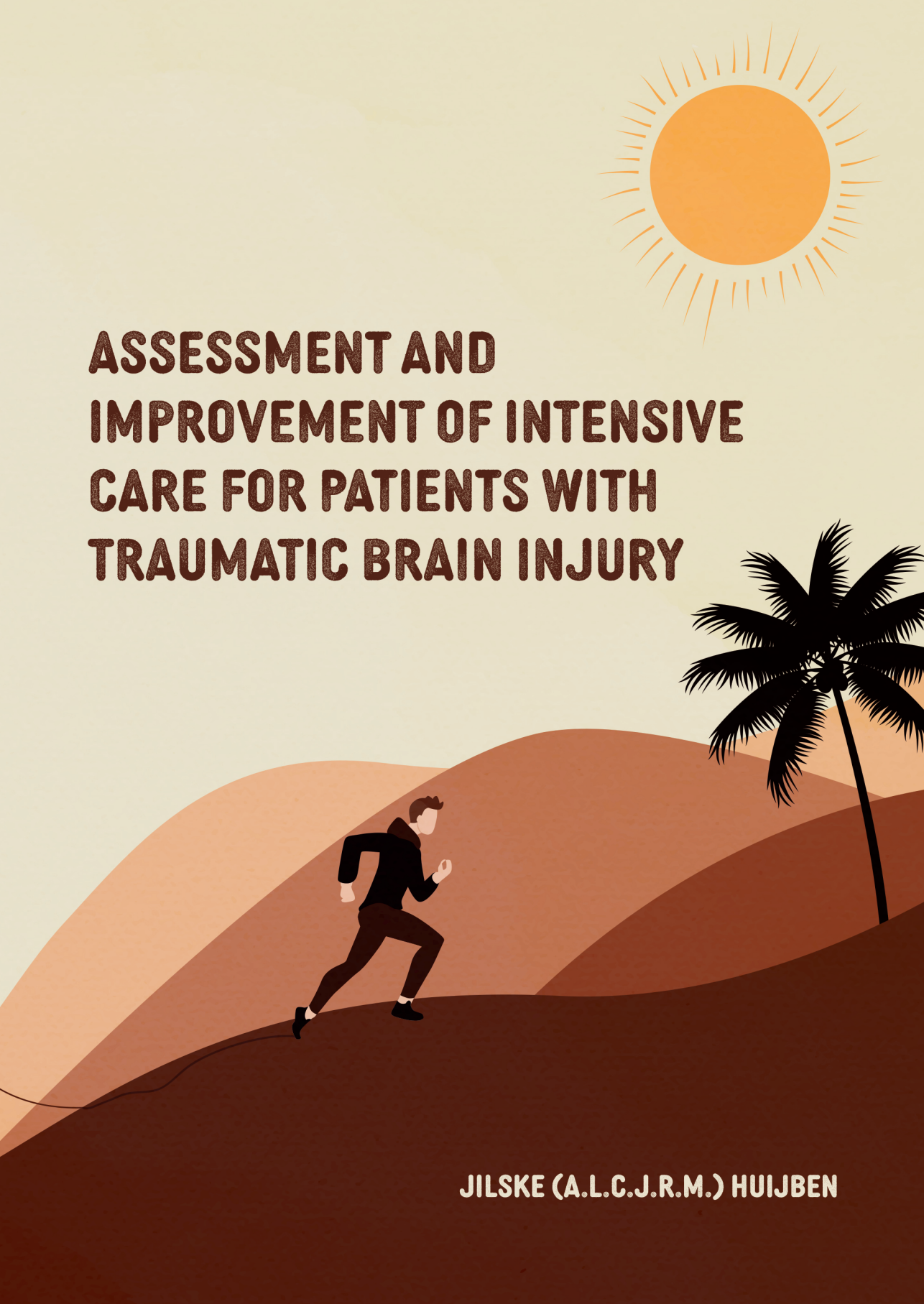
ASSESSMENT AND IMPROVEMENT OF INTENSIVE CARE FOR PATIENTS WITH TRAUMATIC BRAIN INJURY



JILSKE (A.L.C.J.R.M.) HUIJBEN

Assessment and Improvement of Intensive Care for patients with Traumatic Brain Injury

Het evalueren en verbeteren van zorg voor patiënten met traumatisch hersenletsel op de intensive care

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CHAPTER 1

General Introduction

Traumatic Brain Injury

Traumatic Brain Injury (TBI) causes an enormous health and economic burden around the world [1]. TBI has been defined as an 'acute brain injury resulting from mechanical energy to the head from external physical forces' by the World Health Organization. Around half of all people worldwide suffer from a TBI once in their lifetime. TBI is one of the major causes of trauma-related death and hospital admissions in Europe [2]. The global burden of TBI rises, due to falls in high income countries and due to road traffic accidents in lower income countries [3]. Costs are high due to direct health care costs as well as indirect costs, like loss of productivity, as many young people suffer from TBI. Estimated overall costs around the world are US$400 billion, which represents 0.5% of the entire global annual output [4]. In Europe costs were around €33 billion in the year 2010 [5].

TBI encompasses many different injury types, and therefore, TBI is also called a 'heterogeneous syndrome' [6]. It is estimated that around 10-15% of patients with TBI have severe injury [6]. Severe TBI reflects a score of less than 9 points on the Glasgow Coma Scale immediately after the trauma, a scale to assess the depth of the brain injury or coma. These patients need highly specialized care and monitoring at the ICU. A significant proportion of patients admitted to the ICU will die: mortality rates after ICU admission with TBI vary from 30 to 40 percent [7]. When patients survive after ICU admission, they often suffer from life-long disabilities, including physical, cognitive, and emotional impairments. These will also affect the life of family and friends of the patients.

Current ICU treatment strategies

While primary brain injury is regarded as irreversible, secondary injury can potentially be prevented with intensive monitoring and care in patients managed at the ICU.

Monitoring

Both cerebral and systemic monitoring are considered vital to support goal-directed management maintaining the homeostasis of the injured brain. Advanced brain monitoring generally includes intracranial pressure (ICP) assessment. This monitoring is supported by guidelines, but many other modalities are used variably depending on local practices and experiences and are often embedded in research programs of individual institutions. Both ventricular and parenchymal ICP monitoring devices exist. Ventricular ICP monitors can also be used as a treatment intervention by facilitating cerebral spinal fluid drainage. New brain monitoring systems are emerging, like brain tissue PO2, microdialysis, and electrocorticography. On the other end, systemic monitoring (i.e. aimed at assessing volume status and circulation of the body, temperature, coagulation etc) is also vital to ensure stable

physiology and thereby maintain sufficient cerebral blood flow and oxygen supply, and includes invasive blood pressure monitoring, end tidal CO2, and cardiac output.

Intracranial pressure lowering treatments

TBI-specific treatment strategies are mainly based on controlling ICP or, more accurately: intracranial compliance reserve. First tier treatments are CSF drainage, sedatives, hyperosmolar therapies, and fluids; second tier treatments are more aggressive; like decompressive craniectomy, hypothermia, deep hyperventilation, and barbiturate use [8]. Once first tier therapies fail, clinicians can continue towards more intensive therapies, often with more potential for harm; an approach coined as the "staircase approach" [9]. However, the evidence base underlying the individual treatment components of this scaled approach is weak. Recently, the therapy intensity level (TIL) scale has been described and validated [10]. This TIL scale consists of 8 treatment modalities that aim to manage intracranial pressure. With this scale the treatment intensity can be quantified with a maximum score of 38. The treatment intensity may be better for research settings, since application of this scale for clinical practice has been scarce to date. (Table 1)

General and supportive ICU treatments

General and supportive ICU treatments are vital in maintaining blood and oxygen supply to the brain [11, 12]. For example, cerebral blood flow and oxygen delivery might be impaired, if systemic coagulation–and hemoglobin status of the patient is not optimized. This means that coagulation factors and blood transfusions should be carefully considered. However, evidence is lacking on the optimal hemoglobin target level for blood transfusion or coagulation management strategies. Second, the glucose and nutrition status should be optimized as glucose is the main energy nutrient of the brain. Enteral versus parenteral nutrition, nutritional start and duration, and the number of calories provided could all influence the glucose supply and nutrition status of the patient. Still, recommendations on glucose therapy, the aim for caloric intake, and the start of parenteral nutrition are lacking in the BTF guidelines. Overall, optimizing systemic therapies could have an impact on the brain function and long-term outcome [11].

Evidence generation

Evidence-base

Although these ICP targeted and general and supportive treatments form the cornerstones of ICU care for patients with Traumatic Brain Injury, evidence on effectiveness is scarce. Defining best practices is cumbersome. As the last 20 years of research in TBI have shown, it is hard to generate any evidence with a large impact on clinical practice [13]. Also, the Brain Trauma Foundation guidelines give rather general recommendations, since strong

Table 1: Therapy Intensity Level (TIL) scale

Item	Details	Score	Max
Positioning	Head elevation for ICP control	1	
	Nursed flat (180°) for CPP management	1	1
Sedation and neuromuscular blockade	Sedation (low dose as required for mechanical ventilation)	1	
	Higher dose sedation for ICP control (not aiming for burst suppression	2	
	Metabolic suppression for ICP control with high dose barbiturates or propofol	5	
	Neuromuscular blockade (paralysis)	3	8
CSF drainage	CSF drainage low volume (<120 mL /day or < 5 mL/h)	2	
	CSF drainage high volume (≥ 120 mL/ day or ≥5 mL/h)	3	3
CPP management	Fluid loading for maintenance of cerebral perfusion	1	
	Vasopressor therapy required for management of cerebral perfusion	1	2
Ventilatory management	Mild hypocapnia for ICP control [PaCO2 4.6–5.3 kPa (35–40 mmHg)]	1	
	Moderate hypocapnia for ICP control [PaCO2 4.0 - 4.5 kPa (30–35 mmHg)]	2	
	Intensive hypocapnia for ICP control [PaCO2 < 4.0 kPa (<30 mmHg)]	4	4
Hyperosmolar therapy	Mannitol up to2 g/kg/24h	2	
	Mannitol (>2 g/kg/24h)	3	
	Hypertonic saline up to 0.3 g/kg/24h	2	
	Hypertonic saline (>0.3 g/kg/24h)	3	6
Temperature control	Treatment of fever (temperature > 38°C or spontaneous temperature of 34.5°C)	1	
	Cooling for ICP control with a lower limit of 35°C	2	
	Hypothermia below 35°C	5	5
Surgery for intracranial hypertension	Intracranial operation for progressive mass lesion, not scheduled on admission	4	
	Decompressive craniectiomy	5	9
Maximum possible score			38

This table shows the scoring of the Therapy Intensity Level (TIL) as recorded in the CENTER-TBI study. Derived from Zuercher et al. [10].

evidence is still lacking on more specific recommendations (e.g. on timing, type, and duration of treatment). Guideline adherence in centers might improve, when stronger evidence becomes available to support treatment recommendations [14].

Although many Randomized Controlled trial (RCTs) have been performed to generate new evidence in TBI, most did not impact or change clinical practice [13]. This "failure of RCTs" may relate to relatively limited effectiveness of treatments under study, strict enrolment criteria, and low numbers of patients [15]. However, recently, the CRASH-III trial was a randomized placebo-controlled trial (RCT) including 12 737 patients from 175 hospitals in 29 countries across the world. This RCT provided high-level evidence to change clinical practice [16]. However, it was unknown whether the effects were also generalizable to more severe patients with TBI. Another example of a successful RCT is the MRC CRASH-trial, that showed that steroids should be avoided in the treatment of TBI [17].

The disappointing results of most RCTs have drawn attention to an alternative approach; analysis of large observational cohort studies. The main advantages of such studies are the possibility of inclusion of larger numbers of patients and less selected populations; which might increase the generalizability of results to all patients with TBI. The main disadvantage is risk of bias in the analysis of a treatment effect. In a non-randomized design, studying effectiveness is hampered by 'confounding by indication'. This means that the treatment may appear to be associated with a poor outcome, while it was associated with the indication for which the treatment was given. For example, younger patients might receive more aggressive treatments and show an improved outcome, based on their age instead of the treatment itself.

Comparative Effectiveness Research

Previous studies showed variation in ICP monitoring, ICP-directed therapies and general management in patients with TBI [18-21]. Variation between centres can be justified when explained by variability in case-mix severity of local patient populations. Another source of variation is that there are justifiable choices in individualized management of TBI. However, variation may also reflect that we are in a 'low evidence setting', where it is unclear which treatment approach is optimal. Variations in management might impact on outcome. This is the basic tenet underlying comparative effectiveness research: leveraging variability to assess best practices and most effective treatment policies [22]. (Box 1)

Box 1: Comparative Effectiveness Research (CER)

The Institute of Medicine committee has defined comparative effectiveness research (CER) as "the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels." [23]

Quality of care

Quality indicators

The World Health Organization defines quality of care as "the extent to which health care services provided to individuals and patient populations improve desired health outcomes [24]." To achieve high quality of care, health care must be: safe (avoiding preventable injuries and medical errors), effective (evidence-based), timely (reducing delays), efficient (maximize resource use), equitable (equality in gender, race, etc.), and people-centered (based on preferences and culture). Quality indicators have been developed to quantify these dimensions. The intent is to objectively and generalizable assess care over time and across

settings. Quality indicators are subdivided in structure, process and outcome indicators according to Donabedian's popular framework [25]. Structure indicators define the hospital or health system characteristics, such as the nurse-to-bed ratio. Process indicators measure the appropriateness of delivered care, such as the use of ICP monitoring in patients with severe TBI. Outcome indicators refer to the outcomes of delivered care, such as the number of patients with ventilator acquired pneumonia.

Development of quality indicators

The most common approach to develop quality indicators is in a Delphi study, in which experts from different countries and disciplines select a quality indicator set that could measure and assist in improving quality of care. Online questionnaires are often used in a Delphi study where experts can rate the quality indicators in multiple rounds according to different criteria. Ideally quality indicators are based on high level evidence and recommendations in consensus guidelines.

Quality indicators are often directly implemented, while validation in empirical data rarely takes place. Validation in empirical data should increase our insights in the feasibility, validity and usefulness of quality indicators. A quality indicator set should be dynamic and continuous reevaluation is necessary after implementation.

Improvement of care using quality indicators

Quality indicators can be implemented in different ways to improve quality of care. It has been shown that solely the registration of quality of care can already improve patient outcomes over time [26]. This might be due increased knowledge on care performance, clinical discussions or quality improvement programs on how to improve care, or increased financial support of the hospital. As a next step after registering quality indicators, quality improvement programs are often started, e.g. with implementation of bundles of care at the ICU to increase adherence to quality indicators.

In addition, both internal and external benchmarking might contribute to improvement [27]. With internal benchmarking the performance within the centre is benchmarked over time. With external benchmarking multiple (international) centres are involved and their performance is compared. Such comparisons should generate data with feedback to the participating centre, indicating potential areas for improvement.

For TBI, no widely endorsed quality indicators exist yet, which may be due to the fact that the evidence-base is limited. However, quality indicators may also identify areas of variation where evidence is lacking and research is warranted.

CENTER-TBI study

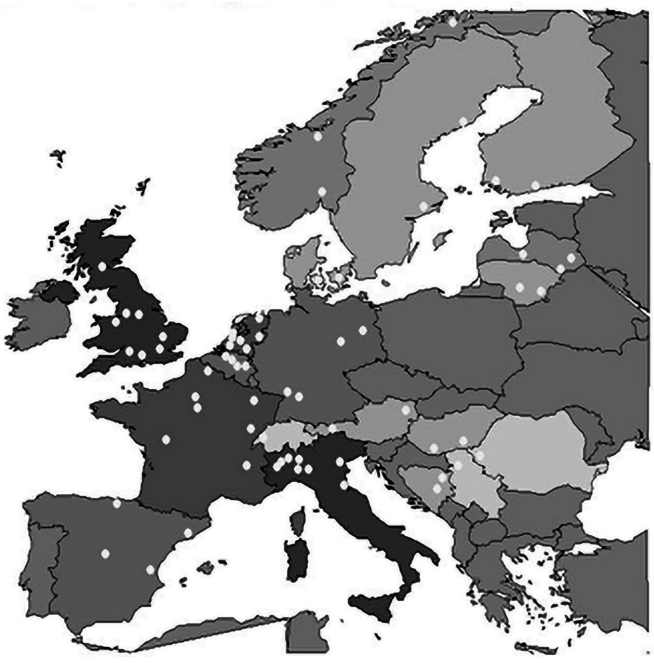
The CENTER-TBI study is a prospective observational cohort study in which neurotrauma centres across Europe participated between December 19, 2014 and December 17, 2017.

The overall aims of CENTER TBI were to provide new, multidimensional insight into TBI characterization, to generate evidence to support treatment recommendations, and to benchmark quality of TBI care across Europe [28].

In total patients from 66 centers (Figure 1) were included in the Core study, which collected detailed data on demographics, injury, imaging, admission, monitoring, treatment, and outcomes. Patients were included in three strata: ER (N= 848; 19%), ICU (N= 2138;47%), and ward (N= 1523; 34%) [29].

In this thesis, the observational CENTER-TBI study is a central data source. A comparative effectiveness research (CER) approach in this study was followed to exploit the heterogeneity and variation between countries, centres, or patients in treatment of TBI.

Figure 1: Number of participating centres in the CENTER-TBI study



Legend figure 1: this figure shows the number of patients participating in each country. The higher the number of participating center per country, the darker the color.

To capture the structures and processes of care at centre-level, questionnaires were sent out to the participating centres: the Provider Profiling questionnaires. An example is shown below about glucose management and caloric intake / nutrition (Box 2). These questionnaires were part of the CENTER- TBI study and extracted information on the structures and processes of care of the participating centers, as perceived by designated local researchers: these included mostly clinicians (neurosurgeons, intensivists, anesthesiologist), but also policymakers and hospital managers.

In the studies presented in this thesis, we used the CENTER-TBI core data, specifically the ICU stratum, and the Provider Profiling data.

Box 2: Example Questions of the Provider Profiling questionnaire

Glucose

64. Is there a standard protocol for glucose management in Traumatic Brain Injury (TBI) in your Intensive Care Unit (ICU) ?
    - o No
    - o Yes

65. What therapy is used in glucose management at your Intensive Care Unit (ICU) ?
    - o No specific therapy
    - o Prophylactic insulin administration (buffered infusion)
    - o Insulin administration to correct hyperglycemias
    - o Tight glycemic control

Caloric intake / nutrition

66. How is nutrition managed at your Intensive Care Unit (ICU) ?
    - o Always parenteral route
    - o Always enteral route
    - o Mostly parenteral route, enteral route on indication
    - o Mostly enteral route, parenteral route on indication
    - o Other……..

67. What caloric intake do you aim for in patients with Traumatic Brain Injury (TBI) at your Intensive Care Unit (ICU) ?

…

In the Provider Profiling questions on treatment protocol were asked, such as timing, thresholds, and treatment choice

Aims and objectives

The overall aim of this thesis is to describe variation in management of TBI patients among European ICUs, and to assess the quality and effectiveness of some components of ICU care for TBI patients.

The two main research questions are:

1) What is the current variation in treatment policies for patients with TBI among European ICUs?
2) What is the quality of ICU care for patients with TBI and how can we improve the effectiveness and safety of treatments?

Thesis outline

Chapter 2 gives an overview of monitoring, treatment and outcomes of TBI patients admitted to the ICU in CENTER-TBI and the between-center variation. Also, the underlying mechanisms for variation in treatment policies are studied. In **Chapter 3,** the Provider Profiling questionnaires are used to describe the variation in treatment strategies to decrease the intracranial pressure in patients with TBI across European centers, specifically ICP monitoring policies, supportive care, and ICP- lowering treatments. **Chapter 4** describes the variation in the use of blood transfusion and coagulation policies among European centers using the provider profiling questionnaires. This chapter provides more details on hemoglobin transfusion thresholds, deep venous thrombosis prophylaxis, and coagulation products. **Chapter 5** reports the between-center variation in the more general supportive and preventive treatment strategies, including circulatory and respiratory management, fever control, use of corticosteroids, nutrition and glucose management, and seizure prophylaxis and treatment, using the provider profiling questionnaires.

Chapter 6 reports the development of quality indicators to measure quality of ICU care based on a Delphi study. **Chapter 7** shows which quality indicators can be used to benchmark and improve quality of care based on real-time patient data from the prospective CENTER TBI study. **Chapter 8** covers a study on the use and effectiveness of high therapy intensity levels at the ICU in the CENTER TBI study. **Chapter 9** describes the variation in pharmaceutical VTE prophylaxis between centres and the association with clinical outcome.

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PART 1

Assessment of variation in Traumatic Brain Injury care among European ICUs

CHAPTER 2

2

Changing Care Pathways and Between-Centre Practice Variations in Intensive Care for Traumatic Brain Injury across Europe

Huijben JA, Wiegers EJA, Lingsma HF, Citerio G, Maas AIR, Menon DK, Ercole A, Nelson D, van der Jagt M, Steyerberg EW, Helbok R, Lecky F, Peul W, Birg T, Zoerle T, Carbonara M, Stocchetti N

Intensive Care Medicine, 2020

Abstract

Purpose: To describe ICU stay, selected management aspects, and outcome of Intensive Care Unit (ICU) patients with traumatic brain injury (TBI) in Europe, and to quantify variation across centers.

Methods: This is a prospective observational multicenter study conducted across 18 countries in Europe and Israel. Admission characteristics, clinical data, and outcome were described at patient- and center-levels. Between-center variation in the total ICU population was quantified with the median odds ratio (MOR), with correction for case-mix and random variation between centers.

Results: A total of 2138 patients were admitted to the ICU, with median age of 49 years; 36% of which were mild TBI (Glasgow Coma Scale; GCS 13-15). Within 72 hours 636 (30%) were discharged and 128 (6%) died. Early deaths and long stay patients (>72 hours) had more severe injuries based on the GCS and neuroimaging characteristics, compared with short stay patients. Long stay patients received more monitoring and were treated at higher intensity, and experienced worse 6-month outcome compared to short-stay patients. Between-center variations were prominent in the proportion of short stay patients (MOR= 2.3, $p<0.001$), use of Intracranial Pressure (ICP) monitoring (MOR= 2.5, $p<0.001$) and aggressive treatments (MOR= 2.9, $p<0.001$); and smaller in 6-month outcome (MOR= 1.2, $p=0.01$).

Conclusions: Half of contemporary TBI patients at the ICU have mild to moderate head injury. Substantial between-center variations exist in ICU stay and treatment policies, and less so in outcome. It remains unclear whether admission of short stay patients represents appropriate prudence or inappropriate use of clinical resources.

Introduction

Traumatic brain injury (TBI) causes a social and economic global burden with about 82,000 deaths in Europe every year [1]. Patients with severe TBI often receive a highly intensive and multidisciplinary approach to prevent or mitigate both secondary brain injury and systemic complications [2]. For less severe TBI cases (without severe extracranial injury), clinicians have to estimate whether they will benefit from ICU admission, since guidelines with high-level evidence on ICU admission criteria are lacking. ICU admission is costly, and might also potentially be inappropriate for the patient, with risk of overtreatment and ICU-related complications, such as infections from multi-resistant bacteria [3].

In previous studies, intensive care admission was described merely for the most severe TBI cases, typically young male victims of high-energy road traffic incidents. In high income countries, however, the aging population and the reduction of road traffic incidents has led to important changes in TBI epidemiology, which now includes older patients, who are often victims of falls, and present with frequent co-morbidities but less severe brain injury. Recent data suggest that the landscape of TBI in Europe is changing and that, correspondingly, ICU admission policies may have been modified, including a larger proportion of milder TBI patients [4, 5].

The aims of this study were

1) to provide a general description of ICU stay, selected management aspects and outcome in TBI patients across Europe and,
2) to quantify variation across centres.

Methods

CENTER-TBI study

The Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI study, registered at clinicaltrials.gov NCT02210221) entails a longitudinal prospective collection of TBI patient data across 63 centers in Europe and Israel between December 19, 2014 and December 17, 2017. Inclusion criteria were: (1) clinical diagnosis of TBI; (2) indication for a brain CT scan; and (3) presentation to the hospital within 24 hours post-injury. The presence of a severe preexisting neurological disorder, potentially confounding outcome assessment, was the only exclusion criterion. The CENTER-TBI study was approved by the medical ethics committees of all participating centres and informed consent from the patient or legal representative was obtained according to local regulations [4, 6].

ICU population and data collection

All patients directly admitted from the Emergency Room or transferred within 24 hours of injury from another hospital to the ICU were analyzed [4]. Patients who deteriorated at the trauma, neurological or neurosurgical ward and were (re)admitted to the ICU were not included. Clinical data were collected at ICU admission, during ICU stay and at ICU discharge. For the current study, we extracted data on demographics, injury, imaging, admission, monitoring, treatment, and outcome characteristics. Patients were stratified using baseline GCS scores as mild (GCS 13-15), moderate (GCS 9-12), or severe TBI (GCS <9) [4].

ICP and ICP-lowering treatments

ICP and cerebral perfusion pressure (CPP) values were collected every two hours. Intracranial hypertension was defined as a value above 20 mmHg, while 60 mmHg was chosen as a threshold for low CPP. To quantify the intensity of ICP-targeted therapies, a recently updated and validated version of the therapy intensity level (TIL) scale was used [7]. This scale summarizes in a score the number and the intensity of treatments. In addition, we analyzed the use of aggressive treatments for raised ICP as hypothermia, intense hypocapnia, barbiturates and decompressive craniectomy.

Outcome

Outcome was measured at six months after injury using the Glasgow Outcome Scale – Extended (GOSE), administered by interview or postal questionnaire. The categories 'vegetative state (GOSE 2)' and 'lower severe disability (GOSE 3)' were combined, resulting in a seven-point ordinal scale.

Statistical analysis

Patient characteristics are described as mean and standard deviation (SD) or as median and interquartile range [IQR]. We defined three groups: early deaths (died within ≤72 hours of ICU admission), short stay (≤72 hours in the ICU) and long stay (>72 hours in the ICU). Patient characteristics, treatments and outcome were compared between these groups with χ^2 - tests for categorical variables and ANOVA and t-tests for continuous variables. We used the IMPACT Core model to calculate expected mortality and proportion with unfavourable outcome (GOSE<5).

The variation between centres was quantified using random effect logistic and ordinal regression models with a random intercept for centre, and expressed as the Median Odds Ratio [8] for:

1) The proportion of patients with a short stay (≤72 hours in the ICU) versus long stay (>72 hours) and early deaths (≤72 hours).

2) The proportion of cases having received ICP monitoring. Also, a sensitivity analysis of the proportion of cases having received ICP monitoring in a subset of patients with a GCS $\leq$ 8 and CT abnormalities was performed.
3) The use of aggressive ICP-lowering treatments (any use of Decompressive Craniectomy, Metabolic Suppression, Hypothermia Therapy or Intensive Hypocapnia)
4) 6-months GOSE outcome

The MOR is a measure of variation in treatments or outcomes between hospitals that is not explained by factors in the model or attributable to chance. The MOR is related to τ^2, which is the variance of the random effects;

$$\mathrm{MOR} = \exp\left[\sqrt{2 \times \tau^2 \times 0.6745}\right] \approx \exp\left(0.95\tau\right).$$

The MOR can be interpreted as the odds ratio for comparing two randomly selected centres. For example, a MOR equal to one, indicates no differences between centres. If there is considerable between-centre variation, the MOR will be large. For example a MOR of 2 for a certain treatment, indicates that if two TBI patients with the same injury severity and characteristics presented to two random centres in our sample, one patient will have an over twofold probability to receive that treatment. To adjust for differences in baseline risk, we included the variables from the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) lab prognostic model [9] and any major extracranial Injury (defined as an Abbreviated Injury Scale (AIS) > 3) [10]. The Likelihood ratio test was used to determine the significance of the between-center variation, comparing a model with and without a random effect for center. The corresponding p-values require a mixture distribution since the null hypothesis is on the boundary of the parameter space) [11].

Statistical analyses were performed in the R statistical software [12]. Multiple imputation was used to handle missing values, with use of the mice package in R [13]. These analyses were based on Version 2.0 of the CENTER-TBI core dataset, accessed using a bespoke data management tool, 'Neurobot' (http://neurobot.incf.org; RRID: SCR_01700).

Results

Patient characteristics

A total of 4509 patients were enrolled in the CENTER-TBI study, 2138 of whom were admitted to the ICU and included in this study. Patients were mostly male (73%). The median age was 49 years (IQR 29-65). A minority were children younger than 18 years (132, 6%), 552 (26%) were older than 65 years and 94 (4%) older than 80 years. Patients with severe TBI constituted (48%) of the ICU admissions, while 720 cases (36%) were classified as mild. Major

Table 1: Baseline characteristics

	Total 2138	**Short stay 636**	**Long stay 1372**	**Early deaths 128**	**P-value**
Age (median (IQR))	49 (29 – 65)	48 (28 – 64)	49 (29 – 64)	62 (40 – 75)	<0.001
>=65 years	552/2138 (26%)	153/636 (24%)	337/1372 (25%)	62/128 (48%)	<0.001
>=80 years	94 /2138(4.4%)	29/636 (4.6%)	52/1372 (3.8%)	13/128 (10%)	0.003
Male sex	1562/2138 (73%)	443/636 (70%)	1023/1372 (75%)	94/128 (73%)	0.07
Severity TBI					<0.001
Mild	720/2009 (36%)	394/607 (65%)	319/1285 (25%)	6/116 (5.2%)	
Moderate	328/2009 (16%)	107/607 (18%)	213/1285 (17%)	8/116 (6.9%)	
Severe	961/2009 (48%)	106/607 (18%)	753/1285 (59%)	102/116 (88%)	
Pupillary Reactivity					<0.001
Both Reacting	1636/2016 (81%)	564/606 (93%)	1040/1287 (81%)	31/122 (25%)	
Both Unreacting	246/2016 (12%)	16/606 (2.6%)	150/1287 (12%)	80/122 (65%)	
One reacting	134/2016 (6.6%)	26/606 (4.3%)	97/1287 (7.5%)	11/122 (9.0%)	
Hypoxia	266/1981 (13%)	38/593 (6.4%)	191/1266 (15%)	37/121 (31%)	<0.001
Hypotension	267/1992 (13%)	36/595 (6.1%)	189/1274 (15%)	42/122 (34%)	<0.001
ISS (median (IQR))	29 (25 – 41)	24 (16 – 29)	34 (25 – 43)	58 (28 – 75)	<0.001
Any major extracranial injury (AIS>=3)	1174/2138 (55%)	283/636 (45%)	823/1372 (60%)	67/128 (53%)	<0.001
CT Characteristics					
Marshall CT Classification					<0.001
I	204/1854 (11%)	110/566 (19%)	90/1179 (7.6%)	3/108 (2.8%)	
II	889/1854 (48%)	330/566 (58%)	553/1179 (47%)	6/108 (5.6%)	
III	152/1854 (8.2%)	19/566 (3.4%)	105/1179 (8.9%)	28/108 (26%)	
IV	28/1854 (1.5%)	4/566 (0.7%)	17/1179 (1.4%)	7/108 (6.5%)	
V/VI	581/1854 (31%)	103/566 (18%)	414/1179 (35%)	64/108 (59%)	
Epidural Hematoma	369/1854 (20%)	120/566 (21%)	234/1179 (20%)	15/108 (14%)	0.22
tSAH	1347/1854 (73%)	318/566 (56%)	930/1179 (79%)	99/108 (92%)	<0.001
Contusion	1032/1854 (56%)	244/566 (43%)	730/1179 (62%)	58/108 (54%)	<0.001
Acute Subdural Hematoma	911/1854 (49%)	192/566 (34%)	633/1179 (54%)	86/108 (80%)	<0.001
Midline Shift	404/1854 (22%)	77/566 (14%)	281/1179 (24%)	54/108 (50%)	<0.001
Basal Cistern Absent or Compressed	586/1854 (32%)	81/566 (14%)	415/1179 (35%)	94/108 (87%)	<0.001

This table shows the baseline characteristics for short stay (stay ≤ 72 hours), Long Stay (stay >72 hours), and early deaths (≤ 72 hours). P-values from ANOVA and chi-square statistics for continuous and categorical characteristics respectively

AIS: Abbreviated Injury Scale. tSAH: traumatic subarachnoid hemorrhage

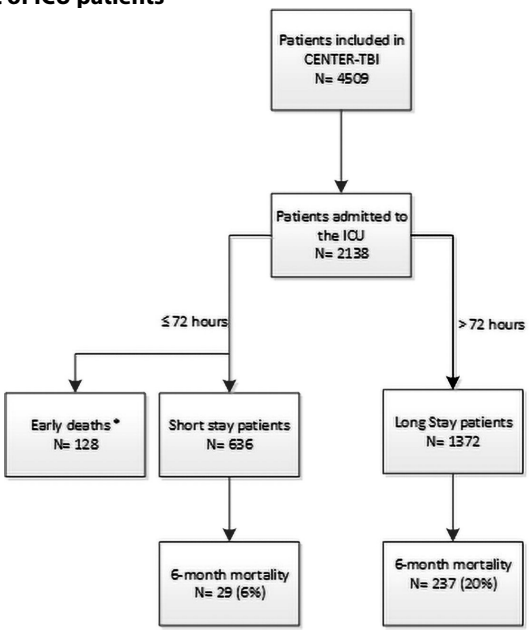
extra-cranial injuries were present in 1174 (55%) patients. (Table 1) More than half of the 54 ICUs have a neuro-ICU available (35, 65%). The median number of ICU beds available was 35 [28-45]. Thirty-eight ICUs had a step-down-unit available (70%). (Table S1) The median number of ICU patients recruited was 28 with an IQR of 15-50 (range 1-140). The median length of stay for the entire ICU cohort was 11 (IQR 3- 26) days.

ICU mortality and discharge rates were high in the first 72 hours, but declined over time (Figure 1, Figure 2). There were 128 (6%) early deaths, 636 (30%) short stay, and 1372 (64%) long stay cases (Figure 2).

Early death patients had a higher median age (62 years) and more severe injuries, both intracranial and extra-cranial, compared to survivors. Demographic features were comparable between short stay and long stay groups, while significant differences were identified with respect to injury severity, CT findings, and pre-admission insults. (Table 1) The main cause of mortality in early death patients was due to initial head injury (78, 81%). (Figure S2)

The most frequent reason for admission in short stay patients were need for frequent neurological observations (340; 54%) and mechanical ventilation (154; 24%) (Figure S3). The long stay patients included 319 patients (25%) classified as mild TBI in whom similar

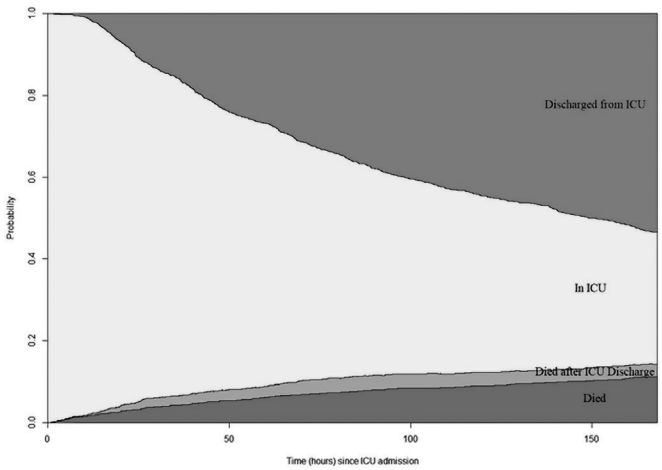
Figure 1: Flowchart of ICU patients



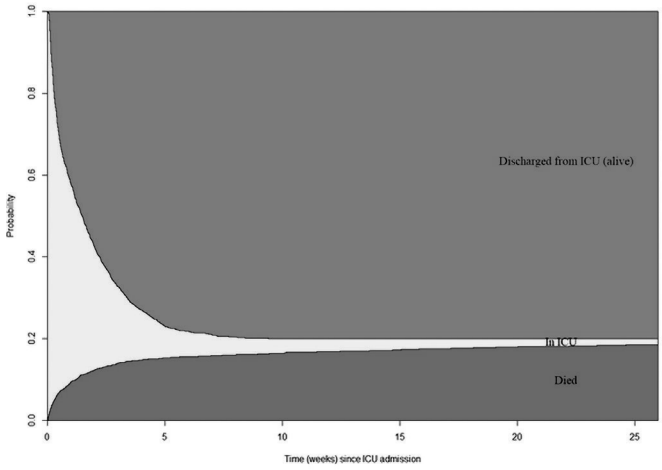
Legend figure 1: this figure shows the flow of patients at the ICU, based on their length of stay. *Patients that died within 72 hours at the ICU

Figure 2: ICU patient flow over time

A



B



Legend 2A] Plot of the dynamic states of patients with TBI that were admitted to the ICU during the first seven days after ICU admission. The y-axis represents the probability to be in one of the possible states (i.e. alive or dead or discharged from ICU) at each time point from ICU admission. *Died after ICU discharge.
Legend 2 B] Plot of the dynamic states of patients with TBI that were admitted to the ICU during the first six months after ICU admission. The y-axis represents the probability the be in one of the possible states (i.e. alive or dead or discharged from ICU) at each point from ICU admission. *Still in ICU

reasons for admission were mentioned (the need for neurological observations (152, 48%), mechanical ventilation (96, 30%).

Monitoring and treatment

Mechanical ventilation for at least 24 hours was most often applied in long stay patients and in patients who died early, when compared to short stay patients (1164 [85%] and 91 [71%];

versus 201 [32%], respectively). A large difference was found in the use of ICP monitoring between long stay and short stay cases (837; 62% versus: 41; 7%, respectively). The main indication for ICP monitoring in short stay patients was surveillance after intracranial operation (31, 76%). Invasive blood pressure monitoring was used in the majority of long stay patients (1227; 90%) and in early deaths (113; 89%); but less frequently (388; 62%) in short stay patients. (Table S2)

Both neurosurgical interventions and extracranial surgery were more common in long stay patients (634; 47% and 467; 34%, respectively) when compared to short stay patients (139; 22% and 122; 19%, respectively). Patients in the short stay group rarely (≤5%) received aggressive ICP treatments (i.e. decompressive craniectomy, metabolic suppression, hypothermia, or intensive hypocapnia). (Table S2)

Complications and Outcome

Long stay patients suffered more complications compared with short stay patients: most commonly ventilator acquired pneumonia (276; 21% versus 3; 0.5%) and cardiovascular complications (125; 9.3% versus 9; 1.5). The overall median hospital length of stay was 11 days (IQR: 3.4-26), while the median hospital length of stay for long stay patients was 18 days (IQR: 7.7-35). When compared to long stay patients, short stay patients were less often discharged to a step down unit (86 [14%] vs 255 [21%] respectively), and more often transferred to the ward (486 [78%] versus 616 [51%]). Long stay patients were also often discharged to other hospitals (174; 14%) and rehabilitation units (95; 8%), while other discharge locations (such as home, other ICU, or nursing home) were rare. (Table 2)

In-hospital mortality for the ICU stratum was 15%; and at six months mortality rose to 21% (data available for 1846 cases), which was lower than expected mortality based on the IMPACT model (30%). Six-month mortality was higher in the long stay patient group compared with the short stay group (20% versus 5.5%).(Table 2)

An unfavorable outcome at six months (GOSE <5) was observed in 43% in the total ICU stratum, 50% (590) in long stay group, and in 15% in short stay group (77). The unfavourable outcome rate in the total ICU stratum was similar to the expected rate based on the IMPACT model (49%)

Between centre- differences

Substantial between-centre differences were found in the proportion of short stay, long stay and early deaths (MOR: 2.3, $p<0.001$, Figure 4). When adjusted for case-mix and random variation, between-centre variation in the proportions of patients in the short stay versus long stay and early death groups was still substantial (MOR: 2.3, $p<0.001$).

Table 2: Outcome and Complications

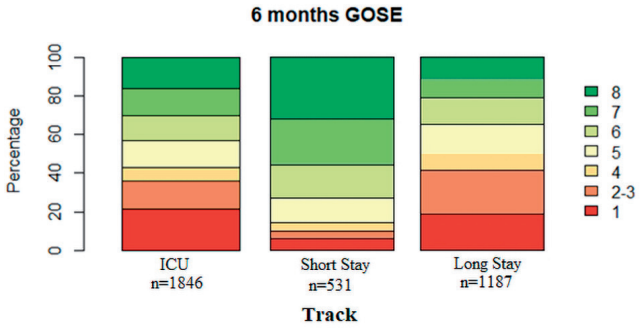
	Total 2138	**Short stay 636**	**Long Stay 1372**	p-value
Outcomes				
6-month Mortality	394/1846 (21%)	29/531 (5.5%)	237/1187 (20%)	<0.001
6-month Unfavorable Outcome (GOSE<5)	795/1846 (43%)	77/531 (15%)	590/1187 (50%)	<0.001
Hospital Length of stay in days (median (IQR))	11 (3.4 – 26)	6.3 (3.0– 11)	18 (7.7 – 35)	<0.001
Discharge Location from ICU				<0.001
General Ward	1102/1840 (60%)	486/623 (78%)	616/1216 (51%)	
Home	15/1840 (0.8%)	11/623 (1.8%)	4/1216 (0.3%)	
Nursing Home	4/1840 (0.2%)	2/623 (0.3%)	2/1216 (0.2%)	
Other	36/1840 (2.0%)	5/623 (0.8%)	30/1216 (2.4%)	
Other Hospital	201/1840 (11%)	27/623 (4.3%)	174/1216 (14%)	
Other ICU	43/1840 (2.3%)	3/623 (0.5%)	40/1216 (3.3%)	
Rehab Unit	98/1840 (5.3%)	3/623 (0.5%)	95/1216 (7.8%)	
Step down/ High Care Unit	341/1840 (19%)	86/623 (13.8%)	255/1216 (21%)	
Complications at the ICU				
Ventilator Acquired Pneumonia	280/2090 (13%)	3/616 (0.5%)	276/1347 (21%)	<0.001
Cardiovascular Complications	155/2091 (7.4%)	9/616 (1.5%)	125/1348 (9.3%)	<0.001
Meningitis	49/2090 (2.3%)	0/616 (0.0%)	48/1347 (3.6%)	<0.001
Seizures	121/2089 (5.8%)	17/616 (2.8%)	99/1346 (7.4%)	<0.001

This table shows the outcomes and ICU complications for patients surviving more than 72 hours after ICU admission. The data is shown for short stay (stay ≤ 72 hours) or long stay (stay >72 hours) patients. Early deaths are not included in this table as these patients represent the outcome in itself (death) and follow-up cannot be described. The categories 'vegetative state (GOSE 2)' and 'lower severe disability (GOSE 3)' were combined resulting in a seven-point ordinal scale.'
GOSE: Glasgow Outcome Scale Extended, ICU: Intensive Care Unit, IQR: interquartile range. P-values from ANOVA and chi-square statistics for continuous and categorical characteristics respectively

Regarding ICP monitoring, after adjustment for case-mix, substantial and significant between-centre variation persisted in the use of ICP monitoring (MOR: 2.5, p<0.001, Figure 4). A sensitivity analyses (with a subset of patient with a GCS <8 and CT abnormalities) confirmed this between-centre variation (MOR: 2.6, p<0.001). After case-mix adjustment, significant between-centre differences were also found in the use of aggressive therapies (MOR: 2.9, p<0.001, Figure 4).

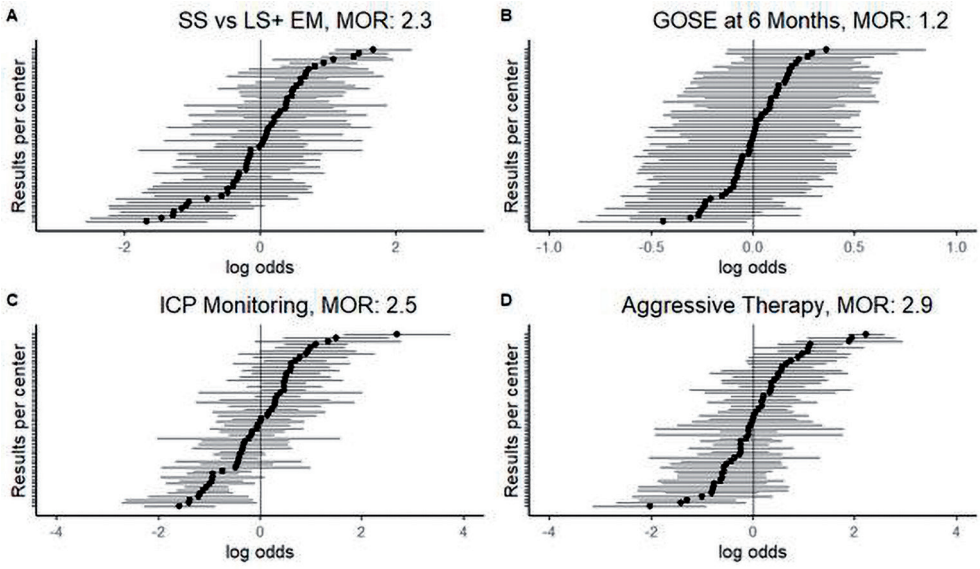
Between-centre variation in outcome was smaller compared to the variation in treatment. The MOR in the total ICU population for six month GOSE was 1.2 (p=0.01, Figure 4).

Figure 3. Six-month Glasgow Outcome Scale Extended.



Legend figure 3: this figure shows the distribution of the functional outcomes at the GOSE after 6 months for all ICU patients, short stay patients, and Long Stay patients.

Figure 4: Between-centre differences in ICU policies and outcome



Legend Figure 4: This panel shows the adjusted differences (adjusted for case-mix with the IMPACT prognostic model) between centres by considering [A] The proportion of patients with a short stay (≤72 hours in the ICU) versus long stay (>72 hours) and early deaths (≤72 hours); long stay and early deaths were treated as one group, since they resemble more severe patients and we aimed to study the proportion in each centre of short stay patients that were discharged alive within 72 hours. [B] GOSE at 6 months for total ICU population, [C] ICP monitoring, [D] Aggressive Therapy (any use of Decompressive Craniectomy, Metabolic Suppression, Hypothermia Therapy or Intensive Hypocapnia during ICU stay). A random effect regression model was used to correct for random variation and adjusted for case-mix severity using the IMPACT variables and the presence of any major extracranial injury. The MOR reflects the between-centre variation; a MOR equal to 1 represents no variation, the larger the MOR, the larger the variation. Significant differences (p-value <0.001) are present for data shown in panels [A], [C], and [D] for panel B (p=0.01)

GOSE: Glasgow Outcome Scale extended, ICP: intracranial pressure, MOR: median odds ratio

Discussion

The aims of this study were to describe ICU admission policies, selected management aspects, and outcome in TBI patients across Europe both at the patient and centre level. A substantial proportion of patients admitted to the ICU were classified on presentation as having a mild or moderate TBI. This is in strong contrast with historical TBI series, such as the USA Traumatic Coma Data Bank study [14] and other studies [15]. However, those series included only severe TBI patients, so that any evaluation of the general ICU admission policies at that time for milder cases is impossible. A more recent study, which analyzed data from 1648 mild TBI patients in 11 US level I trauma centres, showed that about 24 percent of them required admission to the ICU at some stage [16].

Even when compared to these latter data, our findings indicate quite liberal ICU admission rates for less severe cases. This is consistent with the strategies declared by the majority of centres participating in CENTER TBI. When centres were asked (in the Provider Profiling survey; see [5]) if they would admit "patients with a Glasgow Come Score (GCS) between 13 and 15 without CT abnormalities but with other risk factors", 68% of responders reported this as consistent with their centre policy.

Among the cases admitted, we looked at three different patient groups. Around 6% of patients died in the first 3 days after admission, with clearly severe intracranial and extracranial injuries. Patients in this group were significantly older, and only approximately half of those with documented intracranial mass lesions in this group received an operation. In survivors, we studied two distinct groups; those with a brief transition through the ICU and the second characterized by a prolonged ICU treatment. We selected the first 72 hours as criterion to separate these two patient streams, triggered by the high ICU discharge rate during the first 3 days. This separation identified patients with different clinical characteristics, care pathways, and outcomes: long stay patients were more severely injured, required more frequent invasive monitoring (including ICP) and therapies (both surgical and medical), and suffered a worse outcome. In contrast, short stay patients were less severely injured, received less monitoring and treatments, and achieved better outcomes. The most frequently indicated reasons for ICU admission in this latter group were the need for strict neurological observation and mechanical ventilation (which, however, was continued for at least 24 hours only in a third of cases). This may reflect current policy of early intubation at the scene of accident, and/or during initial assessment and evaluation. Cranial and extracranial surgery could also have been alternative indications for a short period of intense post-operative observation in the ICU.

These data can be interpreted in one of two ways. On one hand, the observed practice may represent a prudent strategy, offering close surveillance and assistance to patients

at relatively low risk, but with the opportunity to ensure consistently good outcomes. The risk of deterioration in mild TBI is low but non-negligible. A recent meta-analysis, including 45 studies (for a total of 65724 patients), estimated a 12% incidence of neurological deterioration and 3.5% neurosurgical intervention in mild TBI (characterized as GCS 13-15) [17]. Alternatively, the observed admission strategies may represent costly over-triage, because the ICU is an expensive resource, which should be used wisely. The fact that 11 patients in the short stay group were discharged home directly from the ICU raises strong reservations on their need for intensive care. A previous study in mild TBI patients in the ICU in the USA showed that 17% of cases were over-triaged, with over triaged patients defined as "ICU stay ≤1 day; hospital stay ≤2 days; no intubation; no neurosurgery; and discharged to home"[18]. Our data on ICU admission of mild TBI patients are partially concordant with these findings, and while they do not permit accurate cost-benefit analysis, they clearly indicate a trend in ICU admission policies that deserves attention.

After adjustment for case-mix and random variation between centres, we found significant between-centre proportion of short stay patients discharged alive within 72 hours. This confirms the results of earlier studies that found large variation in admission and discharge policies, primarily for mild TBI patients [5, 18]. This variation might reflect various factors: a search towards more individualized management [2], a lower adherence to guidelines [19], different availability of resources, or various combinations of these different factors. As for monitoring and management variations among centres, heterogeneity was not unexpected: previous studies [19-21] and surveys [22-24] found profound dissimilarities between centres in monitoring and treatment policies similar to our study.

The MOR for outcome between centres (1.2) was significant ($p = 0.01$), but smaller than the MOR for case-mix, ICP monitoring and aggressive therapies (2.5–2.9). This may reflect the small proportion of outcome variance modifiable by differences in management, and/or that differences in individual aspects of management may be discordant and make any outcome impact less easily detectable. Further, between-centre variations in outcome that we demonstrated were smaller than previously reported [25, 26] . This may be because previous analyses were based on older data, collected across multiple studies, and heterogeneity in time and location explained the larger outcome variance in these older reports. It is also possible that over time, a more homogeneous standard of treatment has evolved in Europe and Israel.

Strengths and Limitations

The CENTER-TBI study is unique for its extensive data collection in multiple centres, enrolling TBI patients with varying injury severity across a wide range of European centres. Limitations include that we focused on the ICU while an individual patient's fate, and policies of the center at which treatment is delivered, depend on the continuum of care (from pre-hospital

to rehabilitation). Second, the centres differed in their ICU characteristics, which might potentially contribute to between-centre differences in ICU stay, treatment and outcome. In addition, we might have missed some important case-mix variables in the models that might have contributed to differences between centres (instead of true differences in policies). Third, the low number and non-consecutive enrolment in some centres could result in non-representative recruitment with reference to local ICU admission policy and introduce selection bias. Finally, all centres participating in CENTER TBI are characterized by their commitment to TBI research. They might represent a selected sample of the neurotrauma centres in Europe limiting generalizability.

Future directions

The observed between-centre differences in ICU policies require further research on whether these differences impact patient outcome. Comparative Effectiveness Research (CER) can be used for this purpose [27], requiring adequate covariate adjustment to account for confounders, and adjustment for other treatment policies that might differ between the centers. Variation in ICU performance also provides opportunities for future benchmarking and quality initiatives.

Conclusions

Our results confirm that the current ICU patient population admitted with Traumatic Brain Injury across Europe has changed, compared to previous data, and now includes older patients and a substantial proportion of mild and moderate cases. Sub-populations of patients (which we defined as short stay, long stay, and early mortality groups), are clearly different in injury severities, indications for ICU admission, care pathways, ICU resource utilization, and outcome. Our per-centre analysis identified differences in the proportion of short stay patients and interventions, for instance in the use of ICP monitoring and aggressive therapy, while there were only small differences in outcome.

