Outcome and Comparative Effectiveness Research in Traumatic Brain Injury: A methodological perspective

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Outcome and Comparative Effectiveness Research in Traumatic Brain Injury: A methodological perspective

Uitkomsten en vergelijkend effectiviteitsonderzoek bij traumatisch hersenletsel: Een methodologisch perspectief

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“Life is like a box of chocolates, you never know what you gonna get”

Forrest Gump, 1994

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Part II: Comparative effectiveness research in traumatic brain injury

1

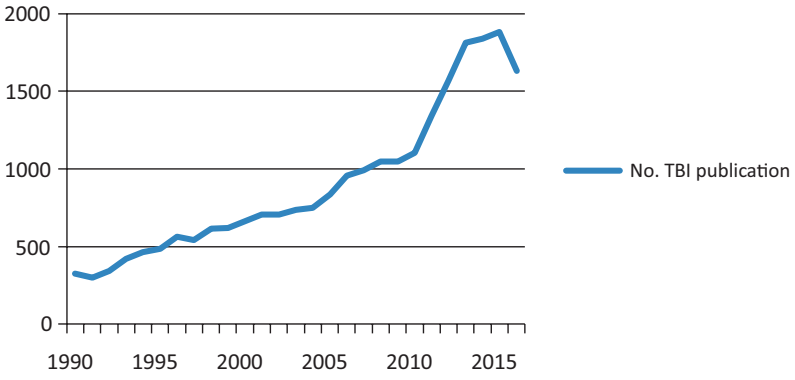
General introduction

Traumatic brain injury (TBI) is one of the leading causes of death and disability worldwide. In Europe, approximately 2.5 million people sustain a TBI annually, of whom 75,000 die.[1,2] Survivors are challenged with a range of disabilities and symptoms that may drastically reduce quality of life and result in huge societal costs.[3-5]

TBI is often referred to as "the most complex disease in our most complex organ". Our brain is an extremely complex structure and a TBI may damage one or more of its areas resulting in various symptoms. The severity of TBI ranges from mild concussion to persistent coma and death, with the large majority of patients at the mild end of the spectrum. The word 'mild' might however be misleading because a substantial part of these patients report cognitive, somatic, and emotional symptoms that may last for months or even years after sustaining a TBI.[6-8] This was already acknowledged by Hippocrates (460-377BC). His famous aphorism *"No head injury is too severe to despair of, nor too trivial to ignore"* indicates that even mild TBI (mTBI) might have serious consequences. Notwithstanding, millennia later, it is still unknown why some patients develop prolonged sequelae following mTBI whereas others recover within a few weeks.

Since TBI is recognized as a serious public health concern, it has emerged as an important topic in medical research. In the year 2016, more than 1,500 papers have been published in English language journals studying TBI in humans, which is a fourfold of the number of papers that was published in the year 1990 (Figure 1). In comparison, the total number of papers in English language journals about human subjects has only doubled since 1990. Nevertheless, all these research endeavors have not yet resulted in major advances in our understanding of TBI, nor in an improvement of patient outcomes.[9-11]

Figure 1. **Number of published papers from 1990 to 2016 on TBI in human subjects**



The following EMBASE search was employed: [article]/lim AND [english]/lim AND [humans]/lim AND [xxxx-xxxx]/py AND ('traumatic brain injury':ab,ti OR 'head injury':ab,ti OR tbi:ab,ti OR concuss*:ab,ti). The total number of papers has increased from 327 in 1990 to 665 (103%) in 2000, to 1233 (277%) in 2010 and to 1631 (400%) in 2016. In comparison, the total number of papers with the search strategy: [article]/lim AND [english]/lim AND [humans]/lim AND [xxxx-xxxx]/py has increased from 146,545 in 1990 to 212,278 (45%) in 2000 to 363,573 (148%) in 2010 and 396,607 (171%) in 2016.

Research in TBI is hampered by the heterogeneity of the patient population, the lack of standardized outcome instruments, and the fact that secondary insults and complications are common and may interact with the effects of a possibly beneficial treatment.[10,12] Moreover, many randomized controlled trials (RCTs) have methodological shortcomings, including a lack of statistical power and focus on isolated disease mechanisms.[10] In addition, prognostic studies often include too many predictors and do not use internal or external validation approaches.[13,14] As a consequence, the evidence derived from many studies is modest.

In this thesis we address two important and emerging topics in TBI research. First, we focus on outcome following TBI, with an emphasis on prevalence, predictors, and prediction modeling. Second, we focus on whether comparative effectiveness research (CER) could contribute to evidence generation in TBI, by analyzing current guideline adherence, treatment variation, and analytical methods. For both purposes, we follow a methodological perspective. This chapter will introduce some concepts related to outcome and CER in TBI. In addition, the research questions will be explained and an outline for this thesis will be provided.

1.1 Traumatic Brain Injury

Traumatic Brain Injury (TBI) is generally defined as "an alteration in brain function or other evidence of brain pathology, caused by an external force"[15] (Box 1). TBI was historically considered a single event. However, it is now recognized as a progressive disease in which both primary and secondary damage might be detrimental,[16] and where final outcome is determined based on complex interactions between genetic make-up, pre-injury characteristics, injury mechanism, secondary complications, and psycho(social) characteristics.[8,17,18]

The incidence of TBI is increasing substantially all over the globe as a consequence of an increase in motor vehicle crashes in low- and middle-income countries and an increase in fall incidents in high-income countries.[5,19] Consistent epidemiological data are however lacking because of heterogeneity in TBI definitions and data collection methods.[11] Consequently, reported annual incidence rates vary from 47 to 849 per 100,000 in the European population.[11]

The severity of TBI is most often indicated by the Glasgow Coma Scale (GCS) score; a score ranging from 3 to 15 based on eye reactivity (e.g. being able to open the eyes), verbal activity (e.g. being confused) and motor activity (e.g. obeying commands).[20] Based on the GCS score, TBI severity is often trichotomized into mild (GCS score 13-15; in some studies 14-15), moderate (GCS score 9-12) and severe (GCS score 3-8). The large majority of TBI patients (70-90%) sustained a mTBI according to this classification.[21] In addition to the GCS score, studies in mTBI patients frequently use additional diagnostic criteria as recommended by the American Congress of Rehabilitation Medicine[22] (Box 1).

Box 1. **Definitions for Traumatic Brain Injury**

Traumatic Brain Injury (Menon et al. 2010)[15]

- An alteration in brain function or other evidence of brain pathology, caused by an external force.
- An alteration in brain functioning includes at least one of the following:
  - Any period of loss or decreased consciousness
  - Any loss of memory before or after the injury
  - Neurologic deficits
  - Any alteration in mental state at time of injury

Mild Traumatic Brain Injury (American Congress of Rehabilitation Medicine)[23]

Same criteria but with the following restrictions:

- Loss of consciousness between 0-30 minutes
- A Glasgow Coma Scale (GCS) of 13-15 after 30 minutes
- Loss of memory no longer than 24 hours

1.2 Outcome following TBI

Studying outcome following TBI aims to identify the objective and subjective burden experienced after sustaining a TBI. Subsequently, factors influencing outcome can be studied to identify patients at enhanced risk for persistent sequelae, which can be defined as the experience of residual symptoms (e.g. fatigue, headache, depression). Outcome research is also critically important in the evaluation of treatment effectiveness; e.g. we can compare outcome in patients receiving and not receiving a particular treatment. Outcome following TBI is however complex and multidimensional and there is no consensus on how and when outcome should be assessed. As a consequence, comparing results of different studies is challenging.

Some studies examining outcome focus on mortality, which is a hard endpoint. Since approximately 40% of patients with severe TBI die,[9] it is considered important in this subgroup of patients. However, mortality rates in mild and moderate TBI are much lower and survivors of TBI are frequently challenged with cognitive, somatic, and emotional symptoms that may drastically influence functioning and quality of life. Therefore, the emphasis of outcome research had shifted towards other outcome measurements including clinical outcome, post-concussion symptoms, psychiatric disorders, and health-related quality of life (HRQoL).[9,24]

1.2.1 Clinical outcome

Clinical outcome refers to the degree to which TBI survivors are able to function independently, fulfill occupational and social roles, and have returned to daily functioning (definition based on Wilson et al.[25]). It is usually measured with either the Glasgow Outcome Scale (GOS; 5-point scale)[26] or the Glasgow Outcome Scale Extended (GOSE; 8-point scale).[25] Both scales divide patients who sustained TBI into groups that allow for a standardized description of recovery.

Scales range from death to good recovery (GOS) or upper good recovery (GOSE). In research practice, both the GOS and GOSE are commonly collapsed into a binary scale (favorable outcome vs. unfavorable outcome). It should however be noted that this results in loss of information and statistical power,[27,28] and should therefore be discouraged. A proportional odds model in which the GOS/GOSE is used as an ordinal outcome variable has been proposed as an alternative.[27,29] In such a model, a summary odds ratio is calculated based on all possible transitions on the scale.[27] As a consequence, all patients who improved with at least one point on the GOS or GOSE can contribute towards demonstrating a beneficial treatment effect, rather than only those patients who shifted from having an unfavorable outcome towards having a favorable outcome. Although the GOSE is recommended as standard end-point measurement for outcome following TBI,[24,30] its ability to detect burden following mTBI can be debated since the large majority of mTBI patients function in the upper levels.[31]

1.2.2 Post-concussion symptoms

Post-concussion symptoms refer to physical (e.g. headache, dizziness), cognitive (e.g. memory deficits, concentration problems), and emotional (e.g. depression, irritability) problems that can be experienced after sustaining a TBI. It has been assumed that post-concussion symptoms are relatively common following injury but resolve within weeks to months in the large majority of patients.[32-34] This assumption has however been challenged by recent prognostic studies reporting that up to 50% of mTBI patients experience persistent post-concussion symptoms.[7,35] Persistence of post-concussion symptoms can be diagnosed according to the International Classification of Diseases Tenth Edition (ICD-10) as Post-Concussion Syndrome (PCS). This diagnosis is however highly controversial, because post-concussion symptoms are neither unique to TBI nor do they cluster together in a predictable manner.[36,37]

Despite controversy on diagnostic criteria, persistent post-concussion symptoms represent a substantial burden to patients and relatives and are associated with reduced HRQoL, lower functioning, and work absentism.[38-40] Therefore, they are currently the topic of active research investigation. Post-concussion symptoms are commonly measured using self-reported questionnaires, among which the Rivermead Post-concussion Questionnaire (RPQ)[41] is the most frequently used. The RPQ is a 16-item questionnaire that measures the prevalence and severity of post-concussion symptoms in comparison to before the injury. There has however been substantial variability among studies in the use of the RPQ; e.g. the scale can be used as a linear total scale[41,42] or can be divided into two (RPQ3 and RPQ13),[43] or three (cognitive, somatic and emotional)[44] subscales. In addition, many studies dichotomize the RPQ into 'PCS' vs. 'no PCS' using different symptoms (all RPQ symptoms vs. only those RPQ symptoms described in the ICD-10 criteria) and different cut-off points (including symptoms that are indicated to be mild or worse or symptoms that are indicated to be moderate or worse).[12] This substantial variation in study design and analysis hampers comparability of studies on post-concussion symptoms, and subsequently slows down evidence generation.

1.2.3 Psychiatric disorders

Psychiatric disorders such as depression and post-traumatic stress disorder (PTSD) are relatively common following TBI.[24,45] They are also more common following TBI than following other injuries.[46] Psychiatric disorders are associated with adverse outcomes, such as lower quality of life,[45] lower societal and occupational participation,[47,48] and less life satisfaction.[47] In addition, they may interfere with rehabilitation interventions[49] and are consequently considered important in outcome assessment following TBI. Psychiatric disorders can be assessed with either self-reported questionnaires or diagnostic interviews. Self-reported questionnaires are relatively efficient in terms of costs and labor intensity, but cannot confirm the presence of a psychiatric disorder. In addition, they might not be reliable in a TBI population as a consequence of memory deficits, attention problems and because of overlap between TBI symptoms and symptoms of a psychiatric disorder.[50-54] Therefore, the use of diagnostic interviews is recommended to reliably assess psychiatric disorders following TBI.

1.2.4. Health-related quality of life (HRQoL)

HRQoL reflects a patient's perspective on how an illness and its treatment affect physical, affective, cognitive, and social daily life aspects.[55-57] HRQoL can be measured with generic (e.g. SF-36) or disease specific measurements (e.g. QOLIBRI). The SF-36 is a frequently used generic HRQoL instrument and yields a profile of eight domains relevant to quality of life, including: physical functioning, role limitations related to physical health problems, role limitations related to emotional health problems, bodily pain, general health perceptions, social role functioning, vitality, and mental health. From these subscales, a physical and mental health summary score can be calculated, which is often performed in studies assessing HRQoL following TBI.[57] However, no convincing validation, such as confirmatory factor analysis, has been performed for the adequacy of this two-dimensional structure in TBI patients.

1.2.5 Outcome prediction following TBI

The identification of prognostic factors for TBI outcome is relevant for both clinical practice and research.[13,18] It might be especially relevant to combine various prognostic factors into a prediction model, which can be defined as a mathematical formula estimating prognosis in individual patients.

For moderate and severe TBI, prognostic modeling is relatively advanced with two well-established models predicting mortality and clinical outcome.[58,59] For mTBI patients, however, prognostic modeling has received relatively limited attention. Information on prognostic factors and the development of a prognostic model can however be used to identify patients at increased risk of long-term sequelae who may benefit from additional monitoring or (preventive) treatment, and thereby has the potential to reduce mTBI burden.

Applying prediction modeling to mTBI patients is challenging because there is lack of standardized outcomes and unequivocal predictors. Next to these challenges, prior prediction modeling studies can be criticized for methodological shortcomings. For example, studies often included too many candidate predictors given the number of patients in their sample.[14] Also, only a limited number of studies used internal validation techniques and more advanced statistical techniques such as shrinkage. This may result in statistical overfitting, meaning that a model performs well in the developmental set but poorly in new patients.[13,60] Furthermore, none of the developed prognostic models for post-concussion symptoms or psychiatric disorders has been externally validated in an independent dataset,[14,61] whereas this is a prerequisite for implementation in clinical practice.[9,60]

1.3 Comparative effectiveness research in TBI

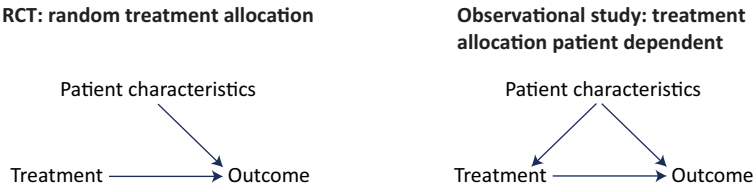
1.3.1 Evidence generation in TBI

The scientific evidence underpinning international guideline recommendations for the medical and surgical management of TBI is weak.[62] Although there have been major advances in the understanding of molecular and cellular mechanisms of TBI,[63] this has not yet resulted in an increase in evidence-based treatment,[5,64] nor has it changed patient outcomes.[10]

Randomized Controlled Trials (RCTs) are regarded the cornerstone of evidence-based medicine. The contribution of RCTs to the field of TBI is however relatively disappointing. According to a 2016 state-of-the-science overview, nearly three-quarters of all RCTs in TBI failed to detect a statistically significant difference between treatment and comparison groups.[10] This might be caused by the limited effectiveness of new interventions, but also by the heterogeneity of TBI,[65] as well as by methodological shortcomings such as small sample sizes and focus on isolated disease mechanisms.[65,66]

Observational studies constitute the main alternative for RCTs. They have the potential to contribute to the evaluation of treatment effectiveness in a real-world setting. A major methodological challenge in observational studies is confounding by indication, referring to a situation where the treatment indication is a confounder in the association between treatment and outcome. For example, aggressive, risky treatments might be more often performed in patients with a relatively unfavorable prognosis compared to patients with a relatively favorable prognosis.[67,68] As a consequence, it remains uncertain whether differences in outcome among treated and non-treated patients are caused by the treatment under study or by differences in patient characteristics between treated and non-treated patients (Figure 2).

Figure 2. **The influence of patient characteristics on treatment allocation in RCTs and observational studies**



1.3.2 Variation in structures and processes of care

Since the current body of evidence underpinning the management of TBI is inconclusive, large between-center variation in both structures and processes of care are expected, which may arise from local traditions, personal preferences, and resource availability.[69-71] Structures refer to the conditions under which patient care is provided (e.g. the number of beds, nurse-to-patient ratio) and processes refer to activities that constitute patient care (e.g. treatment policy). Previous studies investigating structures and processes of TBI care indeed reported substantial heterogeneity among centers.[70,72-76] One might argue that large variation is worrisome since this may imply that some patients are not receiving the best care and are therefore at risk for a less favorable outcome. On the other hand, since we do not know the effectiveness of current structures and processes of care, one might also regard variation as an opportunity to study the comparative effectiveness of interventions that all have the potential to be best practices.

1.3.3 Comparative Effectiveness Research

Comparative Effectiveness Research (CER) refers to "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 improve the delivery of care."[77] CER provides a promising framework to identify best practices for the treatment of TBI.[78] While traditional RCTs are often conducted in rather selected patient populations, CER aims to demonstrate effectiveness of real-life interventions and thereby may directly inform consumers, clinicians and policy makers.[77]

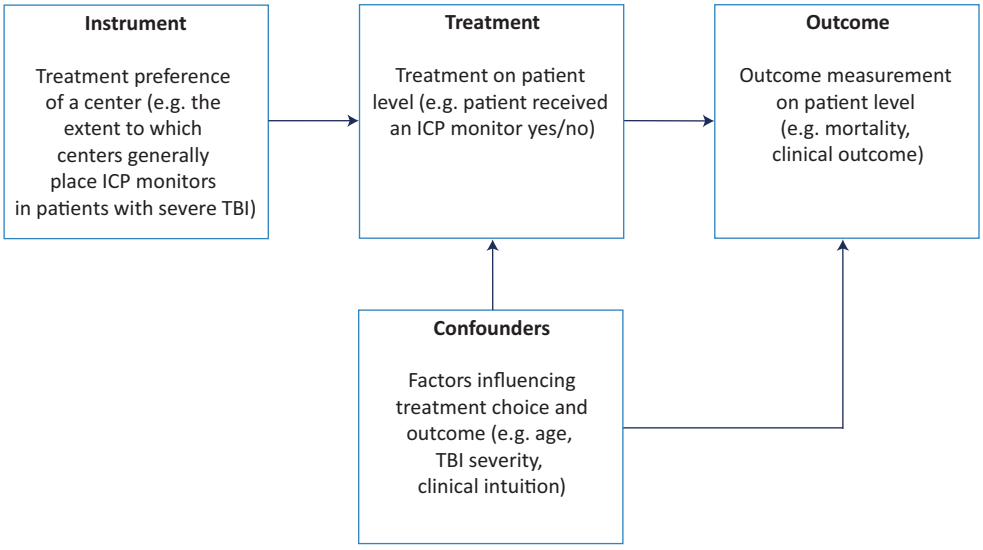
It has been recognized that the methodological quality underpinning CER studies is critically important for its success. Therefore the Good Research for Comparative Effectiveness (GRACE) checklist has been proposed.[79,80] This checklist consists of 11 items with quality criteria about both the data 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.[79] Some of these methods, however, do not take into account the role of unmeasured

confounders (e.g. factors related to clinical intuition), while these factors may comprise important determinants of both treatment indication and patient outcome.

A method that may adjust for unmeasured confounders is instrumental variable analysis. In instrumental variable analysis, the association between an 'instrument' and outcome is analyzed.[81] This instrument should be associated with the treatment under study, should cause the outcome only through the treatment under study and its effect should not be associated with the confounders (Figure 3).[81] Treatment preference may potentially serve as an instrument in multicenter observational CER studies, for example, by comparing patient outcomes in centers with a high preference for a particular intervention to patient outcomes in centers with a lower preference for the intervention. This strategy was recently used in two observational multicenter studies on ICP monitoring.[82,83]

In order to obtain valid estimates of the treatment effect in instrumental variable analyses, it is crucial that the underlying assumptions are met (i.e. instrument is associated with treatment, causes outcome only through the treatment and is not associated with confounders). However, a 2014 systematic review found that these assumptions are often violated.[84] For example, the instrument treatment preference could be associated with geographic location, patient characteristics, facility characteristics and the provision of co-occurring treatments,[84] which may influence the validity of the effect estimate.

Figure 3. **Instrumental variable analysis with treatment preference as instrument**



1.3.4 Valorization of scientific knowledge

Valorization refers to the utilization of research findings in clinical practice. Valorization of research might be accomplished by the conduct of systematic reviews and the development of guidelines. Systematic reviews summarize and weight scientific information on the same topic and provide recommendations that may directly inform doctors and policy-makers. Nevertheless, a recent evidence-mapping approach found that only half of the systematic reviews in the acute management of TBI were current (i.e. included the most recent RCTs) and only two-thirds were complete (i.e. including all available RCTs that met the inclusion criteria of the review, taking into account when the review was conducted). Also, for some topics, there were multiple systematic reviews available with sometimes conflicting conclusions.[85] Hence, current information from systematic reviews might be outdated, incomplete and contradictory, which may decrease the translation of research endeavors to clinical practice.

Guidelines are developed to improve quality of care, reduce practice variation and ensure that evidence-based care is optimally implemented.[86] The use of guidelines might be associated with more favorable outcomes in TBI patients.[87] However, guidelines can only improve patient outcomes if they are based on high-quality evidence, properly implemented and adhered to.

1.4 Aims and outline of this thesis

The aim of this thesis is to expand our knowledge on outcome and opportunities for CER in patients with TBI. We maintain an integrative approach by using a wide range of methodologies, including systematic reviews of the literature, analysis of patient data, survey data and a simulation study to address methodological challenges.
The aim of this thesis was operationalized in the following two main research questions:

1. **What is the prevalence and what are predictors of outcome following TBI?**
    a. What is the prevalence of TBI outcome in terms of persistent post-concussion symptoms, psychiatric disorders and HRQoL?
    b. What are predictors of TBI outcome?
    c. Can we identify patients at greatest risk for suffering post-concussion symptoms?
2. **To what extent can CER contribute to evidence generation in TBI?**
    a. To what extent do clinicians adhere to current evidence from guidelines?
    b. To what extent does variation in structure and process characteristics exist among centers treating patients with TBI?
    c. What is the influence of analytical methods on the estimate of treatment effectiveness in observational studies? And which method may provide a valid estimate in case of confounding by indication?

This thesis consists of two parts. In **Part I (Chapter 2-8)** prevalence and predictors of TBI sequelae are described and the possibility of identifying patients at greatest risk for post-concussion symptoms is examined. Specifically, **Chapter 2** provides an overview of current knowledge on prevalence, predictors, assessment and treatment of post-concussion symptoms. **Chapter 3** examines the influence of definition of post-concussion syndrome on prevalence rates and predictors. **Chapter 4 and 5** study the prevalence and predictors of psychiatric disorders following TBI. Prediction models for six-month post-concussion symptoms were developed and externally validated in **Chapter 6 and 7**. **Chapter 8** assesses HRQoL of Dutch and Chinese TBI patients and examines psychometric properties of the SF-36.

In **Part II (Chapter 9-16)** of this thesis we examine how CER could contribute to evidence generation in TBI. We start with an overview of current guideline adherence in **Chapter 9**. In the **Chapters 10 to 13** we describe variation in structures and processes of care, which is a prerequisite for CER. Specifically we focus on general characteristics (Chapter 10), structures and processes during emergency department and hospital admission (Chapter 11), intracranial pressure monitoring and treatment policy (Chapter 12) and rehabilitation (Chapter 13). **Chapter 14** describes variation of ICU management across five neurotrauma centers in the Netherlands and uses instrumental variable analysis to analyze the effect of intracranial pressure monitoring. The influence of analytical techniques on effect estimates is further examined in **Chapter 15 and 16.**

The results of the studies included in this thesis are further discussed in **Chapter 17**, together with their interpretation and recommendations for future research, policy and clinical practice.

This thesis is part of the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI; European Union FP 7th Framework program; grant 602150) project; a prospective longitudinal observational study that is currently recruiting patients from 68 European neurotrauma centers. CENTER-TBI aims to improve characterization and classification of TBI and to identify best clinical care, by using a comparative effectiveness approach. One of the tasks within CENTER-TBI is the characterization of center characteristics by sending out a survey ('the provider profiling questionnaires') to the participating neurotrauma centers addressing structural and process characteristics of different phases of care. The development of this survey is described in chapter 10 and the results are presented in chapters 10-13. How the results of this survey can be used for the CENTER-TBI CER analyses, will subsequently be described in the discussion section (Chapter 17).

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PART

Outcome following traumatic brain injury

2

Mild traumatic brain injury: A multidimensional approach to post-concussion symptoms

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Abstract

Mild traumatic brain injury (mTBI) can present a substantial burden to patients, relatives, and health systems. Whereas recovery is expected in the majority of patients, a subset continues to report persisting somatic, cognitive, emotional, and/or behavioral problems, referred to as post-concussion syndrome (PCS). However, this term has been subject of debate since the mechanisms underlying post-concussion symptoms and the role of pre- and post-injury-related factors are still poorly understood.

Current evidence and controversies concerning the use of the terms post-concussion symptoms versus syndrome, its diagnosis, etiology, prevalence, assessment and treatment in both adults and children are reviewed. Post-concussion symptoms are dependent on complex interactions between somatic, psychological, and social factors. Progress in understanding has been hampered by inconsistent classification and variable assessment procedures. There are substantial limitations in research to date, resulting in gaps in our understanding, leading to uncertainty regarding epidemiology, etiology, prognosis, and treatment.

Future directions concerning the identification of potential mechanisms, new imaging techniques, comprehensive, multidisciplinary assessment and treatment options are discussed. Longitudinal studies applying standardized assessment strategies, diagnoses, and evidence-based interventions are required in adult and pediatric mTBI populations to optimize recovery and reduce burden of post-concussion symptoms.

Introduction

Mild traumatic brain injuries (mTBI) are among the most common neurologic conditions, representing a substantial burden worldwide.[1,2] A subset of mTBI patients suffers from acute post-concussion symptoms that may manifest as somatic, cognitive, emotional, and/or behavioral problems. In a small portion of mTBI patients, post-concussion symptoms persist over time,[3,4] which is often referred to as post-concussion syndrome (PCS). PCS is usually diagnosed according to the International Classification of Diseases (ICD)-10[5], or following Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria.[6] However, over the last 15 years the concept of PCS as a reliably identifiable, unique syndrome has been questioned.[7,8] Therefore, we will use the term post-concussion symptoms to describe symptoms following mTBI and will refer to persistent post-concussion symptoms when these persist for at least three months after TBI.

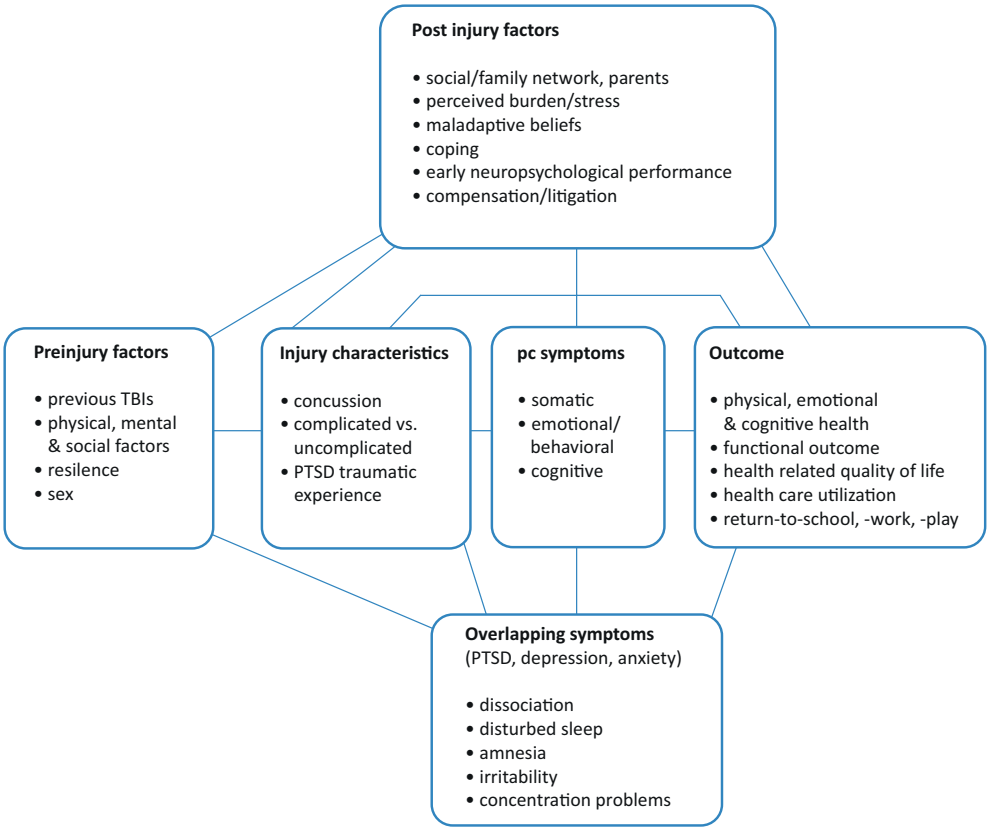
This narrative review (based on a systematic literature search till April 5th 2017, see search strategy and selection criteria and appendix) adds to the literature by summarizing current knowledge on epidemiology, etiology, assessment and treatment of post-concussion symptoms, using a multidimensional comprehensive coverage of topics, both in adults and children. Understanding the various factors leading to post-concussion symptoms (Figure 1), and the complex interactions between temporal onset, biological, psychological and social factors, as well as the relative influence of injury-related and non-injury related factors may contribute towards the understanding, diagnosis and classification of post-concussion symptoms. In addition, an insight into the wide range of assessment methods and possible treatments may provide guidance for both physicians and policy-makers. Furthermore, this review will provide directions for future research and clinical services, including recommendations on the investigation of etiological factors, assessment and treatment of post-concussion symptoms.

Definitions and epidemiology

Mild Traumatic Brain Injury (mTBI)

The American Congress of Rehabilitation Medicine (ACRM)[10] defines mTBI as an "acute brain injury resulting from mechanical energy to the head from external physical forces", with any of the following symptoms: loss of consciousness (LOC) not exceeding 30 minutes, post-traumatic amnesia (PTA) of no more than 24 hours, a score of no less than 13 on the Glasgow Coma Scale (GCS) after 30 minutes post injury (or upon presentation),[11] and an (unspecified) period of confusion (feeling dazed, disoriented, confused), or other transient neurologic abnormalities such as focal signs or seizures.

***Figure 1*. A model for the study of post-concussion symptoms after mTBI**



Modeled after Yeates[9]

Literature on mTBI frequently distinguishes between complicated and uncomplicated mTBI. Most mTBI patients do not show trauma-related abnormalities on computed tomography (CT) scans. However, the term "complicated mTBI" can be used to refer to the, e.g. 5-10% of emergency department (ED) patients[12] showing abnormalities, such as subarachnoid hemorrhage, intracranial contusions, or small extra-axial hematomas.

Controversies related to definitions

Post-concussion symptoms following mTBI refer to somatic symptoms of brain injury (nausea, dizziness, headache, blurred vision, auditory disturbance, fatigue), cognitive deficits involving memory and executive function, or emotional/behavioral changes (disinhibition and emotional lability).[5,6,10] The literature on mTBI frequently uses the term "symptom" to refer to all changes experienced after a concussion, regardless of whether they refer to the patient's subjective report, for which the term "complaints" might be more appropriate. In this review, the term "symptoms" will be applied to remain consistent with the literature.

Post-concussion symptoms do not always cluster in a consistent and predictable manner, and it is controversial whether they truly represent a specific, cohesive, and predictable syndrome.[8,13] Although the term post-concussion symptoms might suggest otherwise, these symptoms are not specific to TBI but are also frequently reported in non-brain injured trauma patients[14], including patients with whiplash injuries[15] and even in healthy adults and children.[16-18]

PCS is usually defined according to DSM-IV or ICD-10 criteria, with both focusing on symptom presentation.[13] These manuals agree on the prerequisite history of brain trauma for the diagnosis of post-concussional disorder (DSM-IV[6]) or PCS (ICD-10[5]). Differences between diagnostic systems are presented in Table 1. An important difference is that DSM-IV requires immediate symptom onset and persistence for at least three months whereas ICD-10 does not. In addition, DSM-IV requires objective evidence of memory or attention deficits (criterion B), but ICD-10 explicitly precludes such evidence (criterion C-3). The variability in terminology and associated criteria of the DSM-IV and ICD-10 hampers accurate identification and diagnosis of patients with PCS.[9] Different classification methods may result in overestimation or underestimation of symptoms, particularly when relying on subjective endorsement of symptoms by patients. This was shown in a cross-sectional study in which 61 patients were referred to a concussion clinic following mTBI.[19]

***Table 1*. Comparison of three definitions of post-concussion symptoms**

	ICD-10	DSM-IV	DSM-5
Headache	✓	✓	
Dizziness	✓	✓	
Fatigue	✓	✓	
Noise intolerance	✓	✓	
Irritability/lability/anxiety/depression	✓	✓	
Sleep problems	✓	✓	
Concentration problems	✓ [A]	✓ [B]	✓ [B]
Memory deficit	✓ [A]	✓ [B]	✓ [B]
Intolerance of alcohol	✓		
Preoccupation with symptoms	✓		
Personality change		✓	
Apathy		✓	
Perceptual-motor			✓ [B]
Social cognition			✓ [B]

Table shows symptoms presented in the International Classification of Diseases (ICD)-10 definition of PCS (diagnosis code F07.02), the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV definition of postconcussional disorder and the DSM-V definition of neurocognitive disorder. [A] Subjective report; [B] Objective test.

