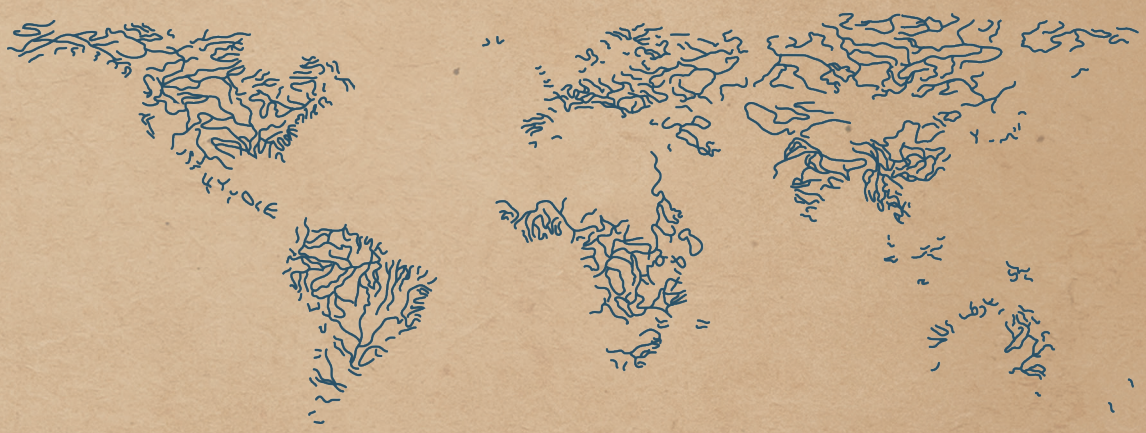
Comparative Effectiveness Research to Improve Neurocritical Care



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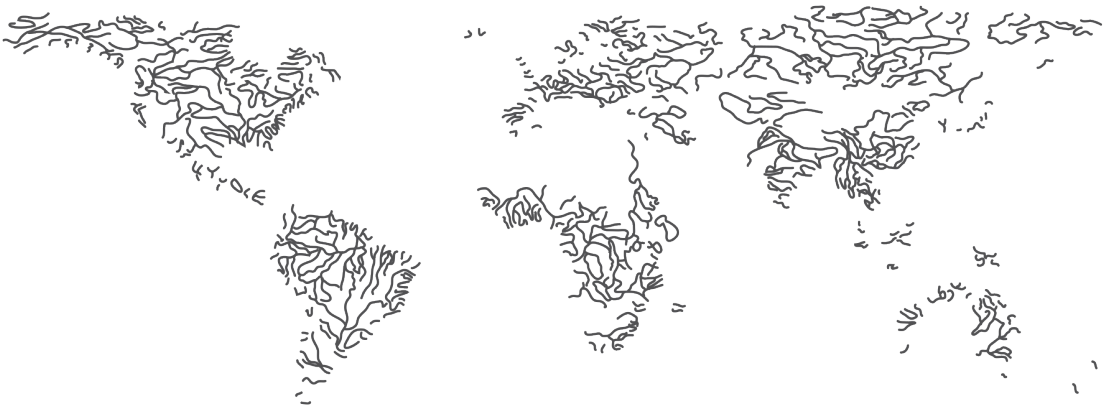
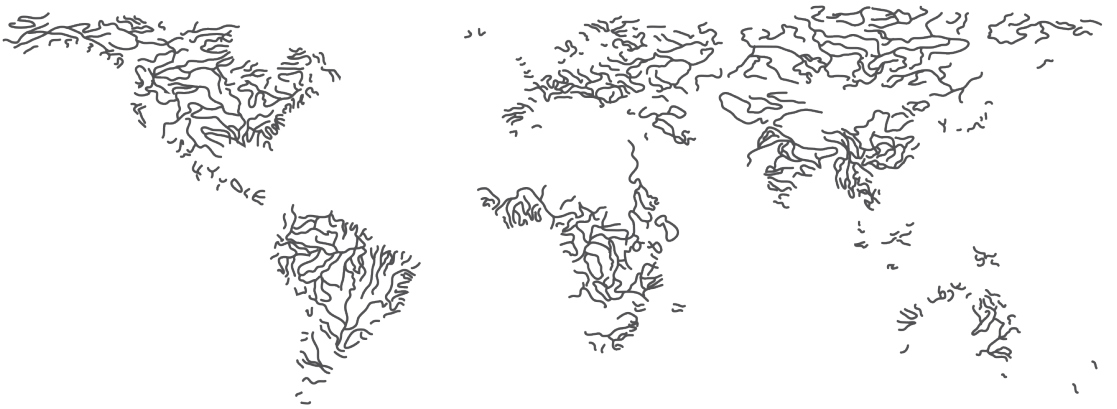


Chapter 1

General Introduction



NEUROCRITICAL CARE

During the Crimean War in the 1850s, Florence Nightingale introduced the origins of ´Critical Care Medicine´. She moved the most seriously ill patients to the beds opposite to the nursing station so that they could be watched more closely[1,2]. In 1923, a special three-bed unit in which specially trained nurses cared for critically ill postoperative neurosurgical patients was created by an American neurosurgeon in the Johns Hopkins Hospital. The poliomyelitis epidemics in the 1940s and the 1950s accelerated the introduction of a new generation of dedicated physicians and professional nurses in special critical care units[1,3]. Rapid advances in both monitoring and measurement technologies triggered new interventions and accelerated the progress in the management of the acutely life-threatened patients[4,5]. During the 1970s and the 1980s, developments in neuro-anaesthesia and neurosurgical techniques allowed more complex operative interventions that required higher levels of care in the postoperative period. In association with immediate access to neurosurgical support in the event of neurological deterioration, the earliest neurocritical care units were established[1,6,7].

Neurocritical care, specifically, is crucial in providing meticulous neuroprotection, mainly by avoiding or minimizing secondary neurological injury, recognizing and treating systemic complications, ultimately to have the best possible recovery for patients[8] (Box 1.1). Neurocritical care can be either provided in general Intensive Care Units (ICUs) or in dedicated neurocritical care units. Dedicated neurocritical care units can bring together a group of highly skilled healthcare providers who by repeatedly caring for similar types of conditions can refine their practices[8,9].

Box 1.1 Definition of Neurocritical Care used for this thesis

Neurocritical Care is a maturing subspecialty of critical care medicine that seeks to integrate content expertise in critical care neurology, skill and experience in general critical care management, and consistent provision of evidence-based practices for patients with brain or spinal cord injuries.

Kramer & Coullaird: Neurocritical Care: A Growing International Collaborative[6]

Two specific patient groups often requiring intensive monitoring and treatments and therefore neurocritical care are patients with Traumatic Brain Injury (TBI) and stroke. TBI and stroke are major public health concerns with an annual incidence in Europe of

2.1 million patients with TBI and 1.1 million patients with stroke[10,11]. Both stroke patients and patients with TBI often experience symptoms of cognitive impairment, next to significant functional impairment, influencing all-day activities, even for years after the event[12,13].

In the past, substantial efforts have been made to optimize treatment strategies for these neurocritical care patients. Several randomized controlled trials (RCTs) proved the benefit of endovascular thrombectomy (EVT) for patients with acute ischemic stroke and large vessel occlusion[14-19]. For patients with TBI, there is no proven single neuroprotective therapy that is highly effective[20]. Guideline recommendations for TBI care have a relatively weak scientific foundation, leaving opportunity for individual treatment preferences depending among others on resource availability, resulting in variation of care[21,22]. Comparative Effectiveness Research (CER) has been proposed to study the most effective treatments and management strategies for patients with TBI admitted to the ICU. CER aims to measure benefits and risks of systems of care and specific interventions in daily clinical practice with the ultimately goal to inform best practices and improve outcomes[23-25].

Systems of care and interventions are all determinants of quality of care, a major topic in health care. Improving quality of care can lead to improved clinical outcomes, lower healthcare costs, and equal access of care in hospitals and countries. But, clinical outcomes are influenced by many factors, which complicates measurement and improvement of quality of care[26]. Quality indicators are measurable aspects of quality of care and have been developed in many clinical fields proving to benefit clinical outcomes[27].

Improving outcomes in neurocritical care patients can be approached in different ways. Treatments that intervene in the pathophysiological pathway of a disease are evident methods to potentially improve outcomes, although in the past this strategy has not always been proven to be effective[28,29]. However, quality of care also plays an important role in daily clinical practice. E.g. the implementation of a new treatment intervening in the pathophysiological pathway is accelerated by adequate quality of care in order to improve clinical outcomes. In this thesis, we will look into to the organization and effectiveness of neurocritical care for patients with stroke and TBI.

TRAUMATIC BRAIN INJURY

Historically, TBI was considered as a disease of predominantly healthy young men. A large living systematic review found a mean age of 27 to 45 in several studies that evaluated the global epidemiological patterns of TBI. The reported proportion of men with TBI was indeed larger than that of women, and ranged from 55% in Sweden to 80% in Ireland[30-32]. A study by Myburgh et al, describing the epidemiological profile of TBI patients in Australia and New Zealand, observed that the mean age of patients with TBI that are admitted to the ICU was 42 years with a large proportion of male patients (74%)[33]. However, over the past years an increased proportion of women and older patients has been observed[34,35]. Older age is known to negatively influence outcome after TBI[36-38].

The epidemiological shift from TBI affecting mainly younger men to older and more women currently occurring, is also reflected by the shift of the leading cause of TBI, namely from road traffic incidents to falls. Road traffic incidents are reported to be the dominant mechanism of injury in most studies that include data from before 2000. Studies that included data from after 2000, however, mainly report falls as the main cause of TBI[39]. The decline of the incidence of TBI resulting from road traffic incidents might be explained by improvements in vehicle safety and safety precautions, as well as road safety mass media campaigns[40,41].

Many patients with TBI require extensive brain monitoring and receive intensive care management and are therefore admitted to the Intensive Care Unit (ICU). In the United Kingdom, approximately 10% of all ICU admissions and about 10% of admission to neurocritical care units are due to TBI[42]. The traditional classification of TBI relies on the Glasgow Outcome Scale (GCS), which consists of three components: Eye, Motor, and Verbal. The classical subdivision of TBI is mild (GCS 13-15), moderate (GCS 9-12), and severe (GCS 3-8)[43-45]. Patients with TBI who are admitted to the ICU generally suffer from moderate or severe injury[46], although some studies report large proportions of mild patients with TBI in the ICU[47].

Patients with TBI admitted to the ICU are at high risk of death and poor functional outcome. ICU mortality in TBI patients is around 18%, and increases to 26% at 6 months. It is estimated that independent survival by 6 months is achieved in only 39% of patients. A large prospective cohort study in Australia and New Zealand recorded favorable outcomes at 12 months in 60% of critically ill TBI patients[33]. Over the past years, a global decline in mortality due to TBI has been observed, although the proportion of independent long-term outcome has not improved[48,49].

STROKE

Each year, approximately 1.1 million European inhabitants suffer a stroke[11,50]. Ischemic stroke accounts for approximately 80% of all stroke cases. The risk for stroke increases with age, which means that women typically have higher stroke risk[51]. The incidence in the elderly population is decreasing, but the aging population and the increase of observed rates in the young adults have led to higher number of stroke cases. Therefore, there is an increased attention for prevention and improved care for stroke patients[11,52,53]. Other major risk factors for stroke, including many preventable risk factors, are high blood pressure, diabetes, heart diseases, smoking, and a family history of stroke[51]. The in-hospital mortality rate for ischemic stroke patients is approximately 10-20%[54,55]. Many survivors face challenges of residual disability which affects their quality of life and is associated with poorer prognosis due to increase in stroke recurrences. In all patients that survive stroke, almost 50% experience a recurrent stroke. Both stroke recurrence and long-term mortality are affected by several modifiable risk factors, and thus amenable to secondary prevention strategies[13].

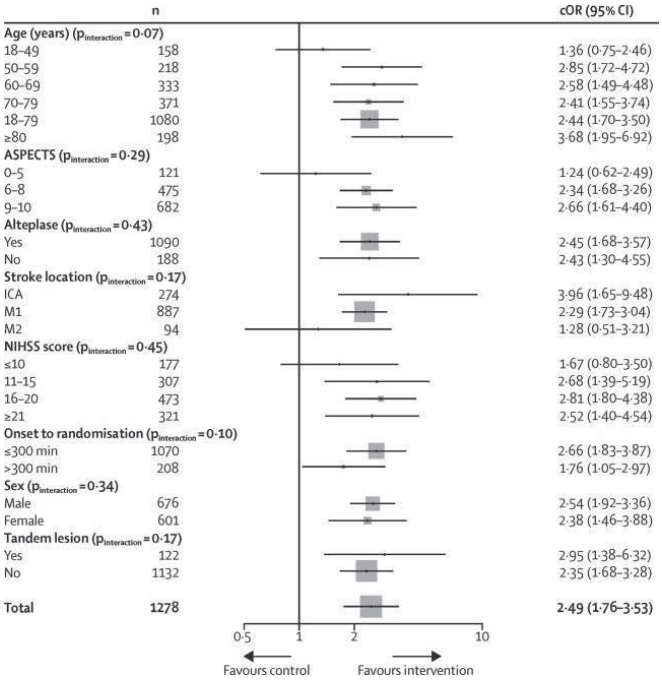


Figure 1.1 Meta-analysis of individual patient data from five randomised trials for the effect of endovascular thrombectomy after large-vessel ischaemic stroke[19]

The aim of treatment in the acute phase is reperfusion of the brain to restore blood flow to the regions of the brain that are ischemic but not yet infarcted. Options for reperfusion therapy that are proven effective include intravenous thrombolysis (IVT) and EVT. The benefit of EVT has been proven in several RCTs, and has revolutionised ischemic stroke treatment[14,16-19] (Figure 1.1). During the procedure of EVT, a catheter is inserted into an artery in the groin or arm and moved towards the blood clot under X-ray guidance. Subsequently, large stroke-causing clots are removed by trapping it in a stent which is then pulled out with the clot, or the clot may be sucked out through a catheter. If the clot cannot be removed, stroke physicians may try to liquefy the clot by applying local thrombolytics[23]. Complications after EVT are low but do occur and include the risk of haemorrhage or the movement of blood clots to parts of the brain that were initially not affected by the stroke[24]. The results of these RCTs have led to the incorporation of EVT in stroke guidelines[56,57].

The effectiveness and potential of EVT has been well-communicated among all stakeholders, but the implementation of EVT into daily clinical practice might be hampered by several organizational aspects. Implementation research is an integrated concept that links research and practice to accelerate the development and delivery of public health approaches, ultimately leading to improved clinical outcomes and lower healthcare costs[58]. When implementation lags behind the evidence, studies on implementation may help to provide insight in effective implementation barriers and to improve delivery of evidence based care.

VARIATION IN CARE

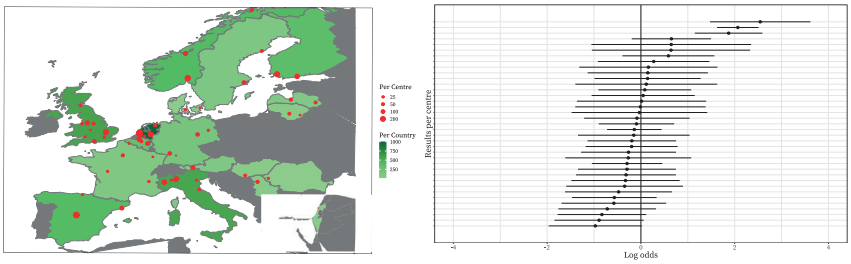
General supportive and preventive measures in the neurocritical care management of TBI aim to prevent or limit secondary brain injury and optimize recovery. To guide such management, the Brain Trauma Foundation (BTF) guidelines have been established[20]. However, although substantial efforts have been made to optimize treatment strategies, there is still no specific neuroprotective therapy that is highly effective to improve clinical outcome after TBI. Challenges arise when conducting research in the TBI field. First, the conventional prognostic subdivision into mild, moderate, and severe has its limitations since it does not accurately capture differences in aetiology and has therefore been described to inadequately characterise the TBI patient[59,60]. Second, clinical research is complicated by individual differences in response to injury and the complexity and cohesion with co-injuries apart from the TBI. Third, informed consent issues can arise with clinical research on time sensitive interventions in the acute setting[61].

Survey studies on ICU management of patients with TBI in European neurotrauma centers found large variation in general supportive and preventive measures, monitoring and treatment policies for intracranial hypertension in patients with TBI admitted to the ICU[21,22]. Practice variation in the management of patients with TBI admitted to the ICU might be an opportunity for different types of research including comparative effectiveness research and as such a potential source of improvement of outcomes among patients with TBI[62]. Studies about practice variation can 1) identify areas of clinical equipoise, 2) serve as hypothesis generation basis for further research, 3) serve as basis for quality of care initiatives or consensus documents when evidence is absent and, 4) inspire local protocols by providing diverse options of practices when evidence is low. Different methods can be used to measure variation (Box 1.2).

Box 1.2 Measuring variation of care

Methods used in this thesis to assess variation

1. Regional plots: Visualization of the proportion of patients with condition that receives treatment
2. Caterpillar plots: The x-axis indicates the mean and 95% CI posterior means per centre, region or country compared to the average proportion for all centres. Random effect regression models are used to correct for random variation and can also be adjusted for case-mix severity.
3. The Median Odds Ratio (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 and can quantify variation. The MOR is related to $\tau 2$, which is the variance of the random effects; 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 variation, the MOR will be large. In analyses that include data from different hospitals, hospitals should be included as effect in the so-called mixed effects model.



The aim of CER is to assess the effectiveness and value of medical interventions or policies (e.g. as covered with the term 'systems of care', such as care bundles or guidelines) in real-life scenarios[25] (Box 1.3). Traditionally, RCTs involve carefully-selected patients and strict and selected (single) treatments, while in clinical practice patients typically present with multiple health problems and may be subjected to numerous interventions and concomitant variations in their application (e.g. temperature management may be applied as only avoidance of fever, or as mild hypothermia). CER is designed to account for the abundance of treatment options by comparisons that are clinically meaningful in a broader representation of the affected population. This is in contrast to traditional RCTs that often have strict inclusion criteria and therefore do not represent all patients that are affected by the disease. Therefore, CER has the potential to reduce variability in clinical practice, aiming to ensure high-quality care for all patients. The biggest challenge for CER in observational data is confounding by indication in which certain patients may preferentially receive one treatment or another based on their characteristics. Advanced statistical analyses such as instrumental variable analyses have been developed to facilitate relevant results from observational CER studies[63,64].

Box 1.3 Definition of Comparative Effectiveness Research used for this thesis

Comparative Effectiveness Research is 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.

Institute of Medicine: Initial national priorities for comparative effectiveness research[60]

IDENTIFYING EFFECTIVE AND HIGH QUALITY CARE

Fluid management

Over the past years, fluid management has gained attention in neurocritical care. Fluid management is the administration of different types and amounts of fluids to optimize oxygenation and perfusion of vital organs. Different types and amounts of fluids may have diverging impact on secondary brain injury given specific fluid properties (e.g. regarding osmolality and reflection-coefficient), and effects on both systemic and cerebral circulation and oxygenation[65]. Several studies in critical care have demonstrated

that fluid overload can be detrimental[6,66-68]. For patients with TBI, this might also be applicable since an increase in ICP will partly originate from tissue oedema, that can be facilitated by too much fluid or low osmolality of fluids administered, or too low amounts of fluids (dehydration, which is regarded as obsolete but may still be applied).

Beta-blockers

Beta blockers, as a class of drugs, are predominantly used to manage abnormal heart rhythms and improve outcome for heart failure, and for example to protect the heart from a second myocardial infarction after a first heart attack. Beta blockers are competitive antagonists that block the receptor sites for the endogenous epinephrine and norepinephrine on adrenergic beta receptors, or the sympathetic nervous system, which mediates the fight-or-flight response[69,70].

Although the exact pathophysiological cascade after TBI is not completely understood, studies have shown that TBI is associated with a hyperadrenergic state which seems detrimental. In the context of a disrupted blood brain barrier, this hyperadrenergic state leads to high local norepinephrine levels and increased cerebral metabolic rate (CMR). The pre-existing ischemia and metabolic crisis can be exacerbated by the increased CMR in the injured brain with defective autoregulation. Therefore, the potential of beta-blockers after TBI has been attributed to block some of the adverse effects of sympathetic activation[71-76]. Another hypothetical pathway may include the positive effect of beta-blockers on diastolic cardiac dysfunction often seen in association with sympathetic over activation: in turn diastolic dysfunction may contribute both to venous congestions and reduced cardiac output, which may both decrease cerebral perfusion and contribute to secondary brain injury[77-80].

Measuring quality of care

Quality of care has become a major topic in health care (Box 1.5[81]). Today, daily clinical practice is evaluated by different stakeholders such as patients, practitioners and managers, with the aim to improve quality of care. There is general consensus that improving quality of care will lead to improved clinical outcomes, lower healthcare costs, and equal access of care in hospitals and countries of similar socio-economic background. However, since clinical outcomes are influenced by many factors, the measurement and improvement of a single aspect of quality of care, to improve outcomes is challenging and complicated[26].

Box 1.5 Definition Quality of Care used for this thesis

Quality of Care is the extent to which health care services provided to individuals and patient populations improve desired health outcomes. In order to achieve this, health care must be safe, effective, timely, efficient, equitable and people-centred.

World Health Organization[79]

Quality indicators are measurable aspects of quality of care and are generally used to assess quality of care. In other clinical fields, quality indicator sets have been developed and proved to benefit quality of care[82,83]. Several definitions and classifications of quality indicators exist. In general, quality indicators are often classified into three types: structure, process, and outcome indicators. Structure indicators define the characteristics of the health system or the hospital in which the care is provided. Process indicators can be measured per patient and refer to the appropriates of the delivered care. Outcome indicators reflect the end result as a consequence of care[27]. Of note however, one might argue whether quality indicators should always be based on high level of evidence or that consensus based indicators reflecting quality of care as judged by relevant stakeholders can be sufficient.

AIMS AND CONTENTS

The overall aim of this thesis is to improve some aspects of neurocritical care, specifically for patients with TBI and stroke. The specific aims of this thesis were:

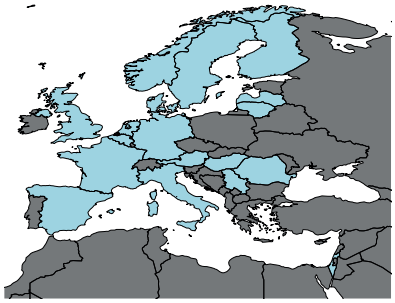
1. To describe the contemporary landscape of neurocritical care in Europe and Australia
    a. To describe patient populations and outcomes
    b. To describe how neurocritical care is organized and implemented
    c. To quantify the variability in management, organization and outcomes between centres, regions and countries
2. To assess the effectiveness and quality of neurocritical care
    a. What is the effectiveness of different fluid management strategies?
    b. What is the effectiveness of beta-blockers?
    c. How may quality of neurocritical care for TBI patients be assessed and can it be investigated in the CENTER-TBI database?

This thesis consists of two parts. In Part I (chapter 2-6) the contemporary landscape of neurocritical care in Europe and Australia is described. Chapters 2-4 provide an overview of the case-mix, care pathways, outcomes in patients with TBI in Europe and Australia and investigate to which extent this differs between centres and countries. In chapter 5, we describe ICU admission practices in patients with mTBI and assess potential overtriage. Specifically, chapter 6 describes how the use of EVT has developed before, during, and after the pivotal EVT trials.

In part II of this thesis we examine how we can improve neurocritical care management and assess quality of care. Chapter 7 describes the association of fluid therapy on outcome after TBI. In chapter 8 we investigate the association between beta-blocker use and outcome in TBI patients. In chapter 9 we aim to develop a quality indicator set for TBI patients in neurocritical care, which is further validated in chapter 10.

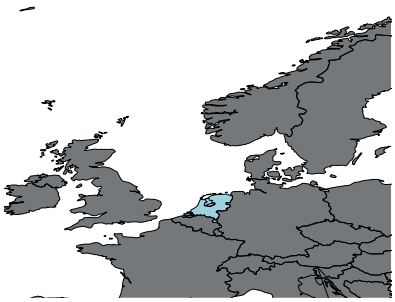
The results of the studies included in this thesis are further discussed in chapter 11, together with their interpretation and recommendations for future research, policy, and clinical practice.

Figure 1.2 Datasets used in this thesis



CENTER-TBI:
Collaborative European NeuroTrauma Effectiveness Research in TBI
Setting:
65 major trauma centres in Europe and Israel
Design:
Prospective observational study
Years of inclusion:
2014-2017
Inclusion criteria:
A clinical diagnosis of TBI, indication for CT scanning, presentation to study centre within 24 hours of injury
Number of patients:
4509 in CENTER-TBI Core Study, 2138 in ICU Stratum

OzENTER-TBI:
Australia-Europe NeuroTrauma Effectiveness Research in Traumatic Brain Injury
Setting:
2 major trauma centres in Australia
Design:
Prospective observational study
Years of inclusion:
2015-2017
Inclusion criteria:
A clinical diagnosis of TBI, indication for CT scanning, presentation to study centre within 24 hours of injury and admission to ICU.
Number of patients:
198



MR CLEAN:
The Multicenter collaboration for endovascular treatment of acute ischemic stroke in the Netherlands
Setting:
17 hospitals in the Netherlands
Design:
Pretrial + Registry: prospective observational study
Trial: Randomized Controlled Trial
Years of inclusion:
2002-2018
Inclusion criteria:
Pretrial + Registry: all patients treated with EVT
Trial: >18 years with acute ischemic stroke and a symptomatic anterior proximal artery occlusion, treated within 6 hours after stroke onset
Number of patients:
Pretrial: 514, Trial: 500, Registry: 3294

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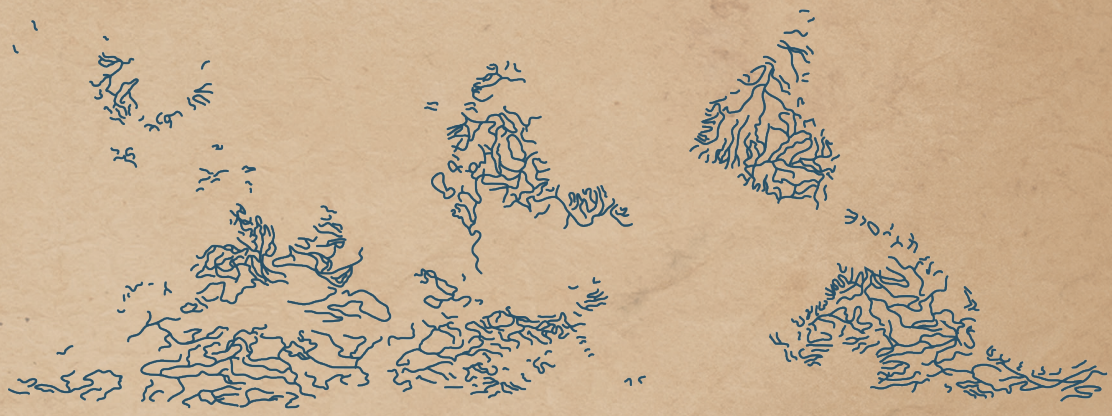
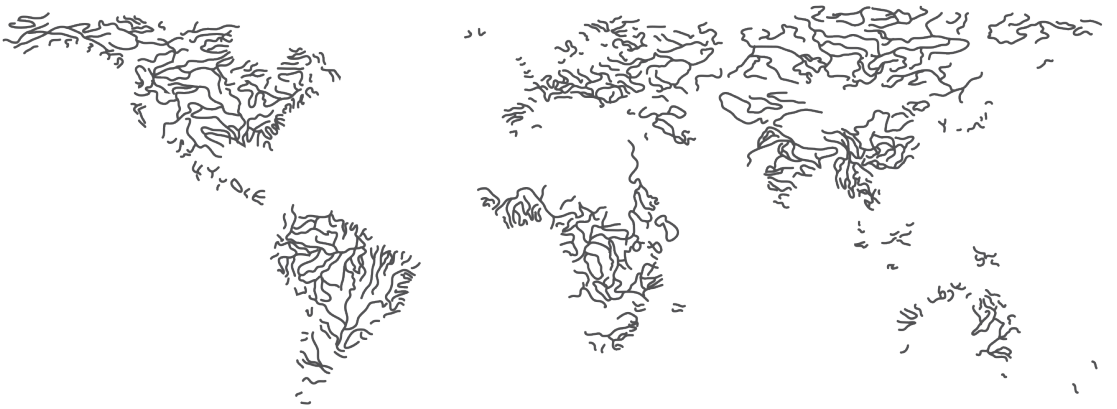


Part I

Variation in patients, care, and outcome



Chapter 2

Case-mix, care pathways, and outcomes in patients with traumatic brain injury in CENTER-TBI: a European prospective, multicentre, longitudinal, cohort study

The Lancet Neurology, 2019

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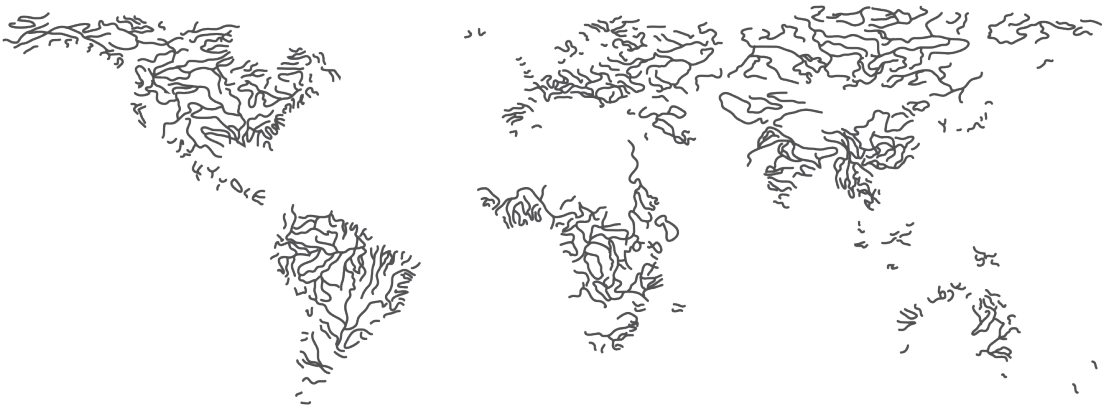
*equal contribution



SUMMARY

Background

The burden of traumatic brain injury (TBI) poses a large public health and societal problem, but the characteristics of patients and their care pathways in Europe are poorly understood. We aimed to characterise patient case-mix, care pathways, and outcomes of TBI.

Methods

CENTER-TBI is a Europe-based, observational cohort study, consisting of a core study and a registry. Inclusion criteria for the core study were a clinical diagnosis of TBI, presentation fewer than 24 h after injury, and an indication for CT. Patients were differentiated by care pathway and assigned to the emergency room (ER) stratum (patients who were discharged from an emergency room), admission stratum (patients who were admitted to a hospital ward), or intensive care unit (ICU) stratum (patients who were admitted to the ICU). Neuroimages and biospecimens were stored in repositories and outcome was assessed at 6 months after injury. We used the IMPACT core model for estimating the expected mortality and proportion with unfavourable Glasgow Outcome Scale Extended (GOSE) outcomes in patients with moderate or severe TBI (Glasgow Coma Scale [GCS] score ≤12). The core study was registered with ClinicalTrials.gov, number NCT02210221, and with Resource Identification Portal (RRID: SCR_015582).

Findings

Data from 4509 patients from 18 countries, collected between Dec 9, 2014, and Dec 17, 2017, were analysed in the core study and from 22782 patients in the registry. In the core study, 848 (19%) patients were in the ER stratum, 1523 (34%) in the admission stratum, and 2138 (47%) in the ICU stratum. In the ICU stratum, 720 (36%) patients had mild TBI (GCS score 13–15). Compared with the core cohort, the registry had a higher proportion of patients in the ER (9839 [43%]) and admission (8571 [38%]) strata, with more than 95% of patients classified as having mild TBI. Patients in the core study were older than those in previous studies (median age 50 years [IQR 30–66], 1254 [28%] aged >65 years), 462 (11%) had serious comorbidities, 772 (18%) were taking anticoagulant or antiplatelet medication, and alcohol was contributory in 1054 (25%) TBIs. MRI and blood biomarker measurement enhanced characterisation of injury severity and type. Substantial inter-country differences existed in care pathways and practice. Incomplete recovery at 6 months (GOSE <8) was found in 207 (30%) patients in the ER stratum, 665 (53%) in the admission stratum, and 1547 (84%) in the ICU stratum. Among patients with moderate-to-severe TBI in the ICU stratum, 623 (55%) patients had unfavourable outcome at 6 months (GOSE <5), similar to the proportion predicted by the IMPACT prognostic model (observed to expected ratio 1.06 [95% CI 0.97–1.14]), but mortality was lower than expected (0.70 [0.62–0.76]).

Interpretation

Patients with TBI who presented to European centres in the core study were older than were those in previous observational studies and often had comorbidities. Overall, most patients presented with mild TBI. The incomplete recovery of many patients should motivate precision medicine research and the identification of best practices to improve these outcomes.

RESEARCH IN CONTEXT

Evidence before this study

In November, 2017, the Commission on Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research in The Lancet Neurology highlighted existing deficiencies in epidemiology and patient characterisation. An extensive literature search was undertaken as a basis for writing the Commission, which went beyond the academic literature and included national and international policy documents and statistical resources. These data were updated through more focused literature reviews for this manuscript. The Commission concluded that concerted efforts are urgently needed to address deficiencies in prevention, care, and research, and recommended that large collaborative studies be done, which could provide the framework for precision medicine and comparative effectiveness research.

Added value of this study

The CENTER-TBI registry and core study provide detailed insights into the contemporary landscape of traumatic brain injury (TBI) in Europe and constitute a unique resource for improving the characterisation of TBI, developing precision medicine approaches, and identification of best practices. The epidemiology of TBI as observed in the CENTER-TBI core study and registry differs from previous observational studies: patients were older, were most commonly injured by a fall, and many had comorbidities. Advanced neuroimaging and blood biomarkers can improve characterisation of injury type and severity. Differentiation of patients by care pathways provided novel insights. Around 95% of patients discharged from the emergency room or admitted to the ward, and a third of those primarily admitted to the ICU, had a so-called mild TBI. However, nearly a third of patients discharged from the emergency room and over half of those admitted to the hospital ward did not attain full recovery. There are substantial national and regional variations in care pathways and clinical management in Europe.

Implications of all the available evidence

The results from CENTER-TBI suggest that TBI should no longer be considered predominantly a disease of otherwise healthy young men. Falls were the most common cause of TBI and should motivate an increased focus for prevention. Mild TBI not only poses the greatest societal burden to health care, but also affects functional recovery and quality of life more than was commonly thought. Improved disease characterisation can contribute to precision medicine approaches through the development of multidimensional classifications of initial injury severity and outcome. Variations in care offer an opportunity for comparative effectiveness research to identify best practice.

INTRODUCTION

The burden of Traumatic Brain Injury (TBI) is widely recognized as a large public health and societal problem. TBI results in 1.5 million hospital admissions and 57,000 deaths in the EU each year[1], but the landscape of TBI in European hospitals is poorly characterized. In November, 2017, a Commission in The Lancet Neurology highlighted the burden posed by TBI to patients, relatives, and society, and provided recommendations to improve patient outcomes through improved prevention, clinical care, and research. One recommendation was for large collaborative observational studies to collect longitudinal data, which could inform improved patient characterization to allow better targeting of therapies, and identify best practices through comparative effectiveness research (CER).

The Collaborative European NeuroTrauma Effectiveness Research (CENTER-TBI) project is a collaborative European study, conducted within the InTBIR Initiative (https://intbir.nih.gov/[2], that was designed to address these needs[3]. The project includes a multicentre, longitudinal, observational cohort study (core study) with highly granular data collection, which included detailed longitudinal clinical and outcome data, neuro imaging repositories, a DNA repository, and a blood and serum biobank; and a registry, which collected basic administrative data. The main aims are to 1) better characterize Traumatic Brain Injury (TBI) as a disease and describe it in a European context, and 2) identify the most effective clinical interventions for managing TBI. Provider Profiles of participating centres were established to characterize structures and processes of care in preparation for comparative effectiveness research[4-10]. We aim to describe the contemporary landscape of TBI in Europe, with a focus on the patient case-mix, care pathways, and outcome in the core study, and to explore generalizability by comparison with data from the Registry.

METHODS

Study design

CENTER-TBI includes a core study (clinicaltrials.gov NCT02210221) and a registry (RRID: SCR_015582)[4]. 65 centres initiated patient enrolment (Figure 2.1). The core study was an prospective observational longitudinal cohort study on patients of all severities of TBI, presenting between December 19, 2014 and December 17, 2017, to centres across Europe and Israel. Inclusion criteria were a clinical diagnosis of TBI, indication for CT scanning, presentation to study centre within 24 h of injury, and informed consent obtained according to local and national requirements[4]. Participants were excluded if they had any severe pre-existing neurological disorder that could confound outcome assessments. Patients were differentiated by care pathway into three strata:

1. ER stratum (patients evaluated in the emergency room (ER) and discharged);
2. Admission stratum (admitted to hospital ward);
3. ICU stratum (primary admission to the intensive care unit).

The assignment to a stratum was prospectively in the core study, and retrospectively in the registry. Generalizability of the core study was assessed through comparison with the Registry, which collected administrative data not requiring consent, and covered a site-specific, convenience-based, time window during the recruitment period of the core study.

The CENTER-TBI study was done in accordance with all relevant laws of the European Union, if directly applicable or of direct effect, and all laws of the country where the recruiting sites were located, including, but not limited to, the privacy and data protection laws and regulations, the laws and regulations on the use of human materials, and all relevant guidance relating to clinical studies from time to time in force including, but not limited to, the International Council on Harmonisation guideline on Good Clinical Practice (CPMP/ICH/135/95) and the World Medical Association Declaration of Helsinki. Informed consent by the patients or the legal representative or next of kin was obtained according to the local legislations for all patients recruited in the core dataset of CENTER-TBI and documented in the electronic case report form. Ethics approval was obtained for each recruiting site. The list of sites, ethics committees, approval numbers, and approval dates is available online[11].

Outcomes

Outcome assessments were done at 6 months after injury. The primary outcome measures were global function and health-related quality of life using the eight-point Glasgow Outcome Scale (GOSE; overall effect of injury, including extracranial injuries)[12], the quality of life after brain injury overall scale (Qolibri-OS)[13], and the 12-item short form health survey (SF-12v2)[14]. Details of data, imaging, biosamples collection and banking, data handling, and analysis are provided in the Supplementary Material.

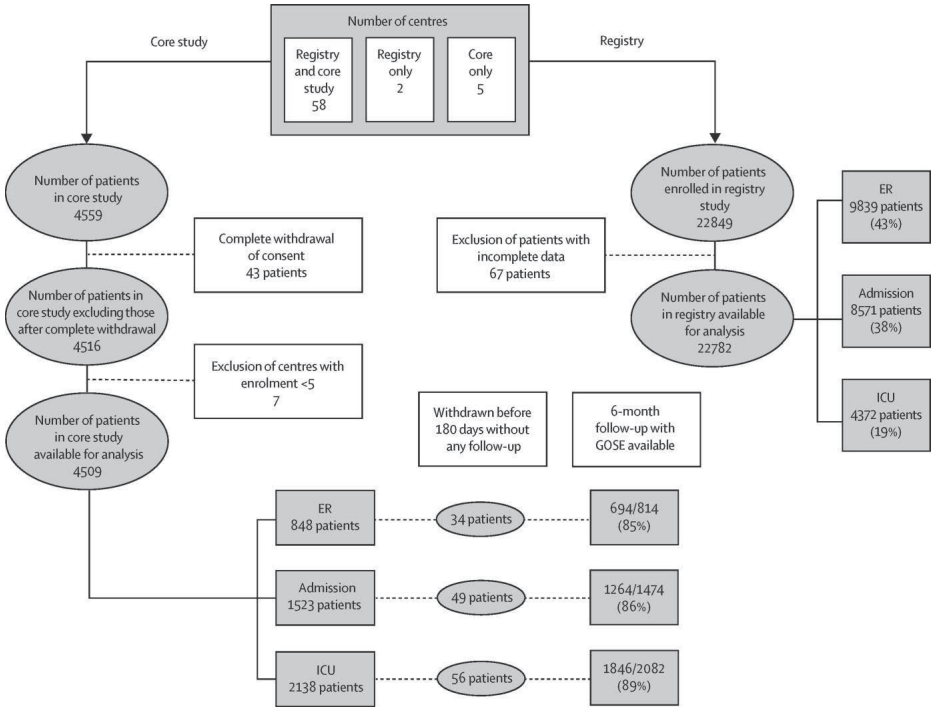


Figure 2.1 Trial profile

The accrual to the emergency room, admission, and intensive care unit strata was defined prospectively in the core study, and retrospectively in the registry. GOSE=Glasgow Outcome Scale Extended.

Data collection, handling, and storage

Clinical data were collected using a web-based electronic case report form, with stratum-specific workflows (QuesGen Systems Incorporated, Burlingame, CA, USA). Variables were coded in accordance with the Common Data Elements scheme established by the US National Institutes of Health's National Institute of Neurological Disorders. Blood was banked for DNA extraction and assayed for protein biomarkers (neuron specific enolase [NSE], S100B, neurofilament light, total tau, glial fibrillary acidic protein [GFAP], and ubiquitin carboxyl-terminal hydrolase L1 [UCHL1]). Patients underwent X-ray CT at admission (repeated if clinically indicated), and MRI was obtained in a subset of patients. We provide data on all admission CT examinations, biomarker data on the first 961 patients, and MRI data on the 504 patients who underwent an initial MRI within 3 weeks of injury.

Data handling and storage

Data were de-identified and stored on a secure database, hosted by the International Neuroinformatics Coordinating Facility in Stockholm, Sweden. Source data verification of major characteristics was undertaken on a quasi-random sample of 1298 (28%) patients by a designated contract research organisation (ICON, Paris, France). Detailed curation was done by a multidisciplinary data curation task force.

Statistical analysis

Data (version 2.0) were accessed using a bespoke data management tool, Neurobot (details available on the SciCrunch Resource Identification Portal, using the Research Resource Identifier RRID/SCR_017004). We report completeness of data, medians, and IQRs for continuous or ordinal variables, and numbers and percentages for categorical variables. All analyses were differentiated by stratum and done in R (version 3.5.1) and RStudio (version 1.0.136). ANOVA was used for comparison of continuous variables across strata. The χ^2 test was used for comparison of categorical variables. No corrections for multiple comparisons were done. For comparisons of characteristics between strata, we assessed compatibility with the null hypothesis of no differences between strata. κ statistics were used to express the agreement between central and local radiological assessment of admission CT scans and for CT versus MR scans. We analysed complete outcome data for the primary outcome measures. Analysis of secondary outcome measures (Supplementary Methods) is ongoing and will be presented elsewhere. For patients with GOSE scores outside the prespecified 5–8-month window (n=988 [22%]), we used a multistate model to impute the 180-day GOSE (msm package[15]). We classified Qolibri-OS scores less than 52 and SF-12v2 summary scores less than 40 as impaired[16]. When there was no SF-12v2 summary score we derived scores using SF-36v2 items when available.

We used the IMPACT core model for the expected mortality and proportion with unfavourable GOSE outcomes among patients with moderate or severe TBI (Glasgow Coma Scale [GCS] score ≤12).[17] Observed mortality and unfavourable GOSE outcomes were compared with expected outcomes and expressed as a ratio with 95% CIs estimated according to a Poisson distribution. The core study is registered with ClinicalTrials.gov, number NCT02210221, and the Resource Identification Portal (RRID: SCR_015582).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

We enrolled 4559 patients in the core study and 22 849 patients in the registry from 65 sites in 19 countries. We analysed data from 4509 (98.9%) patients in the core study and 22 782 (99.7%) in the registry obtained from 18 countries (Figure 2.1). The median number of enrolled patients by centre in the core study was 50 (IQR 21–107), with widely different distributions across strata (Supplementary Figure 2.1 and 2.2). In the core study, 848 (19%) patients in the ER stratum, 1523 (34%) in the admission stratum, and 2138 (47%) were in the ICU stratum. The registry enrolled more patients in the ER and admission strata than did the core study (Figure 2.1).

Overall, the median age was 50 years (IQR 30–66), with 1254 (28%) patients older than 65 years (Table 2.1). Patients in the admission stratum were older (53 years [32–69], 493 [32%] aged >65 years), than were those in the ER and ICU strata. Male patients were overrepresented in every stratum, most notably in the ICU stratum (Table 2.1). At older age, however, the proportion of female patients was higher in the ER and admission strata (Supplementary Figure 2.3). Severe systemic disease was reported in 462 (11%) patients (Table 2.1).

Patients differed between the three strata with respect to socioeconomic characteristics (education, marital, and employment status), medical history (especially frequency of having had a previous TBI), cause of injury, and clinical severity (Table 2.1, Supplementary Table 1-4). An incidental fall was the most common cause of injury in the ER and admission strata (Table 2.1). We found a clear association with age, with high rates of falls in patients younger than 10 years and in patients older than 65 years (Supplementary Figure 2.4). Road-traffic incidents were most common in the ICU stratum (Supplementary Table 2.3). Alcohol use was reported in 144 (64%) violence-related TBIs, in 533 (28%) incidental falls, and in 262 (17%) road-traffic incidents (Supplementary Figure 2.5). Recreational and prescription drug use were reported in 203 (6%) patients.

Clinical severity varied by stratum. In the ER and admission strata, the median baseline GCS was 15, and 826 (99%) patients in the ER stratum and 1409 (95%) in the admission stratum were classified as having mild TBI (GCS 13–15; Table 2.1, Supplementary Figure 2.6). In the ICU stratum, the median GCS was 9 (4–14) and 720 (36%) patients had a GCS greater than 12. Major extracranial injuries (abbreviated injury score ≥3) were reported in 422 (28%) patients in the admission stratum and in 1174 (55%) in the ICU stratum. The body region most commonly injured was thorax and chest (n=742 [35%]), and concomitant serious spinal injuries occurred in 374 (18%) patients (Supplementary Table 2.4).

Table 2.1 Baseline characteristics of patients enrolled in the CENTER-TBI Study

	Overall
Demographic characteristics	
Age (years)	50 (30–66)
>65 years	1254/4509 (27.8%)
Sex	
Male	3023/4509 (67.0%)
Female	
White	4158/4300 (96.7%)
Socioeconomic characteristics	
Years of education (n=3212)	13 (10–16)
Highest level of education	
College or university	850/3566 (23.8%)
Married or living with partner	2070/4075 (50.8%)
Employment status before injury	
Working	1946/3980 (48.9%)
Pre-injury health status and medical history	
Pre-injury ASA-PS classification	
Patient with mild systemic disease	1410/4373 (32.2%)
Patient with severe systemic disease	462/4373 (10.6%)
Previous TBI	402/4158 (9.7%)
Anticoagulants	298/4345 (6.9%)
Platelet aggregation inhibitors	474/4345 (10.9%)
Cause of injury and influence of alcohol	
Cause of injury	
Road traffic incident	1682/4388 (38.3%)
Incidental fall	2024/4388 (46.1%)
Alcohol involved in the injury (yes or suspected)	
All causes	1054/4163 (25.3%)
Road traffic incident	262/1528 (17.1%)
Incidental Fall	533/1918 (27.8%)
Clinical presentation	
GCS	15 (10–15)
Mild (13–15)	2955/4330 (68.2%)
Moderate (9–12)	389/4330 (9.0%)
Severe (3–8)	986/4330 (22.8%)
Pupillary reactivity	
One pupil unreactive	164/4247 (3.9%)
Two pupils unreactive	281/4247 (6.6%)

ER stratum	Admission stratum	ICU stratum	p value*
48 (29–64)	53 (32–69)	49 (29–65)	0.001
209/848 (24.6%)	493/1523 (32.4%)	552/2138 (25.8%)	
			< 0.0001
473/848 (55.8%)	988/1523 (64.9%)	1562/2138 (73.1%)	
810/831 (97.5%)	1452/1508 (96.3%)	1896/1961 (96.7%)	0.33
13 (11–16)	13 (11–16)	12 (10–15)	< 0.0010
			< 0.0001
236/787(30.0%)	334/1304 (25.6%)	280/1475 (19.0%)	
385/797 (48.3%)	717/1426 (50.3%)	968/1852 (52.3%)	0.15
			0.05
427/816 (52.3%)	638/1414 (45.1%)	881/1750 (50.3%)	
			0.56
268/843 (31.8%)	507/1502 (33.8%)	635/2028 (31.3%)	
93/843 (11.0%)	159/1502 (10.6%)	210/2028 (10.4%)	
120/812 (14.8%)	149/1459 (10.2%)	133/1887 (7.0%)	< 0.0001
46/837 (5.5%)	133/1510 (8.8%)	119/1998 (6.0%)	< 0.0009
85/837 (10.2%)	178/1510 (11.8%)	211/1998 (10.6%)	0.38
			< 0.0001
266/836 (31.8%)	490/1499 (32.7%)	926/2053 (45.1%)	
424/836 (50.7%)	761/1499 (50.8%)	839/2053 (40.9%)	
137/828 (16.5%)	384/1452 (26.4%)	533/1883 (28.3%)	< 0.0001
25/260 (9.6%)	76/471 (16.1%)	161/797 (20.2%)	< 0.0001
72/414 (17.4%)	209/730 (28.6%)	252/774 (32.6%)	< 0.0001
15 (15–15)	15 (14–15)	9 (4–14)	< 0.0001
826/832 (99.3%)	1409/1489 (94.6%)	720/2009 (35.8%)	
2/832 (0.2%)	59/1489 (4.0%)	328/2009 (16.3%)	
4/832 (0.5%)	21/1489 (1.4%)	961/2009 (47.8%)	
			< 0.0001
3/795 (0.4%)	27/1436 (1.9%)	134/2016 (6.6%)	
16/795 (2.0%)	19/1436 (1.3%)	246/2016 (12.2%)	

Table 2.1 Baseline characteristics of patients enrolled in the CENTER-TBI Study

	Overall
Hypoxia (prehospital or ER phase)	299/4256 (7.0%)
Hypotension (prehospital or ER phase)	297/4296 (6.9%)
Any major extracranial injury (AIS ≥3)	1642/4509 (36.4%)
CT characteristics	
Any intracranial abnormality at local reading	2268/3924 (57.8%)
Any intracranial abnormality at central reading	2434/4037 (60.3%)
MRI characteristics	
Any intracranial abnormality at central reading	312/504 (61.9%)
Biomarkers†	
NSE (ng/mlL; n=961)	18 (13–27)
S100B (µg/L; n=960)	0.18 (0.09–0.42)
GFAP (ng/mL; n=1010)	4.4 (0.8–17)
NFL (pg/mL; n=1010)	23 (10–60)
Total Tau (pg/mL; n=1010)	4 (1.7–11)
UCHL1 (pg/mL; n=1009)	127 (48–381)
Laboratory measurements	
Haemoglobin (g/dL; n=3846)	14 (12–15)
Glucose (mmol/L; n=3492)	6.9 (5.9–8.3)

Data are median (IQR) or n (%), unless otherwise indicated. ER=emergency room. ICU=intensive care unit. TBI=traumatic brain injury. AIS=abbreviated injury score. ASA-PS=American Society of Anesthesiologists physical status classification system. GCS=Glasgow Coma Scale. S100B=S100 calcium-binding protein B. NSE=Neuron-specific enolase. NFL=neurofilament light. GFAP=glial fibrillary acidic protein. UCHL1=ubiquitin carboxy-terminal hydrolase L1.

The differential recruitment to individual strata in the core study and the registry (Figure 2.1), and the exclusion of patients with pre-existing neurological disease from the core cohort, precluded direct overall comparisons between the two cohorts. When differentiated by stratum, patients in the core study broadly resembled those in the registry (Supplementary Table 2.5). The proportion of patients who had serious extracranial injuries was similar in the core study and the registry in the admission and ICU cohorts (Supplementary Table 2.5), and a similar proportion of patients in the ICU stratum in both study parts arrived intubated at the ER (Supplementary Table 2.5). In the ICU stratum, the frequency of emergency surgical procedures was similar (eg, 297 [14%] patients had received craniotomy for haematoma or contusion in the core study vs 700 [16%] in the registry; Supplementary Table 2.5). In-hospital mortality was

ER stratum	Admission stratum	ICU stratum	p value*
3/818 (0.4%)	30/1457 (2.1%)	266/1981 (13.4%)	<0.0001
4/820 (0.5%)	26/1484 (1.8%)	267/1992 (13.4%)	<0.0001
46/848 (5.4%)	422/1523 (27.7%)	1174/2138 (54.9%)	<0.0001
53/768 (6.9%)	632/1317 (48.0%)	1583/1820 (87.0%)	<0.0001
103/804 (12.8%)	681/1379 (49.4%)	1650/1854 (89.0%)	<0.0001
32/123 (26.0%)	101/180 (56.1%)	179/197 (90.9%)	<0.0001
13 (11–16.8)	14 (11–18)	23 (15–34)	<0.0001
0.07 (0.05–0.12)	0.11 (0.06–0.19)	0.30 (0.15–0.59)	<0.0001
0.3 (0.1–1.0)	1.7 (0.6–5.1)	11 (3.4–31)	<0.0001
8.3 (5.1–15)	16 (8–30)	40 (18–95)	<0.0001
1.2 (0.8–2.0)	2.3 (1.3–4.5)	7.9 (3.3–17)	<0.0001
35 (20–64)	68 (34–122)	275 (109–597)	<0.0001
14 (13–15)	14 (13–15)	13 (12–14)	<0.0001
6 (5.3–7.1)	6.5 (5.7–7.8)	7.3 (6.3–8.9)	<0.0001

**p values were derived from ANOVA for continuous characteristics and χ^2 statistics for categorical characteristics, comparing strata. The p value assessed compatibility with the null hypothesis of no differences between strata. †NSE and S-100B were measured using the e602 module of a Cobas 8000 analyser (Roche Diagnostics International, Rotkreuz, Switzerland) in Pécs, Hungary; and NFL, total tau, GFAP, and UCHL1 using the Quanterix SIMOA Neurology 4-plex kit (Quanterix, Lexington, MA, USA), at the University of Florida, FL, USA.*

similar across strata (eg, 318 [15%] patients in the core ICU stratum and 773 [19%] in the registry ICU stratum; Supplementary Table 2.5). Some differences existed in other baseline and injury characteristics (Supplementary Table 2.5). Patients in the core ER stratum were more frequently injured in road-traffic incidents and had more intracranial abnormalities on CT scanning than did their registry counterparts (Supplementary Table 2.5). Patients in the core admission stratum were younger, more often male, more frequently injured in road traffic incidents, and had more intracranial abnormalities on CT scanning than did those in the registry admission stratum (Supplementary Table 2.5). Patients in the core ICU stratum had a lower baseline GCS than did those in the registry ICU stratum (Supplementary Table 2.5).

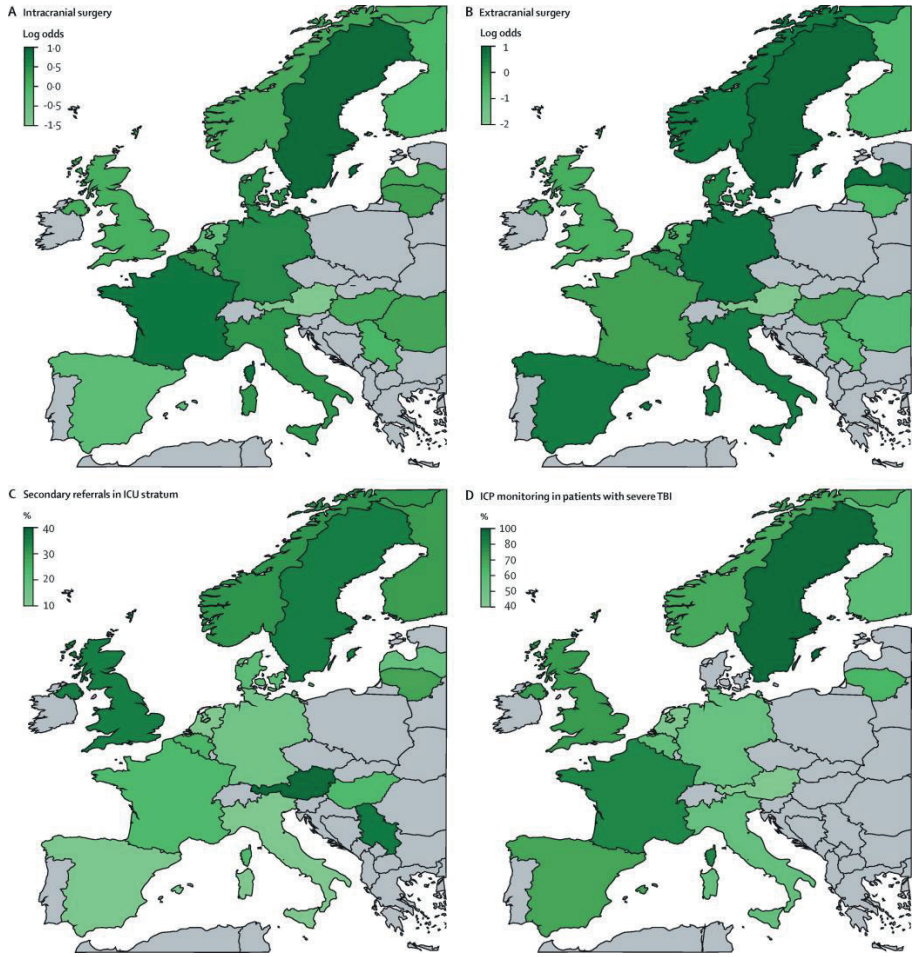


Figure 2.2 Between-country differences in processes of care for TBI in Europe

(A) The log odds ratio of intracranial surgery, representing the log odds of intracranial surgery per contry compared with the overall average, adjusted for IMPACT CT model and stratum. (B) The log odds ratio of extracrianal surgery, representing the log odds of extracranial surgery per country compared with the overall average, adjusted for any major extracranial injury and stratum. (C) The percentage of patients in the intensive care unit stratum (n=2138) referred from another hospital, per country. (D) Percentage of patients with severe TBI (n=958) with ICP monitoring, per country. These analyses were adjusted for baseline characteristics and stratum and might reflect true differences in policy. TBI=traumatic brain injury. ICU=intensive care unit. ICP=intracranial pressure.

Early CT scans showed traumatic intracranial abnormalities in 2434 (60%) of 4037 patients at central review (Table 2.1, Supplementary Table 2.6). The most frequently reported abnormalities were traumatic subarachnoid haemorrhage, contusion, and acute subdural haematoma (Supplementary Table 2.6). Overall, comparisons between central review scores and investigator scores showed good agreement for 3922 initial CT scans (κ 0.79 for any abnormality; Supplementary Table 2.7). However, we found low κ values for traumatic axonal injury (0.35) and cisternal compression (0.54; Supplementary Table 2.7). An early MRI (<3 weeks) showed traumatic intracranial abnormalities in 312 (62%) of 504 patients (Table 2.1). Abnormalities on MRI were found in 60 (30%) of 202 patients with a normal admission CT scan (Supplementary Table 2.8). Conversely, MRI was normal in 32 (18%) of 182 patients with traumatic abnormalities on the CT scan obtained at presentation. MRI showed more contusions and traumatic axonal injuries than did CT, but CT detected more subarachnoid haemorrhage and epidural haematoma (Supplementary Table 2.8).

The CENTER-TBI biobank included serum samples from 3833 patients, whole-blood samples from 3649 patients and plasma samples for haemostasis analyses from 604 patients. Values for S100B, NSE, GFAP, NFL, total tau, and UCHL1 were all highest in the ICU stratum (Table 2.1). Concentrations of biomarkers were significantly associated with the presence of intracranial injuries at CT scans (Supplementary Figure 2.7) and scaled inversely with the GCS (Supplementary Figure 2.8-2.9). The concentrations of different biomarkers showed close correlations (Supplementary Figure 2.9).

731 (16%) patients were transferred from another hospital to the study centre, with substantial variations in secondary referral rates across countries (Table 2.2, Figure 2.2). Most secondary transfers occurred in the ICU stratum (Table 2.2). Secondary referral was associated with a five -times increase in time required to reach definitive treatment at the study centre (median 65 min [IQR 45–100] vs 297 min [211–440]; p<0.001). 591 (62%) patients with a GCS less than 9 received an intracranial pressure monitor (Table 2.2), but there were substantial variations across countries (Figure 2.2). Intracranial surgery was done in 885 (24%) patients and extracranial surgery in 735 (20%) patients (Table 2.2, Supplementary Table 2.9 p 14). An acute subdural haematoma was the most frequent indication for intracranial surgery (n=323; 25% of all intracranial procedures), and an extremity fracture for extracranial surgery (n=457; 35% of all extracranial procedures). Decompressive craniectomy was done in 204 patients (Supplementary Table 2.9).

Table 2.2 Care pathways in the CENTER-TBI core study

	Overall
Referral	
Primary referral	3761/4492 (83.7%)
Time to study centre (min;n=4491)	65 (45–100)
Secondary referral	731/4492 (16.3%)
Time to study centre (min; n=4491)	297 (211–440)
Diagnostic and surgical interventions	
Time from injury to first CT (min; n=3924)	118 (81–199)
ICP monitor placed	924/2159 (42.8%)
GCS ≤8	591/958 (61.7%)
Intracranial surgery	885/3686 (24.0%)
Extracranial surgery	735/3685 (19.9%)
Length of hospital stay	
Length of stay (days; n=4392)	2.8 (1.0–12)
Length of stay for all patients who survived to hospital discharge (days; n=4018)	2.8 (1.0–12)
Hospital discharge destination	
Home	2646/4191 (63.1%)
Rehabilitation Unit	480/4191 (11.5%)
Other Hospital	636/4191 (15.2%)
Nursing Home	49/4191 (1.2%)
Other	17/4191 (0.4%)
In-hospital mortality	363/4191 (8.7%)

Data are n/N (%) or median (IQR), unless otherwise indicated. ER=emergency room. ICU=intensive care unit. ICP=intracranial pressure. GCS=Glasgow Coma Scale.

Only 37 (5%) patients who were initially enrolled in the ER stratum were admitted to hospital (Figure 2.3). Most patients in the ER stratum could be discharged home (Table 2.2). In the admission stratum, most patients went home after a median hospital stay of 2.0 days (IQR 1.0–5.0), and 58 (4%) were discharged directly to a rehabilitation centre (Table 2.2). In the ICU stratum, ICU mortality was 13% (n=272) and most patients were initially discharged to the ward, with a median ICU length of stay of 5.9 days (1.8–15.0) and a total inpatient length of stay of 13 days (5.0–29.0). 518 (27%) patients were subsequently transferred to another hospital, 422 (22%) were further treated at a rehabilitation centre, and 46 (2%) few went to a nursing home (Table 2.2, Figure 2.3).

	ER stratum	Admission stratum	ICU stratum	p-value
	818/847 (96.6%)	1323/1522 (86.9%)	1620/2123 (76.3%)	<0.0001
	62 (42–105)	60 (41–96)	72 (50–101)	
	29/847 (3.4%)	199/1522 (13.1%)	503/2123 (23.7%)	<0.0001
	257 (151–316)	295 (205–428)	301 (218–445)	
	153 (103–273)	112 (75–190)	110 (80–165)	<0.0001
	NA	3	921/2113 (43.6%)	<0.0001
	NA	NA	591/958 (61.7%)	<0.0001
	1	64/1521 (4.2%)	820/2124 (38.6%)	<0.0001
	1	128/1520 (8.4%)	606/2124 (28.5%)	<0.0001
	0.22 (0.14–0.60)	2.0 (0.77–5.0)	11 (3.4–26)	<0.0001
	0.22 (0.14–0.60)	2.0 (1.0–5.0)	13 (5.0–29)	<0.0001
	803/807 (99.5%)	1246/1466 (85.0%)	597/1918 (31.1%)	
	0/807 (0%)	58/1466 (4.0%)	422/1918 (22.0%)	
	0/807 (0%)	118/1466 (8.0%)	518/1918 (27.0%)	
	1/807 (0.1%)	2/1466 (0.1%)	46/1918 (2.4%)	
	0/807 (0%)	0/1466 (0%)	17/1918 (0.9%)	
	3/807 (0.4%)	42/1466 (2.9%)	318/1918 (16.6%)	

**p values were derived from ANOVA for continuous characteristics and χ^2 statistics for categorical characteristics, comparing strata. The p value assessed compatibility with the null hypothesis of no differences between strata.*

Three (0.3%) patients in the ER and 42 (2.8%) in the admission strata died. The in-hospital and 6-month mortality in the ICU stratum was much higher (Table 2.3). A 6-month GOSE score was available for 3804 (84%) patients (Table 2.3, Figure 2.4). Death or severe disability occurred in 795 (43%) patients in the ICU stratum. A GOSE less than 8 was observed in 1547 (84%) patients in the ICU stratum, in 665 (53%) in the admission stratum, and in 207 (30%) in the ER stratum (Table 2.3). This failure to achieve a complete functional recovery was also reflected in quality of life scores. 227 (26%) patients in the ICU stratum, 160 (18%) in the admission stratum, and 91 (19%) in the ER stratum had Qolibri-OS scores of less than 52. SF-12v2 scores showed similar results (Table 2.3). Patients with missing outcomes were generally younger, less educated, and less severely injured (Supplementary Table 2.10).

