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

Dijck, J.T.J.M. van

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Jeroen Theodorus Josephus Maria van Dijck
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Promotor
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Copromotores
Dr. E.J.O. Kompanje, Erasmus Medisch Centrum, Rotterdam
Dr. S. Polinder, Erasmus Medisch Centrum, Rotterdam

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"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

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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.

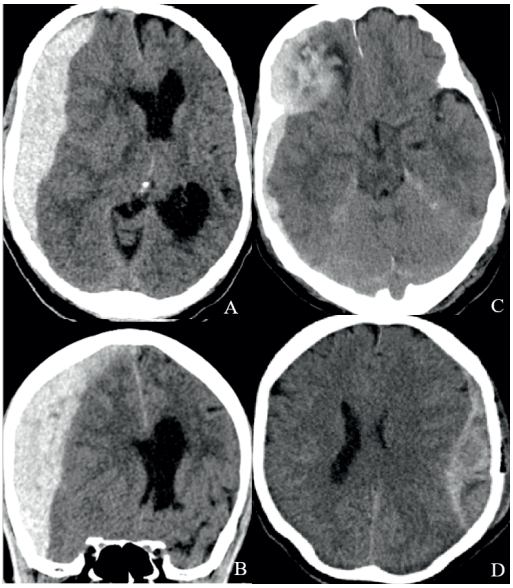

Figure 1. Computed tomography (CT) scans of patients with traumatic intracranial abnormalities. A and B: Subdural hematoma. C: Contusion and parenchymal hematoma. D: Epidural hematoma.

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 centers [32], structures and processes of TBI care [33], monitoring and treatment policies in patients with TBI and intracranial hypertension [34], general supportive and preventive measures at ICUs [35], 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 TBI [39], 0.9% to 8% for moderate TBI [40] 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 patient [3], 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 management [93], allowing choice of relevant and generalizable outcome variables, [95] promoting uniform product safety regulations [94], 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.

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PART I

Patient outcome, in-hospital healthcare consumption, in-hospital costs, and treatment decision-making in severe traumatic brain injury

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 Dijck [1]
Florence C.M. Reith [2]
Inge A.M. van Erp [1]
Thomas A. van Essen [1]
Andrew I.R. Maas [2]
Wilco C. Peul [1]
Godard C.W. de Ruiter [1]

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

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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 studies[15-20] (Figure 1). In addition, a total of 126 manuscripts formed the evidence base for the sections on penetrating brain injury.

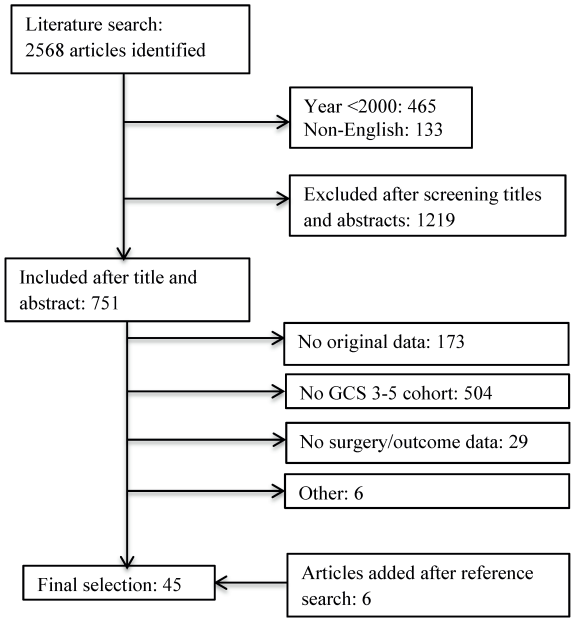

Figure 1: Article selection

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).

