

Florencia, 11 de octubre 2023

| |
|--|
| Referencia: CONCEPTO MEDICO SOLICITADO POR HOSPITAL DEPARTAMENTAL MARIA INMACULADA |
|--|

| |
|------------------------------------|
| Abogado asignado: Ana Maria Dussan |
|------------------------------------|

| |
|--|
| Proceso: Gentil Guevara Dussan c.c 17636255 |
|--|

A. Identidad del perito y datos de ubicación:

A efectos de pronunciarme sobre mi idoneidad y experiencia profesional especializada para rendir el concepto, refiero mi historial educativo.

B. Objeto del concepto medico:

Emitir concepto como especialista en Neurocirugía, sobre la atención que se le brindó a la paciente Gentil Guevara Rojas .

C. Documentos recibidos y analizados:

Recibí y analicé los siguientes documentos:

1. Historia clínica inicial y resumen elaborado por la oficina jurídica HMI
2. Cuestionario remitido por la defensa
3. Guías y literatura científica

D. Técnicas empleadas:

Se analizaron los documentos entregados a partir de los conocimientos que poseo en la especialidad de Neurocirugía y la revisión de la literatura en la misma área.

E. Juramento:

Bajo la gravedad del juramento, que se entiende prestado con la suscripción de este documento, declaro que no me encuentro incurso en ninguna de las causales de exclusión contenida en el artículo 50 del CGP y que acepto el régimen jurídico de auxiliares de la justicia.

También declaro que mi opinión es independiente y corresponde a mi real

convicción profesional, que las conclusiones fueron producto del análisis objetivo que realicé del caso en mi calidad de médico especialista en neurocirugía, sin que haya utilizado métodos distintos a los que utilizo en el ejercicio regular de mi profesión.

Asimismo, manifiesto que no he sido perito ni he participado en la elaboración de otros dictámenes o conceptos periciales en este proceso ni para la misma parte/abogado solicitante. No tengo ningún grado de consanguinidad o parentesco con las partes de este proceso y no he realizado publicaciones relacionadas con la materia del presente dictamen.

1. En el presente caso ¿Qué significado tiene el hecho de que el puntaje en la escala de coma de Glasgow sea 3/15?

Significa que el paciente se encontraba en mal estado neurológico y vital al momento de la valoración; la escala de coma de Glasgow indica estado neurológico global pero también es un indicador de pronóstico, en algunos artículos científicos de hecho en pacientes con escala de coma de Glasgow menor, igual a 4 se consideran NO candidatos quirúrgicos

1. ¿A que se refiere la afirmación de que el paciente era rescatable? Dadas las lesiones que se hallaron al momento de la cirugía: ¿realmente tenía posibilidad de sobrevivir este paciente? ¿Y dado el caso que sobreviviera en que condiciones de vida quedaría?

Probablemente la afirmación era “rescatable” se refería a que tenía baja posibilidad de sobrevivir; a alto costo general (físico y emocional del paciente y su familia). Al haber ingresado en una escala de coma de Glasgow de 3 indica que la mortalidad alcanza el 100% aproximadamente

En el paciente describen hallazgos intra operatorios como laceraciones cerebrales y fragmentos metálicos intra cerebrales correspondientes a esquirlas en hemisferio cerebral izquierdo lo que hubiese condicionado en el paciente alteración del estado de conciencia (coma, estado vegetativo persistente o de mínima conciencia), pérdida completa de la capacidad del lenguaje (tanto para entender como para expresarlo; pérdida completa de la movilidad y sensibilidad del lado contralateral a la lesión.

2. En la demanda que cursa contra el HMI, la parte demandante afirma que si este paciente se hubiese intervenido de inmediato a su ingreso, el resultado

sería diferente. Realmente se esperaría un desenlace diferente dada la descripción de las lesiones en la TAC y en los hallazgos durante la cirugía?

Los daños primarios que sufrió este paciente son deletéreos e irreversibles, los proyectiles por arma de fuego generan una injuria o daño cerebral irreversible, es un daño por cavitación, emisión de energía, necrosis de tejido; estos daños son descritos e identificados en la tomografía al ingreso del paciente a la institución y además son encontrados intra operatoriamente; son descritos como hemorragia, laceración y lesión venosa cerebral, además la lesión que sufrió el paciente por la herida por proyectil de arma de fuego por su lesión de características vasculares lo lleva a hipotensión, sangrado masivo y paro cardio respiratorio

3. Considera de que el hecho de que hubo un espacio de aproximadamente 1 hora y media desde el ingreso hasta la intervención quirúrgica, fue determinante en el fallecimiento de este paciente?

Este tiempo no cambia el pronóstico de este paciente, en este caso lo que influye en la sobrevivida es ; la escala de coma de Glasgow al ingreso, lesiones cerebrales extensas generadas por el proyectil de arma de fuego, lesión venosa cerebral

Cordialmente,



Edith Natalia Hernández Segura
Especialista en Neurocirugía
Cirujana de Epilepsia
Neurocirujana pediátrica
c.c 52898144

Telefono: 3183400994

Email: enataliahernandezs@hotmail.com

Dirección: Carrera 5 # 14 – 75. Provenir. Florencia Caquetá

Bibliografía

Robyn D'Agostino , Alexandra Kursinskis · Management of Penetrating Traumatic Brain Injury: Operative versus Non-Operative Intervention. J Surgery Reserch, 2021 Jan;257:101-106.

Jeroen T van Dijck , Florence C Reith. Decision making in very severe traumatic brain injury (Glasgow Coma Scale 3-5): a literature review of acute neurosurgical management . J Neurosurg Sci. 2018 Apr;62(2):153-177

Mohammad Ahmad Jamous Outcome of Craniocerebral Penetrating Injuries: Experience from the Syrian War . J Neurol Surg . 2019 Sep;80(5):345-352

Jeffrey V Rosenfeld · Randy S Bell. Current concepts in penetrating and blast injury to the central nervous system. World J Surg. 2015 Jun;39(6):1352-62

Hussein Fathalla, Ahmed Ashry. Managing military penetrating brain injuries in the war zone: lessons learn. Neurosurg Focus. . 2018 Dec 1;45(6):E6. doi: 10.3171/2018

Edith Natalia Hernández Segura
Cédula de Ciudadanía N° 52,898,144 de Bogotá DC, Colombia



I. DATOS PERSONALES

FECHA DE NACIMIENTO: 12 - Noviembre -1981
LUGAR: Florencia – Caquetá
DIRECCIÓN RESIDENCIAL: Carrera 5ª N° 14 – 75
Celular: 3183400994
E-mail: nataliahernandezs@hotmail.com

II. PERFIL PROFESIONAL

Neurocirujana con Subespecialidad (Fellow) en Neurocirugía Pediátrica y Alta Especialidad en Cirugía de Epilepsia

Neurocirujana con más de siete años de experiencia, competente para evaluar pacientes con patología neuroquirúrgica en Adultos y Niños, incluyendo: evaluación clínica completa e integral del paciente, diagnóstico clínico y paraclínico, tratamiento médico-quirúrgico en patología de adultos y niños (trauma, tumores craneales y espinales, raquis, disrafismos espinales, hidrocefalias complejas, malformaciones craneofaciales, craneosinostosis, espasticidad y epilepsia clínica y quirúrgica).

III. FORMACIÓN PROFESIONAL

PREGRADO / UNIVERSITARIO:

TÍTULO OBTENIDO: **Medica Cirujana**
INSTITUCIÓN: Fundación Universitaria de Ciencias de la Salud
CIUDAD: Bogotá /Colombia
AÑO: 2006

TITULO OBTENIDO: **Especialista en Neurocirugía.**
INSTITUCIÓN: Fundación Universitaria de Ciencias de la Salud
CIUDAD: Bogotá /Colombia
AÑO: 2012

TITULO OBTENIDO: **Especialista en Cirugía de Epilepsia**
INSTITUCIÓN: Universidad Nacional Autónoma de México (UNAM)
Instituto Nacional de Neurología y Neurocirugía (INNN)
CIUDAD: Ciudad de México, México
AÑO: 2017

TITULO OBTENIDO: **Especialista en Neurocirugía Pediátrica**
INSTITUCIÓN: Universidad Nacional Autónoma de México (UNAM)
Hospital Infantil de México/Federico de Gómez (HIMFG)
CIUDAD: Ciudad de México, México
AÑO: 2019

IV. LOGROS ACADEMICOS

PUBLICACIONES

Craneotomía descompresiva en trauma craneoencefálico: Hospital San José de Bogotá/ Hernández Segura Edith Natalia. Repertorio de Medicina y Cirugía (Index). Vol 21, N° 3 (2012) p. 165 – 171. Disponible en link: <http://catalogo.unisucre.edu.co/cgi-bin/koha/opac-detail.pl?biblionumber=23759>

"Electrocorticographic patterns in epilepsy surgery and long-term outcome". RE: JCNP-D-17-00047R1. Accepted Journal of Clinical Neurophysiology. June 2017

Effects of resective epilepsy surgery on the social determinants of health.
Juvenal Barbosa Ortega | Daniel San-Juan | Natalia Hernández Segura | Mario Alonso Vanegas | David J. Anschel. July 2020

ASISTENCIA A ULTIMOS CONGRESOS /ACTIVIDADES ACADEMICAS

- 1. Curso Work Shop Neuroendoscopia.** 24-30 noviembre 2018. San Luis Potosí – México
- 2. 4° Congreso internacional de Neurocirugía Pediátrica del Hospital Infantil de México** *Participación*
Ciudad de México 7-9 marzo 2018
- 3. Congreso de Neurología pediátrica mexicano.**
Puerto Vallarta – México 22-26 mayo 2017
- 4. Congreso Americano de epilepsia.** *Participación*
Houston – Estados Unidos 2-8 diciembre 201
- 5. Congreso Liga Latinoamericana de epilepsia** *Participación*
Cancún – México. 8-12 agosto 2016
- 6. XXV Simposio Internacional de Neurocirugía.** *Participación*
Cartagena de Indias/Colombia 26 al 28 de marzo 2015
- 7. XXII Simposio Nacional de Neurocirugía.** *Participación.* Barranquilla/Colombia 12 - 15 de noviembre 2015.
- 8. 81st AANS Annual Scientific Meeting.** New Orleans/Estados Unidos. 27 abril - 1 mayo del 2013
- 9. XII Congreso Nacional de Neurocirugía** Bogotá del 9 al 12 de Mayo de 2012.
- 10. 33° congreso Latinoamericano de Neurocirugía.** Bogotá/Colombia 26 - 30 octubre del 2008.
- 11. XII Congreso Nacional de Neurocirugía** Bogotá del 9 al 12 de Mayo de 2012.
- 12. II Encuentro Nacional de Neurocirujanos en formación.** Villa de Leiva/Colombia 23 al 25 de junio 2010

FORMACIÓN ACADÉMICA ASOCIADA

Estancia Formativa en Neurocirugía Pediátrica.

Lugar: Hospital Vall d'Hebron – Barcelona / España

Duración: 1 mayo - 15 septiembre 2011

Promedio: 4.0 (8)

Trabajo: Cambios clínicos de pacientes con hidrocefalia comunicante y no comunicante tratados con sistema de derivación con dispositivos anti gravitatorios.

Curso “Proveedores de reanimación básica y avanzada” (BLS-ACLS). Bogotá. 25 al 27 de junio del 2005.

Workshop for Surgeons and 3° Annual Latin American Approaches in Neurosurgery Course. Dallas /Estados Unidos. Diciembre 11 - 14, 2013.

Curso “Proveedores de reanimación básica y avanzada pediátrica” (PALS).
Febrero Ciudad de México 2017

V. EXPERIENCIA LABORAL

EXPERIENCIA PROFESIONAL

Y RELACIONADA:

INSTITUCIÓN:

FUNCIONES:

TIEMPO LABORAL:

CIUDAD:

11 años de Profesional (2006 – 2017)

Clínica Juan N Corpas.

Neurocirujano General

Febrero de 2012 a Abril 2012.

Bogotá/Colombia

INSTITUCIÓN:

FUNCIONES:

TIEMPO LABORAL:

CIUDAD:

Hospital María Inmaculada.

Neurocirujano General

Abril de 2012 a Enero 2016, y desde 08
marzo 2020 a la fecha .

Florencia/Colombia

INSTITUCIÓN:

FUNCIONES:

TIEMPO LABORAL:

CIUDAD:

Saludcoop - Clínica Santa Isabel.

Neurocirujano General

Noviembre de 2012 a Agosto 2015.

Florencia/Colombia

INSTITUCIÓN:

FUNCIONES:

TIEMPO LABORAL:

CIUDAD:

Clínica UROCAQ

Neurocirujano General

Febrero de 2013 a Octubre 2014.

Florencia/Colombia

INSTITUCIÓN:

FUNCIONES:

TIEMPO LABORAL:

CIUDAD:

CORPOMEDICA

Neurocirujano General

Abril 2015 a Noviembre 2015.

Florencia/Colombia

VI. REFERENCIAS

REFERENCIAS LABORALES

NOMBRE: Oscar Zorro
CARGO: Neurocirujano
ENTIDAD: Hospital Universitario San Ignacio
TELEFONO: 3142172423

NOMBRE: Juan Carlos Ortiz
CARGO: Neurocirujano
ENTIDAD: Hospital Moncaleano – Neiva
TELEFONO: 3108827422

NOMBRE: Camilo Díaz
CARGO: Subgerente
ENTIDAD: Hospital María Inmaculada
TELEFONO: 321 479 4064

REFERENCIAS PERSONALES

NOMBRE: Juvenal Adolfo Barbosa Ortega
PROFESION : Abogado y Ph D Economía,
TELEFONO: 3007294905

NOMBRE: William Renan Rodríguez
PROFESION : Abogado, Docente universitario
TELEFONO: 3015013460





INDICE DERECHO

FECHA DE NACIMIENTO **12-NOV-1981**
BOGOTA D.C
(CUNDINAMARCA)

LUGAR DE NACIMIENTO

1.63

ESTATURA

A+

G.S. RH

F

SEXO

15-MAR-2000 BOGOTA D.C.

FECHA Y LUGAR DE EXPEDICIÓN

REGISTRADOR NACIONAL
JUAN CARLOS GALINDO YACHA



A-1500150-00990190-F-0052898144-20180327

0060476525A 1

49677282

ESTADO CIVIL



La salud
es de todos

Minsalud



COLEGIO MÉDICO
COLOMBIANO
CMC

IDENTIFICACIÓN ÚNICA DEL TALENTO HUMANO EN SALUD

EDITH NATALIA HERNANDEZ SEGURA

C.C. 52898144

MEDICO

F. Universitaria de Ciencias de la Salud

Bogotá D.C.

Grado: 17/06/2005

Rethus: 31/01/2006

ESPECIALIZACIÓN EN NEUROCIRUGÍA





Esta tarjeta es un documento público que se expide de conformidad con la ley 1164 de 2007 y el decreto 4192 de 2010. Si esta tarjeta es encontrada, favor devolver al colegio medico colombiano Av. Carrera 15 # 100-43 Oficina 501 - Edificio Avenida 15 P.H.
Info@colegiomedicocolombiano.org

A handwritten signature in black ink, consisting of stylized, flowing letters, positioned above a horizontal line.

Firma Representante Colegio Medico Colombiano



La Universidad Nacional Autónoma de México



otorga a
Edith Natalia Hernández Segura
el grado de
Especialista en Medicina
(Neurocirugía Pediátrica)

en atención a que demostró tener hechos los estudios conforme a los planes autorizados por el Consejo Universitario y haber sido aprobada en el examen de grado que sustentó el día 11 de octubre de 2018 según constancias archivadas en la misma Universidad.

Por mi Raza hablará el Espíritu
Dado en la Ciudad de México, el día 24 de
enero de 2019.

El Secretario General

Dr. Leonardo Lomeli Varegas

El Rector

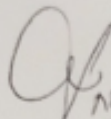
Dr. Enrique Graue Wiechers

Ciudad Universitaria, Cd. Mx.

a 24 de Enero de 2019

anotado a fojas 101 del

libro respectivo.


Natalia Hernández Segura
Firma del Interesado

La Directora General de

Administración Escolar

Mtra. Ivonne Ramírez Wence

| | | | |
|--|---|---|---|
|  | | MÉXICO | 009273 / 2019 |
| SECRETARÍA DE GOBERNACIÓN | | APOSTILLE | |
| (Convention de La Haya du 5 octobre 1961) | | | |
| 1. País (country/pays): México | El presente documento público (This public document / La présente acte public) | | |
| 2. ha sido firmado por: DR. ENRIQUE GRAUE WIECHERS | (has been signed by / a été signé par) | | |
| 3. quien actúa en calidad de: RECTOR. | (acting in the capacity of / agissant en qualité de) | | |
| 4. y está revestido del sello/timbre de: UNIVERSIDAD NACIONAL AUTÓNOMA DE MÉXICO | (bears the seal / est revêtu du sceau / timbre de) | | |
| Certificado (Certified/Attesté) | | | |
| 5. en (at) CIUDAD DE MÉXICO | 6. el día (the day) 01 DE MARZO DE 2019 | LIC. MARTA TERESA URRUTIA CÁRDENAS, DIRECTORA DE COORDINACIÓN POLÍTICA CON LOS PODERES DE LA UNIÓN, EN AUXILIO DEL TITULAR DE LA UNIDAD DE GOBIERNO, CON FUNDAMENTO EN LOS ARTÍCULOS 10 FRACCIÓN I Y 11 ÚLTIMO PÁRRAFO DEL REGLAMENTO INTERIOR DE LA SECRETARÍA DE GOBERNACIÓN. | |
| 7. por (by / par) UNIÓN | | | |
| 8. No. (N°/acus n°) 1 / 8958 / 2019 | 9. Sello/timbre (seal/tamp / sceau/timbre) | 10. Firma (signature) | |
| Tipo de Documento: GRADO DE ESPECIALISTA (Type of document / Type d'acte) | | | |
| Nombre del Titular: EDITH NATALIA HERNANDEZ SEGURA (Name of holder of document / Nom du titulaire) | | | |
| <small>La presente Apostilla certifica la firma, la capacidad del signatario y el sello o el timbre que ostenta. La Apostilla no certifica el contenido del documento para el cual se emite. This Apostille only certifies the signature, the capacity of the signatory and the seal or stamp it bears. It does not certify the content of the document for which it was issued. Cette Apostille ne certifie que la signature, la capacité du signataire ou l'usage du sceau ou du timbre de l'autorité qui l'a émise. Elle ne certifie pas le contenu du document pour lequel elle a été émise. La autenticidad de esta Apostilla y su firma electrónica puede ser verificada en: The authenticity of this Apostille and its electronic signature may be verified at: L'autenticité de cette Apostille et de sa signature électronique peut être vérifiée sur: www.dicoppe.gob.mx/gob.mx/verifica</small> | | | |
| | | Código: (code) 5GT12ATHR |  |

• 185397



República de Colombia
Ministerio de Educación Nacional
y en su nombre la

Fundación Universitaria de Ciencias de la Salud

Personería Jurídica 10917 del 1º de Diciembre de 1976 del Ministerio de Educación Nacional

Facultad De Medicina

En atención a que

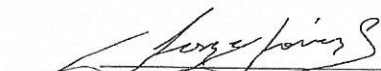
Edith Natalia Hernández Segura

C.C. 52.898.144 de Bogotá D.C.

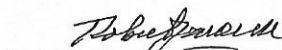
Cumplió satisfactoriamente con todos los requisitos del plan de estudios, le confiere el título de

Especialista En Neurocirugía

En testimonio de ello se firma y refrenda con los respectivos sellos en Bogotá, D.C., a los 10 días del mes de Febrero de 2012


Presidente Consejo Superior


Secretario General


Rector


Decano


Vicerrector


Secretario Académico

Número de Registro 0869 Número de Hoja 94 y 95
Bogotá D.C. 10 de Feb de 2012

El Ministerio de Educación
Nacional certifica para todos
los efectos legales y
académicos en
la institución
superior que expide el presente
documento esta debidamente
reconocida y autorizada por el
Gobierno Nacional.

Atención:
NO SE ASUME LA RESPONSABILIDAD
DEL TEXTO DEL DOCUMENTO

2015 AUG 26 PM 11:15

FIRMA AUTORIZADA

Julia Inés Bocanegra Aldana





Universidad Nacional Autónoma de México
Facultad de Medicina
División de Estudios de Posgrado



otorga el presente

Diploma

a la Médica Especialista en Medicina

**Edith Natalia
Hernández Segura**

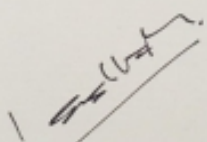
Por haber acreditado el Curso de Posgrado
de Alta Especialidad en Medicina

Cirugía en epilepsia

Impartido del 01 de marzo de 2016
al 28 de febrero de 2017

"Por mi Raza Hablará el Espíritu"
Ciudad Universitaria, Cd. Mx., a 9 de febrero de 2017


Dr. Germán Enrique Fajardo Dolci
Director


Dr. Carlos Lavallo Montalvo
Jefe de la División

BAJO LA INSCRIPCIÓN No. 5250 A FOJAS 125 DEL LIBRO DE REGISTRO DE
DIPLOMAS DE CURSOS DE POSGRADO PARA MÉDICOS ESPECIALISTAS DE LA FACULTAD DE MEDICINA
CON ESTA FECHA QUEDA INSCRITO EL DIPLOMA A FAVOR DE

EDITH NATALIA HERNÁNDEZ SEGURA
EL DÍA 3 DE FEBRERO DE 2017
CIUDAD UNIVERSITARIA, CD. MX, A 9 DE FEBRERO DE 2017

SECRETARIA DE SERVICIOS ESCOLARES

DRA. MARIA DE LOS ANGELES FERNÁNDEZ ALTUNA

SECRETARÍA GENERAL
DIRECCIÓN GENERAL DE ADMINISTRACIÓN ESCOLAR
DIRECCIÓN DE CERTIFICACIÓN Y CONTROL DOCUMENTAL
El que suscribe C.P. AGUSTÍN MERCADO, CERTIFICA
que la firma de la Dra. María de los Ángeles Fernández Altuna es
AUTÉNTICA.
Atentamente
"POR MI RAZA HABLARA EL ESPÍRITU"
Ciudad Universitaria, CDMX, marzo 21 de 2017

C.P. AGUSTÍN MERCADO
DIRECTOR

AMM



DIRECCIÓN GENERAL
ADMINISTRACIÓN ESCOLAR
DIRECCIÓN DE CERTIFICACIÓN
Y CONTROL DOCUMENTAL



MÉXICO
APOSTILLE
(Convention de La Haye du 5 octobre 1961)

021755 / 2017

1. País (country/cays): México El presente documento público
(This public document / Le présent acte public)

2. ha sido firmado por: C.P. AGUSTIN MERCADO
(has been signed by / a été signé par)

3. quien actúa en calidad de: DIRECTOR DE CERTIFICACIÓN Y CONTROL DOCUMENTAL DE LA
(acting in the capacity of / agissant en qualité de) DIRECCIÓN GENERAL DE ADMINISTRACIÓN ESCOLAR

4. y está revestido del sello/ timbre de: UNIVERSIDAD NACIONAL AUTÓNOMA DE MÉXICO
(bears the seal / stamp of / est revêtu du sceau / timbre de)

Certificado
(Certificat)

5. en (at) CIUDAD DE MÉXICO 6. el día (the / le) 14 DE JUNIO DE 2017

7. por (by / par) MARTA TERESA URRUTIA CÁRDENAS, DIRECTORA DE COORDINACIÓN POLÍTICA CON LOS PODERES DE LA
UNIÓN, EN AUSENTO DEL TITULAR DE LA UNIDAD DE GOBIERNO, CON FUNDAMENTO EN LOS ARTÍCULOS 10
FRACCIÓN I Y 11 ÚLTIMO PÁRRAFO DEL REGLAMENTO INTERIOR DE LA SECRETARÍA DE GOBERNACIÓN.

8. No. (N°/issue n°) 1 / 19953 / 2017 9. Sello/ timbre
(seal/stamp / sceau/timbre)

10. Firma
(signature)

Tipo de Documento: DIPLOMA
(Type of document / Type d'acte)
Nombre del Titular: EDITH NATALIA HERNANDEZ SEGURA
(Name of holder of document / Nom du titulaire)

La presente Apostilla está certificada en forma, la expedición del apóstila y el sello o el timbre son
válidos. La Apostilla no se otorga al contenido del documento pero sí a su forma.

Esta Apostilla certifica que el contenido del documento es el que se indica y que el sello o el timbre
son válidos. La Apostilla no se otorga al contenido del documento pero sí a su forma.

Código: (code)
E8FCT7UBR

La autenticidad de esta Apostilla y su firma electrónica puede ser verificada en:
The authenticity of this Apostilla and its electronic signature may be verified at:
L'authenticité de cette Apostilla et de sa signature électronique peut être vérifiée sur:
www.dicopse.unam.mx/verificacion

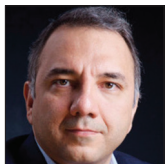
Original Article

Civilian penetrating traumatic brain injury: A 5-year single-center experience

Omid Yousefi¹, Pouria Azami, Roham Borazjani¹, Amin Niakan¹, Mahnaz Yadollahi¹, Hosseinali Khalili¹

Trauma Research Center, Shahid Rajaei (Emtiaz) Trauma Hospital, Shiraz University of Medical Sciences, Shiraz, Iran.

E-mail: Omid Yousefi - omid.y.d@gmail.com; Pouria Azami - pouria.azami95@gmail.com; Roham Borazjani - rohamborazjani@gmail.com; Amin Niakan - aminniakan@gmail.com; Mahnaz Yadollahi - mahnazyadollahi@gmail.com; *Hosseinali Khalili - khalilih16@gmail.com



*Corresponding author:

Hosseinali Khalili,
Trauma Research Center,
Shahid Rajaei (Emtiaz) Trauma
Hospital, Shiraz University of
Medical Sciences, Shiraz, Iran.

khalilih16@gmail.com

Received : 23 December 2022

Accepted : 10 January 2023

Published : 27 January 2023

DOI

10.25259/SNI_1160_2022

Quick Response Code:



ABSTRACT

Background: The aim of this study was to report the demographics and clinical features of patients with penetrating traumatic brain injury (PTBI) during the past 5 years in Rajaei Hospital, a tertiary referral trauma center in Shiraz, southern Iran.

Methods: We conducted a 5-year retrospective evaluation of all patients diagnosed with PTBI who were referred to Rajaei Hospital. We retrieved the following items from the hospital's database and PACS system: patients' demographics, on-admission Glasgow Coma Scale (GCS), presence of trauma to other organs, duration of the hospital and ICU stay, the neurosurgical interventions, any necessity of tracheostomy, duration of ventilator dependency, the entrance point of the trauma in the skull, type of assault, length of trajectory in the brain parenchyma, the number of remaining objects in the brain, the occurrence of any hemorrhagic phenomenon, the cross of the bullet from the midline or coronal suture, and the presence of the pneumocephalus.

Results: A total of 59 patients with a mean age of 28.75 ± 9.40 had PTBI over the 5 years. The mortality rate was 8.5%. Stab wounds, shotguns, gunshots, and airguns were the cause of injury in 33 (56%), 14 (23.7%), 10 (17%), and 2 (3.4%) patients, respectively. The median initial GCS of patients was 15 (3–15). Intracranial hemorrhage was observed in 33 cases, subdural hematoma in 18 cases, intraventricular hemorrhage in eight cases, and subarachnoid hemorrhage in four cases. The mean duration of hospitalization was 10.05 ± 10.75 (ranging from 1 to 62 days). Furthermore, 43 patients experienced ICU admission with mean days of 6.5 ± 5.62 (1–23). The temporal and frontal regions were the most common entrance points, in 23 and 19 patients, respectively.

Conclusion: The incidence of PTBI is relatively low in our center, possibly due to the prohibition of possession or using warm weapons in Iran. Further, multicenter studies with larger sample sizes are needed to determine prognostic factors associated with worse clinical outcomes after PTBI.

Keywords: Gunshot, Penetrating traumatic brain injury, Shotgun, Stab wound, Traumatic brain injury

INTRODUCTION

Traumatic brain injury (TBI) is considered a leading cause of morbidity and mortality in different societies, like Iran.^[23] According to reports, 2.5 million emergency department visits were recorded in the USA due to the TBI.^[7,10]

In Iran, like most of the other regions, the most common underlying cause of TBI is transport accidents, in a way that according to the study, held in our center, 6390 potential years of life lost following TBI were recorded in 2013.^[13]

This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-Share Alike 4.0 License, which allows others to remix, transform, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

©2023 Published by Scientific Scholar on behalf of Surgical Neurology International

Penetrating TBI (PTBI) represents 0.4–1.5% of all TBI cases, but it is believed to cause the highest rate of mortality among TBI patients (up to 42% of TBI-related mortalities).^[7,22]

The majority of PTBI reports reflect the war experiences which are mostly caused by high-velocity missiles and there are not many reports about civilian-based PTBIs in the literature.^[27,33]

The pattern of involvement and piercing objects vary worldwide. In the US, where possession of firearms is not illegal, the annual number of gunshot victims reaches 70/000 cases, which leads up to 30/000 deaths and it is estimated that the target in 14% of all gunshot wounds (GSW) is the brain. It is also believed that the global mortality rate following firearm assaults is increasing.^[2,4]

There are not many reports on the other etiologies of PTBI, such as the shotgun and stab assaults, as there are on gunshots. As a result, the clinical outcomes following PTBI are not favorable in most reports (because they mostly are about gunshots), in a way that a survival rate of 7–15% has been reported after a gunshot to the brain.^[8,10,14]

The aim of the present study is to report the etiology, radiological, and hospitalization characteristics of patients who were admitted to Rajaei Hospital, a tertiary referral trauma center in southern Iran, with the diagnosis of PTBI during the past 5 years.

MATERIALS AND METHODS

All of the patients who were referred to the emergency room of the Rajaei Hospital, a tertiary referral trauma center in Shiraz, southern Iran, with the diagnosis of penetrating brain injury, during the past 5 years were included in the present study.

Patients who passed away before hospital arrival or obtaining brain imaging were excluded from this study. Hospitalization and imaging records of the patients were extracted from the hospital's database and PACS system. By reviewing the obtained brain CT scans, the entrance point, type of assault, length of trajectory, the number of the remaining objects, the occurrence of any hemorrhagic phenomenon, the cross of the bullet from the midline or coronal suture, and the presence of the pneumocephalus were surveyed. The assessment of the injury to the vessels was also conducted by evaluating the CT angiography of the patients.

The information regarding patients' demographics, on-admission Glasgow Coma Scale (GCS), presence of trauma to other organs, duration of the hospital and ICU stay, the neurosurgical interventions, any necessity of tracheostomy, and duration of ventilator dependency were also extracted from the hospitalization records of the patients.

The present study has been approved by the ethics committee of Shiraz University of Medical Sciences and informed

consent has been obtained from the patients and their families for inclusion in this report.

Hospitalization

Based on the findings of the initial brain CT scan, the decision for further interventions was made. Patients were admitted to the ICU when they had significant intracranial hemorrhage (ICH), severe injury to other organs, and on admission GCS of lower than 10.

In cases with suspicion of vascular injury, a brain CT angiography was also obtained.

Cranioplasty and dural repair were performed when indicated, and the removal of the foreign bodies was also conducted when objects were not located in deep-seated or eloquent areas.

In cases with findings in favor of a midline shift of more than 5 mm or raised intracranial pressure, decompressive craniectomy was performed. Following the surgical intervention, patients were transferred to the ICU and then, once they were stable, to the ward.

RESULTS

Of the 59 patients diagnosed with penetrating brain injury, 65 patients were male, and the overall mean age was 28.75 ± 9.40 .

In 10 (17%) patients, the gunshot was the cause of injury, in 14 (23.7%) shotguns, in 33 (56%) stab wounds, and in two patients (3.4%) air guns. All patients affected by firearms, were injured by civilian types, rather than military weapons, and as a result, these types of injuries were considered as low velocity ones.

Thirty-six cases had also injuries to other organs.

The midline cross was observed in four patients, the cross from coronal suture in 14 patients, and the through and through phenomenon in four cases. The mean length of assault trajectory in the brain parenchyma was 21.49 ± 19.3 mm.

ICH was observed in 33 cases, subdural hemorrhage in 18 cases, intraventricular hemorrhage in eight cases, and subarachnoid hemorrhage in four cases. No hemorrhagic phenomenon was observed in 17 cases. The mean volume of the ICH volume was 13.48 ± 14.2 .

The severity of the injury was classified regarding the on-admission GCS of the patients, which is as follows: 1. GCS <8 was categorized as severe, 2. GCS score between 9 and 12 as moderate, and 3. A score of higher than 12 as mild TBI.

The details of the patient's characteristics and imaging findings are provided in [Table 1].

Table 1: On-admission, hospitalization, and imaging characteristics of the patients.

| On admission characteristics | Item | Mean (range)/ Number (percent) | |
|------------------------------|---|--------------------------------|-------|
| On admission characteristics | Cases | 59 | |
| | Age | 28.75±9.40 | |
| | Initial GCS | 11.4 (3–15) | |
| | | Median 15 | |
| | GCS | | |
| | Mild | 35 (59.3%) | |
| | Moderate | 4 (6.8%) | |
| | Severe | 20 (33.9%) | |
| | Blood Pressure | | |
| | SBP | 122±16.5 (55–170) | |
| | DBP | 75±12.6 (31–111) | |
| | Cases with trauma to other organs | 36 (61%) | |
| Imaging findings | Cases with pneumocephalus | 22 (37.3%) | |
| | Depth of tract | 21.49±28.03 | |
| | Cases with assaults crossed over midline | 4 (6.8%) | |
| | Cases with assaults crossed over coronal suture | 14 (23.7%) | |
| | Cases with through and through assaults | 4 (6.8%) | |
| | Cases with assaults having ricochet | 3 (5%) | |
| | Cases with vascular injury | 12 | |
| Course of hospitalization | Days of hospitalization | 10.05±10.75 (1–62) | |
| | Cases with ICU admission | 43 | |
| | Days of ICU stay | 6.5±5.62 (1–23) | |
| | Cases with dependency to ventilator | 28 | |
| | Days of ventilator dependency | 4.17±3.01 | |
| | Cases needing tracheostomy | 7 (11.9%) | |
| | Performed LP | 6 (10.2%) | |
| | Mortalities | 5 (8.5%) | |
| Entrance point | Region | Left | Right |
| | Frontal | 12 | 7 |
| | Temporal | 17 | 6 |
| | Occipital | 4 | - |
| | Parietal | 2 | 3 |
| | Orbital | | 6 |
| | Submandibular | | 2 |

DBP: Diastolic blood pressure, GCS: Glasgow coma scale, ICU: Intensive care unit, LP: Lumbar puncture, SBP: Systolic blood pressure

DISCUSSION

PTBI is defined as an injury to the craniocerebral structures caused by sharp objects with subsequent damage along the trajectory of the piercing insults.^[24,31] PTBI accounted for only 0.4% of all TBIs and based on the setting of occurrence could be categorized into two extended groups: military caused by high-velocity or blast injuries and civilian PTBI (caused by a mixture of high-to-low-velocity injuries).^[31] The literature is scant regarding the features of civilian PTBI.^[24,33] Therefore, the current cross-sectional and registry-based study described the demographic and clinical characteristics of patients with PTBI. We have excluded those who were not alive on hospital arrival or passed away before any documented CT imaging.

It is believed that PTBI has worse clinical outcomes than close blunt head trauma. The overall mortality rate has been reported to vary widely from 34% to 92% in different studies.^[5,10,29,33] Such a high mortality rate is still a significant challenge worldwide. D'Agostino *et al.* performed a secondary analysis of a multicentric study of patients with PTBI who survived more than 72 h after hospital admission to investigate whether the surgical intervention improves the outcomes. They have shown that 48.2% of patients with GCS 3–5 and 8% with GCS>6 died following PTBI.^[5] In our study, only five patients (8.5%) with PTBI died. They all presented to our center with severe TBI following gunshot (two cases) or shotgun injuries (three cases). CT angiography was done in two of these patients showing injuries to bilateral PICA and MCA + PA in another patient.

The low mortality rate did not let us conduct the prognostic statistical analysis; however, by reviewing the literature, several factors are attributed to this rate.

In our study, the mean age was 28.75 years old which was younger than the reported series from Egypt^[33] (a prospective descriptive of 63 patients: age 38.34 ± 15.1), and the US (a retrospective of 26,871 patients with a mean age of 36.2 ± 18)^[27] studies. The previous surveys agreed that younger age is a prognostic factor for improved survival rate.^[3] Deng *et al.* reported a decrease in the mortality rate in younger fire-arm-related victims in the US. The mortality rate was 73.3% in patients >60 years of age and 50.2% in patients between 18 and 29.^[7] Joseph *et al.* showed that survivors following a civilian brain gunshot are younger (28 ± 12 years) than the non-survivors (37 ± 23), although it was not statistically significant.^[12] We believe that the younger age in our population is one of the causes of a higher survival rate than previously reported studies.

In our study, the majority of patients had mild (59.3%) PTBI followed by severe (33.9%) and moderate (6.8%) PTBI. Among patients with severe TBI, 70% had a missile-related injury and in 77.1% of patients with mild PTBI, non-missiles related injuries were the most frequent mechanism. Presenting GCS is influenced by the mechanism of injury and it consequently does affect the final outcomes.

The reported presenting GCS vary widely in the previous studies. Wu *et al.* compared the transbase versus transvauld low-velocity PTBI and showed that the majority of patients with low-velocity of PTBI had mild GCS on hospital arrival (74.1%).^[31] The opposite pattern was reported by Mansour *et al.* where the majority of patients with PTBI and subsequent vascular injuries had severe presenting GCS. In the mentioned study, almost all patients suffered from GSW (71 out of 72 patients).^[17]

The previous studies address several prognostic factors affecting both survival rate and short-to-long-term functional outcomes.^[1,3,11] Ambrosi *et al.* reported that preoperative GCS, pupil conditions, and intracerebral hematomas are prognostic factors among patients following GSW.^[2] In Austria, Marhold *et al.* analyzed 27 patients with PTBI and concluded that initial GCS, trajectory, type of injury (low- or high-velocity), and pupil status are predictors of functional outcomes.^[19]

We have shown that the majority of our patients suffered from a stab wound which is a low-velocity penetrating object. Globally reported, non-missile low-velocity PTBI is a very rare condition. The majority of studies are case reports or series in adult patients and the most frequent causes are occupational, assaults, or self-inflicted.^[9,15,16,21,22,28,30,32]

The civilian PTBI however differs extensively regarding the epidemiology, the underlying mechanisms, and outcomes

between nations. In the US where having gunshot is legal, the majority of assaults are caused by GSW leading to a high-velocity PTBI. In Iran, however, the use of or having a warm weapon is illegal. In contrast to studies from the United States or other regions of the world, the majority of our patients had non-missile and low-velocity stab wounds caused by assault or self-inflicted injuries. PTBI by low-velocity objects causes more localized injuries limited to lacerations or local bleeding along the wound tract. However, gunshots and shotguns are high-velocity (not as high as rifles or ballistic missiles) leading to blast effect and remote damage.^[29]

Shotguns represent a distinct form of ballistic injury due to projectile scatter and variable penetration. Due in part to their rarity, existing literature on shotgun injuries is scarce.^[25] In 2020, Schellenberg *et al.* investigated the epidemiology, injury patterns, and outcomes following shotgun-related PTBI using the National Trauma Data Bank. During 7 years, shotgun PTBI comprised 9% of all firearm injuries. Of included patients, the in-hospital mortality rate was 14% and the head was the most severely injured anatomical location. Unfortunately, this study did not categorize mortality rate by the anatomical locations.^[26] Civilian-based shotgun head injuries are extremely rare in other parts of the world.^[14] In our study, three out of 14 patients with shotgun PTBI have died.

Two of our patients suffering from low-velocity gunshot-related PTBI died in the hospital. The most frequently used weapon in our country is the handgun. Although injuries caused by handguns, hunting rifles, and other “high-velocity” objects have been well-described, events caused by “low-velocity” objects are particularly uncommon.^[34] In our subgroups of shotgun and gunshot injuries, the mortality rate was very low. Therefore, another factor must be attributed as well.

The literature declares that the mortality rate among patients with PTBI is mostly related to missiles' trajectory. By reviewing 27 patients with low-velocity PTBI (stab), Wu *et al.* have shown that injuries through the skull base (transbase) increased the risk of injury to nerves and major vessels, although the patients with transvauld injuries had lower functional outcome scores.^[31] In 2003, Martins *et al.* showed that transventricular (or central type of bihemispheric) PTBI is significantly associated with a higher mortality rate.^[20] DeCuypere *et al.* added deep nuclear and multi-lobar involvement to the transventricular injury as a predictor of dismal survival outcomes among pediatrics following intracranial gunshot injuries.^[6] A systematic review of 1774 patients by Maragos *et al.* has confirmed these patterns of injuries as the mortality predictors.^[18] In our study, of five dead patients, three and two had injuries crossing the midline (biventricular) and coronal plane, respectively. Therefore, our high survival rate may be partially attributed to the trajectories of penetrating objects.

CONCLUSION

PTBI outcomes vary in different centers depending on mostly mechanism of injury. Its incidence and the subsequent mortality rate are relatively low in Iran, possibly due to the prohibition of possession or using warm weapons. Further, multicenter surveys with larger sample sizes are warranted to determine the association of on-admission and imaging characteristics, hospitalization course events, and the final clinical outcomes.

Limitations

Having no follow-up data on neurological deficits and chronic phase complication of the patients is regarded as the main limitation of the current study.

The small sample size is the main limitation of this study, which could have an adverse effect on meaningful comparisons between the subsets.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Publication of this article was made possible by the James I. and Carolyn R. Ausman Educational Foundation.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Aarabi B, Tofighi B, Kufera JA, Hadley J, Ahn ES, Cooper C, *et al.* Predictors of outcome in civilian gunshot wounds to the head. *J Neurosurg* 2014;120:1138-46.
2. Ambrosi PB, Valença MM, Azevedo-Filho H. Prognostic factors in civilian gunshot wounds to the head: A series of 110 surgical patients and brief literature review. *Neurosurg Rev* 2012;35:429-36.
3. Borazjani R, Ajdari MR, Niakan A, Yousefi O, Amoozandeh A, Sayadi M, *et al.* Current status and outcomes of critical traumatic brain injury (GCS= 3-5) in a developing country: A retrospective, registry-based study. *World J Surg* 2022;46:2335-43.
4. Charry JD, Rubiano AM, Puyana JC, Carney N, Adelson PD. Damage control of civilian penetrating brain injuries in environments of low neuro-monitoring resources. *Br J Neurosurg* 2016;30:235-9.
5. D'Agostino R, Kursinkis A, Parikh P, Letarte P, Harmon L, Semon G. Management of penetrating traumatic brain injury: Operative versus non-operative intervention. *J Surg Res* 2021;257:101-6.
6. DeCuyper M, Muhlbauer MS, Boop FA, Klimo P. Pediatric intracranial gunshot wounds: The Memphis experience. *J Neurosurg Pediatr* 2016;17:595-601.
7. Deng H, Yue JK, Winkler EA, Dhall SS, Manley GT, Tarapore PE. Adult firearm-related traumatic brain injury in United States trauma centers. *J Neurotrauma* 2019;36:322-37.
8. Dozier KC, Miranda MA, Kwan RO, Cureton EL, Sadjadi J, Victorino GP. Despite the increasing use of nonoperative management of firearm trauma, shotgun injuries still require aggressive operative management. *J Surg Res* 2009;156:173-6.
9. Finneran MM, Marotta DA, Nardone EM. Nonmissile penetrating head injury with a wooden table leg: An illustrative case. *Clin Case Rep* 2021;9:2424-8.
10. Frösen J, Frisk O, Raj R, Hernesniemi J, Tukiainen E, Barner-Rasmussen I. Outcome and rational management of civilian gunshot injuries to the brain-retrospective analysis of patients treated at the Helsinki University Hospital from 2000 to 2012. *Acta Neurochir* 2019;161:1285-95.
11. Hasar TB, Bir T. Traumatic brain injury due to gunshot wounds: A single institution's experience with 442 consecutive patients. *Turk Neurosurg* 2009;19:216-23.
12. Joseph B, Aziz H, Pandit V, Kulvatunyou N, O'Keeffe T, Wynne J, *et al.* Improving survival rates after civilian gunshot wounds to the brain. *J Am Coll Surg* 2014;218:58-65.
13. Kavosi Z, Jafari A, Hatam N, Enaami M. The economic burden of traumatic brain injury due to fatal traffic accidents in shahid rajaei trauma hospital, shiraz, iran. *Arch Trauma Res* 2015;4:e22594.
14. Kim HR, Go SJ, Sul YH, Ye JB, Lee JY, Choi JH, *et al.* Experience of penetrating gunshot wound on head in Korea. *J Trauma Injury* 2018;31:82-6.
15. Li Z, Chen J, Qu X, Duan L, Huang C, Zhang D, *et al.* Management of a steel bar injury penetrating the head and neck: A case report and review of the literature. *World Neurosurg* 2019;123:168-73.
16. Liu YQ, Zhang QL, Fan XY, Zhang MK, Liu GC. A rare case of craniocervical penetrating injury by a steel bar. *J Craniofac Surg* 2022;33:e365-8.
17. Mansour A, Loggini A, El Ammar F, Ginat D, Awad IA, Lazaridis C, *et al.* Cerebrovascular complications in early survivors of civilian penetrating brain injury. *Neurocrit Care* 2021;34:918-26.
18. Maragkos GA, Papavassiliou E, Stippler M, Filippidis AS. Civilian gunshot wounds to the head: Prognostic factors affecting mortality: Meta-analysis of 1774 patients. *J Neurotrauma* 2018;35:2605-14.
19. Marhold F, Scheichel F, Ladisich B, Pruckner P, Strasser E, Themesl M, *et al.* Surviving the scene in civilian penetrating brain injury: Injury type, cause and outcome in a consecutive patient series in Austria. *Front Surg* 2022;9:923949.
20. Martins RS, Siqueira MG, Santos MT, Zanon-Collange N, Moraes OJ. Prognostic factors and treatment of penetrating gunshot wounds to the head. *Surg Neurol* 2003;60:98-104.
21. Oearsakul T, Kaewborisutsakul A, Jantharapattana K, Khumtong R, Puetpaiboon A, Sangthong B. Multidisciplinary management of a penetrating cerebellar injury by a fishing speargun: A case study and literature review. *Surg Neurol Int* 2021;12:391.
22. Qazi Z, Ojha B, Chandra A, Singh S, Srivastava C, Verma N,

- et al.* Self inflicted stab with a knife: An unusual mode of penetrating brain injury. *Asian J Neurosurg* 2017;12:276-8.
23. Saatian M, Ahmadpoor J, Mohammadi Y, Mazloumi E. Epidemiology and pattern of traumatic brain injury in a developing country regional trauma center. *Bull Emerg Trauma* 2018;6:45-53.
 24. Santiago LA, Oh BC, Dash PK, Holcomb JB, Wade CE. A clinical comparison of penetrating and blunt traumatic brain injuries. *Brain Inj* 2012;26:107-25.
 25. Schellenberg M, Inaba K, Heindel P, Forestiere MJ, Clark D, Matsushima K, *et al.* The diagnostic dilemma of shotgun injuries. *Eur J Trauma Emerg Surg* 2020;46:1351-6.
 26. Schellenberg M, Owattanapanich N, Cremonini C, Heindel P, Anderson GA, Clark DH, *et al.* Shotgun wounds: Nationwide trends in epidemiology, injury patterns, and outcomes from US trauma centers. *J Emerg Med* 2020;58:719-24.
 27. Skarupa DJ, Khan M, Hsu A, Madbak FG, Ebler DJ, Yorkgitis B, *et al.* Trends in civilian penetrating brain injury: A review of 26,871 patients. *Am J Surg* 2019;218:255-60.
 28. Sweeney JM, Lebovitz JJ, Eller JL, Coppens JR, Bucholz RD, Abdulrauf SI. Management of nonmissile penetrating brain injuries: A description of three cases and review of the literature. *Skull Base Rep* 2011;1:39-46.
 29. Turco L, Cornell DL, Phillips B. Penetrating bihemispheric traumatic brain injury: A collective review of gunshot wounds to the head. *World Neurosurg* 2017;104:653-9.
 30. Wahyudi, Zaky A, Islam AA, Rosyidi RM. An extremely rare case: Transorbital penetrating intracranial injury by wooden foreign body. Case report. *Ann Med Surg* 2021;71:102937.
 31. Wu Y, Chen TG, Chen SM, Zhou L, Yuan M, Wang L, *et al.* Trans-base and trans-vault low-velocity penetrating brain injury: A retrospective comparative study of characteristics, treatment, and outcomes. *Chin J Traumatol* 2021;24:273-9.
 32. Xue H, Zhang WT, Wang GM, Shi L, Zhang YM, Yang HF. Transorbital nonmissile penetrating brain injury: Report of two cases. *World J Clin Cases* 2020;8:471-8.
 33. Yousef MS, Attia SM, Ahmed ME, Nabeeh MM. Patterns and outcomes of patients with penetrating head injury. *Egypt J Hosp Med* 2022;87:1010-6.
 34. Zyck S, Toshkezi G, Krishnamurthy S, Carter DA, Siddiqui A, Hazama A, *et al.* Treatment of penetrating nonmissile traumatic brain injury. Case series and review of the literature. *World Neurosurg* 2016;91:297-307.

How to cite this article: Yousefi O, Azami P, Borazjani R, Niakan A, Yadollahi M, Khalili H. Civilian penetrating traumatic brain injury: A 5-year single-center experience. *Surg Neurol Int* 2023;14:28.

Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Journal or its management. The information contained in this article should not be considered to be medical advice; patients should consult their own physicians for advice as to their specific medical needs.

Current Concepts in Penetrating and Blast Injury to the Central Nervous System

Jeffrey V. Rosenfeld · Randy S. Bell ·
Rocco Armonda

Published online: 2 December 2014

© The Author(s) 2014. This article is published with open access at Springerlink.com

Abstract

Aim To review the current management, prognostic factors and outcomes of penetrating and blast injuries to the central nervous system and highlight the differences between gunshot wound, blast injury and stabbing.

Methods A review of the current literature was performed.

Results Of patients with craniocerebral GSW, 66–90 % die before reaching hospital. Of those who are admitted to hospital, up to 51 % survive. The patient age, GCS, pupil size and reaction, ballistics and CT features are important factors in the decision to operate and in prognostication. Blast injury to the brain is a component of multisystem polytrauma and has become a common injury encountered in war zones and following urban terrorist events. GSW to the spine account for 13–17 % of all gunshot injuries.

Conclusions Urgent resuscitation, correction of coagulopathy and early surgery with wide cranial decompression may improve the outcome in selected patients with severe craniocerebral GSW. More limited surgery is undertaken for focal brain injury due to GSW. A non-operative approach may be taken if the clinical status is very poor (GCS 3, fixed dilated pupils) or GCS 4–5 with adverse CT findings or where there is a high likelihood of death or poor outcome. Civilian spinal GSWs are usually stable neurologically and biomechanically and do not require exploration. The indications for exploration are as follows: (1) compressive lesions with partial spinal cord or cauda equina injury, (2) mechanical instability and (3) complications. The principles of management of blast injury to the head and spine are the same as for GSW. Multidisciplinary specialist management is required for these complex injuries.

Introduction

The majority of homicides and suicides involve the use of firearms and disproportionately affect persons <55 years, males and certain minority populations [1]. The experience

of civilian neurosurgeons with penetrating CNS trauma varies depending on their location. CNS blast injuries have been encountered frequently by military surgeons in Iraq and Afghanistan and are increasingly encountered by civilian neurosurgeons because of terrorist bombings in urban environments. Craniocerebral gunshot wounds

J. V. Rosenfeld
Department of Neurosurgery, The Alfred Hospital, Melbourne,
Australia

J. V. Rosenfeld (✉)
Department of Surgery, Monash University, 6th Floor, The
Alfred Centre, 99 Commercial Road, Clayton, Melbourne,
Australia
e-mail: j.rosenfeld@alfred.org.au

J. V. Rosenfeld · R. S. Bell · R. Armonda
Department of Surgery, F. Edward Hébert School of Medicine,
Uniformed Services University of the Health Sciences, Bethesda,
MD, USA

R. S. Bell · R. Armonda
Department of Neurosurgery, MedStar-Georgetown University
Hospital and Washington Hospital Center, Washington, DC,
USA

(GSWs) and blast-injured patients are arguably among the most complex and surgically challenging trauma encountered by neurosurgeons.

This review focuses on current concepts and treatment strategies for penetrating craniocerebral and spinal injury due to gunshot wounds (GSWs), blast injury and knives and other sharp implements. Aggressive management is usually recommended for craniocerebral GSW presenting with Glasgow Coma Score (GCS) 6–12. There is controversy as to how aggressively to treat the craniocerebral GSW in patients with GCS 3–5 [2]. Many authors have advocated an expectant approach because of likely poor outcome or death. However, there has been recent advocacy for a more ‘aggressive’ approach to the management of these patients with evidence emerging of improved survivability. For instance, in one trauma center in Tucson, Arizona, survival rates improved from 10 % in 2008 to 46 % in 2011 [3]. In this review, we describe the likely factors which have resulted in the improved outcomes for these patients and discuss selection of patients for surgery, the principles of surgery and prognosis.

The treatment of penetrating spine injuries remains controversial due to the weak strength of the evidence for different treatment strategies [4]. Military penetrating spinal injury tends to be more destructive than civilian injury and may require more extensive surgery. Civilian neurosurgeons on call for trauma should be prepared to manage penetrating CNS trauma.

This review is based on the current literature, published guidelines and our personal experience of managing patients with penetrating and blast injury to the CNS and does not represent the official policy of either United States Department of Defense or the Australian Defence Force.

Craniocerebral GSW

Epidemiology

Craniocerebral GSWs are the most lethal of civilian firearm injuries with up to 71 % dying at the scene, 66–90 % dying before reaching hospital and survivals of up to 51 % reported of those reaching hospital [3, 5, 6]. The mortality is higher with self-inflicted GSW because of the close range of the weapon. In a recent study of craniocerebral GSW in the State of Maryland, USA, there were 786 patients in a 2-year retrospective study. Five hundred and ninety-four (76 %) died at the scene, and 118 (15 %) died during the course of the hospitalization [5]. Mortality of craniocerebral GSW after admission was 69 % in Aarabi et al.’s study [5] with 30.4 % dead on arrival. Less than 20 % of the total population of craniocerebral GSW will receive neurosurgical treatment [5]. Approximately 50 %

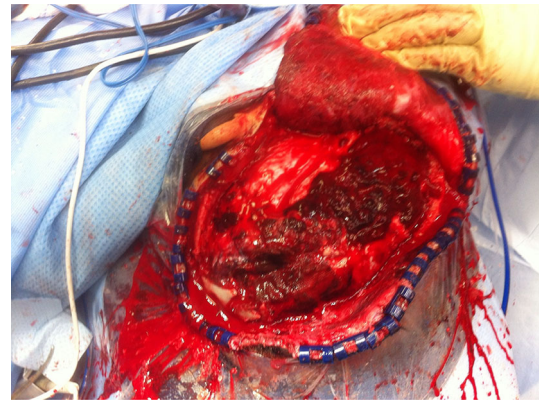


Fig. 1 Operative photograph showing a gunshot wound to the left parietal lobe. The craniotomy has been performed and the dura opened. The upper part of the ear lobe is exposed in the upper operative field. Note the gross hemorrhagic track of the bullet with surrounding swollen brain. The wound was contaminated with dirt

of those craniocerebral GSWs who make it to a trauma center alive are discharged to rehabilitation [5].

Pathophysiology

Ballistic aspects of the wounding should always be considered including the type of weapon used, the proximity of fire, bullet caliber, jacketing and velocity [7, 8]. The volume of injured brain and size of cavitation adjacent to the path of the missile are dependent on the kinetic energy imparted to the brain by the missile. This depends on the velocity of the missile at the point of impact with the head and the thickness of the skull. The extent of brain injury also depends on the size, shape, spin and yaw of the missile, and whether it fragments. The principal pathological effects of craniocerebral GSW are brain swelling, intracranial hemorrhage and penetrating injury with bone and metal fragments and other foreign bodies (see Fig. 1).

Prehospital care

Maintenance of airway, and adequate ventilation, correction of hypoxia and hypotension are crucial to prevent secondary brain injury. Advanced paramedic training and efficient trauma systems may deliver more craniocerebral GSW victims to trauma centers alive.

Emergency room treatment (see Table 1)

In a 5-year retrospective review of 132 civilian patients with craniocerebral GSW, increasing survival was associated with aggressive resuscitation in all patients, and resuscitation with blood products and hyperosmolar fluids were independently associated with survival [3]. GCS 3–5

Table 1 Emergency room treatment of craniocerebral GSW

| |
|--|
| Early aggressive resuscitation ('damage control resuscitation') |
| Correct hypotension, hypoxia |
| Maintain PaCO ₂ in the normal range |
| Hypertonic saline for brain swelling |
| Urgent control of cervical vascular injury |
| Avoid excessive crystalloid |
| Early correction of traumatic coagulopathy with combinations of blood, blood products (fresh-frozen plasma, platelets), cryoprecipitate or prothrombin complex concentrate [3] |
| Surgical airway if gross maxillofacial trauma or facial/respiratory tract burns are present |
| Packing nasal cavity and facial wounds to control hemorrhage |
| Urgent CT scan |
| Tetanus prophylaxis |
| Antibiotic prophylaxis |

and bihemispheric injury should not prevent early resuscitation, but a decision for expectant supportive care should come when the patient has been stabilized and then reassessed as some may improve. It is therefore the post-resuscitation GCS that should be used for decision making. Excessive crystalloid, permissive hypotension, hypoxia and hypercapnia should all be avoided.

Acute traumatic coagulopathy (ATC) may develop in patients with isolated head injury (which includes GSW) and in the setting of multiple injuries with major blood loss and shock [9, 10]. This latter scenario includes multiple gunshot wounds or blast injury. The diagnosis and treatment of acute traumatic coagulopathy should be made rapidly, and replacement of blood and clotting components proceed as soon as possible. Massive transfusion protocols have been developed in many trauma centers [11]. However, the optimal ratio of plasma, packed red cells and platelets to treat acute traumatic coagulopathy is uncertain and remains under investigation [12]. Cryoprecipitate, prothrombin complex concentrates (PCC) and tranexamic acid are variably used in the resuscitation phase [11]. The effect of Vitamin K administration is delayed 6–12 h and so is not useful in the resuscitation phase. Off-label use of recombinant Factor VIIa is an option, but the American Society of Anesthesiologists recommends use on a case-by-case basis because of the risk of serious adverse events [13]. ATC after head injury increases the risk of mortality [14, 15]. Whether early correction of ATC improves outcome remains to be confirmed [11].

Indications for surgery for craniocerebral GSW

Minor pellet injuries to the brain with small entry wounds may only require local debridement, closure and antibiotics. More severe focal injuries with hemorrhage and

Table 2 Clinical factors associated with poor outcome following civilian craniocerebral gunshot wound (GSW) [27, 56]

| |
|--|
| GCS <5 (post-resuscitation) on admission |
| Dilated, unreactive pupil(s) |
| Occipital entry wound |
| Brainstem injury |
| Injury to 'eloquent' brain |
| High-velocity missile injury (e.g., semiautomatic military-type weapons) |
| Hypotension on admission |
| Major intracranial vascular injury |
| High ICP |
| Onset of diabetes insipidus [16] |
| Suicide attempt (because of close range) |
| Increased retrieval time |
| Coagulopathy or disseminated intravascular coagulation (DIC) |
| Advanced age |

Comment: Bilateral frontal lobe injuries (often seen after suicide attempts) have better survival prospects than other bilateral injuries, but cognitive deficits and personality change may be profound

fragments without adverse radiological features may also only require local exploration via a small craniotomy. More severe penetrating injuries will require extensive surgery if a decision is made to operate. This may include decompressive craniectomy, debridement, evacuation of hematomas, dural repair and insertion of an ICP monitor. The great challenge and dilemma for the neurosurgeon treating a severe craniocerebral GSW is whether to pursue surgery and survival of the patient at all costs or alternately, whether to pursue quality of survival and therefore expectant treatment in selected patients. The disadvantage of active treatment, including surgery on patients with a predicted poor prognosis, will result in increased numbers of minimal conscious state (vegetative) and severe disability survivors who may be a burden on their family and the healthcare system.

There are a number of clinical findings and imaging features which are significant determinants of outcome (see Tables 2 and 3). These include age, admission GCS, abnormal pupil reactivity, and the trajectory of the missile and obliteration of the basal cisterns [5, 16]. These should all be considered when deciding to pursue aggressive management and surgery on the individual patient [6]. The current management of penetrating injury to CNS is based mainly on retrospective observational studies [17]. Clinical practice guidelines for the management of civilian and military penetrating brain injury have been published [18, 19].

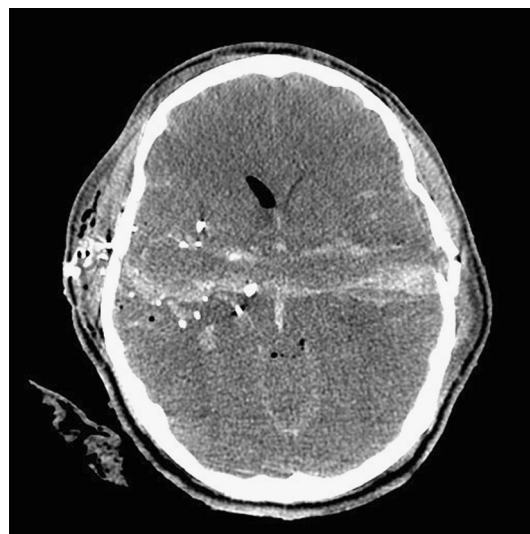
Active management has often been withheld in patients with GCS 3–5, particularly if there is a bihemispheric injury. If the trajectory passes through both thalami and

Table 3 CT features associated with poor outcome following civilian craniocerebral gunshot wound (GSW)

| |
|--|
| Multilobar or bihemispheric injury |
| Ventricular injury with hemorrhage |
| Diffuse fragmentation |
| Missile passing through the geographic center of the brain (i.e., involving the thalamus and basal ganglia) An area 4 cm above the dorsum sellae was described as the <i>zona fatalis</i> [16] |
| Trajectory crossing the x, y and z planes |
| Midline shift >10 mm on CT (Caveat: Kim et al. [16] found midline shift was associated with better outcome presumably because one hemisphere is traversed rather than both hemispheres) |
| Compressed or obliterated basal cisterns |
| Large intracerebral hemorrhage |
| Subarachnoid hemorrhage (SAH) [56] |
| Large volume of contused brain |
| Posterior fossa wound with brainstem involvement |
| ‘ <i>Tram track sign</i> ’ hemorrhage on either side of a dark center track in a perforating injury [16] (see Fig. 1) |

basal ganglia or through the posterior fossa and brainstem, the patient is unlikely to survive or be better than vegetative and should be managed expectantly. Kim et al. [16] performed a Cartesian vector analysis on trajectories on CT scans of 217 civilian through-and-through GSW to the head and found midline brain shift was more common in survivors probably because the injury was predominantly unilateral in these cases. They also found that an area of brain approximately 4 cm above the dorsum sellae when penetrated across the midline led to brain death. They coined the term ‘*zona fatalis*’ for this area. Kim et al. [16] also described the ‘*tram track sign*’ which is a dark central track with a hyperdense line of blood on either side (Fig. 1). This sign was associated with fatal injury ($p = 0.005$) (see Fig. 2).

Surgery is not recommended for a craniocerebral GSW, GCS 3 with fixed dilated pupils following resuscitation and no mass lesion on CT [2]. Kaufman et al. [2] recommend operating on patients with GCS 3, if the pupils are reactive and the patient is hemodynamically stable and, for GCS 4–6, if the pupils are reactive and the patients are not hypotensive or if the pupils are fixed and dilated and there is a motor response. Kaufman et al. [2] have reported some good outcomes in these patient groups. This management is clearly controversial, and other clinical and CT scan adverse factors will need to be considered and may sway the surgeon against surgery in these severe craniocerebral GSW. Patients with GSW who suddenly deteriorate with mass lesions on CT should have immediate surgery [2]. In patients with craniocerebral GSW, if there is an intracranial mass lesion, unequal pupils or reacting pupils, we recommend urgent craniotomy unless there is brainstem or

**Fig. 2** Axial CT scan showing the ‘tram track sign’. The bullet has traversed the cerebral hemispheres with streaks of blood on either side of the low density track. This resulted in a fatal outcome for the patient

bilateral thalamic, basal ganglia injury. Brain swelling with minimal hemorrhage may also be an indication for urgent craniectomy. Each patient should be judged on a case-by-case basis. Based on the current evidence, GCS <5 is not an absolute contraindication for surgery.

The principles of surgery for craniocerebral GSW

The principles of surgery for craniocerebral GSW have been well described. The salient points are as follows: urgent surgery should be undertaken within 1 h of arrival, preferably within 30 min. A surgical airway should be performed if the upper airway affected by swelling or severe injury. Gaining rapid control of hemorrhage in the brain, head and neck is a vital component of the prevention and treatment of shock and coagulopathy in these patients. Urgent packing of the nasal cavity and facial wounds and balloon tamponade of the nasopharynx may be required to control hemorrhage. Current neurosurgical practice favors more aggressive decompression of the brain (unless there is a focal injury) and less aggressive debridement and retrieval of deep bone and metal fragments [20]. Deep exploration for fragments increases the risk of morbidity. Irrigation of the missile track can release debris. Wide decompressive craniectomy should be performed where there is significant cerebral swelling seen on CT [21]. ICP monitoring is performed. The options are ventriculostomy drain which enables CSF venting and therefore treatment of raised ICP and/or a parenchymal ICP monitor.

The risk of infection increases with acute or delayed CSF leak, paranasal sinus continuity with the cranial

Table 4 Criteria for removal of intracranial metal fragments

| |
|---|
| Large fragments in superficial locations |
| Heavy metal toxicity |
| Large fragments within the ventricles |
| Large fragments within the CSF cisterns |
| Fragments that are mobile or associated with intermittent hydrocephalus |
| Fragments/large foreign bodies related to large blood vessels |

cavity, transventricular injury and injuries crossing the midline [22–24] Heavy wound contamination and delayed surgery may also be adverse factors. Therefore, watertight dural closure is essential. The elimination of CSF leak, adequate debridement of contaminated wounds and early surgery are important strategies to reduce infection risk. A duraplasty using pericranium or dural substitute will permit further cerebral expansion and allow for dural closure. Primary scalp closure should be performed. Advancement or rotation scalp flaps may be required to achieve closure.

There is considerable variability in the literature on the use of prophylactic antibiotics [23]. Bayston et al. [25] performed a systematic review of prophylactic antibiotics for penetrating craniocerebral trauma and found only retrospective and anecdotal studies. They recommended broad-spectrum antibiotic prophylaxis for both military and civilian penetrating craniocerebral injury. Staphylococci are important potential pathogens and Gram-negative bacilli may also be involved. Bayston et al. [25] recommended cephalosporin alone or with gentamicin for 5 days as the minimum prophylaxis. When the wounds are contaminated with soil or excreta or where clothing is in-dri-ven, anaerobic cover with metronidazole is recommended. The possibility of delayed fungal infection should be also considered [25]. Broad-spectrum antibiotic cover is also recommended in the penetrating brain injury guidelines [23]. Lin et al. [17] recommended broad-spectrum prophylactic antibiotic cover with vancomycin, gentamycin and metronidazole for 48–72 h.

The experience of craniocerebral penetrating trauma in US military personnel from the Iraq and Afghanistan wars is that broad-spectrum cover was associated with appreciable rates of multi-drug resistant organisms particularly *Acinetobacter* requiring meropenem. Therefore, the current recommendation of the US military guidelines is cephazolin for 5–7 days [26]. We recommend that infectious disease physicians should be involved in the choice and duration of antibiotic prophylaxis for these injuries.

Anticonvulsant prophylaxis is continued for 1 week. Collaboration with ENT, ophthalmology, maxillofacial, plastics and vascular surgeons will be required where there is complex craniofacial wounding. Metal fragments removed at surgery are kept for forensic evidence.

Table 5 Survival for civilian GSW to the head [27] [57]

| GCS after resuscitation | Survival |
|-------------------------|--|
| GCS 3–5 | 0–8.1 % [27], 28 % [3], 100 % in 4 patients [17], 0 % for GCS 3, 4 [16], 5 % [5], 40 % (GCS 3–4) [6] |
| GCS 6–8 | 35.6 % [27], 83.3 % (with 2 lost to F/U) [5] |
| GCS 9–15 | 90.5 % [27], 84.6 % (with 4 lost to F/U) [5] |

Lin et al. [17] have presented useful practical technical advice to enable rapid and successful surgery. Their mantra for treating GSW to the brain is “time is brain”. Perhaps the remarkable recovery in the high profile case of the near-fatal cerebral GSW injury to Congresswoman Gabrielle Giffords in the USA in 2011 which Lin et al. [17] call the ‘Giffords factor’ will encourage a more aggressive and rapid approach to severe craniocerebral GSW. Giffords had surgery about 38 min from arrival at the hospital. Aarabi et al. [5] performed surgery in 28 of 48 resuscitated patients (58 %). There was simple debridement and skin closure in 9 (19 %) patients, and craniotomy or decompressive craniotomy in 19 (40 %) patients. Of the 5 (10 %) who had decompressive craniectomy, 3 were done acutely and 2 for intractable intracranial hypertension.

The complications of craniocerebral GSW

Complications of craniocerebral penetrating injury have been reviewed [18, 27] and include pseudoaneurysm, cerebral vasospasm, cerebral abscess, meningitis, ventriculitis, epilepsy and hydrocephalus. GSW may cause subarachnoid hemorrhage which is associated with cerebral vasospasm. The vasospasm is diagnosed with daily transcranial Doppler studies. Transluminal angioplasty may be required [28, 29]. Pseudoaneurysms, which have a reported incidence of 20–50 % of penetrating head injuries, require early angiographic diagnosis and definitive multimodality treatment [30]. The criteria for digital subtraction angiography (DSA) following penetrating brain injury have been described by Bell et al. [30]. Those are as follows:

1. Penetrating injury through the pterional/orbitofrontal region
2. Known cerebral vessel injury with or without pseudoaneurysm seen at the initial exploration
3. Blast injury with GCS <8 (closed or penetrating)
4. Transcranial Doppler (TCD) evidence of vasospasm
5. Spontaneous, unexplained decrease in the partial pressure of brain oxygen (PbrO₂) [30]

Lead toxicity is uncommon but lead levels should be monitored if there are major embedded metallic fragments.

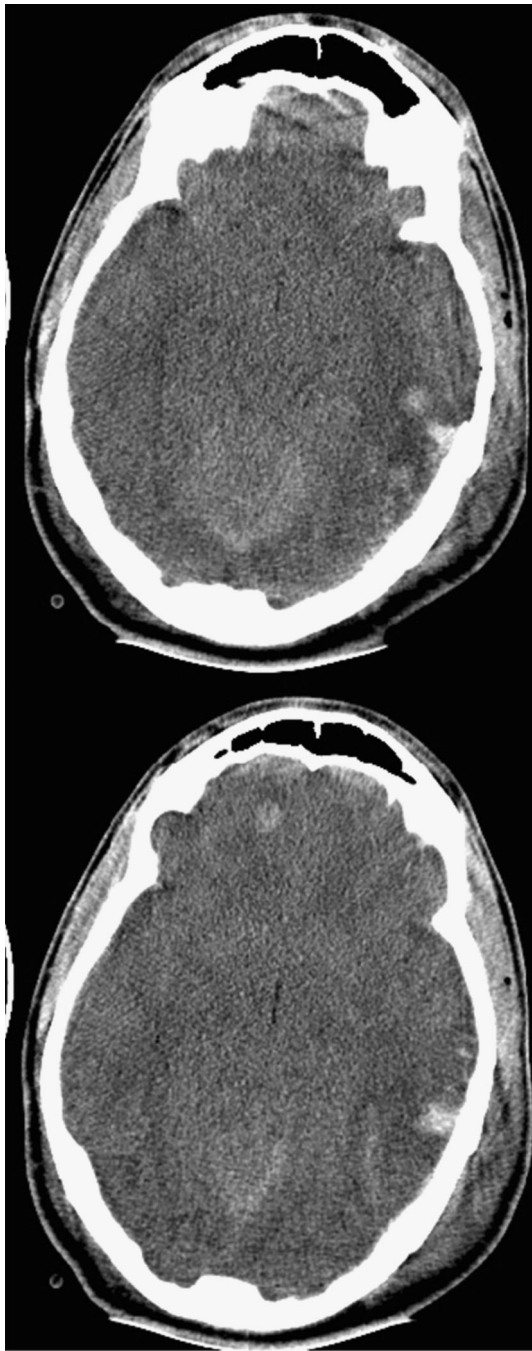


Fig. 3 Axial CT scans showing non-penetrating blast overpressure effect on the brain. *Note* the generally swollen brain with loss of basal cisterns, slit-like third ventricle, loss of *gray-white* differentiation and multiple hemorrhagic contusions

The indications for removal of retained bullet or metal fragments are limited and are outlined in Table 4. Those large fragments located in CSF cisterns or the ventricles should be considered for removal as well as those that are superficially located. Additional indications include heavy metal toxicity symptoms for those in CSF including

delayed lead (Pb) and copper (Cu) toxicities. Delayed extraction of a bullet or a major metal fragment may be aided by stereotactic techniques or fluoroscopic ‘c’ arm [31]. Those fragments embedded in brain tissue that do not migrate and are not easily accessible can be followed with noninvasive imaging.

The prognosis of craniocerebral GSW

Survival correlates with post-resuscitation GCS, but the figures vary considerably between series (see Table 5), particularly in those with low GCS. Gressot et al. [6] retrospectively reviewed 119 patients admitted to hospital with GSW to the head. The overall outcome was 49 % death, 19 % favorable outcome and 35 % had poor outcome. However, of those with an initial GCS of 3–4, only 11 % had a good outcome and 89 % had a poor outcome or death, whereas for those with GCS 5–15, there were 27 % good outcomes and 73 % poor outcome or death. In Aarabi et al.’s [5] series, 20 patients were admitted with GCS 3–5 and 19 (95 %) of those died. Of 8 patients with GCS 6–8, one died, one was severely disabled and 3 had mild to moderate disability. All 4 patients with GCS 9–12 had Glasgow Outcome Score (GOS) of 4 which is a moderate disability (disabled but independent). Of 13 patients with GCS 13–15: 2 died, 7 had GOS 4 and 4 were lost to follow-up. Lin et al. [17] report on 4 patients with GCS <5 on admission with civilian craniocerebral GSW. Two had a unilaterally dilated pupil, 2 had equal and reacting pupils. One had a GCS 3. Three out of 4 were functionally independent at 1 year. Joseph et al. [3] reported survival of 28 % in patients with GCS 3–5 and 22 % in patients with bihemispheric injuries. Of those who presented with a GCS 3–5, 18 % were discharged with a GCS >8. The proportion who became independent is unknown. Glapa et al. [32] reported a series of 72 civilian patients with a mortality of 81 % for GCS ≤8 versus 14 % for GCS >8.

There are many clinical factors associated with poor outcome following civilian craniocerebral GSW. These are outlined in Table 2 and include the time to reach a neurosurgeon, age, GCS post-resuscitation, pupil size and reactivity, and the presence of hypoxia or hypotension. GCS >8 is one of the most important predictive factors for a good outcome [5]. The weapon ballistics should also be considered by the clinician.

Certain CT features are associated with poor outcome following civilian craniocerebral GSW and are outlined in Table 2. The trajectory of the bullet in crossing ‘x’, ‘y’ and ‘z’ planes was more significant on regression analysis than obliteration of basal cisterns and intraventricular hemorrhage [5].

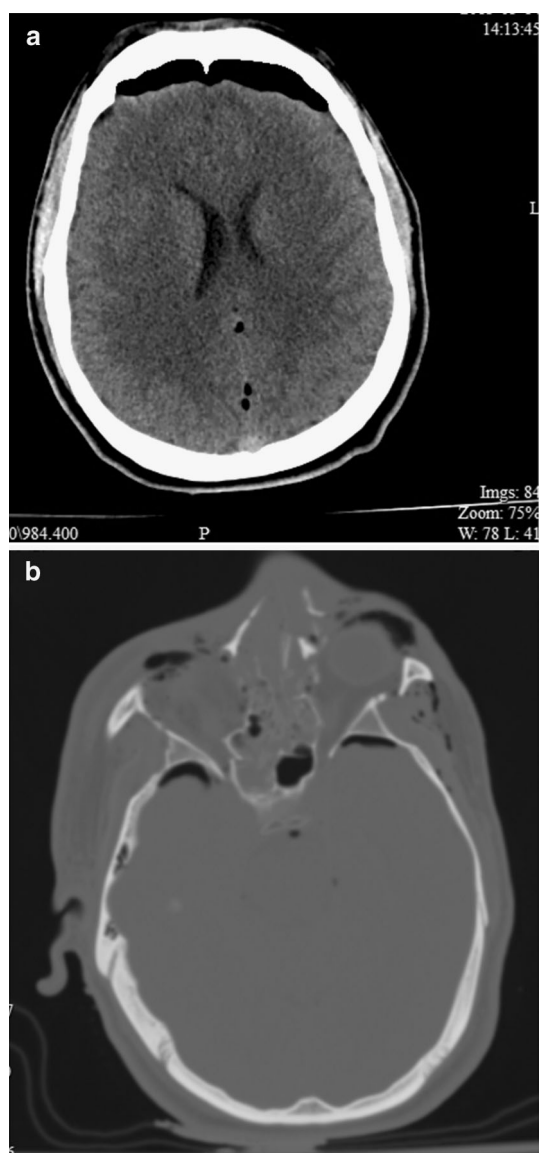


Fig. 4 **a** IED injury in a 23-year-old male causing facial lacerations, right globe disruption, oral lacerations, penetrating neck wound and lower extremity injuries. He had fractures to the midface, right orbit and frontal sinus. Axial CT showing a large frontal aerocele and multiple other small intracranial air bubbles. **b** Axial CT bone windows showing extensive fractures to the nasal bones, ethmoid and sphenoid sinuses and the right orbit

Blast injury to the brain

Blast injuries due to improvised explosive devices (IEDs) have been increasingly encountered in the Iraq and Afghanistan wars and in terrorist events in many countries. The pathophysiology of blast injury is more complex than GSW [33]. Bomb explosions cause injury to the brain by three main mechanisms: (1) the overpressure wave which is transmitted through the skull and is also probably ‘funnelled’ through skull openings (orbits, nasal cavity,

temporal bones and foramen magnum; (2) metal fragments and other foreign bodies penetrating the skull and entering the brain; (3) hot gases generated by the blast cause skin and respiratory burns [33].

The blast wave frequently causes severe cerebral edema (see Fig. 3). Moderate and severe blast injuries frequently involve penetrating craniocerebral injury and are usually a component of polytrauma rather than isolated head injury. These wounds are usually heavily contaminated. Subarachnoid hemorrhage is common. Civilian neurosurgeons should become familiar with the patterns of blast injury and the management.

Principles of management

Multidisciplinary teams are best-equipped to manage these complex injuries of the head and neck, and the treatment has recently been reviewed [33]. A thorough primary and secondary survey are mandatory. The external wounds can be deceptive and do not reveal the extent of internal damage or the trajectory and final position of penetrating fragments. Facial and sinus penetration, orbital injury and skull base disruption are often present given the upward and outward trajectory of blasted fragments (see Fig. 4a, b). With these injury patterns in mind, management principles are guided by rapid cranial decompression [21], early repair of skull base injury with consideration of CSF diversion, early diagnosis and management of traumatic vascular injuries which are common, and delayed facial and cranial reconstruction to allow for resolution of the inevitable local and systemic infections that arise.

Hemicraniectomy also protects patients from the effects of brain swelling during air transport to definitive care [34]. The problem of SAH, vasospasm and pseudoaneurysm described in the craniocerebral GSW section also occurs following blast injury [28–30].

Outcome

In the prospective study of Weisbrod et al. [35], 32 % of those presenting with a GCS 3–5 and 63 % of those with GCS 6–8 achieved functional independence 2 years following severe blast or penetrating TBI. Significant improvement may occur in individuals with severe blast or penetrating TBI over one to 2 years [35, 36].

In a retrospective study of 604 patients, outcomes of a military population with isolated blast and penetrating severe TBI compared favorably with those of a matched civilian population [37]. A lower overall mortality was found in the military population (7.7 vs. 21.0 %; $p < 0.001$; odds ratio 0.32 [0.16–0.61]). This difference was more pronounced in the penetrating group (5.6 vs. 47.9 %; $p < 0.001$; odds ratio, 0.07 [0.02–0.20]) [37].

Many factors may account for the differences, including higher neurosurgical intervention rates and fewer high-velocity single-bullet injuries in the military population [33].

Craniocerebral stab wounds

Craniocerebral penetrating injuries due to knives, arrows, nail guns, spears and other sharp implements are uncommon. Machete injuries to the head are common in parts of Africa. These may cause compound depressed fractures with neurological deficit [38]. The principles of surgery for craniocerebral stab wounds are the same as for GSW. The foreign body should not be removed without surgical control of major vessels in proximity. Most craniocerebral injuries in children are due to sharp objects penetrating the orbit. These may initially appear trivial and are often missed if the foreign body is withdrawn. The child may present with delayed infection including frontal lobe abscess [25].

Spinal GSW

GSW to the spine have been extensively reviewed [4, 27, 39–43].

Epidemiology

GSW to the spine accounts for 13–17 % of all gunshot injuries and occurs predominantly in the thoracic region in civilian practice [4, 44]. Penetrating injury accounts for about half of all spinal cord (SC) injuries in urban centers [45]. The rate of complete SC injury in cervical GSW is about 70 %, and the rate of incomplete injury in lumbosacral injuries is about 70 % [4].

In a recent series of military spine injury, cervical spine was the most common but this included closed injuries [39].

Schoenfeld et al. [46, 47] documented a spine casualty rate of 7.4 % in a cohort of 4,122 soldiers deployed to a combat zone in Iraq and an 11.1 % rate of spinal injuries in a retrospective study of 7,877 combat wounded from Iraq and Afghanistan recorded in the Defence Trauma Registry 2005–2009. These are the highest figures recorded in US military history although blunt injury is also included. The incidence of combat-related spinal trauma was 4.4 per 10,000 [47]. In a series of 701 soldiers injured in Iraq and Afghanistan, SC injury occurred in 12 % of all casualties and represented 4 % of all musculoskeletal wounds [48]. This is thought to be due to the increased use of improvised explosive devices (IEDs). In a series of 90 British military

casualties with penetrating neck injury, 20 (22 %) had cervical spine or spinal cord injury. Only 6 (7 %) of these survived to reach hospital and 4 of the 6 subsequently died within 72 h [49]. Spinal injuries in combat troops are frequently accompanied by adjacent visceral injuries and limb injuries [50]. Blair et al. [51] reported that 28 % of US military spine casualties had isolated penetrating injuries, 66 % had isolated blunt injuries and 5 % had a combination of both.

Pathophysiology

The extent of injury to the spinal cord depends on ballistics, the degree of transection and contusion of the SC, the degree of concussive blast injury of the SC, compression of the cord by hematoma or displaced bone fragments, disruption of SC vasculature and the mechanical stability of the spinal segment(s) involved.

Principles of management of penetrating spinal injury

Acute management includes detailed documentation of neurological status, maintenance of adequate spinal cord oxygenation and perfusion. Exploration of the spine in urban civilian injury is not usually required because the deficit is not usually improved by surgery and there is usually no mechanical stability. However, there is an increased risk of mechanical instability in patients with cervical GSW causing SC injury [52]. A hard cervical collar should be applied until CT or MR is obtained for spine clearance [46]; however, where there is penetrating injury, spinal precautions or application of hard cervical collar should not hinder the management of the acute neck injury and should be re-applied when these procedures are completed [52]. Spinal canal surgical decompression may create instability.

Contaminated wounds should be irrigated and debrided. Injuries to adjacent structures in the neck, torso and pelvis relate to the trajectory of the missile and will require the relevant investigation and treatment. Bullets passing through the gastrointestinal tract risk causing sepsis as they enter the spine. There is scant evidence on the type and duration of antibiotic prophylaxis in penetrating spine trauma. Recommendations vary in the literature from 2 to 10 days [41, 43]. We recommend a minimum 2 days of broad-spectrum antibiotic cover, but would increase the duration if there is bowel content contamination. Steroids are not indicated and may increase the risk of non-spinal complications [4, 41].

Partial SC injury or nerve root injury due to compression by bone, metal fragment or hematoma may benefit from decompression [43]. Surgical decompression of intracanal bullets involving lumbosacral spine, with incomplete

deficit and cauda equina syndrome, may result in motor and sensory improvement [4, 41]. Minimally invasive surgical techniques may be used in selected cases [44, 53].

Surgery is also indicated for complications such as infection and mechanical instability. We recommend repair of persistent external CSF fistulae [45]. The risk of infection including meningitis increases if CSF fistula persists. Migration of metal fragments and late lead poisoning are both uncommon so that preventive surgery is not necessary.

GSW to the atlantoaxial spine is uncommon and often fatal. Ten cases were recently reported by Syre et al. [54]. Unilateral injuries were usually stable and did not need surgery. Unilateral vertebral artery injury is usually well tolerated and vascular complications can be managed with endovascular techniques. Only one patient required fusion for stabilization [54].

Outcome

The outcome is determined primarily by the level of the spinal injury and the severity of neurological deficits rather than the method of treatment.

A US study of 60 adolescents with GSW to the spine included 34 patients with complete neurological deficit [45]. No patient required surgery. At 1 year follow-up, there was no spinal instability and there was significant but non-functional improvement [45]. Improvement of fixed neurological deficit is uncommon. In a retrospective series from New Orleans, Trahan et al. [53] reported 127 (88 %) patients treated conservatively, and only one (0.7 %) improved from ASIA D to E. Of 20 patients who underwent surgery, one (5 %) patient had a clinical improvement from ASIA C to D. Sidhu et al. [4] performed a systematic review of civilian GSW to the spine and found patients in the non-operated group with partial SC injuries had a weighted rate of neurologic recovery of 65.3 and 12.7 % of complete lesions improved, whereas in the operated group, these figures were 53 and 21.5 %, respectively. Sidhu et al. [4] conclude that there is no major benefit for improvement in neurological deficit with surgery. The rate of complications is greater in the operated group, but there is a bias here because these patients may have more severe injuries that require the surgery.

Blast injury to the spine

Blast injuries and high-velocity GSW to the spine which are encountered by military surgeons tend to be more destructive and require exploration more readily than civilian GSW. Internal fixation for instability is more often required. Blast injuries to the spine with penetrating

fragments are usually heavily contaminated and require debridement. Lumbar burst fractures and lumbosacral dissociation may occur in spinal blast injury [39]. Military surgeons recommend decompression for an incomplete neurological injury and continued canal compromise, within 24–48 h of injury with stabilization if there is spinal instability [43].

Spinal stab wounds

Penetrating spinal injuries due to knives or other sharp objects are rare in most settings. The lower cervical and thoracic regions are most commonly affected due to assaults from behind. The management has been well described by Shahlaie et al. [55]. Removal of the foreign body may be beneficial both acutely and in cases of delayed presentation.

Conclusions

Craniocerebral GSW is frequently a devastating injury with 66–90 % of victims dying before they reach hospital and up to 51 % of those treated in hospital surviving. The decision to operate depends on many factors including GCS, age, pupil size and reaction, ballistics and imaging features on CT scan. Once this decision has been made, urgent surgery follows. Improved outcome has been reported in recent series probably because of the rapidity of resuscitation, correction of coagulopathy and surgery. The principles of management of cranial blast injury are similar to GSW. Penetrating spinal injury does not usually require exploration unless the injury is unstable or there is a compression with partial spinal cord or cauda equina injury or complications develop. Multidisciplinary teams including experienced clinicians treating patients with penetrating CNS injury is likely to produce the best outcomes.

Open Access This article is distributed under the terms of the Creative Commons Attribution License which permits any use, distribution, and reproduction in any medium, provided the original author(s) and the source are credited.

References

1. Parks SE, Johnson LL, McDaniel DD et al (2014) Surveillance for violent deaths—national violent death reporting system, 16 states, 2010. *MMWR Surveill Summ* 63:1–33
2. Kaufman HH, Levy ML, Stone JL et al (1995) Patients with Glasgow Coma Scale scores 3, 4, 5 after gunshot wounds to the brain. *Neurosurg Clin N Am* 6:701–714
3. Joseph B, Aziz H, Pandit V et al (2014) Improving survival rates after civilian gunshot wounds to the brain. *J Am Coll Surg* 218:58–65

4. Sidhu GS, Ghag A, Prokuski V et al (2013) Civilian gunshot injuries of the spinal cord: a systematic review of the current literature. *Clin Orthop Relat Res* 471:3945–3955
5. Aarabi B, Tofighi B, Kufera JA et al (2014) Predictors of outcome in civilian gunshot wounds to the head. *J Neurosurg* 120:1138–1146
6. Gressot LV, Chamoun RB, Patel AJ et al (2014) Predictors of outcome in civilians with gunshot wounds to the head upon presentation. *J Neurosurg* 121:645–652
7. Jandial R, Reichwage B, Levy M et al (2008) Ballistics for the neurosurgeon. *Neurosurgery* 62:472–480
8. Powers DB, Delo RI (2013) Characteristics of ballistic and blast injuries. *Atlas Oral Maxillofac Surg Clin North Am* 21:15–24
9. McCully SP, Schreiber MA (2013) Traumatic brain injury and its effect on coagulopathy. *Semin Thromb Hemost* 39:896–901
10. Halpern CH, Reilly PM, Turtz AR et al (2008) Traumatic coagulopathy: the effect of brain injury. *J Neurotrauma* 25:997–1001
11. Mitra B, O'Reilly G, Cameron PA et al (2013) Effectiveness of massive transfusion protocols on mortality in trauma: a systematic review and meta-analysis. *ANZ J Surg* 83:918–923
12. Baraniuk S, Tilley BC, Del Junco DJ et al (2014) Pragmatic randomized optimal platelet and plasma ratios (PROPPR) trial: design, rationale and implementation. *Injury* 45:1287–1295
13. Smith CE BA, Pivalizza EG, Tanaka K, Boral L, Shander A, Waters JH (2014) Massive transfusion protocol for hemorrhagic shock. *American Society of Anesthesiologists, Schaumburg, IL*
14. Epstein DS, Mitra B, Cameron PA et al (2014) Acute traumatic coagulopathy in the setting of isolated traumatic brain injury: definition, incidence and outcomes. *Brit J Neurosurg* 25:1–5
15. Talving P, Benfield R, Hadjizacharia P et al (2009) Coagulopathy in severe traumatic brain injury: a prospective study. *J Trauma* 66:55–61
16. Kim KA, Wang MY, McNatt SA et al (2005) Vector analysis correlating bullet trajectory to outcome after civilian through-and-through gunshot wound to the head: using imaging cues to predict fatal outcome. *J Neurosurg* 57:737–747
17. Lin DJ, Lam FC, Siracuse JJ et al (2012) “Time is brain” the Gifford factor—or: why do some civilian gunshot wounds to the head do unexpectedly well? A case series with outcomes analysis and a management guide. *Surg Neurol Int* 3:98
18. Part 1: guidelines for the management of penetrating brain injury. Introduction and methodology. *J Trauma* 51:S3–S6 (2001)
19. United States Army Institute of Surgical Research Joint Theater Trauma System Clinical Practice Guideline (Neurosurgical management), United States Army, 2012
20. Kazim SF, Shamim MS, Tahir MZ et al (2011) Management of penetrating brain injury. *J Emerg Trauma Shock* 4:395–402
21. Ragel BT, Klimo P Jr, Martin JE et al (2010) Wartime decompressive craniectomy: technique and lessons learned. *Neurosurgery* 28:E2
22. Aarabi B, Taghipour M, Alibai E et al (1998) Central nervous system infections after military missile head wounds. *J Neurosurg* 42:500–509
23. Antibiotic prophylaxis for penetrating brain injury. *J Trauma* 51:S34–S40 (2001)
24. Management of cerebrospinal fluid leaks. *J Trauma* 51:S29–S33 (2001)
25. Bayston R, de Louvois J, Brown EM et al (2000) Use of antibiotics in penetrating craniocerebral injuries. “Infection in Neurosurgery” Working Party of British Society for Antimicrobial Chemotherapy. *Lancet* 355:1813–1817
26. United States Army Institute of Surgical Research Joint Theater Trauma System Clinical Practice Guideline (Management of patients with Severe Head Trauma), 2012
27. Rosenfeld JV (2002) Gunshot injury to the head and spine. *J Clin Neurosci* 9:9–16
28. Armonda RA, Bell RS, Vo AH et al (2006) Wartime traumatic cerebral vasospasm: recent review of combat casualties. *Neurosurgery* 59:1215–1225
29. Armonda R, Tigno T, Hochheimer S et al (2011) Specific clinical applications of transcranial doppler ultrasound for patients with wartime traumatic brain injury. *J Neurotrauma* 28:A5
30. Bell RS, Vo AH, Roberts R et al (2010) Wartime traumatic aneurysms: acute presentation, diagnosis, and multimodal treatment of 64 craniocervical arterial injuries. *Neurosurgery* 66:66–79
31. Elserly T, Anwer H, Esene IN (2013) Image guided surgery in the management of craniocerebral gunshot injuries. *Surg Neurol Int* 4:S448–S454
32. Glapa M, Zorio M, Snyckers FD et al (2009) Gunshot wounds to the head in civilian practice. *Am Surg* 75:223–226
33. Rosenfeld JV, McFarlane AC, Bragge P et al (2013) Blast-related traumatic brain injury. *Lancet Neurol* 12:882–893
34. Bell RS, Mossop CM, Dirks MS et al (2010) Early decompressive craniectomy for severe penetrating and closed head injury during wartime. *Neurosurgery* 28:E1
35. Weisbrod AB, Rodriguez C, Bell R et al (2012) Long-term outcomes of combat casualties sustaining penetrating traumatic brain injury. *J Trauma Acute Care Surg* 73:1523–1528
36. Ecker RD, Mulligan LP, Dirks M et al (2011) Outcomes of 33 patients from the wars in Iraq and Afghanistan undergoing bilateral or bicompartamental craniectomy. *J Neurosurg* 115:124–129
37. DuBose JJ, Barmparas G, Inaba K et al (2011) Isolated severe traumatic brain injuries sustained during combat operations: demographics, mortality outcomes, and lessons to be learned from contrasts to civilian counterparts. *J Trauma* 70:11–18
38. Enicker B, Madiba TE (2014) Cranial injuries secondary to assault with a machete. *Injury* 45:1355–1358
39. Schoenfeld AJ, Lehman RA Jr, Hsu JR (2012) Evaluation and management of combat-related spinal injuries: a review based on recent experiences. *Spine J* 12:817–823
40. Jaiswal M, Mittal RS (2013) Concept of gunshot wound spine. *Asian Spine J* 7:359–364
41. Bono CM, Heary RF (2004) Gunshot wounds to the spine. *Spine J* 4:230–240
42. Heary RFMA (2010) Gunshot injuries to the thoracolumbar spine. *Semin Spine Surg* 22:73–77
43. Klimo P Jr, Ragel BT, Rosner M et al (2010) Can surgery improve neurological function in penetrating spinal injury? A review of the military and civilian literature and treatment recommendations for military neurosurgeons. *Neurosurgery* 28:E4
44. Shen FH, Samartzis D (2013) Operative management of a sacral gunshot injury via minimally invasive techniques and instrumentation. *Asian Spine J* 7:44–49
45. Aryan HE, Amar AP, Ozgur BM et al (2005) Gunshot wounds to the spine in adolescents. *Neurosurgery* 57:748–752
46. Schoenfeld AJ, Goodman GP, Belmont PJ Jr (2012) Characterization of combat-related spinal injuries sustained by a US Army Brigade Combat Team during Operation Iraqi Freedom. *Spine J* 12:771–776
47. Schoenfeld AJ, Laughlin MD, McCrisky BJ et al (2013) Spinal injuries in United States military personnel deployed to Iraq and Afghanistan: an epidemiological investigation involving 7877 combat casualties from 2005 to 2009. *Spine* 38:1770–1778
48. Schoenfeld AJ, Dunn JC, Belmont PJ (2013) Pelvic and extremity wounds among combat-specific personnel serving in Iraq and Afghanistan (2003–2011): a new paradigm in military musculoskeletal medicine. *Injury* 44:1866–1870
49. Ramasamy A, Midwinter M, Mahoney P et al (2009) Learning the lessons from conflict: pre-hospital cervical spine stabilisation following ballistic neck trauma. *Injury* 40:1342–1345
50. Patzkowski JC, Blair JA, Schoenfeld AJ et al (2012) Multiple associated injuries are common with spine fractures during war. *Spine J* 12:791–797

51. Blair JA, Possley DR, Petfield JL et al (2012) Military penetrating spine injuries compared with blunt. *Spine J* 12:762–768
52. Medzon R, Rothenhaus T, Bono CM et al (2005) Stability of cervical spine fractures after gunshot wounds to the head and neck. *Spine* 30:2274–2279
53. Trahan J, Serban D, Tender GC (2013) Gunshot wounds to the spine in post-Katrina New Orleans. *Injury* 44:1601–1606
54. Syre P 3rd, Rodriguez-Cruz L, Desai R et al (2013) Civilian gunshot wounds to the atlantoaxial spine: a report of 10 cases treated using a multidisciplinary approach. *J Neurosurg Spine* 19:759–766
55. Shahlai K, Chang DJ, Anderson JT (2006) Nonmissile penetrating spinal injury. Case report and review of the literature. *J Neurosurg Spine* 4:400–408
56. Levy ML (2000) Outcome prediction following penetrating craniocerebral injury in a civilian population: aggressive surgical management in patients with admission Glasgow Coma Scale scores of 6 to 15. *Neurosurgery* 8:e2
57. Polin RS, Shaffrey ME, Phillips CD et al (1995) Multivariate analysis and prediction of outcome following penetrating head injury. *Neurosurg Clin N Am* 6:689–699



Universiteit
Leiden
The Netherlands

Decision-making in severe traumatic brain injury: patient outcome, hospital costs, and research practice

Dijck, J.T.J.M. van

Citation

Dijck, J. T. J. M. van. (2021, September 16). *Decision-making in severe traumatic brain injury: patient outcome, hospital costs, and research practice*. Retrieved from <https://hdl.handle.net/1887/3210899>

Version: Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/3210899>

Note: To cite this publication please use the final published version (if applicable).

Cover Page



Universiteit Leiden



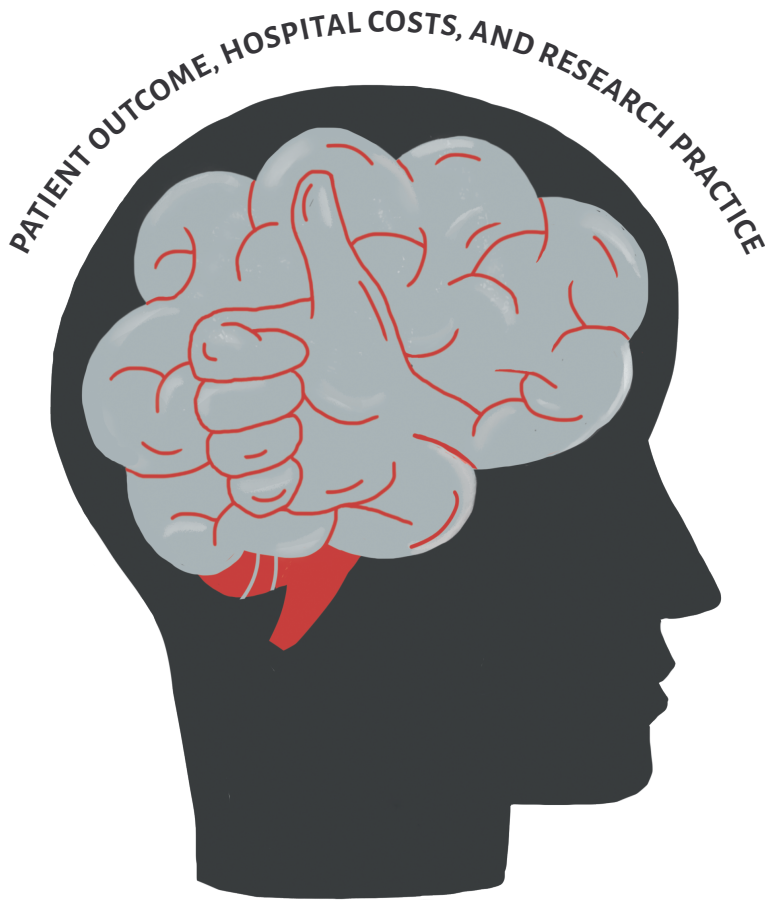
The handle <https://hdl.handle.net/1887/3210899> holds various files of this Leiden University dissertation.