Table 2.3 Outcomes of patients enrolled in the CENTER-TBI core study

	Overall
In-hospital mortality	363/4471 (8.1%)
6-month mortality	473/3804 (12.4%)
6-month GOSE	3804/4509 (84.4%)
6-month GOSE <8	2419/3804 (63.6%)
6-month unfavourable outcome (GOSE <5)	966/3804 (25.4%)
6-month SF-12v2 mental component summary 9 (n=2300)	50 (41–57)
6-month SF-12v2 physical component summary (n=2300)	48 (39–55)
6-month Qolibri-OS (n=2323)	71 (54–83)
6-month SF-12v2 mental component summary <40 (impaired)	551/2300 (24.0%)
6-month SF-12v2 physical component summary <40 (impaired)	661/2300 (28.7%)
6-month Qolibri-OS <52 (impaired)	511/2323 (22.0%)

Data are n/N (%) or median (IQR), unless otherwise indicated. ER=emergency room. ICU=intensive care unit. GOSE=Glasgow Outcome Scale Extended. SF-12v2=12-item short form health survey. Qolibri-OS=quality of life after brain injury overall scale.

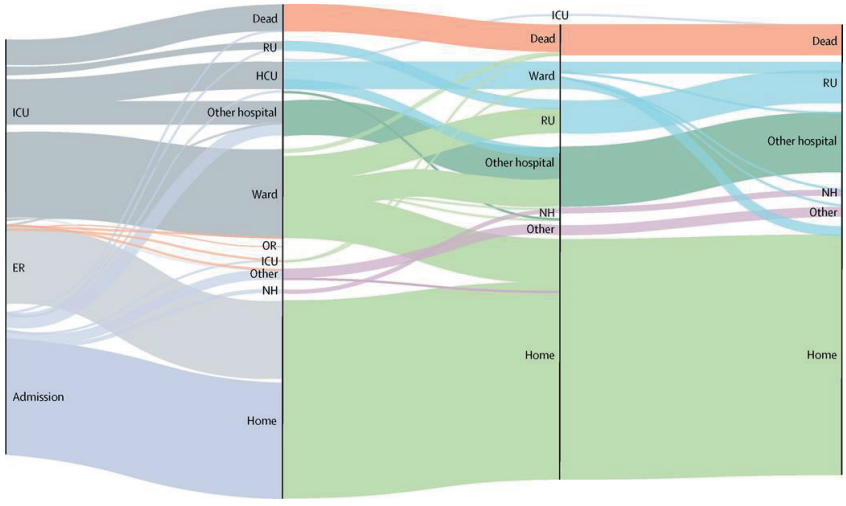


Figure 2.3 Care pathway by stratum in the CENTER-TBI core study (n=4509)

Vertical lines represent the first, second, and third transition of care. For example, most patients from the ER are discharged home and from the ICU most patients go to the ward. The width of each stream reflects the number of patients in that particular stream. The colours have been chosen to allow for clear visual differentiation between streams but do not carry any other intrinsic information. ER=emergency room. ICU=intensive care unit. ED=emergency department. HCU=high care unit. OR=operation room. RU=rehabilitation unit. NH=nursing home.

ER stratum	Admission stratum	ICU stratum	p value*
3/841 (0.4%)	42/1517 (2.8%)	318/2113 (15.0%)	<0.0001
9/694 (1.3%)	70/1264 (5.5%)	394/1846 (21.3%)	<0.0001
694/848 (81.8%)	1264/1523 (83.0%)	1846/2138 (86.3%)	
207/694 (29.8%)	665/1264 (52.6%)	1547/1846 (83.8%)	<0.0001
31/694 (4.5%)	140/1264 (11.1%)	795/1846 (43.1%)	<0.0001
51 (43–57)	51 (42–57)	48 (39–55)	<0.0001
51 (41–56)	50 (40–56)	46 (36–53)	<0.0001
75 (58–91)	75 (58–83)	67 (50–83)	<0.0001
101/480 (21.0%)	184/857 (21.5%)	266/963 (27.6%)	0.002
112/480 (23.3%)	207/857 (24.2%)	342/963 (35.5%)	<0.0001
91/474 (19.2%)	160/866 (18.5%)	260/983 (26.4%)	<0.0001

**p values were derived from ANOVA for continuous characteristics and χ^2 statistics for categorical characteristics, comparing strata. The p value assessed compatibility with the null hypothesis of no differences between strata.*

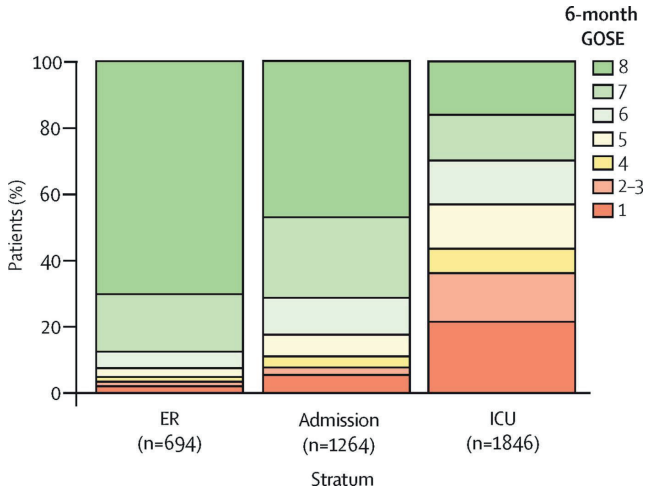


Figure 2.4 GOSE at 6 months by stratum in the CENTER-TBI core study

GOSE 1=dead. GOSE 8=upper good recovery. GOSE categories 2 (vegetative) and 3 (lower severe disability) are combined because differentiation is not possible for assessments done by postal questionnaire. GOSE=Glasgow Outcome Scale Extended. ER=emergency room. ICU=intensive care unit.

All covariates for the IMPACT core model and GOSE were available in 1132 (84%) patients older than 14 years with moderate or severe TBI (GCS ≤12). The 6-month mortality was 347 (30%), and 504 (43%) deaths were expected (observed to expected ratio 0.70, 95% CI 0.62–0.76). An unfavourable outcome (dichotomised at GOSE <5) was seen in 623 (55%) patients, which was not better than expected (1.07, 0.97–1.14).

DISCUSSION

This integrated analysis describes the landscape of TBI in the CENTER-TBI cohorts who presented in European hospitals, which differs substantially from previous observational studies[18,19]. Patients analysed in these cohorts were older, had more comorbidities, and injuries were most frequently caused by falls. The stratification of patients by care pathway showed clear discordances with the GCS-based classification of TBI severity, reflects the care that is provided, and sets a context for comparative effectiveness research. CENTER-TBI highlights the substantial burden and poor outcomes of TBI, particularly for patients with mild TBI. A quarter of patients in the core ER stratum and half in the core admission stratum were not fully recovered at 6 months.

Our study suggests that TBI should no longer be considered predominantly a disease of otherwise healthy young male patients[20]. 28% of the population was older than 65 years, compared with around 10% in previous studies[21]. The most common cause of injury was incidental falls, which increased with age, from around 50% in patients aged 50–60 years to more than 75% in patients older than 80 years. These findings motivate an increased focus on fall prevention in older people. The findings also make a strong case for targeting health-care provision and research for TBI in this population, who have been underserved in the past[22]. Clinical trials generally impose age limits (eg, 65 years) and older patients are consequently disenfranchised from research to improve their outcomes. Including older patients in clinical trials, however, produces additional challenges because of comorbidities, age-related neurocognitive changes, and limited neuropsychiatric metrics[23].

Comorbidities were present in 43% of the population and anticoagulants or platelet aggregation inhibitors were taken by 18%. The highest proportion of previous anticoagulant or antiplatelet therapy was in the admission stratum and might have predicated the need for a period of observation, and driven hospital admission in a substantial subset of patients. Improved prediction of the risks of late lesion development or progression in these patients might avoid unnecessary admission and bring hospital savings.

Alcohol was thought to be a contributory factor in a quarter of cases; recreational and prescription drug use were contributory factors in 6%, broadly in keeping with previous reports[24-26]. Alcohol was highly prominent in violence-related TBI and was involved about twice as often in incidental falls compared with road-traffic incidents. In public health terms, these findings highlight the need for continued efforts to reduce the role of alcohol in injury causation (with an increased focus on fall prevention), while being vigilant about the effects of recreational and prescription drugs.

Conventional characterisation of patients with TBI has relied on the GCS and broad categorisation of structural damage[27]. Our data go beyond these approaches to advance precision medicine in TBI, through detailed structured reporting of CT imaging, the inclusion of MRI, and measurement of blood biomarkers. The structured CT reporting based on the Common Data Elements that we used might be too detailed for routine clinical practice, but could be modified for wider clinical use—eg, by implementing automated pipelines[28]. We showed that MRI in a multicentre international study can be achieved by use of phantoms and healthy controls[29]. MRI detected abnormalities in 30% of CT-negative patients (typically traumatic axonal injury or contusions), and frequently showed more extensive damage in patients who did show CT abnormalities, in keeping with previous reports[30,31]. However, MRI abnormalities were absent in 18% of CT-positive patients, most often in those with traumatic subarachnoid haemorrhage or epidural haematoma. Understanding whether this discordance is due to resolution of abnormalities on later (around 2 weeks) MRI studies, or due to the inherent greater sensitivity of CT for such lesions is crucial, because doing so will inform whether MRI can be safely used as a sole imaging modality in the hyperacute stage after TBI.

We found that biomarker concentrations scaled with the presence of intracranial abnormalities, TBI severity (as defined by GCS), and management pathway (defined by stratum). Our data are concordant with previous reports[32-34] and motivate further research on the role of biomarkers in identifying the need for CT in the patients with least severe injury, selecting CT-negative patients for MRI, and prognostication in all severities of TBI.

We found substantial discordances between conventional stratification of TBI severity (mild, moderate, severe) and care pathways. Patients with mild TBI (GCS >12) constituted a third of patients in the ICU stratum. Plausible explanations for these ICU admissions include advanced age, frailty, comorbidities, increased risks of lesion progression due to use of anticoagulants and antiplatelet drugs, and the need for (extracranial) surgery[35].

We found substantial differences between countries in pre-hospital care and treatment policies, which support the findings of the provider profiling questionnaires[5-10]. These analyses were adjusted for baseline characteristics and stratum and might reflect true differences in policy. Secondary referrals were associated with substantial delays in access to definitive care, which could drive differences in outcomes between countries[36]. These differences—and the substantial between-country differences we found in the use of intracranial pressure monitoring, cranial and extracranial surgery, and ICU and hospital length of stay— represent opportunities to use comparative effectiveness research to identify best practices.

Although patients with moderate-to-severe TBI in the ICU stratum showed a greater survival than was expected, nearly half had unfavourable outcomes and their functional outcomes were no better than were expected by established prognostic schemes. In the ER stratum, 25% of patients had a GOSE less than 8, and hence had not returned to their pre-TBI baseline functioning by 6 months. These functional deficits were also reflected in quality-of-life measures, and impaired Qolibri-OS and SF-12v2 summary scores were seen in about a quarter[16]. These data are sobering and underline the substantial burden of morbidity for patients who are discharged from ERs, often without follow up, and with no therapeutic options[37]. The lower-than-expected mortality in combination with unchanged risk of unfavourable outcomes implies that the number of people living with severe disability from TBI has increased.

Despite broad similarities, we found some differences in terms of case-mix between the core study and registry. Some of these differences were expected because recruitment to the core study excluded patients with pre-existing neurological disorders, which could have confounded outcome assessment. The most notable difference was the lower percentage of patients in the ER stratum in the core study compared with those in the registry. This difference probably reflects research interests of participating centres, which are more focussed on more severe injuries, and on the logistic challenges of obtaining informed consent in an environment conditioned towards a high turnover rate. Analyses of the core data can be misleading because of the non-representative distribution across strata. Moreover, some differences were found within strata (eg, with respect to age, injury characteristics, and clinical characteristics at presentation). Caution is therefore appropriate when interpreting the generalisability of the core study results. Also, the stratum-specific results from the core study can only be generalised to patients without pre-existing major cognitive dysfunction.

Strengths of CENTER-TBI are the complementary nature of the core study and the registry, the broad pan-European perspective, the inclusion of all TBI severities and age groups, the focus on care pathways, the detailed clinical characterisation of patients, and establishment of large neuroimaging and biospecimen repositories. Collaboration within the InTBIR initiative will facilitate comparisons with contemporary cohorts and enable meta-analyses for research questions that require larger numbers (eg, genomics). Appropriate interpretation of the findings from CENTER-TBI requires an accurate understanding of the data and their context.

Several limitations should be acknowledged. We focused only on patients presenting to study hospitals and did not include pre-hospital deaths or patients who were not seen in the hospital setting. Second, recruitment to the core study was not consecutive and was determined by site logistics and research interests, meaning that selection bias is possible. Third, participating institutions were mainly referral centres for neurotrauma and results might not be generalisable to other hospital settings. Fourth, in some countries only one centre participated and consequently, potential intra-country health and health-care disparities (eg, north–south gradients) cannot be assessed. Fifth, the paediatric population was under-represented because participating centres focused mainly on care for adults. Sixth, not all data elements were complete. In many of the ongoing analyses, multiple imputation will be done for efficient statistical analyses[38]. Similarly, follow-up in the analysis cohort was not complete, although the availability of GOSE outcomes for 84% of the enrolled patients compares favourably with other observational studies.

CENTER-TBI provides detailed insights into the contemporary landscape of TBI in Europe. The results suggest that TBI might no longer be considered predominantly a disease of otherwise healthy young men. Mild TBI not only poses a great societal burden to health care, but also affects functional recovery and quality of life in individuals more than is commonly thought. Substantial geographical differences in care pathways and treatment approaches exist, which provide a basis for comparative effectiveness research to establish best practices. The detailed characterisation of patients in the core study, in combination with the neuroimaging repository and CENTER biobank, will contribute to the development of multidimensional classifications of initial injury severity and outcomes, and to precision medicine approaches. These insights could also provide a basis for re-engaging industry in partnerships for developing new diagnostics and therapeutic interventions for TBI.

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SUPPLEMENTARY MATERIAL

Supplementary Methods

Informed Consent and data de-identification

Consent procedures adhered to local and national requirements. Informed consent was preferred, but seldom possible as most patients were rendered mentally incapacitated by their TBI. Efforts were made to identify a legally acceptable representative (e.g. consultee/proxy). Other options included deferred consent and waiver of consent. We specifically sought consent for blood sampling, DNA analyses, and sharing data with other researchers (both within and outside of Europe). Subjects were free to withdraw, or to be withdrawn by their consultee/proxy: options included complete withdrawal (deletion of all data and destruction of biosamples) and partial withdrawal (cessation of new data accrual, but permission to use data and biosamples already collected). Locally collected data were de-identified and patients allocated a randomly generated GUPI (Global Unique Patient Identifier). All date and time entries were zeroed to the Unix epoch, thus permitting analysis of time intervals while preserving de-identification. Potential patient identifiers were removed from free text, both manually and by automated procedures. Images were defaced upon upload.

Biobank

The CENTER-TBI biobank (Pecs, Hungary) stored samples of whole blood, serum and plasma for genetic, biomarker and haemostasis analyses, respectively, for both the current study and legacy research[1]. Biomarker analysis was staged: we report on admission samples from 961 patients to explore the potential utility of candidate biomarkers, which included Neuron Specific Enolase (NSE), S-100B , Neurofilament light (NFL), total tau, glial fibrillary acidic protein (GFAP), and ubiquitin carboxyl-terminal hydrolase L1 (UCHL1). NSE and S-100B were measured on the e602 module of a Cobas 8000 analyzer (Roche Diagnostics International Ltd. Rotkreuz, Switzerland) in Pecs, Hungary. Neurofilament light (NFL), total tau, glial fibrillary acidic protein (GFAP), and ubiquitin carboxyl-terminal hydrolase L1 (UCHL1) were measured using the Quanterix SIMOA Neurology 4-plex kit (Quanterix, Lexington, MA, USA), at the University of Florida, USA.

Neuro-imaging repository

CT scans were obtained in all patients upon presentation. Follow up CT scans were acquired as clinically indicated or by local protocol[1]. MR scans were obtained in a subset of participating centres, and results are provided on analysis of the first 504 early (<3 weeks) studies. Images were scored locally, details captured in the e-CRF,

and subsequently uploaded into a central repository coordinated and maintained by Icometrix (https://icometrix.com/). All uploaded images were read centrally using NINDS CDE-based structured qualitative reporting (https://www.commondataelements.ninds.nih.gov/Doc/SharedForms/F0328_Imaging.docx).

Outcome data

Outcome assessments included disease-specific and health-related quality of life, psychosocial and symptom questionnaires and neuropsychological tests. Outcome assessors underwent face-to face training. Questionnaires were translated into national languages and linguistically validated.[1] Telephone or postal interviews were permitted in addition to face-to-face assessments. Cross-sectional outcome assessments across all strata were performed at 6 months post-injury. We report on the three primary outcome measures as defined on registration of the study (global function and health-related quality of life: GOSE[2] (overall impact of injury, including extracranial injuries), Qolibri-OS[3] and SF-12v2[4]), and on mortality at 6 months after injury. We classified Qolibri-OS scores <52 and SF-12v2 summary scores < 40 as impaired[5]. Secondary outcome instruments used in the study are given in the Tables below.

Secondary outcome Instruments CENTER-TBI

Questionnaire Follow-up* (Telephone interview or postal questionnaire/personal interview)
· Participant Questionnaire Part A
· QOLIBRI
· Post-traumatic Stress Disorder (PCL-5)
· GAD-7
· Rivermead Post Concussion Questionnaire (RPQ)
· SF36v2
· PHQ-9
Neuropsychology Follow-up* (Neuropsychological testing face to face visit)
· Participant Questionnaire Part B
· GOAT
· RAVLT
· TMT
· CANTAB
· 10 meter walk and timed up and go
· JFK Coma Recovery Scale –Revised

Data curation

Data were stored on a secure relational database, hosted by the International Neuroinformatics Coordinating Facility (INCF; www.incf.org) in Stockholm, Sweden. Source data verification of major characteristics was undertaken on a quasi-random sample of 1298 patients (28%) by a designated Contract Research Organization (ICON, Ltd, Paris). A multidisciplinary data curation task force addressed data missingness and plausibility, tested for multivariate consistency by cross-checking variables, and calculated derived variables to aid analyses. The cleaned and fully de-identified database was accompanied by a data dictionary with detailed descriptions of data manipulation or transformation applied, and an explicit record of non-resolvable curation issues. A data management tool, 'Neurobot' (http://neurobot.incf.org) was developed by INCF (RRID: SCR_01700). This facilitated data extractions, with the script storable as a unified resource locator for subsequent reuse, reference, or sharing. Separate repositories were used to store Imaging files (https://icometrix.com/) and high-resolution data (in hdf5 format[6]).

Data analysis

Patients without any GOSE assessment were excluded from analysis (n=705; 16%). The 6-month GOSE scores were available within the 5-8 month protocol window for 2186 (62%) patients. For 988 patients (22%) with scores outside the 5-8 month window, we used a multistate model to estimate the 180-day GOSE. We used the IMPACT Core model for the expected mortality and proportion with unfavourable GOSE outcome among patients with moderate or severe TBI (Glasgow Coma Score < = 12)[7]. Observed mortality and unfavourable GOSE outcomes were compared to expected outcomes and expressed as a ratio with 95% confidence intervals estimated according to a Poisson distribution.

For calculating SF-12v2 summary scores, we used the SF-12v2 questionnaires where complete, supplemented by derived scores using SF-36v2 items when available.

Supplementary Table 2.1 Socio-economic characteristics

Variable	N complete	N (%)
		4509
Years of education (median, IQR)	3212	13 (10 – 16)
Highest level of education	3566	
· None or primary school		641 (18%)
· Currently in or with diploma/degree oriented program		814 (23%)
· Secondary school		1261 (35%)
· College / University		850 (24%)
Marital status	4075	
· Married/living together		2070 (51%)
Employment status before injury	3980	
· Working		1946 (49%)
· Unable to work/sick leave		127 (3.2%)
· Retired		1112 (28%)
· Looking for work		235 (5.9%)
· Student / schoolgoing		486 (12%)
· Homemaker		74 (1.9%)

** p-values from ANOVA and chi-square statistics for continuous and categorical characteristics respectively*

Supplementary Table 2.2 Pre-injury health status and medical history

	N complete	All (N, %)
		4509
Pre-injury ASA-PS classification	4373	
A normal healthy patient		2501 (57%)
A patient with mild systemic disease		1410 (32%)
A patient with severe systemic disease		462 (11%)
Medical history		
Any	4370	2089 (48%)
Cardiovascular disease	4375	1304 (30%)
Endocrine disease	4369	583 (13%)
Diabetic Mellitus		339 (7.8%)
Oncologic	4368	285 (6.5%)
Pulmonary	4369	443 (10%)
Psychiatric	4352	601 (14%)
Previous TBI / concussions		
Previous TBI	4158	402 (9.7%)
Anticoagulants	4345	298 (6.9%)
Platelet aggregation inhibitors	4345	474 (11%)

ASA-PS = The American Society of Anesthesiologists (ASA) physical status classification system, Any Medical History = Cardiovascular disease, Endocrine disease, Oncologic disease, Pulmonary disease, Psychiatric disease, TBI = Traumatic Brain Injury.

ER (N, %) 848 (19%)	Admission (N, %) 1523 (34%)	ICU (N, %) 2138 (47%)	p-value*
13 (11 – 16)	13 (11 – 16)	12 (10 – 15)	<0.001
			<0.001
141 (18%)	224 (17%)	276 (19%)	
152 (19%)	324 (25%)	338 (23%)	
258 (33%)	422 (32%)	581 (39%)	
236 (30%)	334 (26%)	280 (19%)	
385 (48%)	717 (50%)	968 (52%)	0.15
			0.05
427 (52%)	638 (45%)	881 (50%)	
23 (2.8%)	46 (3.3%)	58 (3.3%)	
208 (26%)	438 (31%)	466 (27%)	
48 (5.9%)	88 (6.2%)	99 (5.7%)	
92 (11%)	174 (12%)	220 (13%)	
18 (2.2%)	30 (2.1%)	26 (1.5%)	

ER (N, %) 848 (19%)	Admission (N, %) 1523 (34%)	ICU (N, %) 2138 (47%)	p-value*
			0.56
482 (57%)	836 (56%)	1183 (58%)	
268 (32%)	507 (34%)	635 (31%)	
93 (11%)	159 (11%)	210 (10%)	
			0.21
413 (49%)	737 (49%)	939 (46%)	
235 (28%)	492 (33%)	577 (29%)	
130 (16%)	206 (14%)	247 (12%)	
70 (8.3%)	124 (8.1%)	145 (6.8%)	
63 (7.5%)	110 (7.3%)	112 (5.6%)	
83 (9.9%)	180 (12%)	180 (8.9%)	
127 (15%)	182 (12%)	292 (15%)	
			<0.001
120 (15%)	149 (10%)	133 (7.0%)	
46 (5.5%)	133 (8.8%)	119 (6.0%)	0.001
85 (10%)	178 (12%)	211 (11%)	0.38

** p-values from ANOVA and chi-square statistics for continuous and categorical characteristics respectively*

Supplementary Table 2.3 Cause of injury and intoxications

	N complete	All (N, %) 4509
Cause of injury	4388	
Road traffic incident		1682 (38%)
Incidental fall		2024 (46%)
Violence / assault		245 (5.6%)
Suicide attempt		48 (1.1%)
Other		389 (8.9%)
Alcohol involved in the injury (yes or suspected)	4163	1054 (25%)
Recreational drugs involved in the injury (yes or suspected)	3938	130 (3.3%)
Sedatives or sleeping pills involved in the injury (yes or suspected)	3883	92 (2.4%)

** p-values from ANOVA and chi-square statistics for continuous and categorical characteristics respectively*

Supplementary Table 2.4 Baseline clinical characteristics

	N complete	All (N, %) 4509 (100%)
GCS (median (IQR))	4330	15 (10-15)
Mild (13-15)		2955 (68%)
Moderate (9-12)		389 (9.0%)
Severe (3-8)		986 (23%)
GCS motor score	4397	
M1-3		828 (18,9%)
M4		158 (3.6%)
M5		433 (9.8%)
M6		2978 (68%)
Pupillary reactivity	4247	
One pupil unreactive		164 (3.9%)
Two pupils unreactive		281 (6.6%)
LOC (yes or suspected)	3987	2634 (66%)
PTA (yes or suspected)	3092	1483 (48%)
Hypoxia (prehospital/ER phase)	4256	299 (7.0%)
Hypotension (prehospital/ER phase)	4296	297 (6.9%)
ISS (median (IQR))	4453	16 (9-29)
Major extracranial injury (AIS > =3)		
Any	4509	1642 (36%)
Face	4509	650 (14%)
Thorax/chest	4509	886 (20%)
Abdomen/pelvis	4509	422 (9.4%)
Extremities	4508	513 (11%)
External	4509	92 (2.0%)
Spine	4509	480 (11%)

GCS = Glasgow Coma, M = Motor, LOC = Loss of Consciousness, PTA = Post-Traumatic Amnesia, ISS = Injury Severity Score, AIS = Abbreviated Injury Scale (AIS).

ER (N, %) 848 (19%)	Admission (N, %) 1523 (34%)	ICU (N, %) 2138 (47%)	p-value *
			<0.001
266 (32%)	490 (33%)	926 (45%)	
424 (51%)	761 (51%)	839 (41%)	
61 (7.3%)	100 (6.7%)	84 (4.1%)	
1 (0.1%)	3 (0.2%)	44 (2.1%)	
84 (10%)	145 (9.7%)	160 (7.8%)	
137 (17%)	384 (27%)	533 (28%)	<0.001
12 (1.5%)	28 (2.0%)	90 (5.2%)	<0.001
10 (1.2%)	31 (2.2%)	51 (3.0%)	0.020

ER (N, %) 848 (19%)	Admission (N, %) 1523 (34%)	ICU (N, %) 2138 (47%)	p-value *
15 (15-15)	15 (14-15)	9 (4-14)	<0.001
826 (99%)	1409 (55%)	720 (36%)	
2 (0.2%)	59 (4.0%)	328 (16%)	
4 (0.5%)	21 (1.4%)	961 (48%)	
			<0.001
4 (0.5%)	20 (1.3%)	804 (39%)	
3 (0.4%)	9 (0.6%)	146 (7.0%)	
9 (1.1%)	45 (3.0%)	379 (13%)	
819 (98%)	1417 (95%)	742 (36%)	
			<0.001
3 (0.4%)	27 (1.9%)	134 (6.6%)	
16 (2.0%)	19 (1.3%)	246 (12%)	
391 (49%)	883 (64%)	1360 (75%)	<0.001
284 (35%)	681 (50%)	518 (58%)	<0.001
3 (0.4%)	30 (2.1%)	266 (13%)	<0.001
4 (0.5%)	26 (1.8%)	267 (13%)	<0.001
4 (2-8)	10 (9-17)	29 (25-41)	<0.001
			<0.001
46 (5.4%)	422 (28%)	1174 (55%)	
19 (2.2%)	160 (11%)	471 (22%)	
8 (0.9%)	136 (8.9%)	742 (35%)	
7 (0.8%)	56 (3.7%)	359 (17%)	
17 (2.0%)	124 (8.1%)	372 (17%)	
8 (0.9%)	21 (1.4%)	63 (2.9%)	
10 (1.2%)	96 (6.3%)	374 (18%)	

** p-values from ANOVA and chi-square statistics for continuous and categorical characteristics respectively*

Supplementary Table 2.5 Characteristics of patients enrolled in the CENTER-TBI Registry versus CENTER-TBI Core study.

	ER	
	Core	**Registry**
	848 (19%)	**9839 (43%)**
Demographic characteristics		
Age (median, (IQR))	48 (29 – 64)	50 (29 - 72)
Male sex	473 (56%)	5523 (56%)
Injury characteristics		
Road traffic accident	266 (32%)	2191 (24%)
Incidental fall	424 (51%)	4851 (52%)
Other	146 (17%)	2244 (24%)
Baseline clinical characteristics		
GCS (median, (IQR))	15 (15 – 15)	15 (15 – 15)
Mild (13-15)	826 (99%)	9276 (98%)
Moderate (9 – 12)	2 (0.2%)	96 (10%)
Severe (3 – 8)	4 (0.5%)	55 (0.6%)
GCS motor score (median, (IQR))	6 (6 – 6)	6 (6 - 6)
Pupillary reactivity		
One pupil unreactive	3 (0.4%)	47 (0.5%)
Two pupils unreactive	16 (2%)	81 (0.9%)
Major extracranial injury (AIS> =3)	46 (5.4%)	321 (3.3%)
CT Characteristics		
Any intracranial abnormality	103 (13%)	498 (5.1%)
Key emergency interventions		
Craniotomy for haematoma/contusion	0 (0%)	6 (0%)
Arrived intubated at ED	2 (0.2%)	50 (0.5%)
Status on discharge		
In-hospital mortality	3 (0.4%)	75 (0.8%)

GCS = Glasgow Coma Scale, ICP = Intracranial pressure

	Admission		ICU	
	Core	**Registry**	**Core**	**Registry**
	1523 (34%)	**8571 (38%)**	**2138 (47%)**	**4372 (19%)**
	53 (32 – 69)	64 (40 - 81)	49 (29 – 65)	51 (31 - 68)
	988 (65%)	5133 (60%)	1562 (73%)	3169 (73%)
	490 (33%)	2077 (25%)	926 (45%)	1636 (39%)
	761 (51%)	5237 (64%)	839 (41%)	2039 (49%)
	248 (17%)	910 (11%)	288 (14%)	496 (12%)
	15 (14 – 15)	15 (14 – 15)	9 (4 – 14)	12 (5 – 15)
	1409 (95%)	7735 (94%)	720 (36%)	1466 (49%)
	59 (4.0%)	369 (4.5%)	328 (16%)	423 (14%)
	21 (1.4%)	113 (1.4%)	961 (48%)	1093 (37%)
	6 (6 – 6)	6 (6 - 6)	5 (1 – 6)	5 (1 - 6)
	27 (1.9%)	38 (0.5%)	134 (6.6%)	491 (12%)
	19 (1.3%)	126 (1.6%)	246 (12%)	303 (7.3%)
	422 (28%)	2410 (28%)	1174 (55%)	2312 (53%)
	681 (49%)	3032 (36%)	1650 (89%)	3509 (81%)
	19 (1.2%)	124 (1.5%)	297 (14%)	700 (16%)
	15 (1.0%)	53 (0.6%)	929 (44%)	1776 (41%)
	42 (2.8%)	209 (2.5%)	318 (15%)	773 (19%)

Supplementary Table 2.6 CT characteristics from central review

	N complete	All (N, %) 4509
Marshall CT classification	4037	4037
Diffuse Injury I (no visible pathology)		1633 (41%)
Diffuse Injury II		1527 (38%)
Diffuse Injury III (swelling)		165 (4.1%)
Diffuse Injury IV (shift)		32 (0.8%)
V/VI (Evacuated/Non evacuated mass lesion)		679 (17%)
Any intracranial abnormality	4037	2434 (60%)
Basal cistern absent / compressed	4037	640 (16%)
Midline shift	4037	464 (12%)
Traumatic subarachnoid haemorrhage (tSAH)	4037	1812 (45%)
Epidural Hematoma	4037	445 (11%)
Acute subdural hematoma	4037	1218 (30%)
Diffuse Axonal Injury	4037	368 (9.1%)
Contusion	4037	1301 (32%)

Any intracranial abnormality: Basal cistern absent / compressed, Midline shift, Traumatic subarachnoid haemorrhage, Epidural Hematoma, Acute subdural hematoma, Subacute/chronic subdural hematoma,

Supplementary Table 2.7 Agreement between central and local radiological evaluation of 3,922 admission CT scans.

	Agreement	Frequencies	
	Kappa (95% CI)	Central (N,%)	Site (N,%)
CT+	0.79 (0.77-0.81)	2358 (60%)	2408(61%)
CT-	0.79 (0.77-0.81)	1564 (40%)	1514 (39%)
Epidural hematoma	0.59 (0.55-0.63)	465 (12%)	419 (11%)
Acute subdural hematoma	0.67 (0.65-0.70)	1200 (31%)	1222 (31%)
tSAH	0.67 (0.65-0.70)	1784 (45%)	1500 (38%)
Contusion	0.63 (0.60-0.65)	1278 (33%)	1366 (35%)
TAI	0.35 (0.30-0.40)	359 (9%)	378 (10%)
MLS	0.75 (0.71-0.78)	456 (12%)	576(15%)
Cisternal compression	0.54 (0.50-0.58)	627 (16%)	351 (9%)

Kappa values for a positive and negative CT scan (CT+, CT-, see methodology section) and 7 different CT characteristics. Frequencies in which CT characteristics were reported by the investigator sites and by the central review are shown, with associated McNemar tests for discordance of paired values.

ER (N, %) 848	Admission (N, %) 1523	ICU (N, %) 2138	p-value *
805	1378	1854	< 0.001
716 (89%)	711 (52%)	207 (11%)	
85 (11%)	556 (40%)	886 (48%)	
0 (0.0%)	13 (0.9%)	152 (8.2%)	
0 (0%)	4 (0.3%)	28 (1.5%)	
4 (0.5%)	94 (6.8%)	581 (31%)	
103 (13%)	681 (49%)	1650 (89%)	< 0.001
3 (0.4%)	59 (4.3%)	578 (31%)	< 0.001
3 (0.4%)	58 (4.2%)	403 (22%)	< 0.001
56 (7%)	424 (31%)	1332 (73%)	< 0.001
1 (0.1%)	101 (7.4%)	343 (19%)	< 0.001
21 (2.6%)	298 (22%)	899 (49%)	< 0.001
18 (2.2%)	67 (4.8%)	283 (16%)	< 0.001
25 (3.1%)	254 (19%)	1022 (55%)	< 0.001

Mixed density subdural hematoma, Contusion, Mass lesion, Intraventricular haemorrhage, and Traumatic axonal injury. p-values from ANOVA and chi-square statistics for continuous and categorical characteristics respectively*

Concordance		Discordance		McNemar
CR+/SR+	CR-/SR-	CR-/SR+	CR+/SR-	p-value
2184	NA	224	174	0.014
NA	1340	224	174	0.014
282	320	137	183	0.012
936	2436	286	264	0.371
1329	1967	171	455	0.001
994	2272	372	284	0.001
152	3337	226	207	0.387
402	3292	174	54	0.001
290	3234	61	337	0.001

Frequencies of concordance and discordance are also shown. CR = Central Review, SR = Site Review, NA = Not applicable. tSAH = Traumatic Subarachnoid Hemorrhage, TAI = Traumatic Axonal Injury, MLS = Midline Shift, CI = Confidence Interval.

Supplementary Table 2.8 CT and MR agreement for 384 MR early (<3 weeks) scans (derived from central review)

	Agreement	Frequencies	
	Kappa (95% CI)	**CT (N,%)**	**MR (N,%)**
Any intracranial abnormality	0.52 (0.44-0.61)	182 (47%)	210 (55%)
No intracranial abnormality	0.52 (0.44-0.61)	202 (53%)	174 (45%)
Epidural hematoma	0.64 (0.49-0.79)	34 (9%)	23 (6%)
Acute subdural hematoma	0.47 (0.36-0.58)	75 (20%)	81 (21%)
tSAH	0.48 (0.39-0.58)	122 (32%)	90 (23%)
Contusion	0.65 (0.57-0.74)	84 (22%)	121 (32%)
TAI	0.15 (0.08-0.22)	21 (5%)	135 (35%)
MLS	0.28 (0.05-0.50)	19 (5%)	8 (2%)
Cisternal compression	0.29 (0.05-0.52)	17 (4%)	9 (2%)

Kappa values for Any intracranial abnormality and 7 different imaging characteristics. Frequencies in which the imaging characteristics were reported on CT and MR are shown, with associated McNemar tests for discordance of paired values.

Supplementary Table 2.9 Diagnostic and Surgical interventions

	N completed	**N (%)**
		4509
ICP monitor placed	2340	924 (43%)
Intracranial surgery	3686	885 (24%)
Total number of intracranial surgeries		1290
Decompressive craniectomy		204 (16%)
Depressed skull fracture		54 (4.2%)
Acute subdural hematoma		323 (25%)
Epidural hematoma		134 (10%)
Intracerebral hematoma		32 (2.5%)
Ventriculostomy for CSF drainage		162 (13%)
Other		381 (30%)
Extracranial surgery	3685	735 (20%)
Total number of extracranial surgeries		1305
Maxillofacial		177 (14%)
Extremity fracture		457 (35%)
Laparotomy		65 (5.0%)
Pelvic fracture		64 (4.9%)
Spinal stabilization		117 (9.0%)
Thoracotomy		13 (1.0%)
Other		412 (32%)

CSF = Cerebrospinal Fluid. Percentage for individual types of surgical procedures are in relation to the total number of extracranial and intracranial surgeries performed (as appropriate in each context)

Concordance		Discordance		McNemar
CT+/MR+	CT-/MR-	CT+/MR-	CT-/MR+	p-value
142	150	32	60	0.005
150	142	60	32	0.005
15	346	15	4	0.022
45	273	30	36	0.538
66	238	56	24	0.001
76	255	8	45	0.001
18	246	3	117	0.001
4	361	15	4	0.022
4	362	13	5	0.099

Frequencies of concordance and discordance are also shown. CT = Computed Tomography, MR = Magnetic Resonance. tSAH = Traumatic Subarachnoid Hemorrhage, TAI = Traumatic Axonal Injury, MLS = Midline Shift, CI = Confidence Interval.

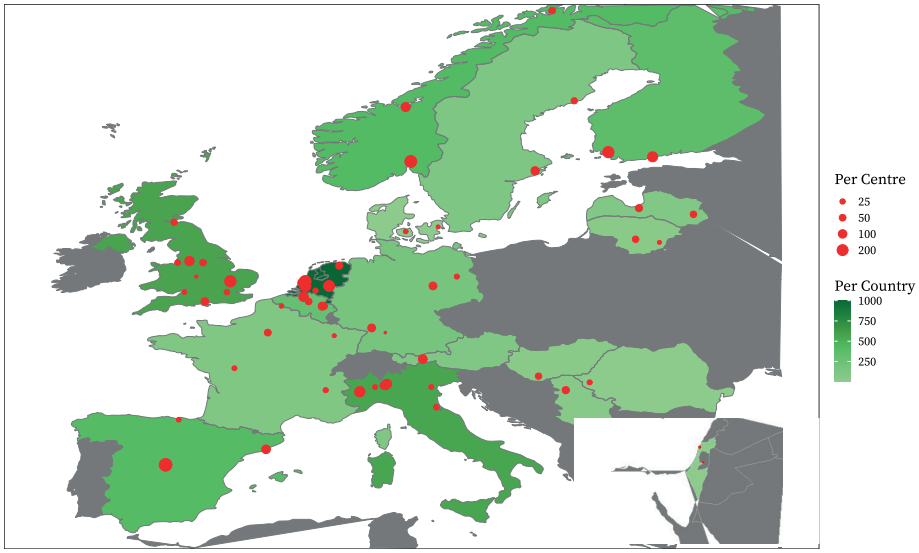
ER (N, %) 848 (19%)	Admission (N, %) 1523 (34%)	ICU (N, %) 2138 (47%)	p-value *
0 (0.0%)	3 (7%)	921 (44%)	<0.001
1 (2.4%)	64 (4.2%)	820 (39%)	<0.001
1	65	1224	
0 (0.0%)	2 (3.1%)	202 (17%)	
0 (0.0%)	9 (14%)	45 (3.7%)	
0 (0.0%)	14 (22%)	309 (25%)	
0 (0.0%)	19 (29%)	115 (9.4%)	
0 (0.0%)	1 (1.5%)	31 (2.5%)	
0 (0.0%)	1 (1.5%)	161 (13%)	
1 (100%)	19 (29%)	361 (30%)	
1 (2.4%)	128 (8.4%)	606 (29%)	<0.001
2	158	1145	
1 (50%)	36 (23%)	140 (12%)	
1 (50%)	56 (35%)	400 (35%)	
0 (0.0%)	4 (2.5%)	61 (5.3%)	
0 (0.0%)	5 (3.2%)	59 (5.2%)	
0 (0.0%)	13 (8.2%)	104 (9.1%)	
0 (0.0%)	2 (1.3%)	11 (1.0%)	
0 (0.0%)	42 (27%)	370 (32%)	

** p-values from ANOVA and chi-square statistics for continuous and categorical characteristics respectively*

Supplementary Table 2.10 Glasgow Outcome Scale – Extended (GOSE) assessed during follow-up: known (*n*=3804) versus unknown (*n*=705)

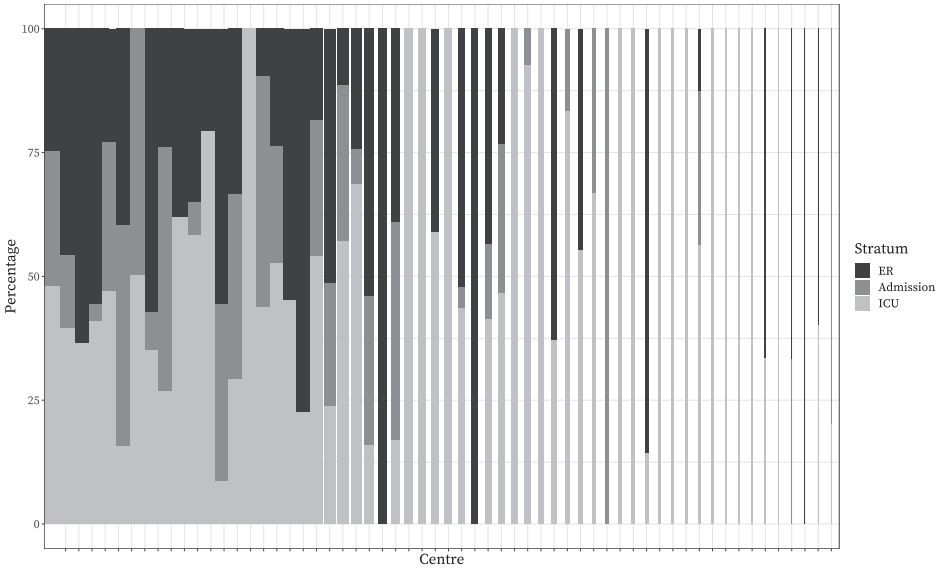
Variable	GOSE available (N, %) 3804 (84%)	GOSE unknown (N, %) 705 (16%)	p-value *
Demographic characteristics			
Age (median (IQR))	51 (30-67)	46 (29-65)	0.14
> =65 years	1069 (28%)	185 (26%)	0.33
Male sex	2537 (67%)	486 (69%)	0.26
Caucasian	3537 (97%)	621 (95%)	0.04
Socio-economic characteristics			
Years of education (median (IQR))	13 (10-16)	12 (10-15)	<0.001
Highest level of education			
College / University	758 (25%)	92 (18%)	0.001
Married/living together	1790 (51%)	280 (48%)	0.18
Employment status before injury			
Working	1669 (49%)	278 (48%)	0.006
Pre-injury health status and medical history			
Pre-injury ASA-PS classification			0.70
A patient with mild systemic disease	1204 (33%)	206 (31%)	
A patient with severe systemic disease	390 (11%)	72 (11%)	
Previous TBI	346 (11%)	56 (8.7%)	0.40
Anticoagulants	249 (6.8%)	49 (7.4%)	0.57
Platelet aggregation inhibitors	418 (11%)	58 (8.5%)	0.05
Cause of injury and use of medication			
Cause of injury			<0.001
Road traffic incident	1454 (39%)	228 (34%)	
Incidental fall	1716 (46%)	308 (45%)	
Alcohol involved in the injury (yes or suspected)	854 (24%)	200 (32%)	<0.001
Baseline clinical characteristics			
GCS baseline (median (IQR))	15 (9-15)	15 (12-15)	<0.001
GCS motor score (median (IQR))	6 (5-6)	6 (6-6)	<0.001
Pupillary reactivity			0.003
One pupil unreactive	141 (3.9%)	25 (3.8%)	
Two pupils unreactive	256 (7.1%)	23 (3.5%)	
Hypoxia (prehospital/ER phase)	270 (7.5%)	28 (4.2%)	0.003
Hypotension (prehospital/ER phase)	273 (7.5%)	24 (3.6%)	<0.001
Major extracranial injury (AIS > =3)			
Spine	427 (11%)	56 (7.9%)	0.003

*ASA-PS = The American Society of Anesthesiologists (ASA) physical status classification system, TBI = Traumatic Brain Injury, GCS = Glasgow Coma Scale, AIS = Abbreviated Injury Scale (AIS). * p-values from ANOVA and chi-square statistics for continuous and categorical characteristics respectively*

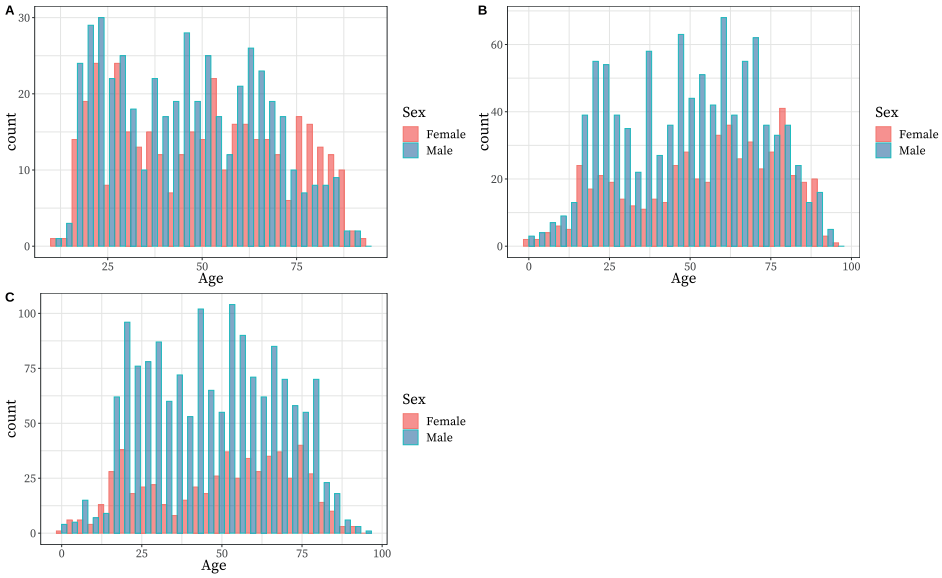


Supplementary Figure 2.1 Participation per study centre & country in the CENTER-TBI Core study (n=4509 patients)

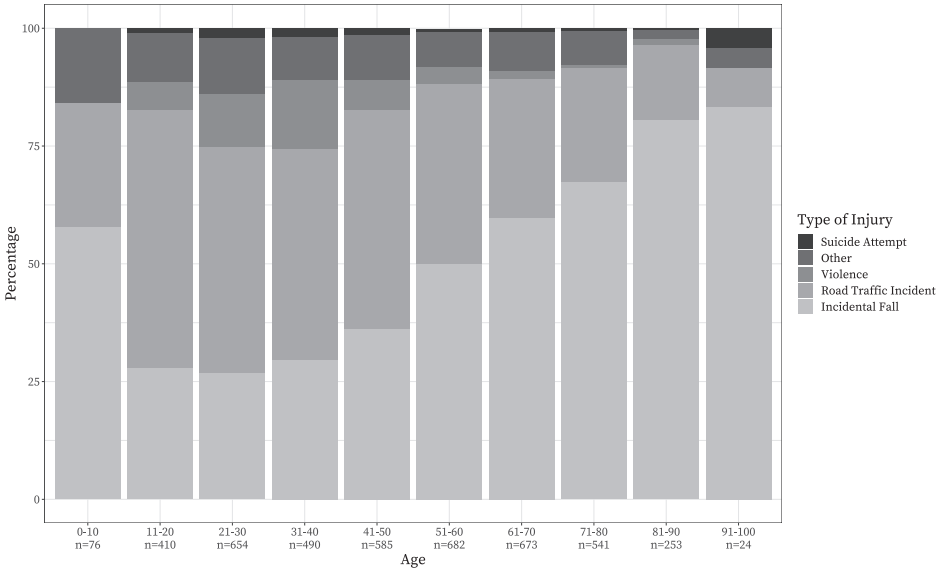
The median enrollment by country was 125 (IQR: 50 – 403) and median by site 50 (IQR: 21 – 107). Four countries accounted for 2563/4509 (57%) of recruited patients (Netherlands: N=7 centres, n=1,006 patients; the UK: N=9 centres, n=578 patients; Italy: N=8 centres, n=560 patients and Norway: N=3 centres, n=419 patients).



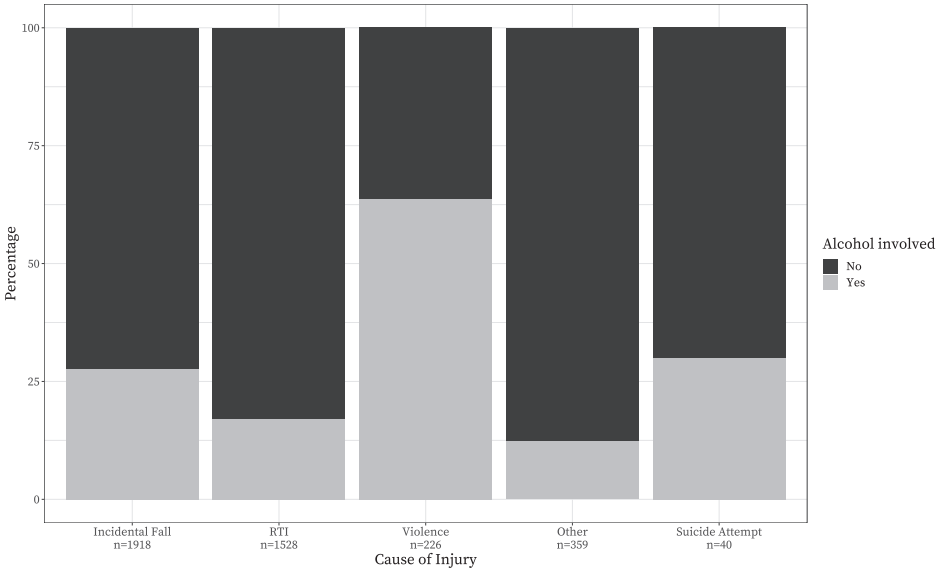
Supplementary Figure 2.2 Enrolment in strata by centre. The width of the bars indicates the total number of patients per centre.



Supplementary Figure 2.3 Age by sex distribution by stratum in the CENTER-TBI Core study (n=4509 patients). The ER stratum included most females and the ratio of females to males increased with older ages in each stratum. A) ER (n=848), B) Admission (n=1523), C) ICU (n=2138)

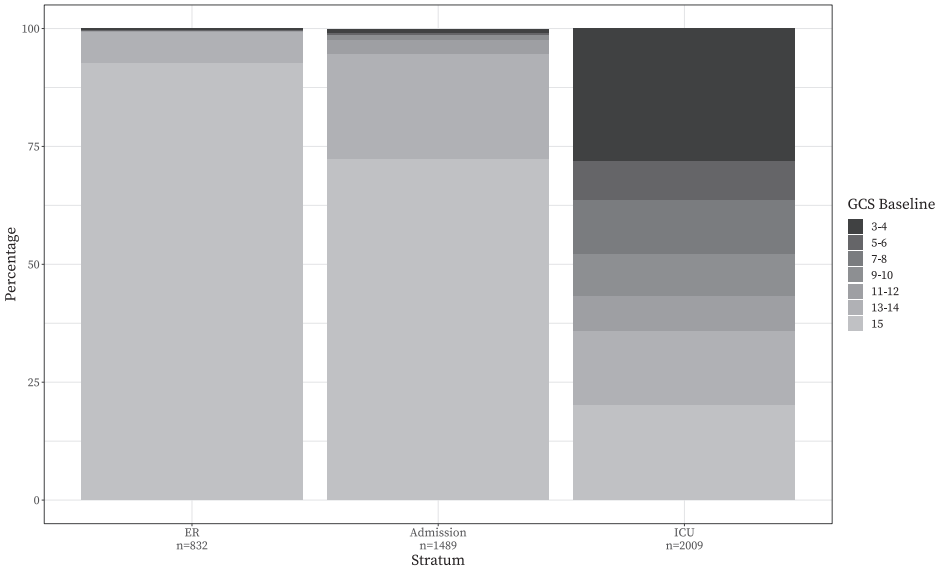


Supplementary Figure 2.4 Cause of Injury by Age Group, CENTER-TBI Core (N=4388)

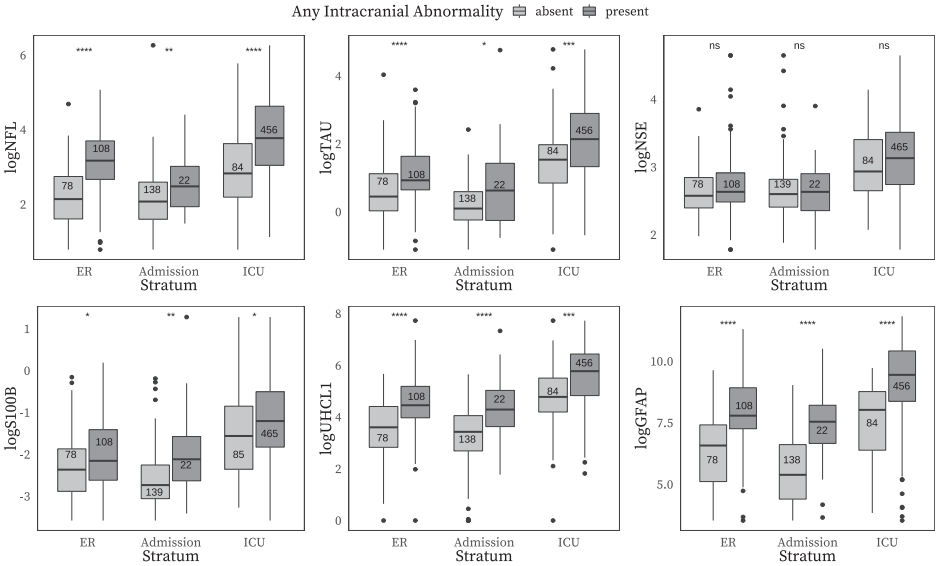


Supplementary Figure 2.5 Alcohol use and Cause of Injury, CENTER-TBI Core (N= 4071)

**RTI = Road Traffic Incident.*

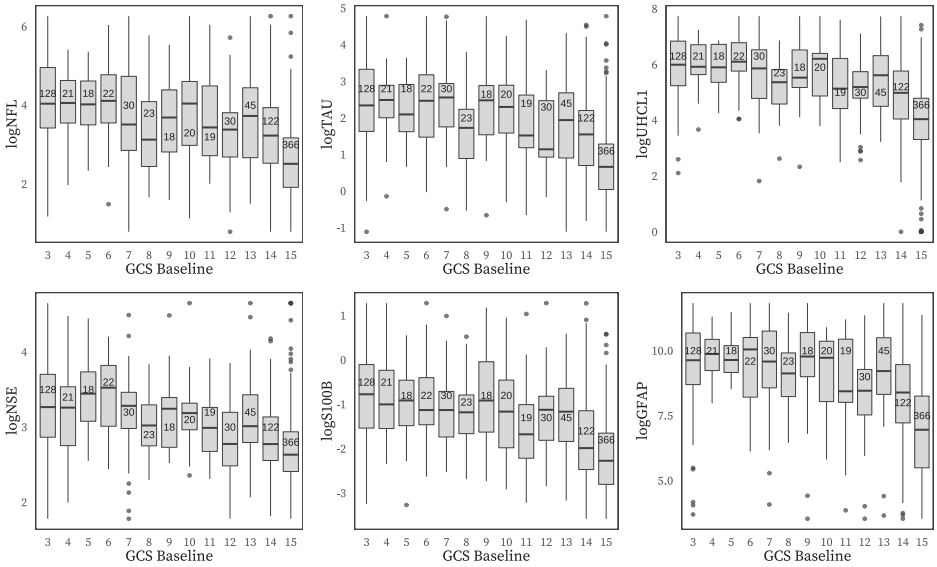


Supplementary Figure 2.6 GCS distribution by stratum, CENTER-TBI- core (N=4344). GCS baseline reflects the GCS score obtained as close as possible to study admission, and is derived from all available scores from the time period pre-hospital to admission to ward/ICU or discharge from the ER.



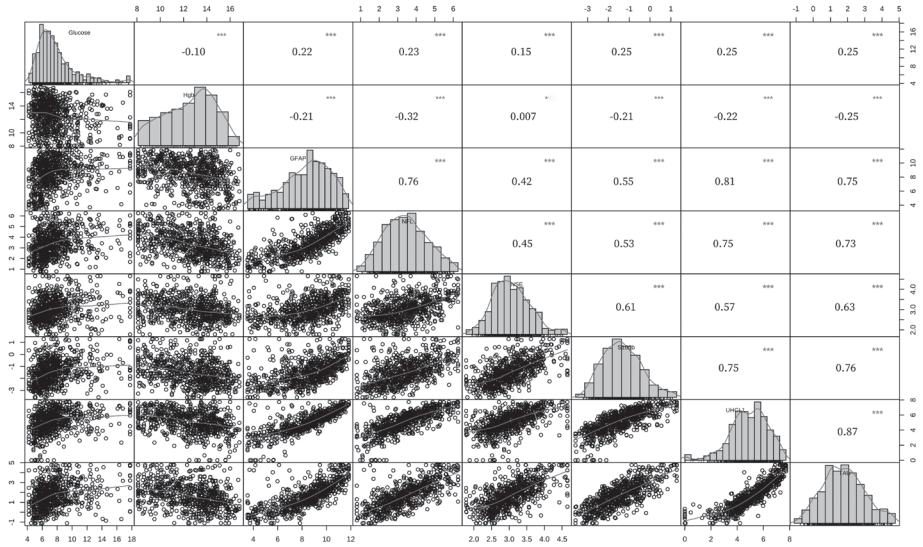
Supplementary Figure 2.7 Biomarkers versus CT Abnormalities by stratum (complete case analysis, n=898)

*[#] NFL = Neurofilament Light, NSE = Neuron-Specific Enolase, UCHL1 = Ubiquitin Carboxy-Terminal Hydrolase L, t-TAU = total TAU1, S100B = S100 calcium-binding protein B, GFAP = Glial Fibrillary Acidic Protein. NSE and S-100B were measured on the e602 module of a Cobas 8000 analyzer (Roche Diagnostics International Ltd. Rotkreuz, Switzerland) in Pecs, Hungary and NF-L, total Tau, GFAP, and UCH-L1 on the Quanterix SIMOA Neurology 4-plex kit (Quanterix, Lexington, MA, USA), at the University of Florida, USA. Differences between biomarker values in patients with any intracranial abnormality versus patients without any intracranial abnormality were tested per stratum with a t-test. The stars above the bars indicate significance: ns: p >0.05, *: p < =0.05, **: p < =0.01, ***: p < =0.001, ****: p < =0.0001.*



Supplementary Figure 2.8 Biomarkers by GCS levels in the CENTER-TBI Core study (n=898)

NFL = Neurofilament Light, NSE = Neuron-Specific Enolase, UCHL1 = Ubiquitin Carboxy-Terminal Hydrolase L, t-TAU = total TAU1, S100B = S100 calcium-binding protein B, GFAP = Glial Fibrillary Acidic Protein. NSE and S-100B were measured on the e602 module of a Cobas 8000 analyzer (Roche Diagnostics International Ltd. Rotkreuz, Switzerland) in Pecs, Hungary and NF-L, total Tau, GFAP, and UCH-L1 on the Quanterix SIMOA Neurology 4-plex kit (Quanterix, Lexington, MA, USA), at the University of Florida, USA.



Supplementary Figure 2.9 Correlation between glucose, hemoglobin, and six biomarkers (GFAP, NFL, NSE, S100B, UHCL1, t-TAU, n=804). Strong correlations were noted, specifically between GFAP, NFL, S100B, UCHL1, and t-TAU (r>0.7). Only weak correlations were noted between biomarkers versus glucose or hemoglobin.

Hgb = Hemoglobin, GFAP = Glial Fibrillary Acidic Protein, NFL = Neurofilament Light, NSE = Neuron-Specific Enolase, S100B = S100 calcium-binding protein B, UCHL1 = Ubiquitin Carboxy-Terminal Hydrolase L1, t-TAU = total TAU. All biomarkers were log transformed.

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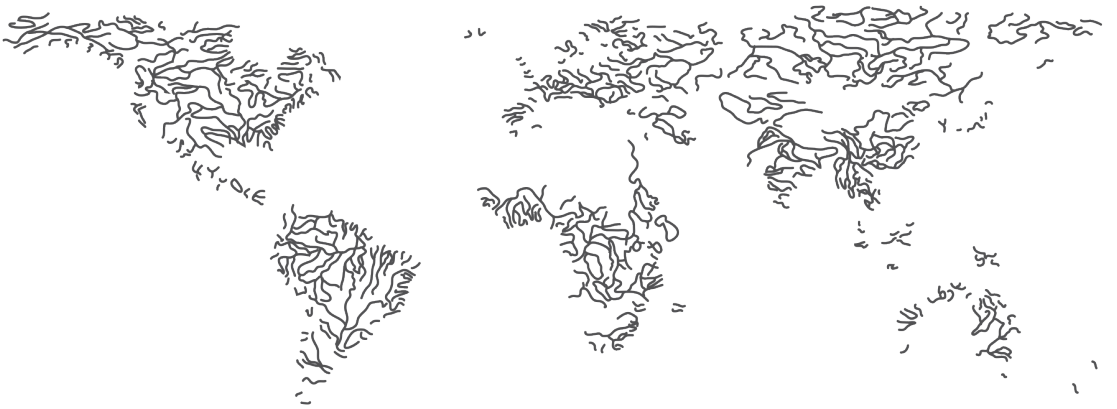

Chapter 3

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

Intensive Care Medicine, 2020

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*equal contribution

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 centres.

Methods
Prospective observational multicentre study conducted across 18 countries in Europe and Israel. Admission characteristics, clinical data, and outcome were described at patient- and centre-level. Between-centre variation in the total ICU population was quantified with the median odds ratio (MOR), with correction for case-mix and random variation between centres.

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-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, $p=0.01$).

Conclusions
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.

Keywords
intensive care unit, traumatic brain injury, intracranial pressure, outcome

Take home message
"Patients with traumatic brain injury admitted to intensive care units are older and often less severe than in previous studies. Substantial between-centre variation exists in ICU admission and treatment policies across Europe"

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 Intensive Care Unit (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:

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

- 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 ≤ 8 and CT abnormalities was performed.
- The use of aggressive ICP-lowering treatments (any use of Decompressive Craniectomy, Metabolic Suppression, Hypothermia Therapy or Intensive Hypocapnia)
- 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;

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

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-centre variation, comparing a model with and without a random effect for centre. 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 extra-cranial injuries were present in 1174 (55%) patients. (Table 3.1) 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%) (Supplementary Table 3.1). 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.

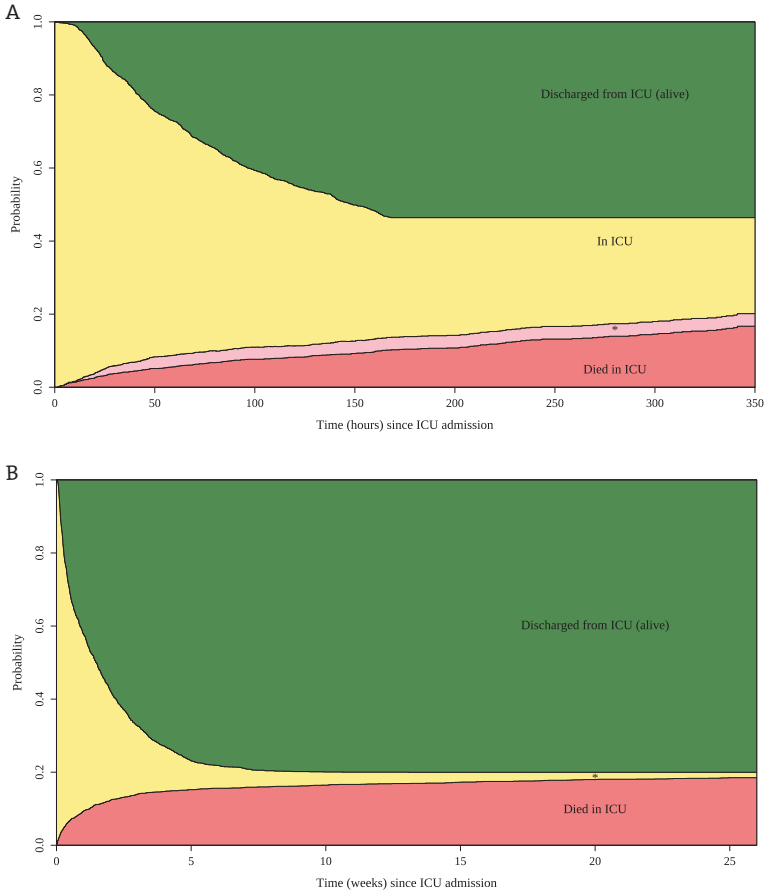

Figure 3.1 Patient flow over time

*a 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. b Plot of the dynamic states of patients with TBI that were admitted to the ICU during the first 6 months 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 point from ICU admission. *Still in ICU*

ICU mortality and discharge rates were high in the first 72 hours, but declined over time (Figure 3.1, Figure 3.2). There were 128 (6%) early deaths, 636 (30%) short stay, and 1372 (64%) long stay cases (Figure 3.2).