Post-concussional disorder was not included in the last DSM-5 edition.[20] Instead, DSM-5 includes "mild neurocognitive disorder due to TBI", a neurocognitive disorder, which strongly suggests – but not formally requires- performance-based, quantifiable evidence of acquired cognitive

deficits after mTBI (Table 1). Importantly, in DSM-5 the most frequently reported post-concussion symptoms are reduced to the status of "associated features". In addition, DSM-5 emphasizes the broad differential diagnoses, especially when symptom severity "appears to be inconsistent with the severity of the TBI".[21]

Prevalence of post-concussion symptoms

Prevalence of post-concussion symptoms varies and depends on pre-injury factors,[14,22] patient population (see panel 1),[23] assessment,[23] analysis strategies, and diagnostic criteria.[23,24] Overall, single symptoms (e.g. headache or depression) are very common[25] (Figure 2), whereas multiple concurrent symptoms are less frequent.[23]

Neuropsychological testing consistently shows minor cognitive deficits within the first two weeks after injury, with some exploratory evidence suggestion deficits lasting up to six months.[26] It has been suggested that self-reported somatic symptoms (headaches, dizziness) are more prevalent immediately after the injury (1-2 weeks)[27], whereas cognitive and emotional symptoms resolve more slowly and may still be above baseline levels at three months post injury.[28] However, as these are cross-sectional analyses, which do not track the evolution of symptoms in single patients, evidence supporting a differential trajectory between self-reported somatic and cognitive/emotional subacute symptoms is limited.

ICD-10 prevalence rates at three months post-injury vary between 6%,[29] 22%[30] and 64%.[24] DSM-IV diagnostic criteria appear to be stricter than ICD-10 criteria leading to lower estimates when using DSM-IV: a cohort study of patients after mTBI found a prevalence of PCS at three months of 64% based on ICD-10 criteria, but only a prevalence of 11% when using DSM-IV.[24]

Only few pediatric studies report prevalence of post-concussion symptoms based on ICD-10 or DSM-IV diagnostic criteria; one-month prevalence for children recruited from ED based on ICD-10 reach 52%[18] and three-month prevalence based on DSM-IV constitutes 29.3%.[31] Some studies define symptomatic children as having an increase at least in one symptom and arrive at estimates between 24.5-52.5% at one month post injury,[18,32] 11-39% after three months, and 2.3% at 12 months,[18] which makes comparison of symptom development trends between children and adults challenging. An additional complication in capturing prevalence rates in children is that younger children may not be able to describe their symptoms reliably. Therefore, such prevalence estimates should be treated with caution.

***Figure 2*. The prevalence of post-concussion symptoms over time**

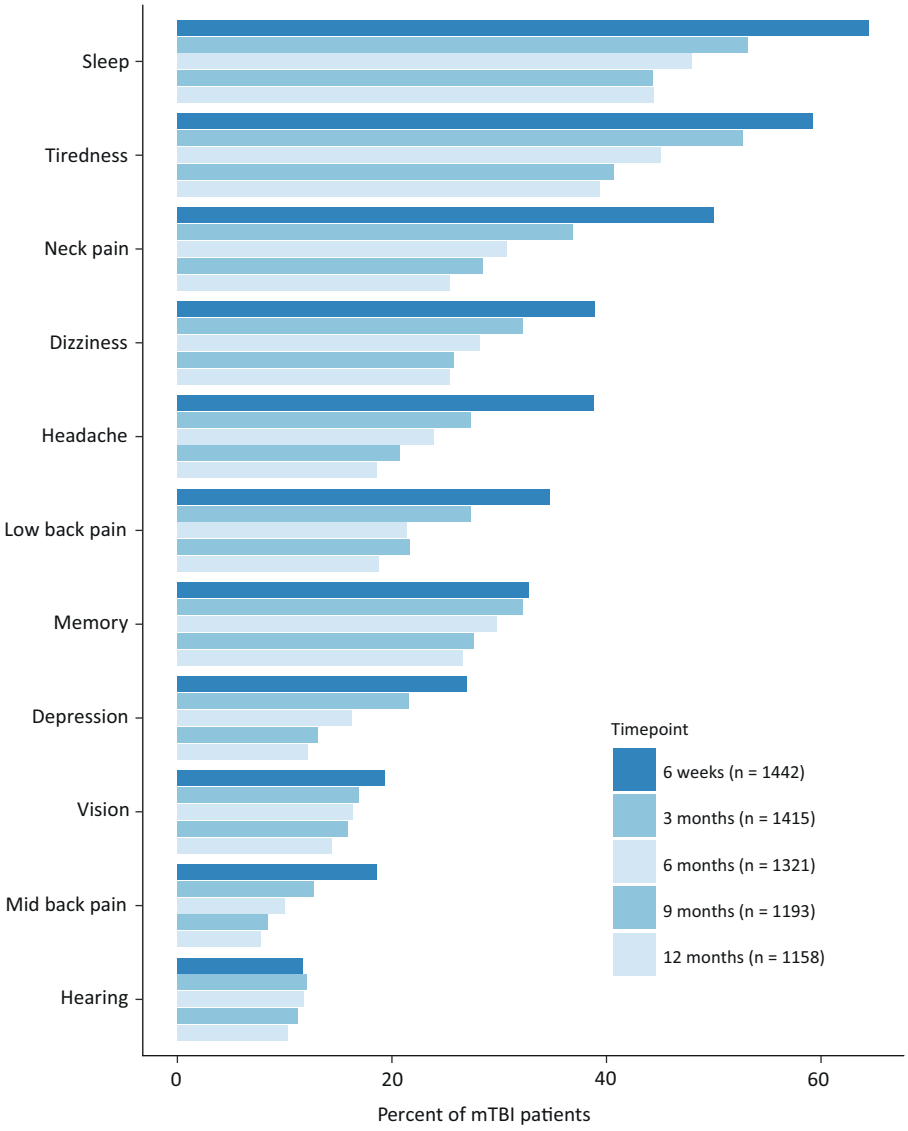


Figure is based on data presented in Hartvigsen et al.[25]

Etiology

Acute and persistent post-concussion symptoms

Acute symptoms post-injury, such as headache, dizziness, sensitivity to light or noise, double vision or tinnitus, are associated with the development of persistent symptoms.[13,33,34] A clinical risk score in children has identified headache, sensitivity to noise, fatigue and answering questions slowly as predictive of post-concussion symptoms at 28 days post-injury.[35] In addition,

the experience of post-concussion symptoms early post-injury (1 week – 1 month) is consistently associated with a higher odds of persistent post-concussion symptoms.[14,36] A 2015 study in 103 patients found that 82% of patients experiencing post-concussion symptoms one year after mTBI had already reported these after one month.[37]

Biological factors and persistent post-concussion symptoms

Several predominantly biological factors, such as diffuse axonal injury, neuro-inflammation, and altered cerebral blood flow have been implicated in the genesis of post-concussion symptoms after mTBI.[38-40] However, these factors have not yet been analyzed in high-quality prognostic studies. The role of biological factors is underlined by findings that repetitive mTBIs is associated with increased symptom prevalence,[41,42] longer time to symptom resolution, [42,43] and (limited) neurocognitive deficits.[44] Similarly, repetitive sub-concussive impacts, e.g. in contact sports, have also been associated with minor long-term neuropsychological sequelae, abnormalities in both neuroimaging and in neuropsychological tests,[45] and even with the development of neurodegenerative conditions such as chronic traumatic encephalopathy (CTE).[45] Although many symptoms of CTE bear similarity with post-concussion symptoms (e.g. irritability, impulsivity, depression, (short-term) memory loss), current evidence on the association of repetitive sub-concussive impacts with CTE is limited and should be considered preliminary.[46]

A major controversy in attempting to identify the role of biological factors in the development of post-concussion symptoms is their weak relationship with injury severity and the high prevalence of PCS-like symptoms in non-brain injured patients, as well as in healthy participants.[14-18,32,36,47]

Even though most studies find higher symptom endorsement in brain-injured patients,[29,37,48-50] the high rate of false-positives needs to be taken into account when validating biological factors. It should be acknowledged that biological factors do not exist in isolation but need to be interpreted in the context of potentially confounding factors, e.g. pre- and post-injury physical and mental health, trauma, and psychosocial factors.[14,49-51]

Psychiatric, psychological, (psycho)-social factors and post-concussion symptoms

Psychiatric factors

Many post-concussion symptoms (e.g. sleep difficulties, irritability and concentration problems) are similar to symptoms of the hyperarousal dimension of posttraumatic stress disorder (PTSD),[50] which may occur following exposure to severe, often life-threatening events. PTSD following TBIs of all severity grades has a pooled prevalence rate of 13.8% (10.2% to 17.4%)[52] and appears to follow TBI more frequently than other traumatic injuries not involving the brain.[38,53]

Given the overlap between post-concussion and PTSD symptoms,[50,53,54] careful differential diagnosis is required. Nevertheless, a prospective study including 534 brain-injured patients and 827 controls found that mTBI was a significant predictor for PTSD but not for post-concussion

symptoms.[50] However, it is unclear, whether these results also hold true for pediatric samples. A smaller prospective study comparing parent-reported post-concussion symptoms and PTSD symptoms in 186 children with mTBI and 99 children with non-head orthopedic injuries reported higher rates of post-concussion symptoms after mTBI but comparable rates of PTSD symptoms.[54]

Almost half of patients with persistent post-concussion symptoms suffer from premorbid depression and anxiety.[38,55] Pre-injury mental health status has repeatedly been shown to predict persistent post-concussion symptoms in adult[36,38,39,56] and pediatric populations.[9,18] However, the question of causality remains unclear, as psychiatric symptoms might be a reaction to experiencing persistent post-concussion symptoms, and/or mental health problems might increase the risk of reporting persisting symptoms.

Psychological factors

Recall biases have been shown to influence reports of post-concussion symptoms after mTBI. Patients after mTBI expecting to experience post-concussion symptoms show higher symptoms rates than patients with lower levels of expectation.[57] Similarly, in some patients the "good-old-days" bias may lead them to underestimate pre-injury symptoms.[39,48]

Malingering, exaggeration, and misattribution of common symptoms may also influence the persistence and worsening of post-concussion symptoms following mTBI. Involvement in litigation and compensation processes may lead to stress, exaggeration, and attribution.[7,58] Malingering is a multidimensional construct defined by the DSM-IV as "intentional production of false or grossly exaggerated physical or psychological symptoms, motivated by the external incentives". This diagnosis has been criticized for poor classification accuracy. Although removed from the index in the DSM-5, codes to identify conditions and criteria for when to consider malingering remain unchanged. Neuropsychological performance based outcomes (PERBOS) have also become an established practice in litigation cases despite the presence potential for bias and possible misinterpretation.[58]

Finally, symptoms commonly occurring in everyday life, such as headache, irritability, sleep disturbance and forgetfulness may be misattributed to brain trauma.[7,30] Extensive assessments for putative somatic origins of such common symptoms may further beliefs that these symptoms are indicative of serious brain damage, leading to hypervigilance and catastrophic attributions, comparable to behaviors seen in patients with somatoform disorders or hypochondriasis.[7,30,53,58,59]

Socio-demographic, social and personality factors

Female sex is consistently associated with greater reporting of persistent post-concussion symptoms.[36] Sex effects appear to be smaller in children.[18,32,47] Some studies found that post-concussion symptoms are associated with lower education in adults[36] and pre-injury learning difficulties in children.[32] Community integration, social support, lifestyle, and family dynamics

may contribute to the development and persistence of post-concussion symptoms in adults[39,60] and children[9] However, conclusive evidence has not yet been established.

Basic personality traits as captured in the five-factor model do not appear to be associated with persistent post-concussion symptoms.[14] However, more specific traits such as high anxiety sensitivity,[61] low resilience,[62] coping styles[30,63] or alexithymia[61] may be associated with persistence of symptoms. However, the cross-sectional design and small sample sizes in these studies hamper the establishment of firm conclusions in this area.

Predicting persistent post-concussion symptoms

The identification of risk factors might be especially useful for clinical practice when combined into a prognostic model predicting patients at risk of poor outcome. However, current models are often based on small samples[64] and lack internal and external validation.[14,36,64] In addition, no model is able to reliably predict outcomes at the individual patient level.[36] Therefore, identification of high-risk patients might best be accomplished by careful and dense follow-up data collection. However, advances in study and modeling methodology and, possibly, the incorporation of advanced imaging and biochemical biomarkers (see Panel 2 for recommendations) may improve the ability to identify at-risk patients in the first week post-injury in the future.

Clinical assessment of post-concussion symptoms

Providing optimal care depends on the early and reliable identification of patients at risk of developing persistent post-concussion symptoms,[8,65] by a multidisciplinary team. Medical examination should include a history of previous TBIs, head and neck injuries, and a detailed description of the number and extent of acute concussion symptoms, preferably using standardized instruments (see Table 2). Special emphasis should also be placed on the assessment of co-morbid injuries and disorders, such as chronic headache, and other pain, cervical-disorders, chronic fatigue, sleep and somatoform disorders.[18,56,65,66] However, checklists should not be solely administered to “diagnose” persistent post-concussion symptoms as a disorder in the absence of a comprehensive multidimensional medical, neurological, and psychiatric and (neuro) psychological evaluation.[55,67]

Since persistence of post-concussion symptoms has been associated with pre-, peri-, and post-injury psychological distress and risk of psychiatric disorders (PTSD, depression, anxiety, substance abuse, somatoform disorders), anamnesis should also include an assessment of pre-injury and current mental health difficulties (see table 2).[14,26,52,55] Finally, information on social and legal factors, such as availability of social support, life stressors, and involvement in legal proceedings needs to be collected.[66]

Table 2. **Selection of Post-Concussion Symptoms Assessments (Adults and Children) based on CDE Recommendations and Frequent Clinical Use**

Assessments	Examinations and instruments	Population
Clinical Examination and History	Standardized medical history and history of injury event, neurological and physical examination including orientation, speech fluency, memory, concentration, dyslexia, dizziness, vertigo, sleep, cranial nerves, motor, sensory and gait assessment; balance and vestibular testing; respiratory and heart rate, blood pressure; Cervical spine range of motion and tenderness; comprehensive headache assessment; neuroimaging (if mandated by neurological deficits)	A/P
	Standardized pre- and post-injury anamnesis of depression, anxiety, stress, dissociation, behavior, and other mental health problems retro- and prospective assessment: e. g. Structured Clinical Interview-DSM, Mini International Neuropsychiatric Interview (v 5.5), Diagnostic Interview Schedule for Children-IV, Neuropsychiatric Rating Schedule (NPRS), Clinician-administered PTSD Scale (CAPS)	
Self-reported Post-Concussion Symptoms	Health and Behavior Inventory*	P
	Neurobehavioral Symptom Inventory **	A
	Post-concussion Symptom Inventory**	P
	Rivermead Post-Concussion Symptom Questionnaire*	A
Neuropsychological Impairments	Behavior Rating Inventory of Executive Function**	P
	Rey Auditory Verbal Learning Test*	A/P
	California Verbal Learning Test for Children*	P
	Delis-Kaplan Executive Function System - Verbal Fluency*	P
	Immediate Post-Concussion Assessment and Cognitive Testing **	A/P
	Trail making test (TMT)*	A
	TRAILS-PRESCHOOL**	P
	Cognitive Battery-NIH Toolbox**	A/P
	Wechsler Abbreviated Scale of Intelligence*	P
	Wechsler Adult Intelligence Scale*	A
	Wechsler Intelligence Scale for Children-IV*/Wechsler Preschool and Primary Scale of Intelligence -III	P
Psychological and Psychiatric Status	Brief-Symptom-Inventory-18*	A
	Beck-Depression Inventory II**	A/P
	Child Behavior Checklist**	P
	Patient Health Questionnaire -9**	A/P
	Screen for Child Anxiety Related Emotional Disorders (SCARED)**	P
	Minnesota Multiphasic Personality Inventory (MMPI)**	A
	Posttraumatic Stress Disorder Checklist (PCL)**	A
	Short Mood and Feelings Questionnaire (SMFQ)**	A/P
	Alcohol Use Disorders Identification Test: Self-Report Version (AUDIT)**	A
Symptom Validity	Test of memory malingering (TOMM)**	A/P
	Medical Symptom Validity Test**	A/P
Family and Environment	Family Assessment Device (FAD)**	A/P
	Child and Adolescent Scale of Environment (CASE) **	P
	Family Burden of Injury Interview (FBII) **	P

* Common Data Elements (CDEs) recommended as basic measure; ** CDEs recommended as supplemental measure;
Abbreviations: A = Adult TBI; P = Pediatric TBI

A variety of symptom checklists exist to assess somatic, emotional, and cognitive post-concussion symptomatology, and require patients to indicate presence, absence, frequency, and intensity of symptoms. Neuropsychological PERBOS include measures of attention, memory, concentration, orientation and executive function and can provide performance-based evidence of symptoms indicating impaired cognition. Standard neuropsychological procedures should be followed to ensure that test results are not unduly influenced by comorbid disorders (e.g., attention deficit hyperactivity disorder, and dyslexia[68,69]), or inadequate understanding of test and questionnaire requirements, or low effort.[70] Until now, only in the field of sport concussion, short reliable and sensitive screening instruments (7-10 minutes) are implemented to identify possible symptoms.[71] A comprehensive overview of instruments suitable for clinical assessment is presented in table 2.

Neuroimaging and persistent post-concussion symptoms

No consensus has been reached on the relevance of imaging indicators of brain abnormalities for prognosis and outcome after mTBI. Several studies have shown that measures derived from magnetic resonance imaging (MRI)[65,72-74] or magnetic resonance spectroscopy (MRS) can reveal structural or functional abnormalities in adults and children with an otherwise normal CT.[18] Thus, for some patients, persistence of post-concussion symptoms may be explained by yet unknown brain abnormalities. However, current evidence is equivocal and the few large-scale, prognostic studies available suggest only small effects,[75] if at all.

Health-related quality of life and post-concussion symptoms

Health-related quality of life (HRQoL) measures supplement functional and mental health outcomes with information on how health conditions influence patients' subjective perspectives on their wellbeing. Post-concussion symptoms have been linked to lower levels of satisfaction with life[60] and HRQoL in adults[76] and children.[77] However, given the association of pre-injury physical and mental health status with persistent post-concussion symptoms, the specificity of these findings is unclear. Further research is needed to isolate the specific effects of persistent symptoms on HRQoL.[11]

Management of patients with post-concussion symptoms

Treatment of post-concussion symptoms is primarily symptom-oriented, and, given the limitations of current treatment guidelines,[78] highly variable.

Pharmacological interventions

The evidence for pharmacological treatment of depression, anxiety, and mood lability after mTBI is limited and conflicting. A meta-analysis evaluating the effectiveness of depression treatment after mTBI found that studies using a pre-post design suggested treatment benefits from selective serotonin reuptake inhibitors.[79] In contrast, the overall effects of controlled trials included in this meta-analysis did not reveal significant differences between treatment and control groups,

with some evidence favoring the control condition.[79] However, a recently published RCT found sertraline to be effective in preventing depression following TBI when administered early after injury.[80] These findings may have considerable therapeutic implications for patients with TBI, but future studies are needed to replicate results before a change in the treatment guidelines could be recommended.

Non-pharmacological interventions

Evidence concerning the benefits of non-pharmacological interventions targeting post-concussion symptoms is limited. Early educational interventions in ED patients after mTBI have received very limited evidence in reducing the incidence and severity of post-concussion symptoms.[81] However, successful interventions may be economical, as a single center RCT focusing on symptom management delivered via telephone counseling demonstrated reduced chronification of post-concussion symptoms during the first three months post injury.[82] However, this finding could not be replicated in a multi-center study of patients with mixed severity TBIs.[83] A recent Cochrane review concluded that most unselected mTBI patients make good recovery and do not necessarily benefit from interventions such as telephone counseling or patient information brochures.[84]

Evidence for beneficial effects of neuropsychological rehabilitation on post-concussion symptoms is still limited. A systematic review found evidence that, particularly when applied early, such approaches may be efficient in reducing self-reported post-concussion symptoms, anxiety and depression, but do not result in a clear reduction of cognitive impairment.[85]

A recent study suggests that cognitive behavioral therapy (CBT) can improve HRQoL in patients with persistent post-concussion symptoms in the context of outpatient rehabilitation services.[86] However, the effect of CBT on post-concussion symptoms was only marginal.[86] Problem orientation and problem-solving skills seem to improve by neuropsychological rehabilitation addressing self-regulation of cognitive and emotional processes,[87] but evidence is limited.

Intervention studies in children and adolescents are highly variable, of limited methodological quality, and evidence to support any particular intervention for post-concussion symptoms in pediatric samples is absent.[88] In adults, as in pediatric populations, well-designed prospective studies focusing on non-pharmacological multidimensional intervention that show improvement on variables such as HRQoL and return to play and work are still lacking.

Rest and post-concussion symptoms

Concerns have been raised regarding the expert-based consensus recommendation for rest after acute concussion, as studies in adults[89] and children[90] indicate that prolonged rest may contribute to prolonged symptomatology,[91] and no reduction in post-concussion symptoms was found in a study on rest interventions.[81]

Vestibular rehabilitation therapy

The traumatic event resulting in mTBI might also have resulted in concomitant cervical soft tissue damage, resulting in "whiplash-related" symptoms such as headache, dizziness and balance dysfunction as well as cognitive and visual dysfunction.[15] A 2014 RCT comparing cervical spine physiotherapy and vestibular rehabilitation therapy (VRT) with a control condition in 58 athletes found that among the intervention group a significantly higher proportion of individuals were medically cleared after eight weeks of treatment.[92] However, a recent systematic review concluded that current evidence for optimal prescription and efficacy of VRT in patients with mTBI is still limited.[93] Thus, further high-level studies evaluating the effects and optimal intervention window of VRT are required

Headaches

Headaches are among the most disabling symptoms after mTBI. Most post-traumatic headaches show clinical features of a recognized primary headache, such as migraine headaches or tension headaches. Post-traumatic migraines may respond to the same abortive and prophylactic treatments as sporadic migraines.[94] In addition, non-pharmacological approaches such as biofeedback, physical therapy, cognitive behavioral therapy, either as primary or adjunctive treatments, have also been successfully applied to persistent post-concussion headaches.[56,95]

Methodological considerations

In this narrative review, we only included prospective cohort studies with at least 100 participants, and reviews, with some exceptions (supplemental material). A total of ten included studies did not meet these criteria.[16,17,19,27,28,48,61,68,69,96] For these topics, there was no prospective study with at least 100 participants available. Therefore, prospective, multicenter research with larger patient samples is needed. In addition, it should be noted that studies fulfilling our quality criteria might still be at risk of bias. Attrition is a recurrent problem,[36,64] that may have influenced the reported prevalence rates, the relevance of etiological factors and also treatment effectiveness. In addition, some studies of etiological factors were based only on univariable analyses, while multivariable assessment is highly recommended because of the multifactorial nature of post-concussion symptoms.

Conclusions and future directions

Despite a sharp increase in studies investigating post-concussion symptoms, controversies and debates still exists pertaining to etiology, diagnosis, pathophysiology, natural history, prevalence, and terminology. The subjective nature of post-concussion symptoms, their low specificity, and the significant overlap with other physical, neurological and psychiatric conditions add additional challenges to these discussions.[8,13,14,16,35,36,47,50,67] The frequent overlap and very individual interplay of post-concussion symptoms with especially pre- and post-injury psychiatric, psychological

and social factors are still under-investigated and necessitates a standardized comprehensive differential diagnosis of comorbid mental conditions, in particular depression, anxiety disorders and PTSD.

In this review, we described possible factors contributing to post-concussion symptoms from a bio-psychosocial perspective. This provides insight into its complex nature and can be used by physicians to estimate risk of persistent symptoms in individual patients. In addition, it may provide targets for prediction modeling in which the explanatory value of different factors contributing to post-concussion symptoms are combined. Currently, no valid model is available to predict post-concussion symptoms.[36,64] Future prediction modeling studies can be improved by using solid methodology (see panel 2). However, the feasibility of prediction modeling can be debated given the complex, controversial and multifactorial nature of post-concussion symptoms. Therefore, investing in routine and economic follow-up methods (e.g. the development of a mobile phone applications) might be prioritized over prediction models.

The frequent reliance on simple symptom questionnaires for diagnosis ignores possible biases[14] and the fact that the major classification systems require several other criteria to be fulfilled, such as performance-based evidence of cognitive impairment.[20] Most questionnaires were developed in and for patients with more severe deficits, thus their sensitivity and specificity in mTBI may be challenged. More refined neuropsychological tests, especially sensitive to assess cognition after mTBI, may support the diagnosis of post-concussion symptoms. Moreover, short screening batteries (computerized and paper and pencil) are required for use in EDs and at general practitioners practices. This is line with international attempts at developing and implementing standards for clinical research (e.g. CDEs),[97] terminology and diagnosis criteria for post-concussion symptoms.

The heterogeneous nature of mTBI and post-concussion symptoms and the lack of reliable biological predictors and clinically useful gold-standard biomarkers still limit the development of disease-modifying therapies. A first step may be the identification of specific biochemical[98] and imaging biomarkers that can complement clinical diagnosis, inform prognosis by identifying patients at risk for post-concussion symptom persistence, and predict treatment response.[72,99]

Large-scale multidimensional, prospective longitudinal studies with several measurement points are strongly required to tackle current challenges in studying post-concussion symptoms. Such designs would allow stratified subgroup analyses to identify patients at risk for developing persistent symptoms, and might help to further early and personalized treatment. Depending on the research question, improved designs should include control groups, to receive insight into spontaneous recovery, and progression, injury severity, frequency, intensity and fluctuation (trauma controls and healthy participants) of post-concussion symptoms.

Due to normal variation in developmental trajectories, outcomes in children after mTBI may be particularly variable. Longitudinal large sample studies (>100) that investigate predictors of post-concussion symptoms in pediatric populations with multiple endpoints, adequate controls are especially important since high neuro- and cognitive plasticity is present here.

Although evidence for effective treatments is limited, a multi-disciplinary approach corresponding to the complex etiology of post-concussion symptoms may be most promising. Such an approach would combine in-depth comprehensive medical and neurological diagnosis with an emphasis on psychiatric differential diagnostics and psychosocial und neuropsychological outcome assessment. Also health management, medical monitoring, and proactive health maintenance interventions require further investigation. Future treatment directions (repetitive transcranial magnetic stimulation, vestibular and vision rehabilitation therapy and aerobic exercise) may offer a solution for the basic pathological processes associated with post-concussion symptoms.[56]

Standardization of treatment and interventions, outcome measures,[97] and follow-up assessment time-points would also enhance reliability and validity of research comparisons and individualized treatment. One might speculate as to whether post-concussion symptoms represent the most valid endpoint for treatment/study after mTBI. Given their low specificity, it may well be that other outcomes (e.g. functional outcome and HRQoL) prove to be more useful.
To summarize, standardization of multidimensional comprehensive diagnostics, treatment and interventions, and follow-up assessment time-points may enhance reliability and validity of research comparisons and refine personalized treatment and care.

This review documents the need for future directions concerning the identification of potential mechanisms, new imaging techniques, comprehensive multidisciplinary assessment and treatment options. Longitudinal-well controlled studies applying standardized, diagnoses, assessment strategies and evidence-based interventions are required in adult and pediatric mTBI populations to optimize recovery and reduce burden of post-concussion symptoms.

Supplemental material is available at www.marysecnossen.nl

Panel 1. **Cohort descriptions: Emergency Department patients versus sports related injuries and military blast injuries**

Patients presenting for care with mTBI represent a diverse group with differing mechanisms of injury and presentations to different points of care within the medical system. Characteristics of these subpopulations differ in terms of injury characteristics as well as patient demographics and likely affect outcomes. Important differences also exist with regard to risk of repeat injury and return to activities which influences clinical management. A broad understanding of these issues is essential to the care of these differing populations of mTBI. A brief comparison of such differences is presented in the table below.

Table: **Cohort Descriptions: Emergency Department vs. Sports-related vs. Military Blast Injuries**

	Emergency department mTBI	Sports mTBI	Military blast mTBI
Mechanism of injury	Higher energy (motor vehicle crashes, falls, direct impact)	Lower energy[102] Angular acceleration	Overpressure[104]
Hospitalization	High rate of hospitalization[100]	Low rate of hospitalization	Unknown
LOC	High incidence LOC	Low incidence LOC (< 10%)	Unknown
Repetitive injury	Uncommon	Common	Possible
Visual deficits	Unknown, but likely[101]	Common (smooth pursuit, saccadic deficits, convergence insufficiency[103])	Common (smooth pursuit, saccadic deficits, convergence insufficiency[105])
Duration	Symptoms may persist for months[59]	Symptoms resolve in 80-90% in 8-10 days[64]	High incidence of PTSD[106]

Summary: In short, mTBI patients are a heterogeneous population with differing pre-injury, injury and post-injury characteristics, all of which likely influence clinical care and recovery. Accounting for these differences in management of patients is paramount to optimize care and ultimate outcomes.

Panel 2. **Methodological recommendations for studies on post-concussion symptoms after mTBI**

Well-designed confirmatory studies with the following characteristics have been called for to better understand post-concussion symptoms and its consequences:

- **Study design**: Prospective inception cohort studies with appropriate control group (e.g. non-brain injured patients, general population) and appropriate follow-up period to differentiate persistent deficits and symptoms due to post-concussion symptoms from the effects of pre-injury (neuro)psychiatric disorders and other non-mTBI factors. Longitudinal analyses strategies to monitor evolution of post-concussion symptoms in single patients.

- **Instruments**: Use crosswalk analysis to compare incidence rates between studies using different post-concussion symptom assessment procedures. At least include anchor items.

- **Studies on predictors / prediction models** (based on Mushkudiani et al.[107] and Steyerberg [108]:
  - Sample size: N > 500
  - Predictors should be based on theory, clinical knowledge or previous research
  - For every predictor considered there should be at least ten cases (i.e. patients classified as having PCS)
  - A liberal *p*-value (e.g. $p < 0.157$)[109] should be used when applying selection procedures
  - Results should be internally validated (e.g. bootstrap validation)
  - Both discrimination and calibration statistics should be mentioned; a score chart is warranted for implementation in clinical practice
  - External validation: external validation in an independent dataset is a prerequisite before implementation in clinical practice. External validation and updating of an existing model should be prioritized against the development of a new model.

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3

Divergent classification methods of post-concussion syndrome after mild traumatic brain injury: Prevalence rates, risk factors and functional outcome

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Submitted

Abstract

Background: Mild Traumatic Brian Injury (mTBI) is a common diagnosis and approximately one-third of mTBI patients experience a variety of cognitive, emotional, psychosocial and behavioral post-concussion symptoms. When a cluster of these symptoms persists for more than three months they are often classified as post-concussion syndrome (PCS). The objective of this study was to determine prevalence rates, risk factors and functional outcome associated with PCS six months after mTBI applying divergent classification methods.

Methods: We performed a post-hoc analysis of 731 mTBI patients recruited in the Radboud University Brain Injury Cohort Study (RUBICS). Follow-up questionnaires at six months after mTBI included the Rivermead Post-Concussion Symptoms Questionnaire (RPQ) and the Glasgow Outcome Scale Extended (GOSE). The RPQ was analyzed according to different classification methods: the mapped International Classification of Diseases (ICD-10)/Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), the RPQ total score, the RPQ3 and the three-factor model using two different cut-off points (mild or worse and moderate or worse).

Findings: Prevalence rates of PCS ranged from 11.4% to 38.7% using divergent classification methods. Six percent of patients experienced PCS according to all eight methods. Applying the divergent classification methods resulted in a different set of predictors being statistically significantly associated with PCS and a different percentage of overlap with functional impairment, measured with the GOSE.

Conclusions: Depending on the classification method and rating score used, prevalence rates of PCS deviated considerably. For future research, consensus regarding the diagnostic criteria for PCS and the analysis of the RPQ should be reached, to enhance comparability of studies regarding PCS after mTBI.

Introduction

Traumatic brain injury (TBI) is a leading cause of death and disability worldwide with an annual incidence of 262 per 100,000 admitted TBI patients in Europe.[1] The large majority (70-80%) of all TBI cases are evaluated as mild TBI (mTBI). In the first weeks following mTBI many patients suffer from post-concussion symptoms comprising physical symptoms (e.g. headaches, dizziness, blurred vision, fatigue and sleep disturbances), cognitive deficits (e.g. poor memory, attention and executive difficulties), and behavioral/emotional symptoms (e.g. depression, irritability, anxiety, emotional lability).[2] For most patients these symptoms will diminish spontaneously,[3] but for a subset of patients (estimated between 5-43%[4-9]) symptoms last for over months and sometimes even longer. When a set of symptoms persists for over three months, it is often referred to as post-concussion syndrome (PCS).

It is challenging to define PCS because there is no consensus with regards to the criteria for diagnosis.[10] The most used criteria for diagnosis are those specified in the International Classification of Diseases (ICD-10)[11] and the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).[2] Even though the ICD-10 and DSM-IV classifications deviate, they both include a head injury with potential loss or alteration of consciousness and the existence of certain symptoms.

A frequently used instrument to assess the presence and severity of post-concussion symptoms is the Rivermead Post-Concussion Symptoms Questionnaire (RPQ).[12] The RPQ was developed by King (1995), who proposed to use the total scale score for analyses.[12] Subsequently, other evaluation methods have been applied. Potter et al. (2006) proposed a ≥ 12 cut-off for the total scale score.[13] Eyres et al. (2005) suggested the use of a two subscale version, one scale containing three items (RPQ3) and one containing 13 items (RPQ13), because of a possible lack of unidimensionality for the RPQ total scale.[14] Smith-Seemiller et al. (2003) recommended a modified scoring system with three subscales (cognitive, emotional and somatic symptoms) or two subscales (collapsing somatic and emotional symptoms versus cognitive symptoms) to be more sensitive.[13,15] The majority of studies however mapped the ICD-10 or DSM-IV criteria to the RPQ.[16-18] Patients are subsequently classified with PCS if they report at least three out of the following symptoms: headaches, dizziness, fatigue, irritability, impaired memory, impaired concentration, and insomnia. Next to heterogeneity in classification methods, there is also no consensus on whether symptoms should be incorporated in the rating for PCS if they are rated as 2 (mild problem) or worse or only if they are rated as 3 (moderate problem) or worse.[19,20]

The application of different classification methods and cut-offs may lead to incomparability of studies assessing PCS. The main objective of this study was to assess the prevalence rate of PCS among patients six months after mTBI, using four divergent classification methods and two different rating scores as cut-off to analyze the RPQ. In addition, we examined the association between PCS, predictors and functional outcome using the divergent classification methods.