Author: Dijck, J.T.J.M. van

Title: Decision-making in severe traumatic brain injury: patient outcome, hospital costs, and research practice

Issue Date: 2021-09-16

Decision-making in Severe Traumatic Brain Injury



J.T.J.M. van Dijck

DECISION-MAKING IN SEVERE TRAUMATIC BRAIN INJURY

PATIENT OUTCOME, HOSPITAL COSTS, AND RESEARCH PRACTICE

J.T.J.M. van Dijck

DECISION-MAKING IN SEVERE TRAUMATIC BRAIN INJURY
PATIENT OUTCOME, HOSPITAL COSTS, AND RESEARCH PRACTICE
PhD thesis, Leiden University, Leiden, the Netherlands

Copyright 2021 J.T.J.M. van Dijck, the Netherlands

All rights reserved. No parts of this thesis may be reproduced or transmitted in any form or by any mean, electronical or mechanical, including photocopy, recording, or in any information storage and retrieval system, without permission in writing from the copyright owner.

| | |
|--------------|---|
| ISBN | 978-94-6332-767-1 |
| Cover Design | Elise Buntinx, (elisebuntinx.be) |
| Lay-out | Ferdinand van Nispen tot Pannerden Citroenvlinder DTP & Vormgeving, my-thesis.nl |
| Printing | CVO drukkers & vormgevers B.V. Ede NL |

The research projects in this thesis were supported by Hersenstichting Nederland (Dutch Brain Foundation) and by The European Union seventh Framework Program (grant 602150)

Publication of this thesis was kindly supported by:
Peter van Dijck & Willemien van Dijck-Kaandorp
ETB-BISLIFE

**DECISION-MAKING IN SEVERE TRAUMATIC
BRAIN INJURY
PATIENT OUTCOME, HOSPITAL COSTS,
AND RESEARCH PRACTICE**

Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Leiden
op gezag van rector magnificus prof.dr.ir. H. Bijl
volgens besluit van het college voor promoties
te verdedigen op 16 september 2021
klokke 13:45 uur

door

Jeroen Theodorus Josephus Maria van Dijck
geboren te Tilburg
in 1990

Promotor

Prof. dr. W.C. Peul

Copromotores

Dr. E.J.O. Kompanje, Erasmus Medisch Centrum, Rotterdam

Dr. S. Polinder, Erasmus Medisch Centrum, Rotterdam

Leden promotiecommissie

Prof. dr. E.W. Steyerberg

Prof. dr. A.M. Stiggelbout

Prof. dr. H.M. Dupuis

Prof. dr. R.H.M.A. Bartels, Radboud Universitair Medisch Centrum, Nijmegen

Prof. dr. W.B.F. Brouwer, Erasmus Universiteit, Rotterdam

Prof. dr. W.P. Vandertop, Amsterdam Universitair Medisch Centrum, Amsterdam

"I think nobody should be certain of anything. If you're certain, you're certainly wrong because nothing deserves certainty. So one ought to hold all one's beliefs with a certain element of doubt, and one ought to be able to act vigorously in spite of the doubt"

Bertrand Russell. 1960

TABLE OF CONTENTS

| | | |
|----------------|---|------------|
| Chapter 1 | General introduction | 9 |
| Part I | Patient outcome, in-hospital healthcare consumption, in-hospital costs, and treatment decision-making in severe traumatic brain injury | 25 |
| Chapter 2 | Decision-making in very severe traumatic brain injury (Glasgow Coma Scale 3-5); a literature review of acute neurosurgical management | 27 |
| Chapter 3 | In-hospital costs after severe traumatic brain injury: a systematic review and quality assessment | 65 |
| Chapter 4 | Functional and patient-reported outcome versus in-hospital costs after traumatic acute subdural hematoma; a neurosurgical paradox | 91 |
| Chapter 5 | Patient outcome, healthcare consumption and in-hospital costs after traumatic brain injury: a Dutch prospective multicenter study | 111 |
| Chapter 6 | The patient with severe traumatic brain injury: clinical decision-making: the first 60 minutes and beyond | 131 |
| Part II | Institutional review board approval and use of informed consent procedures in emergency research with traumatic brain injury patients | 149 |
| Chapter 7 | How do 66 European Institutional Review Boards approve one protocol for an international prospective observational study on traumatic brain injury? Experiences from the CENTER-TBI study | 151 |

| | | |
|------------|--|-----|
| Chapter 8 | Informed consent procedures in patients with an acute inability to provide informed consent: policy and practice in the CENTER-TBI study | 169 |
| Chapter 9 | Informed consent procedures for emergency interventional research in patients with acute traumatic brain injury and ischaemic stroke | 185 |
| Chapter 10 | General summary | 209 |
| Chapter 11 | Samenvatting | 215 |
| Chapter 12 | General discussion and future perspectives | 223 |
| Appendices | | |
| | List of publications | 246 |
| | Dankwoord | 248 |
| | Curriculum vitae | 250 |



CHAPTER 1

GENERAL INTRODUCTION

Worldwide, an estimated fifty to sixty-nine million people a year sustain a traumatic brain injury (TBI).^{1,2} The all-cause, all-severity global yearly incidence of TBI is estimated at 939 cases per 100,000 people, of which an estimated 5.48 million people (73/100,000) suffer severe TBI (s-TBI).² In Europe, there are an estimated 2.5 million new cases of TBI each year.¹ Numbers from The Netherlands show almost 35,000 annual emergency department visits.³ The most common causes of TBI are road traffic accidents and falls.¹ In recent years, the number of falls is increasing, especially in the elderly.^{1,3-7} The medical consequences of TBI are substantial and range from symptoms like headache and fatigue to severe disabilities and even death.⁷⁻¹¹ The high occurrence and acute and chronic consequences of TBI contribute to the substantial healthcare- and socioeconomic burden and cause harm to patients, proxies and societies.¹

Diagnosis and classification

TBI is defined as 'an alteration in brain function, or other evidence of brain pathology, caused by an external force'.¹² It can be diagnosed and classified by using trauma mechanism, clinical severity, presence of structural damage on neuroimaging, and prognostic risk.¹³ Clinical severity is the most frequently used classification method and usually indicated by the level of consciousness as represented by the Glasgow Coma Scale.^{1,14,15} The combined sum score (3 to 15) of the eye (1-4), verbal (1-5) and motor (1-6) components is used to categorize patients in three severity groups: severe TBI (GCS 3-8), moderate TBI (GCS 9-12), and mild TBI (GCS 13-15). These severity groups account for an estimated 8%, 11% and 81% of all TBI patients respectively.²

Although these TBI severity groups are frequently used in clinical practice and research, the clinical presentation of patients within these categories remains highly variable.¹⁶ Variability in TBI is very common and complicates diagnosis, classification and clinical practice. It is the result of differences in patient characteristics, or particulars of trauma, such as type, intensity, direction, and duration of the external forces, but also by uncertainties related to the complexity of the brain.^{1,13} Many aspects of the pathophysiological mechanisms of TBI are still unknown. The mechanism of TBI can be best understood by distinguishing primary and secondary brain injury.^{1,13,17}

Primary and secondary brain injury

Primary brain injury occurs at the time of the initial injury and causes diffuse or localized brain tissue destruction and areas of intracerebral or extracerebral haemorrhage. Primary injury is irreversible by definition and therefore unsuitable

for treatment. It could only be anticipated by preventative measures.¹⁸ More extensive primary injury is usually seen in more severely injured TBI patients, and is likely to be related to the development of secondary brain injury.

Secondary brain injury occurs from insults to the brain in the hours, days or months after the initial injury.^{13,17} It is mainly triggered by hypoxia and hypovolaemia caused by systemic insults or increased intracranial pressure (ICP) as a result of intracranial hematomas, brain swelling, cerebral oedema or ischemia.¹³ Other causes are impaired haemostasis, the consequences of neurotransmitter release, or a damaged blood-brain barrier with leakage of immune cells and a subsequent increased neuroinflammatory response with brain swelling.^{13,17} Secondary injury is considered to be reversible and is suitable for treatment.^{13,17}

Treatment strategies

Immediate treatment in the pre-hospital or hospital setting could prevent or reverse secondary injury and associated brain dysfunction and might therefore be beneficial for patient outcome.^{1,13} Trauma patients are usually treated by using the ATLS (Advanced Trauma Life Support) principle: 'treat first what kills first'.¹⁹ When necessary, this includes the prevention and/or normalisation of hypoxia and hypovolaemia by using intubation, oxygen supplementation, fluid resuscitation, or acute treatment of extracranial injuries, before focussing on the neurological status of the patient.¹⁹ After neurological assessment, a CT scan is made to identify potential treatable or operable traumatic intracranial abnormalities, including diffuse axonal injury, diffuse swelling, subarachnoid haemorrhage, contusions, and epidural or subdural hematomas (Figure 1). Traumatic intracranial hematomas are rare in patients with mild TBI, but occur in 25-35% of patients with s-TBI and in 5-10% of patients with moderate TBI and could require immediate or delayed surgical intervention to prevent secondary injury.^{13,20}

Surgical intervention options include the placement of an ICP monitor or extraventricular drain, a craniotomy with evacuation of a haemorrhagic focus, or a decompressive craniectomy.²⁰ Surgical management is often combined with perioperative ICU treatment that also focusses on the prevention of secondary injury and the optimisation of conditions for brain recovery.^{13,21} The necessary individualised and targeted approaches are nearly only possible at specialised ICUs.²¹ When ICU admission is not required, patients will be admitted to a medium care or general ward. Provided care obviously depends on a patients' clinical condition,

their medical needs and the local possibilities to provide care. Deciding to initiate or withhold surgical and/or non-surgical treatment during the acute treatment decisions-making process is often very difficult for treating physicians.

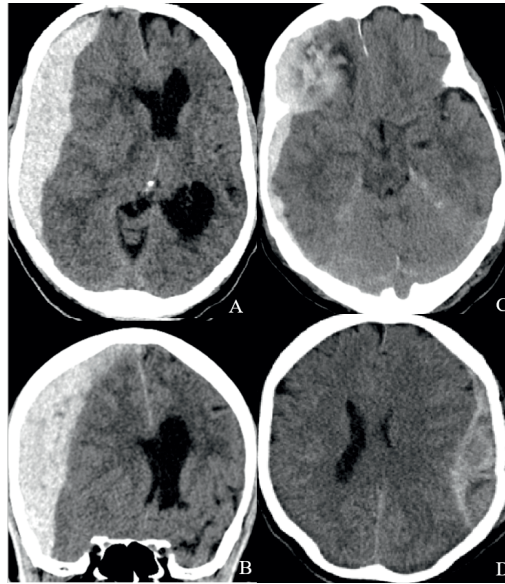


Figure 1. Computed tomography (CT) scans of patients with traumatic intracranial abnormalities. A and B: Subdural hematoma. C: Contusion and parenchymal hematoma. D: Epidural hematoma.

The acute treatment decision-making process

Several evidence-based guidelines, treatment protocols, and consensus-based recommendations are made to support physicians in this decision-making process.^{20,22-26} Despite their existence, adherence to TBI guidelines is generally poor. This is caused by the low evidence level on which recommendations are based^{27,28}, delay between literature search and publication, the fact that recommendations are not restated in subsequent guideline versions, and downgrading of a recommendations' evidence level.²⁹ In addition, there are several areas of uncertainty that are not included in available guidelines because essential evidence is not available.^{23,24}

The extent of the problem of evidence availability is also reported in two recent reviews. The first review of 191 completed randomized controlled trials for acute TBI management found very little translatable evidence because of multiple methodological shortcomings.³⁰ The second investigated systematic reviews on the acute management of moderate to s-TBI patients and concluded a lack of currency, completeness and quality.³¹

The many problems with the availability of high-quality evidence results in a lack of consensus, decision-making difficulties, and an inability to practice evidence-based medicine. This enables treatment variation, which is reported in nearly all fields of TBI management, including the use and implementation of guidelines in European neurotrauma centers³², structures and processes of TBI care³³, monitoring and treatment policies in patients with TBI and intracranial hypertension³⁴, general supportive and preventive measures at ICUs³⁵, and neurosurgical strategies or management.^{36,37}

Future research is needed to improve the quality and completeness of evidence on the treatment of TBI patients. Reliable information on patient outcome and treatment effectiveness is likely to substantially improve the treatment decision-making process for physicians.

Patient outcome

The effectiveness of treatments can be assessed by measuring achieved patient outcome, because the main goal of providing healthcare is to achieve best possible patient outcome. Despite available treatment interventions, TBI patients still show high rates of mortality and unfavourable outcome, especially in patients with s-TBI. In a recent meta-analysis, the in-hospital mortality for moderate TBI and s-TBI patients was 57.2% and the 'all time point' mortality was 65.3% for s-TBI, 34.3% for moderate TBI and 12.3% for mild TBI patients.³⁸ Other studies reported lower mortality rates of 0.45% to 8% for mild TBI³⁹, 0.9% to 8% for moderate TBI⁴⁰ and 39% - 40.4% for s-TBI.

^{41,42}

In addition to mortality rates many investigators report functional patient outcome by using the Glasgow Outcome Score - Extended.⁴³ (Table 1) A so called 'favourable outcome' (GOSE 5-8), indicating independency in daily life, was achieved by 29% - 40% of s-TBI patients, 55.3% - 87% of moderate TBI patients, and 85.4% of mild TBI patients.^{40,41,44} Unfortunately, outcome rates are difficult to generalize because they depend on multiple factors such as age, injury severity, initial neurologic condition and TBI severity (i.e defined by GCS).^{38,45}

Besides short term outcome, many studies report long-term sustained healthcare problems, which are not limited to s-TBI patients, but also reported after mild TBI.^{10,11,46-51} Several authors therefore consider TBI to be a chronic health condition and suggest that it should be addressed as such by healthcare providers, researchers and policymakers.^{52,53}

Table 1 Explanation of Glasgow Outcome Scale (- Extended). ⁴³

| Glasgow Outcome Scale (GOS) | Glasgow Outcome Scale – Extended (GOSE) | Brief description | U/F |
|-----------------------------|---|--|----------------------|
| 1. Death | 1. Death | Death | Unfavourable outcome |
| 2. Vegetative state | 2. Vegetative state | Absence of awareness of self and environment | |
| 3. Severe disability | 3. Lower severe disability | Needs full assistance in daily life | |
| | 4. Upper severe disability | Needs partial assistance in daily life | |
| 4. Moderate disability | 5. Lower moderate disability | Independent, but cannot resume work/school or all previous social activities | Favourable outcome |
| | 6. Upper moderate disability | Some disability exists, but can partly resume work or previous activities | |
| 5. Good recovery | 7. Lower good recovery | Minor physical or mental deficit that affects daily life | |
| | 8. Upper good recovery | Full recovery or minor symptoms that do not affect daily life | |

Patient outcome after TBI and thereby the effectiveness of available, generally unproven, treatment strategies is still considered to be unsatisfactory.^{1,9,21,24,29} A critical appraisal of treatment effectiveness and patient outcome will hopefully decrease the number of patients that achieve an outcome that they would have never wanted and might even prevent associated but ineffective healthcare expenses.^{9,54-56}

In-hospital costs

The annual global economic burden of TBI is estimated to be US\$ 400 billion.¹ Direct costs (i.e. healthcare costs) represent a substantial part of the total economic burden^{3,57-60}, but the indirect costs (i.e. loss of productivity and intangible costs) are considered to be the largest contributor.^{1,61,62} TBI related healthcare costs are increasing annually, which is problematic when healthcare budgets remain restricted.⁶³⁻⁶⁵ These high and rising healthcare costs could endanger the affordability of national healthcare systems and thereby public health.^{66,67} The importance of investigating the cost of care for TBI patients is therefore widely recognized by healthcare professionals and societies.¹ Healthcare professionals and policy makers are nowadays even expected to study the cost-effectiveness of treatments.^{68,69}

When focussing on the hospital setting, patients with s-TBI show the longest hospital or ICU length of stay and have the most (neuro)surgical and medical interventions compared to other TBI severities.^{42,70,71} These patients also show the highest individual costs of all TBI patients.⁷⁰ In The Netherlands, the mean direct and indirect costs for TBI patients were €18,030 per patient³, and when including rehabilitation and nursing home costs, patients with s-TBI costed €40,680 to €44,952.⁷²

Understanding and generalizing the in-hospital costs of individual TBI patients from available literature however remains difficult because methodological heterogeneity of TBI cost studies is high and study quality often inadequate.^{73,74} Input from high quality cost research is essential to achieve a rational and righteous distribution of limited resources, to guarantee the highest quality of care for the lowest costs.⁷³⁻⁷⁵ To achieve this, several difficulties in conducting TBI research have to be improved.

Difficulties in conducting TBI research

Conducting research in patients with TBI is complicated by several factors; largely unknown pathophysiological mechanisms of brain injury, the acute and stressful situation, unavailable necessary information (i.e. trauma mechanism, medical history, use of anticoagulants), and a patients' inability to provide informed consent. As stated, to meet the need for more high-quality research, the efficiency of future research initiatives needs to be improved. This can be achieved by optimizing several aspects of TBI research. This thesis will focus on the use of informed consent procedures and the process of institutional review board approval.

Informed consent

Physicians and researchers are obligated to inform patients and obtain informed consent before executing diagnostic tests or treatment interventions as part of a clinical study.^{76,77} The right to refuse informed consent and thus study participation is internationally recognised and formalised in many declarations, regulations, directives and laws.⁷⁶⁻⁷⁸ Obtaining informed consent respects the principle of autonomous people and their autonomous choices and actions. It establishes a shared responsibility between professionals and patients.

Obtaining patient informed consent is however not possible in patients with an inability to provide informed consent due to acute TBI. As a result of limited formal guidance in this context, most Institutional Review Boards (IRB) have pragmatically accepted that proxies may provide prior consent on behalf of the patient. Because proxies are frequently unavailable or unable to provide informed consent within the limited time window, potentially eligible patients may not always be recruited, and study progress suffers delays.⁷⁹⁻⁸¹

To allow essential emergency research initiatives, several alternatives are introduced to overcome this problem. It is accepted to start the study without prior patient or proxy informed consent with (deferred consent) and without (exception from consent, waiver of consent) the requirement to obtain informed consent for study continuation later.⁸²⁻⁸⁴ As in TBI management, there is substantial practice variation in used informed consent procedures, within and between EU Member States, and also globally.^{85,86} Variation in informed consent procedures complicates multicentre international studies because it may lead to inclusion problems, bias, and delay in institutional review board approval.^{87,88}

Institutional review boards

An institutional review board is usually appointed to review research protocols to ensure their compliance with ethical standards and national laws. IRBs have an essential role in (clinical) research to protect the dignity, fundamental rights, safety, and well-being of research participants and their formal approval is compulsory before a clinical study can start.⁸⁹ Although several international models exist to improve the harmonization of ethical principles, the functioning of IRBs is subject to national legislation and regulation, which refine their structure and function to better serve local needs and cultural preferences.^{90,91} Approval of research protocols submitted to IRBs is subject to these differences, which may complicate the conduct of international research.

Lack of procedural harmonization 'leads to a complex and uncertain framework for ethical review and for participant informed consent, resulting in numerous inefficiencies in observational studies'.⁹² Greater procedural harmonization is generally considered desirable, because it could improve quality and efficiency by decreasing costs, increasing statistical validity,⁹³⁻⁹⁵ optimizing data management⁹³, allowing choice of relevant and generalizable outcome variables,⁹⁵ promoting uniform product safety regulations⁹⁴, and minimizing waste of resources due to inefficiencies.⁹⁴

The efficiency of future research initiatives could be improved by assessing the procedural details, and quantifying the differences, problems and challenges regarding informed consent and IRB procedures. This could improve efficiency and quality of future research initiatives and thereby contribute to the evidence base on patient outcome and treatment cost-effectiveness. This might benefit future treatment decision-making and ultimately patient outcome.

AIM AND OUTLINE OF THIS THESIS

This thesis aims to describe and improve the acute treatment decision-making process and research practice in patients with s-TBI.

The following research questions will be answered to address this aim:

1. What is the outcome of patients with s-TBI?
2. What is the in-hospital healthcare consumption and how high are the in-hospital costs of patients with s-TBI?
3. What challenges are encountered in the acute treatment decision-making process in patients with s-TBI?
4. What difficulties are encountered in current TBI research practice?

Accordingly, this thesis consists of two parts.

Part I is about the challenges of the treatment decision-making process in patients with (s-)TBI and focusses on three factors considered to be important in this process: patient outcome, in-hospital healthcare consumption, and in-hospital costs. *Chapter 2* is a literature review of acute neurosurgical management in patient with very severe TBI (Glasgow Coma Scale 3-5), where several factors related to surgical intervention and patient outcome are investigated. *Chapter 3* is a systematic review and quality assessment of available literature on the in-hospital healthcare consumption and in-hospital costs of patients after sustaining s-TBI. *Chapter 4* presents functional and patient-reported outcome and in-hospital healthcare consumption and in-hospital costs of a retrospectively investigated regional cohort of patients with a traumatic acute subdural hematoma. *Chapter 5* investigates patient outcome, in-hospital healthcare consumption and in-hospital costs of TBI patients that were regionally included in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study. *Chapter 6* summarizes the result of multiple focus group sessions and explores the difficulties of acute decision-making in s-TBI patients.

Part II analyses procedural difficulties in TBI research practice. It focusses on the process of institutional review board approval and the use of informed consent procedures in patients with TBI with an inability to provide informed consent. *Chapter 7* describes how the CENTER-TBI study protocol is reviewed and approved by 66 European institutional review boards. *Chapter 8* analyses the policy and practice regarding informed consent procedures in patients with an acute inability to provide

informed consent in the CENTER-TBI study. *Chapter 9* contains an extensive overview on informed consent procedures for emergency interventional research in patients with acute TBI and ischaemic stroke.

A summary and general discussion are included to complete this thesis.

REFERENCES:

1. Maas AIR, Menon DK, Adelson PD, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. *Lancet Neurol* 2017; **16**(12): 987-1048.
2. Dewan MC, Rattani A, Gupta S, et al. Estimating the global incidence of traumatic brain injury. *J Neurosurg* 2018: 1-18.
3. Scholten AC, Haagsma JA, Panneman MJ, van Beeck EF, Polinder S. Traumatic brain injury in the Netherlands: incidence, costs and disability-adjusted life years. *PLoS One* 2014; **9**(10): e110905.
4. Brazinova A, Rehorcikova V, Taylor MS, et al. Epidemiology of Traumatic Brain Injury in Europe: A Living Systematic Review. *J Neurotrauma* 2018.
5. Majdan M, Plancikova D, Brazinova A, et al. Epidemiology of traumatic brain injuries in Europe: a cross-sectional analysis. *The Lancet Public Health* 2016; **1**(2): e76-e83.
6. Peeters W, van den Brande R, Polinder S, et al. Epidemiology of traumatic brain injury in Europe. *Acta Neurochir (Wien)* 2015; **157**(10): 1683-96.
7. Steyerberg EW, Wiegers E, Sewalt C, et al. Case-mix, care pathways, and outcomes in patients with traumatic brain injury in CENTER-TBI: a European prospective, multicentre, longitudinal, cohort study. *Lancet Neurol* 2019; **18**(10): 923-34.
8. Beck B, Gantner D, Cameron P, et al. Temporal trends in functional outcomes following severe traumatic brain injury: 2006-2015. *J Neurotrauma* 2017.
9. Fountain DM, Kolias AG, Lecky FE, et al. Survival Trends After Surgery for Acute Subdural Hematoma in Adults Over a 20-year Period. *Ann Surg* 2017; **265**(3): 590-6.
10. De Koning ME, Scheenen ME, Van Der Horn HJ, Spikman JM, Van Der Naalt J. From 'miserable minority' to the 'fortunate few': the other end of the mild traumatic brain injury spectrum. *Brain Inj* 2018; **32**(5): 540-3.
11. van der Naalt J, Timmerman ME, de Koning ME, et al. Early predictors of outcome after mild traumatic brain injury (UPFRONT): an observational cohort study. *Lancet Neurol* 2017; **16**(7): 532-40.
12. Menon DK, Schwab K, Wright DW, Maas AI. Position statement: definition of traumatic brain injury. *Arch Phys Med Rehabil* 2010; **91**(11): 1637-40.
13. Maas AIR, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. *Lancet Neurol* 2008; **7**(8): 728-41.
14. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. *The Lancet* 1974; **304**(7872): 81-4.
15. Teasdale G, Maas A, Lecky F, Manley G, Stocchetti N, Murray G. The Glasgow Coma Scale at 40 years: standing the test of time. *Lancet Neurol*; **13**(8): 844-54.
16. Saatman KE, Duhaime AC, Bullock R, Maas AI, Valadka A, Manley GT. Classification of traumatic brain injury for targeted therapies. *J Neurotrauma* 2008; **25**(7): 719-38.
17. Pearn ML, Niesman IR, Egawa J, et al. Pathophysiology Associated with Traumatic Brain Injury: Current Treatments and Potential Novel Therapeutics. *Cell Mol Neurobiol* 2017; **37**(4): 571-85.
18. Iaccarino C, Carretta A, Nicolosi F, Morselli C. Epidemiology of severe traumatic brain injury. *J Neurosurg Sci* 2018; **62**(5): 535-41.
19. The ATLS Subcommittee ACoSCoT, group tIAw. Advanced trauma life support (ATLS®): The ninth edition. *J Trauma Acute Care Surg* 2013; **74**(5): 1363-6.
20. Bullock MR, Chesnut R, Ghajar J, et al. Guidelines for the Surgical Management of Traumatic Brain Injury Author Group. *Neurosurgery* 2006; **58**(3): S2-vi-S-vi.
21. Stocchetti N, Carbonara M, Citerio G, et al. Severe traumatic brain injury: targeted management in the intensive care unit. *Lancet Neurol* 2017; **16**(6): 452-64.
22. Picetti E, Rossi S, Abu-Zidan FM, et al. WSES consensus conference guidelines: monitoring and management of severe adult traumatic brain injury patients with polytrauma in the first 24 hours. *World J Emerg Surg* 2019; **14**: 53.
23. Hutchinson PJ, Kolias AG, Tajsic T, et al. Consensus statement from the International Consensus Meeting on the Role of Decompressive Craniectomy in the Management of Traumatic Brain Injury : Consensus statement. *Acta Neurochir (Wien)* 2019; **161**(7): 1261-74.
24. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. *Neurosurgery* 2017; **80**(1): 6-15.
25. Kochanek PM, Tasker RC, Carney N, et al. Guidelines for the Management of Pediatric Severe Traumatic Brain Injury, Third Edition: Update of the Brain Trauma Foundation Guidelines, Executive Summary. *Neurosurgery* 2019; **84**(6): 1169-78.

26. Hodgkinson S, Pollit V, Sharpin C, Lecky F. Early management of head injury: summary of updated NICE guidance. *BMJ* 2014; **348**: g104.
27. Khormi YH, Gosadi I, Campbell S, Senthilselvan A, O'Kelly C, Zygum D. Adherence to Brain Trauma Foundation Guidelines for Management of Traumatic Brain Injury Patients and Its Effect on Outcomes: Systematic Review. *J Neurotrauma* 2018; **35**(13): 1407-18.
28. Cnossen MC, Scholten AC, Lingsma HF, et al. Adherence to Guidelines in Adult Patients with Traumatic Brain Injury: A Living Systematic Review. *J Neurotrauma* 2016.
29. Volovici V, Steyerberg EW, Cnossen MC, et al. Evolution of Evidence and Guideline Recommendations for the Medical Management of Severe Traumatic Brain Injury. *J Neurotrauma* 2019; **36**(22): 3183-9.
30. Bragge P, Synnot A, Maas AI, et al. A State-of-the-Science Overview of Randomized Controlled Trials Evaluating Acute Management of Moderate-to-Severe Traumatic Brain Injury. *J Neurotrauma* 2016; **33**(16): 1461-78.
31. Synnot A, Bragge P, Lunny C, et al. The currency, completeness and quality of systematic reviews of acute management of moderate to severe traumatic brain injury: A comprehensive evidence map. *PLoS One* 2018; **13**(6): e0198676.
32. Volovici V, Ercole A, Citerio G, et al. Variation in Guideline Implementation and Adherence Regarding Severe Traumatic Brain Injury Treatment: A CENTER-TBI Survey Study in Europe. *World Neurosurg* 2019; **125**: e515-e20.
33. Cnossen MC, Polinder S, Lingsma HF, et al. Variation in Structure and Process of Care in Traumatic Brain Injury: Provider Profiles of European Neurotrauma Centers Participating in the CENTER-TBI Study. *PLOS ONE* 2016; **11**(8): e0161367.
34. Cnossen MC, Huijben JA, van der Jagt M, et al. Variation in monitoring and treatment policies for intracranial hypertension in traumatic brain injury: a survey in 66 neurotrauma centers participating in the CENTER-TBI study. *Crit Care* 2017; **21**(1): 233.
35. Huijben JA, Volovici V, Cnossen MC, et al. Variation in general supportive and preventive intensive care management of traumatic brain injury: a survey in 66 neurotrauma centers participating in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study. *Crit Care* 2018; **22**(1): 90.
36. van Essen TA, den Boogert HF, Cnossen MC, et al. Variation in neurosurgical management of traumatic brain injury: a survey in 68 centers participating in the CENTER-TBI study. *Acta Neurochir (Wien)* 2019; **161**(3): 435-49.
37. van Essen TA, de Ruiter GC, Kho KH, Peul WC. Neurosurgical Treatment Variation of Traumatic Brain Injury: Evaluation of Acute Subdural Hematoma Management in Belgium and The Netherlands. *J Neurotrauma* 2017; **34**(4): 881-9.
38. McIntyre A, Mehta S, Aubut J, Dijkers M, Teasell RW. Mortality among older adults after a traumatic brain injury: a meta-analysis. *Brain Inj* 2013; **27**(1): 31-40.
39. Carroll LJ, Cassidy JD, Cancelliere C, et al. Systematic Review of the Prognosis After Mild Traumatic Brain Injury in Adults: Cognitive, Psychiatric, and Mortality Outcomes: Results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. *Arch Phys Med Rehabil* 2014; **95**(3, Supplement): S152-S73.
40. Einarsen CE, van der Naalt J, Jacobs B, et al. Moderate Traumatic Brain Injury: Clinical Characteristics and a Prognostic Model of 12-Month Outcome. *World Neurosurg* 2018; **114**: e1199-e210.
41. Rosenfeld JV, Maas AI, Bragge P, Morganti-Kossmann MC, Manley GT, Gruen RL. Early management of severe traumatic brain injury. *The Lancet* 2012; **380**(9847): 1088-98.
42. Stein SC, Georgoff P, Meghan S, Mizra K, Sonnad SS. 150 years of treating severe traumatic brain injury: a systematic review of progress in mortality. *J Neurotrauma* 2010; **27**(7): 1343-53.
43. Wilson JT, Pettigrew LE, Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. *J Neurotrauma* 1998; **15**(8): 573-85.
44. McIntyre A, Mehta S, Janzen S, Aubut J, Teasell RW. A meta-analysis of functional outcome among older adults with traumatic brain injury. *NeuroRehabilitation* 2013; **32**(2): 409-14.
45. Krishnamoorthy V, Vavilala MS, Mills B, Rowhani-Rahbar A. Demographic and clinical risk factors associated with hospital mortality after isolated severe traumatic brain injury: a cohort study. *J Intensive Care* 2015; **3**(1): 46.
46. Andelic N, Howe EI, Hellstrom T, et al. Disability and quality of life 20 years after traumatic brain injury. *Brain Behav* 2018; **8**(7): e01018.
47. Forslund MV, Perrin PB, Roe C, et al. Global Outcome Trajectories up to 10 Years After Moderate to Severe Traumatic Brain Injury. *Front Neurol* 2019; **10**: 219.
48. Grauwmeijer E, Heijenbrok-Kal MH, Peppel LD, et al. Cognition, Health-Related Quality of Life, and Depression Ten Years after Moderate to Severe Traumatic Brain Injury: A Prospective Cohort Study. *J Neurotrauma* 2018; **35**(13): 1543-51.

49. Ruet A, Bayen E, Jourdan C, et al. A Detailed Overview of Long-Term Outcomes in Severe Traumatic Brain Injury Eight Years Post-injury. *Front Neurol* 2019; **10**: 120.
50. Moskowitz E, Melendez CI, Dunn J, et al. Long-Term Effects of Decompressive Craniectomy on Functional Outcomes after Traumatic Brain Injury: A Multicenter Study. *Am Surg* 2018; **84**(8): 1314-8.
51. Ventura T, Harrison-Felix C, Carlson N, et al. Mortality after discharge from acute care hospitalization with traumatic brain injury: a population-based study. *Arch Phys Med Rehabil* 2010; **91**(1): 20-9.
52. Wilson L, Stewart W, Dams-O'Connor K, et al. The chronic and evolving neurological consequences of traumatic brain injury. *Lancet Neurol* 2017; **16**(10): 813-25.
53. Stocchetti N, Zanier ER. Chronic impact of traumatic brain injury on outcome and quality of life: a narrative review. *Crit Care* 2016; **20**(1): 148.
54. Beck B, Gantner D, Cameron PA, et al. Temporal trends in functional outcomes after severe traumatic brain injury: 2006-2015. *J Neurotrauma* 2018; **35**(8): 1021-9.
55. Honeybul S, Janzen C, Kruger K, Ho KM. Decompressive craniectomy for severe traumatic brain injury: is life worth living? *J Neurosurg* 2013; **119**(6): 1566-75.
56. Chierigato A, Venditto A, Russo E, Martino C, Bini G. Aggressive medical management of acute traumatic subdural hematomas before emergency craniotomy in patients presenting with bilateral unreactive pupils. A cohort study. *Acta Neurochir (Wien)* 2017; **159**(8): 1553-9.
57. Faul M, Xu L, Wald M, Coronado V. Traumatic brain injury in the United States: emergency department visits, hospitalizations and deaths, 2002-2006. *Atlanta (GA): Centers for Disease Control and Prevention, National Center for Injury Prevention and Control* 2010: 1-74.
58. Garcia-Altes A, Perez K, Novoa A, et al. Spinal cord injury and traumatic brain injury: a cost-of-illness study. *Neuroepidemiology* 2012; **39**(2): 103-8.
59. Tuominen R, Joelsson P, Tenovu O. Treatment costs and productivity losses caused by traumatic brain injuries. *Brain Inj* 2012; **26**(13-14): 1697-701.
60. Humphreys I, Wood RL, Phillips CJ, Macey S. The costs of traumatic brain injury: a literature review. *Clinicoecon Outcomes Res* 2013; **5**: 281-7.
61. Gustavsson A, Svensson M, Jacobi F, et al. Cost of disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol* 2011; **21**(10): 718-79.
62. Olesen J, Gustavsson A, Svensson M, Wittchen HU, Jonsson B. The economic cost of brain disorders in Europe. *Eur J Neurol* 2012; **19**(1): 155-62.
63. Raj R, Bendel S, Reinikainen M, et al. Costs, outcome and cost-effectiveness of neurocritical care: a multi-center observational study. *Crit Care* 2018; **22**(1): 225.
64. Marin JR, Weaver MD, Mannix RC. Burden of USA hospital charges for traumatic brain injury. *Brain injury* 2017; **31**(1): 24-31.
65. Frontera JA, Egorova N, Moskowitz AJ. National trend in prevalence, cost, and discharge disposition after subdural hematoma from 1998-2007. *Crit Care* 2011; **39**(7): 1619-25.
66. Xu K, Soucat A, Kutzin J, et al. New perspectives on global health spending for universal health coverage Geneva: World Health Organization 2018; (WHO/HIS/HGF/HFWorkingPaper/18.2) Licence: CC BY-NC-SA 3.0 IGO: 1-44.
67. Papanicolas I, Woskie LR, Jha AK. Health care spending in the United States and other high-income countries. *JAMA* 2018; **319**(10): 1024-39.
68. De Minister van Volksgezondheid. Kamerbrief over beëindiging 'sluis' nivolumab per 1 maart 2016. 2016. <https://www.rijksoverheid.nl/documenten/kamerstukken/2016/01/28/kamerbrief-over-beeindiging-sluis-nivolumab-per-1-maart-2016>. Accessed on June 22, 2018.
69. Porter M, Lee T. The strategy that will fix health care. *Harv Bus Rev* 2013; **91**(10).
70. Te Ao B, Brown P, Tobias M, et al. Cost of traumatic brain injury in New Zealand: evidence from a population-based study. *Neurology* 2014; **83**(18): 1645-52.
71. Carroll LJ, Cassidy JD, Cancelliere C, et al. Systematic review of the prognosis after mild traumatic brain injury in adults: cognitive, psychiatric, and mortality outcomes: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. *Arch Phys Med Rehabil* 2014; **95**(3 Suppl): S152-73.
72. Saltzherr TP, Goslings JC, Bakker FC, et al. Cost-effectiveness of trauma CT in the trauma room versus the radiology department: The REACT trial. *Eur Radiol* 2013; **23**(1): 148-55.
73. Alali AS, Burton K, Fowler RA, et al. Economic Evaluations in the Diagnosis and Management of Traumatic Brain Injury: A Systematic Review and Analysis of Quality. *Value Health* 2015; **18**(5): 721-34.
74. Lu J, Roe C, Aas E, et al. Traumatic brain injury: methodological approaches to estimate health and economic outcomes. *J Neurotrauma* 2013; **30**(23): 1925-33.

75. Porter ME. A strategy for health care reform-toward a value-based system. *N Engl J Med* 2009; **361**(2): 109-12.
76. Grady C, Cummings SR, Rowbotham MC, McConnell MV, Ashley EA, Kang G. Informed Consent. *N Engl J Med* 2017; **376**(9): 856-67.
77. World Medical Association. WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects 2018. <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>. Accessed July 7, 2020.
78. Wolf SM, Clayton EW, Lawrenz F. The Past, Present, and Future of Informed Consent in Research and Translational Medicine. *The Journal of Law, Medicine & Ethics* 2018; **46**(1): 7-11.
79. Shalowitz DI, Garrett-Mayer E, Wendler D. The accuracy of surrogate decision makers: a systematic review. *Arch Intern Med* 2006; **166**(5): 493-7.
80. Wrigley A. Proxy consent: moral authority misconceived. *J Med Ethics* 2007; **33**(9): 527-31.
81. Ciroldi M, Cariou A, Adrie C, et al. Ability of family members to predict patient's consent to critical care research. *Intensive Care Med* 2007; **33**(5): 807-13.
82. Jansen TC, Kompanje EJ, Bakker J. Deferred proxy consent in emergency critical care research: ethically valid and practically feasible. *Critical Care Med* 2009; **37**(1 Suppl): S65-8.
83. European Commission Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC OJ L158:1–76: 2014.
84. Food and Drug Administration. Department of Health and Human Services. Protection of Human Subjects; Informed Consent and Waiver of Informed Consent Requirements in Certain Emergency Research; Final Rules. Fed Regist 1996; Volume 61, Number 192: 51498–531.
85. Kompanje EJ, Maas AI, Menon DK, Kesecioglu J. Medical research in emergency research in the European Union member states: tensions between theory and practice. *Intensive Care Med* 2014; **40**(4): 496-503.
86. van Belle G, Mentzelopoulos SD, Aufderheide T, May S, Nichol G. International variation in policies and practices related to informed consent in acute cardiovascular research: Results from a 44 country survey. *Resuscitation* 2015; **91**: 76-83.
87. Burns KE, Zubrinich C, Tan W, et al. Research recruitment practices and critically ill patients. A multicenter, cross-sectional study (the Consent Study). *Am J Respir Crit Care Med* 2013; **187**(11): 1212-8.
88. Ecartot F, Quenot JP, Besch G, Piton G. Ethical challenges involved in obtaining consent for research from patients hospitalized in the intensive care unit. *Ann Transl Med* 2017; **5**(Suppl 4): S41.
89. Steering Committee on Bioethics. Guide for Research Ethics Committee Members. 2012. https://www.coe.int/t/dg3/healthbioethic/activities/o2_biomedical_research_en/Guide/Guide_EN.pdf. Accessed on July 7, 2020
90. World Health Organization. Standards and operational guidance for ethics review of health-related research with human participants. 2011.
91. Emanuel E CR, Lie R, et al. The Oxford Textbook of Clinical Research Ethics. Oxford. *Oxford University Press*; Reprint edition 2011.
92. Urushihara H, Parmenter L, Tashiro S, Matsui K, Dreyer N. Bridge the gap: The need for harmonized regulatory and ethical standards for postmarketing observational studies. *Pharmacoepidemiol Drug Saf* 2017; **26**(11): 1299-306.
93. Bowles KH, Potashnik S, Ratcliffe SJ, et al. Conducting research using the electronic health record across multi-hospital systems: semantic harmonization implications for administrators. *J Nurs Adm* 2013; **43**(6): 355-60.
94. Aledort LM. Harmonization of clinical trial guidelines for assessing the risk of inhibitor development in hemophilia A treatment. *J Thromb Haemost* 2011; **9**(3): 423-7.
95. Oliver Daly J. Harmonisation of research outcomes for meaningful translation to practice: The role of Core Outcome Sets and the CROWN Initiative. *Aust N Z J Obstet Gynaecol* 2018; **58**(1): 15-6.





CHAPTER 2

Decision-making in very severe traumatic brain injury (Glasgow Coma Scale 3-5): a literature review of acute neurosurgical management

Authors

Jeroen T.J.M. van Dijk¹

Florence C.M. Reith²

Inge A.M. van Erp¹

Thomas A. van Essen¹

Andrew I.R. Maas²

Wilco C. Peul¹

Godard C.W. de Ruiter¹

Affiliations

1: Department of Neurosurgery, University Neurosurgical Center Holland, LUMC, HMC & Haga Teaching Hospital, Leiden/The Hague, The Netherlands;

2: Department of Neurosurgery, Antwerp University Hospital, Antwerp, Belgium

Citation

van Dijk JTJM, Reith FCM, van Erp IA, et al. Decision-making in very severe traumatic brain injury (Glasgow Coma Scale 3-5): a literature review of acute neurosurgical management. J Neurosurgical Sci. 2018; 62(2):153/177. doi:10.23736/S0390-5616.17.04255-2

ABSTRACT

Introduction: Patients presenting with an early Glasgow Coma Scale (GCS) Score of 3-5 after blunt or penetrating skull-brain assaults are categorized as having sustained a very severe traumatic brain injury (vs-TBI). This category is often overlooked in literature. Impact on patients and families lives however is huge and the question “whether to surgically treat or not” frequently poses a dilemma to treating physicians. Little is known about mortality and outcome, compared to what is known for the group of severe TBI patients (s-TBI) (GCS 3-8). The main goal of this review was creating more awareness for the neurosurgical treatment of this patient group.

Evidence acquisition: A literature search (2000-2017) was conducted discussing “severe TBI (GCS 3-8)”, “(neuro)surgical management” and “outcome”. Ultimately 45 out of 2568 articles were included for further analysis.

Evidence synthesis: Mortality rates and unfavorable outcome are high for s-TBI patients and as expected higher for vs-TBI patients. Mortality rates reach up to 100% for specific subgroups with GCS=3 and bilaterally fixed dilated pupils. Functional outcome was generally poor, but sometimes, although seldom, favorable in specific groups of vs-TBI patients after neurosurgical intervention. Factors like initial GCS, pupillary abnormalities and age seem to be associated with worse outcome.

Conclusions: Overall this literature review showed high rates of unfavorable outcome and mortality for vs-TBI patients. However, some studies, reporting relatively low mortality rates, reported “good” outcome for specific groups of vs-TBI patients. It is concluded that clinical decision-making, in particular those on treatment limitations, should never be taken based on the GCS alone.

INTRODUCTION

Patients with severe traumatic brain injury (s-TBI) are generally defined as those with a Glasgow Coma Scale Score (GCS) between 3 and 8. These patients are, in most instances in Western World, directly intubated and transported to the nearest level I trauma center. Obviously, s-TBI has high emotional, humanitarian and financial impact on patients, their proxy's as well as on society. Of hospitalized TBI patients about 1 out of 25 are classified as having s-TBI.¹ The nature and extent of brain injury in this group may vary from closed to penetrating trauma,^{2,3} including intracranial hematomas (epidural, subdural or hemorrhagic contusion injury) observed in up to 35% of the s-TBI patients and varying degrees of diffuse axonal injury.^{2,4} Mortality rates are high (40%) and chance for clinically favorable outcome, as assessed by the Glasgow Outcome Scale (GOS), relatively low (40%).⁵⁻⁸

Within the population of s-TBI, very severe TBI (vs-TBI) is being proposed by the authors to sub-classify the group of patients with an extremely low initial coma score, categorized as having a very low GCS, ranging between 3 and 5. Obviously, for the latter patients, mortality and severe disability rates are higher, and clinical outcome is worse than for the entire group of severe TBI. Still, this sub-classification is useful to analyze detailed outcome for this group specifically, because vs-TBI is the most challenging group of patients in treatment decision-making for neurosurgeons, traumatologists, intensivists and neurologists. As time is limited in the acute phase, communication with family and friends of the patient is short, if ever performed at all. It creates difficulties for those, who have to determine whether or not to treat these patients surgically in the acute setting. Surgical options, range from inserting an intracranial pressure (ICP) monitoring device up to a large decompressive craniectomy, in order to try to control "severe brain swelling", which may develop secondarily. The latter treatment may increase the chance for survival, but also increases the chance for survival of a patient with severe disability,⁹⁻¹³ which might not be acceptable for all people and to society.

The goal of this literature review was to investigate reported outcome for patients with vs-TBI, in particular the effect of different neurosurgical interventions. Besides important essential factual information, the authors try to identify gaps in the diagnostic and treatment evidence, for which more research will be needed to eventually improve surgical treatment for this important group of TBI patients.

EVIDENCE ACQUISITION

The literature review was conducted according to a predefined search protocol. A systematic review attempt was abandoned as randomized studies and methodological sound prospective studies were lacking. Keywords were “brain injury”, “traumatic”, “surgery”, “neurosurgical procedures”, “operative” and “severe” (Appendix I). The sections discussing penetrating brain injury (PBI) are separately informed by the literature search used for the *Guidelines for the Management of Penetrating Brain Injury*,¹⁴ which was expanded by an additional literature search in Medline. Search terms included “penetrating head or brain injuries”, “brain”, “head”, “wounds” and “gunshot” (Appendix I).

Two reviewers independently selected relevant studies, extracted data and discussed disagreements until consensus was reached. If consensus was not reached one of the senior authors was capable to take the final decision.

Two stages of study selection were needed (Figure 1). First, studies were selected on title and abstract at least containing: (1) s-TBI patients, (2) (neuro) surgical treatment and (3) clinical outcome. Secondly, during full-text screening, only original data studies with patient cohorts (N>10) consisting of vs-TBI patients (early GCS Score 3-5) were included if data on (neuro) surgical treatment and outcome were presented. Studies were excluded when published before 2000 and non-English. Authors excluded series without a detailed initial GCS and only mentioning mean or median scores for obvious clinimetric reasons.

Manuscripts containing information on outcome in vs-TBI in adult populations were subsequently divided based on surgical treatment; ICP monitoring, decompressive craniectomy and other surgical interventions. Studies discussing elderly and pediatric patients were discussed separately. Authors used various synonyms for good or favorable outcome (GOS 4 or 5), representing “moderate disability” and “good outcome” respectively. The same classification and denomination was used in the specific references.

EVIDENCE SYNTHESIS

The search resulted in 2568 manuscripts. After screening of abstracts, 751 studies were selected for full-text assessment. Manuscripts were excluded for three main reasons: 1) no original data (N.=173); 2) no vs-TBI patient cohort (N.=504); 3) no surgical treatment or outcome specified for vs-TBI (N.=29) and other reasons (N.=6). Finally, 39 scientific manuscripts met inclusion criteria. After checking reference lists on possible relevant publications another 6 emerged, resulting in a final selection of 45 studies¹⁵⁻²⁰ (Figure 1). In addition, a total of 126 manuscripts formed the evidence base for the sections on penetrating brain injury.

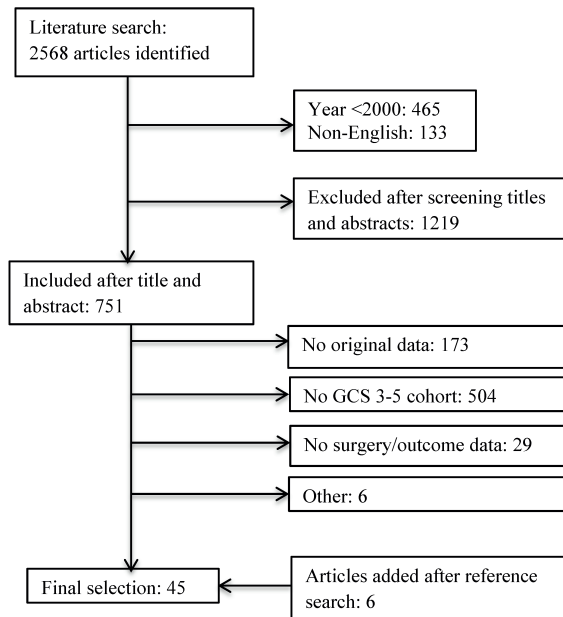


Figure 1: Article selection

Intracranial pressure monitoring

Eight studies from all global continents reported results of ICP guided treatment in vs-TBI patients (Table I).²¹⁻²⁸ Only three studies reported prospective data collection.²¹⁻²³ Cohort sizes varied between 78 and 4880 patients,^{24, 25} presenting male dominance (mean 77%) and young age (mean 42 years).

Table I: ICP Monitoring

| Study information | Purpose | Population | ♂ | Age |
|--|--|---|----|----------------|
| Farahvar (2012) ²¹ USA, 2000-2009 Prospective | Examine 2-week mortality of s-TBI patients with or without ICP monitor. | N=1446 ICP:1202 (83.1%) GCS3-5: 761 | 75 | 36.6 |
| Mauritz (2008) ²² Austria, 1998-2004 Prospective | Reasons for receiving ICP monitoring and factors influencing mortality. | N=1856 1:ICP:1031 (56%) 2:No-ICP:825 GCS3+4: 959 | 73 | 1: 46 2: 53 |
| Dawes (2015) ²³ USA, 2009-2010 Prospective | Determine the impact of ICP monitor placement on inpatient mortality. | N=822 ICP: 378 (46%) GCS3: 449 | 75 | 42 |
| Kim (2014) ²⁴ Korea, 2010-2012 Retrospective | Effect of ICP monitoring on the two-week mortality after early DC in s-TBI | N=78 ICP: 25 (32.1%) GCS3-5: 38 ICP: 10 (26.3%) | 82 | 44 |
| Alice (2017) ²⁵ USA, 2013-2014 Retrospective | Assess both compliance and outcomes of ICP monitoring. | N=4880 GCS3-5 sub: 3352 ICP: 381 (11.4%) | 72 | 50 |
| Griesdale (2010) ²⁶ Canada, 2000-2006 Retrospective | Evaluate guideline adherence and relationship between EVD use and mortality. | N=171 1:EVD: 98 (57%) 2:No EVD: 73 GCS<6: 52 | 77 | 1: 35 2: 42 |
| Haddad (2011) ²⁷ Saudi Arabia, 2001-2008 Retrospective | Examine outcome of ICP monitoring in s-TBI patients. | N=477 ICP: 52 (10.9%) GCS3-4: 231 | 96 | ±28.5 |
| Zeng (2010) ²⁸ China, 2004-2006 Retrospective | Evaluate treatment guided by ICP monitoring in s-TBI patients. | N=136 ICP: 136 (100%) GCS3-5: 58 | 66 | 44.8 |

Table I legend:

* Multivariable logistic regression models predicting 2-week mortality for all-age sample ((OR; 95%CI;P))

** Risk-adjusted mortality rate reduction for ICP monitoring.

*** Logistic regression analyses predicting 2-week mortalities for all 78 patients.

Abbreviations: ♂: Male; s-TBI: severe Traumatic Brain Injury; ICP: Intracranial Pressure; GCS: Glasgow Coma Scale (score); ICU: Intensive Care Unit; ED: Emergency Department; ISS: Injury Severity Score; FIM: Functional Independence Measure; EVD: External Ventricular Drain; GOS: Glasgow Outcome Scale.

Average reported proportion of ICP monitoring in s-TBI was 42% (range: 10.8-83.1%). Two studies specifically assessed guideline adherence and found only 10.8% and 46% of eligible patients receiving ICP monitoring.^{23, 25} A third study found that 86% of patients without an extra ventricular drain would have qualified for having one.²⁶ One study investigated inter-center differences and found that ICP monitoring occurred more often in medium-sized trauma centers compared to large centers (OR 3.09, 95% CI 2.42-3.94).²²

| Type of GCS score. | Outcome measure | Results |
|----------------------------------|-------------------------------------|--|
| Initial day 1 post-resuscitation | 14-day mortality | Mortality (OR; 95% CI; P) <u>GCS6-8 vs. GCS3-5</u> = (0.44; 0.36 - 0.53; <0.0001) ICP monitoring is a statistically significant predictor of 2-week mortality: (0.63; 0.41-0.94; 0.02)* |
| Admission | ICU/Hospital mortality | Mortality: <u>GCS3</u> (N=796): ICU: 48.5%, Hospital: 51.1% <u>GCS>3</u> : ICU: 24.8%, Hospital: 29.3% <u>Age 65 and GCS=3</u> : ICU 67%; Hospital 71.1% Numbers irrespective the presence of ICP monitoring |
| ED | Inpatient mortality | Mortality: <u>GCS(3)</u> : -13.3% (95% CI: -6.0 to -20.5). P:<0.001 <u>GCS(3)+ High ISS (>25)</u> : -32.9% (95% CI: -20.3 to -45.4) P:<0.001** |
| Initial | 2-week mortality | Overall mortality: ICP: 24%, no-ICP: 50.9% (p=0.025) Mortality: <u>GCS3-5</u> : 57.8% <u>GCS3-5</u> : Crude OR 3.625 (1.406-9.343)*** Adjusted OR: 2.506 (0.712-8.822)*** |
| Presentation | Mortality (in hospital)/ FIM (good) | Mortality Overall ICP/no-ICP: 27.2% / 22.4% FIM (good) Overall ICP/no-ICP: 17.8% / 28.7% Mortality: <u>GCS3-5</u> : 26.3%. Overall: 22.9% <u>GCS3-5</u> : Independent predictor of mortality: OR1.84 |
| Best in first 12 hours. | Hospital and 28-day mortality | Hospital mortality (OR; 95% CI; P): <u>GCS<6</u> : 0.76; 0.18-3.2; 0.71, <u>GCS≥6</u> : 5.6; 1.7-18.4; <0.01 28-day mortality (OR; 95% CI; P): <u>GCS<6</u> : 0.47; 0.11-2.1; 0.32, <u>GCS≥6</u> : 5.0; 1.5-16.7; <0.01 |
| Admission | Hospital mortality | Mortality ICP/No-ICP , (OR; 95%CI; P) <u>GCS3-4</u> : 12.9%/ 24.5%, (0.51; 0.17-1.59; 0.25) <u>GCS5-6</u> : 18.2%/ 7%, (3.74; 0.61-22.82; 0.15) <u>GCS7-8</u> : 50%/ 7.2%, (12.89; 3.14-52.95; 0.0004) |
| Admission | GOS (>6M) | <u>GCS3-5</u> : GOS1= 16%, GOS2=12%, GOS3= 24%, GOS4= 10%, GOS5=38% <u>GCS6-8</u> : GOS1= 4%, GOS2=4%, GOS3= 13%, GOS4= 10%, GOS5=69% |

Multiple factors seemed likely to be associated with more frequent placement of an ICP monitoring device, including age (<65 years), female gender, the presence of at least one reactive pupil and more isolated TBI with a higher Abbreviated Injury Scale (AIS) head score and higher Injury Severity Score (ISS).^{22, 23} Increased likelihood ratios for ICP monitoring were also found when the CT-scan showed subdural hematoma, cerebral contusion or diffuse mass effect.²³ Reasons for not providing ICP monitoring included higher age,²¹⁻²³ pupillary abnormalities,²¹ history of cancer,²² cardiac insufficiencies,²² alcoholism, coagulopathy or injury from a fall²³ and a higher estimated mortality as assessed by the treating physician.²² A cohort of 1856 patients, showed ICP rates rise with TBI severity, but interestingly again decreased for vs-TBI.²²

Monitoring ICP, with therapeutic consequences, was reported to be associated with an 8.3% reduction in risk-adjusted mortality rate.²³ Reduction in risk-adjusted mortality rate increased to 13.3% for low GCS Score (3) and to 32.9% in high (>25) and low GCS Score (3) combined.²³ But there was no consensus. Some found a lower GCS Score to be a predictor for mortality^{21, 25} and others showed no significant difference for GCS 5-6 and GCS 3-4 subgroups.²⁷ Even the opposite was found. A higher hospital and 28-day mortality in patients with GCS>5, but not in patients with GCS<6.²⁶

Despite ICP guided treatment, up to 12% was diagnosed as sustaining a persistent vegetative state at 6 months, besides which 24% having severe cognitive and somatic disabilities.²⁸ Favorable outcome (GOS 4-5) was reached in 48% (GCS 3-5) and 79% (GCS 6-8) of patients.²⁸

Although possibly due to selection bias, ICP monitored patients showed longer duration of mechanical ventilation,²⁵⁻²⁷ a higher need for tracheostomy²⁷ and significantly longer intensive care unit (ICU) stay^{22, 25-27} compared to non-ICP monitored patients. Also more complications and poorer functional outcome at discharge are reported.²⁵

Decompressive craniectomy

Seventeen of 45 selected studies concerned decompressive craniectomy (DC) procedures. Results (Table II)^{15-17, 29-42} showed a predominance of young males (age range: 25-56 years) and most cohorts involved less than 50 patients, with one prospective study and other studies being retrospective.²⁹ Most studies used the Glasgow Outcome Scale (GOS) and one study used the modified Rankin Scale (mRS).³⁰

Wide ranges in outcome were identified for overall s-TBI mortality rates (11% to 68.5%).^{30, 31} Rates for vs-TBI patients were higher near 80%,^{32, 33} up to 100% in two GCS=3 subgroups.^{30, 34} Favorable outcome in vs-TBI patients ranged from 0% (mRS 0-2) to 63% (GOS3-5).^{30, 35} Up to 80% of patients with initial GCS≥6 achieved favorable outcome.³⁶

Nine studies investigated outcome of standard DC, without comparing different ICU and surgical treatment methods.^{15-17, 31, 32, 34, 36-38} A bilateral decompression for bilateral injury or diffuse edema/swelling was used in 3.3-34% of total procedures. The identified two typical reasons for performing DC are: 1) directly to prevent secondary injury; 2) posttraumatic ICP elevation, after failed ICU treatment; and 3) posttraumatic

surgical lesions like epidural hematoma (EDH), acute subdural hematoma (ASDH) or cerebral contusions, depending on their location, extent and presence of brain edema and CT recorded midline shift.^{31, 34, 36-38} With 34% of all patients receiving bilateral decompressive surgery for posttraumatic intractable intracranial hypertension, overall 84% achieved unfavorable outcome increasing to 96.6% for vs-TBI.¹⁷

Timing of surgery varied between cohorts from 86% of patients within first hour after admission, to 33% within 6 hours from trauma.^{31, 36} One study with only ASDH patients, showed a 30-day mortality rate of nearly 40 percent. The vs-TBI subgroup showed higher mortality rates (64% vs. 26%) and more 6-month unfavorable outcome (GOS1-3) (91% vs. 55%) compared to patients with GCS>5.³⁴ A second study (79% ASDH) found similar unfavorable outcome rates for vs-TBI patients after 6 months approaching 90%, but found higher mortality rates (79.3%).³² With 86% of cohort being patients with ASDH, Huang *et al.* found 59.7% 30-day mortality for vs-TBI subgroup and 12.4% mortality for GCS 6-8.¹⁶ In other studies ASDH was the most prevalent focal intracranial space-occupying lesion (32-86%).^{16, 17, 30, 31, 38} A study investigating “malignant” brain swelling reported no difference in mortality rates, but worse outcome for vs-TBI patients (70% vs. 16.7%) than GCS>5 patients.³⁷ Within a cohort of 66 vs-TBI patients, neurosurgeons performed 86% of all DC within approximately one hour after admission and this study reported an overall 1-year mortality rate of 11%, with good outcome in 68%.³¹ Worse outcome was reported in patients with higher initial ICPs and GCS<5.³¹ A relatively favorable overall mortality rate (12.5%) was found in Italy, where 37% of GCS 3-5 patients achieved favorable outcome.¹⁵

Five studies compared different surgical techniques and varying timing of surgery.^{30, 35, 39-41} All studies were retrospective and contained a subgroup of GCS 3-5 patients. Early bilateral decompressive craniectomy as a first treatment option in s-TBI was compared to secondary DC for refractory ICP.³⁹ It was shown to be an effective treatment option for ICP control, resulting in overall significant better one-year favorable outcome of 50% and 27.8%, respectively.³⁹ Compared to the GCS 6-8 subgroup, the vs-TBI subgroup showed a 2 times higher rate of mortality (50% vs. 25%) and splits favorable outcome (45% vs. 25%).³⁹ Ultra-early DC (<4 h of trauma onset) compared with DC after 4 hours did not seem to improve patient outcome.³⁰ Worse mortality rates were found for vs-TBI patients (GCS 3:100%, GCS 4-5:82.2%, GCS>5:41%) and showed 0% favorable outcome, compared to 4.7% in GCS>5 patients.³⁰ Another study reported significantly better outcome for patients with GCS 6-8 who were operated within 24 h compared to patients with GCS 3-5, operated within the same time window.⁴¹

Apart from the timing of decompressive surgery, another factor was the surgical technique, which varied, caused by the extent of diffuse swelling and presence of intracranial hematoma. The difference between DC with and without mass evacuation was investigated comparing 93 patients with mass lesions and 71 patients with diffuse injury and swelling.⁴⁰ The first group showed lower mortality (14 vs. 32.4%) and appeared to be a significant predictor to 60-day mortality (OR=0.31). Only good outcome was significantly worse for vs-TBI patients.⁴⁰ Performing large DC (10 cm x (13-15)cm) on patients resulted in overall satisfactory outcome (GOS 3-5) in 71.1% compared to 58.6% in the routine DC group (6-8 cm diameter) ($P<0.05$).³⁵ Superiority was especially seen in vs-TBI patients (63.0% vs. 36.7%, $P<0.01$).³⁵

A higher initial GCS Score, typically compared to GCS 3-5 (vs-TBI) subgroups, was correlated with more favorable outcome in almost all studies.^{15-17, 30-32, 34, 36-41} Patients with GCS 6-8 were more likely to have a good outcome than the GCS 3-5 group (OR 10.0, 95% CI 1.6-60.9).³⁷ A GCS motor-score of 5-6 resulted more in good outcome than a motor-score of 1-4 (OR 4.2, 95% CI 1.1-16.3).³⁷ Pupillary abnormalities were associated with mortality,^{36,40} even up to 100% when bilaterally fixed and dilated³² (except in one study).³⁷ A younger age was associated with a favorable outcome,^{15-17, 30, 31, 34, 38-42} only two studies mentioned no statistical significance between age and prognosis.^{32, 37} Other factors like small size of bone flap,^{31, 35} association of intracranial lesions, midline shift > 15 mm, ICP > 20 at time of DC,³¹ Revised Trauma Score < 5, Charlson Comorbidity Index Scores > 5, glucose > 180 (mg.dL-1), PaO_2 < 160 (mmHg), SO_2 < 96 (%) were all linked to poor prognosis and unfavorable outcome.³⁴

Outcome, hypothetically can be improved by two suggested changes in technique.^{29, 33, 42} A prospective study showed that DC combined with a new multi-dural stabs technique (SKIMS) in patients with ASDH and severe brain edema seems very effective in patients with low GCS.²⁹ Patients with vs-TBI receiving DC with SKIMS showed a mortality of 36.7% and favorable outcome (GOS 4+5) in 30%, while 59% of the conventional group died and 19% achieved favorable outcome.²⁹ Two small retrospective patient series described that creating vascular tunnels during decompressive surgery dropped mortality for GCS < 5 patients with severe brain edema (ICP > 30 mmHg for > 3 hours) from 80% to $\pm 40\%$ and good outcome (GOS 4+5) improved from 10% to $\pm 40\%$.^{33, 42} Series were compared with a historic control group receiving a large bilateral frontotemporo-parietal craniectomy.

Neurosurgical interventions

Eleven studies discussed surgical interventions, mainly craniotomy for hematoma evacuation (Table III).^{19, 43-51} One study used prospectively collected data and six discussed cohorts with exclusively GCS 3-5 patients, with four only including GCS=3 patients.

The choice between surgical intervention or not and which technique showed substantial variation between centers (9-77%). Fewer patients with a cerebral contusion received surgical intervention (34%) compared to patients having an EDH or ASDH (88%, 68%).⁴³ Factors positively associated with quantities of surgical intervention appeared to be fall injury, more severe injuries (according to ISS and head AIS), bradycardia and injuries like skull fractures, EDH and ASDH. Negative associating factors seem to be a diagnosis of intracerebral hemorrhage and hypotension or tachycardia at ED presentation.⁴⁴ Although suffering from more extra-axial bleedings, significantly lower rates of surgical intervention were found in patients with bilaterally fixed dilated pupils, compared to patients with reactive pupils (16.4% vs. 34.8%).⁴⁵ The execution of bilateral surgery instead of unilateral surgery seems to be associated with absence of pupillary response, lower GCS (6.7% vs. 9.2%), more large-volume lesions, complete cistern compression and CT-visible deep lesions.⁴⁶ Timing of surgical intervention was not always mentioned, but 50 and 73% was performed <24 hours^{43, 47} up to 83% within 4 hours in one cohort.⁴⁴ Several studies show lower GCS scores to be linked to worse outcome and higher mortality rates.^{46, 48} Unfavorable outcome (GOS 1-3) in up to 94.11% was found for GCS 3-5 subcategories.⁴⁹

Surgical intervention resulted in improved mortality.^{43, 44, 46, 49} One study found better prognosis for both GCS 6-8 and GCS 3-5 surgical treatment subgroups and poorer outcome for conservative treatment especially in patients with GCS \geq 6.⁴⁶ A significant 4-fold survival benefit was found for surgically treating mass lesions in patients with GCS=3, but this study also found surgery to be significantly related to more complications, especially pneumonia ($P<0.001$).⁴⁴ Significant higher mortality (48% vs. 23%) and poorer outcome was found in the conservative group.⁴³ Two studies reported no significant difference in surgical interventions between survivors and non-survivors and another found no effect from immediate neurosurgery on outcome in patients without a mass lesion.^{44, 50}

Multiple studies report poor outcome and increased mortality rates to be associated with pupillary abnormalities.^{45, 46, 48, 50} In normally bilateral reactive pupils a mortality rate of 23.5% and a good outcome in 1 out of 4 patients is reported⁵⁰ and in another study absence of pupillary response correlated with unfavorable outcome (OR 3.16, 95% CI 1.38-7.25).⁴⁶ In patients with gunshot wound to the head 96% and 100% died when having a unilateral dilated pupil or a medium fixed pupil.⁴⁸ Another study found mortality rates in patients with bilaterally fixed dilated pupils of nearly 80% and good outcome in only 1.5% of patients.⁵⁰ Other possibilities, like unilateral fixed dilated pupils showed good outcome in 27.5% and bilateral fixed, non-dilated pupils achieve good outcome in only 7.5%.⁵⁰ Patients with both a GCS=3 and bilaterally fixed dilated pupils presented good outcome (GOS 4-5) after neurosurgery in 9.3%. In the overall group, difference in good outcome was found between field and post resuscitation GCS of 3 (8.7% vs. 4%).¹⁹ Patients with bilaterally fixed dilated pupils showed increased numbers of extra-axial bleedings (81.4% vs. 56.5%, $P=0.002$), midline shifts (70.0% vs. 24.2%, $P<0.0001$) and herniation (64.3% vs. 11.3%, $P<0.0001$) and ultimately higher mortality compared to patients with RP (100% vs. 42%, $P<0.0001$).⁴⁵ Sometimes, patients with bilaterally fixed dilated pupils were not stable enough to undergo a CT scan.⁴⁵

Aggressive presurgery medical treatment with single high mannitol dosage (90-106g) resulted in significant lower risks of death and persistent vegetative state (OR=0.016) with lower unfavorable outcome (57.1% vs. 95.5%). However at 1 year follow up, more patients survived with severe disabilities.⁵¹

One study showed survival was most positively linked to acute epidural hematomas, followed by cerebral contusions, and worst with acute subdural hematomas.⁴⁷ Another study however, found no correlation between dominant lesions, presence of midline shift and outcome.⁴⁶ Compression of basal cisterns was linked to death (OR 3.24, 1.04-10.12) and unfavorable outcome (OR: 2.74, 1.17-6.42).^{19, 46} For patients with gunshot wounds to the head, especially transventricular or bihemispheric central type trajectory, and bilobar or multilobar wounds are suggested as predictive factors of high morbidity and mortality.⁴⁸

Other factors mentioned to be associated with lower survival or unfavorable prognosis are: higher age^{19, 47, 50, 51} and ICP.⁵⁰ Alcohol, gender, mechanism of injury, hypotension on admission, and extracranial injuries are mentioned not to be related with outcome.⁵⁰

Elderly patients

Five studies focusing on elderly patients matched our criteria (Table IV)^{18, 20, 52-54} and three articles from other categories contained information concerning elderly patients.^{22, 31, 38}

Mortality rates ranged between 53.6% (6 month) and 77% (1 year) for all GCS scores.^{52, 53} For this severity group, surgical management resulted in lower mortality compared to conservative treatment (32.9% vs. 88.1% and 62% vs. 81%).^{18, 52} For vs-TBI patients, results are worse, with rates around 80% even up to 100% after DC.^{18, 20, 53, 54} An earlier discussed study found better outcome in patients younger than 66 years old, which seemed to be a cut-off point, since groups aged <40 and 40-65 showed no differences.³⁸

Almost 6% of GCS 3-4 patients achieved functional recovery (GOS 4-5) 6-months after evacuation of an ASDH.⁵⁴ In another study, GCS 3-4 patients achieved 11% favorable outcome (GOS 4-5) one year after >80% received non-specified neurosurgical intervention.²⁰ Our biggest included cohort showed only 3% of vs-TBI patients with favorable outcome, compared to 13% with less severe injury (GCS 6-15).¹⁸ Both positive and negative association of surgical intervention with outcome was reported.^{18, 20, 52, 53} GCS Score was an important outcome predictor^{18, 52-54} and other factors associated with unfavorable outcome are treatment method, pupillary abnormality, higher trauma severity, closed basal cisterns (100% mortality) and midline shift (≥ 10 or ≥ 15 mm) on first CT-scan.^{20, 52} Age was said to be both a significant^{18, 54} and insignificant predictor⁵³ and also gender associations remained non-conclusive.^{20, 53}

Table II Decompressive Craniectomy

| Study information | Purpose | Population | ♂ | Age | Type of GCS score | Pupils |
|--|---|---|------|-------------------|---------------------------|---|
| Chibbaro (2007) ¹⁵ Italy, 2003-2005 Retrospective | Effects of DC in the treatment of severe head injury | N=48 GCS3-5: 19 | 63 | 47 | Preoperative | BFD: 6 UFD: 18 |
| Huang (2013) ¹⁶ Taiwan, 2006-2008 Retrospective | Investigate factors related to 30-day mortality after DC | N=201 GCS3-5: 67 ASDH: 86% TSAH: 84% CC: 56% EDH: 12% | 72 | 46 | Pre-decompression | Unilateral FP: 12 Bilateral FP: 91 |
| Ucar (2005) ¹⁷ Turkey 2001-2003 Retrospective | Evaluate benefits of DC in intractable ICH | N=100 GCS4-5: 60 ASDH: 32% | 68 | 30 | Initial | NP |
| Bhat (2013) ²⁹ India, 2006-2011 Prospective | Effects of combining DC and multi-dural stabs | N=225 s-TBI ASDH+BE GCS3-4: 30 | > 80 | 65%= 21- 40 | Following trauma | NP |
| Park (2014) ³⁰ Korea, 2007-2013 Retrospective | Outcomes of Ultra-Early DC after s-TBI | N=127 GCS3: 27 GCS4-5: 45 ASDH: 62.2% EDH: 2.4% CC: 32.3% | 76 | 50 | Admission | Many GCS=3 patients with bilateral DP |
| Fotakopoulos (2016) ³¹ Greece, 2009-2013 Retrospective | Clinical outcome after DC in s-TBI patients | N=101 s-TBI. GCS3-5: 60 ASDH :37% BE:30% IP:21% CC:8%, EDH:7% | 80 | 42.8 | Time of intubation | NP |
| Saade (2014) ³² Brazil, 2004-2012 Retrospective | Prognostic factors of DC in treating s-TBI patients | N=56 GCS4-5: 29 ASDH:79% CC:28.6% EDH:18% TSAH:18% | 83 | Most 40- 50 | Admission/ Prehospital | ANI: 48% BFD: 18% Normal: 34% |
| Csokay (2002) ³³ Hungary, 1997-1999 Retrospective | Outcome of a new surgical technique: vascular tunnelling (VT) | N=28 All GCS<5, BE 1: VT: 28 2: Previous cohort: 20 | NP | NP | NP | NP |
| Kalayci (2013) ³⁴ Turkey, 2001-2009 Retrospective | Prognostics and value assessment in DC for ASDH | N=34 GCS3-4: 11 ASDH 100% | 76 | 37 | Preoperative | BFD:12 Unilateral DP: 9 Isocoria: 13 |

| Surgical intervention. | Outcome measure | Results |
|--|---------------------------|---|
| DC($\geq 35\text{cm}^2$): 48 Unilateral: 42 Bilateral: 6 <16h trauma: 28 <48h trauma: 48 | GOS | GOS1: Overall: 12.5%, <u>GCS3-5</u> : 16%, <u>GCS6-8</u> : 11% GOS2: <u>GCS3-5</u> : 37%, <u>GCS6-8</u> : 7% Favourable (GOS4+5): Overall: 55%, <u>GCS3-5</u> : 37%, <u>GCS6-8</u> : 67% <u>LTJU</u> : 2 (Mean FU 14 months) |
| Primary: 187 Secondary: 14 Unilateral: 183 Bilateral: 8 Bifrontal: 10 <24h trauma: 166 | 30-day Mortality | Mortality: Overall: 26.4%, <u>GCS9-15</u> : 4.4%, <u>GCS6-8</u> : 12.4%, <u>GCS3-5</u> : 59.7% >90% died within 14 days. |
| Unilateral: 66% Bilateral: 34% 94 < mean 17.1h 6 after secondary ICP increase. | GOS (6M) | Unfavourable (GOS1-3): Overall: 84%, <u>GCS4-5</u> : 96.6%, <u>GCS6-8</u> : 65% Favourable (GOS4-5): Overall: 16%, <u>GCS4-5</u> : 3.4%, <u>GCS6-8</u> : 25% |
| Conventional DC: 106 Multi-dural stabs technique: 119 | Discharge GOS | Conventional GCS3-4: GOS1: 59%, GOS (2+3): 22%, GOS (4+5): 19% SKIMS GCS3-4: GOS1: 36.7%, GOS (2+3): 33.3%, GOS (4+5): 30% |
| 1: Ultra-early DC<4h: 60 2: DC>4h: 67 | Mortality / mRS | Mortality: Overall: 68.5%, DC<4h: 65.0%, DC>4h: 71.6%, (p: 0.430) Mortality: <u>GCS3</u> : 100%, <u>GCS4-5</u> : 82.2%, <u>GCS>5</u> : 41% Favourable (mRS0-2): <u>GCS3-5</u> : 0%, <u>GCS>6</u> : 4.7% |
| Early DC (± 1 h after admission): 85.9% Secondary: 14.1% (4-6 days). 8.2% bilateral. | GOS (6M/12M) | At surgery: Mortality 1.9%, morbidity 31.9%. 6M (overall): GOS1: 11%, GOS2: 26%, GOS3: 9%, GOS4: 26%, GOS5: 28% 12M (overall): GOS1: 11%, GOS2: 6%, GOS3: 15%, GOS4: 25%, GOS5: 43% Other: >60Y + GCS ≤ 5 (N=11) = 100% GOS<4. Poorer outcome in higher ICP and GCS <5 |
| Unilateral DC: 96.4% Bilateral DC: 3.6% <6h admission: 71.4% | Mortality/GOSE (6M) | Mortality: All: 58.9%, <u>GCS4-5</u> : 79.3%, <u>GCS>5</u> : 37% Unfavourable(GOSE1-4): All: 78.5%, <u>GCS4-5</u> : 89.7% |
| Uni/bilateral FTPC (with/without vascular tunnel construction). <4h admission: 20 | GOS | Group 1: GOS1: 39.3%, GOS4-5: 42.9%, GOS2-3: 17.8% Group 2: GOS1: 80%, GOS4-5: 10%, GOS2-3: 10% |
| Uni/bilateral FTPC ± 5 hours from trauma | Mortality (30d)/ GOS (6M) | 30d: Mortality: Overall: 38.2%, <u>GCS≤ 5</u> : 64%, <u>GCS>5</u> : 26% (P=0.042), <u>GCS3</u> (N=3): 100%, <u>GCS4</u> (N=5): 80% 6M: Mortality: 47%, GOS2: 20%. Favourable (GOS4-5): Overall: 35%, <u>GCS≤ 5</u> : 9%, <u>GCS>5</u> : 45% Unfavourable (GOS1-3): <u>GCS≤ 5</u> : 91%, <u>GCS>5</u> : 55% |

Table II continued

| Study information | Purpose | Population | ♂ | Age | Type of GCS score | Pupils |
|---|--|---|----|------------------|--------------------|---|
| Li (2008) ³⁵ China, 2001-2006 Retrospective | Compare large DC (LDC) with routine DC (RDC) in s-TBI patients | N=263 LDC: 135 -GCS3-5: 54 RDC: 138 -GCS3-5: 49 | 69 | ±47 | Administration | Bilateral DP:38 Unilateral DP: 97 |
| Gouello (2014) ³⁶ France, 2005-2011 Retrospective | Outcome of DC in s-TBI patients | N=60 GCS3-5: 26 Primary: 20 Secondary: 40 | 77 | 33 | Initial management | CSP:43% UnilateralDP:57% Bilateral DP:22% ACR:8% |
| Aarabi (2006) ³⁷ USA, 2000-2004 Retrospective | DC in TBI (malignant brain swelling) | N=50 GCS3-5: 15 BS: 88% | 66 | 25 | Post-resuscitation | ALR:22% |
| Pompucci (2007) ³⁸ Italy, 1994-2004 Retrospective | Effect of DC. | N=55 GCS3-5: 31 No focal lesion: 38% ASDH+ BE: 62% | 63 | 53 | Post-resuscitation | NP |
| Akyuz (2010) ³⁹ Turkey, 2003-2008 Retrospective | Effectiveness of early bilateral DC in s-TBI patients | N=76 GCS4+5: 20 1: Second-tier DC: 36 2: First-tier: 40 | 59 | 1:37.6 2:41.3 | Initial | NP |
| Yuan (2013) ⁴⁰ China, 2005-2009 Comparative | Difference between DC with and without mass evacuation in TBI | N=164 GCS3-5: 51 2 groups. | 75 | 48 | Admission | ALR: 1: 56% 2: 48% |
| Limpastan (2013) ⁴¹ Thailand 2006-2008 Retrospective | Evaluate risk factors influencing outcome after DC in s-TBI | N=159 GCS3-5: 63 | 82 | 36 | Preoperative | 80.3% of deceased group had no pupillary light reflex |
| Csokay (2001) ⁴² Hungary, 1998-2000 Retrospective comparative | Evaluation of new operative technique: vascular tunnelling (VT). | N=20 (19TBI) All GCS<6, BE. 1: VT: 20 2: Previous cohort: 20 | NP | NP | NP | Bilateral DP: 20% Unilateral DP: 35% |

Table II: Abbreviations: ♂: Male; ACR; Absent Corneal Reflex; ALR; Abnormal Light Response; ANI: Anisocoria; ASDH: Acute Subdural Hematoma; BE: Brain Edema; BFDP: Bilateral Fixed Dilated Pupils; BS: Brain Swelling; CC: Cerebral Contusion; CSP: Constricted Symmetrical Pupils; DC: Decompressive Craniectomy; DP: Dilated Pupil(s); EDH: Epidural Hematoma, FP: Fixed Pupil; FTPC: Frontotemporoparietal Craniectomy; GCS: Glasgow Coma Scale; GOS(E): Glasgow Outcome Scale (Extended); ICH: Intracranial Hypertension; ICP: Intracranial Pressure; IP: Intraparanchymal; LTFU: Loss to Follow Up; mRS: modified Rankin Scale; NP: Not Provided; s-TBI: severe Traumatic Brain Injury; TBI: Traumatic Brain Injury; TSAH: Traumatic Subarachnoid Hemorrhage; UFDP: Unilateral Fixed Dilated Pupil.

| Surgical intervention. | Outcome measure | Results |
|--|----------------------------|--|
| LDC: 10cm x (13-15) cm RDC: 6-8 cm diameter | GOS (6M) | Satisfactory (GOS3-5): <u>GCS3-8</u> : LDC 71.1%, RDC: 58.6% (P<0.05), <u>GCS3-5</u> : LDC 63%, RDC 36.7% (P<0.01) LDC (GCS3-5): GOS1: 30%, GOS2: 7%, GOS 3-5: 63% RDC (GCS3-5): GOS1: 57%, GOS2: 6%, GOS 3-5: 37% |
| Unilateral DC: 58. Bilateral DC: 2. Mean size 100cm ² <6h: 33%. 6-24h: 12% | Mortality/ GOS (3/24M) | Mortality : <u>GCS3-5</u> : 50%, <u>GCS6-8</u> : 12%, <u>GCS>8</u> : 12% Unfavourable (GOS2+3) : <u>GCS3-5</u> : 54%, <u>GCS6-8</u> : 20%, <u>GCS>8</u> : 20%. Favourable (GOS4+5) : <u>GCS3-5</u> : 46%, <u>GCS6-8</u> : 80%, <u>GCS>8</u> : 80%. All significant |
| FTPC: 49 Bifrontal:1 <48h: 34% | Mortality/ GOS (3M) | Mortality (30d): <u>Overall</u> : 28%, <u>GCS 3-5</u> : 20%, <u>GCS 6-8</u> : 21.7%, <u>GCS 9-15</u> : 25%. Good outcome (GOS4+5) : <u>Overall</u> : 51.3%, <u>GCS 3-5</u> : 16.7%, <u>GCS6-8</u> : 66.7%, <u>GCS 9-15</u> : 66.7%. |
| Unilateral FTPC:50 Bilateral FTPC: 5 <5h: 29% >10h: 35% | GOS (12- 102M) | GOS1 : <u>Overall</u> : 39%. Favourable (GOS4-5) <u>Overall</u> : 47% <u>GCS3-5</u> : 26.7%, <u>GCS6-8</u> : 76.9%, <u>GCS9-15</u> : 66.7% Unfavourable (GOS1-3) <u>GCS3-5</u> : 76.3%, <u>GCS6-8</u> : 23.1%, <u>GCS9-15</u> : 33.3% Age>65 + GCS3-5 (N=11): 100% |
| Group 1: Unilateral: 22. Bilateral: 14. Group 2: Bilateral:40 | GOS (12M) | Favourable (GOS4+5) : Group 1: 27.8%, Group 2: 50% <u>GCS4-5</u> : GOS1: 50%, GOS2+3: 25%, GOS4+5: 25% <u>GCS6-8</u> : GOS1: 20%, GOS2+3: 35%, GOS4+5: 45% |
| 1: DC for mass lesion: 93 2: DC for diffuse injury and swelling: 71 | Mortality (60d)/ GOS | Overall : GOS1: 22%, GOS4-5: 42% Mortality : Group 1/Group 2: 14% / 32.4% Mortality : <u>GCS3-5</u> : 27.5%, <u>GCS6-8</u> : 26.9%, <u>GCS9-12</u> =13.1%. P=0.197 Good outcome (GOS4-5) (%) : <u>GCS3-5</u> : 29.7%, <u>GCS6-8</u> : 52.6%, <u>GCS9-12</u> : 71.7% P=0.002 |
| ≤24h after admission: 76% (N=122) Unilateral: 88% Bilateral: 12% | GOS (discharge / 6M) | Mortality : <u>Overall</u> : 44.7%, <u>GCS3-5</u> : 59%, <u>GCS>5</u> : 35% (p=0.004). Surgery ≤24h: (discharge) : GOS1 : <u>GCS3-5</u> : 68%, <u>GCS6-8</u> : 42%, GOS4-5 : <u>GCS3-5</u> : 26%, <u>GCS6-8</u> : 41.7% (p=0.013) (6M): GOS1 : <u>GCS3-5</u> : 26.7% <u>GCS6-8</u> : 61.7% GOS4-5 : <u>GCS3-5</u> : 6.7%, <u>GCS6-8</u> : 14.7% (p=0.013) |
| Bilateral FTPC (with/ without vascular tunnel construction). | GOS | Group 1 : GOS1: 40%, GOS4-5: 40%, GOS2-3: 20% Group 2 : GOS1: 80%, GOS4-5: 10%, GOS2-3: 10% |

Tabel III Neurosurgical Interventions

| Study Information | Purpose | Population | ♂ | Age | Type of GCS score | Pupils |
|--|---|---|----|--------------------|---------------------------------------|--|
| Mauritz (2009) ¹⁹ Europe, 2001-2005 Prospective data | Investigate outcome of s-TBI with GCS 3 and BFDP. | N=92 F-GCS3: 100% PR-GCS3: 74 ASDH: 46% EDH: 13% TSAH: 64% | 79 | 32 | Field (F) and Post-resuscitation (PR) | BFDP: 100% ≥1 reactive pupil PR (N=18) |
| Kawamata (2006) ⁴³ Japan, 1998-2001 Retrospective | Effects of surgical excision of necrotic brain tissue in severe cerebral contusion. | N=182 GCS3-5: 58 CC: 182 | NP | 1: 47.8 2: 54.4 | Admission | NP |
| Salottolo (2016) ⁴⁴ USA, 2009-2013 Retrospective | Outcome in TBI treated with cranial surgery (CRANI). | N=541 Surgery: 103 GCS3: 100% ASDH: 58% TSAH: 53% CC/laceration: 40% | 74 | 49 | Presentation | NP |
| Tien (2006) ⁴⁵ Canada, 2001-2003 Retrospective | Mortality of s-TBI+GCS3 comparing BFDP with RP. | N=173 GCS3: 100% | 68 | ±41 | Admission | BFDP:104 Reactive pupils (RP):69 |
| Hu (2015) ⁴⁶ China, 2010-2012 Retrospective | Outcome of traumatic acute bilateral mass lesions. | N=80 GCS3-8:47 GCS3-5:15 ASDH: 42.5% EDH: 21.3% HC: 36.3% | 82 | 46 | Admission | Absent pupillary response: One: 7.5%, Two: 26.3% |
| Bindal (2015) ⁴⁷ India, 2009-2011 Retrospective | Outcome of surgery for supratentorial mass lesions after blunt s-TBI. | N=72, All GCS4 (M2) EDH: 38% CC: 26% ASDH/CC:26% ASDH: 10% | 79 | 19% >60 year | Time operation | NP |
| Martins (2003) ⁴⁸ Brazil, 1994-2000 Retrospective | Evaluate morbidity and mortality in civilians with head gunshot wounds. | N=319. GCS3-5: 125 Damaged dura=265 | 93 | 26 | Admission | Unilateral Dilated Pupils (UDP): 27 Medium Fixed (MF): 38 |
| de Souza (2013) ⁴⁹ Brazil, 1991-2005 Retrospective | Prognostic factors associated with TBI by a firearm projectile. | N=181 GCS3-5: 68 Penetrating 84% Tangential 16% | 85 | 31 | Admission | NP |

| Surgical intervention. | Outcome measure | Results |
|---|--|--|
| Neurosurgery: 43 Not further specified. | GOS (12M) | Total group: Poor outcome (GOS1-3): Field GCS: 91.3%, PR-GCS: 96% Good outcome (GOS4-5): Field GCS: 8.7%, PR-GCS: 4% ≥1 reactive pupil (N=18): Good outcome: 28% After neurosurgery (N=43): Good outcome: 9.3%, non-significant |
| 1: Conservative 66% 2: Surgery 34% Internal decompression with/without external decompression: 90% Only external decompression: 10% <24h in 73% Craniotomy: 87% Craniectomy: 13% <4h arrival: 83% Mean time: 1.9h | GOS (6M) | Surgical GCS3-5 (N=11): GOS1: 55%, GOS2: 0%, GOS3: 27%, GOS4: 9%, GOS5: 9%. Conservative GCS3-5 (N=47): GOS1: 70%, GOS2: 11%, GOS3: 11%, GOS4: 2%, GOS5: 7%. Surgical GCS6-8 (N=21): GOS1: 14%, GOS2: 10%, GOS3: 24%, GOS4: 29%, GOS5: 24% Conservative GCS6-8 (N=58): GOS1: 29%, GOS2: 10%, GOS3: 10%, GOS4: 21%, GOS5: 29% |
| | Mortality (discharge) / favorable (home, rehabilitation) / FIM | Overall mortality GCS=3: 48% (9% Emergency room) Overall survivors (favorable): 74%. Overall FIM: (feeding/ expression/locomotion): 61%, 63%, 38%. Survival: CRANI/no CRANI: 61%/50% (P=0.04) Favorable (home/rehab): CRANI/no CRANI: 39%/39% Matched mass lesion population: Survival: CRANI/no CRANI: 65%/34% Favorable outcome: CRANI/no CRANI: 43%/26% |
| Neurosurgical procedures: BFDP 16.4% and RP 34.8% (P=0.005) | Mortality | Mortality: GCS3 + BFDP: 100% GCS3+RP: 42% (P<0.0001) |
| Conservative 22.5%. Unilateral 48.8%. Bilateral 28.8% (78.3% simultaneously). | Mortality/ GOS (6M) | Overall mortality: 31.3%. Unfavorable (GOS1-3): 56.3% Surgical group: GCS3-5: GOS1: 53.3%, GOS2: 26.7%, GOS3: 20.0% GCS≥6: GOS1: 14.9%, GOS2: 6.4%, GOS3: 17% LTFU: 3.8% |
| EDH:37%, ASDH: 10% Removal contusion/ lobectomy: 33% Persistent brain swelling (DC): 21%. 50% <24h. | Mortality/ GOS | In-hospital mortality: 79%. Overall: 83%. Mortality isolated ASDH: 100%. >60 years: 100% 70% of survivors, operated <24h GOS4-5: Overall: 14%, EDH: 26%, CC: 11%, ASDH/CC: 5% LTFU: 3% |
| Large craniotomy. Surgery in 156 patients. GCS3-5 + Surgery: 26 | Mortality/ GOS (hospital discharge) | Overall mortality: 65% Mortality: GCS3-5: 98.5% (PVS:1.5%), UDP: 96%, MF: 100% After surgery: GCS3-5: Death: 92.5%, PVS: 7.5% GCS6-8: Death: 62.5%, GOS4-5: 22.5% GCS9-12: Death 22%, GOS4-5: 67.5% GCS13-15: Death: 9%, GOS4-5: 91% |
| Surgery: Overall: 91 GCS3-5: 13 | GOS | Satisfactory (GOS3-5): Overall: 50.3%, surgery: 71.4% Poor (GOS1-2): Overall: 49.7%, surgery: 29.9% Poor outcome (GOS 1-2): GCS3-5: 94%, GCS6-8: 40%, GCS-9-12: 25% |

Tabel III continued

| Study Information | Purpose | Population | ♂ | Age | Type of GCS score | Pupils |
|--|---|---|----|------|-------------------|---|
| Chamoun (2009) ⁵⁰ USA, 1997-2007 Retrospective | Outcome of blunt s-TBI patients with GCS=3. | N=189 GCS3: 100% Surgery: 110 Died: 93 | 83 | 36.5 | Presentation | BRP: 1: 41% 2: 12.9% BFDP: 1: 14.6% 2: 59.1% |
| Chierigato(2017) ⁵¹ Italy, 1997-2012 Retrospective | Outcome of medical management in ASDH after craniotomy. | N=115 All ASDH GCS3-4: 100% | 67 | 34 | Presentation | BFDP 100% |
| Weisbrod (2012) ⁵⁹ USA, 2003-2011 Prospective data | Outcomes of combat casualties sustaining penetrating TBI. | N=137 GCS3-5: 31 Gunshot: 31% Blast: 69% | 98 | 25 | Admission | NP |

Table III: Abbreviations: ♂: Male; ASDH: Acute Subdural Hematoma; BFDP: Bilateral Fixed Dilated Pupils; BRP: Bilateral Reactive Pupils; CC: Cerebral Contusion; DC: Decompressive Craniectomy; FIM: Functional Independence Measure; GCS: Glasgow Coma Scale; GOS: Glasgow Outcome Scale; HC: Haemorrhagic Contusion; ICP: Intracranial Pressure; LTFU: Loss to Follow Up; NP: Not Provided; PVS: Persistent Vegetative State; s-TBI: severe Traumatic Brain Injury; TBI: Traumatic Brain Injury; TSAH: Traumatic Subarachnoid Haemorrhage.

Tabel IV Elderly Patients

| Study Information | Purpose | Population | ♂ | Age | Type of GCS score | Pupils |
|---|---|--------------------------------|-----|------|------------------------------|---------------------------------------|
| Shimoda (2014) ¹⁸ Japan, 1998-2011 Retrospective | Benefit of surgery in the elderly after TBI. | N=888 GCS3-5: 421 | 61 | ±76 | Admission | NP |
| Brazinova(2010) ²⁰ Europe, 2001-2005 Prospective | Outcome in elderly TBI patients with GCS3-4. | N=100 GCS3:71 GCS4:29 | 71 | ±74 | Initial | NP |
| Wan (2016) ⁵² China, 2008-2014 Retrospective | Outcome of surgery in severe intracranial hematoma. | N=112 GCS3-5: 40 | ±72 | ±74 | Emergency department arrival | Abnormal: Overall:59 Surgery:38 |
| De Bonis (2011) ⁵³ Italy, 2002-2009 Retrospective | Patient outcome and predictors of survival in TBI and DC. | N=44 GCS3-5: 22 | 59 | 76.7 | Post-resuscitation | NP |
| Benedetto(2017) ⁵⁴ Italy, 2011-2014 Retrospective | Outcome after surgery for traumatic ASDH. | N=67 GCS3-5: 17 ASDH: 67 | 53 | 80.5 | Admission | NP |

Table IV: Abbreviations: ♂: Male; ASDH: Acute Subdural Hematoma; DC: Decompressive Craniectomy; GCS: Glasgow Coma Scale; GOS: Glasgow Outcome Scale; ICP: Intracranial Pressure; ICU: Intensive Care Unit; NP: Not provided; TBI: Traumatic Brain Injury

| Surgical intervention. | Outcome measure | Results |
|---|------------------------------------|--|
| Evacuation ASDH: 72 Evacuation ASDH+DC:12 Surgery EDH: 5 | Mortality/ GOS (6M). LTFU: 7.4% | Overall mortality: 49.2% Good functional outcome (GOS1+2): 13.2% Mortality: BFDP: 79.9%, BRP: 23.5%, evacuation ASDH: 48.3%, ASDH + DC: 50%, EDH 20% Outcome survivors (N=96): GOS1: 22%, GOS2: 8.5%, GOS3: 42.7%, GOS4: 26.8%. |
| Emergent hematoma evacuation: 53 Pre-operative medical therapy -> Aggressive: 13.2%, Reinforced: 45.3% | GOS (1Y) | Not operated (N=62): Mortality: 100% Surgery: Mortality: 75.5%, GOS2: 7.5%, GOS3: 13.2%, GOS4: 1.9%, GOS5: 1.9%. |
| ICP: 80%, Craniotomy: 8%, Craniectomy: 79% -Unilateral 65% -Bilateral: 14% | Mortality/ GOS (6M, 12M, 24M) | Mortality initial admission: 5.8% Including delayed mortality (24M): 7.3% Functional independence (GOS≥4) at 24M: Overall: 68% <u>GCS3-5:</u> 32% <u>GCS6-8:</u> 63% <u>GCS9-11:</u> 74% <u>GCS12-15:</u> 100% GCS3-5: Significant improvement at 2 years from discharge |

| Surgical intervention. | Outcome measure | Results |
|--|--|--|
| Surgery: 478 <4h: 92 | Mortality(6M)/ GOS(6M) | Overall mortality: 71% Unfavorable (GOS1-3): 87% Mortality: Surgery: 62%. No surgery: 81% (P<0.001) Unfavorable: Surgery: 82%. No surgery: 93% (P<0.001) Surgical group: <u>GCS3-5:</u> GOS1: 87%. GOS1-3: 96%, <u>GCS6-15:</u> GOS1: 57%, GOS1-3: 79%, both (P<0.001) |
| Surgery: GCS3: 55 GCS4: 15 ICP monitoring: GCS3: 36 GCS4: 5 | Mortality/ GOS(12M) | ICU-Mortality: 76%. ICU-Outcome: 11% favorable (GOS4-5) Mortality(12M): 80%. Outcome (12M): 11% favorable. |
| Surgery: 62.5% -Craniotomy:10 -DC: 60 GCS3-5: 25 surgery | Mortality (6M)/ favorable (6M) | All Mortality: 53.6%, Favorable (GOS4-5): 68.8%, Mortality: <u>GCS≤5:</u> 77.5%, <u>GCS>5:</u> 40%, Favorable: <u>GCS≤5:</u> 5%, <u>GCS>5:</u> 46% Mortality (surgery): 32.9%, favorable: 47.1% Mortality (conservative): 88.1%, favorable: 4.8% |
| DC: No focal lesion:11 Focal lesion+ brain oedema: 33 | Mortality/ GOS (ICU/hospital discharge, 12-102M) | Overall mortality: ICU 48%, Hospital 57%, 1Y and last follow up: 77%. Bad outcome (GOS1-3): Hospital discharge and 1Y: 82%. Mortality: <u>GCS3-5:</u> 100% Good outcome (GOS4-5): <u>GCS6-8=</u> 20%, <u>GCS>8</u> = 50%. |
| Hematoma evacuation: 67 Second craniotomy: 5 | Mortality (6M)/ GOS (1M/6M) | Overall mortality (1M): 55.1%, (6M): 67.2% Mortality (6M): <u>GCS3-4:</u> 82.4%, <u>GCS14-15:</u> 14.3% Functional recovery (6M): <u>GCS3-4:</u> 5.9%, <u>GCS14-15:</u> 42.9% |

Pediatric patients

Four studies contained pediatric patients, with one using prospectively collected data (Table V).⁵⁵⁻⁵⁸

Brain Trauma Foundation (BTF) Guideline adherence for ICP monitoring in the pediatric cohort was low. Close to 8% of patients meeting criteria was actually monitored and monitoring only showed mortality reduction in patients with a GCS of 3 (OR 0.64, 95% CI 0.43-1.00).⁵⁷ ICP-monitoring was related to significant longer ICU and hospital LOS (12.6 vs. 6.3 and 21.0 vs. 10.4 days) and higher costs.⁵⁷

Although unfavorable outcome (up to 71.6%) and mortality rates were high (range 36-56.7%), favorable outcome was achieved in 40% to 45% of the patients.^{55, 56, 58} In patients with postresuscitation GCS Score 3 and 4; one-year survival was 43.3%, of which almost 12% was normal in every respect and 3% scored GOS=5.⁵⁵

One article mentioned GCS ≤ 5 to be a significant predictor for poor outcome.⁵⁶ Another stated that compared to the GCS 4 patient group, patients with a GCS=3 showed significantly more hypoxia (65.9% vs. 39.1%), single seizure (2.3% vs. 17.4%) and open cisterns on CT scan (68.2% vs. 91.3%) but did not find a statistically significant difference in survival or outcome ($P=0.2$).⁵⁵

A normal pupillary reaction resulted in 87% chance of survival, which dropped to 23% when at least one eye was abnormal. Pupillary abnormalities resulted in 1-year poor outcome (GOS 1-3) in 92% of cases and 0% good outcome (GOS ≥ 4) for the combination of absent pupillary reflex and hypothermia. Pupillary response was considered the factor most predictive of both survival and outcome.⁵⁵

Other negatively correlated factors for survival seemed to be a delayed presentation >150 minutes ($P=0.010$), DC >4 h after hospital arrival ($P=0.042$), intraoperative blood loss >300 mL ($P=0.001$) and mechanism of injury (abuse), hypothermia, hypotension, major concurrent symptoms, midline shift on CT scan, and assessment of the fontanelle.^{55, 56}

Penetrating brain injury

Three articles in our vs-TBI article selection focussed on PBI.^{48, 49, 59} In case of PBI by a firearm projectile, admission GCS of 3-5 resulted in a poor prognosis (GOS 1-3) in up to 94.11%.⁴⁹ A second article, investigating gunshot wounds to the head, presents a

mortality rate of 65% for all patients and 98.5% for patients with admission GCS 3-5.⁴⁸ After surgery, mortality rates dropped to 92.5%, but all survivors were in persistent vegetative state.⁴⁸ In contrast to these dramatic results, one study showed 2-year functional outcome (GOS 4-5) in 66% of all patients and in 32% of patients with admission GCS 3-5.⁵⁹

PBI occurs both in military and civilian setting (Table VI). In the context of civilian population, PBI is mainly caused by gunshot wounds, either self-inflicted or caused by (mass) violence. In combat situations, TBI is most commonly caused by improvised explosive devices (IEDs), but also by artillery, rocket and mortar shells, mines or booby traps, aerial bombs and rocket-propelled grenades.⁶⁰

Emergency management in patients with PBI should include aggressive resuscitation like described in the ATLS guidelines, since it appears to be associated with significant improvement of survival.^{61, 62} Initial mortality after gunshot wounds is high, with one study reporting a prehospital mortality rate of 76% in a civilian PBI population.⁶³ If patients reach the hospital and survive initial resuscitation and stabilization, a head CT scan provides information on bullet trajectory, missile fragments, bony destruction and brain damage, including (hemorrhagic) mass lesions. Hemorrhagic contusion and intraventricular bleeding are the most common CT finding.^{63, 64}

The surgical management for PBI differs in many aspects from that of closed TBI. PBI represents an open and contaminated type of brain injury, for which prophylactic broad spectrum antibiotics is common practice.⁶⁵ Surgical management in PBI consequently should include the prevention of infection⁶⁶ and treatment of CSF fistulas.⁶⁷⁻⁶⁹ Principles of wound debridement have evolved under influence of experience in military settings from extensive debridement with repeated removal of retained fragments to more limited procedures. During the Second World War and Vietnam war, it was disproven that retained bone fragments were linked to the development of brain abscesses.^{67, 70-73} Moreover, studies have revealed significant morbidity and mortality associated with repeated and aggressive surgery to remove retained fragments.⁷⁴⁻⁷⁷ During the Israeli-Lebanese and Croatian conflicts, rapid evacuation and improved medical care, including use of CT-scanning, was broadly available, which led to a less aggressive surgical approach to preserve brain tissue.^{78, 79}

Table V Pediatric Patients

| Study Information | Purpose | Population | ♂ | Age | Type of GCS score | Pupils |
|--|--|--|----|----------------------|---|------------------------------------|
| Fulkerson (2015) ⁵⁵ USA, 1988-2004 Prospective | Clinical outcome in children with TBI. | N=67 1: GCS3:44 2: GCS4:23 | 60 | 1: 49,8M 2: 66.9M | Post-resuscitation (Modified for pediatric) | Asymmetry: 1: 20.4% 2: 13.0% |
| Khan (2014) ⁵⁶ Pakistan, 2000-2010 Retrospective | Risk factors in pediatric patients with DC. | N=25 GCS3-5:11 BE 80% ASDH 24% | 84 | 6 | Presentation | Anisocoria: 24% |
| Alkhoury (2014) ⁵⁷ USA, 2001-2006 Retrospective | Effect of ICP monitoring on survival in s-TBI. | N=4141 GCS3: 1942 GCS4: 167 GCS5: 169 | 62 | ±8.6 | Emergency department | NP |
| Guresir (2012) ⁵⁸ Germany, 2000-2009 Retrospective | Outcome of DC for sustained high ICP. | N=34 DC for TBI: 23 (67.7%) | 60 | 12 | Admission | Normal=6 UDP=7 BDP=10 |

Table V: Abbreviations: ♂: Male; ASDH: Acute Subdural Hematoma; BDP: Bilateral Dilated Pupils; BE: Brain Edema; DBS: Diffuse Brain Swelling; DC: Decompressive Craniectomy; EVD: Extraventricular Drain; GCS: Glasgow Coma Scale; GOS: Glasgow Outcome Scale; ICP: Intracranial Pressure; mRS: modified Rankin Scale; NP: Not provided; R-ICH: Refractory Intracranial Hypertension; s-TBI: severe Traumatic Brain Injury; TBI: Traumatic Brain Injury; UDP: Unilateral dilated pupil.