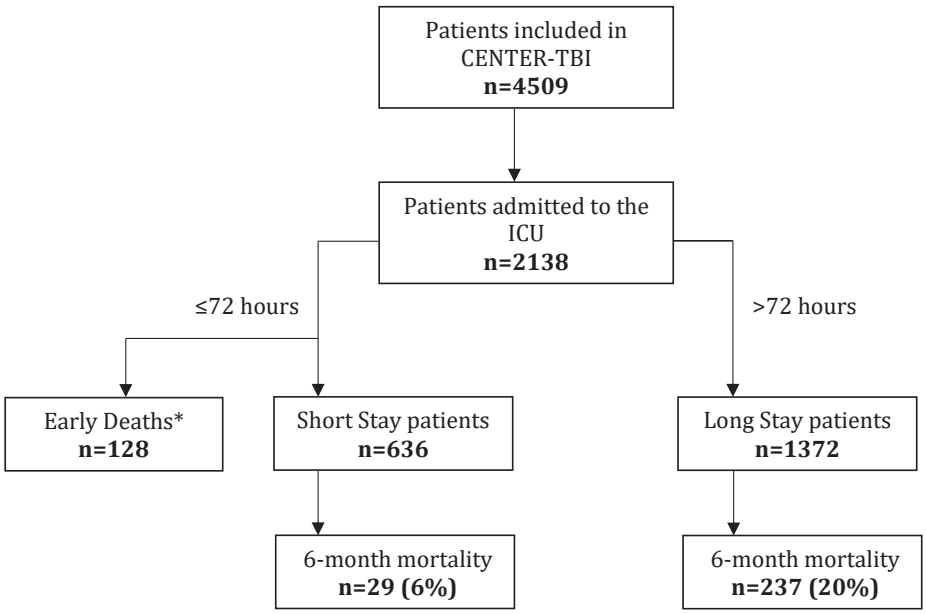

Figure 3.2 Flowchart of ICU patients

*This figure shows the flow of patients at the ICU, based on their length of stay. *Patients who died within 72 h at the ICU*

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 3.1). The main cause of mortality in early death patients was due to initial head injury (78, 81%) (Supplementary Figure 3.2).

The most frequent reason for admission in short stay patients were need for frequent neurological observations (340; 54%) and mechanical ventilation (154; 24%) (Supplementary Figure 3.3). The long stay patients included 319 patients (25%) classified as mild TBI in whom similar reasons for admission were mentioned (the need for neurological observations (152, 48%), mechanical ventilation (96, 30%).

Table 3.1: Baseline characteristics

	Total	**Short stay**
	2138	**636**
Age (median (IQR))	49 (29 – 65)	48 (28 – 64)
> =65 years	552/2138 (26%)	153/636 (24%)
> =80 years	94 /2138(4.4%)	29/636 (4.6%)
Male sex	1562/2138 (73%)	443/636 (70%)
Severity TBI		
Mild	720/2009 (36%)	394/607 (65%)
Moderate	328/2009 (16%)	107/607 (18%)
Severe	961/2009 (48%)	106/607 (18%)
Pupillary Reactivity		
Both Reacting	1636/2016 (81%)	564/606 (93%)
Both Unreacting	246/2016 (12%)	16/606 (2.6%)
One reacting	134/2016 (6.6%)	26/606 (4.3%)
Hypoxia	266/1981 (13%)	38/593 (6.4%)
Hypotension	267/1992 (13%)	36/595 (6.1%)
ISS (median (IQR))	29 (25 – 41)	24 (16 – 29)
Any major extracranial injury (AIS > =3)	1174/2138 (55%)	283/636 (45%)
CT Characteristics		
Marshall CT Classification		
I	204/1854 (11%)	110/566 (19%)
II	889/1854 (48%)	330/566 (58%)
III	152/1854 (8.2%)	19/566 (3.4%)
IV	28/1854 (1.5%)	4/566 (0.7%)
V/VI	581/1854 (31%)	103/566 (18%)
Epidural Hematoma	369/1854 (20%)	120/566 (21%)
tSAH	1347/1854 (73%)	318/566 (56%)
Contusion	1032/1854 (56%)	244/566 (43%)
Acute Subdural Hematoma	911/1854 (49%)	192/566 (34%)
Midline Shift	404/1854 (22%)	77/566 (14%)
Basal Cistern Absent or Compressed	586/1854 (32%)	81/566 (14%)

This table shows the baseline characteristics for short stay (stay ≤ 72 hours), Long Stay (stay >72 hours), and early deaths (≤ 72 hours).

Long stay 1372	Early deaths 128	p-value
49 (29 – 64)	62 (40 – 75)	< 0.001
337/1372 (25%)	62/128 (48%)	< 0.001
52/1372 (3.8%)	13/128 (10%)	0.003
1023/1372 (75%)	94/128 (73%)	0.07
		< 0.001
319/1285 (25%)	6/116 (5.2%)	
213/1285 (17%)	8/116 (6.9%)	
753/1285 (59%)	102/116 (88%)	
		< 0.001
1040/1287 (81%)	31/122 (25%)	
150/1287 (12%)	80/122 (65%)	
97/1287 (7.5%)	11/122 (9.0%)	
191/1266 (15%)	37/121 (31%)	< 0.001
189/1274 (15%)	42/122 (34%)	< 0.001
34 (25 – 43)	58 (28 – 75)	< 0.001
823/1372 (60%)	67/128 (53%)	< 0.001
		< 0.001
90/1179 (7.6%)	3/108 (2.8%)	
553/1179 (47%)	6/108 (5.6%)	
105/1179 (8.9%)	28/108 (26%)	
17/1179 (1.4%)	7/108 (6.5%)	
414/1179 (35%)	64/108 (59%)	
234/1179 (20%)	15/108 (14%)	0.22
930/1179 (79%)	99/108 (92%)	< 0.001
730/1179 (62%)	58/108 (54%)	< 0.001
633/1179 (54%)	86/108 (80%)	< 0.001
281/1179 (24%)	54/108 (50%)	< 0.001
415/1179 (35%)	94/108 (87%)	< 0.001

P-values from ANOVA and chi-square statistics for continuous and categorical characteristics respectively. AIS: Abbreviated Injury Scale. tSAH: traumatic subarachnoid hemorrhage

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 (Supplementary Table 3.2).

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) (Supplementary Table 3.2).

Complications and Outcome

Long stay patients suffered more complications compared with short stay case: 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 3.2).

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 3.2).

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%).

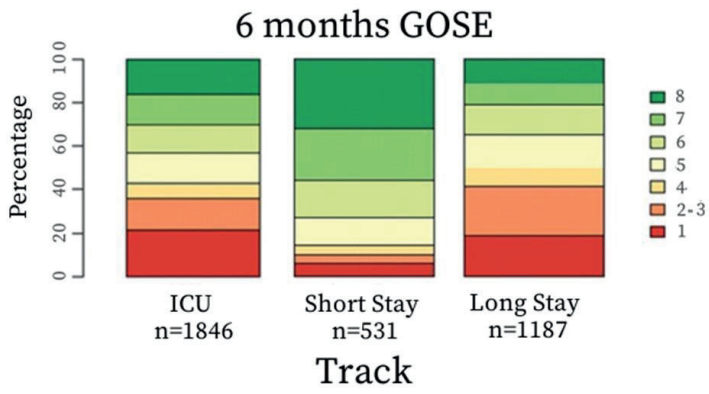

Figure 3.3 Six-month Glasgow outcome scale extended

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

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 3.4). 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, $p < 0.001$).

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 3.4). A sensitivity analyses (with a subset of patient with a GCS $\leq$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 3.4).

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 3.4).

Table 3.2 Outcome and Complications

	Total **2138**
Outcomes	
6-month Mortality	394/1846 (21%)
6-month Unfavorable Outcome (GOSE < 5)	795/1846 (43%)
Hospital Length of stay in days (median (IQR))	11 (3.4 – 26)
Discharge Location from ICU	
General Ward	1102/1840 (60%)
Home	15/1840 (0.8%)
Nursing Home	4/1840 (0.2%)
Other	36/1840 (2.0%)
Other Hospital	201/1840 (11%)
Other ICU	43/1840 (2.3%)
Rehab Unit	98/1840 (5.3%)
Step down/ High Care Unit	341/1840 (19%)
Complications at the ICU	
Ventilator Acquired Pneumonia	280/2090 (13%)
Cardiovascular Complications	155/2091 (7.4%)
Meningitis	49/2090 (2.3%)
Seizures	121/2089 (5.8%)

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.

	Short stay **636**	**Long Stay** **1372**	**p-value**
	29/531 (5.5%)	237/1187 (20%)	<0.001
	77/531 (15%)	590/1187 (50%)	<0.001
	6.3 (3.0– 11)	18 (7.7 – 35)	<0.001
			<0.001
	486/623 (78%)	616/1216 (51%)	
	11/623 (1.8%)	4/1216 (0.3%)	
	2/623 (0.3%)	2/1216 (0.2%)	
	5/623 (0.8%)	30/1216 (2.4%)	
	27/623 (4.3%)	174/1216 (14%)	
	3/623 (0.5%)	40/1216 (3.3%)	
	3/623 (0.5%)	95/1216 (7.8%)	
	86/623 (13.8%)	255/1216 (21%)	
	3/616 (0.5%)	276/1347 (21%)	<0.001
	9/616 (1.5%)	125/1348 (9.3%)	<0.001
	0/616 (0.0%)	48/1347 (3.6%)	<0.001
	17/616 (2.8%)	99/1346 (7.4%)	<0.001

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

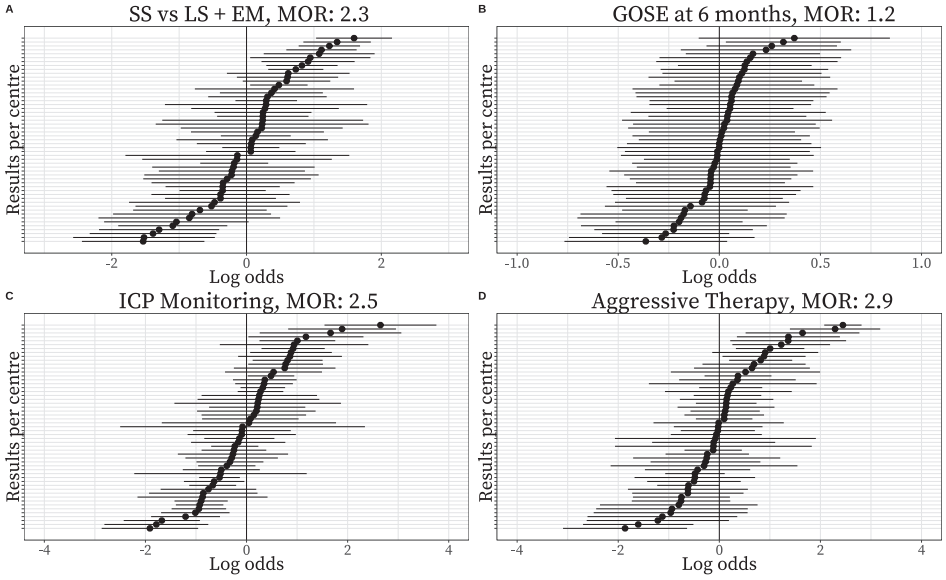

Figure 3.4 Between-centre differences in ICU policies and outcome

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 h in the ICU) versus long stay (> 72 h) and early deaths (≤ 72 h); 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 h. 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 a, c, and d for 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 extra-cranial 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 extra-cranial 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 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 MOR for casemix, 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 centre 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 neuro-trauma 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 centres. 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 include older patients with a substantial proportion of mild and moderate cases. Sub-populations of patients (which we defined as the 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 ICU stay and interventions, for instance in ICP monitoring and use of aggressive therapy, while there were only small differences in outcome.

List of abbreviations

AIS: Abbreviated injury scale; CENTER-TBI: Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury; CPP: Cerebral perfusion pressure; CT: Computer tomography; EDH: Epidural hematoma;; GCS: Glasgow Coma Scale; GOSE: Glasgow Outcome Scale Extended; ICP: Intracranial pressure; ICU: intensive care unit; IMPACT: International Mission for Prognosis and Analysis of Clinical Trials; MOR: Median odds ratio; tSAH: Traumatic Subarachnoid Hemorrhage; TBI: Traumatic brain injury; US: United States

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SUPPLEMENTARY MATERIAL

Supplementary 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	56/54	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	26%
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]		-	

Supplementary Table 1 Continued

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

Supplementary Table 3.2 Treatment Frequency

	Total
	2138
Mechanical Ventilation for at least 24 hours	1456/2138 (68%)
ICP Monitor	921/2113 (44%)
Number of patients with ICP > =20	615/921 (67%)
Number of patients with CPP < 60	674/921 (73%)
Invasive Blood Pressure Monitoring	1728/2111 (82%)
Cranial Surgery	820/2124 (39%)
Extracranial Surgery	606/2124 (29%)
Hypothermia < 35 °C	130/1979 (6.6%)
Mild Hypothermia with a lower limit of 35°C	173/1979 (8.7%)
Intensive Hypocapnia [PaCO2 < 4.0 kPa (30 mmHg)]	82/1977 (4.1%)
Metabolic suppression [1]	404/1979 (20%)
Neuromuscular blockade	436/1978 (22%)
Decompressive craniectomy	212/1979 (11%)

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,

Supplementary Table 3.3 Baseline characteristics stratified by GCS Severity

	Mild
	720
Track	
Short Stay	394 (55%)
Long Stay	319 (44%)
Early Deaths	6 (0.8%)
Age (median (IQR))	53 (33 – 67)
> =65 years	207/720 (29%)
> =80 years	41/720 (5.7%)
Male sex	528/720 (73%)
Pupillary Reactivity	
Both Reacting	660/691 (96%)
Both Unreacting	10/691 (1.4%)
One reacting	21/691 (3.0%)
Hypoxia	35/678 (5.2%)
Hypotension	46/687 (6.7%)
Any major extracranial injury (AIS > =3)	361/720 (50%)

Short stay 636	Long Stay 1372	Early Deaths 128	p-value
201/636 (32%)	1164/1372 (85%)	91/128 (71%)	<0.001
41/627 (6.7%)	837/1359 (62%)	43/127 (34%)	<0.001
13/41 (32%)	563/837 (67%)	39/43 (91%)	
20/41 (49%)	613/837 (73%)	41/43 (95%)	
388/626 (62%)	1227/1358 (90%)	113/127 (89%)	<0.001
139/634 (22%)	634/1260 (47%)	46/128 (36%)	<0.001
122/633 (19%)	467/1361 (34%)	16/128 (13%)	<0.001
4/566 (0.7%)	109/1304 (8.4%)	17/109 (16%)	<0.001
4/566 (0.7%)	157/1304 (12%)	12/109 (11%)	<0.001
2/565 (0.4%)	74/1303 (5.7%)	6/109 (5.5%)	<0.001
27/566 (4.8%)	358/1304 (28%)	19/109 (17%)	<0.001
30/565 (5.3%)	384/1304 (29%)	22/109 (20%)	<0.001
9/566 (1.6%)	187/1304 (14%)	16/109 (15%)	<0.001

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

Moderate 328	Severe 961	p-value
		<0.001
107 (33%)	106 (11%)	
213 (65%)	753 (78%)	
8 (2.4%)	102 (11%)	
54 (32 – 70)	45 (27 – 62)	<0.001
108/328 (33%)	209/961 (22%)	<0.001
16/328 (4.9%)	33/961 (3.4%)	0.08
218/328 (67%)	723/961 (75%)	0.01
		<0.001
277/311 (89%)	634/929 (68%)	
20/311 (6.4%)	202/929 (22%)	
14/311 (4.5%)	93/929 (10%)	
17/308 (5.5%)	190/898 (21%)	<0.001
24/306 (7.8%)	177/904 (20%)	<0.001
147/328 (45%)	600/961 (62%)	<0.001

Supplementary Table 3.3 Continued

	Mild
	720
CT Characteristics	
Marshall CT Classification	
I	120/645 (19%)
II	364/645 (56%)
III	21/645 (3.3%)
IV	6/645 (0.9%)
V/VI	134/645 (21%)
Epidural Hematoma	130/645 (20%)
tSAH	393/645 (61%)
Contusion	301/645 (47%)
Acute Subdural Hematoma	246/645 (38%)
Midline Shift	74/645 (11%)
Basal Cistern Absent or Compressed	93/645 (14%)

This table shows the baseline characteristics stratified by GCS severity. P-values from ANOVA and chi-square statistics for continuous and categorical characteristics respectively.

Supplementary Table 3.4 Treatment frequency stratified by GCS Severity

	Mild
	720
Mechanical Ventilation for at least 24 hours	280/720 (39%)
ICP Monitor	123/716 (17%)
Number of patients with ICP > = 20	75/121 (62%)
Number of patients with CPP < 60	92/120 (77%)
Invasive Blood Pressure Monitoring	453/715 (63%)
Cranial Surgery	177/716 (25%)
Extracranial Surgery	191/716 (27%)
Hypothermia < 35 °C	10/664 (1.5%)
Mild Hypothermia with a lower limit of 35°C	15/664 (2.3%)
Intensive Hypocapnia [PaCO2 < 4.0 kPa (30 mmHg)]	2/663 (0.3%)
Metabolic suppression [1]	51/664 (7.7%)
Neuromuscular blockade	62/663 (9.3%)
Decompressive craniectomy	24/664 (3.6%)

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,

	Moderate 328	Severe 961	p-value
			<0.001
	13/277 (4.7%)	59/827 (7.1%)	
	137/277 (50%)	339/827 (41%)	
	17/277 (6.1%)	104/827 (13%)	
	4/277 (1.4%)	18/827 (2.2%)	
	106/277 (38%)	361/827 (37%)	
	70/277 (25%)	145/827 (18%)	0.02
	222/277 (80%)	657/827 (79%)	<0.001
	191/277 (69%)	479/827 (58%)	<0.001
	163/277 (59%)	454/827 (55%)	<0.001
	71/277 (26%)	240/827 (29%)	<0.001
	84/277 (30%)	347/827 (45%)	<0.001

AIS: Abbreviated Injury Scale. tSAH: traumatic subarachnoid hemorrhage

	Moderate 328	Severe 961	p-value
	235/238 (72%)	850/961 (88%)	<0.001
	148/325 (46%)	591/958 (62%)	<0.001
	97/143 (68%)	405/571 (71%)	<0.001
	106/143 (74%)	433/571 (76%)	<0.001
	285/325 (88%)	892/957 (93%)	<0.001
	142/323 (44%)	445/957 (47%)	<0.001
	78/323 (24%)	300/957 (31%)	0.02
	16/305 (5.2%)	99/913 (11%)	<0.001
	23/305 (7.5%)	127/913 (14%)	<0.001
	12/304 (3.9%)	61/913 (6.7%)	<0.001
	62/305 (20%)	266/913 (29%)	<0.001
	68/305 (22%)	279/913 (31%)	<0.001
	24/305 (7.9%)	152/913 (17%)	<0.001

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

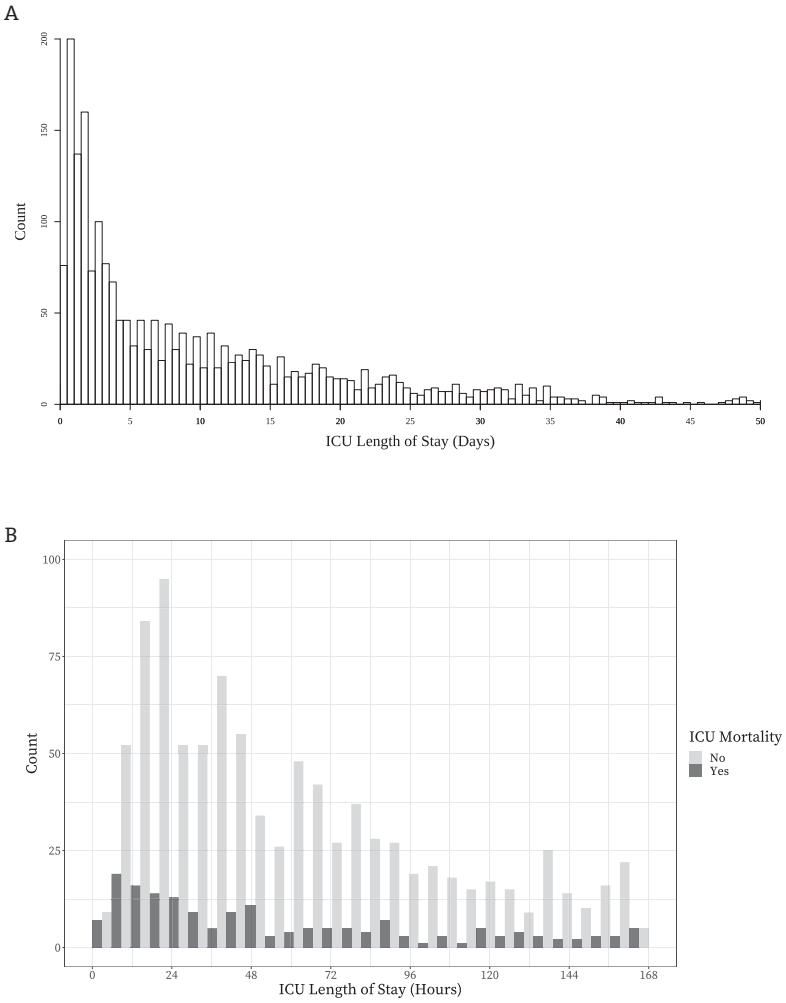
Supplementary Table 3.5 Outcome stratified by GCS severity

	Mild **720**
Outcomes	
6-month Mortality	45/619 (7.3%)
6-month Unfavorable Outcome (GOSE < 5)	136/619 (22%)
Hospital Length of stay in days (median (IQR))	8.2 (3.8 – 16)
Discharge Location from ICU	
General Ward	487/695 (70%)
Home	9/695 (1.3%)
Nursing Home	1/695 (0.1%)
Other	9/695 (1.3%)
Other Hospital	57/695 (8.2%)
Other ICU	10/695 (1.4%)
Rehab Unit	24/695 (3.5%)
Step down/ High Care Unit	98/695 (14%)
Complications at the ICU	
Ventilator Acquired Pneumonia	39/712 (5.5%)
Cardiovascular Complications	33/712 (4.6%)
Meningitis	4/712 (0.6%)
Seizures	29/711 (4.1%)

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,

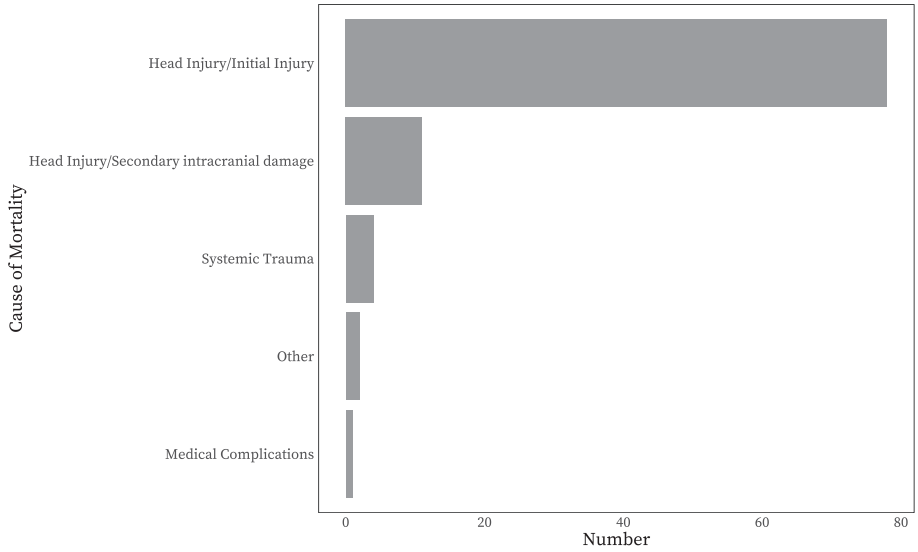
	Moderate **328**	**Severe** **961**	**p-value**
	59/281 (21%)	256/843 (30%)	<0.001
	114/281 (41%)	487/843 (58%)	<0.001
	13 (5.1 – 25)	16 (2.7 – 34)	<0.001
			<0.001
	174/296 (59%)	387/761 (51%)	
	2/296 (0.7%)	3/761 (0.4%)	
	2/296 (0.7%)	1/761 (0.1%)	
	7/296 (2.4%)	19/761 (2.5%)	
	28/296 (9.5%)	105/761 (14%)	
	9/296 (3.0%)	18/761 (2.4%)	
	12/296 (4.1%)	54/761 (7.1%)	
	62/296 (21%)	174/761 (23%)	
	39/324 (12%)	190/947 (20%)	<0.001
	31/324 (9.6%)	81/948 (8.5%)	<0.01
	5/324 (1.5%)	33/947 (3.5%)	<0.001
	26/324 (8.0%)	62/947 (6.5%)	<0.001

ICU: Intensive Care Unit, IQR: interquartile range. P-values from ANOVA and chi-square statistics for continuous and categorical characteristics respectively



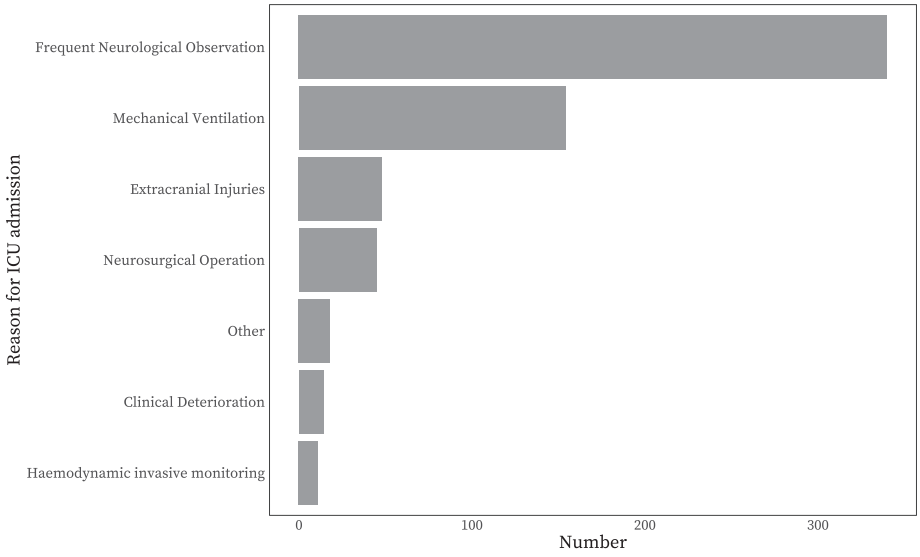
Supplementary Figure 3.1 Length of ICU stay

A] Length of Stay at the ICU for all patients (n=2136), B] Length of Stay at the ICU for the first 7 days, stratified by ICU mortality (data available for 1130 patients)



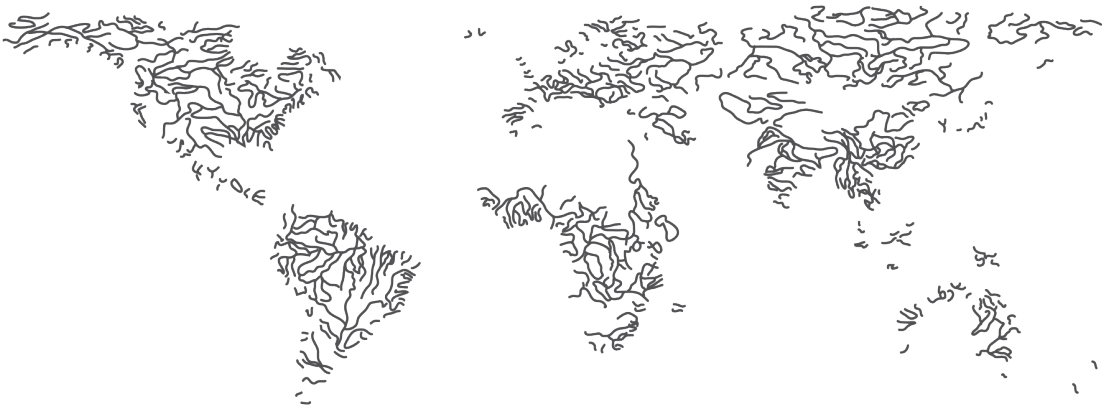
Supplementary Figure 3.2 Cause of Mortality in Early Death Group

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



Supplementary Figure 3.3 Reason for ICU admission for short stay patients

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



Chapter 4

Characteristics, management and outcomes of patients with severe traumatic brain injury in Victoria, Australia compared to United Kingdom and Europe: a comparison between two harmonised prospective cohort studies

Injury, 2021

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ABSTRACT

Objective

The aim of this manuscript is to compare characteristics, management, and outcomes of patients with severe Traumatic Brain Injury (TBI) between Australia, the United Kingdom (UK) and Europe.

Methods

We enrolled patients with severe TBI in Victoria, Australia (OzENTER-TBI), in the UK and Europe (CENTER-TBI) from 2015 to 2017. Main outcome measures were mortality and unfavourable outcome (Glasgow Outcome Scale Extended < 5) 6 months after injury. Expected outcomes were compared according to the IMPACT-CT prognostic model, with observed to expected (O/E) ratios and 95% confidence intervals.

Results

We included 107 patients from Australia, 171 from UK, and 596 from Europe. Compared to the UK and Europe, patients in Australia were younger (median 32 vs 44 vs 44 years), a larger proportion had secondary brain insults including hypotension, (hypotension,) (30% vs 17% vs 21%) and a larger proportion received ICP monitoring (75% vs 74% vs 58%). Hospital length of stay was shorter in Australia than in the UK (median: 17 vs 23 vs 16 days), and a higher proportion of patients were discharged to a rehabilitation unit in Australia than in the UK and Europe (64% vs 26% vs 28%). Mortality overall was lower than expected (27% vs 35%, O/E ratio 0.77 [95% CI: 0.64 – 0.87]. O/E ratios were comparable between regions for mortality in Australia 0.86 [95% CI: 0.49–1.23] vs UK 0.82 [0.51–1.15] vs Europe 0.76 [0.60–0.87]). Unfavourable outcome rates overall were in line with historic expectations (O/E ratio 1.32 [0.96-1.68] vs 1.13 [0.84-1.42] vs 0.96 [0.85-1.09]).

Conclusions

There are major differences in case-mix between Australia, UK, and Europe; Australian patients are younger and have a higher rate of secondary brain insults. Despite some differences in management and discharge policies, mortality was less than expected overall, and did not differ between regions. Functional outcomes were similar between regions, but worse than expected, emphasizing the need to improve treatment for patients with severe TBI.

Key words

Traumatic Brain Injury; Trauma Systems; Intensive Care; Outcome Comparison; Comparative Effectiveness Research

INTRODUCTION

Traumatic Brain Injury (TBI) is a leading cause of death and long-term disability, particularly in young adults. Sixty-nine million individuals worldwide are estimated to sustain a TBI each year[1]. In Australia, TBI accounts for over 1000 Intensive Care Unit (ICU) admissions per year[2]. Half of severe TBI patients will be severely disabled or dead within six months of the injury, with lifetime costs largely due to disabled survivors of an estimated annual hospital costs of €33 billion of indirect and direct costs in Europe[3,4]. For Australia, the lifetime cost for each severe TBI was estimated at $4,8 million[5,6].

Although recent randomised trials of alternative current therapies have provided guidance for clinicians (SAFE-TBI, DECRA, RESCUEicp, POLAR), trials of new therapies have been generally discouraging or require further investigations to resolve uncertainty[7-11]. Guideline recommendations for TBI care are often weak, leaving opportunity for individual treatment preferences and resource availability, resulting in variation of care. Comparative effectiveness research subsequently has been embraced internationally, and uses practice variation to measure benefits and risks of systems of care and interventions in ordinary settings and broader populations, reflecting daily clinical practice[12].

An earlier study that compared outcomes following major trauma involving serious head injury managed in Victoria, Australia and the UK concluded that the absence of an organized trauma system in the UK at that time was associated with increased risk-adjusted mortality compared to management in the inclusive trauma system of Victoria, Australia over these years[13]. However, contemporary global comparisons of patients with severe TBI have been few, are largely limited to North America and Europe, and are hampered by different times, settings and populations. Improved understanding of the benefits and limitations of different approaches to care for TBI patients requires comparisons across trauma care systems, using comparable methods of data collection and comparable time periods. Practice variation in the management of TBI patients admitted to the ICU might then offer opportunities for identification of best practices using comparative effectiveness research.

This study compared demographics, treatment characteristics and outcomes in two prospective harmonised cohorts of severe TBI patients in the state of Victoria Australia (population 6 million; OzENTER), with UK and Europe (CENTER-TBI).

METHODS

Study population

Data came from the Collaborative European NeuroTrauma Effectiveness Research (CENTER-TBI) Core Study and the OzENTER-TBI (Australia-Europe NeuroTrauma Effectiveness Research in Traumatic Brain Injury) Study. Both studies were longitudinal cohort studies with harmonised data points and outcome assessments. The OzENTER-TBI Study was conducted in the two designated adult major trauma centres in Victoria, Australia at different intervals between February 2015 to March 2017. These centres receive 85% of adults with severe TBI from a state population of 6 million. The CENTER-TBI Core study included TBI patients that were admitted to the ICU across 54 centres in the European Union, the United Kingdom (UK) and Israel between 2015 and 2017. Patients or family were given the opportunity to opt-out of data collection in the OzENTER-TBI Study. Ethics approval in the OzENTER-TBI study was granted by Human Research Ethics Committees of the local university, along with the two participating adult major trauma centres. The CENTER-TBI Core study was approved by the medical ethics committees of all participating centres and consent was obtained according to local regulations. More detailed information about the CENTER-TBI Core Study can be found in the study protocol and the publication of the main results[14-16]. Patients of any age were included if they underwent a CT-scan of the brain and were admitted to the ICU within 24 hours of injury. Patients with a pre-existing neurological disorder that would otherwise confound outcome assessment were excluded. For the purpose of the current study, we included all patients with severe TBI, which was defined as a Glasgow Coma Scale (GCS) score of 3-8 at baseline that were admitted to the ICU.

Data Collection

Detailed information on demographics, injury characteristics, and clinical characteristics was collected. Clinical data was collected on a daily basis: at ICU admission, during ICU stay (days 1-7, day 10, day 14, day 21, and day 28), and at ICU discharge. Data collection was undertaken by trained Research Coordinators and entered into an online Case Report Form. CT scans were obtained in all patients upon presentation and centrally reviewed. Follow up CT scans were acquired as clinically indicated. All patients were treated according to local protocol.

Outcome assessment

The eight-point Glasgow Outcome Scale Extended (GOSE; overall effect of injury) was collected at 6 months after injury. The GOSE was measured by either a postal questionnaire or a structured (telephone) interview by a trained assessor[17]. The

categories 'vegetative state (GOSE 2)' and 'lower severe disability (GOSE 3)' were combined resulting in a seven-point ordinal scale. Unfavourable outcome was defined as a GOSE < 5, and favourable outcome as a GOSE > 4.

Statistical analysis

Patients were stratified into three groups: patients that were admitted to a study centre in 1) Australia (OzENTER-TBI Study), 2) the United Kingdom (CENTER-TBI Study), 3) Europe (CENTER-TBI Study). Countries that included less than 50 severe TBI patients were omitted from analysis.

Baseline characteristics were presented as median values with interquartile ranges (IQR) for continuous variables and as frequencies and percentages for categorical variables. ANOVA was used for comparison of continuous variables across strata. The X^2 test was used for comparison of categorical variables.

The IMPACT CT model was used to calculate the expected mortality and expected proportion of patients with unfavourable outcome at 6 months in patients with severe TBI[18]. The IMPACT CT (International Mission for Prognosis and Analysis of Clinical Trials in TBI Computed Tomography) model was developed for predicting 6 month outcome in adult patients with moderate to severe head injury using their key covariates. The model was developed and validated in collaboration with the CRASH trial collaborations both including large numbers of individual patient data. The model discriminates well; and has been validated for the purpose of classification and characterization of large cohorts of patients[19]. Observed to expected (O/E) ratios were calculated with 95% confidence intervals. We performed a sensitivity analysis of the outcome comparison after multiple imputation, with use of the mice package in R. All statistical analyses were performed in R (version 3.5.1) and RStudio (version 1.0.136). CENTER-TBI data was accessed using a bespoke data management tool, 'Neurobot' (http://neurobot.incf.org, RRID: SCR_01700), vs 2.0 (data freeze: June 2019).

Table 4.1 Baseline characteristics of patients with severe TBI in Victoria, Australia, the UK and Europe

Variable Total number of patients	Australia N=107	UK N=171	Europe N=596	p-value
Demographic characteristics				
Age (median (IQR))	32 (23 – 48)	44 (27 – 56)	44 (26 – 62)	0.003
>65 years	13 (12%)	26 (15%)	133 (22%)	0.01
Male sex	84 (79%)	128 (75%)	448 (75%)	0.74
Cause of injury				<0.001
Road traffic incident	64 (60%)	82 (51%)	320 (55%)	
Incidental fall	22 (21%)	50 (31%)	194 (34%)	
Suicide Attempt	6 (5.6%)	3 (1.9%)	18 (3.1%)	
Violence/Assault	9 (8.4%)	12 (7.4%)	6 (1.0%)	
Other	6 (5.6%)	15 (9.3%)	41 (7.1%)	
Missing	-	9	17	
Clinical presentation				
GCS Motor Score - Baseline				0.05
1/2	51 (49%)	76 (46%)	306 (53%)	
3/4	16 (15%)	44 (27%)	134 (23%)	
5/6	38 (36%)	44 (27%)	143 (25%)	
Missing	2	7	13	
Pupillary Reactivity				0.47
Both pupils reactive	79 (76%)	120 (73%)	403 (70%)	
One pupil unreactive	9 (8.7%)	8 (11%)	53 (9.2%)	
Two pupils unreactive	16 (15%)	27 (16%)	122 (21%)	
Missing	3	6	18	
Hypoxia (prehospital/ER phase) Missing	29 (28%) 2	28 (19%) 21	127 (22%) 17	0.23
Hypotension (prehospital/ER phase)	32 (30%)	26 (17%)	120 (21%)	0.03
Missing	0	13	19	
Any major extracranial injury (AIS >=3)	63 (59%)	105 (61%)	405 (68%)	0.08
Spine	17 (16%)	36 (21%)	120 (20%)	0.54
Thorax/Chest	57 (53%)	69 (40%)	262 (44%)	0.10
Abdomen/pelvis	16 (15%)	28 (16%)	121 (20%)	0.28
CT characteristics (central review)				
Epidural Hematoma	28 (29%)	25 (19%)	81 (15%)	0.004
Missing	10	38	56	
Traumatic Subarachnoid Haemorrhage	69 (71%)	105 (80%)	423 (79%)	0.24
Missing	10	39	57	
Contusion	29 (50%)	71 (69%)	204 (51%)	0.02

Table 4.1 Continued

Variable Total number of patients	Australia N=107	UK N=171	Europe N=596	p-value
Missing	49	68	194	
Marshall Classification				0.19
I/II	59 (61%)	61 (46%)	276 (51%)	
III/IV	12 (12%)	18 (14%)	82 (21%)	
V/VI	26 (27%)	54 (41%)	184 (34%)	
Missing	10	38	54	

ANOVA was used for comparison of continuous variables across strata. The X^2 test was used for comparison of categorical variables. P values relate to how likely differences between groups could occur while no differences between groups exist.

RESULTS

In total, 198 patients were included in the OzENTER-TBI Study and 2138 patients were included in the CENTER-TBI ICU Core Study. After excluding patients with missing GCS at baseline (n= 133), patients with no severe GCS (n= 1135), and patients that were included in countries that included less than 50 patients (n= 194), 874 patients were included in this study (Figure 4.1). These patients were from three regions: Victoria, Australia (2 MTCs, N=107), UK (8 MTCs, N=171), and Europe (28 MTCs, N=596, *The Netherlands, Italy, Spain, Belgium, Norway, France each of which had > 50 patients enrolled and were included*).

Patients with severe TBI in Victoria, Australia, compared to those in the UK and Europe, were younger (median: 32 (IQR: 23-48) vs 44 years (IQR: 27-56) and 44 years (IQR: 26 – 62), p:0.003), a higher proportion was injured due to a road traffic incident (60% vs 51% vs 55%, p < 0.001), and a lower proportion due to a fall (21% vs 31% vs 34%). Although a higher proportion of patients in Victoria, Australia and Europe than the UK, were transported direct to the trauma centre from the accident scene (90% vs 89% vs 66%) the transport times (from scene to trauma centre) for primary referrals were similar (median: 97 (IQR: 64-151) vs 105 (IQR: 80 – 127) minutes) in Victoria, Australia and the UK, but shorter in Europe (median: 73 (IQR: 54-100) minutes). In Australia, UK and Europe, two thirds of severe TBI patients were intubated before hospital arrival (67% vs 60% vs 70%). However ICP monitors (75% vs 74% vs 58%, p < 0.001), and intensive therapies (74% vs 71% vs 54%, p < 0.001) were used in a higher proportion of patients in Australia and UK than Europe. Patients' brain injury severities expressed as GCS scores, and pupil reactivities were similar in all regions, but CT scans reported epidural hematomas in a higher proportion of patients in Australia (p=0.004), and contusions in a lower proportion of patients in Europe (p=0.02).

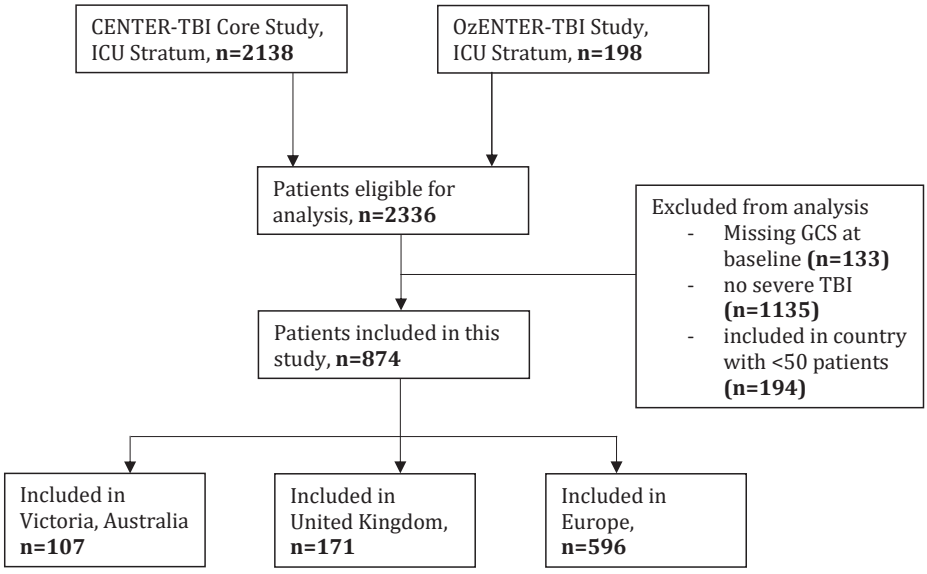

Figure 4.1 Flowchart of included patients

More patients in Victoria, Australia had secondary brain insults recorded in the prehospital and emergency room phases of care. In Australia compared to UK/Europe, hypotension was recorded in 30% vs 17% / 21% (p=0.03), and hypoxia in 28% vs 19% / 22% (p=0.23). Major extracranial injuries were observed in a lower proportion of patients in Australia than in the UK and Europe (59% vs 61% vs 68%, p=0.08), but thorax/chest injuries were observed in a higher proportion of patients in Australia (Table 4.1, Table 4.2).

Both extracranial surgeries and cranial surgeries were performed in more patients in Australia than in the UK and Europe (43% vs 20% vs 36%, p<0.001 and 68% vs 50% vs 42%, p<0.001), but most acute management medical practices were equivalent. Two interventions for refractory intracranial hypertension were used in a lower proportion of patients in Australia than the UK and Europe. These were *intensive hypocapnia* (1.1% vs 8.5% vs 6.7%) (p=0.06), and *decompressive craniectomy* (14% vs 25% vs 15%) (p=0.01). There were no differences in the proportion of patients with large intracranial hematomas (Marshall classification V/VI; 27% vs 41% vs 34%) (Table 4.2).

However, despite the many similarities in other factors, ICU length of stay was substantially shorter in Australia than the UK and Europe, (median: 8.8 vs 13 days vs 11 days, p<0.001), and hospital length of stay was shorter in Australia than in the UK, but similar to Europe (median 17 vs 23 vs 16 days, p<0.001). In Australia although ICU times

were shorter, most TBI deaths (19%) occurred in the ICU, and a further 3% occurred after ICU. In the UK, ICU mortality was 16%, with another 5% occurring later. In Europe, 2% of hospital deaths occurred after ICU. In Australia, the median time from ICU admission to death in ICU was 4.1 days [IQR: 1.2 – 8.9] and the median time from ICU admission to decision of withdrawal of treatment was 3.7 days [IQR: 1.3 – 7.8], compared to 7.1 days [IQR: 3.1 - 13] and 8.0 [IQR: 2.5 – 12] in the UK, and 1.7 days [IQR: 0.6 – 6.4] and 1.1 [IQR: 0.3 – 4.6] days in Europe ($p = 0.031$and $p < 0.01$). Withdrawal of therapy due to very severe brain injury was the primary cause of death in both countries (91% in Australia vs 89% in the UK). In Australia 64% of TBI patients were discharged to a rehabilitation centre compared to 26% in UK and 28% in Europe ($p < 0.001$) where the most common discharge destination was a second hospital.

Table 4.2 Management characteristics of patients with severe TBI in Victoria, Australia, the UK and Europe

Variable **Total number of patients**	**Australia** **N=107**	**UK** **N=171**	**Europe** **N=596**	**p-value**
Referral				
Primary referral	96 (90%)	113 (66%)	531 (89%)	<0.001
Time to study centre (median (IQR)) – minutes	97 (64 – 151)	105 (80 – 127)	73 (54 – 100)	0.70
Secondary referral	11 (10%)	58 (34%)	65 (11%)	<0.001
Time to study centre (median (IQR)) – minutes	439 (308 – 512)	325 (239 – 499)	308 (225 – 435)	0.43
Diagnostic and surgical interventions				
Arrived Intubated	71 (67%)	102 (60%)	416 (70%)	0.04
Missing	*1*	-	*2*	
ICP monitor placed	80 (75%)	126 (74%)	343 (58%)	<0.001
Cranial Surgery	72 (68%)	85 (50%)	248 (42%)	<0.001
Missing	*1*	*1*	*1*	
Extracranial Surgery	45 (43%)	35 (20%)	215 (36%)	<0.001
Missing	3	-	2	
Treatment characteristics				
Intensive Monitoring*	79 (74%)	121 (71%)	319 (54%)	<0.001
Mechanical Ventilation for at least 24 hours	104 (97%)	162 (95%)	510 (86%)	<0.001
Invasive Blood Pressure Monitoring	106 (99%)	163 (96%)	545 (92%)	0.01
Missing	-	*1*	*2*	
Hypothermia <35 °C	15 (16%)	24 (15%)	61 (11%)	0.21
Missing	*13*	*6*	*32*	
Mild Hypothermia with a lower limit of 35°C	23 (24%)	48 (29%)	67 (12%)	<0.001

Table 4.2 Continued

Variable Total number of patients	Australia N=107	UK N=171	Europe N=596	p-value
Missing	*13*	*6*	*32*	
Intensive Hypocapnia [PaCO2 < 4.0 kPa (30 mmHg)]	1 (1.1%)	14 (8.5%)	38 (6.7%)	0.06
Missing	*13*	*6*	*32*	
Metabolic Suppression**	23 (24%)	40 (24%)	183 (32%)	0.06
Missing	*13*	*6*	*32*	
Paralysis	54 (57%)	88 (53%)	171 (30%)	<0.001
Missing	*13*	*6*	*32*	
Decompressive craniectomy	13 (14%)	41 (25%)	84 (15%)	0.01
Missing	*13*	*6*	*32*	

**A combination of ICP Monitor, Invasive Blood Pressure Monitoring, and Mechanical Ventilation for at least 24 hours, **Metabolic suppression for ICP control with high dose barbiturates or propofol. ANOVA was used for comparison of continuous variables across strata. The* X^2 *test was used for comparison of categorical variables. P values relate to how likely differences between groups could occur while no differences between groups exist.*

GOSE at 6 months was available in 776 (89%) patients. The follow-up rate was higher in Victoria (n=99, 93%), compared to UK (n=135, 79%) and similar to Europe (n=542, 91%). Six-month mortalities were 24% vs 30% vs 28%. (table 4.3). Overall, six-month mortality was better than predicted (27% vs 35%, observed to expected ratio 0.77 [95% CI: 0.64 – 0.87]), and similar in Victoria, UK and Europe (0.86 [95% CI: 0.49–1.23] vs 0.82 [0.51–1.15] vs 0.76 [0.60–0.87]). In all 3 regions however, unfavourable non-independent functional outcomes measured by GOSE < =4 were similar to predicted (1.32 [0.96-1.86] vs 1.13 [0.84-1.42] vs 0.96 [0.85-1.09]). Unadjusted unfavourable outcomes rates exceeded 50% (63% vs 65% vs 55%). The unadjusted proportion of survivors with severe disability at 6 months was similar in Australia and the UK (51% and 50%), compared to 37% in Europe (Table 4.3). The observed to expected ratios after multiple imputation were similar to those in complete case analysis (Supplementary Table 4.1).

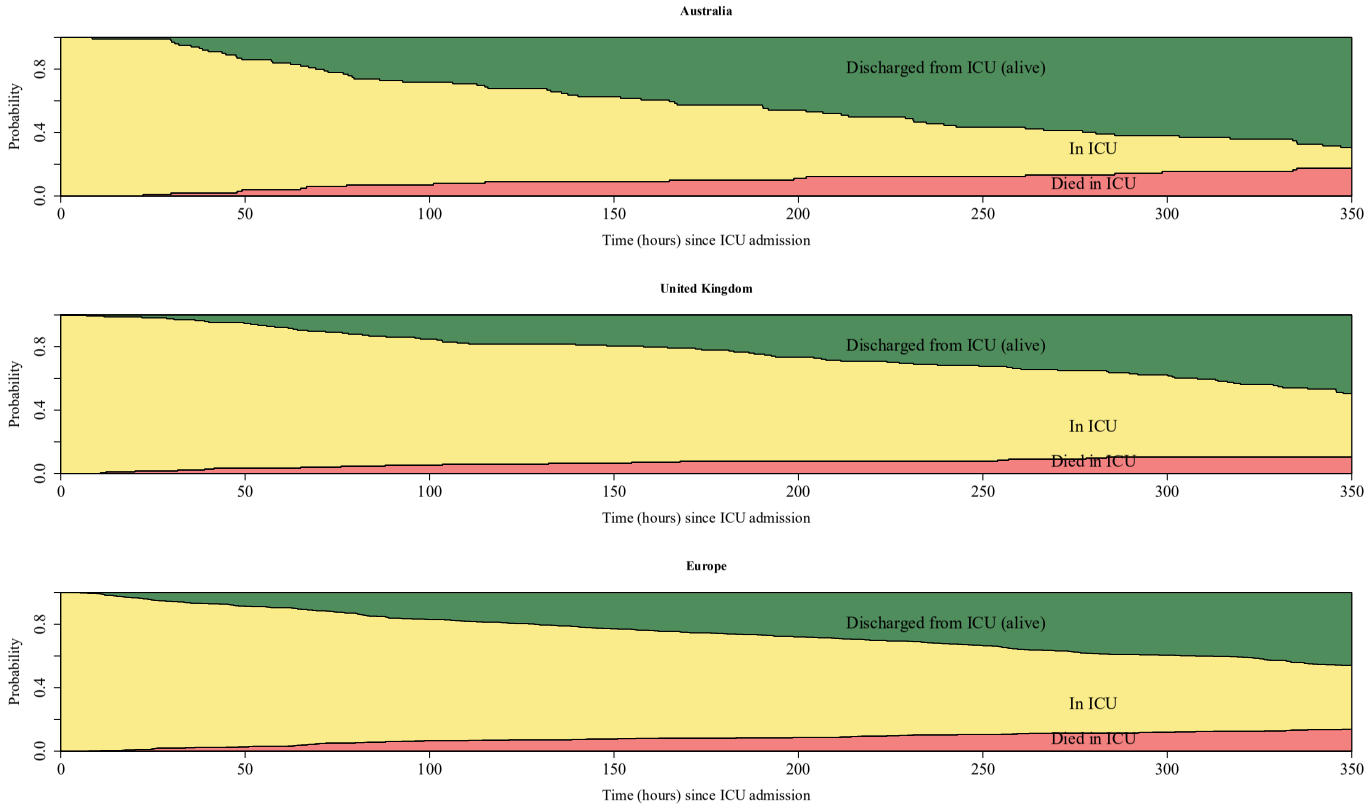

Figure 4.2 Probabilities of state of severe TBI patients during the first two weeks after ICU admission.

The x-axis represents time from ICU admission in hours, y-axis represents the probability to be in one the following states; discharged from ICU, still in ICU, or died in ICU.

Table 4.3 Outcomes among patients with severe TBI in Victoria, Australia, the UK and Europe

Variable **Total number of patients**
Length of Stay
Hospital Length of Stay, median (IQR) – days*
Hospital Length of stay for all patients who survived to hospital discharge, median (IQR) - days
ICU Length of stay, median (IQR) – days
ICU Length of stay for all patients who survived to ICU discharge, median (IQR) – days
Hospital Mortality
ICU Mortality
In-hospital Mortality
Cause of Death (for patients that died in-hospital)
Head injury/initial injury
Head injury/secondary intracranial damage
Systemic Trauma
Other (including medical complications)
Missing
Final Discharge Location
Rehab Unit
Home
Other hospital
Other
Mortality
Missing
6-month Outcome
6-months mortality
Missing
6-month predicted probability of mortality**
Observed versus expected mortality**
6-months unfavourable outcome (GOSE < 5)
Missing
6-month predicted probability of unfavourable outcome **
Observed versus expected unfavourable outcome **
6-month GOSE 2-4 vs 5-8

**Length of stay was missing in: 0, 7, 12 patients. **according to the IMPACT-CT model. ANOVA was used for comparison of continuous variables across strata. The X^2 test was used for comparison of categorical variables. P values relate to how likely differences between groups could occur while no differences between groups exist.*

	Australia N=107	**UK N=171**	**Europe N=596**	**P-value**
	17 (8.8– 30)	23 (8.1– 54)	16 (1.8 – 33)	<0.001
	19 (11 – 32)	30 (12 – 60)	22 (8.6 – 38)	<0.001
	8.8 (4.6 – 15)	13 (5.6 – 20)	11 (3.2 – 21)	0.05
	9.6 (4.9 – 16)	14 (7.4 – 22)	14 (5.6 – 23)	0.02
	20 (19%)	28 (16%)	124 (21%)	0.39
	24 (22%)	36 (21%)	139 (23%)	0.82
				0.21
	20 (83%)	15 (60%)	79 (74%)	
	2 (8.3%)	8 (32%)	15(14%)	
	2 (8.3%)	-	4 (3.7%)	
	-	2 (8%)	9 (8.4%)	
	-	11	32	
				<0.001
	67 (64%)	42 (26%)	153 (28%)	
	7 (6.7%)	33 (20%)	116 (21%)	
	6 (5.7%)	46 (28%)	134 (24%)	
	1 (1.0%)	5 (3.1%)	15 (2.7%)	
	24 (23%)	36 (22%)	139 (25%)	
	2	*9*	*39*	
	24 (24%)	41 (30%)	154 (28%)	0.58
	8	*36*	*54*	
	29%	34%	36%	
	0.86 [0.49 – 1.23]	0.82 [0.51 – 1.15]	0.76 [0.60 – 0.87]	0.72
	62 (63%)	88 (65%)	297 (55%)	0.05
	8	*36*	*54*	
	47%	56%	55%	
	1.32 [0.96 – 1.68]	1.13 [0.84 – 1.42]	0.96 [0.85 – 1.09]	0.10
	38 (51%)	47 (50%)	143 (37%)	0.01

The outcome comparisons with the IMPACT CT model were based on patients in whom both information on predicted outcome and observed outcome was available. A chi-squared goodness of fit was applied to the observed versus expected values.

DISCUSSION

Compared to TBI patients in the UK, and Europe, patients in Victoria, Australia were younger, and higher proportions had road traffic incidents compared to falls, secondary insults in the prehospital and emergency phases of care (predominantly hypotension), and epidural hematomas. A lower proportion received intensive hypocapnia and decompressive craniectomy therapies, and the patients treated in Victoria had shorter times to withdrawal of therapy for severe brain injuries, contributing to shorter ICU and hospital times. The proportion discharged to rehabilitation centres in Victoria was greater than UK and Europe but at 6 months after injury, mortality and functional outcomes in all 3 regions were similar, with unfavourable non-independent living being similar to IMPACT predictions.

The younger age of severe TBI patients in Victoria, Australia compared to the UK, likely reflects patient selection within the Victorian Trauma system, which directs adult trauma patients preferentially to two adult trauma centres, but triages patients 65 years old and over with an isolated TBI related to a low fall, to different neurosurgical centres that did not participate in the OzENTER-TBI. A recent Registry study in Victoria of severe TBI patients reported a 85%:15% patient division between the two major trauma centres of our study and the other hospitals with neurological services, and also a median age of severe TBI patients in the whole state of 41.5 years[20], which is comparable to the UK (44 years), but different to this study (32 years). Selection in Victoria also likely accounts for the lower proportion of falls compared to UK which are more common in the elderly, and the higher rate of road traffic incidents (60% vs 50%). The higher rates of hypotension and hypoxia in Australia may relate to the higher percentage of road traffic incidents in this cohort, with associated greater haemorrhage and thoracic injuries. Our data suggest they are not due to different prehospital intubation rates nor to longer transport times, however they are likely to impact upon patient outcomes. Future research in Australia may optimally be directed towards further improvements in fluid resuscitation and intubation protocols aimed at reducing these secondary insults[21,22].

We found large variation between Australia, the UK and Europe in the use of brain-specific treatments including ICP monitoring, metabolic suppression, intensive hypocapnia, and paralysis. Intensive hypocapnia is little used in Australia due to concerns about short duration of action, and possible adverse implications of cerebral vasoconstriction. Several attempts to improve the quality of evidence for ICP monitoring have been performed in the past, which have been complicated by ethical challenges in randomizing patients between ICP monitoring and no ICP monitoring, and result in low evidence recommendations[23,24]. Recent developments in technology resulted in new monitoring techniques, also known as multimodal monitoring, that can provide

the neuro intensivist with information and assist in management decision making[25,26]. Currently, several collaborations and research efforts are being made to resolve the outstanding questions about the roles and indications for neuro monitoring after TBI and demonstrate unequivocally whether monitor-guided interventions lead to improved outcomes for patients[27]. Another therapeutic option is decompressive craniectomy, which we found to be less common in Australia and Europe than the UK (P=0.01). A current randomised trial is testing decompressive craniectomy after evacuation of intracranial hematomas for brain swelling, but in patients with diffuse severe TBI and combined diffuse and mass lesion TBI, two large randomised trials in 2011 and 2016 found that decompressive craniectomy increased severely disabled survivors at 6 months. At 12 months, neither study showed an increase in patients surviving with a GOSE ≥ 5[7,8,28,29].

ICU and hospital times were 50% shorter for TBI patients in Australia than the UK. Since dying patients consume less hospital time than survivors, timing of death impacts these findings, and in Australia almost all TBI deaths occurred during the first 9 days in ICU. In the UK, ICU stays were longer, yet one third of UK deaths occurred after ICU. It is possible that some of these differences may be because step down care of critically ill patients may have been differentially labelled as ICU or non-ICU care in different hospitals, but such details were unavailable. Since 80% of TBI deaths in both countries were due to such severe head injury that withdrawal of care took place, the unexpected difference in timings of this decision making may be a factor driving reduced hospital times and costs in Australia, compared to the UK.

A higher proportion of patients was discharged to rehabilitation facilities in Victoria than in the comparable countries where a second (less acute) hospital was most common, although this might be explained in part by the younger age of patients in Victoria. However, availability of rehabilitation services in Victoria for road trauma patients who are compensable through the Transport Accident Commission, may be another driver[30]. Lower level RCT evidence and expert opinion suggest that TBI rehabilitation is beneficial in improving the functional outcomes beyond what we would expect from spontaneous recovery[31,32]. However, the probability of receiving rehabilitation is associated with patients' and regional characteristics. Also, it might be challenging to meet the key success criteria for health and rehabilitation services such as inclusion of and access to and inclusion of well-coordinated multidisciplinary processes incorporating the varying needs of the individuals having sustained a TBI. However, our results may also question the beneficial impact of earlier rehabilitation on long term functional outcomes in severe TBI patients. Therefore, future studies should assess the necessity of more extensive multidimensional and standardized assessment of functional and psychological impairments and corresponding rehabilitation needs.

However despite these differences, after adjusting for predicted outcomes using IMPACT CT, patient outcomes at 6 months in all three regions were very similar: mortality tended to be better than predicted, but independent outcomes were not, indicating that the number of people living with severe disability was increased compared to predicted in all regions. Also, we did not observe any substantial differences in outcome between Victoria, Australia, the UK and Europe, confirming the results of a recent study [33]. Although this could be the result of a homogenous standard of treatment in the three regions, this might also suggest that the differences in therapies may be discordant and urges the need for future studies that study the effect of these therapies in isolation. The IMPACT CT prognostic scheme accounts for only about a third of outcome variance, and outcomes in all three regions may have been affected by unmeasured confounders. This, coupled with the large confidence intervals for our estimates of observed/expected unfavourable outcome in Victoria and the UK may mean that significant differences were missed.

Strengths of this study were the enrollment of patients with severe TBI across three large regions and many countries, and the detailed information on demographics, therapies, and outcomes. Limitations were first that our three cohorts were a small proportion of all patients with TBI in Australia, UK, and Europe, and they were not enrolled consecutively which could introduce selection bias. Second, follow-up data was missing in some patients, adding some uncertainty to the interpretation of the outcome comparisons.

This study highlights regional differences in patient characteristics which need to be considered when interpreting and comparing results from clinical studies on TBI from different regions. This collaboration within the InTBIR initiative will enable future meta-analyses for research questions that require larger numbers. Results from observational studies may give rise to new insights in disease mechanisms and rejuvenate industry interests and investment in TBI.

In conclusion, differences exist in case-mix between Victoria, Australia compared to the UK and Europe, including a younger age and a higher rate of secondary brain insults. Despite some differences in management and discharge policies, mortality and functional outcomes are largely similar. Contemporary mortality is better than expected based on historical data, but independent living outcomes may not have improved. These findings are likely driven by increased survival with disability over time and emphasize the need for further global efforts in order to refine recommendations for severe TBI patients.

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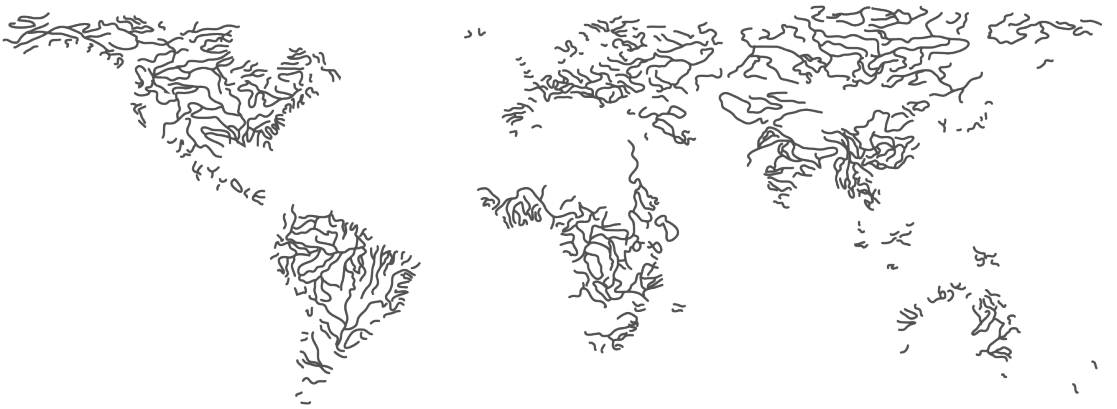
SUPPLEMENTARY MATERIAL

Supplementary Table 4.1 Observed versus Expected Values after multiple imputation

Variable Total number of patients	Australia N=107	UK N=171	Europe N=596	P-value
Observed versus expected mortality*	0.76 [0.46 – 1.08]	0.86 [0.60 – 1.09]	0.76 [0.64 – 0.87]	0.71
Observed versus expected unfavourable outcome *	1.21 [0.91 – 1.51]	1.23 [1.05– 1.40]	1.00 [0.89 – 1.11]	0.11

**according to the IMPACT-CT model. The outcome comparisons with the IMPACT CT model were based on patients in whom both information on predicted outcome and observed outcome was available. A chi-squared goodness of fit was applied to the observed versus expected values.*



Chapter 5

Admission of mild TBI patients to ICU: a CENTER-TBI study

In preparation

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ABSTRACT

Introduction

Patients with mild Traumatic Brain Injury (mTBI) are often admitted to the Intensive Care Unit (ICU), but this might not always be necessary. The aim of this study is to describe ICU admission and potential overtriage of patients with mTBI across Europe to evaluate appropriateness of ICU admission.

Methods

CENTER-TBI was a prospective observational multicentre study conducted across 18 countries in Europe and Israel. We selected patients with mTBI (Glasgow Coma Scale at baseline of 13 to 15) and did mixed effects multivariable analyses to identify patient characteristics and hospital characteristics associated with ICU admission. Further we defined potential 'overtriage' to the ICU: no major extracranial injury, no cranial surgery, not mechanically ventilated at any point during hospital stay and reason of ICU admission for frequent neurological observations.