Tabel 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) GCS6-8 vs. GCS3-5 = (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:** GCS3 (N=796): ICU: 48.5%, Hospital: 51.1% GCS>3: ICU: 24.8%, Hospital: 29.3% Age 65 and GCS=3: ICU 67%; Hospital 71.1% Numbers irrespective the presence of ICP monitoring
ED	Inpatient mortality	**Mortality:** GCS(3): -13.3% (95% CI: -6.0 to -20.5). P:<0.001 GCS(3)+ High ISS (>25): -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**: GCS3-5: 57.8% GCS3-5: 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**: GCS3-5: 26.3%. Overall: 22.9% GCS3-5: Independent predictor of mortality: OR1.84
Best in first 12 hours.	Hospital and 28-day mortality	**Hospital mortality** (OR; 95% CI; P): GCS<6: 0.76; 0.18–3.2; 0.71, GCS≥6: 5.6; 1.7-18.4; <0.01 **28-day mortality** (OR; 95% CI; P): GCS<6: 0.47; 0.11–2.1; 0.32, GCS≥6: 5.0; 1.5-16.7; <0.01
Admission	Hospital mortality	**Mortality ICP/No-ICP,** (OR; 95%CI; P) GCS3-4: 12.9%/ 24.5%, (0.51; 0.17-1.59; 0.25) GCS5-6: 18.2%/ 7%, (3.74; 0.61-22.82; 0.15) GCS7-8: 50%/ 7.2%, (12.89; 3.14-52.95; 0.0004)
Admission	GOS (>6M)	GCS3-5: GOS1= 16%, GOS2=12%, GOS3= 24%, GOS4= 10%, GOS5=38% GCS6-8: 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 fall [23] 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 tracheostomy [27] 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 dilated [32] (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 ±40% and good outcome (GOS 4+5) improved from 10% to ±40%.[33, 42] Series were compared with a historic control group receiving a large bilateral frontotemporoparietal 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≥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 reported [50] and in another study absence of pupillary response correlated with unfavorable outcome (OR3.16, 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 (OR3.24, 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 predictor [53] and also gender associations remained non-conclusive.[20, 53]

Tabel 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	BFDP: 6 UFDP: 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% BFDP: 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	BFDP:12 Unilateral DP: 9 Isocoria: 13

Surgical intervention.	Outcome measure	Results
DC(≥35cm²): 48 Unilateral: 42 Bilateral: 6 <16h trauma: 28 <48h trauma: 48	GOS	**GOS1:** Overall:12.5%, GCS3-5: 16%, GCS6-8:11% **GOS2:** GCS3-5: 37%, GCS6-8: 7% **Favourable (GOS4+5)**: Overall: 55%, GCS3-5: 37%, GCS6-8: 67% LTFU: 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%, GCS9-15: 4.4%. GCS6-8: 12.4%, GCS3-5: 59.7% >90% died within 14 days.
Unilateral: 66% Bilateral: 34% 94 < mean17.1h 6 after secondary ICP increase.	GOS (6M)	**Unfavourable (GOS1-3):** Overall: 84%, GCS4-5: 96.6%, GCS6-8: 65% **Favourable (GOS4-5):** Overall: 16%, GCS4-5: 3.4%, GCS6-8: 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:** GCS3: 100%, GCS4-5: 82.2%, GCS>5: 41% **Favourable (mRS0-2)**: GCS3-5: 0%, GCS>6: 4.7%
Early DC (±1h 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%, GCS4-5: 79.3%, GCS>5: 37% **Unfavourable(GOSE1-4)**: All: 78.5%, GCS4-5: 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%, GCS≤5: 64%, GCS>5: 26% (P=0.042), GCS3 (N=3): 100%, GCS4 (N=5): 80% **6M: Mortality:** 47%, **GOS2**: 20%. **Favourable (GOS4-5):** Overall: 35%, GCS≤5: 9%, GCS>5: 45% **Unfavourable (GOS1-3):** GCS≤5: 91%, GCS>5: 55%

Tabel 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)**:** GCS3-8: LDC 71.1%, RDC: 58.6% (P<0.05), GCS3-5: 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 100cm² <6h: 33%. 6-24h: 12%	Mortality/ GOS (3/24M)	**Mortality**: GCS3-5: 50%, GCS6-8: 12%, GCS>8: 12% **Unfavourable (GOS2+3)**: GCS3-5: 54%, GCS6-8: 20%, GCS>8: 20%. **Favourable (GOS4+5)**: GCS3-5: 46%, GCS6-8: 80%, GCS>8: 80%. All significant
FTPC: 49 Bifrontal:1 <48h: 34%	Mortality/ GOS (3M)	**Mortality** (30d): Overall: 28%, GCS 3-5: 20%, GCS 6-8: 21.7%, GCS 9-15: 25%. **Good outcome (GOS4+5)**: Overall: 51.3%, GCS 3-5: 16.7%, GCS6-8: 66.7%, GCS 9-15: 66.7%.
Unilateral FTPC:50 Bilateral FTPC: 5 <5h: 29% >10h: 35%	GOS (12-102M)	**GOS1**: Overall: 39%. **Favourable (GOS4-5)** Overall: 47% GCS3-5: 26.7%, GCS6-8: 76.9%, GCS9-15: 66.7% **Unfavourable (GOS1-3)** GCS3-5: 76.3%, GCS6-8: 23.1%, GCS9-15: 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% GCS4-5: GOS1: 50%, GOS2+3: 25%, GOS4+5: 25% GCS6-8: 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**: GCS3-5: 27.5%, GCS6-8: 26.9%, GCS9-12=13.1%. P=0.197 **Good outcome (GOS4-5) (%):** GCS3-5: 29.7%, GCS6-8: 52.6%, GCS9-12: 71.7% P=0.002
≤24h after admission: 76% (N=122) Unilateral: 88% Bilateral: 12%	GOS (discharge / 6M)	**Mortality:** Overall: 44.7%, GCS3-5: 59%, GCS>5: 35% (p=0.004). **Surgery ≤24h: (discharge): GOS1**: GCS3-5: 68%, GCS6-8: 42%, **GOS4-5**: GCS3-5: 26%, GCS6-8: 41.7% (p=0.013) **(6M): GOS1**: GCS3-5: 26.7% GCS6-8: 61.7% **GOS4-5**: GCS3-5: 6.7%, GCS6-8: 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%	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%
Craniotomy: 87% Craniectomy: 13% <4h arrival: 83% Mean time: 1.9h	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%
Chieregato(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% GCS3-5: 32% GCS6-8: 63% GCS9-11: 74% GCS12-15: 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**: GCS3-5: GOS1: 87%. GOS1-3: 96%, GCS6-15: 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**: GCS≤5: 77.5%, GCS>5: 40%, **Favorable:** GCS≤5: 5%, GCS>5: 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:** GCS3-5: 100% **Good outcome (GOS4-5):** GCS6-8=20%, GCS>8 = 50%.
Hematoma evacuation: 67 Second craniotomy: 5	Mortality (6M)/ GOS (1M/6M)	**Overall mortality (1M)**: 55.1%, **(6M):** 67.2% **Mortality (6M)**: GCS3–4: 82.4%, GCS14-15: 14.3% **Functional recovery (6M)**: GCS3–4: 5.9%, GCS14-15: 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 (OR0.64, 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 infection [66] 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 abcesses.[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]