Table VI: Differences Civilian & Military patients suffering PBI

| | Civilian | Military |
|-------------------------|---------------------------|---|
| Age | All | Young, healthy |
| Cause | GSW – near contact injury | Explosion; low-velocity shell/shrapnel injury |
| Mechanism | (self-)assault | Mainly explosive blasts |
| Time to hospital | 30-45 minutes | Up to 2,5 hours |
| Protection | None | Body armor and helmets |
| GCS | lower | higher |
| Mortality | 19-88% | 5-30% |

Table VI: Abbreviations: GSW: gunshot wounds; GCS: Glasgow Coma Scale

Over the past decades multiple studies have been published suggesting a less aggressive approach, with an important adjuvant role for antibiotics.^{77, 80-82} However, more recently, Charry *et al.* suggested that early DC as a damage control procedure in civilian patients suffering PBI in a hospital setting with limited resources on ICU neuro-monitoring is a treatment option to improve survival and outcome in these patients.⁸³ Rapid exploration and exenteration of the injured air sinuses is recommended to prevent infectious complications^{84,85}. CSF fistulas pose a very high risk for deep infections^{67, 69, 78} with nosocomial organisms and should be closed watertight, and if needed with placement of lumbar drainage.⁸²

| Surgical intervention | Outcome measure | Results |
|--|--|---|
| Surgery: 1: 55% 2: 87% ICP/EVD: 1: 55% 2: 78% DC: 9 DBS, 15 mass lesions + DBS, 1 R-ICH. Bilateral: 7 | Modified GOS (long term: mean 10.2Y) GOS (5M) | Discharge: Overall mortality: 55.2%, <u>GCS3</u> : GOS1: 61.4%, GOS2: 6.8%, GOS3: 11.4%, GOS4: 15.9%, GOS5: 4.6% <u>GCS4</u> : GOS1: 43.5%, GOS2: 17.4%, GOS3: 17.4%, GOS4: 13.0%, GOS5: 4.6% 1 year (N=29) : GOS1: 56.7, GOS2: 4.5%, GOS3: 10.4%, GOS4: 6.0%, GOS5: 3.0%, "Normal": 11.9%, Unknown: 7.5%. Long term (N=22) : 45% GOS5 or "normal". Overall mortality 36%. GOS5: 40% GCS \leq 5 significant predictor for poor outcome (GOS1-3), (Univariate analysis p=0.009) |
| ICP: 318 -GCS3-5: 224 | Mortality | Mortality ICP (GCS3): OR0.64; 95%CI, 0.43-1.00. No effect on mortality for other GCS groups. |
| DC | mRS (6M) | Only TBI data used: Favorable (mRS0-2) : 40% *We didn't include additional review data. |

DISCUSSION

This literature review shows that mortality rate in vs-TBI patients is high and the chance to reach good outcome low. Moreover good outcome is defined quite heterogeneously. Interestingly however, in some studies low mortality and relatively good outcome rates were reported for specific patient groups. It is difficult to point out exactly what contributed to this better outcome in these patients. Good outcome seemed to be associated with factors that are known to have a positive effect such as higher GCS (at least >5), absence of pupillary abnormalities and lower age (<65 year). Factors, which might have contributed were immediate and accurate treatment. However, because comparison of studies showed huge heterogeneity, correlations between the factors mentioned above and outcome could not be determined. Nevertheless, we strongly suggest that, given the chance for successful recovery, surgical intervention should be considered in every very severe TBI patient.

Importantly, treatment-limiting decisions should not be based on the GCS alone. Although a recent review showed adequate reliability of the GCS Score, the use and general applicability has been widely criticized.⁸⁶ In our review, outcome results are probably more favorable because of the exclusion of patients with a "true" GCS of 3 and inclusion of patients with a "false" GCS of 3 as a result of intubation and sedation.

Indeed, better survival rates were reported in patients with a “false” compared to a “true” GCS of 3 (61% vs. 45%).⁴⁴

Decisions on treatment intensity and in particular withholding and withdrawal of life-sustaining therapies will clearly affect outcome and mortality rates. A random selection of Canadian TBI patients showed that 70% of all deaths were associated with withdrawal of therapy, half within the first three days.⁸⁷ In Oslo, 17% of s-TBI patients had treatment limiting decisions, of which the majority (70%) was made within the first 2 days after injury. In 93% of in-hospital deaths, treatment limiting decisions were documented.⁸⁸ Worryingly, around 80% of physicians felt at best uncomfortable with withdrawal of care decisions and there were major differences among them regarding neuro prognostication and decision-making.⁸⁹ By early withholding/withdrawal, no chance of recovery is offered. The short term of the decision is worrying, given that although the majority (71.4%) of TBI patients with a favorable outcome followed commands (GCS motor score=6) within 1 week, almost 15% regained that ability for the first time from two weeks after injury.

Premature and inappropriate treatment limiting decisions are of particular concern in the elderly. Elderly vs-TBI patients showed higher mortality (80%, 82%, 100%),^{20, 53, 54} compared to the whole s-TBI group (53.6-77%).^{52, 53} In literature a mortality of 78.5% in elderly s-TBI patients was reported, compared to >80% in vs-TBI patients (GCS 3-5) and 92.6% for patients aged >80 years.⁹⁰ Understandably, high mortality rates contribute to the overall belief that aggressive treatment in the elderly population is not effective. A decrease of treatment intensity can have accompanying negative influence on outcome, forming self-fulfilling prophecies.^{91, 92} Despite the reported high mortality rates, two studies showed that realizing good outcome in elderly vs-TBI survivors was not impossible (5.9-11%).^{20, 54} Although severity according to the GCS was lower, a recent meta-analysis reported a similar percentage of 7.9% for elderly s-TBI patients.⁹³

Although surgical intervention can reduce mortality and unfavorable outcome rates, not all studies agree on justifying intervention for vs-TBI patients.^{18, 52} Guidance from evidence is lacking, as patients aged ≥ 65 years are not included in most clinical studies and not in the BTF Guidelines, resulting in absence of guidance, subjective critical care and thus treatment variation. This is of increasing concern because TBI is increasing in the elderly population (>65 years old)^{2, 94} and because elderly patients often necessitate a different approach. Specific features include mostly a low energy

mechanism of trauma (fall), the frequent occurrence of contusions and (sub)acute subdural hematomas, the use of anticoagulants, but also the presence of some degree of brain atrophy that may allow for more volume compensation. Conversely, however, the lack of cognitive reserve may adversely affect outcome.

Future research is needed to identify specific (subgroups of) patients in whom aggressive surgical intervention will result in good outcome, preferably with a certainty that can be useful in multidisciplinary decision-making. Until that time, physicians should not withhold aggressive treatment options in s-TBI patients, young or old, who have some potential of achieving good outcome even with ominous neurological signs. A more reserved attitude regarding aggressive therapy may be justified in patients in whom a combination of different features indicate very low chances of regaining an acceptable quality of life and no signs of any improvement exist following initial optimal therapy.

ICP monitor

We found no consensus of benefit on mortality rates from ICP monitoring because all three possible outcomes were reported: reduced mortality,^{21, 24} no difference and higher mortality.²⁵ The same inconclusiveness was found in a recent review and meta-analysis⁹⁵ and other studies reporting both benefit,^{96, 97} and no benefit.^{98, 99}

Both the sickest and least sick patients appear to receive less ICP monitor placement^{22, 100} and ICP monitoring placement seemed to be influenced by high age,²¹⁻²³ which reflects a tendency towards overall lower intensity of care in elderly TBI patients.⁹²

The reported lower mortality rates for vs-TBI patients compared to s-TBI patients, can be explained by a decreased advantage of ICP monitoring guided therapy for less severe TBI patients with ongoing, potentially disadvantageous, exposure to intensive therapies.²⁵ ICP monitoring guided therapy was associated with increased mortality for GCS 7-8 patients (OR12.89)²⁷ and had a larger protective impact on patients with GCS=3.^{23, 57} Included studies showed ICP monitored patients with longer duration of mechanical ventilation,²⁵⁻²⁷ higher need for tracheostomy²⁷ and significantly longer ICU stays.^{22, 25-27, 57} These results were confirmed by literature^{95, 98} and are likely to influence outcome.

Insertion of ICP monitor would appear to be based on physicians' judgement, rather than guidelines, possibly inducing confounding by indication. More severely injured patients are more likely to receive ICP monitoring guided care, but, because being in a worse condition they are prone for worse outcome. Also, patients can be considered to be unsalvageable and because of withholding aggressive therapy (including ICP monitoring), only the patients with an expected chance of survival get a chance, resulting in better outcome in ICP monitored cohorts.

Lack of adherence to guidelines has been previously reported in various studies. A recent study¹⁰¹ reported major variation in adherence between studies (range 18-100%), with only 31% for the BTF ICP monitoring guidelines, possibly caused by scepticism resulting from the absence of high quality evidence and the invasive character of the intervention.¹⁰¹ Substantial variation in ICP monitoring indications and subsequent treatment decisions is also reported.^{101, 102} We expected high rates of ICP monitoring in included s-TBI cohorts, but found an unweighted mean of 42%. Two studies found poor adherence rates (10.8% and 46% in two studies), corresponding with the literature.^{23, 25, 26} Investigating the effect of adherence on survival, literature delivers non-conclusive evidence of benefit,⁹⁶ no benefit⁹⁹ and even an increase in complications and use of hospital resources.¹⁰³

The relative lack of guideline adherence for ICP monitoring for patients with vs-TBI may also reflect the lack of specific recommendations for this group. International TBI guidelines from BTF and NICE organizations are largely based on best available level III evidence and use GCS 3-8 as s-TBI category.^{104, 105} In the BTF-Guidelines the vs-TBI subgroup is separately mentioned only three times and are considered to be part of the GCS 3-8 s-TBI group.¹⁰⁴ There is no mentioning of the GCS 3-5 subgroup in the 2nd edition of the BTF Guidelines for the Acute Medical Management of s-TBI in Infants, Children, and Adolescents.¹⁰⁶ Recent studies conclude both absence of benefit¹⁰⁷ as higher survival and improved outcome, without higher hospital costs following guidelines.^{108, 109}

We suggest that therapy guided by ICP monitoring following the guideline recommendations should also be used in vs-TBI patients, since positive effects and good outcome are reported. Because worse results are most likely due to complications, ICP monitoring devices should be removed as soon as possible, hopefully avoiding adverse effects of overtreatment.

Decompressive craniectomy

Although it is clear that DC can decrease ICP effectively and good outcome is reported,¹¹⁰ its value remains controversial.^{9-11, 111}

Mortality rates for s-TBI patients after DC range between 11% and 68.5%,^{30, 31} up to 80% for vs-TBI patients^{32, 33} and even 100% for patients with a GCS of 3.^{30, 34} The overall mortality rate difference is most likely the result of different patient samples, with variation in variables associated with worse prognosis. The cohort with 68.5% mortality rate contained more older patients with GCS=3 and bilaterally dilated pupils (50 vs. 42.8 years). The study with 11% mortality (60% vs-TBI), provided no information on pupillary status or potential “false” GCS. The potential beneficial effect of early surgery (<1hour after admission) in 85.9% of patients, remains uncertain. A low mortality rate is not necessarily a good result, since it can be related to a high percentage (37% in GCS 3-5 and 7% in GCS 6-8) of patients remaining in a vegetative state.¹⁵ Since certain traumatic lesions result in worse outcome, by nature of the injury, composition of cohorts regarding traumatic lesions is likely to contribute to confounding by indication and outcome results. One study confirmed this by showing less mortality in s-TBI patients with mass lesion receiving DC compared to DC for diffuse injury and swelling (14 vs. 43.4%).⁴⁰

Factors related to timing of surgery and surgical technique may be relevant to outcome. Two studies studied timing of DC and the first found better results for performing early DC within 4 hours,³⁰ while the second found that early bilateral DC showed better results compared to DC as secondary treatment option.³⁹ Two others mentioned early DC to be related to better outcome, one only for GCS 6-8 subgroup.^{15, 41} Although many physicians will agree with early timing of surgery, a review found that timing of surgery was not significantly related to outcome in 11 out of 16 included studies. Looking at DC studies, 4 out of nine reported a significant effect of time to surgery on patient outcome.¹¹² As is also recommended in the BTF-Guideline, a large sized bone flap resulted in significantly more satisfactory outcome (GOS 3-5), especially in vs-TBI subgroup (63.0% vs. 36.7%, $P<0.01$).³⁵ Thus, according to the present evidence, in cases in which decompressive surgery is decided upon, bone flaps should be made large.

We suggest a certain restraint against the early withholding and withdrawal of therapy, especially because prognostication is still inaccurate and decision can result in potentially avoidable deaths. After the (sub) acute setting, additional treatment

decisions depending on neurological improvement should be made, preferably after proxy consultation.

Penetrating brain injury

The difference between combat and civilian PBI can explain outcome results. Combat casualties include more blast injury and civilian more gunshot wounds. Also, almost 90% of patients (mean age 25 years) underwent neurosurgical intervention. The combination of young healthy military patients with aggressive neurosurgical intervention might be beneficial. However, in the study reporting favorable results there is 43% loss to follow-up and only 22% of total PBI patients were treated at this institution. In the literature, PBI mortality rates range from 23 to 93% with higher rates (87-100%) in presence of well-known risk factors for poor outcome: GCS <5, pupillary abnormalities, hypotension, high ICP and higher age.¹¹³

As in all TBI patients, surgical treatment should be meaningful and the indication for surgery balanced against the likelihood of survival, particularly in patients with a low GCS in the civilian setting. Some authors don't recommend surgical intervention in patients with small to zero change of achieving favorable outcome,^{48, 49} low admission GCS scores and extensive brain injury^{114, 115} or patients with a GCS 3 to 5 without operable hematomas.⁶¹ Nevertheless, it does not preclude possible recovery and some patients may survive. A recent study for example, reported a survival rate of 40% in patients with a GCS of 3-4 on admission, whilst 11% achieved favorable outcome.¹¹⁶ These investigators attribute their better results to a more aggressive management policy.

We believe that clinical (GCS Score and presence of pupillary abnormalities) and radiological signs should guide physicians decision-making. We advocate minimal surgery in civilian PBI cases with a GCS of 3-5 and optimal medical management for at least 24 hours. In case of improvement, more extensive surgery can be considered. An early decompressive craniectomy with watertight dural closure is a valid surgical option. The removal of retained bone fragments at the cost of healthy brain tissue is not advised and in case of dural defects grafting is possible by using autologous materials like fascia lata or periosteum. Finally, the adequate cranialization of violated air sinuses and the watertight closure of CSF fistulas should be performed as soon as possible.

Limitations of the study

Our strict inclusion criteria resulted in the inclusion of studies reporting on surgical treatment and outcome of vs-TBI patients with a definite GCS 3-5. Most included studies were relatively small observational single center cohort studies and only few used prospectively collected data. As is typical for TBI itself, the huge heterogeneity between patient cohorts regarding injury, treatment and outcome, resulted in inevitable selection bias and makes comparing results and drawing conclusions difficult. For this reason, it was considered impossible to conduct a solid meta-analysis. The independent effect of surgical treatment on outcome is also hard to establish because parameters known to be associated with outcome, were often not mentioned or investigated. Results of this review should be interpreted with care and conclusion only drawn with the recognition of the remarks.

Three promising studies (DECRA, RESCUEicp, STITCH) from the past years did not meet our inclusion criteria but unfortunately also didn't change the controversy of decompressive craniectomy.¹¹⁷⁻¹¹⁹ We are looking forward to the results of two ongoing trials, respectively comparing primary DC with craniotomy in adults with an ASDH (RESCUE-ASDH: www.rescueasdh.org) and investigating the effect of therapeutic and prophylactic DC in s-TBI patients with mass lesions (PRECIS).¹²⁰

Future research

Given the current heterogeneity and variability, future research should focus on patient cohorts, (surgical) treatments and outcome measures that are as equal as possible, to improve comparability and generalizability of study results. Alternatively, variability can also contribute to investigating the effectiveness of (surgical) treatment by comparing variation in local practice using a method called "Comparative Effectiveness Research" (CER). International initiatives like CENTER-TBI (www.center-tbi.eu), and a Dutch initiative called Net-QuRe (www.net-quire.nl) are using this method investigating (surgical) treatment effectiveness. Because postdischarge information is considered very important, Net-Qure has a 24 month follow-up period and includes data on the rehabilitation phase. Knowing how much a specific patient will benefit from which specific treatment in terms of functional recovery and quality of life is essential in future decision-making and informed consent conversations. Therefore a long-term follow-up period is necessary and particularly relevant to patients with vs-TBI, as reports show that improvement may not be uncommon between 1 and 3 years after injury.

In addition, a humanistic approach on the quality of life after TBI is needed to explore what can be considered a favorable and desirable outcome for patients, their proxies and for society as a whole. Also, an accurate calculation of hospital and postdischarge healthcare costs following TBI must be undertaken, to improve hospital and public management planning and allocation of appropriate budgets.

Finally, we believe that the currently used s-TBI category remains very heterogeneous. Future research should aim for better characterization and understanding of individual pathophysiology, and identification of subgroups of patients more likely to benefit from specific therapies. Both could hopefully inform more targeted treatment according to specific patient needs.

CONCLUSIONS

The most severely injured TBI patients including patients with penetrating brain injury, frequently confront physicians with great medical and ethical conflicts. This literature review reports that although mortality rates are high and unfavorable outcome is frequent, good outcome is possible for patients with very severe TBI. Multiple different patient and injury specific factors, combined with treatment timing and type of intervention, showed to be related to intervention and outcome. Most important are age, GCS and pupillary abnormalities. Clearly, vs-TBI patients are different from the less severe TBI patients (GCS 6-8) and therefore should be recognized and treated as such. Until the availability of solid evidence, physicians must find an equilibrium between falsely withholding surgical intervention from patients with potential good outcome and aggressive treatment with an inevitable unwanted outcome.

REFERENCES

1. Tagliaferri F, Compagnone C, Korsic M, Servadei F, Kraus J. A systematic review of brain injury epidemiology in Europe. *Acta Neurochir (Wien)* 2006;148:255-68.
2. Maas AIR, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. *Lancet Neurol* 2008;7:728-41.
3. Stocchetti N, Carbonara M, Citerio G, Ercole A, Skrifvars MB, Smielewski P, *et al.* Severe traumatic brain injury: targeted management in the intensive care unit. *Lancet Neurol* 2017;16:452-64.
4. Skandsen T, Kvistad KA, Solheim O, Strand IH, Folvik M, Vik A. Prevalence and impact of diffuse axonal injury in patients with moderate and severe head injury: a cohort study of early magnetic resonance imaging findings and 1-year outcome. *J Neurosurg* 2010;113:556-63.
5. Frost RB, Farrer TJ, Primosch M, Hedges DW. Prevalence of traumatic brain injury in the general adult population: a meta-analysis. *Neuroepidemiology* 2013;40:154-9.
6. Stein SC, Georgoff P, Meghan S, Mizra K, Sonnad SS. 150 years of treating severe traumatic brain injury: a systematic review of progress in mortality. *J Neurotrauma* 2010;27:1343-53.
7. Jennett B, Bond M. Assessment of outcome after severe brain damage. *Lancet* 1975;1:480-4.
8. Wilson JT, Pettigrew LE, Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. *J Neurotrauma* 1998;15:573-85.
9. Honeybul S, Gillett G, Ho K, Lind C. Ethical considerations for performing decompressive craniectomy as a life-saving intervention for severe traumatic brain injury. *J Med Ethics* 2012;38:657-61.
10. Honeybul S, Gillett GR, Ho KM, Lind CR. Neurotrauma and the rule of rescue. *J Med Ethics* 2011;37:707-10.
11. Honeybul S, Ho KM, Lind CR, Gillett GR. Long term outcome following decompressive craniectomy for severe traumatic brain injury: Ethical considerations. *Injury Extra* 2011;42:148.
12. Rogers SJ, Browne AL, Vidovich M, Honeybul S. Defining meaningful outcomes after decompressive craniectomy for traumatic brain injury: existing challenges and future targets. *Brain Inj* 2011;25:651-63.
13. Nakagawa K, Obana KK. Willingness to favor aggressive care and live with disability following severe traumatic brain injury: a survey of healthy young adults in Hawai'i. *Hawaii J Med Public Health* 2014;73:212-6.
14. No authors listed. Part 1: Guidelines for the management of penetrating brain injury. Introduction and methodology. *J Trauma* 2001;51:S3-6.
15. Chibbaro S, Tacconi L. Role of decompressive craniectomy in the management of severe head injury with refractory cerebral edema and intractable intracranial pressure. Our experience with 48 cases. *Surg Neurol* 2007;68:632-8.
16. Huang YH, Lee TC, Lee TH, Liao CC, Sheehan J, Kwan AL. Thirty-day mortality in traumatically brain-injured patients undergoing decompressive craniectomy. *J Neurosurg* 2013;118:1329-35.
17. Ucar T, Akyuz M, Kazan S, Tuncer R. Role of decompressive surgery in the management of severe head injuries: prognostic factors and patient selection. *J Neurotrauma* 2005;22:1311-8.
18. Shimoda K, Maeda T, Tado M, Yoshino A, Katayama Y, Bullock MR. Outcome and surgical management for geriatric traumatic brain injury: analysis of 888 cases registered in the Japan Neurotrauma Data Bank. *World Neurosurg* 2014;82:1300-6.
19. Mauritz W, Leitgeb J, Wilbacher I, Majdan M, Janciak I, Brazinova A, *et al.* Outcome of brain trauma patients who have a Glasgow Coma Scale score of 3 and bilateral fixed and dilated pupils in the field. *Eur J Emerg Med* 2009;16:153-8.
20. Brazinova A, Mauritz W, Leitgeb J, Wilbacher I, Majdan M, Janciak I, *et al.* Outcomes of patients with severe traumatic brain injury who have Glasgow Coma Scale scores of 3 or 4 and are over 65 years old. *J Neurotrauma* 2010;27:1549-55.
21. Farahvar A, Gerber LM, Chiu YL, Carney N, Hartl R, Ghajar J. Increased mortality in patients with severe traumatic brain injury treated without intracranial pressure monitoring. *J Neurosurg* 2012;117:729-34.
22. Mauritz W, Steltzer H, Bauer P, Dolanski-Aghamanoukjan L, Metnitz P. Monitoring of intracranial pressure in patients with severe traumatic brain injury: an Austrian prospective multicenter study. *Intensive Care Med* 2008;34:1208-15.
23. Dawes AJ, Sacks GD, Cryer HG, Gruen JP, Preston C, Gorospe D, *et al.* Intracranial pressure monitoring and inpatient mortality in severe traumatic brain injury: A propensity score-matched analysis. *J Trauma Acute Care Surg* 2015;78:492-501; discussion -2.

24. Kim DR, Yang SH, Sung JH, Lee SW, Son BC. Significance of intracranial pressure monitoring after early decompressive craniectomy in patients with severe traumatic brain injury. *J Korean Neurosurg Soc* 2014;55:26-31.
25. Alice P, Meghan L, Elizabeth B, Alberto A, Kenji I, Demetrios D. Intracranial pressure monitoring in severe traumatic brain injuries: a closer look at level 1 trauma centers in the United States. *Injury* 2017;48:1944-50.
26. Griesdale DE, McEwen J, Kurth T, Chittock DR. External ventricular drains and mortality in patients with severe traumatic brain injury. *Can J Neurol Sci* 2010;37:43-8.
27. Haddad S, Aldawood AS, Alferayan A, Russell NA, Tamim HM, Arabi YM. Relationship between intracranial pressure monitoring and outcomes in severe traumatic brain injury patients. *Anaesth Intensive Care* 2011;39:1043-50.
28. Zeng T, Gao L. Management of patients with severe traumatic brain injury guided by intraventricular intracranial pressure monitoring: a report of 136 cases. *Chin J Traumatol* 2010;13:146-51.
29. Bhat AR, Kirmani AR, Wani MA. Decompressive craniectomy with multi-dural stabs - A combined (SKIMS) technique to evacuate acute subdural hematoma with underlying severe traumatic brain edema. *Asian J Neurosurg* 2013;8:15-20.
30. Park JH, Park JE, Kim SH, Lim YC, You NK, Ahn YH, *et al*. Outcomes of Ultra-Early Decompressive Craniectomy after Severe Traumatic Brain Injury-Treatment Outcomes after Severe TBI. *Korean J Neurotrauma* 2014;10:112-8.
31. Fotakopoulos G, Tsianaka E, Vagkopoulou K, Fountas KN. According to which factors in severe traumatic brain injury craniectomy could be beneficial. *Surg Neurol Int* 2016;7:19.
32. Saade N, Veiga JC, Cannoni LF, Haddad L, Araujo JL. Evaluation of prognostic factors of decompressive craniectomy in the treatment of severe traumatic brain injury. *Rev Col Bras Cir* 2014;41:256-62.
33. Csokay A, Pataki G, Nagy L, Belan K. Vascular tunnel construction in the treatment of severe brain swelling caused by trauma and SAH. (evidence based on intra-operative blood flow measure). *Neurol Res* 2002;24:157-60.
34. Kalayci M, Aktunc E, Gul S, Hanci V, Edebalı N, Cagavi F, *et al*. Decompressive craniectomy for acute subdural haematoma: an overview of current prognostic factors and a discussion about some novel prognostic parameters. *J Pak Med Assoc* 2013;63:38-49.
35. Li G, Wen L, Yang XF, Zheng XJ, Zhan RY, Liu WG. Efficacy of large decompressive craniectomy in severe traumatic brain injury. *Chin J Traumatol* 2008;11:253-6.
36. Gouello G, Hamel O, Asehnoune K, Bord E, Robert R, Buffenoir K. Study of the long-term results of decompressive craniectomy after severe traumatic brain injury based on a series of 60 consecutive cases. *ScientificWorldJournal* 2014;2014:1-10.
37. Aarabi B, Hesdorffer DC, Ahn ES, Aresco C, Scalea TM, Eisenberg HM. Outcome following decompressive craniectomy for malignant swelling due to severe head injury. *J Neurosurg* 2006;104:469-79.
38. Pompucci A, De Bonis P, Pettorini B, Petrella G, Di Chirico A, Anile C. Decompressive craniectomy for traumatic brain injury: patient age and outcome. *J Neurotrauma* 2007;24:1182-8.
39. Akyuz M, Ucar T, Acikbas C, Kazan S, Yilmaz M, Tuncer R. Effect of early bilateral decompressive craniectomy on outcome for severe traumatic brain injury. *Turk Neurosurg* 2010;20:382-9.
40. Yuan Q, Liu H, Wu X, Sun Y, Hu J. Comparative study of decompressive craniectomy in traumatic brain injury with or without mass lesion. *Br J Neurosurg* 2013;27:483-8.
41. Limpastan K, Norasetthada T, Watcharasakul W, Vaniyapong T. Factors influencing the outcome of decompressive craniectomy used in the treatment of severe traumatic brain injury. *J Med Assoc Thai* 2013;96:678-82.
42. Csokay A, Nagy L, Novoth B. Avoidance of vascular compression in decompressive surgery for brain edema caused by trauma and tumor ablation. *Neurosurg Rev* 2001;24:209-13.
43. Kawamata T, Katayama Y. Surgical management of early massive edema caused by cerebral contusion in head trauma patients. *Acta Neurochir Suppl* 2006;96:3-6.
44. Salottolo K, Carrick M, Levy AS, Morgan BC, Mains CW, Slone DS, *et al*. Aggressive operative neurosurgical management in patients with extra-axial mass lesion and Glasgow Coma Scale of 3 is associated with survival benefit: A propensity matched analysis. *Injury* 2016;47:70-6.
45. Tien HC, Cunha JR, Wu SN, Chughtai T, Tremblay LN, Brenneman FD, *et al*. Do trauma patients with a Glasgow Coma Scale score of 3 and bilateral fixed and dilated pupils have any chance of survival? *J Trauma* 2006;60:274-8.
46. Hu Y, Sun H, Yuan Y, Li Q, Huang S, Jiang S, *et al*. Acute bilateral mass-occupying lesions in non-penetrating traumatic brain injury: a retrospective study. *BMC Surg* 2015;15:6.

47. Bindal A, Chandra N, Ojha BK, Chandra A, Singh SK, Srivastava C. Outcome of surgery for operable supratentorial mass lesions in patients presenting with decerebration following severe head injury: A retrospective analysis of factors affecting outcome. *Asian J Neurosurg* 2015;10:145-8.
48. Martins RS, Siqueira MG, Santos MT, Zanon-Collange N, Moraes OJ. Prognostic factors and treatment of penetrating gunshot wounds to the head. *Surg Neurol* 2003;60:98-104; discussion.
49. de Souza RB, Todeschini AB, Veiga JC, Saade N, de Aguiar GB. Traumatic brain injury by a firearm projectile: a 16 years experience of the neurosurgery service of Santa Casa de Sao Paulo. *Rev Col Bras Cir* 2013;40:300-4.
50. Chamoun RB, Robertson CS, Copinath SP. Outcome in patients with blunt head trauma and a Glasgow Coma Scale score of 3 at presentation. *J Neurosurg* 2009;111:683-7.
51. Chierigato A, Venditto A, Russo E, Martino C, Bini G. Aggressive medical management of acute traumatic subdural hematomas before emergency craniotomy in patients presenting with bilateral unreactive pupils. A cohort study. *Acta Neurochir (Wien)* 2017;159:1553-9.
52. Wan X, Liu S, Wang S, Zhang S, Yang H, Ou Y, *et al.* Elderly Patients with Severe Traumatic Brain Injury Could Benefit from Surgical Treatment. *World Neurosurg* 2016;89:147-52.
53. De Bonis P, Pompucci A, Mangiola A, Paternoster G, Festa R, Nucci CG, *et al.* Decompressive craniectomy for elderly patients with traumatic brain injury: it's probably not worth the while. *J Neurotrauma* 2011;28:2043-8.
54. Benedetto N, Gambacciani C, Montemurro N, Morganti R, Perrini P. Surgical management of acute subdural haematomas in elderly: report of a single center experience. *Br J Neurosurg* 2017;31:244-8.
55. Fulkerson DH, White IK, Rees JM, Baumanis MM, Smith JL, Ackerman LL, *et al.* Analysis of long-term (median 10.5 years) outcomes in children presenting with traumatic brain injury and an initial Glasgow Coma Scale score of 3 or 4. *J Neurosurg Pediatr* 2015;16:410-9.
56. Khan SA, Shallwani H, Shamim MS, Murtaza G, Enam SA, Qureshi RO, *et al.* Predictors of poor outcome of decompressive craniectomy in pediatric patients with severe traumatic brain injury: a retrospective single center study from Pakistan. *Childs Nerv Syst* 2014;30:277-81.
57. Alkhoury F, Kyriakides TC. Intracranial Pressure Monitoring in Children With Severe Traumatic Brain Injury: National Trauma Data Bank-Based Review of Outcomes. *JAMA Surg* 2014;149:544-8.
58. Guresir E, Schuss P, Seifert V, Vatter H. Decompressive craniectomy in children: single-center series and systematic review. *Neurosurgery* 2012;70:881-8; discussion 8-9.
59. Weisbrod AB, Rodriguez C, Bell R, Neal C, Armonda R, Dorlac W, *et al.* Long-term outcomes of combat casualties sustaining penetrating traumatic brain injury. *J Trauma Acute Care Surg* 2012;73:1525-30.
60. Sayer NA, Chiros CE, Sigford B, Scott S, Clothier B, Pickett T, *et al.* Characteristics and rehabilitation outcomes among patients with blast and other injuries sustained during the Global War on Terror. *Arch Phys Med Rehabil* 2008;89:163-70.
61. Grahm TW, Williams FC, Jr., Harrington T, Spetzler RF. Civilian gunshot wounds to the head: a prospective study. *Neurosurgery* 1990;27:696-700; discussion.
62. Joseph B, Aziz H, Pandit V, Kulvatunyou N, O'Keeffe T, Wynne J, *et al.* Improving survival rates after civilian gunshot wounds to the brain. *J Am Coll Surg* 2014;218:58-65.
63. Aarabi B, Tofighi B, Kufera JA, Hadley J, Ahn ES, Cooper C, *et al.* Predictors of outcome in civilian gunshot wounds to the head. *J Neurosurg* 2014;120:1138-46.
64. Kong V, Odendaal J, Sartorius B, Clarke D, Brysiewicz P, Jerome E, *et al.* Civilian cerebral gunshot wounds: a South African experience. *ANZ J Surg* 2017;87:186-9.
65. Bizhan A, Mossop C, Aarabi JA. Surgical management of civilian gunshot wounds to the head. *Handb Clin Neurol* 2015;127:181-93.
66. Aarabi B. Comparative study of bacteriological contamination between primary and secondary exploration of missile head wounds. *Neurosurgery* 1987;20:610-6.
67. Aarabi B. Causes of infections in penetrating head wounds in the Iran-Iraq War. *Neurosurgery* 1989;25:923-6.
68. Gonul E, Baysefer A, Kahraman S, Ciklatekerlioglu O, Gezen F, Yayla O, *et al.* Causes of infections and management results in penetrating craniocerebral injuries. *Neurosurg Rev* 1997;20:177-81.
69. Meirowsky AM, Caveness WF, Dillon JD, Rish BL, Mohr JP, Kistler JP, *et al.* Cerebrospinal fluid fistulas complicating missile wounds of the brain. *J Neurosurg* 1981;54:44-8.
70. Carey ME, Young H, Mathis JL, Forsythe J. A bacteriological study of craniocerebral missile wounds from Vietnam. *J Neurosurg* 1971;34:145-54.
71. Rish BL, Caveness WF, Dillon JD, Kistler JP, Mohr JP, Weiss GH. Analysis of brain abscess after penetrating craniocerebral injuries in Vietnam. *Neurosurgery* 1981;9:535-41.

72. Pitlyk PJ, Tolchin S, Stewart W. The experimental significance of retained intracranial bone fragments. *J Neurosurg* 1970;33:19-24.
73. Maltby GL. Penetrating craniocerebral injuries; evaluation of the late results in a group of 200 consecutive penetrating cranial war wounds. *J Neurosurg* 1946;3:239-49.
74. Carey ME, Young HF, Rish BL, Mathis JL. Follow-up study of 103 American soldiers who sustained a brain wound in Vietnam. *J Neurosurg* 1974;41:542-9.
75. Hammon WM. Analysis of 2187 consecutive penetrating wounds of the brain from Vietnam. *J Neurosurg* 1971;34:127-31.
76. Chaudhri KA, Choudhury AR, al Moutaery KR, Cybulski GR. Penetrating craniocerebral shrapnel injuries during "Operation Desert Storm": early results of a conservative surgical treatment. *Acta Neurochir (Wien)* 1994;126:120-3.
77. Taha JM, Haddad FS, Brown JA. Intracranial infection after missile injuries to the brain: report of 30 cases from the Lebanese conflict. *Neurosurgery* 1991;29:864-8.
78. Brandvold B, Levi L, Feinsod M, George ED. Penetrating craniocerebral injuries in the Israeli involvement in the Lebanese conflict, 1982-1985. Analysis of a less aggressive surgical approach. *J Neurosurg* 1990;72:15-21.
79. Vrankovic D, Splavski B, Hecimovic I, Glavina K, Dmitrovic B, Mursic B. Analysis of 127 war inflicted missile brain injuries sustained in north-eastern Croatia. *J Neurosurg Sci* 1996;40:107-14.
80. Shoung HM, Sichez JP, Pertuiset B. The early prognosis of craniocerebral gunshot wounds in civilian practice as an aid to the choice of treatment. *Acta Neurochir (Wien)* 1985;74:27-30.
81. Singh P. Missile injuries of the brain: results of less aggressive surgery. *Neurol India* 2003;51:215-9.
82. Cosar A, Gonul E, Kurt E, Gonul M, Tasar M, Yetiser S. Craniocerebral gunshot wounds: results of less aggressive surgery and complications. *Minim Invasive Neurosurg* 2005;48:113-8.
83. Charry JD, Rubiano AM, Puyana JC, Carney N, David Adelson P. Damage control of civilian penetrating brain injuries in environments of low neuro-monitoring resources. *Br J Neurosurg* 2016;30:235-9.
84. Bell RS, Mossop CM, Dirks MS, Stephens FL, Mulligan L, Ecker R, *et al.* Early decompressive craniectomy for severe penetrating and closed head injury during wartime. *Neurosurg Focus* 2010;28:E1.
85. Arendall RE, Meirowsky AM. Air sinus wounds: an analysis of 163 consecutive cases incurred in the Korean War, 1950-1952. *Neurosurgery* 1983;13:377-80.
86. Reith FCM, Van den Brande R, Synnot A, Gruen R, Maas AIR. The reliability of the Glasgow Coma Scale: a systematic review. *Intensive Care Med* 2016;42:3-15.
87. Turgeon AF, Lauzier F, Simard J-F, Scales DC, Burns KEA, Moore L, *et al.* Mortality associated with withdrawal of life-sustaining therapy for patients with severe traumatic brain injury: a Canadian multicentre cohort study. *Can Med Assoc J* 2011;183:1581-8.
88. Robertsen A, Førde R, Skaga NO, Helseth E. Treatment-limiting decisions in patients with severe traumatic brain injury in a Norwegian regional trauma center. *Scand J Trauma Resusc Emerg Med* 2017;25:44.
89. Turgeon AF, Lauzier F, Burns KE, Meade MO, Scales DC, Zarychanski R, *et al.* Determination of neurologic prognosis and clinical decision making in adult patients with severe traumatic brain injury: a survey of Canadian intensivists, neurosurgeons, and neurologists. *Crit Care Med* 2013;41:1086-93.
90. Patel HC, Bouamra O, Woodford M, Yates DW, Lecky FE. Clinical article: mortality associated with severe head injury in the elderly. *Acta Neurochir (Wien)* 2010;152:1353-7; discussion 7.
91. Vigué B, Ract C. Treatments and outcome, the point in head trauma. *Ann Fr Anesth Reanim* 2014;33:110-4.
92. Thompson HJ, Rivara FP, Jurkovich GJ, Wang J, Nathens AB, MacKenzie EJ. Evaluation of the effect of intensity of care on mortality after traumatic brain injury. *Crit Care Med* 2008;36:282-90.
93. McIntyre A, Mehta S, Janzen S, Aubut J, Teasell RW. A meta-analysis of functional outcome among older adults with traumatic brain injury. *NeuroRehabilitation* 2013;32:409-14.
94. Stocchetti N, Paterno R, Citerio G, Beretta L, Colombo A. Traumatic brain injury in an aging population. *J Neurotrauma* 2012;29:1119-25.
95. Yuan Q, Wu X, Sun Y, Yu J, Li Z, Du Z, *et al.* Impact of intracranial pressure monitoring on mortality in patients with traumatic brain injury: a systematic review and meta-analysis. *J Neurosurg* 2015;122:574-87.
96. Peep Talving, Efsthathios Karamanos, Pedro G. Teixeira, Dimitra Skiada, Lydia Lam, Howard Belzberg, *et al.* Intracranial pressure monitoring in severe head injury: compliance with Brain Trauma Foundation guidelines and effect on outcomes: a prospective study. *J Neurosurg* 2013;119:1248-54.
97. Alali AS, Fowler RA, Mainprize TG, Scales DC, Kiss A, de Mestral C, *et al.* Intracranial pressure monitoring in severe traumatic brain injury: results from the American College of Surgeons Trauma Quality Improvement Program. *J Neurotrauma* 2013;30:1737-46.

98. Cremer OL, van Dijk GW, van Wensen E, Brekelmans CJ, Moons KG, Leenen LP, *et al.* Effect of intracranial pressure monitoring and targeted intensive care on functional outcome after severe head injury. *Crit Care Med* 2005;33:2207-13.
99. Shafi S, Diaz-Arrastia R, Madden C, Gentilello L. Intracranial pressure monitoring in brain-injured patients is associated with worsening of survival. *J Trauma* 2008;64:335-40.
100. Biersteker HA, Andriessen TM, Horn J, Franschman G, van der Naalt J, Hoedemaekers CW, *et al.* Factors influencing intracranial pressure monitoring guideline compliance and outcome after severe traumatic brain injury. *Crit Care Med* 2012;40:1914-22.
101. Cnossen MC, Scholten AC, Lingsma HF, Synnot A, Tavender E, Gantner D, *et al.* Adherence to Guidelines in Adult Patients with Traumatic Brain Injury: A Living Systematic Review. *J Neurotrauma* 2016 [Epub ahead of print].
102. Cnossen MC, Huijben JA, van der Jagt M, Volovici V, van Essen T, Polinder S, *et al.* Variation in monitoring and treatment policies for intracranial hypertension in traumatic brain injury: a survey in 66 neurotrauma centers participating in the CENTER-TBI study. *Crit Care Med* 2017;21:233.
103. Aiolfi A, Benjamin E, Khor D, Inaba K, Lam L, Demetriades D. Brain Trauma Foundation Guidelines for Intracranial Pressure Monitoring: Compliance and Effect on Outcome. *World J Surg* 2017;41:1543-9.
104. Carney N, Totten AM, O'Reilly C, Ullman JS, Hawryluk GWJ, Bell MJ, *et al.* Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. *Neurosurgery* 2017;80:6-15.
105. National Clinical Guideline C. National Institute for Health and Clinical Excellence: Guidance. Head Injury: Triage, Assessment, Investigation and Early Management of Head Injury in Children, Young People and Adults. London: National Institute for Health and Care Excellence (UK).
106. Kochanek PM, Carney N, Adelson PD, Ashwal S, Bell MJ, Bratton S, *et al.* Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents--second edition. *Pediatr Crit Care Med* 2012;13 Suppl 1:S1-82.
107. Bennett TD, DeWitt PE, Greene TH, *et al.* Functional outcome after intracranial pressure monitoring for children with severe traumatic brain injury. *JAMA Pediatr* 2017;171:965-71.
108. Graves JM, Kannan N, Mink RB, Wainwright MS, Groner JI, Bell MJ, *et al.* Guideline Adherence and Hospital Costs in Pediatric Severe Traumatic Brain Injury. *Pediatr Crit Care Med* 2016;17:438-43.
109. Vavilala MS, Kernic MA, Wang J, Kannan N, Mink RB, Wainwright MS, *et al.* Acute care clinical indicators associated with discharge outcomes in children with severe traumatic brain injury. *Crit Care Med* 2014;42:2258-66.
110. Zhang D, Xue Q, Chen J, Dong Y, Hou L, Jiang Y, *et al.* Decompressive craniectomy in the management of intracranial hypertension after traumatic brain injury: a systematic review and meta-analysis. *Sci Rep* 2017;7:8800.
111. Honeybul S, Ho KM. The current role of decompressive craniectomy in the management of neurological emergencies. *Brain Inj* 2013;27:979-91.
112. Kim Y-J. The impact of time to surgery on outcomes in patients with traumatic brain injury: A literature review. *Int Emerg Nurs* 2014;22:214-9.
113. Vakil MT, Singh AK. A review of penetrating brain trauma: epidemiology, pathophysiology, imaging assessment, complications, and treatment. *Emerg Radiol* 2017;24:301-9.
114. Suddaby L, Weir B, Forsyth C. The management of 22 caliber gunshot wounds of the brain: a review of 49 cases. *Can J Neurol Sci* 1987;14:268-72.
115. Tsuei YS, Sun MH, Lee HD, Chiang MZ, Leu CH, Cheng WY, *et al.* Civilian gunshot wounds to the brain. *J Chin Med Assoc* 2005;68:126-30.
116. Gressot LV, Chamoun RB, Patel AJ, Valadka AB, Suki D, Robertson CS, *et al.* Predictors of outcome in civilians with gunshot wounds to the head upon presentation. *J Neurosurg* 2014;121:645-52.
117. Cooper DJ, Rosenfeld JV, Murray L, Arabi YM, Davies AR, D'Urso P, *et al.* Decompressive craniectomy in diffuse traumatic brain injury. *N Engl J Med* 2011;364:1493-502.
118. Hutchinson PJ, Kolias AG, Timofeev IS, Corteen EA, Czosnyka M, Timothy J, *et al.* Trial of Decompressive Craniectomy for Traumatic Intracranial Hypertension. *N Engl J Med* 2016;375:1119-30.
119. Mendelow AD, Gregson BA, Rowan EN, Francis R, McColl E, McNamee P, *et al.* Early Surgery versus Initial Conservative Treatment in Patients with Traumatic Intracerebral Hemorrhage (STITCH[Trauma]): The First Randomized Trial. *J Neurotrauma* 2015;32:1312-23.
120. Zhao HX, Liao Y, Xu D, Wang QP, Gan Q, You C, *et al.* Prospective randomized evaluation of therapeutic decompressive craniectomy in severe traumatic brain injury with mass lesions (PRECIS): study protocol for a controlled trial. *BMC Neurol* 2016;16:1-8.



CHAPTER 3

In-hospital costs after severe traumatic brain injury: a systematic review and quality assessment.

Authors:

Jeroen T.J.M. van Dijck MD^{1*}

Mark D. Dijkman MD¹

Robbin H. Ophuis MSc²

Godard C.W. de Ruiter MD PhD¹

Wilco C. Peul MD PhD MBA¹

Suzanne Polinder PhD²

Affiliations:

1. Department of Neurosurgery, University Neurosurgical Center Holland, LUMC, HMC & Haga Teaching Hospital, Leiden/The Hague, The Netherlands;
2. Department of Public Health, Erasmus Medical Center, Rotterdam, The Netherlands

Citation:

van Dijck JTJM, Dijkman MD, Ophuis RH, de Ruiter GCW, Peul WC, Polinder S (2019) In-hospital costs after severe traumatic brain injury: A systematic review and quality assessment. PLoS ONE 14(5):e0216743. <https://doi.org/10.1371/journal.pone.0216743>

ABSTRACT

Background: The in-hospital treatment of patients with traumatic brain injury (TBI) is considered to be expensive, especially in patients with severe TBI (s-TBI). To improve future treatment decision-making, resource allocation and research initiatives, this study reviewed the in-hospital costs for patients with s-TBI and the quality of study methodology.

Methods: A systematic search was performed using the following databases: PubMed, MEDLINE, Embase, Web of Science, Cochrane library, CENTRAL, Emcare, PsychINFO, Academic Search Premier and Google Scholar. Articles published before August 2018 reporting in-hospital acute care costs for patients with s-TBI were included. Quality was assessed by using a 19-item checklist based on the CHEERS statement.

Results: Twenty-five out of 2372 articles were included. In-hospital costs per patient were generally high and ranged from \$2,130 to \$401,808. Variation between study results was primarily caused by methodological heterogeneity and variable patient and treatment characteristics. The quality assessment showed variable study quality with a mean total score of 71% (range 48% - 96%). Especially items concerning cost data scored poorly (49%) because data source, cost calculation methodology and outcome reporting were regularly unmentioned or inadequately reported.

Conclusions: Healthcare consumption and in-hospital costs for patients with s-TBI were high and varied widely between studies. Costs were primarily driven by the length of stay and surgical intervention and increased with higher TBI severity. However, drawing firm conclusions on the actual in-hospital costs of patients sustaining s-TBI was complicated due to variation and inadequate quality of the included studies. Future economic evaluations should focus on the long-term cost-effectiveness of treatment strategies and use guideline recommendations and common data elements to improve study quality.

INTRODUCTION

Healthcare expenditures are rising worldwide and endanger the affordability of national healthcare systems.^{1,2} To secure their future existence, a thoughtful and righteous distribution of limited resources is essential. Policy makers and healthcare professionals are therefore increasingly expected to study the effectiveness of treatments and its associated costs.^{3,4} After all, the input from high quality cost research is required to make healthcare systems efficient and to achieve the highest quality of care for the lowest costs.⁵

Also in the field of traumatic brain injury (TBI), with an estimated total global annual burden of US\$ 400 billion, research efforts are increasingly conducted towards cost-effectiveness.⁶⁻¹⁰ After sustaining a TBI, in-hospital treatment is frequently required and generally associated with high costs.¹¹⁻¹⁴ In the USA, the 2010 TBI-related in-hospital charges totalled US\$ 21.4 billion.¹⁵ In-hospital costs after TBI are increasing annually and represent a substantial part of the total financial TBI burden.¹⁵ The highest individual costs in TBI patients are generally seen in patients with severe TBI (s-TBI).¹⁶ These patients also have the longest hospital or intensive care unit (ICU) length of stay (LOS) and the highest number of (neuro)surgical and medical interventions.¹⁶⁻¹⁸ Despite their substantial healthcare consumption, these vulnerable patients show high rates of mortality and unfavourable outcome. Especially for these patients with poor outcome at high costs, a critical appraisal of treatment cost-effectiveness is essential to avoid ineffective expenditures and improve treatment decision-making.¹⁹⁻²²

Two recent reviews on healthcare costs after TBI have reported about the considerable variation in healthcare costs after TBI between different studies and about the insufficient quality of the available cost studies.^{7,10} These reviews however were mainly focussed on the methodological quality of economic evaluations and therefore did not report the actual in-hospital costs. Insight into in-hospital costs and important components of the costs, such as healthcare utilization and other factors that drive these costs were not provided. This is important information for physicians and policymakers, because this information is needed for decision-making and for correct allocation of resources.

In this systematic review, we have therefore focussed on: (1) providing a detailed insight in the reported in-hospital costs for patients with s-TBI and (2) assessing the (quality of) study methodology.

METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.²³ The study protocol was registered in the PROSPERO International Prospective Register of Systematic Review with registration number CRD42018081131.

Literature search

A final systematic literature search was performed on the 8th of August 2018 using the following databases: PubMed, MEDLINE, Embase, Web of Science, Cochrane library, CENTRAL, Emcare, PsychINFO, Academic Search Premier and Google Scholar. The search strategy was developed and conducted with the assistance of a trained clinical librarian. All relevant information on the literature search can be found in S1 Appendix. In addition to the search, the reference lists of all included articles were manually checked for additional relevant studies.

Inclusion/exclusion criteria

Studies were included when the in-hospital costs or in-hospital charges of a cohort of >10 patients with s-TBI were reported. Because the appellation “severe TBI” encompassed a range of brain injuries considered to be too varied for appropriate comparison the two most widely used classifications for s-TBI were applied: Glasgow Coma Scale (GCS) ≤ 8 and/or Abbreviated Injury Scale (AIS) ≥ 4 .²⁴⁻²⁶ We excluded reviews, commentaries, editorials, conference and meeting abstracts, unpublished data, non-English studies and studies that could not be found or retrieved in full text. Studies were also excluded when in-hospital costs related to acute care were not distinguishable from other costs like indirect non-healthcare related costs (e.g. loss of productivity), (in-hospital) rehabilitation or long-term costs. There were no restrictions on publication date or patient characteristics.

Article selection and data extraction

First, duplicates, non-English and unretrievable records were excluded. Second, two reviewers (JD,MD) independently screened the titles and abstracts of the remaining studies and selected all potential eligible studies. Full-texts were independently reviewed by the same researchers and studies were included according to the above mentioned criteria. During the process, all disagreements were resolved through discussion until consensus or after consulting a third researcher (RO). Data extraction was performed in duplicate using pre-created data extraction sheets. Extracted data was then discussed and combined. Variables that were collected included: study details, study population, definition of TBI (including severity), healthcare consumption, details of costs research methodology and cost outcome results.

Quality assessment

A 19-item checklist was used to assure an accurate quality assessment for the evaluation of in-hospital costs following s-TBI. The checklist was based on the CHEERS statement, which is developed to improve the reporting on economic evaluations.²⁷⁻³⁰ We slightly adjusted the items from the CHEERS statement by specifying items like 'target population and subgroups' in clear definition of illness and TBI severity, because this was deemed necessary for proper interpretation of study results. Also we intentionally left out items like cost perspective, time horizon and discounting costs since these were considered not relevant for short term in-hospital costs. The final checklist covers items in the areas of study details, population, clinical data, cost data and study methodology. All relevant details can be found in S2 Appendix.

The quality assessment was independently performed by three reviewers (JD, MD, RO). Disagreements were reassessed and discussed in several meetings until consensus was reached. All items were scored according to a predefined scoring manual that included four options: yes (1), suboptimal (0.5), no (0) and not applicable (N/A). A double weight was assigned to several items that were considered to be particularly important in calculating and reporting in-hospital costs. Final scores represented study quality and were presented as a percentage of the maximum score per study. Scores per item and item category were also calculated. All items that were not applicable were excluded from score calculation. When studies used a statistical model, items were scored considering the clear use and description of the model input parameters and sources.

Outcome

All relevant data was reported in a descriptive manner. In line with the inclusion criteria, patients were included from three different severity groups as they were reported in the included studies ($GCS \leq 8$, $AIS \geq 4$, $AIS \geq 5$). These subgroups were also used in the text and figures. In one figure, hospital LOS was presented by using black indicators (■) and ICU LOS by white indicators (□). A clear distinction between hospital costs and hospital charges, when known, was made by using black and white indicators respectively. In-text, both the reported hospital charges and hospital costs were presented as in-hospital costs. The Gross Domestic Product (GDP) per capita of the study country was included as reference value, to improve comparability between the reported costs. The reference year that was used, corresponded with the currency year.³¹ All costs, including GDP per capita, were converted to US dollars (2015) using the CCEMG – EPPI-Centre Cost Converter.³² This web-based tool utilizes Gross Domestic Product deflator index values and Purchasing Power Parities conversion rates provided by the International Monetary Fund.³³ In case a reference year was not provided we used the last year in which patients were included or, when unknown, the year of publication. Figures were designed with GraphPad Prism version 7.0.2.

RESULTS

Literature search and study selection

The systematic literature search identified 2372 studies (Fig 1). First, a total of 283 duplicate, non-English or unfindable studies were removed. The remaining 2089 studies were screened on title and abstract, resulting in 204 studies considered eligible for full-text assessment. Studies were excluded because; (1) they did not include a s-TBI cohort defined by a $GCS \leq 8$ and/or $AIS \geq 4$ ($N=134$), (2) they did not report hospital costs for patients with s-TBI ($N=28$) or (3) in-hospital acute care costs were not distinguishable from other costs ($N=13$). No additional studies were identified through the reference check. Ultimately, 25 articles were included in this systematic review.

Study characteristics

The main study characteristics can be found in Table 1. Twelve studies were published after 2010, nine between 2000 and 2019, and four before 2000. Cohort size ranged from 20 to 7774 patients.^{34,35} Nineteen studies were conducted in high income countries of which sixteen in the USA. The majority of studies focused on adult

patients, while some studies focused on paediatric^{34,36-38} and elderly patients.^{35,39} Nineteen studies (76%) had cost research in TBI patients as a research objective. TBI was often only defined by mentioning “TBI” or “head injury” (N=9). Six studies provided only little additional information and nine studies used ICD (N=8) and/or AIS codes (N=2). Severity was defined by GCS (68%), by AIS (28%) or both (4%). The used GCS was obtained at admission (n=7), the emergency department (n=3) and the time remained unknown in 5 studies. A retrospective study design was used in 60%^{35-37,39-50}, followed by a prospective design (16%)^{34,51-53} or a combination of both (12%).⁵⁴⁻⁵⁶ Three studies used a statistical model.^{38,57,58}

Fig 1. Flow chart of the article selection process.

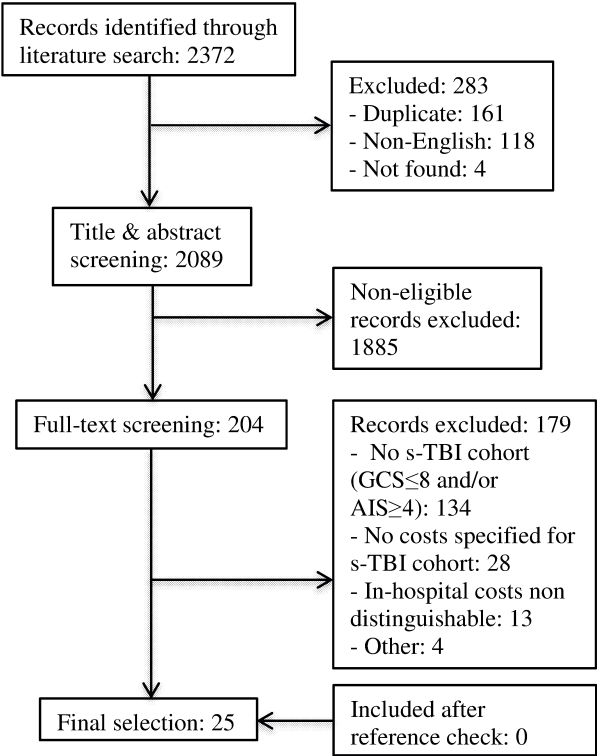


Table 1: Study details & results

| # | Study info ^a | Purpose | Study Design | Patient (N) | Definition of TBI | Severity definition |
|---|--|--|---------------------------------------|-----------------------------------|---|----------------------------|
| 1 | <ul style="list-style-type: none"> - Ahmed ⁴⁰ - 2007 - 2002-2005 - USA | Evaluate the impact of early tracheostomy on s-TBI patients | Retrospective cohort study | 55 s-TBI | TBI, not further specified | GCS≤8 at admission |
| 2 | <ul style="list-style-type: none"> - Albrecht ³⁹ - 2017 - 2008-2012 - USA | Provide charge estimates of TBI treatment for elderly patients | Retrospective cohort study | GCS<9:247 AIS4:688 AIS5:368 | ICD-9-CM codes | GCS<9 at admission, AIS>3 |
| 3 | <ul style="list-style-type: none"> - Andelic ⁵⁷ - 2014 - 2005-2007 - Norway | Estimate long-term cost-effectiveness of rehabilitation trajectories | Decision-tree model | 59 s-TBI | ICD-10 codes | GCS≤8 before intubation |
| 4 | <ul style="list-style-type: none"> - Brooks ⁴¹ - 1995 - 1989-1990 - USA | Determine the costs of health care services for TBI patients | Retrospective cohort study | 28 s-TBI | TBI with AIS>0 | AIS 4 and 5 |
| 5 | <ul style="list-style-type: none"> - Bryant ⁴² - 1993 - NP - USA | Find a high-quality cost-effective strategy for head injury rehabilitation | Retrospective cohort study | 47 s-TBI | TBI, not further specified | GCS≤8 in ED |
| 6 | <ul style="list-style-type: none"> - Fakhry ⁴³ - 2004 - 1991-2000 - USA | Determine effect of following BTF guidelines on outcome and charges | Cohort study with historical controls | 830 s-TBI | TBI defined as blunt traumatic head injury with AIS-head > 2 | GCS≤8 |
| 7 | <ul style="list-style-type: none"> - Farhad ⁴⁴ - 2013 - 1993-1994/2006-2007 - USA | Compare TBI-related hospitalization outcomes between 2 periods | Retrospective analysis of NIS data | 317/288 s-TBI | ICD-9-CM codes | ICD/AIS 4–6 |
| 8 | <ul style="list-style-type: none"> - Graves ³⁶ - 2016 - 2007-2011 - USA | Evaluate guideline adherence on outcome and costs for paediatric s-TBI patients | Retrospective cohort study | 235 s-TBI | ICD-9 codes, head AIS ≥ 3, history of trauma, abnormal admission head CT scan | GCS≤8 at admission |
| 9 | <ul style="list-style-type: none"> - Ibrahim ⁵¹ - 2007 - 2003 - Malaysia | CEA of two neuro monitoring modalities in s-TBI management | Prospective observational CEA study | 62 s-TBI | Severe head injury, traumatic in nature, not further specified | GCS≤8 and CT-scan features |

| Cost data source | Details on cost calculation | Included costs | Currency (Y) / GDP per capita ^b | Results (\$ 2015) ^c (% of GDP per capita) |
|---|---|--|--|--|
| Hospital accounting database | NP, most likely directly obtained from database | Total hospital charges | US\$ (NP) / \$52,876 | - ET (GCS 4.3±1.9): median \$348,858 (660%) (95% CI: \$293,682-\$468,908) - LT (GCS 4.5±1.8): median \$396,917 (751%) (95% CI: \$334,441-\$520,808) |
| Finance and billing department of (trauma) hospital and university | NP, most likely directly obtained from database | Hospital and physician charges. (Cost-to-charge ratio: 140.65%). | US\$ (2012) / \$53,681 | - GCS <9: \$58,899 (110%) ± \$74,194 - AIS 4: \$37,503 (70%) ± \$58,025 - AIS ≥5: \$59,146 (110%) ± \$87,230 |
| Expected costs calculated from a reimbursement system using diagnosis related groups (DRG) | DRG reimbursement multiplied by the DRG cost weight for each patient | Total acute hospitalization costs for first 5 years post-injury | NOK (2009) / \$87,894 | - All: \$112,808 (128%) ± \$68,327 - Trajectory 1: \$123,526 (141%) ± \$50,911 - Trajectory 2: \$101,822 (116%) ± \$81,725 |
| Charges are obtained directly from all service providers | Services and billing records were added up to calculate actual/estimated charges | Initial care charges including EMS, acute care charges and physicians charges of initial hospitalization | US\$ (1993) / \$40,211 | - Acute care: \$123,303 (307%) - Physicians: \$25,767 (64%) - Emergency Medical Services (EMS): \$1,855 (5%) |
| Costs are estimated from financial records of the health maintenance organization (HMO) | Unit costs are multiplied by utilized services | Acute medical care costs using actual operational costs. | US\$ (NP) / \$40,211 | - All: \$24,205 (60%) |
| Trauma registry and individual chart review | NP, most likely directly obtained from registry of charts | Total charges (hospital room, critical care, nursing services, direct and indirect expenses, general hospital charges) | US\$ (1997) / \$44,428 | - 1991-1994 (GCS 4.0): \$51,634 (116%) - 1995-1996 (GCS 3.5): \$42,558 (96%) - 1997-2000 (GCS 3.5): \$40,002 (90%) |
| National Inpatient Sample (NIS) database (1993-1994/2006-2007) | NP, most likely directly obtained from database | Total charges of hospitalization | US\$ (2006-2007) / \$53,764 | - 1993-1994: \$21,427 ± \$21,315 - corrected for inflation: \$29,999 (56%) - 2006-2007: \$65,002 (121%) ± \$60,900 |
| Total charged amounts most likely from hospitals, CCR from HCUP-KID or institution's billing office | Obtained charges converted to costs with institution specific cost-charge ratio (CCR) | Total costs of hospitalization + ICU care | US\$ (2012) / \$53,681 | - Hospital mean: \$106,969 (199%) (95% CI: \$96,355 - \$117,582) - ICU mean: \$84,843 (156%) (95% CI: \$76,364 - \$93,322) |
| All treatment costs measured using budget information | Macro and micro costing approach | Only direct provider costs calculated during admission | US\$ (2002) / \$5,379 | - Group 1 (GCS median 5.5, IQR 2.0): \$10,356 ± \$6,526 (121%) - Group 2 (GCS median 6.0, IQR 2.0): \$11,646 ± \$8,168 (152%) |

Table 1: Study details & results

| # | Study info ^a | Purpose | Study Design | Patient (N) | Definition of TBI | Severity definition |
|----|--|--|--|-------------------------------|---|--|
| 10 | - Jaffe ³⁴ - 1993 - 1987-1988 - USA | Assess acute and rehab costs of paediatric TBI patients | Prospective cohort study | 20 s-TBI | Non-penetrating TBI with loss of consciousness | GCS≤8, at ED or before paralyzing agents |
| 11 | - Lehmkuhl ⁵⁴ - 1993 - 1989-1992 - USA | Investigate factors that influence hospital charges for persons with TBI | Retrospective and prospective cohort study | 111 s-TBI, 108 vs-TBI | TBI, defined as brain tissue damage caused by external force | GCS≤8, lowest score in first 24 hours |
| 12 | - Li ³⁵ - 2017 - 2001-2007 - China | Epidemiological characteristics of elderly TBI patients | Retrospective analysis of Chinese Trauma Database data | 5238 s-TBI 2536 c-TBI | ICD-9-CM codes | AIS4: severe AIS5-6: critical |
| 13 | - Martini ⁴⁵ - 2009 - 2004-2007 - USA | Resource utilization of brain tissue oxygen monitoring | Retrospective cohort study | 629 s-TBI | TBI, not further specified | GCS≤8 at admission |
| 14 | - McGarry ⁴⁶ - 2002 - 1997-1999 - USA | Examine treatment outcomes and costs of TBI | Retrospective analysis of database | 2580 s-TBI 1147 c-TBI | ICD-9-CM codes | ICD/AIS4: severe ICD/AIS5: critical |
| 15 | - Morris ⁴⁷ - 2008 - 2000-2005 - England/ Wales | Investigate cost of care for hospitalised TBI patients | Retrospective analysis of database | 2460 s-TBI 2573 c-TBI | TBI defined using 1998 AIS codes | AIS4: severe AIS5: critical |
| 16 | - Palmer ⁵⁵ - 2001 - 1994-1999 - USA | Report impact of TBI guideline implementation on outcome in s-TBI patients | Cohort study using retro- and prospective data | 93 s-TBI | Closed head injury and evidence of brain injury on examination or CT-scan | GCS≤8 at admission |
| 17 | - Prang ⁴⁸ - 2012 - 1995-2004 - Australia | Describe details of care services after transport related TBI | Analysis of a compensation database | 316 s-TBI | Transport related-TBI, not further specified. | GCS3–8: severe |
| 18 | - Salim ⁵² - 2008 - 2000-2004 - USA | Evaluate outcome of ARDS in patients with s-TBI | Prospectively collected cohort in ARDS dataset | 28 s-TBI+ ARDS 56 s-TBI | Blunt trauma patients with TBI, AIS defined. | Head AIS ≥ 4 |
| 19 | - Schootman ⁴⁹ - 2003 - 1996 - USA | Hospitalization charges for acute care in TBI patients in the USA | Population based descriptive study | 1789 s-TBI | ICD-9-CM codes | ICD/AIS 4-6 |
| 20 | - Siddiqui ⁵⁶ - 2015 - 2002-2009 - Pakistan | Identify impact of early tracheostomy in s-TBI patients | Cohort study using retro- and prospective data | 100 s-TBI | TBI, not further specified | GCS<8 |

| Cost data source | Details on cost calculation | Included costs | Currency (Y) / GDP per capita ^b | Results (\$ 2015) ^c (% of GDP per capita) |
|--|--|--|--|---|
| Hospital/physician charges from hospitals and physicians billing office | NP, most likely directly obtained from billing office | Charges used as proxy for costs. Initial acute care | US\$ (1988) / \$38,048 | - GCS3-8: \$93,934 (247%) (range: \$8,881–\$328,857) - AIS4: \$32,375 (85%) (\$16,378–\$81,852) - AIS5: \$145,573 (383%) (\$36,096–\$328,857) |
| Copy of final billed charges submitted to designated payer | NP, most likely the submitted charges | Hospitalization costs (billed charges) for acute care excluding physicians fee | US\$ (1989–1992) / \$45,150 | - GCS6-8: \$90,291 (200%) ± \$72,243 - GCS3-5: \$141,813 (314%) ± \$84,216 |
| Chinese Trauma Database dataset. | NP, most likely directly obtained from dataset | Hospitalization costs | US\$ (NP) / \$3,039 | - AIS4: \$2,130 (70%) ± 3,881 - AIS5-6: \$3,586 (118%) ± 5,384 |
| Hospital administrative records | Charges converted to costs with institution specific CCR | Hospital costs | US\$ (2007) / \$54,204 | - Group 1 (GCS 5.6 ± 2.3): \$116,387 (215%) ± \$85,034 - Group 2 (GCS 5.1 ± 2.2): \$143,453 (265%) ± \$88,079 |
| Billed charges from a large multihospital database | Charges converted to costs with CCR | Hospitalization costs of acute treatment | US\$ (1999) / \$47,467 | - AIS4: \$23,017 (48%) - AIS5: \$45,981 (97%) |
| Trauma Audit and Research Network database and reference unit costs from different sources | Resource use from database and unit count multiplied by unit costs for other costs | National Health Service hospital costs | £ (NP) / \$49,803 | - AIS4: \$16,110 ± \$30,088 (60%) - AIS5: \$29,504 ± \$29,944 (60%) |
| Patient records and/or financial data | NP, most likely directly obtained from records or financial data | Hospital charges | US\$ (NP) / \$47,467 | - Before implementation (GCS 6.4 ± 0.7): \$268,902 (567%) ± \$31,761 - After implementation (GCS 6.9 ± 0.5): \$401,808 (846%) ± \$27,364 |
| Accepted claims from Compensation Research Database | Mean costs calculated for each service category | Direct cost of healthcare over 5-year period post-injury | AUD \$ (2009) / \$46,885 | - Acute hospital services: \$45,384 (98%) ± \$38,720 |
| Hospital's trauma registry | NP, most likely directly obtained from trauma registry | Hospital charges | US\$ (NP) / \$51,638 | - TBI+ARDS group (GCS 4 ± 2): \$258,790 (501%) ± \$296,186 - TBI group (GCS 5 ± 2): \$142,074 (275%) ± \$198,248 |
| National Inpatient Sample (NIS) of 1996 | Database contains patient-level clinical and resource use information | Hospitalization billed charges for acute care | US\$ (1996) / \$43,035 | - Mean \$47,004 (109%) ± \$3,238; - Median \$20,886 |
| Institution's billing department | NP, most likely directly obtained from billing department | Inpatient treatment costs (ED, ICU, ward, lab, imaging, surgery) | US\$ (2009) / \$1,105 | - Group 1 (GCS 5.4 ± 1.7): \$8,811 (797%) - Group 2 (GCS 6.0 ± 1.7): \$10,934 (990%) |

Table 1: Study details & results

| # | Study info ^a | Purpose | Study Design | Patient (N) | Definition of TBI | Severity definition |
|----|---|--|---|----------------------------|--|--|
| 21 | - White ³⁷ - 2001 - 1991-1995 - USA | Determine predictors in paediatric s-TBI patients | Retrospective cohort study | 136 s-TBI | Non-penetrating head injury, not further specified | GCS≤8 at admission to ED |
| 22 | - Whitmore ⁵⁸ - 2012 - N/A - USA | Determine the cost-effectiveness of treatment strategies in s-TBI patients | Decision-analytical model | N/A | TBI, not further specified | GCS≤8 and motor component of ≤5 at admission |
| 23 | - You ⁵⁰ - 2018 - 2015-2016 - Malaysia | Assign costs to treatment of surgically treated patients with TBI | Retrospective cohort study | 26 s-TBI | ICD-10 codes | GCS3-8 on presentation |
| 24 | - Yuan ⁵³ - 201) - 2004 - China | Acute treatment costs for TBI | Prospective observational multicentre study | 2500 s-TBI | TBI diagnosis was made by admitting neurosurgeons or ER physicians and confirmed by CT | GCS≤8 at admission |
| 25 | - Zapata-Vazquez ³⁸ - 2017 - N/A - Mexico | Cost-effectiveness of ICP monitoring in paediatric s-TBI patients | Decision-tree model | Based on 33 s-TBI patients | TBI, not further specified | GCS3-8 |

This table shows the main study characteristics and results

AIS, Abbreviated Injury Scale; ARDS, Adult Respiratory Distress Syndrome; BTF, Brain Trauma Foundation; CCR, Cost to Charge Ratio; CEA, Cost Effectiveness Analysis; CT, Computed Tomography; c-TBI, critical TBI; DRG, Diagnosis Related Groups; ED, Emergency Department; EMS, Emergency Medical Services; ET, Early Tracheostomy; GCS, Glasgow Coma Scale; HCUP-KID, Healthcare Cost and Utilization Project - Kids' Inpatient Database; HMO, Health Maintenance Organization; ICD-10, International Classification of Diseases, 10th Revision; ICD-9-CM, International Classification of Diseases, Ninth Revision; ICP, Intracranial Pressure; ICU, Intensive Care Unit; LOS, Length of Stay; LT, Late Tracheostomy; N/A, not applicable; N, Number; NIS, National Inpatient Sample; NP, Not provided; s-TBI, severe Traumatic Brain Injury; TBI, Traumatic Brain Injury; vs-TBI, very severe Traumatic Brain Injury; Y, Year

Legend:

^a Name first author [reference #] - year of publication - Cohort inclusion period - Study country.

^b GDP per capita from year of currency and converted to \$ 2015.

^c When available, severity defined by GCS was further specified by adding the mean GCS ± SD. (Unless stated otherwise)

| Cost data source | Details on cost calculation | Included costs | Currency (Y) / GDP per capita ^b | Results (\$ 2015) ^c (% of GDP per capita) |
|---|---|---|--|---|
| NP: "were available" | Charges converted to costs using hospital based CCR | Hospitalization costs | US\$ (1998) / \$45,866 | - Survivors (CCS 5.4±1.9): \$12,247 (27%) (\$2,199-\$127,555) - Non-survivors (CCS 3.4±0.8): \$7,081 (15%) (\$2,305-\$32,622) |
| Obtained from literature and Medicare reimbursement rates | Cost calculations follow general principles earlier described in literature and methods section | Direct acute medical care costs, primarily associated with the initial hospitalization | US\$ (2011) / \$52,910 | - Comfort care: GOS1: \$60,582 (115%) GOS2-3: \$111,067 (210%) GOS4-5: \$43,753 (83%) - Routine care: GOS 1: \$77,410 (146%) GOS 2-3: \$136,309 (258%) GOS4-5: \$52,167 (99%) - Aggressive care: GOS1-5: \$124,725 (236%) |
| Hospital revenue department, finance department and financial reports | Micro- and macro-costing methods. Activity units multiplied by unit costs | Total cost of treatment (including hospitalization, surgery and investigations) | US\$ (2016) / \$9,416 | - GCS3-8: \$8,964 (95%) ± \$5,753 |
| Unsubsidized total hospital billings | NP, most likely directly obtained from hospital billings | Total acute hospitalization treatment costs | US\$ (2004) / \$1,859 | - GCS3-8: median \$3,115 (168%) (\$1,468 - \$6,046) - Isolated TBI: \$2,844 (153%) - TBI with other injury: \$3,207 (173%) |
| Most costs taken from official journal of the federation. Medicine price catalog, ICP probe price provided by supplier. | Amount of supplies directly obtained from hospital price | Costs of hospitalization (direct medical costs + clinical complications) medicines, laboratory, imaging, surgery, LOS ICU/Ward. | Mex\$ (2015) / \$9,291 | - ICP monitoring group (CCS 5.5±1.7): \$66,263 (713%) ± \$31,436 - Control group (CCS 7.0±1.5): \$41,783 (450%) ± \$10,622 |

Quality of study methodology

The results of the quality assessment are presented in detail in S1 Table. Study quality was variable with an average total score of 71% and a range of 48% to 96%. Seven studies achieved a score above 80%, representing "high quality".^{36,38,39,47,50,53,58} Especially items in the 'cost data' subgroup scored poorly (49%). All but one study mentioned their cost data source, but a clear description was missing in 24%. Also, the design and methods of costs analysis were not mentioned in 36% and were unclear in another 16%. Eleven studies properly assessed hospital activity data but only three studies appropriately valued and reported unit costs. Hospital costs were disaggregated in 20% of studies and in 52% charges were reported instead of costs. Major assumptions were tested in a sensitivity analysis in only 16% and a reference year was missing in 14% of the studies. The subgroups 'study details', 'population' and 'methodology'

had the highest scores (100%, 87% and 78%). There were infrequent statements on source of funding and conflicts of interest, unsatisfying TBI definitions and inadequate evaluation of study findings.

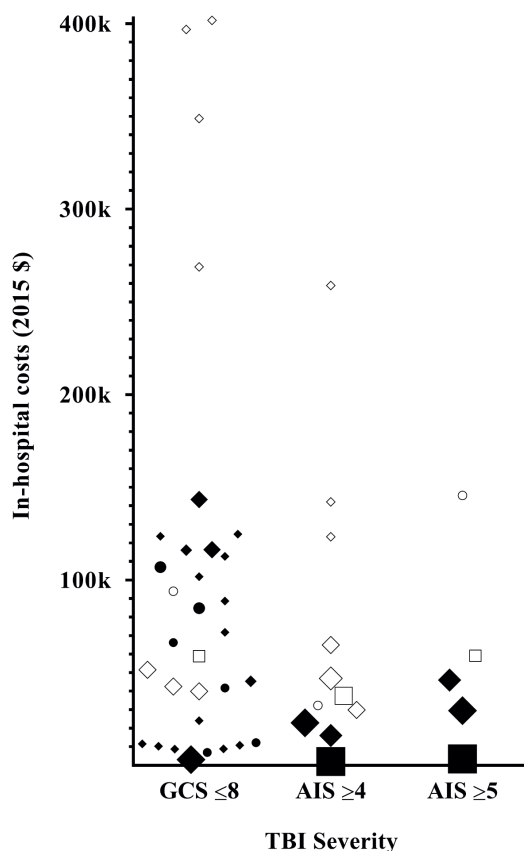


Fig 2. In-hospital costs and in-hospital charges of a patient with s-TBI

Figure 2 shows the in-hospital costs and in-hospital charges of a patient with s-TBI, as reported in the included studies. Black indicators represent in hospital costs, while white indicators represent in-hospital charges. A bigger indicator size, represents a bigger study cohort size.

- ○ : Paediatric
- ◆ ◇ : Adult
- □ : Elderly

Hospital costs & healthcare consumption

The median reported in-hospital costs per patient were \$55,267 (mean \$87,634) and ranged from \$2,130 to \$401,808 (Fig 2). The lowest costs were seen in studies from China, Pakistan and Malaysia (\$2,130 to 10,356)^{35,50,51,53,56} and in a subgroup of paediatric non-

survivors in the USA (\$7,081).³⁷ The highest in-hospital costs (\$258,790 to \$401,808) were found in three studies describing different patient cohorts from the USA.^{40,52,55} The in-hospital costs as percentage of the GDP per capita (median 128%, mean 234%) were highly variable and ranged from 15% to 990%.^{37,56} Mean percentages were not significantly different between high and lower income countries and between charges and costs (204% vs. 333% and 289% vs. 202%).

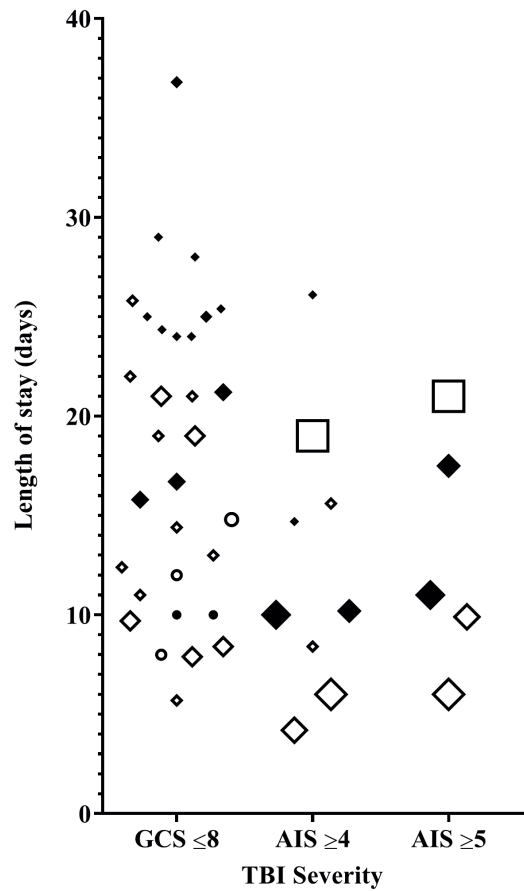


Fig 3. ICU and hospital length of stay of a patient with s-TBI

Figure 3 shows the ICU and hospital length of stay of a patient with s-TBI, as reported in the included studies. Black indicators represent hospital length of stay, while white indicators represent ICU length of stay. A bigger indicator size, represents a bigger study cohort size.

- ○ : Paediatric
- ◆ ◇ : Adult
- □ : Elderly

Fourteen studies reported LOS for patients with s-TBI, also showing major variation (Fig 3).^{35,36,38,40,43,45-47,50-52,54-56} ICU LOS ranged from 7.9 to 25.8 days ($GCS \leq 8$)^{40,43}, 6 to 19 days ($AIS \geq 4$) and 6 to 21 days ($AIS \geq 5$).^{35,47} Hospital LOS ranged from 10 to 36.8 days ($GCS \leq 8$)^{38,54}, 10 to 26.1 days ($AIS \geq 4$)^{47,52} and 11 to 17.5 days ($AIS \geq 5$).^{46,47}

Some studies reported costs related to acute care to be 46% to 67% of total hospitalization costs, while inpatient rehabilitation costs accounted for 26% to 41%.^{41,42,54,57} Various studies found that costs related to hospital LOS and ICU LOS were the main drivers of hospital costs.^{36,38,39,47,50,53} Costs related to ICU care comprised the biggest part of total hospital costs (51-79%), followed by costs related to ward admission (12-38%), surgery (4-8%) and imaging/laboratory (<3%).^{36,38,47} Physician charges were reported to be 12% to 20% of total costs.^{39,41} One study included the salary of paramedics and found salary to be the most important contributor (71-79%) to total provider costs.^{39,41,51} The majority of costs, up to 90%, were made in the first year after trauma and were generally associated with TBI-related hospitalization costs.^{41,48,57} The share of acute hospital services (18%) and rehabilitation (27%) on total costs decreased when a long-term follow-up period was used.⁵²

Several studies provided some additional information on clinical factors that were associated with reported costs. A higher TBI severity was generally related with an increased LOS and costs.^{34,35,37-39,41,42,46-50,53,54} Even among patients with a s-TBI, patients with a $GCS 3-5$ or $AIS=5$ were more expensive than patients with a $GCS 6-8$ or $AIS=4$, respectively.^{34,35,39,40,46,47,54} A higher overall injury severity was also related with higher costs.^{39,47,53} Male gender was linked with higher costs^{35,39,53} and two studies mentioned that a higher age was more expensive.^{47,50} Costs were also influenced by trauma mechanism and were higher for motor vehicle accidents and gunshot wounds and lower after an assault to the head.^{34,35,39,46,53,54} The use of surgical intervention, intracranial pressure monitoring or mannitol were all related to longer LOS and higher costs.^{37,38,45,53,54} Also, the introduction of guidelines and evidence based medicine protocols appeared to increase LOS and hospital costs^{43,55}, while improvement of guideline adherence did not change ICU and hospital costs in another study.³⁶ Three studies related costs to outcome and found lower costs for patients that died or made a good recovery.^{37,53,58}

DISCUSSION

This systematic review demonstrates that the in-hospital costs related to acute care for patients with s-TBI are generally high and increase with severity of TBI and overall severity of the injury. Both healthcare consumption and in-hospital costs are highly variable between studies and associated with factors such as mechanism of injury and treatment strategy.

Three previous reviews on costs after TBI were generally in line with our results, but results were difficult to compare with the present review due to differences in study objectives and substantial variation between the included studies that was mainly caused by differing methodological and clinical characteristics.^{7,59,60} Elaborating on these reviews, we specifically investigated the in-hospital costs related to acute care for patients with s-TBI aiming to reduce variation and improve study comparability. Methodological and clinical heterogeneity remained present, likely contributing to the variation in in-hospital costs between studies. The highest in-hospital costs were found in studies from the USA that reported charges instead of costs. Because hospital charges are not actual costs and usually higher than hospital costs, this increased total amounts. Charges are also often non-transparent and the resultant of deals between hospitals and insurance companies or other stakeholders. It is therefore preferred to calculate and report total costs by using healthcare utilization with its corresponding unit costs. Also, USA healthcare expenditures are twice as high as expenditures in other high-income countries.^{2,61} While healthcare utilization patterns were rather similar between high-income countries, the higher expenditures were especially caused by higher prices of labour, goods, pharmaceuticals and administrative costs.^{2,62} Large international differences were also seen between European countries when assessing injury related hospitalization costs.⁶³ Likewise, the lowest in-hospital costs were found in studies from lower-income countries, which is also in accordance with literature.⁶⁴ These absolute costs are lower because of lower prices, lower treatment intensity and higher mortality rates with associated lower resource utilization.^{64,65} In-hospital costs reported as percentage of GDP per capita were however not significantly different between high and low income countries, suggesting a similar financial impact for patients. Differences in costs might also be caused by hospital associated factors (e.g. level of trauma center, volume, treatment protocols) and by the major epidemiological differences of trauma populations between countries.⁶ The different timeframes included in this review could also contribute to variation, since treatment strategies have changed over time and healthcare costs have been increasing globally over the years.^{15,64,66} Comparing in-hospital costs from different healthcare systems in different timeframes is therefore problematic.

As in literature, the identified in-hospital costs increase with higher TBI severity.^{9,16,60,67} Costs increase because they primarily consist of costs related to LOS and surgical interventions and because the utilization of both is higher in more severely injured TBI patients.⁶⁸⁻⁷¹ After all, healthcare expenses are equal to utilization multiplied by associated prices.⁶² Also in other studies, physician charges are another important contributor to in-hospital costs.^{2,72} Length of stay results and its variability seemed to be in accordance with literature, but were difficult to compare due to this variation.^{68,69} Like in previous research, extracranial injuries and overall injury severity contributed to higher healthcare consumption and in-hospital costs.^{67,69,73-75} Distinguishing costs that are related to TBI or associated extracranial injuries is nearly impossible. Therefore, four studies explicitly investigated patients with isolated-TBI.^{44,51,53,56} Motor vehicle accidents and gunshot wounds were reported to be related to higher costs, most likely because of higher injury severity and accompanying extracranial injuries. Although a higher age is often considered to be more expensive, only few studies mentioned this and comparison between the age groups did not show obvious differences in LOS or in-hospital costs.^{15,63,67,73}

Hospital and acute care costs were reported to be important constituents of total costs followed by in-patient rehabilitation. However, the limitations of a short follow-up period have been recognized before.⁷ Although the in-hospital costs are obviously an important part, post-discharge rehabilitation and other long term care costs are also major contributors to the total costs after TBI.¹² When including the enormous long-term or lifetime costs and the loss of productivity, the share of in-hospital costs on the total burden significantly decreases.^{12,14,76} A long-term follow up period would provide a better overview for two reasons. First, the assessment of patient outcome will be more accurate, because health problems might persist, improve or deteriorate several years after trauma.^{77,78} Second, the cost analysis will be more comprehensive, since a changing health situation influences healthcare consumption and productivity for both patients and relatives. Therefore, especially for establishing the cost-effectiveness of treatments, a long-term follow-up should be included.

The identified most important reasons for (outcome) variation were probably all caused by different study objectives. Study objectives determined study methodology and consequently also the studied participants, interventions and outcome. Although most study objectives included costs research, the major differences between them likely caused the aforementioned methodological and clinical heterogeneity. Heterogeneity has earlier been reported for TBI cost studies and complicates study comparison and outcome interpretation.^{7,10,59,60} Heterogeneity is not limited to TBI

cost research, but is very common in general TBI research and likewise complicates comparability, generalizability and interpretation of other studies.⁷⁹⁻⁸²

Study quality also influenced interpretation of study results, since poor methodological quality compromises quality and therefore value of data. Two recent reviews specifically assessed the methodological quality of TBI cost evaluation studies and identified important limitations regarding the adherence to the methodological principles of economic evaluations.^{7,10} More specifically, these limitations include not reporting all relevant costs on a long-term or lifetime horizon, not discounting future costs, not performing incremental analysis of cost-effectiveness and applying sensitivity analysis. Our quality assessment found variable and overall inadequate study quality. Only few studies were considered high quality and especially items concerning the calculation and reporting of costs scored poorly. Cost results were often provided without relevant context. A description of costs analysis methods, required to understand and interpret the results, was frequently missing. Studies also rarely calculated in-hospital costs by transparently multiplying healthcare consumption with associated unit costs. Almost no study reported the highly informative and important disaggregated costs. Even reference years were missing in several studies. Because several studies did not focus on reporting costs after TBI, they might have scored low on our quality assessment, despite appropriately investigating their specific study objectives.

Strengths and limitations

This systematic review benefits from an extensive literature search in multiple databases and strict inclusion criteria, which improve study comparability and interpretation of results. The PRISMA guidelines were used during the review process and the quality assessment made use of a checklist that was based on the CHEERS statement and allowed the critical appraisal of the included articles. Although the assignment of scores is partly subjective, our experiences regarding the quality assessment using this checklist were positive. In addition, this is by our knowledge, the first detailed overview of in-hospital costs in patients with s-TBI.

This study also has several limitations. The article selection criteria resulted in the exclusion of some patients, that were severely injured but lacked the required severity classification. Also, regarding in-hospital costs, studies were excluded that not clearly distinguished acute care in-hospital costs from rehabilitation costs, indirect costs or other non in-hospital costs. Data from these patients could have contributed to our results, but the introduction of additional methodological and clinical heterogeneity

would have compromised comparability and interpretation of study results. In addition, the used TBI severity criteria have their limitations. The GCS has been criticized for its general applicability although it shows adequate reliability in a recent review.^{24,83} A patient can be scored 'false-low' due to intubation and sedation overestimating injury severity, while the severity of patients who quickly deteriorate after admission will be underestimated. Also, a decreased GCS is not always caused by TBI and could also be caused by extracranial injury alone.⁸⁴ Last, patients could be at the lower or the higher end of the spectrum within the GCS 3-8 group. This could have substantial impact on study results, because severity is related to costs. Regarding AIS, the classification system changed over time and the 2005 version codes similar injuries with a lower severity score compared to the 1998 version.⁸⁵ Also, some researchers suggest using AIS \geq 5 as severe, instead of AIS \geq 4.⁸⁶ Despite this, using both criteria is very relevant because they are the most widely used criteria for s-TBI.²⁴ Limiting the selection to patients with s-TBI improves comparability, but fails to assess the financial burden caused by minor and/or moderate TBI. Although individual costs are lower for these injuries, the total burden on society is much higher because of their more frequent occurrence.¹⁶ Although the distinction is clearly made throughout, including hospital charges and hospital costs may have compromised comparability of study results. Since both are frequently reported, it did however make a comprehensive review of in-hospital expenses possible and points out the difficulty of cost research. Last, the focus on in-hospital costs, dramatically underestimated the total financial burden caused by s-TBI.^{12,14,76}

Future research

Because a righteous and ethical distribution of limited healthcare resources is essential to secure the future existence of successful healthcare systems around the world, policymakers increasingly request high quality evidence regarding the cost effectiveness of treatments.³ To improve the future quality of TBI cost research, investigators should equalize methodological and clinical heterogeneity by using specific methodological guidelines and common data elements.^{27,87} As seen in this systematic review, one of the biggest challenges in TBI cost research is heterogeneity. Checklists could be helpful, but the development of international guidelines on economical evaluations for TBI patients is preferred. Patient outcome should be investigated along with the financial burden of treatments. Therefore, cost-effectiveness analysis should be included in upcoming trials investigating TBI treatment strategies. Patients from all ages should be investigated because all are confronted with the consequences of TBI. Because TBI related consequences and associated costs are variable over time, economic evaluations should include a long-term or even lifetime horizon.⁶ All associated costs

adding to the total burden on society, like indirect costs and loss of productivity, should be included to accurately map expenditures. Also, health and financial implications for family and proxies deserve investigation. Last, the use of accurate cost calculation methods using exact healthcare consumption and cost price data could further improve the accuracy of cost calculations and thus outcome results.^{88,89}

CONCLUSIONS

We conclude that healthcare consumption and in-hospital costs for patients with s-TBI are generally high. In-hospital costs mostly consist of costs related to LOS and surgical interventions. The major variation of study results is primarily caused by methodological and clinical heterogeneity. Study quality was variable but often inadequate and especially items considered important in calculation and reporting of in-hospital costs scored poorly. High quality future economic evaluations could guide physicians and policy-maker in improving clinical decision-making and resource allocation. Studies should therefore focus on the long-term cost-effectiveness of treatments and improve both study quality and equality by using guidelines and common data elements.

Supporting information available online.

S1 Appendix. Literature search strategy:

<https://doi.org/10.1371/journal.pone.0216743.s001> (DOCX)

S2 Appendix. Quality assessment information: <https://doi.org/10.1371/journal.pone.0216743.s002> (DOCX)

S1 Table. PRISMA 2009 checklist:

<https://doi.org/10.1371/journal.pone.0216743.s003> (DOC)

S2 Table. Results of the quality assessment:

<https://doi.org/10.1371/journal.pone.0216743.s004> (DOCX)

REFERENCES

1. Xu K, Soucat A, Kutzin J, et al. New perspectives on global health spending for universal health coverage Geneva: World Health Organization 2018; (WHO/HIS/HGF/HFWorkingPaper/18.2) Licence: CC BY-NC-SA 3.0 IGO: 1-44.
2. Papanicolas I, Woskie LR, Jha AK. Health care spending in the United States and other high-income countries. *Jama* 2018; 319(10): 1024-39.
3. Health. DMO. Kamerbrief over beeindiging 'sluis' nivolumab per 1 maart 2016. 2016. <https://www.rijksoverheid.nl/documenten/kamerstukken/2016/01/28/kamerbrief-over-beeindiging-sluis-nivolumab-per-1-maart-2016> (accessed 22 June 2018).
4. Porter M, Lee T. The strategy that will fix health care. *Harv Bus Rev* 2013; 91(10).
5. Porter ME. A strategy for health care reform-toward a value-based system. *N Engl J Med* 2009; 361(2): 109-12.
6. Maas AIR, Menon DK, Adelson PD, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. *The Lancet Neurology* 2017; 16(12): 987-1048.
7. Alali AS, Burton K, Fowler RA, et al. Economic evaluations in the diagnosis and management of traumatic brain injury: a systematic review and analysis of quality. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2015; 18(5): 721-34.
8. Alali AS, Naimark DM, Wilson JR, et al. Economic evaluation of decompressive craniectomy versus barbiturate coma for refractory intracranial hypertension following traumatic brain injury. *Crit Care Med* 2014; 42(10): 2235-43.
9. Ho KM, Honeybul S, Lind CRP, Gillett GR, Litton E. Cost-effectiveness of decompressive craniectomy as a lifesaving rescue procedure for patients with severe traumatic brain injury. *The Journal of trauma* 2011; 71(6): 1637-44.
10. Lu J, Roe C, Aas E, et al. Traumatic brain injury: methodological approaches to estimate health and economic outcomes. *Journal of neurotrauma* 2013; 30(23): 1925-33.
11. Faul M, Xu L, Wald M, Coronado V. Traumatic brain injury in the United States: emergency department visits, hospitalizations and deaths, 2002-2006. *Atlanta (GA): Centers for Disease Control and Prevention, National Center for Injury Prevention and Control* 2010: 1-74.
12. Scholten AC, Haagsma JA, Panneman MJ, van Beeck EF, Polinder S. Traumatic brain injury in the Netherlands: incidence, costs and disability-adjusted life years. *PLoS One* 2014; 9(10): e110905.
13. Garcia-Altes A, Perez K, Novoa A, et al. Spinal cord injury and traumatic brain injury: a cost-of-illness study. *Neuroepidemiology* 2012; 39(2): 103-8.
14. Tuominen R, Joellsson P, Tenovu O. Treatment costs and productivity losses caused by traumatic brain injuries. *Brain Inj* 2012; 26(13-14): 1697-701.
15. Marin JR, Weaver MD, Mannix RC. Burden of USA hospital charges for traumatic brain injury. *Brain Inj* 2017; 31(1): 24-31.
16. Te Ao B, Brown P, Tobias M, et al. Cost of traumatic brain injury in New Zealand: evidence from a population-based study. *Neurology* 2014; 83(18): 1645-52.
17. Carroll LJ, Cassidy JD, Cancelliere C, et al. Systematic review of the prognosis after mild traumatic brain injury in adults: cognitive, psychiatric, and mortality outcomes: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. *Arch Phys Med Rehabil* 2014; 95(3 Suppl): S152-73.
18. Stein SC, Georgoff P, Meghan S, Mizra K, Sonnad SS. 150 years of treating severe traumatic brain injury: a systematic review of progress in mortality. *Journal of neurotrauma* 2010; 27(7): 1343-53.
19. Beck B, Gantner D, Cameron PA, et al. Temporal trends in functional outcomes after severe traumatic brain injury: 2006-2015. *Journal of neurotrauma* 2018; 35(8): 1021-9.
20. Honeybul S, Janzen C, Kruger K, Ho KM. Decompressive craniectomy for severe traumatic brain injury: is life worth living? *Journal of neurosurgery* 2013; 119(6): 1566-75.
21. Fountain DM, Kolias AG, Lecky FE, et al. Survival trends after surgery for acute subdural hematoma in adults over a 20-year period. *Annals of surgery* 2017; 265(3): 590-6.
22. Chieragato A, Venditto A, Russo E, Martino C, Bini G. Aggressive medical management of acute traumatic subdural hematomas before emergency craniotomy in patients presenting with bilateral unreactive pupils. A cohort study. *Acta neurochirurgica* 2017; 159(8): 1553-9.

23. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals of internal medicine* 2009; 151(4): 264-9.
24. Brazinova A, Rehorcikova V, Taylor MS, et al. Epidemiology of traumatic brain injury in Europe: a living systematic review. *Journal of neurotrauma* 2016; <http://doi.org/10.1089/neu.2015.4126>.
25. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet (London, England)* 1974; 2(7872): 81-4.
26. Gennarelli TA, Wodzin E. AIS 2005: A contemporary injury scale. *Injury* 2006; 37(12): 1083-91.
27. Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS) statement. *BMJ* 2013; 346:f1049.
28. Drummond M, Sculpher M, Torrance G, O'Brien B, Stoddart G, Buskens E. Methods for the economic evaluation of health care programmes. 3rd edition. *Oxford: Oxford University Press* 2005.
29. Costa N, Derumeaux H, Rapp T, et al. Methodological considerations in cost of illness studies on Alzheimer disease. *Health Econ Rev* 2012; 2(1): 18.
30. Molinier L, Bauvin E, Combescurre C, et al. Methodological considerations in cost of prostate cancer studies: a systematic review. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2008; 11(5): 878-985.
31. Bank TW. <https://data.worldbank.org/indicator/NY.GDPPCAPCD?end=2015&start=1960>.
32. Campbell and cochrane economics methods group and the evidence for policy and practice information and coordinating centre. CCEMG – EPPI-centre cost converter (v.1.5). <http://eppi.ioe.ac.uk/costconversion> 04 June 2018).
33. Shemilt I, Thomas J, Morciano M. A web-based tool for adjusting costs to a specific target currency and price year. *Evidence and Policy* 2010; 6(1): 51-9.
34. Jaffe KM, Massagli TL, Martin KM, Rivara JB, Fay GC, Polissar NL. Pediatric traumatic brain injury: acute and rehabilitation costs. *Arch Phys Med Rehabil* 1993; 74(7): 681-6.
35. Li Y, Zhou J, Chen F, Zhang J, Qiu J, Gu J. Epidemiology of traumatic brain injury older inpatients in Chinese military hospitals, 2001-2007. *J Clin Neurosci* 2017; 44: 107-13.
36. Graves JM, Kannan N, Mink RB, et al. Guideline adherence and hospital costs in pediatric severe traumatic brain injury. *Pediatr Crit Care Med* 2016; 17(5): 438-43.
37. White JR, Farukhi Z, Bull C, et al. Predictors of outcome in severely head-injured children. *Crit Care Med* 2001; 29(3): 534-40.
38. Zapata-Vazquez RE, Alvarez-Cervera FJ, Alonzo-Vazquez FM, et al. Cost Effectiveness of Intracranial Pressure Monitoring in Pediatric Patients with Severe Traumatic Brain Injury: A Simulation Modeling Approach. *Value Health Reg Issues* 2017; 14: 96-102.
39. Albrecht JS, Slejko JF, Stein DM, Smith GS. Treatment charges for traumatic brain injury among older adults at a trauma center. *J Head Trauma Rehabil* 2017; 32(6): E45-E53.
40. Ahmed N, Kuo YH. Early versus late tracheostomy in patients with severe traumatic head injury. *Surg Infect (Larchmt)* 2007; 8(3): 343-7.
41. Brooks CA, Lindstrom J, Mccray J, Whiteneck GG. Cost of medical-care for a population-based sample of persons surviving traumatic brain injury. *J Head Trauma Rehabil* 1995; 10(4): 1-13.
42. Bryant E, Sundance P, Hobbs A, Jenkins J, Rozance J. Managing costs and outcome of patients with traumatic brain injury in an HMO setting. *J Head Trauma Rehabil* 1993; 8(4): 15-29.
43. Fakhry SM, Trask AL, Waller MA, Watts DD, Force INT. Management of brain-injured patients by an evidence-based medicine protocol improves outcomes and decreases hospital charges. *J Trauma* 2004; 56(3): 492-9.
44. Farhad K, Khan HMR, Ji AB, Yacoub HA, Qureshi AI, Souayah N. Trends in outcomes and hospitalization costs for traumatic brain injury in adult patients in the United States. *Journal of neurotrauma* 2013; 30(2): 84-90.
45. Martini RP, Deem S, Yanez ND, et al. Management guided by brain tissue oxygen monitoring and outcome following severe traumatic brain injury. *Journal of neurosurgery* 2009; 111(4): 644-9.
46. McGarry LJ, Thompson D, Millham FH, et al. Outcomes and costs of acute treatment of traumatic brain injury. *The Journal of trauma* 2002; 53(6): 1152-9.
47. Morris S, Ridley S, Lecky FE, Munro V, Christensen MC. Determinants of hospital costs associated with traumatic brain injury in England and Wales. *Anaesthesia* 2008; 63(5): 499-508.
48. Prang KH, Ruseckaite R, Collie A. Healthcare and disability service utilization in the 5-year period following transport-related traumatic brain injury. *Brain Inj* 2012; 26(13-14): 1611-20.