Results

A total of 1498 patients patients with mTBI were included, 365 (24%) were admitted to the ICU. The percentage of ICU admission for patients with mTBI in 32 centres ranged from 4.6% to 80%. The following characteristics were associated with ICU admission: lower GCS at baseline (OR: 0.68, 95% CI: 0.49 – 0.83), higher ISS (OR: 1.17, 95% CI: 1.15 – 1.20), epidural hematoma (OR: 2.18, 95% CI: 1.22 – 3.91), traumatic subarachnoid hemorrahge (OR: 2.20, 95% CI: 1.51 – 3.22), availability of a dedicated neuro-ICU (OR: 2.10, 95% CI: 1.21 – 3.64), admission to a level II or level II trauma centre (OR: 6.88, 95% CI: 2.76 –17), the availability of stepdown beds (OR: 2.36, 95% CI: 1.20 – 4.65), admission to ICU in case of bed shortage (OR: 2.44, 95% CI: 1.36 – 4.35), and admission of TBI patients to the same ICU (OR: 2.19, 95% CI: 1.34 – 3.58). Sixty-five (18%) of patients met the criteria for overtriage. Patients that were overtriaged had worse outcome at 6 months than patients admitted to the ward (unfavorable outcome: 10, 17% versus 88, 9.5%).

Discussion

In Europe, a substantial part of mTBI patients is admitted to the ICU. Next to patient characteristics, ICU admission of mTBI patients seems to be determined by local organizational factors. The low number of patients that were overtriage suggests efficient and rationalized clinical decision making by physicians.

INTRODUCTION

Traumatic Brain Injury (TBI) is a major public health concern with an annual incidence of 2.5 million in Europe[1]. The large majority of TBIs can be classified as mild TBI (mTBI)[2], which is generally indicated by an admission Glasgow Coma Scale (GCS) score of 13-15. Most patients with mTBI recover completely in the ensuing weeks to months without the necessity of medical or neurosurgical interventions[3,4].

However, in approximately 1%, the initially identified mTBI will deteriorate into a life-threatening condition, necessitating immediate and intensive medical and neurosurgical interventions[5,6]. For this reason, patients with mTBI are often admitted to the Intensive Care Unit (ICU) for close monitoring in order to quickly identify and act upon any deterioration. A recent meta-analysis found that clinical deterioration among patients with mTBI was 11%[7], suggesting that for some patients with mTBI ICU admission might not be necessary.

Furthermore, earlier studies found large variation in the admission of patients with mTBI to the ICU[8,9]. Studies that investigated outcome in patients with mTBI were unable to detect a clear benefit of ICU admission versus acute care admission[10-13]. This was further supported by a recent study in the United States, which found that 17% of the mTBI patients admitted to the ICU is possibly overtriaged[8].

The aim of this study is to describe ICU admission and potential overtriage of patients with mTBI across Europe to evaluate appropriateness of ICU admission.

METHODS

Study population

The Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) study is a multicentre longitudinal prospective observational cohort study across 63 centres in Europe and Israel between 2015 and 2017. Patients were included in the CENTER-TBI study if they 1) had a clinical diagnosis of TBI; 2) arrived within 24 hours of injury; 3) and had an indication for a brain CT-scan. The presence of a severe preexisting neurological disorder was the only exclusion criterion, since this could potentially confound outcome assessment. Patients were included in one of the following CENTER-TBI strata:

1. ER stratum (patients evaluated in the ER and discharged)
2. Admission stratum (patients admitted from ER to the hospital but not to the ICU)
3. ICU stratum (patients admitted directly from ER or another hospital to the ICU)

The CENTER-TBI study was approved by the medical ethics committees of all participating centres and informed consent was obtained according to local regulations[14,15].

In this study, we included all patients with a GCS score of 13-15 at baseline. We excluded patients that were secondary referred or patients that were included in hospitals that only included patients in either the admission stratum or the ICU stratum.

Data Collection

The CENTER-TBI study collected detailed information on demographics, injury characteristics and clinical characteristics. Clinical data was collected on a daily basis: at ICU admission, during ICU stay (days 1-7, day 10, day 14, day 21, day 28), and at ICU discharge. In each centre, data was collected and interpreted by physicians and/or research assistants and entered in an online data entry and analysis platform (Quesgen Inc.). For the purpose of the current study, we extracted data on demographics, injury, imaging, admission, monitoring, treatment, and outcome characteristics. Neuroworsening was defined as 1) a decrease in GCS motor score of 2 or more points; 2) a new loss of pupillary reactivity or development of pupillary asymmetry > = 2 mm); 3 deterioration in neurological or CT status sufficient to warrant immediate medical or surgical intervention.

Imaging

CT scans were obtained in all patients upon presentation. Follow up CT scans were acquired as clinically indicated. Images were stored locally, details captured in the e-CRF, and subsequently, once anonymized, uploaded into a central repository coordinated and maintained by Icometrix (https://icometrix.com/). All uploaded images were read centrally using NINDS CDE-based structured qualitative reporting. The Morris-Marshall Classification was used to grade the severity of the traumatic Subarachnoid Hemorrhage (tSAH). The Morris-Marshall Classification is classified as follows: Grade 0: No CT evidence of traumatic subarachnoid hemorrhage (tSAH); Grade 1: tSAH present only in one location; Grade 2: tSAH present at only one location, but quantity of blood fills that structure, or tSAH is at any two sites, filling, neither of them; Grade 3: tSAH present at two sites including the tentorium, filled with blood; and, Grade 4: tSAH present at three or more sites, and being of any quantity.

Outcome

Outcome was measured at six months with the Glasgow Outcome Scale – Extended (GOSE) by either a postal questionnaire or a telephone interview. The categories 'vegetative state (GOSE 2)' and 'lower severe disability (GOSE 3)' were combined resulting in a seven-point ordinal scale. The 8 categories are: Dead, Vegetative State, Lower Severe Disability, Upper Severe Disability, Lower Moderate Disability, Upper Moderate Disability, Lower Good Recovery, and Upper Good Recovery. The categories 'vegetative state (GOSE 2)' and 'lower severe disability (GOSE 3)' were combined resulting in a seven-point ordinal scale[16].

Hospital characteristics

Characteristics of the participating centres were collected a priori by sending an online survey about structures and processes of care to all centres (i.e. provider profiling)[17]. For the purpose of the current study, we extracted the following hospital characteristics: level I or level II trauma centre, availability of a dedicated neuro-ICU, the frequency of GCS assessment, availability of step-down beds, whether TBI patients are always admitted to the same ICU, whether the admission policy to the ICU is influenced by shortage of ICU beds, if centres admit patients with mTBI with anticoagulants, contusion, CT abnormalities, Epidural Hematoma's, and post-operatively.

Overtriage

To examine to which extent patients admitted to the ICU may have been overtriaged, we used the definition of an early study[8]. Patients must fulfill all criteria in order to be categorized as overtriaged:

- No major extracranial injury (AIS > =3)
- Admitted to the ICU straight from ER
- ICU length of stay less than or equal to 1 day
- Total Hospital Length of Stay of 2 days or less
- Was not intubated at any point during hospital stay
- Did not undergo neurosurgical intervention;
- And discharged from the hospital to home- or self-care

As we observed large differences between centres in length of stay that might be largely explained by differences between policies, we also created a second definition[18]:

- No major extracranial injury
- No cranial surgery
- Was not mechanically ventilated at any point during hospital stay
- Reason of admission for frequent neurological observations

Statistical Analysis

Baseline characteristics of the study population were reported as frequencies and percentages for categorical variables and as medians and interquartile ranges for continuous variables. These characteristics were described for the total study populations, as well as for patients that were admitted to the ward and admitted to the ICU separately.

Between-centre differences

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

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

The MOR can be interpreted as the odds ratio for comparing two randomly selected centres. For example, an MOR equal to one, indicates no differences between centres. If there is considerable between-centre variation, the MOR will be large[19]. For adjustment purposes, we included the variables from the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) prognostic model (age, GCS motor score, pupillary reaction, hypoxia, hypotension, CT Marshall Classification, traumatic Subarachnoid Hemorrhage (tSAH), Epidural Hematoma (EDH), first glucose and first Hemoglobin)[20], and any major extracranial injury (AIS > =3).

Factors associated with ICU admission

Factors associated with ICU admission were studied using multivariable logistic regression analyses with ICU admission (yes/no) as an outcome and all baseline characteristics and hospital characteristics as independent variable. All variables with a p-value < 0.15 were considered for multivariable analysis. Subsequently, all patient and hospital characteristics were added in a multivariable model. In a second, multivariable model the hospital characteristics were added together with a random intercept for centre. The Nagelkerke R^2 was used to measure the variance between the multivariable model with only fixed effects, and the multivariable model including a random intercept for centre.

Patients that were initially admitted to the ward, but transferred to the ICU later were analyses in het admission group.

All statistical analyses were performed in R studio. All continuous variables were tested for non-linearity. Missing data was handled using multiple imputation. CENTER-TBI data was accessed using a bespoke data management tool, 'Neurobot' (http://neurobot.incf.org, RRID: SCR_01700), vs 2.1.

RESULTS

Study population

In total, 4509 patients were included in the CENTER-TBI core study. After exclusion of patients that did not have information on GCS baseline (n= 179), with moderate or severe TBI (n= 1357), that were discharged after ER (n= 826), included in a centre that only included patients in admission stratum or ICU stratum (n= 310), or were transferred from another centre (n= 321), 1498 patients were eligible for analysis. In total, 372 (25%) patients were directly admitted to the ICU, and 1122 (75%) patients were admitted to the ward of which 30 (2.7%) patients were transferred to ICU later (Figure 5.1, Supplementary Table 5.1).

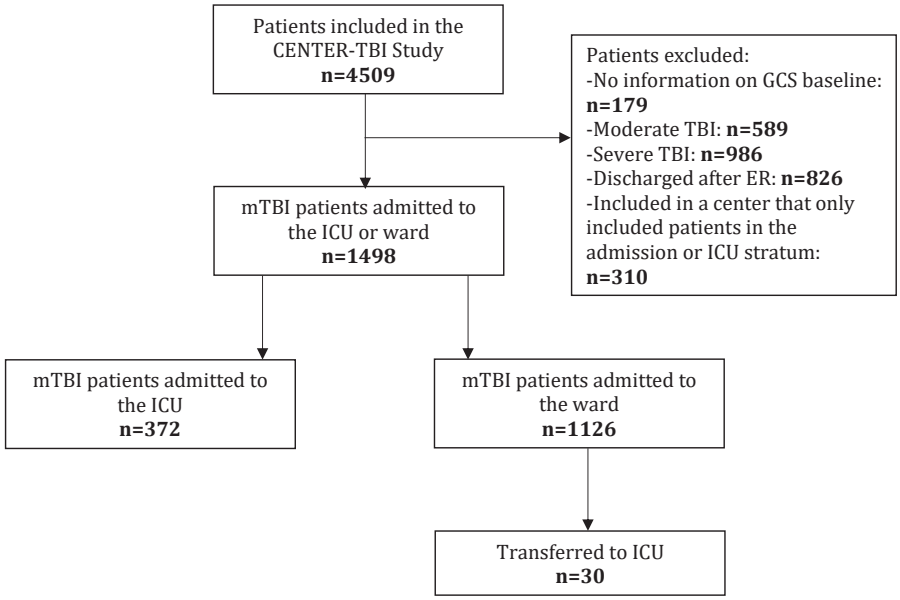

Figure 5.1 Flowchart of included patients in the CENTER-TBI study

Baseline characteristics

Overall, the median age was 53 (IQR: 33 – 68), with 470 (31%) older than 65 years. Patients admitted to the ward (53, IQR: 34 – 69) and ICU (51, IQR: 32 – 66) had similar age. Male patients were overrepresented in both strata, with 274 (74%) in the ICU stratum, and 716 (64%) in the group of patients that was admitted to the ward. In patients admitted to the ICU, 39 (11%) patients had severe systemic disease, 24 (6.7%) had a prior indication of anticoagulants and 36 (10%) had a prior indication of antiplatelets, versus 124 (11%), 105 (9.4%), and 128 (11%) in patients that were admitted to the ward. Major extracranial injuries (abbreviated injury score ≥ 3) were reported in 351 (31%) in the admission to the ward stratum and in 227 (61%) in the ICU stratum. In the ICU stratum, more patients had epidural hematoma (55, 16% versus 70, 6.7%) and traumatic subarachnoid hemorrhages (183, 53% versus 315 (30%). (Table 5.1) The main reason for ICU admission was the need for frequent neurological observations (n = 200, 54%) (Supplementary Figure 5.1).

Table 5.1 Baseline characteristics of all mTBI patients admitted in the CENTER-TBI study, stratified by stratum

	Total	**Admission**	**ICU**
	1498	**1126**	**372**
Baseline characteristics			
Age (median (IQR))	53 (33 – 68)	53 (34 – 69)	51 (32 – 66)
≥ 65 years	470 (31%)	371 (33%)	99 (27%)
Male sex	990 (66%)	716 (64%)	274 (74%)
Pupillary Reactivity			
Both reacting	1405 (98%)	1060 (98%)	345 (96%)
One reacting	28 (1.9%)	18 (1.7%)	5 (1.4%)
Both unreacting	8 (0.6%)	3 (0.3%)	10 (2.8%)
Hypoxia prehospital or at ER	41 (2.8%)	19 (1.7%)	22 (6.1%)
Hypotension prehospital or at ER	50 (3.4%)	20 (1.8%)	30 (8.3%)
Pre-Injury ASAPS Classification			
A patient with mild systemic disease	489 (33%)	381 (34%)	108 (29%)
A patient with severe systemic disease	163 (11%)	124 (11%)	39 (11%)
Use of anticoagulants	129 (8.7%)	105 (9.4%)	24 (6.7%)
Use of antiplatelets	168 (11%)	128 (11%)	40 (10%)
Arrived Intubated	49 (3.3%)	5 (0.4%)	44 (12%)
Cause of Injury			
Incidental Fall	717 (48%)	565 (51%)	152 (41%)
Road Traffic Accident	561 (38%)	390 (35%)	171 (46%)
Any major extracracranial injury	578 (39%)	351 (31%)	227 (61%)
ISS (median (IQR))	13 (9 – 20)	10 (9 – 17)	25 (16 – 34)

Table 5.1 Continued

	Total	Admission	ICU
	1498	1126	372
Imaging characteristics			
Epidural Hematoma	125 (8.9 %)	70 (6.7 %)	55 (16%)
Traumatic Subarachnoid Hemorrhage	498 (36%)	315 (30%)	183 (53%)
Contusion	318 (23%)	179 (17%)	139 (40%)
Subdural Hematoma	287 (21%)	185 (18%)	102 (29%)
Marshall Classification			
Grade I	654 (47%)	558 (53%)	96 (28%)
Grade II	622 (45%)	439 (42%)	183 (53%)
Grade III	20 (1.4%)	8 (0.8%)	12 (3.5%)
Grade IV	3 (0.2%)		3 (0.9%)
Grade V/VI	98 (7.0%)	45 (4.3%)	53 (15%)
Morris-Marshall Classification			
Grade 1	368 (26%)	253 (24%)	115 (33%)
Grade 2	94 (6.7%)	48 (4.6%)	46 (13%)
Grade 3	19 (1.4%)	8 (0.8%)	11 (3.2%)
Grade 4	16 (1.1%)	5 (0.5%)	11 (3.2%)

Between-centre differences

All patients included in this study were included in 32 centres in 14 countries. The percentage of ICU admission for patients with mTBI in these centres ranged from 4.6% to 80%. The percentage of overtriage for definition II ranged from 10% to 75% (Supplementary Figure 5.3, 5.4). After case-mix adjustment, significant between-centre differences for ICU admission for patients with mTBI were observed (MOR: 2.91, $p < 0.001$) (Figure 5.2).

Factors associated with ICU admission

In univariable analysis, the following patient characteristics were associated ($p < 0.15$) with ICU admission and therefore considered for multivariable analysis: age younger than 45 years, male sex, GCS baseline, GCS Motor, hypotension, hypoxia, Injury Severity Scale (ISS), Loss of Conciousness, neuroworsening, patient with mild systemic disease, subarachnoid hemorrhage and epidural hematoma (Supplementary Table 5.4).

The following hospital characteristics were associated with ICU admission: availability of a dedicated neuro-ICU, trauma Level II or III, availability of stepdown beds, bed shortage, the admission of TBI patients to the same ICU (Supplementary Table 5.5).

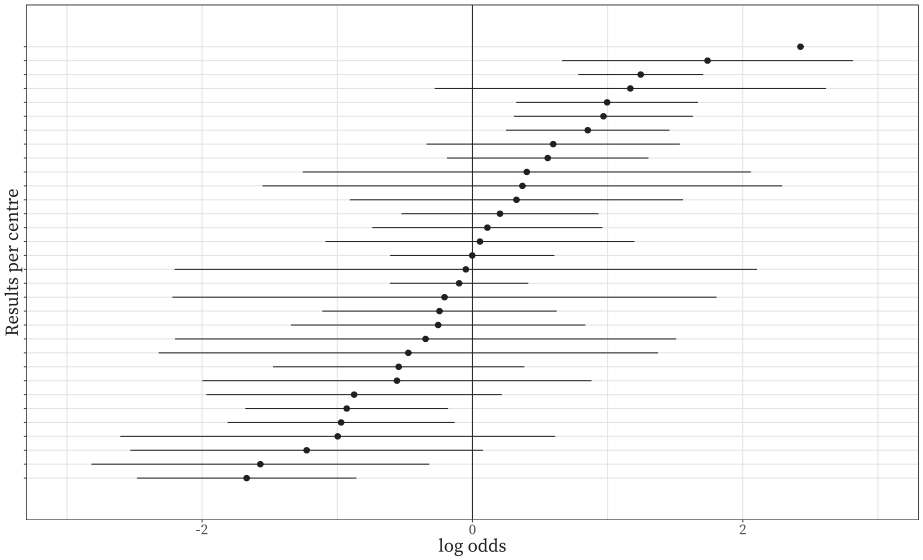

Figure 5.2 Between-centre differences, proportion of mTBI patients admitted to the ICU versus ward

Median Odds Ratio: 2.55. A random effect regression model was used to correct for random variation and was adjusted for case-mix severity using the IMPACT variables (Age, GCS Motor Score, Pupillary Reactivity, Hypoxia, Hypotension, Marshall CT Classification, Epidural Hematoma, Traumatic Subarachnoid Hemorrhage, First Hemoglobin, First Glucose), ISS, and a random intercept for centre.

In multivariable analysis including a random intercept for centre, the following patient characteristics and hospital characteristics remained associated with ICU admission: GCS Baseline (OR per point increase: 0.68, 95% CI: 0.49 – 0.83, p = 0.01), ISS (OR per point increase: 1.17, 95% CI: 1.15 – 1.20, p < 0.001), Epidural Hematoma on CT (OR: 2.18, 95% CI: 1.22 – 3.91), p < 0.001), traumatic subarachnoid hemorrhage (OR: 2.20, 95% CI: 1.51 – 3.22), p < 0.0001) availability of a dedicated neuro-ICU (OR: 2.10, 95% CI: 1.21 – 3.64, p < 0.001), trauma level II or III (OR: 6.88, 95% CI: 2.76 – 17, p < 0.001), availability of stepdown beds (OR: 2.36, 95% CI: 1.20 – 4.65, p = 0.01), bed shortage (OR: 2.44, 95% CI: 1.36 – 4.35, p = 0.01), and admission of TBI patients to the same ICU (OR: 2.19, 95% CI: 1.34, 3.58, p = 0.002). The Nagelkerke R^2 increased from 0.54 to 0.57 after adding a random intercept for centre (Table 5.2).

Overtriage

In the ICU stratum, 145 (39%) did not have major extracranial injuries, 231 (63%) patients were not mechanically ventilated at any point during hospital stay, and 294 (79%) patients did not undergo neurosurgical intervention. An ICU length of stay less than or equal to 1 day was observed in 77 (21%) patients, a total hospital length of stay of 2 days or less was observed in 117 (1433 patients. About 60% (n=194) of

the patients was discharged from hospital to home or self-care. In total, 6 (1.6%) of mTBI met all criteria for the first definition for overtriage, 65 (18%) met all criteria for the second definition of overtriage.

Table 5.2 Multivariable Associations with ICU admission

	Fixed effects		Random effects	
Variable	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Patient characteristics				
GCS Baseline, per point increase	0.69 (0.52 – 0.90)	0.01	0.68 (0.49 – 0.83)	0.01
ISS	1.17 (1.15 – 1.20)	<0.001	1.17 (1.15 – 1.20)	<0.001
Epidural Hematoma	2.14 (1.21 – 3.81)	0.01	2.18 (1.22 – 3.91)	<0.001
Traumatic Subarachnoid Hemorrhage	2.17 (1.49 – 3.16)	<0.001	2.20 (1.51 – 3.22)	<0.001
Nagelkerke R^2		0.47		0.58
Hospital characteristics				
Availability of dedicated Neuro-ICU	1.99 (1.30 – 3.05)	0.02	2.10 (1.21 – 3.64)	<0.01
Trauma Level II or III	6.93 (3.22 – 15)	0.01	6.88 (2.76 – 17)	<0.001
Availability of Stepdown beds	2.32 (1.27 – 4.25)	0.01	2.36 (1.20 – 4.65)	0.01
Bed shortage	2.57 (1.63 – 4.04)	<0.001	2.44 (1.36 – 4.35)	0.003
Admission of TBI patients to the same ICU	2.15 (1.44 – 3.22)	<0.001	2.19 (1.34 – 3.58)	0.002
Nagelkerke R^2		0.10		0.16
Nagelkerke R^2	**0.54**		**0.57**	

Table 5.3 Number of patients meeting criteria for overtriage according two different definitions

Criteria	**Overtriage – I**	**Overtriage - II**
No major extracranial injury	145(39%)	145 (39%)
ICU length of stay less than or equal to 1 day	77 (21%)	
Total Hospital Length of Stay of 2 days or less	117 (33%)	
Was not mechanically ventilated at any point during hospital stay	231 (63%)	231 (63%)
Did not undergo neurosurgical intervention	294 (79%)	294 (79%)
And discharged from the hospital to home- or self-care	194 (60%)	
Reason for ICU admission for frequent neurological observations		200 (54%)
Fulfilling all criteria	**6 (1.6%)**	**65 (18%)**

Patients that were overtriaged according to definition II were younger (median: 43 versus 52), had less often hypoxia (2, 3.1% versus 19, 6.8%), injury due to road traffic incident (24, 37% versus 146, 48%), but more often had Epidural Hematomas (44, 72% versus 139, 49%) and Traumatic Subarachnoid Hemorrhage (44, 72% versus 139, 49%)

compared to patients admitted to the ICU but not overtriaged (Table 5.3, Supplementary Table 5.2). Patients that were overtriaged had worse outcome at 6 months than patients admitted to the ward (unfavorable outcome: 10, 17% versus 88, 9.5%) (Figure 5.3).

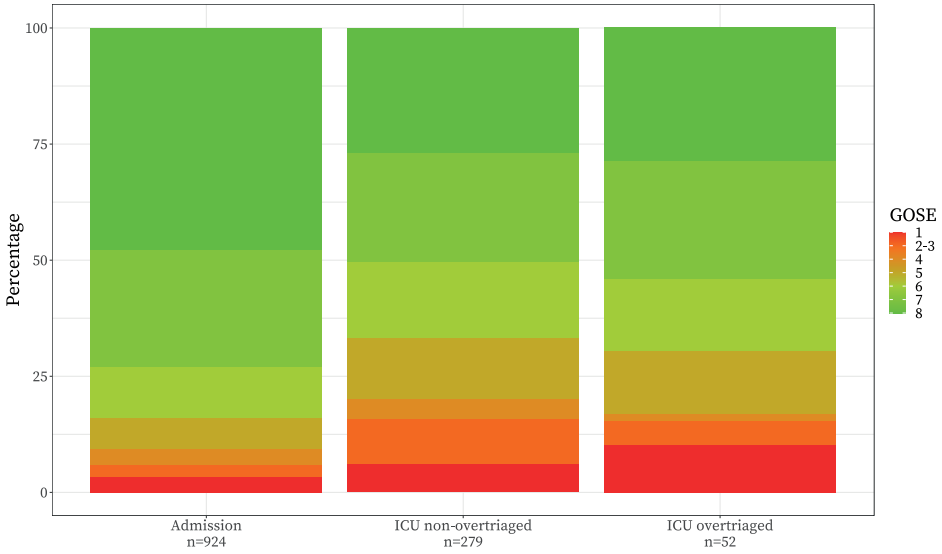

Figure 5.3 Outcome GOSE, stratified per stratum

DISCUSSION

The aim of this study was to describe ICU admission and potential overtriage of patients with mTBI across Europe to evaluate appropriateness of ICU admission. We found that a substantial part of mTBI patients are admitted to the ICU, often because of extracranial injuries. We also identified a number of patient characteristics and hospital characteristics that were associated with ICU admission. Overtriage in mTBI patients admitted to the ICU in Europe appears to be generally low.

The results of our multivariable analysis suggest that patients with lower GCS at baseline and higher ISS were more likely to be admitted to ICU. Previous studies suggested that mTBI patients with lower GCS at baseline and the presence of extracranial injuries, indicating higher ISS, have worse outcomes [21,22]. Therefore, these results seem intuitive and suggest that some factors placing patients at greater risk of deterioration prompt triage to the ICU for close monitoring. Unsurprisingly, we also observed that patients with any intracranial abnormality on admission CT were more likely to be admitted

to ICU. CT abnormalities have been associated with poor neurological outcomes and indicates a higher risk of an expansion of intracranial hematoma and the need for surgical evacuation[7]. However, we also observed that a substantial proportion of patients with tSAH that were admitted to ICU, had isolated tSAH. It has been reported that patients with isolated SAH are more likely to be overtriaged and are at very low risk of requiring interventions[8,23,24].

Compared to a recent study in the United States, we observed substantial lower rates of overtriage. Since this definition was arbitrarly defined and included criteria on length of stay which is known to be substantially contributed to centre policies[25,26], we also defined a second definition. This resulted in a higher number of patients that were overtriaged. We observed that outcomes in patients that were overtriaged according to this definition were worse than patients that were admitted to the ward. An explanation for this might be that the definition was too strict and did not fully capture all patients that needed ICU admission. Alternatively, patients in ICU might have been overtreated resulting in worse outcomes compared to patients admitted to the ward. The fact that patients that were overtriaged patients received few treatments, did however not support this theory (Supplementary Table 5.6).

We observed that there is large variation in ICU admission policies between countries in Europe and that this could not only be attributed to random variation. Patients that were admitted to hospitals that were designated as level II or level III trauma centres, having a dedicated neuro-intensive care unit or step-down unit, or in which the policy of ICU admission is influenced in case of bed shortage, were more likely to be admitted to ICU. The availability of a dedicated neuro-intensive care unit and a step-down unit have both been associated with lower healthcare costs, improvement of outcome and some key metrics of quality of care[27,28].

Strengths and Limitations

This study's strength lies in the use of a multicentre and granular database spanning several countries. As such, we have been able to examine the patterns of ICU admission across centres of both patients characteristics and centre characteristics.

However, this study does have several limitations. Although mTBI is usually defined by a GCS score 13-15, almost 40% of the European neurotrauma centres participating in the CENTER-TBI study previously indicated to use more restrictive criteria (GCS 14-15)[29]. Unfortunately, we were unable to estimate the effect of ICU admission over ward triage on outcome. Although comparative effectiveness research has been proposed as the solution in observational studies, we were unable to use these methods that could deal

with confounding by indication in this study. Propensity score matching is known for creating experimental conditions using observational data, some pitfalls to this method should be acknowledged. Propensity methods only address observed bias and cannot adjust for unmeasured confounding[30]. In this study, the severity of mTBI might confound the relationship between ICU admission and outcome: more severe mTBI patients would more often be admitted to the ICU and have worse outcomes. Instrumental variable analysis has been proposed as the solution to deal with unmeasured confounding[31,32]. However, statistical efficiency was lacking to perform instrumental variable analysis in this study.

Future implications

The observed between-centre differences in ICU admission policies require further research on whether these differences impact patient outcome and quality of care. Prognostic models can be useful to inform clinical decision-making regarding ICU admission. Future studies should assess which patients indicators capture the definition of overtriage.

Conclusions

In Europe, a substantial part of mTBI patients is admitted to the ICU. Next to patient characteristics, ICU admission of mTBI patients seems to be determined by local organizational factors. The low number of patients that were overtriaged and the worse outcomes of patients admitted to the ICU compared to the ward suggests efficient and rationalized clinical decision making by physicians.

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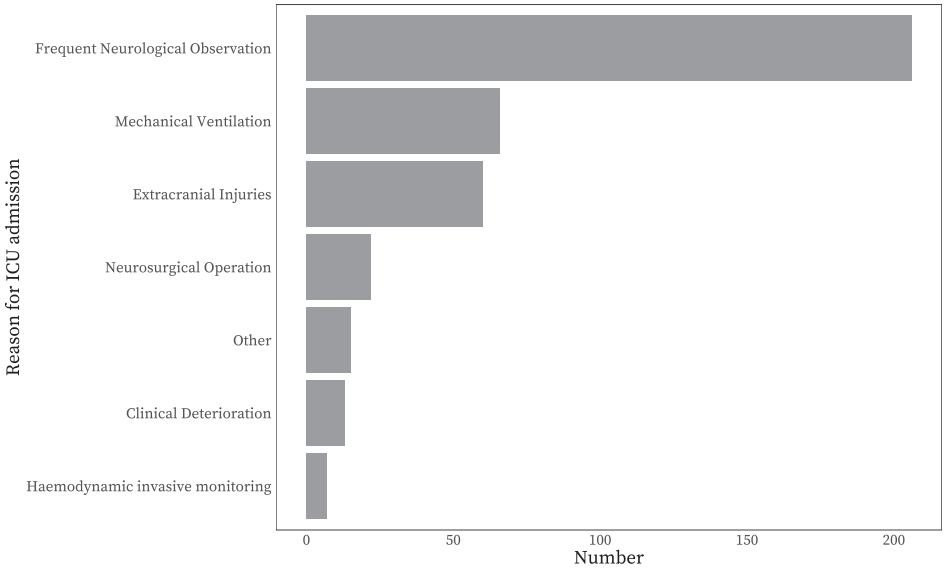
SUPPLEMENTARY MATERIAL

Supplementary Table 5.1 Patient characteristics of patients that were transferred from ward to ICU versus those who were not

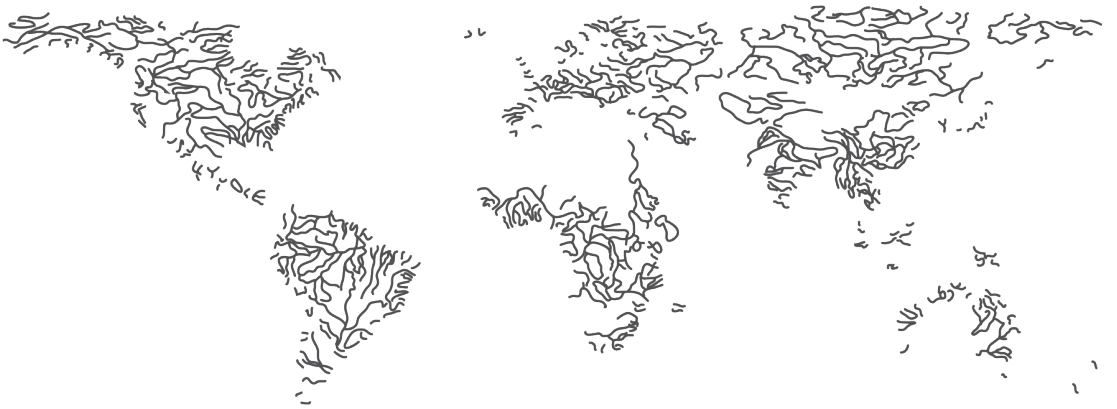
	No	**Yes**
	1096	**30**
Baseline characteristics		
Age (median (IQR))	53 (34 – 69)	61 (48 – 76)
· ≥65 years	357 (33%)	14 (47%)
Male sex	692 (63%)	24 (80%)
Pupillary Reactivity		
· Both reacting	1030 (98%)	30 (100%)
· One reacting	18 (1.7%)	
· Both unreacting	3 (0.3%)	
Hypoxia prehospital or at ER	15 (1.4%)	4 (15%)
Hypotension prehospital or at ER	18 (1.7%)	2 (7.4%)
Pre-Injury ASAPS Classification		
· A patient with mild systemic disease	370 (34%)	11 (38%)
· A patient with severe systemic disease	116 (11%)	8 (28%)
Use of anticoagulants	102 (9.4%)	3 (10%)
Use of antiplatelets	125 (11%)	3 (10%)
Arrived Intubated	5 (0.5%)	0 (0%)
Cause of Injury		
· Incidental Fall	556 (51%)	9 (31%)
· Road Traffic Accident	377 (35%)	13 (45%)
Any major extracracranial injury	336 (31%)	15 (50%)
ISS (median (IQR))	10 (9 – 17)	18 (13 – 26)
Imaging characteristics		
Epidural Hematoma	66 (6.4%)	4 (16%)
Traumatic Subarachnoid Hemorrhage	302 (30%)	13 (52%)

Supplementary Table 5.2 Patients characteristics of patients who were overtriaged according to the second definition versus those were not. All patients were included in the ICU stratum

	No	**Yes**
	306	**65**
Baseline characteristics		
Age (median (IQR))	52 (33 – 67)	43 (30 – 62)
· ≥65 years	83 (27%)	16 (25%)
Male sex	222 (73%)	51 (79%)
Pupillary Reactivity		
· Both reacting	283 (95%)	61 (98%)
· One reacting	9 (3%)	1 (1.6%)
· Both unreacting	5 (1.7%)	0 (0%)
Hypoxia prehospital or at ER	19 (6.8%)	2 (3.1%)
Hypotension prehospital or at ER	30 (10%)	0 (0%)
Pre-Injury ASAPS Classification		
· A patient with mild systemic disease	92 (30%)	37 (12%)
· A patient with severe systemic disease	37 (12%)	2 (3.4%)
Use of anticoagulants	19 (6.4%)	5 (7.7%)



Supplementary Figure 5.1 Reason for ICU admission for short stay patients



Chapter 6

Path From Clinical Research to Implementation: Endovascular Treatment of Ischemic Stroke in the Netherlands

Stroke, 2020

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ABSTRACT

Prior to 2015, endovascular treatment (EVT) for acute ischemic stroke was considered a promising treatment option. Based on limited evidence, it was performed in several dedicated stroke centres worldwide on selected patients. Since 2015, EVT for patients with intracranial large vessel occlusion has quickly been implemented as standard treatment in many countries worldwide, supported by the revised international guidelines based on solid evidence from multiple clinical trials. We describe the development in use of EVT in the Netherlands before, during, and after the pivotal EVT trials.

We used data from all patients who were treated with EVT in the Netherlands from January 2002 until December 2018. We undertook a time-series analysis to examine trends in the use of EVT using Poisson regression analysis. Incidence Rate Ratios (IRR) per year with 95% confidence intervals (95%CI) were obtained to demonstrate the impact and implementation after the publication of the EVT trial results. We made regional observation plots, adjusted for stroke incidence, to assess the availability and use of the treatment in the country.

In the build-up to the MR CLEAN trial, a slow increase of EVT patients was observed, with 0.2% of all ischemic stroke patients receiving EVT. Before the trial results were formally announced, a statistically significant increase in EVT-treated patients per year was observed (IRR:1.72 [95%CI: 1.46–2.04], and after the trial publication an immediate steep increase was seen, followed by a more gradual increase (IRR:2.14 [95%CI: 1.77–2.59]. In 2018, the percentage of ischemic stroke patients receiving EVT increased to 5.8%.

A well-developed infrastructure, a pragmatic approach towards the use of EVT in clinical practice, in combination with a strict adherence by the regulatory authorities to national evidence-based guidelines has led to successful implementation of EVT in the Netherlands. Ongoing efforts are directed at further increasing the proportion of stroke patients with EVT in all regions of the country.

INTRODUCTION

Endovascular therapy (EVT) in patients with acute ischemic stroke has been proven highly effective in randomized controlled trials[1-7]. The Multicenter Clinical trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial was the first to publish positive results in January 2015, immediately followed by several other trials[1].

Before the start of the MR CLEAN trial in December 2010, several studies had provided data suggesting that EVT might be beneficial, although convincing evidence was lacking[8,9]. The Dutch stroke guideline of 2008 mentioned EVT as a rescue treatment, preferably provided within the context of randomized trials. In the Netherlands, EVT for acute ischemic stroke was not reimbursed until 2013, when reimbursement to centres was made conditional on participation in the MR CLEAN trial. This reimbursement policy is still in place and reinforced by guidelines and quality criteria provided by the professional societies and endorsed by regulating authorities.

In the early 2000s, two stroke centres started providing EVT as an experimental treatment in selected patients, inspired by the results of early trials and by local clinical experience[10]. After 2005, other centres gradually followed. Still, prior to initiation of the MR CLEAN trial in 2010 there were 2 centres in the Netherlands which had treated more than 50 patients with IAT. Currently, 17 comprehensive stroke centres provide EVT in the Netherlands for a population of 17,182,000 inhabitants.

The European Stroke Organisation recently stated that in 2030, 95% of eligible patients across Europe should have access to reperfusion therapy and EVT rates should be over 5% in all European countries[11]. Although considerable efforts have been made, a recent study showed large differences between countries in terms of access to appropriate acute stroke treatment[12]. Gaining understanding in the trends of EVT over time might not only provide insight into the accessibility, but also about the implementation of new treatments in daily clinical practice.

In this article we describe the trends in number of patients with acute ischemic stroke who were treated with EVT, and the accessibility of EVT in the Netherlands in three time periods: before, during, and after the completion of the MR CLEAN trial.

MATERIALS AND METHODS

The data of the MR CLEAN TRIAL have been made publicly available at the [Virtual International Stroke Trials Archive (VISTA)] and can be accessed at http://www.virtualtrialsarchives.org/vista/. Individual patient data of the MR CLEAN pre-trial Registry and the MR CLEAN Registry cannot be made available under Dutch law, as we did not obtain patient approval for sharing individual patient data, even in coded form. However, all syntax files and output of statistical analyses will be made available upon reasonable request.

Study population

We analyzed data from the MR CLEAN pre-trial period, the MR CLEAN trial and MR CLEAN Registry.

In the pre-trial period we retrospectively and prospectively collected data of all patients with acute ischemic stroke who received EVT in the Netherlands from October 2002 until a centre started participation in the MR CLEAN trial, which included its first patient in December 2010[13].

Patient selection criteria and methods of the MR CLEAN trial have been reported previously[14]. In short, the MR CLEAN trial was a clinical trial in which patients with a proximal intracranial arterial occlusion in the anterior circulation were randomized to either EVT with usual care or usual care alone. Treatment should be started within 6 hours after onset of stroke symptoms. All patients or their legal representatives provided written informed consent before randomization in the MR CLEAN trial. The study protocol of the MR CLEAN trial was approved by a central medical ethics committee and the research board of each participating centre.

Directly after inclusion of the last patient in the trial by March 2014 and before the presentation of the MR CLEAN trial results at the World Stroke Conference in October 2014, all EVT-treated patients were enrolled in the MR CLEAN Registry, which is as a prospective, multicentre, observational study. For our current analysis, we used data from all patients registered until December 31, 2018[15]. The MR CLEAN Registry was approved by the medical ethics committee of the Erasmus MC, Rotterdam, The Netherlands (MEC-2014-235). We assume that no patients were treated outside the MR CLEAN trial during the study period and that all patients treated before and after the trial are registered in either one of the registries.

Statistical analysis

We analyzed differences between three time periods (pre-trial period, MR CLEAN trial and MR CLEAN Registry). Patients in the MR CLEAN trial who were randomized to usual care were also included, since EVT was considered in these patients.

We used Poisson regression or negative binomial regression to determine whether the incidence ratio of EVT changed during the pre-trial period and MR CLEAN Registry with the denominator being the count of EVT in each year. We then computed incidence rate ratios (IRR) with 95% confidence intervals (CI), using the first year of the time period as reference point. Data were checked for potential over-dispersion (variance greater than the mean) to ensure that the assumptions of a Poisson distribution were met. All analyses were adjusted for the number of stroke patients per year[16-28].

We calculated the use of EVT as a proportion of all patients in the Netherlands who were hospitalized with acute ischemic stroke (including cerebral hemorrhages) between 2002 and 2018, which was based on reports of the Dutch Heart Association[22-26]. Linear regression was used to estimate the number of ischemic stroke patients for years in which another definition of stroke was used or years in which only the number of patients hospitalized with acute stroke was reported.

Maps of the Netherlands at province level were created using R package tmap[29]. Geographical and demographical information was obtained from Statistics Netherlands and Kadaster[30,31]. The number of EVT-treated patients by province was based on the location of first-hospital admission. The density of EVT-treated patients was averaged by dividing the total number of patients by respectively the years of patient enrollment and number of stroke patients per province. The latter was based on anonymized data obtained from central hospital registration systems.

All statistical analyses were performed in R statistical software 3.4.2 (R Foundation for Statistical Computation, Vienna).

RESULTS

In this 16-years' time period, 6394 patients were treated with EVT. In the pretrial period (2002-2010), 514 patients were treated with EVT. During the MR CLEAN trial (2010-2014), 500 patients were included of whom 233 patients were randomized to intervention. In the ongoing MR CLEAN Registry started directly after inclusion of the last patient in the MR CLEAN trial in March 2014, 5335 patients were registered until December, 2018.

Table 6.1 Baseline characteristics

	In total October 2004 –June 2016 N = 4308
Age, y, median (IQR)	70 (58 – 79)
Men, n. (%)	2299 (53)
NIHSS†, median (IQR)	16 (11 – 20)
SBP‡, mean mmHg (SD)	149 (28)
Intravenous alteplase treatment, n. (%)	3217 (75)
Onset to groin puncture time (min) – median (IQR)	205 (155 – 270)

*Abbreviations: *mRS: modified Rankin Scale, †NIHSS: National Institutes of Health Stroke Scale, ‡SBP: Systolic Blood Pressure. mRS was missing in 373 patients,*

Of all treated patients, 2299 (53%) patients were men; 59% in the pre-trial period, 58% in MR CLEAN trial and 52% in the MR CLEAN Registry. The median age was 70 years (interquartile range (IQR): 58–79); 62 in pre-trial patients (IQR 51 – 71), 66 (IQR 55–76) during the MR CLEAN trial, and 71 (IQR 61 – 80) in the MR CLEAN Registry. The time from onset to groin puncture was 205 minutes (IQR 155–270). A median onset to groin puncture time of 237 minutes (IQR 190–315) was observed in the pre-trial population, which had increased to 260 (IQR 210–311) in the MR CLEAN trial and decreased to 195 (IQR 150–260) in the MR CLEAN Registry. All baseline characteristics significantly differed between study periods (Table 6.1).

Trend analyses

From 2006 onwards, a gradual increase in thrombectomies was observed (Figure 6.1). In the build-up to the MR CLEAN trial, more centres provided EVT and a sharper increase was observed which continued during the MR CLEAN trial. After the last inclusion in the MR CLEAN trial, the same level of increase was observed until the results of the EVT trials were presented in October 2014. After the presentation of the MR CLEAN trial results at the World Stroke Conference in October 2014, the number of patients treated with EVT increased steeply (Figure 6.1). During the pre-trial period and following the steep increase that occurred immediately after the trial, in the MR CLEAN Registry period, a statistically significant gradual increase in EVT-treated patients per year was observed (pre-trial: IRR: 1.72 [95%CI: 1.46 – 2.04], $p < 0.001$, MR CLEAN Registry: IRR: 2.14 [95% CI: 1.77 – 2.59], $p < 0.001$).

Regional differences

During the pre-trial period, patients were predominantly treated in Utrecht, a province in the centre of the Netherlands. During the trial phase, a similar pattern was observed, although the number of patients treated in other regions increased. After announcement of the trial results, the distribution of EVT-treated patients spread more evenly across the Netherlands (Figure 6.2).

Pre-trial October 2004 – December 2010 N = 514	MR CLEAN trial December 2010 – March 2014 N = 500	MR CLEAN Registry April 2014 – October 2017 N = 3294	p-value
62 (51 – 71)	66 (55 – 76)	71 (61 – 80)	< 0.001
305 (59)	292 (58)	1702 (52)	< 0.001
16 (12 – 21)	16 (12 – 21)	16 (11 – 20)	< 0.001
148 (24)	145 (25)	150 (28)	0.01
323 (64)	445 (89)	2449 (75)	< 0.001
237 (190 – 315)	260 (210 – 311)	195 (150 – 260)	< 0.001

NIHSS was missing in 189 patients, SBP was missing in 189 patients. MR CLEAN Registry contains information on baseline characteristics up to October, 2017.

Proportion of acute ischemic stroke patients receiving EVT

In 2010, 23771 patients were hospitalized with acute ischemic stroke in the Netherlands, of whom 170 (0.5%) received EVT. In 2014, 217 (0.8%) acute ischemic stroke patients received EVT. After the MR CLEAN trial, the percentage of acute ischemic stroke patients treated with EVT increased to 3.1% in 2015. In 2018, 29244 patients were admitted with acute ischemic stroke of whom 1712 (5.8%) received EVT (Figure 6.3, Supplementary Table 6.1).

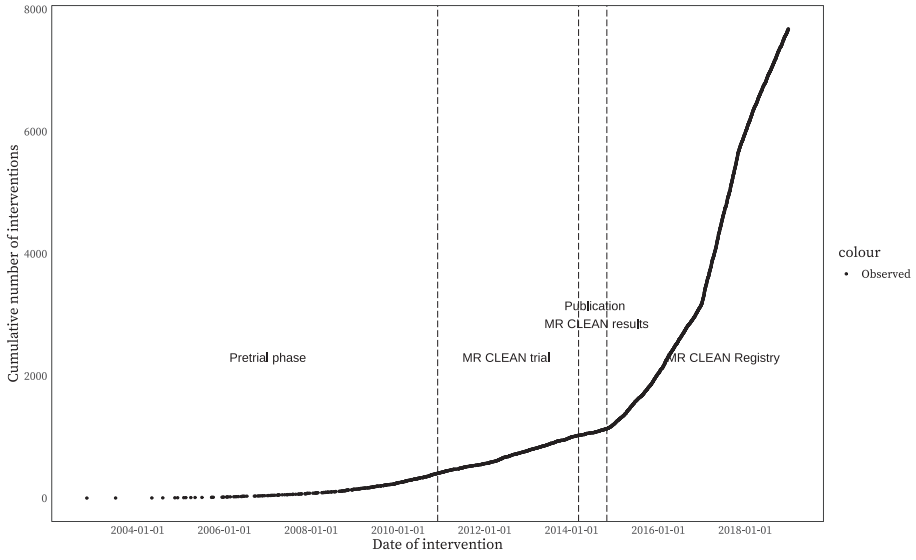

Figure 6.1 Trends over time regarding the use of endovascular treatment (EVT) in patients with acute ischemic stroke, presenting the observed number of EVT procedures.

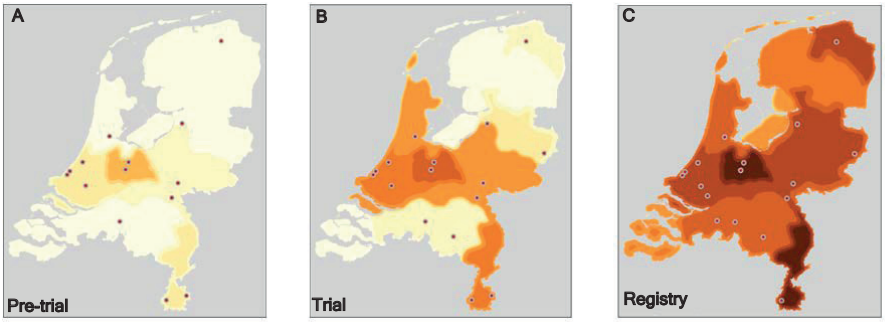

Figure 6.2 Maps of the coverage of EVT in the Netherlands per province in three different time periods (Pre-trial, MR CLEAN Trial, MR CLEAN Registry)

Pre-trial period; October 2002- December 2010, MCR CLEAN Trial: December 2010 – March 2014, MR CLEAN Registry: April 2014 – October 2017. Number of EVT-treated patients for each province are indicated per province. The density of EVTs was averaged by dividing the total number of treated patients by the average incidence during the observation period in that province. The red dots indicate intervention centres.

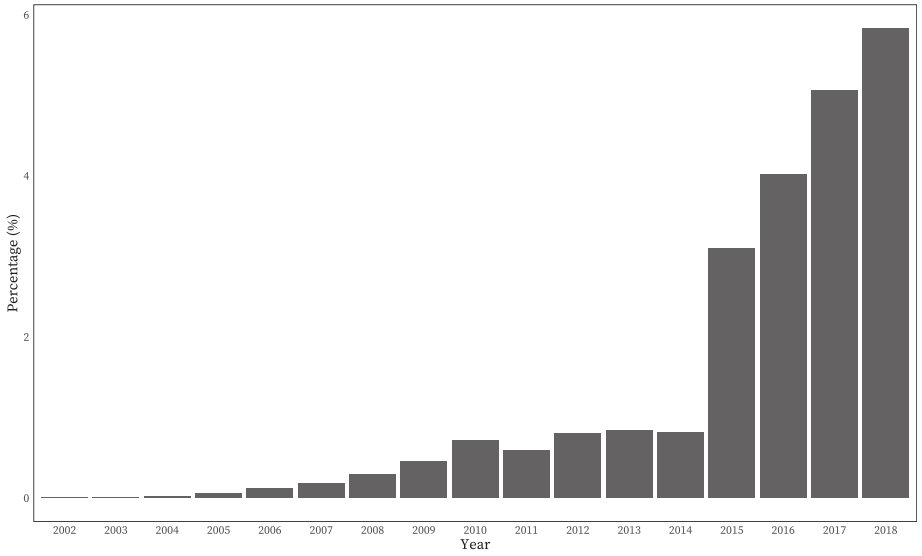

Figure 6.3 Proportion of ischemic stroke patients receiving endovascular treatment in the Netherlands per year

DISCUSSION

We described the trends in use of EVT before, during, and after the MR CLEAN trial expressed as the coverage of EVT in the Netherlands across different regions and the proportion of stroke patients who received with EVT.

Our time-trend analysis showed increasing rates of treated patients in three consecutive time periods. In the pre-trial period, the number of treated patients before the MR CLEAN trial in the Netherlands was low. This was probably due to conservative recommendations in national guidelines that recognized the low level of evidence for this treatment, and to the fact that EVT was not reimbursed in that time period. During the pre-trial period, a strict policy regarding non-evidence based treatments was maintained by insurance companies, government and professional societies.

A strict national policy of evidence-based guidelines is meant to provide the best evidence based care to the majority of patients. However, it has to be acknowledged that the pioneering centres, that provided EVT as an experimental treatment when guidelines were not yet accommodating this intervention, played an important role in the pre-trial development of acute stroke networks and treatment experience necessary to successfully perform a randomized clinical trial.

The adherence to guideline-based treatment strategies continued until the steep increase of EVT-treated patients just after the results of MR CLEAN were formally announced at the World Stroke Conference in October, 2014[32]. From the last inclusion in the trial until the presentation of these results, the use of EVT increased with the same level as during the MR CLEAN trial. The sharp acceleration of EVT use after October 2014 indicates that centres and physicians quickly adopted EVT and rapidly reorganized their acute stroke care to be able to provide this new treatment to more patients, even ahead of incorporation of EVT in national guidelines in 2017.

The Netherlands belong to the countries with one of the highest annual proportion of patients with ischemic stroke receiving EVT[12]. In 2017, 5.1% of the acute ischemic stroke patients received EVT[12]. In the United States during the same time period, 3.3% of ischemic stroke patients treated with EVT in selected centres[33].

It has been estimated that about 10% of the patients with ischemic stroke are eligible for EVT[34,35]. Therefore, it could be roughly estimated that almost 50% of the number of ischemic stroke patients eligible for EVT actually received this treatment in 2018. This implies that many patients who are eligible still do not receive the treatment. This can

be partially explained by the fact that a lot of patients arrived more than 6 hours after symptom onset, and treatment of patient in this late treatment window was not yet included in national and European guidelines[36,37]. Another explanation might be that not yet all patients who might benefit from EVT are being recognized in time pre-hospital and in-hospital, even though CTA has been advised as standard diagnostic procedure for all patients with acute ischemic stroke[38]. Also, in current clinical practice, most suspected stroke patients are first transported to the nearest hospital for immediate treatment with IVT, which can lead to delay of the start of EVT and worse outcomes because of additional time needed for transfer to an endovascular capable centre[39].

Acute stroke care in the Netherlands is organized as follows. A national network for acute medical care has been established, with expert committees for subsections for acute stroke care, trauma, obstetrics, acute psychiatry and acute myocardial infarction. The acute stroke care expert committee consists of vascular neurologists representing all stroke centres in the region, a GP, ambulance service coordinators and a secretary. Every region has a regional network protocol for acute stroke care, based on the national stroke guideline and the requirements proposed by the national societies of neurology and radiology. The regional protocol prescribes the pathway from onset to ER of primary stroke centre and intervention centre. Triage systems are being evaluated for implementation in prehospital settings, but meanwhile all patients are being transferred to the most nearby hospital with IVT available[40] (Supplementary Figure 6.1).

Our density plots show that some regions implemented EVT earlier and with a faster rate than other regions. These between-region differences indicate that access to EVT in the Netherlands can still be improved. Increasing the availability of EVT might contribute to equally divided stroke care in the Netherlands, although the number of stroke units per ischemic stroke patients is already at a very high level[12]. Considering that patients treated with EVT at higher volume centres have better outcomes than those treated at lower volume centres and that time is brain, especially in EVT-eligible stroke patients[41-43], a careful trade-off between centralization and accessibility of acute stroke care should be made[44].

Experience from related medical areas, for instance from cardiology, could provide valuable lessons and some guidance. In the eighties and nineties, patients with large myocardial infarction were being treated with thrombolytics. But when the superiority of the more effective and safer percutaneous coronary intervention (PCI) had been established, the country-wide introduction of this therapy was hampered and delayed by almost a decade by the specific requirements that the hospitals offering this form of treatment had to meet. Not infrequent and serious complications associated with

the PCI procedure mandated the presence of on-site cardiac surgery in the early years following the introduction of PCI, and limited the number of sites that could offer optimal treatment. Both technical as well as organizational developments, subsequently made the requirements of on-site cardiac surgery less of an issue, and gradually enabled the development of PCI-programs in hospitals without on-site cardiac surgery from the year 2002 onwards. Since then, the number of sites offering primary PCI for large myocardial infarctions increased from 16 to 30, more than sufficient to treat all patients with large myocardial infarctions within a reasonable time-frame[45].

Inspired by this example, professional societies, governmental agencies and insurance companies concluded that one stroke intervention centre per million inhabitants should be sufficient. Hospitals are supported in providing EVT, given the relatively small effect on hospital costs but substantial cost savings in the social service sector[46,47]. To facilitate the development of EVT centres in the Netherlands and to ensure sufficient quality, requirements have been kept at an essential minimum of 50 EVT procedures per centre per year and include 24/7 availability, sufficient facilities and trained personnel (Table 6.2). These requirements were proposed by the Dutch Society for Neurology and the Dutch society for Radiology, and adopted by insurance companies and regulatory bodies. However, the requirements for EVT centres are being updated, because of the extension of the time window for reperfusion treatment based on advanced perfusion imaging[48-52]. National guidelines require acquisition of NCCT and CTA (or MRI/MRA) in all patients with acute ischemic stroke, and are being updated with perfusion imaging for late window ischemic stroke patients.

More than a decade ago, criteria were established by the national professional societies that require a two-year training in neuro-intervention with certification that is open to all medical specialties but in practice to neurologists, radiologists, and neurosurgeons[53]. Almost all interventionists in the Netherlands are radiologists. For general interventional radiologists who want to qualify for endovascular treatment of ischemic stroke, a short additional training is required that amounts to doing at least 25 thrombectomies, 50 digital subtraction angiographies, 200 other endovascular procedures and assessment of 200 NCCT and 50 or more head/neck CTA or MRAs under supervision.

Interestingly, during the trial onset to groin times had increased by about one hour and after the trial a gradual decrease was noted The increase may be attributed to the consent and randomization procedure in the trial, whereas improved awareness, logistics and increasing experience has led to the gradual decrease after the trial. Median age of EVT treated patients, likely because trial results and guidelines point out that high age by itself should not be considered as a contra-indication for EVT[54] (Supplementary Figure 6.2-6.4).

Table 6.2 Quality criteria for primary stroke centres providing intravenous alteplase treatment, and for stroke-intervention centres providing endovascular treatment for ischemic stroke, established by the professional societies for Radiology and Neurology in 2017.

Primary stroke centres should
1) admit and treat at least 100 acute stroke patients annually (mean of last 3 years),
2) have a median door-to-needle time of less than 45 minutes,
3) have CT and CTA of cervical and intracranial vessels 24/7 available, with direct assessment provided by or supervised by a radiologist,
4) have treatment with intravenous alteplase 24/7 available, with the treatment carried out by or under supervision of a neurologist, who has direct access to neuroimaging,
5) have a stroke-team 24/7 available, with a stroke nurse under supervision of a neurologist,
6) have stroke unit with 24/7 care and 24/7 admission through ER,
7) have neurosurgery available 24/7 or collaboration with a nearby neurosurgical centre,
8) have a registry of acute stroke patients, which includes the percentage of patients treated with intravenous alteplase and the number of patients admitted within 4.5 hours after onset of stroke
9) participate in a regional stroke service and have a regional coordinator, and
10) have arrangements with an intervention centre for endovascular treatment and with the regional ambulance service for rapid transfer of patients eligible for endovascular treatment.
Stroke intervention centres should
1) fulfill the criteria for primary stroke centres,
2) have a multidisciplinary team at least consisting of a neurologist, radiologist, interventionalist and anesthesiologist,
3) provide EVT on a 24/7 basis with the multidisciplinary team,
4) have arrangements with at least one other centre in the same region in order to provide EVT when because of unusual circumstances EVT is not available in their own centre,
5) have at least 2 angio-suites, of which one is readily available with sufficient and appropriate personnel,
6) be equipped with an intensive care unit and a stroke unit
7) have a local protocol, which includes description of logistics, responsibilities of all involved professionals, patients' safety and benchmarks for door to needle and door to groin puncture time.
8) have neurologists with vascular expertise available 24/7.
9) have at least 3 interventionalists,
10) perform at least 50 EVT procedures per year
11) have at least 20 EVT procedures per interventionalist per year (procedures done by 2 interventionalists count for both)
12) have median door to groin puncture times of less than 60 minutes, and
13) have a local registry of quality of care parameters concerning logistics, complications and technical as well as clinical outcomes (at least door to groin puncture time and onset to groin puncture time, eTICI and mRS at 3 months).

Our study has some limitations. No information about the residence of the EVT-treated patients was available for all time periods. Therefore, we estimated the coverage of EVT in the Netherlands based on the first-hospital admission. Since not all patients are at home at the moment of their stroke onset and the first hospital is often close to the place of stroke onset, this should reflect daily clinical care.

Our study only describes EVT in the Netherlands, and it does only touch upon factors that have facilitated its rapid implementation. Comparisons with other countries may help in this regard. Still, several factors may have played an important role in the implementation of EVT in the Netherlands, including the dense population (17 million people living on an area of 33671 km^2, for an average population density of 510/km^2), the dense highway network, the large number of primary stroke centres (85, 5 per million inhabitants) and EVT centres (17, 1 per million inhabitants)[12], and last, an ambulance network which has to comply with the requirement that every patient should be picked up within 15 minutes after calling 112, and should be delivered at the ER of the most nearby primary stroke centre within 30 minutes.

CONCLUSION

A well-developed infrastructure, a pragmatic approach towards the use of EVT in clinical practice, in combination with a strict adherence by the regulatory authorities to national evidence-based guidelines has led to successful implementation of EVT in the Netherlands. Ongoing efforts are directed at further increasing the proportion of stroke patients with EVT in all regions of the country.

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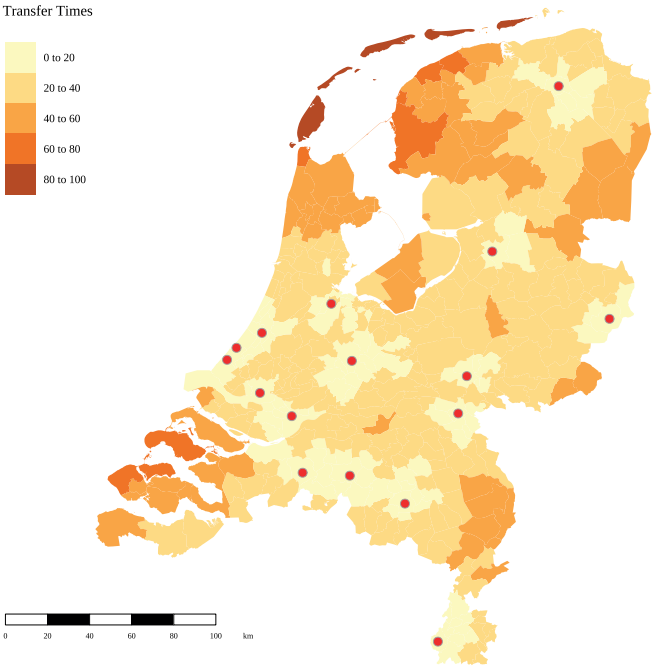
SUPPLEMENTARY MATERIAL

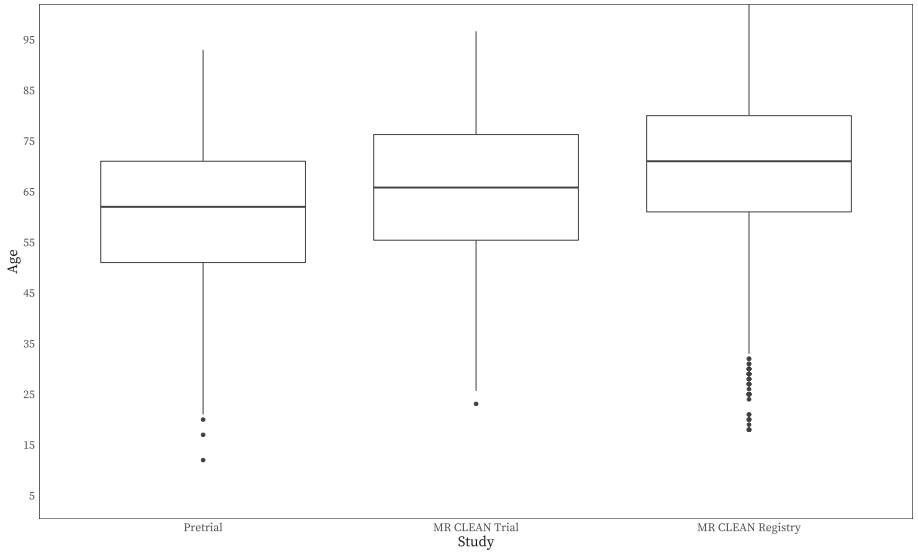
Supplementary Table 6.1 Number of (ischemic stroke) patients and (proportion) treated with EVT

Year	Stroke Patients (n)	Ischemic Stroke Patients (n)	EVT-treated patients (n)	% EVT-treated / Ischemic Stroke
2002	26919	18304	1	0.005%
2003	27924	18988	1	0.005%
2004	28928	19671	4	0.02%
2005	29993	20395	11	0.05%
2006	30938	21038	24	0.1%
2007	31943	21721	39	0.2%
2008	32948	22405	65	0.3%
2009	33952	23807	104	0.4%
2010	34958	23771	170	0.7%
2011	35962	24454	145	0.6%
2012	36967	25138	200	0.8%
2013	37792	25699	216	0.8%
2014	39145	26726	217	0.8%
2015	39699	26266	812	3.1%
2016	41047	28368	1138	4.0%
2017	41685	29244	1478	5.1%
2018	42844	29356	1712	5.8%

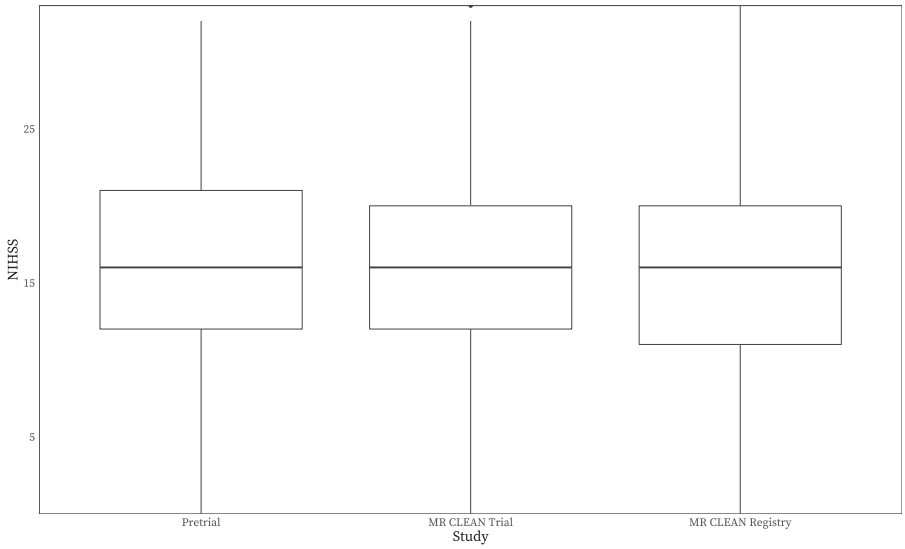
Numbers are obtained from several reports of the Dutch Heart Association.