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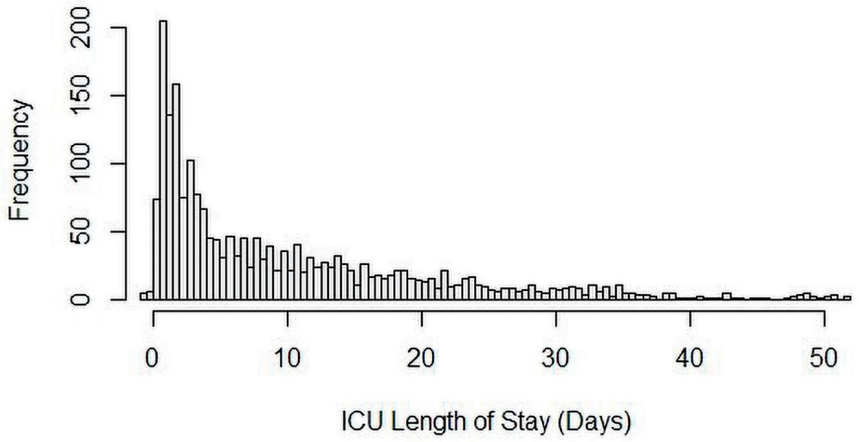
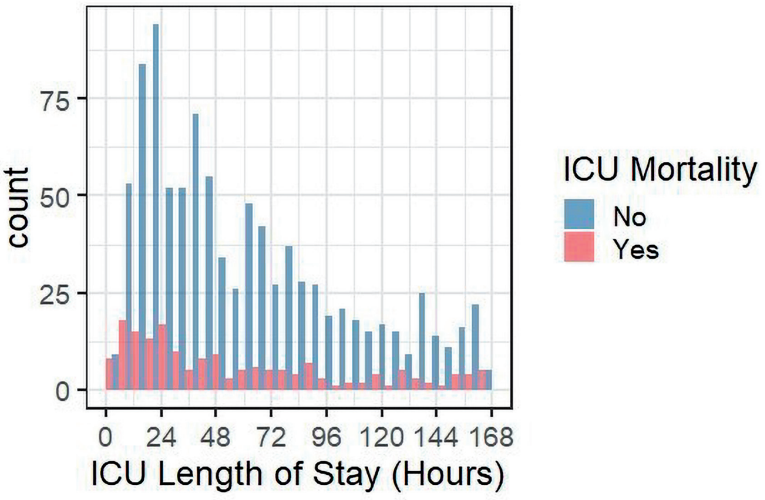
Figures as supplementary material

Figure 1: Length of ICU stay

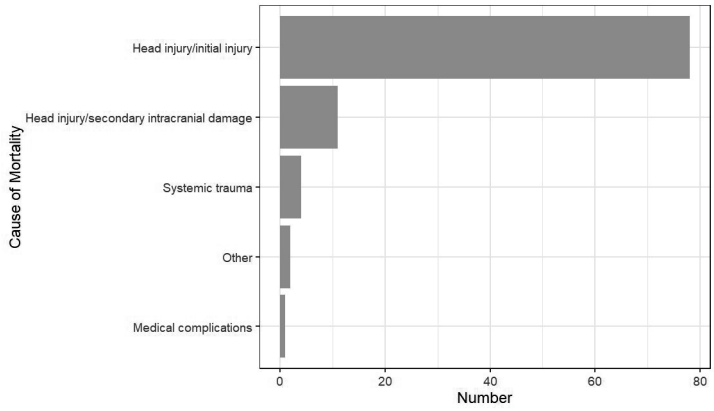


Legend Figure 1A] Length of Stay at the ICU for all patients (n=2138)



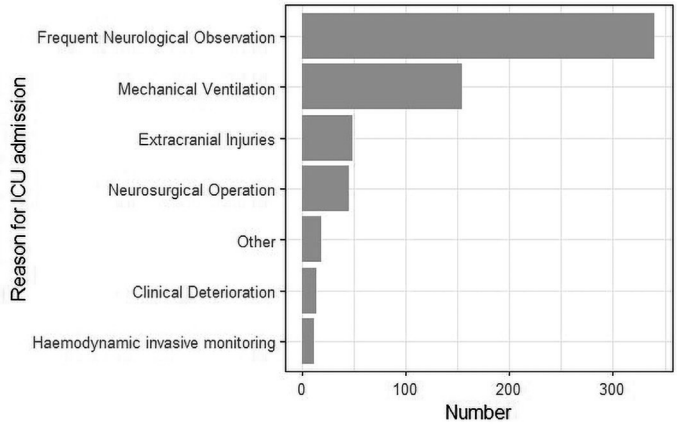
Legend Figure 1B] Length of Stay at the ICU for the first 7 days, stratified by ICU mortality (data available for 1130 patients)

Figure 2: Cause of Mortality in Early Death Group



Legend Figure 2: This figure shows the cause of mortality in the early death patients (N=96) Only one reason per patient could be entered by clinicians.

Figure 3: Reason for ICU admission for short stay patients



Legend Figure 3: This figure shows the reasons for ICU admission for the short stay patients (N=631). Only one reason per patients could be entered by clinicians.

Table 1: Centre characteristics of participating centres

Centre characteristics	Centre-level (N=54)		Patient-level (N=2138)	
	N	%	N	%
Centre				
Academic	51/54	94%	2030/2138	95%
Nonacademic	3/54	6%	108/2138	5%
Location [a]				
Northern Europe	20/54	37%	695/2074	33%
Western Europe	19/54	35%	863/2074	40%
Southern Europe	12/54	22%	556/2074	26%
Eastern Europe	2/54	4%	23/2074	1%
Israel	1/54	2%	1/2074	0%
Higher income country [b]				
Yes	48/54	89%	2072/2138	97%
No	6/54	11%	66/2138	3%
Centre location [c]				
Urban	53/54	98%	2122/2138	99%
Suburban	1/54	2%	16/2138	1%
Trauma designation [d]				
Level I	37/54	69%	1569/2138	73%
Level II	4/54	7%	86/2138	4%
Level III	1/54	2%	140/2138	7%
No designation/NA	12/54	22%	343/2138	16%
Dedicated neuro-ICU available				
Yes	35/54	65%	1471/2138	69%
No	19/54	35%	667/2138	31%
Step-down beds available [e]				
Yes	38/54	70%	1583/2138	74%
No	16/54	30%	555/2138	36%
Electronic patient records at the ICU				
Yes	42/54	78%	1814/2138	85%
No	12/54	22%	324/2138	15%
Number of ICU beds available (median, IQR)	35 [28-45]		-	

This table describes the centre characteristics at centre-level and the representing number of patients (patient-level).
a) Location is based on United Nations geoscheme: Northern Europe = Norway (N = 163), Sweden (N = 87), Finland (N = 132), Denmark (N = 3), the United Kingdom and Ireland (N = 271), and Baltic States: Latvia (N = 10), Lithuana (N = 23); Western Europe = Austria (N = 109), Belgium (N = 193), France (N = 115), Germany (N = 87), and the Netherlands (N = 359); Southern Europe = Serbia (N = 10), Italy (N = 293) and Spain (N = 195); Eastern Europe = Romania (N = 3), Hungary (N = 20); b) *Higher income:* Austria, Belgium, Denmark, Finland, France, Germany, Israel, Italy, the Netherlands, Norway, Spain, Sweden, the UK and Switzerland; *Relatively low income:* Bosnia Herzegovina, Hungary, Latvia, Lithuania, Romania and Serbia. c) Urban: A hospital location very near to a city and situated in a crowded area. Suburban: between urban and rural (an hospital location in or very near to the countryside in an area that is not crowded.) d) Level I trauma centre: A regional resource centre that generally serves large cities or population-dense areas. A level I trauma centre is expected to manage large numbers of severely injured patients (at least 1,200 trauma patients annually or have 240 admissions with an Injury Severity Score of more than 14). It is characterized by 24-hour in-house availability of an attending surgeon and the prompt availability of other specialties (e.g. neurosurgeon, trauma surgeon). Level II trauma centre: A level II trauma centre provides comprehensive trauma care in either a population-dense area in which a level II trauma centre may supplement the clinical activity and expertise of a level I institution or occur in less population-dense areas. In the latter case, the level II trauma centre serves as the lead trauma facility for a geographic area when a level I institution is not geographically close enough to do so. It is characterized by 24-hour in-house availability of an attending surgeon and the prompt availability of other specialties (e.g. neurosurgeon, trauma surgeon). Level III trauma centre: A level III trauma centre has the capacity to initially manage the majority of injured patients and have transfer agreements with a level I or II trauma centre for seriously injured patients whose needs exceed the facility's resources. e) A step-down bed or a medium care facility is a facility in between the ICU and the hospital ward. It is often used for patients who improved at the ICU and no longer need the intensivity of ICU care, but are also not well enough to be cared for on a routine hospital ward. The care provided in stepdown/intermediate care beds is less intensive than the care provided at the ICU but more intensive than hospital ward care
ICU: Intensive Care Unit, ISS: Injury Severity Scale, NA: not applicable, TBI: Traumatic Brain Injury

Table 2: Treatment frequency

	Total 2138	Short stay 636	Long Stay 1372	Early Deaths 128	p-value
Mechanical Ventilation for at least 24 hours	1456/2138 (68%)	201/636 (32%)	1164/1372 (85%)	91/128 (71%)	<0.001
ICP Monitor	921/2113 (44%)	41/627 (6.7%)	837/1359 (62%)	43/127 (34%)	<0.001
Number of patients with ICP>=20	615/921 (67%)	13/41 (32%)	563/837 (67%)	39/43 (91%)	
Number of patients with CPP <60	674/921 (73%)	20/41 (49%)	613/837 (73%)	41/43 (95%)	
Invasive BP Monitoring	1728/2111 (82%)	388/626 (62%)	1227/1358 (90%)	113/127 (89%)	<0.001
Cranial Surgery	820/2124 (39%)	139/634 (22%)	634/1260 (47%)	46/128 (36%)	<0.001
Extracranial Surgery	606/2124 (29%)	122/633 (19%)	467/1361 (34%)	16/128 (13%)	<0.001
Hypothermia <35 °C	130/1979 (6.6%)	4/566 (0.7%)	109/1304 (8.4%)	17/109 (16%)	<0.001
Mild Hypothermia with a lower limit of 35°C	173/1979 (8.7%)	4/566 (0.7%)	157/1304 (12%)	12/109 (11%)	<0.001
Intensive Hypocapnia [PaCO2 < 4.0 kPa (30 mmHg)]	82/1977 (4.1%)	2/565 (0.4%)	74/1303 (5.7%)	6/109 (5.5%)	<0.001
Metabolic suppression [1]	404/1979 (20%)	27/566 (4.8%)	358/1304 (28%)	19/109 (17%)	<0.001
Neuromuscular blockade	436/1978 (22%)	30/565 (5.3%)	384/1304 (29%)	22/109 (20%)	<0.001
Decompressive craniectomy	212/1979 (11%)	9/566 (1.6%)	187/1304 (14%)	16/109 (15%)	<0.001

This table shows the treatment and monitoring characteristics for short stay (stay ≤ 72 hours), long stay (stay >72 hours), and early deaths (≤ 72 hours).
1) High dose barbiturates or propofol
CPP: cerebral perfusion pressure, ICP: Intracranial Pressure, mmHg: millimeters mercury, kPa: kilopascal, $PaCO_2$: partial pressure of carbon dioxide in arterial blood. P-values from ANOVA and chi-square statistics for continuous and categorical characteristics respectively

Table 3: Baseline characteristics stratified by GCS Severity

	Mild 720	Moderate 328	Severe 961	p-value
Track				<0.001
Short Stay	394 (55%)	107 (33%)	106 (11%)	
Long Stay	319 (44%)	213 (65%)	753 (78%)	
Early Deaths	6 (0.8%)	8 (2.4%)	102 (11%)	
Age (median (IQR))	53 (33 – 67)	54 (32 – 70)	45 (27 – 62)	<0.001
>=65 years	207/720 (29%)	108/328 (33%)	209/961 (22%)	<0.001
>=80 years	41/720 (5.7%)	16/328 (4.9%)	33/961 (3.4%)	0.08
Male sex	528/720 (73%)	218/328 (67%)	723/961 (75%)	0.01
Pupillary Reactivity				<0.001
Both Reacting	660/691 (96%)	277/311 (89%)	634/929 (68%)	
Both Unreacting	10/691 (1.4%)	20/311 (6.4%)	202/929 (22%)	
One reacting	21/691 (3.0%)	14/311 (4.5%)	93/929 (10%)	
Hypoxia	35/678 (5.2%)	17/308 (5.5%)	190/898 (21%)	<0.001
Hypotension	46/687 (6.7%)	24/306 (7.8%)	177/904 (20%)	<0.001
Any major extracranial injury (AIS>=3)	361/720 (50%)	147/328 (45%)	600/961 (62%)	<0.001
CT Characteristics				
Marshall CT Classification				<0.001
I	120/645 (19%)	13/277 (4.7%)	59/827 (7.1%)	
II	364/645 (56%)	137/277 (50%)	339/827 (41%)	
III	21/645 (3.3%)	17/277 (6.1%)	104/827 (13%)	
IV	6/645 (0.9%)	4/277 (1.4%)	18/827 (2.2%)	
V/VI	134/645 (21%)	106/277 (38%)	361/827 (37%)	
Epidural Hematoma	130/645 (20%)	70/277 (25%)	145/827 (18%)	0.02
tSAH	393/645 (61%)	222/277 (80%)	657/827 (79%)	<0.001
Contusion	301/645 (47%)	191/277 (69%)	479/827 (58%)	<0.001
Acute Subdural Hematoma	246/645 (38%)	163/277 (59%)	454/827 (55%)	<0.001
Midline Shift	74/645 (11%)	71/277 (26%)	240/827 (29%)	<0.001
Basal Cistern Absent or Compressed	93/645 (14%)	84/277 (30%)	347/827 (45%)	<0.001

This table shows the baseline characteristics stratified by GCS severity. P-values from ANOVA and chi-square statistics for continuous and categorical characteristics respectively
AIS: Abbreviated Injury Scale. tSAH: traumatic subarachnoid hemorrhage

Table 4: Treatment frequency stratified by GCS Severity

	Mild 720	Moderate 328	Severe 961	p-value
Mechanical Ventilation for at least 24 hours	280/720 (39%)	235/238 (72%)	850/961 (88%)	<0.001
ICP Monitor	123/716 (17%)	148/325 (46%)	591/958 (62%)	<0.001
Number of patients with ICP>=20	75/121 (62%)	97/143 (68%)	405/571 (71%)	<0.001
Number of patients with CPP <60	92/120 (77%)	106/143 (74%)	433/571 (76%)	<0.001
Invasive Blood Pressure Monitori28ng	453/715 (63%)	285/325 (88%)	892/957 (93%)	<0.001
Cranial Surgery	177/716 (25%)	142/323 (44%)	445/957 (47%)	<0.001
Extracranial Surgery	191/716 (27%)	78/323 (24%)	300/957 (31%)	0.02
Hypothermia <35 °C	10/664 (1.5%)	16/305 (5.2%)	99/913 (11%)	<0.001
Mild Hypothermia with a lower limit of 35°C	15/664 (2.3%)	23/305 (7.5%)	127/913 (14%)	<0.001
Intensive Hypocapnia [PaCO2 < 4.0 kPa (30 mmHg)]	2/663 (0.3%)	12/304 (3.9%)	61/913 (6.7%)	<0.001
Metabolic suppression [1]	51/664 (7.7%)	62/305 (20%)	266/913 (29%)	<0.001
Neuromuscular blockade	62/663 (9.3%)	68/305 (22%)	279/913 (31%)	<0.001
Decompressive craniectomy	24/664 (3.6%)	24/305 (7.9%)	152/913 (17%)	<0.001

This table shows the treatment and monitoring characteristics stratified by GCS severity
1) High dose barbiturates or propofol
CPP: cerebral perfusion pressure, ICP: Intracranial Pressure, mmHg: millimeters mercury, kPa: kilopascal, PaCO2 : partial pressure of carbon dioxide in arterial blood. P-values from ANOVA and chi-square statistics for continuous and categorical characteristics respectively

Table 5: Outcome stratified by GCS severity

	Mild 720	Moderate 328	Severe 961	p-value
Outcomes				
6-month Mortality	45/619 (7.3%)	59/281 (21%)	256/843 (30%)	<0.001
6-month Unfavorable Outcome (GOSE<5)	136/619 (22%)	114/281 (41%)	487/843 (58%)	<0.001
Hospital Length of stay in days (median (IQR))	8.2 (3.8 – 16)	13 (5.1 – 25)	16 (2.7 – 34)	<0.001
Discharge Location from ICU				<0.001
General Ward	487/695 (70%)	174/296 (59%)	387/761 (51%)	
Home	9/695 (1.3%)	2/296 (0.7%)	3/761 (0.4%)	
Nursing Home	1/695 (0.1%)	2/296 (0.7%)	1/761 (0.1%)	
Other	9/695 (1.3%)	7/296 (2.4%)	19/761 (2.5%)	
Other Hospital	57/695 (8.2%)	28/296 (9.5%)	105/761 (14%)	
Other ICU	10/695 (1.4%)	9/296 (3.0%)	18/761 (2.4%)	
Rehab Unit	24/695 (3.5%)	12/296 (4.1%)	54/761 (7.1%)	
Step down/ High Care Unit	98/695 (14%)	62/296 (21%)	174/761 (23%)	
Complications at the ICU				
Ventilator Acquired Pneumonia	39/712 (5.5%)	39/324 (12%)	190/947 (20%)	<0.001
Cardiovascular Complications	33/712 (4.6%)	31/324 (9.6%)	81/948 (8.5%)	<0.01
Meningitis	4/712 (0.6%)	5/324 (1.5%)	33/947 (3.5%)	<0.001
Seizures	29/711 (4.1%)	26/324 (8.0%)	62/947 (6.5%)	<0.001

This table shows the outcomes and ICU complications stratified by GCS severity. The categories 'vegetative state (GOSE 2)' and 'lower severe disability (GOSE 3)' were combined resulting in a seven-point ordinal scale.' GOSE: Glasgow Outcome Scale Extended, ICU: Intensive Care Unit, IQR: interquartile range. P-values from ANOVA and chi-square statistics for continuous and categorical characteristics respectively

CHAPTER 3

3

Variation in Monitoring and Treatment policies for intracranial hypertension in Traumatic Brain Injury

Cnossen MC, Huijben JA, van der Jagt M, Volovici V, van Essen T, Polinder S, Nelson D, Ercole A, Stocchetti N, Citerio G, Peul WC, Maas AIR, Menon D, Steyerberg EW, Lingsma HF

Crit Care, 2017

Abstract

Background: No definitive evidence exists on how intracranial hypertension should be treated in patients with traumatic brain injury (TBI). It is therefore likely that centers and practitioners individually balance potential benefits and risks of different intracranial pressure (ICP) management strategies, resulting in practice variation. The aim of this study was to examine variation in monitoring and treatment policies for intracranial hypertension in patients with traumatic brain injury.

Methods: A 29-item survey on intracranial pressure (ICP) monitoring and treatment was developed based on literature and expert opinion, and pilot-tested in 16 centers. The questionnaire was sent to 68 neurotrauma centers participating in the Collaborative European Neurotrauma Effectiveness Research (CENTER-TBI) study.

Results: The survey was completed by 66 centers (97% response rate). Centers were mainly academic hospitals (n = 60, 91%) and designated level I trauma centers (n = 44, 67%). The Brain Trauma Foundation guidelines were used in 49 (74%) centers. Approximately ninety percent of the participants (n = 58) indicated placing an ICP monitor in patients with severe TBI and computed tomography abnormalities. There was no consensus on other indications or on peri-insertion precautions. We found wide variation in the use of first- and second-tier treatments for elevated ICP. Approximately half of the centers were classified as having a relatively aggressive approach to ICP monitoring and treatment (n = 32, 48%), whereas the others were considered more conservative (n = 34, 52%).

Conclusions: Substantial variation was found regarding monitoring and treatment policies in patients with traumatic brain injury and intracranial hypertension. The results of this survey indicate a lack of consensus between European neurotrauma centers and provide an opportunity and necessity for comparative effectiveness research.

Introduction

Secondary brain injury associated with elevated intracranial pressure (ICP) is an important cause of mortality and morbidity in patients with severe traumatic brain injury (TBI) [1]. Therefore, identifying high ICP and optimizing its management is believed to be critically important. Yet, no definitive evidence exists on how ICP should be monitored and treated [2]. Patient and treatment heterogeneity make conducting randomized controlled trials (RCTs) challenging; the majority of RCTs to-date have non-significant findings [3]. On the other hand, observational studies, which are easier to conduct, are at risk for confounding by indication, hampering causal inference [4, 5].

In the absence of conclusive evidence, treatment policy is usually based on local practices, individual preferences and resource availability [6-9]. It is likely that centers and practitioners individually balance potential benefits and risks of different ICP management strategies, which may result in some centers being relatively aggressive while others being more conservative in their treatment policies.

A novel and promising approach in estimating treatment effectiveness is to exploit this variation by comparing standard practices between different centers or countries which is referred to as comparative effectiveness research (CER) [10, 11]. The Collaborative European Neurotrauma Effectiveness Research in TBI (CENTER-TBI) study (grant: 602150) is currently recruiting and will use CER methodology to study treatment effectiveness of ICP management [10]. As a first step, we examined self-perceived practices of ICP monitoring and associated treatment policies, by sending a survey to the centers participating in the CENTER-TBI study. This survey aims to provide insight into variability in ICP management across Europe. Topics identified as showing substantial between-center variation that are plausibly associated with patient outcome will be selected for CER, and their treatment effectiveness can be studied once the CENTER-TBI patient-level data becomes available.

Methods

Study Sample

All centers participating in the prospective longitudinal observational CENTER-TBI study (https://www.center-tbi.eu) were asked to complete a set of questionnaires on structures and processes of care for patients with TBI. Questionnaires were sent to 71 centers from 20 countries between 2014 and 2015 [12]. Three centers dropped-out from the CENTER-TBI study, resulting in 68 eligible centers from Austria (n = 2), Belgium (n = 4), Bosnia Herzegovina (n = 2), Denmark (n = 2), Finland (n = 2), France (n = 7), Germany (n = 4), Hungary (n = 2), Israel (n = 2), Italy (n = 9), Lithuania (n = 2), Latvia (n = 3), the Netherlands

(n = 7), Norway (n = 2), Romania (n = 1), Serbia (n = 1), Spain (n = 4), Sweden (n = 2), the United Kingdom (n = 9) and Switzerland (n = 1).

Questionnaire development and administration

A set of questionnaires to measure structure and process of TBI care was developed based on available literature and expert opinion, and has been comprehensively described in a previous publication [12]. Pilot-testing was undertaken in 16 of the participating centers and feedback was incorporated into the final questionnaire design.

One of the questionnaires contained 29 questions on ICP monitoring and treatment at the ICU. In most questions, we explicitly asked for the 'general policy' which was defined as the treatment or monitoring modality estimated to be used in more than 75% of patients, recognizing that there might be exceptions. In some questions, we asked for quantitative estimations. The representatives of the centers could indicate how often they used a particular monitoring or treatment strategy (never 0-10%, rarely 10-30%, sometimes 30-70%, frequently 70-90%, always 90-100%). The options 'frequently' and 'always' were interpreted as representing the general policy, in line with a previous report [13].

Analyses

We calculated frequencies and percentages for all variables related to the number of responders for that variable. We examined factors associated with a relatively aggressive ICP monitoring and treatment strategy with the Chi-squared or Fisher's exact test as appropriate. Centers were classified as being relatively aggressive if they: (a) place an ICP monitor in patients with a Glasgow Coma Scale (GCS) score ≤ 8 and an abnormal head computed tomography (CT) scan, and (b) if they generally perform at least one out of three second-tier treatments that represented a maximum therapy intensity (barbiturates, decompressive craniectomy and hypothermia < 35° Celsius) [14].

We examined whether there were differences between and within geographic regions in the use of first and second-tier treatments. Countries were divided into seven geographic regions (Northern Europe, Western Europe, UK, Southern Europe, Eastern Europe, Baltic States and Israel). Within each region, we examined the percentage of centers that indicated that the particular treatment was their general policy. In addition, we assessed the influence of geographic region on treatment decision by performing logistic regression analysis with treatment as dependent variable (general policy yes/no) and geographic region (categorical variable) as independent variable. The Nagelkerke R^2 was reported, representing the proportion of variation in treatment that can be explained by geographic region. Analyses were performed using the Statistical Package for Social Sciences (SPSS) version 21 [15].

Results

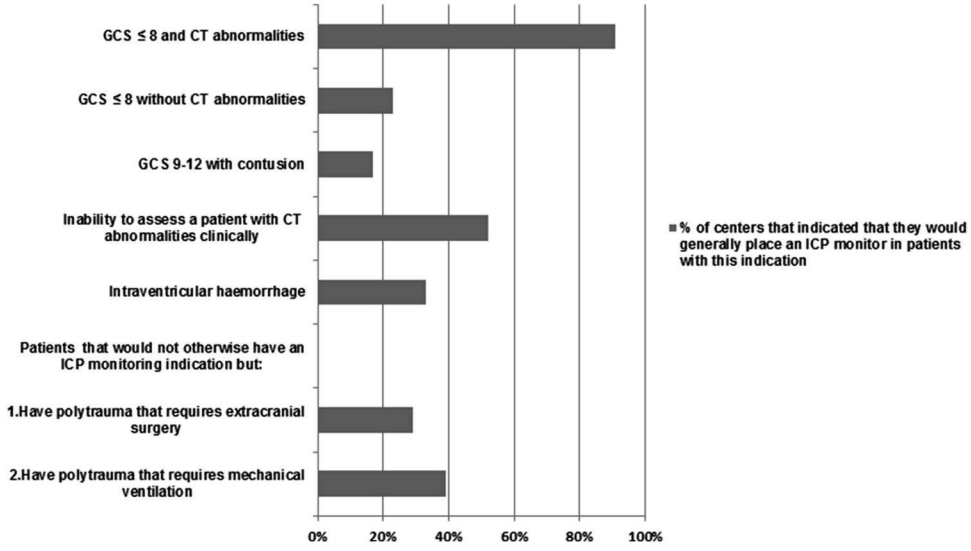
Participating centers

Sixty-six centers (97% response rate) completed the questionnaire on ICP monitoring and treatment in severe TBI patients. Questionnaires were mainly completed by intensive care physicians (n = 33, 50%) and neurosurgeons (n = 23, 35%). Most centers (n = 60, 91%) had an academic affiliation and 44 (67%) were designated level I trauma. Centers had a median of 33 (interquartile range 22-44) ICU beds in total and treated a median of 92 (interquartile range 52-160) severe TBI patients annually. Forty-three (65%) centers operated a 'closed' ICU model; an 'open' model was adopted in three (5%) centers and a 'mixed' model in 20 (30%) centers. Approximately half (n = 39) of the centers had a dedicated neurosciences ICU. Approximately three-quarters of sites (n = 49, 74%) indicated that they used the 2007 Brain Trauma Foundation (BTF) guidelines or institutional guidelines that were based on the BTF guidelines.

Indications for ICP monitoring

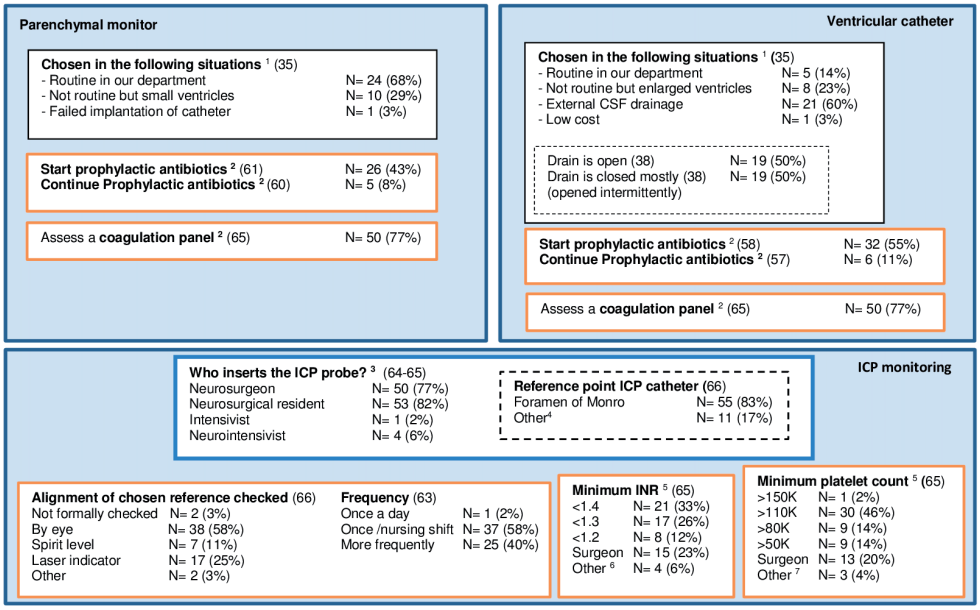
The majority of participants (n = 58, 91%) indicated that they would generally place an ICP monitor in patients with GCS ≤ 8 and CT abnormalities (Figure1). ICP monitors were less often considered for other indications, e.g. GCS ≤ 8 without CT abnormalities (n = 15, 23%), inability to assess a patient with CT abnormalities clinically (e.g. due to sedatives;

Figure 1: Indications for ICP monitoring placement



Legend figure 1: figure presents percentage of centers that indicated that they would generally place an ICP monitor in patients with the described characteristics.
Question is completed by 64/66 centers.
Abbreviations. CT = Computed Tomography; GCS = Glasgow Coma Scale; ICP = Intracranial Pressure

Figure 2A: Algorithm for ICP management: ICP monitoring



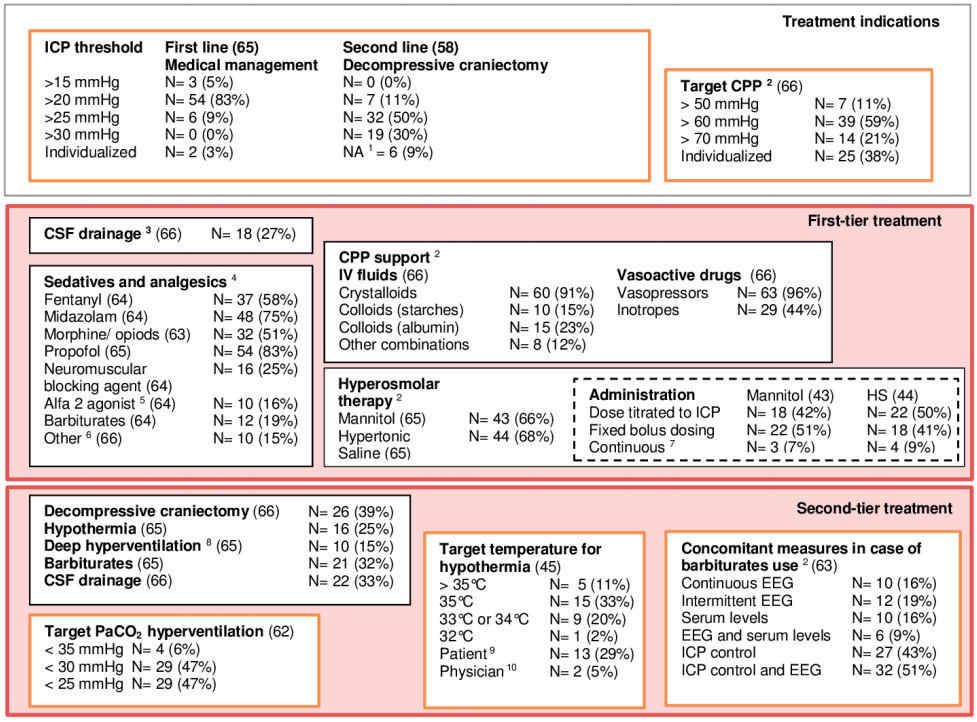
Legend figure 2A: the blue box represents ICP monitoring with the policy for parenchymal monitor on the left and ventricular catheter on the right. Orange boxes are checkpoints during the ICP monitoring process. The N represents the number of centers that indicated this answer as general policy with a corresponding percentage (%). The number in parenthesis after the titles represents the number of centers that completed this question. *Abbreviations.* CSF: cerebrospinal fluid, ICP: intracranial pressure, INR: International Normalized Ratio **1)** Centers that indicated these situations as top 1 of the top 3 reasons for choosing a ventricular or parenchymal catheter **2)** Frequently and always summed **3)** Arterial blood pressure, midauricular level, ventrix motor, NA (we only use parenchymal monitors), room air, calibrated by device and meatus externa **4)** Prior to insertion ventricular catheter for ICP monitoring **5)** Depending on other factors such as the use of platelet aggregation inhibitors **6)** Multiplate and rotem analysis prior to surgery if concerns

n = 11, 17%), and intraventricular hemorrhage (n = 21, 33%). Around one-third of the participants would place an ICP monitor in polytrauma patients (GCS > 8) who require extracranial surgery or mechanical ventilation but would not otherwise have an indication for ICP monitoring. Patient-specific reasons for not monitoring ICP included: the risk of raised ICP was considered low (n = 40, 62%), patients were considered unsalvageable (n = 37, 57%) or GCS > 8 (n = 37, 57%).

Variability in monitoring and treatment of intracranial hypertension

There is large variation in monitoring and treatment characteristics among European centers treating patients with TBI (Figure 2a and b).

Figure 2B: Algorithm for ICP management: treatment indications, first- and second- tier treatment



Legend figure 2B: the red box represents ICP treatment with first-tier treatment on top and second-tier treatment at the bottom. Orange boxes are checkpoints during the ICP treatment process. The N represents the number of centers that indicated this answer as general policy with a corresponding percentage (%). The number in parenthesis after the titles represents the number of centers that completed this question. *Abbreviations.* CSF: cerebrospinal fluid, CPP: cerebral perfusion pressure, EEG: electro-encephalogram, HS: hypertonic saline, ICP: intracranial pressure, IV: intravenous
1) Decompressive craniectomy is (almost) never performed in our hospital **2)** Multiple answers were possible **3)** Only if ventricles are enlarged **4)** Frequently and always summed **5)** Clonidine or dexmedetomidine **6)** Sufentanil (4), reminfentanyl (2), beta blockers (1), alfentanil (2), esketamine (1) **7)** Standard continuous infusion **8)** PaCO2 < 30 mmHg **9)** Variable, depends on patient **10)** Variable, depends on physician

Parenchymal and ventricular ICP devices

Both parenchymal and ventricular ICP devices were available in more than half of centers (n = 38, 59%).One-third (n = 21) of the participants indicated that they used only parenchymal monitors, whereas five (8%) participants indicated that they used only ventricular catheters. In centers that used both types of monitors, parenchymal monitors were typically used routinely, with ventricular catheters placed either when the ventricles were enlarged or when cerebrospinal fluid (CSF) drainage was indicated. When a ventricular drain was used, half of the participants indicated that their local practice was generally to leave the drain open (n = 19, 50%), and the other half indicated a policy of intermittent drainage (n = 19, 50%) (Figure 2a).

Precautions with ICP monitor placement

Half of the participants (55% ventricular catheter and 43% parenchymal sensor) indicated that they generally administered prophylactic antibiotics prior to the insertion of an ICP monitor, which was continued in around 10% of the centers. The majority of participants (n = 50, 77%) generally assessed the patient's coagulation status prior to ICP monitor insertion. There was wide variability regarding the minimum international normalized ratio and minimum platelet count considered safe for device insertion (Figure 2a).

Additional neuromonitoring

Half of the participants (n = 33) indicated that they generally used at least one additional neuromonitoring device. Transcranial Doppler was generally applied in 24 (38%) centers and brain tissue oxygenation in 12 (19%) centers.

First-tier treatment of elevated ICP

The majority of participants indicated an ICP threshold for medical treatment above 20 mmHg (n = 54, 83%, Figure 2). There was less consensus on cerebral perfusion pressure (CPP) treatment thresholds; 39 participants (59%) indicated a threshold of 60 mmHg in their center, whereas 25 (38%) indicated individualized CPP targets.

Propofol (n = 54, 83%), midazolam (n = 48, 75%), fentanyl (n = 37, 58%) and morphine (n = 32, 51%) were generally used as part of first-tier treatment in patients with elevated ICP, whereas the use of alpha 2 agonists (n = 10, 16%) and barbiturates (n = 12, 19%) was less frequent. Neuromuscular blocking agents were generally used in 16 (25%) centers. Participants typically preferred a specific combination of sedatives and analgesics as part of first-tier treatments; i.e. 50 participants (76%) indicated they used 2-4 out of 8 sedatives and analgesics as general policy and the other interventions only infrequently.

Regarding the use of osmotic therapy, two-thirds of the participants indicated generally using mannitol (n = 43, 65%) and/or hypertonic saline (n = 44, 67%). Seventeen participants indicated the use of mannitol, but not hypertonic saline, as their general policy, whereas 18 participants indicated the opposite. Fourteen (22%) participants indicated to generally using hypertonic saline in conjunction with mannitol (Figure 2). Crystalloids were the most commonly used intravenous (IV) fluids to augment CPP (n = 60, 91%), while other fluids (starches, albumin and other combinations) were less often used (12-23%). Vasopressors were generally used in almost all centers to support CPP (n = 63, 96%). Among the parameters that are used to titrate vasoactive drugs, mean arterial pressure targets (n = 51, 77%) and transpulmonary thermodilution monitoring by means of pulse contour cardiac output (n = 35, 53%) were most often used.

Second-tier treatments for refractory intracranial hypertension

Among the second-tier treatments, decompressive craniectomy (n = 26, 39%), barbiturates (n = 21, 32%) and CSF drainage (n = 22, 33%) were the most often employed (Figure 2). Hypothermia and hyperventilation ($PaCO_2$ < 30 mmHg) were the general policy in 24.6% and 15.4% of the centers respectively, while approximately one-third of the participants indicated to never use hypothermia and hyperventilation. Participants typically preferred one (n = 27, 42%) or two (n = 20, 31%) second-tier treatments and indicated to use the other options infrequently. Details on indications for, administration of and targets of second-tier treatments show a high degree of variability.

Factors associated with aggressive monitoring and treatment policies

Around half of the centers were classified as using an aggressive ICP monitoring and treatment policy (n = 32, 48%). Centers with an open or mixed ICU model more often applied an aggressive ICP management style in comparison to centers with a closed ICU model (p = .05). We did not find significant associations between aggressiveness and any of the other factors studied (Table 1).

The influence of geographic region on treatment decisions

The use of first and second-tier treatments varied substantially within and between geographic regions (Table 2). Morphine and CSF drainage showed the largest within-region variation with approximately half of the participants within each region stating to generally use these treatments. Between-region differences were especially pronounced for barbiturates as first-tier treatment. Barbiturates were mainly used in the Baltic states and Eastern Europe and geographic region explained 63% of the variance in barbiturate use. In addition, the use of mannitol varied substantially across regions with all participants in the Baltic states, Eastern Europe and Israel indicating to generally use mannitol, while only 11% of the participants in Northern Europe stated to generally use mannitol. In Northern Europe, Western Europe and the UK, propofol, midazolam, morphine and hypertonic saline are generally applied as first-tier treatment, while participants in Southern Europe, the Baltic States, Eastern Europe also indicated to generally use fentanyl, barbiturates, CSF drainage and mannitol.

Discussion

We found substantial variation in the general approaches to ICP monitoring and treatment among 66 European neurotrauma centers. The majority of centers indicated that they would insert an ICP monitor in patients with severe TBI and an abnormal head CT. There was however no consensus on other indications, nor was there consensus on peri-insertion precautions. The use of both first- and second-tier treatments for elevated ICP varied widely

Table 1: Factors associated with an aggressive ICP management style

Factor	Relatively aggressive centers (n = 32)	Relatively conservative centers (n = 34)	p-value
ICU organization			.05
- Closed	17 (40%)	26 (60%)	
- Open/Mixed	15 (65%)	8 (35%)	
Dedicated neuro ICU			.96
- Available	19 (49%)	20 (51%)	
- Not available	13 (48%)	14 (52%)	
BTF guidelines used[Ł]			.48
- Yes	25 (51%)	24 (49%)	
- No	7 (41%)	10 (59%)	
Volume†			.82
- High-volume	17 (47%)	19 (53%)	
- Low-volume	15 (50%)	15 (50%)	
Income country‡			.83
- High income	27 (49%)	28 (51%)	
- Relatively low income	5 (46%)	6 (54%)	
Geographic location[Ł]			.84
- Northern Europe	4 (44%)	5 (56%)	
- Western Europe	13 (52%)	15 (48%)	
- UK	3 (43%)	4 (57%)	
- Southern Europe	5 (42%)	7 (58%)	
- Baltic States	2 (40%)	3 (60%)	
- Eastern Europe	3 (50%)	3 (50%)	
- Israel	2 (100%)	0 (0%)	

Ł BTF guidelines or institutional guidelines that were broadly based on the Brain Trauma Foundation (BTF) guidelines
†Relatively high volume (number of severe TBI patients admitted to the ICU higher than the median number of severe TBI patients admitted to the ICU (n = 92)) vs. relatively low volume (number of severe TBI patients admitted to the ICU lower than or equal to the median number of severe TBI patients admitted to the ICU.
‡ The division into relatively high and low income was based on a 2007 report by the European Union.[21] High-income = Austria, Belgium, Denmark, Finland, France, Germany, Israel, Italy, the Netherlands, Norway, Spain, Sweden, United Kingdom and Switzerland; Relatively low-income = Bosnia Herzegovina, Bulgaria, Hungary, Latvia, Lithuania, Romania and Serbia.
ŁNorthern Europe = Norway, Sweden, Finland and Denmark; Western Europe = Austria, Belgium, France, Germany, Switzerland and the Netherlands; Southern Europe = Italy and Spain; Eastern Europe = Hungary, Romania, Serbia and Bosnia Herzegovina; Baltic states = Latvia and Lithuania.

between centers and regions. We found that half of the centers employed a relatively aggressive ICP management approach while the other half showed a more conservative approach.

Table 2: Within- and between-region variation in first- and second-tier treatments for elevated intracranial pressure

Variable	Northern Europe (N =9)	Western Europe (N = 25)	UK (N =7)	Southern Europe (N =12)	Baltic States (N = 5)	Eastern Europe (N = 6)	Israel (n = 2)	Nagelkerke R^2
First-tier treatments								
Propofol	78%	76%	100%	92%	80%	67%	100%	0.14
Midazolam	67%	76%	29%	75%	100%	83%	100%	0.22
Fentanyl	44%	44%	29%	67%	100%	100%	50%	0.31
Morphine	56%	48%	57%	50%	40%	33%	50%	0.02
Neuromuscular blocking agents	0%	16%	29%	25%	40%	67%	50%	0.25
Alfa 2 agonists	33%	12%	0%	17%	40%	0%	0%	0.22
Barbiturates	11%	8%	0%	0%	80%	83%	0%	0.63
CSF drainage	33%	24%	0%	25%	60%	50%	0%	0.20
Mannitol	11%	67%	43%	83%	100%	100%	100%	0.46
Hypertonic Saline	89%	71%	86%	58%	40%	33%	100%	0.20
Second-tier treatments								
Decompressive craniectomy	33%	36%	29%	33%	80%	33%	100%	0.16
Hypothermia	22%	25%	71%	25%	0%	0%	0%	0.29
Deep hyperventilation	0%	13%	0%	33%	20%	33%	0%	0.24
Barbiturates	11%	29%	14%	33%	80%	67%	0%	0.25
CSF drainage	56%	28%	43%	33%	20%	17%	50%	0.08

Note. Table presents the percentage of participants within each geographic region that indicated that the first- or second-tier treatment was their general policy. Nagelkerke R2 was derived from a logistic regression analysis with treatment (general policy yes/no) as dependent variable and geographic region (categorical variable) as independent variable. Nagelkerke R2 represents the proportion of variance of the treatment variable that is accounted for by geographic region.
Northern Europe = Norway, Sweden, Finland and Denmark; Western Europe = Austria, Belgium, France, Germany, Switzerland and the Netherlands; Southern Europe = Italy and Spain; Eastern Europe = Hungary, Romania, Serbia and Bosnia Herzegovina; Baltic states = Latvia and Lithuania.

Strengths of this study include the high response rate (97%), the extensive development process of the questionnaire, and the comprehensive examination of both monitoring and treatment. In addition, since our survey was completed by centers that are currently collecting patient-level data for the CENTER-TBI study, the results of this study can directly be used as input for the CER analyses, once the patient-level data becomes available. A limitation of our study is that the included centers represent a selected group of European neurotrauma centers that are prominent in the field of neurotrauma care and research. Consequently, the picture obtained might be skewed. In addition, this study is dependent on perceived practices rather than on clinical data. Although we repeatedly emphasized

confidentiality of results, we cannot exclude that some physicians presented (even subconsciously) a more favorable image or presented individual treatment preferences rather than the general policy in a center. A further limitation is that we asked for isolated general treatments but did not assess specific combinations. In clinical practice, however, different treatments are used simultaneously and outcome might be determined by the combination of treatments provided rather than by one particular intervention [14].

The substantial variation in strategies for ICP management in our study was in line with previous survey studies in Europe and the United States [7, 13, 16-18]. For example, Hesdorffer et al.[13] found that mannitol, hypertonic saline and hyperventilation were generally used in half of their centers. Guidelines have been proposed to reduce treatment variation in medicine.[19] However, although the large majority of participants stated they adhere to the BTF guidelines, there was wide variation in both monitoring and treatment of elevated ICP. In addition, some participants claimed using treatments that are discouraged in the BTF guidelines. For example, one-fifth of the participants specified to use barbiturates as first-tier treatment, while this is a second-tier treatment in the BTF guidelines [20]. The discrepancy between BTF guidelines and reported policies indicates that there is little consensus among neurotrauma centers with respect to ICP management. This might be due to the relatively small evidence-base underpinning the guidelines [3].

Our study has several implications for the planned CER analyses. We found wide variation for most of the topics studied, which enables analyzing effectiveness of ICP management on the hospital-level. Analyzing effectiveness on the hospital-level might be especially useful for treatments that were indicated to be used 'rarely', 'sometimes' or 'frequently' by the large majority of participants. For these treatments, patient characteristics play an important role and these can dramatically confound conventional patient level analyses [4, 5]. Caution should however be applied in the interpretation of the effects of treatments that are solely performed in some regions but not in others. For example, barbiturates as first-tier treatment are often performed in the Baltic States and Eastern Europe but not in other regions. A harmful or beneficial effect could therefore also be attributed to other aspects of care in the particular regions rather than barbiturate use itself. In principle, it is possible to adjust statistically for between-center differences other than the treatment variable of interest with a random-effects model with a random intercept for center. However, when correlations between the treatment variable of interest and other factors that differ between centers are strong, as for the first line use of barbiturates and region, this might not be sufficiently captured by the random-effects model. In such a case differences in outcome cannot be attributed with certainty to the treatment under study. Based on current findings, we would therefore recommend prioritizing the following topics for CER because of feasibility of the center-level approach:

(1) ICP monitoring in patients with other indications than GCS ≤ 8 and CT abnormalities;
(2) parenchymal vs. ventricular monitoring (with and without CSF drainage);
(3) use of first-tier treatments for elevated ICP (including use of neuromuscular blocking agents, mannitol vs hypertonic saline vs mannitol + hypertonic saline, fentanyl vs no fentanyl, fluid management),
(4) use of second-tier treatments (including decompressive craniectomy vs barbiturates vs hypothermia) and
(5) the effect of an aggressive ICP management policy versus a more conservative approach.

Conclusion

Substantial variation was found in the monitoring and treatment of patients with severe traumatic brain injury and intracranial hypertension. These results indicate a lack of consensus among European neurotrauma centers and provide an important opportunity and necessity for comparative effectiveness research to support the development of optimal treatment protocols for these severely affected patients.

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CHAPTER 4

Variation in Blood Transfusion and Coagulation Management in Traumatic Brain Injury at the Intensive Care Unit

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Background Our aim was to describe current approaches and to quantify variability between European intensive care units (ICU)s in patients with TBI. Therefore, we conducted a provider profiling survey as part of the 'Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury' (CENTER-TBI) study.

Methods The ICU Questionnaire was sent to 68 centers from 20 countries across Europe and Israel. For this study, we used ICU questions focused on 1) hemoglobin target level (Hb-TL), 2) coagulation management, and 3) deep venous thromboembolism (DVT) prophylaxis.

Results Seventy-eight participants, mostly intensivists and neurosurgeons of 66 centers completed the ICU questionnaire. For ICU-patients, half of the centers (N=34; 52%) had a defined Hb-TL in their protocol. For patients with TBI, 26 centers (41%) indicated a Hb-TL between 70 and 90 g/l and 38 centers (59%) above 90 g/l. To treat trauma related hemostatic abnormalities the use of fresh frozen plasma (N=48; 73%) or platelets (N=34; 52%) was most often reported, followed by the supplementation of vitamin K (N=26; 39%). Most centers reported using DVT prophylaxis with anticoagulants frequently or always (N=62; 94%). In the absence of hemorrhagic brain lesions, 14 centers (21%) delayed DVT prophylaxis until 72 hours after trauma. If hemorrhagic brain lesions were present, the number of centers delaying DVT prophylaxis for 72 hours increased to 29 (46%).

Conclusion Overall, a lack of consensus exists between European ICUs on blood transfusion and coagulation management. The results provide a baseline for the CENTER-TBI study and the large between-center variation indicates multiple opportunities for comparative effectiveness research.

Introduction

The management of hemorrhage and disordered coagulation is a common and critically important challenge in trauma patients. This is particularly the case for patients with severe traumatic brain injury (TBI) where physicians have to balance the risks of progressive hemorrhage in the brain against secondary thrombotic complications including deep venous thrombosis (DVT). Many controversies continue to exist regarding the appropriate management for optimizing blood and coagulation status.

Transfusion thresholds for anaemia are a particularly controversial area in TBI. According to the guidelines [1, 2], transfusion in general critically ill patients is recommended at a restrictive hemoglobin target level (Hb-TL) of 70 g/l rather than a liberal Hb-TL of 90 g/l or 100g/l. Whether such target levels also apply to patients with TBI is unclear. [3, 4] Inappropriate use of blood products exposes patients to a number of systemic risks and may even lead to progressive hemorrhagic injury following TBI. [3] However, cerebral oxygenation may be improved with higher hemoglobin concentrations [5, 6] whereas restrictive transfusion thresholds may predispose to brain tissue hypoxia and may increase the risk of early mortality. [7] On the other hand, a recent large retrospective cohort study indicated that a restrictive blood transfusion policy was not associated with increased mortality and can be cost-effective in patients with TBI. [8] An additional challenge for the management of both blood–and coagulation status is the presence of coagulopathy.[9] Both pro- and anticoagulatory abnormalities can be observed after TBI in around one out of three patients. [10-12] Coagulopathy at admission is associated with increased mortality and poor neurological outcome. [12-14] Coagulopathy may result from defective clot initiation, poor clot formation or hyper fibrinolysis. Acidosis, hypothermia, coagulation factor consumption or dilution, and the more recently described acute coagulopathy of trauma-shock which results from widespread endothelial activation after hypoperfusion may contribute to coagulopathy. [15] Finally, patients with TBI are at increased risk of venous thromboembolism (VTE) (around 20%) [16] compared with general ICU patients (around 6-8%). [17] Here, the balance between the prevention of VTE and the risk of (progressive) hemorrhage of the brain depends largely on the timing of thromboprophylaxis with anticoagulants. However, current Brain Trauma Foundation guidelines do not make clear recommendations on coagulation management. [18]

In summary, no definitive evidence exists to guide physicians in determining the transfusion and coagulation management in patients with (severe) TBI. This will likely lead to variations in management. Our aim was to describe and quantify variability in European ICUs for blood transfusion and coagulation management in patients with TBI, using a survey among European neurotrauma centers participating in the Collaborative European Neurotrauma Effectiveness Research in TBI (CENTER-TBI) study. [19, 20]

Methods

Participating centers

This study is part of the prospective, longitudinal 'Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury' (CENTER-TBI) study in 68 centers from 20 countries across Europe and Israel. In 2014, before the start of inclusion of patients, the principle investigators of each center were asked to complete a set of questionnaires on structure and process of care: 'the Provider Profiling Questionnaires'. [19, 20] The questionnaires were about TBI management irrespective of systemic injuries. One of these questionnaires concerned ICU management.

Provider Profiling Questionnaire

The provider profiling questionnaire was developed in a systematic manner. The literature (including guidelines and available surveys) was reviewed and experts of various disciplines (neurosurgeons, (neuro)intensivists, neurologists, emergency department physicians, rehabilitation physicians, medical ethicists, health care economists and epidemiologists) were consulted throughout the different phases in the development process. Preliminary questionnaires were pilot-tested in 16 of the participating centers for unexpected or missing values and ambiguity, and received feedback was incorporated. For more information about the development, administration and content of the total set of provider profiling questionnaires, see Cnossen et al., 2016. [19] In this study, we focus on 10 questions (with additional sub questions) on hemoglobin target levels, trauma related coagulation management, and use and timing of thromboprophylaxis.

Hemoglobin target level and coagulation management

Participants were explicitly asked for their general policy rather than for individual treatment preferences. General policy was defined as 'the way the large majority of patients (>75%) with a certain indication would be treated'. The ICU questionnaire consisted mostly of multiple-choice questions and one open question; the Hb-TL in the protocol at the ICU for the general ICU population. For the hemoglobin unit conversion from mmol/L towards g/L we multiplied with the factor 1.6 and then rounded up to tens.