Tabel 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%	Modified GOS (long term: mean 10.2Y)	**Discharge:** Overall mortality: 55.2%, GCS3: GOS1: 61.4%, GOS2: 6.8%, GOS3: 11.4%, GOS4: 15.9%, GOS5: 4.6% GCS4: 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".
DC: 9 DBS, 15 mass lesions + DBS, 1 R-ICH. Bilateral: 7	GOS (5M)	**Overall mortality** 36%. GOS5: 40% GCS≤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-analysis [95] 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 tracheostomy [27] 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 study [101] 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 benefit [99] 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 benefit [107] 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-qure.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.

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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 MD[1]

Robbin H. Ophuis MSc[2]

Godard C.W. de Ruiter MD PhD[1]

Wilco C. Peul MD PhD MBA[1]

Suzanne Polinder PhD[2]

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

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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≤8, AIS≥4, AIS≥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≤8 and/or AIS≥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.

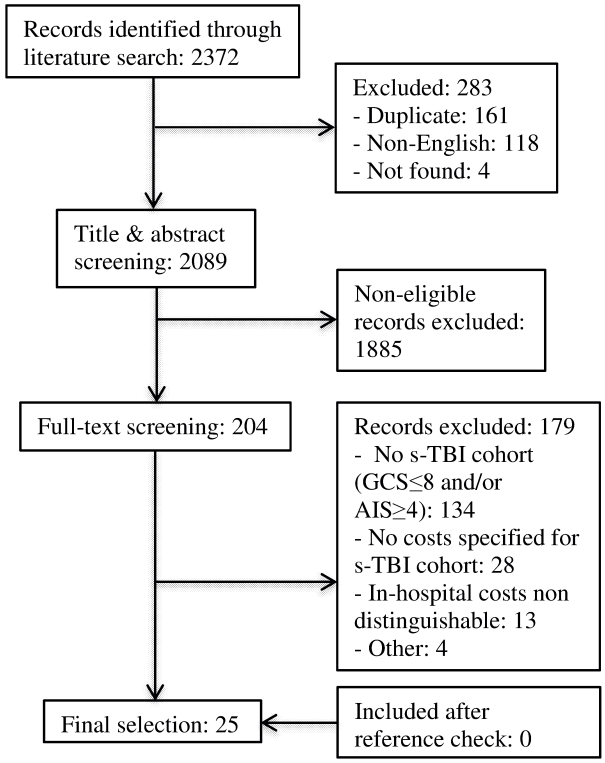

Table 1: Study details & results

#	Study info [a]	Purpose	Study Design	Patient (N)	Definition of TBI	Severity definition
1	- 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	- 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	- 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	- 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	- 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	- 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	- 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	- 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	- 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 (GCS 5.4±1.9): $12,247 *(27%)* ($2,199-$127,555) - Non-survivors (GCS 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: $3,207 *(173%)*
Most costs taken from official journal of the federation. Medicine price catalog, ICP probe price provided by supplier.	Amount of supplies multiplied by unit price	Costs of hospitalization (direct medical costs + clinical complications) medicines, laboratory, imaging, surgery, LOS ICU/Ward.	Mex$ (2015) / $9,291	- ICP monitoring group (GCS 5.5±1.7): $66,263 *(713%)* ± $31,436 - Control group (GCS 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.