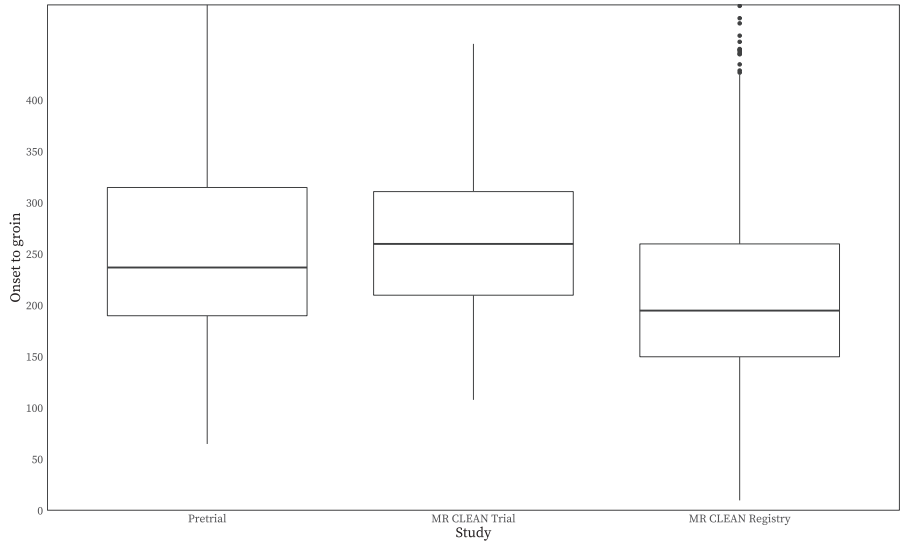
Supplementary Figure 6.1 Map of average transfer time per municipality to the nearest stroke-intervention centre in minutes



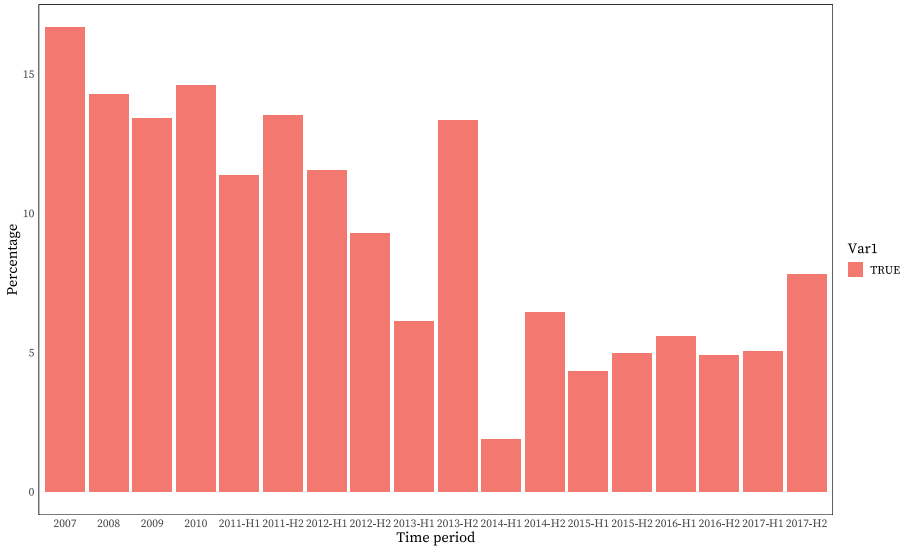
Supplementary Figure 6.2 Age per study period



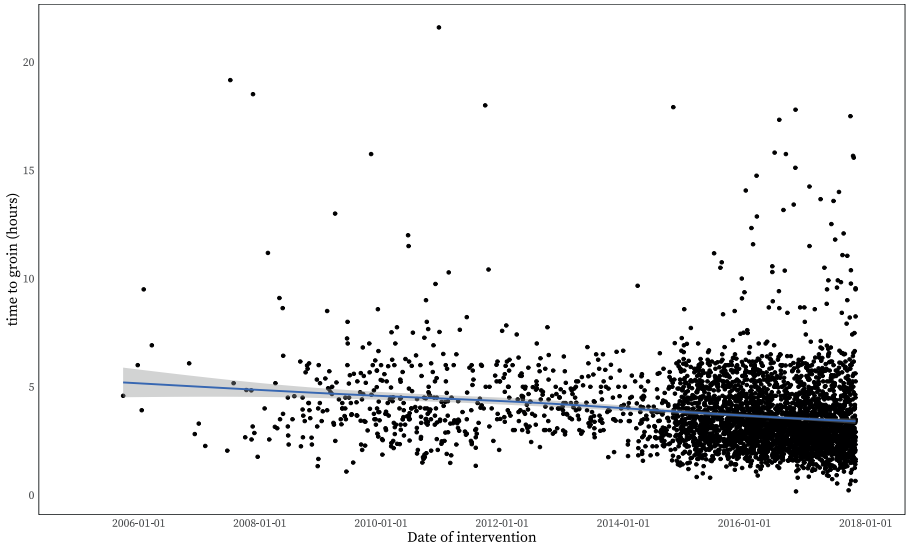
Supplementary Figure 6.3 NIHSS per study period



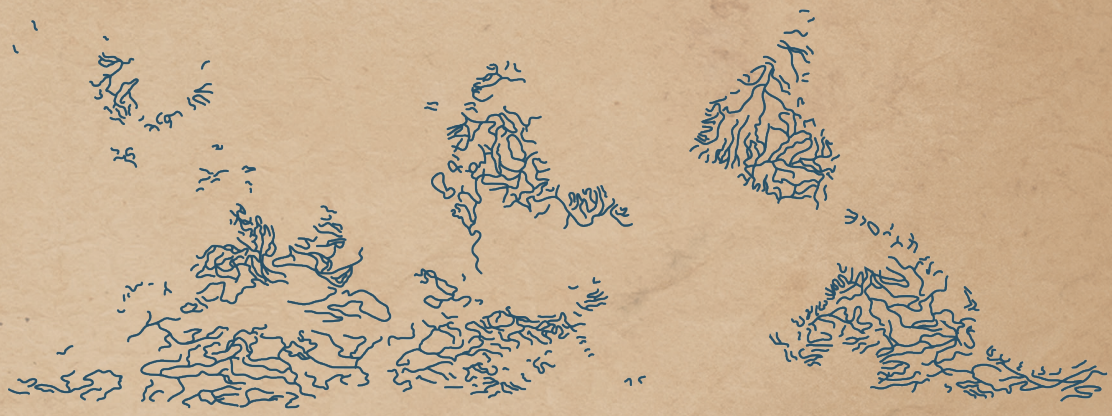
Supplementary Figure 6.4 Time from onset to groin puncture per study period



Supplementary Figure 6.5 Percentage of patients undergoing endovascular thrombectomy outside the time window of 6 hours, from 2007 to 2018.

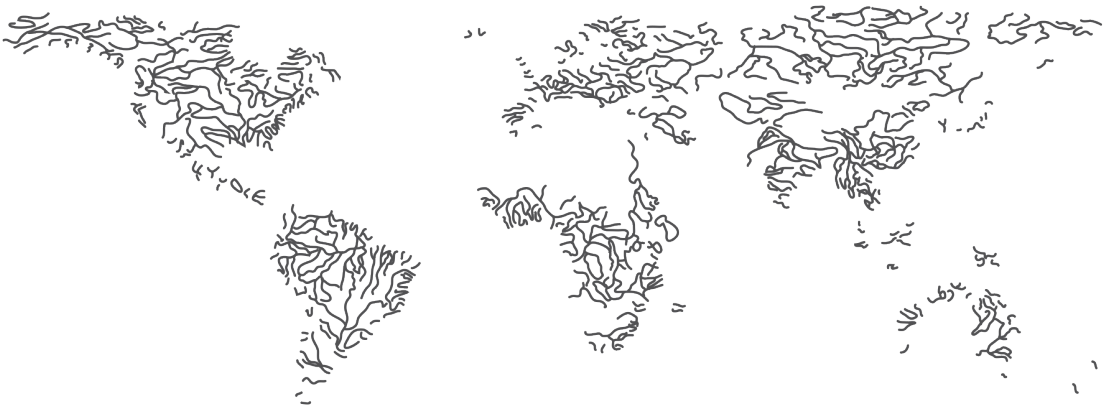


Supplementary Figure 6.6 Time from onset to groin (hours) by date of intervention, in patients undergoing endovascular thrombectomy, from 2006 to 2018.



Part II

Identifying effective care



Chapter 7

Fluid Balance and Outcome in Critically Ill Patients with Traumatic Brain Injury: a prospective multinational, multicentre comparative effectiveness study

The Lancet Neurology, 2021

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ABSTRACT

Background

Fluid therapy - the administration of fluids to maintain adequate organ tissue perfusion and oxygenation - is essential in patients admitted to the intensive care unit (ICU) with traumatic brain injury (TBI). We aimed to quantify variability in fluid management policies in patients with traumatic brain injury and to study the effect of this variability on patients' outcomes.

Methods

We did a prospective, multicentre, comparative effectiveness study of two observational cohorts: CENTER-TBI in Europe and OzENTER-TBI in Australia. Patients from 55 hospitals in 18 countries, aged 16 years or older with traumatic brain injury requiring a head CT, and admitted to the ICU were included in this analysis. We extracted data on demographics, injury, and clinical and treatment characteristics, and calculated the mean daily fluid balance (difference between fluid input and loss) and mean daily fluid input during ICU stay per patient. We analysed the association of fluid balance and input with ICU mortality and functional outcome at 6 months, measured by the Glasgow Outcome Scale Extended (GOSE). Patient-level analyses relied on adjustment for key characteristics per patient, whereas centre-level analyses used the centre as the instrumental variable.

Findings

2125 patients enrolled in CENTER-TBI and OzENTER-TBI between Dec 19, 2014, and Dec 17, 2017, were eligible for inclusion in this analysis. The median age was 50 years (IQR 31 to 66) and 1566 (74%) of patients were male. The median of the mean daily fluid input ranged from 1.48 L (IQR 1.12 to 2.09) to 4.23 L (3.78 to 4.94) across centres. The median of the mean daily fluid balance ranged from –0.85 L (IQR –1.51 to –0.49) to 1.13 L (0.99 to 1.37) across centres. In patient-level analyses, a mean positive daily fluid balance was associated with higher ICU mortality (odds ratio [OR] 1.10 [95% CI 1.07 to 1.12] per 0.1 L increase) and worse functional outcome (1.04 [1.02 to 1.05] per 0.1 L increase); higher mean daily fluid input was also associated with higher ICU mortality (1.05 [1.03 to 1.06] per 0.1 L increase) and worse functional outcome (1.04 [1.03 to 1.04] per 1-point decrease of the GOSE per 0.1L increase). Centre-level analyses showed similar associations of higher fluid balance with ICU mortality (OR 1.17 [95% CI 1.05 to 1.29]) and worse functional outcome (1.07 [1.02 to 1.13]), but higher fluid input was not associated with ICU mortality (OR 0.95 [0.90 to 1.00]) or worse functional outcome (1.01 [0.98 to 1.03]).

Interpretation

In critically ill patients with traumatic brain injury, there is significant variability in fluid management, with more positive fluid balances being associated with worse outcomes. These results, when added to previous evidence, suggest that aiming for neutral fluid balances, indicating a state of normovolaemia, contributes to improved outcome.

Funding

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RESEARCH IN CONTEXT

Evidence before this study

Almost all patients with traumatic brain injury, with or without polytrauma, receive intravenous fluids. Over the past few decades, the main goal of fluid management has shifted from a dehydration strategy, including negative fluid balance, to normovolaemia (ie, neutral or net zero fluid balance) and mild hypervolaemia (ie, a slightly positive fluid balance). In 2018, the European Society of Intensive Care Medicine (ESICM) consensus on fluid therapy in neurointensive care, which also pertains to patients with traumatic brain injury, reported the findings of an extensive literature search based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to evaluate the quality of evidence and formulate evidence-based treatment recommendations. However, given the absence of high-quality investigations, consensus-based practice recommendations were drafted on optimal fluid resuscitation and maintenance fluid therapy, suggesting clinicians should aim for normovolaemia (which has not been defined in detail), using arterial blood pressure and fluid balance as the main and safety endpoints to titrate fluids, and avoid restrictive fluid therapy (ie, a negative fluid balance). We updated the systematic literature search used for this ESICM consensus (which ran until Jan 19, 2017), excluding studies done in animals, case reports and reviews, and studies of non-traumatic brain injury, using the same search terms in PubMed on Feb 20, 2021: (“brain edema”[MeSH] OR “traumatic brain injury”[All Fields] OR “head trauma”[All Fields] OR “head injury”[All Fields]) AND (“Hemodynamics”[Mesh] OR “Blood volume”[MeSH] OR “Hemodilution”[MeSH] OR “fluid therapy”[Mesh] OR “Hydroxyethyl starch derivatives”[MeSH] OR “crystalloid solutions”[Supplementary Concept] OR “Hypertonic solutions”[MeSH] OR (“albumins”[MeSH Terms] OR “albumins”[All Fields] OR “albumin”[All Fields]) OR (“crystalloid solutions”[Supplementary Concept] OR “crystalloid solutions”[All Fields] OR “crystalloid”[All Fields]) OR “Hydroxyethyl starch”[All Fields] OR (“mannitol”[MeSH

Terms] OR "mannitol"[All Fields]) OR ("glucose"[MeSH Terms] OR "glucose"[All Fields] OR "dextrose"[All Fields]) OR ("sodium chloride"[MeSH Terms] OR ("sodium"[All Fields] AND "chloride"[All Fields]) OR "sodium chloride"[All Fields] OR "saline"[All Fields])) AND ("humans"[MeSH Terms] AND English[lang]) NOT (child* OR infant* OR pediatrics). No additional relevant studies were retrieved.

Added value of this study

In this comparative effectiveness study of a large cohort of patients admitted to the intensive care unit (ICU) with traumatic brain injury in Europe (CENTER-TBI) and Australia (OzENTER-TBI), we found that the mean daily fluid balance was often in the normovolaemia to mild hypervolaemia range, as indicated by a neutral to positive fluid balance. Fluid management varied substantially between ICUs. Positive daily mean fluid balances were common and consistently associated with higher ICU mortality and worse functional outcome.

Implications of all the available evidence

Our findings, in combination with previous evidence, argue for a more rigorous policy of normovolaemia, carefully avoiding both hypervolaemia and hypovolaemia as indicated by mean neutral fluid balances, given the harm associated with both mean negative and positive fluid balances. However, further research is needed to establish how to implement this knowledge while still respecting individualised approaches (eg, based on haemodynamic monitoring) and taking into account cerebral perfusion pressure.

INTRODUCTION

Traumatic Brain Injury (TBI) is one of the major causes of premature death and disability worldwide[1]. Intensive care management of patients with traumatic brain injury predominantly involves monitoring of intracranial pressure and cerebral perfusion pressure[2]. However, the effect of systemic therapies, including fluid therapy (the administration of different intravenous fluids for maintenance of adequate organ tissue perfusion and oxygenation), in critically ill patients with traumatic brain injury is understudied.

Fluid therapy is essential in critically ill patients with traumatic brain injury. Fluid restriction could have adverse consequences on outcome[3], whereas fluid overload could cause systemic complications (eg, pulmonary oedema) or brain oedema and increased intracranial pressure[3, 4]. Historically, the importance and goals of fluid management in patients with traumatic brain injury have varied and shifted, from dehydration therapy

(aimed at limiting cerebral oedema) in the 1970s to 1990s[5], towards normovolemia or even hypervolemia[3, 6, 7]. These changing insights are reflected in previous versions of the Brain Trauma Foundation (BTF) Guidelines with recommendations ranging from "euvolemia… by adequate fluid replacement" to a focus on maintaining cerebral perfusion pressure above 70mmHg", with fluids or vasopressors, or both[8]. In the 2007 and 2016 versions of the BTF guidelines, recommendations on fluid management were discarded because of the absence of high-quality evidence[9, 10]. Notably, these last two versions also discarded the higher than 70mmHg target for cerebral perfusion pressure, following the trial by Robertson and colleagues[11] , that found a five-times higher incidence of adult respiratory distress syndrome and a significantly more positive fluid balance when aiming for a cerebral perfusion pressure higher than 70mmHg.

In summary, best practices guidelines for fluid management in patients with traumatic brain injury remain controversial. Potentially as a result, previous studies have shown substantial practice variation regarding fluid management[3]. Although variability in clinical practice is in principle undesirable, it also provides the opportunity to relate between-centre differences in management to differences in outcome[2, 12, 13]. In this prospective, multicentre, comparative effectiveness study, we aimed to quantify the variability in fluid management policies for patients with traumatic brain injury across intensive care units (ICUs) in Europe and Australia, and to study the association between fluid therapy and outcomes.

METHODS

Study Design and Participants

The Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) study is an ongoing, multicentre longitudinal prospective observational cohort study being done in 63 centres from 18 countries across Europe and Israel. Data were collected between Dec 19, 2014, and Dec 17, 2017. Patients were included in the study if they were admitted to the ICU within 24 h of injury with a clinical diagnosis of traumatic brain injury and had a CT scan of the brain. Patients were excluded if they had a severe pre-existing neurological disorder that would confound outcome assessment[13]. The OzENTER-TBI (Australia-Europe NeuroTrauma Effectiveness Research in Traumatic Brain Injury) study was an entirely ICU-based study that collected detailed data from patients with traumatic brain injury admitted to the ICU of two major trauma centres in Australia between Feb 1, 2015, and March 31, 2017. The OzENTER-TBI study was prospectively harmonised with and followed the same inclusion criteria as the CENTER-TBI study. For this analysis, we included patients aged 16 years or older who were admitted to the ICU in either study.

The CENTER-TBI study was approved by the medical ethics committees of all participating centres (https://www.center-tbi.eu/project/ethical-approval)[13]. All patients or their proxies provided written informed consent within 24 hours after injury. In the OzENTER-TBI study, ethical approval was granted by the human research ethics committees of Monash University, Melbourne, VIC, Australia, and of the two participating adult major trauma hospitals (The Alfred Hospital and the Royal Melbourne Hospital, Melbourne, VIC, Australia). For patients in OzENTER-TBI, patients or family members were given two opportunities to opt out of data retention and outcome assessments, but if family members could not be located, patients were included in the study with informed consent waived by the three human research ethics committees.

Procedures

CENTER-TBI and OzENTER-TBI collected detailed information about demographics, injury characteristics, clinical characteristics, laboratory values, monitoring, treatment intensity level, and outcomes. Furthermore, on a daily basis, serum sodium was documented, as well as details of whether colloids or osmotic therapy had been administered (yes or no). At each centre, data were collected and interpreted by physicians or research assistants, or both, and entered on an online data entry and analysis platform (QuesGen; Burlingame, CA, USA).

A site coordinator was designated in each centre to streamline data collection. Data collection was supported by ICON (Paris, France), a professional contract research organisation, and source data verification of major characteristics was done by ICON at all sites on a quasirandom sample of 1298 (28%) patients. For the purpose of this study, we extracted data on demographics, injury, and clinical and treatment characteristics. All patients were treated according to local hospital protocols, which were informed by the Brain Trauma Foundation guidelines in 49 (75%) of 65 centres in CENTER-TBI[14].

Fluid balance was calculated as the difference between fluid input (all intravenous fluids including any crystalloid, hyperosmotic, or colloid fluids, blood products, enteral fluids, and renal replacement therapy fluids) and fluid loss (urine output, enteral losses, drain losses, and dialysis effluent-dialysate from continuous renal replacement therapy) per day in the ICU. Insensible fluid losses were not considered. On the case report form, cumulative fluid input was requested over a 24 h period, including fluids that were given in the operating room on days 1–7 and on days 10, 14, 21, and 28. We calculated the mean daily fluid balance and mean daily fluid input during ICU stay per patient. This estimate accounts for the fact that the number of measurements might differ per patient because of mortality or discharge from the ICU.

Outcomes

Primary outcomes were ICU mortality and the Glasgow Outcome Scale Extended (GOSE) at 6 months. The GOSE was measured by either a postal questionnaire or an interview, depending on the preference of the centre, outcome assessor, or patient, or a combination of the above[12]. The categories "vegetative state" and "lower severe disability" were combined, as these categories could not be differentiated for assessments based on postal questionnaires. Unfavourable outcome was defined as a GOSE score less than 5.

Statistical analyses

Baseline characteristics of included patients were presented as median values with IQRs for continuous variables and as frequencies and percentages for categorical variables. ANOVA was used for comparison of continuous variables across strata. The χ^2 test was used for comparison of categorical variables.

To assess between-centre variation in fluid management, we used a linear mixed-effects model to estimate the mean balance and mean input per centre with corresponding 95% CIs. The variables from the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) prognostic models (age, Glasgow Coma Scale [GCS] motor score, pupillary reaction, hypoxia, hypotension, CT Marshall classification, traumatic subarachnoid haemorrhage, epidural haematoma, first glucose, and first haemoglobin), and any major extracranial injury (Abbreviated Injury Scale [AIS] ≥ 3) were assessed upon hospital admission only and added as independent variables to adjust for case-mix severity[15]. Hypotension was defined as a measured systolic blood pressure lower than 90 mmHg at least once before hospital admission or in the emergency department

In patient-level analyses, the associations between fluid balance and fluid input and outcome were analysed with a random-effects logistic regression (for ICU mortality) and ordinal regression (for GOSE), with adjustment for the IMPACT variables, any major extracranial injury, and a random intercept for centre. In a secondary analysis we also adjusted for cerebral perfusion pressure and serum sodium (see legend, Supplementary Table 7.12) and for mean arterial pressure (Supplementary Table 7.13). Additionally, we used propensity score matching (see legend, Supplementary Table 7.14).

Table 7.1 Baseline characteristics

	Total n=2125
Age, years	50 [31-66]
Age ≥65 years	572/2125 (27%)
Male sex	1566/2125 (74%)
Pre-injury ASA-PS Classification	
A normal healthy patient	1167/2035 (57%)
A patient with mild systemic disease	658/2035 (32%)
A patient with severe systemic disease	210/2035 (10%)
History of cardiovascular disease	596/1995 (30%)
Use of anticoagulants	117/1999 (5.9%)
Use of antiplatelets	222/1999 (11%)
GCS Baseline	9 [4-14]
Severity TBI	
Mild (GCS: 13 – 15)	681/2029 (34%)
Moderate (GCS: 9 – 12)	340/2029 (17%)
Severe (GCS: 3 – 8)	1008/2029 (50%)
Pupillary reaction	
Both reacting	1637/2030 (81%)
Both unreactive	250/2030 (12%)
One reacting	143/2030 (7%)
Hypoxia Prehospital or at ER	300/1993 (15%)
Hypotension Prehospital or at ER	305/2010 (15%)
Any major extracranial injury (AIS ≥3)	1202/2125 (57%)
Marshall CT Classification	
I	183/1879 (10%)
II	901/1879 (48%)
III	153/1879 (8%)
IV	28/1879 (2%)
V/VI	614/1879 (33%)
Epidural Hematoma	364/1877 (19%)
Traumatic Subarachnoid Haemorrhage	1392/1873 (74%)
Treatments during ICU stay	
Any use of vasopressors during ICU stay	1145/2002 (57%)
ICP Monitor	993/2125 (47%)
Colloids	338/2107 (16%)
Any Hypertonic Saline or Mannitol	582/2125 (27%)
Hypertonic Saline	463/2125 (22%)

	Fluid Balance < = median (0.37L) n=1063	Fluid Balance > median (0.37L) n=1062	p-value
	47 [30-64]	52[31-67]	0.0090
	264/1063 (25%)	308/1062 (29%)	0.0034
	805/1063 (76%)	761/1062 (72%)	0.037
	604/1022 (59%)	563/1013 (56%)	0.27
	318/1022 (31%)	340/1013 (34%)	
	100/1022 (9.8%)	110/1013 (11%)	
	285/1018 (28%)	311/977 (32%)	0.068
	55/1007 (5%)	62/992 (6.2%)	0.51
	102/1007 (10%)	120/992 (12%)	0.18
	9[4-14]	8[3-13]	0.086
			0.35
	359/1024 (35%)	322/1005 (32%)	
	169/1024 (17%)	171/1005 (17%)	
	496/1024 (48%)	512/1005 (51%)	
			0.092
	837/1015 (83%)	800/1015 (79%)	
	110/1015 (11%)	140/1015 (14%)	
	68/1015 (6.7%)	75/1015 (7.4%)	
	137/1012 (14%)	163/981 (17%)	0.063
	132/1014 (13%)	173/996 (17%)	0.0079
	584/1063 (55%)	618/1062 (58%)	0.14
			0.48
	93/951 (10%)	90/928 (9.7%)	
	473/951 (50%)	428/928 (46%)	
	70/951 (7%)	83/928 (9%)	
	15/951 (2%)	13/928 (1%)	
	300/951 (32%)	314/928 (34%)	
	206/951 (22%)	158/926 (17%)	0.014
	702/947 (74%)	690/926 (75%)	0.89
	527/1008 (52%)	618/994 (62%)	<0.0001
	474/1063 (45%)	519/1062 (49%)	0.053
	132/1053 (13%)	206/1054 (20%)	<0.0001
	263/1063 (25%)	319/1062 (30%)	0.0072
	211/1063 (20%)	252/1062 (24%)	0.035

Table 7.1 Continued

	Total n=2125
Mannitol	276/2125 (13%)
Cranial Surgery	877/2111 (42%)
Extracranial Surgery	651/2110 (31%)
Central Venous Pressure Monitoring	961/2121 (45%)
Cardiac Output Monitoring	292/2122 (14%)
Renal Replacement Therapy	56/2122 (3%)
Clinical Parameters during ICU stay	
Mean CPP during ICU stay	74 [69 – 79]
Mean Sodium during ICU stay	141 (139 – 144)
Complications and Outcomes	
Respiratory Failure	516/2109 (25%)
Ventilator Associated Pneumonia	318/2109 (15%)
ICU Length of Stay - days	6.7[2.1-15.2]
ICU Mortality	283/2112 (13%)
Mortality at 6 months	407/1844 (22%)
Predicted probability of mortality at 6 months – IMPACT model	32%
Unfavourable Outcome at 6 months (GOSE <5)	853/1844 (46%)
Predicted probability of unfavourable outcome at 6 months – IMPACT model	51%

Data are n (%) or median (IQR). The IMPACT model was used to calculate the expected mortality and expected proportion of patients with an unfavourable outcome (GOSE <5) at 6 months. ASA-PS=American Society of Anesthesiologists physical status.

Because of the observational nature of the study, the possibility of residual confounding (beyond confounding variables based on clinical or pathophysiological reasoning or previous research) in a patient-level analysis can never be fully excluded. Therefore, we also analysed the association between fluid management and outcome with instrumental variable analysis, which is less sensitive for confounding by indication. The instrumental variable was mean fluid balance and fluid input per centre, which was calculated by use of a mixed effects linear regression with adjustment for the IMPACT variables, any major extracranial injury, and a random intercept for centre, and expressed as the deviation of the centre-specific mean balance or input from the overall mean. The association of this instrument, the centre-specific deviation, with outcome was tested by use of a mixed-effects ordinal regression model with GOSE as outcome, with adjustment for the IMPACT variables, any major extracranial injury, and a random intercept for centre, to adjust for potential confounding centre characteristics (see also Supplementary Methods).

Fluid Balance <= median (0.37L) n=1063	Fluid Balance > median (0.37L) n=1062	p-value
121/1063 (11%)	155/1062 (15%)	0.033
418/1050 (40%)	459/1061 (43%)	0.12
313/1050 (30%)	338/1060 (32%)	0.32
485/1060 (46%)	476/1061 (45%)	0.71
136/1060 (13%)	156/1062 (15%)	0.24
19/1062 (2%)	37/1060 (4%)	0.021
75 [70 – 80]	73[68 – 78]	0.0020
141 (139 – 143)	141 (139 – 144)	0.22
224/1056 (21%)	292/1053 (28%)	0.00060
145/1056 (14%)	173/1053 (16%)	0.10
6.8[2.2-14.7]	6.5[2.1-15.4]	0.98
97/1057 (9.2%)	186/1055 (18%)	<0.0001
158/928 (17%)	249/916 (27%)	<0.0001
30%	35%	<0.0001
380/928 (41%)	473/916 (52%)	<0.0001
48%	54%	<0.0001

GCS=Glasgow Coma Scale. AIS=Abbreviated Injury Scale. ICU=intensive care unit. ICP=intracranial pressure. CPP=cerebral perfusion pressure. IMPACT=International Mission for Prognosis and Analysis of Clinical Trials in TBI. GOSE=Glasgow Outcome Scale Extended.

In all models, restricted cubic splines were used to test for the non-linearity of the effect of fluid management. For fluid balance, a non-linear association with GOSE at 6 months was observed (Supplementary Figure 7.1) with an inflection point at a fluid balance of 0.0. Therefore, mean daily positive fluid balance (> = 0L) and a mean daily negative fluid balance (< 0L) were analyzed as two separate linear variables and their effect expressed as two separate odds ratios (ORs) and p-values. ORs and 95% CIs for GOSE were reversed, so that an OR above 1 indicates worse outcome, to align the interpretation of these results with those for the effect on mortality.

All statistical analyses were performed in R studio, and a two-sided p value of 0.05 was considered to be statistically significant. Data were accessed using a bespoke data management tool, 'Neurobot' (http://neurobot.incf.org; RRID: SCR_01700), vs 2.1 (data freeze: June 2020). Multiple imputation was used to handle missing values, with use of the Multiple Imputation by Chained Equations (MICE) package in R.

We did sensitivity analyses to explore the consistency of the results in the following subgroups of patients, based on the assumption that fluid management might differ between subgroups: patients with isolated traumatic brain injury (no major extracranial injury; AIS ≥3) versus those with major extracranial injury; patients with hypotension before hospital admission or in the emergency department; patients who were not treated with hypertonic saline versus those who were treated with hypertonic saline; patients who were not treated with mannitol versus those treated with mannitol; patients who survived in the ICU for at least 3 days versus patients who stayed in the ICU for a maximum of 3 days; patients with raised intracranial pressure (>20 mm Hg) versus patients who did not have raised intracranial pressure at least once during ICU stay; patients who had an intracranial pressure monitor versus patients who did not have an intracranial pressure monitor; patients with moderate and severe traumatic brain injury (GCS 13 at baseline) versus patients with mild traumatic brain injury (GCS ≥13); and patients included in CENTER-TBI versus those in the OzENTER cohort. Interactions between fluid balance or fluid input and subgroups were tested by comparing models with and without interaction terms by use of a likelihood ratio test.

To gain more insight into the potential consequences of fluid therapy, we assessed the association of fluid balance and input with intracranial pressure, cerebral perfusion pressure, and the dose of vasopressors. In a subgroup of patients in whom intracranial pressure monitoring was done, the association of daily fluid balance and input with the daily maximum intracranial pressure, mean cerebral perfusion pressure, and dose of noradrenaline (mg) on the following day was analysed with a linear mixed model, including a random intercept for patient to account for multiple observations within one patient and with adjustment for the IMPACT core variables (age, GCS motor score, and pupillary reactivity).

Role of funding source
The funders had no role in study design, data collection, data analysis, data interpretation, the writing of the report, or in the decision to submit for publication.

RESULTS

4509 patients were enrolled in the CENTER-TBI study, of whom 2138 patients were admitted to the ICU. 198 patients admitted to an ICU were enrolled in the OzENTER-TBI Study. We excluded patients, for whom information on fluid therapy was lacking (n=128, including one from the OzENTER Study) and those who were younger than 16 years of age (n=83). 2125 patients from 55 hospitals in 18 countries were therefore eligible for inclusion in this analysis (Figure 7.1).

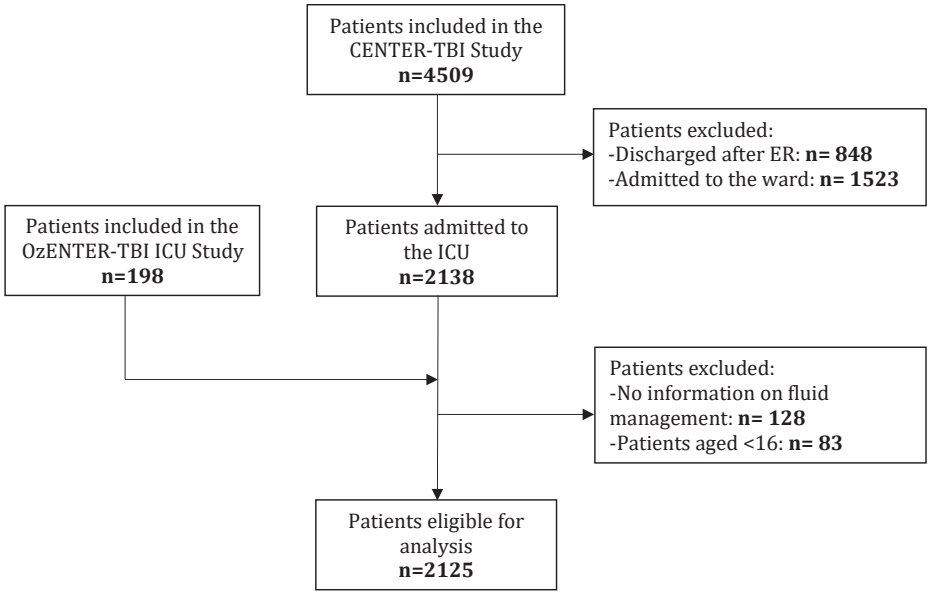

Figure 7.1 Flowchart of included patients

ICU = intensive care unit

The median age was 50 years (IQR 31 to 66) and 1566 (74%) were male. 1202 (57%) had major a extracranial injury (Table 7.1, Supplementary Table 1). Cranial surgery was done in 877 (42%) patients and extracranial surgery was done in 651 (31%). 582 (27%) patients received mannitol, hypertonic saline, or both, 338 (16%) patients received colloids, and 1145 (57%) received vasopressors during ICU stay. 56 (3%) patients received renal replacement therapy. 283 (13%) patients died in the ICU. Considering the whole duration of ICU stay, the median of the mean daily fluid balance was 0.37L (IQR -0.08 to 0.79), and the median of the mean daily fluid input was 2.91L (IQR 2.15 to 3.60) (Supplementary Figure 7.2). Cerebral perfusion pressure was lower in patients with higher than median fluid balance, although the absolute difference was small (73 mmHg versus 75 mmHg, p=0.0015). After 6 months, 853 (46%) patients had an unfavorable outcome (Table 7.1, see also Supplementary Table 7.1 and 7.2). The median of the mean daily fluid balance ranged from -0.85L [IQR -1.51 to -0.49] to 1.13L [IQR 0.99 to 1.37] across centres. The median of the mean daily fluid input ranged from 1.48L [IQR 1.12 to 2.09] to 4.23L [3.78 to 4.94] across centres. After adjustment for case-mix, substantial differences remained in fluid management between centres (Figure 7.2). The 27 (50%) centres with a daily fluid balance higher than the median did cardiac output monitoring less often than the 28 (50%) centres with a daily fluid balance lower than the median (14% (range 0%-70%) vs 21% (range

0%- 100%). The same was true for fluid input: 13% (range 0 to 100) in the 27 (50%) centres with higher than median fluid input versus 22% (0 to 100) in the 28 (50%) centres with lower than median fluid input underwent cardiac output monitoring (Supplementary Table 7.2).

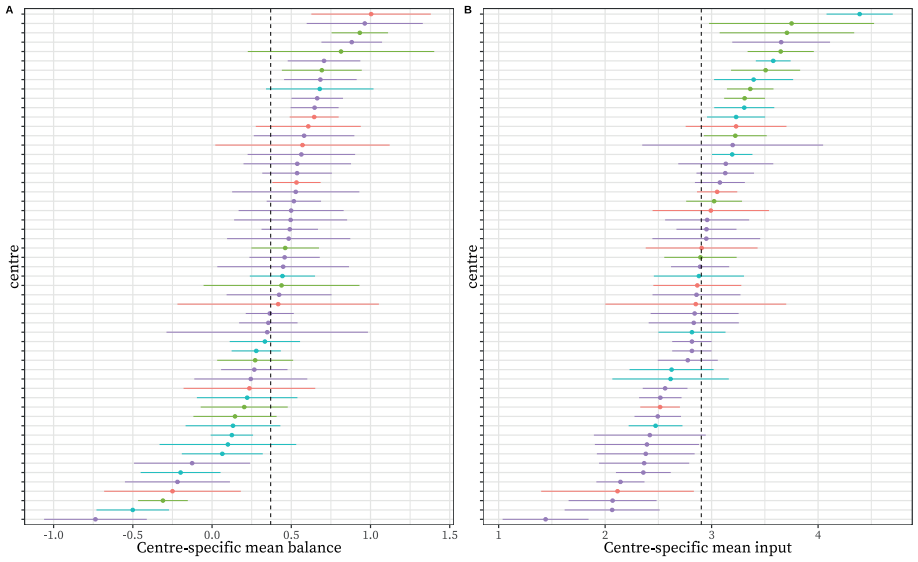

Figure 7.2 Between-centre differences in A] mean daily fluid balance and B] mean daily fluid input

(A) The x-axis indicates the mean fluid balance and 95% CI posterior means per centre compared to the average mean balance for all centres. A random-effect regression model was used to correct for random variation and adjusted for case-mix severity with the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) variables (age, Glasgow Coma Scale [GCS] motor score, pupillary reaction, hypoxia, hypotension, Marshall CT classification, traumatic subarachnoid haemorrhage, epidural haematoma, first glucose, first haemoglobin) and the presence of any major extracranial injury (Abbreviated Injury Scale [AIS] ≥3). The dashed red line represents the overall mean (0.38 L; SD 0.45). (B) The x-axis indicates the mean fluid input and 95% CI posterior means per centre compared to the average input for all centres. A random-effect regression model was used to correct for random variation and adjusted for casemix severity with the same variables as used for the analysis of fluid balance. The dashed red line represents the overall mean (2.91 L; SD 0.63). In both panels, the centres are shown in order of the means. The colour of the dot indicates the region in which the centre was located according to the UN geoscheme.

In our adjusted analysis, a mean daily positive fluid balance was associated with higher ICU mortality (OR 1.10, [95%CI: 1.07-1.12] per 0.1 L increase) and worse functional outcome (1.04 [1.02–1.05]) (Table 7.2, Figure 7.3). A negative mean daily fluid balance was not associated with ICU Mortality (OR 0.96, [95%CI: 0.90–1.01] per 0.1 L increase) or worse functional outcome (0.99, [0.97–1.02]).

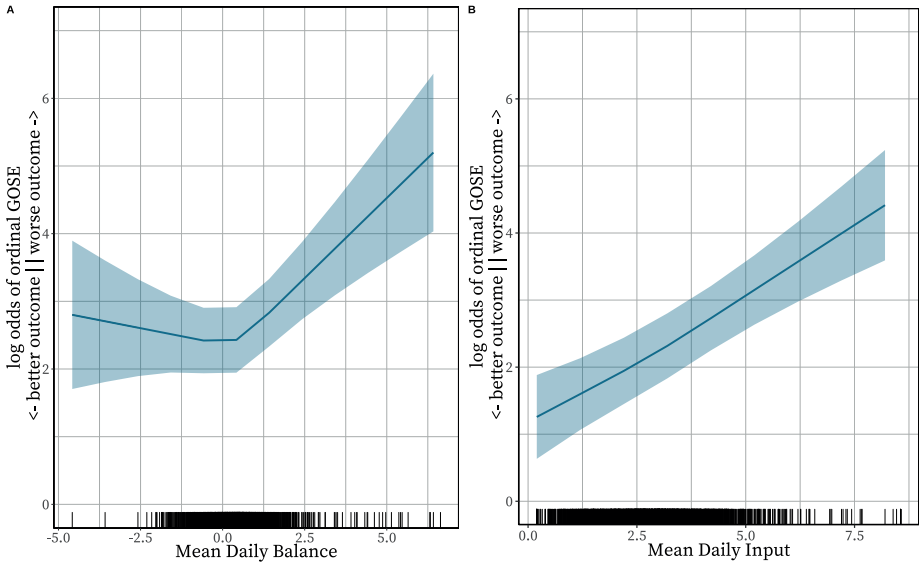

Figure 7.3 Effect Plots for the effect of daily mean of Fluid Balance (A) and Fluid Input (B) on GOSE at 6 months

(A) Effect plot for the log odds of ordinal Glasgow Outcome Scale Extended (GOSE; y-axis) for mean daily fluid balance (x-axis, per L). (B) Effect plot for the log odds of ordinal GOSE (y-axis) for mean daily fluid input (x-axis, per L). In both analyses, increasing log odds indicate worse outcomes, and decreasing log odds indicate better outcomes. This analysis was adjusted for the average patient: age 49 years, Glasgow Coma Scale (GCS) motor score at baseline of 1, both pupils reactive, no hypoxia before hospital admission or in the emergency department, no hypotension before hospital admission or in the emergency department, no epidural haematoma, Marshall CT classification of II, haemoglobin 13 g/dL, glucose 8.4 mmol/L, major extracranial injury (Abbreviated Injury Scale ≥3), and the centre that included the most patients. The average patient was defined according to the mean values for continuous variables and the most frequently occurring category for categorical variables. The shaded area represents 95% CIs. The black lines at the bottom of the x-axis correspond to individual patients' mean daily fluid balance or input during ICU stay.

We observed a linear association between higher mean daily fluid input and higher ICU mortality (OR 1.05, [95%CI: 1.03–1.06] per 0.1 L increase; and between a higher mean daily input and worse functional outcome (OR 1.04, [95%CI: 1.03–1.05] for a 1-point decrease of the GOSE per 0.1L increase) (Table 7.2, Figure 7.3, Supplementary Figure 7.2).

Table 7.2 Associations for mean daily fluid balance and mean daily fluid input with ICU Mortality and 6-month GOSE

	ICU Mortality Worse short-term outcome		GOSE - ordinal Worse outcome at 6 months	
	OR + 95%CI	**p-value**	**OR + 95%CI**	**p-value**
Unadjusted – per 0.1L increase				
Mean daily positive fluid balance	1.10 (1.08 – 1.12)	<0.0001	1.06 (1.04 – 1.07)	<0.0001
Mean daily negative fluid balance	0.98 (0.94 – 1.02)	0.32	1.00 (0.98 – 1.03)	0.71
Mean daily fluid input	1.05 (1.04 – 1.06)	<0.0001	1.05 (1.04 – 1.05)	<0.0001
Adjusted* - per 0.1L increase				
Mean daily positive fluid balance	1.10 (1.07 – 1.12)	<0.00001	1.04 (1.02 – 1.05)	<0.0001
Mean negative fluid balance	0.96 (0.90 – 1.01)	0.11	0.99 (0.97 – 1.02)	0.68
Mean daily fluid input	1.05 (1.03 – 1.06)	<0.00001	1.04 (1.03 – 1.04)	<0.0001

*ICU=intensive care unit. GOSE=Glasgow Outcome Scale Extended. *Adjusted for age, Glasgow Coma Scale (GCS) motor score at baseline, pupillary reactivity, hypoxia, hypotension, Marshall CT classification, epidural haematoma, traumatic subarachnoid haemorrhage, first haemoglobin, first glucose, any major extracranial injury (Abbreviated Injury Scale ≥3), and a random intercept for centre.*

In all sensitivity analyses, similar effect estimates were observed (Supplementary Tables 7.3-7.14), although with less statistical certainty. Higher cerebral perfusion pressure was independently associated with better outcome, whereas higher serum sodium was independently associated with worse outcome. However, these confounders did not explain the association of higher fluid balance and input with worse outcome. In a propensity matched analysis (Supplementary Table 7.14), associations were similar, although with less statistical certainty.

The instrumental variable analyses confirmed the association of higher fluid balance with ICU mortality (OR 1.17, 95%CI: 1.05–1.29 per 0.1 L higher centre mean balance than overall mean balance) and worse functional outcome (1.07, [1.02–1.13], per 0.1 L higher centre mean balance than overall mean balance) but not the association of higher fluid input with ICU mortality (0.95, [0.90-1.00] per 0.1 L higher mean input than the overall mean) or functional outcome (1.01, [0.98–1.03] per 0.1 L higher mean input than the overall input) (Figure 7.4, see legend).

In 993 patients with intracranial pressure monitoring, daily higher positive fluid balance was not associated with higher maximum ICP (beta 0.24, [95% CI: -0.53 to 0.05] for every 1mmHg increase of intracranial pressure per L extra fluid balance), but it was associated with increased use of noradrenalin (beta 0.52, [95%CI: 0.10 to 0.94] for every 1 mg increased use of noradrenalin:), and with lower mean CPP (beta 0.70, [95%CI: 0.43 to 0.97], for every 1 mm Hg decrease of cerebral perfusion pressure per L extra fluid

balance) (Supplementary Figure 7.3). Daily fluid input higher than 3 L was associated with higher maximum ICP (beta 0.49 [95% CI 0.21 to 0.78] for every 1 mm Hg increase of intracranial pressure per L extra fluid input), lower mean cerebral perfusion pressure (beta 0.75 [0.49–1.02], for every 1 mm Hg decrease of cerebral perfusion pressure per L extra fluid input) and increased use of noradrenalin (beta 0.97 [0.56-1.39] for every 1 mg increased use of noradrenalin).

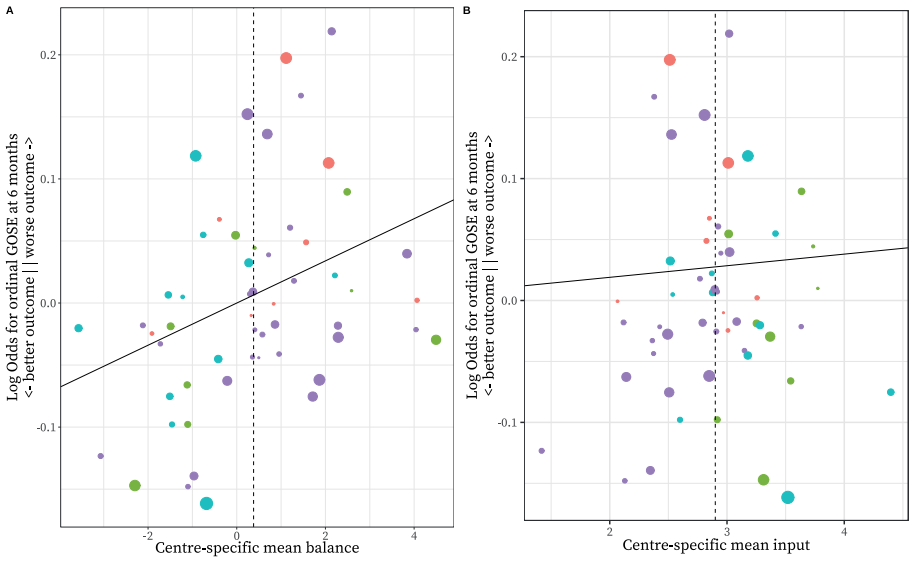

Figure 7.4 Scatterplot for the association between A] centre-specific mean balance and B] centre-specific mean input and log odds for ordinal GOSE at 6 months

(A) Scatterplot for the association between the centre-specific mean fluid balance for all centres and the log odds for ordinal Glasgow Outcome Scale Extended (GOSE) at 6 months. To account for the non-linearity of fluid balance, all centres that had an average negative mean balance were assigned a mean balance of 0. The dashed red line represents the overall mean (0.38 L). (B) Scatterplot for the association between the centre-specific mean fluid input per centre for all centres and the log odds for ordinal GOSE at 6 months. The dashed red line represents the overall mean (2.9 L). In both panels, increasing log odds indicate worse outcomes, and decreasing log odds indicate better outcomes. Both analyses were adjusted for the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT)-extended model (age, Glasgow Coma Scale [GCS] motor score, pupillary reaction, hypoxia, hypotension, Marshall CT classification, traumatic subarachnoid haemorrhage, epidural haematoma, first glucose, first haemoglobin), any major extracranial injury (Abbreviated Injury Scale [AIS] ≥3), and a random intercept for centre. The size of the dot indicates the number of patients per centre. The solid line represents the regression line. The colour of the dot indicates the region in which the centre was located according to the UN geoscheme.

DISCUSSION

In this large, prospective, multicentre study of critically ill patients with traumatic brain injury, we found substantial differences in fluid management policies between centres across Europe and Australia. Furthermore, we found that incrementally positive daily fluid balances were associated with worse clinical outcomes. These findings suggest that positive fluid balance might be an underappreciated factor contributing to adverse outcomes. This finding is clinically relevant since a positive fluid balance could be readily modifiable by less liberal fluid administration. Taken together with the previously published evidence, these results suggest that a policy aimed at stricter avoidance of both hypervolaemia and hypovolaemia during the whole ICU stay, as indicated by a mean overall neutral fluid balance, might improve clinical outcomes in critically ill patients with traumatic brain injury.

The substantial variation in our study is in line with earlier studies showing between-centre differences in intensive care management of patients with traumatic brain injut[2, 13]. Guidelines could help reduce treatment variation in clinical practice, and awareness of guidelines has increased[16]. The variation that we observed might be due to the fact that the Brain Trauma Foundation Guidelines do not include recommendations about fluid management[9]. More recently, a consensus statement on fluid therapy in patients in neurocritical care recommended aiming for normovolemia, integrating more than one circulatory variable to estimate volume status[17]. However the consensus statement also recommended avoiding restrictive fluid policies (negative fluid balances) and using fluid balances as a safety endpoint for fluid therapy. The recommendations did not include a specific statement on potential risks of positive fluid balances. In line with the study by Clifton and colleagues[3], in a subgroup analysis in patients with an ICP monitor, we found that more negative fluid balance was associated with worse outcome, although in the study by Clifton and colleagues[3] positive fluid balances were not associated with worse outcome. However, in a more recent trial by Clifton and colleagues of therapeutic hypothermia in patients with severe traumatic brain injury, higher daily fluid balances with hypothermia were associated with increased intracranial hypertension[4].

In our patient-level analyses, we controlled for measured confounders that are known to be independent predictors of outcome after traumatic brain injury. However, the possibility of residual confounding by indication always remains in observational studies analysed at a patient level. We therefore also performed an instrumental variable analysis[18, 19]. Although this analysis is less sensitive to confounding by indication, it is limited by a decrease in statistical power. This may explain why the association between fluid input and functional outcome was not statistically significant, as opposed

to the association with fluid balance. The concordance between both analyses allows for a less cautious interpretation of the association between positive fluid balance and worse functional outcome[12]. Moreover, the associations were largely similar in subgroup analyses. However, some subgroups were based on factors observed after fluid administration and should be interpreted with caution, and some associations in subgroup analyses had less statistical certainty, which might be explained by the fact that power to detect statistically significant effects within subgroups is by definition low. Additional adjustment for cerebral perfusion pressure and sodium, which were both perceived as strong potential confounders from a clinical perspective (e.g. given that especially low cerebral perfusion pressure could trigger fluid administration), did not have any effect on the association observed. The associations between increased fluid loading, lower cerebral perfusion pressure, and higher noradrenaline usage as a vasopressor are intriguing. However, the fact that lower cerebral perfusion pressure was independently associated with worse outcome when added as covariable, but did not affect the association of fluid balance and outcome, argues against cerebral perfusion pressure being a strong confounder. Nonetheless, this analysis does not imply that adverse effects of fluids are entirely independent from cerebral perfusion pressure [7, 11]. An additional complication in estimating effects of time-varying treatments is the potential of time-varying confounding; low cerebral perfusion pressure triggers fluid administration, which in turn might affect cerebral perfusion pressure. Adjustment for mean cerebral perfusion pressure over ICU stay fails to address this issue and might lead to biased estimates. However, the potential for bias becomes smaller with a longer time between treatment (and confounders) and outcome. The consistency of the effects on ICU mortality and GOSE at 6 months in the analysis with adjustment for (potentially time-varying) confounders such as cerebral perfusion pressure and mean arterial pressure, therefore indicates that the problem of time-varying confounding was unlikely to have had any effect in our study.

Several randomised clinical trials in neurocritical care support the notion that a less liberal fluid policy can be accomplished with the use of advanced hemodynamic monitoring and that such a policy might contribute to improved outcomes in patients with traumatic brain injury[20, 21]. This theory might be congruent with the fact that study centres with lower than median fluid balances did cardiac output monitoring more often than centres with higher than median fluid balances. Moreover, our findings build on a growing evidence base indicating that positive fluid balances may be detrimental in critical care (e.g. in acute respiratory distress syndrome or in septic shock after the resuscitation phase) [11, 17, 22, 23]. Furthermore, a vast body of evidence exists from the critical care literature indicating that large volumes of fluids are often administered unintentionally in intensive care (so-called “fluid creep”), and since we have no reason

to believe that patients with traumatic brain injury are exempt from such incidents, this practice might constitute an important target for improved management of these patients[24]. The SAFE-TBI study showed that fluid resuscitation with albumin 4% (being hypotonic to serum) as opposed to saline in patients with traumatic brain injury resulted in worse outcomes, suggesting that tonicity rather than amounts of fluids alone might have a significant impact[25]. However, adding serum sodium to our analyses, as an indicator of the net impact of hypertonic or hypotonic fluids being administered, did not change our results, while higher serum sodium was independently associated with worse outcome.

What might be the pathophysiological rationale for positive fluid balance being associated with harm in TBI? Capillary hydrostatic back-pressure to the brain might occur due to fluid overload and raised central venous, resulting in fluid accumulation into the brain interstitium. This situation might occur especially in the face of central venous pressure being close to intracranial pressure and when positive end-expiratory pressure is being applied in patients on mechanical ventilation[26]. In the injured brain, this situation will increase traumatic cerebral edema, further facilitated by blood-brain-barrier disruption[27]. Further, experimental studies in rodents and clinical work have indicated that isotonic fluids per se, and especially when given in excess, may increase cerebral or systemic complications[4, 11, 28]. In our analysis, the finding that fluid balance and intake were not strongly related to intracranial pressure may be explained by the fact that raised intracranial pressure is immediately acted upon with various medical therapies to decrease it and that the temporal resolution (up to hourly sampling) of our database may not have been sensitive enough to account for short intermittent intracranial pressure peaks.

Our study has several limitations. First, the case record form of the CENTER-TBI and OzENTER-TBI studies did not capture important physiological variables in detail, including: central venous pressure, positive end-expiratory pressure, fluid intake normalised to body-weight, exact reasons for fluid bolus, cardiac output data when monitored, differentiation between hyperosmolar fluids and maintenance fluids (including gastric feeds, volume administered as vehicle for medication), and the tonicity and amounts of different fluid types. Documentation of these variables over time could have contributed to mechanistic understanding of the associations observed. Second, we did not account for insensible fluid losses resulting in possible over-estimation of fluid balances. However, adding mean temperature to the multivariable analyses did not change our results (data not shown). Third, we recognise that traumatic brain injury is a complex and heterogeneous condition in which multiple treatments are used both during the acute and post-acute phase, and that it remains challenging to determine

any effect of a single treatment or policy on outcome assessed at 6 months. Fourth, the observational data in principle preclude causal inference. However, we applied advanced analytical approaches to deal with confounding by indication, yielding consistent results. The combination of the patient-level and instrumental variable approach with similar results, supports the validity of the main findings. Furthermore, fluid balance and fluid input were captured as continuous variables. This approach results in a gain of statistical power compared to earlier studies which categorized fluid balance and fluid input. Nevertheless, randomized controlled trials are essential to definitively assign causality to the relationships in this study. However, given the need to maintain a target cerebral perfusion pressure, such a trial would not simply address different strategies for fluid therapy; rather it might need to compare vasopressor dominant versus fluid dominant strategies to maintain cerebral perfusion pressure. A controlled before-after study aiming to implement mean neutral fluid balances (e.g. with a stepped wedge design), might be another option. Additionally, such studies might be facilitated by a management protocol using bedside hemodynamic monitors, such as ultrasound or cardiac output monitoring, to assess volume status[29], to align a general policy of avoiding both hypervolemia and hypovolemia with more personalized fluid management where appropriate. Finally, as part of any intervention to improve fluid management, the administration of fluids without a clear physiological rationale should be minimised.

In summary, fluid management of patients with TBI in the ICU varies substantially between centres, with positive fluid balances associated with worse outcomes. Together with the existing evidence, these results suggest that aiming for mean neutral fluid balances more rigorously, thereby avoiding both hypervolemia and hypovolemia, could improve clinical outcomes. However, further research is needed to investigate the implementation of these findings in clinical practice, taking into account cerebral perfusion pressure and adhering to personalized approaches when appropriate, for instance guided by routinely used hemodynamic monitors.

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SUPPLEMENTARY MATERIAL

Supplementary Table 7.1 Baseline characteristics, stratified for study (CENTER-TBI and OzENTER-TBI)

	CENTER-TBI (n=1928) **Fluid Balance** **< = median (0.37L)** **n=1001**
Age – median (IQR)	48 [31-64]
- > =65 years	250/1001 (25%)
Male sex	757/1001 (76%)
Pre-injury ASA-PS Classification	
A normal healthy patient	560/961 (58%)
A patient with mild systemic disease	304/961 (32%)
A patient with severe systemic disease	97/961 (10%)
History of cardiovascular disease	272/964 (28%)
Use of anticoagulants	51/950 (5.4%)
Use of antiplatelets	97/950 (10%)
GCS Baseline – median (IQR)	9 [4-14]
Mild (GCS: 13 – 15)	351/964 (36%)
Moderate (GCS: 9 – 12)	156/964 (16%)
Severe (GCS: 3 – 8)	457/964 (47%)
Pupillary reaction	
Both reacting	794/955 (83%)
Both unreactive	99/955 (10%)
One reacting	62/955 (6.5%)
Hypoxia Prehospital or at ER	118/951 (12%)
Hypotension Prehospital or at ER	120/952 (13%)
Any major extracranial injury (AIS>-3)	560/1001 (56%)
Marshall CT Classification	
- I	92/892 (10%)
- II	436/892 (49%)
- III	67/892 (7.5%)
- IV	13/892 (1.5%)
- V/VI	284/892 (32%)
Epidural Hematoma	193/888 (22%)
Traumatic Subarachnoid Haemorrhage	658/888 (74%)

CENTER-TBI (n=1928)		OzENTER-TBI (n=197)		
Fluid Balance > median (0.37L) n=927	**p-value**	**Fluid Balance <= median (0.37L) n=62**	**Fluid Balance > median (0.37L) n=135**	**p-value**
53 [33-67]	0.002	44[26-62]	44[24-67]	0.83
271/927 (29%)	0.04	14/62 (23%)	37/135 (27%)	0.59
661/927 (71%)	0.04	48/62 (77%)	100/135(74%)	0.74
	0.19			0.58
479/884 (54%)		4/61 (72%)	84/129 (65%)	
301/884 (34%)		14/61 (23%)	39/129 (30%)	
104/884 (12%)		3/61 (4.9%)	6/129 (4.7%)	
275/879 (31%)	0.17	13/54 (24%)	36/98 (37%)	0.16
57/866 (6.6%)	0.32	4/57 (7.0%)	5/127 (4.0%)	0.61
104/866 (12%)	0.25	5/57 (8.8%)	16/126 (13%)	0.60
8 [3-14]	0.04	7 [3-10]	8 [3-13]	0.04
282/872 (32%)	0.18	8/60 (13%)	40/133 (30%)	0.04
145/872 (17%)		13/60 (22%)	26/133 (20%)	
445/872 (51%)		39/60 (65%)	67/133 (50%)	
	0.02			0.17
690/883 (78%)		43/60 (72%)	110/132(83%)	
125/883 (14%)		11/60 (18%)	15/132 (11%)	
68/883 (7.7%)		6/60 (10%)	7/132 (5.3%)	
128/850 (15%)	0.12	19/61 (31%)	35/131 (27%)	0.64
128/864 (15%)	0.19	19/62 (19%)	45/132 (34%)	0.05
536/927 (58%)	0.43	24/62 (39%)	82/135 (61%)	0.01
	0.57			0.18
79/810 (9.8%)		1/59 (1.7%)	11/118 (9.3%)	
370/810 (46%)		37/59 (63%)	58/118 (49%)	
72/810 (8.9%)		3/59 (5.1%)	11/118 (9.3%)	
11/810 (1.4%)		2/59 (3.4%)	2/118 (1.7%)	
278/810 (34%)		16/59 (27%)	36/118 (31%)	
135/808 (17%)	0.01	13/59 (22%)	23/118 (20%)	0.84
607/808 (75%)	0.67	44/59 (75%)	83/118 (70%)	0.68

Supplementary Table 7.1 Continued

	CENTER-TBI (n=1928) **Fluid Balance** **< = median (0.37L)** **n=1001**
Treatment characteristics	
Any use of vasopressors during ICU stay	488/954 (51%)
ICP Monitor	435/1001 (44%)
Colloids	131/991 (13%)
Any administration of hypertonic saline	186/1001 (19%)
Any administration of mannitol	114/1001 (11%)
Cranial Surgery	382/990 (39%)
Extracranial Surgery	288/991 (29%)
Central Venous Pressure Monitoring	438/998 (44%)
Cardiac Output Monitoring	136/998 (14%)
Renal Replacement Therapy	17/1000 (1.7%)
Clinical Parameters during ICU stay	
Mean CPP during ICU stay	75 [70-80]
Mean Sodium during ICU stay	141 [139-144]
Complications and Outcomes	
Respiratory Failure	191/994 (19%)
Ventilator Associated Pneumonia	128/994 (13%)
ICU Length of Stay	6.7 [2.1-15]
ICU Mortality	88/995 (8.8%)
Mortality at 6 months	146/874 (17%)
Predicted probability of mortality at 6 months – IMPACT CT	29%
Unfavourable Outcome at 6 months (GOSE <5)	349/874 (40%)
Predicted probability of unfavourable outcome at 6 months – IMPACT CT	47%

CENTER-TBI (n=1928)		OzENTER-TBI (n=197)		
Fluid Balance > median (0.37L) n=927	**p-value**	**Fluid Balance <= median (0.37L) n=62**	**Fluid Balance > median (0.37L) n=135**	**p-value**
539/884 (61%)	<0.0001	39/54 (72%)	79/110 (72%)	1
442/927 (48%)	0.07	39/62 (63%)	77/135 (57%)	0.53
197/919 (21%)	<0.0001	1/62 (1.6%)	9/135 (6.7%)	0.25
198/927 (21%)	0.14	25/62 (40%)	54/135 (40%)	1
140/927 (15%)	0.02	7/62 (11%)	15/135 (11%)	1
384/926 (42%)	0.22	36/60 (60%)	75/135 (56%)	0.67
272/926 (29%)	0.92	25/59 (42%)	66/134 (49%)	0.47
376/926 (41%)	0.16	47/62 (76%)	100/135 (74%)	0.93
155/927 (17%)	0.07	0/0 (0%)	1/135 (0.7%)	1
33/925 (3.6%)	0.02	2/62 (3.2%)	4/135 (3.0%)	1
74 [69-78]	0.02	76 [72 – 78]	70 [66 – 73]	0.001
141 [139-144]	0.18	139 [137-141]	140 [138-142]	0.43
251/918 (27%)	<0.0001	33/62 (53%)	41/135 (30%)	0.004
144/918 (16%)	0.09	17/62 (27%)	29/135 (22%)	0.46
6.7[2.0-16]	0.68	8.6[4.7 – 12]	5.7 [2.8 – 11]	0.05
162/920 (18%)	<0.0001	9/62 (15%)	24/135 (18%)	0.72
221/795 (28%)	<0.0001	12/54 (22%)	28/121 (23%)	1
34%	<0.0001	42%	38%	<0.0001
399/795 (50%)	<0.0001	31/54 (57%)	74/121 (61%)	0.76
53%	<0.0001	63%	59%	<0.0001

Supplementary Table 7.2 Centre characteristics, stratified for centres that had a mean daily fluid balance and input lower than/equal or higher to the median of all centres

Age – median (IQR)
> =65 years –mean [min-max]
Male sex – mean [min-max]
Pre-injury ASA-PS Classification
A normal healthy patient – mean [min-max]
A patient with mild systemic disease – mean [min-max]
A patient with severe systemic disease – mean [min-max]
History of cardiovascular disease – mean [min-max]
Use of anticoagulants – mean [min-max]
Use of antiplatelets – mean[min-max]
GCS Baseline – median (IQR)
Mild (GCS: 13 – 15) – mean [min-max]
Moderate (GCS: 9 – 12) -mean [min-max]
Severe (GCS: 3 – 8) – mean [min-max]
Pupillary reaction
Both reacting – mean [min-max]
Both unreactive – mean[min-max]
One reacting -mean[min-max]
Hypoxia Prehospital or at ER – mean[min-max]
Hypotension Prehospital or at ER -mean [min-max]
Any major extracranial injury (AIS > -3) -mean [min-max]
Marshall CT Classification
I – mean[min-max]
II– mean[min-max]
III– mean[min-max]
IV– mean[min-max]
V/VI– mean[min-max]
Epidural Hematoma – mean[min-max]
Traumatic Subarachnoid Haemorrhage– mean[min-max]

	Per centre		Per centre	
	Fluid Balance <= median (0.39L) n=28	**Fluid Balance > median (0.39L) n=27**	**Fluid Input <=median (2.96L) n=28**	**Fluid Input >median (2.96L) n=27**
	50 [41 – 55]	52 [46-58]	53 [42 – 58]	48 [43 – 55]
	24% [11%-33%]	29% [20%-38%]	27% [0%-65%]	25% [0-57%]
	76% [56% - 100%]	76% [55%-100%]	77% [60%-100%]	74%[55%-100%]
	60% [22%-92%]	56% [21%-100%]	59%[21%-100%]	57%[22%-100%]
	33% [7.7% -64%]	32% [0%-59%]	33%[0%-79%]	32%[0%-50%]
	7.0%[0%-25%]	13% [0%-46%]	8.3% [0%-46%]	11% [0%-44%]
	30% [7.8%-67%]	32% [0%-62%]	28% [0%-58%]	34%[11%-67%]
	4.8% [0%-33%]	7.5% [0%-38%]	4.5% [0%-21%]	7.8%[0%-38%]
	9.6% [0%-27%]	11% [0%-21%]	11% [0%-27%]	9.7%[0%-19%
	9 [7-12]	7 [6-8]	8 [7-10]	8 [7-11]
	38% [5.3%-100%]	27%[0%-55%]	32% [0%-71%]	33% [8.3%-100%]
	15% [0%-33%]	17% [0%-50%]	16% [0%-50%]	16% [0%-33%]
	47% [0%-89%]	56% [23%-100%]	53% [14%-100%]	50% [0%-83%]
	83% [50%-100%]	80% [56%-100%]	84% [67%-100%]	79% [50%-100%]
	11%[0%-39%]	11%[0%-27%]	10% [0%-29%]	12% [0%-29%]
	5.7% [0%-22%]	9.2%[0%-33%]	6.2% [0%-22%]	8.7% [0%-33%]
	13%[0%-33%]	17%[0%-50%]	14% [0%-50%]	17% [0%-33%]
	14%[0%-43%]	17% [0%-67%]	11 [0%-43%]	19% [0%-67%]
	58% [44%-100%]	51% [45%-100%	53% [0%-100%]	56%[7.7%-100%]
	9.6% [0%-30%]	8.3% [0%-25%]	8.3% [0%-26%]	9.6% [0%-30%]
	50% [33%-100%]	46% [0%-100%]	45% [0%-77%]	51% [27%-100%]
	6.9% [0%-31%]	8.8% [0%-27%]	8.5% [0%-31%]	7.1%[0%-21%]
	1.1% [0%-10%]	1.8%[0%-10%]	2.0% [0%-10%]	0.9% [0%-9.1%]
	33% [0%-67%]	35% [0%-100%]	36% [7.7%-100%]	31% [0%-55%]
	21% [0%-33%]	20% [0%-50%]	20% [0%-50%]	20% [0%-50%]
	77%[54%-100%]	78%[57%-100%]	77% [54%-100%]	78% [55%-100%]

Supplementary Table 7.2 Continued

Treatments during ICU stay
Any use of vasopressors during ICU stay– mean[min-max]
ICP Monitor– mean[min-max]
Colloids– mean[min-max]
Hypertonic Saline – mean[min-max]
Mannitol– mean[min-max]
Cranial Surgery– mean[min-max]
Extracranial Surgery– mean[min-max]
Central Venous Pressure Monitoring– mean[min-max]
Cardiac Output Monitoring – mean[min-max]
Renal Replacement Therapy– mean[min-max]
Clinical Parameters during ICU stay
Mean CPP during ICU stay -median (IQR)
Mean Sodium during ICU stay – median (IQR)
Complications and Outcomes
Respiratory Failure– mean[min-max]
Ventilator Associated Pneumonia– mean[min-max]
ICU Length of Stay – days – median (IQR)
ICU Mortality– mean[min-max]
Mortality at 6 months– mean[min-max]
Predicted probability of mortality at 6 months – IMPACT CT median (IQR)
Unfavourable Outcome at 6 months (GOSE <5)– mean[min-max]
Predicted probability of unfavourable outcome at 6 months – IMPACT CT – median (IQR)

For each centre, the percentage of patients that received or had one of the above categorical characteristics was calculated. For continuous variables, the median value per centre was calculated. Subsequently all centres were stratified according to whether the median of the mean daily fluid balance or input of that centre was higher than the median of that particular centre. Then the mean percentage and corresponding minimum percentage and maximum percentages for all categorical variables and medians for all continuous variables were calculated.