Statistical analysis

Descriptive statistics (frequencies and percentages) were used to describe the treatment policies reported by the participating centers. For some questions in which centers had to indicate how often a certain approach was taken by choosing 'never' (in 0-10% of cases), 'rarely' (in 10-30% of cases), 'sometimes' (in 30-70% of cases), 'frequently' (in 70-90% of cases) and 'always' (90-100% of cases), categories were combined (e.g. combining 'always' and 'frequently') because of low numbers in these categories.

To gain more insight into characteristics that determine treatment policies we divided centers in relatively high- and middle-income countries versus lower-income countries, and in countries from different geographic locations (North and West Europe versus South and East Europe and Israel). The designation into relatively lower-income countries was based on a 2007 report by the European Commission [21], and the designation into geographic location was based on the classification by the United Nations. Analyses were performed using the Statistical Package for Social Sciences (SPSS) version 21. [22]

Results

Participating centers

Sixty-six centers of the 68 centers completed the ICU questionnaire (response rate= 97%). The questionnaire was completed by intensivists (N=33; 50%), neurosurgeons (N=23; 35%), administrative staff (N=11; 17%), neurologists (N=5, 8%), anesthetists (N=5, 8%) and a trauma surgeon (N=1; 2%). Almost all the centers had an academic affiliation (N=60; 91%) and most centers were designated as a level I trauma center (N=44; 67%). Centers had a median of 33 (interquartile range 22-44) beds for general ICU patients and treated a median of 92 (interquartile range 52-160) patients with TBI, of all severities, annually. An extensive overview of all the center characteristics is described in a previous publication. [19]

For the management of TBI at the ICU, most centers indicated to follow the 2007 Brain Trauma Foundation (BTF) guidelines (N=28; 42%) or institutional guidelines (N=21; 32%), which were broadly based on BTF and/or national guidelines. Some centers indicated they did not have specific guidelines for management of TBI (N=11; 17%) or that they developed a guideline independently from available guidelines (N=2; 3%).

Hemoglobin target level

Half of the centers (N=34; 52%) reported to have hemoglobin target levels (Hb-TL) described in their protocol for general/non-TBI ICU patients. The reported Hb-TL varied (open question): 110 g/l (N=1; 3%), 100 g/L (N=8; 28%), 90 g/L (N=4; 14%), 80 g/L (N=9; 31%), 70 g/L (N=5; 18%), 80-100 g/L (N=1; 3%) and 70-80 g/L (N=1, 3%). In non-neurological critically ill patients, 35 of the centers (56%) reported a Hb-TL between 70 g/L and 80 g/L. In patient with TBI, 10 of the centers (16%) indicated to use a Hb-TL between 70 and 80 g/L. The remainder of the centers used higher Hb-TL: between 80 g/L and 90 g/L (N= 16; 25%), between 90g/L and 100 g/L (N=20; 31%), and above 100 g/L (N=18; 28%). (Table 1)

Table 1: Red blood cell transfusion policy [a]

Items questionnaire	Number completed	N	(%)
Protocol at the ICU			
Protocol	65		
- Presence of a protocol with a Hb-TL		34	(52%)
- Absence of a protocol with a Hb-TL		31	(48%)
Transfusion at Hb-TL in protocol (open question)	29		
- 110 g/L		1	(3%)
- 100g/L		8	(28%)
- 90 g/L		4	(14%)
- 80 g/L		9	(31%)
- 70 g/L		5	(18%)
- 80-100 g/L		1	(3%)
- 70-80 g/L		1	(3%)
In non-neurological critically ill patients			
Transfusion at Hb-TL	63		
- > 100 g/L		1	(2%)
- Between 90 g/l and 100g/L		6	(9%)
- Between 80 g/l and 90 g/L		21	(33%)
- Between 70 g/l and 80 g/L		35	(56%)
In patients with TBI [b]			
Transfusion at Hb-TL	64		
- > 100 g/L		18	(28%)
- Between 90 g/l and 100g/L		20	(31%)
- Between 80 g/l and 90 g/L		16	(25%)
- Between 70 g/l and 80 g/L		10	(16%)

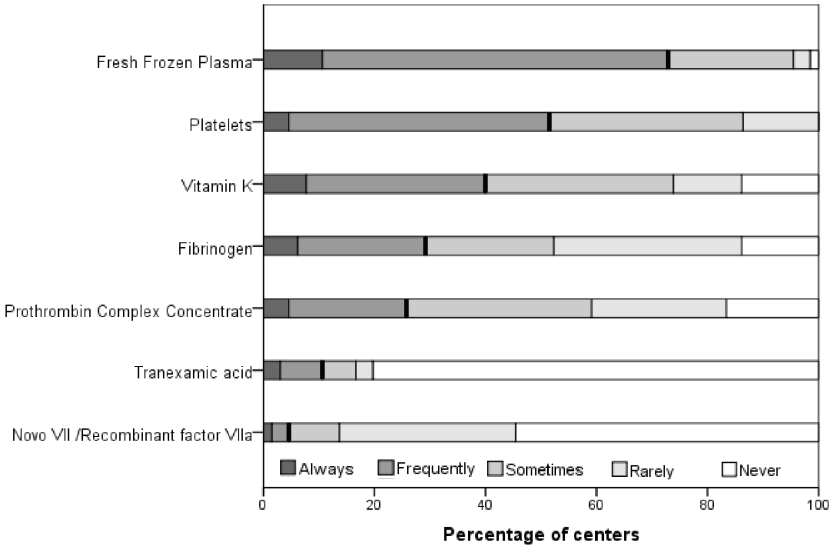
Frequencies and percentage of centers with corresponding answers, ICU: Intensive Care Unit, Hb-TL: hemoglobin target levels, TBI: traumatic brain injury, g/L: grams per liter
a) General policy: the way the large majority of patients (>75%) with a certain indication would be treated at the intensive care b) Policy in the acute phase

Coagulation management

Transfusion with fresh frozen plasma was most often reported for correction of trauma related coagulopathy (N= 48; 73%), followed by the use of platelets (N=34; 52%). Coagulopathy was most often managed with vitamin K (N=26; 39%), fibrinogen (N=19; 29%), Prothrombin Complex Concentrate (N= 17; 26%), Tranexamic acid (N=7; 11%) or recombinant factor VIIa (N=3; 5%). One center reported to use Desmopressin, in addition to Tranexamic Acid. (Figure 1)

Most centers indicated that they use deep venous thrombosis (DVT) prophylaxis with anticoagulants frequently (N=18; 27%) or always (N=44; 67%) in patients with TBI. Fourteen centers (21%) indicated they generally wait 72 hours after trauma before commencing DVT prophylaxis in the absence of hemorrhagic brain lesions. However, twice that number of centers (N=29; 46%) indicated to wait 72 hours after trauma in the presence of hemorrhagic brain lesions. Low molecular weight heparin was most commonly indicated

Figure 1: Trauma related coagulopathy treatment



Legend figure 1: bars represent the percentage of centers that indicated to use this treatment as general policy (the way the large majority of patients >75% with a certain indication would be treated). Bold line represent the border of always and frequently summed. Always: in 90-100% of cases; Frequently: in 70-90% of cases; Sometimes: in 30-70% of cases; Rarely: in 10-30% of cases; Never: in 0-10% of cases

as the prophylactic drug of choice (N=54; 82%), followed by subcutaneous unfractioned heparin (N=7; 11%) and intravenous heparin (N=1; 2%). (Table 2)

Most centers indicated that they would always test a coagulation panel prior to the insertion of a parenchymal sensor (N=45; 69%) or a ventricular catheter (N=46; 71%). The reported minimum platelet count for the insertion of a ventricular catheter was variable: >100 x10^9/L (N=30; 46%), >80 x10^9/L (N=9; 14%) or >50 x10^9/L (N=9; 14%). In most of the remaining centers the minimum platelet count depended on the surgeon (N=13; 20%). Also, the reported minimum International Normalized Ratio (INR) considered safe for placement of a ventricular catheter was variable: <1.4 (N=21; 33%), <1.3 (N=17; 26%) or <1.2 (N=8; 12%). Again, in most of the remaining centers the minimum INR was indicated to depend on surgeon's individual preferences (N=15; 23%). There were no centers that answered 'never' on all questions. (Table 3)

Twenty-nine centers indicated identical policies for coagulation management (always using DVT prophylaxis, and always obtaining a coagulation panel prior to insertion of a parenchymal or ventricular catheter). The majority of these centers are located in South and East Europe and Israel (N=13, 56%) versus (N=16, 37%) in North and West Europe and

Table 2: Coagulation policies, deep venous thrombosis [a]

Items questionnaire	Number completed	N	(%)
DVT prophylaxis			
Frequency of DVT prophylaxis	66		
- Never (0-10%)		1	(2%)
- Rarely (10-30%)		0	(0%)
- Sometimes (30-70%)		3	(4%)
- Frequently (70-90%)		18	(27%)
- Always (90-100%)		44	(67%)
Start in the absence of hemorrhagic lesions	65		
- < 24 hours		26	(40%)
- 24-72 hours		24	(37%)
- > 72 hours		14	(21%)
- Never		1	(2%)
Start in the presence of hemorrhagic lesions	63		
- < 24 hours		5	(8%)
- 24-72 hours		25	(40%)
- > 72 hours		29	(46%)
- Never		4	(6%)
Start after intracranial surgery	64		
- < 24 hours		10	(16%)
- 24-72 hours		31	(48%)
- > 72 hours		21	(33%)
- Never		2	(3%)
Pharmacological DVT prophylaxis	66		
- Subcutaneous unfractioned heparin		7	(11%)
- Intravenous heparin		1	(2%)
- Low-molecular weight heparin		54	(82%)

Frequencies and percentage of centers with corresponding answers
DVT: deep venous thrombosis
a) General policy: the way the large majority of patients >75% with a certain indication would be treated at the intensive care

the majority are located in high income countries (N=26, 47%), versus (N=3, 27%) in lower income countries.

Discussion

This study shows large between-center variation in blood transfusion and coagulation-directed policies in critically ill patients with TBI. More centers indicated a restrictive Hb-TL (between 70 g/l and 80 g/L) in general ICU patients compared to patients with TBI. Reported coagulation management was variable regarding timing of deep venous thrombosis (DVT) prophylaxis with anticoagulants, minimum platelet count and INR values prior to ICP probe insertion, and correction of trauma related coagulopathy.

Table 3: Coagulation policies, ICP monitoring [a]

Items questionnaire	Number completed	N	(%)
Checks prior to insertion of parenchymal sensor for ICP monitoring			
Coagulation panel	65		
- Never (0-10%)		4	(6%)
- Rarely (10-30%)		2	(3%)
- Sometimes (30-70%)		5	(8%)
- Frequently (70-90%)		5	(8%)
- Always (90-100%)		45	(69%)
- Not available [b]		4	(6%)
Checks prior to insertion ventricular catheter for ICP monitoring			
Coagulation panel	65		
- Never (0-10%)		3	(4%)
- Rarely (10-30%)		2	(3%)
- Sometimes (30-70%)		5	(8%)
- Frequently (70-90%)		4	(6%)
- Always (90-100%)		46	(71%)
- Not available [b]		5	(8%)
Minimum platelet count	65		
- >150 x10^9/L		1	(2%)
- >100 x10^9/L		30	(46%)
- > 80 x10^9/L		9	(14%)
- > 50 x10^9/L		9	(14%)
- Depending on the surgeon		13	(20%)
- No minimum		0	(0%)
- Other		3	(4%)
Minimum INR	65		
- <1.4		21	(33%)
- <1.3		17	(26%)
- <1.2		8	(12%)
- Depending on the surgeon		15	(23%)
- No minimum		0	(0%)
- Other		4	(6%)

Frequencies and percentage of centers with corresponding answers
DVT: deep venous thrombosis, ICP: intracranial pressure, INR: International Normalized Ratio, L: Liter
a) General policy: the way the large majority of patients >75% with a certain indication would be treated at the intensive care b) Centers that did not have this technique

The large between-center differences are likely in part explained by a lack of evidence on optimal management of patients with TBI. A majority of centers in our study reported to adhere to the 2007 Brain Trauma Foundation (BTF) guidelines for the treatment of patients with TBI, but this guideline does not provide specific recommendations on red blood cell transfusion or coagulopathy management. Equally, some trauma guidelines have stated policies on blood transfusion and coagulation in trauma patients of which some pertain to patients with TBI, but recommendations are still scarce. [1, 2, 23] A recent update of the Cochrane Review of all Red Cell Transfusion trials reported on 12587 patients identified in 31 randomized trials and suggested that a restrictive rather than liberal transfusion practice improves outcomes, but noted the data was very limited for neurocritical care.[24] Regarding

patients with TBI, several trials have been conducted on blood transfusion management [25, 26], and the reversal of coagulopathy [27, 28], but these all had a limited power. A recent large retrospective single-center study in TBI patients admitted to the intensive care [8] found that transfusion guided by a restrictive Hb-TL was associated with significantly less time with fever, higher cost-effectiveness and had the same risk of mortality compared with a liberal Hb-TL. Another explanation for the variation in management would be the between-center variation in the content of available protocols. E.g. we found that even between centers that do have a protocol on red blood cell transfusion policy, the reported Hb-TL still varied substantially. Overall in patients with TBI, there is no conclusive evidence or clear guidance in guidelines and protocols on blood transfusion and coagulopathy treatment. Still, with an aging TBI demographic with an increased prevalence of comorbidity, coagulation management might even become more complex. Concurrent use of anticoagulant and antiplatelet medication is a growing concern, prior warfarin treatment for example is associated with an increased risk of poor outcome. [29] In addition, coagulation management in TBI is further complicated by the recent introduction of newer anticoagulants, such as direct thrombin inhibitors (dabigatran, argatroban).[30]

For DVT prophylaxis the BTF guidelines do provide a recommendation, which was formulated quite broadly: DVT prophylaxis with anticoagulants can be started if the brain injury is stable and the benefit is considered to outweigh the risk of increased intracranial hemorrhage. Recommendations on the preferred agent, dose, or timing are lacking. [18] In our study only 65% of centers indicated that they always would implement DVT prophylaxis. A review including 15 studies and 4,491 patients on DVT occurrence in TBI published in 2015 showed that DVT incidence is significantly increased (18% versus approximately 2%) when pharmaceutical prophylaxis is not given in the first 8 days.[31] For the timing issue in DVT prophylaxis a novel theoretical prophylaxis protocol, 'the Parkland Protocol' has been recently described.[32] The protocol takes into account the likelihood of natural progression of brain hemorrhage and in that way determines the timing of anticoagulation. The risk classification is based on the stability of the brain hemorrhage at a computed tomography (CT) scan, the modified Berne Norwood criteria (subdural hematoma >8 mm, epidural hematoma >8 mm, contusion or intraventricular hemorrhage >2 cm, multiple contusions per lobe, subarachnoid hemorrhage with abnormal CT angiography), and the presence of an ICP monitor or craniectomy. A randomized controlled trial (RCT) including 62 low risk patients showed the safety of this protocol for this group: no progression of brain hemorrhage with the use of low molecular weight heparin at 24 hours post injury and one DVT with the use of placebo at 24 hours post injury. [33] However, more evidence is needed before this protocol can be widely accepted for the guidelines.

The large between center-variation we found is in line with previous studies. For critically ill trauma patients, several surveys have been conducted to study the management of trauma

related hemorrhage and coagulopathy. [34-36] These studies also found large differences in clinical practices, even among level 1 trauma centers, for example in the use of viscoelastic testing. In the survey of Hamada et al. the reported Hb-TLs in critically ill trauma patients were compared with patients with TBI, and were significantly higher in patients with TBI, like in our study.[37] In addition, two previous surveys were conducted that report the percentage respondents that chose specific Hb-TLs and the rationale for blood transfusion in patients with TBI (coagulation management was not assessed). In the study of Sena et al. a newly developed multiple-choice survey was completed by 312 physicians of the trauma surgery -, neurosurgery -, and ICU department of level I trauma centers in the United States.[38] In the study of Badenes et al. a newly developed multiple-choice survey was used as well, but was completed by 868 respondents, mostly specialists in anesthesiology and intensive care, worldwide.[39] In the study of Sena et al. 55% of respondents chose a restrictive policy of 70 g/l or less. Likewise, in the study of Badenes et al. 50% of respondents chose a low Hb-TL of 70 or 80 g/l, while in our study 16% chose a Hb-TL between 70 and 80 g/. The difference could either be explained by a difference in patient population (severely injured patients with TBI in the study of Sena et al.), by a difference in answer options (we did not have an answer option below 70 g/l), or by a difference in policy between Europe and other continents.

Strengths of our study include the comprehensive development process of the questionnaires and the high response rate of 97%. Limitations include the survey-design, resulting in perceived practices rather than actual practices. Although we explicitly asked for general policy and data were anonymously collected, we cannot exclude differences between current findings and actual treatment in the participating centers. In addition, questions were aimed to assess general policy and contained no specific details on patient characteristics. This is not representative for clinical practice (possibly making the questions more difficult to answer). In addition, we could not make a distinction between pharmaceutical versus mechanical DVT prophylaxis. A further limitation comprises the representativeness of our sample. The majority of centers were Academic level I trauma centers with a special interest in neurotrauma. Findings are therefore not generalizable to non-specialized centers. In addition, differences between centers could represent differences in case-mix instead of true practice.

The practice variability we report supports that evidence on optimal treatment approaches is needed. Such evidence can potentially be obtained in a non-randomized design by comparing outcomes between centers with different treatment policies. Such a Comparative Effectiveness Research approach exploits the existing between-center variation. Data on real time patient management and clinically relevant outcomes in the CENTER-TBI study are now being collected.[20] Future research on blood transfusion and coagulation management in patients with TBI could lead to prevention of progressive brain

hemorrhage and secondary problems like coagulopathy and VTE. For now, the optimal transfusion strategies to correct coagulopathy in terms of the ratio of packed blood cells, fresh frozen plasma (or similar products) and platelets are still being debated. [40] This debate pertains both to optimal strategies with regard to reversal of trauma related coagulopathy and management of coagulopathy induced by conventional agents (such as vitamin K antagonists) and newer ones such as direct thrombin inhibitors. [9, 30, 41] Still, others warn for the use of transfusion considering the possibility of complications of transfusion and unknown effects on (functional) outcome.[42] Also for coagulation (enhancing) products larger studies are needed to prove a positive balance between the beneficial effects in terms of patient outcome and adverse effects on (thromboembolic) complications.[27, 28, 42-45] New evidence is clearly needed on these topics, since control of blood and coagulation status could have a large impact on patient outcome, especially in patients with TBI.

Conclusions

In conclusion, we showed substantial variation in blood and coagulation management of patients with TBI at the ICUs in 66 centers in Europe and Israel participating in the CENTER-TBI study. This variation may be largely attributable to the lack of guidelines and high quality evidence on these topics. The large practice variation provides an opportunity to study the effectiveness of different policies in comparative effectiveness research.

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CHAPTER 5

5

Variation in general supportive and preventive Intensive Care management of Traumatic Brain Injury

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Background General supportive and preventive measures in the intensive care management of traumatic brain injury (TBI) aim to prevent or limit secondary brain injury and optimize recovery. The aim of this survey was to assess and quantify variation in perceptions on ICU management of patients with TBI in European neurotrauma centers.

Methods We performed a survey as part of the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study. We analyzed 23 questions focused on 1) circulatory and respiratory management, 2) fever control, 3) use of corticosteroids 4) nutrition and glucose management, and 5) seizure prophylaxis and treatment.

Results The survey was completed predominantly by intensivists (N=33; 50%) and neurosurgeons (N=23; 35%) from 66 centers (97% response rate). The most common cerebral perfusion pressure (CPP) target was > 60 mmHg (N=39; 60%) and/or an individualized target (N=25; 38%). To support CPP, crystalloid fluid loading (N=60; 91%) was generally preferred over albumin (N=15; 23%), and vasopressors (N=63; 96%) over inotropes (N=29; 44%). The most commonly reported target of partial pressure of carbon dioxide in arterial blood (PaCO2) was 36-40 mmHg (4.8-5.3 kPa) in case of controlled intracranial pressure (ICP < 20mmHg) (N=45; 69%) and PaCO2 target of 30-35 mmHg (4-4.7 kPa) in case of raised ICP (N=40; 62%). Almost all respondents indicated to generally treat fever (N=65; 98%) with paracetamol (N=61; 92%) and/or external cooling (N=49; 74%). Conventional glucose management (N=43; 66%) was preferred over tight glycemic control (N=18; 28%). More than half of the respondents indicated to aim for full caloric replacement within 7 days (N=43; 66%) using enteral nutrition (N=60; 92%). Indications for and duration of seizure prophylaxis varied, and levetiracetam was mostly reported as the agent of choice for both seizure prophylaxis (N=32; 49%) and treatment (N=40; 61%).

Conclusions Practice preferences vary substantially regarding general supportive and preventive measures in TBI patients at ICUs of European neurotrauma centers. These results provide an opportunity for future Comparative Effectiveness Research, since a more evidence-based uniformity in good practices in general ICU management could have a major impact on TBI outcome.

Background

Traumatic brain injury (TBI) is one of the major causes of trauma-related death and hospital admissions in Europe [1]. TBI is recognized as a complex heterogeneous syndrome [2]. The higher vulnerability of this population is reflected by higher mortality rates in patients with TBI compared with non-head injured trauma patients [3]. Therefore, patients with (severe) traumatic brain injury require specialized neuro-intensive care (treatment) at an Intensive Care Unit (ICU) [4].

Case fatality rates in severe TBI are high, ranging from 30% to 40% in unselected observational series [5]. Furthermore, substantial between-country [1] and between center-differences [3, 4, 6] in overall TBI mortality rates exist, which might be partly explained by differences in treatment [7-9].

The key objectives of ICU TBI management are to maintain general physiology and prevent secondary brain injury. A number of brain-specific therapies, such as ICP guided treatment or, less often, brain-metabolic or cerebral vascular autoregulation based goals are employed both clinically or as the subject of clinical research [10]. However, general support of the cardiovascular system, respiratory function, and nutritional or metabolic needs must not be overlooked and could also have a significant impact on outcome [11, 12]. Cerebral metabolic control by seizure or fever management may further contribute to better outcomes [2, 13-15]. At the current time, optimal strategies for general management are only partly established [16, 17]]. This lack of robust evidence may ultimately result in institutional or individual variations in practice which may contribute to variances in outcome.

The aim of this survey study was to assess variation in ICU management perceptions of general supportive and preventive care policies (including for instance circulatory and respiratory management) in patients with TBI in European neurotrauma centers.

Methods

Participating centers

This study is part of the CENTER-TBI study that collects data on patient characteristics, patient management and outcomes in 68 centers from 20 countries across Europe and Israel [18]. All these centers were asked to complete a 'Provider Profiling Questionnaire' [19].

Provider Profiling Questionnaire

The provider profiling questionnaire was developed in several stages. First, literature was explored for evidence, including guidelines and available surveys. Second, a pilot study was

conducted in 16 participating centers in order to receive feedback, to determine ambiguity and to detect unexpected and missing values. Throughout all stages, experts of various disciplines (neurosurgeons, intensivists, neurologists, emergency department physicians, rehabilitation physicians, medical ethicists, health care economists and epidemiologists) were asked for their advice on the development of the questionnaire. Details on the development, administration and content of the complete provider profiling questionnaires have been published previously [19].

General supportive and preventive management

For the purpose of the current study, we focused on 23 questions specifically aimed at general ICU policies. Specifically, we focused on circulatory and respiratory management, fever control, use of corticosteroids, glucose and nutrition management, and seizure prophylaxis and treatment. Most questions were multiple-choice, except for two questions; the aim for caloric intake in TBI patients and the use of corticosteroids for other conditions. Overall, the general policy of a center rather than the individual treatment preference of the respondent was the premise for completion of the questionnaire. General policy is defined as: 'the way the large majority of patients (>75%) with a certain indication would be treated'.

Statistical analysis

We used descriptive statistics (frequencies and percentages) to present the data. Respondents could indicate how frequently certain management strategies were used (never 0-10%, rarely 10-30%, sometimes 30-70%, frequently 70-90%, and always 90-100%). The combined numbers of respondents that indicated 'frequently' and 'always' were interpreted as representing the general policy of a center, in line with previous reports [20, 21]. To describe center characteristics in more detail we divided centers into higher (Austria, Belgium, Denmark, Finland, France, Germany, Israel, Italy, the Netherlands, Norway, Spain, Sweden, the UK and Switzerland) versus relatively lower income countries (Bosnia Herzegovina, Hungary, Latvia, Lithuania, Romania and Serbia), based on a 2007 report by the European Commission [22]; differences were assessed for statistical significance using the Fisher's exact test without correction for multiple comparisons. We used Statistical Package for Social Sciences (SPSS) version 21 [23] for descriptive analyses.

Results

Participating centers

Of the 68 neurotrauma centers participating in this study, 66 (97%) centers completed the questions on general supportive and preventive ICU management. The questionnaire was predominantly completed by intensivists (N=33; 50%) and neurosurgeons (N=23; 35%). Other professionals that assisted in completion of the questionnaire were administrative

staff (N=11; 17%), neurologists (N=5; 8%), anesthesiologists (N=5; 8%) and a trauma surgeon (N=1; 2%).

The majority of centers had an academic affiliation (N = 60, 91%). The majority of centers were designated as level I trauma centers (N= 45; 69%), and a minority as level II (N=4; 6%), level III (N=1; 2%), or no designation (N=15; 23%). More than half of the centers had a dedicated neuroICU (defined as an ICU that is equipped to treat patients with neurological or neurosurgical injury) available (N=39; 59%). The majority of centers adopted a 'closed' ICU organization (the intensivist is primarily responsible for the delivery of care for patients at the ICU) (N= 43; 65%), followed by a 'mixed' ICU organization (the admitting physician, e.g. neurosurgeon is primarily responsible but the care is provided by a intensivist) (N=20; 30%), and a minority adopted an 'open' ICU organization (the admitting physician is primarily responsible for the care at the ICU) (N=3; 5%). Centers indicated to treat a median of 92 (interquartile range 52-160) patients with TBI at their ICU annually. Twenty-eight centers (42%) reported to adhere to the 2007 Brain Trauma Foundation (BTF) guidelines for the management of patients with TBI at their ICU and 21 centers (32%) reported having institutional guidelines that were based on BTF guidelines. The center characteristics and definitions are described in more detail in a previous publication [19].

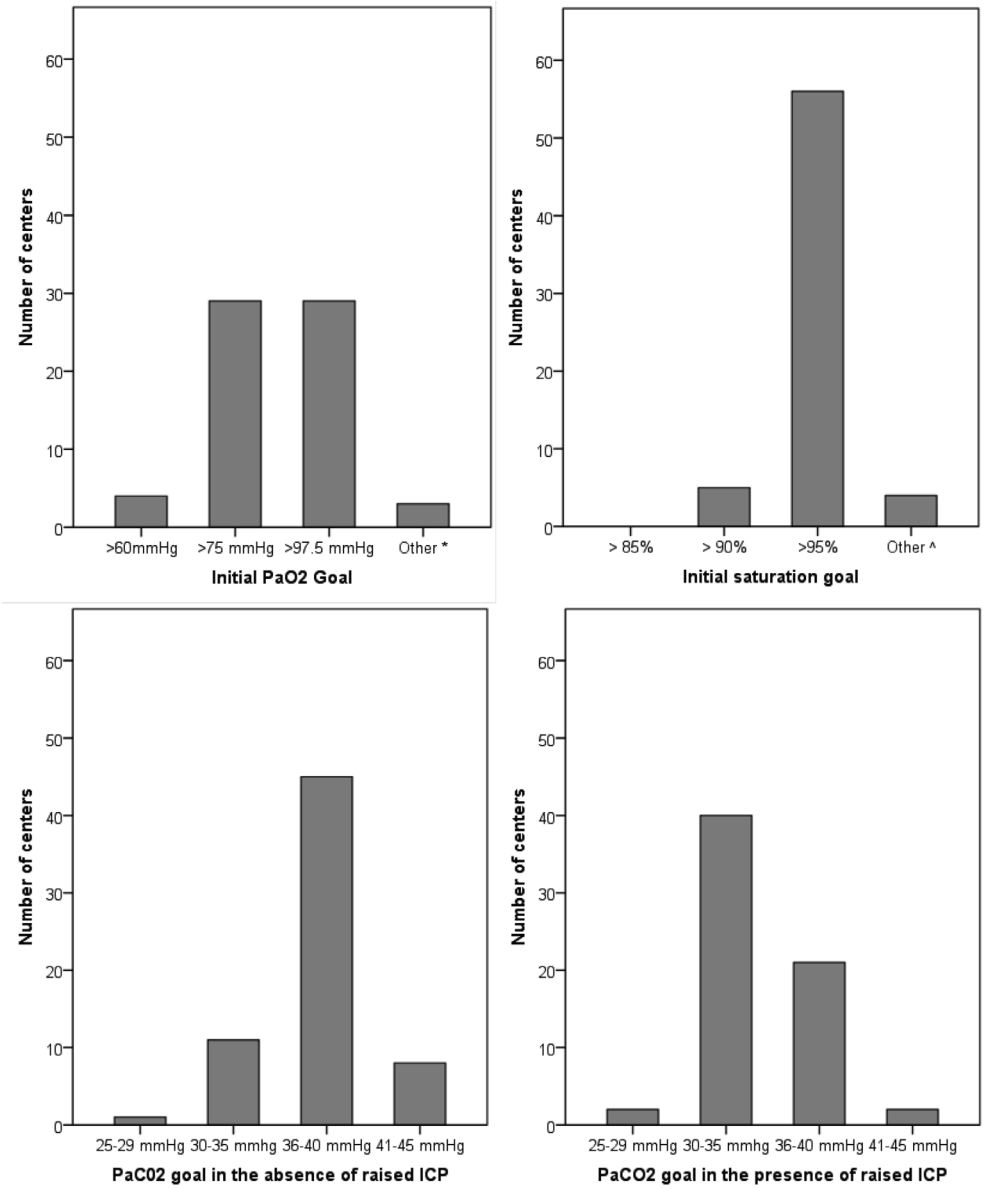
Circulatory and respiratory management

As part of circulatory management, the most frequently mentioned CPP targets were: > 60 mmHg (N=39; 60%) and/or "individualized" (N=25; 38%). Most centers used crystalloids (N=60; 91%) and/or vasopressors (N=63; 96%) for CPP support; inotropes (N=29; 44%) were less frequently – but still regularly–employed. Fifteen centers (23%) reported to use albumin containing solutions for volume expansion. (Supplementary material 1, Table 1)

In mechanically ventilated patients with TBI, initial PaO_2 goals of > 75 mmHg (10 kPa) (N=29; 45%) and > 97.5 mmHg (13 kPa) (N=29; 45%) were most commonly cited as a treatment preference, with an initial arterial oxygen saturation goal of >95% (N=56; 86%). In the absence of raised ICP, most centers indicated a partial pressure of carbon dioxide in arterial blood ($PaCO_2$) goal of 36-40 mmHg (4.8-5.3 kPa) (N=45; 69%). In the presence of raised ICP this shifted towards a lower $PaCO_2$ goal of 30-35 mmHg (4.0-4.7 kPa) (N=40; 62%, Figure 1). The timing of tracheostomy in patients with limited or slow neurological recovery varied substantially from within 1 week (N=13, 20%) to between 1 and 2 weeks (N=36, 55%) and more than 2 weeks (N=16, 25%). (Supplementary material 1, Table 1)

Relatively lower income countries more frequently adopted lower oxygen saturation goals (>90%) compared with saturation targets of >95% which were favoured by higher income countries (N=3/11; 27% vs N= 2/55; 4%, p=0.037). (Supplementary material 2, Table 1)

Figure 1: Mechanical ventilation thresholds



Legend figure 1: Mechanical ventilation thresholds with corresponding answer frequencies. $PaCO_2$: partial pressure of carbon dioxide in arterial blood, PaO_2: partial pressure of carbon dioxide in arterial blood, mmHg: milimiters mercury, 25-29 mmHg ≈ 3.3-3.0 kPa (kilopascal), 30-35 mmHg ≈ 4-4.7 kPa, 36-40 mmHg ≈ 4.8-5.3 kPa, 41-45 mmHg ≈ 5.5-6 kPa, 60 mmHg = 8 kPa, 75 mm Hg = 10 kPa, 100 mmHg =13 kPa * No specific goal (N=1), > 90 mmHg (N=2), ^ > 96% (N=2), >97% (N=1), 92-94% (N=1)

Fever control

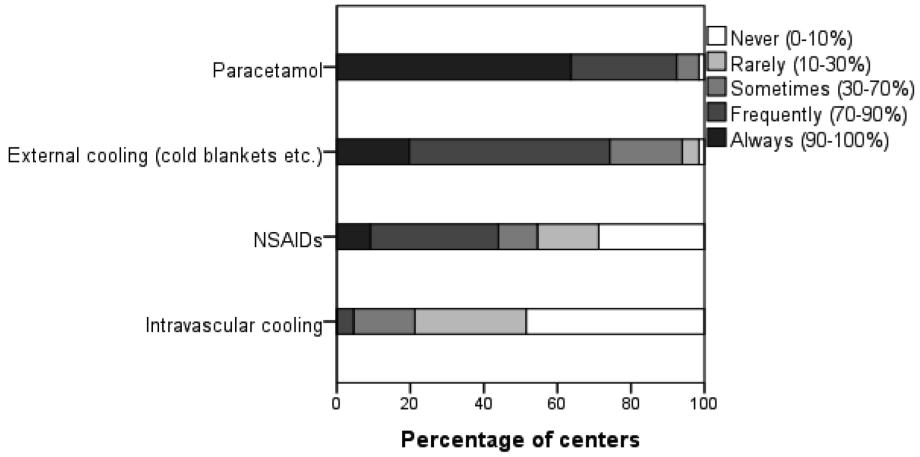
In patients with TBI, the majority of centers indicated that they routinely treat fever (N=65; 98%). One center (2%) reported they would only treat fever "sometimes". The preferred treatments were paracetamol (N=61; 92%) and/or external cooling (N=49; 74%). By contrast, non-steroidal anti-inflammatory drugs (NSAIDs) were less commonly used (N= 29; 44%). Intravascular cooling was also rarely used (N=3; 5%)(Figure 2). (Supplementary material 1, Table 2)

Relatively lower income countries significantly indicated the use of NSAIDs more often than higher income countries (N=11/11; 100% vs N=18/55; 33%, p=0.000). Centers in higher income countries indicated the use of paracetamol significantly more frequently compared with relatively lower income countries (N=53/55; 96% vs N=8/11; 73%, p=0.029). Intravascular cooling was more frequently applied in the lower income group, although this difference did not reach statistical significance. (Supplementary material 2, Table 2)

Use of corticosteroids

Corticosteroids were infrequently used for the primary management of brain injury, although a few respondents indicated that they used them "rarely" (N=5; 8%), "sometimes" (N=2; 3%) or "frequently" (N=1; 2%). However, corticosteroids were used for vasopressor resistant hypotension (N=21; 58%) and, to a lesser extent, sepsis (N=8; 22%) specifically. (Supplementary material 1, Table 3)

Figure 2: Type of fever treatment



Legend figure 2: Type of fever treatment and corresponding percentage of centers that indicated to use this type of fever treatment never (in 0-10% of cases), rarely (in 10-30% of cases), sometimes (in 30-70% of cases), frequently (in 70-90% of cases) or always (in 90-100% of cases). NSAIDs: nonsteroidal anti-inflammatory drugs

Primary use of corticosteroids was significantly more frequently reported by lower income countries compared with higher income countries (N=4/11; 36% vs N=4/55; 7%, p=0.023). (Supplementary material 2, Table 2)

Glucose and nutrition management

The majority of centers stated that their glucose management was protocolised (N=50; 77%). Most centers reported the correction of hyperglycemia as a primary aim (N=43; 66%), while a smaller number implemented tight glycemic control (N=18; 28%). (Supplementary material 1, Table 4)

Most respondents aimed for full caloric replacement within 7 days post-injury (N=43; 66%.). An open question on the goals for caloric intake showed a high variety in reported strategies as well as metrics used (kcal/day, kcal/kg/day and percentages). The enteral route was preferred (N=60; 92%). The timing of parenteral nutrition was highly variable; centers were equally distributed between "as soon as possible" (N=13; 20%), "within 24 hours post-injury" (N=13; 20%), "within 72 hours post-injury" (N=10; 15%), "within 7 days post-injury" (N=17; 26%) and "we do not have rules/guidelines for this" (N=12; 19%).

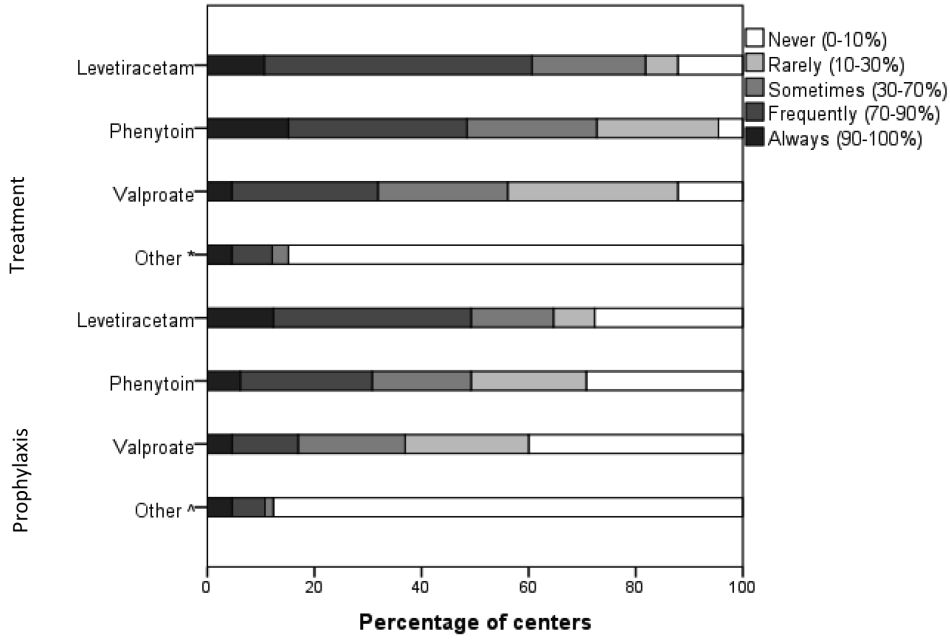
Relatively lower income countries reported using the parenteral route significantly more frequently compared with higher income countries (N=4/11; 36% vs. N=1/55; 2%, p=0.002). (Supplementary material 2, Table 2)

Seizure prophylaxis and treatment

There was little consensus regarding the use of prophylactic antiepileptic drugs (for all indications). Most centers reported to use levetiracetam as the drug of choice for both seizure prophylaxis and treatment (N=32; 49% and N=40; 61%), followed by phenytoin (N=20; 31% and N=32; 48%) (Figure 3). In general, both the reported duration of anti-seizure prophylaxis, as well as the criteria for initiation of anti-epileptic treatment varied considerably. (Supplementary material 1, Table 5)

The choice of agent varied with income, with levetiracetam being less commonly used for both seizure prophylaxis (N= 0/11 vs N=32/55; 59%, p=0.000) and treatment (N=1/11; 9% vs N=39/55; 71%, p=0.000) in the lower income group versus higher income countries, respectively. Instead, lower income countries seemed to favour valproate or phenytoin compared with higher income countries (N=7/11; 64% vs N=14/55; 26%, p=0.029). (Supplementary material 2, Table 2)

Figure 3: Agents used for seizure prophylaxis and treatment



Legend figure 3: Agents for seizure prophylaxis and treatment with corresponding percentage of centers that indicated to never (in 0-10% of cases), rarely (in 10-30% of cases), sometimes (in 30-70% of cases), frequently (in 70-90% of cases) or always (in 90-100% of cases) use the agent.
* Carbamazepine/ phenobarbital, phenobarbital, benzodiazepines, no prophylaxis used in our hospital, carbamazepine (N=3)
^ Phenobarbital, benzodiazepines, carbamazepine (N=4), midazolam/diazepam, lorazepam

Discussion

In this survey, we found varying degrees of consensus between European neurotrauma centers with respect to general supportive and preventive ICU management in patients with TBI. Most variation was found in initial PaO_2 goals for mechanically ventilated patients; CPP targets; the timing of tracheostomy in unconscious patients; nutritional targets; and seizure prophylaxis and treatment.

Large between-center variation was found in topics that are not addressed in the recommendations of the Brain Trauma Foundation (BTF) guidelines (Supplementary material 3), suggesting the role of guidelines in reducing variances in clinical practice. International guidelines (BTF guidelines and guidelines of the American College of Surgeons) do recommend the use of normalized thresholds (e.g. normoglycemia, -capnia, and -thermia) in patients with TBI, although this is not based on high-level evidence [16, 17]. Indeed, randomized controlled trials (RCTs) on these topics are too limited in number

to lead to high-level evidence [10]. Considering CPP targets, the BTF guidelines are unclear whether to use an optimum threshold of >60 or >70 mmHg (and a range of 50 -70 mmHg in the previous BTF guidelines [24]). Despite this ambiguity, a majority of respondents (60%) preferred a target CPP of >60 mmHg. In addition, the current BTF guidelines added that the CPP target might depend on the individual cerebral autoregulatory status, reflected by 38% of respondents who indicated to use an individualized target CPP. The uniformity in reported CPP targets between income groups also suggests that these concepts are widespread. It may be that the willingness to individualize CPP in patients with TBI reflects the growing trend for use of precision medicine [25], where therapies and therapy targets are individualized to patient need, rather than used on a "one size fits all" basis.

Marked variation was also found on topics where consensus was expected based on high-level evidence from RCTs, or the recommendations in the BTF guidelines. The use of steroids for the primary management of TBI was reported by 13% of the respondents (one respondent reported frequent use), but is against the advice of the BTF guidelines and contradicts the prevailing evidence from the CRASH study [26, 27]. However, use in the majority of centers was for vasopressor dependence and/or sepsis, a use in keeping with current guidelines for the management of sepsis [28]. The use of albumin was reported by 23% of the respondents, while the SAFE study showed that albumin was associated with higher mortality rates in patients with TBI [29]. It is difficult to interpret continued use of albumin for volume expansion as a lack of knowledge of the evidence, since worse outcomes in the albumin treated arm in SAFE-TBI may have been the consequence of a hypotonic carrier causing elevated ICP [30], and well informed clinicians may have used albumin that was isotonic or corrected any accompanying hyponatremia. Finally, the use of tight glycemic control was reported by 28% of respondents, while the NICE-SUGAR and CGAO-REA study recommend using moderate instead of tight glucose control in patients with TBI [31, 32].

On the other hand, we found consensus where variation was expected: a high number of centers indicated to use antipyretic agents for treatment of fever, when there is no consensus on the optimal choice of agent and their potentially deleterious side-effect of CPP lowering is well known[33]. This suggests a strong aversion amongst treating clinicians, however, to allow pyrexia in patients with TBI. The choice of NSAID, despite their well-known potentially harmful systemic side-effect profile, as antipyretics in many centers probably also reflects this, although a continuous intravenous infusion instead of intermittent NSAID dosing might improve fever control (with relatively higher CPP) in neurocritical care [34]. In addition, respondents indicated employing below-normal $PaCO_2$ goals (30-35 mmHg) in the presence of raised ICP in mechanically ventilated TBI patients. This was unexpected given the BTF recommendation to avoid prolonged hyperventilation. Furthermore, even patients in whom intracranial hypertension was not a concern were ventilated to normal

carbondioxide (CO_2) tensions showing a reluctance to use permissive ventilatory strategies that have been shown to be effective in reducing mortality in ARDS patients [35].

Our results further suggest that respondents use TBI-specific strategies instead of general strategies (used in general critically ill patients) in the ICU. For example, respondents indicated they frequently or always treat fever, because hyperthermia is associated with worse outcomes in TBI [14, 33] whereas fever is often considered beneficial to some extent in critically ill patients with infections [36].

We found some differences between relatively lower versus higher income countries. It was striking that levetiracetam was significantly more frequently reported by higher income countries as agent of choice for seizure prophylaxis and treatment, while valproate and phenytoin were reported more frequently by lower income countries – although high-level evidence in literature on the agent of choice is lacking [37]. However, there were no clear structural differences in management overall and thus this could not be considered an explanation for the treatment variation. Indeed, some high cost interventions, such as intravascular cooling and parenteral nutrition, were more commonly used in the lower income countries, suggesting that choice of treatment options are not solely based on cost considerations, but also reflected local clinical culture in different institutions.

Our study has several strengths. To our knowledge, this is the first survey that provides an overview of multiple components of general supportive or preventive ICU management in patients with TBI. The survey was developed in several stages with involvement of clinical experts of various disciplines and the response rate of the survey was high (97%). However, this study also has limitations, as the centers participating in the CENTER-TBI study may still be a biased selection of European centers; with a specialist interest in the topic, or a large engagement in research, or more expertise overall. In a small number of centers, the questionnaire was completed by administrative staff (with no clinical expertise). However, presumably this was in close collaboration with a clinician, considering the high number of clinicians that completed the survey and clinical involvement was encouraged throughout the survey. Other limitations are inherent to surveys: the results are self-reported and are not yet confirmed by independent observations in daily practice and therefore represent what the respondents 'believe' is clinical practice and this may not, in fact, reflect reality. Another limitation is that the survey questions represent generalizations and do not include patient factors (such as demographics, lab results, or imaging), or very specific circumstances, while in clinical practice these details influence clinicians' judgement. In line with this, we did not specify time-frames (for ventilation goals) and lab values (for tight glucose control). Also, we asked about general patients with TBI in the survey and did not specify adult or pediatric TBI.

Overall, the practice variation (and consensus) in general ICU management we found might be explained by a lack of evidence (or incomplete implementation of evidence), by the use of individualized approaches or by a tension between general and TBI-specific strategies. We presume that increased and more evidence-based uniformity in good practices in general ICU management might improve outcome in TBI. In fact, general ICU management is part of daily routine (e.g. temperature measurements, lab results and mechanical ventilation) and deviations are generally easily detected and corrected. It is noteworthy that non-neurological complications are frequent; in one report on TBI patients these were more frequent (around 22%) than neurological complications (around 3%) [29]. Our survey showed that future research on individualized management is needed: a high number of respondents reported individualized practices, that implies a trend towards precision medicine. In addition, the existence of practice variation in general ICU management provides direction to Comparative Effectiveness Research (CER) analyses or RCTs. As RCTs in the field of TBI have been disappointing [10], CER might be a promising approach to enhance future knowledge on the effectiveness of general ICU management and understanding in what processes variances occur, as we have attempted to do, is a critical starting point. Hence, in the CENTER-TBI study we will evaluate the effect of different ICU management practices on TBI outcome (after case-mix correction), for example, the difference in patients' outcome between the 13 centers that plan tracheostomy within 1 week, the 36 centers that time tracheostomy between 1 and 2 weeks, and the 16 centers that delay tracheostomy longer than 2 weeks.

Conclusions

This study showed that general supportive and preventive ICU management policies in TBI vary between European neurotrauma centers. These findings stress the need for continued knowledge transfer of existing evidence, further research on optimized individualized management (precision medicine) and as we propose comparative effectiveness research.

Acknowledgement

The authors would like to thank all clinical and research staff at the CENTER-TBI sites for completing the provider profiling questionnaires.