Methods

Study design

Data were obtained from the prospective observational Radboud University Brain Injury Cohort Study (RUBICS).[21-24] All patients with mild, moderate or severe TBI admitted between January 1998 and December 2010 to the emergency department (ED) of the Radboud University Medical Center (RUNMC), a level I trauma center in the Netherlands, were included in the database. The ethical standards committee of the RUNMC had approved this study.

Study participants

The RUBICS database contains information on 2286 patients with mild, moderate and severe TBI. In the current study, 797 patients were selected from the RUBICS database based on the following inclusion criteria: patients' age was 16 years and older, written informed consent given by patients (or guardians), patients suffering from mTBI (GCS 13-15) and admitted to the emergency department of RUNMC between January 2003 and June 2010. Diagnosis of mTBI was based on a Glasgow Coma Scale (GCS, 13-15) after initial resuscitation or followed by sedation and intubation during resuscitation for a non-neurological cause. Exclusion criteria were alcohol or drug abuse or dementia, unknown address, and not able to speak or write Dutch.

Measurements

Clinical data was registered in the ED by a neurologist and/or neurosurgeon and entered by a research nurse into the RUBICS databank. Demographic data (age, sex and educational level), trauma mechanisms, hospitalization, clinical variables and comorbidities were collected with a postal questionnaire which was self-rated by patients or guardians at six months after the trauma.

Assessment of persistent post-concussion symptoms and diagnosis of PCS

The prevalence rates and severity of persistent post-concussion symptoms were assessed with the postal RPQ at six-month follow-up. Patients were asked to rate the severity of 16 different symptoms, commonly found after TBI, over the past 24 hours. In each case, the symptoms were compared with how severe they were before the injury occurred (pre-morbid). The patient was asked to rate the symptoms on a 5-point Likert scale: 0 (not experienced at all), 1 (no more of a problem), 2 (mild problem), 3 (moderate problem) and 4 (severe problem). In the literature, there is not a gold standard concerning the use of the RPQ. Therefore, we used the following classification methods: Mapped ICD-10/DSM-IV, RPQ total score,[12] RPQ 3[14] and three-factor model.[15] Because no clear cut-off was found in the literature for the RPQ13, this scale was not taken into consideration. For each classification method, we used two different rating scores as cut-off (≥ 2 and ≥ 3), resulting in eight different classification methods in total (Panel 1).

Panel 1. **Classification methods regarding Post-Concussion Symptoms**

Variable	**Mapped ICD-10/DSM-IV**	**RPQ Total score** *(Potter, 2006)*	**RPQ3** *(Eyres, 2005)*	**Three-factor model** *(Smith-Seemiller, 2003)*	
No. of symptoms	At least 3 from the list below	All symptoms from the list below	At least 1 symptom from the list below	At least 1 symptom from each scale from the list below	
Eligible symptoms from the RPQ	Headache	Headache	Headache	Cognitive	Forgetfulness, poor memory
	Dizziness	Dizziness	Dizziness		Poor concentration
	Sleep disturbance	Nausea and/or Vomiting	Nausea and/or Vomiting		Taking longer to think
	Fatigue	Noise sensitivity		Emotional	Being irritable, easily angered
	Being irritable, easily angered	Sleep disturbance			Feeling depressed or tearful
	Forgetfulness, poor memory	Fatigue			Feeling frustrated or impatient
	Poor concentration	Blurred vision			Restlessness
		Light sensitivity		Somatic	Headache
		Double vision			Dizziness
		Forgetfulness, poor memory			Nausea and/or Vomiting
		Poor concentration			Noise sensitivity
		Taking longer to think			Sleep disturbance
		Being irritable, easily angered			Fatigue
		Feeling depressed or tearful			Blurred vision
		Feeling frustrated or impatient			Light sensitivity
		Restlessness			Double vision
Cut-off; rating score 2	Three items ≥ 2	≥ 12 (only symptoms ≥ 2)*	≥ 2		Each scale one item ≥ 2
Cut-off; rating score 3	Three items ≥ 3	≥ 12 (only symptoms ≥ 3)	≥ 3		Each scale one item ≥ 3

**Example:* 6 symptoms with rating score 2 qualify as having PCS

Functional outcome

Functional outcome was assessed using the six-month Glasgow Outcome Scale Extended (GOSE), which was completed as a postal questionnaire. The GOSE is a functional measurement scale specifically designed for TBI.[25,26] The instrument evaluates functional outcome through eight categories encompassing consciousness, independence at home and outside the home, work, social and leisure activities, family and friendship and return to normal life.[27] After accumulating these categories an 8-point scale ranging from 1 (dead) to 8 (complete recovery) is established, which has the ability to distinguish between functional outcomes. When there was no available outcome at exactly six months, outcomes measured within a two-month range were also approved. Functional impairment was classified as a GOSE score of ≤ 6.[28]

Statistical analysis

For demographic data (age, sex and educational level), trauma mechanisms, hospitalization, clinical injury variables and comorbidities descriptive analyses were performed. Patients included in current study were compared to those having incomplete RPQ data on demographic variables using Chi-Square tests (categorical variables) and student's *t*-tests (continuous variables).

Prevalence of PCS using the eight divergent classification methods was determined by computing the percentage of patients meeting the specific criteria of each classification method. We subsequently determined overlap between classification methods by calculating the number and percentage of patients diagnosed with PCS according to multiple classification methods.

The univariable associations between predictors and PCS according to multiple classification methods were explored by using Chi-Square tests (categorical variables) and the student's *t*-test (continuous variables). The variables age, gender, education, injury mechanism, injury severity scale (ISS), abbreviated injury score of the head (AISH), comorbidity, traumatic abnormalities on the head computed tomography (CT) scan and hospitalization were considered as risk factors. All characteristics that were significant at $p < 0.20$ in the univariable analyses were included in a stepwise backwards multivariable logistic regression to identify significant risk factors ($p < 0.05$) of PCS. The association between PCS and functional impairment (GOSE ≤ 6) was determined by calculating the percentage of patients for each classification method of PCS that was functionally impaired. Multiple imputation technique with 5 datasets was used to impute missing predictor variables.

All statistical analyses were performed using SPSS version 21 for Windows (IBM SPSS Statistics, SPSS Inc, Chicago, IL).

Results

Study population

In total 797 mTBI patients were included in this study. The six-month follow-up questionnaire was completed by 92% (N = 731) of mTBI patients, who filled in all the items of the RPQ. Patients with a missing six-month RPQ (n = 66) did not differ from those included in this study, except that there was a slight significant difference in age (54 vs. 44) and ISS (7.9 vs. 9.7). The characteristics of our study sample are shown in Table 1. The median age of the respondents was 44 years and 63% were male. Almost half (48%) of the patients were injured due to road traffic accidents and a third due to falls. Approximately 50% of the respondents were admitted to the hospital and they were hospitalized for an average of three days. A total of 35 patients were admitted to the intensive care unit (ICU).

Six-month persistent post-concussion symptoms

The three most frequently reported symptoms on the six-month RPQ were fatigue, forgetfulness/ poor memory and poor concentration (Online Supplement A). Fatigue was endorsed by 308 patients (42.1%) and 32 (4.4%) patients evaluated this as a severe problem. Nausea and/or vomiting was the least reported symptom (n = 42, 5.7%). Approximately one-third of the patients (N = 242) endorsed none of the symptoms (total RPQ score of 0), whereas three patients had an RPQ score of 59, which means they experience severe problems six months after the injury on almost every item. The median score on the RPQ for the study population was 4 (IQR, 4-15).

Prevalence rates of PCS according to the different classification methods

The use of divergent classification methods resulted in prevalence rates for six-month PCS ranging from 11.4% (three-factor model with rating score 3) to 38.7% (mapped ICD-10/DSM-IV with rating score 2; Figure 1.1 and 1.2). Classification methods overlapped substantially; e.g. 95.6% (n = 108) of patients who met the criteria for PCS according to the mapped ICD-10/DSM-IV with rating score 2 also met the criteria for PCS according to the RPQ total score with rating score 2. The lowest amount of overlap was found for the classification methods RPQ3 and three-factor model with rating score 3 (n = 49, 51%) A total of 46 (6.3%) patients met the criteria for PCS according to all classification methods.

Table 1. **Characteristics of the study population**

N	**731**
Gender (male)	463 (63.3%)
Age[1] (years)	44 (27-57)
Education	
Primary education	21 (2.9%)
Secondary education	336 (46.0%)
Higher professional education	108 (14.8%)
Academic education	84 (11.5%)
Unknown	182 (24.9%)
Injury Mechanism	
Road traffic accident	351 (48.0%)
Fall	240 (32.8%)
Sports	77 (10.5%)
Assault	41 (5.6%)
Other/Unknown	22 (3.0%)
Injury characteristics	
ISS[1]	6 (4-14)
AISH[1]	2 (2-2)
Head AIS 3	93 (12.7%)
Head AIS 4	57 (7.8%)
Head AIS 5	11 (1.5%)
Comorbidity[2]	
No pre-existing disease	329 (45.0%)
1 comorbid disease	92 (12.6%)
2 comorbid disease	33 (4.5%)
3 or more comorbidities	40 (5.5%)
Unknown	237 (32.4%)
CT scan	
No CT scan	45 (6.2%)
CT scan, no abnormalities	591 (81.0%)
CT scan, abnormalities	94 (12.9%)
Hospitalization[3]	
Hospital admission	373 (51.0%)
Number of days hospitalized[1]	3 (1-8)
ICU admission	35 (4.8%)

[1] Data are displayed as median, with the first and third quartile given within brackets. 2 Comorbidity is defined as the presence of any co-existing diseases or disease processes additional to injury that the injury patients sustained. The following diseases were assessed as comorbid disease: asthma, chronic bronchitis, chronic non-specific lung disease (not questioned), heart disease, diabetes, back hernia or chronic backache, osteoarthritis, rheumatoid arthritis, and cancer. 3 Hospital or IC admission for one day or more after arrival at emergency department.

Abbreviations: mTBI = mild Traumatic Brain Injury; RPQ = Rivermead Post-Concussion Symptoms Questionnaire; PCS = Post-Concussion Syndrome; ISS = Injury Severity Score; AISH = Abbreviated Injury Scale of the Head; AIS = Abbreviated Injury Scale; CT = computed tomography; IC = intensive care.

Figure 1. **Number of mTBI patients with persistent post-concussion symptoms at six months and the overlap between classification methods**

Figure 1.1 **Rating score 2**

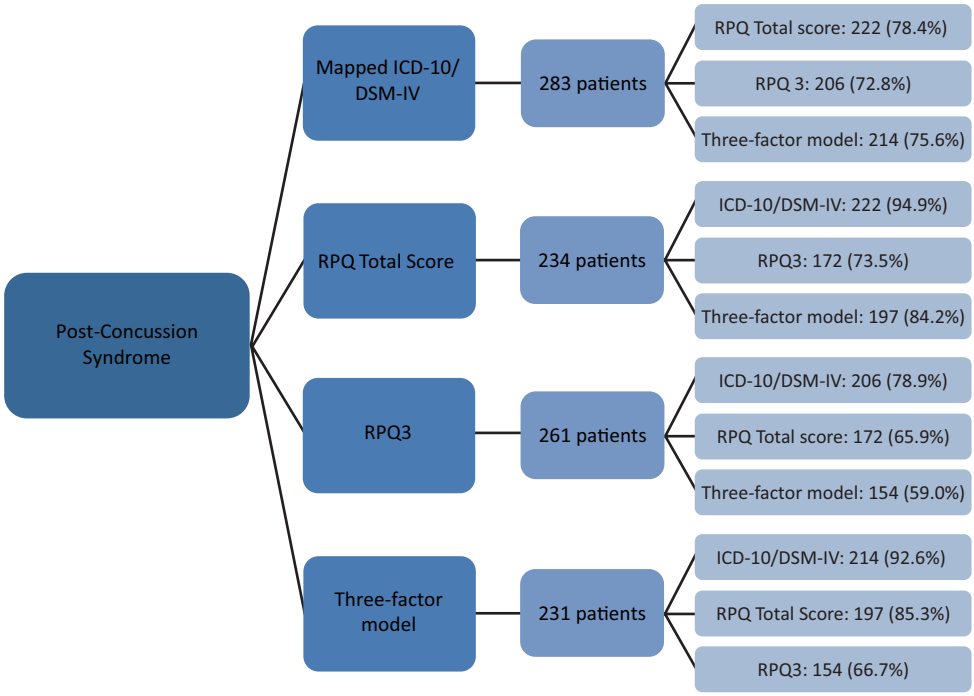
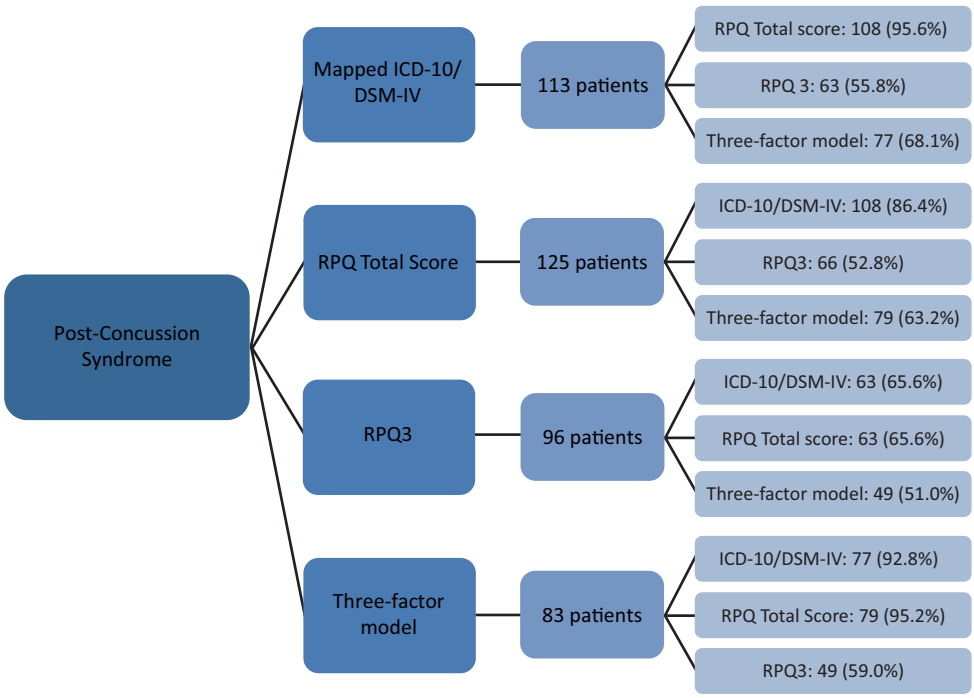


Figure 1.2 **Rating score 3**



Risk factors for PCS

Female gender, lower education and assault were significantly associated with six-month PCS according to all classification methods, whereas traumatic abnormalities on the head CT scan was not statistically significantly associated with PCS according to any of the classification methods (Table 2, Online Supplements B and C). The significance of the predictors ISS, AISH, comorbidity and hospital admission however depended on the classification method used; e.g. hospital admission was a significant predictor for PCS using six out of eight classification methods. Multivariable prediction models explained 8-16% (Nagelkerke R^2) of the variation in PCS according to the different classification methods.

PCS and functional outcome

A total of 198 (27.1%) patients were functionally impaired (GOSE ≤ 6) six months post-injury. There was a significant association between PCS according to all classification methods and functional impairment ($p < .01$). The highest percentage of functional impairment for patients with PCS was found for the RPQ total scale with rating score 3 (72.8%, n = 91), whereas the RPQ3 with rating score 2 recorded the lowest percentage (46.0%, n = 120; Table 3).

***Table 2*. Significant predictors in multivariable model of six-month PCS using divergent classification methods on a $p < 0.05$ level**

	Mapped ICD-10/DSM-IV		RPQ total score		RPQ3		Three-factor model	
Predictor	≥ 2	≥ 3	≥ 2	≥ 3	≥ 2	≥ 3	≥ 2	≥ 3
Gender	●	●	●	●	●	●	●	○
Education	●	●	●	●	●	○	●	●
Injury mechanism (Assault)	●	●	●	●	●	●	●	●
CT abnormalities	○	○	○	○	○	○	○	○
ISS	○	○	●	○	○	○	○	○
AISH	●	○	●	○	○	○	●	●
Comorbidity	●	○	●	○	○	●	●	○
Hospital admission	●	●	●	●	○	○	●	●
Nagelkerke R^2	0.15	0.08	0.16	0.10	0.11	0.11	0.13	0.08

● predictor is statistically significantly ($p < .05$) associated with PCS in multivariable logistic regression analysis.
○ predictor is not statistically significantly ($p < .05$) associated with PCS in multivariable logistic regression analysis.
≥ 2 = rating score 2, indicating mild or worse; ≥ 3 = rating score 3, indicating moderate or worse
Abbreviations: AISH = abbreviated injury severity scale head; CT = computed tomography; DSM = Diagnostic and Statistical Manual; ICD = International Classification of Diseases; ISS = injury severity scale; PCS = post-concussion syndrome; RPQ = Rivermead post-concussion questionnaire

Table 3. **MTBI patients with PCS and functionally impaired (GOSE ≤ 6)**

	Mapped ICD-10/DSM-IV	RPQ total score	RPQ3	Three-factor model
Rating score 2*	51.6% (146)	58.1% (136)	46.0% (120)	54.5% (126)
Rating score 3**	71.7% (81)	72.8% (91)	67.7% (65)	71.7% (59)

* mild or worse; ** moderate or worse

Discussion

The prevalence of PCS six months following mTBI ranged from 11.4% to 38.7%, depending on the classification method and rating score applied. The divergent classification methods in this study additionally influenced the statistical significance of predictors and the association with functional outcome, as measured with the GOSE.

The prevalence rates of PCS in our study are in line with preceding studies, which reported that prevalence rates of PCS after mTBI fluctuate and are estimated to range from 5% to 43%.[4-9] The prevalence rates that were found in the literature were dependent on many aspects, such as case-mix of the sample and setting, but also on the rating score applied and classification method used to identify mTBI patients with PCS. Yeates et al. have pointed out that the inconsistency in definition and classification criteria interferes with the righteous classification and identification of patients with PCS,[29] which ultimately leads to incommensurable prevalence rates and outcomes. Additionally, Waljas et al. have also stated that the rate of PCS diagnosis varies greatly based on which rating scale is being used,[19] which substantiates the decision during this paper to study two different rating scores as cut-off points. Recently, the DSM criteria for PCS have been revised substantially. Since this definition deviates significantly from the DSM-IV (e.g. the term mild neurocognitive impairment (MNI) due to TBI was introduced instead of PCS),[30] it is likely that this will result in even more heterogeneity in prevalence rates. Tator et al. have recently emphasized "a refinement of the definition of PCS"[31] and also the lack of consensus with regard to the definitions of PCS has previously been identified as a problem.[8] This problem presented itself as an opportunity in our study to explore and compare prevalence rates, risk factors and functional outcome when divergent cut-off rating scores and classification methods of the RPQ are applied.

When comparing divergent classification methods, different patients were identified as suffering from PCS. There was a difference of almost 30% in prevalence rates between the classification method with the highest (mapped ICD-10/DSM-IV with rating score 2; 38.7%) and lowest (three-factor model with rating score 3; 11.4%) percentage. Forty-six patients experienced PCS according to all classification methods. The most overlap in identifying the same patients experiencing PCS was found between the mapped ICD-10/DSM-IV and the RPQ total score (95.6%), both with rating score 3. This can be explained by the overlap between symptoms included in both

classification methods and by the fact that six out of seven eligible symptoms from the RPQ enclosed in the mapped ICD-10/DSM-IV are in the top eight most reported symptoms in this population. The lowest percentage of overlap was found between the RPQ3 and the three-factor model (51.0%) when a rating score of 3 was used as a cut-off. This can be explained by the fact that the RPQ3 only defines three somatic symptoms, while four out of the five most reported symptoms (forgetfulness/poor memory, poor concentration, taking longer to think, feeling frustrated or impatient) in this study population are cognitive or emotional, which are captured in the three-factor model. This also is in line with the thought that the RPQ3 measures symptoms that occur more often in the acute phase after a mTBI.[18]

In this study, we found that the classification method used influenced the statistical significance of predictors; i.e. several predictors were statistically significantly associated with PCS using some classification methods but not using others. This might be one of the reasons for the substantial heterogeneity in studies on predictors and prediction modeling for PCS, [32,33] hampering prognostic research.

Although PCS was statistically significantly associated with functional impairment (GOSE ≤ 6), there was variation in the amount of overlap between PCS and functional impairment dependent on the classification methods applied, ranging from 46.0% to 72.8%. Restricting PCS to only those symptoms that are endorsed as 'moderate or worse' resulted in higher overlap between PCS and functional impairment. This may indicate that symptoms endorsed as moderate or worse are more likely to represent clinical relevant symptomatology than symptoms endorsed as mild. This is in line with the findings by Waljas et al (2015),[19] who reported that when using rating score 3 as a cut-off, patients with head injury were successfully distinguished from healthy controls, whereas when rating score 2 was used as cut-off, this resulted in a substantial proportion of healthy controls being diagnosed with PCS.

The present study is unique because eight divergent classification methods concerning PCS were applied and the statistical effect this might have had on predictors associating with PCS and the different percentages seen as functionally impaired, measured by the GOSE were assessed.

Our study had several limitations. Firstly, Ruff et al. have declared that PCS concerns a complex interplay of biological, psychological and social factors, which include prior health, life stressors and compensation/litigation issues.[8] This implies that an overview of many aspects of a patients' current, but also previous life before the trauma, is required for correct assessment. Our study was a post-hoc analysis of prospectively collected data of individuals after mTBI, and there was no pre-injury data available except for pre-existing comorbidity. Additionally, post-concussion symptoms in our study were self-reported, which might have led to more or less reported symptoms on the questionnaire than if the respondents were interviewed by a physician.[34] Response bias might also have played a role during our study. Respondents with symptoms may

have been more likely to participate in the six-month follow-up questionnaires than patients who were currently not experiencing/or had never experienced any symptoms. Furthermore, the RPQ has been argued to not be the most ideal instrument to use in a mTBI population,[35] but there is currently no consensus on what would be a better instrument to use either. Looking at the RPQ total scale, one should keep in mind that even though the total RPQ score has been proposed by the developer of the instrument and is used in most papers till now, Eyres et al. have revalidated the RPQ, and have pointed out that the various items of the RPQ have very low construct validity and in consequence of this should not be computed into a sum score,[14] but into two subscales. A final limitation of our study is that data were collected in one academic hospital, which limits the generalizability of the results, because of differences in case-mix and because patients with severe trauma are more likely to be admitted to the ED of an academic hospital.

During the last decade, a shift from identifying PCS and interpreting it as an exclusive syndrome to recognizing it as being a highly complex and ever changing condition in different settings/ populations can be observed. This development leads to more and more specific research in the area of PCS or as now suggested persistent post-concussive symptoms. This debate and inconsistency concerning definitions, diagnostic criteria, assessment and evaluation of PCS hampers its research and therapy. Standardizing and improving diagnosis and assessment of PCS will facilitate to identify opportunities for intervention when patients suffer from the disabling PCS symptoms or even prevent mTBI patients to develop PCS. In addition, it is recommended to perform sensitivity and specificity analyses on the different classification methods for the RPQ to evaluate their classification accuracy.[18]

Conclusion

Our study showed that prevalence rates of PCS six months after mTBI deviate considerably dependent on the classification method and rating score used. In addition, applying divergent classification methods resulted in a different set of predictors being statistically significantly associated with PCS and a different percentage of overlap with functional impairment, measured with the GOSE. These findings highlight the need for a universal guideline with respect to diagnostic criteria for PCS and a gold standard for analysis of the RPQ to enhance comparability of studies regarding PCS after mTBI.

Supplemental material is available at www.marysecnossen.nl

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4

Prevalence of and risk factors for anxiety and depressive disorders after traumatic brain injury: A systematic review

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Abstract

This review examined the pre- and post-injury prevalence of and risk factors for anxiety disorders and depressive disorders following traumatic brain injury (TBI), based on evidence from studies using structured diagnostic interviews.

A systematic literature search was conducted in EMBASE, MEDLINE, Cochrane Central, PubMed, PsycINFO, and Google Scholar. We identified studies in civilian adults with TBI reporting on the prevalence of anxiety and depressive disorders using structured diagnostic interviews, and assessed their quality. Pooled pre- and post-injury prevalence estimates of anxiety and depressive disorders were computed.

A total of 34 studies described in 68 publications were identified, often assessing anxiety disorders (n = 9), depressive disorders (n = 7), or a combination of disorders (n = 6). Prevalence rates of psychiatric disorders varied widely. Pooled prevalence estimates of anxiety and depressive disorders were 19% and 13% prior to TBI, and 21% and 17% in the first year after TBI. Pooled prevalence estimates increased over time, and indicated high long-term prevalence of Axis I disorders (54%), including anxiety disorders (36%) or depressive disorders (43%). Females, those without employment, and those with a psychiatric history were at higher risk for anxiety and depressive disorders following TBI.

We conclude that a substantial number of patients encounter anxiety and depressive disorders following TBI, and that these problems persist over time. All healthcare settings should pay attention to the occurrence of psychiatric symptoms in the aftermath of TBI to enable early identification and treatment of these disorders and to enhance the recovery and quality of life of TBI survivors.

Introduction

Traumatic brain injury (TBI) often imposes long-term consequences that complicate recovery and rehabilitation.[1] A significant proportion of TBI survivors is diagnosed with psychiatric disorders, with post-traumatic stress disorder (PTSD) and major depression (MD) being the most commonly diagnosed and studied disorders.[1-3]

Anxiety disorders and depressive disorders have a major impact on functional outcome of patients with TBI, and drastically reduce their health-related quality of life (HRQL).[4-9] Due to the high incidence of TBI and the common diagnosis of anxiety and depressive disorders following TBI, this pathology imposes substantial disease burden and economic consequences to both individuals and society. Early identification and treatment of psychiatric disorders in patients with TBI may improve their outcome, psychosocial functioning, and HRQL.[10,11] For early prevention and treatment, insight in the prevalence of and risk factors for anxiety and depressive disorders is needed.

Anxiety and depressive disorders can be diagnosed with use of standard criteria like the Diagnostic and Statistical Manual of Mental Disorders (DSM)[12] or the International Statistical Classification of Diseases and Related Health Problems (ICD).[13] These criteria specify clinical disorders (so called Axis I disorders in DSM) that represent acute symptoms that need treatment. Axis I disorders include a wide range of psychological diagnostic categories, for example substance use, schizophrenia, psychotic disorders, dementia, etc. Common Axis I disorders include anxiety disorders (generalized anxiety disorder (GAD), acute stress disorder (ASD), panic disorder, agoraphobia, specific phobia, social phobia, obsessive-compulsive disorder (OCD), and PTSD), and depressive disorders (dysthymia, bipolar disorder, and major depression).

Previous reviews on psychiatric outcomes after TBI reported a wide range of anxiety and depressive disorders among TBI survivors,[3,14-17] and large variation in prevalence rates.[3,15,17] These reviews found prevalence rates of anxiety as high as 70%,[15] and rates of depressive disorders varying from 25% to 50%.[3,18] The existing reviews, however, focused solely on post-TBI prevalence rates of PTSD,[17,19,20] anxiety disorders,[15] or depressive disorders,[18,21] or included studies with prevalence rates based on both self-report measures and structured diagnostic interviews.[18,22] Research, however, indicated that self-reports from TBI patients may be unreliable due to the overlap between psychiatric symptoms and disorders, memory deficits associated with TBI, and evidence that TBI patients tend to underestimate their functional problems.[10,15] In contrast to self-reports, the use of structured diagnostic interviews enables the clinical examination for the presence of psychiatric disorders according to standard criteria like the DSM or ICD.[23] Use of these criteria in structured diagnostic interviews leads to more accurate prevalence estimates compared to self-report measures.[18,24] Self-report measures may provide an overestimation of psychiatric disorders after TBI, as they do not take into account the pre-existing or co-morbid

conditions of TBI patients, and enable patients to report more symptoms by prompting them with specific questions.[25,26]

The current review was conducted to improve our knowledge on psychiatric outcomes following TBI, which may enable early identification and treatment of these psychiatric disorders and may enhance the recovery and HRQL of patients with TBI. This review provides a full oversight of the prevalence of and risk factors for anxiety and depressive disorders in civilian adults with TBI, based on evidence from structured diagnostic interviews. The current study therefore analyzed existing research that has examined the pre-injury and/or post-injury prevalence of clinically diagnosed anxiety and depressive disorders following TBI, and/or the risk factors influencing the development of anxiety and depressive disorders following TBI.

Methods

Relevant studies were identified through systematic literature searches in the databases EMBASE, MEDLINE, Cochrane Central, PubMed, and PsycINFO. Grey literature was examined via Google Scholar. Search strategies were developed in consultation with a search expert, and included a combination of subheadings and text words (Online Supplement A). Reference lists and citation indices of the included papers and relevant reviews were inspected to identify additional relevant citations. We restricted searches to English-language papers, published in peer-reviewed journals until November 2nd 2015.

Study selection

Study design – We included retrospective and prospective cohort studies, cross-sectional studies, and case-control studies. Reviews, case reports, editorials, and intervention studies were excluded.

Participants – Studies were included if they were conducted in civilian adults (≥ 16 years) with TBI. Studies including a mixed population (e.g. all trauma patients) were only included if they analyzed their results for TBI patients separately. TBI was defined as an alteration in brain function or other evidence of brain pathology, caused by an external cause.[27] There was no restriction in the diagnosis of TBI (e.g. self-reported) or severity of TBI. There was also no restriction in the methods of patient selection (e.g. samples drawn from to the ED or hospital, referral clinics, or outpatient programs).

Psychiatric disorders – We included studies that examined all Axis I disorders or reported on the prevalence of at least one of the underlying anxiety disorders (including generalized anxiety disorder, acute stress disorder, panic disorder, agoraphobia, specific phobia, social phobia, obsessive-compulsive disorder, and posttraumatic stress disorder) or depressive disorders (dysthymia, bipolar disorder, and major depression) – see Box 1. All information on risk factors

for anxiety or depressive disorders (from univariable or multivariable analysis) were extracted from the included studies.

Structured diagnostic interviews – We included studies that used structured diagnostic interviews for the diagnosis of disorders (see Online Supplement B). Studies solely using self-report measures (e.g. checklist or rating scales) or other measures to determine disorders (e.g. own classification system) were excluded.

Multiple publications – To avoid double counting of prevalence rates, we identified publications that were related to the same sample of patients. For studies using data from an overlapping sample, one study was chosen as reference study by giving priority to the largest sample size (e.g. whole sample instead of specific age group or injury mechanism), the assessment of most disorders (e.g. Axis I over solely PTSD), and the focus on reporting prevalence rates (instead of predictors of disorders, or their impact on outcome). Information from all articles was used for analyzing the risk factors for psychiatric disorders following TBI.

Data extraction and risk of bias assessment

The first review author (AS) screened all titles and abstracts and deleted obvious irrelevant citations. After initial selection, the reviewer (AS) screened the remaining citations on title and abstract, and full-text. Any doubt on inclusion was resolved by consulting a second author (JH). Two reviewers (AS and MC) extracted data and assessed the risk of bias of the included studies. Any discrepancies were resolved by discussion or consulting a third author (SP).

We extracted information on the participants (age, gender, injury severity, and injury mechanism), and the assessment (interview, procedure, and timing), prevalence (before and/or after TBI), and risk factors (assessed and significant variables) for the studied psychiatric disorders. For each study the risk of bias was assessed using items on attrition bias (management of loss to follow-up) and reporting bias (primary outcomes missing) from the Research Triangle Institute item bank for observational studies,[28] complemented by items on the assessment of psychiatric disorders (e.g. inter-rater reliability, or assessor blinded to psychiatric history, medical file history, and/or hospitalization variables of participants), study limitations, and statements on causality.

Statistical analysis

TBI severity was assessed and categorized into severity levels (mild / minor, moderate, severe) with use of the classification methods reported in the studies. TBI severity can be classified with use of the Glasgow Coma Scale,[29] which is often categorized into mild or minor (GCS 13-15), moderate (GCS 9-12), and severe TBI (GCS 3-8).[30] Additionally, the American Congress of Rehabilitation Medicine (ACRM) defined mild TBI as a traumatically induced physiological disruption of brain function with a loss of consciousness (LOC) of approximately 30 minutes or less, an initial GCS of 13-15 after 30 minutes, and posttraumatic amnesia (PTA) not greater than 24 hours.[31]

Box 1. **Overview of anxiety disorders and depressive disorders according to the DSM-5***

Disorder	Definition	Symptoms	Duration
Axis I	Clinical disorders	Acute symptoms that need treatment	
Anxiety			
Generalized anxiety disorder (GAD)	Excessive anxiety and worry about a number of events or activities	Restlessness or feeling keyed up or on edge; being easily fatigued; difficulty concentrating or mind going blank; irritability; muscle tension; sleep disturbance	Occurring more days than not and for ≥ 6 months
Acute stress disorder (ASD)	Exposure to actual/threatened death, serious injury, or sexual violation	Intrusion; negative mood; dissociation; avoidance; arousal	3 days to 1 month after trauma exposure
Panic disorder	Recurrent unexpected panic attacks (abrupt surge of intense fear or discomfort)	Palpitations; sweating; shaking; shortness of breath; choking; chest pain; nausea; dizziness; chills or heat sensations; numbness or tingling; derealization; fear of losing control; fear of dying	≥ 1 attack followed by ≥ 1 month of persistent worry, or maladaptive change in behavior
Agoraphobia	Marked fear or anxiety about using public transportation; being in open or enclosed spaces, outside of the home alone, in a crowd; standing in line	Fear or anxiety; avoidance of situation	Persistent, typically lasting ≥ 6 months
Specific phobia	Marked fear or anxiety about an object or situation	Immediate fear or anxiety; avoidance of object or situation	Persistent, typically lasting ≥ 6 months
Social phobia	Marked fear or anxiety about ≥ 1 social situations with exposure to possible scrutiny by others	Fear to act in a way or show anxiety symptoms that will be negatively evaluated; avoidance of social situations	Persistent, typically lasting ≥ 6 months
Obsessive-compulsive disorder (OCD)	Presence of obsessions, compulsions, or both	Experience and ignorance or suppression of recurrent and persistent thoughts, urges, or images; repetitive behaviors or mental acts	Time-consuming (> 1h/day) or interfere with functioning

Box 1. **Continued**

Disorder	Definition	Symptoms	Duration
Post-traumatic stress disorder (PTSD)	Direct experience or witnessing traumatic event, exposure to aversive details or involved friends or family	Persistent re-experiencing of event; avoidance of stimuli; negative alterations in cognitions and mood associated with event; alterations in arousal and reactivity	> 1 month, interfere with functioning
Depression			
Dysthymia	Persistent depressive disorder	Poor appetite/overeating; insomnia/hypersomnia; low energy/fatigue; low self-esteem; poor concentration/difficulty making decisions; feelings of hopelessness	Occurring for most of the day, for more days than not, for ≥ 2 years
Bipolar disorder	Current or past hypomanic episode and major depressive episode	Inflated self-esteem or grandiosity; diminished need for sleep; more talkative than usual or pressure to keep talking; racing thoughts	Interfere with functioning
Major depression		Depressed mood; diminished interest/ pleasure; significant weight loss/gain; insomnia/ hypersomnia; agitation/retardation; fatigue/loss of energy; worthlessness/guilt; diminished ability to think/ concentrate; recurrent thoughts of death, suicidal ideation	Most of the day, nearly every day, interfere with functioning

* Obtained from: American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders, (DSM-5®)*. American Psychiatric Pub.