	Per centre		Per centre	
	Fluid Balance <= median (0.39L) n=28	**Fluid Balance > median (0.39L) n=27**	**Fluid Input <=median (2.96L) n=28**	**Fluid Input >median (2.96L) n=27**
	52% [0% - 91%]	60% [0% - 100%]	53% [0% - 100%]	59% [0% - 91%]
	49% [0%-100%]	50% [18%-94%]	43% [0% - 75%]	56% [19% - 100%]
	19% [0% - 100%]	20% [0% - 100%]	16% [0% - 100%]	23% [0% - 100%]
	20% [0% - 89%]	25% [0%-92%]	19% [0% - 56%]	26% [0% - 92%]
	11% [0%-78%]	20% [0%-100%]	16% [0% - 100%]	16% [0% - 78%]
	46% [7.1%-90%]	50% [6.9%-100%]	42%[6.9%- 100%]	54% [17% - 100%]
	31% [0%-100%]	29% [0%-100%]	21% [0% - 48%]	41% [0% - 100%]
	47% [0%-97%]	40% [0%-100%]	38% [0% - 89%]	50% [0% - 100%]
	21% [0%-100%]	14%[0%-70%]	22% [0% - 100%]	13% [0% - 100%]
	2.2% [0%-11%]	5.3% [0%-35%]	1.8% [0% - 12%]	5.8% [0% - 35%]
	76 [71 – 78]	73 [72 – 75]	74 [71 – 77]	74 [73 – 76]
	141 [140 – 142]	140 [139- 141]	140 [140 – 142]	141 [140 – 142]
	26% [0% - 78%]	26% [0% - 60%]	27% [0% - 57%]	25% [0% - 78%]
	20% [0% - 70%]	14% [0% - 50%]	21% [0% - 70%]	13% [0% - 56%]
	7.5 [4.9 – 12]	6.2 [4.4 – 11]	6.8 [4.1 – 12]	6.9 [5.1 – 10]
	12% [0%-50%]	15% [0%-35%]	14% [0% - 50%]	13% [0% - 35%]
	18% [0% - 64%]	31% [0% - 100%]	25% [0% - 100%]	24% [0% - 74%]
	23% [19% - 28%]	28% [23% -34%]	24% [19% - 28%]	27% [19% - 34%]
	41% [0% - 67%]	53% [0% - 100%]	44% [0% - 100%]	49% [0% - 75%]
	46% [39% - 53%]	53% [46% - 59%]	46% [39% - 53%]	51% [39% - 59%]

**ASA-PS = The American Society of Anesthesiologists (ASA) physical status classification system. CPP: Cerebral Perfusion Pressure. The IMPACT CT model was used to calculate the expected mortality and expected proportion of patients with unfavourable outcome at 6 months in patients included in this study. The IMPACT CT (International Mission for Prognosis and Analysis of Clinical Trials in TBI Computed Tomography) model was developed for predicting 6 month outcome in adult patients with moderate to severe head injury using their key covariates.*

Supplementary Table 7.3a Associations for mean daily fluid balance and mean daily fluid input with ICU Mortality and 6-month GOSE. Sensitivity analysis in patients without any major extracranial injury (n= 923)

	ICU Mortality Worse short-term outcome		GOSE - ordinal worse outcome at 6 months	
	OR + 95%CI	p-value	OR + 95%CI	p-value
Unadjusted – per 0.1L increase				
Mean daily positive fluid balance	1.09 (1.06 – 1.13)	< 0.0001	1.06 (1.03 – 1.08)	< 0.0001
Mean daily negative fluid balance	0.98 (0.93 – 1.05)	0.62	1.00 (0.97 – 1.04)	0.96
Mean daily fluid input	1.03 (1.02 – 1.05)	0.0002	1.04 (1.03 – 1.05)	< 0.0001
Adjusted* - per 0.1L increase				
Mean daily positive fluid balance	1.07 (1.03 – 1.12)	0.0002	1.03 (1.00 – 1.06)	0.02
Mean daily negative fluid balance	0.98 (0.91-1.07)	0.67	0.98 (0.94 – 1.02)	0.34
Mean daily fluid input	1.04 (1.02 – 1.05)	0.0001	1.03 (1.01 – 1.04)	0.0003

Supplementary Table 7.3b Associations for mean daily fluid balance and mean daily fluid input with ICU Mortality and 6-month GOSE. Sensitivity analysis in patients with any major extracranial injury (n= 1202)

	ICU Mortality Worse short-term outcome		GOSE - ordinal worse outcome at 6 months	
	OR + 95%CI	p-value	OR + 95%CI	p-value
Unadjusted – per 0.1L increase				
Mean daily positive fluid balance	1.11 (1.08 – 1.13)	< 0.0001	1.06 (1.04 – 1.07)	< 0.0001
Mean daily negative fluid balance	0.98 (0.93 – 1.04)	0.41	1.01 (0.98 – 1.04)	0.68
Mean daily fluid input	1.06 (1.04 – 1.07)	< 0.0001	1.05 (1.04 – 1.06)	< 0.0001
Adjusted* - per 0.1L increase				
Mean daily positive fluid balance	1.12 (1.08 – 1.15)	< 0.0001	1.04 (1.02 – 1.05)	< 0.0001
Mean daily negative fluid balance	0.95 (0.88 - 1.02)	0.15	0.99 (0.96 – 1.02)	0.62
Mean daily fluid input	1.05 (1.03 – 1.08)	< 0.0001	1.04 (1.02 – 1.05)	< 0.0001

**Adjusted for the IMPACT-extended model (Age, GCS Motor Score at Baseline, Pupillary Reactivity, Hypoxia, Hypotension, Marshall CT Classification, Epidural Hematoma, Traumatic Subarachnoid Hemorrhage, First Hb, First Glucose), and a random intercept for centre. The p-value for interaction between any major extracranial injury and fluid balance was 0.69 for ICU mortality and 0.94 for GOSE at 6 months. The p-value for interaction between any major extracranial injury and fluid input was 0.06 for ICU mortality and 0.18 for GOSE at 6 months.*

Supplementary Table 7.4a Associations for mean daily fluid balance and mean daily fluid input with ICU Mortality and 6-month GOSE. Sensitivity analysis in patients with hypotension in the pre-hospital phase or Emergency Room (n= 305)

	ICU Mortality Worse short-term outcome		GOSE - ordinal Worse outcome at 6 months	
	OR + 95%CI	p-value	OR + 95%CI	p-value
Unadjusted – per 0.1L increase				
Mean daily positive fluid balance	1.09 (1.06 – 1.13)	< 0.0001	1.06 (1.03 – 1.09)	0.0001
Mean daily negative fluid balance	0.94 (0.86 – 1.05)	0.26	0.96 (0.89 – 1.03)	0.25
Mean daily fluid input	1.03 (1.01 – 1.05)	0.001	1.03 (1.01 – 1.05)	0.001
Adjusted* - per 0.1L increase				
Mean daily positive fluid balance	1.10 (1.05 – 1.16)	0.0003	1.04 (1.01 – 1.08)	0.008
Mean daily negative fluid balance	0.92 (0.82 – 1.04)	0.19	0.97 (0.89 – 1.05)	0.46
Mean daily fluid input	1.02 (0.99 – 1.05)	0.16	1.03 (1.00 – 1.05)	0.02

Supplementary Table 7.4b Associations for mean daily fluid balance and mean daily fluid input with ICU Mortality and 6-month GOSE. Sensitivity analysis in patients that did not have hypotension in the pre- hospital phase or Emergency Room (n= 1830)

	ICU Mortality Worse short-term outcome		GOSE - ordinal Worse outcome at 6 months	
	OR + 95%CI	p-value	OR + 95%CI	p-value
Unadjusted – per 0.1L increase				
Mean daily positive fluid balance	1.10 (1.07 – 1.12)	< 0.0001	1.05 (1.04 – 1.07)	< 0.0001
Mean daily negative fluid balance	0.98 (0.94 – 1.04)	0.47	1.01 (0.98 – 1.03)	0.59
Mean daily fluid input	1.05 (1.03 – 1.06)	< 0.0001	1.04 (1.04 – 1.05)	< 0.0001
Adjusted* - per 0.1L increase				
Mean daily positive fluid balance	1.10 (1.06 – 1.13)	< 0.0001	1.03 (1.02 – 1.05)	< 0.0001
Mean daily negative fluid balance	0.96 (0.90 – 1.02)	0.21	1.00 (0.97 – 1.02)	0.93
Mean daily fluid input	1.06 (1.04 – 1.08)	< 0.0001	1.03 (1.02 – 1.04)	< 0.0001

**Adjusted for the IMPACT-extended model (Age, GCS Motor Score at Baseline, Pupillary Reactivity, Hypoxia, Marshall CT Classification, Epidural Hematoma, Traumatic Subarachnoid Hemorrhage, First Hb, First Glucose), and a random intercept for centre. The p-value for interaction between hypotension in the pre-hospital phase or Emergency Room and fluid balance was 0.77 for ICU mortality and 0.64 for GOSE at 6 months. The p-value for interaction between hypotension in the pre-hospital phase or Emergency Room and fluid input was 0.15 for ICU mortality and 0.76 for GOSE at 6 months.*

Supplementary Table 7.5a Associations for mean daily fluid balance and mean daily fluid input with ICU Mortality and 6-month GOSE. Sensitivity analysis in patients that received hypertonic saline (n =463)

	ICU Mortality Worse short-term outcome		GOSE - ordinal Worse outcome at 6 months	
	OR + 95%CI	p-value	OR + 95%CI	p-value
Unadjusted – per 0.1L increase				
Mean daily positive fluid balance	1.14 (1.10 – 1.20)	<0.0001	1.09 (1.06 – 1.13)	<0.0001
Mean daily negative fluid balance	0.95 (0.88 – 1.03)	0.20	0.98 (0.93 – 1.04)	0.49
Mean daily fluid input	1.04 (1.02 – 1.06)	0.0003	1.02 (1.01 – 1.04)	0.005
Adjusted* - per 0.1L increase				
Mean daily positive fluid balance	1.12 (1.07 – 1.18)	<0.0001	1.07 (1.03 – 1.11)	0.0004
Mean daily negative fluid balance	0.93 (0.85 – 1.02)	0.12	0.98 (0.92 – 1.04)	0.48
Mean daily fluid input	1.05 (1.02 – 1.08)	0.0004	1.03 (1.01 – 1.05)	0.002

Supplementary Table 7.5b Associations for mean daily fluid balance and mean daily fluid input with ICU Mortality and 6-month GOSE. Sensitivity analysis in patients that did not receive hypertonic saline (n=1662)

	ICU Mortality Worse short-term outcome		GOSE - ordinal Worse outcome at 6 months	
	OR + 95%CI	p-value	OR + 95%CI	p-value
Unadjusted – per 0.1L increase				
Mean daily positive fluid balance	1.09 (1.07 – 1.12)	<0.0001	1.05 (1.03 – 1.06)	<0.0001
Mean daily negative fluid balance	0.98 (0.94 – 1.04)	0.47	1.01 (0.98 – 1.03)	0.65
Mean daily fluid input	1.04 (1.03 – 1.05)	<0.0001	1.04 (1.03 – 1.05)	<0.0001
Adjusted* - per 0.1L increase				
Mean daily positive fluid balance	1.09 (1.06 – 1.12)	<0.0001	1.03 (1.01 – 1.04)	0.0005
Mean daily negative fluid balance	0.97 (0.92 – 1.02)	0.25	1.00 (0.97 – 1.03)	0.99
Mean daily fluid input	1.03 (1.01 – 1.05)	0.0006	1.03 (1.02 – 1.04)	<0.0001

**Adjusted for the IMPACT-extended model (Age, GCS Motor Score at Baseline, Pupillary Reactivity, Hypoxia, Hypotension, Marshall CT Classification, Epidural Hematoma, Traumatic Subarachnoid Hemorrhage, First Hb, First Glucose), any major extracranial injury (AIS>=3) and a random intercept for centre. The p-value for interaction between any administration of hypertonic saline and fluid balance was 0.15 for ICU mortality and 0.14 for GOSE at 6 months. The p-value for interaction between any administration of hypertonic saline and fluid input was 0.62 for ICU mortality and 0.58 for GOSE at 6 months.*

Supplementary Table 7.6a Associations for mean daily fluid balance and mean daily fluid input with ICU Mortality and 6-month GOSE. Sensitivity analysis in patients that received mannitol (n= 276)

	ICU Mortality Worse short-term outcome		GOSE - ordinal Worse outcome at 6 months	
	OR + 95%CI	p-value	OR + 95%CI	p-value
Unadjusted – per 0.1L increase				
Mean daily positive fluid balance	1.15 (1.10 – 1.22)	<0.0001	1.09 (1.05 – 1.14)	<0.0001
Mean daily negative fluid balance	0.90 (0.80 – 1.04)	0.13	0.93 (0.84 – 1.02)	0.13
Mean daily fluid input	1.05 (1.02 – 1.07)	0.0003	1.03 (1.01 – 1.05)	0.01
Adjusted* - per 0.1L increase				
Mean daily positive fluid balance	1.17 (1.09 – 1.25)	<0.0001	1.08 (1.03 – 1.13)	0.0007
Mean daily negative fluid balance	0.88 (0.75 – 1.03)	0.12	0.92 (0.82 – 1.04)	0.18
Mean daily fluid input	1.05 (1.01 – 1.08)	0.01	1.04 (1.01 – 1.07)	0.005

Supplementary Table 7.6b Associations for mean daily fluid balance and mean daily fluid input with ICU Mortality and 6-month GOSE. Sensitivity analysis in patients that did not receive mannitol (n= 1849)

	ICU Mortality Worse short-term outcome		GOSE - ordinal Worse outcome at 6 months	
	OR + 95%CI	p-value	OR + 95%CI	p-value
Unadjusted – per 0.1L increase				
Mean daily positive fluid balance	1.09 (1.07 – 1.11)	<0.0001	1.05 (1.03 – 1.06)	<0.0001
Mean daily negative fluid balance	0.98 (0.94 – 1.03)	0.46	1.01 (0.98 – 1.03)	0.54
Mean daily fluid input	1.04 (1.03 – 1.05)	<0.0001	1.04 (1.04 – 1.05)	<0.0001
Adjusted* - per 0.1L increase				
Mean daily positive fluid balance	1.09 (1.06 – 1.12)	<0.0001	1.03 (1.01 – 1.04)	0.0001
Mean daily negative fluid balance	0.96 (0.91 – 1.03)	0.25	1.00 (0.98 – 1.03)	0.98
Mean daily fluid input	1.04 (1.02 – 1.06)	<0.0001	1.03 (1.02 – 1.04)	<0.0001

**Adjusted for the IMPACT-extended model (Age, GCS Motor Score at Baseline, Pupillary Reactivity, Hypoxia, Hypotension, Marshall CT Classification, Epidural Hematoma, Traumatic Subarachnoid Hemorrhage, First Hb, First Glucose), any major extracranial injury (AIS>=3) and a random intercept for centre. The p-value for interaction between any administration of mannitol and fluid balance was 0.06 for ICU mortality and 0.08 for GOSE at 6 months. The p-value for interaction between any administration of mannitol and fluid input was 0.41 for ICU mortality and 0.57 for GOSE at 6 months.*

Supplementary Table 7.7a Associations for mean daily fluid balance and mean daily fluid input with ICU Mortality and 6-month GOSE. Sensitivity analysis in patients with an ICU length of stay of at least 3 days (n=1449)

	ICU Mortality Worse short-term outcome		GOSE - ordinal Worse outcome at 6 months	
	OR + 95%CI	p-value	OR + 95%CI	p-value
Unadjusted – per 0.1L increase				
Mean daily positive fluid balance	1.11 (1.08 – 1.14)	<0.0001	1.06 (1.04 – 1.09)	<0.0001
Mean daily negative fluid balance	1.00 (0.94 – 1.07)	0.98	1.02 (0.99 – 1.05)	0.28
Mean daily fluid input	1.04 (1.02 – 1.05)	<0.0001	1.03 (1.02 – 1.04)	<0.0001
Adjusted* - per 0.1L increase				
Mean daily positive fluid balance	1.11 (1.07 – 1.14)	<0.0001	1.05 (1.03 – 1.07)	<0.0001
Mean daily negative fluid balance	0.98 (0.91 – 1.05)	0.58	1.01 (0.98 – 1.04)	0.63
Mean daily fluid input	1.06 (1.03 – 1.08)	<0.0001	1.04 (1.03 – 1.05)	<0.0001

Supplementary Table 7.7b Associations for mean daily fluid balance and mean daily fluid input with ICU Mortality and 6-month GOSE. Sensitivity analysis in patients with an ICU length of stay shorter than days (n=676)

	ICU Mortality Worse short-term outcome		GOSE - ordinal Worse outcome at 6 months	
	OR + 95%CI	p-value	OR + 95%CI	p-value
Unadjusted – per 0.1L increase				
Mean daily positive fluid balance	1.09 (1.06 – 1.11)	<0.0001	1.06 (1.04 – 1.08)	<0.0001
Mean daily negative fluid balance	0.96 (0.91 – 1.01)	0.13	0.98 (0.95 – 1.02)	0.40
Mean daily fluid input	1.07 (1.05 – 1.09)	<0.0001	1.04 (1.03 – 1.05)	<0.0001
Adjusted* - per 0.1L increase				
Mean daily positive fluid balance	1.09 (1.03 - 1.15)	0.004	1.02 (1.00 – 1.04)	0.06
Mean daily negative fluid balance	0.95 (0.85 – 1.07)	0.41	0.99 (0.95 – 1.03)	0.73
Mean daily fluid input	1.07 (1.03 – 1.10)	0.0002	1.02 (1.00 – 1.03)	0.03

**Adjusted for the IMPACT-extended model (Age, GCS Motor Score at Baseline, Pupillary Reactivity, Hypoxia, Hypotension, Marshall CT Classification, Epidural Hematoma, Traumatic Subarachnoid Hemorrhage, First Hb, First Glucose), any major extracranial injury (AIS>=3) and a random intercept for centre. The p-value for interaction between ICU length of stay shorter or longer than three days and fluid balance was 0.08 for ICU mortality and 0.33 for GOSE at 6 months. The p-value for interaction between ICU length of stay shorter or longer than three days and fluid input was 0.29 for ICU mortality and 0.78 for GOSE at 6 months.*

Supplementary Table 7.8a Associations for mean daily fluid balance and mean daily fluid input with ICU Mortality and 6-month GOSE. Sensitivity analysis in patients that had a raised ICP (ICP > 20 mmHg) at least once during ICU stay (n = 516)

	ICU Mortality Worse short-term outcome		GOSE - ordinal Worse outcome at 6 months	
	OR + 95%CI	p-value	OR + 95%CI	p-value
Unadjusted – per 0.1L increase				
Mean daily positive fluid balance	1.13 (1.09 – 1.18)	< 0.0001	1.09 (1.06 – 1.13)	< 0.0001
Mean daily negative fluid balance	0.93 (0.87 – 1.00)	0.04	0.96 (0.91 – 1.02)	0.23
Mean daily fluid input	1.01 (1.00 – 1.03)	0.08	1.01 (0.99 – 1.02)	0.21
Adjusted* - per 0.1L increase				
Mean daily positive fluid balance	1.11 (1.06 – 1.16)	< 0.0001	1.06 (1.02 – 1.09)	0.002
Mean daily negative fluid balance	0.90 (0.82 – 0.98)	0.02	0.97 (0.91 – 1.04)	0.38
Mean daily fluid input	1.02 (1.00 – 1.04)	0.07	1.01 (0.99 – 1.03)	0.16

Supplementary Table 7.8b Associations for mean daily fluid balance and mean daily fluid input with ICU Mortality and 6-month GOSE. Sensitivity analysis in patients that did not have a raised ICP (ICP > 20 mmHg) during ICU stay (n = 1609)

	ICU Mortality Worse short-term outcome		GOSE - ordinal Worse outcome at 6 months	
	OR + 95%CI	p-value	OR + 95%CI	p-value
Unadjusted – per 0.1L increase				
Mean daily positive fluid balance	1.09 (1.07 – 1.12)	< 0.0001	1.04 (1.03 – 1.06)	< 0.0001
Mean daily negative fluid balance	0.98 (0.92 – 1.05)	0.63	1.00 (0.98 – 1.03)	0.74
Mean daily fluid input	1.04 (1.02 – 1.06)	< 0.0001	1.04 (1.03 – 1.05)	< 0.0001
Adjusted* - per 0.1L increase				
Mean daily positive fluid balance	1.10 (1.07 – 1.13)	< 0.0001	1.03 (1.01 – 1.04)	0.0001
Mean daily negative fluid balance	0.99 (0.93 – 1.05)	0.74	1.00 (0.97 – 1.02)	0.74
Mean daily fluid input	1.04 (1.02 – 1.05)	< 0.0001	1.03 (1.02 – 1.04)	< 0.0001

**Adjusted for the IMPACT-extended model (Age, GCS Motor Score at Baseline, Pupillary Reactivity, Hypoxia, Hypotension, Marshall CT Classification, Epidural Hematoma, Traumatic Subarachnoid Hemorrhage, First Hb, First Glucose), any major extracranial injury (AIS > =3) and a random intercept for centre. The p-value for interaction between a raised ICP (ICP > 20 mmHg) at least once during ICU stay and fluid balance was 0.33 for ICU mortality and 0.08 for GOSE at 6 months. The p-value for interaction between a raised ICP (ICP > 20 mmHg) at least once during ICU stay and fluid input was 0.20 for ICU mortality and 0.16 for GOSE at 6 months.*

Supplementary Table 7.9a Associations for mean daily fluid balance and mean daily fluid input with ICU Mortality and 6-month GOSE. Sensitivity analysis in patients that received ICP monitoring during ICU stay (n=993)

	ICU Mortality Worse short-term outcome		GOSE - ordinal Worse outcome at 6 months	
	OR + 95%CI	p-value	OR + 95%CI	p-value
Unadjusted – per 0.1L increase				
Mean daily positive fluid balance	1.13 (1.09 – 1.16)	<0.0001	1.08 (1.05 – 1.10)	<0.0001
Mean daily negative fluid balance	0.94 (0.89 – 1.00)	0.03	0.99 (0.95 – 1.03)	0.54
Mean daily fluid input	1.04 (1.02 – 1.05)	<0.0001	1.02 (1.01 – 1.03)	0.0006
Adjusted* - per 0.1L increase**				
Mean daily positive fluid balance	1.12 (1.08 – 1.15)	<0.0001	1.06 (1.03 – 1.09)	<0.0001
Mean daily negative fluid balance	0.91 (0.85 – 0.98)	0.009	0.98 (0.93 – 1.02)	0.30
Mean daily fluid input	1.05 (1.03 – 1.08)	<0.0001	1.03 (1.02 – 1.05)	<0.0001

Supplementary Table 7.9b Associations for mean daily fluid balance and mean daily fluid input with ICU Mortality and 6-month GOSE. Sensitivity analysis in patients that did not receive ICP monitoring during ICU stay (n=1132)

	ICU Mortality Worse short-term outcome		GOSE - ordinal Worse outcome at 6 months	
	OR + 95%CI	p-value	OR + 95%CI	p-value
Unadjusted – per 0.1L increase				
Mean daily positive fluid balance	1.09 (1.06 – 1.12)	<0.0001	1.05 (1.03 – 1.07)	<0.0001
Mean daily negative fluid balance	1.03 (0.93 – 1.08)	0.93	0.99 (0.96 – 1.02)	0.60
Mean daily fluid input	1.04 (1.03 – 1.06)	<0.0001	1.03 (1.02 – 1.05)	<0.0001
Adjusted* - per 0.1L increase				
Mean daily positive fluid balance	1.09 (1.04 – 1.13)	0.0001	1.02 (1.01 – 1.04)	0.01
Mean daily negative fluid balance	1.06 (0.96 – 1.18)	0.25	1.00 (0.97 – 1.03)	0.77
Mean daily fluid input	1.04 (1.01 – 1.07)	0.005	1.02 (1.01 – 1.03)	0.002

**Adjusted for the IMPACT-extended model (Age, GCS Motor Score at Baseline, Pupillary Reactivity, Hypoxia, Hypotension, Marshall CT Classification, Epidural Hematoma, Traumatic Subarachnoid Hemorrhage, First Hb, First Glucose), any major extracranial injury (AIS>=3) and a random intercept for centre. The p-value for interaction between ICP monitoring and fluid balance was 0.03 for ICU mortality and 0.08 for GOSE at 6 months. The p-value for interaction between ICP monitoring and fluid input was 0.38 for ICU mortality and 0.93 for GOSE at 6 months. **nota bene: interpretation of mean daily negative fluid balance with significant OR<1.0 should be interpreted as follows: a less negative fluid balance (approaching 0) will have and OR of 0.91 with p=0.009, meaning that it is associated with a lower risk of ICU mortality.*

Supplementary Table 7.10a Associations for mean daily fluid balance and mean daily fluid input with ICU Mortality and 6-month GOSE. Sensitivity analysis in patients that had moderate or severe TBI (n=1348)

	ICU Mortality Worse short-term outcome		GOSE - ordinal Worse outcome at 6 months	
	OR + 95%CI	p-value	OR + 95%CI	p-value
Unadjusted – per 0.1L increase				
Mean daily positive fluid balance	1.12 (1.10 – 1.15)	<0.0001	1.08 (1.06 – 1.11)	<0.0001
Mean daily negative fluid balance	0.98 (0.93 – 1.03)	0.40	1.01 (0.98 – 1.04)	0.66
Mean daily fluid input	1.04 (1.03 – 1.05)	<0.0001	1.04 (1.03 – 1.05)	<0.0001
Adjusted* - per 0.1L increase				
Mean daily positive fluid balance	1.11 (1.08 – 1.14)	<0.0001	1.06 (1.04 – 1.08)	<0.0001
Mean daily negative fluid balance	0.96 (0.91 – 1.03)	0.26	1.00 (0.97 – 1.03)	0.87
Mean daily fluid input	1.04 (1.03 – 1.06)	<0.0001	1.04 (1.02 – 1.05)	<0.0001

Supplementary Table 7.10b Associations for mean daily fluid balance and mean daily fluid input with ICU Mortality and 6-month GOSE. Sensitivity analysis in patients that had mild TBI (n=681)

	ICU Mortality Worse short-term outcome		GOSE - ordinal Worse outcome at 6 months	
	OR + 95%CI	p-value	OR + 95%CI	p-value
Unadjusted – per 0.1L increase				
Mean daily positive fluid balance	1.08 (1.04 – 1.13)	0.0001	1.03 (1.01 – 1.05)	0.01
Mean daily negative fluid balance	0.91 (0.83 – 1.00)	0.06	0.98 (0.94 – 1.02)	0.40
Mean daily fluid input	1.05 (1.02 – 1.08)	0.001	1.03 (1.02 – 1.05)	<0.0001
Adjusted* - per 0.1L increase				
Mean daily positive fluid balance	1.07 (1.02 – 1.13)	0.01	1.01 (0.98 – 1.03)	0.57
Mean daily negative fluid balance	0.91 (0.81 – 1.02)	0.10	0.98 (0.94 – 1.02)	0.41
Mean daily fluid input	1.05 (1.01 – 1.10)	0.02	1.03 (1.01 – 1.04)	0.0002

**Adjusted for the IMPACT-extended model (Age, GCS Motor Score at Baseline, Pupillary Reactivity, Hypoxia, Hypotension, Marshall CT Classification, Epidural Hematoma, Traumatic Subarachnoid Hemorrhage, First Hb, First Glucose), any major extracranial injury (AIS>=3) and a random intercept for centre. The p-value for interaction between the severity of TBI and fluid balance was 0.11 for ICU mortality and 0.02 for GOSE at 6 months. The p-value for interaction between the severity of TBI and fluid input was 0.35 for ICU mortality and 0.65 for GOSE at 6 months.*

Supplementary Table 7.11a Associations for mean daily fluid balance and mean daily fluid input with ICU Mortality and 6-month GOSE. Sensitivity analysis in patients from the CENTER-TBI Study (n=1928)

	ICU Mortality Worse short-term outcome		GOSE - ordinal Worse outcome at 6 months	
	OR + 95%CI	p-value	OR + 95%CI	p-value
Unadjusted – per 0.1L increase				
Mean daily positive fluid balance	1.10 (1.08 – 1.12)	<0.0001	1.06 (1.04 – 1.07)	<0.0001
Mean daily negative fluid balance	0.98 (0.94 – 1.02)	0.31	1.00 (0.98 – 1.02)	0.95
Mean daily fluid input	1.04 (1.03 – 1.05)	<0.0001	1.04 (1.04 – 1.05)	<0.0001
Adjusted* - per 0.1L increase				
Mean daily positive fluid balance	1.10 (1.07 – 1.13)	<0.0001	1.04 (1.02 – 1.05)	<0.0001
Mean daily negative fluid balance	0.95 (0.90 – 1.01)	0.09	0.99 (0.97 – 1.02)	0.49
Mean daily fluid input	1.04 (1.03 – 1.06)	<0.0001	1.03 (1.02 – 1.04)	<0.0001

Supplementary Table 7.11b Associations for mean daily fluid balance and mean daily fluid input with ICU Mortality and 6-month GOSE. Sensitivity analysis in patients from OzENTER-TBI Study (n=197)

	ICU Mortality Worse short-term outcome		GOSE - ordinal Worse outcome at 6 months	
	OR + 95%CI	p-value	OR + 95%CI	p-value
Unadjusted – per 0.1L increase				
Mean daily positive fluid balance	1.11 (1.04 – 1.18)	0.002	1.04 (0.99 – 1.09)	0.09
Mean daily negative fluid balance	0.92 (0.66 – 1.28)	0.62	1.07 (0.87 – 1.33)	0.51
Mean daily fluid input	1.10 (1.05 – 1.15)	<0.0001	1.06 (1.03 – 1.09)	<0.0001
Adjusted* - per 0.1L increase				
Mean daily positive fluid balance	1.10 (1.00 – 1.21)	0.04	1.01 (0.96 – 1.06)	0.75
Mean daily negative fluid balance	0.86 (0.58 – 1.27)	0.46	1.12 (0.89 – 1.39)	0.33
Mean daily fluid input	1.11 (1.04 – 1.19)	0.003	1.06 (1.02 – 1.10)	0.002

**Adjusted for the IMPACT-extended model (Age, GCS Motor Score at Baseline, Pupillary Reactivity, Hypoxia, Hypotension, Marshall CT Classification, Epidural Hematoma, Traumatic Subarachnoid Hemorrhage, First Hb, First Glucose), any major extracranial injury (AIS>=3) and a random intercept for centre. The p-value for interaction between study and fluid balance was 0.96 for ICU mortality and 0.90 for GOSE at 6 months. The p-value for interaction between study and fluid input was 0.06 for ICU mortality and 0.26 for GOSE at 6 months.*

Supplementary Table 7.12 Associations for mean daily fluid balance and mean daily fluid input with ICU Mortality and 6-month GOSE. Sensitivity analysis with adjustment for mean CPP and mean sodium

	ICU Mortality Worse short-term outcome		GOSE - ordinal worse outcome at 6 months	
	OR + 95%CI	p-value	OR + 95%CI	p-value
Unadjusted – per 0.1L increase				
Mean daily positive fluid balance	1.13 (1.09 – 1.16)	< 0.0001	1.08 (1.05 – 1.10)	< 0.0001
Mean daily negative fluid balance	0.94 (0.89 – 1.00)	0.03	0.99 (0.95 – 1.03)	0.54
Mean daily fluid input	1.04 (1.02 – 1.05)	< 0.0001	1.02 (1.01 – 1.03)	0.0001
Mean sodium >140 mmol/L – per 1 mmol/L	*1.21 (1.16 – 1.27)*	*< 0.0001*	*1.16 (1.12 – 1.20)*	*< 0.0001*
Mean sodium < =140 mmol/L – per 1 mmol/L	*0.87 (0.76 – 1.00)*	*0.05*	*0.86 (0.77 – 0.96)*	*0.01*
Mean CPP – per 1 mmHg	*0.91 (0.89 – 0.93)*	*< 0.0001*	*0.95 (0.94 – 0.96)*	*< 0.0001*
Adjusted* - per 0.1L increase				
Mean daily positive fluid balance	1.10 (1.06 – 1.15)	< 0.0001	1.05 (1.02 – 1.07)	0.001
Mean daily negative fluid balance	0.91 (0.85 – 0.98)	0.02	0.98 (0.94 – 1.02)	0.37
Mean daily fluid input	1.04 (1.01 – 1.06)	0.003	1.01 (1.00 – 1.03)	0.06
Mean sodium >140 mmol/L per 1 mmol/L	*1.21 (1.14 – 1.28)*	*< 0.0001*	*1.15 (1.11 – 1.19)*	*< 0.0001*
Mean sodium < =140 mmol/L per 1 mmol/L	*0.86 (0.74 – 1.00)*	*0.04*	*0.89 (0.80 – 0.99)*	*0.04*
Mean CPP – per 1 mmHg	*0.94 (0.92 – 0.96)*	*< 0.0001*	*0.97 (0.96 – 0.99)*	*0.0001*

**Adjusted for the IMPACT-extended model (Age, GCS Motor Score at Baseline, Pupillary Reactivity, Hypoxia, Hypotension, Marshall CT Classification, Epidural Hematoma, Traumatic Subarachnoid Hemorrhage, First Hb, First Glucose), any major extracranial injury (AIS > =3), mean CPP, mean sodium, and a random intercept for centre. CPP and sodium were added as covariables in sensitivity analysis as these variables were perceived as important potential confounding factors for the association between fluid management and outcome: lower CPP might trigger fluid administration and hypotonic fluids may aggravate brain injury by increasing cerebral edema, independent from amount of fluids. CPP and sodium were included in the model as mean value over all values that were measured during ICU stay.*

Supplementary Table 7.13 Associations for mean daily fluid balance and mean daily fluid input with ICU Mortality and 6-month GOSE. Sensitivity analysis with adjustment for mean Mean Arterial Pressure (MAP)

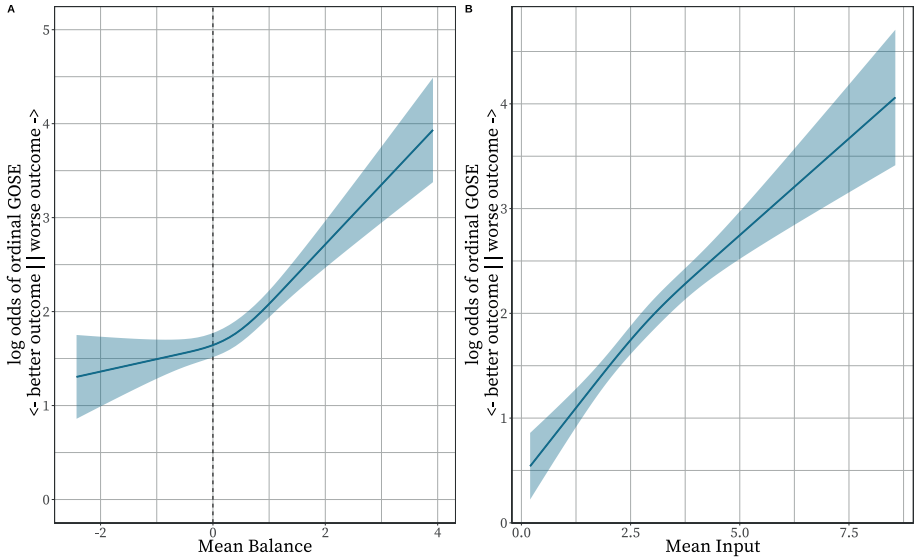
	ICU Mortality Worse short-term outcome		GOSE - ordinal Worse outcome at 6 months	
	OR + 95%CI	**p-value**	**OR + 95%CI**	**p-value**
Unadjusted – per 0.1L increase				
Mean daily positive fluid balance	1.10 (1.08 – 1.12)	<0.0001	1.06 (1.04 – 1.07)	<0.0001
Mean daily negative fluid balance	0.98 (0.94 – 1.02)	0.32	1.00 (0.98 – 1.03)	0.71
Mean daily fluid input	1.05 (1.04 – 1.06)	<0.0001	1.05 (1.04 – 1.05)	<0.0001
Mean MAP – per 1 mmHg increase	0.93 (0.92 – 0.95)	<0.0001	0.96 (0.95 – 0.97)	<0.0001
Adjusted* - per 0.1L increase				
Mean daily positive fluid balance	1.09 (1.06 – 1.12)	<0.0001	1.03 (1.01 – 1.05)	0.0002
Mean daily negative fluid balance	0.94 (0.89 – 1.00)	0.05	0.99 (0.97 – 1.02)	0.74
Mean daily fluid input	1.05 (1.04 – 1.07)	<0.0001	1.03 (1.02 – 1.04)	<0.0001
Mean MAP – per 1 mmHg increase	0.95 (0.94 – 0.97)	<0.0001	0.98 (0.97 – 0.99)	0.0001

**Adjusted for the IMPACT-extended model (Age, GCS Motor Score at Baseline, Pupillary Reactivity, Hypoxia, Hypotension, Marshall CT Classification, Epidural Hematoma, Traumatic Subarachnoid Hemorrhage, First Hb, First Glucose), any major extracranial injury (AIS>=3), mean Mean Arterial Pressure, and a random intercept for centre. Mean Arterial Pressure was included in the model as mean value over all values that were measured during ICU stay.*

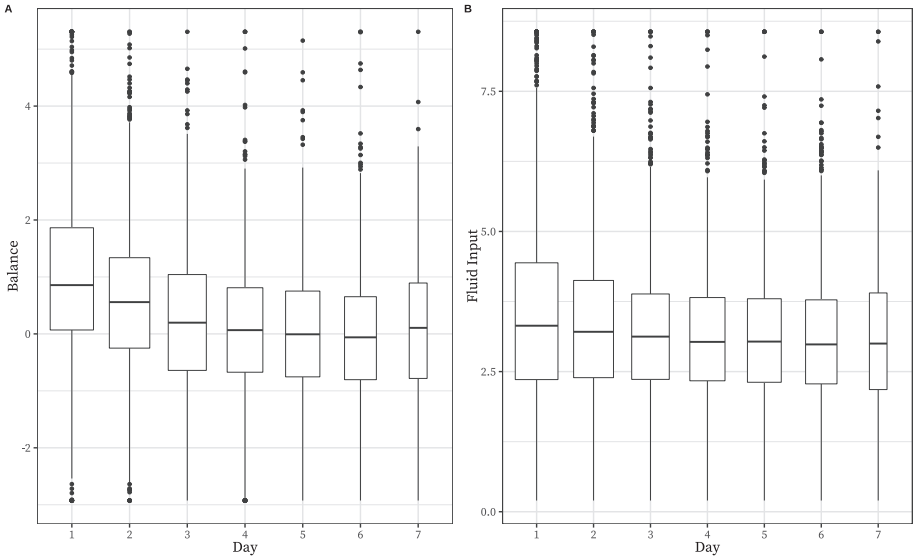
Supplementary Table 7.14 Association of fluid balance and fluid input higher than the median of the mean with outcome in 1214 propensity score matched patients.

	ICU Mortality Worse short-term outcome		GOSE - ordinal worse outcome at 6 months	
	OR + 95%CI	**p-value**	**OR + 95%CI**	**p-value**
Median daily fluid balance	1.53 (1.11 – 2.09)	0.01	1.18 (0.96 – 1.45)	0.11
Median daily fluid input	1.49 (1.05 – 2.13)	0.03	1.68 (1..33 – 2.14)	<0..0001

For each patient, the propensity of having a mean daily fluid balance or mean daily fluid input higher or lower than the median was estimated using multivariable logistic regression analysis with mean daily fluid balance or mean daily fluid input higher or lower than the median as binary dependent variable, and all variables from the IMPACT models, any major extracranial injury (AIS>=3), and a random intercept for centre as independent variables. Patients with higher and lower fluids than the median of all patients were matched based on their propensity. Patients with non-overlapping propensity scores (maximum caliper 0.10) were excluded for the analyses.

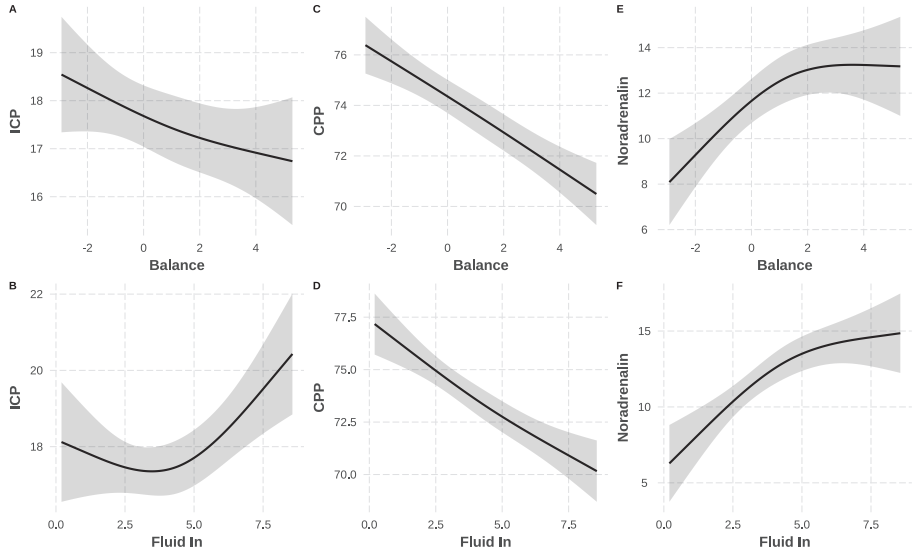


Supplementary Figure 7.1 Linearity of the association between mean daily fluid balance [A] and mean daily fluid input [B] and log odds for ordinal GOSE, unadjusted for case-mix. For fluid balance, a non-linear association with outcome was observed. Therefore, we obtained OR's and p-values for a mean daily positive fluid balance (>=0L) and a mean daily negative fluid balance (<0L) separately. We observed a linear association for fluid input and outcome.



Supplementary Figure 7.2 Fluid input and fluid balance per day

A] Median + IQR Fluid Balance per day, for the first seven days at ICU. The boxes represent the median + corresponding interquartile ranges. B] Median + IQR Fluid Input per day, for the first seven days at ICU. The boxes represent the median + corresponding interquartile ranges. The width of the boxes indicates the number of patients that have a measurement for that particular day.



Supplementary Figure 7.3 The association of daily fluid balance and input with ICP, CPP, and dose of noradrenalin.

The association of daily fluid balance and input with: A+B] maximum ICP, C+D], mean CPP, and E+F] the dose of noradrenalin (mg). All analyses accounted for multiple measures within one patient, and were adjusted for the IMPACT core variables (GCS Motor Score baseline, pupillary reactivity and age).

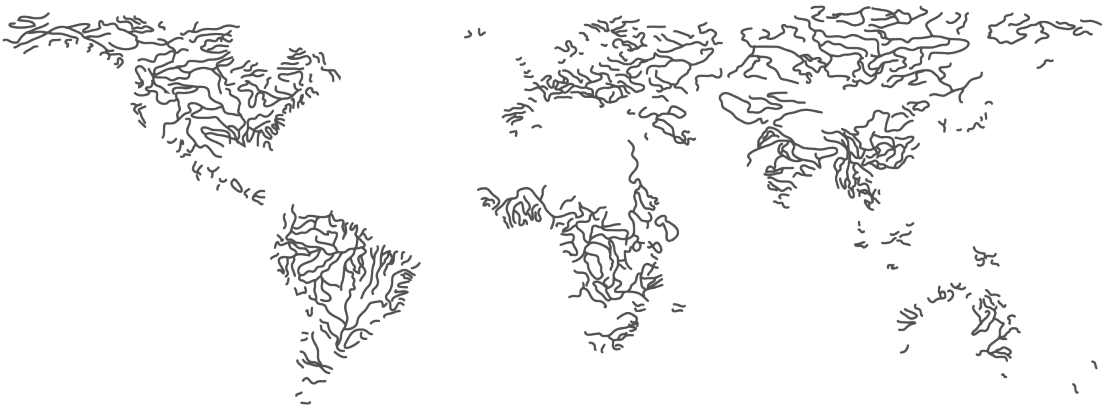
Instrumental variable analysis

Methods

Instrumental variable analysis requires three assumptions to be met: 1) the instrument is associated with the intervention under study; 2) the instrument is not associated with confounders; 3) the instrument is not independently associated with the outcome under study. The first assumption will be tested by quantifying the between center variation in fluid management, independent of patient characteristics. The second assumption will be tested by comparing patient characteristics between centres with higher and lower fluid input and balance. The third assumption cannot be tested but is addressed by using a random effect model with a random intercept for center. In such a model variation between centers that is not explained by the variables in the model is captured in the random centre term. In this way the estimated effect is adjusted for other known and unknown hospital characteristics.

Results

The testable assumptions of the IV analysis were met: there was substantial between center variation in fluid management between centers beyond case-mix (Figure 7.2 in manuscript) and patient characteristics were comparable between centres providing more and less fluids (see this appendix).



Chapter 8

Comparative Effectiveness Research for Beta Blockers in Traumatic Brain Injury

In preparation

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ABSTRACT

Objective
The aim of this study is to describe current beta blocker administration practices in Europe and to investigate the association between early beta-blocker use and outcome in Traumatic Brain Injury (TBI) patients admitted to the ICU.

Design
Prospective, observational cohort study conducted from 2015-2017 (CENTER-TBI study).

Setting
53 centres in 18 European countries.

Patients
TBI patients admitted to the Intensive Care Unit that survived at least 48 hours after injury.

Intervention
Administration of any dose of beta-blockers within the first two days after injury.

Measurements and main results
In total, 1927 patients were included in this study of whom 177 (9.2%) received beta-blockers during the first 2 days after injury. In 37 of the 53 centres, beta-blockers were given within the first 48 hours after injury; in 25 of these 37 centres, beta-blockers were given without a prior indication. After case-mix adjustment, between-centre differences in the early use of beta-blockers remained significant (Median Odds Ratio: 2.5). In 288 matched patients we found no association between beta-blocker use and lower in-hospital mortality (OR: 1.0, 95%CI: 0.4 – 2.7) or improved GOSE (OR: 1.1, 95%CI: 0.7 – 1.7). Sensitivity analysis revealed an association for beta-blocker use and lower in-hospital mortality in patients with isolated TBI (OR 0.5, 95%CI: 0.2–1.3).

Conclusions
Beta-blocker use in TBI patients admitted to the ICU is limited but varies between European ICUs. For patients with isolated TBI, early administration of beta blockers might be associated with improved outcomes. Further research on efficacy and mechanism of beta-blockers is warranted.

INTRODUCTION

Traumatic Brain Injury (TBI) is a major cause of mortality and morbidity worldwide. Long-term neurological impairment is seen in many TBI survivors[1]. Severe functional disability following TBI is a global public health concern[2].

The major determinant of outcome after TBI is the severity of primary injury, which is largely irreversible.[3] However, secondary injury occurs as a result of several factors such as hypoxia, hypotension, increased intracranial pressure and hyperglycemia after primary injury[3,4]. Over the past years, much research on critical care management has been performed[5]. Nevertheless, only a few evidence-based interventions are known for patients with TBI admitted to the Intensive Care Unit that result in improved long-term functional outcome[6,7].

Sympathetic activation is a well-known phenomenon after acute brain injury and in critical illness, and the strong potential of beta-blockade has been shown recently[8-11]. Several pathophysiological mechanisms have been described that support a potential role of beta-blockers to block some of the adverse sympathetic effects in traumatic brain injury[12,13]. These adverse sympathetic effects include cerebral vasoconstriction, systemic inflammation, endothelial disruption, increased metabolic demand including in brain tissue and increased hydrostatic pressures that might contribute to vasogenic cerebral edema[14].

A recent systematic review and meta-analysis showed that use of beta-blockers might significantly decrease mortality after TBI, although the quality of included studies appeared to be very low[15]. Nevertheless, some guidelines recommend consideration of beta-blocker prescription in TBI patients[14]. Current clinical practice and practice variation regarding beta-blockers administration to critically ill TBI patients in Europe is unclear.

The aim of this study is to describe current beta blocker administration practices in Europe and to investigate the association between beta-blocker use within the two first days after injury and outcome in TBI patients admitted to the ICU.

METHODS

Study design

The CENTER-TBI Core study is a prospective observational longitudinal cohort study on patients of all severities of TBI, presenting between December 19, 2014 and December 17, 2017, admitted to 63 centres across Europe and Israel. Inclusion criteria for the CENTER-TBI core study were a clinical diagnosis of TBI, indication for CT scanning of the brain, presentation to study centre within 24 hours of injury, and informed consent obtained according to local and national requirements[16]. The only exclusion criterion was severe pre-existing neurological disorder that could confound outcome assessments. Patients were differentiated by care path into three strata: ER stratum (patients evaluated in the emergency room (ER) and discharged); Admission stratum (admitted to hospital ward); ICU stratum (primary admission to the intensive care unit).

Consent procedures have been described in previous publications about the CENTER-TBI study[1,16,17]. For the purpose of this study, we included patients of all ages in the ICU stratum. Patients that did not have information on beta blocker administration or died within 48 hours after injury were excluded for analysis.

Data collection

Patient data were obtained from the CENTER-TBI Core study, which included detailed information on demographics, injury characteristics, and clinical characteristics. Clinical data on vitals, monitoring, and treatment characteristics were collected on a daily basis: at ER admission, ICU admission, during ICU stay (days 1- 7, day 10, day 14, day 21, day 28), and at ICU discharge. Research assistants and/or physicians collected and interpreted all data and entered these in an online data entry and analysis platform (QuesGen Systems Inc., Burlinghame, CA, USA).

Medication

As part of the CENTER-TBI study, information on all administered drugs prior and during hospital study were prospectively registered. Given the previously defined aim of evaluating the impact of early beta-blockade on outcome and that catecholamines appear to be highest during the first hours after ICU admission [14], patients were allocated to the beta-blocker exposed cases when beta-blockers were administered within 2 days of admission to ICU. Also, information on the time, type, dose, and reason of administration was registered. All patients were treated according to local protocol.

Outcome

Primary outcomes were in-hospital mortality and the Glasgow Outcome Scale – Extended (GOSE) at 6 months. The 8 categories are: Dead, Vegetative State, Lower Severe Disability, Upper Severe Disability, Lower Moderate Disability, Upper Moderate Disability, Lower Good Recovery, and Upper Good Recovery. After combining the categories 'vegetative state (GOSE 2)' and 'lower severe disability (GOSE 3)', the GOSE was assessed at a seven-point ordinal scale. Secondary outcomes were the use of vasopressors and hospital length of stay. To gain more insight in the potential consequences of beta blockers, we assessed the association of beta blockers and daily heart rate, Mean Arterial Pressure (MAP), Intracranial Pressure (ICP), and Cerebral Perfusion Pressure during day 1-7 after ICU admission.

Statistical analysis

Patient characteristics were described as mean and standard deviation (SD) for normal distributions and as median and interquartile range (IQR) for skewed distributions. The variation between centres in early beta blocker use was quantified using random effect logistic and ordinal regression models with a random intercept for centre, and expressed as the Median Odds Ratio[18]. The MOR is a measure of variation between the policies or outcomes of different hospitals that is not explained by factors in the model or chance. The MOR can be shown to be related to τ^2, which is the variance of the random effects;

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

We computed an odds ratio between a patient from the centre with the highest probability for beta-blocker administration and the lowest probability for beta-blocker administration for each pair of patients from different centres. The MOR can be interpreted also as the median value of the distribution of these odds ratios for beta-blocker administration for all pairs of patients in our data. A MOR equal to one indicates no differences between centres[19].

To adjust for confounding, the propensity of receiving beta-blockers within the first two days was estimated using multivariable logistic regression analysis with beta-blockers (yes/no) as an outcome and all variables from the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) prognostic model (age, GCS motor score, pupillary reaction, hypoxia, hypotension, CT Marshall Classification, traumatic Subarachnoid Hemorrhage (tSAH), Epidural Hematoma (EDH), first glucose, and first hemoglobin), any major extracranial injury (AIS >=3), the prior use of beta-blocker and a random intercept for centre as independent variables. Patients with non-overlapping propensity scores (maximum caliper 0.10) were excluded for the effect analyses.

The effect of beta-blocker on GOSE and in-hospital mortality was analyzed with an ordinal and logistic regression model and expressed as Odds Ratios (ORs) with 95% Confidence Intervals (CIs). For adjustment purposes, we included the variables from the IMPACT prognostic model, any major extracranial injury (AIS > =3), and a random intercept for centre. The ordinal regression estimates a common OR for overall health state transitions within the GOSE. The GOSE was converted, so an OR above 1 indicates worse outcome, where an OR below 1 indicates better outcome, to align the interpretation with the effect on mortality.

The effect of beta-blocker use on the median daily heart rate, Mean Arterial Pressure (MAP), intracranial pressure (ICP), and Cerebral Perfusion Pressure (CPP) for day 1 – 7, after injury was assessed using a linear mixed-effects model and presented as estimated ratio of means. A random effect for patient was added to account for repeated measures[20].

A sensitivity analysis was performed in the following patients:
- Isolated TBI
- Staying at the ICU for at least 48 hours
- prior use of beta-blockers before hospital admission

Statistical analyses were performed in the R statistical software[21]. Multiple imputation was used to handle missing values, with use of the mice package in R[22]. (Supplementary Table 8.1) The corresponding R-codes can be found in appendix 1. Data were accessed using a bespoke data management tool, 'Neurobot' (http://neurobot.incf.org; RRID: SCR_01700), vs 2.0 (data freeze: June 2019).

RESULTS

In total, 4509 patients were included in the CENTER-TBI study, 2138 were admitted to the ICU. After excluding patients that did not have information on beta blocker administration (n=135) or died within 48 hours after injury (n=76) were excluded for analysis, resulting in 1927 patients that were eligible for analysis. In 177 (9.2%) patients, beta-blockers were administered during the first 48 hours after injury, of which 71 (44%) had a prior indication for the use of beta-blockers (Table 8.1, Figure 8.1).

Baseline characteristics

Statistically significant differences in baseline characteristics were denoted between the groups of patients that received and not received beta blockers for age (median age: 46 versus 67), hypotension (213 (13%) versus 11 (6.7%), and any major extracranial injury

(1010 (58%) versus 69 (39%). In the beta-blocker group, 44% (n=71) had an indication for beta-blockers before hospital admission (continuation of previous therapy) compared to 5.8% (n=95) in the non-beta-blocker group. In the non-beta-blocker group, more patients had severe TBI (GCS baseline <9) (793 (48%) versus 47 (28%) compared to the beta-blocker group. There were also differences in the use of vasopressors (907 (55%) versus 61 (35%)) and ICP monitoring (799 (46%) versus 61 (35%)) (Table 8.1).

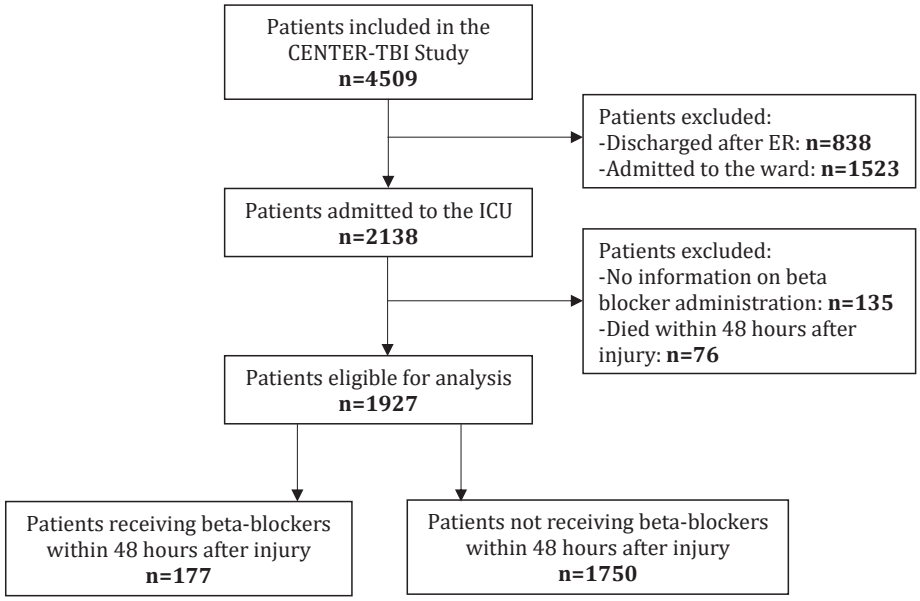

Figure 8.1 Flowchart of Included patients

Beta-blocker characteristics

In 69% (n=123) of patients exposed to beta-blockers, the type of beta-blocker was registered. The most prevalent type was labetalol (n=35, 20%), followed by metoprolol (n=37, 21%). In 124 (70%) patients, the reason for beta-blocker was to decrease blood pressure. Most patients received the beta-blockers orally (n=84, 48%) (Supplementary Table 8.2).

Between-centre differences

In 37 of the 53 centres, beta-blockers were given within the first 48 hours after injury with a minimum of 1.5% to a maximum of 69% of TBI patients admitted to the ICU. In the other 17 centres, beta blockers were not administered in the first 48 hours after injury. In 25 of the 37 centres, beta-blockers were given without a prior indication. After adjustment, significant between-centre differences were observed in the proportion of patients that received beta-blockers (MOR: 2.48, p-value < 0.001.) (Figure 8.2, Supplementary Figure 8.1).

Table 8.1 Baseline Characteristics, stratified for beta-blocker use during ICU stay

	Total 1927	**No beta-blocker 1750**	**Beta-blocker 177**	**p-value**
Baseline characteristics				
Age (median [IQR])	48 (29 – 64)	46 (28 – 62)	67 (51 – 76)	<0.001
Age ≥65 years	471 (24%)	375 (21%)	96 (54%)	<0.001
Male sex	1418 (74%)	1283 (73%)	135 (76%)	0.45
Pupillary Reactivity				0.98
Both unreacting	175 (9.5%)	159 (9.6%)	16 (9.4%)	
One Reacting	122 (6.7%)	110 (6.6%)	12 (7.1%)	
Hypoxia – Yes or Suspected	227 (13%)	214 (13%)	13 (7.8%)	0.07
Hypotension - Yes or Suspected	224 (11%)	213 (13%)	11 (6.7%)	0.03
Any major extracranial injury (AIS>=3)	1079 (56%)	1010 (58%)	69 (39%)	<0.001
Severity TBI				<0.001
Mild	691 (38%)	608 (36%)	83 (49%)	
Moderate	308 (17%)	269 (16%)	39 (23%)	
Severe	840 (46%)	793 (48%)	47 (28%)	
Previous Beta-blocker use	166 (9.2%)	95 (5.8%)	71 (44%)	<0.001
CT characteristics				
Marshall CT Classification				0.07
I	194 (11%)	179 (12%)	15 (10%)	
II	854 (50%)	785 (50%)	69 (47%)	
III	132 (7.7%)	127 (8.1%)	5 (3.4%)	
IV	23 (1.3%)	22 (1.4%)	1 (0.7%)	
V/VI	504 (30%)	446 (29%)	58 (39%)	
Treatment characteristics				
Cranial Surgery	757 (40%)	692 (40%)	65 (37%)	0.56
ICP Monitor	860 (45%)	799 (46%)	61 (35%)	0.01
Outcome Characteristics				
Median heart rate* (median (IQR))	93 (82 – 105)	93 (83 – 105)	88 (79 – 101)	<0.01
Use of vasopressors	979 (54%)	907 (55%)	61 (35%)	0.01
ICU Length of Stay in days (median (IQR))	6.6 (2.1 – 16)	6.7 (2.2 – 16)	4.4 (1.8 – 9.8)	0.001
In-hospital Mortality	208 (11%)	188 (11%)	20 (12%)	0.91
ICU mortality	167 (8.7%)	157 (9.0%)	10 (5.6%)	0.17
Unfavorable outcome at 6 months	660 (40%)	584 (39%)	76 (48%)	0.03

P-values were derived from ANOVA for continuous characteristics and χ^2 statistics for categorical characteristics, comparing patients that received beta-blockers to patients that did not receive beta-blockers. The p-value assessed compatibility with the null hypothesis of no differences between the use of beta-blockers. The median heart rate was calculated for the first seven days from ICU admission.

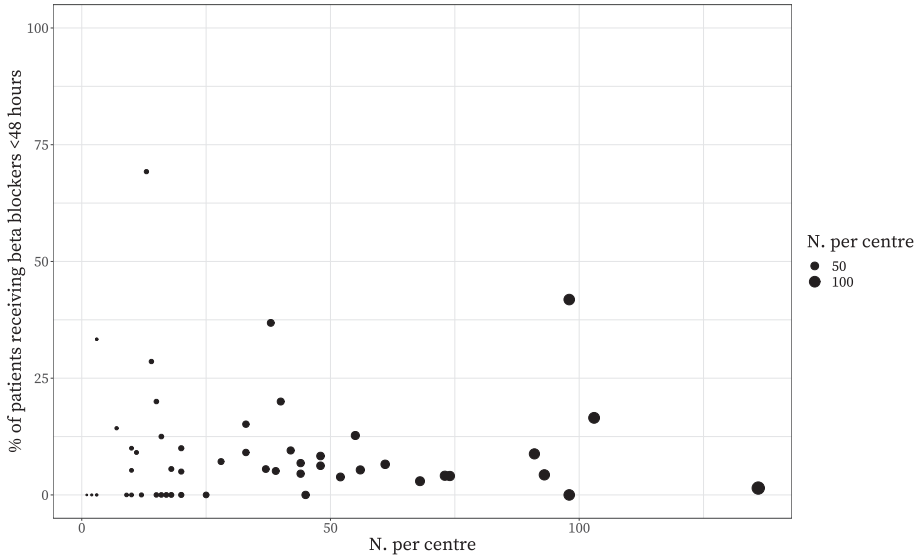

Figure 8.2 The use of administration of beta-blockers within 48 hours per centre

Association with outcome

After propensity score matching, we matched 144 beta-blocker cases to 144 non-beta-blocker cases (Supplementary Table 8.3). Unfavourable outcome was observed in 55 (38%) of the non-beta-blocker group versus 59 (41%) of the beta-blocker group. We did not observe an association between the use of beta-blockers and lower in-hospital mortality (OR: 1.04, 95% CI: 0.41 – 2.65, p = 0.94), improved GOSE (OR: 1.06,95% CI: 0.66 – 1.71, p = 0.80), a reduced use of vasopressor therapy (OR: 0.72, 95%CI: 0.39 – 1.35), p = 0.29) or ICU length of stay (beta: 0.54 (95%CI: -5.1– 6.15), p = 0.85) (Table 8.2, Figure 8.3). After adjustment for patient characteristics, patients with beta blockers had lower heart rate, but higher MAP and CPP (Figure 8.4).