Supplementary material 1: overview of all results

Table 1: Circulatory and respiratory management

Items of the questionnaire	Number completed	N	(%)
Circulatory management			
Target CPP	66*		
- >50 mmHg		7	11
- >60 mmHg		39	60
- >70 mmHg		14	21
- Individualized		25	38
IV fluids for treatment CPP	66*		
- Crystalloids		60	91
- Colloids–starches		10	15
- Colloids–albumin		15	23
- Other combinations		8	12
Vasoactive drugs to support CPP	66*		
- Vasopressors		63	96
- Inotropes		29	44
Respiratory management			
Initial PaO_2 goal [1]	65		
- > 8 kPa (60 mmHg)		4	6
- > 10 kPa (75 mmHg)		29	45
- >13 kPa (100 mmHg)		29	45
- Other [2]		3	4
Initial arterial oxygen saturation goal	65		
- >85%		0	0
- >90%		5	8
- >95%		56	86
- Other [3]		4	6
$PaCO_2$ goal–in the absence of raised ICP	65		
- 25-29 mmHg (≈ 3.3-3.0 kPa)		1	2
- 30-35 mmHg (≈ 4-4.7 kPa)		11	17
- 36-40 mmHg (≈ 4.8-5.3 kPa)		45	69
- 41-45 mmHg (≈ 5.5-6 kPa)		8	12
$PaCO_2$ goal–in the presence of raised ICP	65		
- 25-29 mmHg (≈ 3.3-3.0 kPa)		2	3
- 30-35 mmHg (≈ 4-4.7 kPa)		40	62
- 36-40 mmHg (≈ 4.8-5.3 kPa)		21	32
- 41-45 mmHg (≈ 5.5-6 kPa)		2	3
Timing tracheotomy [4]	65		
- < 1 week		13	20
- 1-2 weeks		36	55
- >2 weeks		16	25

1) In mechanically ventilated patients, 2) No specific goal (N=1), > 12 kPa (N=2), 3) > 96% (N=2), >97% (N=1), 92-94% (N=1), 4) In patients remaining unconscious

* Multiple answers were possible

CPP: Cerebral Perfusion Pressure, ICP: intracranial pressure, IV: intravenous, mmHg: millimeters of mercury, $PaCO_2$: partial pressure of carbon dioxide in arterial blood, PaO_2: partial pressure of oxygen in arterial blood

Table 2: Fever control

Items of the questionnaire	Number completed	N	(%)
Fever [1] treated routinely	66		
- Never (0-10%)		0	0
- Rarely (10-30%)		0	0
- Sometimes (30-70%)		1	2
- Frequently (70-90%)		21	32
- Always (90-100%)		44	66
Type of treatment of fever	66*, **		
- Paracetamol		61	92
- NSAIDs		29	44
- External cooling [2]		49	74
- Intravascular cooling		3	5

1) Core temperature above 38 °C 2) Cold blankets etc
* Multiple answers were possible
** Sum of centers that indicated frequently (70-90% of cases) or always (100% of cases)
NSAIDs: nonsteroidal anti-inflammatory drugs

Table 3: Use of corticosteroids

Items of the questionnaire	Number completed	N	(%)
Primary management with corticosteroids	66		
- Never (0-10%)		57	87
- Rarely (10-30%		5	8
- Sometimes (30-70%)		2	3
- Frequently (70-90%)		1	2
- Always (90-100%)		0	0
Corticosteroids used for other conditions (open question)	36**		
- Vasopressor resistant hypotension		21	58
- Sepsis		8	22
- Other [1]		7	20

1) Adrenal insufficiency, bronchospasm, spinal cord injury, hypopituitarism, hypocortisolism, spinal cord injury, peripheric nerve injury, stress response
* Multiple answers were possible
** Sum of centers that indicated frequently (70-90% of cases) or always (100% of cases)

Table 4: Glucose and nutrition management

Items of the questionnaire	Number completed	N	(%)
Glucose management			
Protocol glucose management	65		
- Presence of a protocol		50	77
- Absence of a protocol		15	23
Glucose therapy	65		
- No specific therapy		2	3
- Prophylactic insulin administration[1]		2	3
- Insulin administration to correct hyperglycemias		43	66
- Tight glycemic control		18	28
Nutrition management			
Aim for full caloric replacement	65		
- At 7 days post-injury		12	19
- < 7 days post-injury		43	66
- >7 days post-injury		10	15
Aim caloric intake (open question)	65		
- 1900 kcal/day[2]		14	22
- 27 kcal/kg/day[3]		32	49
- Other [4]		10	15
- Unknown/no protocol		9	14
Route of nutrition	65		
- Parenteral		5	8
- Enteral[5]		60	92
Start parenteral nutrition	65		
- As soon as possible [6]		13	20
- Within 24 hours post-injury		13	20
- Within 72 hours post-injury		10	15
- Within 7 days post-injury		17	26
- We do not have rules/ guidelines for this		12	19

1) Buffered infusion; 2) median 3) median 4) 100%-130%; 80%ee; 100%; 2 kcal/kg/h; for patients with no resp; variable; based on calorimetry; high 5) Including mostly enteral, parenteral on indication 6) Directly after ICU admission
kcal: kilocalories, kg: kilograms

Table 5: Seizure prophylaxis and treatment

Items of the questionnaire	Number completed	N	(%)
General			
Indications for anti-seizure prophylaxis	66* , **		
- GCS<10		15	23
- Cortical contusion		21	32
- Depressed skull fracture		23	35
- Subdural hematoma		19	29
- Epidural hematoma		12	18
- Intracerebral hematoma		19	29
- Penetrating brain injury		25	38
- Other [1]		5	8
Seizure prophylaxis			
Agents used for seizure prophylaxis	65*, **		
- Phenytoin		20	31
- Levetiracetam		32	49
- Valproate		11	17
- Other [2]		7	11
Duration of anti-seizure prophylaxis	66*		
- 1-3 days		3	5
- 4-7 days		21	32
- > 7 days		6	9
- 3 weeks		2	3
- 3 months		5	8
- Depending on the patient		22	33
- Depending on the physician		12	18
Seizure treatment			
Agents used for seizure treatment	66*, **		
- Phenytoin		32	48
- Levetiracetam		40	61
- Valproate		21	32
- Other [3]		8	12
Initiation of anti-epileptic treatment	66**		
- A single seizure		44	67
- Two or more seizures		61	92

1) Previous seizure, seizure within 24 hours, epileptic fit, ventilated TBI, all severe, EEG confirmed seizures, 2) Carbamazepine/ phenobarbital, phenobarbital, benzodiazepines, no prophylaxis used in our hospital, carbamazepine (N=3), 3) Phenobarbital, benzodiazepines, carbamazepine (N=4), midazolam/diazepam, lorazepam

* Multiple answers were possible

** Sum of centers that indicated frequently (70-90% of cases) or always (100% of cases)

GCS: Glasgow Coma Scale

Supplementary material 2: Variation between higher and lower income countries: variation in thresholds used for circulatory and respiratory management (table 1) and general treatments at the ICU (table 2)

Table 1: Thresholds used for circulatory and respiratory management

Items of the questionnaire	Higher income countries (N=55)	Lower income countries (N=11)	P-value
Respiratory management			
Initial PaO_2 goal (in mechanically ventilated patients)	25 (50%)	4 (50%)	1.000
- > 10 kPa (75 mmHg)	25 (50%)	4 (50%)	
- >13 kPa (100 mmHg)			
Initial arterial oxygen saturation goal			
- >90%	2 (4%)	3 (27%)	0.037
- >95%	48 (96%)	8 (73%)	
$PaCO_2$ goal–in the absence of raised ICP			
- 25-35mmHg	8 (15%)	4 (36%)	0.194
- 36-45 mmHg	46 (85%)	7 (64%)	
$PaCO_2$ goal–in the presence of raised ICP	35 (65%)	7 (64%)	1.000
- 25-35 mmHg	19 (35%)	4 (36%)	
- 36-45 mmHg			
Circulatory management			
Target CPP			
- >50 mmHg	7 (13%)	0 (0%)	0.591
- >60 mmHg	33 (60%)	6 (55%)	0.749
- >70 mmHg	13 (24%)	1 (9%)	0.433
- Individualized	20 (36%)	5 (45%)	0.735

In order to calculate the Fisher exact test a sufficient number per category (answer option) was needed, therefore categories with low numbers were deleted (for PaO_2 goal and saturation goal) or categories were combined (for $PaCO_2$ goal in the presence and absence of raised ICP)
Higher income: Austria, Belgium, Denmark, Finland, France, Germany, Israel, Italy, the Netherlands, Norway, Spain, Sweden, the UK and Switzerland; *Relatively low income:* Bosnia Herzegovina, Hungary, Latvia, Lithuania, Romania and Serbia.
CPP: Cerebral Perfusion Pressure, ICP: intracranial pressure, IV: intravenous, mmHg: millimeters of mercury, $PaCO_2$: partial pressure of carbon dioxide in arterial blood, PaO_2: partial pressure of oxygen in arterial blood

Table 2: Systemic treatments at the ICU

Items of the questionnaire	Higher income countries (N=55)	Lower income countries (N=11)	P-value
Respiratory and circulatory management			
IV fluids			
- Crystalloids	51 (93%)	9 (82%)	0.260
- Colloids- starches	6 (11%)	4 (36%)	0.054
- Colloids- albumin	12 (22%)	3 (27%)	0.703
- Other combinations	5 (9%)	3 (27%)	0.122
Vasoactive drugs to support CPP			
- Vasopressors	52 (95%)	11 (100%)	1.000
- Inotropes	24 (44%)	5 (46%)	1.000
Fever control			
Type of treatment of fever (general policy)			
- Paracetamol	53 (96%)	8 (73%)	**0.029**
- NSAIDs	18 (33%)	11 (100%)	**0.000**
- External cooling	40 (73%)	9 (82%)	0.714
- Intravascular cooling	1 (2%)	2 (18%)	0.070
Corticosteroid use			
Primary management with corticosteroids			
- No	50 (93%)	7 (64%)	**0.023**
- Yes	4 (7%)	4 (36%)	
Glucose and nutrition management			
Glucose therapy			
- Insulin administration to correct hyperglycemias	36 (69%)	7 (78%)	0.713
- Tight glycemic control	16 (31%)	2 (22%)	
Route of nutrition			
- Parenteral	1 (2%)	4 (36%)	**0.002**
- Enteral	53 (98%)	7 (64%)	
Seizure prophylaxis and treatment			
Agents used for seizure prophylaxis (general policy)	16 (29%)	4 (36%)	0.725
- Phenytoin	32 (59%)	0	**0.000**
- Levetiracetam	7 (13%)	4 (36%)	0.080
- Valproate			
Agents used for seizure treatment (general policy)	25 (46%)	7 (64%)	0.333
- Phenytoin	39 (71%)	1 (9%)	**0.000**
- Levetiracetam	14 (26%)	7 (64%)	**0.029**
- Valproate			

In order to calculate the Fisher exact test a sufficient number per category (answer option) was needed, therefore categories were combined (for the primary management with corticosteroids)
Higher income: Austria, Belgium, Denmark, Finland, France, Germany, Israel, Italy, the Netherlands, Norway, Spain, Sweden, the UK and Switzerland; *Relatively low income:* Bosnia Herzegovina, Hungary, Latvia, Lithuania, Romania and Serbia.
CPP: cerebral perfusion pressure, IV: intravenous, NSAIDs: nonsteroidal anti-inflammatory drugs

Supplementary material 3: Comparison with the Brain Trauma foundation recommendations: items of the questionnaire with corresponding recommendations in the Brain Trauma Foundation guidelines for the Management of Severe Traumatic Brain Injury (4th edition)

Table Brain Trauma Foundation guidelines applied to systemic ICU management

Items questionnaire	Recommendations
Respiratory and circulatory management	
$PaCO_2$ goal (in the presence and absence of raised ICP)	Prolonged prophylactic hyperventilation with partial pressure of carbon dioxide in arterial blood (PaCO2) of 25 mm Hg or less is not recommended. Level II B (Chapter 5. Ventilation Therapies) Hyperventilation is recommended as a temporizing measure for the reduction of elevated ICP. (Carney et al.) Hyperventilation should be avoided during the first 24 h after injury when CBF often is reduced critically. (Carney et al.)
Initial PaO_2 goal, arterial saturation goal, timing tracheotomy	-
Target CPP	The recommended target cerebral perfusion pressure (CPP) value for survival and favorable outcomes is between 60 and 70 mm Hg. Whether 60 or 70 mm Hg is the minimum optimal CPP threshold is unclear and may depend upon the patient's autoregulatory status. Level II B (Chapter 13. Cerebral Perfusion Pressure Monitoring)
Intravenous fluids and vasoactive drugs to support CPP	Avoiding aggressive attempts to maintain CPP above 70 mm Hg with fluids and pressors may be considered because of the risk of adult respiratory failure. Level II (Chapter 13. Cerebral Perfusion Pressure Monitoring)
Fever control	
Type of treatment for fever	-
Use of corticosteroids	
	The use of steroids is not recommended for improving outcome or reducing ICP. In patients with severe TBI, high-dose methylprednisolone was associated with increased mortality and is contraindicated. Level I (Chapter 7. Steroids)
Glucose and nutrition management	
Aim for full caloric replacement	Feeding patients to attain basal caloric replacement at least by the fifth day and, at most, by the seventh day post-injury is recommended to decrease mortality. Level II A (Chapter 8. Nutrition)
Route of nutrition	Transgastric jejunal feeding is recommended to reduce the incidence of ventilator-associated pneumonia. Level II B (Chapter 8. Nutrition)
Glucose therapy, aim caloric intake, start parenteral nutrition	-

Continue

Continued

Items questionnaire	Recommendations
Respiratory and circulatory management	
Seizure prophylaxis and treatment	
Agents used for seizure prophylaxis	Prophylactic use of phenytoin or valproate is not recommended for preventing late PTS. Phenytoin is recommended to decrease the incidence of early PTS (within 7 days of injury), when the overall benefit is felt to outweigh the complications associated with such treatment. However, early PTS have not been associated with worse outcomes. Level II A (Chapter 11. Seizure prophylaxis) At the present time there is insufficient evidence to recommend levetiracetam compared with phenytoin regarding efficacy in preventing early post-traumatic seizures and toxicity. (Carney et al.)
Indications for anti-seizure prophylaxis, duration of anti-seizure prophylaxis, agents used for seizure treatment, initiation of anti-epileptic treatment	-

Items of the questionnaire with corresponding recommendations in the Brain Trauma Foundation guidelines for the Management of Severe Traumatic Brain Injury (4th edition), (Carney N, Totten AM, O'Reilly C, Ullman JS, Hawryluk GW, Bell MJ, Bratton SL, Chesnut R, Harris OA, Kissoon N et al: Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. Neurosurgery 2017, 80(1):6-15.)
CPP: cerebral perfusion pressure, ICU: intensive care unit, ICP: intracranial pressure, $PaCO_2$: partial pressure of carbon dioxide in arterial blood, PaO_2: partial pressure of oxygen in arterial blood

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PART 2

Towards improvement in daily Traumatic Brain Injury care

CHAPTER 6

6

Development of a quality indicator set to measure and improve quality of ICU care for patients with Traumatic Brain Injury

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Abstract

Background We aimed to develop a set of quality indicators for patients with Traumatic Brain Injury (TBI) in Intensive Care Units (ICUs) across Europe, and to explore barriers and facilitators for implementation of these quality indicators.

Methods A preliminary list of 66 quality indicators was developed, based on current guidelines, existing practice variation, and clinical expertise in TBI management at the ICU. Eight TBI experts of the Advisory Committee preselected the quality indicators during a first Delphi round. A larger Europe-wide expert panel was recruited for the next two Delphi rounds. Quality indicator definitions were evaluated on four criteria; validity (better performance on the indicator reflects better processes of care and leads to better patient outcome); feasibility (data are available or easy to obtain); discriminability (variability in clinical practice); and actionability (professionals can act based on the indicator). Experts scored indicators on a 5-point Likert scale delivered by an electronic survey tool.

Results The expert panel consisted of 50 experts from 18 countries across Europe, mostly intensivists (N=24; 48%) and neurosurgeons (N=7; 14%). Experts agreed on a final set of 42 indicators to assess quality of ICU care: 17 structure, 16 process, and 9 outcome indicators. Experts are motivated to implement this finally proposed set (N=49; 98%) and indicated routine measurement in registries (N=41; 82%), benchmarking (N=42; 84%), and quality improvement programs (N= 41; 82%) as future steps. Administrative burden was indicated as the most important barrier for implementation of the indicator set (N=48; 98%).

Conclusions This Delphi consensus study gives insight in which quality indicators have the potential to improve quality of TBI care at European ICUs. The proposed quality indicator set is recommended to be used across Europe for registry purposes to gain insight in current ICU practices and outcomes of patients with TBI. This indicator set may become an important tool to support benchmarking and quality improvement programs for patients with TBI in the future.

Background

Traumatic Brain Injury (TBI) causes an enormous health and economic burden around the world [1]. Patients with moderate and severe TBI are at high risk for poor outcomes and often require Intensive Care Unit (ICU) admission. In these patients, evidence-based treatment options are scarce and large differences in outcome and daily ICU practice exist [2-5].

Research to establish more evidence-based and thereby uniform treatment policies for patients with TBI has high priority. Still, breakthrough intervention strategies are scarce [6] and guideline recommendations remain limited. Therefore, new strategies, such as precision medicine and routine quality measurement are being explored to drive research and clinical practice forward [1]. Routine quality measurement using appropriate indicators can guide quality improvement, for example through identifying best practices and internal quality improvement initiatives. The potential of quality indicators to improve care has already been demonstrated in other clinical areas [7], in other ICU populations like sepsis [8] or stroke patients [9], and in children with TBI [10, 11].

However, there are also examples of quality indicators that do not positively affect quality of care. This may be for various reasons, such as lack of validity and reliability, poor data quality, or lack of support by clinicians [12-14]. Deploying poor indicators has opportunity costs due to administrative burden whilst distorting healthcare priorities. An evaluation of a putative quality indicator is inherently multidimensional, and when used to identify best practice or benchmark hospitals, validity and reliability and uniform definitions are all equally important [15, 16].

Although some quality indicator sets for the general ICU exist [17, 18], there are no consensus-based quality indicators specific for the treatment of adult patients with TBI. Delphi studies have been proposed as a first step in the development of quality indicators [19]. The systematic Delphi approach gathers information from experts in different locations and fields of expertise to reach group consensus without groupthink, [19] an approach which aims to ensure a breadth of unbiased participation.

The aim of this study was to develop a consensus-based European quality indicator set for patients with TBI at the ICU, and to explore barriers and facilitators for implementation of these quality indicators.

Methods

This study was part of the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) project [20].

An Advisory Committee (AC) was convened, consisting of 1 neurosurgeon (AM), 3 intensivists (MJ, DM, GC), 1 emergency department physician (FL), and 3 TBI researchers (HL, ES, LW) from 5 European countries. The AC's primary goals were to provide advice on the recruitment of the Delphi panel, to monitor the Delphi process, and to interpret the final Delphi results. During a face-to-face meeting (September 2017), the AC agreed that the Delphi study would initially be restricted to Europe, recruit senior professionals as members of the Delphi panel, and focus on the ICU. The restriction to a European rather than a global set was motivated by substantial continental differences in health funding systems, health care costs, and health care facilities. The set was targeted to be generalizable for the whole of Europe and therefore included European Delphi panelists. The AC agreed to target senior professionals as Delphi panelists as they were expected to have more specialized and extensive clinical experience with TBI patients at the ICU. The AC decided to focus the indicator set on ICU practice, since ICU mortality rates are high (around 40% in patients with severe TBI [21]), large variation in daily practice exists [2-5, 22], and detailed data collection is generally more feasible in the ICU setting due to available patient data management systems or electronic health records (EHRs). We focused on adult patients with TBI.

Delphi panel

The AC identified 3 stakeholder groups involved in ICU quality improvement: 1) clinicians (physicians and nurses) primary responsible for ICU care, 2) physicians from other specialties than intensive care medicine who are regularly involved in the care of patients with TBI at the ICU, and 3) researchers/ methodologists in TBI research. It was decided to exclude managers, auditors, and patients as stakeholders, since the completion of the questionnaires required specific clinical knowledge. Prerequisites to participate were a minimum professional experience of 3 years at the ICU or in TBI research. Stakeholders were recruited from the personal network of the AC (also through social media), among the Principal Investigators of the CENTER-TBI study (contacts from more than 60 Neurotrauma centers across 22 countries in Europe)[20], and from a European publication on quality indicators at the ICU [18]. These experts were asked to provide additional contacts with sufficient professional experience.

Preliminary indicator set

Before the start of the Delphi process a preliminary set of quality indicators was developed by the authors and the members of the AC, based on international guidelines (Brain Trauma Foundation–[23] and Trauma Quality Improvement Program guidelines [24]), ICU practice

variation [3-5], and clinical expertise. Quality indicators were categorized into structure, process and outcome indicators [25]. Overall, due to absence of high-quality evidence on which thresholds to use in TBI management, we refrained from formulating quality indicators in terms of thresholds. For example, we did not use specific carbon dioxide (CO2) or intracranial pressure (ICP) thresholds to define quality indicators for ICP-lowering treatments.

Indicator selection

The Delphi was conducted using online questionnaires. In the first round, the AC rated the preliminary quality indicators on four criteria: validity, discriminability (to distinguish differences in center performance), feasibility (regarding data collection required), and actionability (to provide clear directions on how to change TBI care or otherwise improve scores on the indicator) [26-30][11, 12, 23-25] (table 1). We used a 5-point Likert scale varying from strongly disagree (1) to strongly agree (5). Additionally, an 'I don't know' option was provided to capture uncertainty. Agreement was defined as a median score of 4 (agreement) or 5 (strong agreement) on all criteria . Disagreement was defined as a median score below 4 on at least one of the four criteria [31, 32]. Consensus was defined as an interquartile range (IQR) ≤ 1 (strong consensus) on validity–since validity is considered the key characteristic for a useful indicator [19]- and IQR ≤ 2 (consensus) on the other criteria [31, 32]. Criteria for rating the indicators and definitions of consensus remained the same during all rounds. The AC was able to give recommendations for indicator definitions at the end of the questionnaire. Indicators were excluded for the second Delphi round when there was consensus on disagreement on at least one criterion, unless important comments for improvement of the indicator definition were made. Such indicators with improved definitions were rerated in the next Delphi round.

In the second round the remaining indicators were sent to a larger group of experts. The questionnaire started with a description of the goals of the study and some characteristics of experts were asked. Experts had the possibility to adapt definitions of indicators at the end of a group of indicators on a certain topic (domain). Indicators were included in the final set when there was agreement and consensus, excluded when there was disagreement

Table 1: Selection criteria used to rate the quality indicators

Criteria	Definition
Validity	It is likely that better performance on the indicator reflects better processes of care and leads to better patient outcome
Feasibility	Measurement of the indicator is feasible (data for the indicator are available or easy to obtain)
Discriminability	It is expected that there is variability in clinical practice
Actionability	The indicator can be used to improve quality of care, professionals can act on it

These criteria were used to rate each quality indicator during all Delphi rounds [23-27]

and consensus, and included the next round when no consensus was reached or important comments to improve the indicator definitions were given. As many outcome scales exist for TBI, like the Glasgow Outcome Scale Extended (GOSE), Coma Recovery Scale Revised (CSR-R), Rivermead Post-Concussion Symptoms Questionnaire (RPQ), etc., a separate ranking question was used to determine which outcome scales were preferred (or most important) to use as outcome indicators–to avoid an extensive outcome indicator set (supplement 2, question outcome scales). Outcome scales that received highest ratings (top 3) were selected for round 3 and rated as described above. Finally, exploratory questions were asked for which goals or reasons experts would implement the quality indicators. We only selected experts for the final round that completed the full questionnaire.

In the last round, the expert panel was permitted only to rate the indicators, but could not add new indicators or suggest further changes to definitions. Experts received both qualitative and quantitative information on the rating of indicators (medians and IQRs) from round 2 for each individual indicator. Indicators were included in the final set if there was both agreement and consensus. Final exploratory questions were asked regarding the barriers and facilitators for implementation of the indicator set. For each Delphi round three automated reminder emails and two personal reminders were sent to the Delphi participant to ensure a high response rate.

Statistical analysis

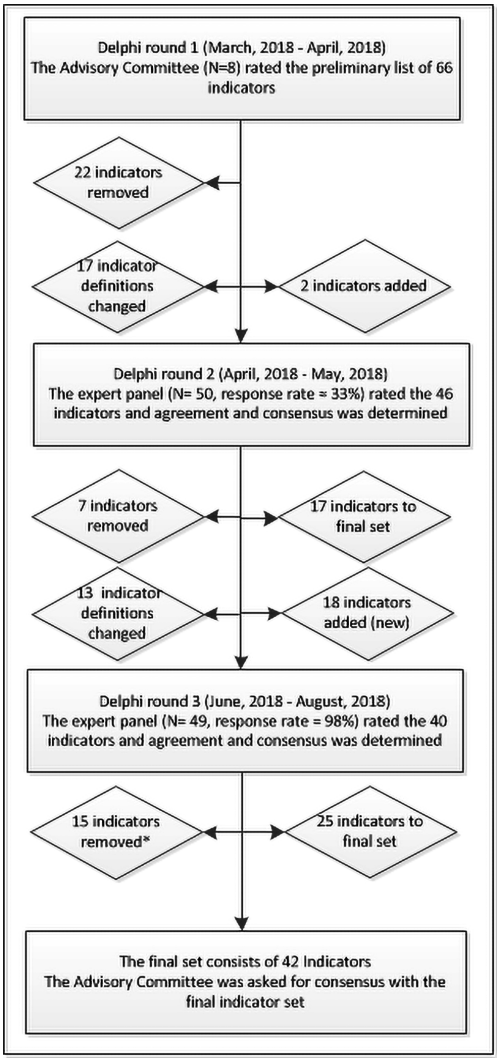
Descriptive statistics (median and interquartile range) were calculated to determine which indicators were selected for the next round and to present quantitative feedback (median and min-max rates) in the third Delphi round. 'I don't know' was coded as missing. A sensitivity analysis after round 3 was performed to determine the influence of experts from Western Europe compared with other European regions on indicator selection (in- or exclusion in final set). Statistical analyses were performed using the R statistical language [33]. Questionnaires were developed using open-source LimeSurvey software [34]. In LimeSurvey, multiple online questionnaires can be developed (and send by email), the response rates can be tracked, and questionnaire scores or responses can easily be exported to a statistical program.

Results

Delphi panel

The Delphi rounds were conducted between March 2018 and August 2018 (figure 1). Approximately 150 experts were invited for round 2, and 50 experts from 18 countries across Europe responded (≈ 33%). Most were intensivists (N=24; 48%), followed by neurosurgeons (N=7; 14%), neurologists (N=5; 10%), and anesthesiologist (N=5; 10%). (Table 2) Most of

Figure 1: Overview of the Delphi process



Legend figure 1: Overview of the Delphi process: time frame, experts' involvement, and indicator selection * 8 indicators were removed based on the sensitivity analyses. The left site of the figure shows the number of indicators that were removed after disagreement and consensus with no comments to improve definitions. In addition, the number of changed indicator definitions is shown. The right site of the figure shows the number of newly proposed indicators (that were rerated in the next Delphi round) and the number of indicators that were included in the final indicator set. After round 2, 17 indicators were included in the final set (and removed from the Delphi process) and after round 3, 25 indicators were included in the final set – a total of 42 indicators. Agreement was defined as a median score of 4 (agreement) or 5 (strong agreement) on all four criteria (validity, feasibility, discriminability, and actionability) to select indicators. Disagreement was defined as a median score below 4 on at least one of the four criteria. Consensus was defined as an interquartile range (IQR) ≤ 1 (strong consensus) on validity–since validity is considered the key characteristic for a useful indicator [19]–and IQR ≤ 2 (consensus) on the other criteria.

Table 2: Baseline characteristics Delphi panel

	N	(%)
Total number of Delphi panelists	50	(100%)
Total number of participating centers	37	(100%)
Gender (N=50)		
Male	40	(80%)
Female	10	(20%)
Profession (N= 50)		
Neurosurgeon	7	(14%)
Intensivist	24	(48%)
Neurologist	5	(10%)
Anesthesiologist	5	(10%)
Trauma surgeon	2	(4%)
Rehabilitation specialist	3	(6%)
Methodologist/ researcher in TBI	3	(6%)
Neurophysiologist	1	(2%)
Number of years of professional experience at the ICU [a] (N= 44)		
3–5 years	4	(9%)
5–10 years	8	(18%)
10–15 years	7	(16%)
> 15 years	25	(57%)
Primary responsible/in charge for the daily care of patients with TBI at the ICU [a] (N= 45)		
Yes	21	(47%)
No	24	(53%)
Location [b] (N= 50)		
Northern Europe	6	(12%)
Western Europe	28	(56%)
United Kingdom	5	(10%)
Southern Europe	8	(16%)
Eastern Europe	2	(4%)
Baltic States	1	(2%)
Center (N= 44)		
Academic	37	(84%)
Nonacademic	7	(16%)
Center location [c] (N= 45)	44	(98%)
Urban	1	(2%)
Suburban		
Trauma designation [d] (N= 45)		
Level I	31	(69%)
Level II	1	(2%)
Level III	7	(15%)
Our center is not officially designated as a trauma center	3	(7%)
Our country does not explicitly designate trauma centers	3	(7%)
Electronic patient records [a] (N=45)		
Yes	43	(96%)
No	2	(4%)
Participation in CENTER-TBI study (N=49)		
Yes	31	(63%)
No	18	(42%)

a) Only asked to those who answered clinician as profession
b) Location is based on United Nations geoscheme: Northern Europe = Norway (1), Sweden (2), Finland (2), and Denmark (1); Western Europe = Austria(1), Belgium (3), France (1), Germany (4), Switzerland (1) and the Netherlands (18); the United Kingdom and Ireland (5), Southern Europe = Portugal (1), Italy (5) and Spain (2); Eastern Europe = Ukraine (1), Serbia (1); Baltic States = Latvia (1)
c) Urban: An hospital location very near to a city and situated in a crowded area.
Suburban: between urban and rural (an hospital location in or very near to the countryside in an area that is not crowded.)
d) Level I trauma center: A regional resource center that generally serves large cities or population-dense areas. A level I trauma center is expected to manage large numbers of severely injured patients (at least 1,200 trauma patients annually or have 240 admissions with an Injury Severity Score of more than 14). It is characterized by 24-hour in-house availability of an attending surgeon and the prompt availability of other specialties (e.g. neurosurgeon, trauma surgeon).
Level II trauma center: A level II trauma center provides comprehensive trauma care in either a population-dense area in which a level II trauma center may supplement the clinical activity and expertise of a level I institution or occur in less population-dense areas. In the latter case, the level II trauma center serves as the lead trauma facility for a geographic area when a level I institution is not geographically close enough to do so. It is characterized by 24-hour in-house availability of an attending surgeon and the prompt availability of other specialties (e.g. neurosurgeon, trauma surgeon).
Level III trauma center: A level III trauma center has the capacity to initially manage the majority of injured patients and have transfer agreements with a level I or II trauma center for seriously injured patients whose needs exceed the facility's resources.
TBI: Traumatic Brain Injury, CENTER-TBI study: Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury study, ICU: Intensive Care Unit [46]

the experts indicated to have 15 years or more experience with patients with TBI at the ICU or another department (N=25; 57%). Around half of the experts indicated that they had primary responsibility for the daily practical care of patients with TBI at the ICU (N=21; 47%). Experts were employed in 37 centers across 18 European countries: mostly in Western Europe (N= 26, 55%). Most experts were from academic (N=37; 84%) trauma centers in an urban location (N=44; 98%). Almost all experts indicated the availability of EHRs in their ICU (N=43; 96%). Thirty-one experts (63%) participated in the CENTER-TBI study. The response rate in round 3 was 98% (N=49).

Indicator selection

The first Delphi round started with 66 indicators (Figure 1). In round 1, 22 indicators were excluded. The main reason for exclusion was poor agreement (median<4) on all criteria except discriminability (supplement 5). Round 2 started with 46 indicators; 17 were directly included in the final set and 7 were excluded, mainly due to poor agreement (median<4) on actionability and poor consensus (IQR>1) on validity. Round 3 started with 40 indicators; 25 indicators were included in the final set. Exclusion of 8 indicators was based on the sensitivity analysis (no consensus in Western Europe versus other European regions) and 7 indicators had low agreement on actionability or no consensus on validity or actionability. During the full Delphi process, 20 new indicators were proposed, and 30 definitions were discussed and/or modified.

The final quality indicator set consisted of 42 indicators on 13 clinical domains (Table 3), including 17 structure -, 16 process, and 9 outcome indicators. For the domains 'precautions

Table 3: Finally proposed set of clinical quality indicators in Traumatic Brain Injury at the ICU

Domain	Indicators
Protocol	
	1. Structure: The existence of a protocol including specific guidelines (like the BTF guidelines or institutional guidelines) for Traumatic Brain Injury patients (yes/no)
	2. Structure: The presence of (some form of) regular audits to check guideline adherence in general at the Intensive Care Unit (ICU) (yes/no) Extra: Audits do not have to be specific for TBI
	3. Structure: The presence of dedicated person(s) to oversee guidelines development and maintenance, including those for patients with TBI, at the ICU (yes/no)
Intensive Care Unit	
	4. Structure: The presence of a step-down unit where patients can still be monitored 24/7, but less intensively than at the ICU (yes/no) Extra: A facility in-between ICU and ward. It is often used for patients who improved at the intensive care and no longer need the intensity of ICU care, but are also not well enough to be cared for at the ward. The care provided in step down beds is less intensive than the care provided at the ICU but more intensive than ward care
	5. Structure: Does your hospital have a dedicated/specialized neurocritical care unit? (yes/no)
	6. Structure: The availability of operating rooms 24 hours per day (yes/no)
	7. Process: Median accident-to-ICU-admission time (process) Extra: Time of the accident/injury to ICU-door-time
Staff	
	8. Structure: A daily meeting between intensivist and neurosurgeon to discuss patients with TBI at the ICU (yes/no)
	9. Structure: Availability of a neurosurgeon (staff) 24/7 within 30 minutes after call (yes/no)
	10. Structure: Total number of disciplines (i.e. neurologist, physiotherapy, occupational therapy) involved during ICU stay
	11. Structure: Certified intensivist present in person 7 days a week during at least day-time (yes/no)
	12. Structure: Intensivist to ICU bed ratio
	13. Structure: ICU nurse to ICU bed ratio
	14. Process: Number of visits by a neurosurgeon/ total number of ICU days in patients with TBI
CT scanning	
	15. Structure: 24/7 availability of a CT scan and radiologist review (yes/no)
ICP monitoring	
	16. Structure: 24/7 availability of a certified person at your center that can insert an ICP monitor within 2 hours after admission at the ICU (yes/no)
	17. Process: Number of severe (GCS 3-8) TBI patients with ICP monitoring/ number of severe TBI patients at the ICU
	18. Outcome: Number of EVD infections in patients with TBI/ total number of patients with TBI at the ICU with an EVD inserted Extra: Only for centers that use ventricular catheters

Domain	Indicators
Deep venous Thrombosis (DVT)	
	19. Process: Number of patients with TBI that receive any DVT prophylaxis/ total number of patients with TBI at the ICU Extra: Timing (application of prophylaxis in days from the injury) and type of DVT prophylaxis (mechanical and/or pharmaceutical) can be registered as well
	20. Process: Number of patients that receive pharmaceutical prophylaxis with low molecular weight heparins/ total number of TBI patients admitted to the ICU Extra: This QI is about the choice of prophylaxis (low molecular weight heparin), not about timing
	21. Process: Number of patients with TBI that receive mechanical DVT prophylaxis (e.g. stockings) initiated within 6 hours/ total number of patients with TBI at the ICU with the possibility to receive stockings Extra: Exclude patients with leg fractures
Glucose and nutrition	
	22. Structure: Do you have a protocol for glucose management available for patients with TBI at your ICU? yes/no
	23. Process: Number of TBI patients with basal full caloric replacement within 5 to 7 days post-injury / number of TBI patients at the ICU
	24. Process: Number of TBI patients with start of (early) enteral nutrition within 72 hours/ number of patients with enteral feeding during ICU stay
	25. Outcome: Number of TBI patients with any blood glucose above 10 mmol/L (180mg/dL, hyperglycemia)/total number of patients with TBI at the ICU Extra: Other values are not necessarily good, only detection of extreme cases
	26. Outcome: Number of TBI patients with any blood glucose below 4 mmol/L (hypoglycemia)/ total number of patients with TBI at the ICU Extra: Other values are not necessarily good, only detection of extreme cases
Surgery	
	27. Structure: The presence of a protocol/ institutional guideline that provide indications for surgery with SDH an EDH (yes/no)
	28. Process: Median door-to-operation time for acute operation of SDH and EDH with surgical indication
Allied health professional	
	29. Process: Number of patients with a support plan (e.g. rehabilitation) after ICU discharge/ number of patients discharged from the ICU Extra: plan consists of physio-, speech-, and occupational therapist goals during hospital stay
	30. Process: Number of patients with TBI visited daily by a physiotherapist during ICU stay/ total number of patients with TBI at the ICU
Assessment scales at the ICU	
	31. Structure: Information on prognosis is discussed with family by one of the treating physicians (ICU physician or neurosurgical physician) at least once during ICU stay
	32. Process: Number of assessments of motor scores of the GCS/ total number of ICU days in patients with TBI
	33. Process: Number of assessments of pupillary responses/ total number of ICU days in patients with TBI
	34. Process: Number of assessments of delirium presence with validated screening tool in conscious TBI patients / total number of ICU days in conscious TBI patients

Continue

Continued

Domain	Indicators
In-hospital outcomes	
	35. Outcome: Number of ICU-deaths among patients with TBI/ total number of ICU-admitted patients with TBI
	36. Outcome: Incidence of ventilator associated pneumonia (VAP) in patients with TBI/ total number of TBI patients with mechanical ventilation at the ICU Extra: Pneumonia defined as 'the presence of new lung infiltrate plus clinical evidence that the infiltrate is of an infectious origin, which includes the new onset of fever, purulent sputum, leukocytosis, and decline in oxygenation.' VAP is defined as a pneumonia occurring >48 hours after endotracheal intubation *American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2005*
	37. Outcome: Number of TBI patients with decubitus grade 2 or higher at the ICU/ number of TBI patients at the ICU Extra (also register the grade): Grade 1: Pressure zone with redness that does not blanch with fingertip pressure, with skin still intact Grade 2: Decubitus ulcer (pressure sore) with skin erosion, blister, partial loss of the epidermis and/or dermis, or skin loss Grade 3: Decubitus ulcer (pressure sore) with loss of all skin layers and damage or necrosis of the subcutaneous tissue, which may extend down to the underlying fascia Grade 4: Decubitus ulcer (pressure sore) with necrosis of muscle, bone, or supportive structures such as tendons or joint capsules
	38. Outcome: Number of patients with TBI with severe sepsis or septic shock/ total number of patients with TBI at the ICU Extra: Sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. For clinical operationalization, organ dysfunction can be represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more, which is associated with an in-hospital mortality greater than 10%. Septic shock should be defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia. *Singer et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) JAMA 2016*
After discharge or follow-up outcomes	
	39. Process: Number of patients with TBI receiving follow-up by a specialist within 2 months after discharge/ total number of patients with TBI discharged (not in rehab clinic)
	40. Process: Number of patients with neuropsychological testing at hospital discharge/ number of patients with TBI discharged from the hospital
Outcome scales at 6 months	
	41. Outcome: The median score of the GOSE from all patients with TBI at 6 months/ number of patients with TBI discharged from the ICU and alive at 6 months
	42. Outcome: The median score of the SF-36 from all patients with TBI at 6 months/ number of patients with TBI discharged from the ICU and alive at 6 months

Final set of indicators after the Delphi rounds per domain. **All outcome indicators will be adjusted for case-mix**

EDH: epidural hematoma, GCS= Glasgow Coma Scale, GOSE = Glasgow Coma Scale – Extended, ICU: Intensive Care Unit SDH: subdural hematoma, SF-36 = 36-item Short Form Survey

ICP monitoring', 'sedatives', 'osmotic therapies', 'seizures', 'fever', 'coagulopathy', 'respiration and ventilation', and 'red blood cell policy' no indicators were included in the final set.

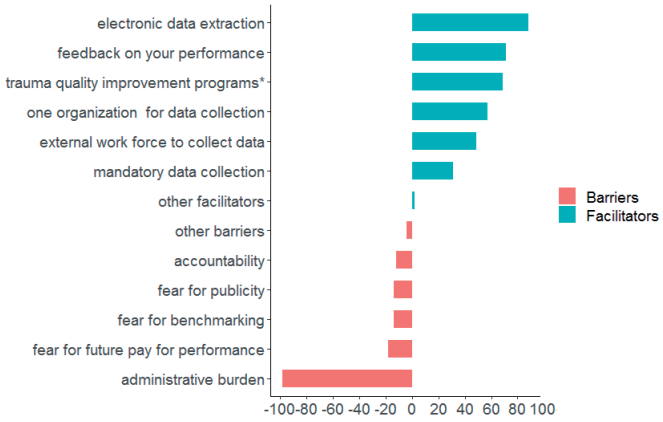
Experts proposed changing the names of the 'short term outcomes' and 'long term outcomes' domains to 'in-hospital outcomes' and 'after discharge or follow-up outcomes'. In round 2, the Glasgow Outcome Coma Scale Extended (GOSE), Quality of life after Brain injury (Qolibri), and Short Form health survey (SF-36) were rated the best outcome scales. However, the Qolibri was excluded in round 3 as outcome indicator, since there was no consensus in the panel on its validity to reflect quality of ICU care. The majority of experts (N=14; 28%) indicated that the outcome scales should be measured at 6 months, but this was closely followed by experts that indicated both at 6 and 12 months (N=13; 26%).

Barriers and facilitators for implementation

Almost all experts indicated that the indicator set should be used in the future (N=49; 98%). One expert did not believe an indicator set should be used at all, because it would poorly reflect quality of care (N=1; 2%).

The majority of experts indicated that the set could be used for registry purposes (N=41; 82%), assessment of adherence to guidelines (N=35; 70%), and quality improvement programs (N=41; 82%). Likewise, the majority of experts indicated that the indicator set could be used for benchmarking purposes (N=42; 84%); both within and between centers. Pay for performance was rarely chosen as a future goal (N=3; 6%). Almost all experts indicated administrative burden as a barrier (N=48; 98%). Overall, experts endorsed facilitators more than the barriers for implementation (figure 2).

Figure 2: Facilitators or barriers for implementation of the quality indicator set



Legend figure 2: Percentage of experts that indicated a certain facilitator or barrier for implementation of the quality indicator set. Other indicated facilitator was 'create meaningful uniform indicators'. Other indicated barriers were 'gaming' (N=1; 2%) and 'processes outside of ICU (e.g. rehabilitation) are hard to query'.
*Participation in trauma quality improvement program

Discussion

Main findings

This three-round European Delphi study including 50 experts, resulted in a quality indicator set with 42 indicators with high-level of consensus on validity, feasibility, discriminability, and actionability, representing 13 clinical domains for patients with TBI at the ICU. Experts indicated multiple facilitators for implementation of the total set, while the main barrier was the anticipated administrative burden. The selection of indicators during the Delphi process gave insight in which quality indicators were perceived as important to improve quality of TBI care. In addition, the indicator definitions evolved during the Delphi process, leading to a final set of understandable and easy to interpret indicators by (clinical) experts. This set serves as a starting point to gain insight in current ICU care for TBI patients, and after empirical validation it may be used for quality measurement and improvement.

Our Delphi resulted in 17 structure, 16 process, and 9 outcome indicators. A large number of structure indicators already reached consensus after round 2; this might reflect that these were more concise indicators. However, during the rounds, definitions for process indicators became more precise and specific. Process indicators must be evidence-based before best practices can be determined: this might also explain that important domains with indicators on daily care in TBI (such as decompressive craniectiomy, osmotic therapies, respiration and ventilation management) did not reach consensus in our Delphi study. Structure, process and outcome indicators have their own advantages and disadvantages. For example, process indicators tend to be inherently actionable as compared to structure and outcome indicators, yet outcome indicators are more relevant to patients [35]. Most indicators that were excluded from the set based on low agreement and lack of consensus on actionability and validity: this indicates that experts highly valued the practicality and usability of the set and were strict on selecting only those indicators that might improve patient outcome and processes of care. Overall, the complete set comprises all different types of indicators.

Existing indicators

Some national ICU registries already exist [17] and in 2012, a European ICU quality indicator set for general ICU quality has been developed [18]. In addition, several trauma databanks already exist [36, 37]. The motivations for selection (or rejection) of indicators in our study can contribute to the ongoing debate on which indicators to collect in these registries. For example, length of stay is often used as outcome measure in current registries; but the Delphi panel commented that determination of length of stay is debatable as an indicator, since hospital structures differ (e.g. step-down units are not standard), and admission length can be confounded by (ICU) bed availability. Although general ICU care is essential for TBI, not all general ICU or trauma indicators are applicable in exactly the same way for

TBI. For example, individualized deep venous thrombosis prophylaxis management in TBI is a priority in view of the risk of progressive brain hemorrhage in contrast to other ICU conditions (e.g. sepsis). Therefore, our TBI-specific indicator set might form a useful addition to current registries.

Strength and limitations

This study has several strengths and limitations. No firm rules exist on how to perform a Delphi study in order to develop quality indicators [19]. Therefore, we extensively discussed methodology and determined strategies with the Advisory Committee. Although the RAND/UCLA Appropriateness Method recommends a panel meeting [38]; no group discussion took place in our study to avoid overrepresentation of strong voices and for reasons of feasibility. However, experts received both qualitative and quantitative information on the rating of indicators to gain insight in the thinking process of the other panel members. Considering the preliminary indictor set, we used the guidelines [23, 24] as a guide to which topics should be included and not as an evidence base. Considering the Delphi panel, the success of indicator selection depends on the expertise of invited members: we assembled a large network of 50 experts from 18 countries across Europe with various professional backgrounds. All participants can be considered as established experts in the field of TBI-research and/or daily clinical practice (around 70% of experts had more than 10 years ICU experience). However, more input from some key stakeholders in quality of ICU care, such as rehabilitation physicians; nurses and allied health practitioners; health care auditors; and TBI patients would have been preferable. We had only three rehabilitation experts on our panel, but increased input from this group of professionals would have been valuable, since they are increasingly involved in the care of patients even at the ICU stage. A number of nurses were invited, but none responded, possibly due to a low invitation rate. This is a severe limitation since nurses play a key role in ICU quality improvement and quality indicator implementation [39, 40]. Therefore, future studies should put even more effort in involving nurses in quality indicator development. Experts were predominantly from Western Europe. Therefore, we performed sensitivity analyses for Western Europe and removed indicators with significant differences compared with other regions to obtain a set generalizable for Europe. The restriction to a European rather than a global set was motivated by substantial continental differences in health funding systems, health care costs, and health care facilities. Finally, some of the responses may have been strongly influenced by familiarity with measures (e.g. SF-36 was selected instead of Qolibri), rather that solely reflecting the value of the measure per se.

Use and implementation

Quality indicators may be used for improvement of care in several ways. First, registration of indicator data itself will make clinicians and other stakeholders aware of their center or ICU performance, as indicators will provide objective data on care instead of perceived

care. Second, as the evidence-base for guidelines is often limited, this indicator set could support refinement of guideline recommendations. This was shown in a study by Vavilala et al., where guideline-derived indicators for the acute care of children with TBI were collected from medical records and were associated with improved outcome [10]. Third, quality indicators can be used to guide and to inform quality improvement programs. One study showed that a TBI-specific quality improvement program was effective, demonstrating lower mortality rates after implementation [41]. Fourth, (international) benchmarking of quality indicators will facilitate discussion between (healthcare) professionals and direct attention towards suboptimal care-processes [17]. Future benchmarking across different hospitals or countries requires advanced statistical analyses such as random effect regression models to correct for random variation and case-mix correction. To perform such benchmarking, case-mix variables must be collected, like in general ICU prognostic models or the TBI-specific prognostic models, such as IMPACT and CRASH [42, 43].

A quality indicator set is expected to be dynamic: ongoing large international studies will further shape the quality indicator set. This is also reflected in the "retirement" of indicators over time (when 90-100% adherence is reached). Registration and use of the quality indicators will provide increasing insight in their feasibility and discriminability and provides the opportunity to study their validity and actionability. Such empirical testing of the set will probably reveal that not all indicators meet the required criteria and thus will reduce the number of indicators in the set; which is desirable, as the set is still quite extensive. For now, based on the dynamic nature of the set and ongoing TBI studies, we recommend to use this consensus-based quality indicator for registry purposes; to gain insight (over time) in current care–and not for changing treatment policies. Therefore, we recommend to regard this consensus-based quality indicator set as a starting point in need of further validation before broad implementation can be recommended. Such validation should seek to establish whether adherence to the quality indicators is associated with better patient outcomes.

To provide feedback on clinical performance, new interventions are being explored to further increase the effectiveness of indicator-based performance feedback, e.g. direct electronic audit and feedback with suggested action plans [44]. A single (external) organization for data collection could enhance participation of multiple centers. International collaborations must be encouraged and further endorsement by scientific societies seems necessary before large-scale implementation is feasible. When large-scale implementation becomes global; there is an urgent need to develop quality indicators for low income countries [36, 45]. An external organization for data collection could also reduce the administrative burden for clinicians. This is a critical issue, since administrative burden was indicated as main barrier for implementation of the whole indicator set, although

experts agreed on the feasibility of individual indicators. In the future, automatic data extraction might be the solution to overcome administrative burden.

Conclusion

This Delphi consensus study gives insight in which quality indicators have the potential to improve quality of TBI care at European ICUs. The proposed quality indicator set is recommended to be used across Europe for registry purposes to gain insight in current ICU practices and outcomes of patients with TBI. This indicator set may become an important tool to support benchmarking and quality improvement programs for patients with TBI in the future.

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CHAPTER 7

7

Quality indicators for patients with Traumatic Brain Injury in European Intensive Care Units

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Abstract

Background: The aim of this study is to validate a previously published consensus-based quality indicator set for management of patients with traumatic brain injury (TBI) at intensive care units (ICUs) in Europe, and to study its potential for quality measurement and improvement.

Methods: Our analysis was based on 2006 adult patients admitted to 54 ICUs between 2014 and 2018, enrolled in the CENTER-TBI study. Indicator scores were calculated as percentage adherence for structure–and process indicators, and as event rates or median scores for outcome indicators. Feasibility was quantified by the completeness of the variables. Discriminability was determined by the between-centre variation, estimated with a random effect regression model adjusted for case-mix severity and quantified by the median odds ratio (MOR). Statistical uncertainty of outcome indicators was determined by the median number of events per centre, using a cut-off of 10.

Results: A total of 26/42 indicators could be calculated from the CENTER-TBI database. Most quality indicators proved feasible to obtain with more than 70% completeness. Sub-optimal adherence was found for most quality indicators, ranging from 26-93% and 20%-99% for structure and process indicators. Significant (p<0.001) between-centre variation was found in 7 process and 5 outcome indicators with MORs ranging from 1.51-4.14. Statistical uncertainty of outcome indicators was generally high; 5 out of 7 had less than 10 events per centre.

Conclusions: Overall, 9 structure, 5 process, but none of the outcome indicators showed potential for quality improvement purposes for TBI patients in the ICU. Future research should focus on implementation efforts and continuous reevaluation of quality indicators.

Background

Limited evidence is available to direct critical care practice in patients with traumatic brain injury (TBI) [1]. Randomized controlled trials have shown limited potential to add evidence translatable to clinical practice and new approaches are being explored to improve care, such as quality of care monitoring. Quality of care registration in patients with TBI could become part of emerging international Intensive Care Unit (ICU) or trauma registries [2-5]. When used over time and across centres, large datasets provide a rich source for benchmarking and quality improvement, i.e. with feedback on performance, between-centre discussions on policies, and opportunities to study best practice.

International registries can contribute to improved patient outcome; by identifying areas in need of quality improvement, informing health policies, and increasing transparency and accountability, as shown in other medical fields, like cancer [6], acute coronary syndrome [7] and cystic fibrosis [8]. Benchmarking TBI management between ICUs can only be reliable, when standardized quality indicators are used and case-mix correction is applied [5]. Quality indicators can be subdivided into structure, process, and outcome indicators [9]. As no quality indicator set is available for patients with TBI, we recently performed a Delphi study to reach consensus on a quality indicator set [10].

The aim of the current study is to validate the consensus-based quality indicator set. We hereto analyzed patients enrolled in a large dataset of patients with TBI from the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study. Data collected for CENTER-TBI included a comprehensive description of ICU facilities and patient outcomes in 54 centres thus providing an opportunity to examine the usefulness of the newly developed indicator set [11]. Based on the validation result the indicator set could be reduced to those that have the greatest potential for implementation.

Methods

Quality indicator set

In this validation study, we applied a previously developed quality indicator set based on a Delphi study to the CENTER-TBI study. The quality indicator set consisted of 17 structure -, 16 process, and 9 outcome indicators for adult patients with TBI at the ICU. It was acknowledged that this initial set would be in need of further validation [10].

Data

The CENTER-TBI study is a multicentre observational cohort study conducted in Europe, which recruited patients between 2014 and 2018 (clinicaltrials.gov NCT02210221) [11, 12].

The Core study contains 4509 patients. Inclusion criteria for the CENTER-TBI study were a clinical diagnosis of TBI, presentation within 24 h of injury, an indication for CT scanning, and the exclusion criterion was a pre-existing (severe) neurological disorder that could confound outcome assessments. We selected ICU patients for this study as the consensus-based indicators were specifically developed for the ICU. So, inclusion criteria for our study were 1) admitted to the ICU and 2) adults older than 18 years. Processes of ICU care (vitals, treatments, and therapy intensity levels) were obtained on a daily basis. Outcomes were assessed at the ICU and at 3, 6, 12, and 24 months. In addition, questionnaires were completed by participating centres on structures and processes of care (Provider Profiling questionnaires [13]).

Indicator scores

We determined whether the indicators could be calculated from the CENTER-TBI database and whether data collection fitted routine practice.

Structure indicator scores at centre-level were calculated based on the Provider Profiling questionnaires and expressed as the number of centres that indicated that the structure was either present or absent.

Process indicators were calculated as the number of patients adherent to the indicator (numerator) divided by the number of patients to which the indicator could have applied per centre (denominator). The denominator could be based on a subset of patients (e.g. excluding patients with leg fractures for the indicator mechanical DVT prophylaxis).

(Crude) outcome indicators were calculated as the event rate of the indicator per centre (numerator) divided by the total number of patients which could have scored on the indicator (denominator). For the Glasgow Outcome Scale Extended (GOSE) and Short Form-36 version 2 (SF-36) the median scores were calculated.

Missing data were disregarded for the denominator so that the indicator adherence scores were based on the number of patients that could be exposed to the indicator. We present the median indicator numbers across centres with interquartile range.

Validation of the quality indicators

The usefulness of the quality indicators was based on three criteria [14]; feasibility[15], discriminability [16, 17], and statistical uncertainty[15, 18, 19]. As no previous studies report thresholds on these criteria, we set a-priori thresholds based on consensus.

1.Feasibility

Feasibility addresses data quality and ease of quality indicator calculation [15].

The feasibility was quantified by the completeness of the variables required to calculate the indicators. We set an arbitrary threshold of >70% completeness of data (of denominator) to determine feasibility.

2.Discriminability
To determine discriminability (between-centre variation), we determined the between-centre differences in adherence to quality indicators to evaluate their potential for benchmarking and quality improvement [16, 17].

Between-centre variation for structure indicators was determined by the number of centres having that structure. We set an arbitrary threshold for moderate discriminability at 80-90% and for poor discriminability at 90%-100% adherence to structure and process indicators. Such high levels of adherence decrease discrimination between centres.

The between-centre variation of process and outcome indicator scores, adjusted for case-mix and statistical uncertainty was quantified with the median odds ratio (MOR) [20]. The MOR represents the odds of being adherent to a specific indicator for two patients with the same patient characteristics from 2 randomly selected centres. The higher the MOR, the larger the between-centre variation (a MOR equal to 1 reflects no variation).

For process and outcome indicators, we considered a low (unadjusted) interquartile range on scores (IQR<10) or non-significant (adjusted) between-centre differences or a MOR of 1.1 or less as poor discriminability. Case-mix and uncertainty adjusted process and outcome indicator scores per centre were presented in caterpillar plots.

3. Statistical uncertainty
Reliability refers to the reproducibility of a quality indicator, and is threatened by unclear indicator definitions [15] and statistical uncertainty [18, 19]. We determined whether we could calculate indicators in a uniform way or made minor changes to definitions. Statistical uncertainty was determined by random variation due to low numbers of events (only applicable to outcome indicators).

Statistical uncertainty for outcome indicators was determined by the median number of events across centres. We set the threshold for high statistical uncertainty at < 10 events.

Statistical analysis

Baseline centre–and patient characteristics are described as frequencies and percentages. Between-centre variation of process and outcome indicator scores was calculated with a random-effect logistic regression analysis. We used a random effect model (random effect for centre) to account for the fact that indicator scores in centres with a small number

of patients can have extreme values due to random variation. Also, only centres with > 10 admitted ICU patients were included. To correct for case-mix we used the extended International Mission for Prognosis and analysis of Clinical Trials in TBI (IMPACT) prognostic model: core (age, motor score, pupillary light reactivity), CT (hypoxia, hypotension, epidural hematoma, traumatic subarachnoid hemorrhage, and Marshall CT classification) and lab (first glucose and hemoglobin) [21] and Injury severity scale score (ISS). The MOR was calculated from the τ^2 (variance of random effects).

Case-mix and uncertainty adjusted process and outcome indicator scores per centre are presented in 'caterpillar' plots. P-values for determining the significance of the between-centre variation were calculated with a likelihood ratio test comparing a model with and without a random effect for centre. A mixture distribution is required to calculate the p-value as the null hypothesis is on the boundary of the parameter space [22].

For the calculation of random effect models, missing data were imputed with multiple (*N*=5) imputation with the MICE package from R [23]. Statistical analyses were performed in R statistical software. Neurobot version 2.1 (data extraction date 23-12-2019) was used.

Results

A total of 26 (11 structure, 8 process, and 7 outcome indicators) of the 42 indicators of the Delphi set could be extracted from the CENTER-TBI database. (Supplementary material 1).