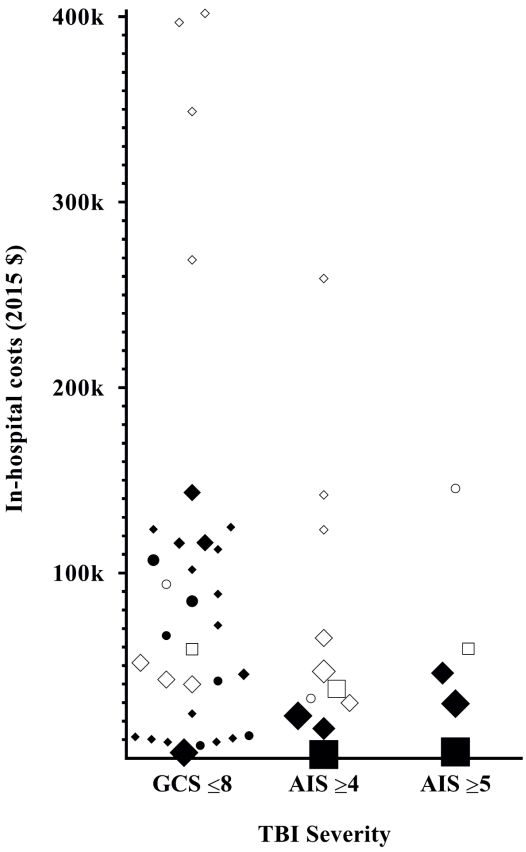

Fig 2. In-hospital costs and in-hospital charges of a patient with s-TBI

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%).

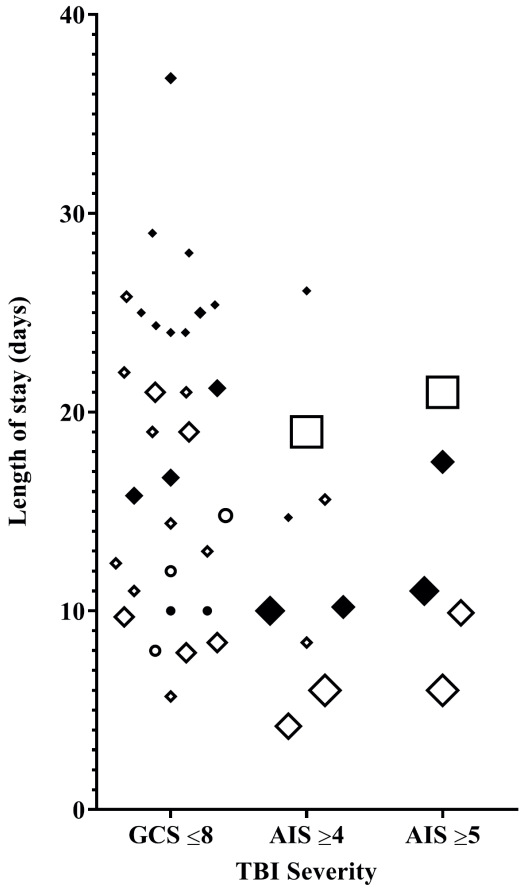

Fig 3. ICU and hospital length of stay of a patient with s-TBI

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≤8) [40,43], 6 to 19 days (AIS≥4) and 6 to 21 days (AIS≥5). [35,47] Hospital LOS ranged from 10 to 36.8 days (GCS≤8) [38,54], 10 to 26.1 days (AIS≥4) [47,52] and 11 to 17.5 days (AIS≥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 GCS3-5 or AIS=5 were more expensive than patients with a GCS6-8 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≥5 as severe, instead of AIS≥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)

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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 MD[1],
Thomas A. van Essen MD[1],
Mark D. Dijkman MD[1],
Cassidy Q.B. Mostert BSc[1],
Suzanne Polinder PhD[2],
Wilco C. Peul MD PhD MBA[1],
Godard C.W. de Ruiter MD PhD[1]

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:

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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≤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 (GCS13-15: 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. Continues variables, like costs and LOS, were presented as mean ± 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
Age (years)	65 ± 17.3
Male	57 (52.8)
Trauma mechanism	
Fall	58 (53.7)
Assault	5 (4.6)
Motor vehicle accident	12 (11.1)
Fall from bike	12 (11.1)
Other	21 (19.4)
TBI severity	
Very severe (GCS3-5)	22 (20.4)
Severe (GCS3-8)	49 (45.4)
Moderate (GCS9-12)	19 (17.6)
Mild (GCS13-15)	40 (37.0)
Clinical parameters	
GCS score	9,63 ± 4.3
Pupil abnormality *	27 (26.7)
Focal Neurologic symptoms	42 (38.9)
Major extracranial injury	12 (11.1)
CT parameters	
Thickness (mm)	13.6 ± 6.1
Midline shift (mm)	11.4 ± 6.6
Concomitant lesion	48 (44.4)
Basal cisterns compressed	39 (36.1)