Pooled prevalence estimates per disorder were determined for three time points: before TBI (pre-injury), during the first year (first year), and after one year (> 1 year). A step-by-step guide was followed to perform a meta-analysis using a random-effects model in a Microsoft Excel spreadsheet.[32] This meta-analysis using Microsoft Excel showed to achieve results comparable with that of using Comprehensive Meta-Analysis Software (CMA), a commercial software package specifically developed to conduct meta-analyses.[32] If studies reported prevalence rates equal to 0%, a prevalence rate of 0.1% was used in our calculations. Studies with a sample size of fewer than 30 patients were excluded from the calculation of pooled prevalence estimates to minimize outlier estimates resulting from small sample sizes. Additionaly, studies that used a sample with self-reported TBI[33,34] or retrospective recall over decades after injury to assess the prevalence of disorders prior to TBI (pre-injury)[35] or the year after injury (first year)[35] were excluded from the calculation of pooled prevalence estimates, as suggested by the Cochrane Collaboration.[36] When only a small number of studies (N ≤ 2) reported on the prevalence of a disorder, no pooled prevalence estimates were calculated for that disorder.

Heterogeneity was assessed with the Q-statistic and I^2-statistic. The Q-statistic is a Chi^2-test for heterogeneity, which assesses whether observed differences in results are compatible with chance alone. A significant Q (low *p*-value) provides evidence of heterogeneity among the effect sizes, and indicates that the variation in effect sizes is beyond chance.[37] The I^2-statistic describes the percentage of variation across studies that is due to heterogeneity rather than chance.[38] An I^2 value of 25% or lower is associated with low heterogeneity, 50% is associated with moderate heterogeneity, and 75% or higher is associated with high heterogeneity.[38]

Results

Literature search

In January 2015, a total of 4,800 unique titles of potentially relevant articles were identified through the extensive search strategy (Online Supplement C). In November, the search strategy was updated and an additional 539 new, unique titles of potentially relevant articles were identified. Screening of the titles and abstracts resulted in a selection of 291 articles that appeared to meet all selection criteria. After screening and selection of the full text papers, we retrieved 34 studies described in 68 publications. The main reasons for exclusion were not using a structured interview, not reporting about TBI patients (separately), or not reporting prevalence rates. Twelve out of the 34 included studies were multiple publications on the same sample of patients, with the number of related studies ranging from 1 (n = 5)[2,33,34,39,40] to 7 (n = 1; Online Supplement D).[41] The 34 studies formed the basis of our review.

Study characteristics

Of the 34 studies, most were conducted in Australia (n = 9),[2,5,42-48] followed by the US (n = 8),[33,34,41,49-53] the UK (n = 4),[24,39,54,55] and Canada (n = 3)[11,56,57] (Table 1). Sample sizes varied

widely, ranging between 16[58] and 476[46] participants. The majority of the participants were males (except in 3 studies with 40-46% males),[54,56,59] with an average age of 29 to 42 years (in 27 out of the 34 studies). Traffic accidents comprised over half of all causes in 16 of the 22 studies that reported on injury mechanism.

TBI severity was often classified using the Glasgow Coma Scale (GCS, n = 15),[5,34,39-41,43,44,49-51,56,58,61,64,66] the definition of mild TBI by the American Congress of Rehabilitation Medicine (ACRM, n = 8),[11,45-48,53,57,65] or the duration of Post Traumatic Amnesia (PTA, n = 3).[24,42,54] Fifteen studies included all TBI severity levels, and twelve only mild TBI.

Axis I disorders (n = 11),[2,5,33-35,39,40,44,48,60,61] acute stress disorder (ASD) and/or post-traumatic stress disorder (PTSD) (n = 9),[24,42,43,45,46,54,55,59,63] (major) depression (n = 7),[11,41,50-52,57,65] and a combination of anxiety disorders and depressive disorders (n = 6)[47,49,53,56,58,64] were the most frequently studied disorders per sample. The three studies on ASD also assessed PTSD, and only included patients with mild TBI (n = 3).[42,46,54] In contrast, 15 of the remaining 31 studies included all TBI severity levels in their assessment of Axis I disorders, PTSD, (major) depression, or both anxiety disorders and depressive disorders.

The most frequently used structured interview was the Structured Clinical Interview for DSM Disorders (SCID, n = 15),[5,11,33,34,40,44,49-52,57,58,60,62,65] followed by the Clinical Assessment PTSD (CAPS, n = 6),[2,24,45,46,48,55] Schedules for Clinical Assessment in Neuropsychiatry / Present State Examination (SCAN/PSE, n = 5),[35,39,41,50,61] and/or Mini International Neuropsychiatric Interview (MINI, n = 3).[2,47,48] Axis I disorders were often assessed with the SCID (n = 6),[5,33,34,40,44,60] or SCAN/PSE (n = 3).[35,39,61] ASD and/or PTSD were diagnosed with use of a range of interviews, including the CAPS (n = 4),[24,45,46,55] Acute Stress Disorder Interview (ASDI, n = 2),[42,54] and Posttraumatic Symptom Scale (PSS, n = 2),[54,59] whereas depressive disorders were commonly assessed with use of the SCID (n = 8).[11,49-52,57,58,65] Five studies used multiple instruments in their assessment of Axis I disorders (MINI and CAPS),[2,48] ASD and PTSD (ASDI and PSS[54] or Composite International Diagnostic Interview, CIDI[42]), and major depression (SCAN/PSE and SCID).[50] Eleven studies reported that the interviews were conducted by one trained (neuro) psychiatrist or psychologist.

Risk of bias

Overall, 21 of the 34 studies reported on attrition, and faced problems of patients who refused to participate (n = 17, 8-58% of study sample),[2,35,40,42-48,54,58,60-63,65] patients who could not be contacted (n = 11, 2-58%),[2,5,35,40,42,43,54,55,61,63,65] and patients who deceased or did not attend appointments (n = 6, 3-36%).[35,39,40,50,62,65] According to these studies, participants often did not differ from those who did not participate. A few studies, however, showed differences in age (participants were older[2,47,50] or younger[59,63] compared to non-responders), and TBI severity (participants had higher[2,63] or lower[43] TBI severity level compared to non-responders).

Table 1. **Study characteristics**

Author, year, country, design	Study population	Inclusion/Exclusion	Sample	Disorder	Interview	Assessment
Bryant, 2010, Australia, A [2]	Mild (ACRM) Admitted to hospital (n = 437)	16-70y Not psychotic or suicidal Randomly selected, stratified by LOS	<45y 73%, 45+y 28%; Male 72%; MVA 76%	Axis I	MINI (DSM-IV, ICD-10) CAPS (DSM-IV)	Telephone interview by trained researchers
Meares, 2011, Australia, A [48]	Mild (ACRM) Admitted to hospital (n = 62)	18-65y Admission < 24h, initial assessment< 14d, IQ ≥ 74 No physical injury due to self-harm; psychotic; pre-existing cognitive impairment; pregnant	35.7y (14.5); Male 68%; MVA: 82% GCS 13 3%, 14 11%, 15 86% PTA < 5m 40%, 6-60m 21% 61m-24h 29%	Axis I	MINI (DSM-IV) CAPS (DSM-IV)	Four trained supervised postgraduate-level psychologists, and Meares. Reimbursement fee $40.00. Multiple imputation (n = 6)
Gil, 2005, Israel, A [60]	Mild Admitted to hospital (n = 120)	18-50y No history of TBI; psychiatric care at time of injury; cognitive deficit; substance abuse; major untreated medical condition	31.4y (2.7); Male 58%; Traffic 90% Upper range GCS 13-15	Axis I	SCID (DSM-IV)	Trained clinician
Gould, 2011A, Australia, A [5]	Compl mild to severe Admitted to rehab. hospital (n = 122)	16-80y No history of TBI; neurological disorder	34.9y (16.2), 16-77; Male 79% GCS 9.2 (4.3), 3-15 PTA 23.6 (22.6), 0.05-121d	Axis I	SCID (DSM-IV-TR)	Not reported
Whelan-Goodinson, 2009, Australia, B/C [44]	Minor to severe (GCS < 15) Admitted to hospital (n = 100)	17-75y No history of TBI; neurological disorder; neurodegenerative disease	*37.2y (14.2), 19-74; Male 71%; MVA 86% GCS 9.1 (4.1), 3-14 PTA 20.8 (17.9), 1-77	Axis I	SCID (DSM-IV)	Clinical computerized version, blinded to medical file history
Deb, 1999, UK, A [39]	Minor to severe (GCS < 15) Admitted to hospital (n = 164)	17+y ICD-9 diagnosis of TBI; Period of LOC; Radiological evidence	Median 43.5y, IQR 28, 18-94; Male 67% GCS 13-14 82%, 3-12 18%	Axis I	SCAN/PSE (ICD-10)	Two trained psychiatrists
Koponen, 2002, Finland, B [35]	Mild to severe Neuropsychiatric evaluation (n = 60)	Neurological symptoms lasting ≥ 1w & LOC ≥ 1m; PTA ≥ 30m; neurol sympt (ex headache; nausea) first 3d; neurorad findings suggesting TBI No history of neurological disorder	29.4y (10.9), 10-53; Male 68% PTA < 24h 50%, > 7d 32%	Axis I	SCAN/PSE (DSM-IV)	Trained research psychiatrist

Table 1. **Continued**

Author, year, country, design	Study population	Inclusion/Exclusion	Sample	Disorder	Interview	Assessment
Koponen, 2011, Finland, A [61]	Mild to severe Attended ED (n = 38)	16-70y Acute brain trauma (< 3d); LOC ≥ 1m; PTA ≥ 30m; neurol sympt (ex headache; nausea) first 3 days, neurorad findings suggesting TBI	41.6y (17.0), 16-67; Male 71%; MVA 26% GCS 13-15 & PTA < 24h 71%	Axis I	SCAN/PSE (DSM-IV)	Trained research psychiatrist
Hibbard, 1998, US, A [33]	Mild to severe Selection quality of life survey (n = 100)	18-65y at time of interview Self-identified TBI ≥ 1y prior to interview No history of neurological disorder	*39.8y (10.2); Male 53%; MVA 62% LOC < 20m 30%, > 1mo 24%	Axis I	SCID (DSM-IV)	Licensed psychologist with extensive background in clinical neuropsych and brain injury
Ashman, 2004, US[1,3] [34]	Mild to severe Hospital, brain injury associations, advertisements, website (n = 188)	18-87y Self-identified TBI No history of neurocognitive disorder; psychotic disorder	40.4y (15.1); Male 53% GCS 13-15 29%, 3-8 62%	Axis I	SCID (DSM-IV)	Clinicians with ≥3y clinical experience
Diaz, 2014, Brazil, A [40]	Severe Admitted to ICU (n = 43)	16+y No gunshot wounds	31.2y (11.9); Male 84%; Traffic: 72% GCS 7-8 37%, 5-6 27%, 3-4 37% PTA ≤ 1mo 51%, > 1mo 49%	Axis I	SCID (DSM-IV)	Two board-certified psychiatrists, blinded to hospitalization variables, additional information by patient relative
Jones, 2005, UK, A [54]	Mild (ACRM) Attended ED (n=131)	18-65y RTA No alcohol/drugs at RTA; psychiatric care at time of injury; fatality involved in RTA	36.8y (12.8), 18-65; Male 40%; Traffic 71%	ASD PTSD	ASDI (DSM-IV) PSS (DSM-IV)	ASDI: Trained masters-level psychologist. PSS: Chartered clinical psychologist with > 10y experience in trauma assessment
Bryant, 1999C, Australia, A [42]	Mild (PTA<24h) Admitted to hospital (n = 79)	16-65y MVA	29.5y (12.6); Male 70%; MVA 100% PTA 9.4 (9.1), 5m-24h	ASD PTSD	ASDI (DSM-IV) CIDI (DSM-III)	Doctoral clinical psychologist with 5y experience in assessing traumatized individuals

Table 1. **Continued**

Author, year, country, design	Study population	Inclusion/Exclusion	Sample	Disorder	Interview	Assessment
Broomhall, 2009, Australia, A [46]	Mild (ACRM) Admitted to hospital (> 24h) (n = 476)	16-65y Not suicidal or psychotic	38y (14.2); Male 73%; MVA 64%	ASD PTSD	CAPS (DSM-IV)	Trained interviewers by a clinical psychologist
Creamer, 2005, Australia, A [45]	Mild (ACRM) Admitted to hospital (> 24h) (n = 189)	18-70y No current psychotic disorder	37.0y (13.7); Male 76%	PTSD	CAPS (DSM-IV)	Telephone interview, trained mental health clinicians
Roitman, 2013, Israel, A [59]	Mild (LOC < 30m) Attended ED (n = 402)	Single MVA Not arrived in coma; LOS>30m; LOS>7d	HI 37.2y (12.7), LOC: 37.2y (12.4) Male HI: 46%, LOC: 63%	PTSD	PSS (DSM-IV)	Telephone interview
Caspi, 2005, Israel, B [62]	Mild to moderate Neurocognitive clinic (n = 120)	18-50y No history of TBI; major psychiatric illness; cognitive deficit; substance abuse; chronic medical condition	35.8y (5.9); Male 59%; Car 84%	Anxiety	SCID (DSM-IV)	Same team of interviewers
Barker-Collo, 2013, New-Zealand, A/B [63]	Mild to severe Multiple sources (BIONIC) (n = 296)	16+y	37.0y (17.9); Male 60%; Traffic 17% Worst GCS 14.1 (2.3) PTA 21.8d (36.4)	PTSD	PDS (DSM-IV)	Trained researcher
Turnbull, 2001, UK, A/C [55]	Mild to severe Attended ED (n = 41)	16-65y No chronic alcohol abuse with repeated ED attendance	35y (11); Male 87%; Traffic 32% PTA none 4%, < 1h 56%, 1-24h 22%, > 1d 18%	PTSD	CAPS (DSM-IV)	Telephone interview by postgraduate psychologist, if > 20 on IES-R subscales
Sumpter, 2005, UK, A [24]	Severe (PTA > 1d) Out-patient and rehabilitation services, voluntary organizations (n = 34)	18+y Severe TBI (PTA > 1d) ≥ 3mo before assessment No scores < 27 on MMSE; severe dysphasia; dyslexia; current treatment for psychosis	*40y (11), 20-60; Male 88%; Traffic 47% PTA 11w (13w), 26h-52w	PTSD	CAPS (DSM-IV)	Not reported

Table 1. **Continued**

Author, year, country, design	Study population	Inclusion/Exclusion	Sample	Disorder	Interview	Assessment
Bryant, 2000 Australia, A [43]	Severe Admitted to rehabilitation unit (n = 96)		34.3y (12.8), 16-71; Male 80% GCS 8.0 (3.8) PTA 37.0 (30.7), 7-143d	PTSD	PTSD-I (DSM-III-R)	Trained rehabilitation consultant
McCauley, 2005, US, A [49]	Mild to moderate Attended ED/admitted to hospital (n = 340)	16+y Arrival to hospital < 24h; blood alcohol level < 200mg/dL No history of substance dependence; mental retardation; major psychiatric disorder; CNS disturbance	DSM PCD: 36.4y (13.6); No PCD: 31.4y (13.3) Male 71%; MVA 70% GCS DSM PCD: 14.7 (1.0); No PCD: 14.6 (1.1)	PTSD Depression	SCID (DSM-IV)	Conducted by bachelors-/masters-level research assistant in the patient's primary language (English or Spanish)
Ponsford, 2011, Australia, A/D [47]	Mild (ACRM) Attended ED (n = 90)	18+y No intubation; anesthesia; breath alcohol > 0.05mg/L; illicit substances; focal neurological signs, seizures, CT abnormalities; upper limb injury (use computer mouse); spinal precautions; history of cognitive impairment, neurological illness, substance abuse, psychiatric impairment affecting functioning	35.0y (13.1); Male 74%; MVA: 41% PTA 103m (191m), 0-24h	Anxiety Depression	MINI (DSM-IV)	Not reported
Al-Adawi, 2007, Oman, A [64]	Mild to severe Neurocogn functioning evaluation (n = 68)	No history of psychiatric disorder; neurological disorder	M: 29.5y (6.9), 17-45; F: 34.9y (7.6), 22-50 Male 69%; MVA 67% GCS 13-15 9%, 9-12 3%, 3-8 41%	Anxiety Depression	CIDI (DSM-IV, ICD-10)	Two trained authors, blinded to results to the HADS
Fann, 1995, US, A [53]	Mild to severe Brain injury rehabilitation clinic (n = 50)	Closed head injuries	38.0y (13.0); Male 74% GCS 13-15 58%, 3-12 42%	Anxiety Depression	DIS (DSM-III)	Psychiatrist

Table 1. **Continued**

Author, year, country, design	Study population	Inclusion/Exclusion	Sample	Disorder	Interview	Assessment
Van Reekum, 1996, Canada, A [56]	Mild to severe TBI rehabilitation program (n = 18)	< 50y MVA≥2y pre-injury No pre-TBI psychiatric history; pre-TBI cognitive deficit Selection female : male ratio of 3 : 1	31.2y (8.5), 19-49; Male 44% GCS 13-15 28%, 9-12 17%, 3-8 56%	Anxiety Depression	SADS-L (DSM-III)	Experienced registered psychiatric nurse
Mauri, 2014, Italy, A/D [58]	Mild to severe Admitted to neurosurgery (n = 16)	18-65y Closed head injury; lesion on CT; LOC ≥ 1m; PTA ≥ 30m No history of unstable neurol conditions; pathol conditions of cardioresp system; psychiatric disorders; substance abuse	40.4y (14.0); Male 63%; MVA 81% GCS 13-15 38%, 9-12 38%, 3-8 25%	Anxiety Depression	SCID (DSM-IV-TR)	Expert clinicians
Rao, 2010, US, D [52]	Mild (LOC < 30m) Attended ED (n = 43)	18+y Closed head injury; GCS < 15 soon after injury No history of TBI; neurological disorder; mood disorder	44.5y (17.5); Male 53%; MVA 45%	Depression	SCID (DSM-IV)	Neuropsychiatrist
Konrad, 2011, Germany, A/D [65]	Mild (ACRM) Attended ED (n = 33)	18-65y No psychopharmacological medication; neurological diseases; MRI contra-indications	*36.7y (12.4); Male 52%; Traffic 55%	Depression	SCID (DSM-IV)	Not reported
Kennedy, 2005, US, A [51]	Mild to moderate Outpatient follow-up system Living assistance program (n = 78)	18+y ≥ 3mo post-injury	38y (12.2), 18-69; Male 69%; MVA 77% GCS 9.3 (4.8), 13-15 45%, 9-12 12%, 3-8 43%	Depression	SCID (DSM-IV)	Three trained research team members, additional information by significant other and medical records
Fedoroff, 1992, US, A [41]	Mild to severe Admitted to shock trauma center (n = 64)	18+y Acute closed head injury No significant multiple system injuries	MD: 26.8y (5.8); No MD: 29.5y (10.7) Male 86% GCS 12-15 17%, 8-15 & intracran surg or focal lesions > 25cc 58%, 3-7 15%	Depression	SCAN/PSE (DSM-III)	Trained research psychiatrist

Table 1. **Continued**

Author, year, country, design	Study population	Inclusion/Exclusion	Sample	Disorder	Interview	Assessment
Rapoport, 2003A, Canada, A [11]	Mild (ACRM) Appointment at TBI clinic (n = 210)	18+y No history of focal brain disease; acute medical illness; schizophrenia; bipolar disorder; dementia	47.3y (19.6), 19-91; Male 60%; MVA 61%	MD	SCID (DSM-IV)	Psychiatrist
Chamelian, 2006, Canada, A [57]	Mild to moderate TBI clinic, tertiary referral center (n = 63)	18-60y	33y (11.7); Male 56% GCS 13.7 (no complications) PTA < 24h 78%, > 24 < 1w 22%	MD	SCID (DSM-IV)	Clinic's neuropsychiatrist, blinded to subjects' cognitive data
Jorge, 2004, US, A/D [50]	Mild to severe Admitted to hospital (n = 91)	Closed head injury No spinal cord injury	36.4y (15.7); Male 59%; MVA 75% GCS 13-15 44%, 9-15 & intracran surg or focal lesions > 15mL 33%, 3-8 23%	MD	SCAN/PSE (DSM-III-R, ICD-10) SCID (DSM-IV)	Psychiatrist

A: Prospective; B: Retrospective; C: Cross-sectional; D: (Nested) Case-control. m=minute; h=hour; d=day; w=week; mo=month; y=year

* Age at assessment

Abbreviations: ACRM = American Congress of Rehabilitation Medicine; ASD = acute stress disorder; ASDI: Acute Stress Disorder Interview; CAPS = Clinician-Administered PTSD Scale for DSM-IV; CIDI = Composite International Diagnostic Interview; DIS = Diagnostic Interview Schedule; CNS = central nervous system; DSM = Diagnostic and Statistical Manual of Mental Disorders; ED = emergency department; GCS = Glasgow Coma Scale; HADS = Hospital Anxiety and Depression Scale; HI = head injury; ICU = intensive care unit; IES-R = Impact of Event Scale – Revised; IQR = interquartile range; LOC = loss of consciousness; LOS = length of stay in hospital; MD = major depression; MINI: Mini International Neuropsychiatric Interview; MMSE = Mini-Mental State Examination; MVA = motor vehicle accident; PCD = post-concussive disorder; PDS = Posttraumatic Stress Diagnostic Scale; PTSD-I = Posttraumatic Stress Disorder Interview; PSE = Present State Examination; PSS = PTSD Symptom Scale; PTA = post-traumatic amnesia; PTSD = post-traumatic stress disorder; RTA = road traffic accident; SADS-L = Schedule for Affective Disorders and Schizophrenia-Lifetime; SCAN = Schedules for Clinical Assessment in Neuropsychiatry; SCID: Structured Clinical Interview for DSM Disorder

With respect to patient selection, two of the 34 studies included patients with self-reported TBI (not medically documented),[33,34] and in another 16 studies participants were drawn from a variety of settings like specialty referral clinics or outpatient programs. Only 6 out of the 34 studies provided information on the inter-rater reliability of the structured diagnostic interviews, which ranged between 80% (n = 2)[34,51] and 100% (n = 4).[2,44-46]

Prevalence rates

Prevalence rates of anxiety and depressive disorders were assessed retrospectively (pre-injury, n = 15),[5,33-35,41,44,47,48,51,53,56,60-62,65] and at approximately 3 months (n = 8),[2,47-50,52,54,58] 6 months (n = 8),[42,43,50,55,57-60] 1 year (n = 10),[2,5,34,35,39,45,50,52,61,63] or more than one year after TBI (n = 12)[24,33-35,40,44,51,53,56,62,64,65] (Figure 1). Of the 12 studies with long-term follow-up, 6 studies had follow-up periods between 1 and 3 years,[34,40,44,53,62,64] 5 studies comprised periods of 5 to 8 years after TBI,[24,33,51,56,65] and one study 31 years after TBI.[35] Overall, a wide range of prevalence rates was reported for Axis I disorders, anxiety disorders and depressive disorders (Table 2).

***Figure 1*. Time points at which prevalence of psychiatric disorders was assessed**

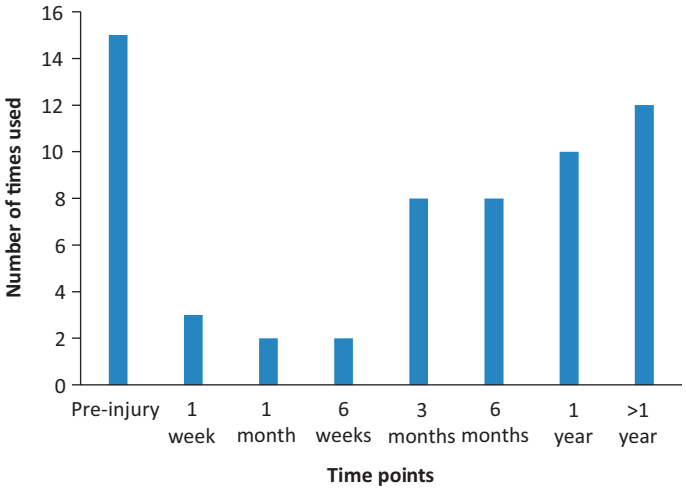


***Table 2*. Prevalence rates of psychiatric disorders before and after TBI**

Disorder	Study	Severity	Pre-injury	< 3 months	3-6 months	1 year	> 1 year	Follow-up (mean, (SD), range)
Axis I	Bryant, 2010	Mild				34.3		1y
	Meares, 2011	Mild	44.6*		32.1			~106.2d (14.9)
	Gil, 2005	Mild	40.8*		10.0			6mo
	Gomez-Hernandez, 1997	Mild to severe	13.8*					[1mo-1y]
	Gould, 2011A	Compl mild to severe	54.1*			45.9[c]		1y (1mo)
	Whelan-Goodinson, 2009	Minor to severe					65.0	3.0y (1.5); 0.5-5.5y
	Deb, 2007	Minor to severe				27.6		1y (1mo)
	Koponen, 2002	Mild to severe	21.7*				40.0	> 10y
	Koponen, 2011	Mild to severe	39.5**			47.4		1y
	Hibbard, 1998	Mild to severe	51.0*					[7.6y (7.1); 1-37y]
	Ashman, 2004	Mild to severe	5.0*	9.0		5.0	0.0	Base, 1, 2y; 3mo-4y
	Diaz, 2014	Severe					56.0	17.8mo (5.7)
Anxiety	Meares, 2011	Mild	41.1*		32.1			~106.2d (14.9)
	Ponsford, 2011	Mild	16.1*	12.5[b]				3mo
	Caspi, 2005	Mild to moderate	19.0*					[2.9y (3.7); 1mo-5y]
	Gould, 2011A	Compl mild to severe	22.1*	13.9	24.6	28.7[c]		6w[67], 6mo[68], 6mo-1y
	Whelan-Goodinson, 2009	Minor to severe	13.0*				38.0	3.0y (1.5); 0.5-5.5y
	Ashman, 2004	Mild to severe	16.0*	27.0		19.0	9.0	Base, 1, 2y; 3mo-4y
	Al-Adawi, 2007	Mild to severe					50.0	18.2mo (12.2); 0mo-5y
	Van Reekum, 1996	Mild to severe	16.7*				38.9	4.9y; 2-9y
	Diaz, 2014	Severe					20.9	17.8mo (5.7)
GAD	Bryant, 2010	Mild			9.8	13.4		3mo, 1y
	Meares, 2011	Mild	14.3*		10.7			~106.2d (14.9)
	Gould, 2011C	Compl mild to severe	1.0*			2.0		1y
	Whelan-Goodinson, 2009	Minor to severe	5.0*				17.0	3.0y (1.5); 0.5-5.5y
	Deb, 1999	Minor to severe				1.8		~1y (4w)
	Koponen, 2002	Mild to severe	0.0*			0.0	1.7	< 1y, > 10y
	Hibbard, 1998	Mild to severe	1.0*				8.0	7.6y (7.1); 1-37y
	Fann, 1995	Mild to severe					24.0	32.5mo (35.1); 1-128mo
	Van Reekum, 1996	Mild to severe	5.6*				27.8	4.9y; 2-9y
	Jorge, 1993D	Mild to severe		10.6	3.0	1.5		31d (IQR 32), 3mo, 1y
	Jorge, 2004	Mild to severe				15.4[d]		1y
	Diaz, 2012	Severe	0.0*				15.1	18.4mo (6)
	Fann, 1995	Mild to severe					24.0	32.5mo (35.1); 1-128mo
	Van Reekum, 1996	Mild to severe	5.6*				27.8	4.9y; 2-9y
	Jorge, 1993D	Mild to severe		10.6	3.0	1.5		31d (IQR 32), 3mo, 1y
	Jorge, 2004	Mild to severe				15.4[d]		1y
	Diaz, 2012	Severe	0.0*				15.1	18.4mo (6)

***Table 2*. Continued**

Disorder	Study	Severity	Pre-injury	< 3 months	3-6 months	1 year	> 1 year	Follow-up (mean, (SD), range)
ASD	Jones, 2005	Mild		21.2				6.0d (1.9)
	Bryant, 1999C	Mild		13.9				7.2d (5.3); 2-25d
	Harvey, 2000	Mild		13.9				1mo
	Broomhall, 2009	Mild		4.6				6.7d (6.9)
	Gould, 2011C	Compl mild to severe	0.0*			1.0		1y
	Whelan-Goodinson, 2008	Minor to severe					11.0	3.0y (1.5); 0.5-5.5y
Panic	Bryant, 2010	Mild			7.4	7.5		3mo, 1y
	Meares, 2011	Mild	10.7*		10.7			~106.2d (14.9)
	Gould, 2011C	Compl mild to severe	2.0*			2.0		1y
	Whelan-Goodinson, 2009	Minor to severe	1.0*				6.0	3.0y (1.5); 0.5-5.5y
	Deb, 1999	Minor to severe				6.7		~1y (4w)
	Koponen, 2002	Mild to severe	0.0*			1.7	6.7	< 1y, > 10y
	Hibbard, 1998	Mild to severe	4.0*				4.0	7.6y (7.1); 1-37y
	Fann, 1995	Mild to severe					4.0	32.5mo (35.1); 1-128mo
	Van Reekum, 1996	Mild to severe					5.6	4.9y; 2-9y
	Jorge, 2004	Mild to severe				2.2[d]		9.4mo (4.2)
	Diaz, 2012	Severe	3.0*				3.0	18.4mo (6)
Agora-phobia	Bryant, 2010	Mild			14.8	12.8		7.2d (9.6), 3mo, 1y
	Meares, 2011	Mild	12.5*		7.1			~106.2d (14.9)
	Gould, 2011C	Compl mild to severe	0.0*			2.0		1y
	Whelan-Goodinson, 2009	Minor to severe	1.0*				1.0	3.0y (1.5); 0.5-5.5y
	Hibbard, 1998	Mild to severe	4.0*				5.0	7.6y (7.1); 1-37y
	Fann, 1995	Mild to severe					2.0	32.5mo (35.1); 1-128mo
Specific phobia	Gould, 2011C	Compl mild to severe	5.9*			6.9		1y
	Whelan-Goodinson, 2009	Minor to severe	0.0*				7.0	3.0y (1.5); 0.5-5.5y
	Koponen, 2002	Mild to severe	8.3*			5.0	13.3	< 1y, > 10y
	Koponen, 2011	Mild to severe	5.3**					[1y]
	Hibbard, 1998	Mild to severe	4.0*				5.0	7.6y (7.1); 1-37y
Social phobia	Bryant, 2010	Mild			6.1	9.0		7.2d (9.6), 3mo, 1y
	Meares, 2011	Mild	10.7*		3.6			~106.2d (14.9)
	Gould, 2011C	Compl mild to severe	7.8*			2.9		1y
	Whelan-Goodinson, 2009	Minor to severe	2.0*				6.0	3.0y (1.5); 0.5-5.5y
	Koponen, 2002	Mild to severe	5.0*			0.0	5.0	< 1y, > 10y
	Koponen, 2011	Mild to severe	5.3**					1y
	Hibbard, 1998	Mild to severe	4.0*				5.0	7.6y (7.1); 1-37y

***Table 2*. Continued**

Disorder	Study	Severity	Pre-injury	< 3 months	3-6 months	1 year	> 1 year	Follow-up (mean, (SD), range)
OCD	Bryant, 2010	Mild			3.2	4.0		3mo, 1y
	Meares, 2011	Mild	10.7*		7.1			~106.2d (14.9)
	Gould, 2011C	Compl mild to severe	0.0*			1.0		1y
	Whelan-Goodinson, 2009	Minor to severe	1.0*				1.0	3.0y (1.5); 0.5-5.5y
	Deb, 1999	Minor to severe				1.2		~1y (4w)
	Hibbard, 1998	Mild to severe	1.0*				9.0	7.6y (7.1); 1-37y
	Van Reekum, 1996	Mild to severe					5.6	4.9y; 2-9y
PTSD	Bryant, 2010	Mild			12.7	13.0		3mo, 1y
	Meares, 2011	Mild	17.9*		19.6			~106.2d (14.9)
	Jones, 2005	Mild		30.4	17.2			44.0d (2.6), 94.3d (2.9)
	Bryant, 1999C	Mild			23.8			6mo
	Creamer, 2005	Mild				15.0		1y
	Gil, 2005	Mild			14.2			6mo
	Roitman, 2013	Mild			31.6[a]			224.9d (39.1)
	Caspi, 2005	Mild to moderate	1.7*				18.3	2.9y (3.7); 1mo-5y
	McCauley, 2005	Mild to moderate			11.5			86.4d (17.4)
	Whelan-Goodinson, 2009	Minor to severe	4.0*				14.0	3.0y (1.5); 0.5-5.5y
	Deb, 1999	Minor to severe				2.4		~1y (4w)
	Koponen, 2002	Mild to severe					0.0	31.4y (4.4); 27-48y
	Koponen, 2011	Mild to severe	0.0**			2.6		1y
	Hibbard, 1998	Mild to severe	6.0*				10.0	7.6y (7.1); 1-37y
	Ashman, 2004	Mild to severe	10.0*	30.0		18.0	21.0	Base, 1, 2y; 3mo-4y
	Barker-Collo, 2013	Mild to severe				17.9		1y
	Turnbull, 2001	Mild to severe			17.1			5mo (3)
	Mauri, 2014	Mild to severe		6.3	6.3			1mo, 3mo
					0.0			6mo
	Jorge, 2004	Mild to severe				7.7[d]		1y
	Alway, 2015A	Moderate to severe	0.5	1.9	4.3	9.4	8.9	56.4d (39.9), Initial-3mo, 3-6mo, 6mo-1y, 1-2y
							8.7	2-3y
							5.6	3-4y
							5.0	4-5y
	Diaz, 2012	Severe	3.0*				3.0	18.4mo (6)
	Sumpter, 2005	Severe					2.9	6y (7); 0.6-34y
	Bryant, 2000	Severe			27.1			6.3mo (1.3); 5-7mo
Depression	Meares, 2011	Mild	25.0*		10.7			~106.2d (14.9)
	Ponsford, 2011	Mild	27.0*	13.5[b]				3mo
	Rao, 2010	Mild			16.3	9.3		3mo, 1y
	Kennedy, 2005	Mild to moderate	50.0*					[76mo (94); 3mo-36y]