Baseline data

Fifty-four centres from 18 countries were included, totaling 2006 adult patients. The median number of ICU patients included per centre was 23 (IQR12-43, range 2-119). Centres were mostly academic centres (*N* = 51; 94%) and designated as Level I trauma centres (*N* = 37; 69%). Most centres were located in Northern (*N*= 20; 37%) or Western Europe (*N*= 19; 35%). (Table 1)

Around 28% of patients admitted to ICU were older than 65 years and mostly male (*N* = 1561; 73%). According to the baseline GCS score, 48% had severe (GCS <9; *N* = 915), 16% moderate (GCS 9-12; *N* = 305), and 48% mild TBI (GCS 13-15; *N* = 671). The majority of patients (*N*= 1963; 96%) suffered from polytrauma. The cause of injury was mostly related to road traffic accidents (*N* = 849; 44%) or incidental falls (*N* = 802; 42%). (Table 1)

Adherence

Regarding structure indicators, sub-optimal adherence rates were found for most indicators, including the presence of a neuro-ICU (*N* = 35; 65%), operation room availability 24 hours

per day (*N* = 40; 75%), and presence of a step-down unit (*N* = 38; 70%) (Supplementary material 2). Patient-to-nurse ratio's varied, with reported ratios of 1 (*N* = 14; 26%), 1-2 (*N* = 23; 43%) , and 2-3 (*N* = 17; 31%) patients per nurse . Adherence was high for 'the existence of a protocol including specific guidelines' (*N* = 47; 89%); 'protocol for glucose management' (*N* = 43; 81%), 'the availability of a neurosurgeon within 30 minutes after call' (*N* = 49; 93%); and 'the 24/7 availability of a CT scan and radiologist review' (N= 50; 91%).

Sub-optimal adherence rates were found for most process indicators, including ICP monitoring in the severe TBI group (median 69%, IQR: 44-82) , basal caloric intake within 5-7 days (*N* = 20%, IQR 3-47), and 'patients that receive DVT prophylaxis with low molecular weight heparins' (median 63%, IQR: 49-78) (Supplementary material 3). Adherence was high for 'enteral nutrition within 72 hours' (median 99%, IQR: 87-100).

For outcome, the centres had a median [IQR] ICU mortality of 12% [9-21], ventilator acquired pneumonia (VAP) incidence of 14% [0-31], and hyperglycemia incidence of 35% [22-45]. The median [IQR] GOSE was 5 [3-7], the SF-36v2 Physical Component Summary (PCS) 46 [37-54], and SF-36v2 Mental Component Summary (MCS) was 46 [36-55]. (Supplementary material 4)

Feasibility

Feasibility of structure indicators was generally high (overall more than 98% available data). Feasibility was low for one process indicator: 'mechanical DVT prophylaxis within 24 hours' (43% available data). Feasibility was high for outcome indicators, except for the SF-36 MCS and PCS scores (28% available data) collected after 6 months (due to loss to follow-up). (Supplementary material 2-4)

Overall, one process and one outcome indicator showed low feasibility (Table 2)

Discriminability

Variation in scores between centres was low for structure indicators (with little room for improvement) for 'existence of a protocol', 'availability of a neurosurgeon 24/7 within 30 minutes after call', and '24/7 availability of a CT scan and radiologist review', due to high overall adherence rates among centres (Supplementary material 2). For process indicators, high variation was found for all indicators (all MORs above 1.5, all $p < 0.001$) except for 'surgery within 4 hours in patients with SDH or EDH' (Figure 1).

For outcome indicators, the between-centre variation was significant as well. The variation between centres was especially high for ventilator acquired pneumonia (VAP) with a MOR of 4.12. Little between-centre variation on the 6-months GOSE was found (MOR= 1.29, p=0.5) (Figure 2).

Table 1: Baseline centre–and patient characteristics

Centre characteristics	Centre-level (N=54)			Patient-level (N=2006)	
	N	%		N	%
Centre					
Academic	51/54	94%		1901/2006	95%
Nonacademic	3/54	6%		105/2006	5%
Centre location [a]					
Urban	53/54	98%		1990/2006	99%
Suburban	1/54	2%		16/2006	1%
Trauma designation [b]					
Level I	37/54	69%		1468/2006	73%
Level II	4/54	7%		84/2006	4%
Level III	1/54	2%		135/2006	7%
No designation/NA	12/54	22%		319/2006	16%
Electronic patient records at the ICU					
Yes	42/54	78%		1690/2006	84%
No	12/54	22%		316/2006	16%
Location [c]					
Northern Europe	20/54	37%		650/2006	33%
Western Europe	19/54	35%		809/2006	40%
Southern Europe	12/54	22%		524/2006	26%
Eastern Europe	2/54	4%		22/2006	1%
Israel	1/54	2%		1/2006	0%
Patient characteristics	**Centre-level (N=54)**			**Patient-level (N=2006)**	
	Median %	IQR	min-max	N	%
Age (years) [d]					
Adults (>= 18 <65 years)	74	63-84	0-100	1454/2006	72%
Elderly (>= 65 years)	26	16-37	0-100	552/2006	28%
Gender					
Male	76	67-83	55-100	1479/2006	74%
Female	25	19-33	6-46	527/2006	26%
TBI severity (GCS) [e]					
Mild 13-15	34	22-43	5-100	671/1891	35%
Moderate 9-12	17	11-21	4-38	305/1891	16%
Severe 3-8	53	40-61	18-100	915/1891	48%
ISS score					
< 16	7	3-14	1-24	76/1963	4%
>=16	100	96-100	76-100	1887/1963	96%
AIS [f]					
Thorax/chest >=3	33	20-40	8-100	654/2006	33%
Abdomen/pelvis >=3	9	6-13	1-33	173/2006	9%
Cause of injury					
Road traffic incident	45	35-55	0-68	849/1921	44%
Incidental fall	40	33-50	11-100	802/1921	42%
Violence/assault	2	0-7	0-43	83/1921	5%
Suicide attempt	0	0-3	0-20	44/1921	2%
Other	6	0-11	0-38	143/1921	7%

This table describes the centre characteristics (at centre-level) and the entire ICU population (patient-level).
a) Urban: A hospital location very near to a city and situated in a crowded area.
Suburban: between urban and rural (an hospital location in or very near to the countryside in an area that is not crowded.)
b) Location is based on United Nations geoscheme: Northern Europe = Norway (*N* = 163), Sweden (*N* = 87), Finland (*N* = 132), Denmark (*N* = 3), the United Kingdom and Ireland (*N* = 271), and Baltic States: Latvia (*N* = 10), Lithuana (*N* = 23); Western Europe = Austria (*N* = 109), Belgium (*N* = 193), France (*N* = 115), Germany (*N* = 87), and the Netherlands (*N* = 359); Southern Europe = Serbia (*N* = 10), Italy (*N* = 293) and Spain (*N* = 195); Eastern Europe = Romania (*N* = 3), Hungary (*N* = 20);
c) Level I trauma centre: A regional resource centre that generally serves large cities or population-dense areas. A level I trauma centre is expected to manage large numbers of severely injured patients (at least 1,200 trauma patients annually or have 240 admissions with an Injury Severity Score of more than 14). It is characterized by 24-hour in-house availability of an attending surgeon and the prompt availability of other specialties (e.g. neurosurgeon, trauma surgeon).
Level II trauma centre: A level II trauma centre provides comprehensive trauma care in either a population-dense area in which a level II trauma centre may supplement the clinical activity and expertise of a level I institution or occur in less population-dense areas. In the latter case, the level II trauma centre serves as the lead trauma facility for a geographic area when a level I institution is not geographically close enough to do so. It is characterized by 24-hour in-house availability of an attending surgeon and the prompt availability of other specialties (e.g. neurosurgeon, trauma surgeon).
Level III trauma centre: A level III trauma centre has the capacity to initially manage the majority of injured patients and have transfer agreements with a level I or II trauma centre for seriously injured patients whose needs exceed the facility's resources.
d) The number of centres that admitted children was 27, therefore the distribution and median is skewed towards 1%. One centre included 1 patient that was an elderly person (therefore max =100%)
e) GCS at baseline: Post stabilization value, if absent prehospital values are used. Intubated/ untestable verbal (V) scores are treated as unknown
f) AIS score of 3 or more reflects serious extracranial injury
AIS: Abbreviated Injury Scale, GCS: Glasgow Coma Scale, ICU: Intensive Care Unit, ISS: Injury Severity Scale, NA: not applicable, TBI: Traumatic Brain Injury

Overall, 5 structure (3 with moderate performance), 2 process, and 4 outcome indicators showed low discriminability. (Table 2)

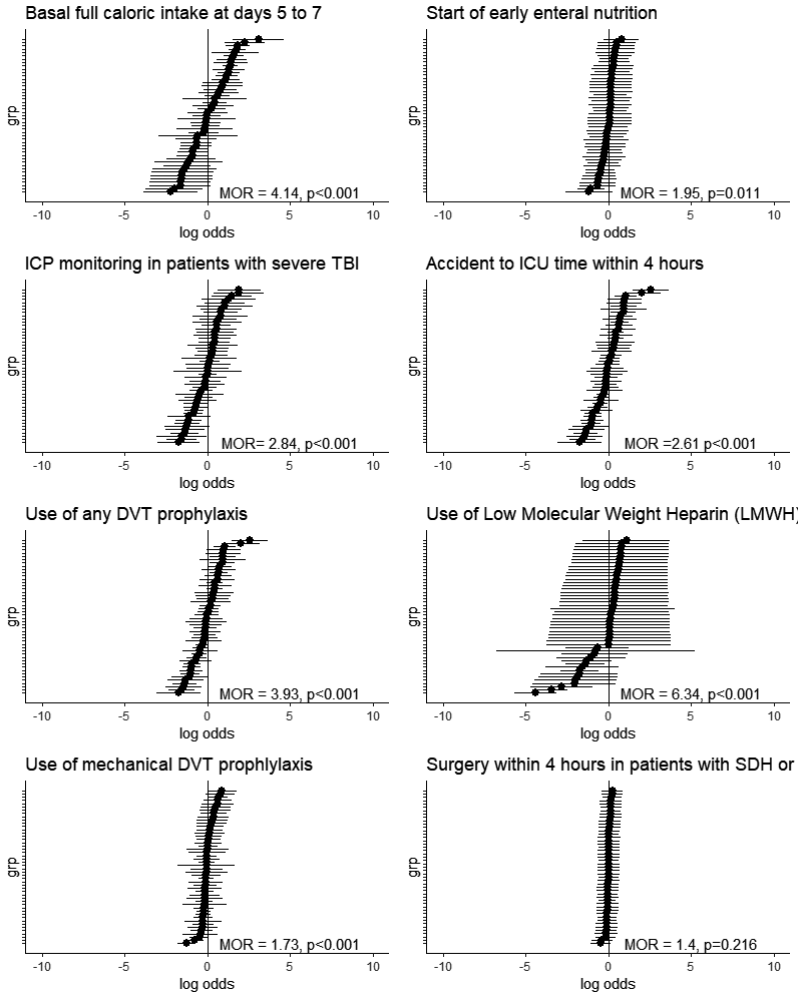
Statistical uncertainty

Four indicator definitions were slightly changed without changing its content (Supplementary material 3 and 4, bold definitions). Median event rates for the outcome indicators hyperglycemia, ICU mortality and Ventilator Associated Pneumonia (VAP) were respectively 8, 4, and 3 events per centre. Median event rates for hypoglycemia and decubitus were zero. All these event rates reflect high statistical uncertainty. (Supplementary material 4)

Discussion

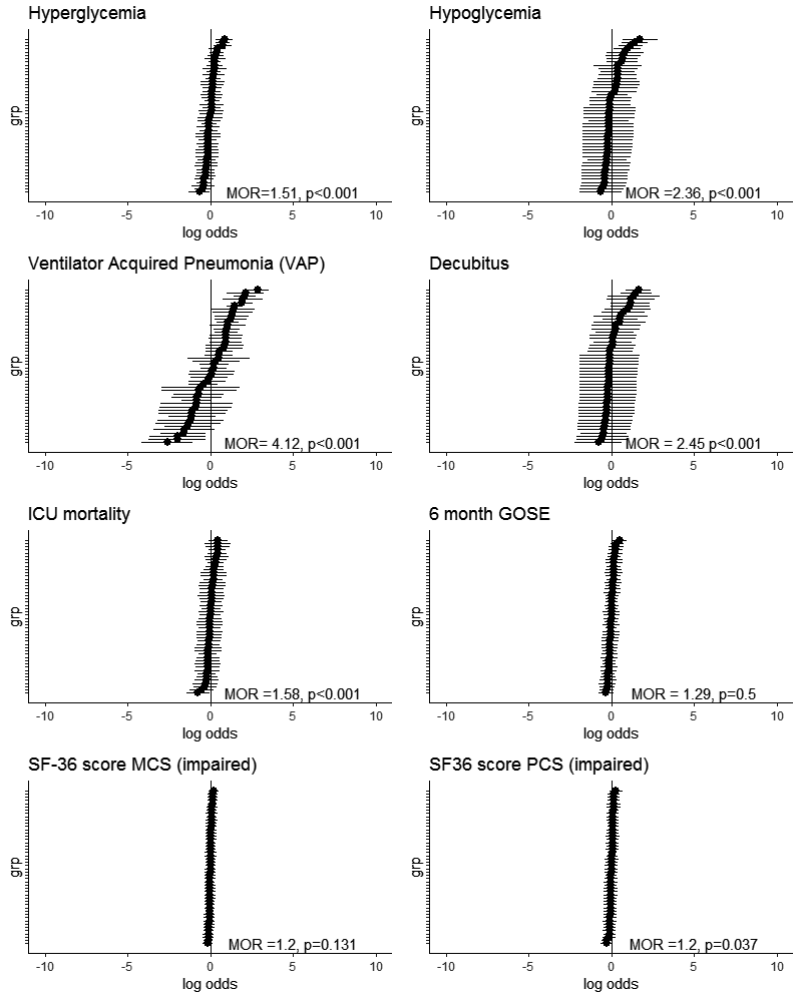
We showed that it was feasible to obtain most quality indicators from a recently proposed, consensus-based, quality indicator set for traumatic brain injury (TBI) at the ICU based on sufficient data completeness. The suboptimal adherence scores in combination with

Figure 1: Adjusted random effect estimates per centre for process indicators



Legend figure 1: This figure shows the between-centre differences for the process indicators (beware of different x-axis). Quality indicator definitions can be found in Supplemental material 3. On the y-axis each dot represents a centre. A centre with an average indicator score has log odds 0 (a positive log odds indicates higher indicator scores and a negative log odds lower indicator scores). The between-centre differences are represented by the shape of the caterpillar plots; the variation in the log odds for individual centres and the corresponding confidence intervals (uncertainty). For example, the use of ICP monitoring shows large variation between centres with small confidence intervals, so there is high variation with low statistical uncertainty. While for use of low molecular weight heparin the variation is large, but the statistical uncertainty is high as well (due to high adherence rates for most centres). The catterpillars were based on non-missing data (after imputation).
'Use of Low Molecular Weight Heparin' reflects the indicator 'Number of patients that receive pharmaceutical prophylaxis with low molecular weight heparins/ total number of TBI patients admitted to the ICU'
'Surgery within 4 hours' reflects the indicator 'Median door-to-operation time for acute operation of SDH and EDH with surgical indication'
DVT: deep venous thrombosis, EDH: epidural hematoma, ICU: Intensive Care Unit, MOR: median odds ratio, SDH: subdural hematoma

Figure 2: Title: Adjusted random effect estimates per centre for outcome indicators



Legend figure 1: This figure shows the between-centre differences for the outcome indicators. Quality indicator definitions can be found in Supplemental material 4. On the y-axis each dot represents a centre. A centre with an average indicator score has log odds 0 (a positive log odds indicates higher indicator scores and a negative log odds a lower indicator scores). Outcome indicator scores were adjusted for case-mix and 'statistical uncertainty' (variation by chance) by using a random effects logistic regression model. The MOR (Median Odds Ratio) represents the between-centre variation: the higher the MOR, the larger the between-centre variation (a MOR equal to 1 reflects no variation). The confidence intervals represent the statistical uncertainty. The catterpillars were based on non-missing data (after imputation). Outcome incidence for decubitus and hypoglycemia were too low to reliably show between-centre variation (high confidence intervals). Impaired SF-36v2 (PCS or MCS) score <=40, CI: Confidence Interval, GOSE: Glasgow Outcome Scale Extended, ICU: Intensive Care Unit, MOR: Median Odds Ratio

Table 2: Overview of indicator performance

	Feasibility	Discriminability	
Panel A. Structure indicators	**% available data**	**adherence score**	
1. The existence of a protocol including specific guidelines (like the BTF guidelines or institutional guidelines) for Traumatic Brain Injury patients (yes/no)	98%	89%	
2. The presence of (some form of) regular audits to check guideline adherence in general at the Intensive Care Unit (ICU) (yes/no)	98%	30%	
3. The presence of dedicated person(s) to oversee guidelines development and maintenance, including those for patients with TBI, at the ICU (yes/no)	98%	83%	
4. Does your hospital have a dedicated/specialized neurocritical care unit? (yes/no)	100%	65%	
5. The availability of operating rooms 24 hours per day (yes/no)	100%	74%	
6. The presence of a step down unit where patients can still be monitored 24/7, but less intensively than at the ICU (yes/no)	100%	70%	
7. Intensivist to ICU bed ratio 1 to <6	100%	50%	
8. ICU nurse to ICU bed ratio 1 to <1.75	100%	26%	
9. Do you have a protocol for glucose management available for patients with TBI at your ICU? yes/no	98%	81%	
10. Availability of a neurosurgeon (staff) 24/7 within 30 minutes after call (yes/no)	100%	91%	
11. 24/7 availability of a CT scan and radiologist review (yes/no)	100%	93%	
	Feasibility	**Discriminability**	
Panel B. Process indicators	**% available data**	**adherence score**	**IQR|MOR**
12. Number of TBI patients with basal full caloric replacement within 5 to 7 days post-injury / number of TBI patients at the ICU at day 5 to 7	100%	20%	44 |4.14
13. Median accident-to-ICU-admission time (reference 0-<4 hours)	99%	35%	26|2.61
14. Number of severe (GCS 3-8) TBI patients with ICP monitoring/ number of severe TBI patients at the ICU Data: baseline GCS	100%	69%	38|2.84
15. Number of patients with TBI that receive any DVT prophylaxis [a]/ total number of patients with TBI at the ICU	97%	80%	34|3.93
16. Number of patients that receive pharmaceutical prophylaxis with low molecular weight heparins/ total number of TBI patients admitted to the ICU that receive pharmaceutical DVT prophylaxis	97%	63%	29|2.6
17. Number of patients with TBI that receive mechanical DVT prophylaxis (e.g. stockings) initiated within 24 hours after ICU admission / total number of patients with TBI at the ICU with the possibility to receive stockings	43%	71%	41|1.73

18. Number of TBI patients with start of (early) enteral nutrition within 72 hours post-injury/ number of patients with enteral feeding during ICU	78%	99%	13|1.95
19. Median door-to-operation time for acute operation of SDH and EDH with surgical indication (reference 0-<4 hours)	100%	64%	29|1.4 [c]
	Feasibility	**Statistical uncertainty***	**Discriminability**
Panel C. Outcome indicators	**% available data**	**Event rates**	**IQR|MOR**
20. Number of TBI patients with any blood glucose above 10 mmol/L (180mg/dL, hyperglycemia)/total number of patients with TBI at the ICU	93%	8/22	23|1.51
21. Number of TBI patients with any blood glucose below 4 mmol/L (hypoglycemia)/ total number of patients with TBI at the ICU	93%	0/22	3| 2.36 [b]
22. Number of ICU-deaths among patients with TBI/ total number of ICU-admitted patients with TBI	99%	4/22	12|1.58
23. Incidence of ventilator associated pneumonia (VAP) in patients with TBI/ total number of TBI patients with mechanical ventilation at the ICU	98%	3/20	31|4.12
24. Number of TBI patients with decubitus at the ICU / number of TBI patients at the ICU	98%	0/22	2| 2.45 [b]
25. The median score of the GOSE from all patients with TBI at 6 months	86%	NA	4 (score)|1.29 [c]
26. The median score of the SF-36 from all patients with TBI at 6 months/ number of patients with TBI discharged from the ICU and alive at 6 months - Physical health - Mental health	28%	NA	17 (score)| 1.2 [c] 19 (score)| 1.2

This table gives an overview of the performance of indicators based on the main results of this study. The colors indicate poor (red), moderate (orange), or good (green) performance on feasibility, discriminability (adherence rates or between-centre variation). The adherence rates and event rates are shown as the median indicator scores across centres. For determination of the feasibility we calculated the amount of available data at patient-level.

Discriminability is determined by adherence rates and between-centre variation: high adherence rates for structures and processes is considered as low discriminability. Discriminability is also reflected in the IQR (unadjusted) and the MOR (adjusted for case-mix and random variation). For outcome indicators the statistical uncertainty (median number of events) was determined.

Feasibility: we determined that >70% available data reflects good performance

Discriminability: the potential for quality improvement was determined by the percentage adherence of centres to structure and process indicators (i.e. with high adherence rates, quality of care cannot be improved that much). We set the threshold for moderate potential for quality improvement at 80-90% and for poor potential at 90%-100%. In addition, we considered a low (unadjusted) interquartile range on scores (IQR<10) or non-significant (adjusted) between-centre differences as poor performance.

* Statistical uncertainty for outcome indicators (the less complications the better the quality of care) was determined by the median number of events/median number of included patients per centre. We set the threshold for poor potential at less than 10 events.

a) Pharmaceutical or mechanical, b) Based on the IQR, c) Based on non-significant between-centre differences

BTF: Brain Trauma Foundation, DVT: Deep Venous Thrombosis , EDH: Epidural hematoma, GCS: Glasgow Coma Scale, ICU: Intensive Care Unit, GOSE: Glasgow Outcome Scale Extended, IQR: Interquartile range, MOR: median odds ratio, OR: Odds Ratio, SDH: Subdural hematoma, TBI: Traumatic Brain Injury

between centre-variation suggest a potential for quality improvement, specifically for process and outcome indicators. However, statistical uncertainty was generally high for outcome indicators, making them less suitable for quality improvement purposes, and benchmarking in particular. Based on the assessment of feasibility, discriminability, and statistical uncertainty, we found 9 structure indicators, 5 process indicators, but none of the outcome indicator out of 26 indicators to be appropriate for quality measurement and improvement in this validation study. Overall, quality of ICU care can be improved for patients with TBI, and our analysis provides a useful case of how quality indicators for ICU care in TBI can be evaluated in a large database.

To our knowledge, this is the first quality indicator set to be developed and validated in adult patients with TBI admitted to the ICU. We have summarized quality indicators with the potential to be used for benchmarking and quality improvement. First, we recommend reducing the initial set by excluding indicators with a low percentage available data (low feasibility), in a given dataset. The low feasibility on some process indicators might be explained by the complexity and high resource needs of collecting data on process indicators. However, feasibility could be improved with automatic data extraction in the future. Second, quality indicators with high between-centre variation (most quality indicators in this study) and suboptimal adherence rates (discriminability) can be used to improve quality of care and for benchmarking. Third, event rates of outcome indicators were generally low (even over a study duration of four years), indicating that outcome indicators have a low potential for quality improvement in this study population due to high statistical uncertainty. However, the threshold of 10 events might be too strict , or alternatively outcome indicator denominators should be restricted to patients with more severe injury, greater organ dysfunction, more interventions, or a longer length of stay to increase the number of events and to increase statistical power. Over time, registration and use of the quality indicators could provide further insights into their role in quality improvement and benchmarking, and allow their re-evaluation and refinement.

Quality of care in critically ill patients with TBI could potentially be improved in various areas, as indicated by a sub-optimal adherence of European ICUs to most quality indicators. The large (adjusted) between-centre variation suggests that some centres significantly outperform others. Wide sharing of best practice and implementation strategies from centres that perform well on quality indicators describing structures and processes of care, and/or registering a low incidence of adverse outcomes could improve performance in centres that perform less well.

Previous studies also report large between-centre differences in processes of TBI care across Europe[24-26]. This between-centre variation could be explained by variation in adherence to guidelines. Although 89% of centres indicated that they complied with the Brain Trauma

Foundation (BTF) guidelines, actual assessment of real-time practice may be different. For example, ICP monitoring in patients with severe TBI (GCS<9) is one of the higher-level evidence recommendations in the BTF guidelines, but we only found adherence rates of 44-82% (IQR) across centres in our study. This implies that there is much to gain in reduction of variation in evidence-based care processes. One previous study reported performance of quality indicators in children with TBI [27]. Although their indicators differed from those in the current study, they found a lower variation in adherence rates (between 68% and 78%). Several registries already exist for general ICU [3, 5] – or trauma care [2, 4]. Some of the outcome indicators we tested are also used in current ICU registries, but did not perform well in our study (decubitus ulcers and hypoglycemia). For example, in our study the outcome score for decubitus ulcers approached 0%, while in Dutch hospitals decubitus was found in around 6% of patients [16].

This study has several strengths. First, we tested the potential of consensus-based quality indicators in a large clinical data set, while most previous studies only report a Delphi study to develop quality indicators and only a few studies pilot-tested quality indicators before implementation [28, 29]. Second, the indicator scores were derived from the CENTER-TBI database, which includes a substantial number of patients with TBI across many ICUs. Indeed, this analysis provides the first opportunity to study indicator performance and between-centre variation in TBI management on a larger scale. The CENTER-TBI database has only one exclusion criterion, so it represents a cohort generalizable to the TBI population across Europe.

Our study also has some limitations. Staffing and organizational data were only partly captured in CENTER-TBI. The structure indicators were based on questionnaires which might be imprecise. Patients of all severities (including early deaths) were included for analyses. We recognize that a selection of patients with a longer ICU stay may have increased between-centre comparability, but we mitigated this issue by correcting all between-centre analyses for case-mix severity. We defined feasibility as the completeness of the data, while other aspects of feasibility, such as accessibility, timeliness, and missing data at center-level could not be addressed [30]. Statistical uncertainty was reflected in the number of event rates, while also other aspects as intra- and inter rater reliability of medical coders are important but could not be addressed. We decided not to test the construct (correlations between indicators) and criterion validity (association with outcome) of the final indicator set as these are hard to test [31];]; for construct validity predetermined correlations between quality indicators are hard to find between different aspects of processes of care and often do not correlate with outcome; and for criterion validity the case-mix adjustment would differ per quality indicator and even very complex models cannot adjust for all residual bias (unmeasured confounding). However, ongoing evaluation of these quality indicators in larger datasets could include assessment of such correlations with outcome.

Future implementation of the quality indicators in a European registry will make it possible to monitor TBI patient data over time and among countries. Feedback from this registry to individual ICUs is essential to make stakeholders aware of their centre performance and help develop internal quality improvement programs. No reference standards for the quality indicators have been defined. Our study also illustrates some pitfalls, since some of these indicators are quite complex and difficult to assess retrospectively. Such data collection could, however, be optimized by routine registration of timing of events and processes, automatic data extraction, and clear definitions. Overall, the methods illustrated in this study can be used to optimize future data collection (with uniform indicator definitions and data quality), to calculate quality indicators (adjusted across centres) and to identify areas in need of further research (due to high variation).

Conclusions

This study validated a consensus-base quality indicator set in a large prospective TBI study (CENTER-TBI). Quality of care in critically ill patients with TBI appears amenable to improvement in various areas as indicated by sub-optimal adherence rates, and between-centre variation for many quality indicators. Further, our analysis generally shows good feasibility and discriminability, but high statistical uncertainty for several outcome indicators. Future research should focus on implementation and quality improvement efforts and continuous reevaluation of the quality indicators.

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Supplementary material 1

Table 1: Exclusion of Delphi quality indicators for application to the CENTER-TBI data

Indicator	Reason for exclusion
Structure indicators	
1. Certified intensivist present in person 7 days a week during at least day-time (yes/no)	1
2. Information on prognosis discussed with family by one of the treating physicians (ICU physician or neurosurgical physician) at least once during ICU stay	2
3. A daily meeting between intensivist and neurosurgeon to discuss patients with TBI at the ICU (yes/no)	2
4. Total number of disciplines (i.e. neurologist, physiotherapy, occupational therapy) involved during ICU stay	1
5. 24/7 availability of a certified person at your centre that can insert an ICP monitor within 2 hours after admission at the ICU (yes/no)	2
6. The presence of a protocol/ institutional guideline that provide indications for surgery with SDH an EDH (yes/no)	1
Process indicators	
7. Number of assessments of delirium presence with validated screening tool conscious TBI patients / total number of ICU days in conscious TBI patients	2
8. Number of patients with TBI visited daily by a physiotherapist during ICU stay/ total number of patients with TBI at the ICU	2
9. Number of patients with TBI receiving follow-up by a specialist within 2 months after discharge/ total number of patients with TBI discharged (not in rehab clinic)	1
10. Number of visits by a neurosurgeon/ total number of ICU days in patients with TBI	2
11. Number of patients with a support plan (e.g. rehabilitation) after ICU discharge/ number of patients discharged from the ICU	2
12. Number of assessments of motor scores of the GCS/ total number of ICU days in patients with TBI	3
13. Number of assessments of pupillary responses/ total number of ICU days in patients with TBI	3
14. Number of patients with neuropsychological testing at hospital discharge/ number of patients with TBI discharged from the hospital	3
Outcome indicators	
15. Number of EVD infections in patients with TBI/ total number of patients with TBI at the ICU with an EVD inserted	1
16. Number of patients with TBI with severe sepsis or septic shock/ total number of patients with TBI at the ICU	1
Reasons for exclusion 1) No identical definition between CENTER-TBI database and quality indicator, 2) Underlying variables not reported in study, 3) data collection for the CENTER-TBI study is different from routine data collection in clinical practice, which impacted on the absolute values of the QI (numerator and/ or denominator), invalidating the QI result.	

Description: This table describes the consensus-based quality indicators (from the Delphi study) that could not be applied to the CENTER-TBI dataset for various reasons

Supplementary material 2

Table 2: Structure indicator scores

	Centre-level (N=54)		
Structure indicators	Number of centres (N)	Missing (N)	Indicator scores Complete cases(%)
1. The existence of a protocol including specific guidelines (like the BTF guidelines or institutional guidelines) for Traumatic Brain Injury patients (yes/no)	47	1	89%
2. The presence of (some form of) regular audits to check guideline adherence in general at the Intensive Care Unit (ICU) (yes/no)			
- Once in the last 5 years	14		26%
- Annually	1		2%
- Several times per year	1		2%
- Overall	16	1	30%
3. The presence of dedicated person(s) to oversee guidelines development and maintenance, including those for patients with TBI, at the ICU (yes/no)			
- Individual	11		21%
- Group	33		62%
- Overall	44	1	83%
4. Does your hospital have a dedicated/specialized neurocritical care unit? (yes/no)	35	0	65%
5. The availability of operating rooms 24 hours per day (yes/no)	40	0	74%
6. The presence of a step down unit where patients can still be monitored 24/7, but less intensively than at the ICU (yes/no)	38	0	70%
7. Intensivist to ICU bed ratio 1 to			
- 0-5	27		50%
- 6-10	22		41%
- >10	5	0	9%
8. ICU nurse to ICU bed ratio 1 to			
- 0-<1	14		26%
- 1-2	23		43%
- >2-3	17	0	31%
9. Do you have a protocol for glucose management available for patients with TBI at your ICU? yes/no	43	1	81%
10. Availability of a neurosurgeon (staff) 24/7 within 30 minutes after call (yes/no)	49	0	91%
11. 24/7 availability of a CT scan and radiologist review (yes/no)	50	0	93%

This table shows the indicator scores of all centres for the structure indicators at both centre and patient-level. Regarding structure indicators, the missing data is a measure for feasibility and the indicator score for discriminability (the percentage of centres that indicated yes compared with no). For the denominator of the indicator scores the total number of centres ($N = 54$) and admitted patients ($N = 2138$) is taken. The complete cases takes the missing data into account. Structure indicators are extracted from the Provider Prefilling database for those centres that participating in the CENTER-TBI study.
BTF: Brain Trauma Foundation, ICU: Intensive Care Unit, TBI: traumatic brain injury

Supplementary material 3

Table 3: Process indicator scores

	Centre-level (N=54)			Patient-level (N=2138)			
		Complete cases		Denom		Complete cases	
	Nr of centres	Median scores	IQR (%)	Nr of patients	Missing	Indicator scores	
Process indicators	(N)	(%)	(Q1-Q3)	(N)	(%)	Num/denom	(%)
1. Number of TBI patients with basal full caloric replacement within 5 to 7 days post-injury / number of TBI patients at the ICU at day 5 to 7 **post-injury**							
Data: 1500/day females or 1750/day males [a]	39	20%	3-47	1084	0%	314/1084	29%
2. Median accident-to-ICU-admission time (hours)							
0-≤4	50	35%	24-50			820/1980	42%
4-≤8	50	41%	30-50			744/1980	37%
>8	51	21%	10-32	2006	1%	416/1980	21%
3. Number of severe (GCS 3-8) TBI patients with ICP monitoring/ number of severe TBI patients at the ICU							
Data: baseline GCS [b]	50	69%	44-82	915	0%	559/915	61%
4. Number of patients with TBI that receive any DVT prophylaxis [c]/ total number of patients with TBI at the ICU							
Any prophylaxis [c]	50	80%	60-94		3%	1472/1950	75%
Mechanical	43	40%	6-71		5%	853/1905	45%
Pharmaceutical	50	65%	54-83		3%	1279/1951	66%
Extra: timing within 72 hours	47	38%	25-81	2006	36%	639/1274	50%
5. Number of patients that receive pharmaceutical prophylaxis with low molecular weight heparins/ total number of TBI patients admitted to the ICU	47	63%	49-78	2006	3%	1244/1948	64%

	Centre-level (N=54)			Patient-level (N=2138)			
		Complete cases		Denom		Complete cases	
	Nr of centres	Median scores	IQR (%)	Nr of patients	Missing	Indicator scores	
Process indicators	(N)	(%)	(Q1-Q3)	(N)	(%)	Num/denom	(%)
6. Number of patients with TBI that receive mechanical DVT prophylaxis (e.g. stockings) initiated within 6 hours **after ICU admission** / total number of patients with TBI at the ICU with the possibility to receive stockings							
Data: initiated within 24 hours	38	71%	50-91	1905	57%	558/821	68%
7. Number of TBI patients with start of (early) enteral nutrition within 72 hours **post-injury**/ number of patients with enteral feeding during ICU	51	99%	87-100	1109	22%	806/ 867	93%
8. Median door-to-operation time for acute operation of SDH and EDH with surgical indication (hours)							
0-≤4							
5-≤8	47	64%	50-79			237/377	63%
>8	33	15%	0-25			60/377	16%
Data: acute operation < 24 hours	30	18%	0-28	377	0%	80/377	21%

This table shows the indicator scores for the process indicators at both centre- and patient-level.
At centre-level, the number of centres represents the number of centres that adhered to the indicator (excluding centres with missing data). For all centres (also non adherent), the median indicator score and IQR is shown (for centres with data available). At patient-level, the indicator scores of complete cases shows the indicator scores taking missing data into account (therefore denominators reflect complete cases). The missing data at patient-level represents the feasibility of an indicator, the IQR and range at centre-level the discriminability. Process indicators are calculated from the CENTER-TBI database. **Bolt indicator definitions** were adjusted as felt more appropriate compared with the definition of the Delphi study, based on the actual data available.
a) Available data/ variable from the CENTER-TBI database b) GCS at baseline: Post stabilization value, if absent prehospital values are used. Intubated/ untestable verbal (V) scores are treated as unknown c) Mechanical or pharmaceutical DVT prophylaxis
Denom: denominator (eligible patients), EDH: Epidural hematoma, ICU: Intensive Care Unit, IQR: Interquartile range, Num: numerator, SDH: subdural hematoma, TBI: traumatic brain injury

Supplementary material 4

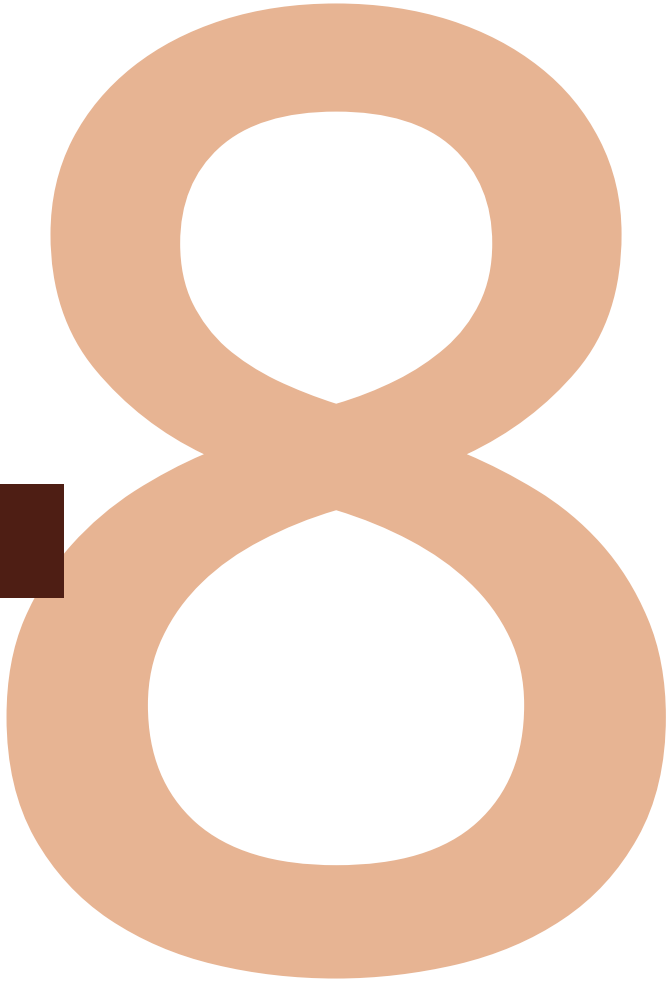
Table 4: Outcome indicator scores

	Centre-level (N=54)			Patient-level (N=2138)			
		Complete cases		Denom		Complete cases	
	Nr of centres	Median scores	IQR (Q1-Q3	Nr of patients	Missing	Indicator scores	
Outcome indicators	(N)	(%)	(%)	(N)	(%)	Num/denom	(%)
1. Number of TBI patients with any blood glucose above 10 mmol/L (180mg/dL, hyperglycemia)/total number of patients with TBI at the ICU [a]	50	35%	22-45	2006	7%	696/1867	37%
2. Number of TBI patients with any blood glucose below 4 mmol/L (hypoglycemia)/ total number of patients with TBI at the ICU [a]	21	0%	0-3	2006	7%	59/1808	3%
3. Number of ICU-deaths among patients with TBI/ total number of ICU-admitted patients with TBI	46	12%	9-21	2006	1%	266/1982	13%
4. Incidence of ventilator associated pneumonia [b] (VAP) in patients with TBI/ total number of TBI patients with mechanical ventilation at the ICU	38	14%	0-31	1432	2%	249/1410	18%
5. Number of TBI patients with decubitus grade 2 or higher at the ICU [c]/ number of TBI patients at the ICU	22	0%	0-2	2006	2%	45/1961	2%
6. The median score of the GOSE from all patients with TBI at 6 months/ number of patients with TBI discharged from the ICU and alive at 6 months	54	5	3-7	2006	14%	5	-

	Centre-level (N=54)			Patient-level (N=2138)			
		Complete cases		Denom		Complete cases	
	Nr of centres	Median scores	IQR (Q1-Q3	Nr of patients	Missing	Indicator scores	
Outcome indicators	(N)	(%)	(%)	(N)	(%)	Num/denom	(%)
7. The median score of the SF-36 from all patients with TBI at 6 months/ number of patients with TBI discharged from the ICU and alive at 6 months							
- Physical health [c]	54	46	37-54			45	
- Mental health [d]	54	46	36-55	1618	72%	45	-

This table shows the median percentage or indicator scores (incidence) of the outcome indicators. At centre-level, the number of centres represents the number of centres where the indicator occurs. For all centres (also non adherent), the median indicator score and IQR is shown. At patient-level, for the denominator of the indicator scores the number of patients in the denominator is taken, disregarding the missing data (denominators reflect complete cases).
The missing data at patient-level represents the feasibility of an indicator, the IQR and range at centre-level the discriminability. Outcome indicators are calculated from the CENTER-TBI database. **Bolt indicator definitions** were adjusted as felt more appropriate compared with the definition of the Delphi study
a) For available lab results b) No extensive definition available in the data, b) No grade available in the data (only yes/no) c) physical component summary d) Mental component summary
Denom: denominator (all eligible patients), EDH: Epidural hematoma, GOSE: Glasgow Coma Scale Extended, ICU: Intensive Care Unit, IQR: Interquartile range, mg/dL: miligrams per deciliter, mmol/L: millimoles per liter, Num: numerator, SDH: subdural hematoma, SF_36: Short Form (36) Health Survey, TBI: traumatic brain injury

CHAPTER 8



Use and impact of high intensity treatments in patients with traumatic brain injury across Europe: a CENTER-TBI analysis

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Abstract

Background: To study variation in, and clinical impact of high Therapy Intensity Level (TIL) treatments for elevated intracranial pressure (ICP) in patients with traumatic brain injury (TBI) across European Intensive Care Units (ICUs).

Methods: We studied high TIL treatments (metabolic suppression, hypothermia (<35oC), intensive hyperventilation ($PaCO_2$ <4 kPa), and secondary decompressive craniectomy) in patients receiving ICP monitoring in the ICU stratum of the CENTER-TBI study. A random effect logistic regression model was used to determine between-centre variation in their use. A propensity score-matched model was used to study the impact on outcome (6-months Glasgow Outcome Score-extended(GOSE)), whilst adjusting for case-mix severity, signs of brain herniation on imaging, and ICP.

Results: 313 of 758 patients from 52 European centres (41%) received at least one high TIL treatment with significant variation between centres (median odds ratio = 2.26). Patients often transiently received high TIL therapies without escalation from lower tier treatments. 38% of patients with high TIL treatment had favourable outcomes (GOSE > 5). The use of high TIL treatment was not significantly associated with worse outcome (285 matched pairs, OR: 1.4, 95% CI [1.0 -2.0]). However, a sensitivity analysis excluding high TIL treatments at day 1 or use of metabolic suppression at any day did reveal a statistically significant association with worse outcome.

Conclusion: Substantial between-centre variation in use of high TIL treatments for TBI was found and treatment escalation to higher TIL treatments were often not preceded by more conventional lower TIL treatments. The significant association between high TIL treatments after day 1 and worse outcomes may reflect aggressive use or unmeasured confounders or inappropriate escalation strategies

Background

Limiting the impact of secondary insults by controlling harmful levels of intracranial pressure (ICP) is an essential part of Traumatic Brain Injury (TBI) care in the intensive care unit (ICU). Interventions used to reduce ICP are typically titrated to balance their clinical effect against their side effects, which may be significant or even life-threatening. The intensity of such interventions can be quantified by the therapy intensity level (TIL) score. The TIL score was first introduced in 1987 [1], and has been revised over the years into a more advanced scoring system [2] which was recently validated [3]. Conceptually, the stepwise approach to treatment of raised ICP aims to use low tier therapies in the first instance, reserving more aggressive (and hazardous) high TIL treatments only for when these fail.

Despite this proposed framework for rational use of ICP therapies, past studies have found wide variations between centres in their deployment [4, 5]. Some of this variation may reflect either therapeutic nihilism or inappropriately aggressive use (as high intensity treatment can be clinically burdensome and consumes more ICU resources). While some studies report efficacy of high TIL therapies when properly targeted in terms of patient group and timing [6], other publications have given rise to concern that they may be ineffective in improving ultimate outcomes, and result in increased survival with severe disability [7], [8].

Therefore, the aim of this study is to investigate the variation in the use of high TIL therapies in clinical practice and explore the impact on clinical outcome in patients with TBI in European ICUs.

Methods

CENTER-TBI study/ study population

Data from the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study were used for this analysis (clinicaltrials.gov NCT02210221). CENTER-TBI recruited patients with TBI, presenting between December 19, 2014 and December 17, 2017 [9, 10]. Inclusion criteria for the CENTER-TBI study were: A clinical diagnosis of TBI, an indication for brain computer tomography (CT) and presentation within 24 hours post-injury. Patients with severe pre-existing neurological disorders were excluded. For this study we selected patients of 14 years and older admitted to the ICU with documented daily measurements on the TIL scale for the first 7 days since admission to the ICU and with ICP monitoring.

Therapy Intensity Level

In the CENTER-TBI study, the most recent TIL scale is used [3] which measures and quantifies the intensity of ICP lowering treatments (and includes common data elements harmonized with the paediatric TIL scale [2]). The TIL scale consists of 8 ICP treatment modalities with corresponding scores for intensity, assessed daily [3] (Supplementary material 1). High intensity ICP-lowering treatment is indicated by the use of one or more of the four treatments representing maximum therapy intensity on the TIL scale: Barbiturates (or high dose sedation) for metabolic (e.g. burst) suppression, secondary decompressive craniectomy, intensive hyperventilation to $PaCO_2$ <4 kPa, and hypothermia <35 °C. We refer to patients who received any of these treatments at any point in time during their ICU stay as the 'high TIL' group. In addition, we excluded patients with decompressive craniectomy on day 1 (i.e. primary decompressive craniectomy) as such patients are likely to have a different pathophysiological trajectory and ICP therapy requirements due to a fundamental difference in intracranial compliance at the start of their ICU course. Such patients are also likely to be a distinct clinical entity (decompression at the time of space occupying lesion evacuation rather than for intractable intracranial hypertension) so their exclusion ensured a homogeneous population for a propensity score analysis. Maximum ICP prior to high TIL treatment (derived from 2 hourly measurements) was used as a measure of ICP burden.

Outcomes

Outcomes were collected at 6-months post-injury. Functional outcome was assessed on the Glasgow Outcome Scale-Extended (GOSE) using either an interview or questionnaire. Categories on the GOSE are: (1) Death, (2) Vegetative State, (3) Lower Severe Disability, (4) Upper Severe Disability, (5) Lower Moderate Disability, (6) Upper Moderate Disability, (7) Lower Good Recovery, and (8) Upper Good Recovery. Patients in categories (2) and (3) on the GOSE were combined in a single category. Health related quality of life (HRQOL) was assessed with the Short Form 36v2 (SF-36) and the Quality of Life after Brain Injury (QOLIBRI) scale. For the SF-36 the Physical Component Summary (PCS) and Mental Component Summary (MCS) are expressed as T-scores. The QOLIBRI Total score has a range from 0 to 100.

Statistical analyses

We stratified the high- and low TIL treatment group and described their baseline characteristics and outcome by frequency / percentages for categorical variables and by median and interquartile ranges (IQR) for continuous variables. Significant group differences were determined with the Chi-square or Fisher's exact test for categorical variables, and ANOVA or Kruskal Wallis test (non-normal distributions) for continuous variables.

Missing data was imputed using multiple imputation (100 imputations, 5 iterations) using the MICE package for R statistical software (version 3.6.0) [11]. The distribution of missingness per variable (prior to imputation) is shown in Supplementary material 2.

To calculate the between-centre variation in the use of high TIL therapies beyond that expected from case-mix severity and random variation, we used a random effects logistic regression model, with high TIL use as dependent variable and centre as random intercept. Covariates used were chosen from the extended International Mission for Prognosis and Analysis of Clinical Trials (IMPACT) prognostic model [12]. In addition, we adjusted for maximum recorded ICP values prior to high TIL treatment (as a surrogate for prior secondary injury and/or difficulty in achieving control), CT variables likely to be associated with the development of intracranial hypertension (brain herniation, cortical sulcus effacement, compression of one of more basal cisterns, midline shift and ventricular compression), as well as extracranial injury severity score (ISS; excluding the head injury component). Centre effects are expressed and plotted as random effects with corresponding confidence intervals at a log odds scale. We also quantified the between-centre variation with the median odds ratio (MOR): the MOR is a measure of the variance of the random effects [13]. The Nakagawa's R^2 for mixed models was calculated to determine the variance in high TIL treatment explained by the variables in the model.

In previous studies, the aggressiveness of TBI management has been quantified based on the percentage use of ICP monitoring in patients who satisfied Brain Trauma Foundation (BTF) guidelines requirements for such monitoring. In order to examine whether this definition of aggressiveness based on use of a monitoring modality actually translated into aggressive management, we examined whether the percentage use of ICP monitoring in centres was related to the random effects of the use of high TIL per in the centre.

Finally, to study the association between high TIL treatment use and outcome, a propensity score matched model was constructed. This analysis determines whether the application of any high TIL therapy resulted in incremental harm (aggressiveness of treatment) beyond that caused by ICP elevation and case-mix severity. The primary outcome was the Glasgow Outcome Score-extended (GOSE) at 6 months, dichotomized into favourable (GOSE>4) and unfavourable (GOSE≤4). We used the random effects logistic regression model above to determine propensity scores for high TIL use. We applied nearest neighbour matching to select patients with a similar propensity scores but different treatment status. We compared the baseline characteristics between matched cases (with no missing data) and tested group differences (should be non-significant) and calculated the standardized mean differences (which should be low) to check match validity. In the matched cases, we compared the result of high versus low TIL treatment using a logistic regression with 6-month unfavourable GOSE as primary outcome. Two sensitivity analyses were performed to check whether the treatments were applied appropriately as high TIL practice. The first of these excluded high TIL treatments on day 1 to more faithfully reflect escalation of ICP therapy and discard non-treatment confounds (for example, hypothermia on day 1 may be injury related). Secondly, we considered the possibility that the use of barbiturates may

have simply reflected therapy to target early / transient difficulties in controlling in ICP, rather than a sustained escalation of therapy. Consequently, the second sensitivity analysis excluded all barbiturate use as a high TIL treatment.

Analyses were performed using R statistical software [14]. The dataset was stored and accessed using the Opal [15] datamart. Dataset downloaded 06-02-2020 (Neurobot release 2.1)

Results

Baseline characteristics

A total of 758 patients from 52 centres in Europe received ICP monitoring with documented TIL measurements during their ICU stay (Figure 1). Of these, 313 patients (41.3%) received high TIL treatments at least once during their ICU stay. Table 1 summarises these groups. Patients who received high TIL treatment were generally younger, had better preinjury health status, and suffered from more severe brain trauma. Multimodal cerebral monitoring was generally more often used in high TIL patients.

Patients requiring high TIL treatment generally had longer ICU stays and had a longer duration of mechanical ventilation (Table 2). Overall, high TIL and low TIL patients were discharged from the ICU with similar GCS scores. The complication rate was similar in the two groups, except for metabolic complications (high TIL:14.0%, versus low TIL: 7.3% p=0.004) (abnormalities in renal or liver function and electrolyte derangements).

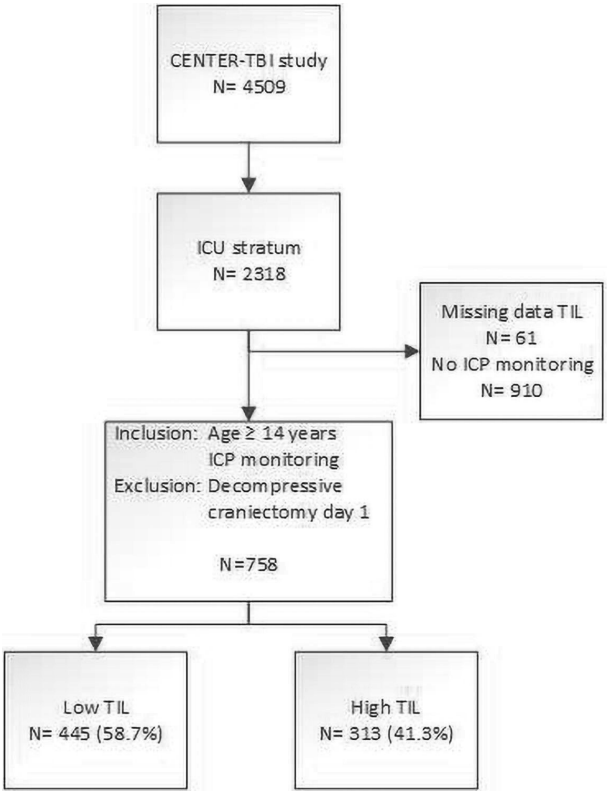
Patterns of high TIL therapy use

Of the 313 patients, most received metabolic suppression while a minority of cases received intensive hyperventilation, intensive hypothermia, or secondary decompressive craniectomy (Supplementary material 3). In general, TIL peaked after day 2, except for hypothermia (which was most commonly applied on day 1). In the majority of cases receiving high TIL treatment, head elevation, vasopressors and higher dose sedation had been used, but cerebrospinal fluid (CSF) drainage, hyperosmolar therapies, and being nursed flat were recorded only in a minority of instances. Mean TIL scores in the high TIL group were below 10 points.