49. Schootman M, Buchman TG, Lewis LM. National estimates of hospitalization charges for the acute care of traumatic brain injuries. *Brain Inj* 2003; 17(11): 983-90.
50. You X, Liew BS, Rosman AK, Dcsn, Musa KI, Idris Z. The estimated cost of surgically managed isolated traumatic head injury secondary to road traffic accidents. *Neurosurgical focus* 2018; 44(5): E7.
51. Ibrahim MI, Abdullah M, Naing L, Abdullah JM, Idris Z, Aljunid SM. Cost effectiveness analysis of using multiple neuromodalities in treating severe traumatic brain injury in a developing country like Malaysia. *Asian J Surg* 2007; 30(4): 261-6.
52. Salim A, Martin M, Brown C, et al. The presence of the adult respiratory distress syndrome does not worsen mortality or discharge disability in blunt trauma patients with severe traumatic brain injury. *Injury* 2008; 39(1): 30-5.
53. Yuan Q, Liu H, Wu X, et al. Characteristics of acute treatment costs of traumatic brain injury in Eastern China-a multi-centre prospective observational study. *Injury* 2012; 43(12): 2094-9.
54. Lehmkuhl DL, Hall K, Mann N, Gordon W. Factors that influence costs and length of stay of persons with traumatic brain injury in acute care and inpatient rehabilitation. *J Head Trauma Rehabil* 1993; 8(2): 88-100.
55. Palmer S, Bader M, Qureshi A, et al. The impact on outcomes in a community hospital setting of using the AANS traumatic brain injury guidelines. Americans Associations for Neurologic Surgeons. *The Journal of trauma* 2001; 50(4): 657-64.
56. Siddiqui UT, Tahir MZ, Shamim MS, Enam SA. Clinical outcome and cost effectiveness of early tracheostomy in isolated severe head injury patients. *Surg Neurol Int* 2015; 6: 65.
57. Andelic N, Ye J, Tornas S, et al. Cost-effectiveness analysis of an early-initiated, continuous chain of rehabilitation after severe traumatic brain injury. *Journal of neurotrauma* 2014; 31(14): 1313-20.
58. Whitmore R, Thawani J, Grady M, Levine J, Sanborn M, Stein S. Is aggressive treatment of traumatic brain injury cost-effective? *Journal of neurosurgery* 2012; 116(5): 1106-13.
59. Humphreys I, Wood RL, Phillips CJ, Macey S. The costs of traumatic brain injury: a literature review. *ClinicoEconomics and outcomes research : CEOR* 2013; 5: 281-7.
60. Dismuke CE, Walker RJ, Egede LE. Utilization and cost of health services in individuals with traumatic brain injury. *Glob J Health Sci* 2015; 7(6): 156-69.
61. Finkler SA. The distinction between cost and charges. *Annals of internal medicine* 1982; 96(1): 102-9.
62. Institute HCC. 2016 health care cost and utilization report. 2017. <http://www.healthcostinstitute.org/report/2016-health-care-cost-utilization-report/> (accessed 04 June 2018).
63. Polinder S, Meerding WJ, van Baar ME, et al. Cost estimation of injury-related hospital admissions in 10 European countries. *The Journal of trauma* 2005; 59(6): 1283-90; discussion 90-1.
64. Dieleman J, Campbell M, Chapin A, et al. Evolution and patterns of global health financing 1995-2014: development assistance for health, and government, prepaid private, and out-of-pocket health spending in 184 countries. *Lancet (London, England)* 2017; 389(10083): 1981-2004.
65. Georgoff P, Meghan S, Mirza K, Stein SC. Geographic variation in outcomes from severe traumatic brain injury. *World Neurosurg* 2010; 74(2-3): 331-45.
66. Maas AI, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. *The Lancet Neurology* 2008; 7(8): 728-41.
67. Ponsford JL, Spitz G, Cromarty F, Gifford D, Attwood D. Costs of care after traumatic brain injury. *Journal of neurotrauma* 2013; 30(17): 1498-505.
68. Moore L, Stelfox HT, Evans D, et al. Hospital and intensive care unit length of stay for injury admissions: a pan-Canadian cohort study. *Annals of surgery* 2018; 267(1): 177-82.
69. Tardif PA, Moore L, Boutin A, et al. Hospital length of stay following admission for traumatic brain injury in a Canadian integrated trauma system: A retrospective multicenter cohort study. *Injury* 2017; 48(1): 94-100.
70. Su SH, Wang F, Hai J, et al. The effects of intracranial pressure monitoring in patients with traumatic brain injury. *PLoS One* 2014; 9(2): e87432.
71. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the management of severe traumatic brain injury, fourth edition. *Neurosurgery* 2017; 80(1): 6-15.
72. Chen A, Bushmeneva K, Zagorski B, Colantonio A, Parsons D, Wodchis WP. Direct cost associated with acquired brain injury in Ontario. *BMC Neurol* 2012; 12: 76.
73. Spitz G, McKenzie D, Attwood D, Ponsford JL. Cost prediction following traumatic brain injury: model development and validation. *J Neurol Neurosurg Psychiatry* 2016; 87(2): 173-80.

74. Leitgeb J, Mauritz W, Brazinova A, Majdan M, Wilbacher I. Impact of concomitant injuries on outcomes after traumatic brain injury. *Arch Orthop Trauma Surg* 2013; 133(5): 659-68.
75. Davis KL, Joshi AV, Tortella BJ, Candrilli SD. The direct economic burden of blunt and penetrating trauma in a managed care population. *The Journal of trauma* 2007; 62(3): 622-9.
76. Majdan M, Plancikova D, Maas A, et al. Years of life lost due to traumatic brain injury in Europe: A cross-sectional analysis of 16 countries. *PLoS medicine* 2017; 14(7): e1002331.
77. Stocchetti N, Zanier ER. Chronic impact of traumatic brain injury on outcome and quality of life: a narrative review. *Critical care (London, England)* 2016; 20(1): 148.
78. McMillan TM, Teasdale GM, Stewart E. Disability in young people and adults after head injury: 12-14 year follow-up of a prospective cohort. *Journal of neurology, neurosurgery, and psychiatry* 2012; 83(11): 1086-91.
79. Cnossen MC, Huijben JA, van der Jagt M, et al. Variation in monitoring and treatment policies for intracranial hypertension in traumatic brain injury: a survey in 66 neurotrauma centers participating in the CENTER-TBI study. *Critical care (London, England)* 2017; 21(1): 233.
80. Cnossen MC, Polinder S, Andriessen TM, et al. Causes and consequences of treatment variation in moderate and severe traumatic brain injury: a multicenter study. *Crit Care Med* 2017; 45(4): 660-9.
81. van Essen TA, de Ruiter GC, Kho KH, Peul WC. Neurosurgical Treatment Variation of Traumatic Brain Injury: Evaluation of Acute Subdural Hematoma Management in Belgium and The Netherlands. *Journal of neurotrauma* 2017; 34(4): 881-9.
82. Greene NH, Kernic MA, Vavilala MS, Rivara FP. Variation in adult traumatic brain injury outcomes in the United States. *J Head Trauma Rehabil* 2018; 33(1): E1-E8.
83. Reith FC, Van den Brande R, Synnot A, Gruen R, Maas AI. The reliability of the Glasgow Coma Scale: a systematic review. *Intensive care medicine* 2016; 42(1): 3-15.
84. Becker A, Peleg K, Olsha O, Givon A, Kessel B, Israeli Trauma G. Analysis of incidence of traumatic brain injury in blunt trauma patients with Glasgow Coma Scale of 12 or less. *Chinese journal of traumatology = Zhonghua chuang shang za zhi* 2018; 21(3): 152-5.
85. Carroll CP, Cochran JA, Price JP, Guse CE, Wang MC. The AIS-2005 revision in severe traumatic brain injury: mission accomplished or problems for future research? *Ann Adv Automot Med* 2010; 54: 233-8.
86. Savitsky B, Givon A, Rozenfeld M, Radomislensky I, Peleg K. Traumatic brain injury: It is all about definition. *Brain Inj* 2016; 30(10): 1194-200.
87. Maas AI, Harrison-Felix CL, Menon D, et al. Common data elements for traumatic brain injury: recommendations from the interagency working group on demographics and clinical assessment. *Arch Phys Med Rehabil* 2010; 91(11): 1641-9.
88. Hakkaart-van Roijen L, van der Linden N, Bouwmans C, Kanters T, Tan S. Kostenhandleiding: methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. *Zorginstituut Nederland* 2015; (<https://www.zorginstituutnederland.nl/binaries/zinl/documenten/publicatie/2016/02/29/richtlijn-voor-het-uitvoeren-van-economische-evaluaties-in-de-gezondheidszorg/Richtlijn+voor+het+uitvoeren+van+economische+evaluaties+in+de+gezondheidszorg+%28verdiepingsmodules%29.pdf> (accessed 30-03-2018)): 1-120 (accessed on 30-03-2018).
89. Kaplan RS, Porter ME. How to solve the cost crisis in health care. *Harv Bus Rev* 2011; 89(9): 46-52, 4, 6-61.



CHAPTER 4

Functional and patient-reported outcome versus in-hospital costs after traumatic acute subdural hematoma: a neurosurgical paradox?

Authors:

Jeroen T.J.M. van Dijck MD¹,
Thomas A. van Essen MD¹,
Mark D. Dijkman MD¹,
Cassidy Q.B. Mostert BSc¹,
Suzanne Polinder PhD²,
Wilco C. Peul MD PhD MBA¹,
Godard C.W. de Ruiter MD PhD¹

Affiliations:

1. Department of Neurosurgery, University Neurosurgical Center Holland, LUMC, HMC & Haga Teaching Hospital, Leiden/The Hague, The Netherlands
2. Department of Public Health, Erasmus Medical Center, The Netherlands

Citation:

van Dijck JTJM, van Essen TA, Dijkman MD, et al. Functional and patient-reported outcome versus in-hospital costs after traumatic acute subdural hematoma (t-ASDH): a neurosurgical paradox?. *Acta Neurochir (Wien)*. 2019;161(5):875-884. doi:10.1007/s00701-019-03878-5

ABSTRACT

Background: The decision whether to operate or not in patients with a traumatic acute subdural hematoma (t-ASDH) can in many cases be a neurosurgical dilemma. There is a general conception that operating on severe cases leads to the survival of severely disabled patients and is associated with relatively high medical costs. There is however little information on the quality of life of patients after operation for t-ASDH, let alone on the cost-effectiveness.

Methods: This study retrospectively investigated patient outcome and in-hospital costs for 108 consecutive patients with a t-ASDH. Patient outcome was assessed using the Glasgow Outcome Score (GOS) and the Traumatic Brain Injury (TBI) -specific QOLIBRI questionnaire. The in-hospital costs were calculated using the Dutch guidelines for costs calculation.

Results: Out of 108 patients, 40 were classified as having sustained a mild (Glasgow Coma Scale (GCS) 13-15), 19 a moderate (GCS 9-12), and 49 a severe (GCS 3-8) TBI. As expected, mortality rates increased with higher TBI severity (23%, 47% and 61% respectively), whereas the chance for favourable outcome (GOS 4-5) decreased (72%, 47% and 29%). Interestingly, the mean QOLIBRI scores for survivors were quite similar between the TBI severity groups (61, 61 and 64). Healthcare consumption and in-hospital costs increased with TBI severity. In-hospital costs were relatively high (€24,980), especially after emergency surgery (€28,670) and when additional ICP monitoring was used (€36,580).

Conclusions: Although this study confirms that outcome is often “unfavourable” after t-ASDH, it also shows that “favourable” outcome can be achieved, even in the most severely injured patients. In-hospital treatment costs were substantial and mainly related to TBI severity, with admission and surgery as main cost drivers. These results serve as a basis for necessary future research focusing on the value-based cost-effectiveness of surgical treatment of patients with a t-ASDH.

Keywords: Acute subdural hematoma; traumatic brain injury; treatment; patient outcome; healthcare costs

INTRODUCTION

Traumatic brain injury (TBI) is accompanied by an acute subdural hematoma (t-ASDH) in around 10-20% of admitted TBI patients.¹ Despite neurosurgical treatment, the mortality rate is high (40-60%) and outcome often unfavourable (up to 70%).¹⁻⁴ This frequently poses an ethical dilemma for neurosurgeons, especially in the more severe cases. Neurosurgical evacuation of the hematoma, sometimes with additional decompressive craniectomy (DC), can save patients' lives by decreasing intracranial pressure and preventing secondary edema, ischaemia and inflammatory cell death, but at the same time, it may result in the survival of severely disabled patients.^{5,6} Alternatively, early treatment limiting decisions (TLD) reduce any chance of recovery and normally result in death.^{7,8} To assist physicians in these difficult life-or-death decisions, experts in the field have provided statements and guidelines on the preferred treatment strategies in these patients.^{1,9} However, the overall adherence to these guidelines is low, probably because the general conception is that outcome for these patients is rather "unfavourable".¹⁰⁻¹²

Unfortunately, in the literature there is little information on the health-related quality of life (HRQoL) after surgical treatment of patients with a t-ASDH. Until recently researchers used functional indicators like the Glasgow Outcome Scale (GOS) or generic HRQoL instruments because a TBI-specific HRQoL instrument was not available.^{13,14} These methods however lacked the perspective of subjective well-being and were considered to be less sensitive.¹⁵ To overcome these limitations, the Quality Of Life after Brain Injury questionnaire (QOLIBRI) was developed.¹⁵ This TBI-specific HRQoL measure covers six dimensions typically affected after TBI and provides more precise information on quality of life.¹⁵ It has been validated in multiple study settings, but has not been used frequently to measure outcome after t-ASDH in clinical studies.¹⁶ Therefore, the TBI-specific HRQoL was investigated in addition to functional outcome (GOS) after the surgical treatment of patients with a t-ASDH.

Furthermore, we analyzed the in-hospital costs associated with both conservative and different surgical treatments in patients with a diagnosed t-ASDH. Costs for the treatment of TBI are high and annually increasing. In the US for example the national hospital costs for all subdural hematomas were estimated to be \$US1.6 billion in 2007, a 60% increase compared to 1998.¹⁷ There is an increasing pressure from governments, insurance companies and healthcare providers to control healthcare costs.¹⁸ The demand for high quality evidence regarding the cost-effectiveness of treatments is

also seen in TBI, where it lacks and where expensive life-saving surgical treatments can also result in a poor HRQoL.^{19,20}

Because patient outcome and in-hospital costs of patients with a t-ASDH are of great individual and societal importance, the aim of this study is threefold: (1) assess functional outcome and TBI-specific HRQoL, (2) calculate the in-hospital costs and (3) serve as a basis for future research that focusses on the cost-effectiveness of surgical treatment of patients with t-ASDH.

METHODS AND MATERIALS

Study setting

This retrospective cohort study was conducted at the neurosurgical departments of two collaborating level I trauma centres in The Netherlands (Leiden University Medical Center, Leiden and Haaglanden Medical Center, The Hague). The study reports in-hospital costs and long term HRQoL follow-up data of patients that are part of a cohort partly used in a separate study by the same investigators.²¹ The research ethics committees of South-West Holland and Leiden University Medical Center provided ethical approval (study number P12.196).

Patients

All consecutive patients with TBI (2008-2012) treated by the department of neurosurgery were identified by screening the hospital registration system. In addition, the national trauma registry was checked for potential missed inclusions. Inclusion criteria were (1) closed head injury due to a traumatic event (2) direct presentation to the emergency department of a referring or study hospital following trauma (3) a hyperdense, crescent shaped lesion on CT, indicative of an ASDH and (4) age ≥ 16 years. To pursue a homogenous patient cohort, patients were excluded in case of non-survivable extracranial injuries, a non-traumatic ASDH, when the ASDH was accompanied by concomitant intracranial lesions (i.e. intracerebral hematoma or epidural hematoma) requiring immediate surgical management and when the ASDH was secondary to an earlier procedure or penetrating brain injury. Eligibility for the QOLIBRI questionnaire was assessed based on exclusion criteria: $GOS \leq 3$, inability to provide informed consent and inability to understand, cooperate and answer QOLIBRI questions. TBI severity was defined according to the commonly used Glasgow Coma

Score scale (GCS) categories (GCS 13-15: mild, GCS 9-12: moderate, GCS 3-8: severe).²² In addition, a subgroup of patients with a very severe TBI (vs-TBI), represented by a GCS of 3-5, was analysed. The first GCS score documented at the emergency room (ER) was used and in case of intubation and/or sedation, the last score before intubation and/or sedation was used.

Clinical & follow-up data

Data was collected independently by two authors in a predefined database using electronic or paper patient records. It encompassed demographics, patient and trauma specific information and pre and in-hospital parameters including medical/surgical interventions and length of stay. Non-ICU admission included admission on the ward and medium care. Focal neurologic symptoms included paresis, aphasia or cranial nerve deficit. Pupils were defined abnormal when at least one pupil was unresponsive to light upon arrival in the emergency room. CT characteristics were assessed from the first CT-scan. Outcome data included in-hospital mortality and Glasgow Outcome Score (GOS) dichotomized in favourable (GOS 4-5) and unfavourable (GOS 1-3) outcome obtained from discharge or outpatient clinic letters 3-9 months after trauma.¹⁴ To determine the TBI-specific HRQoL, we used the postal Quality of Life after Brain Injury (QOLIBRI) questionnaire. After receiving ethical approval to approach patients, we obtained informed consent and asked patients to complete and return the questionnaire two to six years after trauma. Mortality at this time-point was also noted. The QOLIBRI is a comprehensive 37-item questionnaire investigating six dimensions that are typically affected after TBI.¹⁵ Patients rate their (dis)satisfaction (1-5 scale) on six subscales representing the dimensions: cognition, self, daily life & autonomy, social relationships, emotions and physical problems. Scores are transformed to total scores ranging from 0 (worst possible quality of life) to 100 (best possible quality of life).¹⁵ A score lower than 60 is believed to represent a low or impaired HRQoL.²³ In case patients did not return the questionnaire, the investigators attempted a telephone interview, or family members were asked to assist in completing the forms. In addition, the reason for not returning (e.g. death, persistent unresponsive state etc.) the questionnaire was collected at this time point.

Cost data

Cost data analysis was performed from a health care provider perspective and focussed on in-hospital healthcare costs. The Dutch National Health Care Institute guidelines for healthcare cost calculation were followed.²⁴

First, data on health care consumption were collected from electronic patient records and recorded in a predefined cost assessment database. Units were counted in five main categories: (1) admission; including length of stay (LOS) in (non-)ICU with consultations, (2) surgical interventions, (3) imaging, (4) laboratory; including blood products and (5) other; including transportation and outpatient visits. Since this study focused on in-hospital acute healthcare costs, only post-discharge costs associated with re-admissions and outpatient clinic visits related to the initial trauma were included.

Second, as hospital specific costs prices were not available for external research purposes, units were valued by using external sources in accordance with the guidelines.²⁴ Some units were valued using the reference prices from the guideline, being cost prices based on large patient cohorts.²⁴ The use of these prices is recommended for costs research and preferred for cost outcome interpretation and generalization, because prices are non-site-specific.^{24,25} Units that were not available in the guidelines were valued using the maximum amount per unit that healthcare providers are allowed to charge according to the -The Netherlands Healthcare Authority (NZA)-, an autonomous administrative authority falling under the Dutch Ministry of Health, Welfare and Sport.²⁶ The remaining units were valued by using their average national price, based on declared fees including hospital costs and physicians' fees.²⁷ A detailed overview of all used unit costs and corresponding sources can be found in supplement 1.

Third, we corrected all unit costs expressed in different base years to 2012 EURO using the national general consumer price index (CBS). This year was chosen because it was the last year of patient inclusion. And finally, to calculate in-hospital costs, all counted units were multiplied with its corresponding price and rounded to the nearest ten euros. No discounting of costs was deemed necessary. In January 2012, one euro equalled \$1.28 dollar.

Statistical analysis

Baseline data were presented as absolute numbers and percentages. Continuous variables, like costs and LOS, were presented as mean \pm standard deviation, unless stated otherwise. Subgroups were made based on age, TBI severity, pupillary abnormalities, surgical intervention and outcome. Comparison between groups was done by using an independent t-test. A p-value of <0.05 was considered statistically significant. All analyses were performed using IBM's statistical package for social sciences version 23 (SPSS). Figures were designed with GraphPad Prism version 7.02.

RESULTS

Out of 294 initially identified TBI patients, 140 patients did not have a t-ASDH, 6 had penetrating injuries, 9 required surgery for concomitant intracranial lesions and 31 patients were excluded following the other exclusion criteria. Ultimately, 108 patients were included in this study. The final study cohort included 57 males (52.8%) and had a mean age of 65 years (range 18–91) (Table 1). Most ASDH patients (N=49) sustained a severe TBI (s-TBI) followed by mild (N=40) and moderate TBI (N=19). Of patients with s-TBI, 22 were classified as having sustained a vs-TBI. A quarter of all patients had at least 1 non-reactive pupil (N=27) and 38.9% had focal neurologic symptoms. A concomitant intracranial hematoma that not required surgical intervention was present in 44.4% of patients and 11.1% had clinically relevant extracranial injuries. Neurosurgical intervention was performed in 90 patients (60 craniotomies, 29 decompressive craniectomies and 1 burr hole) and an ICP monitoring device was placed in 40 patients. Most of the conservatively treated patients (N=18) were classified as mild TBI (83%).

Table 1. Patient cohort information

| | | | |
|---------------------------|------------|-----------------------------|-------------|
| Number of patients | 108 | Number of patients | 108 |
| Age (years) | 65 ± 17.3 | Age (years) | 65 ± 17.3 |
| Male | 57 (52.8) | Male | 57 (52.8) |
| Trauma mechanism | | Treatment | |
| Fall | 58 (53.7) | Conservative | 18 (16.7) |
| Assault | 5 (4.6) | Emergent surgical | 90 (83.3) |
| Motor vehicle accident | 12 (11.1) | intervention: | |
| Fall from bike | 12 (11.1) | - Craniotomy | - 60 (55.6) |
| Other | 21 (19.4) | - Decompressive craniectomy | - 29 (26.9) |
| TBI severity | | (DC) | |
| Very severe (GCS3–5) | 22 (20.4) | - ICP monitoring | - 40 (37.0) |
| Severe (GCS3–8) | 49 (45.4) | In-hospital mortality | 41 (37.9) |
| Moderate (GCS9–12) | 19 (17.6) | Functional outcome | |
| Mild (GCS13–15) | 40 (37.0) | GOS1–3 (unfavourable) | 56 (51.9) |
| Clinical parameters | | GOS4–5 (favourable) | 50 (46.3) |
| GCS score | 9.63 ± 4.3 | Missing GOS | 2 (1.9) |
| Pupil abnormality * | 27 (26.7) | QOLIBRI response | |
| Focal Neurologic symptoms | 42 (38.9) | FU time, months | 46 ± 16 |
| Major extracranial injury | 12 (11.1) | Yes | 25 (23.1) |
| CT parameters | | No (died; too disabled) | 53 (48.5) |
| Thickness (mm) | 13.6 ± 6.1 | No, other | 30 (27.8) |
| Midline shift (mm) | 11.4 ± 6.6 | | |
| Concomitant lesion | 48 (44.4) | | |
| Basal cisterns compressed | 39 (36.1) | | |

Table 1 provides general information about the patient cohort.

Legend:

N (%) or mean ± SD, unless stated otherwise

*At least one pupil unresponsive to light upon arrival in the emergency room (missing for 7 patients)

Abbreviations:

SD, standard deviation; GCS, Glasgow Coma Score; CT, computed tomography; DC, decompressive craniectomy; ICP, intracranial pressure; GOS, Glasgow outcome score; QOLIBRI, quality of life after brain injury; FU: Follow-up

Patient outcome

In-hospital mortality was 38% and mortality increased to 44% during follow up (mean 37 ± 17 months). Mortality ranged from 23% for initial mild-TBI to 64% for patients with vs-TBI (Table 2). Favourable outcome (GOS 4-5) was seen in 46% of all patients, 72% of patients with mild-TBI and in 23% of patients with vs-TBI (Figure 1). High rates of unfavourable outcome (GOS 1-3) were seen in patients with a GCS of 3 (90%), ICP monitoring (75%), decompressive craniectomy (72%), pupillary abnormalities (70%) and age < 65 (63%).

Twenty-five patients (42% of survivors) returned a completed QOLIBRI questionnaire. Return percentages were lower for patients with higher initial severity scores (9% for vs-TBI and 35% for mild TBI) and lower for patients with worse functional outcome (4% for GOS 1-3 vs. 46% for GOS 4-5). Mean QOLIBRI scores however were rather similar between TBI severity groups (61 ± 25 for s-TBI and 64 ± 24 for mild TBI). Patients with post-trauma pupillary abnormalities (49.8), ICP monitoring (55.1) and patients with unfavourable outcome (GOS 1-3) (50.5) showed mean QOLIBRI scores suggesting an impaired HRQoL. Patients receiving a craniotomy showed better scores (68.4) than patients receiving a decompressive craniectomy (53.2).

Healthcare consumption

Patients with vs-TBI had a significant longer ICU LOS than patients with mild TBI (6 vs. 2 days, $P < 0.001$). (Table 3). Mean LOS for non-ICU admissions was longest for patients with moderate TBI (16 days), followed by 12 and 9 days for patients with vs-TBI and mild TBI. All vs-TBI and 98% of s-TBI patients received cranial surgery, compared to 89.5% of moderate and 62.5% of mild TBI patients. ICP monitoring was most frequently used in patients with vs-TBI and s-TBI (63.6% and 57.1%), but also in 12.5% of patients with mild TBI. ICP monitoring was associated with significant longer ICU and non-ICU LOS compared to non ICP-monitoring.

Table 2. Patient outcome

| Patient category | N | N (%) death [^] | N (%) GOS1-3 | N (%) returned QOLIBRI [#] | QOLIBRI score | QOLIBRI follow up (months) |
|-------------------------------|-----|--------------------------|--------------|-------------------------------------|---------------|----------------------------|
| All patients | 108 | 48 (44) | 56 (53) | 25 (23) | 62.8 ± 23.5 | 37 ± 17 |
| Age ≥65 | 65 | 21 (32) | 29 (45) | 16 (25) | 66.8 ± 22.1 | 38 ± 18 |
| Age <65 | 43 | 19 (44) | 27 (63) | 9 (21) | 55.7 ± 25.6 | 35 ± 16 |
| GCS 3 | 10 | 7 (70) | 9 (90) | 0 | N/A | N/A |
| GCS 3–5 | 22 | 14 (64) | 17 (77) | 2 (9) | 66.0 ± 7.07 | 13 ± 2 |
| GCS 3–8 | 49 | 30 (61) | 35 (71) | 7 (14) | 61.4 ± 24.8 | 34 ± 19 |
| GCS 9–12 | 19 | 9 (47) | 10 (53) | 4 (21) | 61.0 ± 25.5 | 50 ± 21 |
| GCS 13–15 | 40 | 9 (23) | 11 (28) | 14 (35) | 64.0 ± 24.1 | 35 ± 14 |
| Pupillary abnormality | 27 | 15 (56) | 19 (70) | 5 (19) | 49.8 ± 19.4 | 47 ± 23 |
| No abnormalities [*] | 74 | 29 (39) | 32 (43) | 18 (24) | 64.5 ± 24.6 | 32 ± 13 |
| Emergency surgery | | | | | | |
| No | 18 | 3 (17) | 3 (17) | 4 (22) | 56.3 ± 28.6 | 33 ± 15 |
| Craniotomy | 60 | 26 (43) | 32 (53) | 15 (25) | 68.4 ± 21.0 | 36 ± 17 |
| Decompressive craniectomy | 29 | 18 (62) | 21 (72) | 6 (21) | 53.2 ± 26.3 | 42 ± 21 |
| ICP monitoring | 40 | 20 (50) | 30 (75) | 9 (23) | 55.1 ± 20.4 | 36 ± 24 |
| No ICP monitoring | 68 | 28 (41) | 26 (38) | 16 (24) | 67.1 ± 24.7 | 37 ± 13 |
| Outcome (GOS) | | | | | | |
| Favourable | 50 | 4 (8) | N/A | 23 (46) | 63.9 ± 23.3 | 37 ± 17 |
| Unfavourable | 56 | 42 (75) | 56 (100) | 2 (4) | 50.5 ± 2.1 | 37 ± 25 |
| Missing | 2 | | | | | |

Table 2 provides an overview of mortality, functional outcome and health related quality of life per subgroup.

Legend:

Results presented as number (row percentage) and mean ± SD

[#] The response rate is reported as percentage of survivors from the specific category.

^{*}Pupillary abnormality information was missing for 7 patients

[^] Mortality at time of QOLIBRI follow-up

Abbreviations:

LOS, length of stay; GCS, Glasgow Coma Score; ICP, intracranial pressure; QOLIBRI, quality of life after brain injury;

M, months: N/A not applicable.

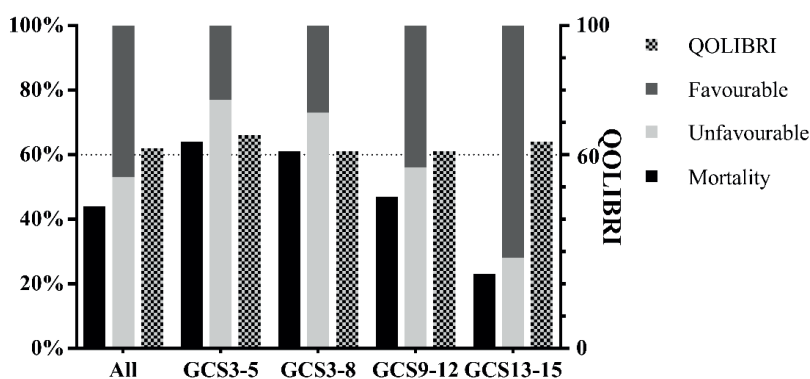


Figure 1. Patient outcome

Fig.1 shows both functional outcome (favourable: GOS 4-5, unfavourable GOS 1-3) and TBI-specific health related quality of life (QOLIBRI) for all patients and for severity subgroups

Table 3. Length of stay and in-hospital costs

| Patient category | N | ICU LOS | Non-ICU LOS | Total costs (€) | Admission costs | Surgery costs |
|-----------------------|-----|---------|-------------|-----------------|-----------------|---------------|
| All patients | 108 | 4 ± 4 | 11 ± 14 | 24,980 ± 17,060 | 14,980 ± 14,000 | 6,890 ± 4,270 |
| Age ≥65 | 65 | 3 ± 3 | 10 ± 12 | 20,820 ± 13,480 | 11,750 ± 10,670 | 6,150 ± 4,040 |
| Age <65 | 43 | 6 ± 5 | 12 ± 16 | 31,260 ± 19,930 | 19,850 ± 16,890 | 8,020 ± 4,410 |
| GCS 3 | 10 | 3 ± 3 | 11 ± 19 | 24,690 ± 18,020 | 13,720 ± 16,310 | 7,940 ± 2,340 |
| GCS 3–5 | 22 | 6 ± 4 | 12 ± 17 | 30,230 ± 16,370 | 19,110 ± 14,910 | 7,710 ± 1,750 |
| GCS 3–8 | 49 | 6 ± 5 | 11 ± 14 | 29,660 ± 17,870 | 18,780 ± 15,890 | 7,520 ± 2,200 |
| GCS 9–12 | 19 | 3 ± 3 | 16 ± 20 | 27,650 ± 15,780 | 15,120 ± 12,600 | 9,230 ± 5,470 |
| GCS 13–15 | 40 | 2 ± 4 | 9 ± 8 | 17,980 ± 14,460 | 10,250 ± 10,610 | 5,010 ± 4,840 |
| Pupillary abnormality | 27 | 7 ± 5 | 13 ± 14 | 33,430 ± 18,330 | 22,480 ± 16,850 | 7,510 ± 1,600 |
| No abnormalities | 74 | 3 ± 4 | 11 ± 14 | 22,220 ± 16,110 | 12,590 ± 12,120 | 6,690 ± 4,940 |
| Emergency surgery | 90 | 5 ± 5 | 12 ± 15 | 28,670 ± 16,230 | 17,120 ± 14,290 | 8,270 ± 3,220 |
| No | 18 | 1 ± 2 | 4 ± 5 | 6,520 ± 4,320 | 4,240 ± 4,160 | 0 |
| Craniotomy | 60 | 4 ± 4 | 12 ± 14 | 26,400 ± 14,680 | 16,040 ± 12,790 | 7,310 ± 3,060 |
| DC | 29 | 6 ± 5 | 11 ± 16 | 33,140 ± 19,070 | 19,950 ± 16,980 | 9,550 ± 3,790 |
| ICP monitoring | 40 | 7 ± 5 | 15 ± 16 | 36,580 ± 16,650 | 23,420 ± 15,260 | 9,340 ± 3,730 |
| No ICP monitoring | 68 | 2 ± 3 | 9 ± 12 | 18,150 ± 13,250 | 10,010 ± 10,480 | 5,460 ± 3,920 |
| Outcome | | | | | | |
| Favourable* | 50 | 3 ± 4 | 11 ± 10 | 20,430 ± 16,540 | 12,320 ± 13,170 | 5,270 ± 3,910 |
| Unfavourable | 56 | 5 ± 5 | 11 ± 16 | 29,230 ± 16,850 | 17,650 ± 14,490 | 8,230 ± 4,100 |
| Dead at discharge | 41 | 5 ± 4 | 6 ± 10 | 25,340 ± 12,450 | 13,890 ± 10,070 | 8,180 ± 3,770 |

Table 3 provides an overview of length of stay and in-hospital costs per subgroup. In-hospital costs are divided between costs related to admission and surgical intervention.

Legend:

Mean ± SD; All costs in € and LOS in days.

* GOS outcomes not available for 2 patients

Abbreviations:

N, number; LOS, length of stay; GCS, Glasgow Coma Score; ICU, Intensive Care Unit; DC, decompressive craniectomy; ICP, intracranial pressure.

Healthcare Costs

Mean in-hospital costs were € 24,980 per patient and primarily the result of costs related to admission (€ 14,980) and surgical intervention (€ 6,890). Mean in-hospital costs were significantly higher for vs-TBI (€ 30,230), s-TBI (€ 29,660) and moderate TBI (€ 27,650) subgroups compared to the mild TBI (€ 17,980) subgroup ($P < 0.05$) (Table 3). For these severity subgroups, mean costs specifically related to ICU admission were € 13,230, € 13,150, € 7,550 and € 5,460 respectively (Figure 2). Patients' healthcare utilization were more expensive after surgical intervention than conservative treatment (€ 28,670 vs. € 6,520). Patients with a decompressive craniectomy showed the highest cost specifically related to surgery. Patients with additional ICP monitoring (€ 36,580) showed highest total costs, of which 64% was related to admission. A lower initial GCS and pupillary abnormalities show an increase in patient LOS and in-hospital costs, except for patients with a GCS of 3. Other characteristics associated with significantly increased total costs were: age < 65, a concomitant intracranial hematoma that not required surgical intervention, presence of pupillary abnormalities and unfavourable outcome.

Five patients (23%) from the vs-TBI subgroup achieved favourable outcome (GOS4-5) at mean in-hospital costs of € 132,610 per patient. Mean costs for patients achieving favourable outcome were € 103,790 for s-TBI patients (N=14; 29%), € 58,150 for moderate TBI patients (N=9; 47%) and € 24,800 per mild-TBI patient (N=29; 72%). Mean in-hospital costs were highest (€ 246,920) for one patient from the GCS=3 subgroup (N=10) that reached favourable outcome.

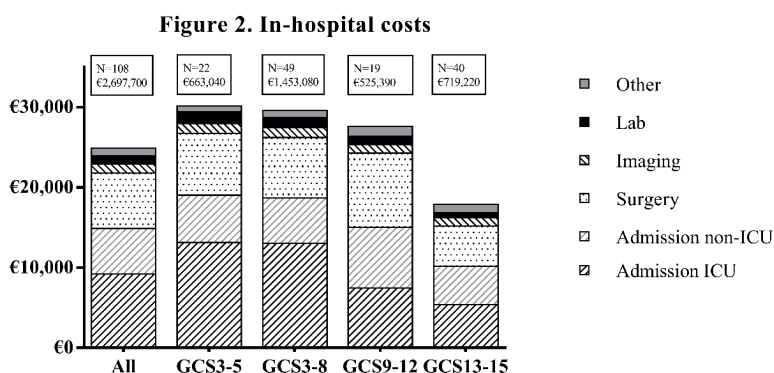


Figure 2. In-hospital costs

Fig.2 shows mean and total in-hospital costs for all patients and for severity subgroups. Also, a distinction has been made between investigated cost categories to show their share to the total in-hospital costs

DISCUSSION

“Favourable” outcome with a good HRQoL was achieved in an important quarter proportion of the seemingly most severely injured patients. This retrospective cohort study, however, also shows high rates of mortality and so called “unfavourable” outcome in patients with a t-ASDH and relatively high healthcare consumption and in-hospital costs. These costs increased with higher injury severity scores and in patients with a surgical intervention. The majority of costs were related to (ICU) admission and surgical intervention. According to the investigators, this study shows a trend that surgical treatment of t-ASDH can realize favourable outcome in s-TBI at for society acceptable in-hospital costs.

Patient outcome

Accurate comparison of the reported patient outcome results with literature is challenging because outcome in TBI is highly variable and dependent on patient characteristics, circumstances, social context and treatment.^{2-4,12,28} Nonetheless, the important result that even the most severely injured TBI patients can, although a small number, achieve favourable outcome (GOS) and good quality of life (QOLIBRI) is supported by recent literature.^{29,30}

Our QOLIBRI results are not applicable to study patients with a cognitive dysfunction and/or impaired self-awareness that is too severe to complete the questionnaire. The unmeasured HRQoL of these patients might have negatively influenced the reported HRQoL per TBI severity group. The applicability of the QOLIBRI for all patients with TBI remains unclear since it has only been validated in patients without substantial post-traumatic cognitive restraints.¹⁶ Proxy completion is impossible for many QOLIBRI items and misses the essence of measuring the ‘self-perceived’ HRQoL. It also remains unclear whether the cut-off point of 60 is satisfying for quantifying a good HRQoL.²³ Therefore, validity should be confirmed for patients with TBI associated persisting cognitive restraints or suitable new (HRQoL) measurement options need to be developed.

In contrast to earlier published reports on t-ASDH, the mean cohort age of 65 years was relatively high, but in accordance with changing TBI epidemiology.³¹ Also, a large number of patients had an initial low GCS and/or pupillary abnormalities. These three factors are known to negatively influence outcome and sometimes these patients are

even considered unsalvageable.^{3,28,29} Nevertheless, neurosurgical intervention was performed in up to 98% of patients with s-TBI. This percentage is high compared to other studies, but seems rational, since neurosurgical evacuation of the hematoma and/or DC can be lifesaving and prevent secondary injury by decreasing ICP.^{2,3,6,32} The high percentage can also be explained by the specific selection of patients with a t-ASDH where neurosurgical consultation was considered necessary, suggesting a higher vulnerability. Although the present study did not evaluate treatment effectiveness, a separate analysis by the authors seemed to support the more aggressive approach.²¹ Even so, superiority between hematoma evacuation or DC remains unknown and no clinical trial has proven primary DC to be effective in improving patient outcome.^{4,33} Surgical intervention is even controversial because patients may survive with ‘unacceptable’ severe disabilities with an accompanying high burden on proxies and society.⁵ This is fundamental in neurosurgical treatment decision-making and as a result, a ‘surgical’ treatment strategy as seen in this study, which follows the guidelines, is not standard day-to-day care in all hospitals.^{3,10,21,32}

Instead, treatment limiting decisions in s-TBI are common in some countries and often made within the first 2 days after trauma.^{7,8} Limiting treatment offers no serious chance of recovery and regularly results in quick death.^{7,8} We acknowledge that these decisions are sometimes inevitable and could be in a patients’ best interest when there is no realistic chance to achieve a “favourable” outcome. But what can be considered a favourable or an unfavourable outcome after s-TBI and vs-TBI?

Therefore, according to the investigators, it would be catastrophic to limit or withhold treatment in patients that could have still benefitted from it. Physicians should be careful in making early treatment limiting decisions when there is still uncertainty, because uncertainty implies a possibility for favourable outcome. Unfortunately, uncertainty in predicting who will benefit from what treatment is very common. There is substantial variation in the perception of neurologic prognosis among physicians and high treatment variation.^{10,12,34} In line with some literature, we believe that treatment limiting decisions in the early phase cannot be justified, because prognostication is not yet accurate enough.³⁵ In a later stage, when clinical and neurological improvement remain absent, further treatment might be considered futile with more certainty. Then, treatment limiting decisions should be discussed with all involved healthcare professionals and proxies.

Healthcare consumption & in-hospital costs

The costs related to admission and surgical intervention cost categories appeared to be the most important contributors to the reported in-hospital costs. In literature, costs related to ICU admission were also high and in-hospital costs also increased with higher injury and TBI severity (defined by GCS), ICP monitoring and surgical intervention.³⁶⁻⁴⁰ The surprisingly lower LOS and in-hospital costs for elderly patients in this study could be explained by the fact that only 33.8% of elderly patients was classified as severe, compared to 62.8% of patients younger than 65.

Overall, the reported healthcare consumption and in-hospital costs seem to be quite similar to literature.^{38,40,41} However, comparison was difficult due to substantial methodological variation and often inadequate methodology of available TBI cost studies.^{19,20} The detailed calculation of healthcare consumption and in-hospital costs is an important strength of this study. The electronic patient file setup reduced the risk to a minimum that unregistered activities contributed to an underestimation of in-hospital resource utilization. Still, the numbers in this study are an enormous underestimation of the total healthcare consumption and total costs associated with t-ASDH and TBI, because the majority of costs are indirect and arise after hospital discharge.^{40,42,43} Also, interpretation and generalization of the results should be done carefully since included patients represent a specific selection of patients with a t-ASDH with a suspected higher vulnerability, where patients with a concomitant hematoma requiring surgical intervention were excluded. Also, the inevitable presence of coexisting injuries causes that results are not solely attributable to TBI.

Despite these remarks, the reported costs give rise to the question whether or not the in-hospital costs may be justified by the achieved outcome. The mean in-hospital costs per patient appear to be acceptable for all TBI severity groups. However, when adding up the in-hospital costs that are made to have one patient achieve a favourable outcome, especially the most severely injured patients appear to be expensive. Unfortunately, true cost-effectiveness could not be established in this study and because there is no consensus in literature, additional research is needed to establish cost-effectiveness and justification of expenses in TBI care.⁴⁴⁻⁴⁷

Future perspective

Future research should establish long-term outcome of ASDH patients after different treatment strategies. A high-quality cost-effectiveness research should incorporate

a long-term follow up and should use accurate resource utilization and cost price information.^{48,49} Future research should also explore the societal impact of t-ASDH, including productivity loss of both patients and proxies. Investigators should aim at comparability and generalizability by using common data points and guideline recommendations.⁵⁰ Ultimately, researchers should explore what health states and associated costs can be considered 'acceptable' to patients, proxies and society.

CONCLUSIONS

Although outcome was often "unfavourable", several of the most severely injured patients, often even considered unsalvageable, achieved favourable outcome on both GOS and QOLIBRI. Associated hospital costs were relatively high, especially for the most severely injured patients, but may be justified considering the realized favourable outcome in part of these patients. Patients should not prematurely be considered unsalvageable and adequate (surgical) therapy should not be withheld in the acute phase. More research is necessary to establish the cost-effectiveness of treatment strategies for patients with a t-ASDH.

REFERENCES

1. Bullock M, Chesnut R, Ghajar J, et al. Surgical management of acute subdural hematomas. *Neurosurgery* 2006; **58**(3 Suppl): S16-24.
2. Leitgeb J, Mauritz W, Brazinova A, et al. Outcome after severe brain trauma due to acute subdural hematoma. *J Neurosurg* 2012; **117**(2): 324-33.
3. Fountain D, Kolias A, Lecky F, et al. Survival trends after surgery for acute subdural hematoma in adults over a 20-year period. *Annals of surgery* 2017; **265**(3): 590-6.
4. Phan K, Moore J, Griessenauer C, et al. Craniotomy versus decompressive craniectomy for acute subdural hematoma: systematic review and meta-analysis. *World Neurosurg*; **101**: 677-85.
5. Honeybul S, Gillett G, Ho K, Lind C. Ethical considerations for performing decompressive craniectomy as a life-saving intervention for severe traumatic brain injury. *Journal of medical ethics* 2012; **38**(11): 657-61.
6. Maas A, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. *The Lancet Neurology* 2008; **7**(8): 728-41.
7. Robertsen A, Førde R, Skaga N, Helseth E. Treatment-limiting decisions in patients with severe traumatic brain injury in a Norwegian regional trauma center. *Scand J Trauma Resusc Emerg Med* 2017; **25**: 44.
8. Wilson W, McMillan T, Young A, White M. Increased trends in the use of treatment-limiting decisions in a regional neurosurgical unit. *British journal of neurosurgery* 2017; **31**(2): 254-7.
9. Carney N, Totten A, O'Reilly C, et al. Guidelines for the management of severe traumatic brain injury, fourth edition. *Neurosurgery* 2017; **80**(1): 6-15.
10. van Essen T, de Ruiter G, Kho K, Peul W. Neurosurgical treatment variation of traumatic brain injury: evaluation of acute subdural hematoma management in Belgium and The Netherlands. *Journal of neurotrauma* 2017; **34**(4): 881-9.
11. Cnossen M, Scholten A, Lingsma H, et al. Adherence to guidelines in adult patients with traumatic brain injury: a living systematic review. *Journal of neurotrauma* 2016: No pagination.
12. Cnossen M, Polinder S, Andriessen T, et al. Causes and consequences of treatment variation in moderate and severe traumatic brain injury: a multicenter study. *Critical care medicine* 2017; **45**(4): 660-9.
13. Polinder S, Haagsma J, van Klaveren D, Steyerberg E, van Beeck E. Health-related quality of life after TBI: a systematic review of study design, instruments, measurement properties, and outcome. *Popul Health Metr* 2015; **13**: 4.
14. Wilson J, Pettigrew L, Teasdale G. Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. *Journal of neurotrauma* 1998; **15**(8): 573-85.
15. von Steinbüchel N, Wilson L, Gibbons H, et al. Quality of life after brain injury (QOLIBRI): scale development and metric properties. *Journal of neurotrauma* 2010; **27**(7): 1167-85.
16. von Steinbüchel N, Wilson L, Gibbons H, et al. Quality of life after brain injury (QOLIBRI): scale validity and correlates of quality of life. *Journal of neurotrauma* 2010; **27**(7): 1157-65.
17. Frontera JA, Egorova N, Moskowitz AJ. National trend in prevalence, cost, and discharge disposition after subdural hematoma from 1998-2007. *Critical care medicine* 2011; **39**(7): 1619-25.
18. Parliamentary letter, Ministry of Health (2016). <https://www.rijksoverheid.nl/documenten/kamerstukken/2016/01/28/kamerbrief-over-beeindiging-sluiss-nivolumab-per-1-maart-2016> (accessed July 30 2018).
19. Lu J, Roe C, Aas E, et al. Traumatic brain injury: methodological approaches to estimate health and economic outcomes. *Journal of neurotrauma* 2013; **30**(23): 1925-33.
20. Alali A, Burton K, Fowler R, et al. Economic evaluations in the diagnosis and management of traumatic brain injury: a systematic review and analysis of quality. *Value Health* 2015; **18**(5): 721-34.
21. van Essen T, Dijkman M, Cnossen M, et al. Comparative effectiveness of surgery for traumatic acute subdural hematoma in an aging population. *Journal of neurotrauma* 2018; **0**(ja): null.
22. Teasdale G, Jennett B. Assessment of coma and impaired consciousness; a practical scale. *Lancet* 1974; **304**(7872): 81-4.
23. Wilson L, Marsden-Loftus I, Koskinen S, et al. Interpreting quality of life after brain injury scores: cross-walk with the short form-36. *Journal of neurotrauma* 2017; **34**(1): 59-65.

24. Hakkaart-van Roijen L, van der Linden N, Bouwmans C, Kanter T, Tan S. Kostenhandleiding: methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. . *Zorginstituut Nederland* 2015; Geactualiseerde versie 2015(<https://www.zorginstituutnederland.nl/binaries/zinl/documenten/publicatie/2016/02/29/richtlijn-voor-het-uitvoeren-van-economische-evaluaties-in-de-gezondheidszorg/Richtlijn+voor+het+uitvoeren+van+economische+evaluaties+in+de+gezondheidszorg+%28verdiepingsmodules%29.pdf> (accessed 30-03-2018)).
25. Tan S, Bakker J, Hoogendoorn M, et al. Direct cost analysis of intensive care unit stay in four european countries: applying a standardized costing methodology. *Value Health* 2012; **15**(1): 81-6.
26. Nederlandse Zorgautoriteit. Tarieventabel DBC-zorgproducten en overige producten - per 1 januari 2012 (PUC_12710_22). https://puc.overheid.nl/nza/doc/PUC_12710_22/1/ (accessed March 29 2018).
27. Nederlandse Zorgautoriteit. Open data van de Nederlandse Zorgautoriteit. www.opendisdata.nl (accessed March 29 2018).
28. Greene N, Kernic M, Vavilala M, Rivara F. Variation in adult traumatic brain injury outcomes in the United States. *The Journal of head trauma rehabilitation* 2018; **33**(1): E1-E8.
29. van Dijk J, Reith F, van Erp I, et al. Decision making in very severe traumatic brain injury (Glasgow Coma Scale 3-5): a literature review of acute neurosurgical management. *Journal of neurosurgical sciences* 2018; **62**(2): 153-77.
30. Soberg H, Roe C, Anke A, et al. Health-related quality of life 12 months after severe traumatic brain injury: a prospective nationwide cohort study. *Journal of rehabilitation medicine* 2013; **45**(8): 785-91.
31. Maas A, Menon D, Adelson P, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. *The Lancet Neurology* 2017; **16**(12): 987-1048.
32. Kwon H, Choi K, Yi H, Chun H, Lee Y, Kim D. Risk factors of delayed surgical intervention after conservatively treated acute traumatic subdural hematoma. *J Korean Neurosurg Soc* 2017; **60**(6): 723-9.
33. Hutchinson P, Kolias A, Timofeev I, et al. Trial of decompressive craniectomy for traumatic intracranial hypertension. *The New England journal of medicine* 2016; **375**(12): 1119-30.
34. Turgeon A, Lauzier F, Burns K, et al. Determination of neurologic prognosis and clinical decision making in adult patients with severe traumatic brain injury: a survey of Canadian intensivists, neurosurgeons, and neurologists. *Critical care medicine* 2013; **41**(4): 1086-93.
35. Geurts M, Macleod MR, van Thiel GJ, van Gijn J, Kappelle LJ, van der Worp HB. End-of-life decisions in patients with severe acute brain injury. *The Lancet Neurology* 2014; **13**(5): 515-24.
36. Marin J, Weaver M, Mannix R. Burden of USA hospital charges for traumatic brain injury. *Brain injury* 2017; **31**(1): 24-31.
37. Albrecht J, Slejko J, Stein D, Smith G. Treatment charges for traumatic brain injury among older adults at a trauma center. *The Journal of head trauma rehabilitation* 2017; **32**(6): E45-E53.
38. Tardif P, Moore L, Boutin A, et al. Hospital length of stay following admission for traumatic brain injury in a Canadian integrated trauma system: A retrospective multicenter cohort study. *Injury* 2017; **48**(1): 94-100.
39. Fountain D, Kolias A, Laing R, Hutchinson P. The financial outcome of traumatic brain injury: a single centre study. *British journal of neurosurgery* 2016; **31**(3): 1-6.
40. Raj R, Bendel S, Reinikainen M, et al. Costs, outcome and cost-effectiveness of neurocritical care: a multicenter observational study. *Crit Care* 2018; **22**(1): 225.
41. Kalanithi P, Schubert R, Lad S, Harris O, Boakye M. Hospital costs, incidence, and in-hospital mortality rates of traumatic subdural hematoma in the United States: Clinical article. *J Neurosurg* 2011; **115**(5): 1013-8.
42. Garcia-Altes A, Perez K, Novoa A, et al. Spinal cord injury and traumatic brain injury: a cost-of-illness study. *Neuroepidemiology* 2012; **39**(2): 103-8.
43. Tuominen R, Joelsson P, Tenovu O. Treatment costs and productivity losses caused by traumatic brain injuries. *Brain injury* 2012; **26**(13-14): 1697-701.
44. Whitmore R, Thawani J, Grady M, Levine J, Sanborn M, Stein S. Is aggressive treatment of traumatic brain injury cost-effective? *J Neurosurg* 2012; **116**(5): 1106-13.
45. Ho K, Honeybul S, Lind C, Gillett G, Litton E. Cost-effectiveness of decompressive craniectomy as a lifesaving rescue procedure for patients with severe traumatic brain injury. *J Trauma* 2011; **71**(6): 1637-44.
46. Malmivaara K, Kivisaari R, Hernesniemi J, Siironen J. Cost-effectiveness of decompressive craniectomy in traumatic brain injuries. *Eur J Neurol* 2011; **18**(4): 656-62.

47. Alali A, Naimark D, Wilson J, et al. Economic evaluation of decompressive craniectomy versus barbiturate coma for refractory intracranial hypertension following traumatic brain injury. *Critical care medicine* 2014; **42**(10): 2235-43.
48. Porter M, Lee T. The strategy that will fix health care. . *Harvard Business Review* 2013; (91): .
49. Keel G, Savage C, Rafiq M, Mazzocato P Time-driven activity-based costing in health care: a systematic review of the literature. *Health Policy* 2017; **121**(7): 755-63.
50. Maas A, Harrison-Felix C, Menon D, et al. Common data elements for traumatic brain injury: recommendations from the interagency working group on demographics and clinical assessment. *Arch Phys Med Rehabil* 2010; **91**(11): 1641-9.



CHAPTER 5

Functional outcome, in-hospital healthcare consumption and in-hospital costs for hospitalized traumatic brain injury patients: A Dutch prospective multicenter study.

Authors:

Jeroen T.J.M. van Dijck MD¹,
Cassidy Q.B. Mostert BSc¹,
Alexander P.A. Greeven MD²,
Erwin J.O. Kompanje PhD^{3,4},
Wilco C. Peul MD PhD MBA¹,
Godard C.W. de Ruiter MD PhD¹,
Suzanne Polinder PhD⁵

Affiliations:

1. Department of Neurosurgery, University Neurosurgical Center Holland, LUMC, HMC & Haga Teaching Hospital, Leiden/The Hague, The Netherlands;
2. Department of Surgery, Haga Teaching Hospital, The Hague, The Netherlands;
3. Department of Intensive Care, Erasmus MC - University Medical Centre Rotterdam, Rotterdam, The Netherlands;
4. Department of Medical Ethics and Philosophy of Medicine, Erasmus MC—University Medical Centre Rotterdam, Rotterdam, The Netherlands;
5. Department of Public Health, Erasmus MC - University Medical Centre Rotterdam, Rotterdam, The Netherlands.

Citation:

van Dijck JTJM, Mostert CQB, Greeven APA, et al. Functional outcome, in-hospital healthcare consumption and in-hospital costs for hospitalised traumatic brain injury patients: a Dutch prospective multicentre study. *Acta Neurochir (Wien)*. doi:10.1007/s00701-020-04384-9

ABSTRACT

Background: The high occurrence and acute and chronic sequelae of traumatic brain injury (TBI) cause major healthcare and socioeconomic challenges. This study aimed to describe outcome, in-hospital healthcare consumption and in-hospital costs of patients with TBI.

Methods: We used data from hospitalized TBI patients that were included in the prospective observational CENTER-TBI study in three Dutch Level I Trauma Centres from 2015 to 2017. Clinical data was completed with data on in-hospital healthcare consumption and costs. TBI severity was classified using the Glasgow Coma Score (GCS). Patient outcome was measured by in-hospital mortality and Glasgow Outcome Score – Extended (GOSE) at 6 months. In-hospital costs were calculated following the Dutch guidelines for cost calculation.

Results: A total of 486 TBI patients were included. Mean age was 56.1 ± 22.4 years and mean GCS was 12.7 ± 3.8 . Six-month mortality (4.2%-66.7%), unfavourable outcome ($\text{GOSE} \leq 4$) (14.6%-80.4%), and full recovery ($\text{GOSE} = 8$) (32.5%-5.9%) rates varied from patients with mild TBI (GCS13-15) to very severe TBI (GCS3-5). Length of stay (8 ± 13 days) and in-hospital costs (€11,920) were substantial and increased with higher TBI severity, presence of intracranial abnormalities, extracranial injury, and surgical intervention. Costs were primarily driven by admission (66%) and surgery (13%).

Conclusion: In-hospital mortality and unfavourable outcome rates were rather high, but many patients also achieved full recovery. Hospitalized TBI patients show substantial in-hospital healthcare consumption and costs, even in patients with mild TBI. Because these costs are likely to be an underestimation of the actual total costs, more research is required to investigate the actual costs-effectiveness of TBI care.

Keywords: Traumatic brain injury; in-hospital costs; mortality; functional outcome

INTRODUCTION

Recent estimates indicate that worldwide up to sixty-nine million people a year sustain a traumatic brain injury (TBI).¹ The high incidence of TBI and the associated acute and chronic sequelae cause substantial healthcare and socio-economic challenges.² Available treatments are unfortunately still largely unproven or unsatisfactory.¹⁻⁴ Patients suffer from the medical consequences of TBI, which range from headache and fatigue to severe disabilities and even death.⁵⁻⁹ The total global accompanying costs of around US\$ 400 billion a year are a major challenge from a socioeconomic perspective.² Especially considering the fact that TBI related healthcare costs are rising, while healthcare budgets remain limited.¹⁰ The in-hospital costs related to TBI represent a substantial part of the total utilized resources.¹¹ Unfortunately, understanding and generalizing the in-hospital costs of individual TBI patients from available literature remains difficult because methodological heterogeneity of TBI cost studies is high and study quality often inadequate.¹²⁻¹⁴

Accurate insight in TBI related costs is essential to substantiate research initiatives that aim to improve treatment efficiency. It also guides policymakers on the rational allocation of resources without compromise of patient outcome. To allow healthcare professionals to continue to provide optimal care for their patients, high quality cost-analysis studies are urgently needed.^{13,14}

Therefore, the aim of this study is to describe outcome, in-hospital healthcare consumption and in-hospital costs of hospitalized TBI patients.

MATERIALS AND METHODS

This study followed the recommendations from the 'Strengthening the Reporting of Observational Studies in Epidemiology' STROBE statement.¹⁵

Study design and patients

Patients were included in three level 1 trauma hospitals from January 2015 to September 2017. All hospitals are located in an urban area in the mid-Western part of the Netherlands and participated in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) project. The CENTER-

TBI Core study (clinicaltrials.gov NCT02210221; RRID: SCR_015582) is a prospective multicentre longitudinal observational study conducted in 65 centers across Europe and Israel.¹⁶ The project aimed to improve TBI characterization and classification and to identify best clinical care. The responsible institutional review board (METC Leiden) approved this study (P14.222).

Patients were included in the CENTER-TBI Core study using the following criteria: (1) clinical diagnosis of TBI, (2) clinical indication for head CT scan, (3) presentation to study center within 24 hours after injury and (4) informed consent following Dutch requirements, including patient, proxy and deferred consent. Patients were excluded when they had a severe pre-existing neurological disorder that would confound outcome assessments or in case of insufficient understanding of the Dutch or English language.

Clinical data

Clinical data were prospectively collected by using a web-based electronic case report form (CRF) (QuesGen System Incorporated, Burlingame, CA, USA). Data were obtained from electronic patient files and patient interviews and when necessary initially recorded on a hardcopy CRF. Data collection was completed by a local research staff that was specifically trained for this project. The site's principal investigator supervised the project. Data were de-identified by using a randomly generated GUPI (Global Unique Patient Identifier) and was stored on a secure database, hosted by the International Neuroinformatics Coordinating Facility (INCF; www.incf.org) in Stockholm, Sweden.

Data was extracted in December 2019 (version 2.1) using a custom-made data access tool Neurobot (<http://neurobot.incf.org>), developed by INCF (RRID: SCR_017000). Extracted data included: baseline demographic, trauma and injury information, results of neurological assessments, imaging (first head CT scan) and patient outcome. This database was merged with separately collected data on in-hospital healthcare consumption and in-hospital costs, which is explained later. Discrepancies were resolved by source data verification.

Baseline Glasgow Coma Scale (GCS) Total Score, GCS Motor Score and pupillary reactivity variables were collected. TBI severity was then classified by using the GCS (GCS13-15; mild TBI, GCS9-12; moderate TBI, GCS3-8; severe TBI, GCS3-5; very severe TBI).¹⁷ These values were derived variables that were centrally calculated using the

IMPACT methodology, taking a post stabilisation value and if absent work back in time towards prehospital values. Out of 19 missing GCS values, 8 were completed by using emergency department arrival GCS score. Intubation was calculated as a GCS Verbal score of 1. Major extracranial injury was defined by AIS body region ≥ 3 . Characteristics from the first head CT-scan were assessed by a central review panel.¹⁸ Six out of seven missing central assessments were completed by using the assessments of local radiologists. Outcome data included in-hospital mortality and 6-month Glasgow Outcome Score – Extended (GOSE). GOSE outcome was dichotomized in favourable (GOSE ≥ 5) and unfavourable (GOSE ≤ 4).¹⁹

In-hospital healthcare consumption

We collected in-hospital healthcare consumption data from electronic patient records by using a predefined cost assessment database. The Dutch National Health Care Institute Guidelines for healthcare cost calculation were followed.²⁰ Units (e.g. number of admission days, number of diagnostics) were collected independently by two researchers from the electronic patient files. There were five main categories: (1) admission; including length of stay (LOS) in (non-)ICU with consultations, (2) surgical interventions, (3) imaging, (4) laboratory; including blood products and (5) other; including ambulance transportation and outpatient visits.²¹ Non-ICU admission was defined as admission to a ward or medium care. In-hospital healthcare consumption and costs were calculated for all included patients. (Supplement 1)

In-hospital costs

We focused on the in-hospital costs from a healthcare perspective. Costs of re-admissions and costs of visits to the Outpatient Clinic related to the trauma were also included. The methods and reference prices as described in the Dutch Guidelines for economic healthcare evaluations were used to calculate in-hospital costs.²⁰ Costs were calculated by multiplying the number of consumed units with the corresponding guideline reference price. Guideline reference prices are based on non-site specific large patient cohorts which improves their generalizability and interpretation.²⁰ When reference prices were not mentioned, the remaining units were valued by using amounts per unit as reported by The Netherlands Healthcare Authority (NZa) (i.e. diagnostics)²² or by using their average national price, based on declared fees (i.e. surgical interventions, consultations).²³ All costs were converted to the last year of patient inclusion (2017) using the national general consumer price index (CBS) and rounded to the nearest ten euros. One EURO equalled \$1.05 dollar on the 1st of January 2017. (Supplement 1)

Statistical methods

Data were analyzed using descriptive statistics. Baseline data were presented as absolute numbers and percentages. Continuous variables, like LOS and costs, were presented as mean \pm standard deviation or median (interquartile range 25-75). Subgroups were made using age, TBI severity, pupillary abnormalities, intracranial abnormalities, surgical intervention and outcome. ANOVA and χ^2 were used for comparison of continuous and categorical variables across different subgroups. A p-value of <0.05 was considered statistically significant. All analyses were performed using IBM's statistical package for social sciences version 25.0 (SPSS). Figures were designed using GraphPad Prism 8.

RESULTS

A total of 486 patients with TBI were included in this study. Patients had a mean age of 56.1 ± 22.4 years and were predominantly male (60.5%). (Table 1) Nearly all patients sustained a closed head injury (98.4%). TBI was mainly caused by incidental falls (54.3%) or road traffic accidents (36.2%) and occurred on streets (56.2%) or at home (31.5%). The mean baseline GCS was 12.7 ± 3.8 and mean injury severity score (ISS) was 20 ± 16 . Patients sustained mild TBI (N=354, 72.8%), moderate TBI (N=43, 8.8%) and severe TBI (N=78, 16.1%), of which 51 were very severe (10.5%). Loss to follow-up was 14.2% and not significantly different between severity groups.

Table 1 Patient characteristics and outcome

| | All (N=486) | Mild TBI (N=354) | Moderate TBI (N=43) | Severe TBI (N=78) | Very severe TBI (N=51) | P value* |
|-------------------------|-------------|------------------|---------------------|-------------------|------------------------|----------|
| Male | 294 (60.5) | 211 (59.6) | 25 (58.1) | 54 (69.2) | 36 (70.6) | 0.265 |
| Age (years) | 56.1 ± 22.4 | 56.6 ± 22.2 | 58.5 ± 22.4 | 52.2 ± 22.6 | 50.9 ± 23.3 | 0.222 |
| ≤18 | 25 (5.1) | 21 (5.9) | 1 (2.3) | 2 (2.6) | 2 (3.9) | 0.467 |
| 19-64 | 255 (52.5) | 184 (52.0) | 21 (48.8) | 46 (59.0) | 30 (58.8) | |
| ≥65 | 206 (42.4) | 149 (42.1) | 21 (48.8) | 30 (38.5) | 19 (37.3) | |
| Stratum Admission ICU | 319 (65.6) | 288 (81.4) | 16 (37.2) | 9 (11.5) | 5 (9.8) | <0.001 |
| | 167 (34.4) | 66 (18.6) | 27 (62.8) | 69 (88.5) | 46 (90.2) | |
| Location of injury | | | | | | 0.137 |
| Street/highway | 273 (56.2) | 201 (56.8) | 22 (51.2) | 45 (57.7) | 31 (60.8) | |
| Home/domestic | 153 (31.5) | 113 (31.9) | 11 (25.6) | 25 (32.1) | 15 (29.4) | |
| Work/school | 14 (2.9) | 8 (2.3) | 5 (11.6) | 1 (1.3) | 1 (2.0) | |
| Sport/recreational | 18 (3.7) | 14 (4.0) | 2 (4.7) | 1 (1.3) | 0 (0.0) | |
| Public location | 25 (5.1) | 15 (4.2) | 3 (7.0) | 6 (7.7) | 4 (7.8) | |
| Other/unknown | 2 (0.6) | 3 (0.9) | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| Cause of injury | | | | | | 0.136 |
| Road traffic accident | 176 (36.2) | 125 (35.3) | 14 (32.6) | 35 (44.9) | 25 (49.0) | |
| Incidental fall | 264 (54.3) | 200 (56.5) | 21 (48.8) | 35 (44.9) | 20 (39.2) | |
| Non-intentional injury | 12 (2.5) | 8 (2.3) | 2 (4.7) | 1 (1.3) | 1 (2.0) | |
| Violence/assault | 10 (2.1) | 8 (2.3) | 2 (4.7) | 0 (0.0) | 0 (0.0) | |
| Suicide attempt | 3 (0.6) | 0 (0.0) | 1 (2.3) | 2 (2.6%) | 2 (3.9) | |
| Other/unknown | 21 (4.3) | 13 (3.6) | 3 (7.0) | 5 (6.4) | 3 (5.9) | |
| Glasgow Coma Score | 12.7 ± 3.8 | 14.7 ± 0.6 | 10.6 ± 0.9 | 4.7 ± 1.9 | 3.5 ± 0.7 | N/A |
| GCS Motor score | 5.3 ± 1.6 | 6.0 ± 0.4 | 5.0 ± 1.3 | 2.3 ± 1.7 | 1.4 ± 0.8 | |
| GCS 13-15 | 354 (72.8) | 354 (100) | - | - | - | |
| GCS 9-12 | 43 (8.8) | - | 43 (100) | - | - | |
| GCS 3-8 | 78 (16.1) | - | - | 78 (100) | - | |
| GCS 3-5 | 51 (10.5) | - | - | 51 (65.4) | - | |
| Missing | 11 (2.3) | - | - | - | - | |
| Pupillary abnormalities | | | | | | <0.001 |
| Both reacting | 423 (87.0) | 343 (98.0) | 39 (90.7) | 38 (48.7) | 19 (37.3) | |
| One reacting | 14 (2.9) | 5 (1.4) | 2 (4.7) | 7 (9.0) | 4 (7.8) | |
| Both non-reacting | 37 (7.6) | 2 (0.6) | 2 (4.7) | 33 (42.3) | 28 (54.9) | |
| Missing | 12 (2.5) | 4 (1.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | |

Table 1 continued

| | All (N=486) | Mild TBI (N=354) | Moderate TBI (N=43) | Severe TBI (N=78) | Very severe TBI (N=51) | P value* |
|----------------------------|-------------|------------------|---------------------|-------------------|------------------------|----------|
| Findings first CT scan | | | | | | |
| Intracranial abnormalities | 263 (54.1) | 160 (45.2) | 30 (69.8) | 68 (87.2) | 43 (84.3) | <0.001 |
| Contusion | 130 (26.7) | 68 (19.2) | 22 (51.2) | 38 (48.7) | 26 (51.0) | <0.001 |
| Traumatic SAH | 185 (38.1) | 101 (28.5) | 26 (60.5) | 56 (71.8) | 37 (72.5) | <0.001 |
| Epidural hematoma(s) | 47 (9.7) | 27 (7.6) | 7 (16.3) | 13 (16.7) | 9 (17.6) | <0.001 |
| Subdural hematoma(s) | 136 (28.0) | 68 (19.2) | 22 (51.2) | 43 (55.1) | 28 (54.9) | <0.001 |
| Skull fracture(s) | 180 (37.0) | 97 (27.4) | 25 (58.1) | 55 (70.5) | 39 (76.5) | <0.001 |
| Compressed basal cisterna | 88 (18.1) | 30 (8.5) | 9 (20.9) | 47 (60.3) | 34 (66.7) | <0.001 |
| Midline shift >5mm | 65 (13.4) | 21 (5.9) | 10 (23.3) | 31 (39.7) | 20 (39.2) | <0.001 |
| Mass lesion >25 cc | 80 (16.5) | 26 (7.3) | 14 (32.6) | 37 (47.4) | 26 (51.0) | <0.001 |
| Uninterpretable** | 10 (2.1) | 5 (1.4) | 4 (9.3) | 0 (0.0) | 0 (0.0) | |
| Injury Severity | | | | | | |
| Brain Injury AIS | 3.1 ± 1.2 | 2.7 ± 0.9 | 3.7 ± 1.2 | 4.6 ± 1.2 | 4.8 ± 1.2 | <0.001 |
| ISS | 20 ± 16 | 15 ± 9 | 22 ± 16 | 39 ± 22 | 43 ± 21 | <0.001 |
| In-hospital mortality | 60 (12.3) | 8 (2.3) | 8 (18.6) | 42 (53.8) | 32 (62.7) | <0.001 |
| GOS-E at 6 months | 5.72 ± 2.55 | 6.5 ± 1.8 | 4.6 ± 2.7 | 2.9 ± 2.7 | 2.4 ± 2.5 | |
| Favourable/unfavourable*** | 72.9%/27.1% | 85.4%/14.6% | 55.3%/44.7% | 29.0%/71.0% | 19.6%/80.4% | |
| 1 | 73 (15.0) | 15 (4.2) | 10 (23.3) | 45 (57.7) | 34 (66.7) | <0.001 |
| 2/3 | 17 (3.5) | 10 (2.8) | 6 (14.0) | 1 (1.3) | 0 (0.0) | |
| 4 | 23 (4.7) | 19 (5.4) | 1 (2.3) | 3 (3.8) | 3 (5.9) | |
| 5 | 25 (5.1) | 18 (5.1) | 5 (11.6) | 2 (2.6) | 1 (2.0) | |
| 6 | 38 (7.8) | 31 (8.8) | 4 (9.3) | 3 (3.8) | 1 (2.0) | |
| 7 | 110 (22.6) | 93 (26.3) | 4 (9.3) | 10 (12.8) | 4 (7.8) | |
| 8 | 131 (27.0) | 115 (32.5) | 8 (18.6) | 5 (6.4) | 3 (5.9) | |
| Loss to follow up | 69 (14.2) | 53 (15.0) | 5 (11.6) | 9 (11.5) | 5 (9.8) | 0.650 |

Table 1 legends:

Caption: Table 1 shows patient characteristics and patient outcome that are reported for all patients because baseline CCS data was missing for 11 patients. Also, data from 1 CT-scan could not be retrieved.

Legend: Values are reported as: *** Calculated excluding missings. Favourable and unfavourable were defined as GOS-E 5-8 and GOS-E 1-4 respectively.

Number (percentage)

Mean ± SD

* p values were derived from ANOVA for continuous characteristics and χ^2

statistics for categorical characteristics, comparing TBI severity categories

(severe TBI, moderate TBI, mild TBI). The p value assessed compatibility with

the null hypothesis of no differences between TBI severity categories.

** Numbers from TBI severity subgroups do not always match the numbers

SAH: subarachnoid hemorrhage

Abbreviations:

AIS: abbreviated injury scale

CT-scan: Computed Tomography scan

GCS: Glasgow Coma Score

GOS-E: Glasgow Outcome Score—Extended

ICU: Intensive care unit

SAH: subarachnoid hemorrhage

Patient outcome

Mean in-hospital mortality was 12.3% and ranged from 2.3% for patients with mild TBI to 62.7% for patients with very severe TBI. (Table 1) The 6-month GOSE follow-up was available for 417 patients (85.8%). Favourable outcome (GOSE \geq 5) was achieved by 85.4% of patients with mild, 55.3% with moderate, 29.0% with severe, and 19.6% with very severe TBI. (Figure 1) A GOSE of 2-4 was found in 40 survivors (8.2%), of which 17 (3.5%) were in a vegetative state (GOSE=2) or required full assistance in daily life (GOSE=3). Nearly a third of patients reported full recovery (GOSE=8) after mild (32.5%), 18.6% after moderate, 6.4% after severe, and 5.9% after very severe TBI.

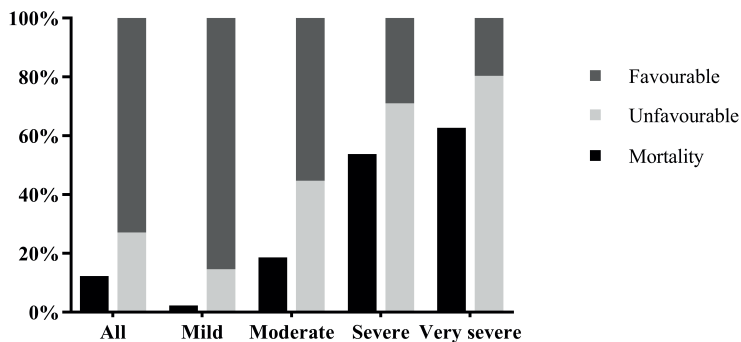


Figure 1. Patient outcome

Figure 1 shows in-hospital mortality and functional outcome (favourable: GOSE 5-8, unfavourable GOSE 1-4) at 6 month follow-up for patients with TBI in different severities.

Length of stay and surgical interventions

Mean total LOS was 8 days (2 days on ICU and 6 days non-ICU). LOS significantly increased with TBI severity, presence of major extracranial injury, surgical intervention(s) and presence of all types of intracranial abnormalities except epidural hematoma. (Table 2, Figure 2) Patients that required ICP monitoring and/or a decompressive craniectomy showed longest mean LOS (27 and 28 days respectively). LOS was short in patients without intracranial abnormalities (5 days). Patients with two non-reacting pupils also showed a significantly shorter LOS (5 days) compared to those with either one (17 days) or two reacting pupils (8 days).

A total of 126 patients (27.2%) received a surgical intervention, of which 67 intracranial (13.8%) and 65 extracranial (13.4%). Intracranial surgery was significantly more common in more severely injured TBI subgroups (6.2% for mild, 34.9% for moderate, and 35.9% for severe TBI). (Table 2).

Table 2. Length of stay and in-hospital costs

| Patient category | N | Total LOS | ICU LOS | Non-ICU LOS | Total costs |
|-------------------------------|-----|-----------|---------|-------------|---------------------------------|
| All patients | 486 | 8 ± 13 | 2 ± 5 | 6 ± 10 | 11,920; 5,200 (2,780-12,500) |
| <u>Age</u> | | | | | |
| ≤18 | 25 | 3 ± 4 | 1 ± 4 | 2 ± 2 | 6,100; 2,550 (1,830-6,470) |
| 19-64 | 255 | 8 ± 15 | 2 ± 5 | 6 ± 11 | 12,640; 4,560 (2,720-12,630) |
| ≥65 | 206 | 8 ± 11 | 2 ± 5 | 7 ± 8 | 11,720; 6,240 (3,070-13,060) |
| <u>TBI severity</u> | | * | * | * | * |
| GCS 13-15 | 354 | 6 ± 8 | 1 ± 3 | 5 ± 6 | 7,800; 3,880 (2,550-8,630) |
| GCS 9-12 | 43 | 14 ± 15 | 4 ± 6 | 10 ± 12 | 20,210; 12,480 (5,370-27,220) |
| GCS 3-8 | 78 | 15 ± 22 | 6 ± 9 | 9 ± 18 | 26,600; 12,340 (7,730-41,260) |
| GCS 3-5 | 51 | 14 ± 20 | 6 ± 8 | 7 ± 17 | 26,350; 12,500 (7,730-42,430) |
| <u>Pupil reactivity</u> | | * | * | * | * |
| Both reacting | 423 | 8 ± 13 | 2 ± 5 | 6 ± 10 | 11,270; 4,650 (2,700-12,290) |
| One reacting | 14 | 17 ± 16 | 8 ± 11 | 9 ± 7 | 31,940; 13,600 (5,070-51,490) |
| None reacting | 37 | 5 ± 6 | 3 ± 5 | 2 ± 5 | 13,210; 8,210 (6,220-14,060) |
| <u>Early CT scan</u> | | | | | |
| Yes abnormalities | 263 | 10 ± 15* | 3 ± 6* | 7 ± 11* | 15,780; 8,240 (3,690-15,750)* |
| No abnormalities | 212 | 5 ± 8 | 0 ± 2 | 4 ± 7 | 6,490; 3,180 (2,350-6,670) |
| Contusion | 139 | 12 ± 16* | 3 ± 6* | 8 ± 13* | 18,060; 9,810 (4,100-21,560)* |
| Traumatic SAH | 185 | 11 ± 17* | 3 ± 7* | 8 ± 13* | 17,730; 9,090 (4,130-20,640)* |
| Epidural hematoma(s) | 47 | 10 ± 15 | 3 ± 6 | 8 ± 11 | 16,320; 8,240 (3,170-14,060) |
| Subdural hematoma(s) | 136 | 11 ± 16* | 3 ± 6* | 8 ± 12* | 16,670; 8,800 (4,210-20,290)* |
| Skull fracture(s) | 180 | 9 ± 15* | 3 ± 6* | 7 ± 11 | 15,450; 8,190 (3,350-16,560)* |
| Compressed basal cisterna | 88 | 12 ± 18* | 4 ± 7* | 8 ± 13 | 21,000; 10,520 (6,500-26,030)* |
| Midline shift >5mm | 65 | 12 ± 15* | 4 ± 7* | 8 ± 12 | 21,290; 12,410 (6,810-26,440)* |
| Mass lesion >25 cc | 80 | 12 ± 18* | 5 ± 8* | 8 ± 13 | 21,590; 11,840 (6,960-25,230)* |
| <u>Surgical intervention:</u> | | | | | |
| Intracranial surgery | 67 | 21 ± 23* | 8 ± 9* | 13 ± 18* | 36,870; 26,440 (13,210-48,500)* |
| No intracranial surgery | 419 | 6 ± 8 | 1 ± 4 | 5 ± 7 | 7,930; 4,110 (2,600-8,960) |
| ICP monitoring | 40 | 27 ± 28* | 12 ± 9* | 16 ± 22* | 47,260; 41,850 (21,480-63,500)* |
| No ICP monitoring | 446 | 6 ± 9 | 1 ± 4 | 5 ± 7 | 8,750; 4,510 (2,640-10,900) |
| Craniotomy | 33 | 19 ± 21* | 7 ± 9* | 12 ± 16* | 33,200; 21,410 (12,210-42,430)* |
| Decompressive craniectomy | 24 | 28 ± 27* | 11 ± 9* | 17 ± 21* | 49,750; 41,970 (26,400-68,830)* |
| Extracranial surgery | 65 | 12 ± 14* | 2 ± 6 | 10 ± 12* | 19,960; 13,900 (10,740-24,630)* |
| No extracranial surgery | 421 | 7 ± 13 | 2 ± 5 | 6 ± 9 | 10,680; 4,130 (2,610-10,050) |
| <u>In hospital mortality</u> | | | * | * | |
| Yes | 60 | 7 ± 9 | 4 ± 6 | 3 ± 6 | 17,250; 9,020 (6,540-22,550) |
| No | | 8 ± 13 | 2 ± 5 | 7 ± 10 | 11,170; 4,530 (2,640-11,890) |
| <u>GOSE 6 months</u> | | * | * | * | * |
| 1 | 73 | 9 ± 13 | 4 ± 7 | 4 ± 10 | 18,240; 8,960 (5,860-21,560) |
| 2/3 | 17 | 30 ± 29 | 7 ± 9 | 23 ± 21 | 36,190; 17,260 (12,290-48,500) |
| 4 | 23 | 8 ± 8 | 2 ± 6 | 6 ± 6 | 13,160; 7,940 (2,890-15,700) |
| 5 | 25 | 9 ± 8 | 2 ± 3 | 7 ± 6 | 13,080; 10,150 (3,840-15,130) |
| 6 | 38 | 7 ± 8 | 1 ± 2 | 7 ± 7 | 10,480; 5,350 (3,330-13,220) |
| 7 | 110 | 7 ± 9 | 1 ± 5 | 5 ± 7 | 9,100; 4,010 (2,780-9,550) |
| 8 | 131 | 4 ± 4 | 0 ± 1 | 4 ± 4 | 5,780; 3,210 (2,310-7,260) |

Table 2 legends:

Caption: Table 2 shows the length of stay and the in-hospital costs of patients with traumatic brain injury.

Legend:

Values are reported as:

Mean ± SD or Mean; Median (IQR 25-75)

*P value <0.05: p values were derived from ANOVA for continuous characteristics. The p value assessed compatibility with the null hypothesis of no differences in mean values between row categories.

Costs were rounded to the nearest ten euros

Favourable and unfavourable were defined as GOSE 5-8 and GOSE 1-4 respectively.

| Admission costs | Surgery costs | Radiology costs | Laboratory costs |
|---------------------------------|------------------------------|-----------------------------|-----------------------------|
| 7,900; 2,670 (1,430-7,090) | 1,490; 0 (0-1,820) | 840; 670 (350-1,080) | 650; 130 (59-580) |
| | | * | |
| 4,110; 1,840 (1,180-2,600) | 650; 0 (0-0) | 460; 300 (130-440) | 210; 50 (0-70) |
| 8,230; 2,440 (1,370-6,810) | 1,760; 0 (0-3,160) | 900; 780 (370-1,160) | 620; 100 (60-470) |
| 7,940; 3,800 (1,840-7,620) | 1,270; 0 (0-0) | 810; 650 (350-980) | 740; 200 (70-780) |
| * | * | * | * |
| 4,900; 2,050 (1,430-5,250) | 1,000; 0 (0-0) | 720; 570 (310-930) | 330; 80 (60-240) |
| 13,900; 8,680 (2,500-18,910) | 3,010; 0 (0-4,520) | 1,140; 890 (480-1,560) | 1,170; 570 (160-1,820) |
| 18,630; 6,570 (2,670-26,410) | 2,950; 0 (0-4,520) | 1,240; 980 (720-1,650) | 1,660; 730 (240-2,550) |
| 18,140; 6,230 (2,670-30,600) | 2,790; 0 (0-4,530) | 1,310; 1,010 (760-1,940) | 1,730; 790 (240-2,980) |
| * | * | | * |
| 7,540; 2,600 (1,430-7,070) | 1,400; 0 (0-0) | 830; 650 (340-1,070) | 560; 110 (60-480) |
| 22,330; 6,420 (2,890-33,050) | 4,210; 3,840 (0-7,440) | 1,250; 1,290 (290-2,260) | 2,330; 1,120 (370-4,480) |
| 7,570; 2,670 (2,340-7,210) | 1,800; 0 (0-4,520) | 880; 840 (660-1,010) | 1,160; 570 (210-1,230) |
| | | | |
| 10,830; 4,340 (1,880-10,290)* | 1,860; 0 (0-3,720)* | 930; 760 (400-1,190)* | 940; 240 (70-1,080)* |
| 3,860; 1,840 (1,180-3,950) | 870; 0 (0-0) | 700; 500 (290-920) | 260; 70 (60-190) |
| 12,740; 5,580 (2,340-15,670)* | 2,190; 0 (0-3,720)* | 970; 800 (500-1,210)* | 1,010; 370 (70-1,230)* |
| 12,250; 4,930 (2,340-13,520)* | 2,120; 0 (0-4,520)* | 990; 840 (450-1,280)* | 1,080; 400 (80-1,280)* |
| 11,390; 4,670 (1,840-11,520) | 1,980; 0 (0-1,820) | 910; 790 (400-1,140) | 720; 220 (60-710) |
| 11,180; 4,680 (1,880-13,170)* | 2,290; 0 (0-4,520) | 950; 790 (460-1,200)* | 1,100; 410 (100-1,350)* |
| 10,620; 4,140 (1,970-12,300)* | 1,730; 0 (0-3,160) | 900; 770 (400-1,190) | 900; 240 (60-1,070)* |
| 13,890; 5,710 (2,670-17,210)* | 3,190; 1,580 (0-4,520)* | 1,080; 860 (590-1,520)* | 1,460; 570 (200-1,930)* |
| 13,950; 6,530 (2,670-16,940)* | 3,630; 4,520 (0-4,530)* | 1,050; 820 (570-1,480)* | 1,420; 770 (240-1,910)* |
| 14,620; 6,630 (2,670-15,060)* | 3,230; 3,530 (0-4,520)* | 1,120; 840 (590-1,540)* | 1,420; 560 (220-1,520)* |
| | | | |
| 24,970; 15,560 (6,740-33,050)* | 6,670; 4,530 (4,520-8,250)* | 1,510; 1,230 (840-2,100)* | 2,300; 1,480 (570-4,280)* |
| 5,170; 2,400 (1,430-5,300) | 670; 0 (0-0) | 730; 600 (310-960) | 390; 90 (60-300) |
| 33,670; 26,530 (13,100-50,180)* | 7,220; 5,430 (4,520-8,250)* | 1,690; 1,710 (870-2,310)* | 2,880; 1,960 (1,040-4,780)* |
| 5,590; 2,500 (1,430-5,840) | 980; 0 (0-0) | 760; 630 (310-980) | 450; 110 (60-400) |
| 21,790; 11,900 (5,690-26,650)* | 7,200; 4,530 (4,520-9,060)* | 1,300; 970 (610-1,750)* | 1,890; 1,080 (500-2,750)* |
| 34,370; 26,530 (14,120-50,400)* | 8,880; 8,240 (4,530-10,500)* | 1,840; 1,880 (1,110-2,310)* | 3,230; 2,850 (1,290-4,940)* |
| 11,620; 6,190 (3,350-13,510) | 5,010; 3,350 (3,160-6,490)* | 1,250; 1,190 (750-1,680)* | 820; 310 (130-1,070) |
| 7,320; 2,500 (1,430-6,400) | 950; 0 (0-0) | 770; 610 (310-970) | 630; 110 (60-530) |
| | * | | * |
| 10,790; 4,330 (2,670-14,540) | 2,320; 0 (0-4,520) | 980; 840 (640-1,160) | 1,490; 910 (240-1,940) |
| 7,490; 2,500 (1,430-6,740) | 1,380; 0 (0-0) | 820; 640 (310-1,070) | 530; 100 (60-420) |
| * | * | * | * |
| 11,890; 4,520 (2,670-13,520) | 2,370; 0 (0-4,520) | 980; 820 (570-1,200) | 1,510; 970 (240-1,960) |
| 26,570; 13,010 (5,420-34,890) | 4,710; 3,720 (0-7,070) | 1,850; 1,750 (1,320-2,260) | 2,060; 1,460 (220-4,280) |
| 8,420; 2,890 (1,620-8,270) | 1,760; 0 (0-3,250) | 1,180; 1,040 (270-1,800) | 670; 120 (60-460) |
| 8,180; 5,140 (2,220-11,600) | 1,930; 0 (0-1,820) | 900; 830 (520-1,140) | 730; 180 (70-920) |
| 6,210; 2,790 (1,370-6,430) | 1,810; 0 (0-3,160) | 1,000; 880 (530-1,190) | 370; 80 (60-370) |
| 6,130; 2,030 (1,430-5,840) | 840; 0 (0-0) | 770; 650 (370-980) | 410; 80 (60-360) |
| 3,560; 1,880 (1,180-4,570) | 670; 0 (0-0) | 560; 410 (270-780) | 220; 70 (60-200) |

Abbreviations:

AIS: abbreviated injury scale

CT-scan: Computed Tomography scan

GCS: Glasgow Coma Score

GOSE: Glasgow Outcome Score – Extended

ICU: Intensive care unit

SAH: subarachnoid hemorrhage

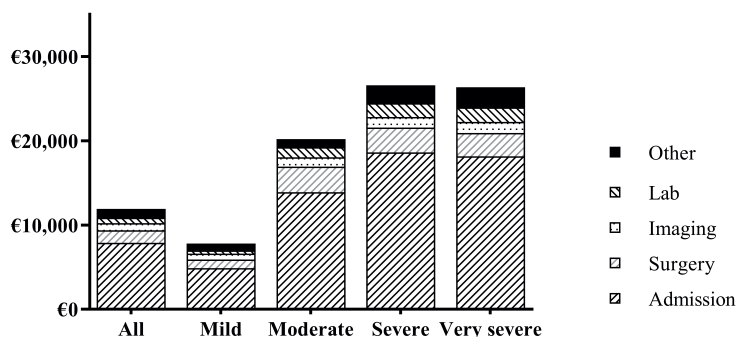


Figure 2. In-hospital healthcare consumption & in-hospital costs

Figure 2 shows the mean in-hospital costs for patients with TBI, specified per severity category and per cost category to show their contribution to the total in-hospital costs.

In-hospital costs

Mean in-hospital costs were €11,918. €7,896 was related to admission (66%), € 1,493 to surgery (13%), and € 1,042 to other (9%). (Table 2) Costs related to radiology (7%) and laboratory (5%) were smaller contributors. Average in-hospital costs were € 7,795 for mild, €20,207 for moderate € 26,595 for severe, and € 26,349 for very severe TBI patients. (Figure 2) Presence of intracranial abnormalities on the first CT-scan nearly doubled total in-hospital costs (€ 15,783 vs. € 8,238). Intracranial surgery or ICP monitoring quadrupled the costs (respectively € 36,866 vs. € 7,928 and € 47,255 vs. € 8,748). Patients with a decompressive craniectomy (€ 49,754), 'regular' craniotomy (€ 33,195) or extracranial surgery (€ 19,957) were also more expensive compared to non-surgically treated patients. Patients with a 6-month GOSE score of 8 showed the lowest in-hospital costs of € 5,774, while patients with a GOSE score of 2/3 showed costs of € 36,190.

DISCUSSION

The current study found substantial in-hospital healthcare consumption and high in-hospital costs for hospitalized TBI patients, even after mild TBI. Both length of stay and in-hospital costs increased with TBI severity and presence of intracranial abnormalities and extracranial injuries. The most important cost drivers were admission and surgical intervention. Patients from all TBI severity categories were able to achieve full recovery, even after sustaining very severe TBI. Nonetheless, mortality and unfavourable outcome rates were high and the majority of patients reported remaining deficits or disabilities after 6 months.

Study cohort

The predominance of male gender, injury mechanisms (road traffic accidents and falls) and distribution of TBI severity were in accordance with recent literature.^{1,24-26} The mean age of 56 years was rather high compared to earlier research²⁴, but matched changing epidemiological patterns.² The number of intracranial CT abnormalities in mild TBI patients was higher compared to literature (45.2% vs. 16.1%).²⁷ This is likely caused by different inclusion criteria (hospital admission after TBI vs. ED presentation with head CT after suspected TBI) and differences in accuracy between central and local radiological reading.¹⁸ The number of patients with major extracranial injury (AIS \geq 3) and pupillary abnormalities was also higher compared to literature^{28,29} and the overall CENTER-TBI Core study cohort.⁹ These factors, with other factors like comorbidities and use of anticoagulants, could have negatively influenced patient outcome and/or increased the reported in-hospital healthcare consumption and in-hospital costs in this study.

Patient outcome

Mortality rates were generally high, but difficult to compare with other studies due to methodological differences.^{2,30,31} One meta-analysis reported higher 'all time point' mortality rates for patients of all TBI severities³², while other studies showed lower mortality rates for mild TBI³³, moderate TBI³¹, and severe TBI.^{30,34} Favourable outcome (6-month GOSE) rates were generally higher in literature.³⁵⁻³⁰⁻³¹ Differences in patient outcome can largely be explained by patient related factors that are known to be associated with worse outcome. Such factors include higher age, higher injury severity, poorer initial neurologic condition and higher TBI severity (defined by GCS) and are reported above average in our cohort.^{32,36,37} For instance, the inclusion of patients with a GCS=3 and/or bilateral pupillary abnormalities influences the comparison of patient outcome, as they are typically excluded in literature because of their often-perceived dismal prognosis.³⁸ That even the most severely injured patients were able to achieve favourable outcome and even full recovery, although rarely, has been reported previously.³⁶

The increase in mortality rates (12.3% to 15%) and data on persisting deficits and disabilities after 6 months confirm the need for increased vigilance and attention for rehabilitation or long-term care opportunities. Sustained health problems after TBI have also been reported by long-term follow up studies³⁹⁻⁴², some reporting deterioration between 5 and 10 years⁴³, others reporting remaining functional limitations up to 20 years after moderate and severe TBI.⁴⁴ Long term impairments are not limited to severe TBI, but are also reported after mild TBI.^{7,8} Despite the short 6-month follow up, our results support statements that consider TBI to be an acute

injury resulting into a chronic health condition that requires continued care for most patients. TBI should therefore be addressed as such by healthcare providers, researchers and policymakers.^{45,46}

Length of stay

Healthcare consumption in terms of length of stay and surgical intervention was substantial. However, when comparing our overall results to numbers for patients (age <65) from Canada, our mean LOS (days) was shorter for all patients (8 vs. 13), for patients with mild TBI (6 vs. 9) and severe TBI (15 vs. 22) but similar for moderate TBI (14 vs. 14).⁴⁷ Median LOS was also shorter for mild TBI (3 vs. 9), moderate TBI (7 vs. 11) and severe TBI (7 vs. 12) compared to recent numbers from England and Wales.²⁵ In a review on hospital costs for severe TBI patients, total LOS ranged between 10 and 36.8 days and ICU LOS between 7.9 and 25.8 days.¹² The large ranges are exemplary for the existing variation, that is primarily caused by patient case-mix and treatment-related factors.⁴⁸ Several factors that we found to be associated with an increased total LOS were also mentioned in literature: lower GCS, higher TBI severity and the presence of extracranial injury^{47,49}, ICP monitoring^{50,51} and decompressive craniectomy.^{52,53}

There were several exceptions. For instance, the most severely injured TBI patients were sometimes admitted to the ward because of treatment limiting decisions shortly after presentation.⁵⁴ This could explain the lower LOS and lower in-hospital costs for very severe TBI patients and patients with two non-reacting pupils. Similarly, some mild TBI patients could have been admitted to the ICU because of (suspected) deterioration or over-triage or non-TBI related issues such as age, comorbidities, and concomitant extracranial injuries.^{55,56}

In-hospital costs

The median costs and interquartile range indicate that costs were skewed by a small group of patients with very high costs. The reported costs were generally similar to available literature. One Dutch study reported that the direct and indirect costs for all TBI patients were €18,030.⁵⁷ Costs were higher for Dutch patients with severe TBI (range €40,680 - €44,952), but these costs included rehabilitation and nursing home costs.⁵⁸ A recent systematic review reported median in-hospital costs per patient with severe TBI of €55,267 (range €2,130 to €401,808).¹² Mean hospital and healthcare charges for TBI in the USA were \$36.075 and \$67.224 respectively.^{59,60} Differences between studies could be explained by variation, methodological heterogeneity, differences in case mix, but also by geographical location. For example, healthcare expenditures in

the USA are generally double of other high-income countries due to prices of labour, goods, pharmaceuticals and administrative costs, while healthcare utilization was similar.⁶¹ These issues are also reported in non-TBI literature.^{62,63}

As in other studies, the main cost drivers in this current study were LOS and/or admission (66%), surgery (12%), radiology (7%), labs (4%) and other costs (11%).^{60,64,65} In-hospital costs were generally higher for the more severely injured patients^{59,64}, with a lower GCS^{12,64,66-68} or pupillary abnormalities.²¹ Higher costs were related to an increased healthcare consumption with longer LOS^{60,66}, specialized intensive care unit (ICU) treatment⁶⁰ and a more frequent use of ICP monitoring^{50,65,69} and surgical procedures.^{21,64,70} The presence of TBI normally increases the LOS of general admissions⁴⁷, but extracranial injury and higher overall injury severity in addition to TBI also contributed to higher in-hospital healthcare consumption and in-hospital costs.^{49,70,71} It is however impossible to distinguish costs related to extracranial injury from costs related to TBI because these costs are too intertwined.

Compared to the hospital costs for other diseases in the Netherlands, the in-hospital costs for TBI patients were high, especially when TBI severity increased. The hospital costs for patients with ischaemic stroke (€5,328)⁷², transient ischaemic attack (€2,470)⁷², appendicitis (€3700), colorectal cancer (€9,777 – €19,417)⁷³ were lower, while costs were higher for patients with non-small cell lung cancer (€33,143)⁷⁴ or patients receiving extracorporeal life support treatment (€106,263).⁷⁵

Strengths and limitations

The accurate calculation of in-hospital healthcare consumption and in-hospital costs of a large prospective multicenter cohort is a strength of the current study. There are also several limitations. The GCS is usually used to determine TBI severity²⁴, but its general applicability as a severity measure is also criticized.⁷⁶ The GCS could have been influenced by intoxication, pharmacological sedation, prehospital intubation, extracranial injury and could thereby have over- and underestimated injury severity.⁷⁷ This could have influenced study results. In a similar way, patient outcome was measured by using in-hospital mortality and GOSE. Critics state that the GOSE insufficiently accounts for the multidimensional nature of TBI outcome.² Unfortunately, earlier reported problems with acquiring the disease related health related quality of life outcome measure QOLIBRI resulted in too many missing data points to be useful for this manuscript.²¹ Another limitation is the short-term follow up, because it is known that patient outcome and costs can change over time.^{43,45,46}

TBI patients that visited the ER but did not require hospitalisation were not included in this study. A precise calculation and comparison of costs was therefore not possible. Costs of these patients are expected to be substantially lower compared to admitted patients since important cost drivers (admission and surgery) are not applicable. Following the unit costs in Supplement 1 (ER, imaging, labs), the average costs are likely to be somewhere between €500 - €1.000. A reduction in number of admitted mild TBI patients, when safe and possible, might result in substantial cost savings, especially since its incidence is high.

The direct costs of TBI (all consumed resources within the health-care sector) are generally considered to be smaller than the indirect costs (loss of productivity and intangible costs).^{2,78,79} Because of the focus on in-hospital costs, our study results dramatically underestimate the exact total costs related to TBI.^{57,80,81} The reported in-hospital costs are also likely to be an underestimation, despite our accurate calculations. More accurate numbers could be achieved by using hospitals' actual cost prices, rather than approximations from guidelines or governmental organizations. These numbers were unfortunately unavailable. Including an accurate complete cost overview is however essential for future cost-effectiveness studies.^{66,80-82}

Future TBI research initiatives should include the combination of long-term outcome and complete economic perspective, because this can improve the objectivity of future treatment decision-making. When striving for cost-effectiveness, people should however not forget the individual aspects of care and the social utility of providing care for severely injured patients.⁸³

CONCLUSIONS

Hospitalized TBI patients show substantial in-hospital healthcare consumption and high in-hospital costs, even in patients with mild TBI. These costs are likely to be an underestimation of the actual total costs after TBI. Although patients from all TBI severity categories were able to achieve full recovery, mortality and unfavourable outcome rates were high and increased with TBI severity, intracranial abnormalities, extracranial injury and surgical intervention. Future studies should focus on the long-term effectiveness of treatments in relation to a complete economic perspective.

REFERENCES

1. Dewan MC, Rattani A, Gupta S, et al. Estimating the global incidence of traumatic brain injury. *J Neurosurg* 2018; 1-18.
2. Maas AIR, Menon DK, Adelson PD, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. *Lancet Neurol* 2017; **16**(12): 987-1048.
3. Volovici V, Steyerberg EW, Cnossen MC, et al. Evolution of Evidence and Guideline Recommendations for the Medical Management of Severe Traumatic Brain Injury. *J Neurotrauma* 2019; **36**(22): 3183-9.
4. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. *Neurosurgery* 2017; **80**(1): 6-15.
5. Beck B, Gantner D, Cameron P, et al. Temporal trends in functional outcomes following severe traumatic brain injury: 2006-2015. *J Neurotrauma* 2017.
6. Fountain DM, Kolias AG, Lecky FE, et al. Survival Trends After Surgery for Acute Subdural Hematoma in Adults Over a 20-year Period. *Ann Surg* 2017; **265**(3): 590-6.
7. De Koning ME, Scheenen ME, Van Der Horn HJ, Spikman JM, Van Der Naalt J. From 'miserable minority' to the 'fortunate few': the other end of the mild traumatic brain injury spectrum. *Brain Inj* 2018; **32**(5): 540-3.
8. van der Naalt J, Timmerman ME, de Koning ME, et al. Early predictors of outcome after mild traumatic brain injury (UPFRONT): an observational cohort study. *Lancet Neurol* 2017; **16**(7): 532-40.
9. Steyerberg EW, Wiegers E, Sewalt C, et al. Case-mix, care pathways, and outcomes in patients with traumatic brain injury in CENTER-TBI: a European prospective, multicentre, longitudinal, cohort study. *Lancet Neurol* 2019; **18**(10): 923-34.
10. Frontera JA, Egorova N, Moskowitz AJ. National trend in prevalence, cost, and discharge disposition after subdural hematoma from 1998-2007. *Crit Care Med* 2011; **39**(7): 1619-25.
11. Raj R, Bendel S, Reinikainen M, et al. Costs, outcome and cost-effectiveness of neurocritical care: a multi-center observational study. *Crit Care* 2018; **22**(1): 225.
12. van Dijk J, Dijkman MD, Ophuis RH, de Ruiter GCW, Peul WC, Polinder S. In-hospital costs after severe traumatic brain injury: A systematic review and quality assessment. *PLoS One* 2019; **14**(5): e0216743.
13. Alali AS, Burton K, Fowler RA, et al. Economic Evaluations in the Diagnosis and Management of Traumatic Brain Injury: A Systematic Review and Analysis of Quality. *Value Health* 2015; **18**(5): 721-34.
14. Lu J, Roe C, Aas E, et al. Traumatic brain injury: methodological approaches to estimate health and economic outcomes. *Journal of neurotrauma* 2013; **30**(23): 1925-33.
15. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for reporting observational studies. *Preventive Medicine* 2007; **45**(4): 247-51.
16. Maas AI, Menon DK, Steyerberg EW, et al. Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): a prospective longitudinal observational study. *Neurosurgery* 2015; **76**(1): 67-80.
17. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet* 1974; **2**(7872): 81-4.
18. Vande Vyvere T, Wilms G, Claes L, et al. Central versus Local Radiological Reading of Acute Computed Tomography Characteristics in Multi-Center Traumatic Brain Injury Research. *J Neurotrauma* 2019; **36**(7): 1080-92.
19. Wilson JT, Pettigrew LE, Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. *J Neurotrauma* 1998; **15**(8): 573-85.
20. Hakkaart-van Roijen L vdLN, Bouwmans CAM, Kanter TA, Tan SS. Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. . Zorginstituut Nederland; Geactualiseerde versie 2015(<https://www.zorginstituutnederland.nl/binaries/zinl/documenten/publicatie/2016/02/29/richtlijn-voor-het-uitvoeren-van-economische-evaluaties-in-de-gezondheidszorg/Richtlijn+voor+het+uitvoeren+van+economische+evaluaties+in+de+gezondheidszorg+%28verdiepings-modules%29.pdf> (accessed 30-03-2018)).
21. van Dijk J, van Essen TA, Dijkman MD, et al. Functional and patient-reported outcome versus in-hospital costs after traumatic acute subdural hematoma (t-ASDH): a neurosurgical paradox? *Acta Neurochir (Wien)* 2019.
22. Zorgautoriteit N. Tarieventabel DBC-zorgproducten en overige producten - per 1 januari 2012 (PUC_12710_22). https://puc.overheid.nl/nza/doc/PUC_12710_22/1/. (accessed Accessed March 29 2018).
23. Zorgautoriteit DN. Open data van de Nederlandse Zorgautoriteit.
24. Brazinova A, Rehorcikova V, Taylor MS, et al. Epidemiology of Traumatic Brain Injury in Europe: A Living Systematic Review. *Journal of neurotrauma* 2018.
25. Lawrence T, Helmy A, Bouamra O, Woodford M, Lecky F, Hutchinson PJ. Traumatic brain injury in England and Wales: prospective audit of epidemiology, complications and standardised mortality. *BMJ Open* 2016; **6**(11): e012197.
26. Majdan M, Plancikova D, Brazinova A, et al. Epidemiology of traumatic brain injuries in Europe: a cross-sectional analysis. *Lancet Public Health* 2016; **1**(2): e76-e83.