Number of patients	108
Age (years)	65 ± 17.3
Male	57 (52.8)
Treatment	
Conservative	18 (16.7)
Emergent surgical intervention:	90 (83.3)
- Craniotomy	- 60 (55.6)
- Decompressive craniectomy (DC)	- 29 (26.9)
- ICP monitoring	- 40 (37.0)
In-hospital mortality	41 (37.9)
Functional outcome	
GOS1-3 (unfavourable)	56 (51.9)
GOS4-5 (favourable)	50 (46.3)
Missing GOS	2 (1.9)
QOLIBRI response	
FU time, months	46 ± 16
Yes	25 (23.1)
No (died; too disabled)	53 (48; 5)
No, other	30 (27.8)

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

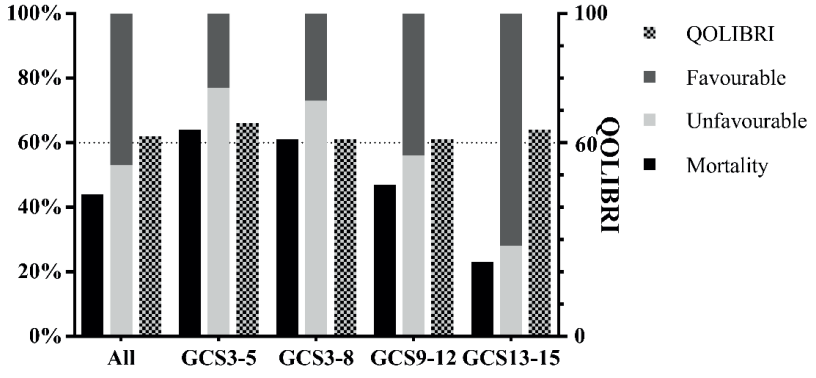

Figure 1. Patient outcome

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

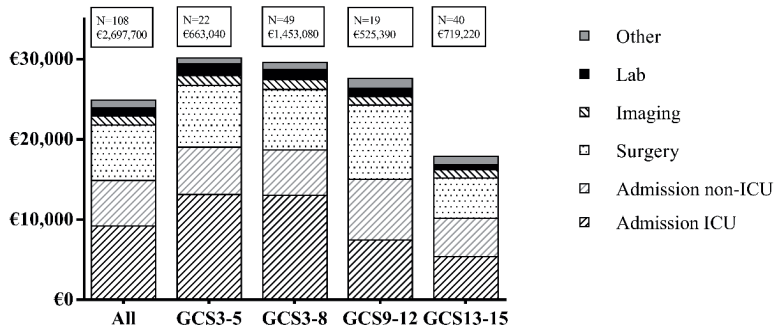

Figure 2. In-hospital costs

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.

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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 MD[1],
Cassidy Q.B. Mostert BSc[1],
Alexander P.A. Greeven MD[2],
Erwin J.O. Kompanje PhD[3,4],
Wilco C. Peul MD PhD MBA[1],
Godard C.W. de Ruiter MD PhD[1],
Suzanne Polinder PhD[5]

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.

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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 (GOSE≤4) (14.6%-80.4%), and full recovery (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_01700). 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 ± 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						<0.001
Admission	319 (65.6)	288 (81.4)	16 (37.2)	9 (11.5)	5 (9.8)	
ICU	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)	
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)	51 (100)	
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
GOSE 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%	<0.001
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
Legend:
Values are reported as:
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 that are reported for all patients because baseline GCS data was missing for 11 patients. Also, data from 1 CT-scan could not be retrieved.
*** Calculated excluding missings. Favourable and unfavourable were defined as GOSE 5-8 and GOSE 1-4 respectively.
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

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≥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.