Between centre variation

Our study included 52 centres from 18 countries in the CENTER-TBI study. The median number of patients per centre was 11.5 [IQR: 5-19]. Most centres used barbiturates (N= 46) while fewer centres used intensive hyperventilation (N= 21), hypothermia below 35°C (N=32), and decompressive craniectomy (N= 26). Based on treatment frequencies, there

Figure 1: Flowchart: patient inclusion



Legend figure 1: his flowchart is showing the inclusion of high TIL patients. High TIL patients were defined as patients receiving any treatment during ICU stay representing maximum therapy intensity of the TIL scale: Barbiturates for metabolic suppression, (secondary) decompressive craniectomy, intensive hyperventilation to PaCO2 <4 kPa, and hypothermia <35 °C at any point during their ICU stay.

was a high degree of between centre variation in treatment choice. Overall, significant between centre variation beyond case mix and random variation (p<0.001) was found in the use of high TIL treatments (MOR = 2.26). (Figure 2, Supplementary material 7). The Nakagawa's R^2 showed that model variables 'explained' 8.7% of the (pseudo)variance in high TIL treatment use. Comparing measures of aggressiveness, the percentage use of ICP monitoring in patients who satisfied BTF guidelines was not related to the use of high TIL therapies by the centre (Figure 3)

Impact of high TIL treatment on outcome

Although unfavourable outcome was more frequent in the high TIL group (62.5% versus 53.0%, p=0.019)- a high proportion of high TIL patients nevertheless achieved a favourable outcome at 6 months (GOSE ≥ 5: N= 105; 37.5%). Mortality was significantly higher in the

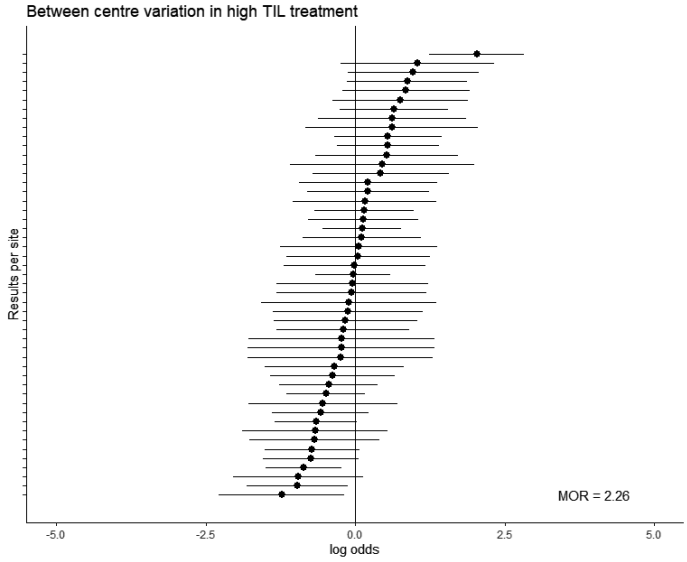
Table 1: Baseline patient and monitoring characteristics

	Low TIL (*N*=445)		High TIL (*N*=313)		*p*-value
Age (median, IQR)	51 [30.0-65.0]		41 [27.0-65.0]		<0.001
Gender, male (*N*,%)	326/445	(73.3)	235/313	(75.1)	0.632
Injury severity (GCS at baseline)					
Mild >=13 (*N*, %)	77/414	(18.6)	29/296	(9.8)	0.002
Moderate >=9–<13(*N*, %)	78/414	(18.8)	51/296	(17.2)	0.653
Severe <9 (*N*, %)	259/414	(62.6)	216/296	(73.0)	0.005
ISS without head injury (median, IQR)	10 [0.0-25.0]		13 [0.0-25.0]		0.286
CT (*N*,%)					
tSAH	306/367	(83.4)	228/253	(90.1)	0.023
EDH	73/366	(19.9)	58/254	(22.8)	0.443
Marshall (*N*, %)					
1	11/367	(3.0)	5/253	(2.0)	<0.001
2	168/367	(45.8)	94/253	(37.2)	
3	30/367	(8.2)	57/253	(22.5)	
4	8/367	(2.2)	5/253	(2.0)	
5	2/367	(0.5)	2/253	(0.8)	
6	148/367	(40.3)	90/253	(35.6)	
Preinjury ASA (*N*, %)					0.001
1) Normal healthy	230/428	(53.7)	194/296	(65.5)	
2) Mild systemic disease	144/428	(33.6)	88/296	(29.7)	
3) Severe systemic disease	51/428	(11.9)	13/296	(4.4)	
4) Severe systemic disease, a constant threat to life	3/428	(0.7)	1/296	(0.3)	
Cause of injury (*N*, %)					0.295
Road traffic incident	212/430	(49.3)	148/301	(49.2)	
Incidental fall	166/430	(38.6)	106/301	(35.2)	
Violence/assault	15/430	(3.5)	18/301	(6.0)	
Suicide attempt	10/430	(2.3)	4/301	(1.3)	
Other	27/430	(6.3)	25/301	(8.3)	
Prehospital [1] (*N*, %)					
Hypoxia	89/445	(20.0)	39/313	(12.5)	0.009
Hypotension	80/445	(18.0)	47/313	(15.0)	0.329
Lab [1] (median, IQR)					
Hemoglobin (g/dL)	13.1 [11.6-14.4]		13.2 [11.9-14.3]		0.694
Glucose (mmol/L)	7.9 [6.7-9.9]		7.8 [6.7-9.8]		0.933
Type ICP monitor (*N*, %)					0.511
Ventricular	53/445	(11.9)	38/312	(12.2)	
Ventricular + inbuilt sensor	7/445	(1.6)	10/312	(3.2)	
Parenchymal	366/445	(82.2)	250/312	(80.1)	
Other	19/445	(4.3)	14/312	(4.5)	
Multimodal cerebral monitoring (*N*, %)					
Jugular oximetry	9/445	(2.0)	20/312	(6.4)	0.004
Brain tissue $P_{bt}O_2$	84/445	(18.9)	65/312	(20.8)	0.555
Transcranial Doppler	34/444	(7.7)	78/312	(25.0)	<0.001
Microdialysis	48/445	(10.8)	30/311	(9.6)	0.700
Continuous EEG	21/445	(4.7)	38/311	(12.2)	<0.001
Electrocorticography	4/444	(0.9)	1/311	(0.3)	0.610

	Low TIL (*N*=445)		High TIL (*N*=313)		*p*-value
Systemic monitoring (N, %)					
Invasive blood pressure monitoring	432/445	(97.1)	306/312	(98.1)	0.530
Cardiac output	74/444	(16.7)	80/312	(25.6)	0.003
Pulse oximetry	436/445	(98.0)	303/312	(97.1)	0.600
End tidal CO_2	335/444	(75.5)	213/312	(68.3)	0.036
Central venous pressure	261/444	(58.8)	190/312	(60.9)	0.612
Mechanical ventilation					
Present	416/441	(94.3)	287/312	(92.0)	0.261

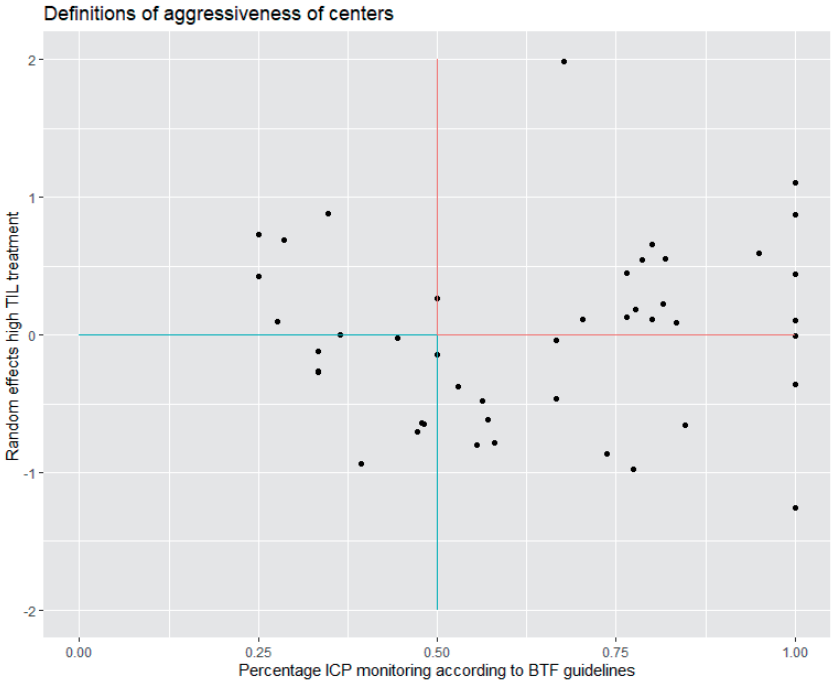
This table describes the baseline characteristics of patients with a high versus a low therapy intensity level (TIL). High TIL was defined as any high intensity treatment (decompressive craniectomy excluding day 1, barbiturates, intensive hypothermia, intensive hyperventilation) during the ICU stay. Significant group differences were determined by using the chi-square or Fisher's exact test (non-normal distributions) for categorical variables and an ANOVAS or Kruskal Wallis test (non-normal distributions) for continuous variables.
1) IMPACT, first available
ASA score: American Society of Anesthesiologists (ASA) Physical Status score, CO_2: carbon dioxide, CT: Computed tomography, CRBSI: catheter-related blood-stream infection EEG: electroencephalogram, GCS: Glasgow Coma Scale, ICP: intracranial pressure, ISS: injury severity score, IQR: interquartile range, $P_{bt}O_2$: brain tissue partial pressure of oxygen, TIL: therapy intensity level

Figure 2: Between-centre variation in high TIL use



Legend figure 2: this figure shows the between-centre variation in the use of high TIL (Therapy Intensity Level) treatment. The use of high TIL per centre was adjusted for case-mix severity, brain herniation on imaging, maximum ICP value at the day of the start of high TIL treatment and random variation per centre with a random effects logistic regression model. For each centre the random effect with corresponding 95% CI is plotted (average effect is log odds of zero). The MOR reflects the odds of high TIL treatment between two randomly selected centres for patients with the same case-mix severity (a higher MOR reflects larger between-centre variation) The MOR represents the median odds ratio; the higher the MOR the larger the between-centre variation (a MOR of 1 reflects no variation)

Figure 3: Definitions of aggressiveness



Legend figure 3: this figure illustrates the concordance between two definitions to identify aggressiveness of centers. On the x-axis is the definition of aggressiveness according to previous studies: the percentage of patients receiving ICP monitoring according to the BTF guidelines (GCS<8 and abnormal CT, or normal CT and 2 or more of the following: hypotension, age> 40 years, unilateral or bilateral motor posturing, or systolic blood pressure (BP) <90 mmHg). This percentage ICP monitoring was calculated in the ICU database (including all patients). On the y-axis is the definition of aggressiveness according to our study: the random effects of high TIL treatment per centers (log odds of receiving high TIL treatment). The upper right quadrant shows the centers that are both identified as aggressive by the previous definition (threshold 50% ICP monitoring) and the definition in our study (threshold random effect of zero).The lower left quadrant shows the centers that are identified as non-aggressive centers by both definitions. The two other quadrants show a discrepancy between the definitions of aggressiveness. Overall, there is no relationship between aggressiveness defined using ICP monitoring rates and actual use of aggressive therapies for ICP control.

high TIL group (20.2% versus 13.3%, p= 0.016) (Figure 4). The data on Health-Related Quality of Life (HRQOL) is less complete than the GOSE, since in addition to loss to follow-up there are no scores for patients who die. Both groups had similar scores on the SF-36v2 MCS and PCS and the QOLIBRI total score. (Table 2)

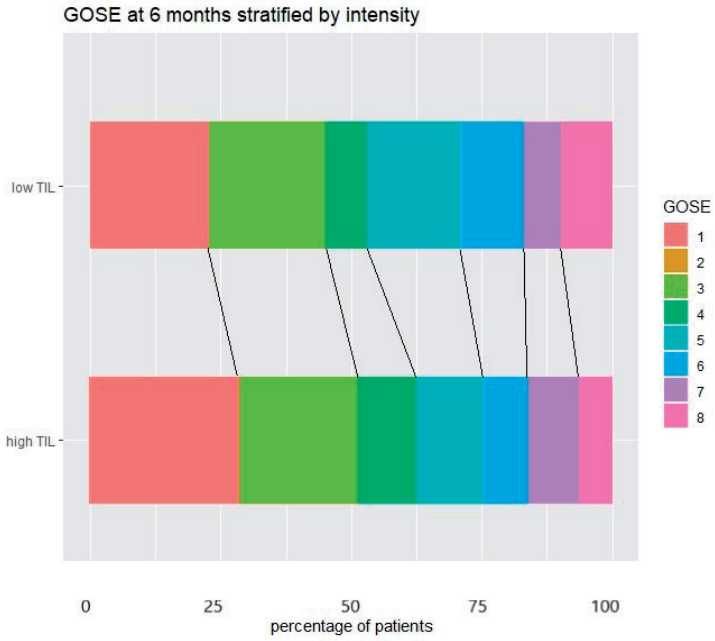
A total of 280 treated (high TIL) patients were well matched in terms of their baseline characteristics (Supplementary material 8) and maximum ICP prior to TIL treatment did not differ between groups (Supplementary material 9). With correction for maximum ICP prior to high TIL treatment; high TIL treatment was not significantly associated with unfavourable outcome (OR: 1.4, 95% CI [0.98 – 1.96], p=0.068). However, after the sensitivity analyses the

Table 2: Patient outcomes

	Low TIL (*N*=445)		High TIL (*N*=313)		*p*-value
General ICU outcomes (median, IQR)					
Length of ICU stay	11 [5.8-19]		17 [10-26]		<0.001
Duration of ventilation	8 [4.0-15]		14 [8-21]		<0.001
Time to obey commands	6 [2.0-11]		13 [7- 21]		<0.001
ICU systemic complications (*N*, %)					
Cardiovascular	52/441	(11.8)	34/307	(11.1)	0.853
CRBSI	20/441	(4.5)	7/307	(2.3)	0.154
DVT	5/441	(1.1)	7/307	(2.3)	0.351
Pulmonary embolus	10/441	(2.3)	5/307	(1.6)	0.728
Metabolic [1]	32/441	(7.3)	43/307	(14.0)	0.004
Pressure sores	20/441	(4.5)	15/307	(4.9)	0.962
Respiratory failure	156/441	(35.4)	123/307	(40.1)	0.219
VAP	107/441	(24.3)	85/307	(27.7)	0.332
UTI	36/441	(8.2)	30/307	(9.8)	0.527
Other	38/441	(8.6)	32/307	(10.4)	0.480
ICU discharge outcomes					
ICU mortality (*N*, %)	59/442	(13.3)	62/307	(20.2)	0.016
GCS discharge score					
Mild >=13 (*N*, %)	121/445	(27.2)	75/313	(24.0)	0.360
Moderate >=9–<13(*N*, %)	13/445	(2.9)	13/313	(4.2)	0.475
Severe <9 (*N*, %)	311/445	(69.9)	225/313	(71.9)	0.607
Outcomes after 6 months					
GOSE					
GOSE <8 (*N*, %)	344 /381	(90.3)	262/280	(93.6)	
GOSE <5 (*N*, %)	202/381	(53.0)	175/280	(62.5)	0.171
GOSE=1 (N, %)	107/381	(28.1)	63/280	(22.6)	0.019
Qolibri					
Impaired (<52) (*N*, %)	32/ 173	(18.5)	29/121	(24.0)	0.321
SF-36 MCS					
Impaired (<40) (*N*, %)	57/173	(32.9)	40/117	(34.2)	0.926
SF-36 PCS					
Impaired (<40) (*N*, %)	57/173	(32.9)	40/117	(34.2)	0.926

This table describes the outcomes of patients stratified by high versus a low therapy intensity level treatment. High TIL was defined as any high intensity treatment (decompressive craniectomy excluding day 1, barbiturates, intensive hypothermia, intensive hyperventilation) during ICU stay. Significant group differences were determined by using the chi-square or Fisher's exact test (non-normal distributions) for categorical variables and an ANOVA or Kruskal Wallis test (non-normal distributions) for continuous variables.
1) Significant variation in proportion of abnormal lab values for high TIL vs. low TIL patients, i.e. creatinine (24.8% vs. 20.1%, p<0.001), sodium (50.1% vs. 39.7%, p<0.001), ASAT (49.1% vs 49.2%, p=0.865), and ALAT (39.3% vs. 37.9%, p=0.020)
CRBSI: Catheter-related bloodstream infection, DVT: Deep Venous Thrombosis, GCS: Glasgow Coma Scale, GOSE: Glasgow Outcome Scale Extended, ICU: Intensive Care Unit, Qolibri: Quality of life after brain injury total score, SF-36 MCS: Short Form-36v2 Mental Component Summary, SF-36 PCS: Short Form-36v2 Physical Component Summary, TIL: therapy intensity level, VAP: ventilator acquired pneumonia

Figure 4: Functional outcome at 6 months



Legend figure 4: this figure shows the functional outcome (GOSE) at 6 months for patients who receive low therapy and high therapy intensity. GOSE 1: Death, 2: Vegetative state, 3: Severe disability lower, 4:Severe disability upper, 5: Moderate disability lower, 6: Moderate disability upper, 7: Good recovery lower, 8: Good recovery upper. Patients in categories (2) and (3) on the GOSE were combined in a single category. GOSE: Glasgow Outcome Scale Extended, TIL: Therapy Intensity Level were combined in a single category. GOSE: Glasgow Outcome Scale Extended, TIL: Therapy Intensity Level

Table 3: Adjusted outcome after high TIL versus low TIL treatment (propensity score matched model)

Main analysis				**Sensitivity analyses**					
High TIL treatment				High TIL treatment after day 1			High TIL treatment excluding barbiturates		
	Nr	OR [95% CI]	*p*	Nr	OR [95% CI]	*p*	Nr	OR [95% CI]	*p*
Unfavourable GOSE ≤4	280	1.4 [1.0-2.0]	0.068	250	1.5 [1.1-2.2]	0.023	114	2.5 [1.4-4.7]	0.004

This table describes the differences in outcome after receiving high Therapy Intensity Level (TIL) treatment versus low TIL treatment. Overall high TIL was defined as any high intensity treatment (decompressive craniectomy excluding day 1, barbiturates, intensive hypothermia, intensive hyperventilation) during ICU stay. The primary outcome is the GOSE after 6 months. We used a multivariate propensity score matched model with correction for centre effects (random intercept). Nearest neighbour matching was used to select patients with the similar propensity scores and different treatment status. Covariates used for matching were IMPACT variables and 'ISS without head injury 'and in the final model we corrected for maximum ICP values prior to treatment. For the sensitivity analyses we only selected patient with high TIL treatments after day 1 or excluded patients receiving barbiturates.
CI: confidence interval, GOSE: Glasgow Outcome Scale Extended, ICP: intracranial pressure, ICU: intensive care unit, Nr: number of matches, OR: odds ratio, TIL: therapy intensity level

association with worse outcome became significant for high TIL after day 1 (OR: 1.5 CI [1.1-2.2], p=0.023) and high TIL excluding barbiturates (OR: 2.5 CI [1.4-4.7] *p*=0.004). (Table 3)

Discussion

To our knowledge, this is the first study to quantify treatments using the TIL scale in real-world clinical practice across centres in Europe. We report substantial between-centre variation in the choice and use of high TIL treatments in patients with TBI admitted to the ICU across Europe. Further, we did not observe a systematic progression in therapy intensity, exhausting low-tier treatments before escalating to more intensive therapies: instead high tier therapies were often used early in the course of treatment. This was unexpected, because progressive approach to treatment is recommended by the Brain Trauma Foundation guidelines [16] and forms part of the standard protocol in previous large clinical trials. In line with previous observational studies, we found relatively infrequent use of intensive hyperventilation, or decompressive craniectomy [17, 18]. In contrast, we found a relatively liberal use of barbiturates/deep sedation for metabolic suppression [19]. We found significant between centre variation in high TIL therapy use, beyond that accounted for by case-mix severity and random variation, both in terms of choice of therapy (e.g. use of hypothermia in a centre) and overall frequency of use (corrected for case-mix severity and random variation). This variation in high TIL treatment at centre-level suggests that, apart from disease severity, the clinical decision to use high TIL treatment is also based on institutional policy and culture.

After correction for ICP control, no statistically significant association was found between the use of high TIL treatment and functional outcome at 6 months. However, when excluding high TIL treatment at day 1 or barbiturates from high TIL treatment there was a statistically significant association with worse outcome. This may reflect some unquantified aspect of disease severity that is not captured by the available covariates but nevertheless translates into both TIL and outcome differences. Alternatively, this could mean that there is indeed some harm from residual high TIL therapies, in which case the use of these therapies before less hazardous low TIL options are exhausted could expose patients to unnecessary risks. Still, high-level evidence is lacking about the use of individual lower TIL therapies like CSF drainage and hyperosmolar fluids. This might explain why centres are cautious to apply these lower TIL treatments as standard use before proceeding to higher TIL treatment. Future studies are needed to confirm these findings as the sample size might have been insufficient to detect an association and to determine if a certain patient subgroup might benefit. High TIL treatments were associated with increased duration of ventilation and longer lengths of stay although we did not find a higher complication rate, at least for the metrics recorded. While we matched the two groups on available factors known to

influence outcome, it is also possible that other aspects of the clinical course which we could not capture are also important in a clinician's decision to institute high TIL therapies (residual confounding).

An important finding is that a large proportion of patients receiving high TIL treatments nevertheless recovered to good functional outcome (moderate disability to good recovery) at 6 months. High TIL treatment might be an appropriate final resource for patients with refractory high ICP values and may be beneficial in this group. Nevertheless, since there could be risks of such treatments, this emphasises the need for their rational use. More work is required to understand if outcome benefits could result from a more consistently gradated and progressive application of treatment intensity and/or a shift from institutional policies towards individualized medicine.

Previous studies have defined highly intensive (aggressive) treatment for ICP control in different ways [4-7, 20]. Cnossen *et al.* explored various definitions for aggressive treatment; such as the definitions 'use of ICP monitoring in more than 50% in patients meeting the BTF guidelines criteria' and 'aggressiveness based on a TIL score (any of the following: osmotic therapy, hyperventilation, cerebrospinal fluid drainage, vasopressors for cerebral perfusion pressure support, hypothermia, barbiturates, and neurosurgical intervention)'[4]. Bulger *et al.* also defined aggressiveness as 'the use of ICP monitoring according to the BTF guidelines in more than 50% of patients' [5]. However, this definition of aggressiveness (use of ICP monitoring) did not correlate with measured aggressiveness of therapy in our study, defined in our dataset as the likelihood of using high TIL therapies. We conclude that the previous use of higher use of ICP monitoring as a marker of aggressive TBI management in a centre may be flawed.

Several recent large trials have studied the impact on outcome of individual high TIL treatments, such as decompressive craniectomy [6, 8] or intensive hypothermia [21], but there is a need to assess other hazardous ICP-directed therapies (such as intensive hyperventilation and barbiturate coma) in this setting.[16] Our analysis targeted integrated assessment of all of these therapies, but the heterogeneity and lack of a uniform tiered approach to their use suggest that comparative effectiveness research (CER) approaches to exploring these therapies may have problems.

This study has a number of limitations that need to be discussed. First, the definition of a high TIL treatment is to some extent arbitrary as it is based on expert opinion rather than concrete outcome data. We considered metabolic suppression as a second-tier treatment, based on the recommendation in BTF guidelines that barbiturates should be considered a second-tier therapy (for raised ICP refractory to maximum treatment) [16]. However, our data suggest that in many centres others might consider this a first-tier/early therapy, in

keeping with results from our Provider Profiling exercise [22]. In addition, we have no data on whether short durations of metabolic suppression in the early phase of illness carry the same risks as prolonged metabolic suppression employed as a treatment for refractory ICP in a later stage. Second, we do not have detailed data on how carefully these treatments were implemented, which is a significant omission. For example, the methods and rates of cooling or re-warming could affect both the efficacy and harm associated with intensive hypothermia. Finally, incomplete data on ICP monitoring made it difficult to accurately define a metric for poor ICP control before escalation of therapy and hence made propensity matching difficult. As poorly controlled ICP is likely to be a driver for escalation of therapy (or for continuing high TIL therapy), and also a marker of poor outcome, the absence of these data makes a rigorous covariate-adjusted comparison of high and low- TIL therapy groups difficult.

Future directions

Further work will be needed to explore the process by which clinical decisions to proceed to more intensive treatments are undertaken and determine the best way that hazardous therapies should be introduced in a rational tiered treatment plan. The evidence base to choose a particular high TIL treatment over another is limited, since the evidence on benefit from these therapies is either absent or conflicting [6-8, 21]. This lack of evidence helps to explain high between-centre variation in choice of treatment, and currently means that the initiation and choice of high TIL interventions is only driven by patient characteristics to a very limited extent and is primarily based on institutional policies. A better identification of subgroups of patients who benefit from such therapies would allow better targeting of either individual interventions, or high intensity therapies in general. We also need to explore whether more rigorous ICP control, with higher intensity therapies, may, in a subgroup of patients, prevent refractory intracranial hypertension, reduce ICU stay, and possibly improve outcome. The search for patient and monitoring characteristics that identify such a subgroup could allow a precision medicine approach to ICP management.

Conclusions

We show substantial variation amongst European centres in the choice and use of ICP-lowering treatments for patients with TBI. We found a no statistically significant association between the use of high TIL therapies and worse outcome after 6 months although a significant association did become apparent when day 1 or high dose sedation was excluded. However, this difference may have been flawed because of incomplete propensity matching of the high TIL and control groups due to unmeasured covariates. In any case, our results do not support a nihilistic view of patients who receive high TIL treatments; One third of high TIL patients achieved a favourable functional outcome, and high TIL

treatment might have contributed to this. Further studies need to confirm whether and when high TIL treatments can be used as a safe final resort. More consistent use of low-tier treatments before escalating management to high TIL therapies, and data that support a rational choice of high TIL therapies, could both contribute to improved clinical outcome.

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The authors would like to thank all patients for their participation in the CENTER-TBI study. In addition, the authors would like to thank all principal investigators and researchers for ICU data collection and for sharing their valuable expertise.

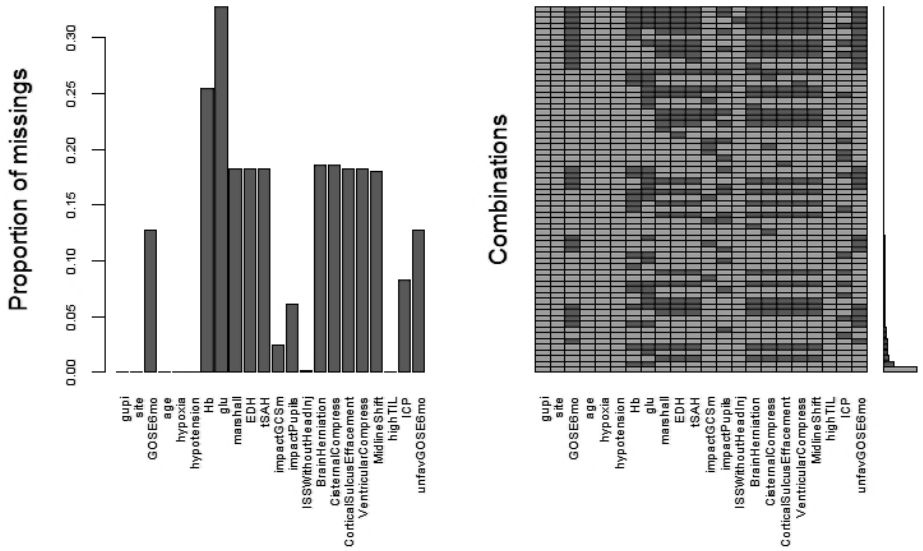
Supplementary material 1.

Table 1: Therapy Intensity Level scale

Item	Details	Score	Max
Positioning	- Head elevation for ICP control	1	
	- Nursed flat (180°) for CPP management	1	1
Sedation and neuromuscular blockade	- Sedation (low dose as required for mechanical ventilation)	1	
	- Higher dose sedation for ICP control (not aiming for burst suppression	2	
	- Metabolic suppression for ICP control with high dose barbiturates or propofol	5	
	- Neuromuscular blockade (paralysis)	3	8
CSF drainage	- CSF drainage low volume (<120 mL /day or < 5 mL/h)	2	
	- CSF drainage high volume (≥ 120 mL/ day or ≥5 mL/h)	3	3
CPP management	- Fluid loading for maintenance of cerebral perfusion	1	
	- Vasopressor therapy required for management of cerebral perfusion	1	2
Ventilatory management	- Mild hypocapnia for ICP control [PaCO2 4.6–5.3 kPa (35–40 mmHg)]	1	
	- Moderate hyppocapnia for ICP control [PaCO2 4.0–4.5 kPa (30–35 mmHg)]	2	
	- Intensive hypocapnia for ICP control [PaCO2 < 4.0 kPa (<30 mmHg)]	4	4
Hyperosmolar therapy	- Mannitol up to2 g/kg/24h	2	
	- Mannitol (>2 g/kg/24h)	3	
	- Hypertonic saline up to 0.3 g/kg/24h	2	
	- Hypertonic saline (>0.3 g/kg/24h)	3	6
Temperature control	- Treatment of fever (temperature > 38°C or spontaneous temperature of 34.5°C)	1	
	- Cooling for ICP control with a lower limit of 35°C	2	
	- Hypothermia below 35°C	5	5
Surgery for intracranial hypertension	- Intracranial operation for progressive mass lesion, not scheduled on admission	4	
	- Decompressive craniectiomy	5	9
Maximum possible score			38

This table shows the scoring of the Therapy Intensity Level (TIL) as recorded in the CENTER-TBI study. Derived from Zuercher et al. [3]. High TIL therapies are shown in bold

Supplementary material 2. Missing data



This figure shows the proportion of missing data in the original data (before imputation). In the left panel the proportion of missingness per variable is shown. In the combination plot (grid) all patterns of missing (darker) and observed data are shown. For example, the bottom row shows all patients with complete data, above that the patients with the combination missing data for Hb and gluc, ect. The bars on the right of the combination plot show the frequency of occurrence of the combinations

Supplementary material 3.

Table 3: Frequencies of treatments on the TIL scale (high TIL patients)

Days at the ICU Total number patients[1]	Day 1 312	Day 2 310	Day 3 304	Day 4 297	Day 5 290	Day 6 283	Day 7 280
Positioning							
- Head elevation	258 (85.1)	268 (88.2)	267 (88.4)	257 (87.1)	251 (87.5)	241 (86.1)	230 (84.9)
- Nursed flat	31 (10.2))	32 (10.5)	30 (9.9)	30 (10.2)	27 (9.4)	22 (7.9)	21 (7.7)
Sedation & neuromuscular blockade							
- Low dose sedation	190 (62.5)	184 (60.5)	175 (57.9)	163 (55.3)	169 (58.9)	148 (52.9)	139 (51.3)
-Higher dose sedation	196 (64.5)	210 (68.9)	204 (67.5)	192 (65.1)	168 (58.7)	150 (53.6)	129 (47.6)
-**Metabolic suppression**	128 (42.4)	148 (48.8)	154 (51.2)	142 (48.5)	131 (45.6)	113 (40.4)	103 (38.0)
- Neuromuscular blockade	105 (34.7)	108 (35.5)	92 (30.6)	77 (26.2)	86 (30.0)	72 (25.7)	62 (22.9)
CSF drainage							
- CSF drainage	46 (15.2)	64 (21.1)	65 (21.7)	71 (24.2)	79 (27.9)	78 (28.0)	76 (28.1)
CPP management							
- Fluid loading	123 (40.7)	122 (40.1)	99 (32.9)	91 (31.0)	85 (29.6)	75 (26.8)	55 (20.3)
- Vasopressors	203 (67.0)	231 (76.0)	222 (73.8)	204 (69.4)	187 (65.2)	170 (60.7)	152 (56.1)
Ventilatory management for ICP control							
- Mild hypocapnia	119 (39.3)	131 (42.7)	134 (43.1)	127 (43.2)	126 (43.9)	111 (39.6)	106 (39.1)
- Moderate hypocapnia	42 (13.9)	60 (19.7)	48 (15.9)	51 (17.3)	46 (16.0)	35 (12.5)	30 (11.1)
- **Intensive hypocapnia**	9 (3.0)	14 (4.6)	15 (5.0)	8 (2.7)	11 (3.8)	10 (3.6)	13 (4.8)
Hyperosmolar therapy							
- Mannitol [2]	42 (14.0)	36 (11.8)	45 (15.0)	36 (12.2)	31 (10.8)	31 (11.1)	19 (7.0)
- Hypertonic saline [3]	71 (23.5)	72 (23.8)	66 (21.9)	55 (19.1)	56 (19.5)	55 (19.6)	52 (19.2)
- Mannitol high[4]	6 (2.0)	13 (4.3)	9 (3.0)	4 (1.3)	4 (1.4)	5 (1.8)	8 (3.0)
- Hypertonic saline high [5]	31 (10.3)	39 (12.9)	22 (7.3)	25 (8.5)	24 (8.4)	23 (8.0)	19 (7.0)
Temperature control							
- Treatment of fever >38 °C	50 (16.5)	76 (24.9)	71 (23.5)	77 (26.1)	101 (36.1)	101 (36.1)	104 (38.4)
- Mild hypothermia ≥35°C	18 (5.9)	28 (9.2)	30 (9.9)	35 (11.9)	39 (13.6)	36 (12.9)	28 (10.3)
- Hypothermia <35°C	36 (11.9)	17 (5.6)	18 (6.0)	12 (4.1)	15 (5.2)	17 (6.1)	12 (4.4)
Surgery for intracranial hypertension							
- Intracranial operation	20 (6.6)	16 (5.2)	10 (3.3)	5 (1.7)	5 (1.7)	4 (1.4)	2 (0.7)
-Decompressive craniectomy	0 *	11 (3.6)	8 (2.6)	11 (3.7)	7 (2.4)	12 (4.3)	9 (3.3)
Mean TIL score	9.0	9.8	9.7	9.3	9.5	9.1	8.5

This table shows the number and percentages of high TIL patients receiving ICP-lowering treatments on the TIL scale.
Each row shows the number of patients (frequency) that receive that treatment (a patient could receive multiple treatments per topic) Bolt treatment are regarded as high TIL treatment
Low dose sedation as required for mechanical ventilation; higher dose sedation for ICP control (not aiming at burst suppression); metabolic suppression for ICP control (with high dose barbiturates or propofol); mild hypocapnia (PaCO2 4.6-5.3 kPa), moderate hypocapnia (PaCO2 4.0-4.5 kPa), intensive hypocapnia (PaCO2 < 4.0 kPa); intracranial operation for progressive mass lesion not scheduled on admission). Percentages take missing values into account
* Decompressive craniectomies were excluded from day 1. This represents the incidence per day (in our analyses this is the prevalence)
1) receiving high TIL somewhere during their stay (e.g. for day 2 could be received at day 1 and vice versa), 2) 2 g/kg/24 hours, 3) 0.3 g/kg/24hours, 4) > 2 g/kg/24 hours, 5) > 0.3 g/kg/24 hours
ICU: intensive care unit, TIL: therapy intensity level

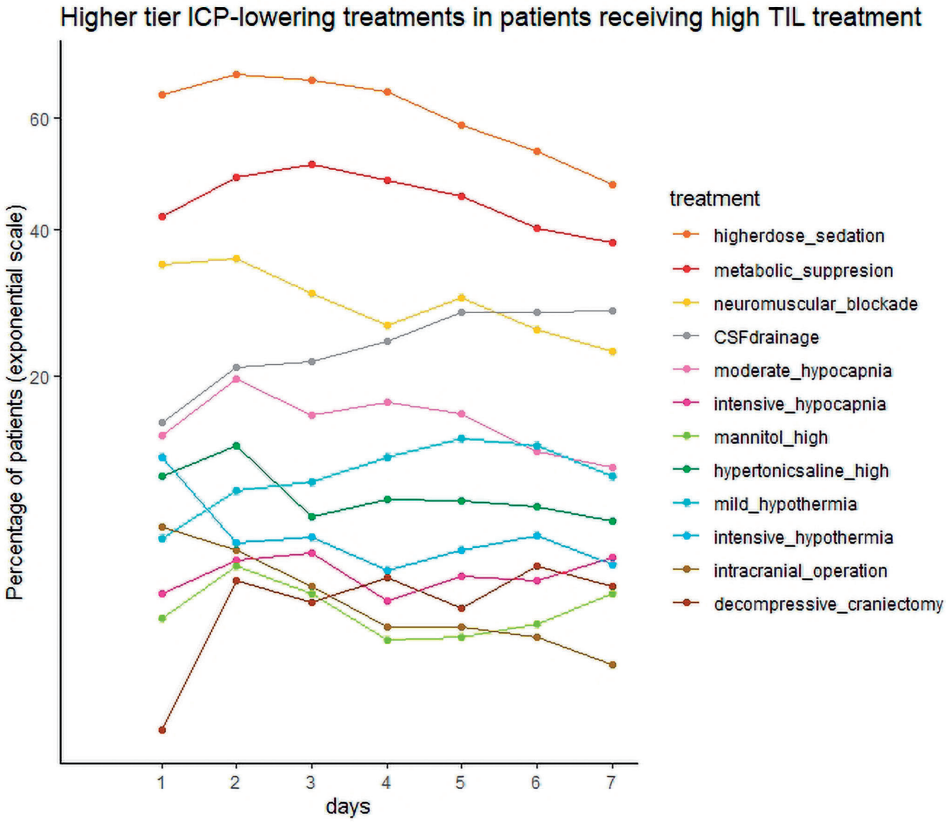
Supplementary material 4.

Table 2: Frequencies of treatments on the TIL scale (all patients)

Days at the ICU Total number patients	Day 1 745	Day 2 742	Day 3 719	Day 4 698	Day 5 665	Day 6 634	Day 7 614
Positioning							
- Head elevation	608 (85.5)	623 (87.0)	583 (84.1)	551 (83.0)	515 (81.6)	488 (81.7)	451 (78.6)
- Nursed flat	75 (10.6)	71 (9.9)	68 (9.8)	62 (9.4)	55 (8.7)	39 (6.5)	38 (6.6)
Sedation & neuromuscular blockade							
- Low dose sedation	490 (68.8)	451 (63.0)	403 (58.1)	366 (55.1)	358 (56.7)	313 (52.4)	288 (50.2)
- Higher dose sedation	319 (44.8)	352 (49.2)	328 (47.4)	292 (44.0)	253 (40.2)	215 (36.0)	187 (32.6)
- Metabolic suppression	128 (18.0)	148 (20.7)	154 (22.3)	142 (21.5)	131 (20.8)	113 (18.9)	103 (17.9)
- Neuromuscular blockade	158 (22.2)	147 (20.5)	118 (17.1)	105 (15.8)	110 (17.4)	90 (15.1)	81 (14.1)
CSF drainage							
- CSF drainage	91 (12.8)	119 (16.6)	123 (17.8)	123 (18.6)	134 (21.3)	133 (22.3)	131 (22.9)
CPP management							
- Fluid loading	302 (42.5)	268 (37.5)	211 (30.5)	172 (26.0)	142 (22.5)	130 (21.8)	104 (18.1)
- Vasopressors	476 (66.5)	505 (70.5)	460 (66.5)	408 (61.6)	354 (56.1)	295 (49.6)	247 (43.0)
Ventilatory management for ICP control							
- Mild hypocapnia	265 (37.2)	292 (40.8)	268 (38.7)	235 (35.5)	211 (33.4)	187 (31.3)	168 (29.3)
- Moderate hypocapnia	69 (9.7)	86 (12.1)	68 (9.8)	68 (10.3)	58 (9.2)	50 (8.4)	43 (7.5)
- Intensive hypocapnia	9 (1.2)	14 (2.0)	15 (2.2)	8 (1.2)	11 (1.7)	10 (1.7)	13 (2.3)
Hyperosmolar therapy							
- Mannitol [1]	62 (8.7)	59 (8.2)	65 (9.4)	48 (7.3)	45 (7.1)	46 (7.7)	31 (5.4)
- Hypertonic saline [2]	113 (15.9)	119 (16.6)	97 (14.0)	81 (12.2)	78 (12.4)	70 (11.7)	70 (12.2)
- Mannitol high[3]	9 (1.2)	14 (2.0)	10 (1.4)	6 (0.9)	5 (0.8)	7 (1.2)	10 (1.7)
- Hypertonic saline high [4]	42 (5.9)	47 (6.6)	30 (4.3)	29 (4.4)	27 (4.3)	28 (4.7)	26 (4.5)
Temperature control							
- Treatment of fever >38 °C	138 (19.4)	178 (24.8)	178 (25.7)	200 (30.2)	231 (36.6)	214 (35.8)	216 (37.6)
- Mild hypothermia ≥35°C	27 (3.8)	40 (5.6)	43 (6.2)	46 (6.9)	48 (7.6)	49 (8.2)	40 (7.0)
- Hypothermia <35°C	36 (5.1)	17 (2.4)	18 (2.6)	12 (1.8)	15 (2.3)	17 (2.8)	12 (2.1)
Surgery for intracranial hypertension							
- Intracranial operation	53 (7.5)	22 (3.1)	11 (1.6)	5 (0.8)	6 (0.9)	5 (0.8)	2 (0.3)
- Decompressive craniectomy	0 *	11 (1.5)	8 (1.2)	11 (1.7)	7 (1.1)	12 (2.0)	8 (1.4)
Mean TIL score	6.7	6.9	6.6	6.2	6.2	6.0	5.7

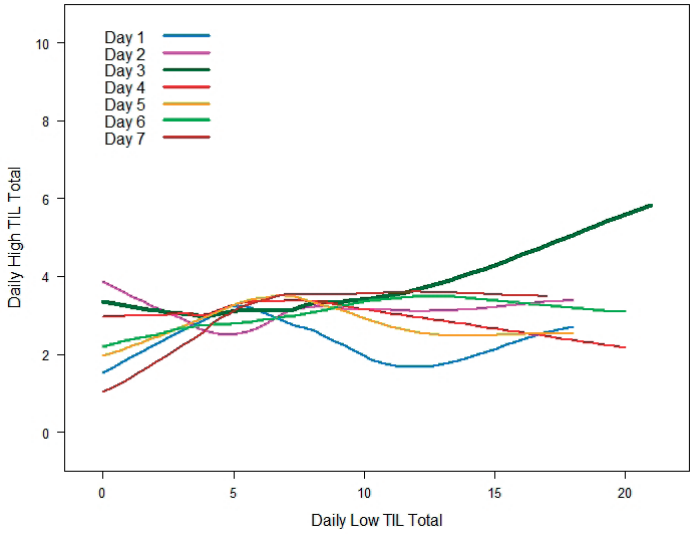
This table shows the number and percentages of ICP-monitored patients receiving ICP-lowering treatments on the TIL scale.
Each row shows the number of patients (frequency) that receive that treatment (a patient could receive multiple treatments per topic)
Low dose sedation as required for mechanical ventilation; higher dose sedation for ICP control (not aiming at burst suppression); metabolic suppression for ICP control (with high dose barbiturates or propofol); mild hypocapnia (PaCO2 4.6-5.3 kPa), moderate hypocapnia (PaCO2 4.0-4.5 kPa), intensive hypocapnia (PaCO2 < 4.0 kPa); intracranial operation for progressive mass lesion not scheduled on admission). Percentages take missing values into account
* Decompressive craniectomies were excluded from day 1. This represents the incidence per day (in our analyses this is the prevalence)
1) 2 g/kg/24 hours, 2) 0.3 g/kg/24hours, 3) > 2 g/kg/24 hours, 4) > 0.3 g/kg/24 hours
ICU: intensive care unit, TIL: therapy intensity level

Supplementary material 5



This figure shows the proportion of patients that receive first and second tier treatments of the high TIL patients across 7 days at the Intensive Care Unit. Decompressive craniectiomies at day 1 were excluded. Mannitol_high: >2 g/kg/24h, hypertonicsaline_high: > 0.3 g/kg/24h

Supplementary material 6



This figure shows the daily high TIL scores (cumulative score of the high TIL treatments) plotted against the daily low TIL scores (cumulative score for low TIL treatments). It shows that at the same high TIL scores a variety of low TIL treatment (scores) is applied (in some cases even no low TIL treatment). Also, the figure shows mainly at day 3 (dark green) higher TIL treatments are applied including higher low TIL scores.
TIL: therapy intensity level

Supplementary material 7.

Table 4: Percentages of high TIL treatment across centres

Treatment use	Number of centres (N, %)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1. Barbiturates	46 (88.5)							
Mean %		18	22	25	22	19	17	17
IQR		0-27	0-36	0-40	0-35	0-28	0-24	0-25
Min-max		0-100	0-80	0-100	0-100	0-78	0-75	0-100
2. Hypothermia below 35 °C	32 (61.5)							
Mean %		5	4	2	1	2	2	1
IQR		0-6	0-0	0-0	0-0	0-0	0-0	0-0
Min-max		0-50	0-100	0-20	0-14	0-33	0-25	0-14
3. Intensive hyperventilation	21 (40.4)							
Mean %		2	3	4	1	1	1	1
IQR		0-0	0-0	0-0	0-0	0-0	0-0	0-0
Min-max		0-50	0-50	0-100	0-33	0-14	0-25	0-25
4. Decompressive craniectomy	26 (50.0)	*						
Mean %			2	2	1	1	1	1
IQR			0-0	0-0	0-0	0-0	0-0	0-0
Min-max			0-50	0-20	0-17	0-17	0-17	0-17
Overall high TIL use	47 (90.4)							
Mean %		42	43	43	43	43	42	43
IQR		25-51	27-52	27-56	27-56	27-55	26-57	27-59
Min-max		0-100	0-100	0-100	0-100	0-100	0-100	0-100

This table describes the between-centre variation for high TIL treatments across the days. The number of centres are the centres that actually apply the individual treatments. The mean percentage represents the mean percentage of patients across centres that receive the therapy, while the IQR and min-max represents the variation in treatment use between centres.

* We excluded patients with decompressive craniectomy at day 1 as we considered this a different treatment group

IQR: interquartile range, min: minimum, max: maximum, TIL: therapy intensity level

Supplementary material 8.

Table 5: Baseline patient characteristics matched dataset (complete cases)

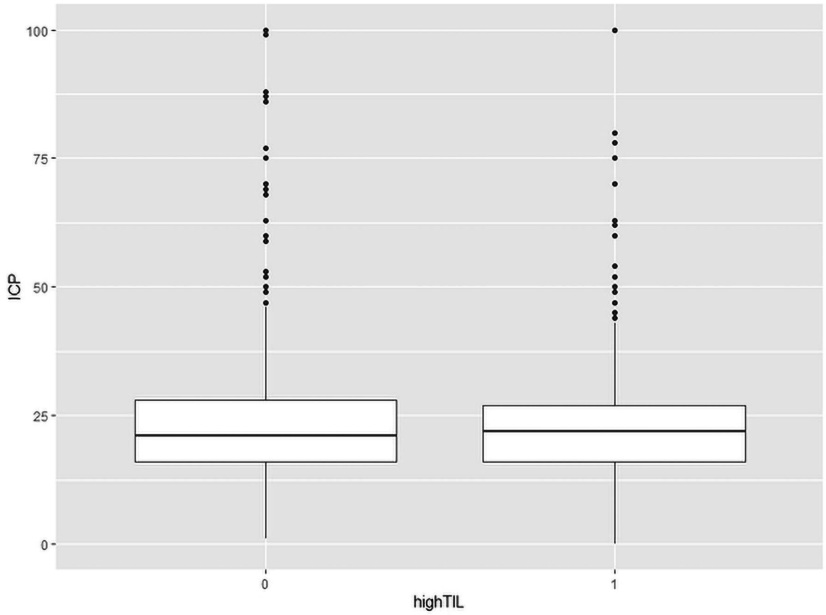
	Low TIL (*N*= 152)	High TIL (*N*= 127)	*p*-value	Standardized mean difference
IMPACT variables				
Age (median, IQR)	48 [27.0- 62.2]	42.0 [26- 58.5]	0.361	0.103
GCS motor score (N, %)				
1	68 (44.7)	64 (50.4)	0.244	
2	7 (4.6)	9 (7.1)		
3	7 (4.6)	7 (5.5)		
4	10 (6.6)	14 (11.0)		
5	36 (23.7)	20 (15.7)		
6	24 (15.8)	13 (10.2)		
GCS pupils (N, %)				
0	116 (76.3)	98 (77.2)	0.898	
1	13 (8.6)	12 (9.4)		
2	23 (15.1)	17 (13.4)		
Marshall (N, %)				
1	2 (1.3)	1 (0.8)	0.006	
2	74 (48.7)	43 (33.9)		
3	14 (9.2)	32 (25.2)		
4	5 (3.3)	4 (3.1)		
5/6	57 (37.5)	47 (37.0)		
Hypoxia (N, %)	21 (13.8)	18 (14.2)	1.000	
Hypotension (N, %)	19 (12.5)	17 (13.4)	0.968	
Hemoglobin (median, IQR)	13.2 [11.6- 14.4]	13.1 [11.8- 14.2]	0.769	.015
Glucose (median, IQR)	8.1 [6.8- 9.8]	7.8 [6.7- 9.6]	0.494	0.110
CT variables				
EDH (N, %)	35 (23.0)	27 (21.3)	0.835	
tSAH (N, %)	128 (84.2)	117 (92.1)	0.067	
Brain herniation (N, %)	32 (21.1)	28 (22.0)	0.956	
Cortical sulcus effacement (N, %)	38 (25.0)	31 (24.4)	1.000	
Ventricular compression(N, %)	52 (34.2)	52 (40.9)	0.301	
Midline shift(N, %)	42 (27.)	32 (25.2)	0.747	
Additional variables				
ISS without head injury (median, IQR	13 [1-25]	9 [0-25]	0.645	0.020
Max ICP [a] (median, IQR)	22 [16-31]	22 [14.5-26]	0.105	0.149

This table describes the baseline characteristics of the matched cases with complete data (as the dataset was imputed, this table could only be completed for complete cases). Significant group differences were determined by using the chi-square or Fisher's exact test (non-normal distributions) for categorical variables and an ANOVA or Kruskal Wallis test (non-normal distributions) for continuous variables.

a) max ICP prior to treatment

GCS: Glasgow Coma Scale, IMPACT: International mission for prognosis and analysis of clinical trials in TBI, ISS: injury severity score, IQR: interquartile range, TIL: therapy intensity level

Supplementary material 9. Maximum ICP values prior to start high TIL use per treatment group



This figure shows the differences in maximum ICP values prior to high TIL treatment between patients with a high TIL (1) versus a low TIL treatment (0). The median ICP for low TIL is 22 [16-28] and for high TIL 22 [16-27]. This difference is not statistically significant.

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CHAPTER 9

9

Pharmaceutical Venous Thrombosis Prophylaxis in Critically Ill Traumatic Brain Injury patients

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Abstract

Background: To describe the use of pharmaceutical venous thrombo-embolic (pVTE) prophylaxis in patients with traumatic brain injury (TBI) in European Intensive Care Units (ICUs) and to study the association with outcome.

Methods: We included 2006 patients admitted to the ICU >= 18 years from the CENTER-TBI study. VTE events were recorded based on clinical symptoms. Variation between 54 centres in application of pVTE prophylaxis was assessed with a random effect model, adjusted for case-mix severity and quantified with the Median Odds Ratio (MOR). The association between pVTE prophylaxis with outcome (Glasgow Outcome Scale Extended at 6 months) was assessed at centre-level and patient-level. A time-dependent Cox survival regression analysis was conducted to determine the effect of pVTE prophylaxis on clinical outcome.

Results: Among 2006 ICU patients, 56 (2%) had a clinical VTE during hospital stay. Substantial between-centre variation in the use of pVTE prophylaxis was found (MOR: 2.69, p<0.001). Most patients 1279 (64%) received pVTE prophylaxis. A moderate association with improved outcome was found at the centre-level (OR: 1.2 [0.7-2.1]), and patient-level (propensity adjusted OR: 1.4 [1.1-1.7]) with similar results in subgroup analyses. Survival was higher with the use of pVTE prophylaxis during hospital stay (p<0.001). We found no clear effect on CT progression (OR:0.9 CI [0.6-1.2]).

Conclusion: Policies for pVTE prophylaxis vary substantially between European centers. The use of pVTE prophylaxis may be associated with improved outcome. Further research is warranted to confirm and elucidate the associations found.

Background

Prevention of venous thromboembolism (VTE) is less straightforward in patients with traumatic brain injury (TBI) compared with non-neurologic patients admitted to the intensive care unit (ICU), because clinicians have to weigh the risks of progression of cerebral hemorrhage against the risks of VTE [1].