***Table 2*. Continued**

Disorder	Study	Severity	Pre-injury	< 3 months	3-6 months	1 year	> 1 year	Follow-up (mean, (SD), range)
	Caspi, 2005	Mild to moderate	8.0*					[2.9y (3.7); 1mo-5y]
	Gould, 2011A		23.0*	8.2	18.0[c]	32.8		6w[67], 6mo[68], 6mo-1y
	Whelan-Goodinson, 2009	Compl mild to severee	17.0*				46.0	3.0y (1.5); 0.5-5.5y
	Deb, 1999	Minor to severe				12.8		~1y (4w)
	Koponen, 2011	Minor to severe	0.0**			5.3		1y
	Ashman, 2004	Mild to severe	20.0*	35.0		24.0	21.0	Base, 1, 2y; 3mo-4y
	Al-Adawi, 2007	Mild to severe					57.4	18.2mo (12.2); 0mo-5y
	Jorge, 2004	Mild to severe				51.6[d]		1y
	Gomez-Hernandez, 1997	Mild to severe	0.0*					[1mo-1y]
	Diaz, 2014	Mild to severe					27.9	17.8mo (5.7)
Dysthymia	Meares, 2011	Severe	0.02*		0.0			~106.2d (14.9)
	Gould, 2011C	Mild	3.9*			1.0		1y
	Whelan-Goodinson, 2009	Compl mild to severe	0.0*				1.0	3.0y (1.5); 0.5-5.5y
	Koponen, 2002	Minor to severe					0.0	31.4y (4.4); 27-48y
	Hibbard, 1998	Mild to severe*	1.0*				3.0	7.6y (7.1); 1-37y
	Fann, 1995	Mild to severe					14.0	32.5mo (35.1); 1-128mo
	Meares, 2011	Severe	0.02*		0.0			~106.2d (14.9)
	Fedoroff, 1992	Mild to severe	0.0*	3.0	7.7	7.0		~36.6d (15.8), 3mo[69], 1y[69]
		Mild to severe			2.3			6mo[69]
	Jorge, 2004					9.9[d]		1y
Bipolar disorder	Gould, 2011C	Mild to severe	0.0*			2.0		1y
	Koponen, 2002	Mild to severe	0.0*			0.0	1.7	31.4y (4.4); 27-48y
	Koponen, 2011	Mild to severe	5.3**					[1y]
	Hibbard, 1998	Mild to severe	0.0*				2.0	7.6y (7.1); 1-37y
	Fann, 1995	Mild to severe					0.0	32.5mo (35.1); 1-128mo
	Van Reekum, 1996	Mild to severe	0.0*				16.7	4.9y; 2-9y
	Jorge, 1994	Mild to severe		1.9				31d (IQR 32)
	Diaz, 2012	Severe	3.0*				6.1	18.4mo (6)
MD	Bryant, 2010	Mild			17.9	17.4		7.2d (9.6), 3mo, 1y
	Meares, 2011	Mild	23.2*		10.7			~106.2d (14.9)
	Konrad, 2011	Mild	3.0*				9.1	6.0y; 4.8-7.3y
	Rapoport, 2003A	Mild		16.7				49.0d (30.0)
	McCauley, 2005	Mild to moderate			15.0			86.4d (17.4)
	Kennedy, 2005	Mild to moderate	14.0*				30.0	76mo (94); 3mo-36y
	Chamelian, 2006	Mild to moderate				7.9		6mo
	Gould, 2011C	Compl mild to severe	13.7*			29.4		1y

***Table 2*. Continued**

Disorder	Study	Severity	Pre-injury	< 3 months	3-6 months	1 year	> 1 year	Follow-up (mean, (SD), range)
	Whelan-Goodinson, 2009	Minor to severe	17.0*				45.0	3.0y (1.5); 0.5-5.5y
	Koponen, 2002	Mild to severe	0.0*			10.0	10.0	31.4y (4.4); 27-48y
	Koponen, 2011	Mild to severe	10.5**			7.9		1y
	Hibbard, 1998	Mild to severe	17.0*				61.0	7.6y (7.1); 1-37y
	Fann, 1995	Mild to severe	12.0*				26.0	32.5mo (35.1); 1-128mo
	Van Reekum, 1996	Mild to severe	22.2*				61.1	4.9y; 2-9y
	Mauri, 2014	Mild to severe		62.5	50.0			1mo, 3mo
					43.8			6mo
	Fedoroff, 1992	Mild to severe	0.0*	25.8				~36.6d (15.8)
	Jorge, 2004	Mild to severe		16.5	9.9			Initial, 3mo
					6.6			6mo
	Diaz, 2012	Severe	6.1*				30.3	18.4mo (6)

Axis I also includes disorders other than anxiety or depressive disorders (e.g. substance use, schizophrenia, psychotic disorders, dementia, etc.) * Lifetime pre-injury prevalence; ** Prevalence in 12-month period before TBI [a] Assessed at on average 7 months after TBI [b-d] Prevalence measured over a period of time: last 3 months[b]; 6 to 12 months[c]; during 1st year[d]
d=day; w=week; mo=month; y=year. *Abbreviations:* ASD = acute stress disorder; GAD = Generalized Anxiety Disorder; HI = head injury; IQR = interquartile range; MD = major depression; OCD = Obsessive Compulsive Disorder; PTSD = post-traumatic stress disorder

Pre-injury

In total, 14 of the 15 studies that assessed the history of psychiatric disorders before TBI used the same diagnostic interview to assess the pre-injury and post-injury disorders, while 1 study used questions to assess the personal history of psychiatric disorders.[70] The 15 studies showed widely varying prevalence rates of pre-injury Axis I disorders (5-54%, with 40-54% in 5 out of 8 studies),[5,33,48,60,61] anxiety disorders (13-41%), and depressive disorders (0-50%, with 17-27% in 5 of the 9 studies reporting on pre-injury rates),[5,34,44,47,48] irrespective of TBI severity. The 15 studies also reported varying pre-injury rates of the other disorders: GAD 0-14%, panic 0-11%, agoraphobia 0-13%, specific phobia 0-8%, social phobia 2-11%, OCD 0-11%, PTSD 0-18%, dysthymia 0-4%, bipolar disorder 0-5%, major depression 0-23%, and absence of ASD (0%, n = 1).[71] A history of dysthymia or bipolar disorders prior to TBI was rarely reported. A few studies reported absence of disorders (a prevalence rate of 0%), which may be explained due to the assessment of disorders after a long period of time,[6,35,44] the measure used for diagnosis of disorders (PSE),[41,70] or inclusion of only patients with severe TBI,[6] with causes other than MVA,[61] or those admitted to a rehabilitation hospital.[71] Additionally, two studies that assessed Axis I disorders in patients with mild TBI generally reported relatively high prevalence rates of all disorders, which may be related to their measures used for diagnosis of the disorders (MINI/CAPS).[2,48]

Post-injury

In the first year after TBI, prevalence rates of Axis I disorders ranged from 10-34% in mild TBI, to 5-47% in studies with all TBI severity levels. Additionally, substantial prevalence rates were reported of post-injury anxiety disorders (13-32%), especially ASD (14-21% in 3 of the

5 studies)[42,54,72] and PTSD (12-32% in 12 of the 17 studies),[2,34,42,43,45,48,49,54,55,59,60,63] or depressive disorders (5-52%, 11-35% in 6 of the 8 studies),[5,34,39,47,48,52] especially major depression (7-63%, 15-29% in 6 of the 11 studies).[2,11,41,49,50,71] Major depression tended to be more frequently diagnosed in patients with more severe TBI, as 8-18% of the patients with mild TBI received this diagnosis versus 7-63% in patients with all TBI severity levels.

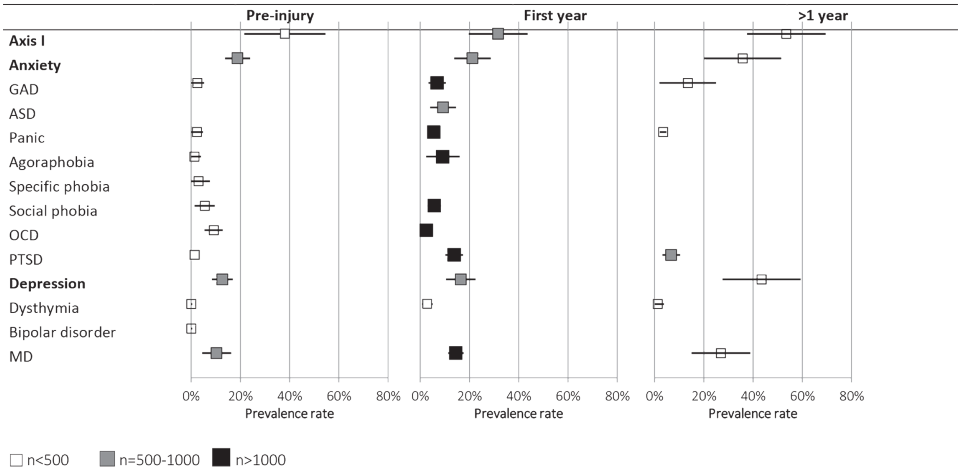
Even years after TBI, patients were diagnosed with psychiatric disorders, with prevalence rates of Axis I disorders as high as 40% (more than 10 years after TBI)[35] and 65% (3 years after TBI).[44] Prevalence of anxiety ranged from 9-50% after on average 1.5 to 5 years of follow-up,[34,40,44,56,64] and rates for depressive disorders were up to 21-57% after follow-up periods of on average 1.5 to 3 years.[34,40,44,64] Long-term prevalence rates were almost all higher than (or equal to) the rates before TBI, in all studies that measured both pre-injury and long-term prevalence of psychiatric disorders.[6,33-35,44,51,53,56,62,65]

Although the prevalence of dysthymia after TBI was generally low (0-3% in 5 of the 8 studies),[33,35,44,48,71] a few studies also reported a prevalence rate of 0% (absence of disorder) for GAD, social phobia, PTSD, and bipolar disorder. These studies, however, had a long follow-up period (more than 30 years after TBI),[35] a small sample size (n = 16),[58] or included solely patients admitted to neurosurgery,[58] or a TBI rehabilitation clinic.[53]

Pooled prevalence estimates

Figure 2 provides an overview of the overall pooled prevalence estimates per disorder by time point (also see Online Supplement E). Highest variation in prevalence rates across studies was seen prior to TBI in agoraphobia (moderate heterogeneity: I^2 = 66%, p = 0.05), and depressive

Figure 2. **Forest plot of pooled prevalence rates per psychiatric disorder**



Axis I also includes disorders other than anxiety or depressive disorders (e.g. substance use, schizophrenia, psychotic disorders, dementia, etc.)

disorders (high heterogeneity: $I^2 = 82\%$, $p < 0.01$). Highest pooled prevalence rates were retrieved for Axis I disorders (n = 5, 38% before TBI; n = 6, 32% in the first year; n = 3, 54% after one year), including anxiety disorders (n = 6, 19%; n = 5, 21%; n = 3, 36%), and depressive disorders (n = 8, 13%; n = 10, 17%; n = 3, 43%). Overall, the pooled prevalence rates increased over time in all disorders, except panic disorder, PTSD, and dysthymia (slight decrease).

Table 3. **Risk factors associated with psychiatric disorders after TBI***

Disorder	Patient-related	Injury-related	Follow-up related
Axis I	Younger age (18-64 year)[39,78] (2|8) Less education[39,78] (2|6) Pre-injury unemployment[5] (1|3) History of psychiatric disorders[33,39,71,78] (4|5) History of alcohol consumption[39,78] (2|2)	More severe TBI[33] (1|7)	Shorter[34], longer[71] time post-injury (2|2) Poorer GOS[39,78] (2|2) Lower MMSE score[39,78] (2|2)
Anxiety	Older age[5,76,86] (3|6) Female gender[33,34] (2|6) Pre-injury unemployment[76] (1|2) Pre-injury anxiety disorders[5,75,76] (3|4)	Less[56], more (symptoms)[58] severe TBI (1|4)	
ASD	History of psychiatric disorders[79] (1|2)		Shorter[79], longer[46] hospitalization (2|2)
PTSD	Older age[60] (1|9) Female gender[34] (PTSD severity)[63] (2|5) History of psychiatric disorders[60,74] (PTSD severity)[63] (3|4)	Higher LOC[59] (PTSD severity)[63] (2|2) Shorter PTA duration[74] (1|8)	Shorter time post-injury[34] (1|4) PCS/PCD[49,84,85] (3|3) Memory of traumatic event[55,60,62] (3|3) Poorer GOSE[74] (1|1) Lower QOLI[74] (1|1)
Depression	Older age[52,87] (2|12) Female gender[34,75] (2|11) Less education[75] (1|11) History of psychiatric disorders[80,81] (2|6), depression[75] (1|2) History of substance abuse[80] (1|4)	Lesion location[52,69,83] (3|3) Abnormal CT result[87] (1|3)	Shorter[34], longer[75] time post-injury (2|5)
MD	Older[82], younger (16-59 year)[11] age (2|6) Pre-injury unemployment[50] (1|4) (No)[33] History of psychiatric disorders[41] (2|2), depression[41,50,82] (3|3) History of substance abuse[11] (1|6)	MVA[10] (1|3) Lesion location[41,50,69] (3|3)	PCS/PCD[49,84] (2|2)

Axis I also includes disorders other than anxiety or depressive disorders (e.g. substance use, schizophrenia, psychotic disorders, dementia, etc.)

* Only risk factors which appear to be significant in 2 or more studies were presented.

In brackets: Number of studies in which the risk factor reached significance | Number of studies in which the risk factor was assessed.

Abbreviations: ASD = acute stress disorder; GOS = Glasgow Outcome Scale; MMSE = Mini-Mental State Examination; LOC = loss of consciousness; MD = major depression; MVA = motor vehicle accident; PCS/PCD = post-concussion symptoms/disorder (e.g. concentration deficits, dizziness, fatigue, headaches, sensitivity to sound, and visual disturbances); PTSD = post-traumatic stress disorder

Risk factors

In total, 30 articles assessed risk factors for psychiatric disorders, including 24 (71%) of the 34 reference studies and six related articles.[2,40,42,44,73,74] The most often assessed risk factors were age (n = 22), gender (n = 19), education (n = 18), marital or relationship status (n = 12), and TBI severity or GCS (n = 14). Other frequently studied factors were personal history of psychiatric

disorders prior to TBI (n = 11), employment, ethnicity, duration of PTA, and time post-injury (all n = 10), history of alcohol or substance abuse before TBI (n = 6), and involvement in litigation (n = 6). Females,[33,34,63,75] those without employment,[5,50,76,77] and those with a history of psychiatric disorders[5,33,39,41,50,60,63,71,73,75,76,78-82] or substance abuse prior to TBI[11,39,63,78,80] were at higher risk for psychiatric disorders following TBI (Table 3). Location of the brain lesion showed to be related to the risk of depressive disorders.[41,50,52,69,83] Furthermore, psychiatric disorders were associated with worse outcomes on measures like the GOS,[39,78] MMSE,[39,78] or complications such as PCS/PCD,[49,84,85] and memory of the traumatic event.[55,60,62] Contrasting findings were reported with respect to patients age, showing an increased risk of psychiatric disorders in older[5,52,60,76,82,86,87] and younger[11,39,78] patients.

Discussion

Our systematic review aimed to provide insight into the prevalence of and risk factors for anxiety disorders and depressive disorders after TBI, collected with structured diagnostic interviews. Our findings showed that a substantial number of patients had a history of anxiety disorders (19%) or depressive disorders (13%) before TBI, or were diagnosed with those disorders in the first year after TBI (21% and 17%). The pooled prevalence estimates of psychiatric disorders increased over time, and indicated that years after TBI, half of the participants (54%) were diagnosed with Axis I disorders, including anxiety disorders (36%) or depressive disorders (43%). Females, those without employment, and those with a history of psychiatric disorders or substance abuse prior to TBI seem to be at higher risk for anxiety or depressive disorders following TBI.

Quality of the evidence

Several limitations of the included studies need to be considered. First, the studies faced difficulties in differential diagnosis of overlapping disorders (e.g. ASD and post-concussive effects) and overlapping symptoms between TBI and disorders, which may have led to higher[79] or lower[88] prevalence rates of disorders. The included studies however all used structured diagnostic interviews to examine the presence of psychiatric disorders according to standard criteria like the DSM or ICD. The use of structured diagnostic interviews by clinical experts (e.g. one trained psychiatrist or psychologist) enables more stringent assessment of psychiatric outcomes after TBI than self-report measures.[18] However, regardless of the method of assessment, patients may report more symptoms due to concerns about pending litigations.[89]

Second, the history of psychiatric disorders prior to TBI was often retrospectively assessed (e.g. with use of the structured interview), in some studies even years after TBI. Relying on recall of symptoms over such long periods may be less reliable.[90]

Third, several studies reported on a small number of subjects,[6,24,52,56,58,65,85,91] and their conclusions may not apply to all patients with TBI. Although most of the 34 included studies had difficulties

in contacting and interviewing all eligible patients, there is a need for a thorough and reliable assessment of the psychiatric outcome in all survivors of a TBI. Participation rates may be increased by using face-to-face recruitment and data collection, by using mail and Internet for contacting and informing patients, and by lowering the participant burden (for example by conducting interviews at home).[92]

Prevalence rates

Consistent with findings in the literature,[1-3] anxiety disorders (mainly PTSD) and depressive disorders (mainly major depression) were the most common and frequently studied disorders following TBI.

There was considerable variation in the post-injury prevalence rates of disorders among the patient samples of the included studies. The wide variation in prevalence rates of pre- and post-injury prevalence rates of anxiety and depressive disorders between studies has been reported previously[1,3,15,93] and can be explained by differences in study design, characteristics of the patients, definitions, methods of assessment, and measures used to assess the psychiatric outcomes.

Our findings indicate that a history of psychiatric disorders before the TBI was common in TBI survivors, as approximately one in three adults (38%) had pre-injury Axis I disorders (often including substance abuse disorder), one in five (19%) a history of anxiety disorders, and one in eight (13%) a history of depressive disorders before TBI. According to our pooled prevalence estimates, prevalence rates of anxiety disorders were lower before TBI (19%) than in the first year after TBI (21%). In contrast, three studies that reported on pre- and post-injury prevalence rates of depressive disorders, indicated prevalence of depressive disorders to be higher before TBI than in the first year after TBI.[5,47,48] In line with these findings, the included studies in our review that also reported on the community base rate of psychiatric disorders showed that patients with TBI had lower pre-injury rates of anxiety disorders than the general population (for example PTSD: 6% pre-TBI versus 8% in US adults[33]; 2% pre-TBI versus 6% in Australian population[71]).

Although a history of psychiatric disorders before TBI was common, several studies reported a substantial share of novel disorders.[2,35,44] These studies showed that numerous participants experienced Axis I disorders (78%), including anxiety disorders (74%) or depressive disorders (72%) for the first time following injury.[35,44] However, a history of psychiatric disorders prior to TBI was significantly associated with a higher risk for psychiatric disorders in the aftermath of a TBI.[5,33,39,41,50,60,63,71,75,76,78-82]

A few of the included studies reported on the prevalence of co-morbid psychiatric disorders and indicated that 72-77% of those with a post-injury depressive disorder also had a co-morbid anxiety disorder, and 69% of those with an anxiety disorder also had a co-morbid depressive

disorder.[44,50,71] According to findings of Gould et al, anxiety disorders tended to precede or emerge at the same time as depressive disorders.[71]

The pooled prevalence estimates of psychiatric disorders indicated that psychiatric disorders did increase over time, even after mild TBI. The increase of prevalence rates of disorders over time was a phenomenon that was also found within some of the included studies.[2,5] This may be explained by the ongoing stressors and problems that may occur after the traumatic event, which may add to the maintenance of disorders after TBI.[2,94] Additionally, the delayed onset of psychiatric disorders may occur due to psychosocial changes, as after the physical recovery insight into social, cognitive and emotional disability develops.[71,95,96] Another explanation may be that a greater cognitive resource (e.g. higher education level before a TBI) may decrease the vulnerability to cognitive deficits after TBI, and may have a protective role in the development of psychiatric disorders.[97] Although the included studies in our review assessed education level[5,6,11,24,34,39,41,50-53,58,60,62,76,77,87,98] and pre-morbid IQ[24,58,82] as risk factors for psychiatric disorders following TBI, only few of them reached significance showing less education to be associated with higher prevalence of anxiety and depressive disorders following TBI.[39,75,78] In contrast, longitudinal results of Ashman et al showed that the risk of having an Axis I disorder decreased 3 to 6 years post-injury.[34] However, Koponen et al found high rates of current psychiatric disorders 30 years after TBI,[35] which suggests that the vulnerability of developing psychiatric disorders may remain throughout the life of a person with TBI.

Our pooled estimates of depressive disorders (MD: 15% first year, 27% > 1 year; dysthymia: 3% and 1%) were in line with those of a recent review of Osborn et al, in which 27% of the TBI survivors were clinically diagnosed with major depression and/or dysthymia after TBI.[18] We, however, computed pooled prevalence estimates over time, showing lower estimates of major depression and dysthymia in the first year after TBI (15% and 3%), but higher estimates in the long-term (27% and 1%). Additionally, a review of van Reekum et al overall reported higher mean prevalence rates of major depression and PTSD compared to our pooled estimates: MD 44%[22] versus 15% in the first year and 27% after one year in our review; PTSD 14%[22] versus 14% and 7% in our review. Their review, however, did not specify prevalence of disorders over time, and included data from both structured diagnostic interviews and self-report measures.[22] Osborn et al showed that, in comparison to structured diagnostic interviews, the use of self-report measures leads to far higher prevalence rates.[18]

Risk factors

The included studies in our review reported different directions of risk factors like the patients' age,[11,82] TBI severity level,[33,56,58] time post-injury,[34,71,75] and length of stay in the hospital.[46,79] However, these findings are not necessarily inconsistent. For example, in the studies that reported that younger people were more at risk of having a psychiatric disorder after TBI, the younger group comprised all those aged 18-64 years,[39,78] or 16-59 years.[11] However, the relationship

between age and psychiatric disorders after TBI is controversial, with studies showing contrasting findings on whether[52,87] or not[11] older patients are at increased risk of psychiatric disorders after TBI.

Additionally, inconsistent findings were reported on TBI severity, as more severe TBI was related to a higher risk for Axis I disorders[33] and the number of anxiety symptoms,[58] whereas less severe TBI was related to higher risk for anxiety disorders.[56]

The studies in our review tended towards higher prevalence rates of major depression among patients with more severe TBI, as 8-18% of the patients with mild TBI received this diagnosis versus 7-63% in patients with all TBI severity levels. However, the severity of TBI has not emerged as a significant risk factor of depressive disorders in previous studies.[5,18,51,53,56,70,76,80,99]

Female gender was identified as a risk factors for psychiatric disorders after TBI in several studies.[33,34,75] This is underpinned by the fact that the included studies with a high share of women (≥ 70%, n = 5) tended to report somewhat higher prevalence rates of anxiety disorders than the samples with relatively more men (on average 6-12% higher rates), OCD (2-6%), PTSD (3-8%), depressive disorders (4-12%), and major depression (< 1-5%).
Finally, several studies included in this review reported depressive disorders being associated with lesion location, with higher rates of disorders in patients with left frontal abnormality,[41,50,52,80,83] left anterior lesions,[41,69,80,83] left[41] or right hemisphere lesions,[41,83] cortical lesions,[41] and parieto-occipital lesions.[41] Although investigations determining the relationship between lesion location and depressive symptoms have proven inconsistent,[100] lesion site may influence the nature of depression but does not fully explain the occurrence and severity of depressive disorders.[101]

Strengths and limitations

Our review adds to the knowledge on psychiatric outcomes of TBI in civilian adults, by providing pooled prevalence estimates over time and insight into the risk factors associated with the full spectrum of anxiety disorders and depressive disorders. Our findings are based on evidence from structured diagnostic interviews, and emphasize that the prevalence of anxiety and depressive disorders after TBI is high and persists over time.

This review has limitations. First, because of our decision to only include studies on anxiety and depressive disorders following TBI, other psychiatric outcomes (e.g. including substance use disorders, schizoaffective disorders, or psychotic disorders) were not specifically taken into account. Second, the review solely focused on the prevalence of psychiatric disorders following TBI in civilian adults aged 16 years or older. Therefore, information on the prevalence of anxiety and depressive disorders among children or adolescents and military personnel is missing. Military personnel and veterans have a higher exposure to emotional trauma,[25] and therefore show higher rates of psychiatric disorders (e.g. PTSD) than the civilian populations.[26] Third, this

review did not elaborate on the cognitive impairments (e.g. deficits in attention, processing speed, and working memory) or post-concussion symptoms (e.g. dizziness, fatigue, and headaches) which may contribute or interact with psychiatric outcome after TBI.[82,86] Fourth, only a few of the studies included in this review reported on the percentage of novel disorders after TBI.[2,35,44,61] Research is needed to gain more insight into the prevalence of new versus recurrent anxiety disorders and depressive disorders after TBI. Finally, it was difficult to compare study results, due to the differences in study objectives, design, methodology and study population, including differences in definitions of TBI, inclusion and exclusion criteria, and interviews used to assess psychiatric disorders. Some of the studies in this review included participants with self-reported TBI (not medically documented) or from a variety of outpatient or rehabilitation settings. The studies assessed disorders in patients with varying TBI severity levels. As mild TBI is likely to be very different from severe TBI on many aspects, pooling of the data across these TBI severity levels may lead to an under- or overestimation of the prevalence rates amongst different cohorts. In addition, some studies (n = 3) reported prevalence over a period of time instead of point prevalence, and sometimes used different diagnostic criteria. Research showed that the latter variation in diagnostic criteria surprisingly provided different prevalence estimates, despite the overlap between these criteria.[18] All the previous factors might have influenced the prevalence estimates of anxiety disorders and depressive disorders provided in this review. To enable comparisons between studies, consensus should be reached on standard definitions (e.g. for TBI, and TBI severity levels), study methods (e.g. which structured interview to use, which time points), and reporting styles (e.g. how to report on pre-injury and post-injury prevalence rates).

Implications for practice and research

Our review showed that, even years after TBI, a substantial number of patients experience psychiatric disorders. This underscores the need for recognition and treatment of anxiety and depressive disorders in all healthcare settings.[10,11,58] Ideally, the routine treatment of patients with TBI should include a psychiatric evaluation and follow-up. Overall, early identification and treatment of psychiatric disorders may enhance the recovery of TBI survivors, their capacity to work, their HRQL and functional outcome, and may reduce the high costs associated with disability in TBI.[102-104]

As only a few of the studies included in this review reported on the percentage of novel disorders after TBI,[2,35,44,61] research is needed to gain more insight into the prevalence of new versus recurrent anxiety and depressive disorders after TBI. Additionally, due to the increased risk of psychiatric disorders over time, it is recommended to assess the psychiatric outcome of patients soon after TBI (within one month), and after 3, 6, 12, and 24 months. Future studies on the psychiatric outcomes of TBI survivors should assess the prevalence of the full range of anxiety disorders and depressive disorders, with use of structured diagnostic interviews, and should

investigate the increased risk for these disorders among females, the unemployed, and those with a history of psychiatric disorders prior to TBI.

Conclusions

Research conducted with the best available assessment instruments shows that a substantial number of patients encounter anxiety and depressive disorders before and after TBI, and that prevalence rates increase with time since injury. The pooled prevalence estimates provide insight into the magnitude of anxiety disorders and depressive disorders following TBI, and indicate that these disorders persist over time. All healthcare settings should pay attention to the occurrence of psychiatric symptoms in the aftermath of TBI, especially in females, those without employment, and those with a history of psychiatric disorders or substance abuse prior to TBI.

Supplemental material is available at www.marysecnossen.nl

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5

Predictors of major depression and posttraumatic stress disorder following traumatic brain injury: A systematic review and meta-analysis

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Abstract

Although major depressive disorder (MDD) and posttraumatic stress disorder (PTSD) are prevalent after traumatic brain injury, little is known about which patients are at risk for developing them. We systematically reviewed the literature on predictors and multivariable models for MDD and PTSD after TBI. We included 26 observational studies. MDD was associated with female gender, pre-injury depression, post-injury unemployment and lower brain volume, whereas PTSD was related to shorter posttraumatic amnesia, memory of the traumatic event and early post-traumatic symptoms. Risk of bias ratings for most studies were acceptable, although studies that developed a multivariable model suffered from methodological shortcomings.

Introduction

Traumatic brain injury (TBI), which is defined as "an alteration in brain function, or other evidence of brain pathology, caused by an external force",[1] comprises a serious public health concern with 262 per 100,000 patients admitted to the hospital each year.[2] A substantial percentage of TBI patients develop psychiatric disorders in the first year post-injury,[3,4] among which major depressive disorder (MDD) and posttraumatic stress disorder (PTSD) are the most frequently reported.[4-7] MDD and PTSD after TBI are associated with functional impairments[3,8,9] and a decrease in health-related quality of life (HRQL).[9] They subsequently interfere with rehabilitative interventions and negatively affect recovery from TBI.[3] Moreover, they are associated with high direct and indirect costs,[10-12] resulting in a tremendous individual and societal burden.

Although the significance of MDD and PTSD after TBI is well established, the literature yields limited information about which patients are at risk of developing these psychiatric conditions. This knowledge could be used to flag patients who might benefit from additional monitoring or (preventive) therapeutic interventions, which have shown to be effective in people at risk for MDD and PTSD.[13-15] Multivariable models, which combine a number of characteristics to predict MDD or PTSD, might be particularly useful for this purpose.

To our knowledge, there is currently one systematic review assessing psychological and psychosocial predictors of PTSD.[16] The authors found that comorbid depression and anxiety, acute stress disorder (ASD), psychological processes (coping styles and attribution) and psychosocial variables (role impairment and reintegration) were associated with PTSD post-TBI.[16] The authors, however, included all factors *associated with* PTSD, rather than factors *predicting* PTSD. It is therefore unclear whether these specific factors predicted PTSD or were predicted by PTSD. Moreover, they included self-reported measurements to diagnose PTSD. Self-reported measurements might not be reliable in a TBI population because of overlap between psychiatric symptoms and TBI symptoms (e.g. anxiety, irritability, fatigue), memory deficits, low self-awareness, attention problems and evidence that TBI patients tend to underestimate their problems.[17-22] Structured diagnostic interviews, such as the structured clinical interview for diagnostic and statistical manual of mental disorders (SCID), constitute a better alternative as these interviews distinguish psychopathology symptoms from TBI symptoms and are less influenced by TBI related problems such as memory deficits.[18]

The objective of this systematic review and meta-analysis was to examine univariable predictors of and multivariable models for MDD and/or PTSD following TBI using structured diagnostic interviews.

Material and methods

Information sources

We conducted a comprehensive literature search until October 2016. The search strategy was developed in consultation with a search expert using a combination of subheadings and text words (Online Supplement A). The following databases were searched: EMBASE, MEDLINE, Cochrane Central, PubMed, PsycINFO and Google Scholar. Reference lists and citation indices of included papers and relevant reviews were further inspected to identify any additional publications. The search strategy was restricted to studies published in peer-reviewed English language journals. We did not use any date restrictions.

Study selection

We selected studies examining univariable predictors of and/or multivariable models for MDD and PTSD after TBI. We used the following inclusion and exclusion criteria to determine eligibility of a study:

Participants – civilian adults (age ≥ 16) who sustained TBI. TBI was defined as "an alteration in brain function or other evidence of brain pathology, caused by an external force".[1] We included patients with mild, moderate and severe TBI (as defined by the study authors). We excluded military patients since there are major differences between military and civilian TBI. In the military, approximately 75% of the TBIs involve blast exposures,[23] which may have unique injury mechanisms.[24] In addition, mental health symptoms are more prevalent in the military than in civilians,[25] which might also be due to other causes than the sustained TBI.

Outcome measurement – MDD and/or PTSD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) classification systems. We restricted our inclusion criteria to studies that used a structured diagnostic interview to diagnose MDD and PTSD, as structured diagnostic interviews are regarded as the gold standard in diagnosing psychopathology[19] and better distinguish psychiatric symptoms from TBI symptoms. Moreover, structured diagnostic interviews are less influenced by potential memory deficits, low self-awareness and over- or underestimation by TBI patients. In addition, with respect to PTSD, clinical interviews can be used to specifically anchor the interview to the event in which the patient was injured.[26]

Predictors – we selected studies that examined at least one predictor of or multivariable model for MDD or PTSD after TBI. To be included, studies had to report at least one of the following: 1) baseline differences in predictors between patients diagnosed with MDD or PTSD (MDD+ and PTSD+) and patients not diagnosed with MDD or PTSD (MDD- and PTSD-; i.e. means and standard deviations for continuous predictors and number of patients for categorical predictors), 2) descriptive statistics (e.g., results from *t*-test, chi-square test, *p*-value) or 3) statistics from the

multivariable model (e.g., odds ratio, Area Under the Curve (AUC), Nagelkerke R^2). To be included as a predictor, these factors must have preceded the diagnosis of MDD or PTSD. Preceding was defined as either 1) being measured earlier than the psychiatric diagnosis (in prospective studies) or 2) obviously preceding the diagnosis of MDD or PTSD such as gender, age and computed tomography (CT) abnormalities (in retrospective, cross-sectional and case-control studies). Multivariable models were defined as models that combined at least two factors to predict a clinical outcome,[27,28] in our case MDD or PTSD.