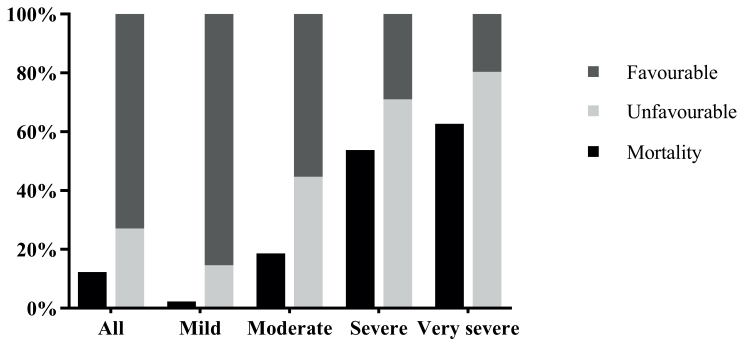

Figure 1. Patient outcome

Figure 1 shows in-hospital mortality and functional outcome (favourable: GOS 5-8, unfavourable GOS 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)
Age					
≤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)
TBI severity		*	*	*	*
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)
Pupil reactivity		*	*	*	*
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)
Early CT scan					
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)*
Surgical intervention:					
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)
In hospital mortality			*	*	
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)
GOSE 6 months		*	*	*	*
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

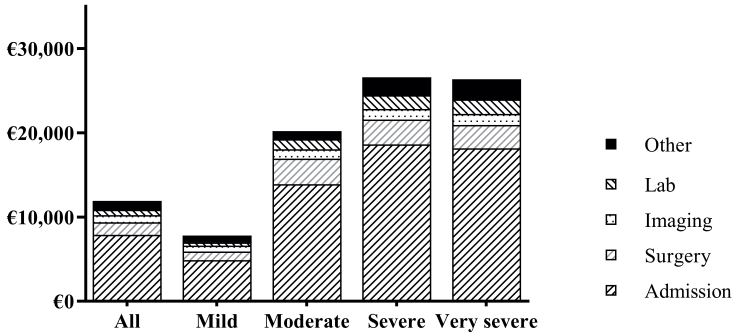

Figure 2. In-hospital healthcare consumption & in-hospital costs

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 research [24], 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≥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 severities [32], while other studies showed lower mortality rates for mild TBI [33], moderate TBI [31], 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 studies [39-42], some reporting deterioration between 5 and 10 years [43], 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) treatment [60] 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 admissions [47], 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 severity [24], 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.

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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, MD[1]

Ronald H.M.A. Bartels, MD PhD[2]

Jan C.M. Lavrijsen, MD PhD[3]

Gerard M. Ribbers, MD PhD[4,5]

Erwin J.O. Kompanje, PhD[6]

Wilco C. Peul, MD PhD MBA[1]

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

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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**, 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 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, 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 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. [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).

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' 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.

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PART II

Institutional review board approval and use of informed consent procedures in emergency research with traumatic brain injury patients

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

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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 regulations [8] 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 Country	Centers (N)	Central or local IRB review	IRB decision on study type
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.

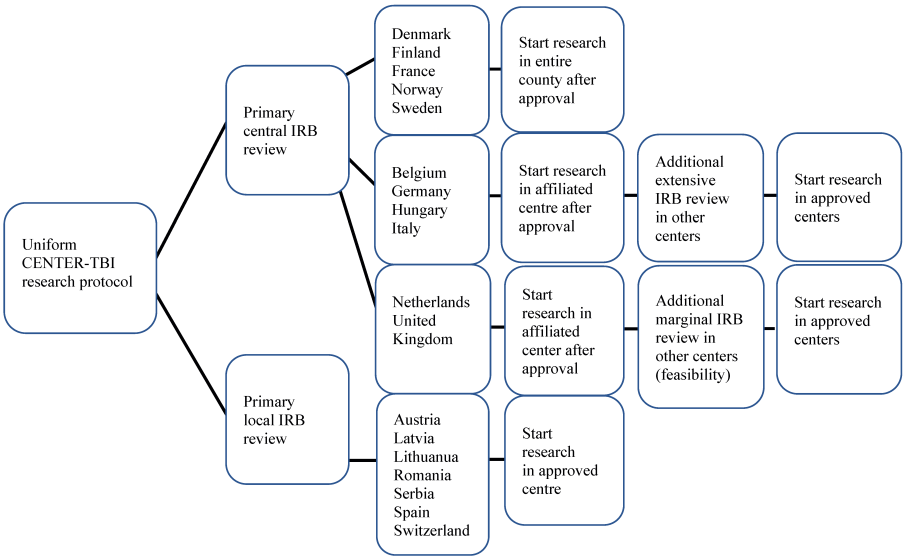

Figure 1: Flowchart of IRB review and approval processes in the CENTER-TBI study

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.