27. Isokuortti H, Iverson GL, Silverberg ND, et al. Characterizing the type and location of intracranial abnormalities in mild traumatic brain injury. *Journal of neurosurgery* 2018; **129**(6): 1588-97.
28. Watanabe T, Kawai Y, Iwamura A, Maegawa N, Fukushima H, Okuchi K. Outcomes after Traumatic Brain Injury with Concomitant Severe Extracranial Injuries. *Neurol Med Chir (Tokyo)* 2018; **58**(9): 393-9.
29. van Leeuwen N, Lingsma HF, Perel P, et al. Prognostic value of major extracranial injury in traumatic brain injury: an individual patient data meta-analysis in 39,274 patients. *Neurosurgery* 2012; **70**(4): 811-8; discussion 8.
30. Rosenfeld JV, Maas AI, Bragge P, Morganti-Kossmann MC, Manley GT, Gruen RL. Early management of severe traumatic brain injury. *The Lancet* 2012; **380**(9847): 1088-98.
31. Einarsen CE, van der Naalt J, Jacobs B, et al. Moderate Traumatic Brain Injury: Clinical Characteristics and a Prognostic Model of 12-Month Outcome. *World Neurosurg* 2018; **114**: e1199-e210.
32. McIntyre A, Mehta S, Aubut J, Dijkers M, Teasell RW. Mortality among older adults after a traumatic brain injury: a meta-analysis. *Brain injury* 2013; **27**(1): 31-40.
33. Carroll LJ, Cassidy JD, Cancelliere C, et al. Systematic Review of the Prognosis After Mild Traumatic Brain Injury in Adults: Cognitive, Psychiatric, and Mortality Outcomes: Results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. *Archives of Physical Medicine and Rehabilitation* 2014; **95**(3, Supplement): S152-S73.
34. Stein SC, Georgoff P, Meghan S, Mizra K, Sonnad SS. 150 years of treating severe traumatic brain injury: a systematic review of progress in mortality. *J Neurotrauma* 2010; **27**(7): 1343-53.
35. McIntyre A, Mehta S, Janzen S, Aubut J, Teasell RW. A meta-analysis of functional outcome among older adults with traumatic brain injury. *NeuroRehabilitation* 2013; **32**(2): 409-14.
36. van Dijk JT, Reith FC, van Erp IA, et al. Decision making in very severe traumatic brain injury (Glasgow Coma Scale 3-5): a literature review of acute neurosurgical management. *Journal of neurosurgical sciences* 2018; **62**(2): 153-77.
37. Krishnamoorthy V, Vavilala MS, Mills B, Rowhani-Rahbar A. Demographic and clinical risk factors associated with hospital mortality after isolated severe traumatic brain injury: a cohort study. *Journal of Intensive Care* 2015; **3**(1): 46.
38. Tien HC, Cunha JR, Wu SN, et al. Do trauma patients with a Glasgow Coma Scale score of 3 and bilateral fixed and dilated pupils have any chance of survival? *J Trauma* 2006; **60**(2): 274-8.
39. Grauwmeijer E, Heijenbrok-Kal MH, Peppel LD, et al. Cognition, Health-Related Quality of Life, and Depression Ten Years after Moderate to Severe Traumatic Brain Injury: A Prospective Cohort Study. *Journal of neurotrauma* 2018; **35**(13): 1543-51.
40. Ruet A, Bayen E, Jourdan C, et al. A Detailed Overview of Long-Term Outcomes in Severe Traumatic Brain Injury Eight Years Post-injury. *Frontiers in neurology* 2019; **10**: 120.
41. Moskowitz E, Melendez CI, Dunn J, et al. Long-Term Effects of Decompressive Craniectomy on Functional Outcomes after Traumatic Brain Injury: A Multicenter Study. *The American surgeon* 2018; **84**(8): 1314-8.
42. Ventura T, Harrison-Felix C, Carlson N, et al. Mortality after discharge from acute care hospitalization with traumatic brain injury: a population-based study. *Arch Phys Med Rehabil* 2010; **91**(1): 20-9.
43. Forslund MV, Perrin PB, Roe C, et al. Global Outcome Trajectories up to 10 Years After Moderate to Severe Traumatic Brain Injury. *Frontiers in neurology* 2019; **10**: 219.
44. Andelic N, Howe EI, Hellstrom T, et al. Disability and quality of life 20 years after traumatic brain injury. *Brain and behavior* 2018; **8**(7): e01018.
45. Wilson L, Stewart W, Dams-O'Connor K, et al. The chronic and evolving neurological consequences of traumatic brain injury. *The Lancet Neurology* 2017; **16**(10): 813-25.
46. Stocchetti N, Zanier ER. Chronic impact of traumatic brain injury on outcome and quality of life: a narrative review. *Critical Care* 2016; **20**(1): 148.
47. Tardif PA, Moore L, Boutin A, et al. Hospital length of stay following admission for traumatic brain injury in a Canadian integrated trauma system: A retrospective multicenter cohort study. *Injury* 2017; **48**(1): 94-100.
48. Moore L, Stelfox HT, Evans D, et al. Hospital and Intensive Care Unit Length of Stay for Injury Admissions: A Pan-Canadian Cohort Study. *Annals of surgery* 2018; **267**(1): 177-82.
49. Davis KL, Joshi AV, Tortella BJ, Candrilli SD. The direct economic burden of blunt and penetrating trauma in a managed care population. *J Trauma* 2007; **62**(3): 622-9.
50. Su SH, Wang F, Hai J, et al. The effects of intracranial pressure monitoring in patients with traumatic brain injury. *PloS one* 2014; **9**(2): e87432.
51. Piccinini A, Lewis M, Benjamin E, Aiolfi A, Inaba K, Demetriades D. Intracranial pressure monitoring in severe traumatic brain injuries: a closer look at level 1 trauma centers in the United States. *Injury* 2017; **48**(9): 1944-50.
52. Keita S, Kazuhiro S, Jun T, Hidenori H, Akio M. In-hospital mortality and length of hospital stay with craniotomy versus craniectomy for acute subdural hemorrhage: a multicenter, propensity score-matched analysis. *Journal of Neurosurgery JNS* 2019: 1-10.
53. Rush B, Rousseau J, Sekhon MS, Griesdale DE. Craniotomy Versus Craniectomy for Acute Traumatic Subdural Hematoma in the United States: A National Retrospective Cohort Analysis. *World Neurosurg* 2016; **88**: 25-31.
54. Robertsen A, Førde R, Skaga NO, Helseth E. Treatment-limiting decisions in patients with severe traumatic brain injury in a Norwegian regional trauma center. *Scand J Trauma Resusc Emerg Med* 2017; **25**(1): 44-.

55. Bonow RH, Quistberg A, Rivara FP, Vavilala MS. Intensive Care Unit Admission Patterns for Mild Traumatic Brain Injury in the USA. *Neurocrit Care* 2019; **30**(1): 157-70.
56. Marinowitz C, Lecky FE, Townend W, Borakati A, Fabbri A, Sheldon TA. The Risk of Deterioration in GCS13-15 Patients with Traumatic Brain Injury Identified by Computed Tomography Imaging: A Systematic Review and Meta-Analysis. *Journal of neurotrauma* 2018; **35**(5): 703-18.
57. Scholten AC, Haagsma JA, Panneman MJ, van Beeck EF, Polinder S. Traumatic brain injury in the Netherlands: incidence, costs and disability-adjusted life years. *PLoS One* 2014; **9**(10): e110905.
58. Saltzherr TP, Goslings JC, Bakker FC, et al. Cost-effectiveness of trauma CT in the trauma room versus the radiology department: The REACT trial. *European Radiology* 2013; **23**(1): 148-55.
59. Marin JR, Weaver MD, Mannix RC. Burden of USA hospital charges for traumatic brain injury. *Brain Injury* 2017; **31**(1): 24-31.
60. Albrecht JS, Slejko JF, Stein DM, Smith GS. Treatment Charges for Traumatic Brain Injury Among Older Adults at a Trauma Center. *J Head Trauma Rehabil* 2017.
61. Papanicolaou I, Woskie LR, Jha AK. Health Care Spending in the United States and Other High-Income Countries. *Jama* 2018; **319**(10): 1024-39.
62. Cnossen MC, Polinder S, Andriessen TM, et al. Causes and Consequences of Treatment Variation in Moderate and Severe Traumatic Brain Injury: A Multicenter Study. *Critical care medicine* 2017; **45**(4): 660-9.
63. Polinder S, Meerding WJ, van Baar ME, Toet H, Mulder S, van Beeck EF. Cost estimation of injury-related hospital admissions in 10 European countries. *J Trauma* 2005; **59**(6): 1283-90; discussion 90-1.
64. Morris S, Ridley S, Lecky FE, Munro V, Christensen MC. Determinants of hospital costs associated with traumatic brain injury in England and Wales. *Anaesthesia* 2008; **63**(5): 499-508.
65. Zapata-Vazquez RE, Alvarez-Cervera FJ, Alonzo-Vazquez FM, et al. Cost Effectiveness of Intracranial Pressure Monitoring in Pediatric Patients with Severe Traumatic Brain Injury: A Simulation Modeling Approach. *Value in health regional issues* 2017; **14**: 96-102.
66. Ponsford JL, Spitz G, Cromarty F, Gifford D, Attwood D. Costs of care after traumatic brain injury. *Journal of neurotrauma* 2013; **30**(17): 1498-505.
67. Te Ao B, Brown P, Tobias M, et al. Cost of traumatic brain injury in New Zealand: evidence from a population-based study. *Neurology* 2014; **83**(18): 1645-52.
68. Ho KM, Honeybul S, Lind CR, Gillett GR, Litton E. Cost-effectiveness of decompressive craniectomy as a lifesaving rescue procedure for patients with severe traumatic brain injury. *J Trauma* 2011; **71**(6): 1637-44; discussion 44.
69. Martini RP, Deem S, Yanez ND, et al. Management guided by brain tissue oxygen monitoring and outcome following severe traumatic brain injury. *Journal of neurosurgery* 2009; **111**(4): 644-9.
70. Yuan Q, Liu H, Wu X, et al. Characteristics of acute treatment costs of traumatic brain injury in Eastern China—a multi-centre prospective observational study. *Injury* 2012; **43**(12): 2094-9.
71. Spitz G, McKenzie D, Attwood D, Ponsford JL. Cost prediction following traumatic brain injury: model development and validation. *Journal of neurology, neurosurgery, and psychiatry* 2016; **87**(2): 173-80.
72. Buisman LR, Tan SS, Nederkoorn PJ, Koudstaal PJ, Redekop WK. Hospital costs of ischemic stroke and TIA in the Netherlands. *Neurology* 2015; **84**(22): 2208-15.
73. Govaert JA, van Dijk WA, Fiocco M, et al. Nationwide Outcomes Measurement in Colorectal Cancer Surgery: Improving Quality and Reducing Costs. *J Am Coll Surg* 2016; **222**(1): 19-29.e2.
74. van der Linden N, Bongers ML, Coupe VM, et al. Costs of non-small cell lung cancer in the Netherlands. *Lung Cancer* 2016; **91**: 79-88.
75. Oude Lansink-Hartgring A, van den Hengel B, van der Bij W, et al. Hospital Costs Of Extracorporeal Life Support Therapy. *Critical care medicine* 2016; **44**(4): 717-23.
76. Becker A, Peleg K, Olsha O, Givon A, Kessel B. Analysis of incidence of traumatic brain injury in blunt trauma patients with Glasgow Coma Scale of 12 or less. *Chinese journal of traumatology = Zhonghua chuang shang za zhi* 2018; **21**(3): 152-5.
77. Salottolo K, Carrick M, Levy AS, et al. Aggressive operative neurosurgical management in patients with extra-axial mass lesion and Glasgow Coma Scale of 3 is associated with survival benefit: A propensity matched analysis. *Injury* 2016; **47**(1): 70-6.
78. Gustavsson A, Svensson M, Jacobi F, et al. Cost of disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol* 2011; **21**(10): 718-79.
79. Olesen J, Gustavsson A, Svensson M, Wittchen HU, Jonsson B. The economic cost of brain disorders in Europe. *Eur J Neurol* 2012; **19**(1): 155-62.
80. Majdan M, Plancikova D, Maas A, et al. Years of life lost due to traumatic brain injury in Europe: A cross-sectional analysis of 16 countries. *PLoS medicine* 2017; **14**(7): e1002331.
81. Tuominen R, Joelsson P, Tenovu O. Treatment costs and productivity losses caused by traumatic brain injuries. *Brain injury* 2012; **26**(13-14): 1697-701.
82. Chen A, Bushmeneva K, Zagorski B, Colantonio A, Parsons D, Wodchis WP. Direct cost associated with acquired brain injury in Ontario. *BMC neurology* 2012; **12**: 76.
83. Honeybul S, Gillett GR, Ho KM, Lind CR. Neurotrauma and the rule of rescue. *Journal of medical ethics* 2011; **37**(12): 707-10.



CHAPTER 6

The patient with severe traumatic brain injury: clinical decision-making: the first 60 min and beyond.

Authors:

Jeroen T.J.M. van Dijck, MD¹

Ronald H.M.A. Bartels, MD PhD²

Jan C.M. Lavrijsen, MD PhD³

Gerard M. Ribbers, MD PhD^{4,5}

Erwin J.O. Kompanje, PhD⁶

Wilco C. Peul, MD PhD MBA¹

On behalf of all focus group participants.

Affiliations:

1. Department of Neurosurgery, University Neurosurgical Center Holland, LUMC, HMC & Haga, Leiden/The Hague, The Netherlands
2. Department of Neurosurgery, Radboud University Medical Center, Geert Grooteplein-Zuid 10, 6525 GA, Nijmegen, The Netherlands.
3. Department of Primary and Community Care, Radboud University Medical Centre, Nijmegen, The Netherlands.
4. Department of Rehabilitation Medicine, Erasmus University Medical Centre, Rotterdam, The Netherlands.
5. Rijndam Rehabilitation, Rotterdam, The Netherlands.
6. Department of Intensive Care Medicine, Erasmus Medical Centre, PO Box 2040, 3000 CA Rotterdam, The Netherlands

Citation:

van Dijck JTJM, Bartels RHMA, Lavrijsen JCM, et al. The patient with severe traumatic brain injury: clinical decision-making: the first 60 min and beyond. *Curr Opin Crit Care*. 2019; 25 (6):622-629 doi: 10.1097 MCC.0000000000000671.

ABSTRACT

Purpose of review: There is an urgent need to discuss the uncertainties and paradoxes in clinical decision-making after severe traumatic brain injury (s-TBI). This could improve transparency, reduce variability of practice and enhance shared decision-making with proxies.

Recent findings: Clinical decision-making on initiation, continuation and discontinuation of medical treatment may encompass substantial consequences as well as lead to presumed patient benefits. Such decisions, unfortunately, often lack transparency and may be controversial in nature. The very process of decision-making is frequently characterized by both a lack of objective criteria and the absence of validated prognostic models that could predict relevant outcome measures such as long-term quality and satisfaction with life. In practice, while treatment-limiting decisions are often made in patients during the acute phase immediately after s-TBI, other such severely injured TBI patients have been managed with continued aggressive medical care, and surgical or other procedural interventions have been undertaken in the context of pursuing a more favorable patient outcome. Given this spectrum of care offered to identical patient cohorts, there is clearly a need to identify and decrease existing selectivity, and better ascertain the objective criteria helpful towards more consistent decision-making and thereby reduce the impact of subjective valuations of predicted patient outcome.

Summary: Recent efforts by multiple medical groups have contributed to reduce uncertainty and to improve care and outcome along the entire chain of care. Although an unlimited endeavor for sustaining life seems unrealistic, treatment-limiting decisions should not deprive patients of a chance on achieving an outcome they would have considered acceptable.

Keywords: Traumatic brain injury; decision-making; medical ethics; prognosis; end of life

INTRODUCTION

Many patients who sustain severe traumatic brain injury (s-TBI) die after trauma or survive with (severe) disabilities.^{1*, 2, 3*, 4*, 5} Performing lifesaving (surgical) interventions may result in survival, but there is no common opinion on how to define an unfavorable outcome, nor on the time horizon of assessing such outcome.^{5, 6, 7, 8, 9*} Treatment-limiting decisions likely result in clinical deterioration and death.^{10, 11, 12**} Most acute treatment decisions are poorly supported by high-quality evidence and prognostic algorithms, leaving shared decision-making complex.^{8, 13*, 14, 15*} Perhaps in light of such lack of clarity, non-adherence to guidelines and substantial treatment variation remains pervasive.^{16, 17, 18*}

Therefore, we examine such treatment paradoxes by reviewing the literature and reporting on several interdisciplinary panel meetings that focused on clinical decision-making in initiating or withholding (surgical) intervention to patients after s-TBI. This position paper was written following a series of discussions with an expert panel of professionals from different backgrounds, and should serve as a starting point for further discussions rather than constitute a final outcome process.

Professional code of physicians

Physicians practice medicine by working according to several codes of conduct and by following four universally accepted moral principles in medical ethics (Table 1).^{19, 20, 21, 22, 23}

Autonomy of the patient is inherently compromised in patients with s-TBI, and proxies are often absent during the acute phase, improperly designated, or incapable of substitute informed decision-making.^{24*, 25, 26**} Physicians then are responsible for selecting a strategy they consider in line with a patients' best interests, i.e. *beneficence*. However, both medical and surgical or procedural interventions carry risks of inducing harm, creating a difficult equilibrium between beneficence and *non-maleficence*.^{2, 9*, 27, 28} Lastly, *justice* requires the fair distribution of benefits, risks and limited medical goods and services. As such, resources should ethically be restricted when used on so-called ineffective and disproportional treatment efforts, as it will deprive other patients of potentially effective treatments

Table 1: Moral principles in medical ethics

| Principle | Description |
|-------------------|--|
| 1. Autonomy | A norm of respecting and supporting autonomous decisions. |
| 2. Beneficence | A group of norms pertaining to relieving, lessening, or preventing harm and providing benefits and balancing benefits against risks and costs. |
| 3. Nonmaleficence | A norm of avoiding the causation of harm. |
| 4. Justice | A group of norms for fairly distributing benefits, risks, and costs. |

Treatment-limiting decisions

Treatment-limiting decisions, including withholding lifesaving (surgical) interventions or withdrawal of life-sustaining medical treatment, are sometimes made within the first two days after s- TBI, allowing for, and leading to death, further deterioration and depriving patients a chance for recovery.^{10, 12^{8*}, 29⁹} Furthermore, defining recovery is relative, as it may encompass the entire spectrum from saving a patients' life, achieving good health related quality of life, to entire satisfaction with one's recovery.^{1⁸, 4⁸, 30, 31⁸, 32⁸}

Although withdrawal of life-sustaining measures can be morally justified, and in line with patients' and proxies' preferences and values, it should be noted that such decisions are typically based on non-data driven clinical prognostication and the goal of achieving survival with an imprecisely defined 'favorable' outcome.^{33^{**}} As 'favorable' outcome has been reported in even some of the most severely injured patients, treatment-limiting decisions in patients that might have achieved 'favorable outcome' must therefore arguably be difficult to uphold on ethical and moral grounds.^{2, 4⁸}

Reasons for treatment-limiting decisions

Several recent studies have aimed to identify what specific reasons or values constitute decision-making in severe brain injuries by medical teams, proxies or patients, but much remains unexplained.^{10, 12^{8*}, 18⁸, 34⁸, 35, 36} Physicians are likely to include their personal valuation of predicted patient outcome in their treatment considerations based on a mix of factors such as religious background, personal and clinical experience, culture, national legislation, and even the socio- economic status of the patient.^{18⁸, 37} This introduces the risk of selectivity and is not evidence- based medicine.^{18⁸}

To elaborate on this, the authors, specialists in neurosurgery, intensive care medicine, rehabilitation, chronic care, anthropology and medical-ethics, executed a multiple occasion professionally led focus group discussion. We explored and described the process and reasoning of decision-making in this manuscript and propose several reasons that would legitimize treatment- limiting decisions (Table 2).

Table 2: Reasons, including potential outcome perspectives, to strongly consider treatment-limiting decisions.

| # | Proposed reasons in random order |
|----|---|
| 1. | Brain death, from a patient perspective (not considering interests regarding organ donation procedures) ^{38,39} |
| 2. | (chronic) Unresponsive wakefulness syndrome ^{40**} , ^{41**} |
| 3. | Minimally conscious state—(minus), (i.e. visual pursuit, localization of noxious stimuli, appropriate smiling or crying to emotional stimuli) ^{40,42} |
| 4. | An available, unquestionable, written and signed specific advance directive of the patient that prohibits treatment in a specific situation (possibly related to expected outcome) |
| 5. | A proxy opinion that is unquestionably based on patient preferences and that is not in conflict with the attending medical teams' considerations, that prohibits treatment in a specific situation (possibly related to expected outcome) |
| 6. | A patient's view (or when necessary a reconstructed vision through surrogates) on life and quality of life is contrary to the outcome that can be expected from the best available prognostic models. |
| 7. | Treatment costs along the whole chain of care that are not cost-effective and higher than the maximum amount that has been decided by national legislation |

'Acceptable' versus 'unacceptable' outcome

Valuation of outcome is probably one of the most important aspects in decision-making, but exact definitions of acceptable or unacceptable outcome after s-TBI remain elusive.^{18*, 43} In literature, 'upper severe disability' (Glasgow Outcome Scale - Extended) and 'the inability to walk' or 'functionally dependent' (Modified Rankin Scale of 4) are sometimes considered favorable outcomes, while most physicians and researchers would classify this outcome degree as unfavorable.^{43, 44} Most competent individuals, irrespective of age, religion or background, consider survival with unfavorable outcome on the Glasgow Outcome Scale (GOS) unacceptable. However, survivors with so-called 'unfavorable outcome' after decompressive craniectomy for s-TBI and caregivers of patients after decompressive craniectomy appear to change their definition of 'a good quality of life' (QOL) and would have provided retrospective consent for the intervention.^{9*, 32*} Clearly, the favorable/unfavorable cut-off point used in prognostic models and TBI studies does not necessarily represent an acceptable/unacceptable outcome for patients.^{9*, 43}

Healthy individuals are generally unable to predict accurately what future QOL would be acceptable or unacceptable to them, because they often underestimate their ability to adapt to levels of disability they previously considered unacceptable.⁴⁵ The absence of a linear connection between disabilities and experienced QOL known as the disability paradox is seen in patients with severe disabilities reporting a good QOL (i.e. s-TBI, locked-in syndrome, Duchenne).^{9*, 46, 47} This does not validate

lifesaving/sustaining interventions in all patients, but suggests that physicians should acknowledge that an unacceptable outcome in their opinion may not necessarily be unacceptable to patients.

Determining cut-off points of acceptability is highly arbitrary and nearly impossible because of countless outcome possibilities and substantial variation in peoples' ever-changing desires and interpretations of a 'good life'. For instance, a life could be worth sustaining regardless of any favorability classifications because it has intrinsic value to relatives and friends, or because of cultural or religious reasons.^{48*}

Prognostic uncertainty

Accurate outcome prediction remains unavailable, although it has huge consequences on decision-making and it is crucial for patients, proxies and physicians.^{18*, 35, 45, 49, 50} Physicians are frequently unable to make accurate predictions and although prognostication may be considered straightforward at the extremes of the spectrum, it remains difficult in the middle.^{29*, 36, 45} This is disturbing, since a physician's perception on long-term prognosis likely influences treatment decisions. The long-term physical, cognitive, emotional and behavioral outcome after TBI is determined by injury characteristics as well as by contextual factors of the patient and the caregiver. Such issues are not covered in the CRASH and IMPACT prognostic models that focus on mortality and severe disability at 6 months post injury. Although helpful in estimating survival, these models do not cover outcomes such as independence in daily living and ultimately perceived satisfaction with life.^{45*, 51, 52, 53*, 54**}

The reasons for failure of prediction are; (1) the heterogeneous nature of s-TBI and concurring comorbidities and their unknown effect on outcome;^{50, 55, 56*, 57} (2) unclear/incomplete clinical information, including a patient's neurological state or level of consciousness;^{58, 59} (3) largely unknown pathophysiological mechanisms of brain injury and inherent degree of plasticity;^{50, 60**, 61*, 62, 63, 64*} (4) prediction models do not include long-term (health-related) QOL, although long-term outcome changes have been reported and patients/proxies value this outcome;^{3*, 28, 31*, 65, 66} (5) prediction models are based on large retrospective data sets that do not necessarily reflect current or future treatment strategies.^{8, 67, 68*, 69}

Balancing between beneficence and non-maleficence in clinical decision-making after s-TBI is a process of weighing the chance between favorable and non-favorable

outcome based on clinical expertise and subjective evaluations with ill-defined clinical endpoints.⁴⁵ Yet, it is considered common sense that lifesaving interventions should be withheld when the predicted risk of 'unfavorable' outcome is high, while depriving a patient of a possible favorable outcome can be seen as inappropriate care. The approach to treat all patients with the potential to survive inherently includes the risk of survival with an unacceptable outcome. All physicians should appreciate and communicate the existing multi-dimensional uncertainty, and decisions should not be guided by assumptions that falsely confer a sense of certainty.^{29*, 33**}

The risk of selection bias and self-fulfilling prophecies should be noted. Assumptions on poor prognosis that lead to treatment-limiting decisions and probably contribute to a worse outcome and possibly death in selected cases.^{12**, 33**, 70}

Improving prognostication

In clinical care the estimated prognosis is based on clinical characteristics, subjective evaluation of the clinician and contextual information at a short interval post onset. However, prognosis after s-TBI is dynamic in which the passage of time changes the predicted probability of a favorable outcome.^{71*, 72} In case of prognostic uncertainty and a small chance of 'acceptable' outcome, full critical care treatment should be initiated and continued to allow for best possible recovery. Information on clinical progress, neurological recovery, the patient's treatment and outcome preferences (when necessary through proxies), and multidisciplinary discussion (ideally with moral council) need to be included in decision-making - and this information only becomes available with time.

Striving for personalized care is promising and allows for appreciation of the general injury applied in an individualized context.⁷³ In the subacute phase, frequent re-evaluation and communication are essential; when treatment has become disproportionate, given the outcome, withdrawal of life-sustaining measures can be considered even at later moments in time. Despite the associated increased healthcare consumption and costs, the survival of patients with severe disabilities and the longer period of suffering for patients/proxies can be legitimized if more patients survive with acceptable outcome.

Patient, proxy or shared decision-making

Values, preferences and treatment wishes of patients (when necessary obtained through proxies) are to be respected and should be incorporated in clinical decision-making. Patient with s-TBI are incapable to decide, and their preferences have rarely been discussed with proxies or recorded in an (written) advance directive.^{18*, 48*} Proxies are then confronted with difficult treatment dilemmas, but information as desired by proxies is not always provided and a patients' social circumstances and preferences are not always included in physicians' decision-making process.^{34*, 35} Proxies might also misjudge or deliberately misrepresent patients' preferences.^{24*, 74}

Proxies are mostly unprepared, confused by uncertainty and hope, and unequipped to fully understand the uncertainties of prognostication and clinical decision-making.^{7, 75} This puts a high burden on the clinician's shoulders. Although medical paternalism is increasingly replaced by 'shared decision-making', the latter remains a difficult, if not impossible proposition when required in neurocritical care.^{26**, 76*} To improve conversations with proxies, it is recommended to provide early, frequent, understandable, honest, and consistent multidisciplinary communication about the patient's condition, consequences of actions, and prognosis, while acknowledging an acceptable level of uncertainty. Although specific needs are highly variable because perceptions are different and often inconsistent with reality, physicians must align unrealistic expectations with medical reality; in case of conflicts, moral deliberation could be helpful and otherwise professional judgement should prevail.

Considerations from a societal perspective

'The rule of rescue' is a powerful ethical proclivity ingrained in human nature, possible even more in acute care physicians, to rescue those in immediate danger, regardless of risks or costs.⁷⁷ 'Performing against the odds' heroism is often in conflict with the utilitarian approach, which aims at the overall performance of the entire healthcare system instead of the entire focus being on the benefits of a single individual.

In this context, it is considered difficult to justify lifesaving neurosurgical interventions resulting in unacceptable outcome at enormous healthcare costs. The ethical question transcends from individual values to societal and political valuation of life related to costs. Studies assessing in hospital costs after s-TBI however, suggest rather an 'acceptable' degree of in-hospital treatment costs, although variation is high and study quality generally poor.^{2, 78} Studies on the long-term costs of patients after s-TBI or patients with severe disorders of consciousness are unfortunately scarce, prohibiting

solid conclusions. Admittedly, money that has been spent cannot be used to treat other patients with possibly more effective treatments. This perspective, however, should not be a prominent variable in arguing for, or against early treatment-limiting decisions. Depriving some patients of recovery to an acceptable outcome should be absolutely minimized in societal decision-making.

Nonetheless, there must be a point where TBI is so severe and patient outcome so unacceptable as to justify the enormous associated healthcare costs. Establishing this point is necessary because healthcare costs increase and healthcare budgets are limited. Therefore, the cost-effectiveness of interventions should be evaluated, and weighted to the maximum amount. Limitations on costs to maintain life have already been set by politicians. For example, the cut-off of cost-effective treatments in The Netherlands is €80.000 per quality adjusted life year.⁷⁹ The justification and number of this cut-off should not be determined solely by politicians, but also involve the contributions of experienced physicians and other health-care professionals.

A commonly perceived advantage of including this economic perspective in decision-making is the objectivity of the criterion to decide whether or not to perform an intervention. We should, however, not forget that focusing on cost-benefit analyses fails to recognize individual aspects of care and the social utility of caring for those most in need. People obtain benefit from the belief that they live in a compassionate and humane society where patients in need will not be ignored merely on the basis of costs.

Acute and chronic care

Because of the chronic consequences of s-TBI, many patients and proxies need adequate lifelong care to optimize outcome.^{80, 81} Specialized rehabilitation, long-term care and patience are essential for recovery.^{14, 82*, 83, 84**} Caretakers and researchers of both subacute and chronic care should collaborate closely and become familiar with the needs, challenges and possibilities along the entire chain of care.

Regrettably, in some healthcare systems, patients without enough progress of recovery during rehabilitation are discharged to nursing homes lacking proper rehabilitation or diagnostic oversight, depriving them of opportunities to recover.^{75, 85} This seems unfair, since “normal” recovery processes of patients and their brains still remain largely unknown, and subtle progress is known to be missed due to a physician’s generally poor evaluation.^{1*, 28, 59, 60**, 61*} Many novel rehabilitation initiatives have been developed, and also improved coping interventions appear now to be more effective.^{62, 64*, 85, 86, 87, 88}

Until we really know what is best, providing appropriate care is something that we as a society morally owe to all patients, while not discounting that catastrophic conditions such as unresponsive wakefulness syndrome or minimally conscious state are accompanied by severe disabilities and enormous challenges.^{41**},⁸⁹ Although the gravity of the outcome could be obscured by the gratitude of survival, many will doubt this is a life worth living.⁷⁵

Future research

Future research initiatives will focus on; (1) the effectiveness of new diagnostic and treatment modalities including short- and long-term functional outcome and health-related QOL, along the whole chain of care;^{90,91} (2) the measurement of well-being and impact on proxies and society; (3) establishing values of dignified existence (i.e. with ex-patients, proxies, physicians); (4) specialized education programs for professionals and patients/proxies on the topic of s-TBI; (5) improving the reliability of prognostic models by machine learning.^{92*,93}

Although these initiatives seem promising, and will likely improve TBI care when successful, we should not underestimate the difficulties in conducting traditional studies, such as the variation between patients, injuries and healthcare systems, but also the variety and potential boundaries of ethics and culture. Randomization of severely injured TBI patients, as one example, is considered inappropriate by many physicians. Prospective, large, multi-centered, compared-effectiveness research initiatives might provide necessary evidence in the future.⁵⁰

CONCLUSIONS

Decision-making in s-TBI is highly complicated due to uncertainty regarding treatment cost- effectiveness, prognostication and unacceptability of outcome, which are caused by a lack of scientific evidence and also by different societal and individual values. Physicians absolutely do not intentionally deprive patients of a chance on achieving an outcome they would have considered acceptable. Research collaborations between medical specialties and across the borders of traditional sciences of medicine, sociology and philosophy might lead to practical evidence, reduced uncertainty and improved care and outcome for s-TBI patients.

KEY POINTS

1. Although multiple recent efforts have contributed to reduce uncertainty and to improve care and outcome for severe traumatic brain injury (s-TBI) patients along the entire chain of care, there remain many uncertainties and paradoxes and a lack of objective criteria in clinical decision-making after s-TBI.
2. Although important for decision-making, well-validated prognostic models predicting long-term outcome on quality of life and satisfaction with life after s-TBI are currently unavailable.
3. Some of the most severely injured TBI patients have been reported to have achieved 'favorable' outcome and (surgical) interventions are generally considered beneficial for patient outcome.
4. To further improve s-TBI care, future research should identify and decrease the existing selectivity and identify objective criteria in decision-making and reduce the impact of subjective valuations of predicted patient outcome.

REFERENCES

1. *Grauwmeijer E, Heijnenbroek-Kal MH, Peppel LD, *et al.* Cognition, health-related quality of life, and depression ten years after moderate to severe traumatic brain injury: A prospective cohort study. *J Neurotrauma* 2018; 35:1543-1551. Long term health-related quality of life is an increasingly popular and important outcome measure in follow-up studies. This is one of the few studies that reports the long-term quality of life after severe traumatic brain injury
2. van Dijk JT, Reith FC, van Erp IA, *et al.* Decision making in very severe traumatic brain injury (Glasgow Coma Scale 3-5): A literature review of acute neurosurgical management. *J Neurosurg Sci* 2018; 62:153-177.
3. * Ruet A, Bayen E, Jourdan C, *et al.* A detailed overview of long-term outcomes in severe traumatic brain injury eight years post-injury. *Front Neurol* 2019; 10:120. Studies including long-term outcome outcome after severe traumatic brain injury are rare, although long-term outcome is considered highly important in clinical decision-making. This recent study assesses the specific determinants of long-term outcome (8 years) after severe traumatic brain injury
4. * van Eijck M, van der Naalt J, de Jongh M, *et al.* Patients with diffuse axonal injury can recover to a favorable long-term functional and quality of life outcome. *J Neurotrauma* 2018; 35:2357-2364. This is one of the few available studies in diffuse axonal injury using the QOLIBRI as disease specific health-related quality of life measure. This study shows that long-term favourable outcome can be achieved in patients with diffuse axonal injury.
5. Moskowitz E, Melendez CI, Dunn J, *et al.* Long-term effects of decompressive craniectomy on functional outcomes after traumatic brain injury: A multicenter study. *Am Surg* 2018; 84:1314-1318.
6. Pujari R, Hutchinson PJ, Koliak AG. Surgical management of traumatic brain injury. *J Neurosurg Sci* 2018; 62:584-592
7. McGowan T. Will you forgive me for saving you? *N Engl J Med* 2018; 379:8-9.
8. Carney N, Totten AM, O'Reilly C, *et al.* Guidelines for the management of severe traumatic brain injury, fourth edition. *Neurosurgery* 2017; 80:6-15
9. * Honeybul S. Long-term outcome following severe traumatic brain injury: Ethical considerations. *J Neurosurg Sci* 2018; 62:599-605. This article discusses existing ethical considerations regarding long-term outcome after sustaining severe traumatic brain injury. It contains a comprehensive overview of available evidence, ethical considerations and future considerations.
10. Robertsen A, Forde R, Skaga NO, *et al.* Treatment-limiting decisions in patients with severe traumatic brain injury in a Norwegian regional trauma center. *Scand J Trauma Resusc Emerg Med* 2017; 25:44
11. Jochems D, van Wessem KJP, Houwert RM, *et al.* Outcome in patients with isolated moderate to severe traumatic brain injury. *Crit Care Res Pract* 2018; 2018:3769418
12. ** Leblanc G, Boutin A, Shemilt M, *et al.* Incidence and impact of withdrawal of life- sustaining therapies in clinical trials of severe traumatic brain injury: A systematic review. *Clin Trials* 2018; 15:398-412. There is much uncertainty on the impact of withdrawal of life-sustaining therapies on patient outcome as reported in randomized clinical trials of patients with severe traumatic brain injury. Because the decision to withdraw life-sustaining therapies has the potential to influence the (interpretation of) results of these clinical trials this study is important to consider when conducting future studies in traumatic brain injury or other diseases.
13. * Synnot A, Bragge P, Lunny C, *et al.* The currency, completeness and quality of systematic reviews of acute management of moderate to severe traumatic brain injury: A comprehensive evidence map. *PLoS One* 2018; 13:e0198676. Important research findings in traumatic brain injury are frequently reported in systematic reviews. However, quality of these systematic review is not always sufficient. This also compromises its generalizability for clinical purposes. This study shows that many systematic review lack completeness and quality
14. Bayley MT, Lamontagne ME, Kua A, *et al.* Unique features of the INESSS-ONF rehabilitation guidelines for moderate to severe traumatic brain injury: Responding to users' needs. *J Head Trauma Rehabil* 2018; 33:296-305
15. * Stocchetti N, Poole D, Okonkwo DO. Intracranial pressure thresholds in severe traumatic brain injury: We are not sure : Prudent clinical practice despite dogma or nihilism. *Intensive Care Med* 2018; 44:1321-1323. Uncertainty is an important aspect of clinical decision-making in severe traumatic brain injury. Acknowledging this uncertainty is another important aspect, which makes this article specifically on ICP thresholds interesting.

16. Volovici V, Ercole A, Citerio G, *et al.* Variation in guideline implementation and adherence regarding severe traumatic brain injury treatment: A CENTER-TBI survey study in Europe. *World Neurosurg* 2019.
17. van Essen TA, den Boogert HF, Cnossen MC, *et al.* Variation in neurosurgical management of traumatic brain injury: A survey in 68 centers participating in the CENTER- TBI study. *Acta Neurochir (Wien)* 2019; 161:435-449
18. * Boyer F, Audibert G, Baumann C, *et al.* [decision-making regarding treatment limitation after severe traumatic brain injury: A survey of French neurosurgeons]. *Neurochirurgie* 2018; 64:401-409. Decision-making in traumatic brain injury is not well understood. Surveys as reported in this article help understand why physicians make decisions and could explain treatment variation or identify future research directives.
19. Czech H, Druml C, Weindling P. Medical ethics in the 70 years after the nuremberg code, 1947 to the present. *Wien Klin Wochenschr* 2018; 130:159-253
20. Beauchamp TC, Childress JF. Principles of biomedical ethics. 7th ed. New York: Oxford University Press; 2013.
21. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. *JAMA* 2013; 310:2191-2194.
22. Parsa-Parsi RW. The revised Declaration of Geneva: A modern-day physician's pledge. *JAMA* 2017; 318:1971-1972
23. World Medical Association Declaration of Taipei on ethical considerations regarding health databases and biobanks. Published October 2016 [Available from: <https://www.wma.net/policies-post/wma-declaration-of-taipei-on-ethical-considerations-regarding-health-databases-and-biobanks/>. Accessed: May 17, 2019.
24. * Turnbull AE, Chessare CM, Coffin RK, *et al.* More than one in three proxies do not know their loved one's current code status: An observational study in a Maryland ICU. *PLoS One* 2019; 14:e0211531. Decisions in clinical practice are frequently discussed with proxies, especially in mentally incapacitated patients. This article reports the accuracy of proxy decision-making.
25. Frey R, Herzog SM, Hertwig R. Deciding on behalf of others: A population survey on procedural preferences for surrogate decision-making. *BMJ Open* 2018; 8:e022289.
26. ** Grignoli N, Di Bernardo V, Malacrida R. New perspectives on substituted relational autonomy for shared decision-making in critical care. *Crit Care* 2018; 22:260. This viewpoint article describes the clinical environment of mentally incapacitated patients where treatment decisions have to be made. New perspectives on substituted relational autonomy are discussed in an attempt to improve shared decision-making in critical care.
27. Gopalakrishnan MS, Shanbhag NC, Shukla DP, *et al.* Complications of decompressive craniectomy. *Front Neurol* 2018; 9:977.
28. Forslund MV, Perrin PB, Roe C, *et al.* Global outcome trajectories up to 10 years after moderate to severe traumatic brain injury. *Front Neurol* 2019; 10:219
29. * Pratt AK, Chang JJ, Sederstrom NO. A fate worse than death: Prognostication of devastating brain injury. *Crit Care Med* 2019; 47:591-598. The authors elaborate on the uncertainties on prognosticating devastating brain injury in the ICU. Supportive care is recommended for at least 72 hours to maximize the potential for recovery and minimize secondary injury.
30. van Dijk J, van Essen TA, Dijkman MD, *et al.* Functional and patient-reported outcome versus in-hospital costs after traumatic acute subdural hematoma (t-ASDH): A neurosurgical paradox? *Acta Neurochir (Wien)* 2019; 161:875-884.
31. * Andelic N, Howe EI, Hellstrom T, *et al.* Disability and quality of life 20 years after traumatic brain injury. *Brain Behav* 2018; 8:e01018. One of the longest follow-up studies in traumatic brain injury, concluding that functional limitations persist even decades after the injury.
32. * Waqas M, Malik N, Shamim MS, *et al.* Quality of life among patients undergoing decompressive craniectomy for traumatic brain injury using Glasgow Outcome Scale Extended and Quality Of Life after Brain Injury scale. *World Neurosurg* 2018; 116:e783-e790. Quality of life outcome measures are important for understanding the true consequences of medical interventions. This article shows the consequences on quality of life of a controversial surgical intervention like a decompressive craniectomy.
33. ** Lazaridis C. Withdrawal of life-sustaining treatments in perceived devastating brain injury: The key role of uncertainty. *Neurocrit Care* 2019; 30:33-41. Highly interesting article about the importance of existing uncertainties on prognostication of perceived devastating brain injury. It discusses the possibility that many withdrawal of life-sustaining treatments are made prematurely and are made based on false assumptions.
34. * Unterhofer C, Hartmann S, Freyschlag CF, *et al.* Severe head injury in very old patients: To treat or not to treat? Results of an online questionnaire for neurosurgeons. *Neurosurg Rev* 2018; 41:183-187. The decision-making processes in traumatic brain injury are not well understood. These questionnaires could be helpful in understanding the specific factors of influence in decision- making processes.

35. Quinn T, Moskowitz J, Khan MW, *et al.* What families need and physicians deliver: Contrasting communication preferences between surrogate decision-makers and physicians during outcome prognostication in critically ill TBI patients. *Neurocrit Care* 2017;27:154-162.
36. Detsky ME, Harhay MO, Bayard DF, *et al.* Discriminative accuracy of physician and nurse predictions for survival and functional outcomes 6 months after an ICU admission. *JAMA* 2017; 317:2187-2195.
37. Letsinger J, Rommel C, Hirschi R, *et al.* The aggressiveness of neurotrauma practitioners and the influence of the impact prognostic calculator. *PLoS One* 2017; 12:e0183552.
38. van Veen E, van der Jagt M, Cnossen MC, *et al.* Brain death and postmortem organ donation: Report of a questionnaire from the CENTER-TBI study. *Crit Care* 2018;22:306.
39. Lesieur O, Gentleuil L, Leloup M. A few realistic questions raised by organ retrieval in the intensive care unit. *Ann Transl Med* 2017; 5:S44.
40. ** Rohaut B, Eliseyev A, Claassen J. Uncovering consciousness in unresponsive ICU patients: Technical, medical and ethical considerations. *Crit Care* 2019; 23:78. Comprehensive overview of unconscious ICU patients which is highly informative for clinical practice. It also discusses medical and ethical considerations including prognostication and medical decision-making which are especially difficult in this particular patient category.
41. ** Giacino JT, Katz DI, Schiff ND, *et al.* Practice guideline update recommendations summary: Disorders of consciousness. *Neurology* 2018; 91:450. One of the most important recent articles regarding disorders of consciousness. It contains a summary of the latest guideline recommendations.
42. Bruno MA, Majerus S, Boly M, *et al.* Functional neuroanatomy underlying the clinical subcategorization of minimally conscious state patients. *J Neurol* 2012;259:1087-1098.
43. Honeybul S, Ho KM, Gillett GR. Long-term outcome following decompressive craniectomy: An inconvenient truth? *Curr Opin Crit Care* 2018; 24:97-104.
44. Olivecrona M, Honeybul S. A study of the opinions of Swedish healthcare personnel regarding acceptable outcome following decompressive hemicraniectomy for ischaemic stroke. *Acta Neurochir (Wien)* 2018; 160:95-101.
45. Ho KM. Predicting outcomes after severe traumatic brain injury: Science, humanity or both? *J Neurosurg Sci* 2018; 62:593-598.
46. Rousseau MC, Baumstarck K, Alessandrini M, *et al.* Quality of life in patients with locked-in syndrome: Evolution over a 6-year period. *Orphanet J Rare Dis* 2015;10:88.
47. Andrews JG, Wahl RA. Duchenne and Becker muscular dystrophy in adolescents: Current perspectives. *Adolesc Health Med Ther* 2018; 9:53-63.
48. * Span-Sluyter CAMFH, Lavrijsen JCM, van Leeuwen E, *et al.* Moral dilemmas and conflicts concerning patients in a vegetative state/unresponsive wakefulness syndrome: Shared or non-shared decision making? A qualitative study of the professional perspective in two moral case deliberations. *BMC Medical Ethics* 2018; 19:10. This study discusses several important moral dilemmas and conflicts in patients in an unresponsive wakefulness syndrome. These considerations could also be useful for physicians not necessarily confronted with this particular patient subgroup.
49. Kompanje EJ. Prognostication in neurocritical care: Just crystal ball gazing? *Neurocrit Care* 2013; 19:267-268.
50. Maas AIR, Menon DK, Adelson PD, *et al.* Traumatic brain injury: Integrated approaches to improve prevention, clinical care, and research. *Lancet Neurol* 2017; 16:987-1048.
51. Collaborators MCT, Perel P, Arango M, *et al.* Predicting outcome after traumatic brain injury: Practical prognostic models based on large cohort of international patients. *BMJ* 2008; 336:425-429.
52. Steyerberg EW, Mushkudiani N, Perel P, *et al.* Predicting outcome after traumatic brain injury: Development and international validation of prognostic scores based on admission characteristics. *PLoS Med* 2008; 5:e165.
53. * Moskowitz J, Quinn T, Khan MW, *et al.* Should we use the impact-model for the outcome prognostication of TBI patients? A qualitative study assessing physicians' perceptions. *MDM Policy Pract* 2018; 3:2381468318757987. There are many different views on the use of prediction models like the IMPACT and CRASH models. This qualitative study assesses the perception of physicians.
54. ** Dijkland SA, Foks KA, Polinder S, *et al.* Prognosis in moderate and severe traumatic brain injury: A systematic review of contemporary models and validation studies. *J Neurotrauma* 2019. doi: 10.1089/neu.2019.6401 This systematic review focuses on prognostication in moderate and severe traumatic brain injury. Because this is a very important factor in clinical decision-making, an assessment of the validity of these models is very important.

55. Malec JF, Ketchum JM, Hammond FM, *et al.* Longitudinal effects of medical comorbidities on functional outcome and life satisfaction after traumatic brain injury: An individual growth curve analysis of NIDILRR traumatic brain injury model system data. *J Head Trauma Rehabil* 2019; 34: E24-35. doi:10.1097/HTR.0000000000000459.
56. * Humble SS, Wilson LD, Wang L, *et al.* Prognosis of diffuse axonal injury with traumatic brain injury. *J Trauma Acute Care Surg* 2018; 85:155-159. This study assessed the association between the presence of diffuse axonal injury and long-term outcomes but found no reasons to attribute the presence of this injury to future neurologic function or quality of life.
57. Henninger N, Compton RA, Khan MW, *et al.* "Don't lose hope early": Hemorrhagic diffuse axonal injury on head computed tomography is not associated with poor outcome in moderate to severe traumatic brain injury patients. *J Trauma Acute Care Surg* 2018; 84:473-482.
58. Reith FC, Synnot A, van den Brande R, *et al.* Factors influencing the reliability of the Glasgow Coma Scale: A systematic review. *Neurosurgery* 2017; 80:829-839.
59. Kondziella D, Friberg CK, Frokjaer VG, *et al.* Preserved consciousness in vegetative and minimal conscious states: Systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* 2016; 87:485-492.
60. ** Vrselja Z, Daniele SG, Silbereis J, *et al.* Restoration of brain circulation and cellular functions hours post-mortem. *Nature* 2019; 568:336-343. This revolutionary study demonstrates that an intact large mammalian brain possesses an underappreciated capacity for restoration of microcirculation and molecular and cellular activity after a prolonged post-mortem interval. This could influence thoughts on treatment limiting-decisions, research initiatives in humans and future treatment strategies.
61. * O'Leary R A, Nichol AD. Pathophysiology of severe traumatic brain injury. *J Neurosurg Sci* 2018; 62:542-548. The pathophysiology of severe traumatic brain injury is not well understood. This article summarizes the present knowledge on this topic.
62. Piradov MA, Chernikova LA, Suponeva NA. Brain plasticity and modern neurorehabilitation technologies. *Herald of the Russian Academy of Sciences* 2018; 88:111-118.
63. Kaur P, Sharma S. Recent advances in pathophysiology of traumatic brain injury. *Curr Neuropharmacol* 2018; 16:1224-1238.
64. * Crosson B, Rodriguez AD, Copland D, *et al.* Neuroplasticity and aphasia treatments: New approaches for an old problem. *J Neurol Neurosurg Psychiatry* 2019; 90:1147-1155. doi: 10.1136/jnnp.2018.319649. This review provides an overview of new approaches in neuroplasticity in aphasia treatment, which is gaining attention in traumatic brain injury literature.
65. Baricich A, de Sire A, Antoniono E, *et al.* Recovery from vegetative state of patients with a severe brain injury: A 4-year real-practice prospective cohort study. *Functional neurology* 2017; 32:131-136.
66. Illman NA, Crawford S. Late-recovery from "permanent" vegetative state in the context of severe traumatic brain injury: A case report exploring objective and subjective aspects of recovery and rehabilitation. *Neuropsychol Rehabil* 2018; 28:1360-1374.
67. Gutowski P, Meier U, Rohde V, *et al.* Clinical outcome of epidural hematoma treated surgically in the era of modern resuscitation and trauma care. *World Neurosurg* 2018; 118:e166-e174.
68. * Scerrati A, De Rosa S, Mongardi L, *et al.* Standard of care, controversies, and innovations in the medical treatment of severe traumatic brain injury. *J Neurosurg Sci* 2018; 62:574-583. Innovations in medicine are warranted, also in severe traumatic brain injury patients. This article provides an overview of care and innovations in medical treatment.
69. Aidinoff E, Groswasser Z, Bierman U, *et al.* Vegetative state outcomes improved over the last two decades. *Brain Inj* 2018; 32:297-302.
70. Christakis N. Death foretold: Prophecy and prognosis in medical care. Chicago: Chicago press; 1999.
71. * Rubin ML, Yamal JM, Chan W, *et al.* Prognosis of 6-month glasgow outcome scale in severe traumatic brain injury using hospital admission characteristics, injury severity characteristics, and physiological monitoring during the first day post-injury. *J Neurotrauma* 2019; 36: 2417-2422. doi: 10.1089/neu.2018.6217 Improvement of prognostic models is important since it contributes to more accurate decision-making. This study finds that certain predictors after the first day after injury could result in more accurate prediction models.
72. Harvey D, Butler J, Groves J, *et al.* Management of perceived devastating brain injury after hospital admission: A consensus statement from stakeholder professional organizations. *Br J Anaesth* 2018; 120:138-145.
73. Chow N, Busse JW, Gallo L. Evidence-based medicine and precision medicine: Complementary approaches to clinical decision-making. *Precision Clinical Medicine* 2018; 1:60-64.

74. Fried TR, Zenoni M, Iannone L, *et al.* Assessment of surrogates' knowledge of patients' treatment goals and confidence in their ability to make surrogate treatment decisions. *JAMA Intern Med* 2019; 179:267-268.
75. Fins JJ. *Rights come to mind*. Cambridge University Press; 1 edition (August 11, 2015) 2015.
76. * Khan MW, Muehlschlegel S. Shared decision making in neurocritical care. *Neurosurg Clin N Am* 2018; 29:315-321. There is much debate on the use of shared-decision making in neurocritical care. The authors discuss the general use of shared decision-making and ways to improve this.
77. Honeybul S, Gillett GR, Ho KM, *et al.* Neurotrauma and the rule of rescue. *J Med Ethics* 2011; 37:707-710.
78. van Dijk J, Dijkman MD, Ophuis RH, *et al.* In-hospital costs after severe traumatic brain injury: A systematic review and quality assessment. *PLoS One* 2019; 14:e0216743.
79. Zorginstituut Nederland. Ziektelast in de praktijk - de theorie en praktijk van het berekenen van ziektelast bij pakketbeoordelingen. 2018. https://www.zorginstituutnederland.nl/binaries/zinl/documenten/rapport/2018/05/07/ziektelast-in-de-praktijk/Ziektelast+in+de+praktijk_definitief.pdf. Accessed: May 17, 2019.
80. Wilson L, Stewart W, Dams-O'Connor K, *et al.* The chronic and evolving neurological consequences of traumatic brain injury. *Lancet Neurol* 2017; 16:813-825.
81. Vespa P. Traumatic brain injury is a longitudinal disease process. *Curr Opin Neurol* 2017; 30:563-564.
82. * Marklund N, Bellander BM, Godbolt A, *et al.* Treatments and rehabilitation in the acute and chronic state of traumatic brain injury. *J Intern Med* 2019. doi: 10.1111/joim.12900. Rehabilitation is essential in the care of a patient with (severe) traumatic brain injury. Improvement of coordinated interdisciplinary rehabilitation for traumatic brain injury patients is necessary. The authors highlight this need and describe new approaches in rehabilitation.
83. Ratan RR, Schiff ND. Protecting and repairing the brain: Central and peripheral strategies define the new rehabilitation following traumatic brain injury. *Curr Opin Neurol* 2018; 31:669-671.
84. ** Konigs M, Beurskens EA, Snoep L, *et al.* Effects of timing and intensity of neurorehabilitation on functional outcome after traumatic brain injury: A systematic review and meta-analysis. *Arch Phys Med Rehabil* 2018; 99:1149-1159. This systematic review and meta-analysis states that early neurorehabilitation in trauma centers and more intensive neurorehabilitation in rehabilitation facilities promote functional recovery in patients with moderate to severe traumatic brain injury.
85. Graff HJ, Christensen U, Poulsen I, *et al.* Patient perspectives on navigating the field of traumatic brain injury rehabilitation: A qualitative thematic analysis. *Disabil Rehabil* 2018; 40:926-934.
86. Douglas JM, Knox L, De Maio C, *et al.* Effectiveness of communication-specific coping intervention for adults with traumatic brain injury: Preliminary results. *Neuropsychol Rehabil* 2019; 29:73-91.
87. Semprini M, Laffranchi M, Sanguineti V, *et al.* Technological approaches for neurorehabilitation: From robotic devices to brain stimulation and beyond. *Front Neurol* 2018; 9:212.
88. ** Thibaut A, Schiff N, Giacino J, *et al.* Therapeutic interventions in patients with prolonged disorders of consciousness. *Lancet Neurol* 2019; 18:600-614. The therapeutic options for patients with disorders of consciousness are often considered to be scarce. New clinical data and new treatment options pose new possibilities for this specific patient subcategory and are described in this article.
89. Avesani R, Dambruoso F, Scandola M, *et al.* Epidemiological and clinical characteristics of 492 patients in a vegetative state in 29 Italian rehabilitation units. What about outcome? *Funct Neurol* 2018; 33:97-103.
90. Kochanek PM, Jackson TC, Jha RM, *et al.* Paths to successful translation of new therapies for severe traumatic brain injury in the golden age of traumatic brain injury research: A pittsburgh vision. *J Neurotrauma* 2019. doi: 10.1089/neu.2018.6203.
91. Wang KK, Yang Z, Zhu T, *et al.* An update on diagnostic and prognostic biomarkers for traumatic brain injury. *Expert Rev Mol Diagn* 2018; 18:165-180.
92. * Rau CS, Kuo PJ, Chien PC, *et al.* Mortality prediction in patients with isolated moderate and severe traumatic brain injury using machine learning models. *PLoS One* 2018; 13:e0207192. New developments in prognostication for moderate and severe traumatic brain injury include the use of machine learning models.
93. Hale AT, Stonko DP, Brown A, *et al.* Machine-learning analysis outperforms conventional statistical models and ct classification systems in predicting 6-month outcomes in pediatric patients sustaining traumatic brain injury. *Neurosurg Focus* 2018; 45:E





CHAPTER 7

How do 66 European Institutional Review Boards approve one protocol for an international prospective observational study on traumatic brain injury? Experiences from the CENTER-TBI study.

Authors

| | |
|--|---|
| Marjolein Timmers ^{* 1} | David K. Menon ⁷ |
| Jeroen T.J.M. van Dijck ^{* 2} | Giuseppe Citerio ^{8,9} |
| Roel P.J. van Wijk ² | Nino Stocchetti ^{10,11} |
| Valerie Legrand ³ | Erwin J.O. Kompanje ^{1,12} |
| Ernest van Veen ^{1,4} | The CENTER-TBI investigators and participants |
| Andrew I.R. Maas ^{5,6} | ^{*Shared first authorship} |

Affiliations:

- 1: Department of Intensive Care, Erasmus MC - University Medical Centre Rotterdam, Rotterdam, the Netherlands.
- 2: Department of Neurosurgery, Leiden University Neurosurgery Centre Holland, LUMC-HMC & Haga Hospital, Leiden & The Hague, The Netherlands.
- 3: ICON plc, South County Business Park Leopardstown Dublin 18, Ireland.
- 4: Department of Public Health, Erasmus MC - University Medical Centre Rotterdam, Rotterdam, the Netherlands.
- 5: Department of Neurosurgery, Antwerp University Hospital, Edegem, Belgium.
- 6: University of Antwerp, Antwerp, Belgium.
- 7: Department of Anaesthesia, University of Cambridge, Cambridge, United Kingdom.
- 8: School of Medicine and Surgery, University of Milan-Bicocca, Milan, Italy.
- 9: San Gerardo Hospital, ASST-Monza, Italy.
- 10: Department of Physiopathology and Transplantation, Milan University, Milan, Italy.
- 11: Neuro ICU Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico Milano, Milan, Italy.
- 12: Department of Medical Ethics and Philosophy of Medicine, Erasmus MC - University Medical Center Rotterdam, Rotterdam, the Netherlands.

Citation:

Timmers M, van Dijck JTJM, van Wijk RPJ, et al. How do 66 European institutional review boards approve one protocol for an international prospective observational study on traumatic brain injury? Experiences from the CENTER-TBI study. *BMC Med Ethics*. 2020;21(1):36. doi:10.1186/s12910-020-00480-8

ABSTRACT

Background: The European Union (EU) aims to optimize patient protection and efficiency of health-care research by harmonizing procedures across Member States. Nonetheless, further improvements are required to increase multicenter research efficiency. We investigated IRB procedures in a large prospective European multicenter study on traumatic brain injury (TBI), aiming to inform and stimulate initiatives to improve efficiency.

Methods: We reviewed relevant documents regarding IRB submission and IRB approval from European neurotrauma centers participating in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI). Documents included detailed information on IRB procedures and the duration from IRB submission until approval(s). They were translated and analyzed to determine the level of harmonization of IRB procedures within Europe.

Results: From 18 countries, 66 centers provided the requested documents. The primary IRB review was conducted centrally (N=11, 61%) or locally (N=7, 39%) and primary IRB approval was obtained after one (N=8, 44%), two (N=6, 33%) or three (N=4, 23%) review rounds with a median duration of respectively 50 and 98 days until primary IRB approval. Additional IRB approval was required in 55% of countries and could increase duration to 535 days. Total duration from submission until required IRB approval was obtained was 114 days (IQR 75-224) and appeared to be shorter after submission to local IRBs compared to central IRBs (50 vs. 138 days, $p=0.0074$).

Conclusion: We found variation in IRB procedures between and within European countries. There were differences in submission and approval requirements, number of review rounds and total duration. Research collaborations could benefit from the implementation of more uniform legislation and regulation while acknowledging local cultural habits and moral values between countries.

Keywords: Research Ethics Committees; European Union; Health-care Research; CENTER-TBI; Harmonization.

BACKGROUND

A Research Ethics Committee or Institutional Review Board (collectively referred to as IRB in the remainder of this manuscript) is appointed to review research protocols to ensure their compliance with ethical standards and national laws. IRBs have an essential role in (clinical) research to protect the dignity, fundamental rights, safety, and well-being of research participants and their formal approval is compulsory before a clinical study can start.¹ Although several international models exist to improve the harmonization of ethical principles, the functioning of IRBs are subject to national legislation and regulation, which refine their structure and function to better serve local needs and cultural preferences.²⁻³ Approval of research protocols submitted to IRBs is subject to these differences, which may complicate the conduct of international research.

Managing variations in IRB procedures is important because of the increasing number of research initiatives which involve multiple European Union (EU) Member States.⁴⁻⁶ Variation could be improved by harmonization of European law, which is the process of creating uniformity in laws, regulations and practices between countries. Regarding research and IRB procedures, lack of procedural harmonization 'leads to a complex and uncertain framework for ethical review and for participant information consent, resulting in numerous inefficiencies in observational studies'.⁷ Greater procedural harmonization is generally considered desirable, because it could improve quality and efficiency of healthcare research by decreasing costs, increasing statistical validity,⁸⁻¹⁰ optimizing data management,¹⁰ allowing choice of relevant and generalizable outcome variables,⁹ promoting uniform product safety regulations⁸ and minimizing waste of resources due to inefficiencies.⁸

Although most IRBs have websites that describe the local submission process and provide access to submission guidelines and forms, up to date systematic information on IRB procedures and their level of harmonization in European health-care research is scarce. We are aware of only one previous meta-analysis on IRB procedures across European countries from 2005 to 2007 that was also related to research involving acutely mentally incapacitated individuals.⁶ The Collaborative European Neurotrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study is a large observational study conducted in many countries across Europe that provides a unique opportunity to assess European IRB policies and procedures.¹¹

This study aims to improve the efficiency of future research initiatives by quantifying the differences in IRB procedures through analyzing the procedural details, problems and challenges that researchers encountered in obtaining IRB approval for the general research protocol of the CENTER-TBI study.

METHODS

Study setting

The Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI, www.center-tbi.eu) Core study is a prospective observational study on traumatic brain injury (TBI), which was conducted between December 2014 and December 2017 in 63 neurotrauma centers across Europe and Israel.¹¹⁻¹² The study included patients with TBI of all severities, and aims to improve characterization of TBI, in order to facilitate the development of precision medicine approaches and to identify best practices by using a comparative effectiveness research (CER) approach.¹¹⁻¹⁴ In the context of the project high-quality Personal Health related Data (PHD) were collected with repositories for neuro-imaging, DNA, and serum biomarkers. Prior to the study start and collection of clinical data, a uniform CENTER-TBI research protocol including all relevant documents was sent to all responsible IRBs to ensure its legal, ethical and statistical soundness and to obtain IRB approval.

A total of 68 centers from 19 countries initially submitted applications for IRB approval. Because this article focuses on IRB approval in Europe, two centers from Israel were excluded from our analysis. The 66 center that participated in this present study are from Austria (N=2), Belgium (N=5), Denmark (N=2), Finland (N=2), France (N=7), Germany (N=4), Hungary (N=3), Italy (N=8), Latvia (N=3), Lithuania (N=2), the Netherlands (N=7), Norway (N=3), Romania (N=1), Serbia (N=1), Spain (N=4), Sweden (N=2), Switzerland (N=1), and the United Kingdom (UK), (N=9). Sixty-one European centers were initiated and actively enrolled patients in the study.

Data collection and administration

All IRB submission documents, communication records and approval documents were collated per center by the Contract Research Organization, ICON plc (ICON), directly after final approval of IRBs.¹⁵ ICON is a global company operating in the healthcare industry that was responsible for the clinical monitoring of CENTER-TBI data. The received IRB documents were obtained in 15 different languages (Danish, Dutch,

English, Finnish, French, German, Hungarian, Italian, Latvian, Lithuanian, Norwegian, Romanian, Serbian, Spanish, and Swedish) and were partly translated before analysis. The authors contacted the principle investigators to obtain additional information to minimize the amount of unclear or missing data. Identifiable information was deleted to protect the privacy of stakeholders. This resulted in a final set of documents, that was analyzed for this study.

Analyses

We assessed the IRB review procedures by using the final set of documents and aimed to answer the following research questions in order to evaluate differences in obtaining IRB approval (1) Was the study considered to be observational or interventional? (2) Was the research protocol to be submitted to a central IRB or local IRB for primary IRB review and primary IRB approval? (3) Was additional IRB review required after primary IRB approval had already been obtained? If yes, to what extent? (4) How many review rounds were conducted before primary IRB approval was obtained? What were the reasons? (5) What was the time between protocol submission and obtaining the required IRB approval to start the study? The use of 'primary' in this context should be interpreted as first in an order and 'additional' as second in an order, without including a statement on importance.

To elaborate on the fifth question, we reconstructed six timeframes regarding the primary IRB review procedure: (1) time between protocol submission and primary IRB approval or first IRB reaction, (2) time between first IRB reaction and first reaction of researcher, (3) time between first reaction of researcher and primary IRB approval or second IRB reaction, (4) time between second IRB reaction and second reaction researcher, (5) time between second reaction researcher and primary IRB approval, and (6) total time between protocol submission and primary IRB approval. The existence of these timeframes naturally depended on the actual procedure. Data on any additional IRB review focused only on the duration of this particular review until the required IRB approval was obtained.

In order to assess regional variation, countries were grouped into six regions based on the United Nation geo-scheme: Baltic States (Latvia, and Lithuania), Eastern Europe (Hungary, Romania, and Serbia), Northern Europe (Denmark, Finland, Norway, and Sweden), Southern Europe (Italy, and Spain), the United Kingdom (UK), and Western Europe (Austria, Belgium, France, Germany, the Netherlands, Switzerland).¹⁶ Incomplete data was marked 'Missing' (M) and all timeframes were reported in days.

To determine significant differences between the time from submission till approval of the research protocol between primary local IRBs and primary central IRBs, we performed a Mann-Whitney U test (continuous). Analyses were performed using R version 3.6.0. Finally, a descriptive analysis of questions, comments and answers from both IRB and researcher during the IRB review procedure was performed to summarize the problems and challenges that researchers encountered in obtaining IRB approval. IRB reactions were categorized and reported by their appearance: (1) Procedure, (2) Blood collection and biomarkers, (3) MRI, (4) Privacy and data security, (5) Other.

RESULTS

A total of 66 neurotrauma centers from 18 countries were included in this analysis. Most centers were located in Western Europe (N=26, 39%) and least in Eastern Europe (N=5, 8%) and the Baltic States (N=5, 8%). Most participating centers were from the UK (N=9), followed by Italy (N=8), The Netherlands and France (N=7) (Table 1). In all countries the local principal investigators were responsible to submit the general CENTER-TBI research protocol for IRB review and IRB approval.

Observational or interventional

The majority of countries (N=14, 78%) considered the study to be observational, while others judged it to be observational with diagnostic interventions (The Netherlands), interventional (France, Hungary) and observational and interventional (Serbia) (Table 1).

Primary central or primary local IRB review

Primary IRB review started directly after protocol submission and was considered 'central' when submitted to a central institution or an institution that was part of a national network (N=11, 61%). There were three options: (1) Primary central IRB approval had a national impact and applied to all participating centers within a country, without the need for additional IRB review (N=5; Denmark, Finland, France, Norway, Sweden). (2) Primary central IRB approval only allowed study start in the research centers associated with the approving IRB. Other participating centers in the country required approval after an additional extensive local IRB review. This involved the re-evaluation of the entire protocol and applicable ethics (N=4; Belgium, Germany, Hungary, Italy). (3) Primary central IRB approval only allowed study start in the research centers associated with the approving IRB. Other participating centers

required additional approval after marginal local IRB review, mainly assessing local feasibility (N=2; UK, The Netherlands) (Figure 1).

Table 1: Baseline study information

| Region | Centers (N) | Central or local IRB review | IRB decision on study type |
|-----------------|-------------|-----------------------------|---|
| Country | | | |
| Baltic States | 5 | | |
| Latvia | 3 | Local ^a | Observational |
| Lithuania | 2 | Local | Observational |
| Eastern Europe | 5 | | |
| Hungary | 3 | Central | Interventional |
| Romania | 1 | Local | Observational |
| Serbia | 1 | Local | Observational and Interventional |
| Northern Europe | 9 | | |
| Denmark | 2 | Central | Observational |
| Finland | 2 | Central | Observational |
| Norway | 3 | Central | Observational |
| Sweden | 2 | Central | Observational |
| Southern Europe | 12 | | |
| Italy | 8 | Central | Observational |
| Spain | 4 | Local | Observational |
| United Kingdom | 9 | | |
| United Kingdom | 9 | Central ^b | Observational |
| Western Europe | 26 | | |
| Austria | 2 | Local | Observational |
| Belgium | 5 | Central | Observational |
| France | 7 | Central | Interventional |
| Germany | 4 | Central | Observational |
| Netherlands | 7 | Central | Observational with diagnostic interventions |
| Switzerland | 1 | Local | Observational |

Table 1 legend:

^a Latvia has a local review procedure, but, after approval had been obtained for the first center, other centers did not require additional approval.

^b In the UK, the research protocol had to be submitted to an external national committee that was not associated to the submitting center. After primary approval by this national committee, all centers (including the submitting center) required additional IRB approval.

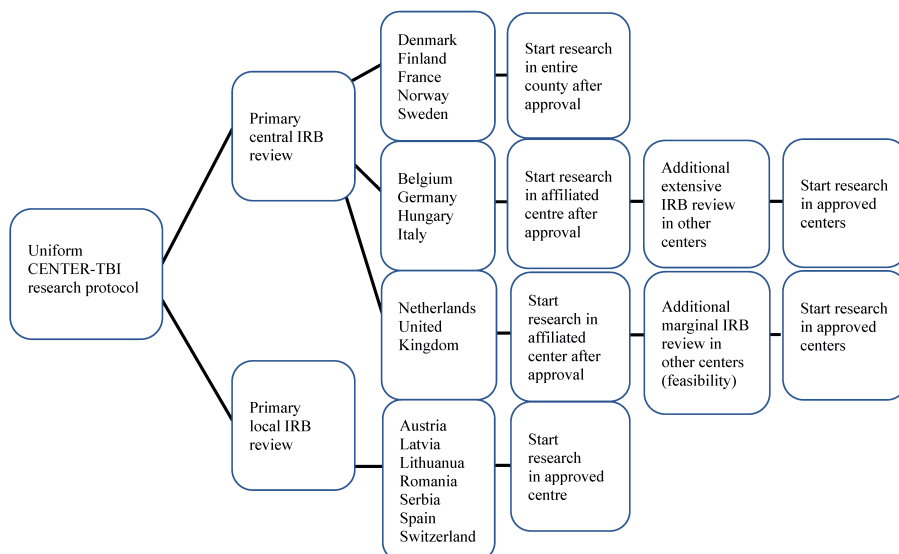


Figure 1: Flowchart of IRB review and approval processes in the CENTER-TBI study

Primary IRB review was considered ‘local’ when the protocol was submitted to an independent ‘local’ IRB. Obtained primary local IRB approvals only applied to the associated research centers and allowed study start without any additional requirements (N=7; Austria, Switzerland, Spain, Lithuania, Latvia, Romania, Serbia). Primary local IRB review could be performed simultaneously in each independent IRB (Figure 1).

For every protocol submission, there were two outcome options after IRB review: (1) the required (primary or additional) IRB approval had been obtained and the study could start, or (2) researchers were asked to answer questions or make protocol changes, which was followed by an extra IRB review round. This process varied between IRBs and was repeated until the required IRB approval was eventually obtained. None of the submissions in this study were rejected.

IRB review rounds

Eight countries (44%), including all countries from Eastern Europe and the Baltic State, obtained primary IRB approval in the first round after submission, while six countries (Austria, Belgium, France, Finland, Spain and UK) required one extra review round and four countries (Denmark, Germany, Norway and Sweden) required two extra review rounds (Figure 2). Extra review rounds were found in 73% of centers after primary central IRB submission and in 20% after primary local IRB submission.

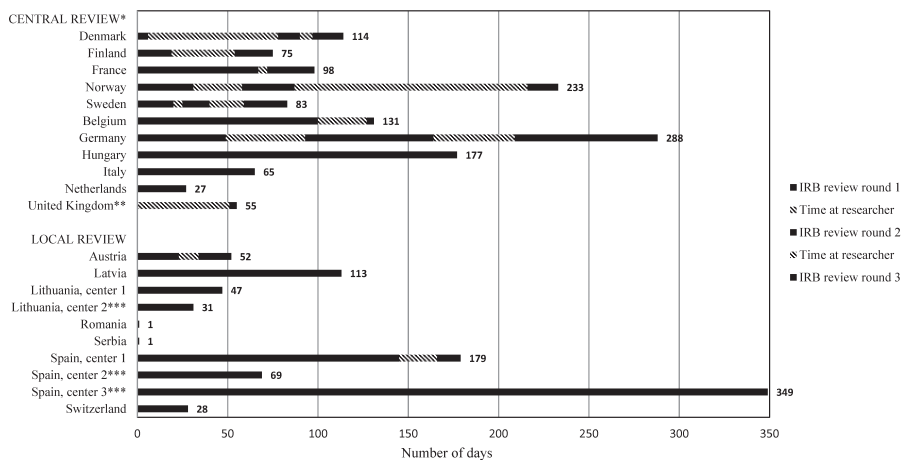


Figure 2. Detailed overview of primary IRB review and duration.

Figure 2 legend:

This figure provides a detailed overview of the number of primary local and central IRB review rounds and their duration in days. *The number of review rounds was only reported for the initial center of each country.

Information on the first review round was missing. *Only the total number of days was available

Several IRBs commented on different aspects of the protocol: selection criteria (n=3, 38%), patient/proxy consent (n=4, 50%), and information forms (n=3, 38%). Also, specific questions were asked on possible non-standard care factors in particular MRI scans (N=4), blood sample collection (N=4). Four questions were asked about privacy and data security, mainly related to the period after study completion. All relevant information can be found in the supplementary files.

Duration from protocol submission to IRB approval

The median time from protocol submission until the required IRB approval was obtained to start the study was 114 days (IQR 75-224). The fastest required IRB approval was obtained after one day in Serbia and Romania, whereas the longest time was found in a center in the UK (535 days). Obtaining central IRB approval (138 days, IQR: 91-229) took significantly longer ($p=0.0074$) than obtaining local IRB approval (50 days, IQR: 29-102) (Table 2).

Table 2. Duration of protocol submission until required IRB approval before study start.

| | Duration (days)* | Centers (N) | Missing (N) |
|----------------|------------------|-------------|-------------|
| All centers | 114 (75-224) | 58 | 8 |
| Local review | 50 (29-102) | 10 | 4 |
| Central review | 138 (91-229)** | 48 | 4 |
| - Central (1) | 98 (94-114) | 16 | 0 |
| - Central (2) | 189 (140-270) | 17 | 3 |
| - Central (3) | 104 (62-224) | 15 | 1 |

Legend:

*Duration was reported in median number of days (IQR).

**Group difference between local and central review were significant ($P=0.0074$, Mann-Whitney U).

Local review: Obtained primary local IRB approvals only applied to the associated research centers and allowed study start without any additional requirements

Central (1): Primary central IRB approval with national impact, applying to all center within a country, without the need for additional local IRB review.

Central (2): Primary central IRB approval only allowed study start in the research centers associated with the approving IRB. Other participating centers required approval after additional extensive local IRB review.

Central (3): Primary central IRB approval only allowed study start in the research centers associated with the approving IRB. Other participating centers required approval after additional marginal local IRB review.

In Norway and Denmark, the majority of time from submission to primary central IRB approval was spent by researchers (67% and 69%, respectively), while in France (95%) and Hungary (71%) most time was consumed by IRBs. Regarding primary local IRB submissions, researchers only accounted for 12% of time in Spain and 21% in Austria (Figure 2).

Additional IRB review rounds after primary central IRB review were required in 55% of countries. An additional marginal (feasibility) review had a median duration of 104 days (IQR: 62-224), whereas an additional extensive IRB review took 189 days (IQR: 140-270) (Table 3).

Variation between centers within countries was least in Lithuania (31 to 47 days), Germany (288 to 312 days), Belgium (131 to 155 days), and Hungary (177 to 204 days), compared to Spain (69 to 349 days), the Netherlands (27 to 224 days), the UK (58 to 535 days), and Italy (65 to 288 days) (Table 3).

Table 3. Duration from submission to required IRB approval before study start per country and study center.

| Country | Central or local IRB review | Duration in days | | | | | | | | |
|-----------------|-----------------------------|------------------|-----|-----|-----|-----|-----|-----|-----|-----|
| | | Centre | | | | | | | | |
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Denmark | Central (1) | 114 | 114 | | | | | | | |
| Finland | Central (1) | 75 | 75 | | | | | | | |
| France | Central (1) | 98 | 98 | 98 | 98 | 98 | 98 | 98 | | |
| Norway | Central (1) | 233 | 233 | 233 | | | | | | |
| Sweden | Central (1) | 83 | 83 | | | | | | | |
| Belgium | Central (2) | 131 | 138 | 141 | 257 | M | | | | |
| Germany | Central (2) | 288 | 296 | 312 | M | | | | | |
| Hungary | Central (2) | 177 | 200 | 204 | | | | | | |
| Italy | Central (2) | 65 | 70 | 139 | 141 | 155 | 261 | 273 | 288 | |
| Netherlands | Central (3) | 27 | 46 | 91 | 209 | 223 | 224 | M | | |
| United Kingdom* | Central (3) | 58 | 61 | 63 | 84 | 104 | 157 | 229 | 282 | 535 |
| Austria | Local | 52 | M | | | | | | | |
| Latvia | Local | 113 | M | M | | | | | | |
| Lithuania | Local | 31 | 47 | | | | | | | |
| Romania | Local | 1 | | | | | | | | |
| Serbia | Local | 1 | | | | | | | | |
| Spain | Local | 69 | 179 | 349 | M | | | | | |
| Switzerland | Local | 28 | | | | | | | | |

Table 3.

Central (1): Primary central IRB approval with national impact, applying to all center within a country, without the need for additional local IRB review to start study.

Central (2): Primary central IRB approval only allowed study start in the research centers associated with the approving IRB. Other participating centers required approval after additional extensive local IRB review to start study.

Central (3): Primary central IRB approval only allowed study start in the research centers associated with the approving IRB. Other participating centers required approval after additional marginal local IRB review to start study.

*In the UK, the research protocol had to be submitted to an external national committee not associated to the submitting center. After primary approval by this national committee, all centers required additional IRB approval.

Local review: Obtained primary local IRB approvals only applied to the associated research centers and allowed study start without any additional requirements

M = Missing

DISCUSSION

This study shows variation in IRB procedures between and within European countries, indicating a lack of uniform legislation and regulation, or inconsistencies in how such legislation or regulation were implemented. In some countries, a primary central IRB approval was sufficient for study initiation, while others required an additional IRB review at the participating site. Also, the number of review rounds, duration until IRB approval, and the nature of questions and comments from the IRBs varied. Not all IRBs considered the study to be observational, demonstrating a different way of

understanding the study. The apparent lack of integration and harmonization in this context suggests that the efficiency of European research collaborations could benefit from improving knowledge on the existing variation in procedures, inefficiencies and differences in value systems between and within countries.

The duration from protocol submission to required IRB approval was highly variable and ranged from one day up to nearly one year. In literature, differences between IRB procedures were also reported and IRB review durations varied from weeks to several months.^{6,17} The difference in total duration between primary central and primary local IRB approval could respectively be overestimated and underestimated by the short primary IRB review times in Serbia and Romania and the missing data of the first review round for the UK. The difference is not necessarily related to the number of review rounds, but might be more explained by the reason and nature (primary central/local review or extensive/marginal additional local review) of the extra review round(s), the accompanying amount of work and the working speed of both IRB and research team. The influence of the latter was substantiated by our data as responding to questions from the IRB seemed to account for an important part of time in several countries (e.g. Denmark and Norway), while the majority of time in other countries (e.g. Belgium, Spain and France) was accounted for by the time taken in primary evaluation by IRBs. The exact reasons for these 'delays' could however not be derived from our data and deserves further study. They might be caused by the difficulty of requirements or questions, although, according to the communication records, IRBs mainly requested extra explanation of research procedures. Based on the IRB information requests in this study, special attention should be given to the description of inclusion criteria, informed consent procedures, patient information forms, non-standard care procedures, privacy and data security. A quick response by investigators and agreeing on a maximal turnover time of 1 month to 2 months for IRBs could already minimize substantial delay. This is also in correspondence with literature, where IRB turnover time targets range from 30 to 60 days.¹⁷⁻¹⁸

The question whether CENTER-TBI was an observational or an interventional study did not appear to be a clear explanation for differences in number and duration of review rounds. Interventional studies are generally subject to a more extensive review process, where observational study reviews may be more marginal. Nonetheless, duration was short in France and long in the UK. CENTER-TBI is registered as an observational study, in which 'the investigator is not acting upon study participants, but instead observing natural relationships between factors and outcomes'.¹⁹ Two IRBs considered the study

to be purely interventional. Interventional studies are studies 'where the researcher intercedes as part of the study design'.¹⁹ An explanation for this opposing classification is that the IRBs did and did not consider the following procedures to be standard-of-care: (1) Different amounts of additional blood draws at presentation and follow-up. (2) Neuropsychological assessments and outcome questionnaires up to a 24-month follow-up. (3) Additional MRIs at sites participating in the MRI sub-study.

Extra work without clear benefits delays projects and should be avoided when possible. An additional IRB review after primary central IRB approval is usually double work and could result in an extra delay of weeks to more than a year, without always having clear benefits over the already obtained primary approval.¹⁷ Cancelling potentially unnecessary (extensive) additional IRB review procedures could not only reduce turnover time, but also reduce costs. The exact costs of European IRB review procedures are unfortunately unknown, but the direct costs of an IRB review and approval in the US have been calculated to be \$107,544 (\$82,610 in IRB fees and \$24,934 in labor).²⁰

Delays in obtaining IRB approval not only adversely affect study initiation, but are also associated with several other risks. Long procedures with many feedback rounds will delay study start, frustrate researchers and might even endanger meeting subsidiary demands. Researchers might attempt to speed up the process by changing the protocol or submitting the protocol to IRBs that are considered to be less strict but able to process the submission the quickest. This does not necessarily serve primary research objectives and might even hamper quality and generalizability of study results.

Optimization of IRB review procedures is urgently needed as multinational collaborations in healthcare research are increasing and even promoted by multiple European research grants.^{4-5,21} Harmonization and adequate implementation of regulatory and ethical standards between European countries could improve the present situation.^{7,22} The EU already aims to freely cooperate across borders by defining common standards and removing legal obstacles, but true harmonization of Member State laws in a research context has clearly not been established yet.²¹⁻²⁴ For example, the General Data Protection Regulation (GDPR) aimed to ensure a fair and transparent processing of personal data and aimed to improve patients' control over their own data.²⁵ The implementation and use of the GDPR however showed the difficulty of harmonization in the protection of the EU citizens in this context. This was especially caused by the possibility for European countries to use their own national legislation in addition to the GDPR, which does not improve the desired harmonization.

Harmonization remains a highly complex process due to variation of national regulations that are based on national customs, culture, ethics, religion and other beliefs. ⁶ Harmonization of laws is designed to incorporate different legal systems under a basic framework. To overcome the highly complex process of harmonization in the area of research, it has been suggested to combine similarities between legislations and regulations of countries under a basic framework like a European research directive. A framework should acknowledge these local cultural or religious beliefs, as disregarding them is neither feasible nor desirable. While the desirable goal of harmonizing regulation will certainly benefit research in the future, both IRBs and researchers will have to put in efforts until that time. IRBs can accelerate the turnover by only requiring central IRB approval and researchers should respond quicker and more comprehensively to questions from IRBs, preventing the repetition of questions.

Strengths and limitations

The CENTER-TBI study provides a unique opportunity to provide comprehensive insight in the procedural differences between European IRBs. The study benefits from its large size and because the data acquisition process increased the quality and completeness of documents. Despite the quality of the documents, results were still dependent on the recorded information. Therefore, we could not always identify causal factors for variation, which is something to look for in future initiatives. The data on IRB review procedures in an observational study conducted with mentally incapacitated patients in neurotrauma centers might not be generalizable for other research settings.

CONCLUSIONS

This study shows variation between IRB procedures across Europe, which pose major challenges to large European research collaborations. Differences are likely caused by the lack of harmonization, integration and implementation of national legislations and regulations. To optimize efficiency for multinational European studies in context of obtaining IRB approval, the encountered differences and inefficiencies should be studied further and policymakers should evaluate the opportunities to optimize regulatory harmonization, while acknowledging the boundaries of national sovereignty and local cultural preferences.

Supplementary files

Available online: <https://bmcomedethics.biomedcentral.com/articles/10.1186/s12910-020-00480-8#Sec14>

REFERENCES

1. Guide for Research Ethics Committee Members, Steering Comm. on Bioethics, revised version 3 December 2010, Council of Europe April (2012).
2. Emanuel E, Crouch R, Lie R, et al. The Oxford Textbook of Clinical Research Ethics. Oxford: Oxford University Press, Reprint edition 2011.
3. Standards and operational guidance for ethics review of health-related research with human participants, World Health Organization (2011).
4. Innovative Medicine Initiative, IMI mission and objectives. <https://www.imi.europa.eu/about-imi/mission-objectives>. Accessed August 3, 2019.
5. European Commission, Horizon 2020 - The Framework Programme for Research and Innovation. <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52011DC0808&from=EN>. Published 2011. Accessed September 3, 2019.
6. Tridente A, Holloway P, Hutton P, et al. Methodological challenges in European ethics approvals for a genetic epidemiology study in critically ill patients: the GenOSept experience. *BMC Med Ethics* 2019;20:30.
7. Urushihara H, Parmenter L, Tashiro S, et al. Bridge the gap: The need for harmonized regulatory and ethical standards for postmarketing observational studies. *Pharmacoepidemiol Drug Saf*. 2017;26:1299-1306.
8. Aledort L. Harmonization of clinical trial guidelines for assessing the risk of inhibitor development in hemophilia A treatment. *J Thromb Haemost*. 2011;9(3):423-427.
9. Oliver Daly J. Harmonisation of research outcomes for meaningful translation to practice: The role of Core Outcome Sets and the CROWN Initiative. *Aust N Z J Obs Gynaecol*. 2018;58:15-16.
10. Bowles K, Potashnik S, Ratcliffe S, et al. Conducting research using the electronic health record across multi-hospital systems: semantic harmonization implications for administrators. *J Nurs Adm*. 2013;43:355-360.
11. Maas A, Menon D, Steyerberg E, et al. Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): a prospective longitudinal observational study. *Neurosurgery*. 2015;76:67-80.
12. Steyerberg E, Wieggers E, Sewalt C, et al. Case-mix, care pathways, and outcomes in patients with traumatic brain injury in CENTER-TBI: a European prospective, multicentre, longitudinal, cohort study. *The Lancet Neurol*. 2019;18:923-934.
13. Maas A, Menon D, Adelson P, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. *Lancet Neurol*. 2017;16:987-1048.
14. Cnossen M, Polinder S, Lingsma H, et al. Variation in structure and process of care in traumatic brain injury: Provider profiles of European Neurotrauma Centers participating in the CENTER-TBI study. *PLoS One*. 2016;11(8):e0161367.
15. ICON plc. <http://www.iconplc.com>. Accessed August 8, 2019.
16. United Nations, Standard country or area codes for statistical use (M49). <https://unstats.un.org/unsd/methodology/m49/>. Published 1999. Accessed September 5, 2019.
17. Mascette A, Bernard G, Dimichele D, et al. Are central institutional review boards the solution? The National Heart, Lung, and Blood Institute Working Group's report on optimizing the IRB process. *Acad Med*. 2012;87:1710-1714.
18. Adams P, Kaewkungwal J, Limphattharacharoen C, et al. Is Your Ethics Committee Efficient? Using "IRB Metrics" as a Self-Assessment Tool for Continuous Improvement at the Faculty of Tropical Medicine, Mahidol University, Thailand. *PLoS ONE* 2014;9(11):e113356.
19. Thiese M. Observational and interventional study design types; an overview. *Biochem Med*. 2014;24(2):199-210.
20. Ravina B, Deuel L, Siderowf A, et al. Local institutional review board (IRB) review of a multicenter trial: local costs without local context. *Ann Neurol*. 2010;67(2):258-260.
21. Consolidated version of the Treaty on the Functioning of the European Union. Official Journal of the European Union C 326/47, 26 October (2012).
22. Henshall C, Mardhani-Bayne L, Fronsdaal KB, et al. Interactions between health technology assessment, coverage, and regulatory processes: emerging issues, goals, and opportunities. *Int J Technol Assess Heal Care*. 2011;27(3):253-260.
23. Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General data Protection Regulation) Official journal of the European Union L 119/1, 4 May (2016)
24. European Commission. The European Union. What it is and what it does. Luxembourg: Publications Office of the European Union 2018. doi:10.2775/665897
25. Timmers M, Van Veen E-B, Maas A, et al. Will the Eu Data Protection Regulation 2016/679 Inhibit Critical Care Research? *Med Law Rev*. 2019;27:59-78.



CHAPTER 8

Informed consent procedures in patients with an acute inability to provide informed consent: policy and practice in the CENTER-TBI study

Authors:

Roel P.J. van Wijk^{1*},
Jeroen T.J. M. van Dijck^{1*},
Marjolein Timmers²,
Ernest van Veen^{2,3},
Giuseppe Citerio^{4,5},
Hester F. Lingsma³,
Andrew I.R. Maas^{6,7},

David K. Menon⁸,
Wilco C. Peul¹,
Nino Stocchetti^{9,10},
Erwin J.O. Kompanje^{2,11},
The CENTER-TBI investigators and participants
*Contributed equally to the study

Affiliations:

1. University Neurosurgical Center Holland, LUMC, HMC & Haga, Leiden & The Hague, the Netherlands.

2. Department of Intensive Care, Erasmus MC - University Medical Centre Rotterdam, Rotterdam, the Netherlands.

3. Centre for Medical Decision Making, Department of Public Health, Erasmus MC - University Medical Centre Rotterdam, Rotterdam, the Netherlands.

4. School of Medicine and Surgery, University of Milan-Bicocca, Milan, Italy. OrcidID 0000-0002-5374-3161.

5. San Gerardo Hospital, ASST-Monza, Italy.

6. Department of Neurosurgery, Antwerp University Hospital, Edegem, Belgium.

7. University of Antwerp, Antwerp, Belgium.

8. Department of Anaesthesia, University of Cambridge, Cambridge, United Kingdom.

9. Department of Physiopathology and Transplantation, Milan University, Milan, Italy.

10. Neuro ICU Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico Milano, Milan, Italy.

11. Department of Medical Ethics and Philosophy of Medicine, Erasmus MC - University Medical Centre Rotterdam, Rotterdam, the Netherlands.

Citation:

R.P.J. van Wijk¹, J.T.J.M. van Dijck¹, M. Timmers, E. van Veen, G. Citerio, H.F. Lingsma, A.I.R. Maas, D.K. Menon, W.C. Peul, N. Stocchetti, E.J.O. Kompanje, The CENTER-TBI investigators and participants. Informed consent procedures in patients with an acute inability to provide informed consent: policy and practice in the CENTER-TBI study. *Journal of Critical Care* 2020. DOI: 10.1016/j.jcrc.2020.05.004.

ABSTRACT

Purpose: Enrolling traumatic brain injury (TBI) patients with an inability to provide informed consent in research is challenging. Alternatives to patient consent are not sufficiently embedded in European and national legislation, which allows procedural variation and bias. We aimed to quantify variations in informed consent policy and practice.

Methods: Variation was explored in the CENTER-TBI study. Policies were reported by using a questionnaire and national legislation. Data on used informed consent procedures were available for 4498 patients from 57 centres across 17 European countries.

Results: Variation in the use of informed consent procedures was found between and within EU member states. Proxy informed consent (N=1377;64%) was the most frequently used type of consent in the ICU, followed by patient informed consent (N=426;20%) and deferred consent (N=334;16%). Deferred consent was only actively used in 15 centres (26%), although it was considered valid in 47 centres (82%).

Conclusions: Alternatives to patient consent are essential for TBI research. While there seems to be concordance amongst national legislations, there is regional variability in institutional practices with respect to the use of different informed consent procedures. Variation could be caused by several reasons, including inconsistencies in clear legislation or knowledge of such legislation amongst researchers.

Keywords: Traumatic brain injury; Informed consent; European union; Ethics.

BACKGROUND

Patient informed consent is one of the basic principles underpinning clinical research. Patients have the right to be informed about a proposed study and should have the opportunity to make an autonomous decision on study participation. It is however impossible to obtain patient informed consent from patients with an acute inability to provide informed consent due to an acute illness such as traumatic brain injury (TBI).¹ Research with TBI patients is however essential to optimize treatments and improve patient outcome. Therefore, several pragmatic alternatives are available in case patient informed consent could not be obtained.²

Proxy informed consent is the most frequently used alternative. Close family members or unrelated appointed legally authorized representatives are selected in accordance with applicable national or local regulations. These so-called proxies have the legal right to provide informed consent on behalf of the patient.³ Proxies are however often unavailable in the acute setting or are unable to make a valid judgment for several other reasons.⁴⁻⁹ This is especially complicated in emergency research where time is scarce.

To overcome this, some research settings allow an independent physician to decide on behalf of the patient. In many European countries, it is also accepted to include and randomize patients in emergency research settings without prior patient- or proxy informed consent and ask consent for study continuation later (deferred consent procedure).^{3,10} Researchers can also use the so-called 'exception from consent' and 'waiver of consent' procedures, which allow study start without prior patient- or proxy informed consent without the requirement of informed consent for study continuation.^{11,12}

The relative pros and cons of different informed consent procedures have led to substantial regulatory variation within and between European Union (EU) Member States and globally.^{13,14} The EU has replaced the Data Protection Directive and the Clinical Trials Directive by the General Data Protection Regulation and the Clinical Trials Regulation to harmonize informed consent procedures.^{3,15-17} Unfortunately, neither regulation addresses the specific situations of patients with an acute inability to provide informed consent in detail, and neither clearly differentiates between acute or chronic mental conditions. Although the General Data Protection Regulation provides

for exemptions from patient informed consent procedures for observational research by leaving room for national legislation, informed consent in clinical emergency research is not mentioned in national law in 12 EU Member States.^{13,18}

The lack of clear directions in European and national legislation may be expected to result in substantial practice variation in consent procedures for patients with an acute inability to provide informed consent.¹⁹ The use of different informed consent procedures in international multi-center studies could cause recruitment inefficiency, non-homogenous patient inclusion, selection bias, asymmetrical randomisation, and limited external validity of study results.^{20,21} Clearly, optimization of informed consent procedures and harmonization of regulations is important for future research initiatives.

The aim of this study is to inform researchers and policymakers on the use and challenges of informed consent procedures in a large prospective observational study including patients with an acute inability to provide informed consent due to TBI. Therefore, we investigated local policy and observed practice of informed consent procedures in the Collaborative-European-Neuro-Trauma-Effectiveness-Research in Traumatic Brain Injury (CENTER-TBI) study.²²

MATERIALS AND METHODS

CENTER-TBI and study sample

The CENTER-TBI project includes a large prospective observational study on TBI conducted in 63 neurotrauma centres across Europe and Israel.²⁰⁻²¹ CENTER-TBI had a follow up period of 12 to 24 months and required extra blood samples and, in a subpopulation, MRI scans in addition to standard care. For this particular study, we excluded four centres with low inclusion rates (<five patients) and 2 centres from Israel, because we focussed on European centres. All remaining centres (N=57) from 17 European countries obtained IRB approval and were analyzed. (See Suppl Table 1).

Policy: Provider profiling and national legislation

Investigators of each study center completed “Provider Profiling” questionnaires prior to recruitment to the CENTER-TBI Core study. The questionnaires aimed to characterize general healthcare processes and, specifically for this present study, the use of informed consent procedures. (see Suppl file 1). These questions were about the acceptance and

use of informed consent procedures in general and not specifically for the CENTER-TBI study. The question mentioning the 'deferred consent/waiver of consent' alternatives was used to assess the possibility of study start without prior informed consent in emergency research and was named deferred consent in this article. Answers explicitly represent a general consensus at the centres, rather than an individuals' preference, in an attempt to capture the actual policy of all study centres. Responses were collected and stored by using a secure online database (QuesGen Systems Incorporated, Burlingame, CA, USA).²³ Detailed information on the provider profiling questionnaires has been published previously.²⁴ An additional analysis of national regulations that were applicable at the time of study was performed and compared with the results of the questionnaire and actual observed informed consent procedures.¹³

Practice: CENTER-TBI Core study

The CENTER-TBI Core study (clinicaltrials.gov NCT02210221; RRID: SCR_015582) was conducted between December 2014 and December 2017.²⁵ Enrolment criteria were a clinical diagnosis of TBI, indication for CT-scanning, and presentation to study centre within 24h of injury. Approval from an IRB or any other appropriate ethics review body was obtained by all centres and informed consent procedures followed local and national requirements. On enrolment, patients were differentiated by care pathway: ER stratum (discharged from emergency room), Admission stratum (hospital ward), and ICU stratum (admission to the intensive care unit (ICU)). For this study, informed consent practice was pragmatically observed in the ICU stratum (N=2137) of CENTER-TBI, since we focussed on patients with an acute inability to provide informed consent. The presence of the inability to provide informed consent was very unlikely in patients from the ER and Admission stratum because nearly all sustained mild TBI and provided informed consent themselves.

Clinical data included details on the type and time of informed consent and were collected and de-identified using a web-based electronic case report form (QuesGen) and stored on a secure database, hosted by the International Neuroinformatics Coordinating Facility (INCF; www.incf.org) in Stockholm, Sweden.²⁶

Analyses

Data (Version 1.0, released: 01/11/2018) was extracted via the custom-made data access tool Neurobot (<http://neurobot.incf.org>), developed by INCF. Descriptive statistics were used to obtain frequencies and percentages. For analysis of potential differences

between regions we grouped countries into six regions based on the United Nations geo-scheme (See Suppl Table 1).²⁷ Due to the agreed anonymity of participating sites, it was not always possible to display all differences between countries, as some countries have only 1 or 2 participating sites. Potential differences between centres in one country were analyzed in countries with three or more participating centres. Analyses were performed using R version 3.6.0.

RESULTS

All 57 participating centres completed the provider profiling questionnaire. The majority was completed by principal investigators and medical professionals (N=20), IRB members (N=15), and staff members (N=13). (See Suppl Table 2) Most centers were academic hospitals (91%) with a designation as Level I trauma centre (68%). Thirty (53%) centres had a department of medical ethics and 28 (49%) had extensive neurotrauma research experience, with five or more research applications over the previous five years. (See Suppl Table 3)

Policy

Alternatives for patient informed consent were widely accepted. (Table 1 & Fig 1). Most IRBs allowed the use of proxy informed consent (79%) for acutely mentally incapacitated patients, while consent by an independent physician was less frequently allowed (37%). The majority of centers considered deferred consent (82%) for emergency research to be a valid alternative.

Table 1. Number of study centres (%) that allow the use of an informed consent procedure in acutely mentally incapacitated patients.

| Informed consent procedure | Yes N (%) | No N (%) | Unknown N (%) |
|-------------------------------------|--------------|-------------|------------------|
| Proxy informed consent | 45 (79) | 11 (19) | 1 (2) |
| Consent by an independent physician | 21 (37) | 30 (53) | 6 (10) |
| Deferred consent | 47 (83) | 7 (12) | 3 (5) |

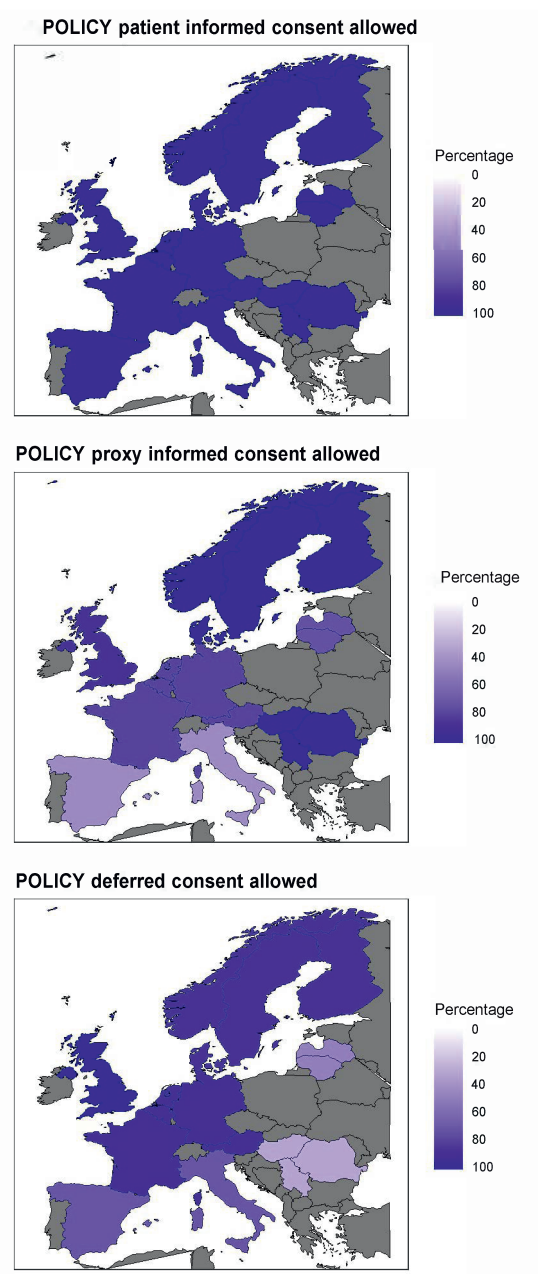


Figure 1: Reported policy on types of consent in acutely mentally incapacitated patients in Europe. (Percentage of centres in one country that allow the type of consent in the questionnaire)

Substantial variation in informed consent policies was noted between regions in Europe. All centres in Northern and Eastern Europe reported prior proxy informed consent to be valid (100%), in contrast to centres in The Baltic States (75%), Southern Europe (45%), the United Kingdom (UK) (89%) and Western Europe (81%). Regarding Southern Europe, especially Italian centers (62%) reported proxy informed consent to be invalid. (See Suppl Table 4).