Table 8.2 Association of beta-blocker administration with outcome in 276 propensity score matched patients.

	Use of beta-blocker within 48 hours	
	OR (95% CI)	**p-value**
Primary outcomes		
In-hospital mortality	1.04 (0.41 - 2.65)	0.94
GOSE at 6 months	1.06 (0.66 – 1.71)	0.80
Secondary outcomes		
Use of vasopressors	0.72 (0.39 – 1.35)	0.29
Hospital Length Of Stay (beta)	0.54 (-5.1– 6.15)	0.85

**Glasgow Outcome Scale Extended – an OR >1 indicates worse outcome*

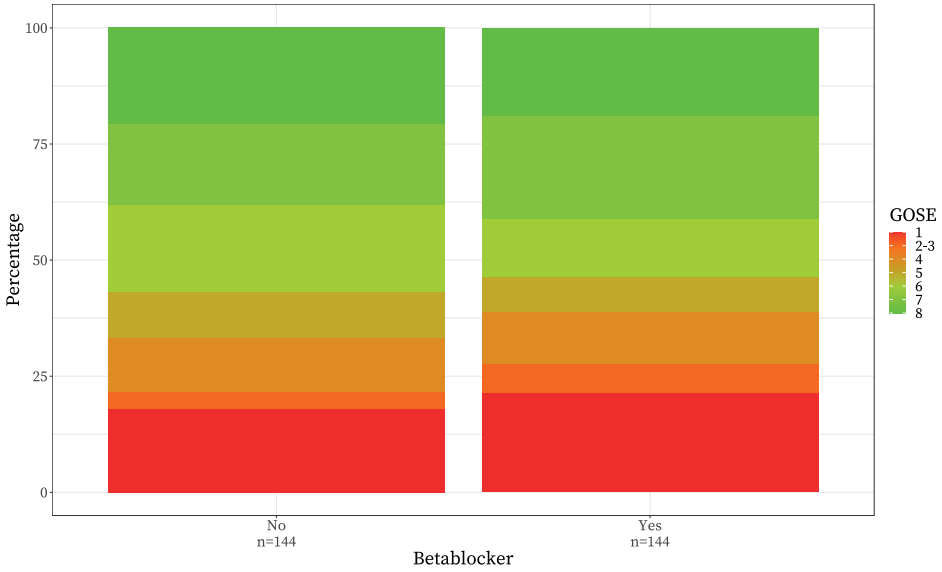

Figure 8.3 Use of Beta-blocker and 6-month GOSE, after propensity-score matching

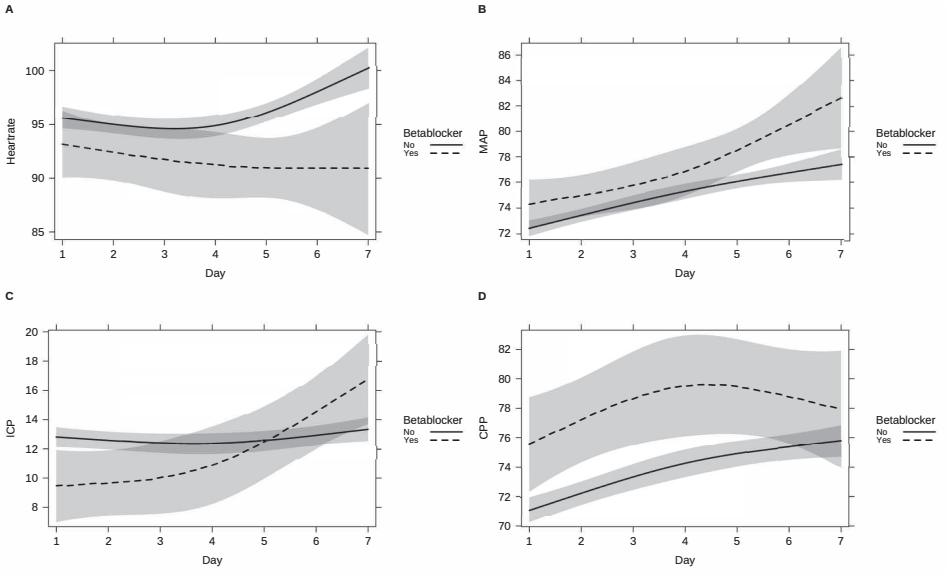

Figure 8.4 Association of Beta-blocker use with A] mean heart rate per day, B] Mean arterial pressure, C] ICP, and D] CPP after adjustment for IMPACT core, linear mixed model

Sensitivity analysis

In sensitivity analysis, we observed an association for beta-blocker use and lower in-hospital mortality in patients with isolated TBI (OR 0.48, 95% CI: 0.18 – 1.28, p=0.14). We did not observe an association for the use of beta-blockers in any of the other prespecified subgroups (Supplementary Table 8.4-8.7).

DISCUSSION

The aim of this study was to describe current beta blocker use in ICU admitted TBI patients in Europe and to investigate the association between beta-blocker use and outcome. Beta-blockers were administered within the first two days after injury in almost 10% of patients. Also, we found significant between-centre differences in prescription rates. We did not find an association between early beta-blocker use and in-hospital mortality and functional outcome at 6 months. However, for patients with isolated TBI, early administration of beta blockers was associated with improved outcomes.

Compared to other prospective observational cohort studies the use of beta-blockers in TBI patients appeared to be lower in this study[23,24]. For example, a recent multi-centre study in the United States and Canada reported that 50% of the adult TBI patients that required intensive care unit admission received beta-blockers[23].

We found considerable between-centre differences in the use of beta-blockers for TBI patients. Although the Brain Trauma Foundation (BTF) guidelines do not include any recommendations about the use of beta-blockers, we found regular prescription in practice.[7] This supports the results of an earlier study that concluded substantial variability in the use and implementation of guidelines in neurotrauma centres in Europe[25]. The variation of beta-blocker use may also originate from the general poor quality of evidence that underpins current TBI guidelines and the fact that current guidelines contain contrasting recommendations[7].

Our findings are partially in contrast to a recent meta-analysis and RCT that found an association of beta-blocker use with improved in-hospital survival[14,26]. Our results argue against a beneficial effect of beta blockers on outcome for all TBI patients in general. This might be a consequence of selection bias introduced by the reduction in confounders through propensity score matching, and the smaller sample size as compared with earlier studies. Patients were matched according to the IMPACT variables, which are well validated for TBI[20]. However, sensitivity analyses revealed that patients without any major extracranial injury might benefit from early beta-blocker administration.

Sympathetic activation is a well-known phenomenon after TBI. As a result, serum catecholamine levels rise which has been associated with worse neurologic outcome and increased in-hospital mortality. Earlier studies concluded that the increase of catecholamine levels in the acute phase of TBI correlates with worsening GCS and functional outcome, indicating a possible detrimental effect of sympathetic hyperactivity on survival and functional outcome[27,28]. Beta-blockers have the ability to block the sympathetic adrenoceptors and thus mitigate such detrimental effects[29]. These adverse sympathetic effects may facilitate secondary brain injuries due to pleiotropic effects of catecholamines on the brain (increased metabolic demand, increasing the risk of ischemia; decreased cerebral blood flow due to vasoconstriction; decreased or increased cardiac output; inflammation and endothelial disruption)[30,31].

While the discussion above addresses some of the current thinking about how beta-blockers might influence the course of TBI, some inferences are counterintuitive. The patients who had a need for beta-blockers for hypertension (which was the dominant indication for use) arguably had the greatest activation of their sympathoadrenal system, and might (given the earlier discussion) be expected to have worse outcomes, but this was not the case. Indeed, the beta-blocker group, despite therapy had higher mean arterial pressure for much of their ICU stay, and though their heart rate was lower, the two groups only showed significant divergence of heart rate only after the first 48 hours. Consequently, while use of beta-blockers might have mitigated the effects of this catecholamine surge, alternate explanations for our results should be considered. It is possible that the need for beta-blockers may have identified patients with less severe haemodynamic compromise, or less intensive sedation, both of which may have predisposed to better outcomes. Alternatively (or in addition), the higher CPP that accompanied the higher MAP in the beta-blocker group may have translated into a lower risk for episodes of significant cerebral hypoperfusion. On the other hand, studies in other populations have suggested in line with our results that beta-blockers may paradoxically result in decreased need for vasopressors[11].

Strengths and limitations

This is a large study with patients enrolled in multiple centres across Europe and Israel. Other strengths lie in the fact that we were able to assess both the prior use of beta-blockers and the use of beta-blockers in-hospital.

Some limitations must be denoted. First, we were unable to perform a sensitivity analysis to assess the effect of beta-blocker administration in different types of beta-blockers. It is known that there is a difference between lipophilic and hydrophilic beta-blockers, since this trait of different beta-blockers determines whether they pass the blood-brain-

barrier[29]. Further, an important limitation is that we did not have data on atrial fibrillation (AF). AF may have guided beta blocker use (which is a legitimate indication), rather than local practice variation and individual preferences of physicians. We used propensity score matching to adjust for confounding. Although propensity score matching is known for creating experimental conditions using observational data, some pitfalls should be acknowledged. Propensity methods only addresses bias introduced by observed variables and cannot adjust for unmeasured confounding[32]. Instrumental variable analysis has been proposed as the solution to deal with unmeasured confounding[33,34]. However, we were unable to perform instrumental variable analysis because statistical efficiency was lacking due to too low numbers of patients being exposed to beta blockers.

Future implications

The variability between centres in the use of beta-blockers probably reflects the low evidence level based on observational studies. Future studies should also focus on intermediate outcomes (e.g. heart rate) to further corroborate that decreasing sympathetic overstimulation may improve clinical outcomes in specific patient groups. Eventually randomised clinical trials are needed with the right physiological targets to assess whether improved outcomes can be established.

Conclusion

In conclusion, variability in early beta-blocker use exists among TBI patients admitted to European ICUs, but their use is quite low (around 10%). We did not find an association between early administration of beta-blockers and outcome, therefore our results do not support the current early use for critically ill TBI patients. However, for patients with isolated TBI, early administration of beta blockers might be associated with improved outcomes. Further research on efficacy and mechanism of beta-blockers are warranted, taking our results and others into account.

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SUPPLEMENTARY MATERIAL

Supplementary Table 8.1 Missing Data

	Total 1927
Baseline characteristics	
Age (median [IQR])	0 (0%)
Age ≥65 years	0 (0%)
Male sex	0 (0%)
Pupillary Reactivity	93 (4.8%)
Hypoxia – Yes or Suspected	129 (6.7%)
Hypotension- Yes or Suspected	118 (6.1%)
Any major extracranial injury (AIS > =3)	0 (0%)
Severity TBI	88 (4.6%)
Previous Beta-blocker use	115 (6.0%)
CT characteristics	
Marshall CT Classification	220 (11%)
Treatment characteristics	
Cranial Surgery	11 (0.6%)
Extracranial Surgery	10 (0.5%)
ICP Monitor	1 (0.1%)
Outcome Characteristics	
Median heart rate	14 (0.7%)
Use of vasopressors	102 (5.3%)
ICU Length of Stay in days (median (IQR))	2 (0.1%)
Hospital Length of Stay in days (median (IQR))	73 (3.8%)
ICU mortality	10 (0.5%)
Unfavorable outcome at 6 months	266 (14%)

Supplementary Table 8.2 Characteristics of beta-blockers

Characteristics	N (%)
Type of Beta-blocker	
Labetalol	35 (20%)
Metoprolol	37 (21%)
Propanolol	2 (1.1%)
Other	49 (28%)
Missing	54 (31%)
Reason for Beta-blocker use	
Anti-hypertensive to lower blood pressure	154 (87%)
Other	1 (0.6%)
Missing	22 (12%)
Route	
Continuous intravenous	24 (14%)
Intermittent intravenous	54 (31%)
Oral	84 (48%)
Missing	15 (8.5%)

Supplementary Table 8.3 Baseline characteristics after propensity score matching

	No beta-blocker 144	Beta-blocker 144	p-value
Age (median (IQR))	63 (49 – 73)	64 (49 – 75)	0.98
Male Sex	102 (71%)	111 (72%)	0.28
Pupillary Reactivity			0.55
Both unreacting	11 (7.6 %)	11 (7.6%)	
One Reacting	9 (6.2%)	14 (9.7%)	
Hypoxia	12 (8.3%)	10 (6.9%)	0.82
Hypotension	11 (7.6%)	11 (7.6%)	1
Any Major Extracranial Injury	59 (41%)	64 (44%)	0.63
Marshall CT classification			0.72
I	9 (6.2%)	15 (10%)	
II	59 (41%)	58 (40%)	
III	8 (5.6%)	7 (4.9%)	
IV	1 (0.7%)	2 (1.4%)	
V/VI	67 (47%)	62 (43%)	
Epidural Hematoma	24 (17%)	17 (12%)	0.31
Traumatic Subarachnoid Hemorrhage	106 (74%)	110 (76%)	0.68
In-hospital Mortality	17 (12%)	22 (15%)	0.49
Unfavourable outcome at 6 months	55 (38%)	59 (41%)	0.64

Supplementary Table 8.4 Association of beta-blocker administration with outcome in isolated TBI patients

	Use of beta-blocker within 48 hours	
	OR (95% CI)	**p-value**
Primary outcomes		
In-hospital mortality	0.48 (0.18 – 1.28)	0.14
GOSE at 6 months*	0.85 (0.42 – 1.71)	0.63
Secondary outcomes		
Use of vasopressors	0.49 (0.21 – 1.14)	0.09
Hospital Length Of Stay	-0.31 (-6.69– 6.09)	0.92

**Glasgow Outcome Scale Extended – an OR >1 indicates worse outcome.*

Supplementary Table 8.5 Association of beta-blocker administration with outcome in patients with an ICU stay of at least 48 hours

	Use of beta-blocker within 48 hours	
	OR (95% CI)	**p-value**
Primary outcomes		
In-hospital mortality	0.87 (0.29 – 2.64)	0.80
GOSE at 6 months*	0.99 (0.54 – 1.84)	0.98
Secondary outcomes		
Use of vasopressors	0.54 (0.28 – 1.03)	0.06
Hospital Length Of Stay	4.50 (-4.84– 11)	0.27

**Glasgow Outcome Scale Extended – an OR >1 indicates worse outcome.*

Supplementary Table 8.6 Association of beta-blocker administration with outcome without a primary indication for the use of beta-blockers

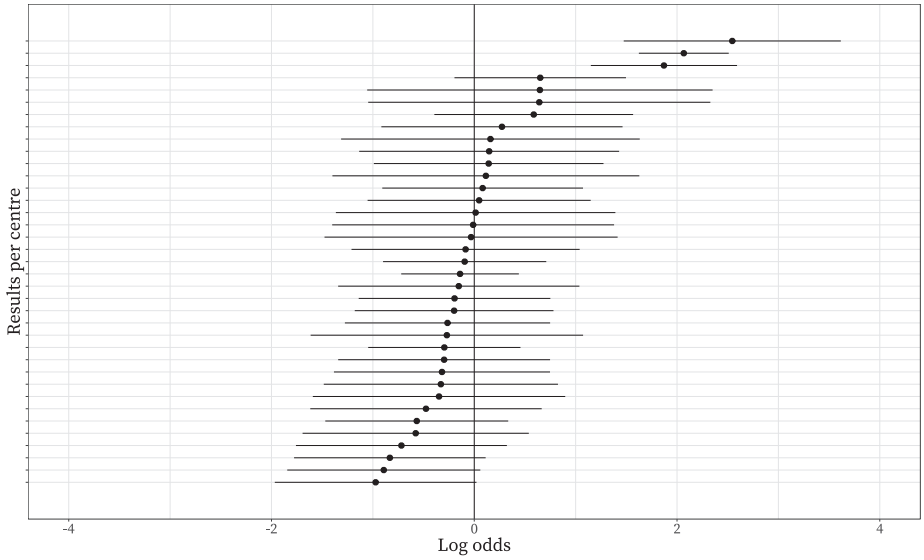
	Use of beta-blocker	
	OR (95% CI)	**p-value**
Primary outcomes		
In-hospital mortality	0.86 (0.27 – 2.66)	0.78
GOSE at 6 months*	0.87 (0.38 – 2.00)	0.72
Secondary outcomes		
Use of vasopressors	0.81 (0.37 – 1.79)	0.59
Hospital Length Of Stay	4.27 (-0.03 – 8.57)	0.05

**Glasgow Outcome Scale Extended – an OR >1 indicates worse outcome*

Supplementary Table 8.7 Association of beta-blocker administration with outcome in patients with a primary indication for the use of beta-blockers

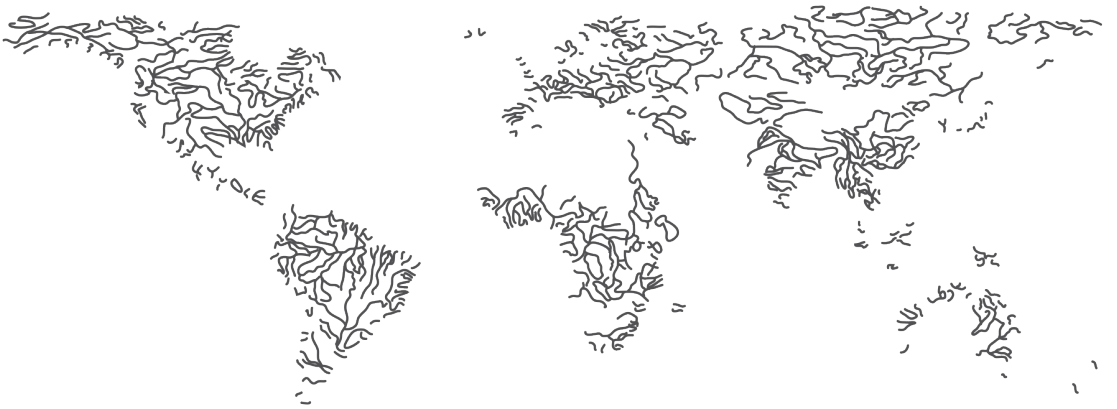
	Use of beta-blocker	
	OR (95% CI)	**p-value**
Primary outcomes		
In-hospital mortality	1.22 (0.37 – 4.02)	0.74
GOSE at 6 months*	1.09 (0.57 – 2.11)	0.79
Secondary outcomes		
Use of vasopressors	0.61 (0.26 – 1.44)	0.25
Hospital Length Of Stay (per day increase)	-0.96 (-6.16– 4.25)	0.72

**Glasgow Outcome Scale Extended – an OR>1 indicates worse outcome*



Supplementary Figure 8.1 Caterpillar plot for the administration of beta-blockers in the first 48 hours after injury

This panel shows the differences between centres with respect to the the administration of beta-blockers in the first 48 hours after injury A random effect regression model was used to correct for random variation and adjusted for case-mix severity using the IMPACT variables, prior indication for beta blockers and 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. A centre with average outcome has log odds 0, a positive log odds indicates higher mortality. Lines indicate 95% posterior interval. Significant differences are indicated by the p-value.



Chapter 9

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

Critical Care 2019

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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 indicators, 16 process indicators, 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.

Keywords

Quality indicators, Benchmarking, Traumatic brain injury, Intensive care unit, Trauma registry, Quality of care

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 the 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 while 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 centres 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 (Additional file 1: Questionnaire round 1). Quality indicators were categorized into structure, process, and outcome indicators[25]. Overall, due to the 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 (Additional files 1, 2, and 3). In the first round, the AC rated the preliminary quality indicators on four criteria: validity, discriminability (to distinguish differences in centre 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](Table 9.1). 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 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), and Rivermead Post-Concussion Symptoms Questionnaire (RPQ), 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 (Additional file 2, question outcome scales). Outcome scales that received the 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.

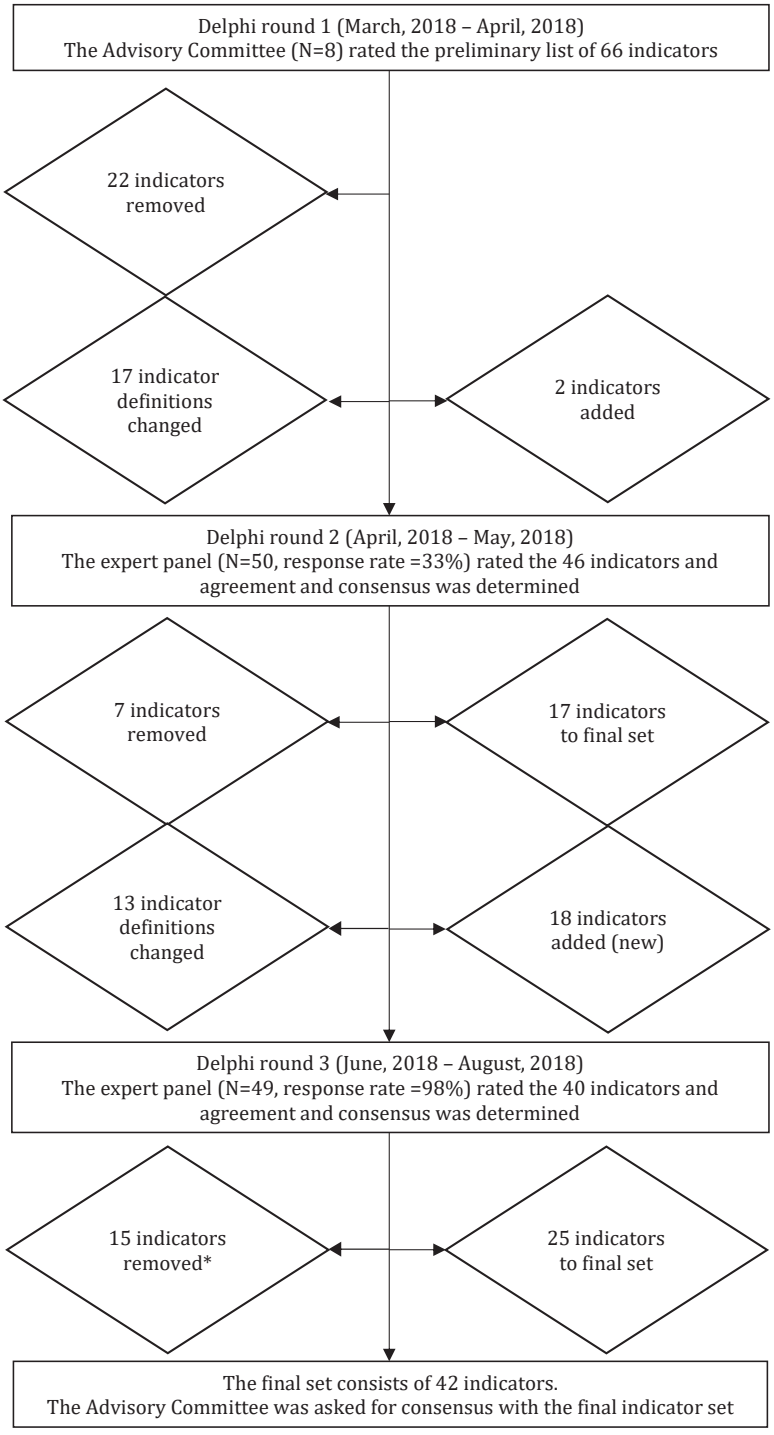
Table 9.1 Selection criteria used to rate the quality indicators

Criteria	Definition
Validity	It is likely that better performance on the indicator reflects better processes of care and leads to a 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, and professionals can act on it

These criteria were used to rate each quality indicator during all Delphi rounds[26-30]

Figure 9.1 Overview of the Delphi process

*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. The 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. The disagreement was defined as a median score below 4 on at least one of the four criteria. The 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.* ►


Delphi round 1 (March, 2018 – April, 2018)
The Advisory Committee (N=8) rated the preliminary list of 66 indicators
22 indicators removed
17 indicator definitions changed
2 indicators added
Delphi round 2 (April, 2018 – May, 2018)
The expert panel (N=50, response rate =33%) rated the 46 indicators and agreement and consensus was determined
7 indicators removed
17 indicators to final set
13 indicator definitions changed
18 indicators added (new)
Delphi round 3 (June, 2018 – August, 2018)
The expert panel (N=49, response rate =98%) rated the 40 indicators and agreement and consensus was determined
15 indicators removed*
25 indicators to final set
The final set consists of 42 indicators.
The Advisory Committee was asked for consensus with the final indicator set

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 the 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 9.1). 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 anesthesiologists (N = 5, 10%) (Table 9.2). Most of 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 centres across 18 European countries: mostly in Western Europe (N = 26, 55%). Most experts were from academic (N = 37, 84%) trauma centres 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 9.1). In round 1, 22 indicators were excluded. The main reason for exclusion was poor agreement (median < 4) on all criteria except discriminability (Additional file 4). Round 2 started with 46 indicators; 17 were directly included in the final set and 7 were excluded, mainly due to a 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.

Table 9.2 Baseline characteristics Delphi panel

	Number	Percent
Total number of Delphi panelists	50	100
Total number of participating centres	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
UK	5	10
Southern Europe	8	16
Eastern Europe	2	4
Baltic States	1	2
Centre (*N* = 44)		
Academic	37	84
Nonacademic	7	16
Centre location [c](*N* = 45)		
Urban	44	98
Suburban	1	2
Trauma designation [d](*N* = 45)		
Level I	31	69

Table 9.2 Continued

	Number	Percent
Level II	1	2
Level III	7	15
Our centre is not officially designated as a trauma centre	3	7
Our country does not explicitly designate trauma centres	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

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-h 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. TBI traumatic brain injury, CENTER-TBI study Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury study, ICU intensive care unit a) Only asked to those who answered clinician as a 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 UK 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 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 1200 trauma patients annually or have 240 admissions with an Injury Severity Score of more than 14). It is characterized by 24-h in-house availability of an attending surgeon and the prompt availability of other specialties (e.g., neurosurgeon, trauma surgeon)

The final quality indicator set consisted of 42 indicators on 13 clinical domains (Table 9.3), including 17 structure indicators, 16 process indicators, and 9 outcome indicators. For the domains "precautions 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 an outcome indicator, since there was no consensus in the panel on its validity to reflect the 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 the 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 centres. 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 9.2).

Table 9.3 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 a 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 h per day (yes/no)
7. Process: Median accident-to-ICU-admission time (process) Extra: Time of the accident/injury to ICU-door-time

Table 9.3 Continued

Domain Indicators	
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 min after the 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 centre that can insert an ICP monitor within 2 h 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 centres that use ventricular catheters
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 h/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 h/number of patients with enteral feeding during ICU stay

Table 9.3 Continued

Domain Indicators
25. Outcome: Number of TBI patients with any blood glucose above 10 mmol/L (180 mg/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
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 a decline in oxygenation,". VAP is defined as pneumonia occurring > 48 h after endotracheal intubation[35]

Table 9.3 Continued

Domain Indicators
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 the 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 the 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%. The 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 mmHg or greater and serum lactate level greater than 2 mmol/L (> 18 mg/dL) in the absence of hypovolemia[36]
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

The 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.

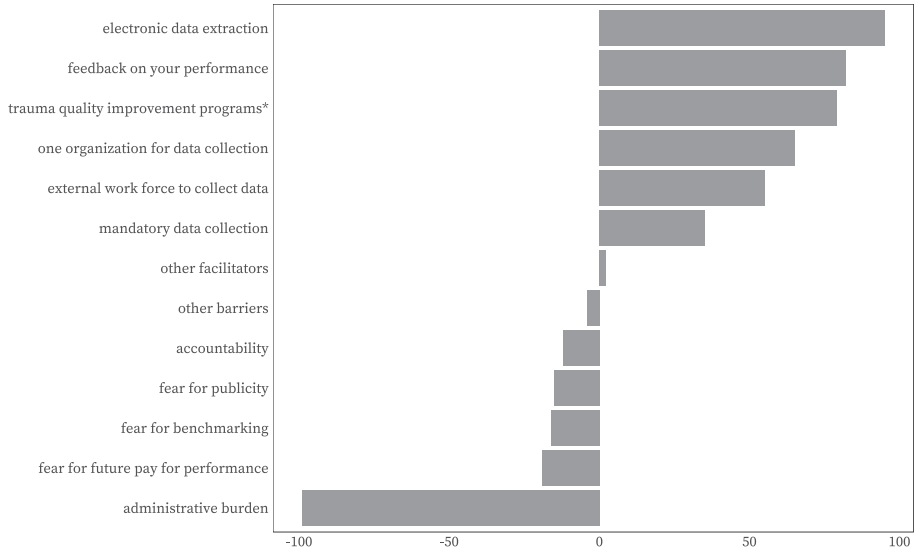


Figure 9.2 Facilitators or barriers for implementation of the quality indicator set

*Percentage of experts that indicated a certain facilitator or barrier forimplementation 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 the 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 into 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 indicators, 16 process indicators, 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 craniectomy, 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[37]. Most indicators were excluded from the set due to 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[38,39]. 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 an outcome measure in current registries, but the Delphi panel commented that determination of the 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 the methodology and determined strategies with the Advisory Committee. Although the RAND/ UCLA Appropriateness Method recommends a panel meeting[40], 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 into 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 of ICU experience). However, more input from some key stakeholders in the 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[41,42]. Therefore, future studies should put even more efforts 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 the improvement of care in several ways. First, registration of indicator data itself will make clinicians and other stakeholders aware of their centre 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[43]. Fourth, (international) benchmarking of quality indicators will facilitate discussion between (health care) 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[44,45]. 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 into 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[46]. A single (external) organization for data collection could enhance participation of multiple centres. 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[38,47]. 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 the 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 the 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.

All additional files are accessible via: https://ccforum.biomedcentral.com/articles/10.1186/s13054-019-2377-x#Sec17.

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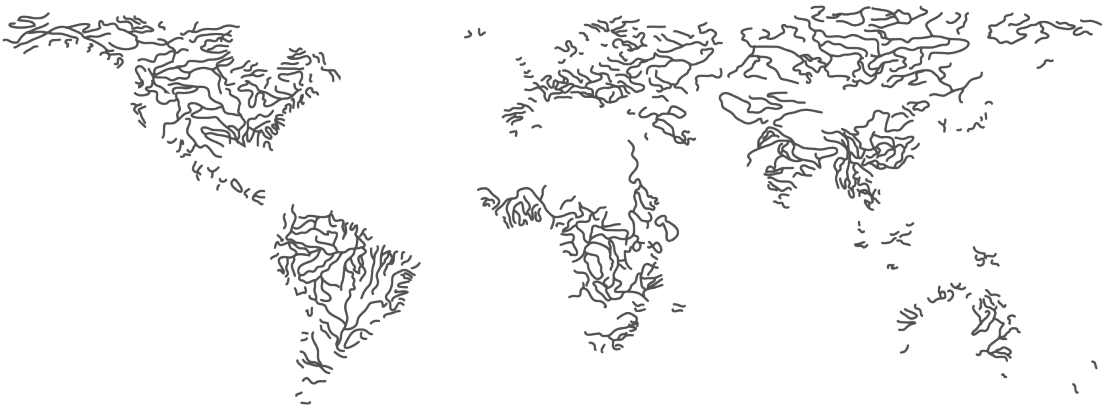

Chapter 10

Quality indicators for patients with Traumatic Brain Injury in European Intensive Care Units: a CENTER-TBI study

Critical Care 2020

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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 2138 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). Reliability 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 30%-89% and 28%-76% for structure and process indicators. Significant ($p < 0.001$) between-centre variation was found in 5 process and 5 outcome indicators with MORs ranging from 1.17 to 4.15. Reliability of outcome indicators was generally low; 5 out of 7 had less than 10 events per centre.

Conclusions

Overall, 9 structure, 4 process, and 1 outcome indicator 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.

Trial registration

The core study was registered with ClinicalTrials.gov, number NCT02210221, registered 08/06/2014, https://clinicaltrials.gov/ct2/show/NCT02210221?id=NCT02210221&draw=1&rank=1 and with Resource Identification Portal (RRID: SCR_015582).

Keywords

quality indicators; benchmarking; traumatic brain injuries; intensive care units; quality of health care

BACKGROUND

Limited evidence is available to direct critical care practice in patients with traumatic brain injury (TBI)[1]. Randomized controlled trials have shown a 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 an 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.

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[10]. 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, the 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.

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.

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 two 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.

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 score (ISS). The MOR was calculated from the $\tau 2$ (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 (Additional file 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 10.1). 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 10.1).

Table 10.1 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	75
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					

Table 10.1 Baseline centre - and patient characteristics

Centre characteristics	**Centre-level (N=54)**			**Patient-level (N=2006)**	
	N	**%**		**N**	**%**
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

GCS: Glasgow Coma Scale, ICU: Intensive Care Unit, ISS: Injury Severity Scale, NA: not applicable, TBI: Traumatic Brain Injury

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 h per day (N = 40; 75%), and presence of a step-down unit (N = 38; 70%) (Additional file 2). Patientto-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) (Additional file 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] (Additional file 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) (Additional files 2, 3, 4). Overall, one process and one outcome indicator showed low feasibility (Table 10.2).

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 (Additional file 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 10.1). 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-month GOSE was found (MOR = 1.29, $p = 0.5$) (Figure 10.2). Overall, five structure (three with moderate performance), two process, and four outcome indicators showed low discriminability (Table 10.2).

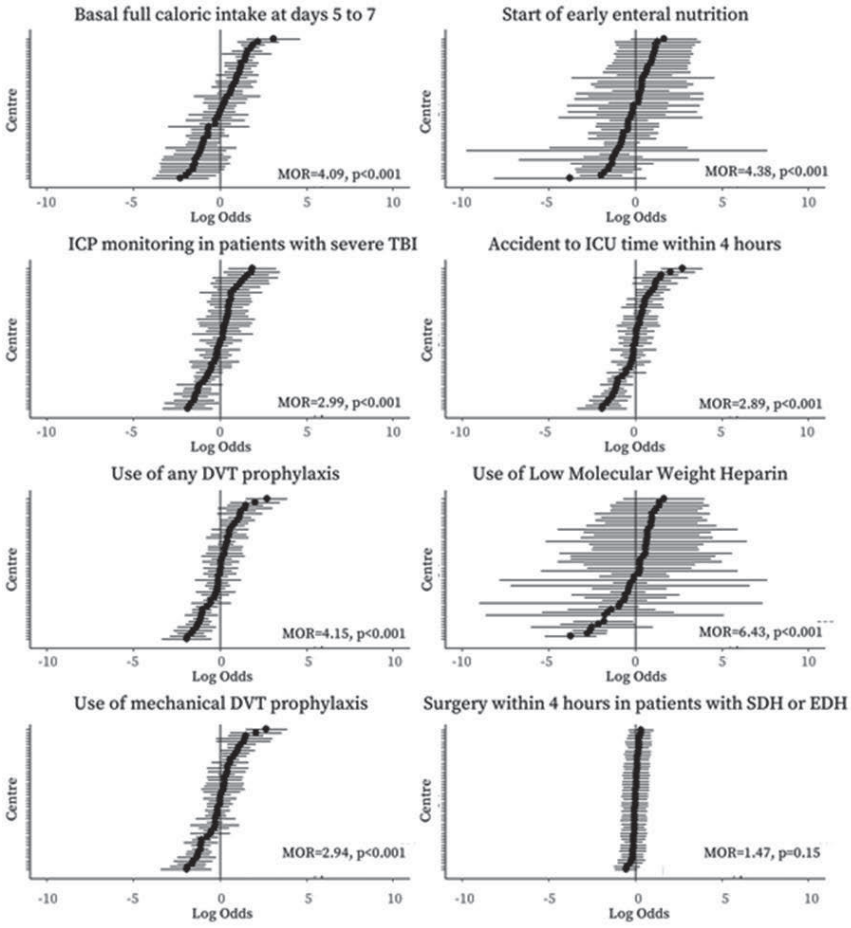

Figure 10.1 Adjusted random effect estimates per centre for process indicators

This figure shows the between-centre differences for the process indicators (beware of different x-axis). Quality indicator definitions can be found in supplement table 3. 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).

DVT: deep venous thrombosis, EDH: epidural hematoma, ICU: Intensive Care Unit, MOR: median odds ratio, SDH: subdural hematoma

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 10.2).

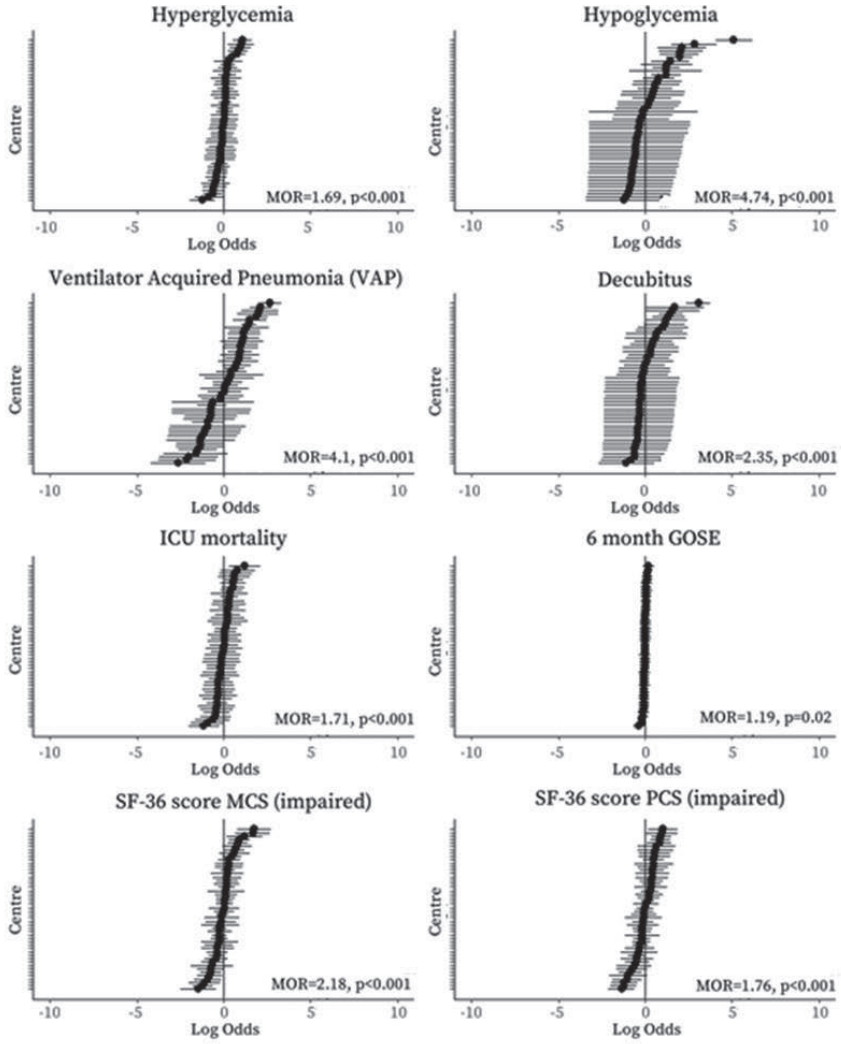

Figure 10.2 Adjusted random effect estimates per centre for outcome indicators

This figure shows the between-centre differences for the outcome indicators. 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 hypoglyecemia were too low to reliably show between-centre variation (high confidence intervals). Impaired SF-36 (PCS or MCS) score < =40.CI: Confidence Interval, GOSE: Glasgow Outcome Scale Extended, ICU: Intensive Care Unit, MOR: Median Odds Ratio

Table 10.2 Overview of indicator performance

Panel A. Structure indicators
The existence of a protocol including specific guidelines (like the BTF guidelines or institutional guidelines) for Traumatic Brain Injury patients (yes/no)
The presence of (some form of) regular audits to check guideline adherence in general at the Intensive Care Unit (ICU) (yes/no)
The presence of dedicated person(s) to oversee guidelines development and maintenance, including those for patients with TBI, at the ICU (yes/no)
Does your hospital have a dedicated/specialized neurocritical care unit? (yes/no)
The availability of operating rooms 24 hours per day (yes/no)
The presence of a step down unit where patients can still be monitored 24/7, but less intensively than at the ICU (yes/no)
Intensivist to ICU bed ratio 1 to <6
ICU nurse to ICU bed ratio 1 to <1.75
Do you have a protocol for glucose management available for patients with TBI at your ICU? yes/no
Availability of a neurosurgeon (staff) 24/7 within 30 minutes after call (yes/no)
24/7 availability of a CT scan and radiologist review (yes/no)
Panel B. Process indicators
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
Median accident-to-ICU-admission time (reference 0-<4 hours)
Number of severe (GCS 3-8) TBI patients with ICP monitoring/ number of severe TBI patients at the ICU Data: baseline GCS
Number of patients with TBI that receive any DVT prophylaxis [a]/ total number of patients with TBI at the ICU
Number of patients that receive pharmaceutical prophylaxis with low molecular weight heparins/ total number of TBI patients admitted to the ICU
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
Number of TBI patients with start of (early) enteral nutrition within 72 hours post-injury/ number of patients with enteral feeding during ICU
Median door-to-operation time for acute operation of SDH and EDH with surgical indication (reference 0-<4 hours)

Feasibility	Discriminability
% available data	adherence score
98%	89%
98%	30%
98%	83%
100%	65%
100%	74%
100%	70%
100%	50%
100%	26%
98%	81%
100%	91%
100%	91%

Feasibility	Discriminability	
% available data	adherence score	IQR|MOR
100%	20%	44 |4.14
99%	35%	26|2.61
100%	69%	38|2.84
97%	80%	34|3.93
0%	100%	2|6.34 [b]
43%	71%	41|1.73
78%	99%	13|1.95 [b]
100%	64%	29|1.4 [c]

Table 10.2 Continued

Panel C. Outcome indicators
Number of TBI patients with any blood glucose above 10 mmol/L (180mg/dL, hyperglycemia)/total number of patients with TBI at the ICU
Number of TBI patients with any blood glucose below 4 mmol/L (hypoglycemia)/ total number of patients with TBI at the ICU
Number of ICU-deaths among patients with TBI/ total number of ICU-admitted patients with TBI
Incidence of ventilator associated pneumonia (VAP) in patients with TBI/ total number of TBI patients with mechanical ventilation at the ICU
Number of TBI patients with decubitus at the ICU / number of TBI patients at the ICU
The median score of the GOSE from all patients with TBI at 6 months
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

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 reliability (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).

Statistical uncertainty

Four indicator definitions were slightly changed without changing its content (Additional files 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 (Additional file 4, Table 10.2).

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 between-centre variation suggest a potential for quality

Feasibility % available data	Reliability Event rates	Discriminability IQR|MOR
93%	8/22	23|1.51
93%	0/22	3| 2.36 [b]
99%	4/22	12|1.58
98%	3/20	31|4.12
98%	0/22	2| 2.45 [b]
86%	NA	4 (score)|1.29 [c]
28%	NA	17 (score)| 1.2 [c] 19 (score)| 1.2

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. Reliability 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.

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 nine structure indicators, five process indicators, but none of the outcome indicators out of 26 indicators to be appropriate for quality measurement and improvement in this validation study. Overall, the 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 4 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 a more severe injury, greater organ dysfunction, more interventions, or 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 the reduction of variation in evidence-based care processes. One previous study reported the 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 dataset, 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 a centre level, could not be addressed[30]. Statistical uncertainty was reflected in the number of event rates, while also other aspects as intra- and interrater 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 the 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 be aware of their centre performance and help develop internal quality improvement programmes. 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 re-evaluation of the quality indicators.

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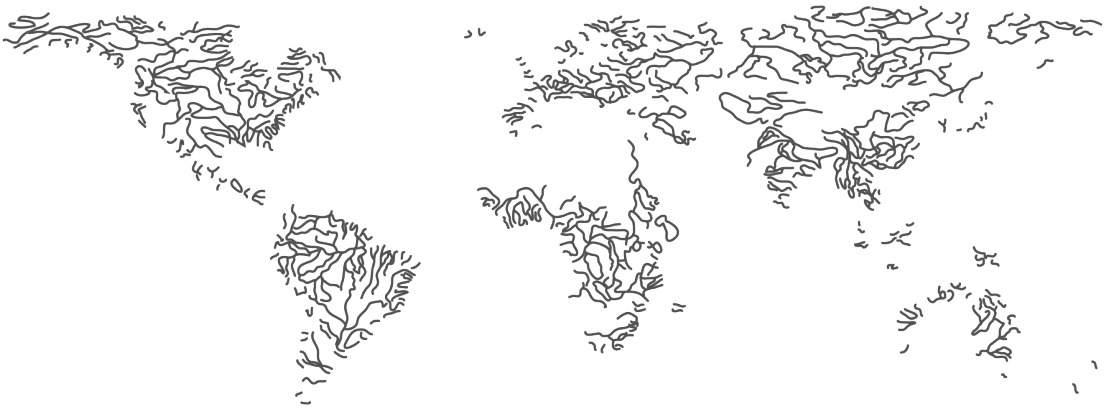
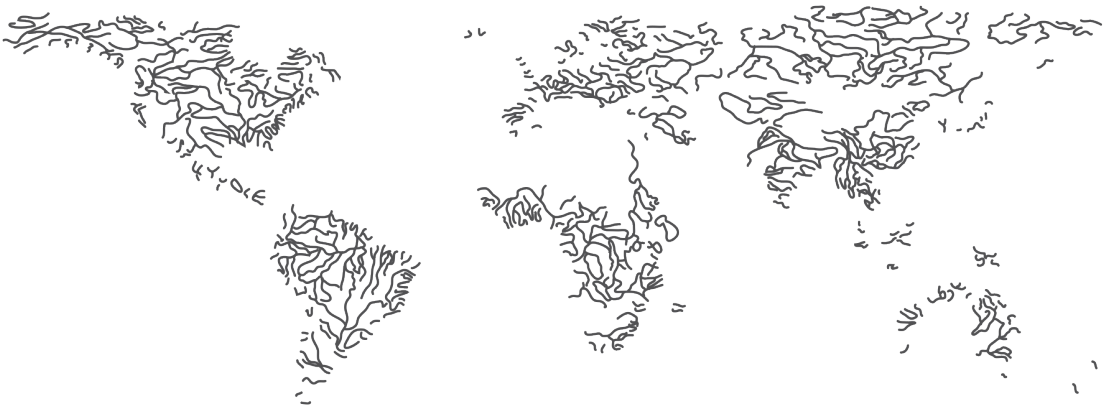


Chapter 11

General Discussion



MAIN FINDINGS

This thesis had two aims. We first examined the contemporary landscape of neurocritical care in Europe and Australia. We observed in chapter two and chapter three that around a quarter of patients with Traumatic Brain Injury (TBI) in neurocritical care are older than 65 years of age. A substantial part of patients with TBI in neurocritical care were classified as mild TBI (mTBI) according to the Glasgow Coma Scale (GCS) classification, and more than half of the patients suffered from major extracranial injury. We identified in chapter 3 three patterns of patients with TBI in neurocritical care: patients that died within 72 hours after Intensive Care Unit (ICU) admission, patients that were discharged within 72 hours after ICU admission, and patients that stayed in the ICU for longer than 72 hours. Though patients with moderate to severe TBI in the ICU stratum showed a greater survival than expected, nearly half experienced unfavourable outcome and their functional outcome was no better than expected by established prognostic schemes. Also, we observed in chapter 2-4 that there is large variation between centres, regions, and countries regarding to case-mix, specific interventions, and management aspects in neurocritical care for patients with TBI. Despite the large variation in neurocritical care practices that we observed, variation in outcome between centres and between countries were smaller and/or undetectable. For the access of Endovascular Thrombectomy (EVT) for patients with acute ischemic stroke, we found in chapter 6 that the differences between regions in the Netherlands reduced over time.

We then assessed how we can make neurocritical care more effective and of higher quality. We concluded in chapter 7 that maintaining neutral fluid balance is not general practice in European and Australian neurocritical care units, while it may contribute to better clinical outcomes. We observed that patients who received more fluids and had higher daily fluid balances during ICU stay, had worse outcomes compared to patients with negative daily fluid balance. We depicted in chapter 8 that beta-blockers use in patients with TBI in neurocritical care varies substantially between European centres. We demonstrated that there is no association between the early administration of beta-blockers and improved outcome, implying that the benefit of beta-blockers may be less than previously presumed. However, subgroup analysis revealed that for patients with isolated TBI, early administration of beta blockers might be associated with improved outcomes. We also developed and validated a quality indicator set in chapter 9 and chapter 10 that can be used to standardize structures and process of care and benchmark results of individual hospitals.

In this final chapter the results and interpretation are summarized and discussed per research question. Also, we discuss the methodological considerations and implications for clinical practice, policy, and research.

INTERPRETATION OF THE FINDINGS

Variation in patients, care, and outcome

The distribution of patients in neurocritical care follows the trend in the general population over the past years: an increasing proportion of elderly patients is admitted to neurocritical care after stroke or TBI[1]. For patients with TBI in neurocritical care, about 25% is older than 65 years, and about 5% constitutes of octogenarians. Compared to past series, in which about 10% of patients was older than 65 years, the proportion of elderly with TBI admitted to neurocritical care substantially increased (chapter 2-3)[2,3]. For acute ischemic stroke, we showed in chapter 6 that in 2014 to 2017 more than 50% of the patients with acute ischemic stroke that received EVT was older than 71 years. In the time period of 2004 up to 2010, the median age of patients with acute ischemic stroke receiving EVT was 62 years reflecting the growth of evidence. As clinical trials often include upper age limits, elderly patients are consequently excluded from research to improve their outcome, and therefore evidence for and experience with treatment in elderly is relatively limited[4,5,6]. The growing evidence for the effectiveness for EVT in octogenarians and nonagenarians has contributed to a changed attitude towards EVT in elderly patients with acute ischemic stroke patients, especially in the Netherlands[7,8].

In chapter 3 we observed that the age of patients with TBI in neurocritical care dying within 72 hours after ICU admission is substantially higher than patients that were discharged within 72 hours or staying at the ICU for longer than 72 hours. On the one hand this might confirm the results of previous studies that indicate that elderly patients are at higher risk for worse outcome compared to younger patients[9-12]. On the other hand, our results may also be the result of treatment limitations that have been proposed by a recent study observing a decrease of management intensity with advanced age[13]. For patients with TBI, in which there is no evidence for a specific neuroprotective therapy that is highly effective to improve clinical outcomes, these findings make a strong case for targeting health care provision and research in TBI in this population. As TBI patients in neurocritical care are most often injured due to incidental falls, there should be a refocus of research efforts to prevent TBI in the older adult. Specific environmental modifications and the addressing of clinical factors in vulnerable patients, including appropriate medication management have been suggested as prevention measures for TBI in the elderly[14-16].

In chapter 2, we observed that about a third of patients with TBI in neurocritical care was classified as mTBI according to the GCS classification. Many of these patients with mTBI suffered from major extracranial injuries. In chapter 3 and 5, we observed that the group of patients that were discharged from neurocritical care within 72 hours, mainly consisted of patients with mTBI. These short stay patients, compared with patients that stayed in the

ICU for longer, were less severely injured, received less monitoring and treatments, and achieved better outcomes. The most frequently indicated reasons for short stay patients and patients with mTBI were the need for strict neurological observation and mechanical ventilation. It is unclear whether admission of short stay patients and patients with mTBI represents appropriate prudence or inappropriate use of clinical resources. The risk of deterioration in mTBI is low but non-neglible; close surveillance and assistance to patients with mTBI could help in the early detection of neurological deterioration. Simultaneously, admission of patients that do not benefit from ICU admission leads to inefficient and expensive care since ICU beds are expensive and scarce[17].

More appropriate use of limited ICU resources especially for patients with mTBI requires an early risk stratification tool that can be practically implemented to guide selective risk-based ICU use. Although several mortality risk scores have been developed for patients with TBI[18,19], the performance of these risk scores has not been evaluated for the purpose of predicting early need for ICU level care. For other clinical fields, for example for patients with non-ST-segment-elevation myocardial infarction, risk scores to guide decision making regarding the most appropriate level of care by selecting a threshold score have been developed[20]. The development of such a tool for patients with mTBI is challenging and requires large multicentre studies and validation studies. In addition, the terminology 'mild TBI' in the traditional classification by GCS suggests a well-defined and favourable course of disease. However, as observed in this thesis and confirmed by many other studies, many patients with mTBI in neurocritical care have long hospital length of stays and poor outcomes are not uncommon[21,22]. The refinement and implementation of suggested multidimensional classification methods could therefore be relevant to predict care pathways better than with GCS only[23].

We observed in chapter 3 and 4 that the in-hospital mortality rate for patients with TBI in neurocritical care was 15%, which increased to 21% after 6 months. Mortality at 6 months was lower than predicted by the IMPACT prognostic model. These data can be interpreted in different ways. First, the study population in our observational study differs from the study population the IMPACT-model was originally derived from[18], implying that the IMPACT-model might not be entirely valid in our dataset. Second, it might well be that the processes and structures of care have improved over time, leading to a decrease in mortality rates. However, the rate of unfavourable outcome (GOSE < 5) was similar to that predicted by the IMPACT prognostic model. Third, there might be a growing awareness of self-fulfilling prophecy among physicians regarding patients with very severe injury. As a result, patients with deplorable prognosis might receive treatment resulting in survival with functional limitations compared to past decades in which these patients might not always have been given the benefit of the doubt[24,25].

For patients with severe TBI, we observed in chapter 4 that only 50% was able to live independently after 6 months. In addition, the self-reported quality of life of patients with TBI is sorrowful; about 36% of all patients with TBI report unfavourable quality of live up to 10 years after injury, implying a huge burden on society[26]. TBI rehabilitation has been proven to confer additional benefit in improving the functional outcomes compared with spontaneous recovery[27,28]. However, the probability of receiving rehabilitation is associated with patients' and regional characteristics[29]. Also, it might be challenging to meet the key success criteria for health and rehabilitation services such as inclusion of and access to well-coordinated multidisciplinary processes incorporating the varying needs of the patients. Therefore, future studies should assess the necessity of more extensive multidimensional and standardized assessment of functional and psychological impairments and corresponding rehabilitation needs.

Ideally, neurocritical care should be organized to deliver evidence-based treatments in a timely manner to all patients that might benefit from proven effective treatments. Before the results of the pivotal EVT trials were published, stroke guidelines recognized the low level of evidence for EVT and were very conservative in their recommendations[30-32]. Some pioneering centres however provided EVT as an experimental treatment when guidelines were not yet accommodating this intervention, leading to the development of acute stroke networks and treatment experience which was necessary to successfully perform a Randomized Clinical Trial (RCT)[33].

The aim of the European Stroke Organization (ESO) is that in 2030, 95% of eligible patients across Europe should have access to EVT and EVT rates should be over 5% in all European countries[34]. In a previous study, it was observed that the Netherlands belong to one of the countries in Europe with the highest annual proportion of patients with ischemic stroke receiving EVT[35] (Figure 11.1). In chapter 7, we estimated that in 2018 approximately 50% of the number of ischemic stroke patients eligible for EVT actually received EVT. To approach the aim of the ESO, further efforts are needed. At the moment, ongoing efforts are made that evaluate prehospital stroke scales to identify patients that are likely to have an intracranial large vessel occlusion, which could allow for direct transportation of EVT eligible patients to an endovascular-capable centre without delaying IVT for the other patients[36]. Other organizational aspects that are thought to further improve outcomes for ischemic stroke patients are promoting prenotification of hospitals by emergency medical service, rapid activation of the entire stroke team, and provision of feedback to the stroke team on their performance[37-39].

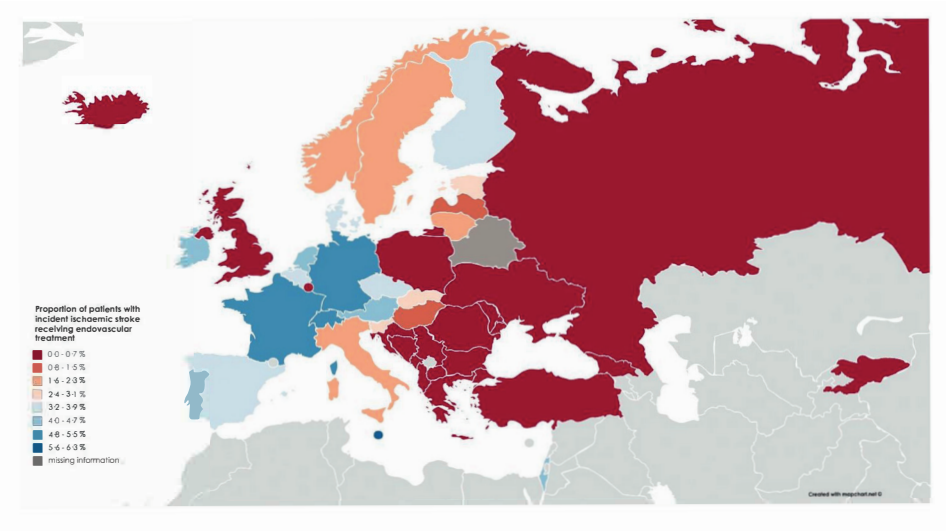


Figure 11.1 Chloropleth map showing contemporary annual estimates of the proportion of patients with incident ischaemic stroke receiving EVT in 42 European countries[40]

Organizational aspects can also play an important role in the decision to admit patients with mTBI to the ICU. We found in chapter 5 that centres with a designated neurocritical care unit and that had step-down beds available were more likely to admit patients to ICU than centres that did not have such facilities. In a dedicated neurocritical care unit (='closed'), similar types of patients are repeatedly treated by the same healthcare professionals. This is in contrast to an 'open' ICU in which healthcare professionals treat all types of patients. The idea of a dedicated neurocritical care unit is that treating increased volumes of similar type of patients leads to more experienced health care providers. Ideally, this results in improved patient outcomes. Strong evidence that a dedicated unit improves outcomes exists for patients with stroke and subarachnoid hemorrhage, but there is less evidence for patients with TBI[41-45]. Also, existing studies have notable limitations. For example, 'before and after' studies, are susceptible to a 'Hawthorne effect', whereby practice patterns change over time, in part because clinicians know that their practices are being audited and therefore become more focused on the practice being studied[46]. Moreover, it is likely that other positive changes were introduced at participating centres over time, apart from the implementation of a neurocritical care services. Therefore, it is more likely that concomitant system changes must occur in order to improve outcomes[41]. A theoretical framework on the impact of designated neurocritical care units is shown in Table 11.1.

Table 11.1 Pros of an 'open' ICU versus a 'closed' ICU[47]

Open Model	Closed Model
Less conflict	Known to be associated with decreased mortality and reduced ICU length of stay
Admitting physicians or surgeons may have better familiarity with patients	Better coordination of critical care services
Admitting specialists continue care after ICU discharge – continuity of care	Cohesive treatment strategy
Cost-saving measures	More efficient use of resources
Minimizes handovers	Focused management by specialists in a critical care environment

In chapter 2-4, we found considerable variation in the use of interventions and selected management aspects available in neurocritical care. Treatments available for TBI patients that were highly variable among European centres were ICP monitoring and Aggressive Therapy (any use of Decompressive Craniectomy, Metabolic Suppression, Hypothermia Therapy or Intensive Hypocapnia during ICU stay). In daily clinical practice, physicians use ICP monitoring to early detect any rise in ICP and if necessary subsequently adjust treatment strategy. There is no high level evidence supporting ICP monitoring, although several attempts for improving quality of evidence for ICP monitoring have been performed in the past. Research in ICP monitoring has been complicated by ethical challenges in randomizing patients between ICP monitoring and no ICP monitoring. External validity from a published RCT was low for Europe since this RCT was performed in lower income countries[48,49]. The clinical rationale of using ICP monitoring is to monitor secondary damage to brain cells. However, it has been argued that an increase of ICP occurs in the late stadium of secondary injury. From a pathophysiological perspective, the viability of brain cells depends on an uninterrupted supply of oxygen (and glucose), suggesting that close monitoring of oxygen levels of brain cells could be an effective marker of secondary injury. Currently, several collaborations and research efforts are ongoing to resolve the outstanding questions about the optimal strategy of neuromonitoring (including ICP monitoring and continuous brain oxygen tissue monitoring) and whether this leads to improved outcomes for patients[50-52].

Despite the considerable variation in the use of interventions and selected management aspects, we found minor variation in outcomes between centres and Australia, Europe, and the United Kingdom in chapter 3 and chapter 4. 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 difference less easily detectable. Or, in other words, there may be a 'regression to the mean' effect

caused by balance between centres in opposing treatments regarding their effect on outcome. Also, 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[53]. It is also possible that over time, a more homogeneous standard of treatment has evolved in Australia, Europe, and Israel. However, the large variation we still observe might discouragingly indicate the minor potential of treatment effects on outcome. Ultimately, the refinement of evidence for critical TBI patients might follow the same observation as we had observed in chapter 6: an increase of evidence contributes to a decrease of differences between regions.

IDENTIFYING EFFECTIVE CARE

Fluid management

We observed in chapter 7 an consistent association between incremental daily net-positive fluid balances and worse clinical outcomes. The pathophysiological concept of fluid overload and worse outcome is well-accomplished and is described through different pathways. First, capillary hydrostatic back-pressure to the brain might occur due to fluid overload and raised central venous pressure (CVP), resulting in fluid accumulation into the brain interstitium[54]. In the injured brain, this will cause cerebral edema, further facilitated by blood-brain-barrier disruption[55]. Second, experimental and clinical work has indicated that excess isotonic increase systemic complications[56-60] (Figure 11.2). The lungs are one of the organs in which adverse effects of fluid overload are most evident[61,62]. Derangements in the capillary permeability, which occurs in SIRS, combined with an increased hydrostatic pressure, as induced by aggressive fluid resuscitation, results in major interstitial edema that can lead to important clinical consequences. The kidneys are susceptible to functional impairment due to positive fluid balance or accompanying abdomen injury, causing venous congestion and subsequent interstitial edema[63-65]. Deeper mechanistic studies are mandatory to understand the relative contributions of each component of fluid therapy on different organ systems.

So, how to optimize fluid management in patients with TBI in neurocritical care? Malbrain et al introduced the 'ROSE' concept of phases of critical illness in septic shock starting with the resuscitation phase. During this resuscitation phase patient require rapid intravascular fluid repletion to maintain organ function. The goal of this phase is early adequate goal directed fluid management and fluid balance will subsequently be positive due to a significant amount of fluids accumulating in the interstitial space. The next phase, the optimisation phase, occurs within hours to days and is marked by ischaemia and reperfusion. In this phase, patients in an unstable, or shock state require

titrating of fluids to achieve sufficient cardiac output and adequate organ perfusion and oxygenation. Over days, the stabilisation phase evolves and fluids should only be administered for maintenance of minimally required circulating blood volume and replacement. Malbrain et al recommended to aim for a neutral or negative fluid balance in this phase. The final phase, the evacuation phase, takes place in patients who do not transition from the 'ebb' phase of shock to the 'flow' phase. This phase requires late goal directed fluid removal ('de-resuscitation') to achieve negative fluid balance[67].

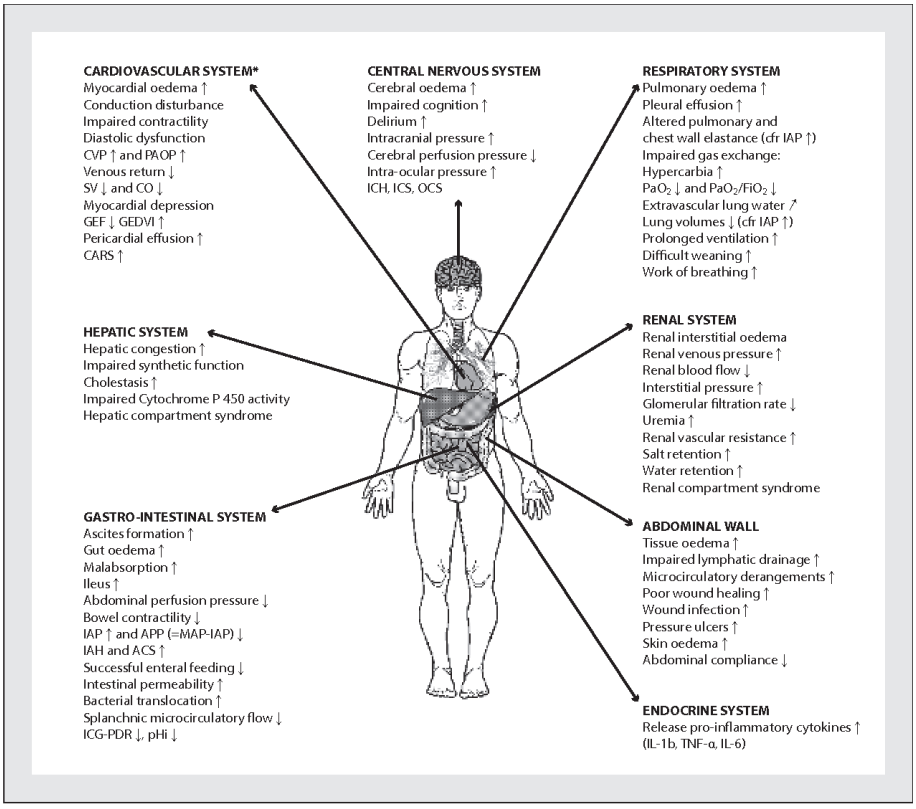


Figure 11.2 Possible pathophysiological effects of fluid-overload on end-organ function[66]

IAP= intra-abdominal pressure, IAH= intra-abdominal hypertension, ACS= abdominal compartment syndrome, ICH= intra-cranial hypertension, ICS= intracranial compartment syndrome, OCS= ocular compartment syndrome, CARS= cardio abdominal renal syndrome

This concept might also be partially true for patients with TBI. Especially patients with extracranial injury and patients requiring surgery require quick administration of fluids in the initial phase. As we assessed the mean fluid balance during ICU stay we were not able to provide an effect of the fluid therapy per separate day. Based on

our findings and findings of earlier studies, we would nevertheless recommend to keep the administration of fluids at an absolute minimum and only for normal maintenance and replacement. In chapter 7, we also observed that despite the minor differences in prognostic characteristics, centres that had a positive fluid balance lower than the mean more often performed hemodynamic monitoring. This might indicate that close monitoring of patients might be a proxy of randomization between centres with higher and lower fluid balance and aids in achieving optimal fluid balances in critical ill patients without jeopardizing patients outcomes by having too negative fluid balances or too positive balances which could both have detrimental effects[68].