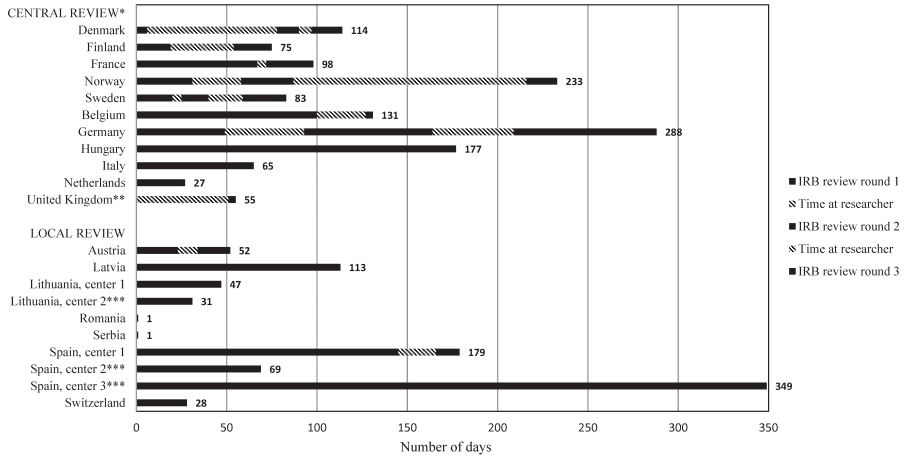

Figure 2. Detailed overview of primary IRB review and duration.

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://bmcmedethics.biomedcentral.com/articles/10.1186/s12910-020-00480-8#Sec14

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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*], David K. Menon [8], Jeroen T. J. M. van Dijck [1*], Wilco C. Peul [1], Marjolein Timmers [2], Nino Stocchetti [9,10], Ernest van Veen [2,3], Erwin J.O. Kompanje [2,11], Giuseppe Citerio [4,5], The CENTER-TBI investigators and participants, Hester F. Lingsma [3], *Contributed equally to the study, Andrew I.R. Maas [6,7],

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.

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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)

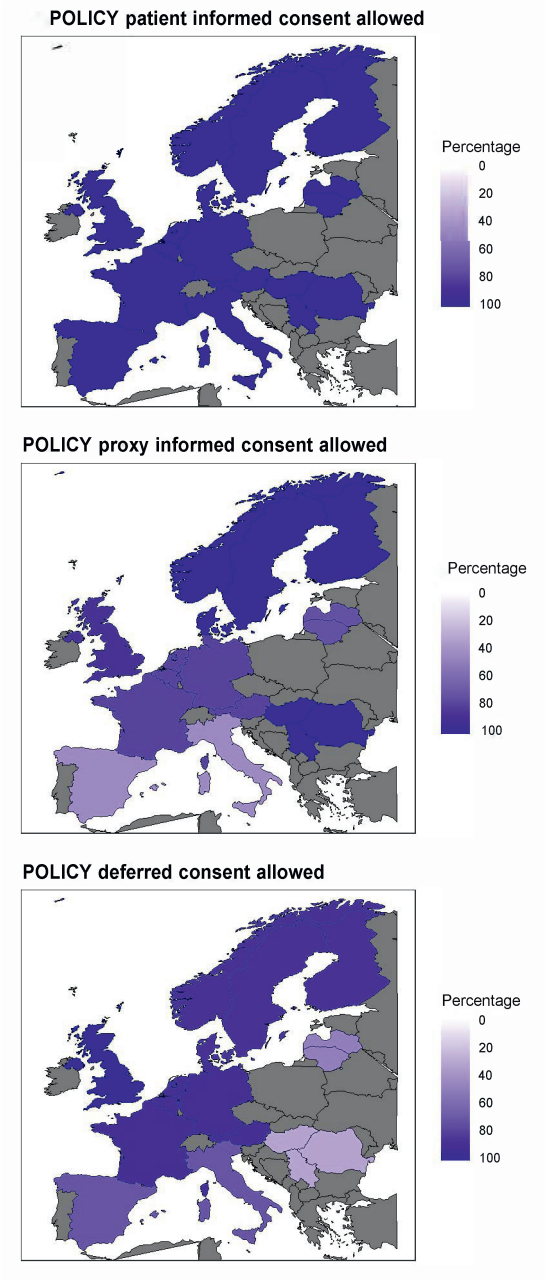

Figure 1: Reported policy on types of consent in acutely mentally incapacitated patients in Europe. (Percentage of centres in one country that allow the type of consent in the questionnaire)

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

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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. Janssen [4]
Paul J. Nederkoorn [7]
Mathieu van der Jagt [1]
Giuseppe Citerio [8]
Nino Stocchetti [9,10]
Diederik W.J. Dippel [4]
Wilco C. Peul [3]
*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 Fransesco Sforza 35, 20122 Milano, Italy.
10: Neuro ICU Fondazione IRCCS Ca Granda Ospedale Maggiore Policlinico Milano, Milan, Italy. Address: Via Fransesco Sforza 28, 20122 Milano, Italy.

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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 early [26] 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 Waiver of informed consent	6 (10%)	5 (7%)
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 Helsinki [2] 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 reconsent 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 Helsinki [2] 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 trial [60] 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 Helsinki [2] 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 study [68] 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).