Study design – we included retrospective- and prospective cohort studies, cross-sectional studies, and case-control studies.

Data extraction and assessment of risk of bias

One author (MC or ASc) screened citations on title and abstract, and then again on full-text, excluding those that did not meet the inclusion criteria. Any doubts were resolved by consulting a senior member of the team (JH or SP). As an audit of performance, a random 20% of the full text screening was repeated by the other reviewer (MC or ASc) and concordance rates were calculated accordingly. The search process was documented according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flowchart.[29]

We developed a data extraction form based on the basis of the Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modeling Studies (CHARMS) checklist[30] and subsequently extracted information on type of prediction modeling study, target population, participants, outcome measurements, candidate predictors, sample size, handling of missing values and model development methods. We additionally extracted baseline information on univariable associations between predictors and outcome by collecting means and standard deviation (SD) for MDD+/PTSD+ and MDD-/PTSD- group (continuous predictors) or number of patients with and without the predictor in MDD+/PTSD+ and MDD-/PTSD- groups (categorical predictors). We further extracted univariable and multivariable statistics and effect measurements, if available.

Risk of bias, which refers to the risk of systematic errors which may result in the over-or underestimation of effects[31] was assessed using the Quality in Prognostic Studies (QUIPS) risk of bias tool. The QUIPS has been recommended by the Cochrane Prognosis Methods Groups and has acceptable inter-rater reliability.[32] We included information on the following domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding and statistical analysis and presentation. Each domain was subsequently rated as 'low', 'moderate' or 'high' risk of bias. A domain obtained the score 'low risk' if all individual items of the domain were rated as 'low risk'. A domain was rated as 'moderate risk' if at least one and maximum 50% of the items implied a high risk of bias or an unknown risk of bias, and a study received a score of high risk if > 50% of the items implied a high risk of bias or an unknown risk of bias.

We applied a quality threshold for study inclusion in the meta-analyses; that is, studies were omitted from the meta-analyses if they obtained a high score on at least two out of the following QUIPS domains: study participation, study attrition, prognostic factor measurement, outcome measurement and statistical analysis and presentation. Such a strategy is recommended by Cochrane.[33] We did not include study confounding as criterion since we aimed to perform a meta-analysis with univariable predictors. Studies were additionally excluded from the meta-analyses if they included less than 20 patients. The data extraction and risk of bias were done independently by one author (MC) with the data and decisions checked by a second author (ASc). Any discrepancies were resolved by discussion with a senior member of the team (SP).

Data synthesis

We performed meta-analyses of univariable predictors of MDD and PTSD. Predictors were included in the meta-analysis if univariable data (mean (SD) or numbers in MDD+/PTSD+ and MDD-/PTSD- groups) were reported in two or more studies measuring the same predictor. Studies were excluded from the meta-analyses if they measured the predictor differently from other studies (e.g. age dichotomized into two age groups instead of continuous), if they obtained a high risk of bias on at least two QUIPS domains (excluding confounding) of if they included less than 20 patients. If a study assessed predictors for multiple time points or multiple outcomes (e.g. chronic depression, late onset depression and recovered depression) scores were combined, or if this was not possible, the time point or outcome that was closest to that in the other studies in the same meta-analysis was chosen. We used Review manager (Revman) version 5.3[34] to perform the meta-analyses. All tests were two-sided and a *p*-value of 0.05 was considered statistically significant. We used Mantel-Haenszel statistic for categorical predictors as this method is recommended by Cochrane[31] and inverse variance to analyze continuous predictors since this is not possible with the Mantal-Haenszel statistic. For all analyses, random effect models were used as we expected heterogeneity in time span and measurements. For dichotomous predictors, we reported the pooled odds ratio (pOR) and confidence interval (CI) and for continuous predictors, we reported the pooled mean difference (pMD) and CI. Heterogeneity was determined using I^2 and was defined as high when I^2 was ≥ 50% (substantial heterogeneity according to Cochrane[31]). In that case, pooled results should not be calculated, or at the very least, be interpreted with caution.

Since we included studies using the DSM-IV, DSM-III or ICD-10 criteria, we may have introduced heterogeneity in the association between predictor and the diagnosis of MDD or PTSD. We therefore performed sensitivity analyses in which we excluded studies using other criteria than the DSM-IV.

Predictors that were reported in at least two studies, but not included in the meta-analyses were narratively described. Multivariable models of MDD and PTSD were narratively described

by comparing model performance (e.g. AUC / Nagelkerke R^2 / calibration) and methods (e.g., number of candidate predictors).

Multiple publications

Multiple publications were dealt with by selecting one main study based on the following criteria: 1) the study that uses multivariable analyses; 2) the study with the largest number of patients included; and 3) the study with the largest number of predictors. If a second paper was written on the basis of the same data as the 'main study' but mentioned any new predictors, only the information on these new predictors was extracted from the study.

Results

Study selection

A total of 9695 citations were identified through the electronic search strategy (Figure 1). After removing duplicates, 6291 were screened on title and abstract and 5966 citations were excluded. We obtained 325 citations in full text of which 295 were subsequently excluded. The most common reason for exclusion was using self-reported measurements instead of a structured diagnostic interview (n = 144). The 20% audit on full text screening obtained a concordance rate of 100% between two review authors. Five additional citations were found via reference lists and citation indices. We included 26 studies (reported in 36 publications) in the narrative synthesis. Of these, 14 studies were included in the meta-analyses.

Study characteristics

Of the 26 studies included, the majority (n = 17) were prospective cohort studies.[19,26,35-49] Four studies used a retrospective cohort design,[50-53] three a cross-sectional design,[54-56] and two were case-control studies.[5,57] Studies were published between 1992 and 2016 and were conducted all over the globe, but mainly in high-income countries such as the United States (n = 7) and Australia (n = 5). Patients were recruited from general hospitals in the majority of studies (n = 9). Other studies included self-identified TBI patients (n = 3), patients admitted to a trauma center (n = 4) or ICU (n = 1) or patients in the post-acute phase in a rehabilitation unit (n = 3) or neuropsychological/neurocognitive TBI clinic (n = 6). The large majority of studies derived their patients from a single center (n = 20; Table 1).

Forty-two percent (n = 11) included patients with mild, moderate and severe TBI. The diagnosis of MDD/PTSD was determined according to the DSM-IV criteria in the large majority of studies (n = 20). Five studies used the DSM-III criteria[36,38,39,46,51] and one study the ICD-10 criteria of MDD/PTSD.[40]

Table 1. **Study characteristics of 26 studies examining predictors of or multivariable models for MDD and PTSD after TBI**

Study	Study Design, setting	Study population	Inclusion and exclusion criteria	Patient characteristics*	No. predictors	Disorder and no. pt with disorder	Interview	Timing Outcome	Assessment
Alway, Y. (2015) *Related: Alway (2015b)*	Pros cohort, Australia	Consecutive mod and sev TBI admitted to hospital (n=203)	PTA > 24h; age 16-80y; no prior TBI / neurological disorder; residence in Australia, sufficient English language	Age: 34y; ±16y 78% male GCS: 9.3; ±4.3 80% MVA	5	PTSD (n = 27)[A]	SCID (DSM-IV)	3m-5y	Face-to face interview at initial assessment; telephone interview at follow-up.
Ashman, T.A. (2004) *Related: Hibbard (2004)*	Cross-sectional, longitudinal, and cross-sequential, US	Self-identified mild to sev TBI from community (n = 188)	US residents in the community 3m-4y post-injury; age 18-87; capable of giving informed consent; no acquired brain injury/ neurocognitive disorder/ psychotic disorder	Age: 40y; ±15y 53% male GCS 13-15: 29%, 3-12: 62% Unknown:9%	3 MDD / 3 PTSD	MDD (n = 66)[B] &PTSD (n = 56)[B]	SCID (DSM-IV)	1y-6y	Interview by clinician with ≥ 3y experience
Barker-Collo (2013)	Pros and retro cohort, New-Zealand	Mild to sev TBI, from a large incidence and outcome study or self-referred (n = 296)	Age ≥ 16	Age: 37y; ±18y 60% Male Worst GCS: 14.1; ±2.3 30% falls, 24% assault, 17% traffic	17	PTSD (n = 53)	PDS (DSM-IV)	1y	Interview by trained researchers
Bryant, R.A. (1998) *Related: Harvey (2000)*	Pros cohort, Australia	Consecutive MVA victims admitted to trauma hospital (n = 63)	Exclusion: inability to be interviewed with aid of an interpreter; not medically fit; taking narcotic analgesia 4weeks after trauma; PTA > 24h	Age: 29y; ±13y[C] 70% Male[C]	25	PTSD (n = 15)	CIDI (DSM-III)	6m	Interview by clinical psychologist blinded for ASD status
Bryant, R.A. (2000)	Pros cohort, Australia	Sev TBI admitted to rehab unit (n = 96)	Exclusion: inability to be interviewed with aid of an interpreter; insufficient cognitive abilities	Age: 34y; ±13y 80% Male	5	PTSD (n = 26)	PTSD-I (DSM-III)	6m	Interview by rehab consultant

Table 1. **Continued**

Study	Study Design, setting	Study population	Inclusion and exclusion criteria	Patient characteristics*	No. predictors	Disorder and no. pt with disorder	Interview	Timing Outcome	Assessment
Caspi, Y. (2005)	Retro cohort, Israel	Mild to mod TBI admitted to neurocogn clinic (n = 120)	Age: 18-50y, fluent in Hebrew; no active chronic medical condition; no pre-injury psychiatric illness, substance abuse, cognitive deficits or brain damage	Age: 36y; ±6y 59% Male 84% car accident	4	PTSD (n = 22)	SCID-I (DSM-IV)	3y	Interview
Deb, S. (2007)	Pros cohort, UK	Minor to sev TBI admitted to hospital (n = 165)	Any of the following: unconsciousness; evidence of skull fracture on X-rays; contusion/hemorrhage on CT or MRI; focal neurological signs; GCS < 15	Age: young group: 36; elderly group: 79 67% Male 82% mild, 13% mod, 5% sev TBI	1	MDD (n = 24)	SCAN (ICD-10)	1y	Interview by two trained psychiatrists
Diaz, A.P. (2012)	Pros cohort, Brazil	Consecutive sev TBI admitted to ICU (n = 33)	GCS ≤ 8 within 48h; age ≥ 18y; resident of the Florianopolis metropolitan area; no gunshot injury	Age: 31y; ±11y 88% Male GCS: 7-8 46%; 5-6 30%; 3-4 24%	7	MDD (n = 10)	SCID (DSM-IV)	18m	Interview by two board-certified psychiatrist, blinded for hospital data
Fedoroff, J. P. (1992) *Related: Jorge 1993, Jorge 1993b*	Pros cohort, US	Consecutive mild to sev TBI admitted to shock trauma center (n = 64)	Acute closed HI; no open HI, no spinal cord injury, no multiple system injury, no decreased consciousness or aphasia	Age: MDD 27y; ±6y; no MDD: 30y; ±11y 86% male GCS: 12-15 17%; 8-15 & intracran surg or focal lesions > 35 cc 58%; 3-7 15%	25	MDD (n = 17)	PSE (DSM-III)	1m	Interview by trained research psychiatrist
Gil, S. (2005)	Pros cohort, Israel	Mild TBI admitted to surgical ward (n = 120)	Age 18-50y; fluent in Hebrew Exclusion: psychiatric care at time of injury; prior HI; cognitive deficits; substance abuse; major untreated medical condition	Age: 31y; ±3y 58% male 90% traffic accident GCS: 13-15 100%	16	PTSD (n = 17)	SCID (DSM-IV)	6m	Interview by trained clinician

Table 1. **Continued**

Study	Study Design, setting	Study population	Inclusion and exclusion criteria	Patient characteristics*	No. predictors	Disorder and no. pt with disorder	Interview	Timing Outcome	Assessment
Gould, K.R. (2011) *Related: Gould (2011b) and Schonberger (2011)*	Pros cohort, Australia	Consecutive TBI admissions to a rehab hospital (n = 122)	Mild, mod or sev TBI; age 16-80; no previous TBI/ neurological disorder; residence in Australia; sufficient cognitive and English ability	Age: 35; 16y GCS: 9.15; ±4.3	7	MDD (n = 40)	SCID (DSM-IV)	12m	Interview
Hibbard, M.R. (1998)	Pros cohort, US	Mild to sev TBI randomly selected for quality of life survey (n = 100)	TBI ≤ 1y prior to interview; age 18-65; resident of New York State; living in the community; no nontraumatic brain injury	Age[D]:40y; ±10y 53% Male 62% MVA	5 MDD / 1 PTSD	MDD (n = 48) & PTSD (n = 17)	SCID (DSM-IV)	8y	Interview by licensed psychologist with background in clinical neuropsychology and brain injury
Jorge, R.E. (2004) *Related: Jorge, R.E. (2007)*	Pros case-control, US	Consecutive mild to sev TBI admitted to hospital (n = 91)	Exclude: penetrating HI; spinal cord injury; sev comprehension deficits	Age: 36y; ±16y 59% Male 44% mild, 33% mod, 23% sev TBI 75% MVA	32	MDD (n = 30)	PSE and SCID-I (DSM-IV)	9m	Interview by psychiatrist
Kennedy, R.E. (2005)	Pros cohort, US	Mild to mod TBI admitted to neuropsych clinic (n = 78)	3m post-injury; age ≥ 18	Age: 38y; ±12y 69% male Mean GCS: 9.3; ±4.8 77% MVA	10	MDD (n = 23)	SCID (DSM-IV)	76m	Interview by three trained research team members

Table 1. **Continued**

Study	Study Design, setting	Study population	Inclusion and exclusion criteria	Patient characteristics*	No. predictors	Disorder and no. pt with disorder	Interview	Timing Outcome	Assessment
Koponen, S. (2002) *Related: Koponen 2005*	Retro cohort, Finland	Mild to sev TBI seen for neuropsych evaluation (n = 60)	TBI causing neurological symptoms ≥ 1 week; one of the following: 1) LOC ≥ 1min, 2) PTA ≥ 30 min, 3) neurological symptoms during the first 3d 4) neuroradiological findings suggesting TBI. No nontraumatic neurological illness	Age: 29y; ±11y 68% Male	2	MDD (n = 16)	SCAN (DSM-III)	31y	Interview by trained research psychiatrist
Levin, H.S. (2005)	Pros cohort, US	Consecutive mild TBI admitted to level I trauma hospital (n = 129)	Hospital arrival ≤ 24h; BAL ≤ 200 mg/dl; age ≥16y; fluent in English or Spanish; resident in catchment area Exclusion: undocumented alien; incarcerated; homeless; active military service; spinal cord injury; previous TBI requiring hospitalization; pre-injury substance dependence, mental retardation, psychiatric disorders or other central nervous system disturbances; no preexisting condition preventing outcome measurement	Age: 32; ±13y 67% male GCS: 14.8; ±0.5 67% MVA	8	MDD (n = 15)	SCID (DSM-IV)	3 m	Interview
Li, L. (2016)	Pros cohort, China	Consecutive mild TBI patients at the ED of 3 hospitals (n = 43)	LOC < 20min, PTA < 24h, GCS 13-15, no abnormal CT/MRI findings	Age: PTSD 35.8y ± 7.6; no PTSD 36.7y ± 7.1 49% male	9	PTSD (n = 21)	CAPS	6m	Interview

Table 1. **Continued**

Study	Study Design, setting	Study population	Inclusion and exclusion criteria	Patient characteristics*	No. predictors	Disorder and no. pt with disorder	Interview	Timing Outcome	Assessment
Mauri, M. C. (2014)	Pros case-control, Italy	Consecutive closed HI admitted to neurosurgery (n = 16)	LOC ≥ 1m; PTA ≥ 30 min; neuroradiological evidence of TBI; no pre-injury neurological / cardiorespiratory / psychiatric conditions; no substance abuse	Age: 40y; ±14y 63% Male GCS 10.6; ±4.4 81% MVA	4	MDD (n=10)	SCID (DSM-IV)	1m	Interview by expert clinician
O'Donnell, M.L. (2008)	Pros cohort, Australia	Randomly selected mild TBI patients at 4 level I trauma centers (n = 404)	Age 18-70y; English proficiency, hospitalized ≥ 24h, LOC ≤30 min, GCS 13-15, PTA ≤ 24h, not currently psychotic or suicidal	Age: 37.9y, ± 14y 72% male 62% transport accidents, 17% falls	2 MDD / 2 PTSD	MDD (n = 65) & PTSD (n = 32)	MINI (MDD, DSM-IV); CAPS (PTSD, DSM-IV)	12m	Telephone interview
Rao, V. (2010)	Cross-sectional, US	Closed HI recruited by advertisements in local newspapers (n = 17)	Age ≥ 18y; TBI 3-60m prior to evaluation; no history of diagnosable mood disorder; MMSE > 18, stable medical history; sufficient cognitive capacity	Age: MDD: 53; no MDD 27	38	MDD (n=10)	SCID (DSM-IV)	3-60m	Interview
Rapoport, M.J. (2003) *Related: Rapoport (2003b)*	Pros cohort, Canada	Consecutive mild TBI with appointment at TBI clinic (n = 210)	Non-penetrating mild TBI Exclusion: pre-injury focal brain disease; serious acute medical illness; schizophrenia; bipolar disorder; dementia	Age: 47y; ±20y 60% Male 61% MVA	10	MDD (n=35)	SCID (DSM-IV)	49d	Interview by psychiatrist
Rapoport, M.J. (2005)	Cross-sectional, Canada	Mild and mod TBI attending a TBI clinic (n = 74)	Exclusion: premorbid focal brain disease; serious medical illness; schizophrenia; bipolar disorder; dementia	Age: 35y; ±13y	16	MDD (n=21)	SCID (DSM-IV)	200d	Interview

Table 1. **Continued**

Study	Study Design, setting	Study population	Inclusion and exclusion criteria	Patient characteristics*	No. predictors	Disorder and no. pt with disorder	Interview	Timing Outcome	Assessment
Reekum, R. van (1996)	Pros cohort, Canada	Mild to sev TBI admitted to TBI rehab program. Patients were contacted with a female: male ratio of 3:1 (n=18)	TBI due to MVA ≥ 2y prior to the study; age < 50y; sufficient language, motor and perceptual skill to permit testing; no pre-injury psychiatric disorder; living in the community	Age: 31y; ±9y 44% Male GCS 13-15: 28%; 9-12: 17%; 3-8 56%	4	MDD (n = 9)	SADS-L (DSM-III)	5y	Interview by experienced registered psychiatric nurse
Roitman, P. (2013)	Pros cohort, Israel	Consecutive mild TBI attended ED (n = 402)	MVA survivors Exclusion: arrived to the hospital in coma; LOC > 30 min; admitted to the hospital > 7days	Age: 37y; ±13y 52% male	1	PTSD (n = 127)	PSS (DSM-IV)	8m	Telephone interview
Turnbull, S.J. (2001)	Retro cohort, Scotland	Mild to sev TBI attended ED who respond to a postal questionnaire (n = 53)	Age 16-65; evidence of TBI; no chronic alcohol abuse	Age: 35y; ±11y 87% Male 32% traffic; 60% assault	1	PTSD (n = 11)	CAPS (DSM-IV)	6m	Telephone interview by postgraduate psychologist
Whelan-Goodinson, R. (2010)	Retro cross-sectional, Australia	Mild to sev TBI admitted to rehab unit (n = 100)	GCS < 15; cognitive capable; reliable historians according to treating doctor/ neuropsychologist, sufficiently proficient in English; no previous TBI/neurological disorder	Age: 37y; ±14y 71% male GCS: 9.1; 4.1 86% MVA	13	MDD (n = 46)	SCID (DSM-IV)	0.5-5.5y	Face-to-face or telephone interview

*Patient characteristics: we reported age: mean; SD unless otherwise specified. For injury mechanism, we reported the most occurring mechanism

[A] 27 patients were diagnosed with PTSD during the 5 year follow-up period. [B] MDD or PTSD at any time point during the 5y follow-up period. [C] These results represent 79 patients included in the study; 14 of them were however not included in the prediction analysis due to loss to follow-up. These patients did not differ significantly from the original sample. [D] Age at assessment

Abbreviations: ASD = acute stress disorder; BAL = blood alcohol level; CAPS = Clinician Administrated PTSD scale; CT = computed tomography; DSM = diagnostic and statistical manual; ED = emergency department; HI = head injury; CIDI = Composite International Diagnostic Interview; GCS = Glasgow Coma Scale; ICD = international classification of diseases; LOC = loss of consciousness; MDD = major depressive disorder; MRI = magnetic resonance imaging; MVA = motor vehicle accident; PDS = Posttraumatic Diagnostic Scale; PSE = Present State Examination; PSS = PTSD symptom scale; PTA = posttraumatic amnesia; PTSD = posttraumatic stress disorder; PTSD-I = posttraumatic stress disorder interview; SADS-L = Schedule for Affective Disorders and Schizophrenia; SCAN = Schedules for Clinical Assessment in Neuropsychiatry; SCID-I = Standardized Clinical Interview for DSM-IV; US = United States.

Figure 1. **PRISMA flowchart of the selection process**

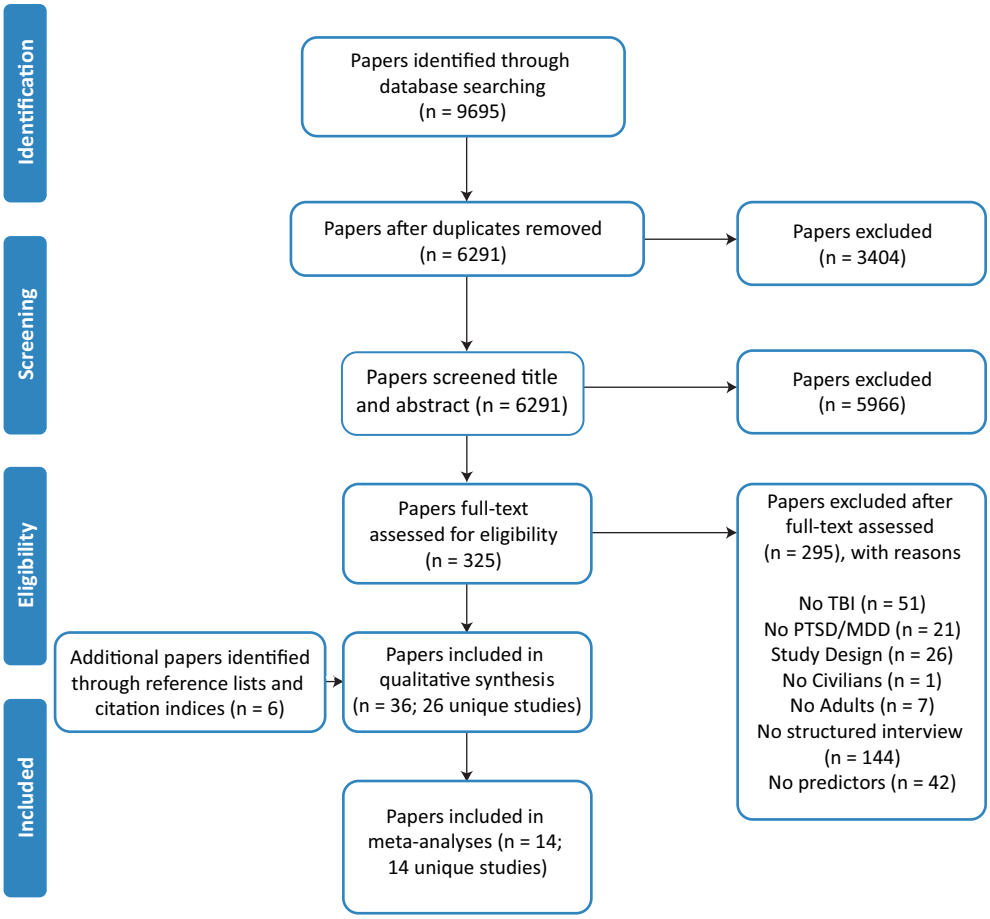

Figure is adapted from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Abbreviations: MDD = Major Depressive Disorder; PTSD = Posttraumatic Stress Disorder; TBI = traumatic brain injury

Fourteen studies examined predictors of MDD,[5,19,36,40-42,44-46,51,52,55-57] nine studies examined predictors of PTSD[35,37-39,47-50,53] and three studies examined both.[26 ,43,54] Nine studies included multiple predictors in a multivariable model to predict MDD (n = 5), PTSD (n =3) or both (n = 1).

Studies included on average 125 patients (range 16 to 404). Studies that assessed predictors of MDD included on average 26 (range 9-65) patients with MDD ('cases') and 83 patients without MDD. Studies that assessed predictors of PTSD included on average 32 patients (range 7-127) with PTSD ('cases') and 142 patients without PTSD. The majority of studies included predominately male patients with a mean age between 30 and 40 years. Motor vehicle accidents (MVA) were the most reported cause of injury. Most predictors were measured during emergency department

(ED) visit or very soon after discharge. Outcome was measured between one month and six years post-injury with the majority of studies measuring MDD/PTSD between three months and one year post-injury (Table 1).

Risk of bias of the studies

The majority of studies (n = 18)[5,19,26,36,38,40,41,43,46-49,51,53,55-58] were scored as high risk of bias for study confounding because they only assessed the effect of predictors in univariable analyses. It is therefore unknown whether the effect of the predictor is independent of other factors. Because we sought to perform a meta-analysis with univariable data, we did not exclude any studies based on a high risk of study confounding from the meta-analysis.

Except for the high risk of study confounding, methodological quality of the included studies was acceptable (Table 2). Study participation[19,43,55] and attrition[40,46,53] were rated at high risk of bias in three studies. Additionally, one study was judged at high risk of bias for prognostic factor measurement[5] and outcome measurement,[53] and six studies were rated at high risk of bias on statistical analysis and reporting.[5,42,47,49,50,53] Three studies[5,49,53] were rated at high risk on two out of five (excluding study confounding) domains and were therefore omitted from the meta-analyses. Two other studies[55] included less than 20 patients and were therefore also excluded from the meta-analyses.

Meta-analyses of univariable predictors

The included studies examined a total of 112 predictors of MDD and 59 predictors of PTSD (Figure 2). Age and gender were most often assessed. The majority of predictors were assessed in only one study. Consequently, only 18 and 6 predictors were included in the meta-analyses for MDD and PTSD, respectively (Table 3, Online Supplement B).

Figure 2. **Frequency of predictors of MDD and PTSD following TBI**

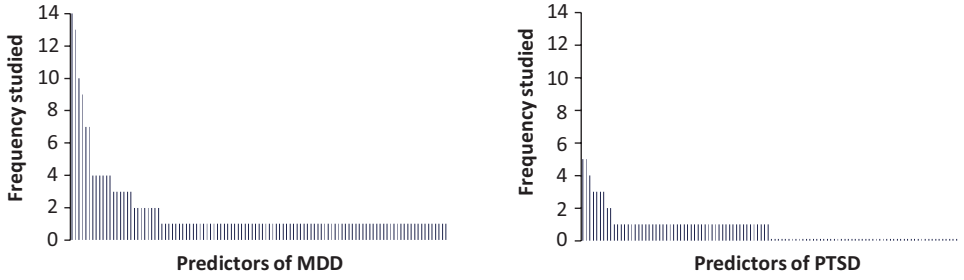

Figure shows how frequent predictors were studied across the included studies. For example, for MDD one predictor (age) is studied in fourteen studies and one predictor (gender) is studied in thirteen studies. The majority of predictors (e.g. MRI abnormalities) were assessed in one study.

Table 2. **Risk of bias assessment**

Study	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analyses and presentation
Alway, Y. (2015)	Moderate	Moderate	Low	Low	Low	Low
Ashman, T.A. (2004)	Moderate	Moderate	Moderate	Low	Low	Moderate
Barker-Collo, S. (2013)	Moderate	Moderate	Low	Low	High	Low
Bryant, R.A. (1998)	Low	Low	Low	Low	High	Low
Bryant, R.A. (2000)	Low	Moderate	Low	Low	High	Low
Caspi, Y. (2006)	Low	Moderate	Low	Low	Low	High
Deb, S. (2007)	Low	High	Low	Moderate	High	Low
Diaz, A.P. (2012)	Low	Low	Low	Low	High	Low
Federoff, J.P. (1992)	Low	Low	Low	Low	High	Low
Gil, S. (2005)	Low	Moderate	Low	Low	Low	Low
Gould, K.R. (2011)	Low	Moderate	Low	Low	Low	High
Hibbard, M.R. (1998)	High	Moderate	Moderate	Low	High	Moderate
Jorge, R.E. (2004)	Low	Low	Low	Low	High	Low
Kennedy, R.E. (2005)	High	Moderate	Low	Low	High	Low
Koponen, S. (2002)	Moderate	Moderate	Moderate	Low	High	Low
Levin, H.S. (2005)	Low	Moderate	Low	Low	Low	Low
Li, L. (2016)	Moderate	Low	Moderate	Low	High	High
Mauri, M.C. (2014)	Moderate	Low	High	Low	High	High
O'Donnell, M.L. (2008)	Low	Low	Low	Low	High	Low
Rao, V. (2010)	High	Low	Low	Low	High	Moderate
Rapoport, M.J. (2003)	Moderate	Low	Moderate	Low	Low	Low
Rapoport, M.J. (2005)	Moderate	Low	Moderate	Low	High	Low
Reekum, R. (1996)	Moderate	High	Low	Low	High	Low
Roitman, P. (2013)	Moderate	Low	Moderate	Low	High	High
Turnbull, S.J. (2001)	Moderate	High	Moderate	High	High	High
Whelan-Goodinson, R. (2010)	Moderate	Low	Low	Low	Moderate	Moderate

Table presents risk of bias assessment according to the Quality in Prognostic Studies (QUIPS) tool.

We found a significant association between the development of MDD and female gender (pOR 1.72, 95% CI 1.19 to 2.48, I^2 = 10%, 8 studies). Additionally, patients with a pre-injury depression had a higher odds on developing MDD post-injury than did patients without a history of depression (pOR 3.86, 95% CI 2.26 to 6.59, I^2 = 0%, 5 studies). Also, patients who were unemployed after sustaining TBI had a higher odds on developing MDD later on than did the employed patients (pOR 2.04, 95%CI 1.10 to 3.79, I^2 = 9%, 3 studies). We further found that patients with a higher admission Glasgow Coma Scale (GCS), which refers roughly to moderate TBI versus severe TBI in these studies, had a higher risk on developing MDD (pMD 0.49, 95% CI 0.02 to 0.97, I^2 = 0%). This was however only assessed in two studies and we did not find a significant association between

GCS after 24 hours and MDD (pMD 0.13, 95%CI -1.29 to 1.56, I^2 = 42%, 2 studies). The association between the other predictors and MDD were all non-significant.

PTSD was significantly associated with a shorter posttraumatic amnesia (PTA; pMD -8.07. 95% CI -15.46 to -0.69, I^2 = 33%, 3 studies) and a memory of the traumatic event (pOR 5.15, 95% CI 2.37 to 11.21, I^2 = 0%, 2 studies). We did not find a significant association between the remainder of predictors and PTSD. Sensitivity analyses with only those studies using the DSM-IV criteria did not result in any differences (Online Supplement C).

***Table 3*. Meta-analyses of univariable predictors of MDD and PTSD following Traumatic Brain Injury**

Predictor	No. of participants (No. of studies)	Pooled effect size meta-analysis OR (95% CI)*	Heterogeneity (I^2)
MDD			
Age (/y, MD (95% CI))	611 (7)	1.20 (-1.96 to 4.36)	49%
Female Gender	768 (8)	1.72 (1.19 to 2.48)	10%
Education (/y, MD (95%CI))	271 (4)	-0.50 (-1.37 to 0.37)	43%
Caucasian race	341 (3)	1.04 (0.61 to 1.75)	0%
Marital status ǂ	610 (6)	1.20 (0.82 to 1.75)	0%
Socioeconomic status ‡	140 (2)	0.69 (0.33 to 1.43)	0%
Pre-injury depression	470 (5)	3.86 (2.26 to 6.59)	0%
Pre-injury psychiatric disorders	426 (4)	1.58 (0.42 to 5.99)	87%
Pre-injury alcohol abuse	244 (2)	1.49 (0.61 to 3.69)	0%
Pre-injury substance abuse	244 (2)	2.02 (0.75 to 5.42)	0%
Pre-injury unemployment	244 (2)	3.80 (0.34 to 42.09)	77%
Family history of psychiatric disorders	234 (2)	1.06 (0.52 to 2.14)	0%
Admission GCS (MD (95% CI))	151 (2)	0.49 (0.02 to 0.97)	0%
24h GCS (MD (95% CI))	138 (2)	0.13 (-1.29 to 1.56)	42%
CT abnormalities	259 (3)	0.70 (0.35 to 1.43)	0%
Brain contusion	101 (2)	1.78 (0.73 to 4.34)	0%
Post-injury unemployment	211 (3)	2.04 (1.10 to 3.79)	9%
Post-injury litigation situation	203 (2)	0.64 (0.16 to 2.53)	0%
PTSD			
Age (/y, MD (95% CI))	717 (5)	1.02 (-1.46 to 3.49)	75%
Female gender	621 (4)	1.27 (0.83 to 1.96)	0%
Education (/y, MD (95% CI))	301 (3)	0.15 (-0.61 to 0.92)	11%
Pre-injury psychiatric disorder	425 (4)	1.32 (0.63 to 2.77)	49%
PTA (MD (95% CI))	477 (3)	-8.07 (-15.46 to -0.69)	33%
Memory of the traumatic event	240 (2)	5.15 (2.37 to 11.21)	0%

*pooled OR (95% CI) unless otherwise specified ǂ married/relationship vs. unattached ‡ Hollinghead classes IV and V vs. lower
Abbreviations: MD = mean difference; MDD = major depressive disorder; OR = odds ratio; TBI = traumatic brain injury; GCS = Glasgow Coma Scale; PTA = posttraumatic amnesia; CT = computed tomography; PTSD = posttraumatic stress disorder; LOC = loss of consciousness

Narrative synthesis of univariable predictors

For MDD, five out of six studies in the narrative synthesis did not find an association between the development of MDD and age[5,40,43,46,52,55] and none of the studies reported a significant association with any other demographic factors and MDD (gender, education, marital status, income; Online Supplement D).[5,19,43,52,55-57,59] For pre-injury variables, patients with a history of psychiatric disorders had a significantly higher risk of developing MDD.[42,57,60] We did not find an association between pre-injury substance and alcohol abuse,[36,42,56] pre-injury unemployment,[52,56] family history of psychiatric disorders,[56,57] pre-injury TBI[17,56] and mechanism of injury and MDD.[19,45,56] For clinical variables, we did not find an association between GCS,[19,36,43,46,57] PTA[51,52,56] and MDD. Bodily injuries were associated with MDD in one out of three studies.[42,52,56]

Three studies analyzed the association between imaging variables and MDD.[55,57,61] Jorge et al.[57] found that the percentage of gray matter in the left lateral frontal cortex and the percentage of gray matter at the left inferior frontal gyrus on magnetic resonance imaging were higher in patients that developed MDD. The influence of brain volume was assessed in two studies that consistently found that a lower brain volume was associated with the development of MDD.[55,61] Early post-injury anxiety and depression were assessed in two studies.[26,42] One study found that early post-injury depression, measured with the SCID, was associated with post-injury MDD and did not found an association between early post-injury anxiety and MDD.[42] Another study reported that the Hospital Anxiety and Depression Survey (HADS) was significantly associated with MDD (AUC 0.72, $p < .01$).[26] This study additionally developed a screening instrument based on pre-injury factors and post-injury irritability and concentration problems, which was also significantly related to MDD (AUC 0.77, $p < .01$).