Acceptance of consent by an independent physician was lower (37%) and variable across European regions. (See Fig. 1 & Suppl Table 4) It was especially considered valid in Germany (100%), the UK (89%), and Spain (67%). None of the centers from The Netherlands, Italy and Norway reported this alternative to be valid, while other countries were inconsistent. (see Suppl Table 5)

The use of the deferred consent procedure was reported valid by most centers in most regions, except Eastern Europe. (see Suppl Table 4) When reported valid, it was mostly regulated by IRB approval (N=36) or by law (N=11). Of countries with ≥ 3 centres, all mentioned that the procedure was valid. (see Suppl Table 5)

Practice

Overall practice

All participating centres (N=57) included 4498 patients. Most patients were admitted to the ICU stratum (N=2137;48%) followed by the Admission stratum (N=1517;34%) and the ER stratum (N=844;19%). Overall, patient informed consent (N=2497;56%) was the most frequently used type of consent, followed by proxy informed consent (N=1635;36%) and deferred consent (N=366;8%) The use of patient informed consent was lower for patients requiring ICU admission (N=426;20%) compared to patients requiring admission to the ward (N=1266;83%). (Table 2)

Table 2. Number of patients (%) and type of used informed consent procedure per stratum in the CENTER-TBI study.

| Consent type Stratum | ER (N=844, 19%) | Admission (N=1517, 34%) | ICU (N=2137, 48%) |
|---|--------------------|----------------------------|----------------------|
| Patient informed consent (N=2497, 56%) | 805 (95) | 1266 (83) | 426 (20) |
| Proxy informed consent (N=1635, 36%) | 35 (4) | 223 (15) | 1377 (64) |
| Deferred consent (N=366, 8%) | 4 (0.5) | 28 (2) | 334 (16) |

Practice in ICU stratum

Proxy informed consent (N=1377;64%) was the most frequently used type of consent in the ICU, followed by patient informed consent (N=426;20%) and deferred consent (N=334;16%) (Table 3). Proxy informed consent was most frequently used in the UK (96%), Southern Europe (80%) and The Baltic States (76%), and less frequently in Northern (56%) and Western Europe (49%). In contrast, deferred consent was most frequently used in Northern (19%) and Western Europe (25%) but infrequently in the UK (0.3%) and the Baltic States (3%) (Table 3). Seven countries (41%) did not use deferred consent. Austria did not use proxy informed consent, but showed the highest number of deferred consents instead (65%). (see Suppl Table 6)

Table 3. Number of patients (%) and type of used informed consent procedures in the ICU stratum per region.

| Answers Regions | Sample Total (N=2137) | Baltic States (N=33) | Eastern Europe (N=33) | Northern Europe (N=391) | Southern Europe (N=546) | United Kingdom (N=271) | Western Europe (N=863) |
|--------------------------|-----------------------------|----------------------------|-----------------------------|-------------------------------|-------------------------------|------------------------------|------------------------------|
| Patient informed consent | 426 (20) | 7 (21) | 11 (33) | 97 (25) | 75 (14) | 10 (4) | 226 (26) |
| Proxy informed consent | 1377 (64) | 25 (76) | 20 (61) | 219 (56) | 433 (79) | 260 (96) | 420 (49) |
| Deferred consent | 334 (16) | 1 (3) | 2 (6) | 75 (19) | 38 (7) | 1 (0.3) | 217 (25) |

Comparison of policy and practice

Proxy informed consent and deferred consent procedures are accepted by national legislation of all displayed countries.^{13,28,29} (Table 4) Some centers however reported proxy or deferred consent procedures to be not accepted. In addition, there was variation between accepted procedures and actually used informed consent procedures. Italy for instance reported a low rate of proxy informed consent acceptance and a high enrolment rate using proxy informed consent.

When also including countries (≤ 3 centres) that could not be displayed, the use of deferred consent in emergency situations was allowed in 10 out of 17 countries. The procedure was not mentioned in national legislation in 6 countries. In the questionnaire, 47 (82%) of the participating centres reported that it was possible to include patients with an acute inability to provide informed consent by using deferred consent. In practice, only 15 centres from seven countries were responsible for 99% (N=330) of the deferred consent cases in the ICU.

Table 4. Comparison of observed practice, national legislation and reported policy regarding informed consent procedures in the CENTER-TBI ICU stratum.

| Country (N) | Patients included using patient informed consent (N (%)) | Proxy informed consent procedures accepted according to national legislation? [13] | Number of centers (%) accepting proxy informed consent according to provider profiling |
|-------------------|--|--|--|
| Belgium (N=4) | 71 (37) | Yes | 4 (100) |
| France (N=5) | 25 (22) | Yes | 5 (100) |
| Germany (N=4) | 24 (28) | Yes | 2 (50) |
| Italy (N=8) | 34 (10) | Yes | 3 (37) |
| Netherlands (N=7) | 68 (19) | Yes | 6 (86) |
| Norway (N=3) | 33 (20) | Yes [28] | 3 (100) |
| Spain (N=3) | 41 (21) | Yes | 2 (67) |
| UK (N=9) | 10 (4) | Yes | 8 (89) |
| Total | 306 | | 33 |

DISCUSSION

Patient informed consent alternatives like proxy informed consent, deferred consent and independent physician consent were widely used in the CENTER-TBI study and were essential to include ICU admitted TBI patients with an acute inability to provide informed consent. Alternatives to patient informed consent are essential in TBI research. Only 20% of ICU patients provided patient informed consent. This study found substantial between and within-country variation in reported accepted informed consent policies and actually used informed consent procedures. Variation could be caused by several reasons and could indicate that either clear national or European legislation is unavailable or that knowledge of such legislation may be inconsistent amongst clinicians and researchers.

The number of patient informed consent (N=2497; 56%) observed in the CENTER-TBI core study was higher than expected. This was partly due to the large number of patients in the ER and Admission strata (>95% with mild TBI) that were able to provide informed consent (87%). In addition, many patients in the ICU stratum had mild TBI (36%).²⁷ This could explain the high number of patient informed consents (20%) in the ICU, but it is also possible that study personnel wrongly considered a patient to have the ability to provide patient informed consent. The CENTER-TBI study did not use or document any assessment of a patients' ability to provide informed consent. Although assessment methods are available and used in some studies, they have important limitations.^{30,31} It is important that researchers formally assess the ability to provide informed consent in all patients when possible. Especially in patients with a

| Patients included using proxy informed consent (N (%)) | Deferred consent accepted in emergency research according to national legislation? [13] | Number of centers (%) accepting deferred consent in emergency research according to provider profiling | Patients included using deferred consent (N (%)) |
|--|---|--|--|
| 122 (63) | Yes | 4 (100) | 0 (0) |
| 90 (78) | Yes | 5 (100) | 0 (0) |
| 54 (62) | Yes | 3 (75) | 9 (10) |
| 279 (79) | Yes | 5 (63) | 38 (11) |
| 154 (43) | Yes | 6 (86) | 137 (38) |
| 94 (58) | Yes [29] | 3 (100) | 36 (22) |
| 154 (79) | Not mentioned | 3 (100) | 0 (0) |
| 260 (96) | Yes | 9 (100) | 1 (0.4) |
| 1207 | | 38 | 221 |

possible episode of an acute inability to provide informed consent. This assessment should ideally be recorded in the case report form to guarantee the validity of patient informed consent.

Alternatives for patient informed consent allowed the inclusion of 80% of ICU stratum patients. Overall, proxy informed consent was the most frequently used alternative. Although it was not always reported to be an accepted informed consent policy for mentally incapacitated patients, it was an accepted procedure by all national laws. Proxies usually prefer to be involved in decision-making, but proxy informed consent has several important limitations.³² Several studies report substantial discrepancies between patients and proxies and conclude that proxies are poor surrogate decision-makers.^{7-9,33} In addition, proxies are not always present in emergency situations, or are too overwhelmed by the stressful situation to provide valid proxy informed consent.^{34,35} Researchers and clinicians should be aware of the many factors that are important in the process of informed consent.³⁶

Fortunately, it was also possible to include patients by using deferred consent when it was impossible to obtain prior patient or proxy informed consent. A total of 45 centres (79%) from ten countries, according to national law, or 47 centres (82%), according to reported policies, were allowed to use this procedure. Nonetheless, only 15 centres (26%) actively (>2 inclusions) used it. There are multiple explanations for this discrepancy. First, the use of deferred consent might be accepted in national legislation, but local IRBs may not have authorised it for the CENTER-TBI study. Also, the use of deferred consent is not ethically neutral and the acceptance by IRBs, healthcare providers, patients and relatives

differ substantially.³⁷⁻⁴² Second, deferred consent was authorised as valid, but its use was not required because proxy or independent physician consent were used. Last, it is also possible that local researchers were unaware of the possibility of deferred consent.

Current European regulations include The Data Protection Directive and the Clinical Trials Directive, which were applicable at the time when patients were included in CENTER-TBI, are or will be superseded by the General Data Protection Regulation and the Clinical Trial Regulation respectively. However, since the General Data Protection Regulation does not apply to anonymized data and alternatives to patient informed consent are left to the legislation of Member States, large improvements in harmonization are not expected.^{19,43} The Clinical Trials Regulation does state that patient informed consent may be deferred in some specific situation and might thereby cause an increase in the use of deferred consent.^{17,19,44-46}

There is a lack of clear regulations on emergency research in mentally incapacitated patients and lack of harmonization regarding informed consent procedures in European Neurotrauma centres. Performing multinational trials is challenging when variations in acceptance of alternatives for patient informed consent exist.^{14,47} Potential issues not only include IRB processing and patient recruitment inefficiency and therefore study delay, but also non-homogenous patient inclusion, selection bias, asymmetrical randomisation, and limited external validity of study results.^{20,21} Although informed consent procedures are bound by national laws, institutional regulations and cultural factors, it could be beneficial for future research initiatives to harmonize procedures and regulations.

This study has several limitations. First, the majority of the participating centres were academic centres specialized in research and neurotrauma resulting in a possible selection bias. Second, by pragmatically focusing on patients from the ICU stratum with the highest likelihood of an inability to provide informed consent, we might have missed a few patients that were included in the ER or ward stratum. Unfortunately, there was no registered formal assessment of the ability to provide informed consent that could have been used to identify patients. Third, in addition to an analysis of national laws, reported informed consent policies were based on the provider profiling questionnaire rather than on actual policies. Although most responses were provided by seniors, the discrepancies could be caused by provider profiling errors due to variable individual understanding of actual policies and/or regulations. It could however also reflect the centres' general consensus or IRB specific directives rather

than national juridical policies. Fourth, it is important to bear in mind that CENTER-TBI is an observational study, although IRBs in three countries considered it to be an interventional study as blood samples were requested. Results on consent policy and practice might be different for interventional studies or randomized controlled trial. This is because the consequences of participation might be bigger and effective retrospective refusal of study participation is not possible as study interventions have already taken place. Although our data are derived from a patient population with TBI, the identified problems and insights have relevance for other conditions that could cause an inability to provide informed consent.

CONCLUSIONS

Alternatives to patient informed consent are essential for studies including TBI patients with an acute inability to provide informed consent. The substantial variation in reported and used informed consent procedures in Europe could be caused by several reasons and could indicate that clear national or European legislation is unavailable or that knowledge of such legislation may be inconsistent amongst clinicians and researchers. Future research initiatives could benefit from clear and harmonized regulations for this subcategory of patients.

HIGHLIGHTS

1. Variation is reported in consent procedures between and within European countries.
2. Discordance between reported consent policy and observed practice was common.
3. Deferred consent was accepted in many countries, but not frequently used.
4. Harmonisation of consent procedures is needed to improve research efficiency.
5. Researchers should verify and document a patients ability to provide informed consent.

Supplementary files

Available online: <https://doi.org/10.1016/j.jcrc.2020.05.004>

REFERENCES

1. World Medical Association. Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. 2018; 2019
2. Grady C, Cummings SR, Rowbotham MC, McConnell MV, Ashley EA, Kang G. Informed Consent. *N Engl J Med* 2017; 376: 856–67. DOI: 10.1056/NEJMr1603773.
3. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC OJ L158:1–76: 2014.
4. Mirr MP. Decisions made by family members of patients with severe head injury. *ACCN* 1991;2:242-51. DOI:10.4037/15597768-1991-2009.
5. Gigon F, Merlani P, Chenaud C, Ricou B. ICU research: The impact of invasiveness on informed consent. *Intens Care Med* 2013;39(7):1282-9. DOI: 10.1007/s00134-013-2908-x.
6. Abramson NS, Meisel A, Safar P. Deferred Consent: A New Approach for Resuscitation Research on Comatose Patients. *JAMA* 1986; 255: 2466–71. DOI:10.1001/jama.255.18.2466.
7. Wrigley A. Proxy consent: moral authority misconceived. *J Med Ethics* 2007; 33: 527–31. DOI:10.1136/jme.2006.019711.
8. Ciroidi M, Cariou A, Adrie C, Annane D, Castelain V, Cohen Y, et al. Ability of family members to predict patient's consent to critical care research. *Intensive Care Med* 2007; 33: 807–13. DOI: 10.1007/s00134-007-0582-6.
9. Shalowitz DI, Garrett-Mayer E, Wendler D. The accuracy of surrogate decision makers: a systematic review. *Arch Intern Med* 2006; 166: 493–7. DOI: 10.1001/archinte.166.5.493.
10. Jansen TC, Kompanje EJO, Bakker J. Deferred proxy consent in emergency critical care research: Ethically valid and practically feasible. *Crit Care Med* 2009;37: (Suppl.):65–68. DOI: 10.1097/CCM.0b013e3181920851.
11. Department of Health and Human Services F and Drug Administration. Protection of Human Subjects; Informed Consent and Waiver of Informed Consent Requirements in Certain Emergency Research; Final Rules. *Fed Regist* 1996; Volume 61, Number 192: 51498–531.
12. U.S Food and Drug Administration. Sec. 50.24 Exception from informed consent requirements for emergency research. *Code Fed Regul Title 21, Vol I, Subchapter A, Part 50, Subpart B*.
13. Kompanje EJO, Maas AIR, Menon DK, Kesecioglu J. Medical research in emergency research in the European Union member states: Tensions between theory and practice. *Intens Care Med* 2014;40:496-503. DOI: 10.1007/s00134-014-3243-6
14. Van Belle G, Mentzelopoulos SD, Aufderheide T, May S, Nichol G. International variation in policies and practices related to informed consent in acute cardiovascular research: Results from a 44 country survey. *Resuscitation* 2015;91:76-83. DOI: 10.1016/j.resuscitation.2014.11.029.
15. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. OJ L21:34: 2001.
16. Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data OJ L281:31–50: 1995.
17. Regulation (EU) No 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) OJ L119:1–88: 2016.
18. European Union GDPR. "Processing of special categories of personal data". OJ L119:Ch. 2 Art. 9. 2016.
19. Timmers M, Van Veen EB, Maas AIR, Kompanje EJO. Will the EU data protection regulation 2016/679 inhibit critical care research? *Med Law Rev* 2019;27:59–78. DOI: 10.1093/medlaw/fwyo23.
20. Ecartot F, Quenot JP, Besch G, Piton G. Ethical challenges involved in obtaining consent for research from patients hospitalized in the intensive care unit. *Ann Transl Med* 2017; 5(suppl):S41. DOI: 10.21037/atm.2017.04.42.
21. Burns KEA, Zubrinich C, Tan W, Raptis S, Xiong W, Smith O, et al. Research recruitment practices and critically ill patients. A multicenter, Cross-sectional study (The Consent Study). *Am J Respir Crit Care Med* 2013;187:1212-7. DOI: 10.1164/rccm.201208-1537OC.
22. Maas AIR, Menon DK, Steyerberg EW, Citerio G, Lecky F, Manley GT et al. Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): a prospective longitudinal observational study. *Neurosurgery* 2015;76(1):67–80. DOI: 10.1227/NEU.0000000000000575.
23. QuesGen Systems, Inc. Available at: <https://www.quesgen.com/> [Accessed October 8, 2019].

24. Crossen MC, Polinder S, Lingsma HF, Maas AI, Menon D, Steyerberg EW. Variation in structure and process of care in traumatic brain injury: provider profiles of European neurotrauma centers participating in the CENTER-TBI study. *Plos One* 2016;11:1. DOI: 10.1371/journal.pone.0161367.
25. Steyerberg E, Wieggers E, Sewalt C, Buki A, Citerio G, De Keyser V, et al. Case-mix, care pathways, and outcomes in patients with traumatic brain injury in CENTER-TBI: a European prospective, multicentre, longitudinal, cohort study. *Lancet Neurol* 2019;18(10):923-34. DOI:10.1016/S1474-4422(19)30232-7.
26. International Neuroinformatics Coordinating Facility (INCF). Available at: <https://www.incf.org/> [Accessed October 8, 2019].
27. United Nations. "Standard Country or Area Codes for Statistical Use (M49)" Available at: <https://unstats.un.org/unsd/methodology/m49/>. [Accessed October 8, 2019].
28. Convention on the protection of human rights and human dignity in connection with the application of biology and medicine: Convention on human rights and biomedicine - ETS no. 164. Chapter 5, Article 17.6
29. Convention on the protection of human rights and human dignity in connection with the application of biology and medicine: Convention on human rights and biomedicine - ETS no. 164. Chapter 5, Article 17.2
30. Johnson-Greene D. Informed consent issues in traumatic brain injury research: current status of capacity assessment and recommendations for safeguards. *J Head Trauma Rehabil* 2010; 25: 145–50. DOI: 10.1097/HTR.0b013e3181d8287d.
31. Feng KL, Person C, Phillips-Sabot J, Williams B, Cai C, Jacobs AN et al. Comparison between a standardized questionnaire and expert clinicians for capacity assessment in stroke clinical trials. *Stroke* 2014; 45: e229–32. DOI: 10.1161/STROKEAHA.114.006395.
32. Barrett KA, Ferguson ND, Athaide V, Cook DJ, Friedrich JO, McDonald E, et al. Surrogate decision makers' attitudes towards research decision making for critically ill patients. *Intensive Care Med* 2012; 38: 1616–23. DOI: 10.1007/s00134-012-2625-x.
33. Ciroidi M, Cariou A, Adrie C, Annane D, Castelain V, Cohen Y. Ability of family members to predict patient's consent to critical care research. *Intensive Care Med* 2007; 33: 807–13. DOI: 10.1007/s00134-007-0582-6.
34. Shepherd V, Hood K, Sheehan M, Griffith R, Wood F. 'It's a tough decision': a qualitative study of proxy decision-making for research involving adults who lack capacity to consent in UK. *Age Ageing* 2019; 48: 903–9. DOI: 10.1093/ageing/afz115.
35. Long B, Clark L, Cook P. Surrogate decision making for patients with severe traumatic brain injury. *J Trauma Nurs* 2011; 18: 204–12. DOI: 10.1097/JTN.0b013e31823a453a.
36. Hall DE, Prochazka AV, Fink AS. Informed consent for clinical treatment. *CMAJ*. 2012;184(5):533–40. DOI:10.1503/cmaj.112120.
37. Topolovec-Vranic J, Santos M, Baker AJ, Smith OM, Burns KE. Deferred consent in a minimal-risk study involving critically ill subarachnoid hemorrhage patients. *Can Respir J* 2014;21:293-6. DOI:10.1155/2014/719270.
38. Honarmand K, Belley-Cote EP, Ulic D, Khalifa A, Gibson A, McClure G, et al. The deferred consent model in prospective observational study evaluating myocardial injury in the intensive care unit. *J Intensive Care Med* 2018;33:475-80. DOI: 10.1177/0885066616680772.
39. Shamy MCF, Dewar B, Chevrier S, Wang CQ, Page S, Goyal M, et al. Deferral of consent in acute stroke trials. Lessons from the ESCAPE trial. *Stroke* 2019; 50:1017-20. DOI: 10.1161/STROKEAHA.118.024096.
40. Woolfall K, Frith L, Gamble C, Gilbert R, Mok Q, Young B, et al. How parents and practitioners experience research without prior consent (deferred consent) for emergency research involving children with life threatening conditions: a mixed method survey. *BMJ Open* 2015;5:e008522. DOI: 10.1136/bmjopen-2015-008522.
41. Eltorki M, Uleryk E, Freedman SB. Waiver of informed consent in pediatric resuscitation research: a systematic review. *Ac Emerg Med* 2013; 20:822-34. DOI: 10.1111/acem.12180.
42. Duffett M, Burns KE, Kho ME, Lauzier F, Meade MO, Arnold DM, et al. Consent in critical care trials: a survey of Canadian research ethics boards and critical care researchers. *J Crit Care* 2011;26:533.e11-533.e22. DOI: 10.1016/j.jcrc.2010.12.009.
43. Chico V. The impact of the General data Protection Regulation on health research. *Br Med Bull* 2018;128:109-18. DOI: 10.1093/bmb/ldyo38.
44. Rumbold JM, Pierscionek B. The Effect of the General Data Protection Regulation on Medical Research. *J Med Internet Res*. 2017;19(2):e47. DOI: 10.2196/jmir.7108.
45. Clarke N, Vale G, Reeves EP, Kirwan M, Smith D, Farrell M. GDPR: an impediment to research? *Ir J Med Sci*. 2019; 188(4):1129-35. DOI:10.1007/s11845-019-01980-2.
46. Van Veen, E.B. Observational health research in Europe: understanding the General Data Protection Regulation and underlying debate. *Eur J Cancer* 2018;104:70-80. DOI: 10.1016/j.ejca.2018.09.032.
47. Tisherman SA, Powell JL, Schmidt TA, Aufderheide TP, Kudenchuk PJ, Spence J, et al. Regulatory challenges for the resuscitation outcomes consortium. *Circulation* 2008; 118:1585–92. DOI: 10.1161/CIRCULATIONAHA.107.764084.



CHAPTER 9

Informed consent procedures for emergency interventional research in patients with traumatic brain injury and ischaemic stroke

Authors:

Erwin J.O. Kompanje*^{1,2}
Jeroen T.J.M. van Dijck*³
Vicky Chalos^{4,5,6}
Sophie A. van den Berg^{4,7}
Paula M. Janssen⁴
Paul J. Nederkoorn⁷

Mathieu van der Jagt¹
Giuseppe Citerio⁸
Nino Stocchetti^{9,10}
Diederik W.J. Dippel⁴
Wilco C. Peul³
*Shared first authorship

Affiliations

1: Department of Intensive Care Adults, Erasmus MC, University Medical Center Rotterdam, the Netherlands. Address: Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands

2: Department of Ethics and Philosophy of Medicine, Erasmus University Rotterdam, the Netherlands. Address: Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands

3: University Neurosurgical Center Holland, LUMC, HMC & Haga Teaching Hospital, Leiden and The Hague, The Netherlands. Address: Albinusdreef 2, 2333 ZA, Leiden, The Netherlands

4: Department of Neurology, Erasmus MC, University Medical Center Rotterdam, the Netherlands. Address: Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands

5: Department of Public Health, Erasmus MC, University Medical Center Rotterdam, the Netherlands. Address: Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands

6: Department of Radiology and Nuclear Science, Erasmus MC University Medical Center, Rotterdam, The Netherlands. Address: Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands

7: Department of Neurology, Amsterdam UMC, The Netherlands. Address: Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.

8: School of Medicine and Surgery, University of Milan-Bicocca, Milan, Italy. Address: Piazza dell'Ateneo Nuovo 1, 20126 Milano, Italy. OrcidID: 0000-0002-5374-3161

9: Department of Physiopathology and Transplantation, Milan University, Milan, Italy. Address: Via Francesco Sforza 35, 20122 Milano, Italy.

10: Neuro ICU Fondazione IRCCS Ca Granda Ospedale Maggiore Policlinico Milano, Milan, Italy. Address: Via Francesco Sforza 28, 20122 Milano, Italy.

Citation:

Kompanje EJO, van Dijck JTJM, Chalos V, et al. Informed consent procedures for emergency interventional research in patients with traumatic brain injury and ischaemic stroke. The Lancet Neurology. 2020. 19(12):1033-1042. doi: 10.1016/S1474-4422(20)30276-3.

ABSTRACT

Health-care professionals and researchers have a legal and ethical responsibility to inform patients before carrying out diagnostic tests or treatment interventions as part of a clinical study. Interventional research in emergency situations can involve patients with some degree of acute cognitive impairment, as is regularly the case in traumatic brain injury and ischaemic stroke. These patients or their proxies are often unable to provide informed consent within narrow therapeutic time windows. International regulations and national laws are criticised for being inconclusive or restrictive in providing solutions. Currently accepted consent alternatives are deferred consent, exception from consent, or waiver of consent. However, these alternatives appear under-utilised despite being ethically permissible, socially acceptable, and regulatorily compliant. We anticipate that, when the requirements for medical urgency are properly balanced with legal and ethical conduct, the increased use of these alternatives has the potential to improve the efficiency and quality of future emergency interventional studies in patients with an inability to provide informed consent.

INTRODUCTION

Health-care professionals and researchers have the legal and ethical responsibility to inform patients before executing procedures as part of a clinical study.^{1,2} Each patient has the right to refuse study participation.² This right is internationally recognised and formalised in many declarations, regulations, directives, and laws.¹⁻⁴ For research involving humans, physicians must consider the applicable international norms and standards, as well as their country's general ethical, legal, and regulatory standards.² From a legal perspective, obtaining informed consent is focused on liability and establishing a shared responsibility between professionals and patients, while from a moral perspective, the focus is mostly on respecting autonomous choices and actions of the patient. The process of informed consent is a multidimensional process that serves several important ethical functions.⁵⁻⁷

Obtaining informed consent is especially challenging in patients with acute medical emergencies with compromised decision-making capacity from traumatic brain injury and ischaemic stroke because: (1) the short therapeutic time window necessitates urgent intervention without unnecessary delay, (2) the acute or life-threatening condition associated with acute cognitive impairment impedes obtaining valid patient informed consent before intervention, and (3) obtaining consent before intervention from proxies is not always possible, because they cannot always be located or contacted within the time window or they are unable to provide consent for other reasons. These difficulties are probably contributing to the international variation in policy and practice regarding consent procedures for emergency research.⁸⁻¹¹

Investigating novel, potentially effective therapeutic options for these patients is essential because traumatic brain injury and ischaemic stroke are associated with high rates of mortality and morbidity, which is a major burden for patients, proxies, and societies.^{12,13} Moreover, many available treatments are still largely unproven or of little benefit.¹²⁻¹⁵ To facilitate research to improve health and functional outcome in these patients, several pragmatic solutions are used to overcome the inability of obtaining patient informed consent before urgent medical intervention. However, the legal basis for these solutions is not universally present.

In this Personal View, we outline the theoretical and ethical basis of four different informed consent procedures in emergency interventional research and their use and

challenges in common practice, focussing on patients with traumatic brain injury and ischaemic stroke with an inability to provide consent. We also provide procedural recommendations for future emergency research initiatives.

Patient informed consent before medical intervention

Patient informed consent before medical intervention is an ethical cornerstone of research involving humans, but obtaining valid patient informed consent before medical intervention for emergency interventional research in traumatic brain injury or ischaemic stroke is challenging. Most patients with severe acute injury from traumatic brain injury or ischaemic stroke have neurological deficits that limit their ability to make or communicate autonomous decisions about research participation. The inability to provide consent is usually caused by a decreased level of consciousness, cognitive impairments, or pharmacological sedation.^{12,13} In patients who are less severely injured, and with variable clinical presentation, this inability can also be difficult to establish.^{12,13} Problems with obtaining consent are frequently caused by factors like cognitive impairment or aphasia.^{16,17} The latter is present in up to 45% of patients in acute stroke trials, of which 30% have severe aphasia.¹⁸ Variability between injuries, and especially injury severity, has implications for how consent might need to be approached. To avert consent problems, researchers have adjusted study protocols by excluding patients with aphasia, left-hemisphere stroke, and moderate or severe cognitive impairment. This approach could, however, cause selection bias and limit external validity of study results.^{10,19–22}

Several measures of capacity have been proposed to provide more accurate measurement of decisional capacity, but all have substantial limitations.^{7,23} We propose several conditions that could be used to help determine the validity of patient consent before intervention (panel 1). When determining consent validity, researchers must balance between two undesirable extremes: (1) having a low threshold for inclusion and a risk of including patients who might not understand what they are agreeing to, and (2) having a high threshold for inclusion and including patients without trying to get their consent at all.

Panel 1. Prerequisites for obtaining valid patient or proxy informed consent before intervention

Disclosure

The patient or proxy should be provided with complete and understandable information about the purpose, duration, potential risks or benefits, and possible other consequences of the study.

Understanding

The patient or proxy should fully understand all provided information.

Authenticity

The patient or proxy can make a judgement, which is consistent with the patient's personal values.

Non-control

The patient or proxy should be able to make a decision without coercion, manipulation, or other undue influences.

Capacity

The patient or proxy should be able to oversee the consequences of providing informed consent and thereby study participation.

Intentionality

The patient or proxy should have the intention to participate in the study.

Time

The patient or proxy should be provided sufficient time to decide on informed consent for study participation.

In the context of emergency interventional research in traumatic brain injury and ischaemic stroke, time constraints make it impossible to await recovery to provide valid patient consent before intervention. Although consent is often obtained in parallel with imaging, laboratory tests, or readying an angiographic suite or operating theatre, obtaining patient consent before intervention could further delay treatment. This approach is problematic because study interventions might need to be delivered in a very short therapeutic time window to be effective.^{24,25} Secondary brain injury after traumatic brain injury can be less severe when treatment is initiated early²⁶ and stroke outcomes are better when reperfusion therapy is administered at the earliest opportunity.^{27,28} A delay of 1 h in reperfusion time in patients with ischaemic stroke is associated with an increase of absolute risk of 6.0–7.7% for unfavourable functional

outcome (modified Rankin Scale score 0–2).^{29,30} The ULTRA-study included patients with decisional capacity without patient consent before intervention because delay in ultra-early administration of the study intervention could compromise its potential effect, and thereby invalidate trial design and trial outcome. Obtaining consent was even considered unethical because patients would have been exposed to unnecessary risk.³¹ Several options to minimise time-to-consent have been suggested, ranging from information leaflets to the use of electronic consenting by telemedicine or smartphones.^{32–34} Nonetheless, many studies have described recruitment problems related to informed consent procedures.^{21,26,35} These problems are not limited to patients in acute care settings, but also occur when patients are exposed to continued and prolonged study activities.

To determine the approaches to informed consent procedures used by traumatic brain injury and ischaemic stroke researchers, we examined a representative sample of randomised controlled trials in emergency traumatic brain injury ($n=70$) and ischaemic stroke ($N=76$) literature (appendix pp 3–16; panel 2). Type of consent was reported in 61 (87%) of 70 randomised controlled trials on traumatic brain injury and in 71 (93%) of 76 randomised controlled trials on ischaemic stroke. Patient consent before medical intervention was mentioned to be the only consent option in 3 (5%) of 61 randomised controlled trials on traumatic brain injury and five (7%) of 71 randomised controlled trials on ischaemic stroke. In total, patient consent before intervention was reported to be an option in 15 (25%) of 61 randomised controlled trials on traumatic brain injury and 68 (96%) of 71 randomised controlled trials on ischaemic stroke (table; panel 3). Obtaining patient consent before intervention was often stated to be impossible because of the sustained brain injury (appendix pp 3, 16–17). In these cases, researchers resorted to three alternatives to patient informed consent before intervention: proxy informed consent before intervention, deferred consent, and exception from informed consent or waiver of consent.

Panel 2: Search strategy and selection criteria

We searched PubMed and Ovid MEDLINE using several strategies. To be informed about the used consent procedures in current traumatic brain injury and ischaemic stroke emergency research practice, we used a representative selection of randomised controlled trials. Data on study design and used consent procedures were extracted. Details on the search strategies, article selection procedures, data extraction, and synthesis of results can be found in the appendix p 3–17. We found articles on the theoretical and conceptual aspects of consent procedures specifically for patients with traumatic brain injury and stroke using search terms, including ‘informed consent’, ‘brain injuries’, ‘head injuries’, and ‘stroke’ (appendix p 18). We focussed on theoretical and conceptual articles about the most commonly used consent procedures (appendix p 20). This search strategy formed the evidence base for this Personal View.

Table. Consent procedures used in randomised controlled trials on traumatic brain injury and ischaemic stroke

| | Traumatic brain injury (N=70) | Ischaemic stroke (N=76) |
|--|-------------------------------|-------------------------|
| Type of consent reported | 61 (87%) | 71 (93%) |
| Patient informed consent before medical intervention | 15 (25%) | 68 (96%) |
| Proxy informed consent before medical intervention | 56 (92%) | 63 (89%) |
| Deferred consent | 8 (13%) | 3 (4%) |
| Exception from informed consent | 6 (10%) | 5 (7%) |
| Waiver of informed consent | | |
| Physician consent or other consent type | 2 (3%) | 2 (3%) |

Panel 3: Comparison of consent procedures in traumatic brain injury and ischaemic stroke literature

There are similarities and differences between the types of consent reported in traumatic brain injury and ischaemic stroke literature (appendix p 16).

First, the patient consent before intervention option was reported to be used less frequently in randomised controlled trials on traumatic brain injury (25%) than in randomised controlled trials on ischaemic stroke (96%; table). This difference does not necessarily mean that patient consent before intervention was impermissible when a participants' consent capacity was intact, but could also mean that it was not considered applicable or relevant for the study population. The difference likely depends on patient and study characteristics and is probably related to a perceived continued ability to provide patient informed consent before intervention after ischaemic stroke in most patients, whereas traumatic brain injury generally has a greater effect on this ability. This might be especially true in the case of more severe traumatic brain injury, additional extracranial injury, and a need for intensive care unit admission.

Second, the reported possibility to use proxy informed consent before intervention was very high in both literature on traumatic brain injury (92%) and ischaemic stroke (88%), and the use of independent physician consent procedures was equally low (3.3% vs 2.8%).

Third, the use of deferred consent and exception from consent was higher in randomised controlled trials on traumatic brain injury (23%) than in those on ischaemic stroke (11%), probably for the same reasons as reported for patient informed consent before intervention differences. There seems to be an increase in randomised controlled trials allowing patient recruitment without patient informed consent before intervention or proxy informed consent before intervention; however, many studies did not use it as an alternative for patient informed consent or proxy informed consent before intervention.

Last, there were more missing descriptions of consent procedures in the literature on traumatic brain injury (13%) than on ischaemic stroke (6.6%), which is likely caused by the inclusion of more dated randomised controlled trials on traumatic brain injury. Nearly all newer studies included a description of informed consent procedures.

Proxy informed consent before intervention

Proxy informed consent before intervention was the most commonly used alternative for patient consent before intervention and used in most randomised controlled trials on traumatic brain injury (56 [92%] of 61) and ischaemic stroke (63 [89%] of 71; table). Proxy informed consent before intervention is provided by an individual who has the legal right to provide consent on behalf of the patient. There are many descriptions in the literature because the legal base that regulates the selection of individuals to act as proxy is variable: consent by a family member, a relative, an appointed person or legally authorised representative; surrogate or substitute decision maker; guardian permission; and sometimes independent physician consent. Independent physicians could serve as proxies for informed consent decisions in two (3%) of 61 randomised controlled trials on traumatic brain injury and in two (3%) of 71 trials on ischaemic stroke. The conditions listed in panel 1 could also be considered to assess validity of proxy informed consent before intervention. Examples of where proxy informed consent before intervention is approved include Australia, Ethiopia, European Union, Chile, China, India, Japan, North America, South Africa, and New Zealand, and is described as valid in the Declaration of Helsinki² and the International Ethical Guidelines for Health-related Research Involving Humans (appendix p 21).⁴

The two main barriers to obtain proxy informed consent before intervention in emergency research are the short therapeutic time window that precludes a consent conversation, and the fact that proxies cannot always be located or contacted.^{21,35,36} As with patient consent before intervention, delaying a timely start of study interventions to obtain proxy informed consent before intervention is undesirable as it can decrease the efficacy of the acute therapy.^{26–28}

A third barrier is that proxy decision-making in research is highly complex and, although proxies prefer to be involved, empirical evidence suggests that proxies might not always be suitable as surrogate decision makers.^{37,38} Substantial discrepancies are described between decisions of patients and proxies in hypothetical scenarios.^{39,40} About 50% of proxies reported to be comfortable with being involved, but many are also emotionally overwhelmed, stressed, distracted, or report symptoms of anxiety and depression.^{37,41–43}

Proxies aim to make a decision that is authentic to the person they represent by balancing factors such as patients values, preferences, and wellbeing.^{38,44–47} Other factors that affected decisions include the time sensitivity of the decision, perceived study risk or benefit, uncertainty of possible outcomes, the complexity of the patient's condition, the use of medical terminology, and communication with physicians and nurses.^{37,47,48} Study participation is often declined because proxies feel unable or unwilling to consider it.^{49,50} Other common reasons to decline consent were being too anxious (67%), fear of experimental treatment (37%), and concerns about risks (33%).⁴⁴ Reasons to provide consent were wanting to help others (91%), contributing to medical progress (88%), and trusting (87%) or not wanting to disappoint the medical team (10%).⁴⁴

In summary, alternatives to patient or proxy informed consent before intervention are sometimes needed in traumatic brain injury or ischaemic stroke emergency interventional research because of the short therapeutic time windows, the deficits caused by traumatic brain injury or ischaemic stroke, and the frequent lack of available proxies. All factors preclude determining a patient's preferences. When patient or proxy informed consent before intervention are not practicable, the use of consent alternatives is imperative.

Deferred consent

This procedure allows participants to be included in studies when patients and proxies are unable to provide valid previous consent within short time frames. The approach was infrequently reported as an option in our analysed sample of randomised controlled trials on traumatic brain injury (eight [13%] of 61) and ischaemic stroke (three [4%] of 71), nearly always in addition to patient and proxy informed consent before intervention (table). It is usually described as deferred patient or proxy consent, retrospective consent, delayed consent, implied consent and consent to continue, or re-consent from patient, and is allowed and practised in places such as Australia, European Union, China, India, Japan, and South Africa. It is described as valid in the Declaration of Helsinki² and in the International Ethical Guidelines for Health-related Research Involving Humans.⁴ After starting study procedures without patient informed consent before intervention or proxy informed consent before intervention, consent must be obtained for study continuation as soon as patients or proxies regain the ability to provide consent. Some authors recommend a time limit of 72 h to prevent unauthorised use of conducting research without previous consent,⁴¹ but there is no

legal or moral ground for this recommendation.⁵² When it remains impossible to get affirmative consent for study continuation for reasons other than death, it could be necessary to withdraw patients from the study. This depends on the specific study circumstances and procedures as reviewed and approved by a responsible institutional review board. When consent for study continuation is provided, already collected data can be used. When study continuation is refused, already collected data can still be used when patients or proxies do not use their right to refuse this.

The procedural particulars depend on local legislation, institutional review board requirements, and their assessment of the relative pros and cons. Respecting local requirements is important, but also has a risk of practice variation and use of different terms or descriptions, both resulting in indistinctness, misunderstanding, and even misuse.^{8–10} Researchers should be aware of this possibility and multinational studies therefore need to be flexible enough to tailor their approach to all applicable requirements.⁵³ Although most researchers use the deferred consent procedure to obtain consent for study continuation, it is sometimes interpreted as a requirement to obtain consent for research activities that have already taken place. However, considering the earlier suggested conditions (panel 1) and the actual meaning of consent (give permission for something to happen or agreement to do something), it can only be concluded that asking and obtaining valid consent is possible only for research activities in the future.

Many patients and proxies report to be willing to participate in a study without previous consent.^{42,50,54,55} Although the deferred consent procedure was not always supported afterwards,⁵⁶ most proxies of patients included in acute care studies (81–100%) without previous informed consent agreed to further participation.^{49,56–58} Only few patients that refused further participation also denied permission for the use of already collected data.⁵⁸ Experienced stress in the setting of an intensive care unit admission was commonly mentioned as reason to endorse the use of a deferred consent procedure.⁴²

A deferred consent procedure is also being used in three ongoing randomised controlled trials on modifications of endovascular treatment for acute ischaemic stroke (MR CLEAN-MED, MR CLEAN-NO IV, MR CLEAN LATE) within the CONTRAST consortium.⁵⁹ On Nov 8, 2019, preliminary data were available for 742 patients of these CONTRAST studies, of whom 664 (90%) patients or proxies provided written consent

after the trial treatment, and 36 (5%) patients died before consent could be obtained. Written consent for study continuation was not obtained in 42 patients (6%), of whom half did not object to the use of already collected data. The observation, that postponing consent until after the study treatment is usually accepted by patients and proxies, has been shown in previous (non-stroke) clinical studies.^{43,55}

In the CONTRAST studies, the median time from admission at the intervention centre to randomisation was 25 min (IQR 16–39), which was shorter than the earlier MR CLEAN trial (76 min; IQR 48–144).⁶⁰ In the MR CLEAN trial⁶⁰ which compared endovascular treatment with usual care versus usual care alone, written patient or proxy informed consent before intervention was obtained based on oral communication and an abbreviated information letter.⁶⁰ Written consent was asked again after the acute phase. Although workflow has improved substantially over time, the difference between these time intervals could suggest that valuable time is lost when using patient consent or proxy informed consent before intervention. This additional time can delay intervention, which could negatively affect effectiveness of the acute intervention.^{29,30}

Emergency research in acute traumatic brain injury and ischaemic stroke often includes patients who die after being included without patient or proxy informed consent before intervention. Exclusion of included patients who have died before consent was obtained is obviously undesirable, as it reduces statistical power, introduces selection bias, causes asymmetrical randomisation, and decreases external validity.^{41,61} When privacy is guaranteed, using already collected data is judged to be ethically valid.^{41,61} Explicit proxy consent is not required in these circumstances. Retrospective removal of study patients from a database, after randomisation, for any reason, not just death, is even considered to be a threat to the scientific integrity of the trial. Scientific integrity is necessary for any trial to be ethically justifiable.

Exception from consent

Exception from consent was used in six (10%) of 61 randomised controlled trials on traumatic brain injury and in five (7%) of 71 on ischaemic stroke and is also called waiver of informed consent. By contrast to the deferred consent procedure, patient or proxy informed consent are not required for continuation of study-related activities if the patient or a proxy never becomes available to engage in an informed consent process,

despite diligent good-faith efforts by the researchers. It is particularly practiced in North America and Ethiopia, and described as valid in the Declaration of Helsinki² and in the International Ethical Guidelines for Health-related Research Involving Humans.⁴ In an effort to improve the progress in emergency research involving patients unable to provide informed consent, the US American Food and Drugs Administration (FDA) published guidelines in 1996, describing the exception from informed consent requirements for emergency research and the waiver of informed consent (appendix p 21). Since the guidelines, exception from informed consent has been available for use in emergency research for US FDA regulated products and waiver of informed consent for non-FDA regulated products.

With this alternative, a study can start without patient or proxy informed consent before intervention. Relevant information on study participation and use of data should be communicated to patients or proxies at the earliest opportunity. Refusal of study continuation or use of already obtained data should always be respected. The exception from informed consent procedure could be necessary when patients are exposed to continued and prolonged study activities while obtaining patient or proxy informed consent before intervention is not possible. The participant remains in the study by default.

Community consultation or public disclosure are specifically required to support the use of exception from informed consent or waiver of informed consent and aim to protect the rights and welfare of study participants.⁶² In community consultation, representatives from general communities (geographic community) or from the population at risk for the condition (condition-oriented community) are recruited. It aims to involve and engage community members with research initiatives by using public fora, community groups, or face-to-face and telephone surveys. Public disclosure involves notifying the community in advance that patients will be enrolled in a study in an emergency situation without patient or proxy informed consent before intervention. After the study, results will be communicated to participants and the public. It remains unclear whether patients, proxies, health-care providers, administrators, or a general population should be considered to be the community.⁶³ Although some reports are positive and participants satisfied,^{64,65} community consultation and public disclosure are also challenging, time consuming, and costly.^{66,67}

A study⁶⁸ reviewed 28 completed and published acute care studies between 1996 and 2018, that used exception from informed consent or waiver of informed consent.⁶⁸ Only 359 (0.6%) of 63 947 study enrolments were withdrawn or did not provide consent for continued study participation.⁶⁸ Acceptance of the exception from informed consent procedure was high and varied by the specifics of the situation.^{65,69}

Implications for research practice

The difficulties regarding patient and proxy informed consent before study intervention in traumatic brain injury and ischaemic stroke emergency interventional research can result in many lost research opportunities when alternatives for informed consent are not facilitated.⁴³ Based on the sample of randomised controlled trials, patient recruitment without patient and proxy informed consent before study intervention seems to be increasingly used in recent years, but still many studies do not use it. The use and efficiency of consent procedures in traumatic brain injury and ischaemic stroke emergency research should be improved.

Selecting an appropriate informed consent procedure for a study is difficult and depends on many factors, often related to each other. Factors include local legislation, institutional review board requirements, and study details such as methods, interventions, and patient characteristics. We propose use of a flow chart to guide investigators or regulators to select the most appropriate informed consent procedures based on several study particulars (figure). Informed consent procedures should be used as overlapping and complementary strategies to solve different challenges of a study. Researchers should first determine whether the therapeutic time window allows time for an informed consent procedure. If there is time, it should also be determined whether it is feasible to obtain valid patient or proxy informed consent before intervention within the time window. The conditions suggested in panel 1 could be used as a starting point to assess consent validity. If both are not practicable, the determination of a patient's wishes regarding study participation should be considered not possible. Researchers should then consider the option of using an alternative procedure like deferred consent or exception from informed consent or waiver of informed consent. This choice mainly depends on local legislation and study details. A non-exclusive list of prerequisites of both procedures, based on existing legislation, as listed in appendix p 21, can be found in panel 4. These prerequisites are not intended to be conclusive, but could assist researchers in determining the appropriateness of the procedure. All procedural decisions should adhere to applicable legislation.

The use of deferred consent or exception from informed consent or waiver of informed consent procedures seems necessary and acceptable in traumatic brain injury and ischaemic stroke emergency interventional research. The seriousness of the potential threats to the welfare and protection of study participants, the scientific integrity of a trial, and public trust in research should however never be underestimated.^{70,71} Independent institutional review boards or steering committees are charged with the protection of patients, researchers, and the public as a whole, balancing and judging their interests. Several safeguards are used in the process: a rigorous evaluation of study protocols, oversight in study procedures such as patient screening, recruitment, consent procedure, and independent safety monitoring.⁷ Other safeguards could consist of including and consulting more representatives of patients on institutional review boards to weigh in on the ethics of different trial approaches in patients where patient or proxy informed consent before intervention is not possible.

Panel 4. A list of prerequisites for the use of deferred consent and exception from consent procedures.

General prerequisites for the use of deferred consent and exception from consent procedures

- 1 The patient has an acute life-threatening situation or an acute medical condition that necessitates urgent (study) procedures because delayed treatment can negatively affect intervention effectiveness or patient outcome. Due to the urgency of the situation, the patient or proxies are unable to provide valid informed consent before intervention.
- 2 The medical condition causes an inability to provide informed consent before intervention by patient or proxy.
- 3 There is scientific information that supports the potential for the study treatment to provide a direct benefit to the patient. Available standard treatments are unproven (the scarcity of high-quality evidence that the treatment is effective) or unsatisfactory (the treatment is unsatisfactory due to safety or efficacy issues that require investigation).
- 4 The risks and burden of study participation are considered acceptable compared with standard treatment, given the potential direct benefit of the study treatment.
- 5 Researchers or physicians are unaware of any objections for study participation (eg, a written advanced directive).

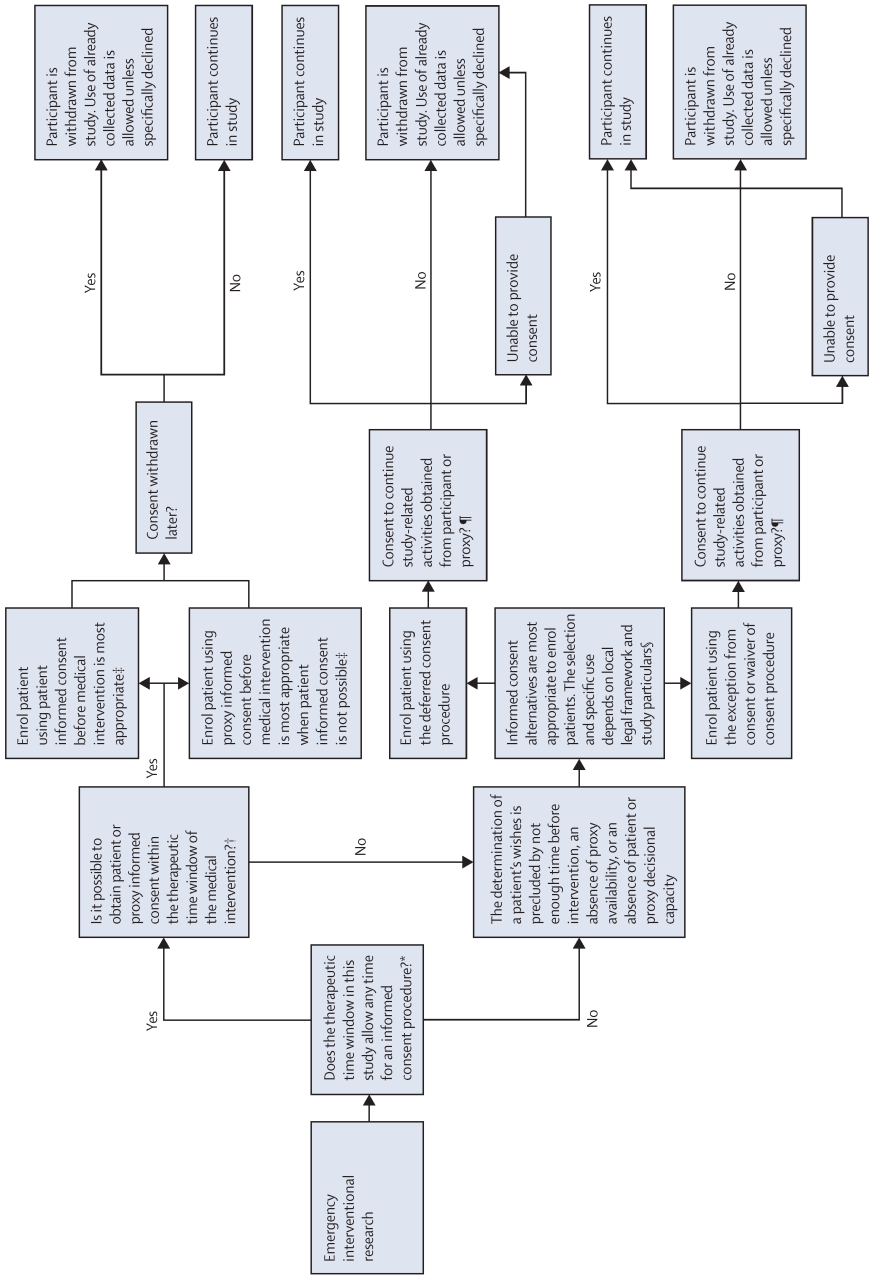


Figure: Flow chart for the selection of appropriate informed consent procedures in emergency interventional research

Proposed flowchart to guide investigators or regulators to select the most appropriate informed consent procedure based on several traumatic brain injury or ischaemic stroke study particulars. Studies could use multiple informed consent procedures in their informed consent strategy. Informed consent procedures should be used as overlapping and complementary strategies to solve different challenges of a study. This flowchart could be best seen as a legal and ethical framework that could be considered in any research setting. It is not binding, and a chosen informed consent strategy should always follow applicable legislation and must be evaluated and approved by the responsible institutional review boards. *Some emergency interventional studies on traumatic brain injury and ischaemic stroke use a very narrow therapeutic time window (ie, mins) that does not allow any time for an informed consent procedure. Obtaining patient or proxy informed consent before intervention is not possible in these situations, because the intervention is immediate. Obtaining informed consent can delay the study intervention. In some studies, any delay of study intervention is problematic because it could compromise the potential effect of the experimental treatment, making the fair interpretation of results difficult. Obtaining informed consent and delaying the study intervention could also be considered unethical because patients would be exposed to unnecessary risk. In other studies, where the therapeutic time window of traumatic brain injury or ischaemic stroke intervention is wider (ie, several hrs), there might be an opportunity to obtain patient or proxy informed consent. †There are many reasons why it could not be possible to obtain patient or proxy informed consent before intervention even when this could have been possible within the therapeutic time window. Reasons include an absence of available proxies, and a patient's or proxy's inability to provide informed consent. ‡Strategies to optimise and support patient or proxy decision-making could help to optimise informed consent procedures. §The use of deferred consent or exception from consent or waiver of consent procedures depends on study particulars and local legal frameworks, including requirements from institutional review boards. Details can be found in the main text of the manuscript and cited references. Their use should be carefully considered and evaluated by researchers and institutional review boards. ¶Informed consent to continue study-related activities should be obtained as soon as the patient or a proxy can provide informed consent. In case a proxy provided informed consent first, informed consent should be verified with the patient when this becomes possible.

- 6 It is reasonably impossible to prospectively identify individuals that are likely to become eligible for study participation in the future, in such a way that patient or proxy informed consent before intervention could be obtained.
- 7 It is practically impossible to undertake the emergency research when patient or proxy informed consent before intervention is required to start study-related activities.
- 8 A comprehensive disclosure of study information and study participation to patients and proxies is required at the earliest possible (practicable) opportunity.
- 9 If the patient dies during the study before informed consent has been obtained, the already collected data can be used according to the study protocol, without the need for proxy informed consent. Proxies should be informed about study participation at the earliest possible (practicable) opportunity.
- 10 The use of this alternative for patient or proxy informed consent before intervention is accepted by local legislation. Institutional review boards have reviewed and approved the study protocol to prevent misconduct and ascertain patient safety.

Specific prerequisites for deferred consent

- 1 It is considered possible to continue essential study-related activities, such as additional interventions or follow-up, when patient or proxy informed consent is required to continue study-related activities. For example, patients or proxies are not expected to have a prolonged inability to provide valid informed consent.
- 2 Patient or proxy informed consent is required for continuation of study-related activities and should be obtained from the patient or proxy at the earliest possible (practicable) opportunity after regaining the ability to provide informed consent. When study continuation is refused, the patient or proxy has the right to refuse the use of already obtained data.
- 3 There are no pre-study requirements such as community consultation or public disclosure.

Specific prerequisites for exception from consent

- 1 It is practically impossible to continue essential study-related activities, such as additional interventions or follow-up, when patient or proxy informed consent is required to continue study-related activities. For example, patients or proxies are expected to have a prolonged inability to provide valid informed consent.
- 2 Written patient or proxy informed consent is not required for continuation of study-related activities if the patient or a proxy never becomes available to engage in an informed consent process despite diligent good-faith efforts by the researchers. Patients or proxies should be informed about their right to refuse the use of obtained data.
- 3 To increase acceptance of the proposed study protocol, pre-study requirements such as community consultation or public disclosure could be required.

Conclusions and future directions

There is an urgent need to investigate novel therapeutic options that are potentially effective for patients with traumatic brain injury and ischaemic stroke. A thorough consideration of the multidimensional process of informed consent is required to increase the feasibility and quality of future emergency research initiatives. Researchers should be aware of the international legal and ethical conditions and possibilities. Implementing this knowledge could improve study protocol and procedures.

Supported by an extensive literature base, we conclude that obtaining patient or proxy informed consent before intervention is often not possible in emergency interventional research in patients with traumatic brain injury or ischaemic stroke. This impossibility is primarily caused by the importance of very narrow therapeutic windows, the inability to provide informed consent, or the frequent absence of surrogate decision makers. Generally accepted alternatives, such as deferred consent and exception from informed consent or waiver of informed consent, appear underutilised in traumatic brain injury and ischaemic stroke emergency interventional research, despite being ethically permissible, socially acceptable, and regulatorily compliant. Not being able to use these alternatives complicates emergency interventional research in these patients. Being able to use them, when appropriate, has the potential to optimally test interventions earlier in a patient's course when they are most likely to be effective. If done properly, it also creates an opportunity for more generalisable and equitable clinical trial participation and results. Using these alternatives appears consistent with the desires of most patients most of the time.

Institutional review boards have an important role to prevent misconduct and protect patient safety by reviewing and approving study protocols. Study procedures should be overseen during the study. Researchers should aim to optimise the use of overlapping and complementary informed consent strategies based on the particular circumstances of a study, especially the requirements and constraints on obtaining patient or proxy informed consent before intervention. Harmonisation of laws and regulations between countries should be pursued, while respecting national sovereignty and local cultural preferences. All measures will further improve the efficiency and quality of emergency research initiatives involving patients with an inability to provide informed consent before medical intervention, regardless of disease.

Supplementary files

Available online: [https://www.thelancet.com/cms/10.1016/S1474-4422\(20\)30276-3/attachment/5b005065-3e21-4ff7-ab02-887d63fod4e9/mmc1.pdf](https://www.thelancet.com/cms/10.1016/S1474-4422(20)30276-3/attachment/5b005065-3e21-4ff7-ab02-887d63fod4e9/mmc1.pdf)

REFERENCES

- 1 Grady C, Cummings SR, Rowbotham MC, McConnell M V, Ashley EA, Kang G. Informed Consent. *N Engl J Med* 2017; **376**: 856–67.
- 2 World Medical Association. Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. 2018; 2019. <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/2194>.
- 3 Wolf SM, Clayton EW, Lawrenz F. The Past, Present, and Future of Informed Consent in Research and Translational Medicine. *J Law, Med Ethics* 2018; **46**: 7–11.
- 4 Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO). International Ethical Guidelines for Health-related Research Involving Humans, Fourth Edition. Geneva. 2016. <https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf>.
- 5 Dickert NW, Eyal N, Goldkind SF, et al. Reframing Consent for Clinical Research: A Function-Based Approach. *Am J Bioeth* 2017; **17**: 3–11.
- 6 Bruni T, Graham M, Norton L, Gofton T, Owen AM, Weijer C. Informed consent for functional MRI research on comatose patients following severe brain injury: balancing the social benefits of research against patient autonomy. *J Med Ethics* 2019; **45**: 299–303.
- 7 Johnson-Greene D. Informed consent issues in traumatic brain injury research: current status of capacity assessment and recommendations for safeguards. *J Head Trauma Rehabil* 2010; **25**: 145–50.
- 8 Kompanje EJ, Maas AI, Menon DK, Kesecioglu J. Medical research in emergency research in the European Union member states: tensions between theory and practice. *Intensive Care Med* 2014; **40**: 496–503.
- 9 van Belle G, Mentzelopoulos SD, Aufderheide T, May S, Nichol G. International variation in policies and practices related to informed consent in acute cardiovascular research: Results from a 44 country survey. *Resuscitation* 2015; **91**: 76–83.
- 10 Majersik JJ. Ethics and Bias in Clinical Trial Enrollment in Stroke. *Curr Cardiol Rep* 2019; **21**: 49.
- 11 van Wijk RPJ, van Dijk JTM, Timmers M, et al. Informed consent procedures in patients with an acute inability to provide informed consent: Policy and practice in the CENTER-TBI study. *J Crit Care* 2020; **59**: 6–15.
- 12 Maas AIR, Menon DK, Adelson PD, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. *Lancet Neurol* 2017; **16**. DOI:10.1016/S1474-4422(17)30371-X.
- 13 Campbell BC V, De Silva DA, Macleod MR, et al. Ischaemic stroke. *Nat Rev Dis Prim* 2019; **5**: 70.
- 14 Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2019; **50**: e344–418.
- 15 Carney N, Totten AM, O'Reilly C, et al. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. *Neurosurgery* 2017; **80**: 6–15.
- 16 Mendyk AM, Labreuche J, Henon H, et al. Which factors influence the resort to surrogate consent in stroke trials, and what are the patient outcomes in this context? *BMC Med Ethics* 2015; **16**: 26.
- 17 Janssen PM, Chalos V, van den Berg SA, et al. Neurological Deficits in Stroke Patients that May Impede the Capacity to Provide Informed Consent for Endovascular Treatment Trials. *J Stroke Cerebrovasc Dis* 2019; : 104447.
- 18 Ali M, Lyden P, Brady M. Aphasia and Dysarthria in Acute Stroke: Recovery and Functional Outcome. *Int J Stroke* 2015; **10**: 400–6.
- 19 Hotter B, Ulm L, Hoffmann S, et al. Selection bias in clinical stroke trials depending on ability to consent. *BMC Neurol* 2017; **17**: 206.
- 20 Thomalla G, Boutitie F, Fiebach JB, et al. Effect of informed consent on patient characteristics in a stroke thrombolysis trial. *Neurology* 2017; **89**: 1400–7.
- 21 Stanley RM, Johnson MD, Vance C, et al. Challenges Enrolling Children Into Traumatic Brain Injury Trials: An Observational Study. *Acad Emerg Med* 2017; **24**: 31–9.
- 22 Mendelson SJ, Aggarwal NT, Richards C, O'Neill K, Holl JL, Prabhakaran S. Racial disparities in refusal of stroke thrombolysis in Chicago. *Neurology* 2018; **90**: e359–64.

- 23 Feng KL, Person C, Phillips-Sabol J, *et al.* Comparison between a standardized questionnaire and expert clinicians for capacity assessment in stroke clinical trials. *Stroke* 2014; **45**: e229–32.
- 24 Gomez CR. Time Is Brain: The Stroke Theory of Relativity. *J Stroke Cerebrovasc Dis* 2018; **27**: 2214–27.
- 25 Zinkstok SM, Beenen LF, Luitse JS, Majoie CB, Nederkoorn PJ, Roos YB. Thrombolysis in Stroke within 30 Minutes: Results of the Acute Brain Care Intervention Study. *PLoS One* 2016; **11**: e0166668.
- 26 Mohamadpour M, Whitney K, Bergold PJ. The Importance of Therapeutic Time Window in the Treatment of Traumatic Brain Injury. *Front Neurosci* 2019; **13**: 7.
- 27 Saver JL, Goyal M, van der Lugt A, *et al.* Time to Treatment With Endovascular Thrombectomy and Outcomes From Ischemic Stroke: A Meta-analysis. *JAMA* 2016; **316**: 1279–89.
- 28 Emberson J, Lees KR, Lyden P, *et al.* Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet* 2014; **384**: 1929–35.
- 29 Fransen PSS, Berkhemer OA, Lingsma HF, *et al.* Time to Reperfusion and Treatment Effect for Acute Ischemic Stroke: A Randomized Clinical Trial. *JAMA Neurol* 2016; **73**: 190–6.
- 30 Mulder MJHL, Jansen IGH, Goldhoorn R-JB, *et al.* Time to Endovascular Treatment and Outcome in Acute Ischemic Stroke: MR CLEAN Registry Results. *Circulation* 2018; **138**: 232–40.
- 31 Post R, Germans MR, Coert BA, Rinkel GJE, Vandertop WP, Verbaan D. Update of the Ultra-early TRanexamic Acid after Subarachnoid Hemorrhage (ULTRA) trial: statistical analysis plan. *Trials* 2020; **21**: 199.
- 32 Haussen DC, Craft L, Doppelheuer S, *et al.* Legal authorized representative experience with smartphone-based electronic informed consent in an acute stroke trial. *J Neurointerv Surg* 2020; **12**: 483–5.
- 33 Shoirah H, Wechsler LR, Jovin TG, Jadhav AP. Acute Stroke Trial Enrollment through a Telemedicine Network: A 12-Year Experience. *J Stroke Cerebrovasc Dis* 2019; **28**: 1926–9.
- 34 Berge E, Stapf C, Al-Shahi Salman R, *et al.* Methods to improve patient recruitment and retention in stroke trials. *Int J Stroke* 2016; **11**: 663–76.
- 35 Kim D-H, Saver JL, Starkman S, *et al.* Enrollment Yield and Reasons for Screen Failure in a Large Prehospital Stroke Trial. *Stroke* 2016; **47**: 232–5.
- 36 Burns KE, Zubrinich C, Tan W, *et al.* Research recruitment practices and critically ill patients. A multicenter, cross-sectional study (the Consent Study). *Am J Respir Crit Care Med* 2013; **187**: 1212–8.
- 37 Barrett KA, Ferguson ND, Athaide V, *et al.* Surrogate decision makers' attitudes towards research decision making for critically ill patients. *Intensive Care Med* 2012; **38**: 1616–23.
- 38 Shepherd V, Hood K, Sheehan M, Griffith R, Wood F. 'It's a tough decision': a qualitative study of proxy decision-making for research involving adults who lack capacity to consent in UK. *Age Ageing* 2019; **48**: 903–9.
- 39 Bryant J, Skolarus LE, Smith B, Adelman EE, Meurer WJ. The accuracy of surrogate decision makers: informed consent in hypothetical acute stroke scenarios. *BMC Emerg Med* 2013; **13**: 18.
- 40 Newman JT, Smart A, Reese TR, Williams A, Moss M. Surrogate and patient discrepancy regarding consent for critical care research. *Crit Care Med* 2012; **40**: 2590–4.
- 41 Jansen TC, Kompanje EJO, Druml C, Menon DK, Wiedermann CJ, Bakker J. Deferred consent in emergency intensive care research: what if the patient dies early? Use the data or not? *Intensive Care Med* 2007; **33**: 894–900.
- 42 Terry MA, Freedberg DE, Morris MC. An Alternative Consent Process for Minimal Risk Research in the ICU. *Crit Care Med* 2017; **45**: 1450–6.
- 43 Ecarnot F, Quenot JP, Besch G, Piton G. Ethical challenges involved in obtaining consent for research from patients hospitalized in the intensive care unit. *Ann Transl Med* 2017; **5**: S41.
- 44 Mehta S, Quittnat Pelletier F, Brown M, *et al.* Why substitute decision makers provide or decline consent for ICU research studies: a questionnaire study. *Intensive Care Med* 2012; **38**: 47–54.
- 45 Hwang DY, Knies AK, Mampre D, *et al.* Concerns of surrogate decision makers for patients with acute brain injury: A US population survey. *Neurology* 2020; **94**: e2054–68.
- 46 Devnani R, Slaven JE, Bosslet GT, *et al.* How Surrogates Decide: A Secondary Data Analysis of Decision-Making Principles Used by the Surrogates of Hospitalized Older Adults. *J Gen Intern Med* 2017; **32**: 1285–93.
- 47 Burns KE, Prats CJ, Maione M, *et al.* The Experience of Surrogate Decision Makers on Being Approached for Consent for Patient Participation in Research. A Multicenter Study. *Ann Am Thorac Soc* 2017; **14**: 238–45.

- 48 Long B, Clark L, Cook P. Surrogate decision making for patients with severe traumatic brain injury. *J Trauma Nurs* 2011; **18**: 204–12.
- 49 Topolovec-Vranic J, Santos M, Baker AJ, Smith OM, Burns KE. Deferred consent in a minimal-risk study involving critically ill subarachnoid hemorrhage patients. *Can Respir J* 2014; **21**: 293–6.
- 50 Woolfall K, Frith L, Gamble C, Gilbert R, Mok Q, Young B. How parents and practitioners experience research without prior consent (deferred consent) for emergency research involving children with life threatening conditions: a mixed method study. *BMJ Open* 2015; **5**: e008522.
- 51 Rebers S, Aaronson NK, van Leeuwen FE, Schmidt MK. Exceptions to the rule of informed consent for research with an intervention. *BMC Med Ethics* 2016; **17**: 9.
- 52 Jansen TC, Kompanje EJ, Bakker J. Deferred proxy consent in emergency critical care research: ethically valid and practically feasible. *Crit Care Med* 2009; **37**: S65–8.
- 53 CRASH-3 trial collaborators. Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. *Lancet* 2019; **394**: 1713–23.
- 54 Whitesides LW, Baren JM, Biros MH, *et al*. Impact of individual clinical outcomes on trial participants' perspectives on enrollment in emergency research without consent. *Clin Trials* 2017; **14**: 180–6.
- 55 Furyk J, McBain-Rigg K, Watt K, *et al*. Qualitative evaluation of a deferred consent process in paediatric emergency research: a PREDICT study. *BMJ Open* 2017; **7**: e018562.
- 56 Shamy MCF, Dewar B, Chevrier S, *et al*. Deferral of Consent in Acute Stroke Trials. *Stroke* 2019; **50**: 1017–20.
- 57 Harron K, Woolfall K, Dwan K, *et al*. Deferred Consent for Randomized Controlled Trials in Emergency Care Settings. *Pediatrics* 2015; **136**: e1316–22.
- 58 Honarmand K, Belley-Cote EP, Ulic D, *et al*. The Deferred Consent Model in a Prospective Observational Study Evaluating Myocardial Injury in the Intensive Care Unit. *J Intensive Care Med* 2018; **33**: 475–80.
- 59 CONTRAST consortium. <https://www.contrast-consortium.nl> (accessed Jan 1, 2020).
- 60 Berkhemer OA, Fransen PSS, Beumer D, *et al*. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med* 2015; **372**: 11–20.
- 61 Jansen TC, Bakker J, Kompanje EJ. Inability to obtain deferred consent due to early death in emergency research: effect on validity of clinical trial results. *Intensive Care Med* 2010; **36**: 1962–5.
- 62 United States Department of Health and Human Services. Food and Drug Administration. Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors. Exception From Informed Consent Requirements for Emergency Research. 2013. <https://www.fda.gov/media/80554/download>.
- 63 Eltorki M, Uleryk E, Freedman SB. Waiver of informed consent in pediatric resuscitation research: a systematic review. *Acad Emerg Med* 2013; **20**: 822–34.
- 64 Fehr AE, Pentz RD, Dickert NW. Learning from experience: a systematic review of community consultation acceptance data. *Ann Emerg Med* 2015; **65**: 162–71.e3.
- 65 Feldman WB, Hey SP, Franklin JM, Kesselheim AS. Public Approval of Exception From Informed Consent in Emergency Clinical Trials: A Systematic Review of Community Consultation Surveys. *JAMA Netw open* 2019; **2**: e197591–e197591.
- 66 Eubank L, Lee KS, Seder DB, *et al*. Approaches to community consultation in exception from informed consent: Analysis of scope, efficiency, and cost at two centers. *Resuscitation* 2018; **130**: 81–7.
- 67 Harvin JA, Podbielski JM, Vincent LE, *et al*. Impact of Social Media on Community Consultation in Exception From Informed Consent Clinical Trials. *J Surg Res* 2019; **234**: 65–71.
- 68 Klein L, Moore J, Biros M. A 20-year Review: The Use of Exception From Informed Consent and Waiver of Informed Consent in Emergency Research. *Acad Emerg Med* 2018; **25**: 1169–77.
- 69 Dickert NW, Scicluna VM, Baren JM, *et al*. Patients' perspectives of enrollment in research without consent: the patients' experiences in emergency research-progesterone for the treatment of traumatic brain injury study. *Crit Care Med* 2015; **43**: 603–12.
- 70 Johnson LR, Siddaiah R. Use of deferred consent for enrolment in trials is fraught with problems. *BMJ* 2015; **351**: h4609.
- 71 Goldstein CE, Weijer C, Brehaut JC, *et al*. Ethical issues in pragmatic randomized controlled trials: a review of the recent literature identifies gaps in ethical argumentation. *BMC Med Ethics* 2018; **19**: 14.



CHAPTER 10

GENERAL SUMMARY

Humans have sustained traumatic brain injuries (TBI) from the beginning of their existence and will most likely be confronted with this devastating disease until their extinction. Even after thousands of years of experience in treating patients with TBI, decisions regarding the optimal treatment strategy remain difficult for both healthcare workers as policy makers. In this thesis, consisting of two parts, we aimed to describe and improve the acute treatment decision-making process and research practice in patients with TBI.

Part I investigated the challenges of the treatment decision-making process in patients with (severe) TBI and focussed on three factors considered to be important in this process: patient outcome, in-hospital healthcare consumption, and in-hospital costs.

Chapter 2 was a literature review of acute neurosurgical management in patient with very severe TBI (Glasgow Coma Scale 3-5). It showed major variation in treatment strategies between forty-five included studies. Mortality rates were high, and the chance to reach a so called 'favourable outcome' was low. Some studies however, did report favourable outcome rates for specific patient groups (lower age, lower TBI severity and absence of pupillary abnormalities). In addition to patient and injury related factors, also the type and timing of an intervention appeared to be related with outcome. It was not possible to establish causality due to the high variation between studies and due to the methodological limitations of individual studies.

Chapter 3 was a systematic review that investigated the in-hospital costs of patients after sustaining severe TBI (Glasgow Coma Scale 3-8). The twenty-five included articles showed generally high in-hospital healthcare costs (median €44,660; range €1,720 – €324,660; mean €70,810). The in-hospital costs were primarily driven by costs related to both general ward (12% – 38%) and ICU (51% – 79%) length of stay and surgical interventions (4% – 8%). The length of stay (LOS) in the ICU ranged from 8 to 26 days and hospital LOS ranged from 10 to 37 days. Consumption and costs increased with higher TBI severity. Drawing firm conclusions was difficult, due to the inadequate quality of the included studies and variation of study results, caused by methodological and clinical heterogeneity. It was concluded that future economic evaluations could improve their quality, accuracy of cost calculation, and reporting of costs, by using guideline recommendations and common data elements.

Chapter 4 and *chapter 5* reported on patient outcome and on in-hospital healthcare consumption and in-hospital costs of two different patient cohorts. The first cohort consisted of 108 consecutive patients with a traumatic acute subdural hematoma and

the second cohort consisted of 486 TBI patients that were regionally included in the CENTER-TBI study. Following the recommendations made in *chapter 3*, we used the Dutch guidelines for economic healthcare evaluations to ascertain the quality of costs calculation. Both studies reported high rates of mortality and unfavourable outcome, as defined by the Glasgow Outcome Scale score. These rates increased with higher TBI severity, presence of intracranial abnormalities, extracranial injury and need for surgical intervention. Despite high rates of mortality and unfavourable outcome, both studies also showed that patients with severe TBI could achieve favourable outcome. Even the most severely injured patients were able to achieve favourable outcome.

Both studies found substantial in-hospital healthcare consumption and generally high in-hospital costs, even in patients with mild TBI (Glasgow Coma Score 13-15). Average in-hospital costs were €7,800 for mild, €20,210 for moderate €26,600 for severe, and €26,350 for very severe TBI patients (*chapter 5*). Increase in healthcare consumption and costs was associated with several factors, including higher TBI severity (lower Glasgow Coma Score), presence of pupillary abnormalities, presence of major extracranial injury, presence of intracranial abnormalities on CT scan, use of intracranial pressure monitoring, and performed surgical interventions(s). In-hospital costs were primarily driven by costs related to admission and surgical intervention. This was in accordance with the results from *chapter 3*.

Chapter 6 was the result of multiple focus group sessions with medical professionals in the field of neurosurgery, intensive care medicine, rehabilitation, chronic care, anthropology and medical ethics. It described the process and reasoning of decision-making and proposed several reasons that could legitimize treatment-limiting decisions in patients with severe TBI (initial Glasgow Coma Score of 3-8). We also discussed the professional code of physicians, treatment-limiting decision, unacceptability of patient outcome, prognostic uncertainty, shared decision-making difficulties, healthcare costs, societal perspective, and importance of specialized rehabilitation and long-term care. Despite multiple efforts to improve care and outcome of TBI patients, it was concluded that decision-making remains highly complicated. The majority of uncertainty was caused by a lack of high-quality scientific evidence on treatment effectiveness and inaccurate outcome prediction. But there was also uncertainty on the acceptability of outcome, due to different societal and individual values.

Part II analysed procedural difficulties in TBI research efficiency by focussing on the process of institutional review board approval and the use of informed consent procedures in patients with TBI with an inability to provide informed consent.

Chapter 7 analysed the process of institutional review board approval around Europe. Major variation was found in how the CENTER-TBI study protocol was reviewed and approved by 66 European institutional review boards. The reported variation between and within European countries with regard to submission and approval requirements, number of review rounds and total duration was not beneficial for study efficiency. It was concluded that future research initiatives could benefit from the implementation of more uniform legislation and regulation while acknowledging local cultural and ethical arrangements between countries.

Chapter 8 and *chapter 9* focussed on the use of informed consent procedures in patients with traumatic brain injury with an inability to provide informed consent for emergency research.

Chapter 8 showed variation and discordance between reported and observed informed consent procedures in intensive care patients that were believed to have an inability to provide informed consent between and within European countries from the CENTER-TBI study. Proxy informed consent and deferred consent procedures appeared to be essential informed consent alternatives in studying TBI patients with an acute inability to provide informed consent. However, the deferred consent procedure was only actively used in a third of the centers where it was considered to be a valid method of consent. The study concluded that the reported European variation in informed consent procedures indicated inconsistencies in clear legislation or knowledge of such legislation among researchers. This could be optimized for the benefit of future research initiatives.

Chapter 9 was an extensive overview that discussed all relevant aspects on the use of informed consent procedures in emergency interventional research in patients with TBI and stroke that have an acute inability to provide informed consent. It was found that currently accepted consent alternatives such as deferred consent and exception/waiver of consent appear under-utilized, despite being ethically permissible, socially acceptable, and regulatory compliant. We concluded that when the requirements for medical urgency are properly balanced with legal and ethical conduct, the increased use of these alternatives has the potential to improve efficiency and quality of future emergency interventional studies in patients with an inability to provide informed consent.

The general discussion of this thesis will elaborate on the role of patient outcome and in-hospital costs in the acute treatment decision-making process in patients with s-TBI



CHAPTER 11

SAMENVATTING

Al sinds het begin van haar bestaan wordt de mensheid geconfronteerd met de ernstige gevolgen van traumatisch hersenletsel. Dat zal in de toekomst niet anders zijn. Ondanks duizenden jaren aan ervaring in het behandelen van patiënten met traumatisch hersenletsel is de besluitvorming rondom die behandeling erg moeilijk. Dit proefschrift had als doel enkele factoren te onderzoeken die belangrijk zijn bij het nemen van behandelbeslissingen. Ook werd er gekeken naar mogelijkheden om het doen van onderzoek naar traumatisch hersenletsel te verbeteren.

Deel 1 onderzocht de uitdagingen bij het nemen van acute behandelbeslissingen bij patiënten met ernstig traumatisch hersenletsel. Er werd gekozen om de focus te leggen op drie factoren, die allen belangrijk werden geacht in dit proces: uitkomst van de patiënt, zorgconsumptie in het ziekenhuis en kosten van de ziekenhuiszorg.

Hoofdstuk 2 was een literatuurstudie die zich richtte op de acute neurochirurgische behandeling van patiënten met zeer ernstig traumatisch hersenletsel (Glasgow Coma Score 3–5). Het werd duidelijk dat er tussen de 45 geïncludeerde studies grote variatie bestond in behandelstrategie. De sterfte onder patiënten was hoog en de kans om een zo genoemde ‘goede’ uitkomst te behalen bleek klein. Die ‘goede’ uitkomst werd vooral behaald door patiënten met een lagere leeftijd en/of een minder ernstige vorm van traumatisch hersenletsel. In aanvulling op de patiënt- en trauma gerelateerde factoren bleken het type en de timing van de interventie ook van invloed te zijn op de uiteindelijk behaalde uitkomst. Het was door de hoge mate van variatie tussen de studies en door methodologische beperkingen niet mogelijk om causaliteit vast te stellen.

Hoofdstuk 3 was een systematische literatuurstudie die de ziekenhuiskosten van patiënten met ernstig traumatisch hersenletsel (Glasgow Coma Score 3–8) onderzocht. De 25 geïncludeerde studies toonden over het algemeen hoge ziekenhuiskosten (mediaan €44,660; range €1,720–€324,660; gemiddeld €70,810). De ziekenhuiskosten bleken voornamelijk veroorzaakt te worden door kosten gerelateerd aan de opname op de intensive care (51%–79%) of de verpleegafdeling (12%–38%) en door chirurgische interventies (4%–8%). De duur van opname op de verpleegafdeling en de intensive care varieerde respectievelijk van 10 tot 37 en van 8 tot 26 dagen. Wanneer de ernst van het traumatisch hersenletsel toenam, stegen ook de intramurale zorgconsumptie en de zorgkosten. Het was moeilijk om conclusies te trekken over de exacte kosten van patiënten met traumatisch hersenletsel door de variatie tussen studies en omdat de kwaliteit van de geïncludeerde studies hiervoor onvoldoende was. Er werd

geconcludeerd dat toekomstige kosten evaluaties door het gebruik van aanbevelingen uit handleidingen voor kostenonderzoek en 'common data elements' hun kwaliteit zouden kunnen verbeteren. Er is vooral extra aandacht gewenst op het gebied van kostenberekening en het beschrijven van de gemaakte kosten.

Hoofdstuk 4 en *5* rapporteerden de uitkomsten van de patiënten van twee verschillende cohorten met daarbij een overzicht van de zorgconsumptie en de ziekenhuiskosten. Het eerste cohort bestond uit 108 patiënten met een traumatisch acuut subduraal hematoom en het tweede cohort bestond uit 486 patiënten met traumatisch hersenletsel die regionaal geïnccludeerd waren in de CENTER-TBI studie. We hebben gebruik gemaakt van de Nederlandse richtlijn voor gezondheids-economische evaluaties met als doel de rapportage en kwaliteit van de kostenberekening te verbeteren. Beide studies vonden een hoge mortaliteit en veel patiënten met een 'ongunstige' uitkomst (definitie Glasgow Outcome Scale). Deze getallen werden hoger als de ernst van het traumatisch hersenletsel toenam, bij aanwezigheid van intracranieële afwijkingen of extracranieële verwondingen, en wanneer een chirurgische interventie noodzakelijk was. Ondanks het feit dat veel patiënten met ernstig traumatisch hersenletsel een slechte uitkomst hadden, lieten beide studies zien dat patiënten uit die groep ook een 'gunstige' uitkomst konden behalen. Zelfs enkele patiënten met zeer ernstig traumatisch hersenletsel behaalden een zogenaamde 'gunstige' uitkomst.

Beide studies vonden dat de zorgconsumptie en bijhorende ziekenhuiskosten van deze patiënten behoorlijk hoog waren, zelfs voor patiënten met mild traumatisch hersenletsel (Glasgow Coma Score 13-15). Gemiddeld waren de ziekenhuiskosten voor een patiënt met mild traumatisch hersenletsel €7,800. De kosten voor patiënten met matig (GCS 9-12: €20,210), ernstig (GCS 3-8: €26,600), en zeer ernstig (GCS 3-5: €26,350) traumatisch hersenletsel waren hoger (*hoofdstuk 5*). De toename in zorgconsumptie en kosten in het ziekenhuis waren gerelateerd aan verschillende factoren: ernstiger traumatisch hersenletsel (lagere GCS, aanwezigheid pupil afwijkingen, intracranieële afwijkingen op CT-scan), aanwezigheid ernstig extracranieel letsel, gebruik van intracranieële drukmeting en chirurgische interventie(s). De ziekenhuiskosten werden primair gedreven door kosten veroorzaakt door opname en chirurgische interventies, zoals ook werd gezien in *hoofdstuk 3*.

Hoofdstuk 6 kwam tot stand naar aanleiding van verschillende focusgroep sessie met medisch professionals op de gebieden neurochirurgie, intensive care geneeskunde, revalidatiegeneeskunde, chronische zorg, antropologie en medische ethiek. Het proces van behandelbeslissingen en de overwegingen in die besluitvorming werd besproken. Ook werden een aantal redenen geformuleerd waarbij behandelbeperkingen bij patiënten met ernstig traumatisch hersenletsel gelegitimeerd zouden kunnen zijn. Daarnaast werd gesproken over professionele code van artsen, behandelbeperkende beslissingen, de beoordeling van patiënten uitkomst, prognostische onzekerheid, shared decision-making, zorgkosten, maatschappelijk perspectief, belang van revalidatie en lange termijn denken. Ondanks alle inspanningen om de zorg en uitkomsten voor patiënten met traumatisch hersenletsel te verbeteren, werd geconcludeerd dat de besluitvorming erg moeilijk blijft. Het grootste deel van de onzekerheid in die besluitvorming wordt veroorzaakt door het gebrek aan hoog kwalitatief bewijs voor de effectiviteit van behandelingen en onzekerheid in prognose stelling. Daarnaast is er onzekerheid over hoe acceptabel een bepaalde uitkomst voor een patiënt is, gezien de grote individuele verschillen tussen patiënten.

Deel II analyseerde enkele problemen bij het doen van onderzoek naar traumatisch hersenletsel. Hierbij lag de focus op het verkrijgen van goedkeuring van medisch ethische toetsingscommissies en op het gebruik van informed consent bij patiënten met traumatisch hersenletsel die zelf geen toestemming voor studiedeelname konden geven.

Hoofdstuk 7 onderzocht de processen die in Europa nodig waren om toestemming van de medisch ethische toetsingscommissie te krijgen voor het starten van de CENTER-TBI studie. Er bleek grote variatie te bestaan in hoe het CENTER-TBI studie protocol werd beoordeeld en goedgekeurd door 66 Europese medisch ethische toetsingscommissies. Er was variatie tussen en binnen Europese landen. Die variatie was voornamelijk te zien op gebied van indiening, goedkeuringsvereisten, aantal ronden, en totale duur van het proces. Allen werden niet bevorderlijk gevonden voor het doen van onderzoek op een zo efficiënt mogelijke manier. We concludeerden dat toekomstige internationale onderzoeksinitiatieven baat zouden kunnen hebben bij de implementatie van uniforme wetgeving, die tegelijkertijd rekening houdt met lokale culturele en morele gebruiken van landen.

Hoofdstuk 8 en hoofdstuk 9 richtte zich op het gebruik van informed consent in patiënten met traumatisch hersenletsel die zelf geen toestemming voor studie deelname konden geven

Hoofdstuk 8 liet variatie en strijdigheid zien tussen gerapporteerde en geobserveerde informed consent procedures in patiënten met een onvermogen tot het geven van toestemming voor studie deelname. Het gaat om patiënten uit de CENTER-TBI studie, die opgenomen waren op de intensive care. De variatie was aanwezig tussen, maar ook binnen Europese landen. Toestemming van een patiënt vertegenwoordiger en uitgestelde toestemming bleken essentieel om patiënten met traumatisch hersenletsel en een onvermogen om zelf toestemming te geven te includeren. Desalniettemin werd de mogelijkheid om patiënten met uitgestelde toestemming te includeren slechts gebruikt in een derde van de centra die vonden dat dit een geldige methode was. Er werd geconcludeerd dat de Europese variatie in het gebruik van informed consent procedures een aanwijzing kan zijn voor onduidelijkheden in wetgeving, of voor het gebrek aan kennis van die wetgeving bij onderzoekers. Hier liggen kansen voor verbetering en die verbetering zou een positief effect kunnen hebben op toekomstige studies.

Hoofdstuk 9 was een overzichtsartikel van de belangrijkste aspecten van het gebruik van informed consent procedures in interventie onderzoek in een spoedsetting bij patiënten met traumatisch hersenletsel of een beroerte, die zelf geen toestemming kunnen geven. Mogelijkheden voor het gebruik van geaccepteerde alternatieven voor het verkrijgen van toestemming, zoals uitgestelde toestemming of vrijstelling van toestemming, lijken onvoldoende te worden benut. Dit ondanks dat deze alternatieven ethisch en maatschappelijk verantwoord zijn en dat het gebruik binnen de geldende regels kan. Het op een correcte manier gebruiken van deze alternatieven kan van groot belang zijn voor het verbeteren van de efficiëntie en de kwaliteit van toekomstige interventie studies in een spoedsetting met patiënten die geen toestemming kunnen geven.

De hierna volgende discussie van dit proefschrift bevat een beschouwing over de rol die de uitkomst van de patiënt en de ziekenhuiskosten spelen bij het nemen van acute behandelbeslissingen bij patiënten met ernstig traumatisch hersenletsel.



CHAPTER 12

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Humans have suffered from the consequences of traumatic brain injuries (TBI) from the beginning of mankind and will continue to do so in the future. For ages, people have attempted to minimize the consequences of TBI by examining and treating affected individuals.¹ Extensive experience and improvements in medical treatments from the last century resulted in substantial progress in the survival and outcome of severe TBI (s-TBI) patients (Glasgow Coma Score (GCS) of 3–8).^{2–5}

Patients with s-TBI (29%–40%)^{6,7} and vs-TBI (GCS 3–5; 19.6%–23%)^{6,7} are nowadays able to achieve so-called ‘favourable’ outcome.^{8,9} Most s-TBI patients (40%–65%)^{6,7} however still die or survive with long-term disabilities^{2,3,8–11}, which also negatively affects the quality of life of most proxies.^{12–14} Outcome is usually worse in patients with higher TBI severity (i.e. lower GCS, pupillary abnormalities), intracranial abnormalities on first CT scan, extracranial injuries and need for surgical intervention.^{3,6,7,15–17} Despite all available patient outcome data, it remains challenging to interpret, generalize, value, and use this data for acute treatment decision-making.

Acute treatment decisions are poorly supported by high- or even moderate quality evidence and accurate prognostic algorithms, leaving ample room for uncertainty.^{18–23,47} Also, available guidelines do not cover all relevant topics due to a lack of supporting evidence.¹⁸ Non-adherence to guidelines and treatment variation seem understandable in light of such lack of certainty.^{24–27} It even remains unclear how specific factors substantiate the acute treatment decision-making process.^{28–31} As a result, the decision to initiate acute treatment or not in s-TBI patients or discontinue critical care in the subacute period poses major medical and ethical dilemmas to physicians.

This *general discussion* elaborates on the role of patient outcome and in-hospital costs in the acute treatment decision-making process in s-TBI patients.

Main findings and interpretation

Patient outcome

Providing healthcare is about doing ‘right’ for individual patients and about better health for populations.³² Physicians have a responsibility to customize treatment strategies to achieve best possible patient outcome that is respectful of and responsive

to individual patient preferences, needs, and values.³² Choosing an acute treatment strategy that is proportional and leads to best possible patient outcome is however difficult. This is mainly caused by uncertainties on future patient outcome, especially regarding outcome prediction and outcome valuation.

Patient outcome prediction

Because providing healthcare is about patient outcome in the future, it is necessary to use a prediction of that outcome for acute treatment decisions. Knowing what specific outcome will be achieved after a specific treatment is likely to improve decision-making.^{30,31,33-35}

Unfortunately, physicians appear to be unable to make accurate outcome predictions (Table 1).^{22,33,36,37} Validated prognostic models, such as IMPACT and CRASH^{38,39}, have been developed to assist physicians with TBI outcome prediction, but they have not been widely implemented in clinical care.⁴⁰⁻⁴⁴ Although IMPACT and CRASH models display good discriminative ability in validation studies^{40,41}, they are, like experienced physicians, considered to be too inaccurate on individual level predictions. Heterogeneity between individual patients with variable injuries, pathophysiology, and treatments makes prognostication difficult and uncertain. Another limitation of available prognostic models is that they only include robust short-term outcome measures like mortality and functional outcome. Although robustness is a good epidemiological attribute of clinical studies it misses personal human properties like long-term physical, cognitive, emotional and behavioural outcome, or satisfaction with life.^{33,38-45} This is problematic, because these long-term consequences of s-TBI are highly relevant to include in outcome assessment.⁴⁶

Table 1. Difficulties in outcome prediction in TBI patients (chapter 6)⁴⁷

| # | Difficulties in random order. |
|---|--|
| 1 | The heterogeneous nature of s-TBI and concurring comorbidities and their unknown effect on outcome. |
| 2 | Unclear/incomplete clinical information, including the patient's neurological state and level of consciousness. |
| 3 | Largely unknown pathophysiological mechanisms of brain injury and inherent degree of brain plasticity. |
| 4 | Prediction models do not include long-term (health-related) quality of life, although long-term changes have been reported and patients/proxies are known to value this outcome. |
| 5 | Prediction models are based on large retrospective data sets that do not necessarily reflect current or future treatment strategies. |

High prognostic accuracy is indispensable when a prediction is used to substantiate individual acute treatment decisions. Relatively small mathematical inaccuracies

can have disastrous clinical consequences. It remains unknown how high this accuracy must be and what cut-offs should be used for decision-making. There are peer reviewed recommendations that consider it reasonable to pursue non-aggressive care in patients with a >85% chance of death or 'unfavourable' outcome.³⁴ If a physician would have followed this recommendation, a 28-year old patient with a CRASH-model predicted risk of death at 14 days of 91.8% and a risk of an 'unfavourable outcome' at 6 months of 95.7%, that achieved 'favourable' outcome and was able to live independently, would have probably died after treatment-limiting decisions.⁴⁸

Despite many efforts to improve outcome prediction, there is substantial inaccuracy in today's prognostic abilities. Every effort must be made to prevent that patients are unfairly deprived of potentially beneficial care because of erroneous prognostication or poorly chosen cut-offs. It is therefore essential that inherent uncertainties of outcome prediction are acknowledged in the acute decision-making process. Only the best possible approximation of expected patient outcome should be used and opportunities to improve prognostic accuracy should be explored.

Patient outcome valuation

Valuation of predicted patient outcome is about judging the favourability of a patients' future health status and about defining how 'acceptable' or 'unacceptable' that health status is to patients, proxies and societies. Its importance for acute treatment decision-making seems obvious. Common sense dictates that acute treatment should be initiated or continued when outcome is judged 'acceptable', and withheld or discontinued when outcome is judged 'unacceptable'.

A cut-off point for 'acceptability' of outcome would be useful, but an exact definition of 'acceptable' or 'unacceptable' outcome remains elusive, and is probably impossible to determine.^{49,50} Any cut-off point will be highly arbitrary and can never account for the countless outcome possibilities and numerous variations in peoples' specific contexts, and ever-changing desires or interpretations of well-being or 'the good life'. Life can be judged worth sustaining because it has intrinsic value to relatives and friends, or because of cultural or religious reasons.⁵¹ (*chapter 6*)

Several scales and checklists have been developed to quantify the individual and societal impact of TBI, and to improve the assessment of medical treatment efficacy.⁵² Nonetheless, the most frequently used measures have important limitations in specifying the individual 'acceptability' of outcome. The reliability of

these measures for outcome valuation and their usefulness in the acute decision-making process of s-TBI patients remains disputed.

Patient mortality

The most frequently used and most straightforward outcome measure. Death is usually considered to be the worst possible outcome that should be prevented at any cost.⁵³ However, in s-TBI patients, survival with severe post-traumatic deficits can be a fate worse than death.⁵⁴⁻⁵⁸ When considering the possibility of very severe cognitive, emotional, and physical disabilities, life and death are not necessarily equal to 'acceptable' and 'unacceptable'. As such, acute treatment decisions should not solely be based on predicted mortality.

Functional outcome

The Glasgow Outcome Scale (GOS) is the most highly cited outcome measure in brain injury studies.⁵⁹⁻⁶¹ Its use as TBI outcome measure is recommended by many organizations.⁶⁰ It assesses multiple aspects of life to determine the impact of TBI on patient functional outcome with a focus on social recovery. It uses dichotomous endpoints, in which 'favourable' outcome (the ability to function independently, see Table 2), is usually considered to be the 'acceptable' outcome. The introduction of the Glasgow Outcome Scale Extended (GOSE) and the structured interview⁶¹ have solved points of criticism on validity and lack of sensitivity in the higher functional end of the scale, but there are remaining issues.^{52,60,61}

The 'favourable'/'unfavourable' division remains arbitrary and ignores a patients' or proxy's perception of satisfaction with life. Patients with severe disability who are dependent in daily life (defined as 'unfavourable') can still judge their health status to be 'acceptable'.⁶⁰ But the other way around is also possible. Some studies classify 'upper severe disability' (GOS-E) to be 'favourable', while probably most physicians, researchers and healthy individuals would classify this outcome as 'unacceptable' within their own social and cultural context.^{50,62}

Instead of using dichotomized outcome, sliding dichotomy or proportional odds methods are considered to be more informative. These methods are increasingly popular, but still have insufficient sensitivity to detect all changes. Subtle changes can be highly valuable for a patients' wellbeing, without having a measurable impact on pre-defined categories.⁶⁰

The GOS/GOSE is a very useful functional outcome measure, but does not include the essential subtleties of well-being. The use of 'favourable' and 'unfavourable' as substitutes for 'acceptable' and 'unacceptable' outcome is inadequate. These terms should not be interpreted or used as such in acute treatment decision-making.

Table 2 Explanation of Glasgow Outcome Scale (- Extended). ⁶¹

| Glasgow Outcome Scale (GOS) | Glasgow Outcome Scale – Extended (GOSE) | Brief description | |
|-----------------------------|---|--|--------------|
| 2. Death | 2. Death | Death | Unfavourable |
| 3. Vegetative state | 3. Vegetative state | Absence of awareness of self and environment | |
| 4. Severe disability | 6. Lower severe disability | Needs full assistance in daily life | |
| | 7. Upper severe disability | Needs partial assistance in daily life | |
| 9. Moderate disability | 10. Lower moderate disability | Independent, but cannot resume work/school or all previous social activities | Favourable |
| | 11. Upper moderate disability | Some disability exists, but can partly resume work or previous activities | |
| 8. Good recovery | 12. Lower good recovery | Minor physical or mental deficit that affects daily life | |
| | 13. Upper good recovery | Full recovery or minor symptoms that do not affect daily life | |

Health-Related Quality of Life (HRQoL)

HRQoL measures focus on a patient's view on the impact of TBI and a certain health status on their (quality of) life. They are a multi-dimensional concept including physical, mental, emotional, and social functioning. Generic HRQoL instruments are designed to investigate particular interventions or populations. ⁶³ Disease-specific HRQoL measures have been specifically designed for a disease and are assumed to be more sensitive to that disease, allowing more precise outcome information.

The Quality of Life after Brain Injury (QOLIBRI) is an example of a TBI-specific HRQoL measure. ⁶⁴ The applicability of the QOLIBRI in s-TBI patients however remains unclear. Most s-TBI patients suffer from cognitive impairment and communicative difficulties. Patients are hardly able to complete the questions, and, likely for this reasons, the QOLIBRI has only been validated in patients without substantial post-traumatic cognitive restraints. ⁶⁵ Proxies are often unable to adequately substitute a patients view. ⁵² The QOLIBRI cut-off point of 60 (score 0 to 100) for quantifying a 'good' HRQoL also remains unclear and is prone for subjectivity. ⁶⁶ Generic HRQoL instruments like the SF-36, EQ-5D, or WHOQOL-BREF are also considered to be less useful in patients with moderate or severe TBI (GCS 3-12). ^{67,68}

Individualized approach

The alternative of simply asking individual s-TBI patients in the acute setting to value their predicted outcome could be helpful, but is impossible. Patients after s-TBI have an inability to participate in the decision-making process by definition and their preferences, needs, and values are therefore unknown.³¹ Written advanced directives are rarely available and patients have rarely discussed preferences with proxies.^{49,51} In addition, proxies, as surrogate decision-makers, are mostly unavailable, unprepared, confused by uncertainty and hope, and unequipped to fully understand the uncertainties of acute clinical decision-making. Proxies might even misjudge or misrepresent patients' preferences.^{69,70}

As mentioned in *chapter 6*, even without mental incapacity due to s-TBI, individuals are generally unable to predict accurately what future quality of life would be 'acceptable' or 'unacceptable' to them. People often underestimate their ability to adapt to a level of disability they previously considered 'unacceptable'.³³ Survivors of s-TBI that had achieved a so-called 'unfavourable outcome' defined by the Glasgow Outcome Scale (Table 2) after a decompressive craniectomy, or their caregivers, appeared to have changed their perception of 'a good quality of life'. They were satisfied and would even have provided retrospective consent for the intervention.^{71,72} This absence of a linear connection between disabilities and experienced quality of life is known as the disability paradox⁷³ and is also seen in patients suffering from locked-in syndrome or Duchenne.^{72,74-76}

A physician's perspective

Given the reservations regarding a patient's or proxies preferences, it is inevitable that a physician's outcome valuation is included in the acute treatment decision-making process. Although physicians have an important role in protecting a patient's interests, their valuation and subsequent acute treatment-decisions might not always honour a patients' preferences. Their valuations can be influenced by local policy, specialized medical training, personal and professional experiences, but also by individual values, religious beliefs, and cultural background. This might jeopardize the objective selection of an individualized healthcare strategy that aims to achieve 'acceptable' patient outcome.

An important risk in decision-making is a physicians' strong belief in high mortality and 'unfavourable' outcome rates, as it is likely to contribute to clinical nihilism and the overall belief that treatment is ineffective.⁴⁷ This focus on poor prognosis is not necessarily in line with reported patient outcome^{6,7} but might lead to withholding, withdrawing, or decreasing intensity of potentially beneficial treatment(s). The

negative feedback makes other involved carers (i.e. nurses) pessimistic, which can result in limited care efforts, which in turn negatively influences patient outcome.⁷⁷

Not realizing their own contribution, worse outcome will initially confirm their individual beliefs and later spread by the inclusion in clinical studies or when included in prognostic models.⁷⁷ As much as 63% of deaths in trials investigating s-TBI patients were registered after decisions to withdraw life-sustaining therapies.⁷⁸ Trial mortality rates could have been influenced by this large number of withdrawals, and could further contribute to maintain the belief in poor prognosis, resulting in more withdrawals of care and worse outcome.⁷⁸ Physicians need to be aware of this self-fulfilling prophecy and its potential effect on treatment decision-making.⁷⁹

Some restraint in treatment-limiting decisions in the acute phase might be prudent given the uncertainties on patient outcome prediction and outcome valuation and the irreversible consequences of these decisions.

Can we fix the acute treatment decision-making process?

Acute treatment decision-making in s-TBI patients is highly complex and many problems with uncertainty in outcome prediction and outcome valuation will be difficult to solve. Despite this complexity, physicians will continue to make treatment decisions at the best of their abilities. An improvement in the quality of these inevitable acute treatment decisions could be achieved by deliberately delaying early treatment-limiting decisions in s-TBI patients with substantial prognostic uncertainty. This may not only prevent premature treatment-limiting decisions, but also means that these patients will receive optimal acute treatment, which hopefully allows best possible recovery, probably at the cost of increasing neuro-critical care costs.