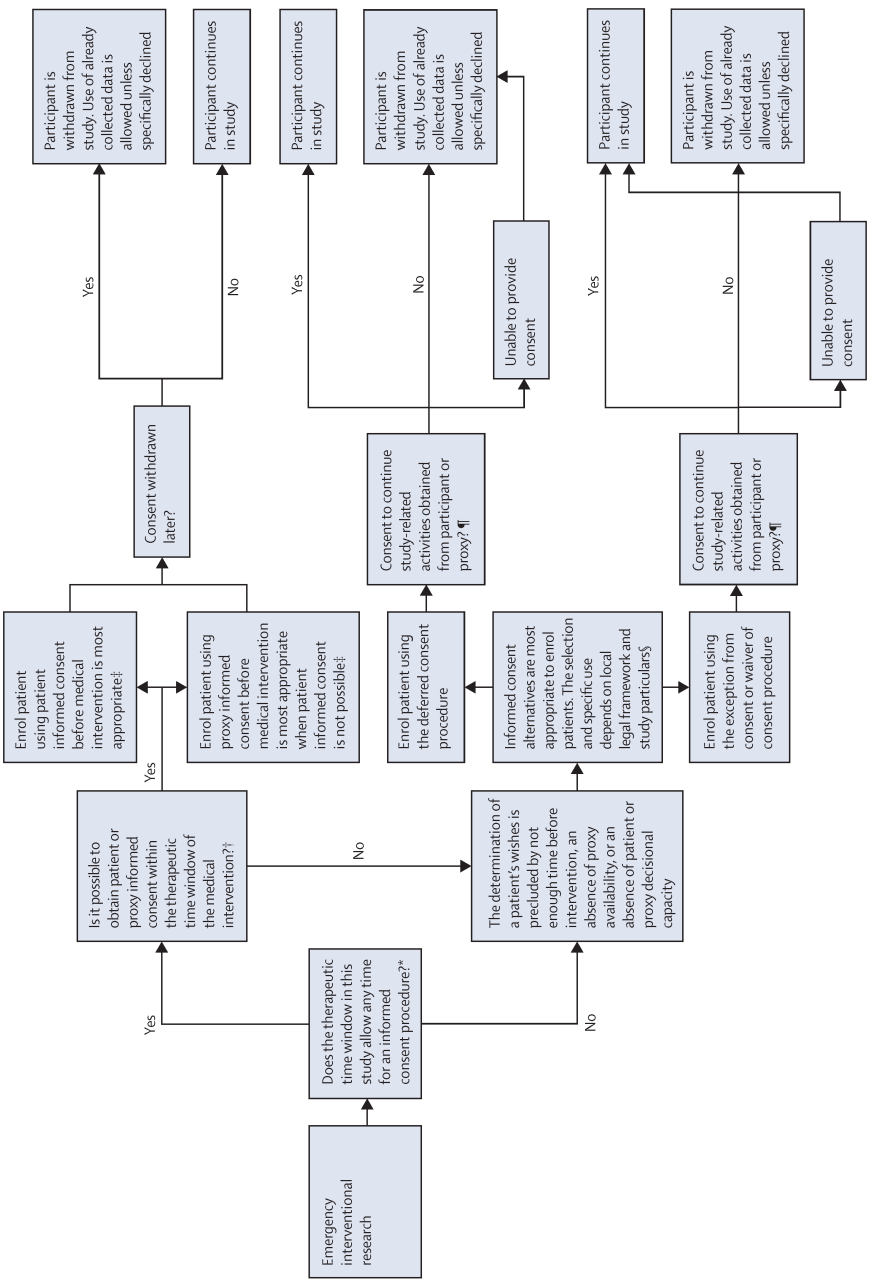

Figure: Flow chart for the selection of appropriate informed consent procedures in emergency interventional research

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-ab02-887d63f0d4e9/mmc1.pdf

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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 geïncludeerd 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 intracraniële afwijkingen of extracraniële 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, intracraniële afwijkingen op CT-scan), aanwezigheid ernstig extracranieel letsel, gebruik van intracraniële 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, valuate, 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 mathemathical 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 todays' 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 interview [61] 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 usefull 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 paradox [73] 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 whishes. [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 succesfull 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 product [104], 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-effective [112-115], 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 it's 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 management [133], 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.

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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. Kompanje[1], J.T.J.M. van Dijck[1], 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 Wijk[1], J.T.J.M. van Dijck[1], 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. Timmers[1], J.T.J.M. van Dijck[1], 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

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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.

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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.

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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.

Stellingen behorende bij het proefschrift

DECISION-MAKING IN SEVERE TRAUMATIC BRAIN INJURY

PATIENT OUTCOME, HOSPITAL COSTS, AND RESEARCH PRACTICE

door Jeroen Theodorus Josephus Maria van Dijck

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 Nietsche. 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.