Guidelines for patients with TBI only state that the use of pharmaceutical VTE prophylaxis (pVTE prophylaxis) 'may be considered'[2]. In addition, RCTs on the effectiveness of pVTE prophylaxis are scarce in TBI [3]. This lack of high-level evidence could result in substantial variation in pVTE prophylaxis policies. Previous studies reported wide variation in incidence rates of deep venous thrombosis (DVT) and pulmonary embolism (PE) [4], but more recent studies suggest that the incidence rates of clinical VTE are low [5]. When incidences of VTE are indeed low, this raises the question whether patients with brain injuries should be given pVTE prophylaxis, especially in the acute phase during ICU care when risk of progression of intracranial hemorrhage is substantial. Previous studies have yielded conflicting results on the effectiveness and safety of pVTE prophylaxis [6-9]. However, these studies often focus on CT progression or VTE incidence alone, as opposed to long term outcome.

The aim of this study is to describe the use of pVTE prophylaxis in ICU patients with TBI in European neurotrauma centres and to study the association of pVTE prophylaxis with outcome.

Methods

CENTER-TBI study

This study is part of the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study, in which 54 ICUs from 18 countries in Europe and Israel participated [10]. Criteria to enter a patient in the CENTER-TBI study were 1) a clinical diagnosis of TBI, 2) indication for a head CT, and 3) presentation within 24 hours after initial trauma. The single exclusion criterion was a previous history of neurological disease that could interfere with clinical outcome assessment. A more extensive description of the study and patient characteristics can be found in previous publications [10, 11]. The CENTER-TBI study included patients in three strata: Emergency Room, Ward, and Intensive Care Unit (ICU). Inclusion criteria for the current analysis selected patients from the CENTER-TBI Core study who were 1) admitted to the ICU and 2) older than 18 years. Ethics approval was obtained at each participating site. Consent for study participation was obtained according to local legislation from patient, legal representative or next of kin, for all patients recruited [12].

Pharmaceutical prophylaxis

Detailed data on VTE prophylaxis were collected. Both the start and duration of pVTE prophylaxis were recorded, as well as the type of drug for pharmaceutical prophylaxis. Use of pVTE prophylaxis in this study was defined in two ways: 1) any use of pharmaceutical DVT prophylaxis at any time during or after ICU stay and 2) use of pharmaceutical DVT prophylaxis during ICU stay.

Outcomes

The presence of a DVT or PE during hospital admission was recorded based on clinical symptoms (so without routine leg ultrasound). The Extended Glasgow Outcome Scale (GOSE) at 6 months and CT progression were the primary outcome measures. CT progression was recorded by clinicians during ICU and later hospital stay.

Statistical analyses

Baseline characteristics were described for patients primarily admitted to the ICU with and without pVTE prophylaxis. Group differences were determined with Chi-square tests for categorical variables and ANOVA for continuous variables.

For the effects of pVTE prophylaxis on 6 month outcome, several analytical approaches were used at patient and centre-level. At patient level, an unadjusted proportional odds model was applied to assess the uncorrected relation between the use of pVTE prophylaxis and ordinal GOSE. To correct for confounding the following variables were added: age, pupils, motor, hypotension, hypoxia, EDH, tSAH, Marshall, ISS, first glucose, first hemoglobin, presence of a central venous catheter, invasive blood pressure monitoring, comorbidity, ASA, prior anticoagulant use, use of tranexamic acid at ED or ICU, cranial surgery, and extracranial surgery. We conducted multivariate proportional odds regression analysis using these covariates, a random effect for centre, and 6-month outcome. In addition, we also undertook a propensity-matched analysis, using the above covariates and pVTE prophylaxis as outcome, including centre as a random effect. Patients that score similar on these characteristics (i.e. with similar propensity scores) were matched with the nearest neighbor method. In the matched data (selection of patients with similar characteristics) the GOSE was compared between those receiving any pharmaceutical prophylaxis and those not receiving any pharmaceutical prophylaxis. In this analysis we additionally corrected for the covariates.

At centre-level, an instrumental variable (IV) analysis was performed with the percentage use of pVTE prophylaxis per centre as instrument, centre as random intercept, 6 month GOSE as outcome and adjustment for the confounders as described for the patient-level analyses. We restricted this analysis to centers that contributed over 10 patients to the analysis cohort. IV assumptions were checked by studying the similarity in case-mix severity

of centres with lower versus more frequent use of VTE prophylaxis. Aggressive centers were defined as those using more pVTE prophylaxis than the median use, while non-aggressive centers were defined as those that used less pVTE prophylaxis than the median use.

A multivariate model with pharmaceutical VTE prophylaxis as outcome and a random effect for centre was used to quantify between centre variation using the Median Odds Ratio (MOR) [13], which were visualized using caterpillar plots. Adjusted random effects at country-level, are visualized in a map of Europe. The higher the random effect, the more likely a country is to use pVTE prophylaxis, even after correction for case-mix and random variation.

The analyses described above were repeated with pVTE prophylaxis during ICU stay as independent variable, and in several subgroups: isolated TBI patients (without major extracranial injury), patients with any traumatic intracranial lesion on CT, patients with an ICU stay of more than 72 hours, and patients with contusions on first imaging.

As the outcome of pharmaceutical VTE prophylaxis is also dependent on timing of treatment, we undertook a time-dependent Cox survival analysis. This Cox survival analysis was conducted with pVTE prophylaxis as time-dependent covariate (including start and stop dates) and mortality as event. The Cox survival model with pVTE as a time-dependent covariate has two features. First, it only uses data when the patient is still 'at risk' of receiving pVTE, i.e. in the hospital. Second, it takes into account the timing of pVTE, i.e. patients switch from control to intervention group at the exact day they receive pVTE prophylaxis. This model was corrected using the same confounders as described above (age, pupils, motor, hypotension, hypoxia, EDH, tSAH, Marshall, ISS, first glucose, first hemoglobin, presence of a central venous catheter, invasive blood pressure monitoring, comorbidity, ASA, prior anticoagulant use, use of tranexamic acid).

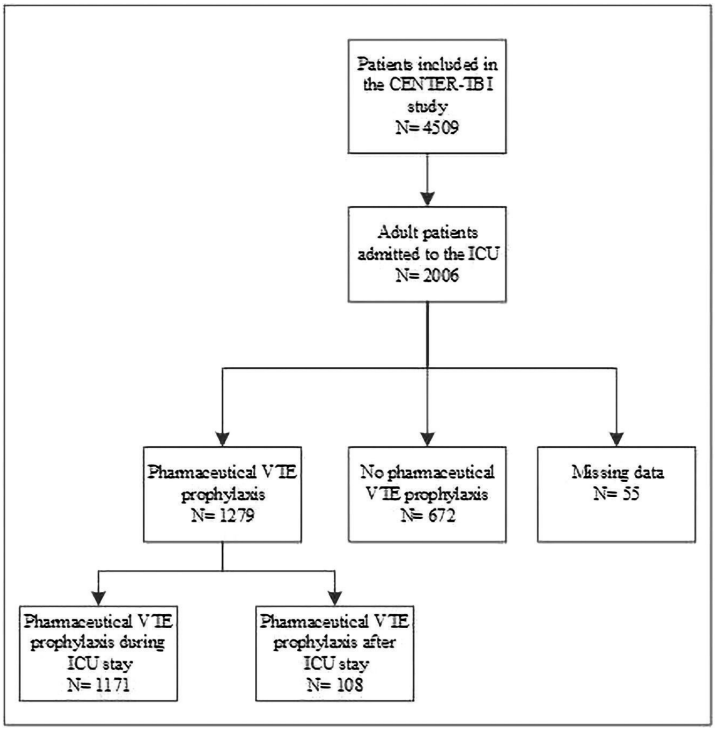
A logistic regression model was used to study the effect of pVTE prophylaxis on CT progression, corrected for the confounders as described above.

R statistical software was used for analyses. Missing data were imputed with the mice package [14]. Data were extracted from Neurobot (version 2.1)

Results

A total of 4509 patients participated in the CENTER-TBI study. Of these, 2006 adult patients were included in the ICU stratum. The majority of these patients received pharmaceutical VTE–(N=1279, 64%) while around a third received no pVTE prophylaxis (N=672, 34%). Most

Figure 1: Flowchart patient inclusion current study



Legend figure 1: Flowchart of the use of pVTE prophylaxis at ICU stay or not, including missing values. CENTER-TBI: Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury, ICU: Intensive Care Unit, VTE: venous thrombotic event

patients received pVTE prophylaxis during ICU stay (N= 1171) in a minority of patients (N= 108) pVTE prophylaxis was started after ICU stay. (Figure 1)

Mechanical VTE prophylaxis was applied in around half of the cases that received pVTE prophylaxis (N=657; 53%) and only in a minority with no pVTE prophylaxis (N= 193; 29%). (Table 1)

Baseline characteristics

Patients who sustained more severe injuries, based on the Glasgow Coma Scale (GCS) and Injury Severity Scale (ISS), were more likely to receive pVTE prophylaxis. Groups were similar regarding age and sex. A substantial proportion of patients with severe injuries received no pharmaceutical DVT prophylaxis (N=272, 43%). We found no significant differences in brain injuries on CT between the pVTE and non-pVTE groups, except more contusion in the pVTE group. Factors increasing the likelihood for VTE were central venous catheter, invasive blood pressure monitoring, cranial surgery, use of tranexamic acid, and extracranial surgery. The median length of hospital stay in patients receiving pVTE prophylaxis was 20

Table 1: Baseline characteristics in all ICU admitted patients

N= 1951	No pVTE prophylaxis hospital stay N= 672		pVTE prophylaxis hospital stay N= 1279		P-value	No pVTE prophylaxis at the ICU N= 780		Received pVTE prophylaxis at the ICU N= 1171		P-value
Age (median, IQR)	52 [33-68]		51 [33-65]		0.266	53 [34-68]		51 [32-64]		0.031
Gender, male (N,%)	485	(72.2)	950	(74.3)	0.343	564	(72.3)	871	(74.4)	0.335
Mechanical DVT prophylaxis	193	(28.8)	657	(53.4)	<0.001	251	(32.3)	599	(53.2)	<0.001
ISS (median, IQR)	26 [17-41]		32 [25-43]		<0.001	26 [18-38]		33 [25-43]		<0.001
GCS (N,%)										
Mild	270	(42.3)	382	(31.3)	<0.001	316	(42.3)	336	(30.2)	<0.001
Moderate	97	(15.2)	206	(16.9)	0.383	121	(16.2)	182	(16.4)	0.981
Severe	272	(42.6)	633	(51.8)	<0.001	310	(41.5)	595	(53.5)	<0.001
CT (N,%)										
tSAH	435	(73.5)	832	(75.1)	0.504	505	(73.4)	762	(75.3)	0.410
EDH	116	(19.5)	209	(18.8)	0.775	137	(19.9)	188	(18.5)	0.538
Contusion	311	(52.2)	653	(58.9)	0.009	367	(53.0)	597	(59.0)	0.017
Marshall (N, %)					0.514					0.315
I	64	(10.7)	117	(10.5)		74	(10.7)	107	(10.6)	
II	260	(43.6)	529	(47.7)		305	(44.1)	484	(47.7)	
III	50	(8.4)	89	(8.0)		55	(7.9)	84	(8.3)	
IV	8	(1.3)	18	(1.6)		8	(1.2)	18	(1.8)	
V/VI [a]	214	(35.9)	357	(32.2)		250	(36.1)	321	(31.7)	
Preinjury ASA (N, %)					0.495					0.196
Normal healthy	363	(57.4)	682	(55.4)		409	(55.5)	636	(56.5)	
Mild systemic disease	198	(31.3)	416	(33.8)		241	(32.7)	373	(33.1)	
Severe systemic	63	(10.0)	124	(10.1)		76	(10.3)	111	(9.9)	
Severe systemic, life threat	8	(1.3)	9	(0.7)		11	(1.5)	6	(0.5)	
Cause of injury (N, %)					0.003					0.030
Road traffic incident	247	(38.0)	582	(47.1)		299	(39.7)	530	(46.8)	
Incidental fall	304	(46.8)	485	(39.3)		346	(45.9)	443	(39.1)	
Violence/assault	34	(5.2)	47	(3.8)		35	(4.6)	46	(4.1)	
Suicide attempt	15	(2.3)	28	(2.3)		16	(2.1)	27	(2.4)	
Other	50	(7.7)	93	(7.5)		57	(7.6)	86	(7.6)	

Continue

Continued

N= 1951	No pVTE prophylaxis hospital stay N= 672		pVTE prophylaxis hospital stay N= 1279		P-value	No pVTE prophylaxis at the ICU N= 780		Received pVTE prophylaxis at the ICU N= 1171		P-value
General VTE risk factors (N, %)										
BMI>25	275	(55.7)	554	(52.7)	0.293	322	(55.5)	507	(52.5)	0.269
History of VTE	4	(0.6)	15	(1.2)	0.321	6	(0.8)	13	(1.1)	0.606
Central venous catheter	207	(31.1)	586	(45.9)	<0.001	244	(31.6)	549	(46.9)	<0.001
Invasive bp monitoring	488	(72.9)	1127	(88.2)	<0.001	575	(74.0)	1040	(88.9)	<0.001
Cranial Surgery	201	(30.0)	562	(44.2)	<0.001	246	(31.7)	517	(44.5)	<0.001
Extracranial surgery	105	(15.7)	451	(35.5)	<0.001	129	(16.6)	427	(36.7)	<0.001
Use of tranexamic acid	33	(4.9)	106	(8.3)	0.008	36	(4.6)	103	(8.8)	0.001
Comorbidity [b]	146	(21.7)	225	(17.6)	0.032	177	(22.7)	194	(16.6)	0.001
Length of ICU stay	2 [1-6]		10 [4-19]		<0.001	2 [1-6]		11 [4-19]		<0.001
Length of hospital stay	7 [3-14]		20 [11-36]		<0.001	8 [3-17]		21 [11-37]		<0.001
Prior medication (N, %)					0.980					0.535
Anticoagulants	35	(5.6)	63	(5.2)		44	(6.1)	54	(4.9)	
PAI	64	(10.2)	126	(10.4)		81	(11.2)	109	(9.9)	
Both	5	(0.8)	11	(0.9)		6	(0.8)	10	(0.9)	

This table shows the baseline characteristics of TBI patients admitted to the ICU stratified by the use of pharmaceutical DVT prophylaxis (at any time during stay)
a) Since a Marshall score of V rarely occurred; score V and VI are condensed b) cardiac (arrhythmia, valvular heart disease, congenital heart disease, thromboembolic heart disease, ischemic heart disease), renal (renal insufficiency or failure), oncologic, hepatic, or sickle cell disease
ASA: American Society of Anesthesiologists; bp: blood pressure; EDH: Epidural hematoma; ISS: Injury Severity Scale; PAI: platelet aggregation inhibitors; tSAH: traumatic subarachnoid hemorrhage; VTE: venous thromboembolism

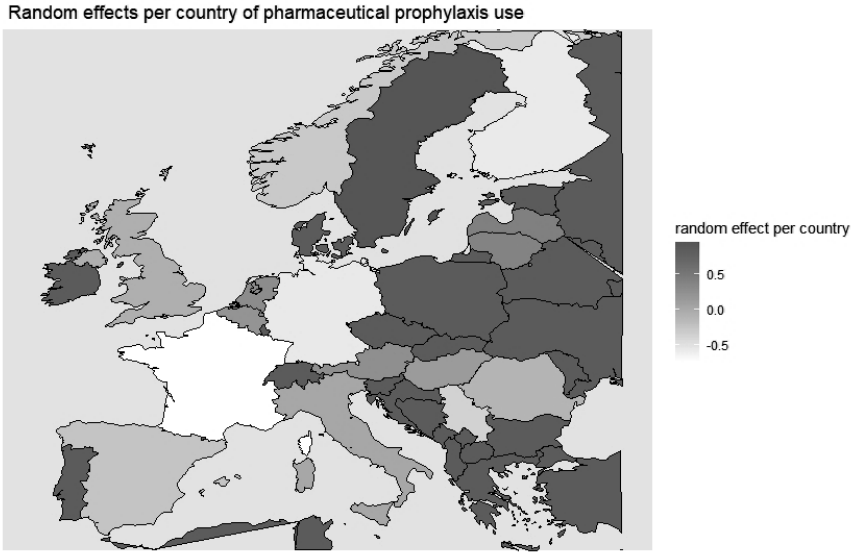
days [IQR: 11-36] versus 7 days [IQR: 3-14] in patients without pVTE prophylaxis. A similar pattern was seen for patients receiving pVTE prophylaxis during ICU stay versus patients receiving no pVTE prophylaxis or after ICU stay. (Table 1)

Overall, DVT incidence rates at the ICU (N=22; 1%) and during hospital stay (N=25; 2%) were low. Further, recorded clinical PE incidence rates were low at the ICU (N=20;1%) and during hospital stay (N=24; 2%). VTE events occurred in 56 patients of whom N= 49 (88%) received pVTE prophylaxis and N=7 (13%) did not receive pVTE prophylaxis during hospital stay.

Pharmaceutical prophylaxis practices

Most patients received Low Molecular Weight Heparins (LMWH): dalteparin (N=227; 18%), nadroparin [N=230; 18%], tinzaparin [N=48; 4%], enoxaparin [N=517, 41%], and parnaparin [N=4; 0%] as agents of choice, while unfractionated heparin [N=32; 3%] use was rare. The

Figure 2: Random effects per country of pharmaceutical VTE prophylaxis use



Legend figure 2: This figure shows the variation at country level in the use of pVTE prophylaxis. This variation is corrected for case-mix severity and random variation (adjusted random effects per centre).

median duration of pVTE prophylaxis was 11 days [CI: 5-23]. The median start of pVTE prophylaxis was 54.5 hours after the injury [CI: 15-109]. (Supplementary material 1)

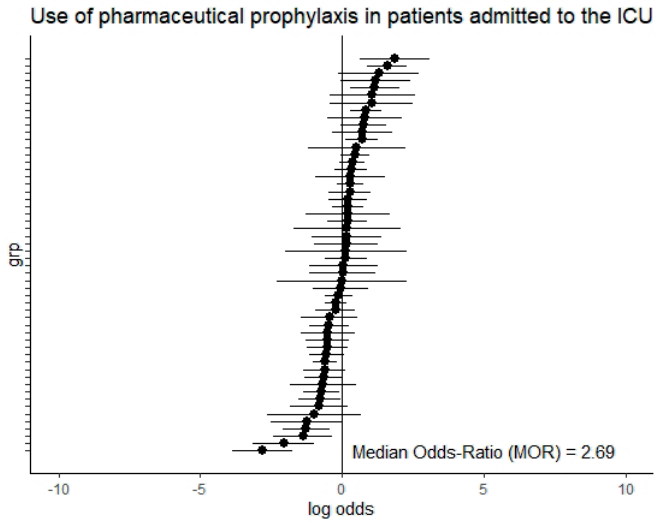
Overall, between-centre differences in application of pVTE prophylaxis were high after case-mix and random variation-correction: a MOR of 2.69 was found (p<0.001). (Figure 2) There was substantial variation in application of pVTE prophylaxis between countries in Europe, with the highest use in Sweden, while in France the use of pharmaceutical DVT prophylaxis was relatively low (Figure 3).

Associations with outcome

At patient-level, both the adjusted multivariate model (OR: 1.4 [1.1-1.7]) as well as the propensity score model (OR: 1.5 [1.1-2.0]) showed better 6-month GOSE scores in patients with pVTE prophylaxis started at some point during the hospital stay (Table 2).

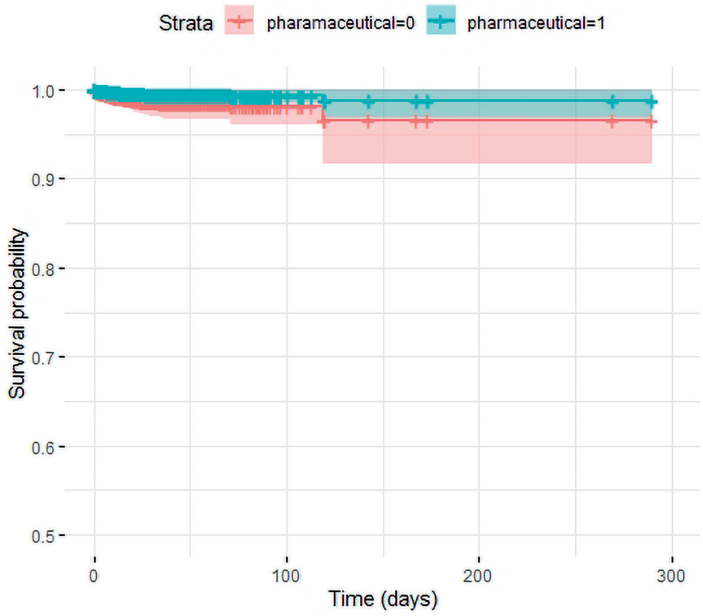
At centre-level, no major differences in patient population (case-mix) between aggressive and non-aggressive centres were found for patient characteristics regarding injury severity (Supplementary material 2). A comparable association between pVTE prophylaxis and outcome was found, but this did not reach significance. (OR:1.2 [0.7-2.1]). (Table 2).

Figure 3: Adjusted random effects per centre: use of pharmaceutical prophylaxis in patients admitted to the ICU



Legend figure 3: Variation in pVTE prophylaxis between centres in Europe. These centre effects are corrected for case-mix severity per centre and random variation (to show variation beyond chance).

Figure 4: Time-dependent cox survival curve



Legend figure 4: This figure shows the time-dependent cox survival curve for the use of pVTE prophylaxis. The difference in survival is significant ($p<0.001$) favoring the use of VTE prophylaxis. Beware the y-axis of survival starts at 0.5. Time is in days.

Table 2: Associations pharmaceutical VTE prophylaxis with six-month outcome

	Centre-level		Patient-level						
	IV analyses [a]		Unadjusted		Adjusted		Propensity score [b]		
Inclusion criteria	OR	[CI]	OR	[CI]	OR	[CI]	Matches	OR	[CI]
Prophylaxis during or after ICU stay									
ICU *N*= 2006	1.2	[0.7-2.1]	1.0	[0.8-1.2]	1.4	[1.1-1.7]	612	1.5	[1.1-2.0]
Subgroup analyses									
Isolated TBI [c] *N*= 900	1.0	[0.5-2.1]	0.9	[0.7-1.1]	1.2	[0.9-1.6]	340	1.3	[0.9-1.9]
Any CT lesion [d] *N*= 1558	1.0	[0.5-2.0]	1.1	[0.9-1.3]	1.5	[1.2-1.9]	494	1.7	[1.2-2.4]
Patients with a long ICU stay N= 1315	1.1	[0.5-2.2]	1.1	[0.9-1.4]	1.6	[1.2-2.2]	237	4.3	[2.3-8.0]
Patients with contusions on imaging N=984	1.2	[0.6-2.5]	1.2	[0.9-1.5]	1.3	[1.0-1.7]	290	1.2	[0.8-1.9]
Prophylaxis during ICU stay *									
ICU *N*= 2006	1.4	[0.8-2.5]	0.9	[0.7-1.1]	1.3	[1.0-1.6]	706	1.2	[0.9-1.5]

This table describes the association of use of pVTE prophylaxis with GOSE at 6 months (a higher score represents a better functional outcome) among patients admitted to the ICU. The intervention is the number of patients receiving pVTE prophylaxis during or after ICU, the control group received no pVTE prophylaxis. We conducted 4 subgroup analyses, one with exclusion of major extracranial injuries (isolated TBI), one limited to patients with hemorrhagic CT abnormalities, one with a longer ICU stay, and one in patients with contusions on CT.

We also conducted analyses with pVTE exposure during ICU stay: * Intervention group is patients who received pVTE prophylaxis at the ICU. Control group received pVTE prophylaxis after ICU stay or no pVTE prophylaxis at all.

Details of each individual analysis are as follows: At centre-level, an instrumental variable analyses was performed with the percentage pVTE prophylaxis as instrument, centre as random intercept, corrected for case-mix (extended IMPACT model and VTE risk factors), and ordinal GOSE as outcome. The analysis was restricted to centres that contributed more than 10 patients to the analysis. At patient-level, the unadjusted model shows the relation between pharmaceutical prophylaxis use and GOSE without added confounders. The adjusted proportional odds model was corrected for case-mix. A propensity score matched model was matched on baseline characteristics and VTE risk factors between cases (receiving pharmaceutical DVT prophylaxis) and controls (without pVTE prophylaxis). In this matched dataset, the difference outcome was determined between cases and controls.

a) OR per 100% increase (no use of prophylaxis or use in every patient) corrected for case-mix, as described above. However, for the isolated TBI patient subgroup, the ISS was not included in the analysis due to high covariance, with subgroup selection criteria b) Propensity matching used nearest neighbour with adjustment for predictors (qlogis). Analyses are pooled over different imputed datasets with different numbers of matches (nr of matches is mean of matches in imputed datasets), c) Exclusion major extracranial injury, d) Any traumatic intracranial CT abnormality

CT: Computer tomography, GOSE: Glasgow Outcome Coma Scale, ICU: intensive care unit, ISS: Injury Severity Scale, OR: odds ratio, pVTE prophylaxis: pharmaceutical Venous Thrombosis Events prophylaxis

Analysis of pVTE prophylaxis in the subgroup analyses at patient-level showed similar results, although not all significant. Effect estimates for the use of pVTE prophylaxis during ICU stay were similar as well.

The survival analyses also showed a beneficial effect of pVTE prophylaxis on survival ($p<0.001$) (Figure 4). No effect on CT progression was found (OR:0.9 CI [0.6-1.2]).

Discussion

Substantial variation at country- and centre-level was found in the use of pVTE prophylaxis, beyond case-mix differences and random variation. The use of pVTE prophylaxis was associated with improved outcome after 6 months, when administered at the ICU or afterwards at the ward. Overall, this indicates that VTE prophylaxis seems safe and might even improve outcomes in critically ill TBI patients. However, given the low incidence of clinically evident VTEs, the pathophysiology explaining this association is not clear from this analysis.

We found a low reported incidence of VTE in patients with TBI in neurotrauma centres in Europe. Although higher incidences of VTE have been reported in previous studies in TBI [4, 15], others reported similar or even lower percentages compared with our study [3, 5]. The discrepancy between higher incidences in other studies, may be partly explained either by a lack of routine lower limb screening with ultrasound for DVT or clinical underreporting of DVT in our study. The incidence of VTE in patients not receiving pVTE prophylaxis was higher, but only slightly. These findings are concordant with a large study which used leg ultrasound for the detection of VTE, and despite a higher overall incidence, showed no significant reduction with pVTE therapy [4]. However, in our study, no conclusion on these outcomes (DVT and PE) could be drawn as the statistical power was very low. Substantial variation was found in VTE prophylaxis practices between centres and countries. To our knowledge, no previous studies have described between-centre variation in pVTE prophylaxis. These variations were observed at both at centre and country-level, and persisted despite correction for random variation and case-mix, suggesting that application of pVTE prophylaxis is driven by hospital policy and local clinical culture.

The association between pVTE prophylaxis and potentially improved functional outcome after 6 months suggests that the benefits of pVTE prophylaxis may outweigh the risks. This result was consistent among all level analyses performed, strengthening the finding of the direction of the effect (better outcome) and rendering the possibility of a harmful effect less likely. Also, no effect of pVTE prophylaxis on CT expansion was found. Previous large studies on the effectiveness of pVTE prophylaxis did not translate to high level evidence [16]. At

centre-level, the analyses did not reach significance, but interpretation of these results is difficult as the statistical power at centre-level was very low[17]. Similar associations with outcome after 6 months were found with the use of pVTE prophylaxis during ICU stay. The survival analyses also showed an improvement in survival during hospital stay. Overall, our results suggest that providing pVTE prophylaxis might improve outcome.

The mechanisms behind possibly improved outcome might be less straightforward than currently thought, given the low incidence of clinical VTE. When taken at face value the outcome associations found may appear to be less likely caused by a decrease of VTE in patients treated with pVTE prophylaxis (given very low incidence in our study) and may therefore indicate a protective effect of this treatment due to mechanisms not yet elucidated. One hypothesis might be that pVTE prophylaxis might reduce microthrombi in the penumbra of contusional lesions [18-20]. The hypothesis was substantiated by a beneficial result of pVTE prophylaxis in the subgroup analyses with patients with contusions. Others might argue that patients without pVTE prophylaxis would receive mechanical VTE prophylaxis instead. However, this was not confirmed in our results (only around a third of patients without pVTE prophylaxis received mechanical prophylaxis instead).

This study has several strengths and limitations. In the CENTER-TBI study multiple neurotrauma centres participated from different countries, enabling us to study between-centre variation and effectiveness at centre-level. Several statistical methods were applied. These methods complement each other in their advantages and disadvantages [17]. For example, centre-level analyses (instrumental variable analyses) is suitable to abolish effects of unmeasured confounding, whereas the power of patient-level analyses is higher, in spite of only being able to adjust for measured confounders. Further, we performed survival analysis to correct for the substantial difference in length of stay between patients with and without pVTE.

This study also has its limitations. CT progression during hospital stay was scored by clinicians subjectively without accounting for a time component. Further routine CT follow-up was not prescribed at specific time points in the protocol. So, it could be that pVTE prophylaxis was administrated after the CT progression occurred. Also, CT progression was not clearly defined (e.g. only progression of cerebral bleeding or other traumatic lesions). Finally, the longer length of ICU and hospital stay in patients receiving pVTE prophylaxis compared with the non-pVTE group suggest the possibility of different subpopulations (and a potential higher risk profile in patients receiving pVTE). However, although residual confounding cannot be excluded, the IV analyses and the different statistical approaches should account for residual confounding and show similar directions of the effect.

Despite these limitations, it is likely that the routine use of pVTE prophylaxis in patients with TBI might improve their outcome. The various complementary approaches to statistical analysis show a significant association between pVTE prophylaxis and better functional outcome. We found no clinically relevant increase in CT progression. pVTE prophylaxis would therefore appear safe and beneficial. The reversal of effect (although not significant) in some subgroups in the IV analyses may indicate lower benefit in some subgroups (e.g. those with isolated TBI), which requires further study.

Future studies are needed to elucidate the mechanism behind the beneficial effect of pVTE prophylaxis and to determine the best time to initiate prophylaxis. An additional quantitative volumetric analysis of CT progression would be sensitive. In the ideal scenario, a Randomized Controlled Trial (RCT) should be considered to confirm our findings, which were obtained in an observational study utilizing comparative effectiveness approaches. However, the extreme heterogeneity of the TBI population in the ICU may render a strict protocol with standardization on when to apply the pVTE prophylaxis challenging.

Conclusion

In conclusion, substantial between-centre variation exists in the use of pVTE prophylaxis, while pVTE prophylaxis might be associated with improved 6-month functional outcome and lower mortality rates, without CT progression. Therefore, although VTE prophylaxis is likely to be safe, further research should be conducted to confirm and elucidate the associations and should be aimed at a better selection of patients more likely to benefit from this treatment.

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Supplementary material 1

Table 1: Baseline characteristics aggressive versus non-aggressive centres (Instrumental variable analyses)

N= 1962 (Centres>10 patients)	Non-aggressive centre Prophylaxis <median% N= 970		Aggressive centre Prophylaxis >=median% N= 992		P-value
Age (median, IQR)	51 [34-66]		52 [32-66]		0.960
Gender, male (N,%)	719	(74.1)	723	(72.9)	0.568
Mechanical DVT prophylaxis	266	(29.4)	578	(60.0)	<0.001
ISS (median, IQR)	26 [20-41]		32 [25-43]		<0.001
GCS					0.003
Mild	354	(38.9)	300	(31.8)	
Moderate	130	(14.3)	172	(18.3)	
Severe	427	(46.9)	470	(49.9)	
CT (N,%)					
tSAH	647	(74.7)	624	(74.2)	0.851
EDH	160	(18.4)	161	(19.1)	0.754
Contusion	492	(56.7)	475	(56.3)	0.927
Marshall (N, %)					0.006
I	91	(10.5)	94	(11.1)	
II	436	(50.2)	359	(42.5)	
III	74	(8.5)	66	(7.8)	
IV	9	(1.0)	17	(2.0)	
V/VI	259	(29.8)	308	(36.5)	
Preinjury ASA (N, %)					0.007
1) Normal healthy	514	(56.9)	522	(54.5)	
2) Mild systemic disease	278	(30.8)	340	(35.5)	
3) Severe systemic	98	(10.8)	92	(9.6)	
4) Severe systemic constant threat to life	14	(1.5)	3	(0.3)	
Cause of injury (N, %)					0.001
Road traffic incident	368	(39.8)	465	(48.7)	
Incidental fall	416	(45.0)	364	(38.2)	
Violence/assault	40	(4.3)	42	(4.4)	
Suicide attempt	28	(3.0)	16	(1.7)	
Other	72	(7.8)	67	(7.0)	

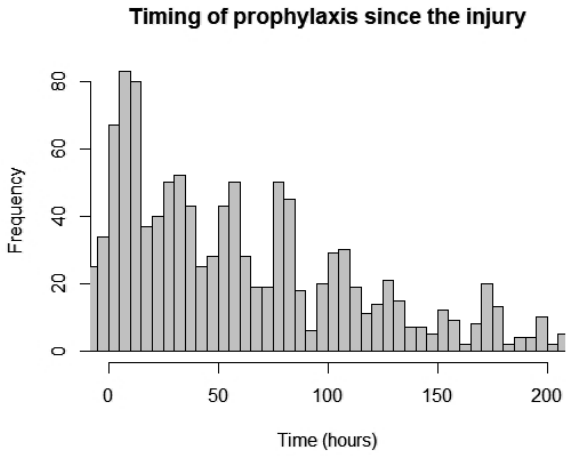
Continue

Continued

N= 1962 (Centres>10 patients)	Non-aggressive centre Prophylaxis <median% N= 970		Aggressive centre Prophylaxis >=median% N= 992		P-value
General VTE risk factors (N, %)					
BMI>25	389	(54.1)	430	(53.4)	0.828
History of VTE	7	(0.7)	12	(1.2)	0.383
Central venous catheter	375	(39.6)	423	(42.8)	0.159
Invasive blood pressure	747	(78.8)	862	(87.2)	<0.001
Cranial Surgery	319	(32.9)	442	(45.0)	<0.001
Extracranial surgery	242	(25.0)	317	(32.2)	<0.001
Comorbidity [1]	178	(18.4)	194	(19.6)	0.533
Length of ICU stay	6 [2-14]		7 [2-16]		0.167
Length of hospital stay	13 [7-28]		16 [7-31]		0.036
Prior medication (N, %)					0.957
Anticoagulants	48	(5.4)	52	(5.5)	
PAI	91	(10.3)	101	(10.8)	
Both	7	(0.8)	9	(1.0)	

This table shows the baseline characteristics of TBI patients admitted to an aggressive centre (ICU) or non-aggressive centre. Aggressiveness is based on more patients than the median percentage patients receiving pharmaceutical prophylaxis in that centre. The median percentage of use in centres is 65%, aggressive centres used more than this median percentaged compared with non-aggressive centres.
1) cardiac (arrhythmia, valvular heart disease, congenital heart disease, thromboembolic heart disease, ischemic heart disease), renal (renal insufficiency or failure), oncologic, hepatic, or sickle cell disease
ASA: American Society of Anesthesiologists, EDH: Epidural hematoma, ISS: Injury Severity Scale, PAI: platelet aggregation inhibitors, tSAH: traumatic subarachnoid hemorrhage VTE: venous thromboembolism

Supplementary material 2



This figure shows the variation in start time of pVTE prophylaxis after the injury. The x-axis shows the time in hours since the injury and the y-axis shows how many patients received pVTE prophylaxis at that starting time.

CHAPTER 10

10

General discussion

General discussion

The overall aim of this thesis was to describe variation in management of traumatic brain injury (TBI) patients among European ICUs, and to assess the quality and effectiveness of ICU care for TBI patients.

The specific research questions were:

1) What is the current variation in treatment policies in patients with TBI across European ICUs?

We have found substantial variation in ICU policies for patients with TBI between European neurotrauma centres assessed with the Provider Profiling questionnaires (Chapter 3-5). This was confirmed in the patient data from the CENTER-TBI study (Chapter 2) showing variation in structures and processes of care, but less so in outcome.

2) What is the quality of ICU care and what is the effectiveness and safety of treatments in routine critical care?

We have developed a quality indicator set specific for TBI (Chapter 6), upon validation, 9 structure, 5 process, but none of the outcome indicators showed potential for quality improvement purposes (Chapter 7). Further, we found that high TIL treatment might be associated with worse outcome after 6 months (Chapter 8) and that pharmaceutical VTE prophylaxis might be associated with improved outcome after 6 months (Chapter 9).

Practice variation

Main findings

In **Chapter 2**, we described ICU stay, selected management aspects, and outcome of Intensive Care Unit (ICU) patients with traumatic brain injury (TBI) in Europe, and quantified variation across centres. A total of 2138 patients were admitted to the ICU; 36% of which were mild TBI (Glasgow Coma Scale; GCS 13-15). Early deaths and long stay patients (>72 hours) had more severe injuries based on the GCS and neuroimaging characteristics, compared with short stay patients. Long stay patients received more monitoring and were treated at higher intensity, and experienced worse 6month outcome compared to short-stay patients. Between-centre variations were prominent in the proportion of short stay patients admitted to the ICU, use of Intracranial Pressure (ICP) monitoring, and aggressive treatments, but smaller in 6-month outcome.

With the Provider Profiling questionnaires, substantial between-center variation in ICU policies was found for ICP monitoring -, blood transfusion and coagulation -, and general supportive and preventive management (**Chapter 3-5**). Questionnaires were mostly completed by intensivists and neurosurgeons. Regarding ICP monitoring and treatment, approximately half of the centers were classified as using a more aggressive approach to ICP monitoring and treatment. For blood transfusion and coagulation policies, most centres indicated a low Hb- target level (between 70g/L and 80 g/L) in general (non-TBI ICU patients). Coagulation management was variable regarding timing of DVT prophylaxis, minimum platelet and INR values prior to ICP probe insertion, and correction of trauma related coagulopathy. For general and supportive treatment, most variation was found in initial PaO2 goals for mechanically ventilated patients, CPP targets, the timing of tracheostomy in unconscious patients, nutritional targets, and seizure prophylaxis and treatment. Overall, variation in treatment policies were mainly found for treatments that lack (or have incomplete) recommendations in the Brain Trauma Foundation (BTF) guidelines.

Reflection on findings

Overall, we found that a large number of mild patients with TBI were admitted to the ICU. We tried to explain this high proportion of admitted mild patients by stratifying patients in short stay (<=72 h) and long stay (>72 h) at the ICU. Among the short stay patients, we expected most mild patients. Indeed, a large proportion of mild patients (65%) was only admitted for a short stay. These patients received less intensive monitoring and treatment. This raises the question whether ICU admission of these short stay (mild) patients was justified or that these patients could also have been treated at the ward. Centers had different proportion of short stay admissions (beyond case-mix severity and random variation). The classification into mild, moderate and severe which is often solely based on the Glasgow Coma Scale prior to hospital arrival seems to have limited value to determine the need for intensive care. Other patient characteristics might also be important to determine severity, like injury mechanism or extracranial injury or items of the IMPACT prognostic score. Prediction models for ICU admission criteria (and early deterioration) clearly require further evaluation to optimize ICU admission policies.

Practice variation between centres was found both in the profiling questionnaires as in the CENTER-TBI patient data. In the patient data, variation could be adjusted for case-mix severity and random variation, but remained substantial. Some discrepancies can exist between results from the PP questionnaires and patient data. For example, the use of mannitol and hypertonic saline was indicated as general policy by 66% of centres, while in patient data of the CENTER-TBI study this was only applied in less than 20% for hypertonic saline or less than 10% for mannitol. This could indicate that questions in the Provider Profiling were less clear or prone to interpretation. This could also indicate that actual daily

practice is different from what clinicians think they do. This renders the results from the Provider Profiling questionnaires less reliable compared to the results of the patient data.

Between-centre variation in structures and processes of care were larger compared with between-centre variation in outcome after 6 months (GOSE). This may reflect the small proportion of outcome variance modifiable by differences in management, and/or that differences in individual aspects of management may be discordant and make any impact on outcome after 6 months less easily detectable. In our study on quality indicators, we showed that variation in clinically relevant (short term) outcome parameters, such as complications or mortality at the ICU, is larger [1]. This might be because outcome at short term is more directly influenced by treatments and thus differences are more easily detectable compared with outcome after 6 months.

Surprisingly, we found marked variation in processes of care that may be considered as general policy based on large clinical studies and consensus (e.g. from guidelines). For example, the use of tight glycemic control was reported by 28% of respondents, while the NICE-SUGAR and CGAO-REA studies recommend using moderate instead of tight glucose control in patients with TBI [2, 3]. Second, use of steroids was reported by 13% of the centers (one center reported frequent use); against the recommendation of the BTF guidelines and evidence from the CRASH study [4].

Between-center variations in clinical practice can be explained by several mechanisms. First, the Brain Trauma Foundation guidelines, specific for patients with TBI, lack high-level evidence to guide many aspects of clinical practice [5]. This was confirmed by the high between-centre variation that was mainly found for items that lack recommendations in the guidelines. In addition, while most centres indicate that they adhere to the guidelines, adherence rates in clinical practice might be different. For example, 70% of patients that should have received an ICP monitor according to indications in the BTF guidelines did not receive ICP monitoring in clinical practice. Deviations from the BTF guidelines might be justified, for many reasons. Still, previous studies suggest that higher adherence rates to the guidelines result in better outcome [6]. Second, due to the heterogeneity and complexity of TBI, clinicians could choose a more individual approach in which patient characteristics, vitals, lab values etc. guide their treatment policies. In this case, between-centre variation might represent optimal care for the patient population in individual centres and the fact that a "one size fits all" approach often is inappropriate. Finally, variation could be explained by a tension between general and TBI-specific strategies (some centres apply policies for non-neurologic patients to patients with TBI).

Quality of care

Main findings

With a Delphi study we developed standardized quality indicators that can be used to measure quality of care over time and across international borders. With the quality indicators, quality of care can be registered and monitored in a uniform way using clear definitions approved by international experts. Experts agreed on a final set of 42 indicators to assess quality of ICU care: 17 structure indicators, 16 process indicators, and 9 outcome indicators. **(Chapter 6)** These quality indicators were validated in the CENTER-TBI database, by determining the feasibility, discriminability, and reliability. Most quality indicators proved feasible to obtain with high completeness. Sub-optimal adherence was found for most quality indicators, ranging from 26-93% and 20%-99% for structure and process indicators. Significant between-centre variation, representing discriminability of the indicators was found in 7 process and 5 outcome indicators. Reliability of outcome indicators was generally low; 5 out of 7 had less than 10 events per centre. Overall, 9 structure, 5 process, but none of the outcome indicators showed potential for quality improvement purposes for TBI patients in the ICU, based on the CENTER-TBI data. **(Chapter 7)**

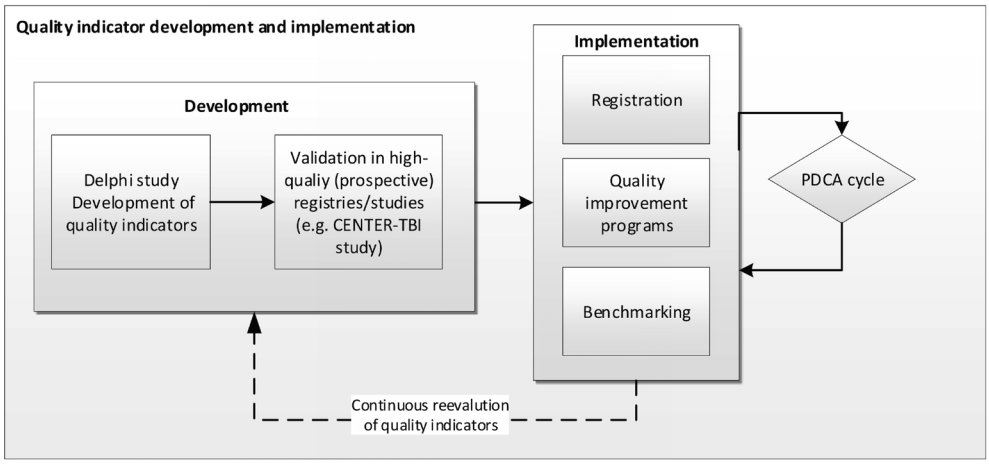
Reflection on findings

There is a large discrepancy between the quality indicators formulated and deemed appropriate by experts for benchmarking and quality improvement versus the results of the validation study. The validation study eliminated almost half of the indicators that the experts had provided, mainly outcome indicators due to low reliability. This might be because we set the (strict) threshold for reliability at 10 events per centre. Experts might not have realized that this threshold is so strict, but indictors with less outcomes per centers run a high risk of reflecting only chance variation. However, from a clinical perspective, each event reflects a complication in a human life, even rare events can have a high impact.

Scores on the indicators varied substantially between centres indicating that improvement in various clinical areas is needed. Scores were suboptimal indicating that some centers seemed to outperform others and that these centers with varying scores to the indicators could learn from the existing between-center differences. This also provides the opportunity for benchmarking and quality of care improvement (Figure 1). Centres could improve their care using feedback on performance, betweencentre discussions on policies, and by studying best practice. On the other end, the registration of care could already improve quality of care by identifying areas in need of quality improvement, informing health policies, and increasing transparency and accountability [7, 8].

Based on our studies we propose the following framework.

Figure 1: Quality indicator development and implementation



Legend figure 1: this figure shows the phases of quality indicator development and implementation. Implementation shows 3 different strategies for quality improvement which can all include feedback on performance; this feedback would again result in better registration, quality improvement programs and benchmarking initiatives. Once the quality indicators are implemented continuous re-evaluation is needed, and when necessary quality indicators need to be adjusted, this is shown by the PDCA cycle. PDCA stands for plan-do-check-act. So, plan the implementation, do (performance of) the implementation, check the result and act on results found.

Effectiveness of interventions

Main findings

In the final two chapters we aimed to evaluate the effectiveness and safety of several ICU treatments. First, we studied high TIL (therapy intensity level) treatments (high dose barbiturates, hypothermia (<35 °C), intensive hyperventilation (PaCO2 <4 kPa), and secondary decompressive craniectomy) in patients receiving ICP monitoring in the ICU **(Chapter 8).** In total, 41% of patients received at least one high TIL treatment during ICU stay, with significant between-centre variation in their use. Patients often did not receive all (or even most) first-tier treatment prior to receiving high TIL treatments. High TIL treatment was significantly associated with unfavorable outcome. Finally, we studied the use of pharmaceutical VTE prophylaxis in patients with TBI. **(Chapter 9)** Substantial between-center variation in the use of pharmaceutical VTE prophylaxis was found. Patient-level analyses pointed towards a favorable outcome with the use of prophylaxis during hospital stay. Hospital-level analyses did not reach significance. Also, no effect of pharmaceutical VTE prophylaxis on CT progression was found.

Reflection on findings

We studied the use, effectiveness and safety of certain ICU interventions regarded as "high intensity" treatments in more detail. High intensity treatment might be defined in different ways. We defined high intensity treatment as the use high dose barbiturates, hypothermia (<35 ºC), intensive hyperventilation (PaCO2 <4 kPa), and secondary decompressive craniectomy at any point during ICU stay. This was based on the TIL scale that was recently validated. Others might argue that high intensity should be based on a high TIL score (sum score of all treatments) or that other treatments should be seen as aggressive (e.g. CSF drainage).

The high therapy intensity level (TIL) treatments were associated with worse outcome after 6 months. Although this might reflect a true effect indicating harm, several biases might explain this apparent result. First, we showed that high TIL treatments were already given before other options with low TIL treatment were exhausted. This might indicate that some patients are treated aggressively, while they might benefit from less aggressive treatment approaches and thereby avoid medical overtreatment and associated side effects which may be substantial. Second, the use of high TIL treatment was predicted based on clinical and imaging characteristics (propensity scores). Sometimes patients with low propensity scores received high TIL and vice versa. This indicates that the used propensity scores do not predict the use of high TIL that well. So, it could be that some residual confounding remained despite correction for disease severity and other factors that influence the use of high TIL. On the other hand, it could also indicate that some milder cases unjustly received high TIL. In this case, high TIL treatment should be targeted towards the more severe cases to improve outcome and avoid over treatment.

When studying the use of pharmaceutical VTE (venous thrombosis embolism) prophylaxis we found low incidences of DVT and PE (under 2%). This might reflect underreporting in clinical practice (since the diagnosis is solely based on clinical symptoms) because leg ultrasound is not used as routine screening tool (as in other studies). The number of VTE did not differ between patients receiving pharmaceutical VTE prophylaxis and patients who did not receive prophylaxis but statistical power was too low to conduct statistical analyses with VTE as outcome.

We found an association of pharmaceutical VTE prophylaxis with favorable outcome. This was mainly found in patient-level analysis (including the subgroup analyses). At centre-level the power was too low to detect a significant treatment effect. To correct for exposure to pharmaceutical VTE prophylaxis over time we included a survival analyses with time varying covariates. Also, mortality over time was lower when pharmaceutical VTE prophylaxis was applied. Since the VTE incidence was similar between patient groups, other mechanisms than prevention of VTE might contribute to the potential beneficial effect

of pharmaceutical VTE prophylaxis. However, our research was not designed to elucidate potential mechanisms beyond DVT or CT progression.

Methods to study effectiveness in observational data

In this thesis, several methods were used to study the effectiveness and safety of interventions and to adjust for confounding and their advantages and disadvantages are summarized below. (Table 1)

Table 1: Advantages of various statistical analyses

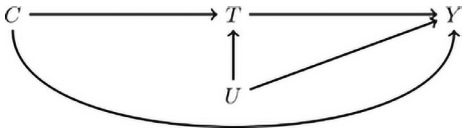
	Statistical power	Correction for unmeasured confounders	Subgroup analyses
Centre-level			
IV analyses	-	+	-
Patient-level			
Propensity score adjustment	+/-	-	-
Regression analyses	+	-	+/-

This table shows the advantages and disadvantages of various statical models. Only IV analyses can correct for unmeasured confounding in observational studies.

At the individual patient-level, a propensity score matching model was used. Based on patient characteristics the chance of receiving the treatment is calculated (propensity scores) and based on the propensity scores patients are matched. However, this reduces the number of patients available for analyses; as only matched patients are eligible for analyses. Another method at patient-level is a logistic or proportional odds regression analyses with correction for confounders. However, a limitation of these patient-level models is that all confounders need to be determined and unmeasured confounders are not taken into account.

In the CENTER-TBI study detailed patient data was available, including CT and MRI, lab, and physiological data. Missing data were generally low in frequency; in that case, missings were imputed. Imputation increased statistical power and provided the opportunity to use all relevant data to correct for confounders. However, we cannot rule out that some unmeasured confounding remained. Subgroup analyses with the propensity score adjustment method are complicated. They can show a reverse effect: in the subgroup the confounding relation could reemerge with the additional problem of systematically excluded cases [9].

Figure 2. Correcion for confounding in IV-analyses



This figure shows the center-level approach, where U represents the instrument (way around confounders) C:confounders, T: treatment, U: instrument, Y:outcome

At centre-level, IV analyses (CER analyses) were conducted that in theory are not biased by confounders at the patient level. This may be achieved by determining treatment preference or aggressiveness (instrument) at centre-level. In IV analyse a random intercept corrects for (un)measured confounders (or the hospital effect) beyond all included factors in the model, including the instrument. This instrument is stronger when higher between-centre variation exists.

In the CENTER-TBI study between-centre variation in structures, processes and outcome of care was high and 54 centres admitted ICU patients, providing the requirements for CER. The CER methodology limits confounding, while at the same time losing statistical power (as the analyses is at centre-level). In our results this was reflected in large confidence intervals. In addition, we cannot exclude that some residual confounding remained. Subgroup analyses often showed a reverse effect compared with the primary analyses, this may be explained by a truly different effect in the subgroups but also by small sample sizes. Further, if treatment preferences per center differ between subgroups, it might be argued that the instrument needs to be determined per subgroup analysis.

Clinical implications

Practice variation

Insight in current hospital policies across Europe, could make physicians aware of other treatment protocols and options. Exchange of knowledge between centres (benchmarking) could generate new ideas on how to improve care. Practice variation provides opportunities to study clinical topics and start research initiatives. Indeed, high practice variability pinpoints areas where clinical equipoise may exist and that should be investigated further in clinical trials.

Our research showed that the ICU admission and discharge policies varied substantially among centres which might reflect the overuse of ICU resources (for example when more short stay patients are admitted who could also have been safely managed outside the ICU). ICU admissions are costly. For example, one frequent reason for ICU admission of mild

patients was neurological observation. One could argue whether ICU admission is necessary for this group of patients. Our findings support further discussion on ICU admission and discharge policies across Europe.