The necessity for more time

The proposed strategy provides more time to measure and collect early key critical care variables to improve prognostic ability and to reconstruct a patients' preferences, values, and treatment wishes.^{31,80-82} This valuable information on clinical progress, neurological recovery, and a complete, objective and consistent evaluation of rapidly evolving imaging modalities (i.e. CT and MRI) only becomes available with extra time and will substantially improve diagnostics and prognostication.⁸³⁻⁸⁶ More time also allows multidisciplinary counsel including moral deliberation on individual patient or proxy preferences. All this additional information is highly valuable, and indispensable for a decision-making process.^{31,87,88}

Although delaying treatment-limiting decisions seems to be a viable solution to improve decision-making, it is not common practice. Treatment-limiting decisions are reported within 2 days after injury in up to 70% of s-TBI patients.^{78,89,90} Although physicians have best intentions, these early decisions deprive patients of a chance for successful recovery and usually result in clinical deterioration and death.^{78,89} Limiting treatment within 2 days after injury seems to be disproportional and morally unjustified given the uncertainties on future outcome.⁸²

It remains unknown how much extra time is necessary to sufficiently improve prognostic accuracy to avoid the withholding of potentially beneficial treatments. The Neurocritical Care Society recommends to use a 72-hour observation period for devastating brain injury patients to determine clinical response and delay decisions regarding withdrawal of life-sustaining treatment.⁹¹ Longer decision-making intervals of a week or even 10 days have also been recommended, awaiting adequate control of cerebral edema, injurious neuroinflammation, and associated intracranial hypertension.^{92,93} Delaying any conclusions about prognosis to after 72 hours is also advised for brain injury after cardiac arrest.⁹⁴

Treatment-limiting decisions

There are advantages of the proposed strategy, but an unrestricted endeavour for sustaining life by providing optimal acute treatment to all s-TBI patients is undesirable and unrealistic for two main reasons:

First, providing acute treatment might be considered disproportional from a patients perspective. Treatment can be against patients' and proxies' preferences and values.^{78,89,95} When achieved outcome becomes 'unacceptable', or when a combination of different features indicates very low chances of regaining an 'acceptable' outcome, or when treatment has become disproportionate given the outcome, treatment-limiting decisions should be considered. Treatment-limiting decisions can be inevitable and morally justified. Death is unwanted, but catastrophic conditions such as unresponsive wakefulness syndrome or minimally conscious state are accompanied by very severe disabilities and enormous challenges for both patients and proxies that should not be disregarded.^{96,97} Many will doubt this is a human life worth living.⁹⁸ (*chapter 6*)

Several reasons to consider early treatment-limiting decisions are listed in textbox 1 (*chapter 6*).⁴⁷ This list is meant to serve as a starting point for further discussion, rather than constitute a final list of reasons. Although all focus group participants from *chapter*

6 were highly regarded experts in the field, clinical situations might not be similar to the Dutch situation and their expert opinion might not be shared. This could limit the generalizability and practicality of the list, but emphasises that continued discussions and research on treatment-limiting decisions are essential.

Textbox 1: Reasons, including potential outcome perspectives, to strongly consider treatment-limiting decisions (chapter 6) ⁴⁷

1. Brain death, from a patient's perspective (not considering interests regarding organ donation procedures). ^{99,100}
2. (chronic) Unresponsive wakefulness syndrome. ^{96,101}
3. Minimally conscious state – (minus) (i.e. visual pursuit, localization of noxious stimuli, appropriate smiling or crying to emotional stimuli). ^{101,102}
4. An available, unquestionable, written and signed specific advance directive of the patient that prohibits treatment in a specific situation (possibly related to expected outcome).
5. A proxy opinion that is unquestionably based on patient preferences and that is not in conflict with the attending medical teams' considerations, that prohibits treatment in a specific situation (possibly related to expected outcome).
6. A patient's view (or when necessary a reconstructed vision through surrogated) on life and quality of life is contrary to the outcome that can be expected from the best available prognostic models.
7. From a societal perspective, treatment costs along the whole chain of care that are not cost-effective and higher than the maximum amount that has been decided by national legislation.

The societal perspective

Second, treatment can be considered disproportional from a societal perspective. Healthcare is not only about individuals but also about improving health of populations. ^{12-14,32} The proposed strategy of providing acute treatment to more s-TBI patients is likely to substantially increase in-hospital costs. On a large scale, this might affect restricted healthcare budgets and jeopardize vulnerable healthcare systems or societal health. ^{3,103} This is undesirable in a time where politicians are already struggling to restrict the increasing worldwide economic burden of healthcare. ¹⁰³ Despite governmental restrictions, The Netherlands, with 17.3 million inhabitants

in 2019, spent as much as €80.9 billion on healthcare in 2019, an increase of 4.8% compared to 2018.¹⁰⁴ This accounts for 10% of total gross domestic product¹⁰⁴, similar to many other high-income countries: 11.5% (9.6%–12.4).¹⁰³ Although treating more s-TBI patients could be legitimized by more patients with improved and hopefully ‘acceptable’ outcome, the future of healthcare systems requires prudence and optimal use of restricted resources.

Justice, as one of four moral principles in medical ethics (Table 3), requires the fair distribution of benefits, risks and limited medical goods and services.¹⁰⁵⁻¹⁰⁷ With respect to its many variations, this is in line with the principle of utilitarianism, which seeks to maximize the well-being of most of the people, instead of the individual.^{108,109} Incorporating these principles in acute treatment decision-making could mean that resources, potentially beneficent for an individual patient, are ethically restricted for the wellbeing of the entire society. In line with this, resources should not be used on so-called ineffective and disproportional treatments in s-TBI patients with a very low chance of achieving ‘acceptable’ outcome, because it will deprive other patients of potentially effective treatments.¹¹⁰ Cost-effectiveness analyses and concepts such as value-based healthcare can be used to substantiate acute treatment decision-making and prevent inefficient use of limited healthcare resources.

Table 3: Moral principles in medical ethics

| Principle | Description |
|-------------------|--|
| 1. Autonomy | A norm of respecting and supporting autonomous decisions. |
| 2. Beneficence | A group of norms pertaining to relieving, lessening, or preventing harm and providing benefits and balancing benefits against risks and costs. |
| 3. Nonmaleficence | A norm of avoiding the causation of harm. |
| 4. Justice | A group of norms for fairly distributing benefits, risks, and costs. |

In-hospital costs

The true cost-effectiveness and feasibility of the proposed strategy has not been investigated in *this thesis*, and also remains unknown based on the in-hospital healthcare consumption and in-hospital costs that are reported in *chapter 3, 4 and 5*.^{6,7,111} It is also difficult to make statements based on available literature, since cost-effectiveness literature in s-TBI is scarce and inconclusive. Some studies report TBI treatment to be cost-effective¹¹²⁻¹¹⁵, while others report the opposite.^{113,116} The feasibility of the proposed strategy remains unclear and requires further investigation with actual cost-effectiveness analyses.

Cost-effectiveness aside, the average in-hospital costs of s-TBI patients (€26,595)⁶ that would be associated with the proposed strategy seem to be acceptable compared to the in-hospital costs for other diseases in the Netherlands. Costs were lower compared to the in-hospital costs of s-TBI for patients with ischaemic stroke (€5,328)¹¹⁷, transient ischaemic attack (€2,470)¹¹⁷, appendicitis (€3,700), colorectal cancer (€9,777–€19,417)¹¹⁸, percutaneous coronary intervention (€14,037) or coronary artery bypass grafting (€17,506)¹¹⁹. In-hospital costs were higher for patients with non-small cell lung cancer (€33,143)¹²⁰, ipilimumab treatment in melanoma patients (€73,739)¹²¹ or patients receiving extracorporeal life support treatment (€106,263).¹²²

Costs also seem to be acceptable when comparing the in-hospital costs for s-TBI patients with the Dutch cut-off point for cost-effective treatments of €80,000 per Quality-adjusted Life Year (QALY).¹²³ Although the comparison of reported in-hospital costs with the €80,000 cut-off point for cost-effectiveness analyses is not entirely appropriate, and although there are always few patient outliers with very high costs, the costs of nearly every TBI patient studied in *this thesis* was lower than €80,000.

Both comparisons are illustrative, but have obvious limitations. First, analyses should not only assess in-hospital costs, but all costs associated with s-TBI, including out of hospital and other indirect costs. Only using in-hospital costs results in a major underestimation of the total costs related to s-TBI. Especially when patients survive with severe disabilities, chronic care after hospital discharge, but also loss of productivity, have substantial economic and societal impact.

Including an economic perspective in decision-making is regarded as reasonable because of its objectivity. Focusing on the economic perspective however also fails to recognize individual aspects of care and the social utility of caring for those most in need. People obtain benefit from the belief that they live in a compassionate and humane society where patients in need will not be ignored merely based on costs. Still, there must be a point where TBI is so severe and patient outcome so 'unacceptable' that it does not justify the associated costs. For future decision-making, it would be very helpful to know where that point is.

FUTURE RESEARCH

The treatment of patients with s-TBI deserves scientific and public attention given the considerable medical and economic burden for patients, proxies, and societies. Treatment decision-making will benefit most from knowing which specific patient will benefit from which specific treatment in terms of cost-effectiveness and patient outcome. Accurate prognostication and the determination of the 'acceptability' of outcome are essential parts of the acute treatment decision-making process. Future studies should focus on investigating:

1. New diagnostic and treatment modalities including their (cost-) effectiveness and their effect on short- and long-term patient outcome.^{124,125}
2. The (patho)physiological mechanisms of brain injury and its plasticity.^{3,126-130}
3. Reliable, reproducible, validated, free and easy to use outcome assessment tools that are sensitive for disabilities commonly present in s-TBI survivors.⁵²
4. Methods to improve the reliability of prognostic or machine learning models.^{131,132}
5. The influence of human values, including a dignified existence and the wellbeing of patients, proxies and society.

Different study designs will be required to answer different research questions. Randomized controlled trials (RCTs), the cornerstone of evidence-based medicine, might provide answers to point 1, 3 and 4. Although very little translatable evidence has been derived from 191 completed RCTs for acute TBI management¹³³, more sophisticated large multi-centre RCTs in priority areas might still be able to make a valuable contribution.¹³³

To allow RCTs in the hyper acute setting of TBI and to increase their quality, efficiency and contribution to the evidence base, optimized research protocols are needed to overcome several complicating factors in the acute and stressful setting, such as; unavailable necessary information (i.e. trauma mechanism, medical history, use of anticoagulants), and a patients' inability to provide informed consent. A rigorous research protocol is essential for any study to be successful and to obtain institutional review board approval. The increased use of informed consent alternatives, such as deferred consent or exception from consent, has the potential to improve efficiency and quality of future emergency interventional studies in patients with an inability to provide informed consent.¹³⁴

Another method to answer research questions related to point 1 and 4 is called “Comparative Effectiveness Research” (CER). With this method, the effectiveness of (surgical and critical care) treatment is investigated by comparing variation between local practices. This method is used in recent TBI research initiatives like CENTER-TBI, TRACK-TBI and Net-QuRe.^{119,135,136} CER is a well-known and promising method to assess treatment effectiveness in TBI, but there are also some important limitations.¹³⁷ Studies are generally expensive because many centres and participants must be included to reach sufficient statistical power. Also, effect estimates largely depend on the used analytical method. When a RCT or CER design is not possible, the focus should be on patient cohorts, surgical treatments and outcome measures that are as equal as possible. It is highly recommended to use the well-known common data elements.¹³⁸ This will improve comparability and generalizability of study results and allow data analyses in large meta-analyses. Point 2 is basically fundamental research and point 3 and 5 require a more humanistic approach to the topic.

CONCLUSION

Decision-making dilemmas in the acute treatment of s-TBI patients are common. They are caused by insufficient evidence and by uncertainties in outcome prediction and outcome valuation. To decrease uncertainty and improve decision-making, treatment-limiting decisions in a selection of s-TBI patients should be delayed to after at least 72 hours after injury. These patients will receive optimal acute treatment. Although the feasibility and cost-effectiveness of the proposed strategy requires further investigation, it prevents premature treatment-limiting decisions and allows the collection of essential information to improve the identification of patients that will benefit from specific treatment strategies. At the same time, it could prevent ‘unacceptable’ patient outcome and inefficient use of limited healthcare resources in threatened healthcare systems. Including an economic perspective in decision-making is reasonable and essential, but the individual aspects of care and the social utility of caring for those most in need should not be disregarded. Although it is unlikely that all uncertainty will ever be resolved, researchers and ethicists should continue to try to reduce uncertainty in decision-making by improving the scientific quality of evidence.

REFERENCES:

- Sanchez GM, BurrIDGE AL. Decision making in head injury management in the Edwin Smith Papyrus. *Neurosurgical focus* 2007; **23**(1): E5.
- Stein SC, Georgoff P, Meghan S, Mizra K, Sonnad SS. 150 years of treating severe traumatic brain injury: a systematic review of progress in mortality. *J Neurotrauma* 2010; **27**(7): 1343-53.
- Maas AIR, Menon DK, Adelson PD, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. *The Lancet Neurology* 2017; **16**(12): 987-1048.
- Teasdale G, Jennett B. ASSESSMENT OF COMA AND IMPAIRED CONSCIOUSNESS: A Practical Scale. *The Lancet* 1974; **304**(7872): 81-4.
- Teasdale G, Maas A, Lecky F, Manley G, Stocchetti N, Murray G. The Glasgow Coma Scale at 40 years: standing the test of time. *The Lancet Neurology* 2014; **13**(8): 844-54.
- van Dijk J, Mostert CQB, Greeven APA, et al. Functional outcome, in-hospital healthcare consumption and in-hospital costs for hospitalised traumatic brain injury patients: a Dutch prospective multicentre study. *Acta neurochirurgica* 2020; **162**(7): 1607-18.
- van Dijk J, van Essen TA, Dijkman MD, et al. Functional and patient-reported outcome versus in-hospital costs after traumatic acute subdural hematoma (t-ASDH): a neurosurgical paradox? *Acta neurochirurgica* 2019; **161**(5): 875-84.
- Rosenfeld JV, Maas AI, Bragge P, Morganti-Kossmann MC, Manley GT, Gruen RL. Early management of severe traumatic brain injury. *Lancet (London, England)* 2012; **380**(9847): 1088-98.
- McIntyre A, Mehta S, Janzen S, Aubut J, Teasell RW. A meta-analysis of functional outcome among older adults with traumatic brain injury. *NeuroRehabilitation* 2013; **32**: 409-14.
- Grauwmeijer E, Heijenbroek-Kal MH, Peppel LD, et al. Cognition, Health-Related Quality of Life, and Depression Ten Years after Moderate to Severe Traumatic Brain Injury: A Prospective Cohort Study. *J Neurotrauma* 2018; **35**(13): 1543-51.
- Ruet A, Bayen E, Jourdan C, et al. A Detailed Overview of Long-Term Outcomes in Severe Traumatic Brain Injury Eight Years Post-injury. *Frontiers in neurology* 2019; **10**: 120.
- Carlozzi NE, Kratz AL, Sander AM, et al. Health-related quality of life in caregivers of individuals with traumatic brain injury: development of a conceptual model. *Arch Phys Med Rehabil* 2015; **96**(1): 105-13.
- Kratz AL, Sander AM, Brickell TA, Lange RT, Carlozzi NE. Traumatic brain injury caregivers: A qualitative analysis of spouse and parent perspectives on quality of life. *Neuropsychol Rehabil* 2017; **27**(1): 16-37.
- Qadeer A, Khalid U, Amin M, Murtaza S, Khaliq MF, Shoaib M. Caregiver's Burden of the Patients With Traumatic Brain Injury. *Cureus* 2017; **9**(8): e1590.
- Gao G, Wu X, Feng J, et al. Clinical characteristics and outcomes in patients with traumatic brain injury in China: a prospective, multicentre, longitudinal, observational study. *The Lancet Neurology* 2020; **19**(8): 670-7.
- Steyerberg EW, Wiegers E, Sewalt C, et al. Case-mix, care pathways, and outcomes in patients with traumatic brain injury in CENTER-TBI: a European prospective, multicentre, longitudinal, cohort study. *The Lancet Neurology* 2019; **18**(10): 923-34.
- Krishnamoorthy V, Vavilala MS, Mills B, Rowhani-Rahbar A. Demographic and clinical risk factors associated with hospital mortality after isolated severe traumatic brain injury: a cohort study. *J Intensive Care* 2015; **3**: 46.
- Carney N, Totten AM, O'Reilly C, et al. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. *Neurosurgery* 2017; **80**(1): 6-15.
- Synnot A, Bragge P, Lunny C, et al. The currency, completeness and quality of systematic reviews of acute management of moderate to severe traumatic brain injury: A comprehensive evidence map. *PLoS one* 2018; **13**(6): e0198676.
- Bayley MT, Lamontagne ME, Kua A, et al. Unique Features of the INESSS-ONF Rehabilitation Guidelines for Moderate to Severe Traumatic Brain Injury: Responding to Users' Needs. *The Journal of head trauma rehabilitation* 2018; **33**(5): 296-305.
- Stocchetti N, Poole D, Okonkwo DO. Intracranial pressure thresholds in severe traumatic brain injury: we are not sure: Prudent clinical practice despite dogma or nihilism. *Intensive care medicine* 2018; **44**(8): 1321-3.
- Kompanje EJ. Prognostication in neurocritical care: just crystal ball gazing? *Neurocrit Care* 2013; **19**(3): 267-8.

23. Hawryluk GWJ, Rubiano AM, Totten AM, et al. Guidelines for the Management of Severe Traumatic Brain Injury: 2020 Update of the Decompressive Craniectomy Recommendations. *Neurosurgery* 2020; **87**(3): 427-34.
24. van Essen TA, de Ruiter GC, Kho KH, Peul WC. Neurosurgical Treatment Variation of Traumatic Brain Injury: Evaluation of Acute Subdural Hematoma Management in Belgium and The Netherlands. *J Neurotrauma* 2017; **34**(4): 881-9.
25. van Veen E, van der Jagt M, Citerio G, et al. End-of-life practices in traumatic brain injury patients: Report of a questionnaire from the CENTER-TBI study. *J Crit Care* 2020; **58**: 78-88.
26. van Essen TA, den Boogert HF, Cnossen MC, et al. Variation in neurosurgical management of traumatic brain injury: a survey in 68 centers participating in the CENTER-TBI study. *Acta neurochirurgica* 2019; **161**(3): 435-49.
27. Volovici V, Ercole A, Citerio G, et al. Variation in Guideline Implementation and Adherence Regarding Severe Traumatic Brain Injury Treatment: A CENTER-TBI Survey Study in Europe. *World neurosurgery* 2019; **125**: e515-e20.
28. Unterhofer C, Hartmann S, Freyschlag CF, Thome C, Ortler M. Severe head injury in very old patients: to treat or not to treat? Results of an online questionnaire for neurosurgeons. *Neurosurgical review* 2018; **41**(1): 183-7.
29. de Kort FAS, Geurts M, de Kort PLM, et al. Advance directives, proxy opinions, and treatment restrictions in patients with severe stroke. *BMC palliative care* 2017; **16**(1): 52.
30. Quinn T, Moskowitz J, Khan MW, et al. What Families Need and Physicians Deliver: Contrasting Communication Preferences Between Surrogate Decision-Makers and Physicians During Outcome Prognostication in Critically Ill TBI Patients. *Neurocrit Care* 2017; **27**(2): 154-62.
31. Turgeon AF, Dorrance K, Archambault P, et al. Factors influencing decisions by critical care physicians to withdraw life-sustaining treatments in critically ill adult patients with severe traumatic brain injury. *CMAJ* 2019; **191**(24): E652-E63.
32. Reuben DB, Tinetti ME. Goal-oriented patient care--an alternative health outcomes paradigm. *The New England journal of medicine* 2012; **366**(9): 777-9.
33. Ho KM. Predicting outcomes after severe traumatic brain injury: science, humanity or both? *Journal of neurosurgical sciences* 2018; **62**(5): 593-8.
34. Letsinger J, Rommel C, Hirschi R, Nirula R, Hawryluk GWJ. The aggressiveness of neurotrauma practitioners and the influence of the IMPACT prognostic calculator. *PloS one* 2017; **12**(8): e0183552.
35. Williamson T, Ryser MD, Abdelgadir J, et al. Surgical decision making in the setting of severe traumatic brain injury: A survey of neurosurgeons. *PloS one* 2020; **15**(3): e0228947.
36. Geurts M, de Kort FAS, de Kort PLM, van Tuijl JH, Kappelle LJ, van der Worp HB. Predictive accuracy of physicians' estimates of outcome after severe stroke. *PLoS One* 2017; **12**(9): e0184894.
37. Pratt AK, Chang JJ, Sederstrom NO. A Fate Worse Than Death: Prognostication of Devastating Brain Injury. *Crit Care Med* 2019; **47**(4): 591-8.
38. Collaborators MCT, Perel P, Arango M, et al. Predicting outcome after traumatic brain injury: practical prognostic models based on large cohort of international patients. *BMJ* 2008; **336**(7641): 425-9.
39. Steyerberg EW, Mushkudiani N, Perel P, et al. Predicting Outcome after Traumatic Brain Injury: Development and International Validation of Prognostic Scores Based on Admission Characteristics. *PLOS Medicine* 2008; **5**(8): e165.
40. Raj R. Prognostic Models in Traumatic Brain Injury. *Dissertation University of Helsinki* 2014.
41. Majdan M, Lingsma HF, Nieboer D, Mauritz W, Rusnak M, Steyerberg EW. Performance of IMPACT, CRASH and Nijmegen models in predicting six month outcome of patients with severe or moderate TBI: an external validation study. *Scand J Trauma Resusc Emerg Med* 2014; **22**: 68.
42. Maeda Y, Ichikawa R, Misawa J, et al. External validation of the TRISS, CRASH, and IMPACT prognostic models in severe traumatic brain injury in Japan. *PloS one* 2019; **14**(8): e0221791-e.
43. Roozenbeek B, Lingsma HF, Lecky FE, et al. Prediction of outcome after moderate and severe traumatic brain injury: external validation of the International Mission on Prognosis and Analysis of Clinical Trials (IMPACT) and Corticoid Randomisation After Significant Head injury (CRASH) prognostic models. *Critical care medicine* 2012; **40**(5): 1609-17.
44. Han J, King NK, Neilson SJ, Gandhi MP, Ng I. External validation of the CRASH and IMPACT prognostic models in severe traumatic brain injury. *J Neurotrauma* 2014; **31**(13): 1146-52.

45. Moskowitz J, Quinn T, Khan MW, et al. Should We Use the IMPACT-Model for the Outcome Prognostication of TBI Patients? A Qualitative Study Assessing Physicians' Perceptions. *MDM policy & practice* 2018; **3**(1): 2381468318757987.
46. Corrigan JD, Hammond FM. Traumatic brain injury as a chronic health condition. *Arch Phys Med Rehabil* 2013; **94**(6): 1199-201.
47. van Dijk J, Bartels R, Lavrijsen JCM, Ribbers GM, Kompanje EJO, Peul WC. The patient with severe traumatic brain injury: clinical decision-making: the first 60min and beyond. *Current opinion in critical care* 2019; **25**(6): 622-9.
48. Nelson CG, Elta T, Bannister J, Dzandu J, Mangram A, Zach V. Severe Traumatic Brain Injury: A Case Report. *Am J Case Rep* 2016; **17**: 186-91.
49. Boyer F, Audibert G, Baumann C, et al. [Decision-making regarding treatment limitation after severe traumatic brain injury: A survey of French neurosurgeons]. *Neuro-Chirurgie* 2018; **64**(6): 401-9.
50. Honeybul S, Ho KM, Gillett GR. Long-term outcome following decompressive craniectomy: an inconvenient truth? *Current opinion in critical care* 2018; **24**(2): 97-104.
51. Span-Sluyter C, Lavrijsen JCM, van Leeuwen E, Koopmans R. Moral dilemmas and conflicts concerning patients in a vegetative state/unresponsive wakefulness syndrome: shared or non-shared decision making? A qualitative study of the professional perspective in two moral case deliberations. *BMC medical ethics* 2018; **19**(1): 10.
52. Nichol AD, Higgins AM, Gabbe BJ, Murray LJ, Cooper DJ, Cameron PA. Measuring functional and quality of life outcomes following major head injury: common scales and checklists. *Injury* 2011; **42**(3): 281-7.
53. Honeybul S, Gillett GR, Ho KM, Lind CR. Neurotrauma and the rule of rescue. *Journal of medical ethics* 2011; **37**(12): 707-10.
54. McGowan T. Will You Forgive Me for Saving You? *The New England journal of medicine* 2018; **379**(1): 8-9.
55. . <https://www.theguardian.com/society/2017/jul/20/when-life-is-a-fate-worse-than-death-assisted-dying> (accessed November 4 2020).
56. Hillman K, Athari F, Forero R. States worse than death. *Current opinion in critical care* 2018; **24**(5): 415-20.
57. Rubin EB, Buehler AE, Halpern SD. States Worse Than Death Among Hospitalized Patients With Serious Illnesses. *JAMA internal medicine* 2016; **176**(10): 1557-9.
58. Graham M. A Fate Worse Than Death? The Well-Being of Patients Diagnosed as Vegetative With Covert Awareness. *Ethical Theory and Moral Practice* 2017; **20**(5): 1005-20.
59. Jennett B, Bond M. Assessment of outcome after severe brain damage. *Lancet (London, England)* 1975; **1**(7905): 480-4.
60. McMillan T, Wilson L, Ponsford J, Levin H, Teasdale G, Bond M. The Glasgow Outcome Scale — 40 years of application and refinement. *Nature Reviews Neurology* 2016; **12**(8): 477-85.
61. Wilson JT, Pettigrew LE, Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. *J Neurotrauma* 1998; **15**(8): 573-85.
62. Olivecrona M, Honeybul S. A study of the opinions of Swedish healthcare personnel regarding acceptable outcome following decompressive hemicraniectomy for ischaemic stroke. *Acta neurochirurgica* 2018; **160**(1): 95-101.
63. Coons SJ, Rao S, Keininger DL, Hays RD. A comparative review of generic quality-of-life instruments. *Pharmacoeconomics* 2000; **17**(1): 13-35.
64. von Steinbüchel N, Wilson L, Gibbons H, et al. Quality of Life after Brain Injury (QOLIBRI): scale development and metric properties. *J Neurotrauma* 2010; **27**(7): 1167-85.
65. von Steinbüchel N, Wilson L, Gibbons H, et al. Quality of Life after Brain Injury (QOLIBRI): scale validity and correlates of quality of life. *J Neurotrauma* 2010; **27**(7): 1157-65.
66. Wilson L, Marsden-Loftus I, Koskinen S, et al. Interpreting Quality of Life after Brain Injury Scores: Cross-Walk with the Short Form-36. *J Neurotrauma* 2017; **34**(1): 59-65.
67. Findler M, Cantor J, Haddad L, Gordon W, Ashman T. The reliability and validity of the SF-36 health survey questionnaire for use with individuals with traumatic brain injury. *Brain Inj* 2001; **15**(8): 715-23.
68. Chiu WT, Huang SJ, Hwang HF, et al. Use of the WHOQOL-BREF for evaluating persons with traumatic brain injury. *J Neurotrauma* 2006; **23**(11): 1609-20.
69. Turnbull AE, Chessare CM, Coffin RK, Needham DM. More than one in three proxies do not know their loved one's current code status: An observational study in a Maryland ICU. *PloS one* 2019; **14**(1): e0211531.

70. Fried TR, Zenoni M, Iannone L, O'Leary JR. Assessment of Surrogates' Knowledge of Patients' Treatment Goals and Confidence in Their Ability to Make Surrogate Treatment Decisions. *JAMA internal medicine* 2019; **179**(2): 267-8.
71. Waqas M, Malik N, Shamim MS, Nathani KR, Abbasi SA. Quality of Life Among Patients Undergoing Decompressive Craniectomy for Traumatic Brain Injury Using Glasgow Outcome Scale Extended and Quality of Life After Brain Injury Scale. *World neurosurgery* 2018; **116**: e783-e90.
72. Honeybul S. Long-term outcome following severe traumatic brain injury: ethical considerations. *Journal of neurosurgical sciences* 2018; **62**(5): 599-605.
73. Ubel PA, Loewenstein G, Schwarz N, Smith D. Misimagining the unimaginable: the disability paradox and health care decision making. *Health Psychol* 2005; **24**(4s): S57-62.
74. Rousseau M-C, Baumstarck K, Alessandrini M, Blandin V, Billette de Villemeur T, Auquier P. Quality of life in patients with locked-in syndrome: Evolution over a 6-year period. *Orphanet J Rare Dis* 2015; **10**: 88-.
75. Andrews JC, Wahl RA. Duchenne and Becker muscular dystrophy in adolescents: current perspectives. *Adolesc Health Med Ther* 2018; **9**: 53-63.
76. Honeybul S, Gillett GR, Ho KM, Janzen C, Kruger K. Is life worth living? Decompressive craniectomy and the disability paradox. 2016; **125**(3): 775.
77. Christakis N. Death foretold: Prophecy and prognosis in medical care. Chicago: Chicago press; 1999.
78. Leblanc G, Boutin A, Shemilt M, et al. Incidence and impact of withdrawal of life-sustaining therapies in clinical trials of severe traumatic brain injury: A systematic review. *Clinical trials (London, England)* 2018; **15**(4): 398-412.
79. Izzy S, Compton R, Carandang R, Hall W, Muehlschlegel S. Self-fulfilling prophecies through withdrawal of care: do they exist in traumatic brain injury, too? *Neurocritical care* 2013; **19**(3): 347-63.
80. Vedantam A, Robertson CS, Gopinath SP. Clinical characteristics and temporal profile of recovery in patients with favorable outcomes at 6 months after severe traumatic brain injury. *Journal of neurosurgery* 2018; **129**(1): 234-40.
81. Rubin ML, Yamal JM, Chan W, Robertson CS. Prognosis of 6-month Glasgow Outcome Scale in severe traumatic brain injury using hospital admission characteristics, injury severity characteristics, and physiological monitoring during the first day post-injury. *J Neurotrauma* 2019.
82. Harvey D, Butler J, Groves J, et al. Management of perceived devastating brain injury after hospital admission: a consensus statement from stakeholder professional organizations. *Br J Anaesth* 2018; **120**(1): 138-45.
83. Smith LGF, Milliron E, Ho M-L, et al. Advanced neuroimaging in traumatic brain injury: an overview. 2019; **47**(6): E17.
84. Jain S, Vyvere TV, Terzopoulos V, et al. Automatic Quantification of Computed Tomography Features in Acute Traumatic Brain Injury. *J Neurotrauma* 2019; **36**(11): 1794-803.
85. Yuh EL, Cooper SR, Ferguson AR, Manley CT. Quantitative CT improves outcome prediction in acute traumatic brain injury. *J Neurotrauma* 2012; **29**(5): 735-46.
86. Vande Vyvere T, De La Rosa E, Wilms G, et al. Prognostic Validation of the NINDS Common Data Elements for the Radiologic Reporting of Acute Traumatic Brain Injuries: A CENTER-TBI Study. *J Neurotrauma* 2020; **37**(11): 1269-82.
87. Grignoli N, Di Bernardo V, Malacrida R. New perspectives on substituted relational autonomy for shared decision-making in critical care. *Crit Care* 2018; **22**(1): 260.
88. Khan MW, Muehlschlegel S. Shared Decision Making in Neurocritical Care. *Neurosurgery clinics of North America* 2018; **29**(2): 315-21.
89. Robertsen A, Førde R, Skaga NO, Helseth E. Treatment-limiting decisions in patients with severe traumatic brain injury in a Norwegian regional trauma center. *Scandinavian journal of trauma, resuscitation and emergency medicine* 2017; **25**(1): 44.
90. Williamson T, Ryser MD, Ubel PA, et al. Withdrawal of Life-Supporting Treatment in Severe Traumatic Brain Injury. *JAMA Surg* 2020; **155**(8): 723-31.
91. Souter MJ, Blissitt PA, Blosser S, et al. Recommendations for the Critical Care Management of Devastating Brain Injury: Prognostication, Psychosocial, and Ethical Management : A Position Statement for Healthcare Professionals from the Neurocritical Care Society. *Neurocritical care* 2015; **23**(1): 4-13.
92. Jha RM, Kochanek PM, Simard JM. Pathophysiology and treatment of cerebral edema in traumatic brain injury. *Neuropharmacology* 2019; **145**(Pt B): 230-46.

93. Xue M, Yong VW. Neuroinflammation in intracerebral haemorrhage: immunotherapies with potential for translation. *The Lancet Neurology* 2020; **19**(12): 1023-32.
94. Cronberg T, Greer DM, Lilja G, Moolaert V, Swindell P, Rossetti AO. Brain injury after cardiac arrest: from prognostication of comatose patients to rehabilitation. *The Lancet Neurology* 2020; **19**(7): 611-22.
95. Turgeon AF, Lauzier F, Simard JF, et al. Mortality associated with withdrawal of life-sustaining therapy for patients with severe traumatic brain injury: a Canadian multicentre cohort study. *CMAJ* 2011; **183**(14): 1581-8.
96. Giacino JT, Katz DI, Schiff ND, et al. Practice guideline update recommendations summary: Disorders of consciousness: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology; the American Congress of Rehabilitation Medicine; and the National Institute on Disability, Independent Living, and Rehabilitation Research. *Neurology* 2018; **91**(10): 450-60.
97. Avesani R, Dambruoso F, Scandola M, et al. Epidemiological and clinical characteristics of 492 patients in a vegetative state in 29 Italian rehabilitation units. What about outcome? *Functional neurology* 2018; **33**(2): 97-103.
98. J.J. Fins. Rights come to mind: Cambridge University Press; 2015.
99. van Veen E, van der Jagt M, Cnossen MC, et al. Brain death and postmortem organ donation: report of a questionnaire from the CENTER-TBI study. *Crit Care* 2018; **22**(1): 306.
100. Lesieur O, Gentileuil L, Leloup M. A few realistic questions raised by organ retrieval in the intensive care unit. *Ann Transl Med* 2017; **5**(Suppl 4): S44.
101. Rohaut B, Eliseyev A, Claassen J. Uncovering Consciousness in Unresponsive ICU Patients: Technical, Medical and Ethical Considerations. *Crit Care* 2019; **23**(1): 78.
102. Bruno MA, Majerus S, Boly M, et al. Functional neuroanatomy underlying the clinical subcategorization of minimally conscious state patients. *J Neurol* 2012; **259**(6): 1087-98.
103. Papanicolas I, Woskie LR, Jha AK. Health Care Spending in the United States and Other High-Income Countries. *JAMA* 2018; **319**(10): 1024-39.
104. Stocchetti N, Carbonara M, Citerio G, et al. Severe traumatic brain injury: targeted management in the intensive care unit. *The Lancet Neurology* 2017; **16**(6): 452-64.
105. Czech H, Druml C, Weindling P. Medical Ethics in the 70 Years after the Nuremberg Code, 1947 to the Present. *Wiener klinische Wochenschrift* 2018; **130**(3): 159-253.
106. Parsa-Parsi RW. The Revised Declaration of Geneva: A Modern-Day Physician's Pledge. *JAMA* 2017; **318**(20): 1971-2.
107. Beauchamp TC CJ. Principles of biomedical ethics. 7th ed. New York: Oxford University Press; 2013.
108. Porter ME, Lee TH. The Strategy That Will Fix Health Care. *Harvard Business Review* 2013; **October 2013 Issue**
109. MacKillop E, Sheard S. Quantifying life: Understanding the history of Quality-Adjusted Life-Years (QALYs). *Soc Sci Med* 2018; **211**: 359-66.
110. Kompanje EJ, Piers RD, Benoit DD. Causes and consequences of disproportionate care in intensive care medicine. *Curr Opin Crit Care* 2013; **19**(6): 630-5.
111. van Dijk J, Dijkman MD, Ophuis RH, de Ruiter GCW, Peul WC, Polinder S. In-hospital costs after severe traumatic brain injury: A systematic review and quality assessment. *PloS one* 2019; **14**(5): e0216743.
112. Whitmore RG, Thawani JP, Grady MS, Levine JM, Sanborn MR, Stein SC. Is aggressive treatment of traumatic brain injury cost-effective? *Journal of neurosurgery* 2012; **116**(5): 1106-13.
113. Ho KM, Honeybul S, Lind CR, Gillett GR, Litton E. Cost-effectiveness of decompressive craniectomy as a lifesaving rescue procedure for patients with severe traumatic brain injury. *J Trauma* 2011; **71**(6): 1637-44; discussion 44.
114. Malmivaara K, Kivisaari R, Hernesniemi J, Siironen J. Cost-effectiveness of decompressive craniectomy in traumatic brain injuries. *European Journal of Neurology* 2011; **18**(4): 656-62.
115. Alali A, Burton K, Fowler R, et al. Economic evaluations in the diagnosis and management of traumatic brain injury: a systematic review and analysis of quality. *Value Health* 2015; **18**(5): 721-34.
116. Knott R.J. HA, Higgins A., Nichol A., French C., Little L., Haddad S., Presneill J. Cost-Effectiveness of Erythropoietin in Traumatic Brain Injury: A Multinational Trial-Based Economic Analysis. *Journal of Neurotrauma* 2019; **36**(17): 2541-8.
117. Buisman LR, Tan SS, Nederkoorn PJ, Koudstaal PJ, Redekop WK. Hospital costs of ischemic stroke and TIA in the Netherlands. *Neurology* 2015; **84**(22): 2208-15.

118. Govaert JA, van Dijk WA, Fiocco M, et al. Nationwide Outcomes Measurement in Colorectal Cancer Surgery: Improving Quality and Reducing Costs. *J Am Coll Surg* 2016; **222**(1): 19-29.e2.
119. Maas AI, Menon DK, Steyerberg EW, et al. Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): a prospective longitudinal observational study. *Neurosurgery* 2015; **76**(1): 67-80.
120. van der Linden N, Bongers ML, Coupe VM, et al. Costs of non-small cell lung cancer in the Netherlands. *Lung Cancer* 2016; **91**: 79-88.
121. Franken MG, Leeneman B, Jochems A, et al. Real-world healthcare costs of ipilimumab in patients with advanced cutaneous melanoma in The Netherlands. *Anti-cancer drugs* 2018; **29**(6): 579-88.
122. Oude Lansink-Hartgring A, van den Hengel B, van der Bij W, et al. Hospital Costs Of Extracorporeal Life Support Therapy. *Critical care medicine* 2016; **44**(4): 717-23.
123. Nederland Zorgautoriteit. Ziekte last in de praktijk - de theorie en de praktijk van het berekenen van ziekte last bij pakketbeoordelingen. 2018. https://www.zorginstituutnederland.nl/binaries/zinl/documenten/rapport/2018/05/07/ziekte last-in-de-praktijk/Ziekte last+in+de+praktijk_definitief.pdf.
124. Kochanek PM, Jackson TC, Jha RM, et al. Paths to Successful Translation of New Therapies for Severe Traumatic Brain Injury in the Golden Age of Traumatic Brain Injury Research: A Pittsburgh Vision. *Journal of neurotrauma* 2019.
125. Wang KK, Yang Z, Zhu T, et al. An update on diagnostic and prognostic biomarkers for traumatic brain injury. *Expert review of molecular diagnostics* 2018; **18**(2): 165-80.
126. Vrselja Z, Daniele SG, Silbereis J, et al. Restoration of brain circulation and cellular functions hours post-mortem. *Nature* 2019; **568**(7752): 336-43.
127. O'Leary RA, Nichol AD. Pathophysiology of severe traumatic brain injury. *Journal of neurosurgical sciences* 2018; **62**(5): 542-8.
128. Hylin MJ, Kerr AL, Holden R. Understanding the Mechanisms of Recovery and/or Compensation following Injury. *Neural Plast* 2017; **2017**: 7125057.
129. Piradov MA, Chernikova LA, Suponeva NA. Brain Plasticity and Modern Neurorehabilitation Technologies. *Herald of the Russian Academy of Sciences* 2018; **88**(2): 111-8.
130. Kaur P, Sharma S. Recent Advances in Pathophysiology of Traumatic Brain Injury. *Current neuropharmacology* 2018; **16**(8): 1224-38.
131. Rau CS, Kuo PJ, Chien PC, Huang CY, Hsieh HY, Hsieh CH. Mortality prediction in patients with isolated moderate and severe traumatic brain injury using machine learning models. *PLoS One* 2018; **13**(11): e0207192.
132. Hale AT, Stonko DP, Brown A, et al. Machine-learning analysis outperforms conventional statistical models and CT classification systems in predicting 6-month outcomes in pediatric patients sustaining traumatic brain injury. *Neurosurgical focus* 2018; **45**(5): E2.
133. Bragge P, Synnot A, Maas AI, et al. A State-of-the-Science Overview of Randomized Controlled Trials Evaluating Acute Management of Moderate-to-Severe Traumatic Brain Injury. *J Neurotrauma* 2016; **33**(16): 1461-78.
134. Kompanje EJO, van Dijck J, Chalos V, et al. Informed consent procedures for emergency interventional research in patients with traumatic brain injury and ischaemic stroke. *The Lancet Neurology* 2020; **19**(12): 1033-42.
135. Van Essen TA, Volovici V, Cnossen MC, et al. Comparative effectiveness of surgery in traumatic acute subdural and intracerebral haematoma: study protocol for a prospective observational study within CENTER-TBI and Net-QuRe. *BMJ Open* 2019; **9**(10): e033513.
136. Investigators T-T. Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI). ClinicalTrials.gov Identifier: NCT02119182. 2014. <https://clinicaltrials.gov/ct2/show/study/NCT02119182>.
137. Cnossen M. Outcome and comparative effectiveness research in traumatic brain injury : a methodological perspective [Ph.D. thesis]: Erasmus University Rotterdam; 2017.
138. Meeuws S, Yue JK, Huijben JA, et al. Common Data Elements: Critical Assessment of Harmonization between Current Multi-Center Traumatic Brain Injury Studies. *J Neurotrauma* 2020; **37**(11): 1283-90.



APPENDICES

LIST OF PUBLICATIONS

J.T.J.M. van Dijck, E.J.O. Kompanje, P.J. Nederkoorn, W.C. Peul, D.W.J. Dippel. Advanced consent for acute stroke trials. *The Lancet Neurology* 2021 Mar; 20(3):170-171. DOI: 10.1016/S1474-4422(21)00028-4

E.J.O. Kompanje¹, J.T.J.M. van Dijck¹, V. Chalos, S.A. van den Berg, P.M. Janssen, P.J. Nederkoorn, M. van der Jagt, G. Citerio, N. Stocchetti, D.W.J. Dippel, W.C. Peul. Informed consent procedures for emergency research in patients with traumatic brain injury and ischaemic stroke. *The Lancet Neurology* 2020. DOI: 10.1016/S1474-4422(20)30276-3

J.T.J.M. van Dijck, C.Q.B. Mostert, A.P.A. Greeven, W.C. Peul, G.C.W. de Ruiter, S. Polinder. Patient outcome, healthcare consumption and in-hospital treatment costs after traumatic brain injury; a Dutch prospective multicenter study. *Acta Neurochirurgica* 2020. DOI:10.1007/s00701-020-04384-9

R.P.J. van Wijk¹, J.T.J.M. van Dijck¹, M. Timmers, E. van Veen, G. Citerio, H.F. Lingsma, A.I.R. Maas, D.K. Menon, W.C. Peul, N. Stocchetti, E.J.O. Kompanje, The CENTER-TBI investigators and participants. Informed consent procedures in patients with an acute inability to provide informed consent: policy and practice in the CENTER-TBI study. *Journal of Critical Care* 2020. DOI: 10.1016/j.jcrc.2020.05.004.

M. Timmers¹, J.T.J.M. van Dijck¹, R.J. van Wijk, V. Legrand, E. van Veen, A.I.R. Maas, D.K. Menon, G. Citerio, N. Stocchetti, E.J.O. Kompanje, The CENTER-TBI investigators and participants. How do 66 European Institutional Review Boards approve one protocol for an international Prospective Observational study on traumatic brain injury? Experiences from the CENTER-TBI study. *BMC Medical Ethics* 2020. DOI: 10.1186/s12910-020-00480-8

J.A.N. van Gent, T.A. van Essen, M.H.A. Bos, S.C. Cannegieter, J.T.J.M. van Dijck, W.C. Peul. Coagulopathy after hemorrhagic traumatic brain injury, an observational study of the incidence and prognosis. *Acta Neurochirurgica* 2019. DOI: 10.1007/s200701-019-04111-Z

J.T.J.M. van Dijck, R.H.M.A. Bartels, J.C.M. Lavrijsen, G.M. Ribbers, E.J.O. Kompanje, W.C. Peul. The patient with severe traumatic brain injury – Clinical decision-making. *Current Opinion in Critical Care* 2019. DOI: 10.1097/MCC.0000000000000671

J.T.J.M. van Dijck, M.D. Dijkman, R.H. Ophuis, G.C.W. de Ruiter, W.C. Peul, S. Polinder. In-hospital costs after severe traumatic brain injury: A systematic review and quality assessment. *PLoS One* 2019. DOI: 10.1371/journal.pone.0216743.

J.T.J.M. van Dijck, M.D. Dijkman, R.H. Ophuis, G.C.W. de Ruiter, W.C. Peul, S. Polinder. Correction: In-hospital costs after severe traumatic brain injury: A systematic review and quality assessment. *PLoS One* 2019. DOI: 10.1371/journal.pone.0219529.

J.T.J.M. van Dijck, T.A. van Essen, M.D. Dijkman, C.Q.B. Mostert, S. Polinder, W.C. Peul, G.C.W. de Ruiter. Functional and patient-reported outcome versus in-hospital costs after traumatic acute subdural hematoma (t-ASDH): a neurosurgical paradox? *Acta Neurochirurgica* 2019. DOI: 10.1007/s00701-019-03878-5.

E. van Veen, M. van der Jagt, M.C. Cnossen, A.I.R. Maas, I.D. de Beaufort, D.K. Menon, G. Citerio, N. Stocchetti, W.J.R. Rietdijk, J.T.J.M. van Dijck, E.J.O. Kompanje, CENTER-TBI investigators and participants. Brain death and post-mortem organ donation: report of a questionnaire from the CENTER-TBI study. *Critical Care* 2018. doi: 10.1186/s13054-018-2241-4

J.T.J.M. van Dijck, F.C. Reith, I.A. van Erp, T.A. van Essen, A.I.R. Maas, W.C. Peul, G.C.W. de Ruiter. Decision-making in very severe traumatic brain injury (Glasgow Coma Scale 3-5): a literature review of acute neurosurgical managements. *Journal Neurosurgical Sciences* 2018. DOI: 10.23736/S0390-5616.17.04255-2.

H.A. Leijdesdorff, J.T.J.M. van Dijck, P. Krijnen, I.B. Schipper. Ongevallen met een scootmobiel. Een groeiend probleem. *Nederlands Tijdschrift voor Geneeskunde* 2014.

H.A. Leijdesdorff, J.T.J.M. van Dijck, P. Krijnen, C.L.A.M. Vleggeert-Lankamp, I.B. Schipper. Injury Pattern, Hospital Triage, and Mortality of 1250 Patients with Severe Traumatic Brain Injury Caused by Road Traffic Accidents. *Journal of Neurotrauma* 2014. DOI: 10.1089/neu.2013.3111.

DANKWOORD

Het proces dat heeft geleid tot dit proefschrift was niet mogelijk geweest zonder de hulp van vele anderen. Ik ben iedereen die hieraan heeft bijgedragen dankbaar en kijk met veel plezier terug op alle samenwerkingen.

Prof. dr. W.C. Peul, hooggeleerde promotor, beste Wilco. Ik ben je heel dankbaar voor de kans om als arts en onderzoeker bij je aan de slag te gaan. Onze inhoudelijke gesprekken, maar vooral je bevologenheid, scherpheid en optimisme hebben me enorm gemotiveerd. Bedankt voor de uitstekende begeleiding en samenwerking.

Dr. E.J.O. Kompanje, weledelzeergeleerde copromotor, beste Erwin. Van je filosofische kijk op de materie heb ik veel geleerd. De manier waarop je ingewikkelde problematiek aan de koffietafel in Barendrecht heel concreet wist te maken zal ik niet snel vergeten. Bedankt voor alles!

Dr. S. Polinder, weledelzeergeleerde copromotor, beste Suzanne. Veel dank voor al je hulp bij dit proefschrift. Zonder jouw expertise en snelle feedback was dit nooit gelukt. Door je enthousiasme en positiviteit kreeg ik altijd weer goede moed. Ik kijk met veel plezier terug op onze samenwerking.

Dr. G.C.W. de Ruiter, beste Godard. Via jou ben ik bij de neurochirurgie terecht gekomen en met dit onderzoek gestart. Ik heb veel geleerd van je scherpe commentaren en hoop ooit je tekstuele superioriteit te benaderen. Hartelijk dank voor de uitstekende begeleiding.

Beste Thomas, Daniel, Ranjit, Mark, Inge, Cassidy, Roel, Lianne, Majanka, Gerard, Renée, Yvon, Veronique, Mirjam, Marjon, Eline, Joyce, Lidwien, Michelle, Jolanda, Jan, Alexander, CENTER-TBI en Net-Qure onderzoekers, UCOMPS, mede-auteurs, focusgroep deelnemers, en alle UNCH collega's. Veel dank voor de goede, leuke en productieve samenwerking van de afgelopen jaren. Ik hoop dat we nog een mooie tijd tegemoet gaan.

Vrienden en familie. Het maakt me blij dat er zoveel mooie mensen in mijn leven zijn die het mogelijk maken er optimaal van te kunnen genieten. Dank voor de vele mooie momenten!

Lieve pap, mam, Willemijn, en Sjoerd. Dank voor jullie steun en relativerende commentaar. De perfecte basis van liefde en onvoorwaardelijke steun geeft je als zoon en broer de vrijheid en mogelijkheid om te doen wat je graag doet. Jullie zijn mijn grootste voorbeelden.

Lieve Maren. Ik kan me niemand anders aan mijn zijde voorstellen en ben zeer dankbaar voor alles in ons leven. Ik ben erg trots op alles wat je doet en kijk uit naar onze toekomst!

CURRICULUM VITAE

Jeroen T.J.M. van Dijck was born on April 28th 1990 in Tilburg, The Netherlands. After moving to Mierlo and finishing his secondary school (VWO, Strabrecht College, Geldrop) in 2008, he attended medical school at Leiden University Medical Center (LUMC). He obtained his medical degree in 2015 and worked as a general surgery resident not in training (ANIOS) at the Haga Teaching Hospital in The Hague. The first preparations for this thesis were made during this period. From the end of 2016 until the end of 2018 he worked as a PhD student and resident not in training (ANIOS) at the neurosurgery department of the LUMC. Afterwards, he started at the Haaglanden Medical Center (HMC) as a neurosurgical resident not in training (ANIOS). As of January 2020, he is a neurosurgical resident in training (AIOS) at the University Neurosurgical Center Holland in LUMC, HMC & Haga Teaching Hospital, Leiden/The Hague under supervision of prof. dr. W.C. Peul.

DECISION-MAKING IN SEVERE TRAUMATIC BRAIN INJURY

PATIENT OUTCOME, HOSPITAL COSTS, AND RESEARCH PRACTICE

door Jeroen Theodorus Josephus Maria van Dijk

1. Patients with severe TBI and very severe TBI, often considered unsalvageable, are able to achieve favourable outcome. (*this thesis*)
2. The in-hospital costs of patients with TBI are relatively high, but seem to be acceptable. (*this thesis*)
3. Patients with severe TBI should not prematurely be considered unsalvageable, and adequate (surgical) treatment should not be withheld in the acute phase. (*this thesis*)
4. The use of informed consent alternatives has the potential to improve efficiency and quality of future emergency interventional studies in patients with TBI with an inability to provide informed consent. (*this thesis*)
5. Science may provide the most useful way to organize empirical, reproducible data, but its power to do so is predicated on its inability to grasp the most central aspects of human life after severe TBI: hope, fear, love, hate, beauty, envy, honor, weakness, striving, suffering, virtue. (*based on Paul Kalanithi. When Breath Becomes Air. 2016*)
6. If we have our own why in life after severe TBI, we shall get along with almost any how. (*based on Friedrich Nietzsche. Die Götzen-Dämmerung – Twilight of the Idols. 1895*)
7. The essence of treating patients with severe TBI is choosing what not to do. (*based on Michael Porter. What is strategy? 1996*)
8. But I have seen a severely wounded brain healed. (*Claudius Galenus. Galen's refutation. AD 129-200*)
9. Er moet door dokters meer gelezen en minder geschreven worden. (*gebaseerd op Andreas Kinneging. De onzichtbare Maat. 2020*).
10. Promoveren is als wielrennen; soms bergaf met wind in de rug, maar meestal klimmen met wind op kop.



THE AGA KHAN UNIVERSITY

eCommons@AKU

Section of Neurosurgery

Department of Surgery

July 2011

Management of penetrating brain injury.

Syed Faraz Kazim
Aga Khan University

Muhammad Shahzad Shamim
Aga Khan University

Muhammad Zubair Tahir
Aga Khan University

S. Ather Enam
Aga Khan University

Shahan Waheed
Aga Khan University

Follow this and additional works at: https://ecommons.aku.edu/pakistan_fhs_mc_surg_neurosurg



Part of the [Neurology Commons](#), and the [Surgery Commons](#)

Recommended Citation

Kazim, S., Shamim, M., Tahir, M., Enam, S., Waheed, S. (2011). Management of penetrating brain injury.. *Journal of Emergencies, Trauma, and Shock*, 4(3), 395-402.

Available at: https://ecommons.aku.edu/pakistan_fhs_mc_surg_neurosurg/26



[J Emerg Trauma Shock](#). 2011 Jul-Sep; 4(3): 395–402.

PMCID: PMC3162712

doi: [10.4103/0974-2700.83871](https://doi.org/10.4103/0974-2700.83871)

Management of penetrating brain injury

[Syed Faraz Kazim](#), [Muhammad Shahzad Shamim](#), [Muhammad Zubair Tahir](#), [Syed Ather Enam](#), and [Shahan Waheed](#)

Section of Neurosurgery, Department of Surgery, Aga Khan University Hospital, Karachi, Pakistan

Address for correspondence: Dr. Syed Ather Enam, E-mail: ather.enam@aku.edu

Received 2010 Aug 13; Accepted 2010 Oct 10.

[Copyright](#) : © Journal of Emergencies, Trauma, and Shock

This is an open-access article distributed under the terms of the Creative Commons Attribution-Noncommercial-Share Alike 3.0 Unported, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

This article has been [cited by](#) other articles in PMC.

Abstract

[Go to:](#)

Penetrating brain injury (PBI), though less prevalent than closed head trauma, carries a worse prognosis. The publication of *Guidelines for the Management of Penetrating Brain Injury* in 2001, attempted to standardize the management of PBI. This paper provides a precise and updated account of the medical and surgical management of these unique injuries which still present a significant challenge to practicing neurosurgeons worldwide. The management algorithms presented in this document are based on *Guidelines for the Management of Penetrating Brain Injury* and the recommendations are from literature published after 2001. Optimum management of PBI requires adequate comprehension of mechanism and pathophysiology of injury. Based on current evidence, we recommend computed tomography scanning as the neuroradiologic modality of choice for PBI patients. Cerebral angiography is recommended in patients with PBI, where there is a high suspicion of vascular injury. It is still debatable whether craniectomy or craniotomy is the best approach in PBI patients. The recent trend is toward a less aggressive debridement of deep-seated bone and missile fragments and a more aggressive antibiotic prophylaxis in an effort to improve outcomes. Cerebrospinal fluid (CSF) leaks are common in PBI patients and surgical correction is recommended for those which do not close spontaneously or are refractory to CSF diversion through a ventricular or lumbar drain. The risk of post-traumatic epilepsy after PBI is high, and therefore, the use of prophylactic anticonvulsants is recommended. Advanced age, suicide attempts, associated coagulopathy,

Glasgow coma scale score of 3 with bilaterally fixed and dilated pupils, and high initial intracranial pressure have been correlated with worse outcomes in PBI patients.

Keywords: Medical management, penetrating brain injury, surgical management

INTRODUCTION

[Go to:](#)

Penetrating brain injury (PBI) includes all traumatic brain injuries which are not the result of a blunt mechanism.[1] Although less prevalent than closed head trauma, PBI carries a worse prognosis.[2] In civilian populations, PBIs are mostly caused by high velocity objects, which result in more complex injuries and high mortality.[3] PBI caused by non-missile, low-velocity objects represents a rare pathology among civilians, with better outcome because of more localized primary injury,[2,4] and is usually caused by violence, accidents, or even suicide attempts.[3–11]

Despite the efforts of law enforcement agencies, these injuries unfortunately continue to be frequently encountered in large trauma centers as well as in metropolitan and large community emergency departments.[1] The formulation of standard medical and surgical management algorithm for PBI patients is essential. In 1995, the American Association of Neurological Surgeons and the Brain Trauma Foundation collaborated to formulate evidence-based *Guidelines for the Management of Severe Head Injury*[12] which were periodically revised and last updated as third edition in 2007.[13] However, they did not address the management of patients injured by penetrating objects such as gun shots and stab wounds. In the spring of 1998, the International Brain Injury Association, the Brain Injury Association, USA, the American Association of Neurological Surgeons, and the Congress of Neurological Surgeons began work on this task. Thus, *Guidelines for the Management of Penetrating Brain Injury*[14] was published in 2001, which attempted to standardize both the medical and surgical management of penetrating craniocerebral trauma. These guidelines were based on available literature at that time and have not been revised for almost a decade.

In this paper, we have reviewed the contemporary management guidelines of PBI. For this purpose, the current literature on various parameters related to PBI available on PubMed and MEDLINE was reviewed. The *Guidelines for the Management of Penetrating Brain Injury* was thoroughly evaluated and compared with literature published after 2001. The objective of this document is to provide a precise and updated account of the medical and surgical management of these unique injuries which still present a significant challenge to practicing neurosurgeons worldwide.

BALLISTIC PRINCIPLES AND PATHOPHYSIOLOGY OF PBI

[Go to:](#)

Optimum management of PBI requires a good understanding of the mechanism of injury and its pathophysiology. As most of the PBIs are caused by missiles or projectiles, an understanding of ballistics is imperative. Ballistics is the study of the dynamics of projectiles; wound ballistics is the study of the projectile's action in tissue.[14]

The ability of bullets, shrapnel, and low-velocity objects such as knives and arrows to penetrate the brain is dependent on their energy, shape, the angle of approach, and the characteristics of intervening tissues (skull, muscle, mucosa, etc.).[1,14] Primary

injury to the brain is determined by the ballistic properties (kinetic energy, mass, velocity, shape, etc.) of the projectile and any secondary projectiles, such as bone or metallic fragments.[14] The kinetic energy is defined by the relationship: $E = 1/2mv^2$, which implies that the velocity of the projectile has a greater influence than the mass of the projectile alone.[1]

As the projectile travels through the brain parenchyma, it is preceded by a transient sonic wave (2 μ s) which appears to have minimal influence on surrounding tissue.[15,16] The projectile itself, however, crushes the soft brain tissue in its path, creating a permanent track of injury. This is in addition to the secondary missiles such as bone and metal fragments created from the impact of projectile on the skull. Higher velocity projectiles will also impart an additional temporary cavitation effect in their wake, which is a velocity-related phenomenon. This results from the transmission of the kinetic energy of the projectile to the surrounding tissue, thus rapidly compressing it tangentially from the primary track. This temporary cavity then collapses upon itself only to re-expand in progressively smaller undulating wave-like patterns. Every cycle of temporary expansion and collapse creates significant surrounding tissue injury to the brain. This can result in shear-like injury of the neurons or can result in epidural hematomas, subdural hematomas, or parenchymal contusions.[17]

An important principle to understand is the influence of air-resistance on the ballistics of a missile. A projectile loses its kinetic energy rapidly as it travels through the air because of its resistance.[17] This loss of kinetic energy is related to the decrement in its velocity which in turn is dependent on the shape of the projectile. The sharper the nose of a bullet, the less the velocity will be decreased by air resistance. The rounder the nose of a bullet or more irregular the shape (as in shrapnel), the quicker the velocity slows and kinetic energy decreases. Projectiles traveling at higher velocities carry more kinetic energy, and thus cause more damage.[1] Additionally, a PBI is expected to be much more severe in case of a close range firearm injury as maximum amount of initial kinetic energy is transferred to the brain tissue.

EMERGENCY MANAGEMENT OF PBI

[Go to:](#)

Immediately after arrival of the patient in the emergency department, a primary survey and stabilization of the patient with regard to the airway, breathing, cervical spine, and circulation including external hemorrhage should be achieved.[18] After resuscitation, an inspection of the superficial wound should be done. The skin, especially the scalp, must be examined meticulously for wounds as it may be covered by blood-matted hair.[18] An entrance wound should be identified and its location recorded as well as any exit wounds when they exist. The superficial scalp should also be observed for powder burns, which would imply a close range firearm injury.[1] Any CSF, bleeding, or brain parenchyma oozing from the wound should be noted; the size of the deficit should also be documented.[1] To examine the head and neck thoroughly, the cervical collar should be removed, but strict spine precautions must be employed. Hemotympanum suggests a skull base fracture. All orifices must be checked for retention of foreign bodies, the missile, teeth, and bone.[18,19] After careful examination of the wound, a detailed neurological examination should be performed, and the post-resuscitative glasgow coma scale (GCS) of the patients should be documented.[1] Clinical features suggestive of raised intracranial pressure (ICP) must be documented carefully. Neurological examination, which should be followed by a complete examination of other organ systems, is recommended as PBI patients may have multiple organ injuries.

[18] A detailed medical history from family or friends and a chronology of the incidence from a witness is warranted. Initial laboratory evaluation must include an arterial blood gas, electrolytes, complete blood count, coagulation profile, type and cross match, and an alcohol and drug screen.[19] Once the initial evaluation is done, the patient should be transferred to radiology for a neuroimaging study as described in the following sections.

NEUROIMAGING IN THE MANAGEMENT OF PBI

[Go to:](#)

The utility of various neuroimaging methods used in patients with PBI lies on the potential management and prognostic implications of these modalities.[20,21] Important findings include: entry and exit sites; intracranial fragments; missile track and its relationship to both blood vessels and air-containing skull-base structures; intracranial air; transventricular injury; basal ganglia and brain stem injury; missile track crossing the midline; multi-lobar injury; basal cisterns effacement; brain parenchymal herniation and associated mass effect.[20,21] Neuroimaging is vital for surgical decision making, the type of surgery, the size and site of craniotomy, the route for extraction of foreign body, etc. as well as the decision to choose non-surgical management, which is also not uncommon in PBI.

Plain films

Plain radiographs of the skull can be of considerable value in identifying the cranial wound(s), the location of missile and bone fragments, and the presence of intracranial air [Figure 1].[20] However, evaluating the projectile trajectory with plain radiographs alone can be misleading in the presence of intracranial ricocheting or fragmentation.[20] Besides, the availability of computed tomography (CT) scanning largely precludes the use of plain radiography, and it is not routinely recommended.



[Figure 1](#)

The skull X - ray (antero - posterior view) is of a neurologically intact, young male patient who presented after a bomb exploded near a political rally. The patient was asymptomatic except for a small puncture wound on scalp, causing minimal bleeding. ...

COMPUTED TOMOGRAPHY

[Go to:](#)

Computed tomography (CT) scanning of the head is now the primary modality used in the neuroradiologic evaluation of patients with PBI.[20] This is because CT scanning is quick and provides improved identification of in-driven bone and missile fragments, characterization of the missile trajectory, evaluation of the extent of brain injury, and detection of intracranial hematomas and mass effects [Figure 2].[20,22–26] All patients with craniocerebral gunshot injury should be imaged emergently with unenhanced

CT regardless of whether or not there is evidence of penetration on clinical examination.[21] In addition to the standard axial views with bone and soft tissue windows, coronal and sagittal sections are also helpful for patients with skull base involvement or high convexity injuries.[20] Postoperatively, CT scan can be helpful in evaluating the development of intracranial hematomas, the presence of residual foreign body, and the extent of cerebral edema.[20,25,26]



[Figure 2](#)

The computed tomography (CT) scan of brain showing left frontal penetrating injury causing multiple fractures and pneumocranium. Multiple bone fragments are displaced within brain parenchyma resulting in contusion and edema. This male patient, a blast ...

MAGNETIC RESONANCE IMAGING

[Go to:](#)

Magnetic resonance imaging (MRI) is generally not recommended for use in the acute management of PBI, as it is time consuming and can be potentially dangerous when there are retained ferromagnetic objects because of possible movement of the object in response to the magnetic torque.[1,3] However, MRI can be a useful neuroradiologic modality, if the PBI is caused by a wooden object.[20,27]

CEREBRAL ANGIOGRAPHY

[Go to:](#)

Cerebral angiography (either CT or catheter) is recommended in patients with PBI where there is an increased risk of vascular injury. This would include those cases where the wound's trajectory is through or near the Sylvian fissure (location of M1 and M2 segments of the middle cerebral artery), the supraclinoid carotid artery, the vertebrobasilar vessels, the cavernous sinus region or the major dural venous sinuses.[20,21] Peripheral branches of the middle cerebral artery followed by the anterior cerebral artery are more vulnerable in craniocerebral penetrating injury than the internal carotid artery.[21,28] The development of otherwise unexplained subarachnoid hemorrhage (SAH) or delayed hematoma could also suggest the presence of a vascular injury, and thus warrant angiography.[20,29]

INTRACRANIAL PRESSURE MONITORING

[Go to:](#)

The concept and management of Intracranial pressure (ICP) is based on Monro–Kellie doctrine.[30] According to this doctrine, since the total skull volume is a constant entity, ICP is dependent on the volume of cranial contents. Under physiological conditions, these contents are brain tissue, cerebrospinal fluid (CSF), and vasculature (blood volume).[31] Even small increments in volume can lead to larger increases in ICP because of the rigidity of the skull. Following trauma, there may be mass lesions that need to be incorporated into this equation. Brain volume may increase because of edema (predominantly cytotoxic after trauma).[31] Vascular volume can increase if venous outflow is blocked or if there is an increased cerebral blood flow (CBF) because of

seizures, pyrexia, or loss of autoregulation.[31] CSF volume may increase because of blockade of outflow tracts or hindrance with reabsorption.[31]

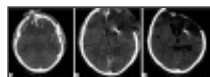
ICP monitoring has been well documented to be an important predictor of prognosis in severe *nonpenetrating* traumatic brain injury (TBI) as intracranial hypertension (ICH) is clearly associated with worse recovery and optimum control of elevated ICP leads to a better outcome.[12,13] However, very little clinical data are available on the indications and applications of ICP monitoring in PBI patients.[1] The only published studies on the role of ICP monitoring in PBI are from military settings, and there is a lack of literature from centers attending civilian PBI patients. Nonetheless, the available data suggest a higher frequency of raised ICP in PBI patients,[1,25,32–34] and when present, raised ICP is documented to be a predictor of worse prognosis.[26,35] Nagib *et al.* reported in their series of 13 patients with PBI that outcome was superior in those who never manifested ICH.[26] Crockard recorded ICP in 20 patients very early after PBI and found a very high mortality associated with elevated ICP, and a much better outcome in those in whom ICH never manifested.[32]

Unfortunately, in comparison with the *Guidelines for the Management of Traumatic Brain Injury*, there is little clinical evidence to evaluate the beneficial effect of management of ICP on outcomes of patients with PBI.[1,36] However, because of this short coming, general guidelines for ICP management in nonpenetrating TBI have been applied to PBI patients as well. In cases, where ICP is monitored and ICH is present, treatment measures are the same, which are used in nonpenetrating TBI, i.e. hyperventilation, mannitol, CSF drainage, high-dose barbiturates, and more recently, decompressive craniectomy.[1,36]

SURGICAL MANAGEMENT OF PBI

[Go to:](#)

Treatment of small entrance bullet wounds to the head with local wound care and closure in patients whose scalp is not devitalized and have no significant intracranial pathologic findings is recommended in the *Guidelines for the Management of Penetrating Brain Injury*. [37] More extensive wounds with nonviable scalp, bone, or dura should be debrided more extensively before primary closure or grafting to secure a watertight wound [Figure 3a – c]. [37] When there is significant mass effect, necrotic brain tissue should be debrided and safely accessible bone fragments should be removed.[38] Intracranial hematomas with significant mass effect should be evacuated. Routine surgical removal of bone or missile fragments lodged distant from the entry site especially in the eloquent areas of the brain is not recommended. Although removal of these foreign bodies from eloquent cortex may decrease the risk of posttraumatic epilepsy,[39] it has been documented to correlate with worse outcomes and higher morbidity,[1,23,37,40] A conservative approach toward cerebral debridement in general has, thus, been recommended.



[Figure 3](#)

(a) Axial computed tomography (CT) scan of the brain showing compound expansile skull fracture with multiple bone fragments along the trajectory and global cerebral edema. Basal cisterns are totally effaced. This 35 - year old patient came to us within ...

Surgical treatment should be performed within 12 h of the injury to decrease the risk of infectious complications.[24,38] Surgical incision should be done in such a fashion so as to incorporate (if possible) the area that needs debridement and vascular supply of the flap. When the trajectory of the missile violates an open air sinus, a water tight closure of the dura should be done as the literature suggests that it may decrease the risk of abscess formation and CSF fistulas.[1,37,41,42]

It is still debatable that which technique, craniotomy, or craniectomy, is best to achieve the most optimal results. No statistically significant advantage of one technique over the other has been described in reports of morbidity and mortality rates associated with the two procedures.[3,43] A recent large study of military patients suffering from severe PBI reported optimum outcomes with early decompressive craniectomy.[44] In military settings, there has been a recent paradigm shift toward an aggressive approach comprising of rapid, far forward cranial decompression with water-tight dural closure followed by rapid evacuation to a major trauma center. This approach, accompanied by subsequent aggressive critical care, has led to better outcomes in wartime PBI patients.[44] However, the wartime injuries differ considerably from the civilian PBI, and the application of military data to civilian population must be done cautiously.

VASCULAR COMPLICATIONS OF PBI

[Go to:](#)

Vascular complications after PBI range from under 5%–40% in various reports.[3,45,46] Features associated with a higher risk of vascular injuries development in missile wounds include orbitofacial or pterional PBI, presence of intracranial hematoma and injuries with fragments crossing two or more dural compartments.[3,7,20,47] All such missile injuries in which large vessel damage is suspected should be explored with cerebral angiography. A four-vessel angiogram is not needed in all cases; only the pertinent ones need to be explored or a CT angiogram may be done. Angiography is also strongly recommended in the case of delayed and/or unexplained SAH or intracranial hematoma development.[3,28,46,48] The importance of angiography in the diagnosis of vascular complications lies in the bad outcome associated with this pathology when it is not aggressively treated. Sometimes vascular injuries are delayed in onset, appearing even weeks or months after the trauma, and an initial negative angiography is not conclusive. When suspicion is maintained, repeating the test 2–3 weeks after the trauma is recommended.[3,7,28,46]

The common vascular complications after PBI include traumatic intracranial aneurysms (TICAs) or arteriovenous fistulas (AVFs), SAH, and vasospasm.[47] These complications are discussed individually in the following text.

Traumatic intracranial aneurysm

Traumatic intracranial aneurysm formation is the most commonly described vascular injury after PBI.[3,7,28,46,48] Approximately 20% of traumatic aneurysms after TBI are caused by PBI.[47] Damage to an arterial wall by PBI causes a TICA. Although rare cases of partial damage to the arterial wall have been described (true TICA), traumatic intracranial aneurysms caused by PBI are mainly false aneurysms.[49–51] Cerebral angiography (CT or conventional) remains the most optimum modality to detect intracranial aneurysms.[28] Once identified, surgical or endovascular repair are the treatment options.[51]

Subarachnoid hemorrhage

The frequency of SAH in PBI patients ranges from 31% to 78%.[\[1,28,52,53\]](#) The presence of SAH after PBI has been documented to correlate significantly with mortality.[\[52\]](#) Additionally, SAH near large vascular territories and intraventricular hemorrhage may lead to poor outcomes.[\[54\]](#)

Vasospasm

A dreaded complication of SAH is the development of vasospasm which is caused by reactive smooth muscle contraction in the walls of the vasculature.[\[1,54\]](#) The subsequent decreased CBF, if severe, can lead to cerebral ischemia and infarction. However, in a study, no significant difference in outcome (3-month Glasgow outcome scale) was noted when PBI patients with/without vasospasm were compared.[\[55\]](#) Vasospasm may be detected by increased velocities on Doppler ultrasound. Treatment may include medical management and/or endovascular angioplasty. Medical management includes hypertension, hypervolemia, and hemodilution, i.e., the conventional HHH therapy.[\[56\]](#)

MANAGEMENT OF CEREBROSPINAL FLUID LEAK

[Go to:](#)

Cerebrospinal fluid leakage is a common complication of PBI. Arendall and Meirowsky reported a 28% instance of CSF leaks.[\[57\]](#) Cerebrospinal fluid leaks after PBI have been documented to be highly predictive of infectious complications.[\[58\]](#) Meirowsky *et al.* reported in Vietnam Head Injury Study the incidence of infection as 49.5% versus 4.6% in 1032 casualties with and without CSF leaks, respectively.[\[59\]](#) Gonul *et al.* in a military series of 148 PBI patients have reported that the variable most highly correlated with intracranial infection was the presence of an acute or delayed CSF leak, which had a 63% infection rate.[\[41\]](#)

Cerebrospinal fluid leak develops because of the dural tear by the missile along with a failure to adequately seal the defect by normal tissue healing processes. CSF leaks can present through the entry or exit sites of the projectile as well as through the ear or nose when the mastoid air cells and the open-air sinuses have been violated, respectively.[\[1\]](#) The *Guidelines for the Management of Penetrating Brain Injury* recommended the surgical correction for CSF leaks which do not close spontaneously or are refractory to CSF diversion through a ventricular or lumbar drain.[\[58\]](#) The injury wounds associated with CSF leaks need to be extensively explored in order to allow watertight closure, either by direct closure of dural defects or by using grafting materials. Synthetic grafts can, however, by virtue of being a foreign body, become a potential source of infection, and they must be used cautiously especially in grossly contaminated wounds.[\[60\]](#) The management of CSF leaks remote from the point of entry or exit may involve CSF diversion. However, the risk of herniation syndromes because of mass effect and/or midline shift must be carefully evaluated before placing a lumbar drain.[\[1\]](#) In refractory leaks, the possibility of hydrocephalus should be explored and permanent CSF diversion considered.

ANTIBIOTIC PROPHYLAXIS FOR PBI

[Go to:](#)

Infectious complications are not uncommon after PBI, and they are also associated with higher morbidity and mortality rates.[61] The risk of local wound infections, meningitis, ventriculitis, or cerebral abscess are particularly high among PBI patients because of the presence of contaminated foreign objects, skin, hair, and bone fragments driven into the brain tissue along the projectile track.[1,62] Infectious complications are more frequent when cerebrospinal fluid leaks, air sinus wounds, transventricular injuries or those ones crossing the midline occur.[3,61] A higher incidence of intracranial infections after PBI is documented in studies on military PBI (4%–11%) as compared to series on civilian PBI (1%–5%).[61]

Staphylococcus aureus is the most frequently associated organism. However, gram negative bacteria also frequently cause intracranial infection after PBI.[61] The administration of broad spectrum antibiotic therapy is deemed necessary in all patients with PBI based on empirical evidence from military series where the rate of infectious complications was as high as 58.8% in the preantibiotic era.[62] In a large retrospective review of civilian PBI data, the rate of infection was documented to be 1%–5% with the use of broad spectrum antibiotics.[63] Based on available literature, it is recommended that broad spectrum antibiotics should be instituted in all PBI cases, and must be started as soon as possible.

There is a considerable variation in the preference for antibiotic regimen for prophylaxis in PBI patients. Cephalosporins, however, are the most preferred antibiotics.[1,3,62,64] Esposito and Walker have recommended the use of intravenous ceftriaxone, metronidazole, and vancomycin for a minimum of 6 weeks for PBI patients.[1]

The “*Infection in Neurosurgery*” Working Party of British Society for Antimicrobial Therapy recommended the following regimen for PBI: intravenous co-amoxiclav 1.2g q 8h, or intravenous cefuroxime 1.5g, then 750mg q 8 h with intravenous metronidazole 500mg q 8 h (or 1g q 12h per rectum or 400mg q 8h by mouth).[65] It is recommended that this regimen should be started as soon as possible after injury and continued for 5 days postoperatively. Based on the available literature, we recommend that antibiotic prophylaxis must be maintained for at least 7–14 days.

ANTISEIZURE PROPHYLAXIS FOR PBI

[Go to:](#)

The risk of posttraumatic epilepsy after PBI is high probably due to direct traumatic injury to the cerebral cortex with subsequent cerebral scarring. It is reported that the more severe the injury to the brain according to the Glasgow outcome scale (GOS) grade, the higher the risk for the development of posttraumatic epilepsy.[1,66,67] About 30%–50% of patients suffering a PBI will develop seizures.[67] It is estimated that up to 10% of them will appear early (first 7 days after the trauma), and 80% during the first 2 years, but about 18% may not have their first seizure until 5 or more years after injury.[39,68] Although the initial studies did not confirm the beneficial effect of the prophylactic anticonvulsants administration, more recent ones recommend the prophylactic anticonvulsants use (e.g., phenytoin, carbamazepine, valproate, or phenobarbital) in the first week after an injury[66,67]. It is acceptable not to use prophylactic anticonvulsants at all in case of smaller, less serious trauma. Besides, the use of anticonvulsants beyond the first 7 days of injury is generally not recommended.[66,67]

PROGNOSTIC FACTORS IN PBI

[Go to:](#)

Age

Increasing age is correlated with a worse prognosis in PBI.[[1](#),[2](#)] Age greater than 50 is documented to be associated with an increased mortality in PBI patients.[[2](#)]

Suicide attempt

Suicide attempt is correlated with a higher mortality in PBI when compared to other causes.[[2](#)] Suicide is an important cause of PBI in civilian population whereas military PBI is commonly associated with shell and shrapnel wounds. Suicide carries a worse prognosis probably because of close range injury.

Mode of injury

PBIs are differentiated into the following types based on mode of injury: penetrating (a foreign object penetrates skull and dura and remains lodged within the intracranial cavity); tangential (a foreign object glances off the skull, often driving bone fragments into the brain); and perforating (a ‘through-and-through’ injury, characterized by entry and exit wounds).[[2](#)] Out of these three, perforating brain injuries are associated with a worse outcome.

Hypotension

Hypotension (systolic blood pressure less than 90 mmHg) is correlated with high mortality in PBI patients.[[53](#)] Hypotension comprises an important complication of traumatic brain injury. The incidence of hypotension in PBI patients varies from 10% to 50%.[[2](#)]

Coagulopathy

Coagulopathy in PBI patients is associated with high mortality, however, the evidence is not sufficient.[[69](#)] Coagulation studies available include prothrombin time, thrombin time, partial thromboplastin time, fibrinogen level, fibrin degradation products, and platelet count.[[2](#)]

Respiratory distress

Respiratory distress in PBI patients is associated with worse prognosis.[[70](#)] Although a consistent definition is lacking, respiratory distress in PBI patients is defined as a respiratory rate of less than 10, apnea, or respiratory depression.[[2](#)]

Glasgow coma scale

Low GCS is associated with an unfavorable outcome in both civilian and military PBI.[[2](#)] In nonpenetrating TBI, patients with a GCS score <8 are described as having severe injuries, and patients with GCS scores of 9–12 are classified as moderate. In PBI

patients, large proportions of civilian patients are admitted with a GCS score of 3–5. However, in military series, patients have a better GCS score, ranging from 13 to 15.[2]

Pupillary size and light reflex

Bilaterally fixed and dilated pupils are highly predictive of mortality in PBI patients.[69] An abnormal pupillary light reflex may be an indirect indicator of cerebral herniation or possible brain stem injury. Measurement of pupillary reactivity includes measurement of the light reflex and size of the pupils.[2]

Intracranial pressure

Raised ICP is predictive of high mortality.[26,35] Brain trauma, whether closed or penetrating, leads to increased ICP. The limited literature available on ICP monitoring in PBI patients suggests that a raised ICP during initial 72 h of injury carries worse prognosis.[2]

CT scan findings

Several CT scan findings have been documented to be associated with worse outcome. These include bihemispheric lesions, multilobar injuries, intraventricular hemorrhage, uncal herniation, and subarachnoid hemorrhage.[1,2]

CONCLUDING REMARKS

[Go to:](#)

The management of PBI differs considerably from *nonpenetrating brain injury* because of the unique mechanism of injury and pathophysiology involved in this type of trauma. The introduction of *Guidelines for the Management of Penetrating Brain Injury* has revolutionized the medical and surgical management of PBI during the last decade. There has been a paradigm shift toward a less aggressive debridement of deep seated fragments and a more aggressive antibiotic prophylaxis in an effort to improve outcomes. However, there is still a need for large scale multicenter randomized controlled trials to evaluate the current guidelines. Research in this area is highly warranted as PBI patients still present a significant challenge to practicing neurosurgeons worldwide.

Footnotes

[Go to:](#)

Source of Support: Nil

Conflict of Interest: None declared.

REFERENCES

[Go to:](#)

1. Esposito DP, Walker JP. Contemporary management of penetrating brain injury. *Neurosurg Q.* 2009;19:249–54.

2. Part 2. Prognosis in penetrating brain injury. *J Trauma*. 2001;51:S44–86. [[PubMed](#)]
3. Gutiérrez-González R, Boto GR, Rivero-Garvía M, Pérez-Zamarrón A, Gómez G. Penetrating brain injury by drill bit. *Clin Neurol Neurosurg*. 2008;110:207–10. [[PubMed](#)]
4. Khalil N, Elwany MN, Miller JD. Transcranial stab wounds: Morbidity and medicolegal awareness. *Surg Neurol*. 1991;35:294–9. [[PubMed](#)]
5. Haddad FS, Manktelow AR, Brown MR, Hope PG. Penetrating head injuries: A trap for the unwary. *Injury*. 1996;27:72–3. [[PubMed](#)]
6. Chibbaro S, Tacconi L. Orbito-cranial injuries caused by penetrating non-missile foreign bodies. Experience with eighteen patients. *Acta Neurochir (Wien)* 2006;148:937–41. [[PubMed](#)]
7. du Trevou MD, van Dellen JR. Penetrating stabwounds to the brain: The timing of angiography in patients presenting with the weapon already removed. *Neurosurgery*. 1992;31:905–11. [[PubMed](#)]
8. Costantinides F. A fatal case of accidental cerebral injury due to power drill. *Am J Forensic Med Pathol*. 1982;3:241–3. [[PubMed](#)]
9. Kelly AJ, Pople I, Cummins BH. Unusual craniocerebral penetrating injury by a power drill: Case report. *Surg Neurol*. 1992;38:471–2. [[PubMed](#)]
10. Navarro-Celma JA, Mir Marin MA, Aso Escario J, Castellano Arroyo M. A report of a suicide by means of an electric drill. *Acta Med Leg Soc (Liege)* 1989;39:247–9. [[PubMed](#)]
11. Schmeling A, Lignitz E, Strauch H. Case reports of suicide with an electric drill. *Arch Kriminol*. 2003;211:65–72. [[PubMed](#)]
12. Bullock R, Chesnut RM, Clifton G, Ghajar J, Marion DW, Narayan RK, et al. Guidelines for the management of severe head injury. Brain Trauma Foundation. *J Neurotrauma*. 1996;13:641–734. [[PubMed](#)]
13. Bullock R, Chestnut RM, Clifton G. Guidelines for the management of severe head injury-3rd edition. *J Neurotrauma*. 2007;24:S1–106.
14. Part 1: Guidelines for the management of penetrating brain injury. Introduction and methodology. *J Trauma*. 2001;51:S1–6. [[PubMed](#)]
15. Barach E, Tomlanovich M, Nowak R. A pathophysiologic examination of the wounding mechanisms of firearms: Part 1. *J Trauma*. 1986;26:225–35. [[PubMed](#)]
16. Carey ME. Experimental missile wounding of the brain. *Neurosurg Clin N Am*. 1995;6:629–42. [[PubMed](#)]

17. Ordog GJ, Wasserberger J, Balasubramaniam S. Wound ballistics: Theory and practice. *Am Emerg Med.* 1984;13:1113–22. [[PubMed](#)]
18. Blissitt PA. Care of the critically ill patient with penetrating head injury. *Crit Care Nurs Clin North Am.* 2006;18:321–32. [[PubMed](#)]
19. Eckstein M. The pre-hospital and emergency department management of penetrating wound injuries. *Neurosurg Clin North Am.* 1995;6:741–51. [[PubMed](#)]
20. Neuroimaging in the management of penetrating brain injury. *J Trauma.* 2001;51:S7–11. [[PubMed](#)]
21. Offiah C, Twigg S. Imaging assessment of penetrating craniocerebral and spinal trauma. *Clin Radiol.* 2009;64:1146–57. [[PubMed](#)]
22. Aarabi B. Comparative study of bacteriological contamination between primary and secondary exploration of missile head wounds. *Neurosurgery.* 1987;20:610–6. [[PubMed](#)]
23. Chaudhri KA, Choudhury AR, al Moutaery KR, Cybulski GR. Penetrating craniocerebral shrapnel injuries during “Operation Desert Storm”: Early results of a conservative surgical treatment. *Acta Neurochir (Wien)* 1994;126:120–3. [[PubMed](#)]
24. Helling TS, McNabney WK, Whittaker CK, Schultz CC, Watkins M. The role of early surgical intervention in civilian gunshot wounds to the head. *J Trauma.* 1992;32:398–400. [[PubMed](#)]
25. Levi L, Borovich B, Guilburd JN, Grushkiewicz I, Lemberger A, Linn S, et al. Wartime neurosurgical experience in Lebanon, 1982–85, I: Penetrating craniocerebral injuries. *Isr J Med Sci.* 1990;26:548–54. [[PubMed](#)]
26. Nagib MG, Rockswold GL, Sherman RS, Lagaard MW. Civilian gunshot wounds to the brain: Prognosis and management. *Neurosurgery.* 1986;18:533–7. [[PubMed](#)]
27. Green BF, Kraft SP, Carter KD, Buncic JR, Nerad JA, Armstrong D. Intraorbital wood. Detection by magnetic resonance imaging. *Ophthalmology.* 1990;97:608–11. [[PubMed](#)]
28. Vascular complications of penetrating brain injury. *J Trauma.* 2001;51:S26–8. [[PubMed](#)]
29. Levy ML, Rezai A, Masri LS, Litofsky SN, Giannotta SL, Apuzzo ML, et al. The significance of subarachnoid hemorrhage after penetrating craniocerebral injury: Correlations with angiography and outcome in a civilian population. *Neurosurgery.* 1993;32:532–40. [[PubMed](#)]
30. Mokri B. The Monro-Kellie hypothesis: Applications in CSF volume depletion. *Neurology.* 2001;56:1746–8. [[PubMed](#)]
31. Chesnut RM. Care of central nervous system injuries. *Surg Clin North Am.* 2007;87:119–56. [[PubMed](#)]

32. Crockard HA. Early intracranial pressure studies in gunshot wounds of the brain. *J Trauma*. 1975;15:339–47. [[PubMed](#)]
33. Lillard PL. Five years experience with penetrating craniocerebral gunshot wounds. *Surg Neurol*. 1978;9:79–83. [[PubMed](#)]
34. Sarnaik AP, Kopec J, Moylan P, Alvarez D, Canady A. Role of aggressive intracranial ressure control in management of pediatric craniocerebral gunshot wounds with unfavorable features. *J Trauma*. 1989;29:1434–7. [[PubMed](#)]
35. Miner ME, Ewing-Cobbs L, Kopaniky DR, Cabrera J, Kaufmann P. The results of treatment of gunshot wounds to the brain in children. *Neurosurgery*. 1990;26:20–5. [[PubMed](#)]
36. Intracranial pressure monitoring in the management of penetrating brain injury. *J Trauma*. 2001;51:S12–5. [[PubMed](#)]
37. Surgical management of penetrating brain injury. *J Trauma*. 2001;51:S16–25. [[PubMed](#)]
38. Hubschmann O, Shapiro K, Baden M, Shulman K. Craniocerebral gunshot injuries in civilian practice: Prognostic criteria and surgical management experience with 82 cases. *J Trauma*. 1979;19:6–12. [[PubMed](#)]
39. Salazar AM, Jabbari B, Vance SC, Grafman J, Amin D, Dillon JD. Epilepsy after penetrating head injury, I.Clinical correlates: A report of the Vietnam Head Injury Study. *Neurology*. 1985;35:1406–14. [[PubMed](#)]
40. Hammon WM. Analysis of 2187 consecutive penetrating wounds of the brain from Vietnam. *J Neurosurg*. 1971;34:127–31. [[PubMed](#)]
41. Gönül E, Baysefer A, Kahraman S, Ciklatekerlioğlu O, Gezen F, Yayla O, et al. Causes of infections and management results in penetrating craniocerebral injuries. *Neurosurg Rev*. 1997;20:177–81. [[PubMed](#)]
42. Aarabi B, Taghipour M, Alibaii E, Kamgarpour A. Central nervous system infections after military missile head wounds. *Neurosurgery*. 1998;42:500–9. [[PubMed](#)]
43. Rish BL, Dillon D, Caveness WF, Mohr JP, Kistler P, Weiss GH. Evolution of craniotomy as a debridement technique for penetrating craniocerebral injuries. *J Neurosurg*. 1980;53:772–5. [[PubMed](#)]
44. Bell RS, Mossop CM, Dirks MS, Stephens FL, Mulligan L, Ecker R, et al. Early decompressive craniectomy for severe penetrating and closed head injury during wartime. *Neurosurg Focus*. 2010;28:E1. [[PubMed](#)]
45. Nathoo N, Boodhoo H, Nadvi SS, Naidoo SR, Gouws E. Transcranial brainstem stab injuries: A retrospective analysis of 17 patients. *Neurosurgery*. 2000;47:1117–22. [[PubMed](#)]
46. Levy ML, Rezai A, Masri LS, Litofsky SN, Giannotta SL, Apuzzo ML, et al. The significance of subarachnoid hemorrhage after penetrating craniocerebral injury: Correlations with angiography and outcome in a civilian population. *Neurosurgery*. 1993;32:532–40. [[PubMed](#)]

47. Rao GP, Rao NS, Reddy PK. Technique of removal of an impacted sharp object in a penetrating head injury using the lever principle. *Br J Neurosurg*. 1998;12:569–71. [[PubMed](#)]
48. Kieck CF, de Villiers JC. Vascular lesions due to transcranial stab wounds. *J Neurosurg*. 1984;60:42–6. [[PubMed](#)]
49. Aarabi B. Traumatic aneurysms of brain due to high velocity missile head wounds. *Neurosurgery*. 1988;22:1056–63. [[PubMed](#)]
50. Aarabi B. Management of traumatic aneurysms caused by high velocity missile headwounds. *Neurosurg Clin N Am*. 1995;6:775–97. [[PubMed](#)]
51. Haddad FS, Haddad GF, Taha J. Traumatic intracranial aneurysms caused by missiles: Their presentation and management. *Neurosurgery*. 1997;28:1–7. [[PubMed](#)]
52. Kaufman HH, Makela ME, Lee KF, Haid RW, Jr, Gildenberg PL. Gunshot wounds to the head: A perspective. *Neurosurgery*. 1986;18:689–95. [[PubMed](#)]
53. Aldrich EF, Eisenberg HM, Saydjari C, Foulkes MA, Jane JA, Marshall LF, et al. Predictors of mortality in severely head-injured patients with civilian gunshot wounds: A report from the NIH Traumatic Coma Data Bank. *Surg Neurol*. 1992;38:418–23. [[PubMed](#)]
54. Shimura T, Mukai T, Teramoto A, Toda S, Yamamoto Y, Nakamura T, et al. Clinicopathological studies of craniocerebral gunshot wound injuries. *No Shinkei Geka*. 1997;25:607–12. [[PubMed](#)]
55. Kordestani RK, Counelis GJ, McBride DQ, Martin NA. Cerebral arterial spasm after penetrating craniocerebral gunshot wounds: Transcranial Doppler and cerebral blood flow findings. *Neurosurgery*. 1997;41:351–9. [[PubMed](#)]
56. Muench E, Horn P, Bauhuf C, Roth H, Philipps M, Hermann P, et al. Effects of hypervolemia and hypertension on regional cerebral blood flow, intracranial pressure, and brain tissue oxygenation after subarachnoid hemorrhage. *Crit Care Med*. 2007;35:1844–51. [[PubMed](#)]
57. Arendall RE, Meinowsky AM. Air sinus wounds: An analysis of 163 consecutive cases incurred in the Korean War, 1950–1952. *Neurosurgery*. 1983;13:377–80. [[PubMed](#)]
58. Management of cerebrospinal fluid leaks. *J Trauma*. 2001;51:S29–33. [[PubMed](#)]
59. Meirowsky AM, Caveness WF, Dillon JD, Rish BL, Mohr JP, Kistler JP, et al. Cerebrospinal fluid fistulas complicating missile wounds of the brain. *J Neurosurg*. 1981;54:44–8. [[PubMed](#)]
60. Vrankoviæ D, Heæimoviæ I, Splavski B, Dmitroviæ B. Management of missile wounds of the cerebral dura mater: Experience with 69 cases. *Neurochirurgia*. 1992;35:150–5. [[PubMed](#)]

61. Antibiotic prophylaxis for penetrating brain injury. *J Trauma*. 2001;51:S34–40. [[PubMed](#)]
62. Whitaker R. Gunshot wounds of the cranium: With special reference to those of the brain. *Br J Surg*. 1916;3:708–35.
63. Benzel EC, Day WT, Kesterson L, Willis BK, Kessler CW, Modling D, et al. Civilian craniocerebral gunshot wounds. *Neurosurgery*. 1991;29:67–71. [[PubMed](#)]
64. Kaufman HH, Schwab K, Salazar AM. A national survey of neurosurgical care for penetrating head injury. *Surg Neurol*. 1991;36:370–7. [[PubMed](#)]
65. Bayston R, de Louvois J, Brown EM, Johnston RA, Lees P, Pople IK. Use of antibiotics in penetrating craniocerebral injuries. “Infection in Neurosurgery” Working Party of British Society for Antimicrobial Chemotherapy. *Lancet*. 2000;355:1813–7. [[PubMed](#)]
66. Aarabi B, Taghipour M, Haghnegahdar A, Farokhi MR, Mobley L. Prognostic factors in the occurrence of posttraumatic epilepsy after penetrating head injury suffered during military service. *Neurosurg Focus*. 2000;8:e1. [[PubMed](#)]
67. Antiseizure prophylaxis for penetrating brain injury. *J Trauma*. 2001;51:S41–3. [[PubMed](#)]
68. Caveness WF, Meierowsky AM, Rish BL, Mohr JP, Kistler JP, Dillon JD, et al. The nature of posttraumatic epilepsy. *J Neurosurg*. 1979;50:545–53. [[PubMed](#)]
69. Shaffrey ME, Polin RS, Phillips CD, Germanson T, Shaffrey CI, Jane JA. Classification of civilian craniocerebral gunshot wounds: A multivariate analysis predictive of mortality. *J Neurotrauma*. 1992;9:S279–85. [[PubMed](#)]
70. Jacobs DG, Brandt CP, Piotrowski JJ, McHenry CR. Transcranial gunshot wounds: Cost and consequences. *Am Surg*. 1995;61:647–53. [[PubMed](#)]

Articles from Journal of Emergencies, Trauma, and Shock are provided here courtesy of **Wolters Kluwer -- Medknow Publications**

Managing military penetrating brain injuries in the war zone: lessons learned

Hussein Fathalla, MD, PhD, Ahmed Ashry, MD, PhD, and Ahmed El-Fiki, MD, PhD

Division of Neurosurgery, Cairo University Hospital, Cairo, Egypt

OBJECTIVE Managing penetrating military brain injuries in a war zone setting is different than managing common civilian penetrating brain injuries. Triage, i.e., deciding on which patients to treat or not treat, and which to be flown back home, is essential to avoid wasting valuable limited resources. In this study the authors aim to identify reliable predictors of mortality and poor outcome to help develop a protocol for treating their patients in the battlefield. They also demonstrate all the lessons learned from their collective experience regarding some of the controversial management issues.

METHODS This study was a retrospective review of 102 patients with penetrating military missile head injuries treated by the authors in various facilities in northern Sinai between 2011 and 2018. Patient demographics, clinical characteristics, imaging characteristics, postoperative complications, and Glasgow Outcome Scale (GOS) scores were recorded for each patient. Several variables associated with mortality and poor outcome that were derived from the literature were analyzed, in addition to variables obtained by direct observation by the authors over time.

RESULTS There were 50 patients (49%) with GOS score of 1 (death), 12 patients (11.8%) with GOS score of 2 (survivors in persistent vegetative state), and 40 survivors (39.2%) with varying degrees of disability on the last follow-up evaluation. The authors identified an anatomical danger zone that was found to predict mortality when traversed. Bilateral dilated fixed pupils and low Glasgow Coma Scale score on admission were also found to be independent predictors of mortality and poor outcome. Based on these findings, a protocol was developed for managing these patients in the war zone.

CONCLUSIONS Managing military penetrating head injuries in the war zone is different than civilian gunshot head injuries encountered by most neurosurgeons in urban cities. The authors developed a simple protocol for managing military penetrating injuries in the war zone. They also describe important lessons learned from this experience.

<https://thejns.org/doi/abs/10.3171/2018.8.FOCUS18371>

KEYWORDS military neurosurgery; penetrating brain injuries; bullet injuries; danger zone

SINCE the Egyptian revolution in 2011, the Sinai Peninsula has witnessed an insurgency that led to the undertaking of multiple military operations by the Egyptian army against terrorism. Starting in 2011 with Operation Eagle, these operations continued throughout the years until the present time. Security conditions started improving in 2018 with a major campaign, i.e., Comprehensive Operation Sinai, which has wiped out most of the militant strategic locations. Inevitably, Egyptian neurosurgeons accumulated tremendous experience dealing with military-grade penetrating head injuries.

Managing penetrating military injuries in a war zone setting is different than managing the common civilian penetrating brain injuries that we usually encounter in our practice due to a variety of factors:^{3,4,7,8} 1) technical factors

(missile caliber and velocity); 2) lack of sophisticated medical facilities in a war zone; 3) lack of equipment and supplies; and 4) lack of sufficient medical personnel and experienced neurosurgeons on site. The general rule in medical practice is to treat every human soul and as physicians we have an ethical obligation to do this. In a war zone, however, with such poor conditions, important decisions have to be made. Having a treatment protocol and algorithm is a must to avoid wasting valuable limited resources. Such a protocol will help triage, that is, deciding whom to treat or not treat, and whom to fly back home. Deciding if a patient will be treated or not is a nightmare for any neurosurgeon, as we are perfectionists and accustomed to doing the best for our patients no matter the conditions. Without evidence-based guidelines, such decisions become ethical

ABBREVIATIONS GCS = Glasgow Coma Scale; GOS = Glasgow Outcome Scale.

SUBMITTED July 25, 2018. **ACCEPTED** August 20, 2018.

INCLUDE WHEN CITING DOI: 10.3171/2018.8.FOCUS18371.

TABLE 1. Demographics

| Variable | No. of Patients (%) |
|---------------------------------|---------------------|
| Sex | |
| Female | 2 (2.0) |
| Male | 100 (98.0) |
| Age (yrs) | |
| 10–20 | 16 (15.7) |
| 21–30 | 76 (74.5) |
| 31–40 | 6 (5.9) |
| 41–50 | 2 (2.0) |
| 51–60 | 2 (2.0) |
| Mean age \pm SD | 25 \pm 1.8 |
| Admission GCS score | |
| 3–5 | 37 (36.3) |
| 6–12 | 32 (31.4) |
| 13–15 | 33 (32.3) |
| Type of hospital | |
| Inside war zone | 41 (40.2) |
| Civilian hospital | 61 (59.8) |
| Type of injury | |
| Bullet | 60 (58.8) |
| Blast | 42 (41.2) |
| Entry wound | |
| Frontal | 27 (26.5) |
| Temporal | 17 (16.7) |
| Parietal | 22 (21.6) |
| Occipital | 13 (12.7) |
| Posterior fossa | 12 (11.8) |
| Face | 11 (10.8) |
| Surgical procedures | |
| None | 28 (27.4) |
| Debridement | 70 (68.6) |
| Hematoma evacuation | 22 (21.6) |
| Bullet extraction | 47 (46.1) |
| Decompressive craniotomy | 18 (17.6) |
| GOS score | |
| 1 | 50 (49.0) |
| 2 | 12 (11.8) |
| 3 | 18 (17.6) |
| 4 | 10 (9.8) |
| 5 | 12 (11.8) |
| Median FU \pm SD (range), mos | 17 \pm 3.2 (3–27) |

FU = follow-up.

dilemmas, especially with an inexperienced young neurosurgeon in the field. Moreover, in those whom we decide to treat, certain surgical and management controversies arise, such as indications of decompressive craniectomy,^{3,7,11} bone reconstruction,¹¹ dural closure,^{2,11} and indications to extract bullets.^{2,8,9}

The authors of this paper have a collective experience of treating more than 100 patients with military missile

head injuries since 2010, managed in various war zone medical facilities. In this study, a retrospective review of these patients aided by guidelines from the literature has led to the identification of reliable predictors of mortality and poor outcome and thus assistance in deciding which patients to treat and how to treat them in the battlefield. We also demonstrate all the lessons learned from our collective experience regarding some of the previously stated controversial management issues.

Methods

This is a retrospective review of 102 patients with penetrating military missile head injuries treated by the authors in various war zone facilities in northern Sinai between 2011 and 2018. Patients with extracranial penetrating injuries were excluded from the study as they may affect the outcome and survival. Patient demographics, clinical characteristics, imaging characteristics, missile trajectories and paths, and surgical data were recorded for each patient. Glasgow Coma Scale (GCS) scores were obtained and recorded at admission and before and after the initial resuscitation; however, for our analysis, we decided to define the term “admission GCS score” as the postresuscitation GCS score. During the hospital stay, GCS score continued to be recorded as part of our hourly neurological examinations until the patient’s condition improved and he or she was discharged home or to a rehabilitation center. Glasgow Outcome Scale (GOS) score was recorded at the point of discharge, and subsequently during follow-up clinic visits at 1 month, 3 months, and then 6-month intervals. Our primary outcome measure was the GOS score at the 1-year follow-up or the last available follow-up visit. Secondary outcome measures were all the complications that occurred in our patients during the hospital stay and after discharge, up to the last follow-up available.