We did not evaluate the composition of fluids that were given, which is of importance for clinicians to determine how patients' fluid input and fluid balance can be minimized. A study by Rass et al evaluated fluids' composition in patients with non-traumatic subarachnoid hemorrhage (Figure 11.3). They concluded that nutritional compound accounted for the highest proportion of fluids administered (31%)[69]. Although this may represent a modifiable factor, patients need nutrition, therefore this factor will probably not be very significant in fluid optimisation. That study also demonstrated that intravenous fluids accounted for another one third of fluids given to the patients. For clinicians in neurocritical care, this emphasizes the potential for fluid minimization by means of meticulously avoiding fluids without a strict clinical indication, but also by less liberal volumes of fluid administrated as vehicles for IV drugs. Furthermore, the application of vitamins and electrolyte substitution may be added to other maintenance fluid compounds, instead of being given in separate fluid bolus. Finally, awareness of the existence and potential harm of unintended fluid overload should likely be improved: this has been coined 'fluid creep' in recent literature and has been shown in other settings to be potentially harmful[56-58].

Beta-blockers

In chapter 8, we found that patients with critical TBI that received beta blockers within the first 48 hours after injury did not have better clinical outcomes than patients that did not receive beta blockers within the first 48 hours after injury. This association did not change for patients that did not have a prior indication for beta blockers. However, for patients without major extracranial injury, we found that there might be a hospital association for the use of beta blockers within 48 hours after injury and lower in-hospital mortality. The clinical evidence to support beta blocker use after TBI was noted in retrospective reviews that observed lower mortality when patients with TBI received beta blockers[70-73]. Most of these studies excluded patients with major extracranial injury and therefore our results are in line with these studies.

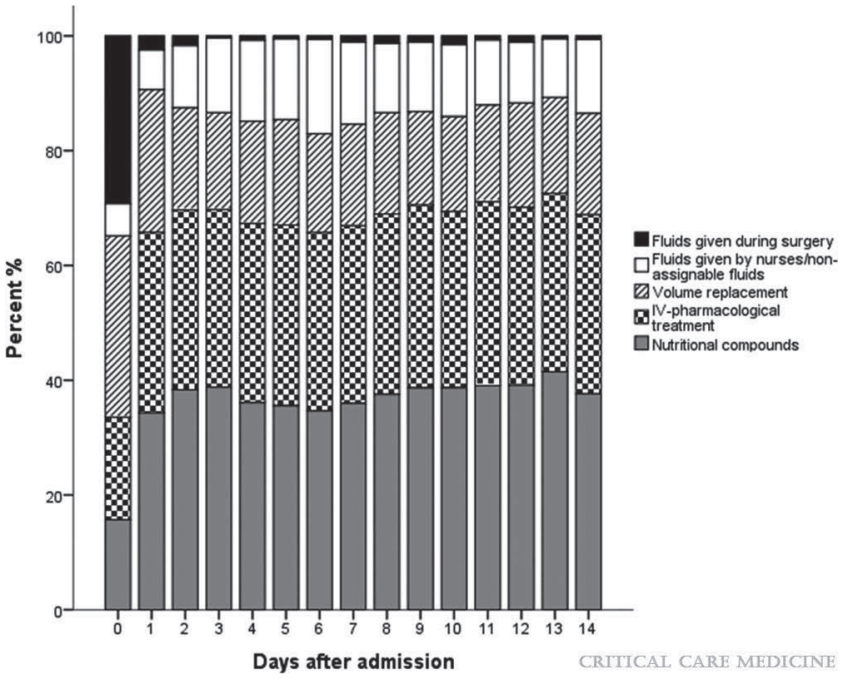


Figure 11.3 The composition of fluids given during the first 15 days of admission with the following contributors to fluid intake in patients with nontraumatic subarachnoid hemorrhage[69]

The composition of fluids given during the first 15 d of admission with the following contributors to fluid intake: nutritional compounds (31%), IV drugs (30%), volume substitution (17%), fluids given during surgery (3%), and fluids given by nurses or nonassignable fluids (19%).

Our data lacked granularity to demonstrate the effectiveness of a single subgroup of beta blockers. We observed that in our study population, labetalol was the most registered type of beta blocker. One study demonstrated superiority of propranolol when compared to other beta blockers[70]. Propranolol is a nonspecific B-adrenergic receptor antagonist that crosses the blood-brain barrier[74]. Propranolol has been shown to block the beta adrenergic signalling, relieve oxidative and inflammatory stress, decrease hypoxia, and improve cerebral glucose metabolism in a dose-dependent manner[72,75,76]. This data is also consistent with other types of brain injury in neurocritical care, for example, a recent meta-analysis also suggested mortality benefit of beta-blockade for patients with non-traumatic subarachnoid hemorrhage[77].

However, whether beta blockers might be protective is yet to be established. In case of a benefit, the exact mechanism should be unravelled. Therefore, future studies are warranted to further elucidate the benefit of beta blockers. Ideally, these studies also

take into account the type, dose and timing of beta blockers. For example, a double-blind RCT that allocates patients to the use of beta blockers versus placebo at different time points could be a potential design. Primary and secondary outcomes should focus on clinical outcomes such as in-hospital mortality and long-term functional outcome, but also on physical parameters such as mean arterial blood pressure, heart rate, and serum glucose. Effects of beta-blockers on paroxysmal sympathetic hyperactivity (PSH), which is present in a substantial minority of patients who survive traumatic brain injury, should also be subject of further study. PSH is a state of sympathetic hyperactivity, that can persist for weeks of months, consisting of periodic episodes of increased heart rate and blood pressure, sweating, hyperthermia and which is associated with worse outcomes[78,79]. Furthermore, the interaction of beta blockers with cardiac output, cardiac power, diastolic dysfunction, venous congestion and heart rate should be studied: e.g. beta-blockers are known to be effective in diastolic cardiac dysfunction, which in turn is reported as a feature of severe brain dysfunction and has been associated with adverse outcomes as well[64,80-82].

Quality Indicators

Together with 50 experts from 18 countries across Europe we identified 42 quality indicators that assessed quality of neuro-intensive care for TBI patients. This quality indicator set was further validated in the CENTER-TBI study and resulted in 9 structure, 5 process, and 1 outcome indicators showing potential for quality improvement purposes for critical TBI patients. A recent study by Haas et al83, investigated the association between quality of acute stroke care defined by overall adherence to evidence-based quality indicators and early outcome in German acute care hospitals. The authors concluded that higher quality of care measured by adherence to a set of evidence-based process QI's for the early phase of stroke treatment was associated with lower in-hospital mortality83 (Figure 11.4). Alternatively, lower in-hospital mortality might also have led to improved adherence to a set of evidence-based process QI's. We decided not to test the correlations between indicators and association with outcome of the final indicator set for TBI at the ICU. The expected correlations between quality indicators and outcome are hard to define, and the power of our study would be too low to detect an outcome effect. We therefore cannot exclude the possibility that the observed associations in the study by Haas et al were caused by residual confounding[83]. However, evaluation of these quality indicators in larger datasets has the potential to include assessment of such correlations with outcome.

Nevertheless, we also identified some potential pitfalls with the introduction of quality indicator sets. For example, some of our quality indicators are quite complex and difficult to assess retrospectively. This might be the reason why studies in other clinical fields reported that adherence to quality indicators is moderate[84-86] and that, especially

from the perspective of the intensivist, the (number of) quality indicators in the ICU setting should be manageable and practical[87]. Natural language processing (NLP) can be an efficient way of automatically extracting and structuring this information. NLP, a form of artificial intelligence, focuses on the interpretation and manipulation of all data that is spoken or written by humans. NLP is therefore a potentially pivotal technique for enabling quality measurement from Electronic Health Record Data[88,89]. In other clinical fields, such as colonoscopy care, NLP has been proven to support quality improvement[90,91]. Further, the adherence to and acceptance of the quality indicator set for TBI at the ICU will be facilitated when more evidence on best practices and effective treatments will become available. Therefore, the acceptance and application of our quality indicator set may be challenging at this time, in spite of the rigorous process underlying its development and validation. In any way, it represents a 'call to arms' for more evidence generation supporting the management of critically ill TBI patients.

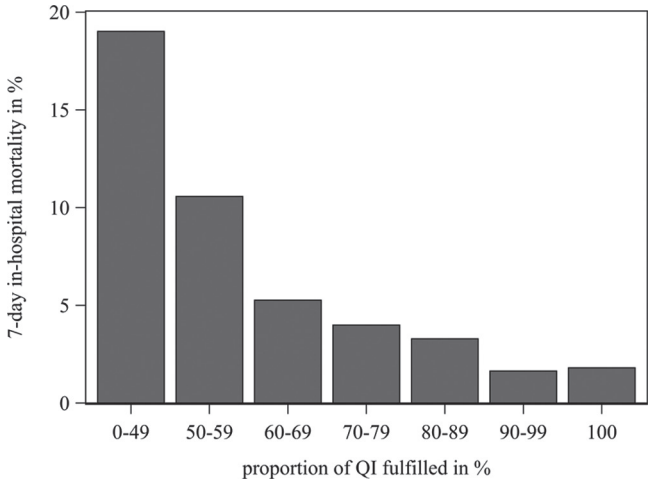


Figure 11.4 Association between 7-day in-hospital mortality and proportion of quality indicators fulfilled[83]

Association Between Adherence to Quality Indicators and 7-Day In-Hospital Mortality After Acute Ischemic Stroke. Association between 7-day in-hospital mortality and proportion of quality indicators fulfilled. This study included 388012 patients with acute ischemic stroke in 736 hospitals.

Methodological considerations: Comparative Effectiveness Research

The studies on fluid management and beta blockers are examples of Comparative Effectiveness Research (CER) using observational data. While RCTs have led to major advances in the field of ischemic stroke, in the field of TBI advances in provision of care have resulted from observational studies, guideline development, and meta-analyses of individual patient data. Why have RCTs led to major successes in the field of ischemic

stroke, but not in the field of TBI? First, the pathophysiology of stroke is substantially different from TBI and might offer more opportunities to reverse the primary cause. Second, there is less heterogeneity in the aetiology, pathology, mechanisms, and outcome in stroke versus TBI. Third, it should be noted that RCTs in stroke often have shorter inclusion periods, more patients enrolled and the methodology are less criticised compared to RCTs in TBI. As an explanation, neurosurgery might be less prone to clinical equipoise compared to neurology; it has been described that neurosurgeons have intrinsically less doubt about their own actions compared to neurologists[92,93].

CER provides a promising framework to identify best practices for the treatment of TBI. There are several large observational studies ongoing in TBI, but also in other neurological diseases. In stroke, large national registries such as the MR CLEAN Registry studied the practice variation and the prognostic impact of this variation[94,95]. Subsequently, these practice variation studies have led to the initiation of the MR CLEAN MED trial to investigate the effect of periprocedural medication[96]. In Guillain Barre syndrome, a large prospective observational study (the International GBS Outcome Study) concluded substantial variability in treatment practices[97,98]. In one separate study, the investigators used propensity score matching to study the effect of one or two intravenous immunoglobulin courses on outcome[99]. Following this observational study, a RCT was performed to further elucidate the effect[100]. Despite the success and novel insights of both observational examples, the examples also demonstrate that obtaining causal inference from observational remains challenging and further RCTs were initiated. It has been recognized that the methodological quality underpinning CER studies is critically important for its success. Therefore, the Good Research for Comparative Effectiveness (GRACE) checklist has been proposed[101]. This checklist consists of 11 items with quality criteria about both the data and the methods used in CER studies, including items on adequate recording of treatment, the use of validated outcome measurements, and adjustment for confounding factors. For confounding factors, the GRACE checklist recommends considering restriction, stratification, multivariable analysis, propensity score matching, instrumental variables or other approaches[101,102]. To strengthen credibility of research findings and since all methods for causal inference have their strengths and limitations, it has been recommended to use different methods and observe whether findings are concordant across different methods[103,104].

This thesis exploited different methods to deal with confounding. For our study on fluid management, we performed our analyses on both per patient level and per centre level. For the per patient analysis, we used multivariable regression. In the multivariable analyses, we adjusted for the IMPACT-extended model, including the severity of

extracranial injuries and a random intercept for study centre. Extracranial injuries were added as adjustment variables since the proportion of extracranial injuries that we observed in our data was higher than the populations IMPACT was originally derived on and are known to be an important prognostic factor for mortality[18,19,105]. By including a random intercept for study centre, we aimed to control for unmeasured confounding caused by variation between centres in case-mix[106,107].

We also performed a per centre analysis since it can theoretically adjust for unmeasured confounders. The per centre analysis, also known as instrumental variable (IV) analyses, used a substitute variable (the instrument: study centre), as level of analysis. The analyses for the impact of fluid balance on outcome showed concordant findings and therefore strengthened our interpretation of a potentially causal effect of fluid balance on outcome. To address the effectiveness of beta-blockers in improving outcomes among critical TBI patients we used propensity score matching. We used measured patient characteristics, to calculate the chance ('propensity') of being exposed to receive beta-blockers, and added the propensity as a covariate to match patients that received beta-blockers and that not received beta-blockers.

The results of this thesis touched upon different advantages of CER. First, by measuring the variations for given treatments, we were able to observe current clinical practice and treatment patterns. Second, we ensured that the participating patients were similar to the average patients seen in the daily clinical practice (chapter 2-3). Third, our studies were conducted in settings that are similar to those in which the participating hospitals are accustomed to in practice. Therefore, these hospitals did not have to alter treatment settings compared to a setting of an RCT to accomplish similar results of the interventions. Moreover, we were able to measure improvements in health care outcome.

However, we also encountered some challenges during the conduction of this CER. For example, in assessing the effectiveness of beta blockers, the large confidence intervals indicated uncertainty and larger datasets would be required to obtain sufficient statistical power. Also, multivariable regression and propensity score matching are frequently used methods in observational research, but have been criticized since both methods cannot adequately address unmeasured confounders[108-110]. For example, many decisions in daily clinical practice are based on clinical institution, which often cannot be captured in the data and thereby may leave residual confounding[111]. Thereby, the results of the different statistical analyses for the impact of fluid input (as opposed to fluid balance) on outcome were conflicting and creates uncertainty in interpreting the impact of fluid input on outcome. Nevertheless, uncertainty among different statistical

methods might be preferable over choosing one method that is possibly invalid. In addition, transparency and validity of observational studies may increase by prospective registration of protocols and by publication of statistical analysis plans before data have been accessed to discern data-driven analyses from pre-planned analyses[112,113].

Recommendations in guidelines are used to support clinicians in decision making regarding best practices. It is common practice to classify recommendations according a hierarchical system of classifying evidence. In this hierarchy, RCTs are given the highest level of evidence since they are designed to be unbiased and have a low risk of systematic errors[114,115]. The results of the studies in this thesis are based on observational studies, and are therefore generally considered to be subject to higher risk of bias. Evidence following our results will be thus regarded as lower level of evidence. However, it is suggested that if designed properly, the level of evidence for CER can approach or surpass those from an RCT[116].

Do the results of the CER on fluid management have the ability to approach a level of evidence to support clinical decision making or are additional RCTs necessary? First, the design of a RCT in the context of fluid management is challenging and is hampered by several factors:

1) It is difficult to measure 'volume' and create a 'volume target' in every patient and it is likely that not every patients requires invasive hemodynamic monitoring to still avoid both hypo- and hypervolemia/fluid overload. However, selecting which patient requires hemodynamic monitoring (including cardiac output for volume status) and when is challenging.
2) Fluid balance may be a surrogate target and it is difficult to define a precise target that is appropriate for every patient at each point in time.
3) The interaction of fluid management and target CPP should be taken into account and currently two 'schools' seems to exist on how to increase CPP when deemed too low: some suggest to start with fluid loading, while others are more inclined to avoid fluids and use vasopressors.

Second, the results of our study showed a firm signal including sufficient power of the analysis (all patients received fluids) and a consistent signal for fluid balance among different statistical approaches. Third, there are pathophysiological explanations that explain the underlying mechanism of the results, making our conclusion biologically plausible (Figure 11.5). Therefore, it could be argued that the results observed in chapter 7 have the ability to sufficiently underpin future guidelines.

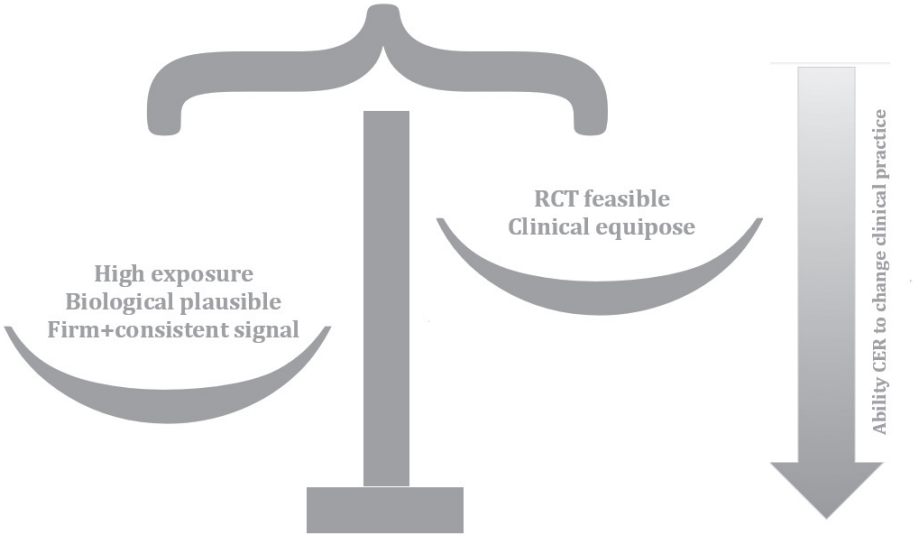


Figure 11.5 Ability of CER to change clinical practice

Nevertheless, in the case of equipoise on best practices regarding fluid management among critical care physicians, a prospective controlled before-after study, e.g. with a cluster RCT could be performed. For implementation, a stepped wedge design, might be a realistic option. The stepped-wedge design includes an initial period in which no patients are exposed to the intervention, which will constitute 'current routine fluid management'. Subsequently, at regular intervals (the 'steps), one cluster (or a group of patients) is randomised to cross from the control to the intervention under evaluation. This process continues until all clusters have crossed over to the intervention (Figure 11.6). Finally, the study ends with all patients are exposed to the intervention. Throughout the study, data collection continues, and all hospitals contribute observations under both control and intervention observation periods. Given the pragmatic study design, this design has been mentioned as a great potential for robust scientific evaluations that might otherwise not be possible[117-119]. The intervention, in the case of fluids, should take into account several issues, among which target CPP, avoiding fluids for which no strict clinical indication exists (fluid creep) the fluid balance target and whether this should be a daily, hourly or longer-term aim (e.g. mean fluid balance during the whole ICU admission), with the ultimate goal to avoid bot hyper- and hypovolemia more rigorously the during the routine fluid management (pre-intervention) period.

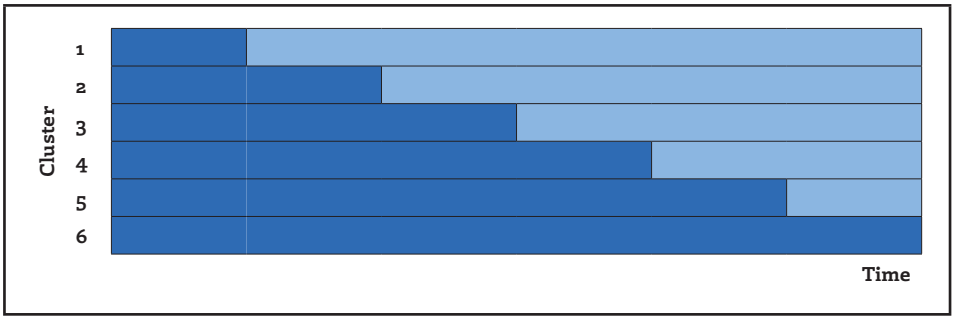


Figure 11.6 Schematic illustration of the stepped wedge study

RECOMMENDATIONS

Based on the content of this thesis and its interpretation, we formulated specific recommendations for research, policy, and clinical practice that are summarized below.

Recommendations for research

1. Assess the effect of multimodal monitoring-based management (including a strict monitoring-based protocol) in patients with TBI admitted to neurocritical care on clinical outcomes
2. Consider different analytical methods for a research question and do not only publish the most appropriate method, but also report the results of all reasonable analytical methods
3. Publish statistical analysis plans ahead of the main publication
4. Perform a stepped-wedge design study to assess the effect of fluid therapy, that is more strictly aimed at avoiding both hypo- and hypervolemia, on outcome
5. Develop an ICU admission prediction model that aids to obtain maximum benefit of ICU admission for mild TBI patients
6. Stimulate funds and researchers to explore treatment indications and pathophysiological pathways in neurocritical care for octogenarians and nonagenarians
7. Perform a RCT that investigates the efficacy of beta blockers including different types, timing and doses of betablockers in patients with TBI
8. Evaluate the correlations between indicators and association with outcome of the final indicator set in large datasets to support, further validate and improve the ICU-TBI indicator set
9. Update the IMPACT model to predict outcomes among patients with TBI admitted to neurocritical care in the contemporary landscape
10. Assess the necessity of more extensive multidimensional and standardized assessment of functional and psychological impairments and corresponding rehabilitation needs

Recommendations for policy

1. Identify elderly people at risk for incidental falls and further develop and implement fall prevention strategies
2. Use natural language processing to accelerate and improve data collection necessary for benchmarking using quality indicator sets
3. Investigate the contribution of quality indicator sets in the improvement of neurocritical care
4. Improve and facilitate adherence by clinicians to quality indicator sets in neurocritical care
5. Facilitate the implementation of prehospital stroke scales that identify patients that are likely to have an intracranial large vessel occlusion, which could allow for direct transportation of EVT eligible patients to an endovascular-capable centre without delaying IVT for the other patients

Recommendations for clinical practice

1. Maintain mean neutral fluid balances in patients with TBI in neurocritical care, rather than allowing consistently positive fluid balances throughout the ICU admission
    a. Be careful to avoid a high level of 'fluid creep' in critically ill patients with TBI
    b. Discuss in case of low CPP whether you should solve this with fluids or with vasopressors
2. Consider the initiation of beta blockers in patients with isolated TBI that show physiological signs of hyperadrenergic state or in patients without contraindication and previous use before ICU admission
3. Consider using the ICU-TBI quality indicator set when quality improvement initiatives are deployed at your ICU in critically ill patients with TBI

In conclusion, in this thesis we found that the landscape of neurocritical care is changing. Patients are older, a substantial proportion have mTBI and stay in the ICU for less than 72 hours. Although mortality was better than expected, functional outcomes were worse than expected, emphasizing the need to improve treatment for patients with TBI. We observed large variation between centres, regions, and countries regarding to case-mix, specific interventions, and management aspects in neurocritical care for patients with TBI, but variation in outcome between centres and countries were smaller. For the access of EVT for patients with acute ischemic stroke, differences between regions in the Netherlands reduced over time.

Less fluids are associated with improved outcomes, but are not common practice. Also, there is variation in the administration of beta blockers to patients with TBI. The administration of beta blockers was only in subgroups associated with improved outcomes. We developed and validated a quality indicator set that can be used to standardize structures and process of care and benchmark results of individual hospitals.

Based on the content of this thesis and its interpretation, we formulated specific recommendations for research, policy and clinical practice, including an increased focus for fall prevention in the elderly, and performing a RCT that investigates the efficacy of different types, timing and doses of betablockers in patients with TBI. For clinical practice, we recommend to maintain neutral fluid balances in patients with TBI.

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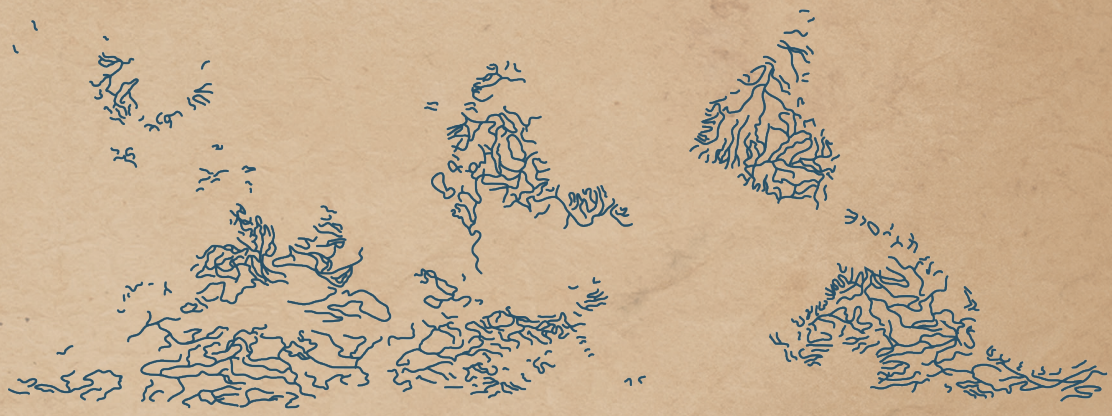
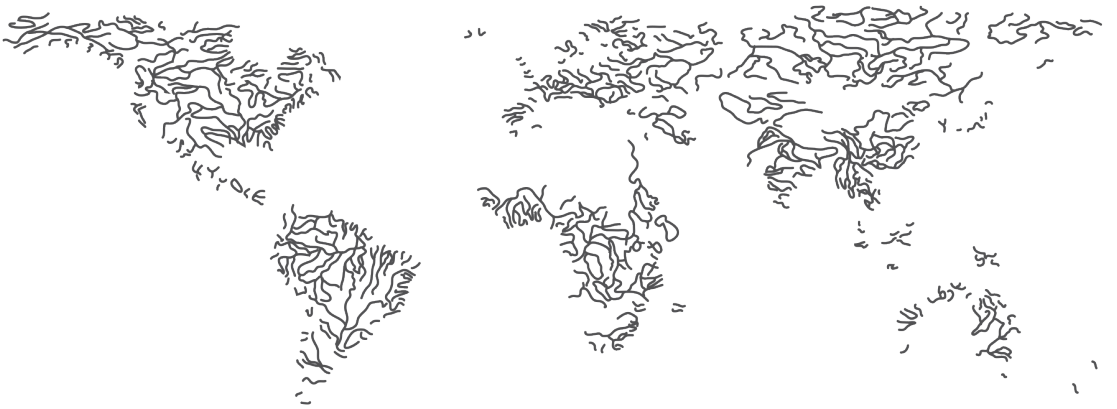
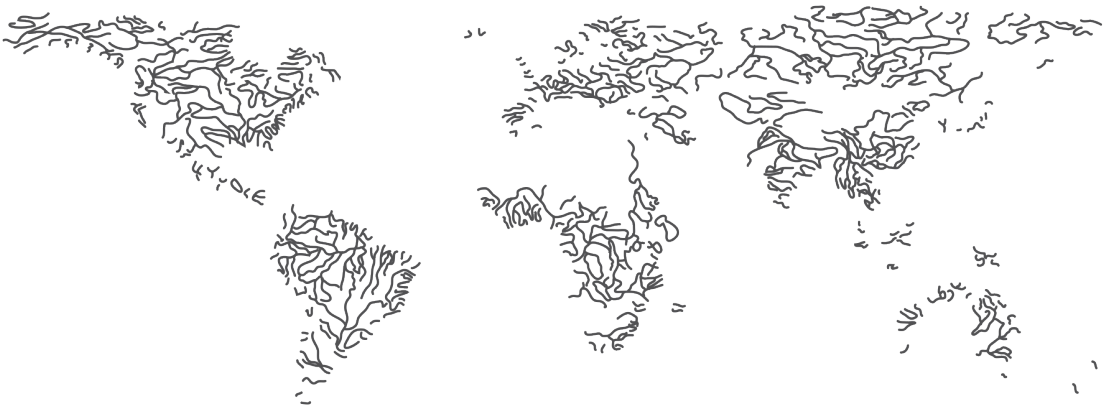


Appendices



Appendices

Summary



SUMMARY

Introduction

Diseases in neurocritical care, in particular traumatic brain injury (TBI) and stroke, are major public health concerns with an annual incidence in Europe of 2.1 million patients with TBI and 1.1 million patients with stroke. Patients with TBI and stroke are often admitted to neurocritical care. Neurocritical care is crucial in providing meticulous neuroprotection, mainly by avoiding or minimizing secondary neurological injury, recognizing and treating systemic complications, ultimately to have the best possible recovery for patients.

Several randomized controlled trials (RCTs) proved the benefit of endovascular thrombectomy (EVT) compared with best medical care for patients with acute ischemic stroke. For patients with TBI, there is no proven specific neuroprotective therapy that is highly effective. Guideline recommendations for TBI care are often weak, leaving opportunity for individual treatment preferences and resource availability, resulting in variation of care. Comparative Effectiveness Research (CER) has been proposed to optimize treatments and management strategies for TBI patients admitted to neurocritical care. CER is designed to account for the abundance of treatment options by comparisons that are clinically meaningful in a broader representation of the affected population.

Improving outcomes in neurocritical patients can be approached in different ways. Treatments that intervene in the pathophysiological pathway of a disease are evident methods to improve outcomes. Over the past years, fluid management has gained attention in neurocritical care. Several studies in critical care have demonstrated that fluid overload can be detrimental, which might also be applicable for patients with TBI. Beta-blockers might have the potential to block some of the adverse effects of sympathetic activation after TBI. However, quality of care also plays an important role in daily clinical practice. Quality indicators are measurable aspects of quality of care and have been developed in many clinical fields proving to benefit patients' outcomes.

The overall aim of this thesis was to improve some aspects of neurocritical care. In specific, the following questions were answered:

1. To describe the contemporary landscape of neurocritical care in Europe and Australia
    d. To describe patient populations and outcomes
    e. To describe how neurocritical care is organized and implemented
    f. To quantify the variability in management, organization and outcomes between centres, regions and countries regions and countries

2. To assess the effectiveness and quality of neuro-critical care
    d. What is the effectiveness of different fluid management strategies?
    e. What is the effectiveness of beta-blockers?
    f. How may quality of neurocritical care for TBI patients be assessed and can it be investigated in the CENTER-TBI database?

Part I: Variation in patients, care and outcome

In chapter 2-4 the contemporary landscape of TBI patients in neurocritical care in Australia and Europe was investigated. We analyzed individual patient data from two different prospective observational cohort studies that were performed across 56 centres in 19 countries. We observed that patients with TBI in neurocritical care are older than previous studies reported, and constitute for a substantial proportion of mild TBI patients. Also, many patients stay in the ICU for a short period of time. The observed mortality rate was lower than expected according to the IMPACT model, which was at a cost of higher rates of unfavourable outcomes. Although the variation in treatments and selected management aspects was large, the variation in outcomes was minor.

The large proportion of mild TBI patients in neurocritical care was further studied in chapter 5. We observed that there are large differences between centres in the decision of admission of mTBI patients to either the ICU or the ward. The admission of mTBI patients is largely explained by the presence of extracranial injuries and other patient characteristics like CT abnormalities. However, we also identified hospital characteristics that were associated with a higher likelihood of ICU admission. Overtriage in Europe is lower than in the USA and Canada.

In chapter 6, we performed a multicentre study in 6394 patients that were treated with EVT the Netherlands during the time period of 2002 and 2018, to describe the development in use of EVT in the Netherlands before, during, and after the pivotal EVT trials. Our time-series analyses demonstrated that the combination of pragmatic approach towards the use of EVT in clinical practice, in combination with a strict adherence by the regulatory authorities to national evidence-based guidelines had led to successful implementation of EVT in the Netherlands. It could be roughly estimated that almost 50% of the number of ischemic stroke patients eligible for EVT actually received this treatment in 2018, although some regional differences still exist.

Part II: Identifying effective care

In chapter 7 we performed a large multicentre cohort study that quantified variability in current fluid therapy in TBI patients across European and Australian ICUs and to study the effect of fluid therapy on outcome after TBI. We observed that patients who received more

fluid and had higher daily fluid balances during ICU stay had worse outcomes compared to patients with negative daily fluid balance. We concluded that maintaining neutral fluid balance is not general practice in European and Australian neurocritical care units, while it may contribute to better clinical outcomes. The confirmation of our results in the per-centre analysis, the simplicity of implementation, and the absence of a pathophysiological friction indicates that we might make headway to make care for critical TBI patients more effective.

Chapter 8 described the current beta blocker administration practices in Europe and investigated the association between beta-blocker use within the first two days after injury and outcome in TBI patients admitted to the ICU. We demonstrated that there is no association between the early administration of beta-blockers and improved outcome, implying that the benefit of beta-blockers may be less than previously presumed. Also, patients that were given beta-blockers short after injury because of centre-policy did not have lower mortality rates or improved long-term functional outcome. However, subgroup analysis revealed that for patients with isolated TBI, early administration of beta blockers might be associated with improved outcomes. Further research on efficacy and the mechanism of beta-blockers is warranted.

Together with 50 experts from 18 countries across Europe we identified 42 indicators that assessed quality of neuro-intensive care for TBI patients in chapter 9. The wide motivation across experts to implement this finally proposed set suggested that there is support to make care more effective. The quality indicator set was further validated in the CENTER-TBI study in chapter 10 and resulted in 9 structure, 5 process, and 1 outcome indicators showing potential for quality improvement purposes for critical TBI patients. The indicator set may become an important tool to support benchmarking and quality improvement programs for patients with TBI in the future.

Discussion

Compared to past series, in which about 10% of patients was older than 65 years, the proportion of elderly with TBI admitted to neurocritical care substantially increased. As clinical trials often include upper age limits, and elderly patients are consequently disenfranchised from research to improve their outcome, evidence and experience with treatment in elderly is limited. The growing evidence for the effectiveness for EVT in octogenarians and nonagenarians has probably contributed to a changed attitude towards EVT in elderly patients with acute ischemic stroke patients. As TBI patients in neurocritical care are most often injured due to incidental falls, there should be a refocus of research efforts to prevent TBI in the older adult. Specific environmental modifications and the addressing of clinical factors in vulnerable patients, including appropriate medication management have been suggested as prevention measures for TBI in the elderly.

We observed that the group of patients that were discharged from neurocritical care within 72 hours, mainly consisted of patients with mTBI. These short stay patients, compared to patients that stayed in the ICU for longer, were less severe injured, received less monitoring and treatments, and achieved better outcomes. The most frequently indicated reasons patients that stayed in the ICU for a maximum of 72 hours were the need for strict neurological observation and mechanical ventilation. On the one hand, the observed practice may represent a prudent strategy, offering close surveillance and assistance to patients at relatively low risk. On the other hand, the observed admission strategies may represent costly over-triage, because ICU is an expensive resource, which should be used wisely. Rational resource use decision making requires an early risk stratification tool that can be practically implemented to guide selective risk-based ICU use. To develop such a tool for patients with mTBI, large multicentre studies and validation studies are necessary.

Mortality at 6 months was lower than predicted by the IMPACT prognostic model. The study population in our observational study differs from the study population the IMPACT-model was originally derived on, implying that the IMPACT-model might not be fully validate in our dataset. Alternatively, it might well be that the processes and structures of care have improved over time, leading to a decrease in mortality rates. However, the rate of unfavourable outcome (GOSE < 5) was similar to that predicted by the IMPACT prognostic model. In addition, the self-reported quality of life of patients with TBI is sorrowful, implying a huge burden on society. Therefore, future studies should assess the necessity of more extensive multidimensional and standardized assessment of functional and psychological impairments and corresponding rehabilitation needs.

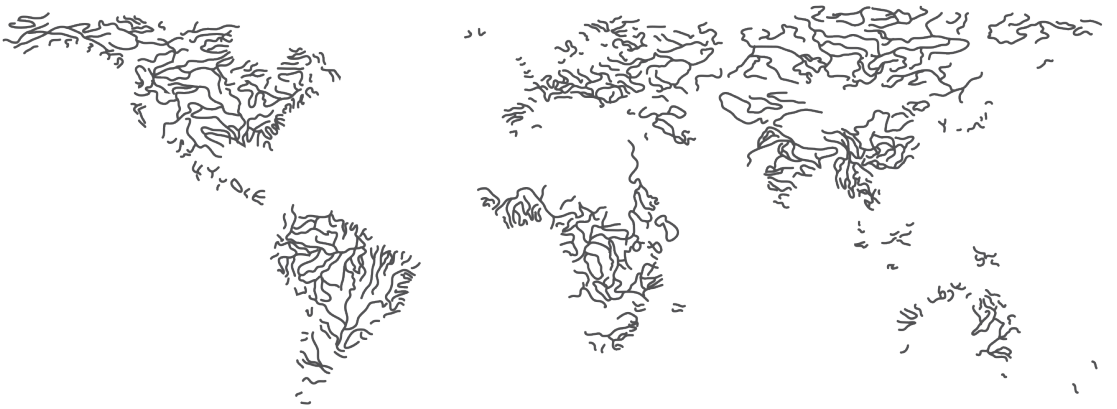
Treatments available for TBI patients that were highly variable among European centres were ICP monitoring and Aggressive Therapy (any use of Decompressive Craniectomy, Metabolic Suppression, Hypothermia Therapy or Intensive Hypocapnia during ICU stay). Recent developments in technology resulted in new monitoring techniques, also known as multimodal monitoring, that can provide the neuro-intensivist with information and assist in management decision making. Currently, several collaborations and research efforts are being made to resolve the outstanding questions about the roles and indications for neuro monitoring after TBI and demonstrate unequivocally whether monitor-guided interventions lead to improved outcomes for patients. Despite the considerable variation in the use of interventions and selected management aspects, we found minor variation in outcomes between centres and Australia, Europe, and the United Kingdom. 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 difference less easily detectable.

Optimizing fluid management strategies in neurocritical care has the strong potential to improve outcomes among patients with TBI admitted to neurocritical care. We observed a consistent association between incremental daily net-positive fluid balances and worse clinical outcomes. A pathophysiological rationale is that capillary hydrostatic back-pressure to the brain might occur due to fluid overload and raised central venous pressure (CVP), resulting in fluid accumulation into the brain interstitium. This situation might occur especially in the face of CVP being close to ICP and when positive end-expiratory pressure (PEEP) is being applied in patients on mechanical ventilation. In the injured brain, this will cause cerebral edema, further facilitated by blood-brain-barrier disruption. Several studies in critical care contemplated about the detrimental effect of fluid overload for different organ systems. The lungs are one of the organs in which adverse effects of fluid overload are most evident. Deeper mechanistic studies are mandatory to understand the relative contributions of each component of fluid therapy on different organ systems.

Patients with critical TBI that received beta blockers within the first 48 hours after injury did not have better clinical outcomes than patients that did not receive beta blockers within the first 48 hours after injury. However, for patients without major extracranial injury, we found that there might be a possible association for the use of beta blockers within 48 hours after injury and lower in-hospital mortality. Future studies are warranted to further elucidate the benefit of beta blockers. Ideally, these studies also take into account the type, dose and timing of beta blockers.

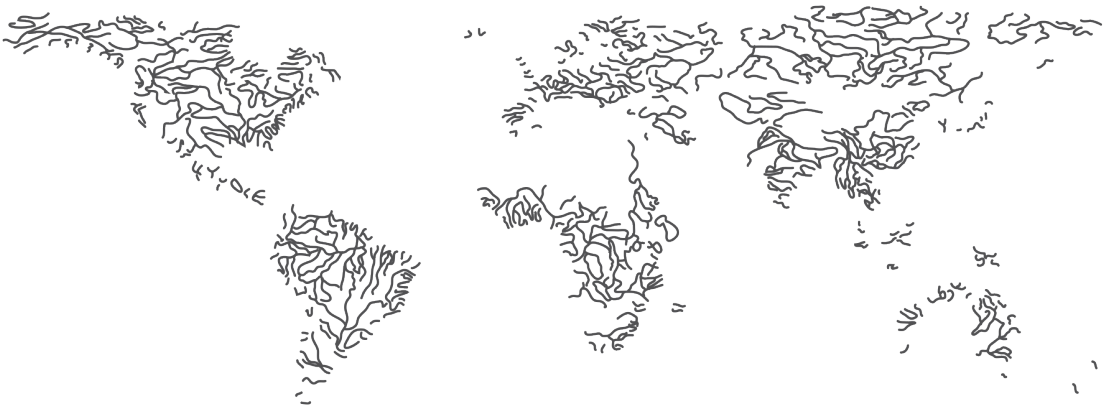
Together with 50 expert from 18 countries across Europe we identified 42 indicators that assessed quality of neuro-intensive care for TBI patients. This quality indicator set was further validated in the CENTER-TBI study and resulted in 9 structure, 5 process, and 1 outcome indicators showing potential for quality improvement purposes for critical TBI patients. We decided not to test the correlations between indicators and association with outcome of the final indicator set. However, evaluation of these quality indicators in larger datasets has the potential to include assessment of such correlations with outcome. Nevertheless, we also identified some pitfalls coming along with the introduction of quality indicator sets, such as the fact that some quality indicators are quite complex and difficult to assess retrospectively. Natural language processing (NLP) can be an efficient way of automatically extracting and structuring this information.

Based on the content of this thesis and its interpretation, we formulated specific recommendations for research, policy and clinical practice, including an increased focus for fall prevention in the elderly, and performing a RCT that investigates the efficacy of different types, timing and doses of betablockers in patients with TBI. For clinical practice, we recommend to maintain neutral fluid balances in patients with TBI.



Appendices

Samenvatting



SAMENVATTING

Traumatisch hersenletsel en beroerte zijn veel voorkomende aandoeningen en vormen een groot probleem voor de volksgezondheid. Patiënten met traumatisch hersenletsel of een beroerte worden vaak opgenomen op een afdeling die specifiek is toegespitst op neuro-intensieve geneeskunde. Het verlenen van adequate neuro-intensieve geneeskunde is cruciaal in het voorkomen van secundaire neurologische schade en het tijdig herkennen en behandelen van systemische complicaties. Het ultieme doel van neuro-intensieve zorg is dat patiënten zo snel mogelijk kunnen functioneren zoals zij voor het ongeval danwel het optreden van een beroerte in staat waren.

Meerdere gerandomiseerde studies in patiënten met een ischemische beroerte hebben aangetoond dat endovasculaire therapie vergeleken met standaard therapie effectief blijkt te zijn in het verbeteren van functionele uitkomsten. Echter, voor traumatisch hersenletsel, is er tot dusver geen behandeling gevonden die uitkomsten evident verbetert. De richtlijnen voor zorg bij patiënten met traumatisch hersenletsel zijn daarom gebaseerd op bewijs van lage kwaliteit. Hierdoor zullen ziekenhuizen en artsen eerder geneigd zijn hun eigen behandelstrategie te bepalen, hetgeen kan leiden tot variatie van zorg bij dezelfde type patiënten. In verschillende studies wordt 'Comparative Effectiveness Research (CER)' beschreven als de methode om behandelingen en het beleid voor patiënten met traumatisch hersenletsel die neuro-intensieve zorg moeten krijgen te verbeteren.

Om uitkomsten van patiënten die neuro-intensieve zorg nodig hebben te verbeteren, kunnen er verschillende strategieën worden gevolgd. Zo kunnen behandelingen die aangrijpen op het pathofysiologische mechanisme van de aandoening geoptimaliseerd worden. Voor patiënten met traumatisch hersenletsel zijn er bijvoorbeeld diverse pathofysiologische mechanismen dat optimaliseren van het vochtbeleid kan leiden tot verbeterde uitkomsten. Daarnaast kan de kwaliteit van zorg worden verbeterd, hetgeen niet alleen eventueel kan leiden tot betere klinisch uitkomsten maar ook tot lagere kosten van de gezondheidszorg en gelijke toegang tot behandeling. Kwaliteitsindicatoren zijn meetbare aspecten van kwaliteit van zorg die in veel verschillende klinische velden ontwikkeld zijn en kunnen voor patiënten met traumatisch hersenletsel wellicht ook een gunstig effect op uitkomst hebben.

Dit proefschrift had als doel om bepaalde aspecten van zorg voor neuro-intensieve patiënten met een beroerte of traumatisch hersenletsel te verbeteren. Specifiek werden de volgende vragen beantwoord:

1. Wat is de huidige organisatie en samenstelling van de neuro-intensieve geneeskunde in Europa?
    a. Wat zijn karakteristieken van patiënten en hun uitkomsten?
    b. Hoe wordt de neuro-intensieve geneeskunde georganiseerd en geïmplementeerd?
    c. Wat is de variabiliteit in de behandelingen, organisatie en uitkomsten tussen ziekenhuizen, regio's en landen?
2. Hoe maken we de zorg voor patiënten op de neuro-intensive geneeskunde effectiever en van betere kwaliteit?
    a. Wat is de effectiviteit van verschillende vochttherapieën?
    b. Wat is de effectiviteit van bètablokkers?
    c. Wat is de rol van kwaliteitsindicatoren?

Deel I: Variatie in patiënten, zorg en uitkomsten

In hoofdstuk 2-4 werden de karakteristieken van patiënten die met traumatisch hersenletsel op de neuro-intensieve geneeskunde in Europa en Australië werden opgenomen beschreven. Daarvoor analyseerden we individuele patiëntdata van twee verschillende prospectieve observationele cohort studies die werden uitgevoerd over 56 centra in 19 landen. We toonden aan dat patiënten ouder zijn dan werd gerapporteerd in vorige studies. Daarbij vonden we dat een aanzienlijk deel van de opgenomen patiënten mild traumatisch hersenletsel heeft in tegenstelling tot ernstig traumatisch hersenletsel. We concludeerden tevens dat een aanzienlijk deel van de patiënten slechts voor korte tijd op de intensive care ligt opgenomen. Het overlijdenspercentage was lager dan we aanvankelijk zouden verwachten volgens het prognostisch model 'IMPACT'. Wel vonden we meer patiënten met een verminderde functionaliteit op lange termijn dan het aanvankelijk hadden verwacht middels 'IMPACT'. Ondanks grote variatie in behandelvoorkeur tussen centra en landen, vonden we weinig variatie in uitkomsten.

Het grote aandeel van patiënten met mild traumatisch hersenletsel op de intensive care werd verder onderzocht in hoofdstuk 5. Er bestaan grote verschillen tussen ziekenhuizen in de beslissing of patiënten worden opgenomen op de afdeling of de intensive care. Het opnemen van patiënten met mild traumatisch hersenletsel wordt grotendeels verklaard door de aanwezigheid van extra-cranieel letsel en andere patiëntkarakteristieken zoals CT-afwijkingen. Tevens hebben we ook een aantal ziekenhuiskarakteristieken kunnen identificeren die geassocieerd zijn met een hogere kans om opgenomen te worden op de intensive care versus de afdeling. Overtriage is in Europa een stuk minder dan in de Verenigde Staten en Canada.

In hoofdstuk 6 hebben we een grote multicenter studie gedaan in 6394 patiënten die zijn behandeld met endovasculaire therapie gedurende de periode 2002-2018. Het doel hiervan was om te beschrijven hoe het verloop in het gebruik van endovasculaire therapie rondom baanbrekende studies te beschrijven. Onze tijdsanalyse liet zien dat de combinatie van een pragmatische benadering van het gebruik van endovasculaire therapie in de dagelijkse klinische praktijk, in combinatie met een strikte naleving van nationale richtlijnen heeft geleid tot een succesvolle implementatie van endovasculaire therapie in Nederland. Grof geschat krijgt inmiddels ongeveer meer dan 50% van de patiënten met ischemische beroerte die in aanmerking zouden komen, ook de daadwerkelijke behandeling. In het begin dat deze behandeling werd aangeboden in Nederland, waren er grote regionale verschillen in Nederland. Deze verschillen zijn er nog steeds, maar zijn de afgelopen jaren met het toenemen van het bewijs wel afgenomen.

Deel 2: Identificeren van effectieve zorg

In hoofdstuk 7 hebben we een grote multicenter prospectieve cohort studie uitgevoerd dat als doel had om de variabiliteit in huidige vochttherapieën bij patiënten die met traumatisch hersenletsel op de neuro-intensieve geneeskunde in Europa en Australië opgenomen worden te kwantificeren en te relateren aan uitkomst. Allereerst zagen we substantiële verschillen tussen ziekenhuizen in hun strategieën voor vochttherapieën. De analyse voor uitkomst hebben we zowel op patiëntniveau als centrumniveau uitgevoerd. Beide analyses toonden aan dat zowel een hogere dagelijkse vochtinput en een dagelijkse positieve vochtbalans waren geassocieerd met slechtere uitkomsten. De eenvoud van implementatie en de pathofysiologische rationale impliceert dat het nastreven van een neutrale vochtbalans kan leiden tot betere uitkomsten bij patiënten met traumatisch hersenletsel.

Hoofdstuk 8 beschreef het huidige beleid om bètablokkers toe te dienen binnen twee dagen na ongeval bij ziekenhuizen in Europa en te onderzoeken of er enige relatie is tussen het gebruik van bètablokkers en uitkomst. Ondanks dat er nauwelijks bewijs is voor het geven van bètablokkers bij patiënten met traumatisch hersenletsel, zijn er nog steeds enkele ziekenhuizen in Europa die wel consistent bètablokkers voorschrijven. Echter konden we geen effect vinden voor het gebruik van bètablokkers op uitkomst. Voor patiënten zonder extra-cranieel letsel zou vroege toediening van bètablokkers mogelijk wel kunnen leiden tot verbeterde uitkomsten. Verder onderzoek naar de werkzaamheid en het mechanisme van bètablokkers bij patiënten met traumatisch hersenletsel is echter noodzakelijk.

Samen met 50 experts uit 18 verschillende landen in Europa hebben we in hoofdstuk 9 42 indicatoren geïdentificeerd die de kwaliteit van neuro-intensieve geneeskunde voor patiënten met traumatisch hersenletsel beoordelen. We zagen dat er brede motivatie was onder de deelnemende experts om de uiteindelijk voorgestelde set te implementeren in de dagelijkse praktijk. De set met kwaliteitsindicatoren werd verder gevalideerd in de CENTER-TBI studie in hoofdstuk 10 en resulteerde in negen structuur-, vijf proces- en één uitkomst indicator(en) die mogelijk kunnen leiden tot kwaliteitsverbetering bij patiënten met ernstig traumatisch hersenletsel. De set met kwaliteitsindicatoren kan in de toekomst een belangrijk middel worden voor benchmarking en diverse kwaliteitprogramma's.

Discussie

In vergelijking met vorige onderzoeken waarin ongeveer 10% van de patiënten met traumatisch hersenletsel op de neuro-intensieve geneeskunde ouder was dan 65 jaar, vonden wij dat het aandeel van oudere patiënten over de afgelopen jaren aanzienlijk is toegenomen. Aangezien RCTs vaak een leeftijdslimiet hebben zijn oudere patiënten consequent buitengesloten van onderzoek. Het bewijs en de ervaringen met oudere patiënten met traumatisch hersenletsel is dus beperkt. Voor endovasculaire behandeling bij patiënten met een beroerte is er de laatste tijd meer bewijs over de effectiviteit bij 80- en 90-plussers. Zeer waarschijnlijk is dat de verklaring voor de toename over de afgelopen jaren in gemiddelde leeftijd voor patiënten met een beroerte die worden behandeld met endovasculaire therapie. Oudere patiënten met traumatisch hersenletsel lopen het meest vaak een letsel op door een val, hetgeen het belang aantoont om preventieve maatregelen te treffen om een val bij de oudere patiënten te voorkomen. Specifieke omgevingsaanpassing en adequate medicatiesanering zijn voorgesteld als mogelijke preventiemaatregelen voor vallen bij ouderen.

We zagen dat de groep van patiënten die binnen 72 uur van de neuro-intensieve geneeskunde werd ontslagen, vooral bestond uit patiënten met mild traumatisch hersenletsel. Deze groep patiënten die kort op de neuro-intensieve geneeskunde verbleef waren vaak minder ernstig verwond, werden minder agressief behandeld en hadden betere uitkomsten. De meest genoemde redenen om deze patiënten op te nemen waren de noodzaak tot strikte neurologische observatie en beademing. Aan de ene kant kan het observeren van patiënten met een relatief laag risico worden gezien als een prudente strategie waarin tijdig achteruitgang in functie bemerkt zal worden. Aan de andere kant kan deze strategie ook overtriage suggereren, aangezien behandeling op de neuro-intensieve geneeskunde dure zorg is. Het ontwikkelen en implementeren van een tool die kan voorspellen welke patiënten met mild traumatisch hersenletsel een risico hebben op verslechtering en daardoor neuro-intensieve geneeskunde nodig hebben kan een uitkomst bieden om artsen te helpen in hun beslissing welke patiënt opgenomen dient te worden op de intensive care.

Mortaliteit op 6 maanden was lager dan voorspeld door het prognostisch model IMPACT. Enerzijds verschilt onze patiëntenpopulatie van de patiëntenpopulatie waarop het prognostisch model IMPACT op was ontwikkeld, waardoor dit model mogelijk niet volledig valide is in onze dataset. Anderzijds is het goed mogelijk dat processen en structuren van zorg zijn verbeterd over tijd en hebben geleid tot een vermindering van de mortaliteit. Het dient echter vermeld te worden dat het percentage patiënten die een slechte functionele uitkomst hadden 6 maanden na het ongeval gelijk was aan het voorspelde percentage volgens het prognostisch model IMPACT. Daarbij was de zelf-gerapporteerde kwaliteit van leven bij patiënten met traumatisch hersenletsel zeer slecht en impliceert dat een grote last op de gezondheidszorg en de maatschappij. Onderzoek in de toekomst moet daarom ook aandacht hebben voor optimale revalidatie.

Behandelingen die vaak worden gebruikt bij patiënten met traumatisch hersenletsel en zeer variabel was onder Europese ziekenhuizen waren bijvoorbeeld het aanbrengen van een drukmeter of het toepassen van hypothermie. Recente technologische ontwikkelingen hebben geresulteerd in nieuwe monitor technieken, die ook bekend staan als multimodale monitoring. Multimodale monitoring kan de neuro-intensivist helpen bij het maken van beslissingen omtrent de juiste behandeling. Op dit moment zijn er verschillende onderzoeksinitiatieven over de rol en indicaties van gebruik van monitoring na traumatisch hersenletsel. Ondanks de grote variatie in het gebruik van behandelingen en beleidsaspecten, vonden we maar minimale variatie in uitkomst tussen ziekenhuizen en verschillende landen in de westerse wereld. Dit kan er op wijzen dat slechts een zeer klein deel van de variatie uitkomst beïnvloed wordt door de verschillen in aanpak. Een alternatieve verklaring is dat individuele aspecten van aanpak omtrent de patiënt met traumatisch hersenletsel niet samenhangen en daardoor verschil in uitkomst niet aan te tonen is.

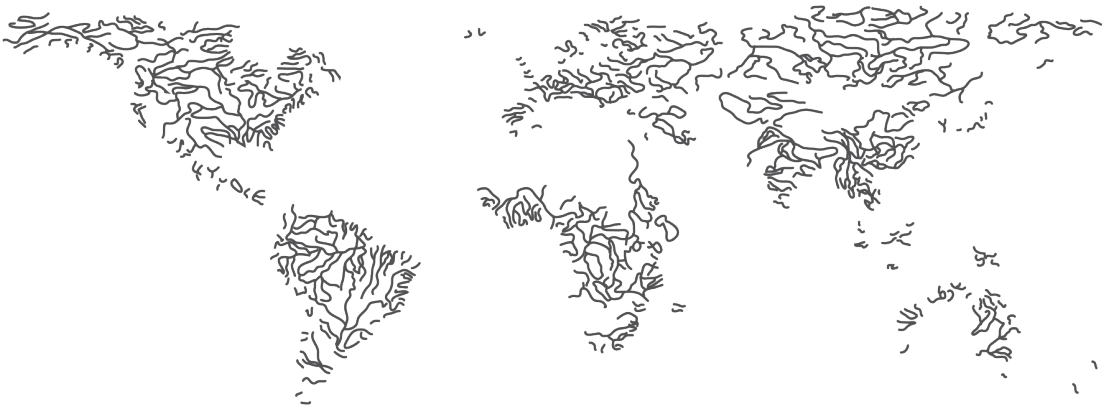
Het optimaliseren van vochtbeleid heeft een evidente potentie om uitkomsten bij patiënten met traumatisch hersenletsel opgenomen op de neuro-intensive geneeskunde te verbeteren. We observeerden namelijk een consistente associatie tussen een hogere vochtbalans en slechtere klinische uitkomsten. Een mogelijke pathofysiologische verklaring die werd besproken is dat capillaire hydrostatische tegendruk naar de hersenen kan optreden als gevolg van vochtoverbelasting en een verhoogde centrale veneuze druk, resulterend in vochtophoping in het herseninterstitium. Verschillende onderzoeken in de intensive care hebben het schadelijke effect van vochtoverbelasting voor verschillende orgaansystemen beschreven. De longen zijn een van de organen waarin de nadelige effecten van vloeistofoverbelasting het duidelijkst zijn. Waarschijnlijk speelt bij patiënten met traumatisch hersenletsel een combinatie van deze pathofysiologische factoren een rol.

We gingen daarnaast verder in op het pathofysiologische effect van het gebruik van bètablokkers bij patiënten met traumatisch hersenletsel. We beschreven welk vervolgonderzoek nodig is om een eventueel effect van bèta-blokkers verder te verdelen. Deze studies zouden dan ook het type, de dosis en optimale timing van bèta-blokkers in acht moeten nemen. Zo hebben eerdere studies bijvoorbeeld aangetoond dat propanolol een betere werking kan hebben dan labetalol.

In dit proefschrift hebben we besloten de correlaties tussen indicatoren en de associatie met uitkomst van deze kwaliteitsindicatoren niet te testen. Echter, het evalueren van kwaliteitsindicatoren in zeer grote datasets heeft de potentie om zulke associaties met uitkomst te beoordelen. Ook hebben we nadelen besproken die evaluatie van kwaliteitsindicatoren lastig maken, zoals de complexiteit en tijdrovende invoer van data. 'Natuurlijke taalverwerking' is mogelijk een efficiënte manier om deze informatie automatisch te extraheren en structuren.

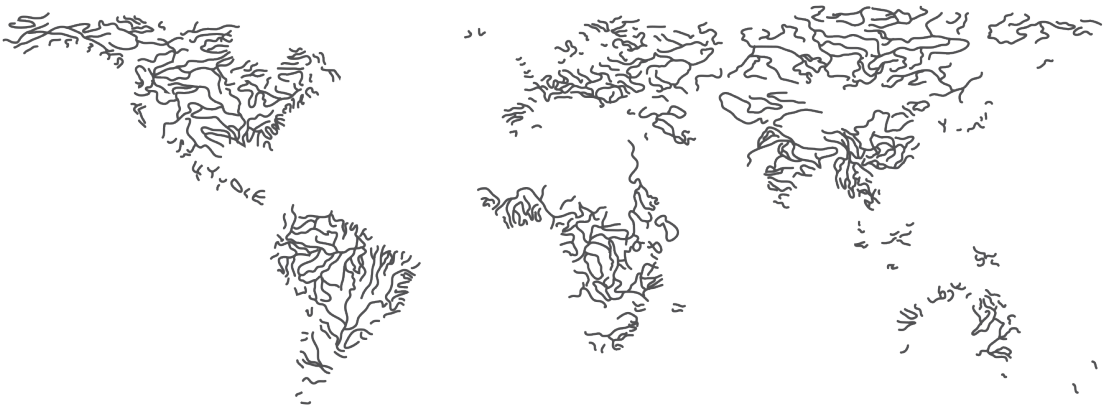
In de discussie werd verder ingedaan op methodologische overwegingen bij het uitvoeren van CER. Verschillende redenen voor het succes van RCTs bij beroerte maar niet bij traumatisch hersenletsel werden benoemd. Tevens beschreven we dat voor het uitvoeren van CER voldoende statische power nodig is en dat het uitvoeren van verschillende analyses kan leiden tot betere interpretatie en acceptatie van de bevindingen.

Op basis van de inhoud van dit proefschrift en de daarbij behorende interpretatie, hebben we specifieke aanbevelingen voor onderzoek, beleid en de klinisch praktijk gedaan. Daarbij hebben we aanbevelingen gedaan om meer aandacht te hebben voor valpreventie maatregelen in de oudere patiënt en het uitvoeren van een gerandomiseerde studie om het mechanisme van verschillende typen, timing en doses van bètablokkers bij patiënten met traumatisch hersenletsel nader te onderzoeken. Voor de klinische praktijk bevelen we aan om de vochtbalans bij patiënten met traumatisch hersenletsel op de neuro-intensieve geneeskunde zo neutraal mogelijk te houden.



Appendices

Acknowledgements



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CENTER-TBI

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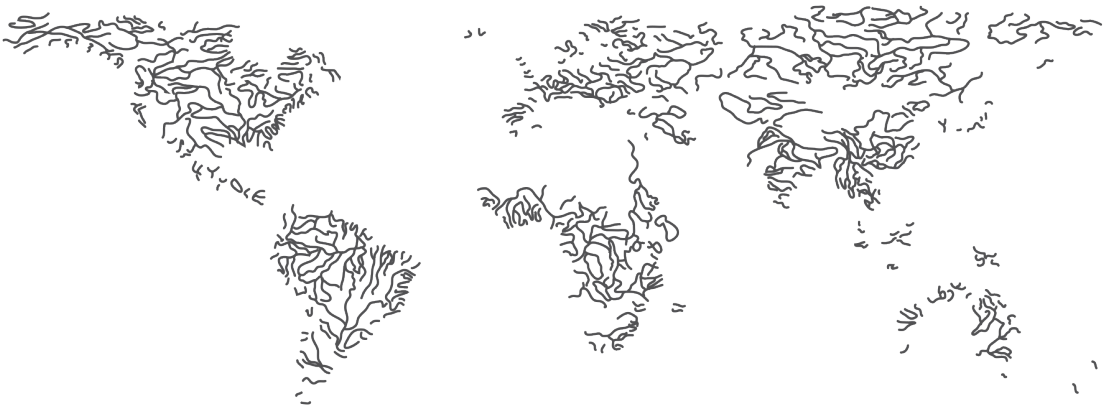
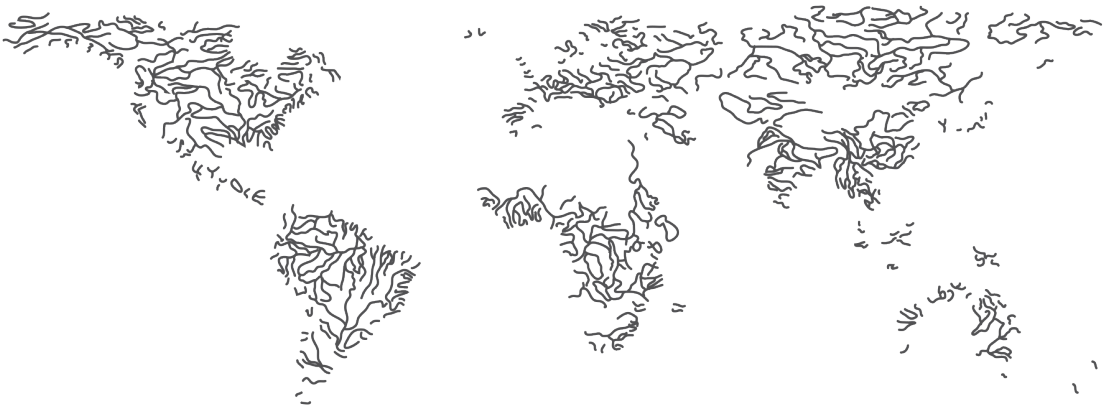
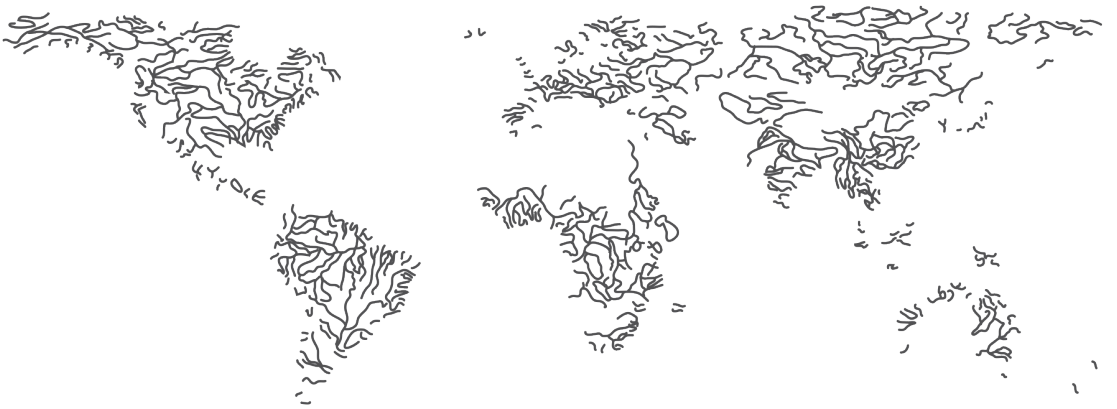




Appendices

List of publications



LIST OF PUBLICATIONS

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