Quality of care

The measurement of quality of care can serve different purposes and stakeholders. First, for clinicians it could provide insight in which clinical areas quality of care can be improved. Quality indicators provide the hospital or ICU with information on how to improve their care and give insight in which clinical areas can be improved most. ICU policies and processes of care can be optimized. This could lead to internal quality of care improvement programs. Second, when quality of care is measured across international borders, centres could compare their policies and learn from each other (benchmarking). Third, with the use of the quality indicators, hospitals can increase their transparency regarding their performance towards other stakeholders (government, health insurance bodies, patients, etc.). With the use of quality indicators hospitals could monitor their quality of ICU care. For now, the quality indicators were developed for patients with TBI, but could be generalizable to other ICU or trauma registries. One Dutch registry (the NICE registry, https://www.stichting-nice.nl/) aimed at benchmarking of Dutch ICUs' quality of care and outcomes already showed interest to add the indicators to their registry. Also, the management of a department can target their financial budget more specifically: when clinical areas are identified where quality of care performance is weak (as measured by the quality indicators), managers could allocate more resources to these specific areas. The use of quality indicators could also increase accountability and transparency (towards patients), but this is not yet recommended in the first stages of implementation. Finally, when quality indicators become part of a registry, when used over time and across countries, this provides a rich data source with possibilities for research.

Effectiveness

Although our research does not provide definitive evidence on effectiveness of interventions studied, we found some interesting associations with outcome. First, aggressive therapies (intensive hypothermia, intensive hyperventilation, decompressive craniectomy, and barbiturates) should be applied with caution and in the right patients. A wider application of a rational step-wise approach (e.g. the staircase approach) with the application of first tier-treatments before second tier treatments might improve patient outcome and might improve comparability of different policies between centers. A prediction model to study which patients (based on patient characteristics) might or might not benefit from high TIL treatments could assist in more appropriate application of TIL components, and should therefore be on the research agenda. We found a beneficial effect of use of pharmaceutical VTE prophylaxis. Some centres did not apply pharmaceutical VTE prophylaxis in any of their

patients, so implementation of pharmaceutical VTE prophylaxis might improve patient outcome.

Research implications

In this thesis we used advanced statistical methods with the final goal to approach causality (between treatment and outcome). However, causal inference remains difficult in observational studies. Therefore, we recommend the application of multiple statistical approaches to address confounding. In this thesis, analyses were conducted at patient-level and at centre-level. Previous studies often use one statistical approach, while we argue that multiple approaches could provide more insight in the true effect. When multiple centres participate in a study, we argue centre-level analyses provides a statistical method that could adjust better for unmeasured confounders and strengthen inferences on causality. Also, practice variation needs to be substantial. All these methods have their advantages and disadvantages [10]. Therefore, conclusions about causality should be made with caution. The results of the interventions we studied in this thesis should be verified in future research. Observational data provide a treasure of information on delivered health care. On the other hand a RCT may provide more definite answers on effectiveness.

The results of this thesis are mainly based on findings from the CENTER-TBI study. This dataset contains one of the largest numbers of TBI patients and centers in history. It was also the start of global collaborations and spin-offs in Australia and China. In future research, international collaboration should remain a priority with ultimately participation world-wide instead of only European-wide. As the CER methods exploits differences between centres and countries, these differences will only enlarge with world-wide participation (including lower income countries). The same applies to quality registries, the more countries or centres participate, the richer the data source and the more opportunities for benchmarking. However, world-wide participation might remain utopia and a logistic nightmare, so an alternative would be to merge international datasets. When common data elements [11] or standardized quality indicators [1] are used, as developed for TBI in this thesis, this becomes more feasible. An alternative way to facilitate large scale research would be automated data extraction from electronic health records. The challenge would be to have consistency in data. Some experiments are currently done on a local scale. With larger data sets, the statistical power of CER will increase, providing more definite answers on quality of care and treatment effectiveness.

Conclusions

Substantial variation exists with respect to ICU policies between centres in Europe. This variation is potentially due to a lack of evidence and guidance in current TBI guidelines. Comparative Effectiveness Research (CER) at centre-level can exploit practice variation to study effectiveness of different ICU policies. Between-centre variation could also provide information to discuss between-centre policies and be an asset for benchmarking.

Quality indicators can be used to register quality of care in a uniform way across centres. Our validation study showed that only a subset of indicators identified in our Delphi study is potentially suitable for benchmarking and quality improvement. Quality indicator scoring in the CENTER-TBI study suggests that most clinical areas could benefit from quality improvement. Continuous reevaluation over time is necessary to refine quality indicators and transform them in order to be better suitable and applicable for quality improvement.

High TIL treatment might be associated with worse outcome after 6 months. A more rational step-wise approach might improve the application of high TIL treatment. For pharmaceutical VTE prophylaxis there may be a positive association with improved outcome after 6 months.

The studies described in this thesis have contributed to improved insight in the current quality of care and practice variation. With the development of quality indicators, which are ideally derived directly from medical records, quality improvement is possible. The results of the comparative effectiveness studies we performed need to be confirmed but the results might guide to the design of future studies.

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Summary

Traumatic Brain Injury (TBI) causes an enormous health and economic burden around the world. TBI has been defined as an 'acute brain injury resulting from mechanical energy to the head from external physical forces' by the World Health Organization. While primary brain injury is regarded as irreversible, secondary injury can potentially be prevented with intensive monitoring and care in patients managed at the ICU. TBI-specific treatment strategies are mainly based on controlling intracranial compliance reserve, through intracranial pressure monitoring and include first-tier and more aggressive second-tier treatment. Although these ICP targeted and general and supportive treatments form the cornerstones of ICU care for patients with Traumatic Brain Injury, evidence on effectiveness is scarce.

Many Randomized Controlled trial (RCTs) have been performed to generate new evidence in TBI, but most did not impact or change clinical practice. The disappointing results of most RCTs have drawn attention to an alternative approach; analysis of large observational cohort studies. Comparative effectiveness research is one method: leveraging variability in clinical practice to assess best (treatment) policies. An alternative method to improve quality of care is the implementation of quality indicators. However, no widely endorsed quality indicators for patients with TBI exist yet, which may be due to the fact that the evidence-base is limited. However, quality indicators may also identify areas of variation where evidence is lacking and research is warranted.

For the studies in this thesis we use data from the CENTER-TBI (the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury) study, a large observational cohort study, including 66 centres in Europe. Of all admitted patients with TBI at the ICU detailed data is collected on demographics, injury, imaging, admission, monitoring, treatment, and outcomes. In addition, to capture the structures and processes of care at centre-level, questionnaires were sent out to the participating centres: the Provider Profiling questionnaires.

The overall aim of this thesis is to describe variation in management of TBI patients among European ICUs, and to assess the quality and effectiveness of some components of ICU care for TBI patients.

The two main research questions are:
1) What is the current variation in treatment policies for patients with TBI among European ICUs?
2) What is the quality of ICU care for patients with TBI and how can we improve the effectiveness and safety of treatments?

Part 1. Assessment of variation in TBI care among European ICUs

In **Chapter 2**, we describe ICU stay, selected management aspects, and outcome of Intensive Care Unit (ICU) patients with traumatic brain injury (TBI) in Europe, and quantify variation across centres. A total of 2138 patients were admitted to the ICU, with median age of 49 years; 36% of which were mild TBI (Glasgow Coma Scale; GCS 13-15). Within 72 hours 636 (30%) patients were discharged and 128 (6%) patients died. Early deaths and long stay patients (>72 hours) had more severe injuries based on the GCS and neuroimaging characteristics, compared with short stay patients. Long stay patients received more monitoring and were treated at higher intensity, and experienced worse 6-month outcome compared to short-stay patients who survived. Between-centre variations were prominent in the proportion of short stay patients (MOR=2.3, p<0.001), use of Intracranial Pressure (ICP) monitoring (MOR = 2.5, p < 0.001), and aggressive treatments (MOR=2.9, p<0.001) and smaller in 6-month outcome (MOR=1.2, p=0.01). In conclusion, half of contemporary TBI patients at the ICU have mild to moderate head injury. Substantial between-centre variations exist in ICU stay and treatment policies, and less so in outcome. It remains unclear whether admission of short stay patients represents appropriate prudence or inappropriate use of clinical resources.

In **Chapter 3**, we identified variation in the ICP monitoring policies in 66 centres in Europe using the Provider Profiling questionnaires. Regarding ICP monitoring devices, some centres indicated that they use an intraparenchymal device, while others use an extraventricular drain as general policy. Regarding indications for ICP monitoring, most centres agreed on placing an ICP monitor in patients with severe TBI and computed tomographic abnormalities (N=58, 91%). No consensus was found on other indications or peri-insertion precautions (like minimum INR or platelet count). Also in the choice, timing, and thresholds of ICP treatment policies we found substantial variation between centres. When centres are subdivided in those using a more or less aggressive approach (based on ICP monitoring use and GCS thresholds and CT criteria for such monitoring and the use of second tier treatments), approximately half of the centers were classified as using a relatively aggressive approach to ICP monitoring and treatment (n = 32, 48%).

In **Chapter 4**, we describe variation in blood transfusion and coagulation management between centres in Europe using the Provider Profiling questionnaires. Sixty-six centres responded to the questionnaires, focused on 1) hemoglobin target level (Hb-TL), 2) coagulation management, and 3) deep venous thromboembolism (DVT) prophylaxis. For ICU-patients, half of the centers (N = 34; 52%) had defined a Hb-TL transfusion threshold in their protocol. For patients with TBI, 26 centers (41%) indicated a Hb-TL between 70 and 90 g/L (= 4.3-5.6 mmol/L) and 38 centers (59%) above 90 g/L. To treat trauma-related

hemostatic abnormalities, the use of fresh frozen plasma (N = 48; 73%) or platelets (N = 34; 52%) was most often reported, followed by the supplementation of vitamin K (N = 26; 39%). Tranexamic acid was used less frequently (N = 7; 11%). Most centers reported using DVT prophylaxis with anticoagulants frequently or always (N = 62; 94%). In the absence of hemorrhagic brain lesions, 14 centers (21%) delayed DVT prophylaxis until 72 h after trauma. If hemorrhagic brain lesions were present, the number of centers delaying DVT prophylaxis for 72 h increased to 29 (46%). Overall, a uniform policy seems to be absent among European ICUs on blood transfusion and coagulation management.

In **Chapter 5**, we assess and quantify variation in perceptions on general intensive care unit (ICU) management of patients with TBI in European neurotrauma centers, with the Provider Profiling questionnaires. We analyzed 23 questions focused on: 1) circulatory and respiratory management; 2) fever control; 3) use of corticosteroids; 4) nutrition and glucose management; and 5) seizure prophylaxis and treatment. The survey was completed predominantly by intensivists (n = 33, 50%) and neurosurgeons (n = 23, 35%) from 66 centers (97% response rate). The most common cerebral perfusion pressure (CPP) target was > 60 mmHg (n = 39, 60%) or an individualized target (n = 25, 38%). To support CPP, crystalloid fluid loading (n = 60, 91%) was generally preferred over albumin (n = 15, 23%), and vasopressors (n = 63, 96%) over inotropes (n = 29, 44%). The most commonly reported target of partial pressure of carbon dioxide in arterial blood (PaCO2) was 36-40 mmHg (4.8-5.3 kPa) in case of controlled intracranial pressure (ICP) < 20 mmHg (n = 45, 69%) and PaCO2 target of 30-35 mmHg (4-4.7 kPa) in case of raised ICP (n = 40, 62%). Almost all respondents indicated to generally treat fever (n = 65, 98%) with paracetamol (n = 61, 92%) and/or external cooling (n = 49, 74%). Conventional glucose management (n = 43, 66%) was preferred over tight glycemic control (n = 18, 28%). More than half of the respondents indicated to aim for full caloric replacement within 7 days (n = 43, 66%) using enteral nutrition (n = 60, 92%). Indications for and duration of seizure prophylaxis varied, and levetiracetam was mostly reported as the agent of choice for both seizure prophylaxis (n = 32, 49%) and treatment (n = 40, 61%).

Part 2. Towards improvement in daily TBI care

In **Chapter 6**, we aimed to develop a set of quality indicators for patients with traumatic brain injury (TBI) in intensive care units (ICUs) across Europe and to explore barriers and facilitators for their implementation. A preliminary list of 66 quality indicators was developed, based on current guidelines, existing practice variation, and clinical expertise in TBI management at the ICU. Eight TBI experts of the Advisory Committee preselected the quality indicators during a first Delphi round. A larger Europe-wide expert panel was recruited for the next two Delphi rounds. Quality indicator definitions were evaluated on four

criteria: validity (better performance on the indicator reflects better processes of care and may contribute to better patient outcomes), feasibility (data are available or easy to obtain), discriminability (captures variability in clinical practice), and actionability (professionals can act based on the indicator). Experts scored indicators on a 5-point Likert scale delivered by an electronic survey tool. The expert panel consisted of 50 experts from 18 countries across Europe, mostly intensivists (N = 24, 48%) and neurosurgeons (N = 7, 14%). Experts agreed on a final set of 42 indicators to assess quality of ICU care: 17 structure indicators, 16 process indicators, and 9 outcome indicators. Experts indicated to be motivated to implement this finally proposed set (N = 49, 98%) and indicated routine measurement in registries (N = 41, 82%), benchmarking (N = 42, 84%), and quality improvement programs (N = 41, 82%) as future steps. Administrative burden was indicated as the most important barrier for implementation of the indicator set (N = 48, 98%). In conclusion, this Delphi consensus study gives insight in which quality indicators have the potential to improve quality of TBI care at European ICUs. The proposed quality indicator set is recommended to be used across Europe for registry purposes to gain insight in current ICU practices and outcomes of patients with TBI. This indicator set may become an important tool to support benchmarking and quality improvement programs for patients with TBI in the future.

In **Chapter 7**, the quality indicators developed with the Delphi method were tested in the CENTER-TBI database as a case study to assess their potential for quality measurement and improvement. We selected 2006 adult patients admitted to 54 ICUs between 2014 and 2018 in the CENTER-TBI database. Indicator scores were calculated as percentage adherence for structure–and process indicators, and as event rates or median scores for outcome indicators. Feasibility was quantified by the completeness of the variables. Discriminability was determined by the between-centre variation, quantified by the median odds ratio (MOR). Reliability of outcome indicators was determined by the median number of events per centre, using a cut-off of 10. A total of 26 of 42 (62%) indicators could be calculated from the CENTER-TBI database. Most quality indicators proved feasible to obtain with more than 70% completeness. Sub-optimal adherence was found for most quality indicators, ranging from 26-93% and 20%-99% for structure and process indicators. Significant ($p<0.001$) between-centre variation was found in 7 process and 5 outcome indicators with MORs ranging from 1.51-4.14. Reliability of outcome indicators was generally low; 5 out of 7 had less than 10 events per centre. Overall, 9 structure, 5 process, but none of the outcome indicators showed potential for quality improvement purposes for TBI patients in the ICU, based on the CENTER-TBI database. Future research should focus on implementation efforts and continuous reevaluation of quality indicators.

In **Chapter 8**, we studied the variation and aggressiveness of high TIL (therapy intensity level) treatments (metabolic suppression, hypothermia (<35 °C), intensive hyperventilation ($PaCO_2$ <4 kPa), and decompressive craniectomy) on outcome in patients receiving ICP

monitoring in the ICU stratum of the CENTER-TBI study. A random effect logistic regression model was used to determine between-centre variation in their use and a propensity score-matched model to study their impact on outcome (6-months Glasgow Outcome Score-extended), whilst adjusting for case-mix severity, clinical signs of brain herniation on imaging, and raised ICP. In total, 313 of 758 patients from 52 European centres (41%) received at least one high TIL treatment, with significant variation in their use between centres (MOR=2.26). Patients often did not transiently received high-TIL therapies escalating from lower tier treatments. 38% of patients with high TIL treatment had favourable outcomes (GOSE > 5). The use of high TIL treatment was not significantly associated with unfavorable outcome (285 matched pairs, OR: 1.4, 95% CI [1.0 -2.0]). However, a sensitivity analyses excluding day 1 high TIL treatments and deep sedation did reveal a significant association with worse outcome. In conclusion, substantial between-centre variation in use of high TIL treatments for TBI was found and treatment escalation to higher TIL treatments were often not preceded by more conventional lower TIL treatments. The association between high TIL treatments and worse outcomes may reflect either side effects of second tier therapies, unmeasured confounding or inappropriate escalation strategies.

In **Chapter 9**, we describe the use of pharmaceutical venous thrombosis embolism (VTE) prophylaxis in patients with traumatic brain injury (TBI) in European Intensive Care Units (ICUs) and to study the association with outcome. We included patients admitted to the ICU >= 18 years from the CENTER-TBI study. VTE were recorded based on clinical symptoms during hospital stay. Variation between centres in application of pharmaceutical VTE (pVTE) prophylaxis during hospital stay was assessed with a random effect model with pVTE prophylaxis as outcome, adjustment for case-mix, and hospital as a random effect, and quantified with the Median Odds Ratio (MOR). The association between VTE prophylaxis -both during ICU stay and during hospital stay- and outcome (Glasgow Outcome Scale Extended [GOSE] at 6 months) was assessed at center-level, using instrumental variable analyses exploiting between center differences, and multivariable logistic regression analyses at the patient-level. Subgroup analyses were conducted for patients with isolated TBI, patients with traumatic lesions on CT, and patients with a long ICU stay (>72 h). A Cox survival regression analysis was conducted with mortality as event and a time-dependent covariate for the use of DVT prophylaxis. The effect of VTE prophylaxis on clinical CT progression as secondary outcome was determined. As a result, among 2006 ICU patients, 1279 (64%) received pVTE prophylaxis and 56 (2%) had a clinical VTE during hospital stay. Substantial between-center variation existed in the use of pVTE prophylaxis (MOR=2.7, p<0.001). There was a moderate association of pVTE prophylaxis during hospital stay with improved outcome at center-level (OR: 1.2 [0.7-2.1]), and a significant effect in patient-level analyses (propensity OR: 1.5[1.1-2.0] and adjusted OR: 1.4 [1.1-1.7]). Similar results were found with pVTE prophylaxis in all subgroup analyses and during ICU stay. We found no clear effect on CT progression (OR:0.9 CI [0.7-1.3]). Survival was higher with the use of pVTE

prophylaxis during hospital stay (time-dependent Cox analyses: p<0.001). In conclusion, we found substantial between-center variation in the use of pVTE prophylaxis in Europe, while our study suggests that the use of pVTE prophylaxis during hospital stay is associated with improved 6-month outcome.

In **Chapter 10** (Discussion) the results and conclusions of the studied described in this thesis were discussed. The overall aim of this thesis was to describe variation in management of TBI patients among European ICUs, and to assess the quality and effectiveness of some components of ICU care for TBI patients.

The first research question was: *what is the current variation in treatment policies for patients with TBI among European ICUs?*

We found substantial variation in ICU policies for patients with TBI between centers in Europe; this was evident both from the results from the Provider Provider questionnaires as patient data from the CENTER-TBI study. Variation was mainly found in structures and processes of care, but less so in outcome.

The second specific research question was: *what is the quality of ICU care for patients with TBI and how can we improve the effectiveness and safety of treatments?*

To assess quality of care, we have developed a quality indicator set specific for TBI. Upon validation, 9 structure, 5 process, but none of the outcome indicators showed potential for quality improvement purposes. Further, we found that high TIL treatment might be associated with worse outcome after 6 months and that pharmaceutical VTE prophylaxis might be associated with improved outcome after 6 months.

Our findings have several implications regarding clinical practice.

Insight in current hospital policies across Europe, could make physicians aware of other treatment protocols and options. Exchange of knowledge between centres (benchmarking) could generate new ideas on how to improve care. Practice variation provides opportunities to study clinical topics and start research initiatives.

The measurement of quality of care can serve different purposes and stakeholders. First, quality indicators provide the hospital or ICU with information on how to improve their care and give insight in which clinical areas can be improved most. Second, when quality of care is measured across international borders, centres could compare their policies and learn from each other (benchmarking). Third, with the use of the quality indicators, hospitals can increase their transparency regarding their performance towards other stakeholders (i.e.

government). Also, with the use of quality indicators hospitals could monitor their quality of ICU care. Finally, when quality indicators become part of a registry, when used over time and across countries, this provides a rich data source with possibilities for research.

Although our research does not provide definitive evidence on effectiveness of interventions studied, we found some interesting associations with outcome. First, aggressive therapies should be applied with caution and in the right patients. A wider application of a rational step-wise approach with the application of first tier-treatments before second tier treatments might improve patient outcome and might improve comparability of different policies between centers. In addition, we found a beneficial effect of use of pharmaceutical VTE prophylaxis. Some centres did not apply pharmaceutical VTE prophylaxis in any of their patients, so implementation of pharmaceutical VTE prophylaxis might improve their patient outcomes.

Our findings also have several implications regarding (future) research.

In this thesis we used advanced statistical methods with the final goal to approach causality. However, causal inference remains difficult in observational studies. Therefore, we recommend the application of multiple statistical approaches to address confounding. Also, the results of the interventions we studied in this thesis should be verified in future research. Observational data provide a treasure of information on delivered health care. On the other hand a RCT may provide more definite answers on effectiveness.

In future research, international collaboration should remain a priority with ultimately participation world-wide instead of only European-wide. As the CER methods exploit differences between centres and countries, these differences will only enlarge with world-wide participation (including lower income countries). The same applies to quality registries, the more countries or centres participate, the richer the data source and the more opportunities for benchmarking. When common data elements or standardized quality indicators are used, as developed for TBI in this thesis, this becomes more feasible. With larger data sets, the statistical power of CER will increase, providing more definite answers on quality of care and treatment effectiveness.

Samenvatting

Traumatisch hersenletsel veroorzaakt een enorme gezondheids–en economische last wereldwijd. Traumatisch hersenletsel wordt gedefinieerd als 'een acuut hersenletsel door een mechanische energie tegen het hoofd door externe fysieke krachten' door de wereld gezondheidsorganisatie. Terwijl de primaire hersenschade wordt beschouwd als irreversibel, kan secundaire hersenschade potentieel worden voorkomen door intensieve zorg en behandeling van patiënten op de IC. Specifieke behandelingen voor traumatisch hersenletsel zijn gebaseerd op het behoud van de intracraniële reserve compliantie, door hersendruk monitoring en bestaat uit eerstelijns en meer agressieve tweedelijns behandeling. Hoewel deze op hersendruk gebaseerde en algemene en ondersteunende behandelingen de hoekstenen zijn voor IC zorg voor patiënten met traumatisch hersenletsel, is het bewijs over de effectiviteit hiervan zeldzaam.

Veel Randomized Controlled Trials (RCTs) zijn uitgevoerd om meer bewijs te genereren, maar de meeste hadden geen impact op de klinische praktijk. De teleurstellende resultaten van de meeste RCTs hebben de focus gelegd op een alternatieve aanpak; analyse van grote observationele cohort studies. Comparative Effectiveness Research is zo'n methode; door middel van variatie in de klinische praktijk, het beste (behandel) beleid bepalen. Een alternatieve methode om de kwaliteit van zorg te verbeteren is de implementatie van kwaliteitsindicatoren. Echter, er bestaat nog geen wijdverbreide geaccepteerde kwaliteitsindicatorenset voor patiënten met traumatisch hersenletsel, waarschijnlijk omdat de evidence-base hiervoor beperkt is. Echter, kwaliteitsindicatoren kunnen ook gebieden identificeren waar bewijs gevonden moet worden en onderzoek noodzakelijk is.

Voor de studies in dit proefschrift gebruiken we data van de CENTER-TBI (the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury) studie, een grote observationele cohort studie met 66 ziekenhuizen in Europa. Van alle opgenomen patiënten met traumatisch hersenletsel op de IC zijn gedetailleerde data verzameld over demografische kenmerken, letsel, beeldvorming, IC-opname, monitoring, behandeling, en uitkomsten. Daarnaast werden vragenlijsten uitgestuurd naar deelnemende ziekenhuizen om structuren en processen van zorg op ziekenhuisniveau te bepalen: de Provider Profiling (PP) vragenlijsten.

Het overkoepelende doel van dit proefschrift is om de variatie te beschrijven in het management van patiënten met traumatisch hersenletsel op Europese Intensive Care's, en om de kwaliteit en effectiviteit van enkele componenten van IC zorg voor patiënten met traumatisch hersenletsel te bepalen.

De twee belangrijkste onderzoeksvragen zijn:

1) Wat is de huidige variatie in behandelbeleid voor patiënten met traumatisch hersenletsel op Europese Intensive Care's?
2) Wat is de kwaliteit van IC zorg voor patiënten met traumatisch hersenletsel en hoe kunnen we de effectiviteit en veiligheid van deze behandelingen verbeteren?

Deel 1. Variatie in behandelingen voor patiënten met traumatisch hersenletsel op de intensive care

Hoofdstuk 2 is een overzichtsartikel waarin verblijfsduur op de IC, management aspecten en uitkomsten van IC patiënten met traumatisch hersenletsel worden beschreven en variatie hierin tussen ziekenhuizen in Europa wordt gekwantificeerd met data uit de CENTER-TBI studie. In totaal zijn er 2138 IC patiënten geïncludeerd met een mediane leeftijd van 49 jaar, waarvan 36% met mild hersenletsel (Glasgow Coma Scale; GCS 13-15), de overige patiënten hadden matig (N=328; 16%) tot ernstig hersenletsel (N=961; 48%). Binnen 72 uur werden 636 patiënten (30%) ontslagen (short stay) en 128 (6%) patiënten overleden (early deaths). Early deaths en long stay patiënten (>72 uur) hadden ernstiger letsel dan long stay patiënten gebaseerd op de GCS en CT in vergelijking met short stay patiënten. Long stay patiënten kregen vaker monitoring en werden intensiever behandeld en hadden een slechtere 6 maand uitkomst vergeleken met short stay patiënten. Tussen-ziekenhuis verschillen waren prominent in het aantal short stay patiënten (MOR=2.3, p<0.001), gebruik van intracraniële druk monitoring (MOR = 2.5, p < 0.001) en agressieve behandelingen (MOR=2.9, p<0.001) maar het verschil was kleiner tussen ziekenhuizen in 6-maand uitkomst (MOR=1.2, p=0.01). We concluderen dat de helft van de huidige opgenomen traumatisch hersenletsel patiënten mild tot matig hersenletsel heeft. Substantiële ziekenhuis verschillen zijn IC verblijfsduur en behandelingen, maar we zien minder verschil in uitkomst. Het blijft onduidelijk of opname van short stay patiënten de juiste mate van voorzichtigheid weergeeft of onjuist gebruik van de IC voorzieningen, dit zou verder onderzocht moeten worden.

In **hoofdstuk 3** wordt het beleid rondom hersendruk monitoring in Europa beschreven. Tot nu toe is er weinig bewijs over hoe intracraniële druk behandeld moet worden bij patiënten met traumatisch hersenletsel. Het is daarom waarschijnlijk dat er veel variatie is tussen ziekenhuizen en clinici. Het doel van dit onderzoek was om de variatie in hersendruk monitoring en behandeling voor verhoogde hersendruk bij patiënten met traumatisch hersenletsel te onderzoeken. Hiervoor is de PP vragenlijst met 29 items ontwikkeld op basis van de literatuur en feedback van klinische experts en getest in 16 ziekenhuizen. Deze vragenlijst is vervolgens gestuurd naar 68 neurotrauma ziekenhuizen die meedoen

aan de CENTER-TBI studie. De vragenlijst is ingevuld door 66 ziekenhuizen (97% response rate). Ziekenhuizen waren voornamelijk academisch (N=44; 67%) en level I trauma centra (N=44; 67%). De Brain Trauma Foundation guidelines werden toegepast in 49 (74%) van de ziekenhuizen. Ongeveer 90% van de ondervraagden (N=58) gaven aan dat zij een hersendruk monitor plaatsen bij patiënten met ernstig hersenletsel en afwijkingen op CT. Er is geen consensus gevonden rondom het beleid van hersendruk monitor insertie. Grote variatie werd gevonden in het gebruik van eerste- en tweedelijns behandeling voor verhoogde hersendruk. Ongeveer de helft van de ziekenhuizen heeft een agressief behandelingsbeleid wat betreft hersendruk monitoring en behandeling (N=32; 48%), terwijl de andere ziekenhuizen als meer conservatief kunnen worden beschouwd (N=34; 52%). Concluderend, er is substantiële variatie gevonden wat betreft het hersendruk monitoring- en behandel beleid voor patiënten met traumatisch hersenletsel en intracraniële druk verhoging. Deze resultaten tonen aan dat er weinig consensus is tussen Europese neurotrauma ziekenhuizen. Verder vergelijkend onderzoek tussen ziekenhuizen (comparative effectiveness research) is dus nodig.

In **hoofdstuk 4** beschrijven we variatie in bloedtransfusie- en stollingsbeleid bij ziekenhuizen in Europa. Wederom werden de PP vragenlijsten beantwoord door 66 ziekenhuizen, met een focus op 1) het hemoglobine level als grens voor bloedtransfusie (Hb-TL), 2) stollingsbeleid,en 3) diep veneuze trombose (DVT) profylaxis. Voor patiënten op de IC gaf de helft van de ziekenhuizen (N=34; 52%) aan dat ze een protocol hadden met een specifieke Hb-TL. Voor patiënten met traumatisch hersenletsel, gaven 36 ziekenhuizen (41%) aan een Hb-TL range van 70 tot 90 g/L en 38 ziekenhuizen (59%) een Hb-TL boven 90 g/L. Voor trauma-gerelateerde stollingsstoornissen werd meestal fresh frozen plasma (N=48; 73%) of bloedplaatjes (n=34; 52%) gebruikt, gevolgd door het toedienen van vitamine K (N=26; 39%). Tranexamic acid werd minder vaak gebruikt (N = 7; 11%). De meeste ziekenhuizen rapporteerden het gebruik van DVT profylaxis met anticoagulantia met vaak tot altijd (N=62; 94%). In de afwezigheid van traumatische hersenbloedingen, gaven 14 ziekenhuizen (21%) aan DVT profylaxis pas na 72 uur te geven. Bij de aanwezigheid van traumatische hersenbloedingen, gaven meer ziekenhuizen dit aan (N=29; 46%). Er is dus geen consensus over het bloedtransfusie- en stollingsbeleid tussen Europese IC's.

In **hoofdstuk 5** gaan we in op de variatie in meer algemeen IC beleid voor patiënten met traumatisch hersenletsel in Europese ziekenhuizen. We maken hierbij opnieuw gebruik van de PP vragenlijsten. Hierbij richten we ons op 23 vragen met betrekking tot 1) circulatie en beademingsbeleid, 2) behandeling van koorts, 3) gebruik van corticosteroïden, 4) voeding en glucose management, 5) profylaxis en behandeling van (epileptische) aanvallen. De vragenlijsten werden meestal ingevuld door intensivisten (N=33; 50%) en neurochirurgen (N=23; 35%) uit 66 ziekenhuizen. De meesten geven aan dat de cerebrale perfusie druk >60 mmHg (N=39;60%) was of een geïndividualiseerd target (N=25; 38%).

Om de cerebrale perfusie druk te behouden, werd meestal kristalloïden (N=60; 91%) gegeven in plaats van albumine (N=15; 23%), en vasopressors (N= 63; 96%) in plaats van inotropica (N= 29; 44%). Meestal werd een partiële druk van carbon dioxide in arterieel bloed ($PaCO_2$) aangegeven van 36-40 mmHg (4.8-5.3 kPa) bij gecontroleerde hersendruk <20 mmHg, en een $PaCO_2$ van 30-35 mmHg (4-4.7 kPa) bij een verhoogde hersendruk (N=40; 62%). De meeste ziekenhuizen gaven aan vaak koorts te behandelen (N=65; 98%) met paracetamol (N=61;92%) en/of externe koeling (N=49; 74%). Conventioneel glucose management (N=43; 66%) werd verkozen boven tight glycemic control (N=18; 28%). Meer dan de helft van de ziekenhuizen richt zich op volledige calorische intake binnen 7 dagen (N=43; 66%) met gebruik van enterale voeding (N=60; 92%). De indicaties en duur van (epileptische) aanvallen voor gebruik van profylaxis varieerden; meestal werd levetiracetam als voorkeursmedicatie aangegeven voor zowel profylaxis (N=332; 49%) als ook behandeling (N=40; 61%).

Deel 2. Richting verbetering van de dagelijkse traumatisch hersenletsel zorg

In **hoofdstuk 6** wordt de ontwikkeling van een kwaliteitsindicatorenset beschreven voor patiënten met traumatisch hersenletsel die worden opgenomen op een IC in Europa. Ook beschrijven we de barrières en facilitators voor implementatie. Eerst werd een lijst met 66 kwaliteitsindicatoren ontwikkeld, gebaseerd op de huidige richtlijnen, variatie in beleid, en klinische expertise van traumatisch hersenletsel management op de IC. Acht experts in traumatisch hersenletsel van de adviserende commissie selecteerden kwaliteitsindicatoren gedurende de eerste ronde. Een groter expert panel uit heel Europa werd geworven voor de volgende twee Delphi rondes. Kwaliteitsindicatoren werden geëvalueerd op basis van 4 criteria; validiteit (betere prestatie op de indicator reflecteert betere processen van zorg en leidt tot betere patiënt uitkomsten), haalbaarheid (data zijn beschikbaar en makkelijk te verkrijgen), discriminatie (variatie in de klinische praktijk), en vervolgbaarheid/ actie (professionals kunnen op basis van de indicator handelen). Experts scoorden de kwaliteitsindicatoren op een 5-punts Likert schaal via een elektronische vragenlijst. Het expert panel bestond uit 50 experts uit 18 landen in Europa en voornamelijk intensivisten (N=24; 48%) en neurochirurgen (N=7;14%). Experts werden het eens over een uiteindelijke set van 42 indicatoren om de kwaliteit van IC zorg vast te stellen: 17 structuur indicatoren, 16 proces indicatoren en 9 uitkomst indicatoren. Experts waren gemotiveerd om deze uiteindelijke set te implementeren (N=42; 98%) met routine metingen in registers (N=41; 82%), benchmarking (N=42; 84%) en kwaliteitsverbetering programma's (N=41; 82%) als vervolgstappen. Administratieve last werd aangegeven als de meest belangrijke barrière voor het implementeren van de kwaliteitsindicatoren set (N=48; 98%). Deze Delphi consensus studie geeft daarmee inzicht in welke kwaliteitsindicatoren potentie hebben

om de kwaliteit van zorg voor patiënten met traumatisch hersenletsel op Europese ICs te verbeteren. We adviseren de voorgestelde kwaliteitsindicatoren set te gebruiken voor registratie in Europa om inzicht te krijgen in de huidige processen van IC zorg en uitkomsten van patiënten met traumatisch hersenletsel. Deze indicatoren set kan een belangrijk middel worden voor benchmarking en kwaliteitsverbeterings programma's voor patiënten met hersenletsel in de toekomst.

In **hoofdstuk 7** worden de kwaliteitsindicatoren die zijn ontwikkeld in de Delphi studie getest in de CENTER-TBI database om te testen of ze gebruikt kunnen worden voor kwaliteitsmeting en verbetering. Hiervoor selecteerden we 2006 volwassen patiënten die werden opgenomen in 54 IC's van 2014 tot 2018. Indicator scores werden berekend als percentage adherentie voor structuur en procesindicatoren en als aantal events of mediane scores voor uitkomst indicatoren. Haalbaarheid werd gekwantificeerd door de volledigheid van de datavariabelen. Discriminatie werd bepaald door de tussen-ziekenhuis variatie, die werd ingeschat door een random effect regressie model gecorrigeerd voor de ernst van de ziekte en gekwantificeerd door de Mediane Odds Ratio (MOR). Betrouwbaarheid van uitkomstindicatoren werd bepaald door het mediane aantal events per ziekenhuis met een grens van 10. In totaal konden 26 van de 42 indicatoren worden berekend in de CENTER-TBI database. De meeste indicatoren hadden een goede haalbaarheid met meer dan 70% data volledigheid. Suboptimale adherentie werd gevonden voor de meeste indicatoren variërend van 26-93% en 20-99% voor stuctuur- en proces indicatoren. Significante ($p<0.001$) tussen-ziekenhuis verschillen werden gevonden voor 7 proces en 5 uitkomst indicatoren met MORs variërend van 1.51-4.14. Betrouwbaarheid van uitkomstindicatoren was over het algemeen laag, 5 van de 7 indicatoren had minder dan 10 events per ziekenhuis. We concluderen dat 9 structuur, 5 proces, maar geen van de uitkomst indicatoren kan worden gebruikt voor kwaliteitsverbeteringsdoeleinden voor patiënten met traumatisch hersenletsel op de IC. Toekomstig onderzoek zou zich moeten richten op implementatie en continue re-evaluatie van de kwaliteitsindicatoren.

In **hoofdstuk 8** bestuderen we het gebruik van intensieve behandelingen (hoge doses barbituraten, hypothermie (<35 °C), intensieve hyperventilatie ($PaCO_2$ <4 kPa) en secundaire decompressive craniectomie) en de associatie met uitkomst bij patiënten met een hersendruk monitor opgenomen op de IC in de CENTER-TBI database. Een random effect logistisch regressie model werd gebruikt om de tussen-ziekenhuis verschillen te bepalen in gebruik en een propensity-score-matching model om de impact op uitkomst te bepalen (6 maanden GOSE (Glasgow Outcome Score-Extended)) met correctie voor confounders zoals ziekte-ernst, klinische symptomen voor cerebrale herniatie op beeldvorming en verhoogde hersendruk. In totaal kregen 318 van de 772 patiënten uit 52 Europese IC's (41%) tenminste 1 intensieve behandeling tijdens verblijf op de IC, met daarbij significante tussen-ziekenhuis verschillen in het gebruik (MOR=2.26). Patiënten kregen niet altijd alle

(of zelfs de meeste) eerstelijns behandelingen voordat ziekenhuizen op deze intensieve behandelingen overgingen. Van de patiënten met intensieve behandelding had 38% een gunstige uitkomst (GOSE > 5). Het gebruik van intensieve behandeling was niet significant geassocieerd met een slechtere uitkomst (285 matching, , OR: 1.4, 95% CI [1.0 -2.0], p=0.068). Echter een sensitiviteitsanalyse met exclusie van intensieve behandeling of diepe sedatie op dag 1 liet een significant verschil zien met slechtere uitkomst. We concluderen dat er substantiële verschillen bestaan tussen ziekenhuizen in het gebruik van intensive hersendruk verlagende behandelingen. Vaak werden de intensieve behandelingen niet vooraf gegaan door de meer conventionele eerstelijns behandelingen. De associatie tussen intensieve behandeling en slechtere uitkomst kan behandelagressiviteit weergeven of ongemeten confounding of onjuiste inzet van eerstelijns behandeling.

In **hoofdstuk 9,** wordt het farmaceutische VTE (veneuze trombose events) profylaxe beleid beschreven en wordt de effectiviteit van het gebruik van farmaceutische VTE profylaxe op uitkomst bestudeerd. Patiëntdata van de CENTER-TBI studie zijn gebruikt. Patiënten opgenomen op de IC en ouder dan 18 jaar zijn geïncludeerd. Om de variatie tussen ziekenhuizen in het gebruik van farmaceutische VTE profylaxe te bepalen is een random effect model gebruikt met farmaceutische VTE profylaxe als uitkomst, gecorrigeerd voor confounders, en ziekenhuis als random intercept, en gekwantificeerd met de Median Odds Ratio (MOR). De associatie tussen farmaceutische VTE profylaxe en uitkomst (GOSE op 6 maanden) werd bepaald op ziekenhuisniveau, met een instrumental variable analyse met het percentage farmaceutische VTE profylaxe per ziekenhuis als instrument en een random intercept voor ziekenhuis en gecorrigeerd voor confounders. Een patiënt-niveau analyse werd uitgevoerd, met gebruik van een propensity score matching model en een adjusted model voor zowel bij prophylaxe tijdens als na ICU opname. Een Cox survival regressie analyse werd uitgevoerd met mortaliteit als event en een tijdsafhankelijke variabele voor het gebruik van farmaceutische VTE. Op patient-niveau werd ook het effect op CT progressie onderzocht. Subgroep analyses werden gedaan voor patiënten met traumatisch hersenletsel zonder extracranieel letsel, voor patiënten met traumatische letsels op CT, en voor patiënten met een lange IC ligduur (>72 uur). In totaal werden 2006 IC patiënten geïncludeerd 1279 (64%) kregen farmaceutische VTE profylaxis en 56 patienten (2%) had een klinische VTE tijdens verblijf in het ziekenhuis. Substantiële tussen-ziekenhuis variatie werd gevonden in het gebruik van farmaceutische VTE profylaxis (MOR=2.7, p<0.001). Een significante associatie op patiënt-niveau (propensity OR: 1.5 [1.1-2.0] and adjusted OR: 1.4 [1.1-1.7]) werd gevonden, op ziekenhuisniveau waren de associaties niet significant. Subgroep analyses bevestigen een significante verbetering op patiënt-niveau. Er is geen effect op CT progressie gevonden (OR:0.9 CI [0.7-1.3]). Overleving was hoger in de groep die farmaceutische VTE profylaxis kreeg toegediend (p<0.001). We concluderen dat er substantieel tussen-ziekenhuis variatie is in het gebruik van farmaceutische VTE profylaxis

in Europa, terwijl de resultaten suggereren dat er een associatie is met verbeterde uitkomst na 6 maanden.

In **hoofdstuk 10** (Discussie) worden de resultaten en conclusies van de studies uit dit proefschrift overwogen. Het overkoepelende doel van dit proefschrift is om de variatie te beschrijven in het management van patiënten met traumatisch hersenletsel op Europese Intensive Care's, en om de kwaliteit en effectiviteit van enkele componenten van IC zorg voor patiënten met traumatisch hersenletsel te bepalen.

De eerste onderzoeksvraag was: *'Wat is de huidige variatie in behandelbeleid voor patiënten met traumatisch hersenletsel op Europese Intensive Care's?*'

We hebben substantiële verschillen gevonden in het IC beleid voor patiënten met traumatisch hersenletsel tussen ziekenhuizen in Europa; dit bleek zowel uit de resultaten van de Provider Profiling vragenlijsten als de patiënt data uit de CENTER-TBI studie. Variatie werd vooral gevonden in de structuren en processen van zorg, maar minder in uitkomst.

De tweede specifieke onderzoeksvraag was: *'Wat is de kwaliteit van IC zorg voor patiënten met traumatisch hersenletsel en hoe kunnen we de effectiviteit en veiligheid van deze behandelingen verbeteren?'*

Om de kwaliteit van zorg te bepalen hebben we een kwaliteitsindicatorenset ontwikkeld specifiek voor traumatisch hersenletsel. Na validatie, 9 structuur, 5 proces, maar geen van de uitkomstindicatoren waren geschikt voor kwaliteitsverbeteringsdoeleinden. Verder vonden we dat hoge intensiteitsbehandelingen mogelijk geassocieerd zijn met slechte uitkomst na 6 maanden en dat farmaceutische VTE profylaxe mogelijk geassocieerd is met verbeterde uitkomst na 6 maanden.

Onze bevindingen hebben enkele implicaties voor de klinische praktijk.

Inzicht in huidig ziekenhuisbeleid in Europa, kan artsen alert maken op andere ziekenhuisprotocollen en opties. Kennisuitwisseling tussen ziekenhuizen (benchmarking) zou nieuwe ideeën kunnen genereren over hoe de zorg te verbeteren. Praktijk variatie biedt mogelijkheden om klinische onderwerpen te bestuderen en onderzoeksinitiatieven te starten.

Het meten van kwaliteit van zorg kan bijdragen aan verschillende doeleinden en stakeholders. Ten eerste, kwaliteitsindicatoren kunnen het ziekenhuis of de IC voorzien van informatie over het verbeteren van zorg en in welke klinische gebieden dit het meest nodig is. Ten tweede, wanneer kwaliteit van zorg gemeten wordt over internationale grenzen,

dan kunnen ziekenhuizen hun beleid vergelijken en leren van elkaar (benchmarking). Ten derde, met het gebruik van kwaliteitsindicatoren kunnen ziekenhuizen hun transparantie verbeteren ten opzichte van andere stakeholders (zoals de overheid). Daarnaast met het gebruik van kwaliteitsindicatoren kunnen ziekenhuizen hun IC zorg monitoren. Ten slotte, wanneer kwaliteitsindicatoren onderdeel worden van een kwaliteitsregistratie, en gebruikt worden door de tijd heen en over landsgrenzen, kan dit een waardvolle database genereren met mogelijkheden voor onderzoek.

Hoewel ons onderzoek geen definitieve antwoorden geeft over de effectiviteit van de bestudeerde interventies, werden enkele interessante associaties met uitkomst gevonden. Ten eerste, agressieve behandelingen moeten met zorg (voorzichtig) toegepast worden en bij de juiste patiënten. Een bredere toepassing van een rationele stapsgewijze aanpak met toepassing van eerstelijns behandelingen vóór het gebruik van tweedelijns (agressievere) behandeling kan de patiënten uitkomsten verbeteren en kan de vergelijking tussen verschillend behandelbeleid tussen ziekenhuizen makkelijker maken. Daarnaast vonden we een gunstig effect van het gebruik van farmaceutische VTE profylaxe. Sommige ziekenhuizen passen helemaal geen farmaceutische profylaxe toe, dus implementatie van farmaceutische VTE profylaxe kan hun patiënt uitkomstmaten verbeteren.

Onze bevindingen hebben ook enkele implicaties voor (toekomstig) onderzoek.

In dit proefschrift gebruiken we enkele geavanceerde statische methoden met als einddoel causaliteit te benaderen. Echter, causale verbanden blijven moeilijk in observationele studies. Daarom bevelen we het gebruik van meerdere statische methoden aan om confounding aan te pakken. Daarom moeten de resultaten van de interventies die wij hebben onderzocht in dit proefschrift geverifieerd worden in toekomstig onderzoek. Observationele data bieden een schat aan informatie over de geleverde zorg. Aan de andere kant kan een RCT meer definitieve antwoorden geven over de effectiviteit.

In toekomstig onderzoek moeten internationale samenwerkingen een prioriteit blijven met uiteindelijk wereldwijde participatie in plaats van alleen Europese. Aangezien de CER methode van verschillen tussen ziekenhuizen en landen gebruik maakt, zullen die verschillen alleen maar toenemen met wereldwijde participatie. Hetzelfde geldt voor kwaliteitsregistraties, hoe meer landen en ziekenhuizen meedoen, hoe beter de data base met meer mogelijkheden voor benchmarking. Wanneer common data elements of gestandaardiseerde kwaliteitsindicatoren worden toegepast, zoals ontwikkeld in dit proefschrift, wordt dit makkelijker haalbaar. Met grotere datasets, verbetert de statische power van CER analyses, waardoor meer definitieve antwoorden gegeven kunnen worden over de kwaliteit van zorg en behandeleffectiviteit.

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2. Ercole A, Brinck V, George P, Hicks R, **Huijben J**, Jarrett M, Vassar M, Wilson L; DAQCORD collaborators. Guidelines for Data Acquisition, Quality and Curation for Observational Research Designs (DAQCORD). **J Clin Transl Sci.** 2020
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4. Meeuws S, Yue JK, **Huijben JA**, Nair N, Lingsma HF, Bell MJ, Manley GT, Maas AIR. Common Data Elements: Critical Assessment of Harmonization between Current Multi-Center Traumatic Brain Injury Studies. **J Neurotrauma** 2020
5. **Huijben J.A.**, Wiegers EJA, Ercole A, de Keizer N.F., Maas AIR, Steyerberg E.W., Citerio G, Wilson L, Polinder S, Nieboer D., Menon D, Lingsma H.F., Quality indicators for patients with Traumatic Brain Injury in European Intensive Care Units: a CENTER-TBI study. **Critical Care** 2020
6. **Huijben J.A.**, Wiegers EJA, Lingsma HF, Citerio G, Maas AIR, Menon DK, Ercole A, Nelson D, van der Jagt M, Haitsma I, Steyerberg EW, Birg T, Zoerle T, Carbonara M, Stocchetti N., Changing care pathways and between-center practice variations in intensive care for traumatic brain injury across Europe: a CENTER-TBI analysis. **Intensive Care Medicine** 2019
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9. Volovici V, Ercole A, Citerio G, Stocchetti N, Haitsma IK, **Huijben JA**, Dirven CMF, van der Jagt M, Steyerberg EW, Nelson D, Cnossen MC, Maas AIR, Polinder S, Menon DK, Lingsma HF. Intensive care admission criteria for traumatic brain injury patients across Europe. **J Crit Care.** 2019
10. Volovici V, **Huijben JA**, Ercole A, Stocchetti N, Dirven CMF, van der Jagt M, Steyerberg EW, Lingsma HF, Menon DK, Maas AIR, Haitsma IK. Ventricular drainage catheters versus intracranial parenchymal catheters for intracranial pressure monitoring-based

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12. Cnossen MC, **Huijben JA**, van der Jagt M, Volovici V, van Essen T, Polinder S, Nelson D, Ercole A, Stocchetti N, Citerio G, Peul WC, Maas AIR, Menon D, Steyerberg EW, Lingsma HF, Variation in monitoring and treatment policies for intracranial hypertension in traumatic brain injury: a survey in 66 neurotrauma centers participating in the CENTER-TBI study. **Crit Care.** 2017

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15. Huijben J, Jansen M, Ginjaar IB, Lammens M, van Putten M, van Alfen N, de Groot IJ., What can we learn from an assisted bicycle training in a girl with dystrophinopathy? A case study. **Journal of child neurology** 2015

About the author

Jilske was born in Breda, the Netherlands, on 16th December 1989, and grew up in Hoeven with her parents, 2 sisters and brother. After graduating cum laude from the gymnasium in Etten-Leur, she started her study medicine at the Radboud University in Nijmegen. During her master program, she was awarded a Radboud Honours scholarship to conduct research in Italy. This research project was granted by the Johanna Kinderfonds to continue for a year at the Radboud UMC Nijmegen.

In September 2016, she started her PhD at the department of Public Health in Rotterdam on the international EU funded CENTER-TBI study under the supervision of prof. Ewout Steyerberg, dr. Hester Lingsma, and dr. Mathieu van der Jagt. Her PhD research focused on the effect of the quality of care and treatments on outcome in patients with Traumatic Brain Injury admitted to the Intensive Care Unit. During her PhD, Jilske went to Cambridge, UK for a research visit of 3 months.

In November 2020, she started working as postdoctoral researcher investigating the therapies for kidney disease within the ERA-EDTA registry at the Amsterdam UMC.

Jilske werd geboren in Breda op 16 december 1989, en groeide op in Hoeven met haar ouders, 2 zussen, en broertje. Na haar gymnasium cum laude behaald te hebben, begon ze haar studie geneeskunde aan de Radboud Universiteit in Nijmegen. Tijdens haar master stage kreeg ze een Radboud Honours award om een onderzoeksproject uit te voeren in Italië. Dit onderzoek werd voort gezet gedurende een jaar op de Raboud UMC in Nijmegen na het verkrijgen van een subsidie van het Johanna Kinderfonds.

Hierna, in september 2016, startte ze haar PhD op de afdeling Public Health in Rotterdam bij de internationale Europese CENTER-TBI studie onder de supervisie van prof. Ewout Steyerberg, dr. Hester Lingsma, en dr. Mathieu van der Jagt. Haar PhD richtte zich op de effecten van de kwaliteit van zorg en behandelingen op uitkomst bij patiënten met traumatisch hersenletsel op de Intensive Care. Tijdens haar PhD ging Jilske voor 3 maanden naar Cambridge in het Verenigd Koninkrijk.

Per 1 november 2020 is Jilske begonnen als postdoc met een onderzoek naar de behandelingen voor nierziekten binnen de ERA-EDTA registratie in het Amsterdam UMC.

Portfolio

Name PhD student: Jilske (A.L.C.J.R.M.) Huijben
Erasmus MC department: Public Health, Medical Decision
Promotor: Ewout W. Steyerberg
Co-promotors: Hester F. Lingsma
Mathieu van der Jagt

	Year	Workload (ECTS)
PhD training		
Weekly seminar of the department of Public Health, Erasmus MC	2016-2020	5
'Principles of Research in Medicine and Epidemiology', Erasmus MC	2016	0.7
'Methods of Public Health Research', Erasmus MC	2016	0.7
'Causal inference', Erasmus MC	2016	1.4
English C1 course, masterclass English, Rotterdam	2017	4
Workshop systematic review, UZA, Antwerpen	2017	0.7
BKO workshop, Erasmus MC	2017	0.3
Data curation workshop, UZA, Antwerpen	2017	1
'Biostatistical methods I: Basic Principles', Erasmus MC	2017	5.7
'Biostatistical methods II: Classical Regression Models', Erasmus MC	2017	4.3
Launch Lancet article, Brussel	2017	0.3
CER workshop, Erasmus MC	2018	2
Conferences and research visits		
IBIA conference New Orleans, poster presentation	2017	1
MICA conference Brussel	2017	0.3
Research meeting, Ospedale Maggiore Policlinico, Milano, Italië	2018	2
Euroneuro conference, Brussel, poster presentation	2018	1
Research visit, Addenbrooke's hospital, Cambridge,UK	2019	2
Teaching		
Supervision community projects bachelor medicine, Erasmus MC	2016	2
Reviewing bachelor thesis bachelor medicine, Erasmus MC	2016	2
Supervision master thesis student medicine, Erasmus MC	2019	1
Total (min 30 ECTS)		42.4

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