The variables studied in order to identify the predictors of mortality for penetrating military head injuries were mainly derived from the literature,^{1,5,6,10} in addition to direct observation by the authors over time, who are all experts in the field of military head injuries.

SPSS software (version 20, IBM Corp.) was used for statistical analysis. Data were presented as mean and range for numerical variables (e.g., age) and as frequency for categorical variables (sex, GCS score, complications, etc.). Mortality and poor outcome in our study were defined as GOS score 1 and 2, respectively. In the univariate analyses the chi-square test, Fisher’s exact test, and Student t-test were used to identify variables associated with mortality. Any variable with a p value < 0.10 was included in a forward stepwise logistic regression model to determine the independent predictors of mortality. These predictors were used to develop a protocol for management.

Results

Study Population

The study population and demographics are listed in Table 1. Of the 102 patients included in this study, the mean age was 25 years. There were only 4 patients over 40 years old, and these were civilians who were shot during

TABLE 2. Complications in survivors (GOS score 2–5)

| Complication | No. of Patients (%) |
|--------------------|---------------------|
| CSF leakage* | 3 (5.8) |
| Infection | 9 (17.3) |
| Brain abscess | 2 (3.8) |
| Meningitis | 3 (5.8) |
| Wound infection | 4 (7.7) |
| Disability | |
| GOS 2 (vegetative) | 12 (23.1) |
| GOS 3 | 18 (34.6) |
| GOS 4 | 10 (19.2) |
| GOS 5 | 12 (23.1) |
| Epilepsy | 11 (21.1) |
| Hydrocephalus | 13 (25.0) |
| Pseudoaneurysm | 3 (5.8) |
| Lead toxicity | 0 (0) |

* All cases of CSF leakage were due to underlying hydrocephalus and were treated with CSF diversion.

terrorist attacks. There were 100 males and only 2 females, a common pattern in penetrating military injuries. The brain injuries in 60 patients were bullet-related while 42 were blast injuries from various explosive devices. Forty-one patients were managed in a warzone medical facility, while 61 were only resuscitated in the war zone and then transferred for management in a nearby civilian hospital in the Sinai cities. Admission GCS score (postresuscitation) was categorized into 3 groups, in which 37 patients presented with scores of 3–5, 32 presented with scores of 6–12, and 33 presented with scores of 13–15. There were 50 patients (49%) with a GOS score of 1 (death), 12 patients (11.8%) with a GOS score of 2 (survivors in persistent vegetative state), and 40 survivors (39.2%) with varying degrees of disability on the last follow-up (Table 2). The GOS scores of these patients according to their admission GCS score are listed in Table 3. The follow-up period ranged from 3 to 27 months. Seventy-four patients had undergone a surgical procedure,⁹ including one or a combination of debridement, bullet extraction, hematoma evacuation, and/or decompressive craniotomy, while 28 patients had no surgical intervention (other than cleaning of wounds and simple suturing of a scalp wound). Those 28 patients had either one or more of the following scenarios: 1) one or more foreign objects from a blast injury,

but of very tiny size and in deep and/or inaccessible locations, so we decided to leave them and only do simple skin debridement and closure; 2) a high risk of mortality and poor outcome, which discouraged us from operating on them; and 3) a traversing bullet or explosive fragment, with an inlet and exit (no retained foreign body) and no other surgical conditions.

Complications in Survivors

There were 52 survivors in this study (GOS score 2–5). Table 2 lists all the complications that occurred on the last follow-up. Of the 52 survivors, there were 12 patients (23.1%) in a persistent vegetative state who never improved. There were 3 patients (5.8%) with CSF leakage from their wounds, which in all 3 cases was due to hydrocephalus and treated with CSF diversion. Various CNS infections such as meningitis, brain abscess, and deep wound infections occurred in 9 patients (17.3%) and were all treated surgically. Eleven patients (21.1%) continued to have epilepsy and needed long-term antiepileptic therapy. Lead toxicity did not occur in any of our patients with retained fragments.

Variables for Mortality

The variables for mortality were chosen based on previously analyzed variables in the literature,^{1,5,6,10} in addition to our own personal observations. For our initial univariate analysis, we included 8 patient-related variables and 10 imaging-related (CT scan) variables (Table 4). One of the imaging-related variables (danger zone) was a direct observation by our team during the period of the study in which we found that there is a certain midline zone that when traversed will almost always cause mortality or poor outcome. This zone was named the “danger zone” (Fig. 1). It is worth noting that all previously described mortality zones in the literature, such as the posterior fossa⁵ and zona fatalis,² were also found to lie within our discovered danger zone.

On univariate analysis, patient-related variables that were found to affect outcome were: admission GCS score, bilateral dilated fixed pupils, hypotension on admission, and diabetes insipidus. Age, sex, and wound entry point did not show statistical significance (Table 4). Imaging-related factors that had a significant association with outcome were: fragments or bullets traversing the danger zone, zona fatalis, posterior fossa, or XYZ planes; and tram track appearance on CT scans (tram track sign is a track of hypodensity surrounded by 2 hyperdense lines and was described by Rosenfeld et al.⁸). Intracerebral

TABLE 3. Relationship between GCS score on admission and GOS score at last follow-up

| GCS Score | GOS Score | | | | | Total |
|-----------|------------|----------------|-----------------------|-------------------------|---------------------------|-----------|
| | 1 (Death) | 2 (Vegetative) | 3 (Severe Disability) | 4 (Moderate Disability) | 5 (Mild or No Disability) | |
| 3–5 | 29 (78.3%) | 6 (16.2%) | 1 (2.70%) | 1 (2.70%) | 0 (0%) | 37 (100%) |
| 6–12 | 16 (50%) | 6 (18.75%) | 3 (9.38%) | 3 (9.38%) | 4 (12.5%) | 32 (100%) |
| 13–15 | 5 (15.15%) | 0 (0%) | 14 (42.42%) | 6 (18.18%) | 8 (24.24%) | 33 (100%) |
| Total | 50 | 12 | 18 | 10 | 12 | 102 |

TABLE 4. Univariate analysis of patient-related and imaging-related variables

| Variable | Death or Vegetative/Total | p Value |
|-------------------------------------|---------------------------|--------------|
| Patient variables | | |
| Age (yrs) | | |
| 10 to <20 | 12/16 | 0.231 |
| 20 to <30 | 42/76 | 0.133 |
| 30 to <40 | 4/6 | 0.612 |
| 40 to <50 | 2/2 | 0.081 |
| 50 to 60 | 2/2 | 0.142 |
| Sex | | |
| Male | 61/100 | 0.093 |
| Female | 1/2 | |
| Admission GCS score | | |
| 3–5 | 35/37 | 0.013 |
| 6–12 | 22/32 | |
| 13–15 | 5/33 | |
| Pupils | | |
| Reactive | 1/21 | |
| Unilateral dilated | 10/30 | |
| Bilateral dilated fixed | 49/51 | 0.004 |
| Wound entry point | | |
| Frontal | 10/27 | 0.744 |
| Temporal | 8/17 | 0.112 |
| Parietal | 17/22 | 0.532 |
| Occipital | 9/13 | 0.861 |
| Posterior fossa | 12/12 | 0.016 |
| Face | 5/11 | 0.443 |
| Hypotension on admission (SBP <90) | 39/46 | 0.037 |
| Diabetes insipidus | 18/22 | 0.024 |
| Meningitis | 0/3 | 0.511 |
| Imaging variables | | |
| Intraventricular hemorrhage | 20/32 | 0.621 |
| Bullet traversing zona fatalis | 7/7 | 0.002 |
| Trajectory crossing XYZ planes* | 9/9 | 0.001 |
| Midline shift >10 mm | 11/31 | 0.188 |
| Compressed basal cisterns | 39/61 | 0.262 |
| Large ICH >30 cm ³ | 17/29 | 0.082 |
| SAH | 38/68 | 0.139 |
| Tram track sign† | 16/21 | 0.042 |
| Trajectory crossing posterior fossa | 17/18 | 0.005 |
| Danger zone | 40/41 | 0.001 |

ICH = intracerebral hemorrhage; SAH = subarachnoid hemorrhage; SBP = systolic blood pressure.

Boldface type indicates statistical significance. GCS score on admission, pupils, hypotension, and diabetes insipidus were significantly associated with mortality and poor outcome. For the imaging variables, zona fatalis, trajectory crossing XYZ plane, and posterior fossa trajectory were significantly associated with outcome. Our danger zone also significantly affected outcome (which includes the previous 3 zones topographically).

* Refers to a single fragment that crosses the coronal, sagittal, and axial planes.

† Tram track sign is a track of hypodensity surrounded by two hyperdense lines and was found to be significant as well.

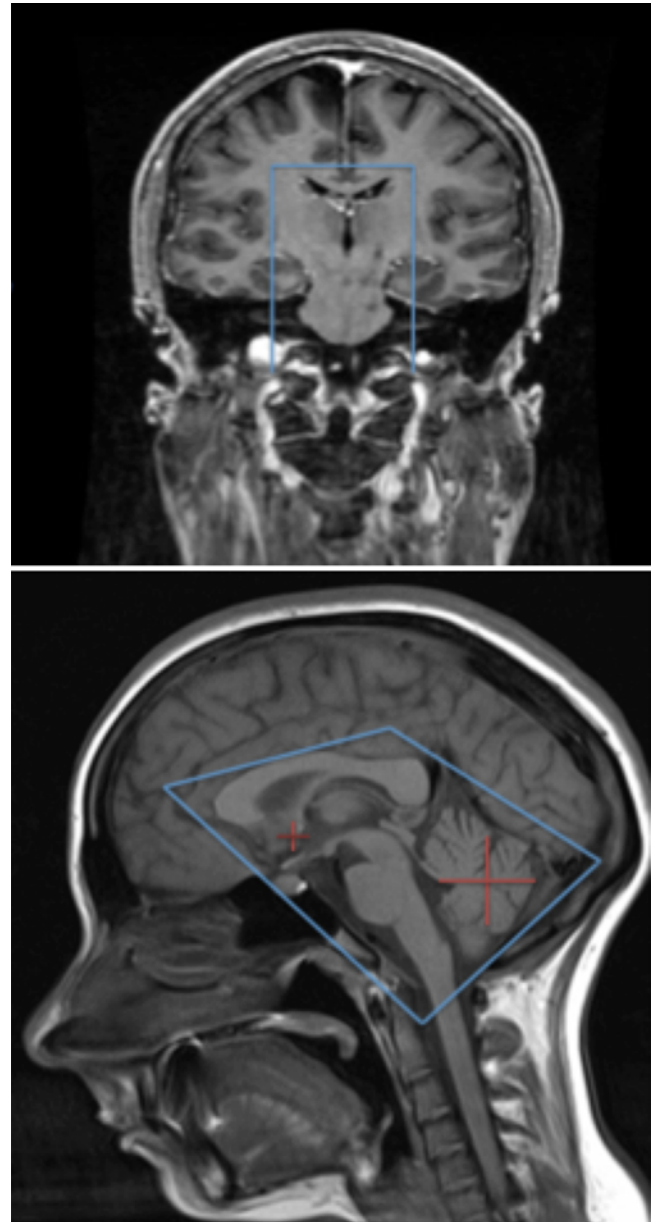


FIG. 1. Upper: Coronal MRI showing the lateral confines of the danger zone. A line extending through the uncus and claustrum bound the zone laterally. **Lower:** Danger zone on sagittal MRI (blue box). The boundaries of this zone are the cingulate gyrus superiorly, body of C2 inferiorly, tentorium and posterior fossa posteriorly, and the anterior commissure anteriorly. As illustrated, the zona fatalis (small red cross) and the posterior fossa (large red cross) lie within the confines of the danger zone.

hematoma, basal cistern compression, midline shift, and subarachnoid hemorrhage had no significant relationship with outcome (Table 4).

When these factors were included in further multivariate analysis (Table 5), the only factors that were found to be significantly associated with mortality and poor outcome were: 1) zona fatalis, 2) posterior fossa trajectory, 3) trajectories crossing the XYZ planes, 4) crossing the danger zone, 5) low admission GCS score (3–6), and 6)

bilateral dilated fixed pupils. Because factors 1, 2, and 3 are components of factor 4 (danger zone), both anatomically and statistically, we decided to use only the danger zone in our analysis and clinical use, as it makes no sense to describe each of them separately when there is a zone that incorporates all of them. Figure 2 illustrates some of our interesting cases.

Based on this previous analysis, we have developed a simple protocol for selecting the best option for treatment in an efficient, time- and cost-effective way (Fig. 3).

Discussion

Numerous literature reviews and studies have identified predictors for mortality in gunshot injuries;^{1,5,6,10} however, this study is unique because it only identifies military head injuries. Military injuries are usually caused by large-caliber bullets and usually cause more extensive injuries than handguns. Also, there are blast injuries from explosive devices and hand grenades that are usually not seen in civilian injuries. Most studies to date mainly addressed a combination of civilian and military injuries and thus were not specific to military-grade weaponry. The significance of this can be demonstrated in the study by Gressot et al.⁵ that elegantly identified and developed a scoring system for mortality in penetrating missile head injuries, in which scores > 2 indicated a 75% chance of mortality. Because injuries in the previous study were both civilian and military injuries, we could not use its scoring system in our series of solely military injuries. In our series, this scoring system will need to be adjusted for a lower threshold for mortality as most of our patients with scores of 1 and 2 would actually have a poor prognosis due to more extensive injuries compared with civilian injuries. This highlights the importance of treating military-grade injuries as a separate entity.

A number of fatal zones have been described in the literature, such as the zona fatalis,⁶ posterior fossa,⁵ and XYZ planes.⁸ Bullets traversing these zones were significantly associated with mortality. The issue here, however, is that most of the studies were again describing penetrating brain injuries in a general sense and were not specific to the more extensive military-grade injuries. Because our study was only addressing large-caliber machine gun injuries and explosive devices, these fatal zones do not apply here and obviously need to be broader and bigger. We were able to identify a broader zone (i.e., the danger zone) that when traversed (Fig. 1), will almost always lead to a poor outcome; 40 of 41 victims with projectiles traversing this zone died or remained in a persistent vegetative state. The projectile in the only patient who survived was a tiny pellet from an explosive device traversing his posterior fossa. He survived and his GOS score was 3 on last follow-up. Our results showed that all previously described fatal zones in the literature lie within the danger zone, further supporting the significance of these zones in the literature. Projectiles passing outside this danger zone, even when crossing the midline, were not found to significantly related to mortality or bad outcomes in our series. Of the 61 victims in whom their projectiles did not traverse the danger zone, only 22 (36%) died or had a bad outcome.

TABLE 5. Multivariate analysis of variables associated with mortality

| Variable | Multivariate p Value |
|--------------------------------|----------------------|
| Danger zone* | 0.001 |
| Zona fatalis | 0.006 |
| Posterior fossa trajectory | 0.014 |
| Trajectory crossing XYZ planes | 0.003 |
| GCS score 3–5 | 0.012 |
| Bilateral dilated fixed pupils | 0.031 |
| Hypotension on admission | 0.283 |
| Diabetes insipidus | 0.151 |
| Tram track sign | 0.082 |

Boldface type indicates statistical significance. Danger zone, bilateral dilated fixed pupils, and GCS score 3–6 on admission were the only factors significantly associated with mortality and poor outcome.

* The zona fatalis, posterior fossa, and XYZ plane intersection were found to be significantly associated with mortality. All 3 zones lie within the danger zone. When the danger zone is analyzed on its own, it is also a significant variable of mortality.

The other 2 variables that were significantly related to mortality in military head injuries were persistent bilateral dilated fixed pupils and low GCS score (3–6) on presentation. It is worth mentioning that these 2 variables do not lead to a 100% mortality rate, unlike the danger zone. Bilateral fixed pupils can be caused by severe hypotensive shock, and can often be reversed if the patient is quickly resuscitated. The presence of these variables alone does not preclude treatment. Based on these findings we have developed a protocol for treatment of military penetrating injuries in the warzone setting (Fig. 3). The protocol also helps identify patients who need to be transferred from the field hospital to a more sophisticated medical facility or flown back home.

It is thus important to emphasize that our protocol of management and deciding whom to treat, based on our identified predictors of mortality, is only applicable in military-grade injuries, and more importantly when treatment is in a warzone medical facility. If such injuries occurred by any chance near a large civilian hospital where supplies and personnel are adequate, then our duty is to treat everyone, and this protocol will not be applicable in this situation.

Lessons Learned

Based on the previous analysis, there are 3 variables that were directly related to mortality in military penetrating injuries. The presence of these 3 variables in a patient presenting in the war field will have an almost 100% poor outcome. The general rule obviously is to treat everyone and do our best, but in the war field where facilities are limited and mass casualties are common, it makes sense to choose whom to treat. Thus, from our experience, any patient presenting with a GCS score of 3–6 with a bilateral dilated fixed pupil and bullet trajectory crossing the danger zone is better left untreated (Fig. 2). Our protocol is described in Fig. 3 and also helps in selecting the best option for treatment in an efficient, time- and cost-effective way.

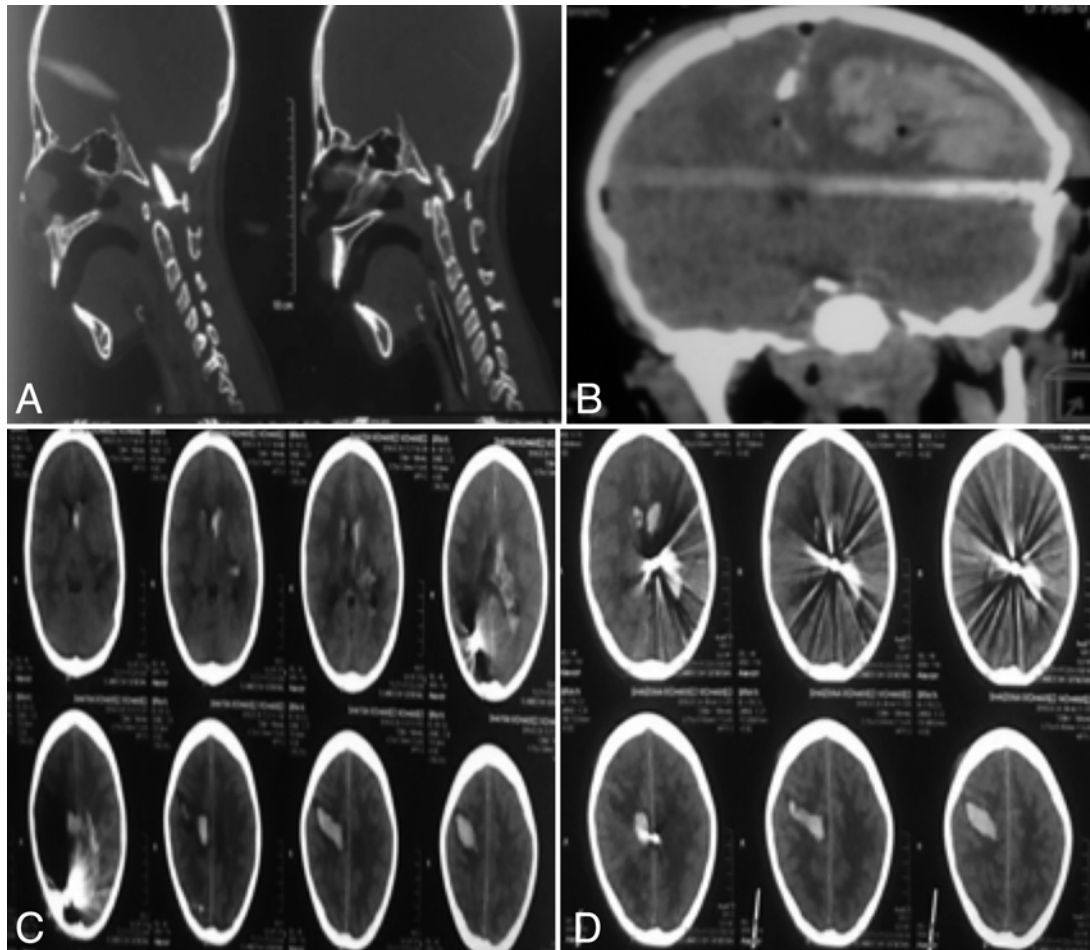


FIG. 2. **A:** Sagittal CT scan of a 15-year-old male victim shot accidentally. Bullet is shown resting at the foramen magnum. The patient presented with a GCS score of 3, lost brainstem reflexes, and died after 48 hours. **B:** Coronal CT scan of a 26-year-old male victim. The bullet trajectory can be seen passing through the danger zone. The patient died within days in the intensive care unit. **C and D:** Axial CT scans, 2 days apart, of one of our first patients in the series, a 22-year-old male victim. The scans show a bullet migrating from the right parietooccipital region to a midline intraventricular location. We have learned to immediately extract large-caliber bullets as early as possible to prevent such complications.

We seldom perform a watertight dural closure in these patients due to the time factor. CSF leakage, however, occurred in only 3 patients and was found to be from hydrocephalus in all 3. We suspect this to be from the heat of the missile causing gliosis and fibrosis in the brain tract and arachnoid. Although we still have no proof of this theory and previous reports¹¹ emphasized its importance, the fact remains that CSF leakage almost never occurred in our patients and when it did, it was usually from hydrocephalus. A watertight dural closure is thus not required from our experience.

In patients in whom decompressive craniectomy is indicated,^{3,7} or aggressive bone debridement is performed, we cover the brain and dura with an extra layer of temporalis fascia, fascia lata, or any thick reinforcing layer. These patients will require future cranioplasty and reconstruction, so these layers will prevent the brain from being directly in contact with the skin and will aid in the surgical dissection of the skin from the brain during the future cranioplasty surgery.

Decompressive craniectomy was performed in 18 patients and 10 survived to the last follow-up evaluations, requiring future cranioplasty. In addition, 14 other patients were aggressively debrided and had large defects also requiring future cranioplasty. These 24 surviving patients underwent cranioplasty 8–12 months later with bone cement, titanium mesh, or their own bone flap implanted in the abdomen with no infection or complications thus far. It appears that 8–12 months is optimal timing for performing cranioplasty and avoiding complications from too early or too late operations. This timing is also consistent with the study by Stephens et al.,¹¹ who performed 108 cranioplasties and had a 12% infection rate, most of them occurring in the time frame of 6–9 months. Further study is necessary to determine whether this timing can be generalized to all populations.

Infection occurred in 17% of the survivors (9 patients), proving to be a not uncommon complication after penetrating military injuries in our series. Of the 9 patients, only 1 patient had a bullet injury while the other 8 had blast in-

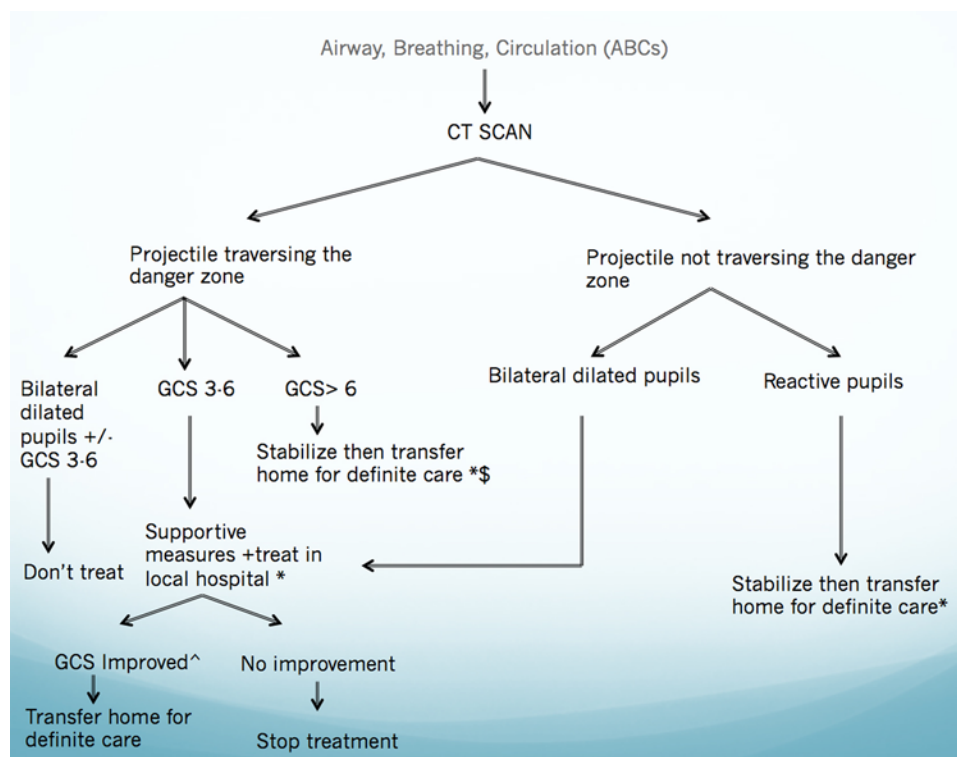


FIG. 3. Suggested protocol for managing military penetrating brain injuries in the war zone. Asterisk (*) = perform emergency surgical procedures, such as hemorrhage evacuation or decompressive craniectomy, promptly before transfer because these cannot wait until the patient is transferred. Caret (^) = the few victims with this specific scenario who survived became vegetative with the exception of only 1 patient. This patient in our series suffered his injury from a small pellet from an explosive device. On last follow-up his GOS score was 3. Dollar sign (\$) = this scenario did not occur in our series.

injuries from nails and other foreign bodies. We have thus learned to take infection more seriously in blast injuries and administer (intravenous) antibiotics for 2 weeks followed by oral therapy for another 2 weeks. We tried this protocol on the last 11 patients with blast injuries in the series and none of them have developed an infection of any kind so far. Moreover, we recommend aggressively debriding any superficial fragments or loose bone in any military-grade penetrating injury given the high incidence of infection.

In case they are chosen for treatment, patients with large-caliber missile injuries (such as AK-47 7.62 × 39-mm bullets) must have their bullets extracted as soon as possible in the war zone hospital if feasible. Unlike small-caliber 9-mm bullets, these bullets tend to migrate easily because of their heavy weight (Fig. 2), so it is advisable to extract them immediately and not delay the procedure until the patient is flown back home.

The most important limitation of this study is its retrospective nature. Future prospective studies are needed to implement this protocol and continue with its development and upgrading.

Conclusions

Managing penetrating military injuries in a war zone setting is different than managing the common civilian penetrating brain injuries that we usually encounter in our practice. We identified 3 predictors of mortality and poor

outcome and used them to develop a simple protocol for managing military penetrating injuries in the war zone. We also describe important lessons learned from this experience.

Acknowledgments

We thank the medical personnel and staff of Hospitals in Northern Sinai for their support and care for our patients. We also wish to express our gratitude for the Egyptian army soldiers and physicians who continue to sacrifice their lives to defend our freedom and values in the war against terrorism.

References

1. Aarabi B, Tofghi B, Kufera JA, Hadley J, Ahn ES, Cooper C, et al: Predictors of outcome in civilian gunshot wounds to the head. *J Neurosurg* **120**:1138–1146, 2014
2. Agarwalla PK, Dunn GP, Laws ER: An historical context of modern principles in the management of intracranial injury from projectiles. *Neurosurg Focus* **28**(5):E23, 2010
3. Bell RS, Mossop CM, Dirks MS, Stephens FL, Mulligan L, Ecker R, et al: Early decompressive craniectomy for severe penetrating and closed head injury during wartime. *Neurosurg Focus* **28**(5):E1, 2010
4. Bell RS, Vo A, Neal C, Tigno J, Roberts R, Mossop C, et al: Military traumatic brain and spinal column injury: a 5-year study of the impact blast and other military grade weaponry on the central nervous system. *J Trauma* **66** (4 Suppl):S104–S111, 2009

5. Gressot LV, Chamoun RB, Patel AJ, Valadka AB, Suki D, Robertson CS, et al: Predictors of outcome in civilians with gunshot wounds to the head upon presentation. **J Neurosurg** **121**:645–652, 2014
6. Kim KA, Wang MY, McNatt SA, Pinsky G, Liu CY, Giannotta SL, et al: Vector analysis correlating bullet trajectory to outcome after civilian through-and-through gunshot wound to the head: using imaging cues to predict fatal outcome. **Neurosurgery** **57**:737–747, 2005
7. Ragel BT, Klimo P Jr, Martin JE, Teff RJ, Bakken HE, Armonda RA: Wartime decompressive craniectomy: technique and lessons learned. **Neurosurg Focus** **28**(5):E2, 2010
8. Rosenfeld JV, Bell RS, Armonda R: Current concepts in penetrating and blast injury to the central nervous system. **World J Surg** **39**:1352–1362, 2015
9. Sakr S, Azzazi A, Elsayed A, Fathalla H: Surgical management of penetrating intracranial bullet injuries. **Neurosurg Q** **26**:37–41, 2016 2014
10. Smith JE, Kehoe A, Harrison SE, Russell R, Midwinter M: Outcome of penetrating intracranial injuries in a military setting. **Injury** **45**:874–878, 2014
11. Stephens FL, Mossop CM, Bell RS, Tigno T Jr, Rosner MK, Kumar A, et al: Cranioplasty complications following wartime decompressive craniectomy. **Neurosurg Focus** **28**(5):E3, 2010

Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Fathalla, El-Fiki. Acquisition of data: Ashry. Analysis and interpretation of data: all authors. Drafting the article: Fathalla. Critically revising the article: Fathalla, El-Fiki. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Fathalla. Statistical analysis: Fathalla. Administrative/technical/material support: Ashry. Study supervision: Fathalla, El-Fiki.

Correspondence

Hussein Fathalla: Cairo University Hospital, Cairo, Egypt.
sehs.fathalla@gmail.com.

Outcome of Craniocerebral Penetrating Injuries: Experience from the Syrian War

Mohammad Ahmad Jamous¹

¹ Department of Neurosurgery, Faculty of Medicine, Jordan University of Science and Technology, Irbid, Jordan

J Neurol Surg A

Address for correspondence Mohammad Ahmad Jamous, MD, PhD, Department of Neurosurgery, Faculty of Medicine, Jordan University of Science and Technology, Irbid, P.O. Box 3030, Jordan (e-mail: mojamous@yahoo.com).

Abstract

Objectives Gunshot wounds to the brain are the most fatal of all firearm injuries. The aim of this study was to evaluate mortality and morbidity in patients with penetrating craniocerebral gunshot injuries and to identify risk factors that affect the outcome.

Patients and Methods A retrospective review from June 2012 to November 2013 of 44 Syrian patients with gunshot wound to the head was performed. A thorough physical examination and computed tomography (CT) of the brain was obtained for all patients at the time of admission. Associated systemic injuries were found in 19 patients (43%). Surgical intervention was performed in 25 patients (57%); the remaining patients were managed conservatively. The patients were followed for a period of 1 to 15 months (range: 6 ± 2 months). Univariate analysis of patient age, sex, type of penetrating object, Glasgow Coma Scale (GCS) score and pupil size on admission, brain CT findings, presence of systemic injuries, and surgical intervention on the patient outcome was performed.

Results Eleven patients (25%) had a bullet injury; the remaining 33 (75%) patients had blast injuries. Initial brain CT revealed different types of skull fractures, intracerebral hemorrhage, and brain edema in all patients. The mortality rate during the follow-up period was 25%. Of the survivors, 25 patients (76%) had a good recovery, eight patients (24%) had a mild disability, and none had a severe disability. The significant factors determining outcome in this series were GCS on admission ($p < 0.005$) and positive pupil reaction to light ($p < 0.05$). The patient age, sex, CT findings, systemic injuries, neurosurgical intervention, and hospital length of stay were not significant prognostic factors ($p > 0.05$).

Conclusions Among various variables, GCS and pupil reactivity were the outcome predictors in patients with penetrating craniocerebral injuries. Age, sex, type of penetrating object, CT findings, and surgical intervention did not have a significant effect on survival for these kinds of injuries.

Keywords

- ▶ penetrating craniocerebral injuries
- ▶ Glasgow Coma Scale
- ▶ Glasgow Outcome Score
- ▶ gunshot wounds
- ▶ pupil reactivity

Introduction

Penetrating craniocerebral injuries occur when the dura mater is breached by a foreign body. Such injuries are typically the result of gunshot or blast wounds to the head, and traditionally and historically they are associated with

battlefield trauma and war injuries. In recent years, severe penetrating craniocerebral injuries have been witnessed in civilian populations due to ruthless militant and terrorist attacks in areas of political turmoil translated into chaotic wars as in areas of the so-called Arab Spring such as Yemen, Libya, and Syria.

received
October 22, 2018
accepted after revision
January 11, 2019

© Georg Thieme Verlag KG
Stuttgart · New York

DOI <https://doi.org/10.1055/s-0039-1683878>.
ISSN 2193-6315.

Penetrating craniocerebral injuries are usually fatal, especially in unprepared civilian populations who are in very close proximity to the blast and wear no helmets or armor. Most patients die at the accident scene or during patient transfer to the hospital; this group of patients does not get the chance to receive medical care in hospitals and hence to be studied by researchers. Only the very few fortunate survivors are available for medical teams to assess and evaluate.

The mortality rates in penetrating craniocerebral injuries among victims who survive to receive medical care in hospital varies between 10% and 90%.^{1,2} The clinical condition of the patient at the time of admission, manifested by the Glasgow Coma Scale (GCS) and pupil reaction to light, are the main factors affecting survival.² The more efficient the transfer system to the hospital, the lower the mortality rate.

Because there are few survivors, articles examining the recovery and outcome of such injuries are limited. The management strategy for these patients is still controversial and usually based on the experience of the neurosurgeon that differs according to the geographic area and wartime surgical experience. There are no solid guidelines for the type and timing of surgical intervention and for the selection of patients for such interventions.

Craniocerebral penetrating injuries have been a prominent injury of the Arab Spring era in different countries in the area. We are sharing our experience in managing patients with craniocerebral penetrating injuries transferred from Syria to King Abdulla University Hospital (KAUH) located within 10 km of the Jordanian-Syrian border. This report presents the assessment of 44 Syrian patients with penetrating craniocerebral injury and evaluates the possible predictive factors.

Patients and Methods

The charts of patients with penetrating craniocerebral injury from the Syrian crisis managed at KAUH over an 18-month period from June 2012 to November 2013 were collected and analyzed retrospectively. A total of 44 Syrian patients were managed in the neurosurgical department. Overall, 39 patients were male and 5 female. Patient ages ranged from 11 months to 63 years (range: 25 ± 14.4 years). To examine the effect of patient age on the outcome, we divided our patient into two groups: < 40 years (38 patients) and ≥ 40 years (6 patients). A total of 33 patients had a blast injury; the remaining 11 patients had a gunshot injury. The GCS on admission ranged from 3 to 15 (8 ± 5). The presence of one or both fixed and dilated pupils was found in 11 patients.

Computed tomography (CT) of the brain was performed for all patients at the time of admission and showed different types of skull fractures, intracranial hemorrhage (►Fig. 1), brain injuries, and brain edema (►Fig. 2a, b) in all patients. Significant midline shift (> 5 mm) was found in 10 patients (►Fig. 3). Some patients had foreign bodies in the brain parenchyma together with disintegrated bullets and shrapnel

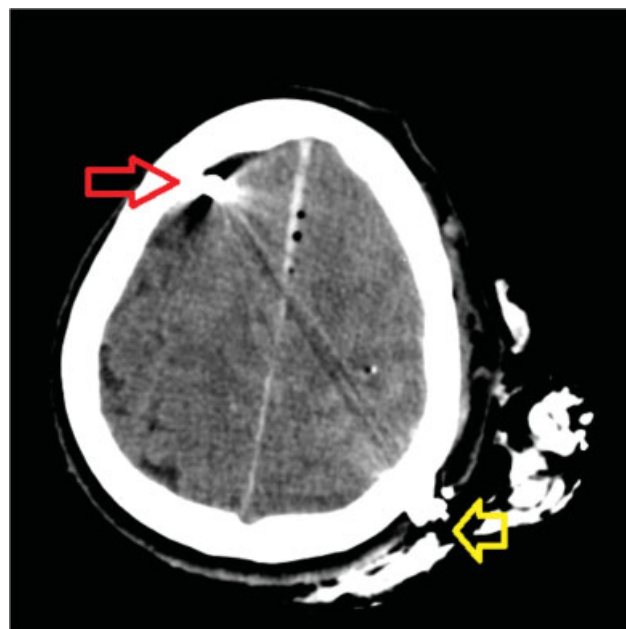


Fig. 1 Brain computed tomography scans of a 20-year-old woman after a blast injury showing left parietal entry (yellow arrow) with the tram-track sign. Shrapnel is present in the right frontoparietal area with metal artifact (red arrow). No midline shift was observed. She presented with a Glasgow Coma Scale score of 3/15, ruptured left eye globe, and normal size and light reactivity of the right pupil. She underwent a left temporoparietal craniotomy. Glasgow Outcome Score was 4/5 (aphasia).

nel (►Fig. 4a, b). Associated systemic injuries were found in 19 patients (43%).

All patients had surgical wound debridement and closure of the dura. Superficial foreign bodies and bone fragments were usually removed when cleaning and debriding the scalp wound. Deep foreign bodies were usually left in place to avoid unnecessary brain damage. Intensive medical management to control the elevated intracranial pressure (ICP) included hyperosmolar therapy, hyperventilation, and maintaining brain perfusion for all patients.

Decompressive craniectomy (DC) was performed in 19 patients (43%); the remaining patients were managed conservatively. The decision for DC was made by the attending neurosurgeon on an individual basis and on clinical and radiologic factors. Decreasing patient's level of consciousness two or more grades on GCS and/ or change in pupil size and reactivity, associated with expansion of an intracranial hematoma or increasing brain edema or midline shift > 5 mm, were considered indications for DC. The patients were followed for a period that varied from 1 to 15 months (6 ± 2 months).

The Glasgow Outcome Score was used to evaluate the patient's outcome (►Table 1). The mortality rate during the follow-up period was 25%. Of the survivors, 25 patients (76%) had a good recovery, 8 patients (24%) had a mild disability, and none of them had a severe disability. The outcome was either death in 11 (25%) or survival in 33 (75%) patients.

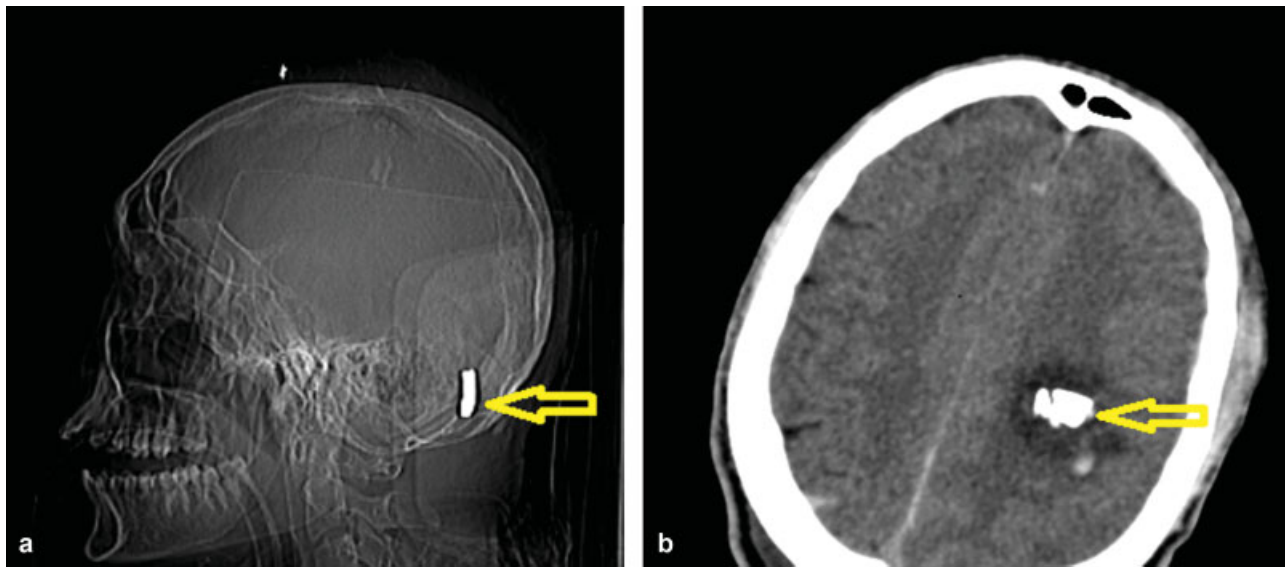


Fig. 2 A 21-year-old man with a bullet injury to the head. (a) The brain computed tomography (CT) scout lateral view shows intact shrapnel (arrow) in the posterior fossa. (b) CT scan shows bone fragments located deep in the parietal white matter with surrounding edema. He presented with Glasgow Coma Scale Score of 8/15 and bilateral reactive pupils. He was treated conservatively, and his Glasgow Outcome score was 4/5 (aphasia).

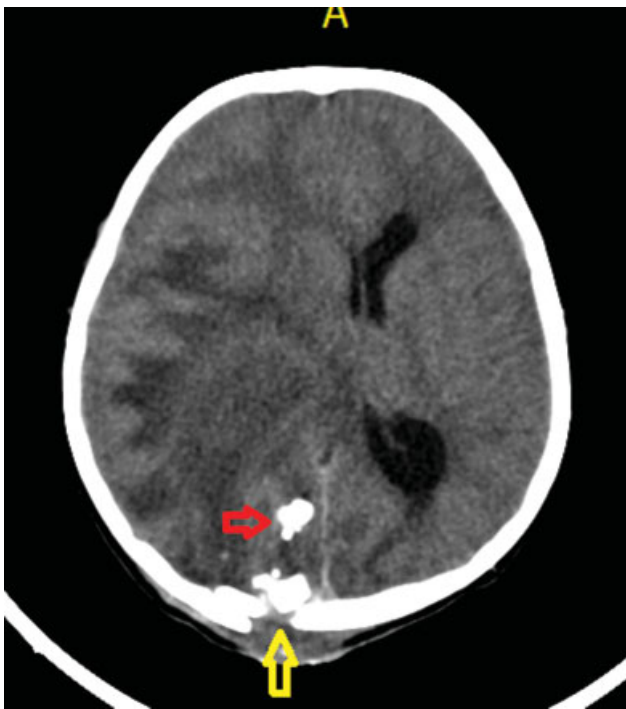


Fig. 3 A 26-year-old man with a blast injury presented with Glasgow Coma Scale score 14/15 and bilateral reactive pupils. Computed tomography shows multiple intracranial metallic shrapnel (arrows) in the deep frontoparietal white matter producing various artifacts. He was treated with a craniotomy and wound debridement. The Glasgow Outcome Score was 5/5 (no deficit).

The effect of different factors on patient mortality was analyzed. A p value < 0.05 was considered to indicate statistical significance. The Statistical Package for the Social Sciences (SPSS) v.14 (IBM, Inc., Armonk, New York, United States) was used to perform all inferential statistical analysis.

Data were analyzed and results expressed as mean \pm standard deviation (SD) for all descriptive variables.

Results

A total of 44 patients with penetrating craniocerebral gunshot wounds presented to KAUH between June 2012 and November 2013. Most of these patients were young, with a mean (\pm SD) age of 25 ± 14.4 years. There were 39 male and 5 female patients. The GCS on admission ranged from 3 to 15 (8 ± 5). Twenty patients had a GCS of 3 to 7, six patients had a GCS of 8 to 12, and 18 patients had a GCS of 13 to 15. Patients were categorized into two groups according to age: older and younger than 40 years ($p = 0.612$). The effect of sex ($p = 0.128$), type of penetrating injury ($p = 0.315$), midline shift on CT scan ($p = 0.213$), and DC ($p = 0.861$), hospital length of stay, and the presence of systemic injuries ($p = 0.922$) on the final outcome was also analyzed. The hospital stay was grouped in two segments: < 1 month and > 1 month. Seven (36.84%) of those who stayed < 1 month died compared with four (16%) of those who stayed > 1 month who died ($p > 0.05$).

► **Table 2** shows a univariate analysis for all the prognostic factors just described. The analysis showed that the only significant factors affecting survival were GCS on admission ($p < 0.005$) and pupil reaction to light ($p < 0.05$).

Discussion

Penetrating craniocerebral injuries from either a gunshot or blast are associated with high mortality rates; 71% of the deaths usually take place at the accident scene³; 66 to 90% take place during transfer or immediately after reaching the hospital⁴; and the overall survival rate is ~ 10 to 15%.⁵

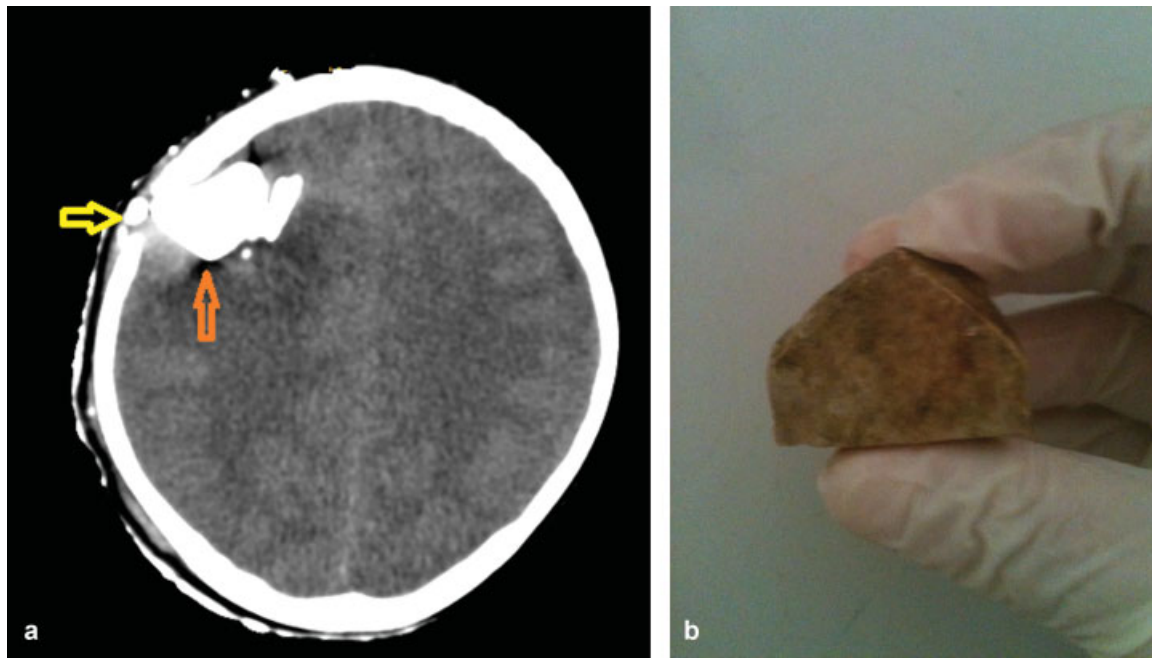


Fig. 4 A 5-year-old male victim of a blast injury presented with Glasgow Coma Scale score 3/15, small right pupil with sluggish reaction to light, and a fixed dilated pupil. (a) Computed tomography shows right frontal bone fracture with bone defect (yellow arrow) and a large intracranial foreign body (orange arrow). He underwent right decompressive craniectomy and removal of foreign bodies. (b) The largest foreign body was a 3 × 3-cm stone as shown after removal.

Table 1 Glasgow Outcome Scale in 44 patients with penetrating craniocerebral injury

| Patients | | | | | |
|-----------------------|---------------------|--|--------------------------------------|--|---|
| Glasgow Outcome Scale | Death | Survivor | | | |
| | <i>n</i> = 11 (25%) | <i>n</i> = 33 (75%) | | | |
| | | 2: persistent vegetative state <i>n</i> = 0 | 3: severe disability <i>n</i> = 0 | 4: mild disability <i>n</i> = 8 (24%) | 5: good recovery <i>n</i> = 25 (76%) |

The high mortality rate in these types of injuries can be explained by their damage mechanisms causing brain edema, intracranial bleeding, and penetrating injury to the brain introducing bone, metal fragments, and foreign bodies.

The guidelines for management of this type of injuries are still controversial. Medical management to control the high ICP caused by brain hemorrhage and edema is mandatory; however, the indication for surgical intervention is not yet clear.⁶ Our entire group of patients had vigorous medical management for ICP control composed of maintaining partial pressure of carbon dioxide in normal limits, using blood products and hyperosmolar therapy, correction of hypotension and hypoxia, and avoiding excess crystalloids. Surgical management was tailored individually; most patients had minimal surgical intervention for wound debridement, and others underwent major neurosurgical procedures including evacuations of hematoma and DC.

In the series we reviewed the mortality rate was 25%. This low mortality rate can be explained by the fact that this group of patients had less severe injuries and the patients were fortunate enough to reach the hospital.

The contrasting outcome with either death or good outcome (GOS 4 to 5) sounds unusual. It is explained by the close location of KAUH to the Syrian border that played a very significant role in improving the outcome in our series. Most of the dead patients either arrived dead or in very poor condition to the hospital because they did not receive any medical care before arriving. Unfortunately, political issues also prevented and delayed many patients from crossing the border and receiving the needed medical care.

We examined and reviewed the effect of different factors on the mortality of patients with craniocerebral penetrating injuries. The patient's clinical condition at the time of admission reflected by the GCS on admission and pupil

Table 2 Univariate analysis of prognostic factors in 44 patients with penetrating craniocerebral injuries

| Variable | Categories | Descriptive statistics | GOS | | Chi square | p |
|--|------------|------------------------|-------|----------|------------|--------------|
| | | | Died | Survived | | |
| Age, y | < 40 | Freq. | 9 | 29 | 0.257 | 0.612 |
| | | % | 23.68 | 76.32 | | |
| | ≥ 40 | Freq. | 2 | 4 | | |
| | | % | 33.33 | 66.67 | | |
| Sex | Male | Freq. | 8 | 30 | 2.316 | 0.128 |
| | | % | 21.05 | 78.95 | | |
| | Female | Freq. | 3 | 3 | | |
| | | % | 50.00 | 50.00 | | |
| Injury type | Blast | Freq. | 7 | 26 | 1.010 | 0.315 |
| | | % | 21.21 | 78.79 | | |
| | Bullet | Freq. | 4 | 7 | | |
| | | % | 36.36 | 63.64 | | |
| GCS significant correlation to outcome | 3–7 | Freq. | 9 | 11 | 10.489 | 0.005 |
| | | % | 45.00 | 55.00 | | |
| | 8–12 | Freq. | 2 | 4 | | |
| | | % | 33.33 | 66.67 | | |
| | 13–15 | Freq. | 0 | 18 | | |
| | | % | 0 | 100 | | |
| Pupil significant correlation to outcome | Reactive | Freq. | 5 | 26 | 6.198 | 0.013 |
| | | % | 16.13 | 83.87 | | |
| | Fixed | Freq. | 6 | 5 | | |
| | | % | 54.55 | 45.45 | | |
| CT | Yes | Freq. | 4 | 6 | 1.553 | 0.213 |
| | | % | 40.00 | 60.00 | | |
| | No | Freq. | 7 | 27 | | |
| | | % | 20.59 | 79.41 | | |
| Surgeries | No | Freq. | 6 | 19 | 0.031 | 0.861 |
| | | % | 24.00 | 76.00 | | |
| | Yes | Freq. | 5 | 14 | | |
| | | % | 26.32 | 73.68 | | |
| Systemic injury | No | Freq. | 6 | 18 | 0.010 | 0.922 |
| | | % | 25.00 | 75.00 | | |
| | Yes | Freq. | 5 | 14 | | |
| | | % | 26.32 | 73.68 | | |
| Duration | < 1 mo | Freq. | 7 | 12 | 2.501 | 0.114 |
| | | % | 36.84 | 63.16 | | |
| | > 1 mo | Freq. | 4 | 21 | | |
| | | % | 16.00 | 84.00 | | |

Abbreviations: Freq., frequency; GCS, Glasgow Coma Scale score; GOS, Glasgow Outcome Scale

Note: Boldface denotes $p \leq 0.05$.

size and reactions are the main factors that affected survival in our patients. These results were consistent with many different studies, as shown in ►Table 3.

However, patient age, sex, and type of injury (blast versus gunshot) did not influence the mortality in those patients.

Table 3 Studies describing relationship of GCS to final outcome in patients with penetrating craniocerebral injuries

| Study | Type | Year/Country | N (study period) | Site | Outcome measures | Main results | Remarks |
|------------------------------|---------------|--------------|--------------------|-------------------------|------------------|---|--|
| Kaufman et al ⁷ | Retrospective | 1986/USA | 143 (1980–1982) | Gang assaults, suicide | GOS | Survival was directly related to GCS and pupillary reflexes. Other less significant factors were hypoxia and blood alcohol level. | The first large review grading patients with GCS and GOS |
| Aldrich et al ⁸ | Prospective | 1992/USA | 151 (1984–1987) | Civilian gunshot wounds | Clinical picture | All patients who were alert and awake with a normal or near-normal neurologic examination at the time of admission survived with a good outcome. Of the 151 patients, 133 (88%) died. Of the 123 patients with initial GCS of 3–5, 116 (94%) died; of the 20 with an initial GCS of 6–8, 14 (70%) died. | NIH Traumatic Coma Data Bank |
| Graham et al ⁹ | Prospective | 1990/USA | 100 (18 mo) | Military and civilian | GOS | No patient with a GCS score of 3–5 had a satisfactory outcome; however, outcome progressively improved as the GCS score increased. | |
| Benzel et al ¹⁰ | Retrospective | 1991/USA | 120 (1980–1987) | Civilian | Clinical outcome | All awake patients had a good outcome; all comatose patients died. | |
| Clark et al ¹¹ | Retrospective | 1986/USA | 76 (1984–1985) | Civilian | Clinical outcome | Patients with a GCS score of 3 invariably died, with or without surgical intervention. | |
| Shaffrey et al ¹² | Retrospective | 1992/USA | 62 (1984–1990) | Civilian | Clinical outcome | Association between GCS ($p = 0.001$) and initial pupillary response ($p < 0.001$) and prognosis. | |
| Kennedy et al ¹³ | Retrospective | 1993 | 192 | Civilian | Clinical outcome | GCS scores on admission seemed to be the most important factor in predicting survival. | |
| Özkan et al ¹⁴ | Retrospective | 2002/Turkey | 107 (1993–2000) | Civilian | Clinical outcome | Level of consciousness is a reliable indicator of severity of injury and correlates predictably with morbidity and mortality. | |
| Martins et al ¹⁵ | Retrospective | 2003/Brazil | 319 (1994–2000) | Civilian | GOS | Significant correlation between low GCS score and higher mortality ($p < 0.001$). | |

Table 3 (Continued)

| | | | | | | | |
|-----------------------------|---------------|-------------------|----------------------------|----------|------------------|---|-------------------|
| Kim et al ¹⁶ | Retrospective | 2005/USA | 217 (2001–2002) | Civilian | Clinical outcome | GCS score and pupil irregularity were associated with fatal outcome ($p < 0.0001$). | |
| Tsuei et al ¹⁷ | Retrospective | 2005/Taiwan | 16 (1988–2002) | Civilian | GOS | Of the 7 patients with GCS score of > 8 , all survived with good outcomes; of the 9 patients with GCS score < 8 , 8 had poor outcomes; $p < 0.005$. | |
| Glapa et al ¹⁸ | Retrospective | 2007/South Africa | 55 (1999–2005) | Civilian | GOS | Mortality for patients with initial GCS score ≤ 8 was 81% versus 14% for patients with GCS score > 8 ($p \leq 0.0001$). | |
| Kim et al ¹⁹ | Retrospective | 2007/South Korea | 13 (> 22 y) | Civilian | GOS | Admission GCS was the most valuable prognostic factor. Of 9 patients with a GCS score > 8 , 8 patients survived with favorable outcomes; of the 4 patients with a GCS score < 8 , all had unfavorable outcomes. | |
| Hofbauer et al ¹ | Retrospective | 2010/Austria | 85 (1992–2008) | Civilian | GOS | GCS at admission and the status of pupils and hemodynamic situation seem to be the most significant predictors of outcome in penetrating craniocerebral gunshot wounds. | |
| Aarabi et al ³ | Retrospective | 2014/USA | 786 (over a 2-y period) | Civilian | GOS | Admission GCS score, trajectory of the missile track, APR to light, and patency of basal cisterns were significant determinants of outcome in civilian GSWH. | Multicenter study |

Abbreviations: APR, abnormal pupillary response; ICP, intracranial pressure; GSWH, gunshot wound to the head; GCS, Glasgow Coma Score; GOS, Glasgow Outcome Score, NIH, National Institutes of Health.

Conclusion

Penetrating craniocerebral injuries are catastrophic injuries usually associated with a high mortality rate and have been seen increasingly over the last few decades in different parts of the world due to local wars and terrorist attacks. Significant prognostic factors of a good outcome are a high GCS on admission and pupils reactive to light.

Conflict of Interest

None declared.

References

- Hofbauer M, Kdolsky R, Figl M, et al. Predictive factors influencing the outcome after gunshot injuries to the head—a retrospective cohort study. *J Trauma* 2010;69(04):770–775
- DuBose JJ, Barmparas G, Inaba K, et al. Isolated severe traumatic brain injuries sustained during combat operations: demographics, mortality outcomes, and lessons to be learned from contrasts to civilian counterparts. *J Trauma* 2011;70(01):11–16; discussion 16–18
- Aarabi B, Tofighi B, Kufera JA, et al. Predictors of outcome in civilian gunshot wounds to the head. *J Neurosurg* 2014;120(05):1138–1146
- Gressot LV, Chamoun RB, Patel AJ, et al. Predictors of outcome in civilians with gunshot wounds to the head upon presentation. *J Neurosurg* 2014;121(03):645–652
- Joseph B, Aziz H, Pandit V, et al. Improving survival rates after civilian gunshot wounds to the brain. *J Am Coll Surg* 2014;218(01):58–65
- Rosenfeld JV, Bell RS, Armonda R. Current concepts in penetrating and blast injury to the central nervous system. *World J Surg* 2015;39(06):1352–1362
- Kaufman HH, Makela ME, Lee KF, Haid RW Jr, Gildenberg PL. Gunshot wounds to the head: a perspective. *Neurosurgery* 1986;18(06):689–695
- Aldrich EF, Eisenberg HM, Saydjari C, et al. Predictors of mortality in severely head-injured patients with civilian gunshot wounds: a report from the NIH Traumatic Coma Data Bank. *Surg Neurol* 1992;38(06):418–423
- Graham TW, Williams FC Jr, Harrington T, Spetzler RF. Civilian gunshot wounds to the head: a prospective study. *Neurosurgery* 1990;27(05):696–700; discussion 700
- Benzel EC, Day WT, Kesterson L, et al. Civilian craniocerebral gunshot wounds. *Neurosurgery* 1991;29(01):67–71; discussion 71–72
- Clark WC, Muhlbauer MS, Watridge CB, Ray MW. Analysis of 76 civilian craniocerebral gunshot wounds. *J Neurosurg* 1986;65(01):9–14
- Shaffrey ME, Polin RS, Phillips CD, Germanson T, Shaffrey CI, Jane JA. Classification of civilian craniocerebral gunshot wounds: a multivariate analysis predictive of mortality. *J Neurotrauma* 1992;9(Suppl 1):S279–S285
- Kennedy F, Gonzalez P, Dang C, Fleming A, Sterling-Scott R. The Glasgow Coma Scale and prognosis in gunshot wounds to the brain. *J Trauma* 1993;35(01):75–77
- Özkan U, Kemaloglu S, Ozates M, Aydin MD. Analysis of 107 civilian craniocerebral gunshot wounds. *Neurosurg Rev* 2002;25(04):231–236
- Martins RS, Siqueira MG, Santos MT, Zanon-Collange N, Moraes OJ. Prognostic factors and treatment of penetrating gunshot wounds to the head. *Surg Neurol* 2003;60(02):98–104; discussion 104
- Kim KA, Wang MY, McNatt SA, et al. Vector analysis correlating bullet trajectory to outcome after civilian through-and-through gunshot wound to the head: using imaging cues to predict fatal outcome. *Neurosurgery* 2005;57(04):737–747; discussion 737–747
- Tsuei YS, Sun MH, Lee HD, et al. Civilian gunshot wounds to the brain. *J Chin Med Assoc* 2005;68(03):126–130
- Glapa M, Kourie JF, Doll D, Degiannis E. Early management of gunshot injuries to the face in civilian practice. *World J Surg* 2007;31(11):2104–2110
- Kim TW, Lee JK, Moon KS, et al. Penetrating gunshot injuries to the brain. *J Trauma* 2007;62(06):1446–1451



The patient with severe traumatic brain injury: clinical decision-making: the first 60 min and beyond

Jeroen T.J.M. van Dijk^a, Ronald H.M.A. Bartels^b, Jan C.M. Lavrijsen^c, Gerard M. Ribbers^{d,e}, Erwin J.O. Kompanje^f, and Wilco C. Peul^g,
On behalf of all focus group participants

Purpose of review

There is an urgent need to discuss the uncertainties and paradoxes in clinical decision-making after severe traumatic brain injury (s-TBI). This could improve transparency, reduce variability of practice and enhance shared decision-making with proxies.

Recent findings

Clinical decision-making on initiation, continuation and discontinuation of medical treatment may encompass substantial consequences as well as lead to presumed patient benefits. Such decisions, unfortunately, often lack transparency and may be controversial in nature. The very process of decision-making is frequently characterized by both a lack of objective criteria and the absence of validated prognostic models that could predict relevant outcome measures, such as long-term quality and satisfaction with life. In practice, while treatment-limiting decisions are often made in patients during the acute phase immediately after s-TBI, other such severely injured TBI patients have been managed with continued aggressive medical care, and surgical or other procedural interventions have been undertaken in the context of pursuing a more favorable patient outcome. Given this spectrum of care offered to identical patient cohorts, there is clearly a need to identify and decrease existing selectivity, and better ascertain the objective criteria helpful towards more consistent decision-making and thereby reduce the impact of subjective valuations of predicted patient outcome.

Summary

Recent efforts by multiple medical groups have contributed to reduce uncertainty and to improve care and outcome along the entire chain of care. Although an unlimited endeavor for sustaining life seems unrealistic, treatment-limiting decisions should not deprive patients of a chance on achieving an outcome they would have considered acceptable.

Keywords

decision-making, end of life, medical ethics, prognosis, traumatic brain injury

INTRODUCTION

Many patients who sustain severe traumatic brain injury (s-TBI) die after trauma or survive with (severe) disabilities [1^{*},2,3^{*},4^{*},5]. Performing lifesaving (surgical) interventions may result in survival, but there is neither a common opinion on how to define an unfavorable outcome, nor on the time horizon of assessing such outcome [5–8,9^{*}]. Treatment-limiting decisions likely result in clinical deterioration and death [10,11,12^{**}]. Most acute treatment decisions are poorly supported by high-quality evidence and prognostic algorithms, leaving shared decision-making complex [8,13^{*},14,15^{*}]. Perhaps in light of such lack of clarity, nonadherence to guidelines and substantial treatment variation remains pervasive [16,17,18^{*}].

Therefore, we examine such treatment paradoxes by reviewing the literature and reporting on several interdisciplinary panel meetings that

^aDepartment of Neurosurgery, University Neurosurgical Center Holland, LUMC-HMC & Haga, Leiden/The Hague, ^bDepartment of Neurosurgery, Radboud University Medical Center, ^cDepartment of Primary and Community Care, Radboud University Medical Centre, Nijmegen, ^dDepartment of Rehabilitation Medicine, Erasmus University Medical Centre, ^eRijndam Rehabilitation and ^fDepartment of Intensive Care Medicine, Erasmus Medical Centre, Rotterdam, The Netherlands

Correspondence to Jeroen T.J.M. van Dijk, MD, Department of Neurosurgery, Leiden University Medical Center Albinusdreef 2, J-11-R-83 2333ZA, Leiden, The Netherlands. Tel: +31 71 5266987; e-mail: j.t.j.m.van_dijk@lumc.nl

Curr Opin Crit Care 2019, 25:622–629

DOI:10.1097/MCC.0000000000000671

KEY POINTS

- Although multiple recent efforts have contributed to reduce uncertainty and to improve care and outcome for severe traumatic brain injury (s-TBI) patients along the entire chain of care, there remain many uncertainties and paradoxes and a lack of objective criteria in clinical decision-making after s-TBI.
- Although important for decision-making, well validated prognostic models predicting long-term outcome on quality of life and satisfaction with life after s-TBI are currently unavailable.
- Some of the most severely injured TBI patients have been reported to have achieved 'favorable' outcome and (surgical) interventions are generally considered beneficial for patient outcome.
- To further improve s-TBI care, future research should identify and decrease the existing selectivity and identify objective criteria in decision-making and reduce the impact of subjective valuations of predicted patient outcome.

focused on clinical decision-making in initiating or withholding (surgical) intervention to patients after s-TBI. This position paper was written following a series of discussions with an expert panel of professionals from different backgrounds, and should serve as a starting point for further discussions rather than constitute a final outcome process.

PROFESSIONAL CODE OF PHYSICIANS

Physicians practice medicine by working according to several codes of conduct and by following four universally accepted moral principles in medical ethics (Table 1) [19–23].

Autonomy of the patient is inherently compromised in patients with s-TBI, and proxies are often absent during the acute phase, improperly designated, or incapable of substitute informed decision-making [24*,25,26**]. Physicians then are responsible for selecting a strategy they consider in line with a patients' best interests, that is, *beneficence*. However, both medical and surgical or procedural

interventions carry risks of inducing harm, creating a difficult equilibrium between beneficence and non-maleficence [2,9*,27,28]. Lastly, justice requires the fair distribution of benefits, risks and limited medical goods and services. As such, resources should ethically be restricted when used on so-called ineffective and disproportional treatment efforts, as it will deprive other patients of potentially effective treatments.

TREATMENT-LIMITING DECISIONS

Treatment-limiting decisions, including withholding lifesaving (surgical) interventions or withdrawal of life-sustaining medical treatment, are sometimes made within the first 2 days after s-TBI, allowing for, and leading to consequences of death, further deterioration and depriving patients a chance for recovery [10,12**,29*]. Furthermore, defining recovery is relative, as it may encompass the entire spectrum from saving a patients' life, achieving good health-related quality of life, to entire satisfaction with one's recovery [1*,4*,30,31*,32*].

Although withdrawal of life-sustaining measures can be morally justified, and in line with patients' and proxies' preferences and values, it should be noted that such decisions are typically based on nondate-driven clinical prognostication, the goal of achieving survival with an imprecisely defined 'favorable' outcome [33**]. As 'favorable' outcome has been reported in even some of the most severely injured patients, treatment-limiting decisions in patients that might have achieved 'favorable outcome' must, therefore, arguably be difficult to uphold on ethical and moral grounds [2,4*].

REASONS FOR TREATMENT-LIMITING DECISIONS

Several recent studies have aimed to identify what specific reasons or values constitute decision-making in severe brain injuries by medical teams, proxies or patients, but much remains unexplained [10,12**,18*,34*,35,36]. Physicians are likely to

Table 1. Moral principles in medical ethics

| Principle | Description |
|----------------|--|
| Autonomy | A norm of respecting and supporting autonomous decisions. |
| Beneficence | A group of norms pertaining to relieving, lessening, or preventing harm and providing benefits and balancing benefits against risks and costs. |
| Nonmaleficence | A norm of avoiding the causation of harm. |
| Justice | A group of norms for fairly distributing benefits, risks, and costs. |

Table 2. Reasons, including potential outcome perspectives, to strongly consider treatment-limiting decisions

| Number | Proposed reasons |
|--------|---|
| 1 | Brain death, from a patient perspective (not considering interests regarding organ donation procedures) [38,39] |
| 2 | (chronic) Unresponsive wakefulness syndrome [40 ^{aa} ,41 ^{aa}] |
| 3 | Minimally conscious state – (minus) (i.e. visual pursuit, localization of noxious stimuli, appropriate smiling or crying to emotional stimuli) [40 ^{aa} ,42] |
| 4 | An available, unquestionable, written and signed specific advance directive of the patient that prohibits treatment in a specific situation (possibly related to expected outcome) |
| 5 | A proxy opinion that is unquestionably based on patient preferences and that is not in conflict with the attending medical teams' considerations, that prohibits treatment in a specific situation (possibly related to expected outcome) |
| 6 | A patient's view (or when necessary a reconstructed vision through surrogates) on life and quality of life is contrary to the outcome that can be expected from the best available prognostic models. |
| 7 | Treatment costs along the whole chain of care that are not cost-effective and higher than the maximum amount that has been decided by national legislation |

Reasons are reported in random order.

include their personal valuation of predicted patient outcome in their treatment considerations based on a mix of factors, such as religious background, personal and clinical experience, culture, national legislation, and even the socioeconomic status of the patient [18^{*},37]. This introduces the risk of selectivity and is not evidence-based medicine [18^{*}].

To elaborate on this, the authors, specialists in neurosurgery, intensive care medicine, rehabilitation, chronic care, anthropology and medical ethics, executed a multiple occasion professionally led focus group discussion. We explored and described the process and reasoning of decision-making in this manuscript and propose several reasons that would legitimize treatment-limiting decisions (Table 2).

'ACCEPTABLE' VERSUS 'UNACCEPTABLE' OUTCOME

Valuation of outcome is probably one of the most important aspects in decision-making, but exact definitions of acceptable or unacceptable outcome after s-TBI remain elusive [18^{*},43]. In literature, 'upper severe disability' (Glasgow Outcome Scale-Extended) and 'the inability to walk' or 'functionally dependent' (Modified Rankin Scale of 4) are sometimes considered favorable outcomes, whereas most physicians and researchers would classify this outcome degree as unfavorable [43,44]. Most competent individuals, irrespective of age, religion or background, consider survival with unfavorable outcome on the Glasgow Outcome Scale (GOS) unacceptable. However, survivors with so-called 'unfavorable outcome' after decompressive craniectomy for s-TBI and caregivers of patients after decompressive craniectomy appear to change their definition of 'a good quality of life' (QOL) and would

have provided retrospective consent for the intervention [9^{*},32^{*}]. Clearly, the favorable/unfavorable cut-off point used in prognostic models and TBI studies does not necessarily represent an acceptable/unacceptable outcome for patients [9^{*},43].

Healthy individuals are generally unable to predict accurately what future QOL would be acceptable or unacceptable to them, because they often underestimate their ability to adapt to levels of disability they previously considered unacceptable [45]. The absence of a linear connection between disabilities and experienced QOL known as the disability paradox is seen in patients with severe disabilities reporting a good QOL (i.e. s-TBI, locked-in syndrome, Duchenne) [9^{*},46,47]. This does not validate lifesaving/sustaining interventions in all patients, but suggests that physicians should acknowledge that an unacceptable outcome in their opinion may not necessarily be unacceptable to patients.

Determining cut-off points of acceptability is highly arbitrary and nearly impossible because of countless outcome possibilities and substantial variation in peoples' ever-changing desires and interpretations of a 'good life'. For instance, a life could be worth sustaining regardless of any favorability classifications because it has intrinsic value to relatives and friends, or because of cultural or religious reasons [48^{*}].

PROGNOSTIC UNCERTAINTY

Accurate outcome prediction remains unavailable, although it has huge consequences on decision-making and it is crucial for patients, proxies and physicians [18^{*},35,45,49,50]. Physicians are frequently unable to make accurate predictions and although prognostication may be considered

straightforward at the extremes of the spectrum, it remains difficult in the middle [29^{*},36,45]. This is disturbing, as a physician's perception on long-term prognosis likely influences treatment decisions. The long-term physical, cognitive, emotional and behavioral outcome after TBI is determined by injury characteristics as well as by contextual factors of the patient and the caregiver. Such issues are not covered in the CRASH and IMPACT prognostic models that focus on mortality and severe disability at 6 months' post injury. Although helpful in estimating survival, these models do not cover outcomes, such as independence in daily living and ultimately perceived satisfaction with life [45,51,52,53^{*},54^{**}].

The reasons for failure of prediction are: the heterogeneous nature of s-TBI and concurring comorbidities and their unknown effect on outcome [50,55,56^{*},57]; unclear/incomplete clinical information, including a patient's neurological state or level of consciousness [58,59]; largely unknown pathophysiological mechanisms of brain injury and inherent degree of plasticity [50,60^{**},61^{*},62,63,64^{*}]; prediction models do not include long-term (health-related) QOL, although long-term outcome changes have been reported and patients/proxies value this outcome [3^{*},28,31^{*},65,66]; prediction models are based on large retrospective data sets that do not necessarily reflect current or future treatment strategies [8,67,68^{*},69].

Balancing between beneficence and nonmaleficence in clinical decision-making after s-TBI is a process of weighing the chance between favorable and nonfavorable outcome based on clinical expertise and subjective evaluations with ill-defined clinical endpoints [45]. Yet, it is considered common sense that lifesaving interventions should be withheld when the predicted risk of 'unfavorable' outcome is high, whereas depriving a patient of a possible favorable outcome can be seen as inappropriate care. The approach to treat all patients with the potential to survive inherently includes the risk of survival with an unacceptable outcome. All physicians should appreciate and communicate the existing multidimensional uncertainty, and decisions should not be guided by assumptions that falsely confer a sense of certainty [29^{*},33^{**}].

The risk of selection bias and self-fulfilling prophecies should be noted. Assumptions on poor prognosis that lead to treatment-limiting decisions and probably contribute to a worse outcome and possibly death in selected cases [12^{**},33^{**},70].

IMPROVING PROGNOSTICATION

In clinical care the estimated prognosis is based on clinical characteristics, subjective evaluation of the

clinician and contextual information at a short interval post onset. However, prognosis after s-TBI is dynamic in which the passage of time changes the predicted probability of a favorable outcome [71^{*},72]. In case of prognostic uncertainty and a small chance of 'acceptable' outcome, full critical care treatment should be initiated and continued to allow for best possible recovery. Information on clinical progress, neurological recovery, the patient's treatment and outcome preferences (when necessary through proxies), and multidisciplinary discussion (ideally with moral council) need to be included in decision-making – and this information only becomes available with time.

Striving for personalized care is promising and allows for appreciation of the general injury applied in an individualized context [73]. In the subacute phase, frequent re-evaluation and communication are essential; when treatment has become disproportionate, given the outcome, withdrawal of life-sustaining measures can be considered even at later moments in time. Despite the associated increased healthcare consumption and costs, the survival of patients with severe disabilities and the longer period of suffering for patients/proxies can be legitimized if more patients survive with acceptable outcome.

PATIENT, PROXY OR SHARED DECISION-MAKING

Values, preferences and treatment wishes of patients (when necessary obtained through proxies) are to be respected and should be incorporated in clinical decision-making. Patient with s-TBI are incapable to decide, and their preferences have rarely been discussed with proxies or recorded in an (written) advance directive [18^{*},48^{*}]. Proxies are then confronted with difficult treatment dilemmas, but information as desired by proxies is not always provided and a patients' social circumstances and preferences are not always included in physicians' decision-making process [34^{*},35]. Proxies might also misjudge or deliberately misrepresent patients' preferences [24^{*},74].

Proxies are mostly unprepared, confused by uncertainty and hope, and unequipped to fully understand the uncertainties of prognostication and clinical decision-making [7,75].

This puts a high burden on the clinician's shoulders. Although medical paternalism is increasingly replaced by 'shared decision-making', the latter remains a difficult, if not impossible proposition when required in neurocritical care [26^{**},76^{*}]. To improve conversations with proxies, it is recommended to provide early, frequent, understandable, honest, and consistent multidisciplinary communication about

the patient's condition, consequences of actions, and prognosis, while acknowledging an acceptable level of uncertainty. Although specific needs are highly variable as perceptions are different and often inconsistent with reality, physicians must align unrealistic expectations with medical reality; in case of conflicts, moral deliberation could be helpful and otherwise professional judgement should prevail.

CONSIDERATIONS FROM A SOCIETAL PERSPECTIVE

'The rule of rescue' is a powerful ethical proclivity ingrained in human nature, possible even more in acute care physicians, to rescue those in immediate danger, regardless of risks or costs [77]. 'Performing against the odds' heroism is often in conflict with the utilitarian approach, which aims at the overall performance of the entire healthcare system instead of the entire focus being on the benefits of a single individual.

In this context, it is considered difficult to justify lifesaving neurosurgical interventions resulting in unacceptable outcome at enormous healthcare costs. The ethical question transcends from individual values to societal and political valuation of life related to costs. Studies assessing in-hospital costs after s-TBI, however, suggest rather an 'acceptable' degree of in-hospital treatment costs, although variation is high and study quality generally poor [2,78]. Studies on the long-term costs of patients after s-TBI or patients with severe disorders of consciousness are unfortunately scarce, prohibiting solid conclusions. Admittedly, money that has been spent cannot be used to treat other patients with possibly more effective treatments. This perspective, however, should not be a prominent variable in arguing for, or against early treatment-limiting decisions. Depriving some patients of recovery to an acceptable outcome should be absolutely minimized in societal decision-making.

Nonetheless, there must be a point where TBI is so severe and patient outcome so unacceptable as to justify the enormous associated healthcare costs. Establishing this point is necessary because healthcare costs increase and healthcare budgets are limited. Therefore, the cost-effectiveness of interventions should be evaluated, and weighted to the maximum amount. Limitations on costs to maintain life have already been set by politicians. For example, the cut-off of cost-effective treatments in The Netherlands is \$80,000 per quality adjusted life year [79]. The justification and number of this cut-off should not be determined solely by politicians, but also involve the contributions of experienced physicians and other health-care professionals.

A commonly perceived advantage of including this economic perspective in decision-making is the objectivity of the criterion to decide whether or not to perform an intervention. We should, however, not forget that focusing on cost-benefit analyses fails to recognize individual aspects of care and the social utility of caring for those most in need. People obtain benefit from the belief that they live in a compassionate and humane society where patients in need will not be ignored merely on the basis of costs.

ACUTE AND CHRONIC CARE

Because of the chronic consequences of s-TBI, many patients and proxies need adequate lifelong care to optimize outcome [80,81]. Specialized rehabilitation, long-term care and patience are essential for recovery [14,82*,83,84**]. Caretakers and researchers of both subacute and chronic care should collaborate closely and become familiar with the needs, challenges and possibilities along the entire chain of care.

Regrettably, in some healthcare systems, patients without enough progress of recovery during rehabilitation are discharged to nursing homes lacking proper rehabilitation or diagnostic oversight, depriving them of opportunities to recover [75,85]. This seems unfair, as 'normal' recovery processes of patients and their brains still remain largely unknown, and subtle progress is known to be missed because of a physician's generally poor evaluation [1*,28,59,60**,61*]. Many novel rehabilitation initiatives have been developed, and also improved coping interventions appear now to be more effective [62,64*,85-87,88**]. Until we really know what is best, providing appropriate care is something that we as a society morally owe to all patients, while not discounting that catastrophic conditions, such as unresponsive wakefulness syndrome or minimally conscious state are accompanied by severe disabilities and enormous challenges [41**,89]. Although the gravity of the outcome could be obscured by the gratitude of survival, many will doubt this is a life worth living [75].

FUTURE RESEARCH

Future research initiatives will focus on the effectiveness of new diagnostic and treatment modalities including short-term and long-term functional outcome and health-related QOL, along the whole chain of care [90,91]; the measurement of well being and impact on proxies and society; establishing values of dignified existence (i.e. with ex-patients,

proxies, physicians); specialized education programs for professionals and patients/proxies on the topic of s-TBI; improving the reliability of prognostic models by machine learning [92*,93].

Although these initiatives seem promising, and will likely improve TBI care when successful, we should not underestimate the difficulties in conducting traditional studies, such as not only the variation between patients, injuries and healthcare systems but also the variety and potential boundaries of ethics and culture. Randomization of severely injured TBI patients, as one example, is considered inappropriate by many physicians. Prospective, large, multicentered, compared-effectiveness research initiatives might provide necessary evidence in the future [50].

CONCLUSION

Decision-making in s-TBI is highly complicated because of uncertainty regarding treatment cost-effectiveness, prognostication and unacceptability of outcome, which are caused by a lack of scientific evidence and also by different societal and individual values. Physicians absolutely do not intentionally deprive patients of a chance on achieving an outcome they would have considered acceptable. Research collaborations between medical specialties and across the borders of traditional sciences of medicine, sociology and philosophy might lead to practical evidence, reduced uncertainty and improved care and outcome for s-TBI patients.

Acknowledgements

As this manuscript was the result of several focusgroups and we could only list six out of nine participants as authors, we would like to thank Iain Haitisma (neurosurgeon, Erasmus Medical Center, Rotterdam), Ria Reis (professor of medical anthropology, Leiden University Medical Center, Leiden) and Jan Kleijne (former CEO of Meander Medical Center, Amersfoort) for their substantial contribution to both the focusgroups 'and this manuscript. Their contribution was equal to the contribution of the listed authors.

Financial support and sponsorship

This work was supported by Hersenstichting Nederland (Dutch Brain Foundation) for Neurotraumatology Quality Registry (Net-QuRe).

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest

*** of outstanding interest

1. Grauwmeijer E, Heijnenbroek-Kal MH, Peppel LD, *et al.* Cognition, health-related quality of life, and depression ten years after moderate to severe traumatic brain injury: a prospective cohort study. *J Neurotrauma* 2018; 35:1543–1551.
2. van Dijck JT, Reith FC, van Erp IA, *et al.* Decision making in very severe traumatic brain injury (Glasgow Coma Scale 3-5): a literature review of acute neurosurgical management. *J Neurosurg Sci* 2018; 62:153–177.
3. Ruet A, Bayen E, Jourdan C, *et al.* A detailed overview of long-term outcomes in severe traumatic brain injury eight years postinjury. *Front Neurol* 2019; 10:120.
4. van Eijck M, van der Naalt J, de Jongh M, *et al.* Patients with diffuse axonal injury can recover to a favorable long-term functional and quality of life outcome. *J Neurotrauma* 2018; 35:2357–2364.
5. Moskowitz E, Melendez CI, Dunn J, *et al.* Long-term effects of decompressive craniectomy on functional outcomes after traumatic brain injury: a multicenter study. *Am Surg* 2018; 84:1314–1318.
6. Pujari R, Hutchinson PJ, Kolias AG. Surgical management of traumatic brain injury. *J Neurosurg Sci* 2018; 62:584–592.
7. McGowan T. Will you forgive me for saving you? *N Engl J Med* 2018; 379:8–9.
8. Carney N, Totten AM, O'Reilly C, *et al.* Guidelines for the management of severe traumatic brain injury, fourth edition. *Neurosurgery* 2017; 80:6–15.
9. Honeybul S. Long-term outcome following severe traumatic brain injury: ethical considerations. *J Neurosurg Sci* 2018; 62:599–605.
10. Robertsen A, Forde R, Skaga NO, *et al.* Treatment-limiting decisions in patients with severe traumatic brain injury in a Norwegian regional trauma center. *Scand J Trauma Resusc Emerg Med* 2017; 25:44.
11. Jochems D, van Wessem KJP, Houwert RM, *et al.* Outcome in patients with isolated moderate to severe traumatic brain injury. *Crit Care Res Pract* 2018; 2018:3769418.
12. Leblanc G, Boutin A, Shemilt M, *et al.* Incidence and impact of withdrawal of life-sustaining therapies in clinical trials of severe traumatic brain injury: a systematic review. *Clin Trials* 2018; 15:398–412.
13. Synnot A, Bragge P, Lunney C, *et al.* The currency, completeness and quality of systematic reviews of acute management of moderate to severe traumatic brain injury: a comprehensive evidence map. *PLoS One* 2018; 13:e0198676.
14. Bayley MT, Lamontagne ME, Kua A, *et al.* Unique features of the INESSS-ONF rehabilitation guidelines for moderate to severe traumatic brain injury: responding to users' needs. *J Head Trauma Rehabil* 2018; 33:296–305.
15. Stocchetti N, Poole D, Okonkwo DO. Intracranial pressure thresholds in severe traumatic brain injury: we are not sure: prudent clinical practice despite dogma or nihilism. *Intensive Care Med* 2018; 44:1321–1323.
16. Volovici V, Ercole A, Citerio G, *et al.*, CENTER-TBI collaborators. Variation in guideline implementation and adherence regarding severe traumatic brain injury treatment: a CENTER-TBI survey study in Europe. *World Neurosurg* 2019. [Epub ahead of print]
17. van Essen TA, den Boogert HF, Cnossen MC, *et al.*, CENTER-TBI Investigators and Participants. Variation in neurosurgical management of traumatic brain injury: a survey in 68 centers participating in the CENTER-TBI study. *Acta Neurochir (Wien)* 2019; 161:435–449.

18. Boyer F, Audibert G, Baumann C, *et al.* Decision-making regarding treatment & limitation after severe traumatic brain injury: a survey of French neurosurgeons. *Neurochirurgie* 2018; 64:401–409.
Decision-making in traumatic brain injury is not well understood. Surveys as reported in this article help understand why physicians make decisions and could explain treatment variation or identify future research directives.
19. Czech H, Druml C, Weindling P. Medical ethics in the 70 years after the Nuremberg code, 1947 to the present. *Wien Klin Wochenschr* 2018; 130:159–253.
20. Beauchamp TC, Childress JF. Principles of biomedical ethics. 7th ed. New York: Oxford University Press; 2013.
21. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013; 310:2191–2194.
22. Parsa-Parsi RW. The revised declaration of Geneva: a modern-day physician's pledge the revised declaration of Geneva: the modern-day physician's pledge. *JAMA* 2017; 318:1971–1972.
23. World Medical Association Declaration of Taipei on ethical considerations regarding health databases and biobanks. Published October 2016. Available at: <https://www.wma.net/policies-post/wma-declaration-of-taipei-on-ethical-considerations-regarding-health-databases-and-biobanks/>. [Accessed 17 May 2019]
24. Turnbull AE, Chessare CM, Coffin RK, *et al.* More than one in three proxies do & not know their loved one's current code status: an observational study in a Maryland ICU. *PLoS One* 2019; 14:e0211531.
Decisions in clinical practice are frequently discussed with proxies, especially in mentally incapacitated patients. This article reports the accuracy of proxy decision-making.
25. Frey R, Herzog SM, Hertwig R. Deciding on behalf of others: a population survey on procedural preferences for surrogate decision-making. *BMJ Open* 2018; 8:e022289.
26. Grignoli N, Di Bernardo V, Malacrida R. New perspectives on substituted && relational autonomy for shared decision-making in critical care. *Crit Care* 2018; 22:260.
This viewpoint article describes the clinical environment of mentally incapacitated patients where treatment decisions have to be made. New perspectives on substituted relational autonomy are discussed in an attempt to improve shared decision-making in critical care.
27. Gopalakrishnan MS, Shanbhag NC, Shukla DP, *et al.* Complications of decompressive craniectomy. *Front Neurol* 2018; 9:977.
28. Forslund MV, Perrin PB, Roe C, *et al.* Global outcome trajectories up to 10 years after moderate to severe traumatic brain injury. *Front Neurol* 2019; 10:219.
29. Pratt AK, Chang JJ, Sederstrom NO. A fate worse than death: prognostication & of devastating brain injury. *Crit Care Med* 2019; 47:591–598.
The authors elaborate on the uncertainties on prognosticating devastating brain injury in the ICU. Supportive care is recommended for at least 72 h to maximize the potential for recovery and minimize secondary injury.
30. van Dijk J, van Essen TA, Dijkman MD, *et al.* Functional and patient-reported outcome versus in-hospital costs after traumatic acute subdural hematoma (t-ASDH): a neurosurgical paradox? *Acta Neurochir (Wien)* 2019; 161:875–884.
31. Andelic N, Howe EI, Hellstrom T, *et al.* Disability and quality of life 20 years & after traumatic brain injury. *Brain Behav* 2018; 8:e01018.
One of the longest follow-up studies in traumatic brain injury, concluding that functional limitations persist even decades after the injury.
32. Waqas M, Malik N, Shamim MS, *et al.* Quality of life among patients undergoing decompressive craniectomy for traumatic brain injury using Glasgow Outcome Scale Extended and Quality Of Life after Brain Injury scale. *World Neurosurg* 2018; 116:e783–e790.
Quality-of-life outcome measures are important for understanding the true consequences of medical interventions. This article shows the consequences on quality of life of a controversial surgical intervention like a decompressive craniectomy.
33. Lazaridis C. Withdrawal of life-sustaining treatments in perceived devastating && brain injury: the key role of uncertainty. *Neurocrit Care* 2019; 30:33–41.
Highly interesting article about the importance of existing uncertainties on prognostication of perceived devastating brain injury. It discusses the possibility that many withdrawal of life-sustaining treatments are made prematurely and are made based on false assumptions.
34. Unterhofer C, Hartmann S, Freyschlag CF, *et al.* Severe head injury in very old & patients: to treat or not to treat? Results of an online questionnaire for neurosurgeons. *Neurosurg Rev* 2018; 41:183–187.
The decision-making processes in traumatic brain injury are not well understood. These questionnaires could be helpful in understanding the specific factors of influence in decision-making processes.
35. Quinn T, Moskowitz J, Khan MW, *et al.* What families need and physicians deliver: contrasting communication preferences between surrogate decision-makers and physicians during outcome prognostication in critically ill TBI patients. *Neurocrit Care* 2017; 27:154–162.
36. Detsky ME, Harhay MO, Bayard DF, *et al.* Discriminative accuracy of physician and nurse predictions for survival and functional outcomes 6 months after an ICU admission. *JAMA* 2017; 317:2187–2195.
37. Letsinger J, Rommel C, Hirschi R, *et al.* The aggressiveness of neurotrauma practitioners and the influence of the impact prognostic calculator. *PLoS One* 2017; 12:e0183552.
38. van Veen E, van der Jagt M, Cnossen MC, *et al.*, CENTER-TBI investigators and participants. Brain death and postmortem organ donation: report of a questionnaire from the CENTER-TBI study. *Crit Care* 2018; 22:306.
39. Lesieur O, Gentileuil L, Leloup M. A few realistic questions raised by organ retrieval in the intensive care unit. *Ann Transl Med* 2017; 5(Suppl 4):S44.
40. Rohaut B, Eliseyev A, Claassen J. Uncovering consciousness in unresponsive && ICU patients: technical, medical and ethical considerations. *Crit Care* 2019; 23:78.
Comprehensive overview of unconscious ICU patients, which is highly informative for clinical practice. It also discusses medical and ethical considerations including prognostication and medical decision-making, which are especially difficult in this particular patient category.
41. Giacino JT, Katz DI, Schiff ND, *et al.* Practice guideline update recommenda- && tions summary: disorders of consciousness. *Neurology* 2018; 91:450.
One of the most important recent articles regarding disorders of consciousness. It contains a summary of the latest guideline recommendations.
42. Bruno MA, Majerus S, Boly M, *et al.* Functional neuroanatomy underlying the clinical subcategorization of minimally conscious state patients. *J Neurol* 2012; 259:1087–1098.
43. Honeybul S, Ho KM, Gillett GR. Long-term outcome following decompressive craniectomy: an inconvenient truth? *Curr Opin Crit Care* 2018; 24:97–104.
44. Olivecrona M, Honeybul S. A study of the opinions of Swedish healthcare personnel regarding acceptable outcome following decompressive hemicraniectomy for ischaemic stroke. *Acta Neurochir (Wien)* 2018; 160:95–101.
45. Ho KM. Predicting outcomes after severe traumatic brain injury: science, humanity or both? *J Neurosurg Sci* 2018; 62:593–598.
46. Rousseau MC, Baumstarck K, Alessandrini M, *et al.* Quality of life in patients with locked-in syndrome: evolution over a 6-year period. *Orphanet J Rare Dis* 2015; 10:88.
47. Andrews JG, Wahl RA. Duchenne and becker muscular dystrophy in adolescents: current perspectives. *Adolesc Health Med Ther* 2018; 9:53–63.
48. Span-Sluyter CAMFH, Lavrijsen JCM, van Leeuwen E, *et al.* Moral dilemmas & and conflicts concerning patients in a vegetative state/unresponsive wakefulness syndrome: shared or nonshared decision making? A qualitative study of the professional perspective in two moral case deliberations. *BMC Med Ethics* 2018; 19:10.
This study discusses several important moral dilemmas and conflicts in patients in an unresponsive wakefulness syndrome. These considerations could also be useful for physicians not necessarily confronted with this particular patient subgroup.
49. Kompanje EJ. Prognostication in neurocritical care: just crystal ball gazing? *Neurocrit Care* 2013; 19:267–268.
50. Maas AIR, Menon DK, Adelson PD, *et al.*, IntTBI Participants and Investigators. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. *Lancet Neurol* 2017; 16:987–1048.
51. Collaborators MCT, Perel P, Arango M, *et al.* Predicting outcome after traumatic brain injury: practical prognostic models based on large cohort of international patients. *BMJ* 2008; 336:425–429.
52. Steyerberg EW, Mushkudiani N, Perel P, *et al.* Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. *PLoS Med* 2008; 5:e165.
53. Moskowitz J, Quinn T, Khan MW, *et al.* Should we use the impact-model for & the outcome prognostication of TBI patients? A qualitative study assessing physicians' perceptions. *MDM Policy Pract* 2018; 3:2381468318757987.
There are many different views on the use of prediction models like the IMPACT and CRASH models. This qualitative study assesses the perception of physicians.
54. Dijkland SA, Foks KA, Polinder S, *et al.* Prognosis in moderate and severe && traumatic brain injury: a systematic review of contemporary models and validation studies. *J Neurotrauma* 2019; doi:10.1089/neu.2019.6401.
This systematic review focuses on prognostication in moderate and severe traumatic brain injury. As this is a very important factor in clinical decision-making, an assessment of the validity of these models is very important.
55. Malec JF, Ketchum JM, Hammond FM, *et al.* Longitudinal effects of medical comorbidities on functional outcome and life satisfaction after traumatic brain injury: an individual growth curve analysis of NIDILRR traumatic brain injury model system data. *J Head Trauma Rehabil* 2019; 34:E24–E35.
56. Humble SS, Wilson LD, Wang L, *et al.* Prognosis of diffuse axonal injury with & traumatic brain injury. *J Trauma Acute Care Surg* 2018; 85:155–159.
This study assessed the association between the presence of diffuse axonal injury and long-term outcomes but found no reasons to attribute the presence of this injury to future neurologic function or quality of life.
57. Henninger N, Compton RA, Khan MW, *et al.* Don't lose hope early: hemorrhagic diffuse axonal injury on head computed tomography is not associated with poor outcome in moderate to severe traumatic brain injury patients. *J Trauma Acute Care Surg* 2018; 84:473–482.
58. Reith FC, Synnot A, van den Brande R, *et al.* Factors influencing the reliability of the Glasgow Coma Scale: a systematic review. *Neurosurgery* 2017; 80:829–839.
59. Kondziella D, Friberg CK, Frokjaer VG, *et al.* Preserved consciousness in vegetative and minimal conscious states: systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* 2016; 87:485–492.

60. Vrselja Z, Daniele SG, Silbereis J, *et al.* Restoration of brain circulation and cellular functions hours postmortem. *Nature* 2019; 568:336–343.
This revolutionary study demonstrates that an intact large mammalian brain possesses an underappreciated capacity for restoration of microcirculation and molecular and cellular activity after a prolonged postmortem interval. This could influence thoughts on treatment-limiting decisions, research initiatives in humans and future treatment strategies.
61. O'Leary RA, Nichol AD. Pathophysiology of severe traumatic brain injury. *J Neurosurg Sci* 2018; 62:542–548.
The pathophysiology of severe traumatic brain injury is not well understood. This article summarizes the present knowledge on this topic.
62. Piradov MA, Chernikova LA, Suponeva NA. Brain plasticity and modern neurorehabilitation technologies. *Herald of the Russian Academy of Sciences* 2018; 88:111–118.
63. Kaur P, Sharma S. Recent advances in pathophysiology of traumatic brain injury. *Curr Neuroparmacol* 2018; 16:1224–1238.
64. Crosson B, Rodriguez AD, Copland D, *et al.* Neuroplasticity and aphasia & treatments: new approaches for an old problem. *J Neurol Neurosurg Psychiatry* 2019; 90:1147–1155.
This review provides an overview of new approaches in neuroplasticity in aphasia treatment, which is gaining attention in traumatic brain injury literature.
65. Barich A, de Sire A, Antonino E, *et al.* Recovery from vegetative state of patients with a severe brain injury: a 4-year real-practice prospective cohort study. *Functional neurology* 2017; 32:131–136.
66. Illman NA, Crawford S. Late-recovery from 'permanent' vegetative state in the context of severe traumatic brain injury: a case report exploring objective and subjective aspects of recovery and rehabilitation. *Neuropsychol Rehabil* 2018; 28:1360–1374.
67. Gutowski P, Meier U, Rohde V, *et al.* Clinical outcome of epidural hematoma treated surgically in the era of modern resuscitation and trauma care. *World Neurosurg* 2018; 118:e166–e174.
68. Scerrati A, De Rosa S, Mongardi L, *et al.* Standard of care, controversies, and innovations in the medical treatment of severe traumatic brain injury. *J Neurosurg Sci* 2018; 62:574–583.
Innovations in medicine are warranted, also in severe traumatic brain injury patients. This article provides an overview of care and innovations in medical treatment.
69. Aidinoff E, Groswasser Z, Bierman U, *et al.* Vegetative state outcomes improved over the last two decades. *Brain Inj* 2018; 32:297–302.
70. Christakis N. Death foretold: prophecy and prognosis in medical care. Chicago: Chicago press; 1999.
71. Rubin ML, Yamal JM, Chan W, *et al.* Prognosis of 6-month glasgow outcome scale in severe traumatic brain injury using hospital admission characteristics, injury severity characteristics, and physiological monitoring during the first day postinjury. *J Neurotrauma* 2019; 36:2417–2422.
Improvement of prognostic models is important since it contributes to more accurate decision-making. This study finds that certain predictors after the first day after injury could result in more accurate prediction models.
72. Harvey D, Butler J, Groves J, *et al.* Management of perceived devastating brain injury after hospital admission: a consensus statement from stakeholder professional organizations. *Br J Anaesth* 2018; 120:138–145.
73. Chow N, Busse JW, Gallo L. Evidence-based medicine and precision medicine: complementary approaches to clinical decision-making. *Precis Clin Med* 2018; 1:60–64.
74. Fried TR, Zenoni M, Iannone L, *et al.* Assessment of surrogates' knowledge of patients' treatment goals and confidence in their ability to make surrogate treatment decisions. *JAMA Intern Med* 2019; 179:267–268.
75. Fins JJ. Rights come to mind. 1st edition Cambridge: Cambridge University Press; 2015.
76. Khan MW, Muehlschlegel S. Shared decision making in neurocritical care. *Neurosurg Clin N Am* 2018; 29:315–321.
There is much debate on the use of shared decision-making in neurocritical care. The authors discuss the general use of shared decision-making and ways to improve this.
77. Honeybul S, Gillett GR, Ho KM, *et al.* Neurotrauma and the rule of rescue. *J Med Ethics* 2011; 37:707–710.
78. van Dijk J, Dijkman MD, Ophuis RH, *et al.* In-hospital costs after severe traumatic brain injury: a systematic review and quality assessment. *PLoS One* 2019; 14:e0216743.
79. Zorginstituut Nederland. Ziektelast in de praktijk - de theorie en praktijk van het berekenen van ziekte last bij pakketbeoordelingen. 2018. Available at: https://www.zorginstituutnederland.nl/binaries/zinl/documenten/rapport/2018/05/07/ziektelast-in-de-praktijk/Ziektelast+in+de+praktijk_definitief.pdf. [Accessed 17 May 2019]
80. Wilson L, Stewart W, Dams-O'Connor K, *et al.* The chronic and evolving neurological consequences of traumatic brain injury. *Lancet Neurol* 2017; 16:813–825.
81. Vespa P. Traumatic brain injury is a longitudinal disease process. *Curr Opin Neurol* 2017; 30:563–564.
82. Marklund N, Bellander BM, Godbolt A, *et al.* Treatments and rehabilitation in the acute and chronic state of traumatic brain injury. *J Intern Med* 2019; 285:608–623.
Rehabilitation is essential in the care of a patient with (severe) traumatic brain injury. Improvement of coordinated interdisciplinary rehabilitation for traumatic brain injury patients is necessary. The authors highlight this need and describe new approaches in rehabilitation.
83. Ratan RR, Schiff ND. Protecting and repairing the brain: central and peripheral strategies define the new rehabilitation following traumatic brain injury. *Curr Opin Neurol* 2018; 31:669–671.
84. Konigs M, Beurskens EA, Snoep L, *et al.* Effects of timing and intensity of neurorehabilitation on functional outcome after traumatic brain injury: a systematic review and meta-analysis. *Arch Phys Med Rehabil* 2018; 99:1149.e1–1159.e1.
This systematic review and meta-analysis states that early neurorehabilitation in trauma centers and more intensive neurorehabilitation in rehabilitation facilities promote functional recovery in patients with moderate-to-severe traumatic brain injury.
85. Graff HJ, Christensen U, Poulsen I, *et al.* Patient perspectives on navigating the field of traumatic brain injury rehabilitation: a qualitative thematic analysis. *Disabil Rehabil* 2018; 40:926–934.
86. Douglas JM, Knox L, De Maio C, *et al.* Effectiveness of communication-specific coping intervention for adults with traumatic brain injury: preliminary results. *Neuropsychol Rehabil* 2019; 29:73–91.
87. Semprini M, Laffranchi M, Sanguineti V, *et al.* Technological approaches for neurorehabilitation: from robotic devices to brain stimulation and beyond. *Front Neurol* 2018; 9:212.
88. Thibaut A, Schiff N, Giacino J, *et al.* Therapeutic interventions in patients with prolonged disorders of consciousness. *Lancet Neurol* 2019; 18:600–614.
The therapeutic options for patients with disorders of consciousness are often considered to be scarce. New clinical data and new treatment options pose new possibilities for this specific patient subcategory and are described in this article.
89. Avesani R, Dambruoso F, Scandola M, *et al.* Epidemiological and clinical characteristics of 492 patients in a vegetative state in 29 Italian rehabilitation units. What about outcome? *Funct Neurol* 2018; 33:97–103.
90. Kochanek PM, Jackson TC, Jha RM, *et al.* Paths to successful translation of new therapies for severe traumatic brain injury in the golden age of traumatic brain injury research: a Pittsburgh vision. *J Neurotrauma* 2019; doi: 10.1089/neu.2018.6203. [Epub ahead of print]
91. Wang KK, Yang Z, Zhu T, *et al.* An update on diagnostic and prognostic biomarkers for traumatic brain injury. *Expert Rev Mol Diagn* 2018; 18:165–180.
92. Rau CS, Kuo PJ, Chien PC, *et al.* Mortality prediction in patients with isolated moderate and severe traumatic brain injury using machine learning models. *PLoS One* 2018; 13:e0207192.
New developments in prognostication for moderate and severe traumatic brain injury include the use of machine-learning models.
93. Hale AT, Stonko DP, Brown A, *et al.* Machine-learning analysis outperforms conventional statistical models and ct classification systems in predicting 6-month outcomes in pediatric patients sustaining traumatic brain injury. *Neurosurg Focus* 2018; 45:E2.