For PTSD, demographic variables were not associated with PTSD in the studies in the narrative synthesis, except for one study[54] which found that PTSD was more common among women. PTSD was not associated with injury mechanism in three studies[48-50] (Online Supplement D). Also, GCS was not associated with the development of PTSD.[39,48,62] One study reported that patients with loss of consciousness (LOC) had a higher odds on PTSD,[47] whereas two other studies did not find statistical differences.[48,49] One-month PTSD symptoms or symptoms of ASD were significantly associated with PTSD in four studies.[26,35,38,49] Bryant et al.[38] studied individual ASD symptoms and reported that the following symptoms were associated with six-month PTSD: helplessness, numbing, depersonalization, recurrent images and thoughts, avoidance of thoughts or talk, avoidance of places and people, insomnia, irritability and motor restlessness. Post-injury anxiety and depression were related to six-month PTSD in one study.[35] Another study developed a screening instrument for PTSD based on pre-injury, peri-injury and post-injury factors and reported an AUC of 0.91, $p < .001$)[26]

Narrative synthesis of multivariable models

Six studies used a multivariable model to predict MDD (Table 4). On average, models included 6.3 cases (range 1.2-22) for every predictor in the model. None of the studies described whether there were missing values in predictors and if so, how they were handled. Nagelkerke R^2 was calculated in three models,[42,45,52] and ranged from 0.18 to 0.35. The AUC was calculated in one study[44] and indicated good discriminative ability (AUC = 0.86). This model included age, depressive symptoms after one week post-injury and CT results.

Four studies used a multivariable model to predict PTSD. Models included on average 7.7 cases (range 1.1-19). Again, none of the studies described how they handled missing values in predictors. Nagelkerke R^2 was reported for two models[35,50] and ranged from 0.38 to 0.42. Both models included memory of the traumatic event and history of psychiatric disorders. None of the multivariable models for MDD and PTSD used internal or external validation to improve the generalizability.

Discussion

This systematic review provides an overview of univariable predictors of and multivariable models for MDD and PTSD following TBI. We included 26 studies and found that the development of MDD was associated with female gender and a pre-injury depression. Post-injury MDD might also be associated with post-injury unemployment status, early post-injury psychiatric symptoms, a higher GCS and a lower brain volume. The development of PTSD was associated with a shorter PTA and a memory of the traumatic event. It may also be associated with early symptoms (e.g., depression, anxiety, ASD). Only a few studies used a multivariable model to predict MDD or PTSD, of which the majority was of limited quality.

This systematic review included studies over the last 23 years from all over the globe and therefore provides a complete overview of current knowledge about predictors and multivariable models for MDD and PTSD following TBI. Some notes should be made regarding the completeness and applicability of the evidence. First, the large majority of predictors were examined in only one study and therefore were not included in our meta-analyses. For many predictors, we consequently cannot draw firm conclusions. A possible solution might have been to include studies with self-reported outcome measurements since these studies are more common and usually include more patients. However, self-reported measurements are less reliable in TBI patients.[16-18] For example, a 2006 study found that the diagnosis of PTSD varied from 59% to 3% when using self-reported measurements and structured diagnostic interviews, respectively.[20] For MDD, a similar range is reported.[22] In self-reported measurements, the overlap between TBI and the psychiatric disorder is usually not captured. For example, focus on the memory gap following coma without great distress could be inappropriately labeled as intrusive in a self-reported measurement.[20] Also the symptoms sleep problems, irritability and concentration problems, which might be

Table 4. **Multivariable models of MDD and PTSD after TBI**

Study	Timing model use	Number of patients	Number of cases*	Number of candidate predictors	Selection procedure of predictors	Statistical model	Outcome measurement and timing	Summary statistics	Final predictors in model
MDD									
Ashman, T.A. (2004)	Unknown	188	35;24; 21[A]	3	Not reported	Linear random effects longitudinal model	SCID-I 3m-4y	Not reported	Age (OR: 1.00; p = .77), time post-injury (OR: 0.88, p = .23) and time of enrolment in the study (OR: 0.59, p < .001)
Federoff, J.P. (1992)	ED	64	17	14	All CT lesion location variables measured	Logistic regression model with backwards selection (p > .05)	PSE 1m	X^2 = 31.39, df = 6, p = 0.0001	Left hemisphere (b:-2.84, p = 0.04); right hemisphere (b: 2.40, p = 0.03);cortical (b: -3.67, p = 0.01); frontal (b: -3.58, p = .01); left anterior (b: 5.90, p = 0.0003); parietal-occipital (b: 3.75, p = .009)
Gould, K.R. (2011)	At discharge	122	40	7	Not reported	Two logistic regression models (1) pre-injury variables; 2) injury-related variables). Significant variables were entered into a final regression model	SCID-I 12m	Nagelkerke R^2 = 0.20; correct classification rate: 70.7%	Pre-injury counseling (OR: 2.34, p = .073); limb injury (OR: 4.07, p = .009); depressive disorder at initial assessment (OR: 6.04, p = 0.039)
Levin, H.S. (2005)	1 wk	129	15	8	Not reported	Logistic regression with backwards selection (p >.05)	SCID-I 3m	AUC = 0.86	Age (OR: 1.05; 95%CI 1.00 to1.1); CES-D score 1wk (OR: 1.11; 95% CI 1.04 to 1.17); Abnormal CT scan (OR: 7.68; 95% CI 1.36-43.48)

Table 4. **Continued**

Study	Timing model use	Number of patients	Number of cases*	Number of candidate predictors	Selection procedure of predictors	Statistical model	Outcome measurement and timing	Summary statistics	Final predictors in model
Rapoport, M.J. (2003)	ED	210	35	11	Significant differences in univariable analyses	Hierarchical logistic regression model with time post-injury as covariate	SCID-I 49d	Nagelkerke $R^2 = 0.18$	Age (OR: 0.99, SE: 0.05, $p > .05$); pre-injury depression (OR: 0.28, SE: 0.67, $p > .05$), substance abuse (OR: 0.25, SE: 0.67, $p < .05$), time post-injury (OR: 1.00, SE: .001, $p > .05$); gender (OR: 0.50, SE: 0.52, $p > .05$); employment (OR: 0.49, SE: 0.71, $p > .05$); education (OR: 0.52; SE: 0.48, $p > .05$), family history of depression (OR: 0.28, SE = 0.67, $p > .05$), medical history (OR: 1.49, SE: 0.55, $p > .05$), focal CT abnormalities (OR: 0.77, SE: 0.55, $p > .05$), mechanism of injury (OR: 1.66, SE: 1.62, $p > .05$)
Whelan-Goodinson, R. (2010)	ED	100	46	13	Significant in univariable analyses	Logistic regression model	SCID-I a t 0.5-5y	$X^2(6) = 29.10$, $p < .001$, Nagelkerke $R^2 = 0.35$; correct classification absent depression: 80.4%; correct classification presence depression: 67.4%; overall correct classification: 74.2%	Gender (B = 0.48; p = .10); pain (B = -0.97, p = .06); post-injury unemployment (B = 0.48; p = .39); pre-injury depression (B = 1.87; p =.01); years of education (B = 1.87; p = .01); time post-injury (B = 0.32, p = .06)

Table 4. **Continued**

Study	Timing model use	Number of patients	Number of cases*	Number of candidate predictors	Selection procedure of predictors	Statistical model	Outcome measurement and timing	Summary statistics	Final predictors in model
PTSD									
Alway, Y. (2015)	ED	203	27	5	Not reported	Multivariable random-effects logistic regression model adjusting for time post-injury	SCID-I at different follow-up points 3m-5y	Not reported	Age (OR: 0.99; 95%CI: 0.95 to 1.03); female gender (OR: 0.31; 95%CI: 0.05 to 2.08); years of education (OR: 1.06; 95%CI: 0.80 to 1.42); pre-injury psychiatric disorder (OR: 0.84; 95%CI: 0.23 to 3.15); PTA (days; OR: 0.98; 95%CI 0.95 to 1.02)
Ashman, T.A. (2004)	Unknown	188	30;18;21[A]	3	Not reported	Linear random effects longitudinal model	SCID-I 3m-4y	Not reported	Age (OR: 0.98; p =.22), time post-injury (OR: 1.07, p =.74) and time of enrolment in the study (OR: 0.59; p = .003)
Caspi, Y. (2006)	2.9y post-injury	120	22	4	Not reported	Logistic regression model adjusted for co-occuring depressive (BDI) and anxiety (BAI) symptoms	SCID-I 3y	Goodness of fit: 83.42, p < .001; Nagelkerke R^2 = 0.42, p < .001	Memory for the traumatic event (OR: 2.8; 95%CI 1.8-8.9); male gender (OR: 0.5; p >.05); history of psychiatric illness (OR: 0.5, p >.05), age (OR: 1.2, p >.05)
Gil, S. (2005)	1m post-injury	120	17	16	Significant in univariable analyses	Logistic regression model with variables that had shown significant association in univariable analyses	SCID-I 6m	Nagelkerke R^2 = 0.38; p < .001	Memory of traumatic event (OR: 2.2, 95%CI 1.0 to 10.1); acute posttraumatic symptoms (CAPS; OR: 5.3; 95%CI 1.1 to 9.3); acute posttraumatic symptoms (PSS; OR: 5.2; 95%CI 1.0 to 9.4); depressive symptoms (1wk; OR: 5.1; 95%CI 1.0 to 9.2); anxiety symptoms (1 wk; OR: 4.9, 95%CI 1.0 to 9.1), history of psychiatric disorders (OR: 3.7; 95% CI 1.1-8.9)

*Case = number of patients with the outcome of interest, in this case MDD or PTSD

[A]Number of patients with MDD or PTSD at three time points

Abbreviations: AUC = Area Under the Receiver Operating Curve; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; CAPS = Clinician Administrated PTSD scale; CES-D = Center for Epidemiologic Studies Depression Scale; CT = computed tomography; ED = emergency department; MDD = major depressive disorder; PSE = Present State Examination; PTSS = PTSD symptom scale; PTA = posttraumatic amnesia; PTSD = posttraumatic stress disorder; SCID=IV = Standardized Clinical Interview for DSM-IV

indicative of post-concussive syndrome, might be scored as hyperarousal symptoms in self-reported instruments. Reliability of self-reported measurements might further be hampered by memory deficits, low self-awareness and attention problems.[17-22] This is illustrated in a 2001 case report.[63] The inclusion of self-reported measurement might therefore have resulted in the reporting of invalid predictors, compromising the quality of this systematic review.

A second note that could be made regarding the completeness and applicability of evidence is that only a minority of studies used a multivariable model. The majority of results are based on univariable associations. As a consequence, we cannot exclude the possibility that some of the associations that we found were influenced by other factors. Also, factors that are non-significant in this review might comprise important predictors after correction for confounders. Third, the majority of studies included patients with mild, moderate and severe TBI and did not stratify or correct for TBI severity. Lastly, the large majority of studies were underpowered which might have resulted in non-significant findings in the narrative synthesis. This problem was partly captured by performing meta-analyses. This was however only possible for 18 and 6 predictors of MDD and PTSD, respectively.

The risk of bias of most studies developing multivariable models was high. Models included on average six to eight cases for every predictor, while it is recommended to include at least ten.[64,65] Including too many predictors enhances the risk of finding too extreme estimates ('statistical overfitting'), limiting generalizability of findings.[66] Additionally, the majority of studies did not report how they handled missing data and how they selected candidate predictors. Also, none of the studies used internal or external validation. As a consequence, none of the multivariable models could be applied to clinical practice yet.

We found a significant association between female gender and the likelihood of developing MDD in our meta-analysis. This is in line with systematic reviews about gender and depression in the general population; females approximately have a twice as high risk of developing major depression as do males.[67,68] However, this significant association was not found in three studies that were not included in the meta-analysis.[43,55,56] These studies were however underpowered since they included only 48, 10 and 21 cases respectively.

MDD was also associated with the presence of a pre-injury depression, which might be due to the high recurrence rates in MDD. A large prospective study reported that up to 85% of the patients with prior MDD developed a new MDD episode during a 15 years follow-up period.[69] Recurrence of MDD can be triggered by a stressful life event, such as a TBI, although causation is usually multifactorial.[70,71]

MDD was further more prevalent among those reporting post-injury unemployment and early post-injury psychiatric symptoms. This has also been shown in systematic reviews in the general population.[72,73] Unemployment can result in reduced social interactions and status which may subsequently result in depression.[74]

Higher admission GCS, referring predominately to moderate TBI patients compared to severe TBI patients, might also be associated with a higher odds of MDD. However, we did not find an association between 24-hours GCS and MDD and also failed to find an association between GCS as categorical variable and MDD in the narrative synthesis. As a consequence, the association between GCS and MDD remains uncertain.

Lastly, MDD after TBI might also be associated with lower brain volume. This was in line with a 2012 meta-analysis about gray matter abnormalities in MDD.[75] Since this was only assessed in two studies that used relatively low sample sizes, these finding should be interpreted with caution.

PTSD was more likely among patients with a shorter PTA and those with a memory of the traumatic event. A shorter PTA (less amnesia) and a memory of the event basically mean the same thing, and it is suggested that amnesia for the traumatic events minimizes the establishment of cognitive representations and so reduces the likelihood of intrusive symptoms.[50] However, one out of three studies found a significant association between the occurrence of LOC and PTSD, and the two studies assessing the association between PTSD and GCS did not find a significant effect, which might be contradictory to our findings on PTA and memory of the event; i.e., LOC and a low GCS are usually accompanied by at least some PTA. The difference in findings could be attributable to the lack of power in individual studies in the narrative synthesis. Future research is important in confirming the possible association between memory of the traumatic event and PTSD. PTSD was further significantly associated with ASD and early PTSD symptoms. Although studies could not be pooled because of different outcomes reported, four individual studies found a significant association between ASD or PTSD symptoms after one month and PTSD after six or twelve months. This was in line with a systematic review about predictors of sequelae in mild TBI patients[76] and a review about predictors of PTSD using self-reported outcome measurement.[16]

Strengths of this systematic review include the comprehensive search strategy, the restriction to structured diagnostic interviews and the performance of meta-analyses, which improved the statistical power. Additionally, we combined results from the meta-analyses, narrative synthesis and multivariable models to obtain conclusions about the significance of predictors. We thereby integrated all available sources of evidence. A limitation of the use of meta-analyses is that there was between-study variation in time span, TBI severity and outcome measurement, resulting in estimates that are difficult to interpret. Also, the use of I^2 statistic to interpret heterogeneity in the meta-analyses could be considered a limitation. Although I^2 statistic is the best heterogeneity

measurement available, it might be biased and not very precise in small meta-analyses.[77,78] Therefore, overlap in CIs should also be considered when interpreting heterogeneity between studies. A third limitation concerns our screening process, which was conducted by one study author. We however performed an audit and found a 100% concordance between study authors, indicating that screening by two independent reviewers would probably not have resulted in the inclusion of any additional studies.

The results of this systematic review imply that there is still limited knowledge regarding which patients develop MDD and PTSD after TBI. We therefore cannot recommend yet which patients should receive additional follow-up or preventive treatment and advise physicians to be aware in all patients who sustained TBI. Physicians could be extra aware in female patients with a pre-injury history of depression and post-injury unemployment or psychiatric symptoms. Also, a reduction in brain volume might indicate a risk of developing MDD post-injury. Furthermore, patients with a shorter PTA, a clear memory of the traumatic event and patients with early post-traumatic symptoms might be at higher risk of developing PTSD post-TBI.

More research is needed to confirm the relevance of these predictors of MDD and PTSD after TBI, and develop a multivariable model that could be implemented in hospitals and rehabilitation centers.

Future prognostic studies should include a more homogenous group of TBI patients (e.g. only those with mild TBI). It is also recommended that future studies include a large sample size and a limited set of candidate predictors. Selection of candidate predictors could be based on current review, theory or clinical knowledge about etiology of psychiatric disorders. Additionally, the confirmation of specific predictions among different patient samples is critically important to increase our knowledge about predictors of psychiatric sequelae post-TBI.

Conclusion

Our systematic review showed that MDD after TBI was associated with female gender, pre-injury depressive disorder, post-injury unemployment, early post-injury psychiatric symptoms and a lower brain volume, while PTSD was related to PTA, a memory of the traumatic event and early post-traumatic symptoms. Currently available multivariable models of MDD and PTSD after TBI suffer from methodological shortcomings. The findings of the current review, together with clinical knowledge about etiology of psychiatric disorders, could form the basis for future development of a prognostic model from a large sample of TBI patients using solid methodology.

Supplemental material is available at www.marysecnossen.nl

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Development of a prediction model for post-concussive symptoms following mild traumatic brain injury: A TRACK-TBI Pilot study

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Abstract

Post-concussive symptoms occur frequently after mild traumatic brain injury (mTBI) and may be categorized as cognitive, somatic, or emotional. We aimed to: 1) assess whether patient demographics and clinical variables predict development of each of these three symptom categories, and 2) develop a prediction model for six-month post-concussive symptoms.

MTBI patients (Glasgow Coma Scale score 13-15) from the prospective multicenter Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) Pilot study (2010-2012) who completed the Rivermead Post-Concussion Symptoms Questionnaire (RPQ) at six months post-injury were included. Linear regression was utilized to determine the predictive value of candidate predictors for cognitive, somatic, and emotional subscales individually, as well as the overall RPQ. The final prediction model was developed using least absolute shrinkage and selection operator procedure and bootstrap validation.

We included 277 mTBI patients (70% male, median age 42y). No major differences in the predictive value of our set of predictors existed for the cognitive, somatic, and emotional subscales, and therefore one prediction model for the RPQ total scale was developed. Years of education, pre-injury psychiatric disorders and prior TBI were the strongest predictors of six-month post-concussive symptoms. The total set of predictors explained 21% of the variance, which decreased to 14% after bootstrap validation.

Demographic and clinical variables at baseline are predictive of six-month post-concussive symptoms following mTBI; however these variables explain less than one-fifth of the total variance in outcome. Model refinement with larger datasets, more granular variables, and objective biomarkers are needed before implementation in clinical practice.

Introduction

Traumatic brain injury (TBI) is a common and often debilitating injury. In the United States alone, at least 2.5 million people suffer TBIs annually, accounting for 52,000 deaths, 275,000 inpatient hospitalizations, and 1,365,000 emergency room visits.[1] Approximately 70-90% of all TBI is characterized as mild TBI (mTBI) defined by a Glasgow Coma Scale (GCS) score of 13 to 15 upon admission to the emergency department (ED).[2] Many patients recover completely from mTBI in the ensuing weeks to months.[3,4] However, in 5-30% of subjects with mTBI, neurologic, cognitive and/or neuropsychiatric symptoms persist up to one year post-injury, or longer.[5-8] Methodologies to predict those at greatest risk of incomplete recovery are limited, but are the subject of active research incorporating neuroimaging, patient demographics, and genetic polymorphisms. Data from any of these sources may portend poor recovery.[9-13]

Post-concussive syndrome (PCS) is a clinical term used to describe a constellation of post-traumatic symptoms which may be divided into the domains of cognitive (forgetfulness, poor concentration, or slowed processing speed), somatic (headaches, double or blurred vision, photo or phonophobia, dizziness, nausea, disrupted sleep habits, or fatigue) or emotional (irritability, depression, frustration or restlessness).[14-17] The International Classification of Diseases, tenth edition (ICD-10) states that a diagnosis of PCS should include a head injury "usually sufficiently severe to result in loss of consciousness (LOC)," as well as three or more subjective symptoms present for at least four weeks. Symptoms should cause significant clinical impairment.[18]

In civilian populations, estimates suggest that roughly 10-20% of patients experience PCS within six months following mTBI.[14] However, the complaints are non-specific and are also observed in patients with extracranial injuries; because systemic injuries often coexist with neurological injuries, accurate estimates of true prevalence of PCS are difficult to ascertain. The term is not without controversy – for instance, after being included in the DSM-IV as a research diagnosis, PCS has been removed as a standalone disorder from the DSM-5 in favor of "major or mild neurocognitive disorder due to TBI."[19] In addition, there is overlap between the diagnostic criteria for PCS and posttraumatic stress disorder (PTSD),[20] further complicating the diagnosis of PCS. Therefore, it has been suggested that mTBI sequelae are more accurately understood as "post-concussive symptoms" rather than PCS.[5,21] Nevertheless, prior efforts to identify and create prediction models of post-concussive symptoms have relied on surveying the entire constellation of PCS rather than analyzing individual symptoms and/or domains.[22-24]

The Rivermead Post-Concussion Symptoms Questionnaire (RPQ) is one validated metric to survey post-concussive symptoms, relying on self-report as to the presence and severity of 16 symptoms.[16,17,25] It has been widely utilized to characterize outcomes and formally endorse symptomatology across the acute and chronic phases following mTBI.[26-29] The RPQ is composed of individual symptom domains: cognitive deficits, somatic complaints, and emotional complaints

– as described above.[16] Thus, the RPQ permits separate analysis of potential predictors of post-concussive symptoms in each domain. As different domains likely reflect different etiological pathways, one hypothesis is that each domain may be differentially susceptible to patient-specific and clinical factors. Alternatively, these complaints may reflect more global processes and therefore may not demonstrate differential susceptibility. The predictors that overlap across domains (cognitive, somatic, and emotional), and the predictors specific to each domain, warrant further delineation. Utilizing the prospective multicenter Transforming Research and Clinical Knowledge in Traumatic Brain Injury Pilot (TRACK-TBI Pilot) dataset,[30] we investigated whether cognitive, somatic, and emotional symptoms have different predictors, and whether multivariable prediction modeling using patient demographics and clinical variables can be successfully applied to identify those at greatest risk for suffering post-concussive symptoms following mTBI.

Material and methods

This study was conducted and reported according to the criteria of the *Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis* (TRIPOD) statement.[31]

Study design

The TRACK-TBI Pilot study was a multicenter, prospective observational study conducted at three Level I Trauma Centers in the United States: San Francisco General Hospital (SFGH), University of Pittsburgh Medical Center (UPMC), and University Medical Center Brackenridge (UMCB) in Austin, Texas using the National Institute of Neurological Disorders and Stroke (NINDS) TBI Common Data Elements (CDEs) version 1 (https://commondataelements.ninds.nih.gov/TBI.aspx). Eligible subjects were enrolled upon presentation to the ED through convenience sampling at all three sites between April 2010 and June 2012. Institutional Review Board approval was obtained at all sites. Informed consent was obtained for all participants prior to enrollment in the study. For participants unable to provide consent due to their injury, consent was obtained from their legally authorized representative. Participants were re-consented, if cognitively able, at later inpatient and/or outpatient study follow-up assessments. The current analysis focuses on post-concussive symptoms as measured by the RPQ; other outcome measures obtained at six months post-injury included the Glasgow Outcome Scale-Extended (GOS-E), Brief Symptom Inventory – 18 Item, Post-Traumatic Stress Disorder Checklist – Civilian Version, Trailmaking Test, and California Verbal Learning Test, Second Edition, as previously described.[30]

Patient selection

Inclusion criteria for the TRACK-TBI Pilot study were adult patients (age ≥ 16 years) presenting to one of the participating Level I trauma centers suffering external force trauma to the head with sufficient indications to triage to clinically indicated head computed tomography (CT) scan within 24 hours of injury. There were no requirements for visible pathology on CT scan.[30] Exclusion

criteria were pregnancy, comorbid life-threatening disease, incarceration, serious psychiatric and neurologic disorders that would interfere with outcome assessment, and non-English speakers due to limitations in participation with outcome assessments. For the present study, our analysis was restricted to the subset of patients with mTBI, defined by a GCS ≥ 13.

Measurements

To assess the presence/absence and severity of post-concussive symptoms, subjects completed the RPQ at six months following injury, in-person with trained study personnel, preceded by the Galveston Orientation and Amnesia Test to assess capacity. All study personnel were trained on outcome measure administration by a single neuropsychological outcomes coordinator from UPMC. As previously described, the RPQ is a sensitive and validated assessment tool for the presence of post-concussive symptoms[16,17,25-29] and is a "CORE" level NINDS TBI CDE.[32] It is comprised of questions directed toward the following 16 symptoms: headache, nausea or vomiting, dizziness, sensitivity to noise, disrupted sleep, irritability, frustration, fatigue, depression, impaired memory, poor concentration, slowed thinking, blurred vision, double vision, light sensitivity, and restlessness. Each symptom is rated on a 5-point scale to assess whether the symptom has been absent, no more of a problem, or a mild, moderate, or severe problem in the 24 hours prior to completing the questionnaire, compared to pre-injury. As recommended by previous research,[33] the scores 0 and 1 were collapsed into a single category, scored at 0 points. This resulted in a 4-point scale with the following categories: symptom is absent or no more of a problem (0), symptom is mild (1), moderate (2), or severe (3). The total score was determined by adding up all scores 0 to 3, which results in a minimum score of 0 and a maximum score of 48. Subject responses may then be clustered into distinct neuropsychiatric domains: (i) cognitive deficits (impaired memory, poor concentration, slowed thinking), (ii) somatic complaints (headaches, blurred or double vision, noise sensitivity, dizziness, nausea, sleep disturbances, fatigue) and (iii) psychological complaints (irritability, depression, frustration, restlessness).[16]

Selection of candidate predictors

A systematic literature search was performed using subheadings and text words in EMBASE and Google Scholar to identify systematic reviews and prior published prediction model developing studies that assessed predictors of post-concussive symptoms (or related outcomes) following mTBI (see Online Supplement A for the EMBASE search strategy). To maximize the potential application of a prediction model to clinical practice, candidate predictors not readily available in the ED or during initial clinical evaluation were excluded. The following were chosen as candidate predictors: age, gender, years of education, pre-injury seizures, pre-injury migraine or headache, pre-injury psychiatric disorders, blood alcohol level (BAL > 80 mg/dl (U.S. legal limit); ≤ 80 mg/dl; not measured), GCS score, CT abnormalities (present; absent), posttraumatic amnesia (PTA; present; absent; not measured), LOC (present; absent; not measured), and extracranial injury. We further included whether subjects suffered a prior TBI per self-report as a

potential candidate predictor. Prior TBI was assessed using the NINDS TBI CDEs version 1,[34] and classified as yes (with or without hospitalization) or no. Although not found in systematic reviews and previous prediction modeling studies, we hypothesized that deficits from repeated TBIs may be cumulative and thus may result in greater post-concussive symptoms burden. Information on candidate predictors was gathered through abstraction of medical records and from patient interviews during the index hospital visit.

Statistical analyses

Baseline characteristics of the overall study population were reported as medians and interquartile ranges (IQR), and frequencies and percentages, for continuous and categorical variables respectively. To verify whether loss to follow-up resulted in possible bias, we compared baseline characteristics of included patients with those patients who had a missing six-month RPQ (n = 199), using the Pearson chi-square statistic for categorical variables and the Mann-Whitney *U* test for continuous variables. Missing data on candidate predictors were subsequently imputed with a single imputation technique, meaning that values for the missing data points were estimated in a regression model using all other predictor variables and outcomes as independent variables.

We described the RPQ total scale and subscales (mean, SD, range), and assessed the association between the RPQ total scale and subscales and functional outcome (as measured by the GOS-E) as well as intercorrelations between scales, using the non-parametric Spearman's rho correlation coefficient. We subsequently calculated Cronbach's alpha for the RPQ total scales and subscales as a measurement of internal consistency.

To calculate the effect of candidate predictors on the RPQ cognitive, somatic and emotional subscales, we used univariable linear regression models with the candidate predictor of interest as independent variable and the RPQ subscale as dependent variable. To assess the adjusted effect of candidate predictors, we used multivariable linear regression models with all candidate predictors as independent variables. Unstandardized β's and *p*-values were reported. The β coefficient indicates the change in outcome (points on the RPQ scale or subscale) for one unit change in the predictor variable. To enhance comparability of effect estimates for the different subscales, we additionally calculated standardized β coefficients. A standardized β indicates the change in outcome in SDs, for one SD change in the predictor variable.

To assess whether the predictor effects differed across cognitive, somatic and emotional subscales, we tested for interaction between the predictors (summarized in the predicted values of the RPQ total scale) and the subscales. We created three rows per patient in the database: one with the cognitive outcome, one with the somatic outcome, and one with the emotional outcome. We subsequently fitted a random effects model with a random intercept for patient number, the

predicted value of the total RPQ scale based on the full multivariable model, ”outcome type” and an interaction between ”outcome type” and predicted value.

We developed the final model by using the least absolute shrinkage and selection operator (Lasso) method. This method shrinks the β-coefficients in order to obtain less extreme βs to enhance the external validity of a prediction model.[35] Variables with βs that are unstable are shrunk to zero and omitted from the model. It should be noted that Lasso shrinkage focuses on the overall fit rather than statistical significance of individual predictors. As a consequence, predictors with a *p*-value > 0.05 could still be included in the final model. External validity of the final model was further enhanced by performing bootstrap validation with 100 samples.

The interaction test, Lasso shrinkage, and bootstrap validation were analyzed with R (version 3.2.2.) using the *lme4,*[36] *penalized*[37] and *foreign*[38] packages. All other analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 21. A *p*-value < 0.05 was considered statistically significant in all analyses.

Sensitivity analyses

Although a prediction model with a linear outcome is statistically more appealing, models with a binary outcome variable are often preferred for clinical interpretation. We therefore performed multivariable logistic regression analysis with the variables obtained after Lasso shrinkage as independent variables and the dichotomized RPQ scale as dependent variable. For the dichotomization of the RPQ we utilized the eight symptoms mentioned in the ICD-10 criteria. Subjects were subsequently diagnosed with PCS if they meet three or more of the following symptoms: (1) headache, (2) dizziness, (3) fatigue, (4) irritability, (5) insomnia, (6) memory problems, (7) concentration issues, and (8) frustration or depression (in ICD-10 explained as reduced tolerance to stress, emotional excitement or alcohol). It should be recognized that the RPQ could not be used to truly diagnose ICD-10 PCS since the RPQ is based on self-report rather than clinical examination and does not include information on symptom duration and clinical significant impairment. In addition, there is no consensus as to whether symptoms should be included if they are rated as “mild symptom or worse” or if they are rated as “moderate symptom or worse.”[39] We therefore applied both classifications.

We further examined the influence of attrition on estimates of the predictors by simulating three scenarios:

1. The patients lost to follow-up have relatively favorable outcomes in comparison to those included in current study
2. The patients lost to follow-up have similar outcomes to those included in current study
3. The patients lost to follow-up have relatively unfavorable outcomes in comparison to those included in current study

For the first scenario, we simulated the outcome of those lost to follow-up by generating random numbers with the range 0-48 (possible scores on RPQ), a mean of 0.00 (25th percentile of those included), and a SD of 10.0 (actual SD of those included). For the second scenario, we simulated outcome of those lost to follow-up with the range 0-48, a mean of 5.0 (median of those included), and a SD of 10.0 (actual SD of those included). For the third scenario, we simulated outcome with the range 0-48, a mean of 15 (75th percentile of those included), and a SD of 10.0 (actual SD of those included). For simplicity, we did not predetermine the associations between predictors and attrition, while acknowledging that this may play a role in the influence of attrition on effect estimates.

Results

Patient characteristics

The TRACK-TBI Pilot study consisted of 580 TBI subjects, of whom 476 had mTBI (GCS 13-15); 277 subjects (58%) completed six-month RPQ assessment and were included in the current analysis (Figure 1). Included subjects had more years of education (median: 14) than those lost to follow-up (median: 13, $p < 0.01$). No other statistically significant differences existed between those included in the current analysis versus lost to follow-up (Table 1).

***Figure 1*. Flow-chart of included patients in current study**

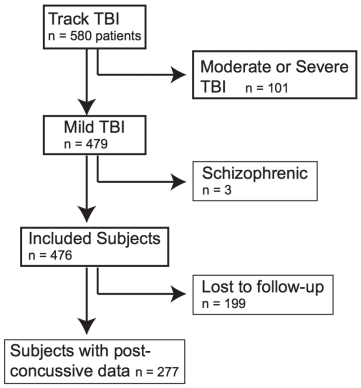

Figure shows patients from the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK TBI) pilot study that were included in current study

Median age for subjects in the current analysis was 42 years (Interquartile range 26-57y) and most (70%) were male. Half of the subjects (n = 141) sustained a traffic accident. Fifty-four percent (n = 147) reported a prior TBI, for whom 88 were hospitalized. By ED triage, 38% were discharged home, 35% were admitted to the ICU or other monitored inpatient bed, 23% were admitted to the ward, and 4% went directly to the operating room.

Table 1. **Baseline characteristics of 277 subjects included in the study compared to 199 subjects lost to follow-up**

	Included subjects (n = 277)		Subjects lost to follow-up (n = 199)		
Variable	**Missing**	**N (%)‡**	**Missing**	**N (%)‡**	***p*-value**
Age (median, IQR range)	-	42 (26-57)	-	43 (27-57)	.66
Gender (Female)	-	84 (30%)	-	51 (26%)	.26
Years of education (median, IQR range)	11	14 (12-16)	7	13 (12-15)	< .01
Pre-injury seizures*	-	30 (11%)	-	18 (9%)	.52
Pre-injury migraine & headache	-	36 (13%)	-	15 (8%)	.06
Pre-injury psychiatric disorders**	-	89 (32%)	-	49 (25%)	.08
Prior TBI	7	147 (54%)	14	84 (45%)	.06
Mechanism of injury	1		-		.11
– Traffic accident		141 (51%)		83 (42%)	
– Fall		84 (30%)		70 (35%)	
– Assault		39 (14%)		40 (21%)	
– Other		12 (5%)		6 (2%)	
BAL	-		-		.41
– ≤ 80 mg/dl (low BAL)		80 (29%)		53 (27%)	
– > 80mg/dl (high BAL)		39 (14%)		37 (19%)	
– Not measured		158 (57%)		109 (54%)	
GCS < 15	-	63 (23%)	-	56 (28%)	.18
CT abnormalities***	-	95 (34%)	-	74 (37%)	.52
PTA	1		2		.38
– Yes or suspected		173 (63%)		112 (56%)	
– No		90 (32%)		72 (37%)	
– Unknown		13 (5%)		13 (7%)	
LOC	2		1		.58
– Yes		190 (69%)		132 (67%)	
– No		66 (24%)		55 (28%)	
– Unknown		19 (7%)		11 (5%)	
Extracranial AIS ≥ 3 in at least one body region	-	36 (13%)	-	32 (16%)	.34
ED disposition	-		-		.33
– Home		105 (38%)		62 (31%)	
– Hospital ward		63 (23%)		42 (21%)	
– Step-down bed or ICU		97 (35%)		88 (44%)	
– Operating room		12 (4%)		7 (4%)	

‡Values are presented as N (%) unless otherwise specified.

p-value presents results of Chi-Square test (categorical variables) or Mann-Whitney *U* test (continuous variables) for the differences between the included subjects and subjects that were lost to follow-up.

* Includes seizures and epilepsy.

** Includes anxiety, depression, sleeping disorders and bipolar disorder.

*** Includes EDH, SDH, SAH, contusion, ICH, IVH, DAI, brain swelling, midline shift, cistern compression, fourth ventricle shift and third ventricle shift.

Abbreviations: BAL = blood alcohol level; ED = emergency department; TBI = traumatic brain injury; GCS = Glasgow Coma Scale; CT = computed tomography; PTA = posttraumatic amnesia; LOC = loss of consciousness; AIS = abbreviated injury scale.

At six-months post-injury, the mean RPQ score was 8.8 (SD = 10.0). Fifty-three percent (n = 147) reported at least three or more out of the eight symptoms defined for PCS by ICD-10 as 'mild or worse,' while 27% (n = 74) reported at least three out of eight symptoms rated as 'moderate or worse.'

RPQ scales

The RPQ cognitive, somatic, and emotional subscales, and the RPQ total scale all demonstrated a skewed distribution with the majority of patients having relatively lower scores (Table 2). Cronbach's alpha was > 0.80 for the subscales and the total scale, indicating adequate internal consistency.[40] The RPQ total scale and subscales demonstrated moderate correlation with the GOS-E at six-months post-injury (r -0.61 to -0.71; $p < 0.01$), indicating that higher RPQ scores were associated with worse functional outcome. Inter-correlations between subscales were moderate (r 0.63 to 0.76; $p < 0.01$).

Table 2. **RPQ outcome scales six months after mild traumatic brain injury**

	Psychometric characteristics						Correlations		
	No. Items	**Mean**	**SD**	**Range**	**Possible range**	**Cronbach's alpha**	**GOSE**	**RPQ cognitive Scale**	**RPQ Somatic Scale**	**RPQ Emotional Scale**
RPQ Cognitive scale	3	2.25	2.74	0-9	0-9	.92	-.61*	-		
RPQ Somatic scale	9	4.32	5.34	0-27	0-27	.85	-.65*	.63*	-	
RPQ Emotional scale	4	2.19	3.07	0-12	0-12	.89	-.64*	.69*	.76*	-
RPQ Total scale	16	8.76	10.03	0-44	0-48	.93	-.71*	.82*	.94*	.90*

* $p < .01$

Results are presented after collapsing the RPQ scores 0 (no problem) and 1 (no more of a problem) together.

Correlation coefficients represent non-parametric Spearman's rho correlation coefficients.

Cognitive scale is based on the items forgetfulness, poor concentration and taking longer to think

Somatic scale is based on the items headache, dizziness, nausea, noise sensitivity, sleep disturbance, fatigue, blurred vision, light sensitivity and double vision

Emotional scale is based on the items irritability, depressed, frustrated and restlessness

Abbreviations: RPQ = Rivermead Post Concussion Questionnaire; SD = standard deviation; GOSE = Glasgow Outcome Scale Extended

Predictors of cognitive, somatic, and emotional post-concussive symptoms

The cognitive, somatic, and emotional subscales were significantly associated with years of education ($p < 0.01$), pre-injury psychiatric disorders ($p < 0.01$), and prior TBI ($p < 0.01$) in both univariable and multivariable linear regression analyses. Strengths of the effect sizes, illustrated with standardized βs, were similar across the three different scales (Online Supplement B). In addition, age, pre-injury seizures, pre-injury migraine and headache, and CT abnormalities were significant predictors for one or more subscales (Table 3). The interaction test between the cognitive, somatic, and emotional outcome subscales and the predicted value of the RPQ total scale was not statistically significant (t = 0.54; SE = 0.02). This indicates that although some differences exist on an individual predictor level, overall predictor effects are similar for the three

subscales. Hence, one prediction model using the RPQ total scale as the outcome measure of choice could be developed from the current dataset – which comprised the next phase of our analysis.

Prediction model of six-month post-concussive symptoms

The RPQ total scale was significantly associated with years of education ($p < 0.01$), pre-injury seizures ($p = 0.03$), pre-injury migraine and headache ($p < 0.01$), pre-injury psychiatric disorders ($p < 0.01$) and prior TBI ($p < 0.01$) in univariable analyses. In a multivariable model, the variables years of education ($p < .01$), pre-injury psychiatric disorders ($p < 0.01$), and prior TBI ($p < 0.01$) were statistically significant. We applied Lasso shrinkage to obtain the final set of independent predictors and their shrunken βs. After shrinkage, the occurrence and severity of persistent post-concussion symptoms (higher scores on the RPQ) were associated with older age, female gender, less years of education, a confirmed or unknown PTA, a confirmed or unknown LOC and the presence of pre-injury migraine and headache, pre-injury psychiatric disorders and prior TBI (Table 4). Comparison of the expected values of the scales with the actual scores resulted in an R^2 of 0.21, which decreased to 0.14 after bootstrap validation. The expected score on the subscales and total scale could be calculated for individual patients by using the regression formula (Table 4, footnote). An example of the calculation for two individual patients is displayed in Box 1.

Sensitivity analyses

Multiple logistic regression analyses with the variables obtained after Lasso shrinkage resulted in the same set of predictors being statistically significant (PCS classified as ≥ 3 'mild or worse' symptoms: years of education OR = 0.84 (95% CI: 0.76-0.93), pre-injury psychiatric disorders OR = 2.05 (95% CI: 1.14-3.68), prior TBI OR = 2.94 (95% CI: 1.71-5.08); PCS classified as ≥ 3 'moderate or worse' symptoms: years of education OR = 0.87 (95% CI: 0.77-0.97), pre-injury psychiatric disorders OR = 3.24 (95% CI: 1.77-5.91), prior TBI OR = 2.08 (95% CI: 1.10-3.93)). Female gender was a statistically significant predictor of PCS classified as ≥ 3 'mild or worse' symptoms (OR 2.02; 95% CI: 1.11-3.68). The Areas under the Curve (AUCs) ranged from 0.74 to 0.76, indicating reasonable discriminative ability (Online Supplement C). We did not apply further model development (e.g., shrinkage, bootstrap validation), since our sample size was too small to develop a valid model with a binary outcome.

When analyzing different scenarios of attrition, the scenarios in which patients lost to follow-up had similar or more favorable outcomes did not result in major changes in effect estimates. However, in the scenario where patients lost to follow-up had relatively unfavorable outcomes, prior TBI was no longer a statistically significant predictor of six-month post-concussive symptoms, while age, GCS, and PTA became significant predictors.

Table 3. **Univariable and multivariable predictors of cognitive, somatic and emotional post-concussive symptoms after six-months in 277 patients with mild traumatic brain injury**

Predictors	RPQ – cognitive (3 items)		RPQ – somatic (9 items)		RPQ – emotional (4 items)	
	Univariable (β, *p*-value)	Multivariable (β, *p*-value)	Univariable (β, *p*-value)	Multivariable (β, *p*-value)	Univariable (β, *p*-value)	Multivariable (β, *p*-value)
Age (/10y)	0.15 (p = .09)	0.11 (p = .23)	0.30 (p = .10)	0.38 (p = .03)	0.02 (p = .83)	0.09 (p = .40)
Gender (Female vs Male)	0.39 (p = .27)	0.58 (p = .10)	0.74 (p = .29)	0.88 (p = .19)	0.05 (p = .90)	0.22 (p = .58)
Years of education (/y)	-0.24 (p < .01)	-0.23 (p < .01)	-0.46 (p < .01)	-0.39 (p < .01)	-0.24 (p < .01)	-0.21 (p < .01)
Pre-injury seizures* (yes vs. no)	1.14 (p = .03)	0.47 (p = .36)	1.85 (p = .07)	-0.001 (p = .99)	1.32 (p = .03)	0.44 (p = .46)
Pre-injury migraine & headache (yes vs. no)	0.86 (p = .08)	0.02 (p = .96)	4.58 (p < .01)	2.82 (p < .01)	1.50 (p = .01)	0.45 (p = .41)
Pre-injury psychiatric disorders** (yes vs. no)	1.57 (p < .01)	0.99 (p = .01)	3.14 (p <.01)	2.04 (p < .01)	1.67 (p <.01)	1.12 (p < .01)
Prior TBI (yes vs. no)	1.08 (p < .01)	1.19 (p < .01)	2.54 (p < .01)	2.04 (p < .01)	1.49 (p < .01)	1.10 (p < .01)
BAL						
– high BAL vs. low/unmeasured	-0.83 (p = .12)	-0.94 (p = .08)	0.50 (p = .64)	0.59 (p = .56)	0.15 (p = .81)	-0.14 (p = .81)
– unmeasured BAL vs. high/low	-0.67 (p = .07)	-0.59 (p = .11)	-0.09 (p = .91)	-0.17 (p = .81)	0.06 (p = .89)	-0.44 (p = .92)
GCS 13 or 14 vs GCS 15	0.17 (p = .67)	0.25 (p = .53)	0.24 (p = .75)	-0.14 (p = .85)	0.66 (p = .14)	0.52 (p = .25)
CT abnormalities*** (yes vs. no)	0.05 (p = .88)	0.46 (p = .22)	-1.32 (p = .05)	-0.35 (p = .62)	-0.90 (p = .02)	-0.42 (p = .33)
PTA						
– yes vs. no/unknown	-1.20 (p = .13)	-1.09 (p = .16)	0.74 (p = .63)	1.24 (p = .40)	-0.02 (p = .99)	-0.09 (p = .92)
– no vs. yes/unknown	-0.94 (p = .25)	-1.20 (p = .15)	0.51 (p = .75)	0.25 (p = .87)	- 0.10 (p = .92)	-0.42 (p = .65)
LOC						
– yes vs. no/unknown	0.36 (p = .59)	0.37 (p = .56)	-1.18 (p = .36)	-1.33 (p = .28)	-0.12 (p = .87)	-0.06 (p = .93)
– no vs. yes/unknown	0.02 (p = .98)	0.10 (p = .89)	-1.85 (p = .18)	-1.55 (p = .26)	-0.82 (p = .31)	-0.56 (p = .50)
Extracranial AIS ≥ 3 in at least one body region (yes vs. no)	-0.41 (p = .40)	-0.45 (p = .34)	-0.37 (p = .70)	-0.19 (p = .83)	-0.41 (p = .45)	-0.46 (p = .39)
R^2		0.20		0.23		0.17

Unstandardized β's and *p*-values are shown for all analyses. The multivariable model is based on all candidate predictors in the table. Cognitive scale is based on the items forgetfulness, poor concentration and taking longer to think Somatic scale is based on the items headache, dizziness, nausea, noise sensitivity, sleep disturbance, fatigue, blurred vision, light sensitivity and double vision

Emotional scale is based on the items irritability, depressed, frustrated and restlessness

*Includes seizures and epilepsy **Includes anxiety, depression, sleeping disorders and bipolar disorder ***Includes EDH, SDH, SAH, contusion, ICH, IVH, DAI, brain swelling, midline shift, cistern compression, fourth ventricle shift and third ventricle shift

Abbreviations: BAL = blood alcohol level; ED = emergency department; TBI = traumatic brain injury; GCS = Glasgow Coma Scale; CT = computed tomography; PTA = posttraumatic amnesia; LOC = loss of consciousness; AIS = abbreviated injury scale.

Box 1. Two cases and their predicted score on the RPQ scale according to our prediction model

Case 1 : Male patient, 65 years, 23 years of education with pre-injury headache or migraine, a pre-injury psychiatric disorder, a prior TBI, LOC, and PTA.

Predicted value total RPQ scale after six months = 14.45 (intercept) + (0.74*0) + (0.05*65) + (-0.79*23) + (2.07*1) + (3.73*1) + (3.71*1) + (-0.47*0) + (-0.38*0) = 9.04 (95% CI: 4.57 – 13.50)

Case 2: Female patient, 30 years, 10 years of education with pre-injury headache or migraine, a pre-injury psychiatric disorder and no prior TBI, LOC and PTA

Predicted value total RPQ scale after six months = 14.45 (intercept) + (0.74*1) + (0.05*30) + (-0.79*10) + (2.07*1) + (3.73*1) + (3.71*0) + (-0.47*1) + (-0.38*1) = 17.45 (95% CI: 13.00 – 21.90)

Expected scores can be calculated with the regression formula in the footnote of Table 4. The 95% Confidence interval can only be calculated with advanced statistical software.

Table 4. Predictors of six-month post-concussive symptoms in 277 patients with mild traumatic brain injury

Predictors	Univariable (β, *p*-value)	Multivariable (β, *p*-value)	LASSO shrinkage (β)
Age (/10y)	0.50 (p = .16)	0.58 (p = .08)	0.53
Gender (Female vs Male)	1.18 (p = .37)	1.68 (p = .19)	0.74
Years of education (/y)	-0.94 (p < .01)	-0.84 (p < .01)	-0.79
Pre-injury seizures* (yes vs. no)	4.30 (p = .03)	0.91 (p = .63)	-
Pre-injury migraine & headache (yes vs. no)	6.95 (p < .01)	3.30 (p = .06)	2.07
Pre-injury psychiatric disorders** (yes vs. no)	6.28 (p < .01)	4.15 (p < .01)	3.73
Prior TBI (yes vs. no)	5.11 (p <.01)	4.34 (p < .01)	3.71
BAL			
– high BAL vs. low/unmeasured	-0.19 (p = .92)	-0.49 (p = .80)	-
– unmeasured BAL vs. high/low	-0.70 (p = .61)	-0.80 (p = .54)	-
GCS 13 or 14 vs GCS 15	1.07 (p = .46)	0.62 (p = .66)	-
CT abnormalities*** (yes vs. no)	-2.17 (p = .09)	-0.31 (p = .82)	-
PTA			
– yes vs. no/unknown	-0.47 (p = .87)	0.06 (p = .98)	-
– no vs. yes/unknown	-0.53 (p = .86)	-1.36 (p = .64)	-0.47
LOC			
– yes vs. no/unknown	-0.94 (p = .70)	-1.02 (p = .66)	-
– no vs. yes/unknown	-2.65 (p = .31)	-2.01 (p = .43)	-0.38
Extracranial AIS ≥ 3 in at least one body region (yes vs. no)	-1.20 (p = .51)	-1.09 (p = .52)	-
R^2		0.23	0.21Ł

Unstandardized β's and *p*-values are shown for all analyses. The multivariable model is based on all candidate predictors in the table. The expected 6-months RPQ score can be estimated with the following formula:
6 month RPQ = 14.45 + (0.05*Age) + (-0.79*Years of education) + (0.74*female gender) + (2.07*pre-injury migraine or headache) + (3.73*pre-injury psychiatric disorder) + (3.71*prior TBI) + (-0.47* no PTA) + (-0.38*no LOC)
*Includes seizures and epilepsy
**Includes anxiety, depression, sleeping disorders and bipolar disorder
***Includes EDH, SDH, SAH, contusion, ICH, IVH, DAI, brain swelling, midline shift, cistern compression, fourth ventricle shift and third ventricle shift
Abbreviations: BAL = blood alcohol level; ED = emergency department; TBI = traumatic brain injury; GCS = Glasgow Coma Scale; CT = computed tomography; PTA = posttraumatic amnesia; LOC = loss of consciousness; AIS = abbreviated injury scale.
ŁR^2 decreased to 0.14 after bootstrap validation with 100 samples.

Discussion

We developed a prediction model to predict six-month post-concussive symptoms following mTBI in a multicenter study with 277 subjects. Post-concussive symptoms were associated with older age, female gender, less education, pre-injury migraine or headache, pre-injury psychiatric problems, prior TBI, PTA, and LOC, of which years of education, presence of pre-injury psychiatric disorders and prior TBI were the most robust predictors. This set of predictors accounted for less than one-fifth of the variance in post-concussive symptoms.

Previous investigations have often reported that PCS is a multidimensional concept.[5,16,17,33,41,42] Therefore, it has been hypothesized that the cognitive, somatic, and emotional RPQ subscales are differentially susceptible to predictor variables. We did not find a difference in the predicted probabilities of the total set of candidate predictors for the three subscales, and therefore, we developed one overall prediction model for six-month post-concussive symptoms using the RPQ total scale. This might indicate that post-concussive symptoms from different domains share etiological factors. However, we did find differences in the predictive ability for some predictors (age, pre-injury seizures, pre-injury migraine and headache, CT abnormalities) and the inter-correlations between the three subscales were modest. Therefore, confirmation of our findings in larger patient samples is necessary to confirm the adequacy of the total RPQ scale as an outcome variable in prognostic research. Our final prediction model has an R^2 of 0.21, which decreased to 0.14 after bootstrap validation. This indicates that less than one-fifth of the variation in post-concussive symptoms could be explained by the predictors in the model. Despite being low for a prediction model, this is consistent with previous studies examining predictors of post-concussive symptoms using the linear RPQ as an outcome measurement. For example, in a systematic review conducted by Silverberg et al.[43] R^2s ranged from 0.06 to 0.89 in six studies that used the RPQ as a continuous outcome measurement, and was only above 0.40 in two studies deemed at high risk of statistical overfitting.[43]

In prior systematic reviews, the most robust predictors of mTBI sequelae were gender, pre-injury mental health, early post-injury neurological functioning, and post-injury anxiety.[43,44] Consistent with this, pre-injury mental health was also a significant predictor in our study. Patients with pre-injury psychiatric disorders are known to be vulnerable to recurrence of the psychiatric disorder[45] or the development of other psychopathology,[46] which might be triggered by a stressful or traumatic event such as mTBI. Other significant predictors in our study were years of education and prior TBI. Both of these were also candidate predictors in the prediction model developed by Stulemeijer et al.[24] but were not found to be statistically significant in their final model, which was confirmed by the systematic review of Silverberg et al.[43] Nevertheless, higher education is associated with return to work in several studies,[24,47,48] and highly educated people generally have improved coping skills, cognitive and financial reserves, and a wider social network to deal with possible consequences of mTBI. The influence of prior TBI on persistent

post-concussion symptoms is less often studied. However, emerging basic science and clinical research on repetitive brain injury suggests that the deleterious effects of brain injury are cumulative.[49] Therefore, inclusion of a history of prior TBI is an important consideration for future work on post-concussive symptoms and other neuropsychiatric sequelae of TBI. The predictors age, gender, pre-injury migraine and headache, PTA and LOC also appeared in our final prediction model because they contributed to the overall model fit. It however should be noted that they were not statistically significantly associated with persistent post-concussion symptoms and their potential as predictors should therefore be examined in future studies.

In creating our prediction model, we attempted to methodologically overcome several of the shortcomings of prior work. Our set of candidate predictors was based on existing literature and was appropriately limited to not exceed the rule of thumb of a maximum of one candidate predictor for every ten cases,[50,51] which limits the risk of statistical overfitting.[50,52] Additionally, we used Lasso shrinkage and bootstrap validation to correct for model optimism, improving generalizability of the model.[50,52] Third, we examined the influence of predictors on the three RPQ subscales and tested whether the total RPQ scale as an outcome variable was adequate. The use of the RPQ as a linear scale might also be regarded as a strength of our study. Since there is no clear cut-off point determining whether a patient should be diagnosed with PCS, dichotomization might result in an arbitrary difference between favorable and unfavorable outcome, limiting its potential for clinical practice. For example, in our study we found that two different classifications of PCS (i.e. PCS ≥ 3 'mild or worse' symptoms vs. PCS ≥ 'moderate or worse' symptoms) resulted in a prevalence difference of 26%. Further, dichotomization results in a loss of information and potentially overoptimistic results.[50] Large sample sizes are needed to prevent statistical overfitting in prognostic studies with a dichotomous outcome, especially when the prevalence of patients with the outcome of interest is relatively low. In our study, we would have needed a total of 599 patients to develop a prediction model with a binary outcome variable (PCS defined as ≥ 3 moderate symptoms or worse). On the other hand, models with a dichotomized outcome are clinically appealing since these models can directly estimate the risk of post-concussive symptoms. In addition, it might be more relevant for clinicians to predict a clinical significant problem (e.g., PCS) rather than predicting an increase on the RPQ scale. The latter may also necessitate clinically relevant cut-off points that are currently unavailable. To improve clinical interpretation, we created a model with a dichotomous outcome for clinical interpretation.

We note several limitations. First, there was a significant proportion of subjects lost to follow-up (42%). Although this percentage is similar to other prospective studies in mTBI research[24,53,54] and patients lost to follow-up did not differ from those who remained, we cannot exclude selection bias. Patients included in our sample may, for instance, differ from those not included on factors that were not measured, or on the severity of their post-concussive symptoms. To estimate the possible effect of attrition on our estimation of predictors, we performed sensitivity analyses in

which we simulated scenarios where patients lost to follow-up had a more favorable, similar, or more unfavorable outcome compared with those included in our study. We did not find major differences in the predictive probability of our set of predictors in the scenarios where patients lost to follow-up had similar or more favorable outcomes than the included patients. This corroborated similar studies analyzing the influence of attrition on predictor estimates.[55,56] However, in the scenario were patients lost to follow-up had less favorable outcomes, additional predictors were associated with post-concussive symptoms, while prior TBI, which is a strong predictor in this study, was no longer statistically significant. The effect of attrition on outcome should therefore be taken into account when interpreting the results of the current study. A second limitation is that our sample size is relatively small for the development of a prediction model.[57] Consequently, our study might not have been sufficiently powered to detect the significance of some of the candidate predictors and current regression coefficients might be relatively unstable.[52] Third, in the present study, the included mild TBI patients were relatively severely injured. For example, 34% of the patients had CT abnormalities, and the majority of patients had PTA and LOC. In addition, 35% of the patients were admitted to step-down beds or the ICU. The relative severity of our study population may have implications for the generalizability to other populations of mTBI patients. Given these limitations, the results of the current study should be considered preliminary; validation in an independent population is needed.

We chose to develop a model with baseline and clinical predictors that can be gathered during the ED visit to maximize the potential application of the model in clinical practice. The inclusion of post-injury characteristics may be less useful as mTBI patients may not receive routine follow-up after leaving the ED.[58] However, since our model explained less than one-fifth of the variation in six-month post-concussive symptoms, additional variables are likely necessary to obtain more reliable predictions. Since early post-injury symptoms have been shown to associate highly with chronic symptoms,[43] the addition of these symptoms could substantially improve our prediction model. Ideally, two models could be developed, validated, and implemented in future ED practices. First, a model based on baseline and clinical characteristics collected at ED presentation with a high sensitivity should be developed. This model could select high-risk patients that should be seen at a follow-up appointment soon after their ED visit. Such a model could be based on current findings and could further be refined with larger datasets, more granular variables and objective biomarkers. At the follow-up appointment, early post-injury symptoms could be further investigated and added to the model. This second model could subsequently identify patients at risk for long-term sequelae, who should be prioritized for preventive or rehabilitative interventions.

Conclusion

Demographic and clinical variables at baseline predict post-concussive symptoms after mild traumatic brain injury, however these variables explain less than one-fifth of the total variance in outcome. Model refinement with larger datasets, more granular variables, and objective biomarkers are needed before implementation in clinical practice.

Supplemental material is available at www.marysecnossen.nl

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7

Prediction of persistent post-concussion symptoms following mild traumatic brain injury: External validation of existing models and the development of a new model

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Abstract

Objectives: To externally validate existing models for persistent post-concussion symptoms, and to develop a new model based on the synthesis of existing models and the addition of complaints at the emergency department.

Methods: Patients with mild traumatic brain injury (Glasgow Coma Scale score 13-15) were prospectively recruited from three Dutch level I trauma centers between 2013-2015 in the UPFRONT study. Persistent post-concussion symptoms were assessed using the Head Injury Severity Checklist at six-month post-injury. Two prognostic models (Stulemeijer et al.; Cnossen et al.) were examined for calibration and discrimination. The final model, based on variables of existing models was developed with the addition of headache, nausea/vomiting and neck pain at emergency department, using logistic regression and bootstrap validation to correct for model optimism.

Results: Overall 591 patients (mean age 51years, 41% female) were included; 241 (41%) developed post-concussion symptoms at six months. Existing models performed poorly at external validation (AUC: 0.57-0.64). The newly developed model included female sex (OR 1.48, 95% CI 1.01-2.18), neck pain at emergency department (OR 2.58, 95% CI 1.39-4.78), two-week post-concussion symptoms (OR 4.89, 95% CI 3.19-7.49) and two-week posttraumatic stress (OR 2.98, 95% CI 1.88-4.73) as statistically significant predictors, with adequate discrimination (AUC after bootstrap validation: 0.75)

Interpretation: Existing prognostic models for persistent post-concussion symptoms perform poorly. A new model including female sex, complaints at emergency department and symptoms after two weeks performed reasonably and warrants further external validation. Prediction research in mild traumatic brain injury should be improved by standardizing definitions and data collection.

Introduction

Mild Traumatic Brain Injury (mTBI) is a common condition in the general population[1] and is associated with substantial burden to patients and relatives and high societal costs.[2] A considerable proportion of patients with mTBI report post-concussion symptoms (PCS), including cognitive (e.g. memory problems, cognitive deficits), somatic (e.g. headache, nausea) and emotional symptoms (e.g. depression, irritability) days to weeks following injury.[2,3] Although it is generally assumed that these symptoms resolve within weeks to months,[2-4] recent prospective studies indicate persistence of post-concussion symptoms (PPCS) in a large subset of patients six months to one year post-injury.[5,6] PPCS is associated with work absenteeism[7,8] and a reduction in health-related quality of life.[7,9] Hence, a current priority in mTBI research is the understanding of the etiology of PPCS.

Despite an abundant number of studies aiming to identify risk factors for PPCS, no study to date has successfully developed a prediction model to identify risk-prone patients.[10-12] Such a model could be used to flag patients at risk for prolonged sequelae who might benefit from additional monitoring or early treatment interventions such as cognitive behavioral therapy.[13] One of the challenges for prognostic modeling in mTBI is the lack of standardized outcome measurement. The Rivermead Post Concussion Questionnaire (RPQ) is often used to assess PPCS but there is a lack of consensus on how this scale should be analyzed and interpreted. Previous studies used the RPQ total scale,[14,15] RPQ subscales[16,17] or mapped the International Classification of Diseases (ICD)-10 diagnosis of Post-Concussion Syndrome[18] to the RPQ. This variation may substantially influence prevalence rates and the relevance of predictors across studies[18-20] and therefore hampers generalizability of prediction research.

Generalizability is further confined by methodological shortcomings of existing prognostic studies, including the use of cross-sectional study designs, small sample sizes in combination with the examination of a large number of candidate predictors, inappropriate handling of missing values, data-driven selection methods and lack of validation.[11] None of the models for PPCS have been externally validated in an independent patient sample,[11] which is necessary to determine model validity and to be able to recommend use in clinical practice.[21,22] Models for functional outcome after mTBI, using the Glasgow Outcome Scale-Extended, have been externally validated but performed poorly.[23]

The aims of this study were: (1) to externally validate existing prognostic models for six-month PPCS in an independent sample of patients with mTBI; and (2) to develop a new model ('The UPFRONT-PPCS model') based on relevant predictors from existing models and complaints at the emergency department (ED). Although prognostic research has focused extensively on pre-injury characteristics (e.g. pre-injury mental health)[10,12] and post-injury characteristics (e.g. two-week PCS and posttraumatic stress),[10,12] the role of acute complaints at the ED (e.g. headache, nausea,

vomiting or neck pain) is less often studied. These complaints have the potential to be relevant predictors,[24,25] and could be easily applied to a prognostic model as they are gathered during standard clinical assessment on ED examination.

Methods

This study was conducted and reported according to the criteria of the 'Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis' (TRIPOD) statement.[26]

Patient population

Data were obtained from a prospective cohort study conducted in three level I trauma centers in the Netherlands (the UPFRONT study).[27] Patients admitted to the EDs of these centers between 2013 and 2015 were included if they were sixteen years or older, had an admission Glasgow Coma Scale (GCS) score of 13-15 and had sufficient comprehension of the Dutch language. Exclusion criteria included drug or alcohol addiction, homelessness, dementia and whiplash injury without loss of consciousness (LOC). The UPFRONT study was approved by the local medical ethics committee of the University Medical Center Groningen, which acted as a central committee for the three participating centers. All patients provided written informed consent.

Measurements

Demographics, pre-injury characteristics and complaints at the ED

Demographics and clinical variables and the presence of a prior TBI were extracted from hospital records. Education was divided into low (less than 11 years of formal education), middle (11-14 years of formal education) and high (more than 14 years of formal education) and LOC and PTA were noted as present or absent. The following symptoms were examined during ED admission: headache, nausea/vomiting and neck pain. Information on pre-injury characteristics was examined with a short questionnaire completed by patients.

Post-concussion symptoms

Post-concussion symptoms (PCS) at two weeks and six months post-injury were assessed with the Head Injury Symptom Checklist (HISC).[28] The HISC consists of 21 frequently reported symptoms and patients were asked to complete each item, for both the pre-injury and current level, on a 3-point scale (never, sometimes, often). The HISC can be directly mapped to the ICD-10 criteria for post-concussion syndrome, since all eight symptoms are examined. Patients were subsequently classified as having PCS (persisting for two weeks) and PPCS (persisting for six months) if they indicated that at least three of the following symptoms were worse than before the injury (difference score of 1 or 2): (1) headache; (2) dizziness; (3); fatigue; (4) irritability; (5) difficulties falling asleep or staying asleep; (6) concentration problems; (7) memory difficulties; or (8) intolerance of alcohol or being anxious.

Posttraumatic stress symptoms

Posttraumatic stress symptoms at two weeks were examined with the Impact of Event Scale (IES);[29] a 15-item questionnaire in which patients have to rate whether they experience intrusive and avoidant posttraumatic stress symptoms on a 5-point Likert scale, resulting in a minimum score of 0 and a maximum score of 75. Scores above 26 were classified as severe, in line with recommendations.[30]

Selection of prognostic models

Existing prognostic models were identified by screening reference lists of systematic reviews on prognosis following mTBI[10,12] and by updating the search strategy of Silverberg et al.[10] until March 2017. Models were considered for our external validation study if they were developed in prospectively collected data on adult (age ≥ 16 years) patients with mTBI (Table 1). To be included, studies had to fulfill at least one out of three quality criteria:[21] 1) A large sample size (N > 500 patients); 2) > 10 cases (patients with PCS) for each candidate predictor consider; or 3) the use of shrinkage or internal validation.

Two models met our eligibility and quality criteria (Online Supplement A).[19,31] Stulemeijer et al.[31] had developed a prediction model based on data from a level I trauma center in the Netherlands (2004-2006) to predict six-month PPCS using the RPQ. They investigated 201 patients among whom 49 developed PPCS. Among the 19 candidate predictors, three (pre-injury physical comorbidities, early PCS, early posttraumatic stress) were included in their final model. The final model had an Area Under the Curve (AUC) of 0.82, which decreased to 0.73 after bootstrap validation.

Cnossen et al.[19] had developed a prediction model based on 277 patients from three level I trauma centers in the United States (2010-2012) applying the RPQ. The RPQ was used as a linear scale and 14 candidate predictors available at the ED were considered. After least absolute shrinkage and selection operator (lasso) procedure and bootstrap validation, the final model with 8 predictors (age, sex, years of education, pre-injury migraine or headache, pre-injury psychiatric disorders, prior TBI, PTA and LOC) explained 14% of the variation in outcome. The final set of predictors was examined in a logistic model with the RPQ dichotomized according to the ICD-10 criteria, resulting in an AUC of 0.74. A list of included and excluded studies as well as detailed characteristics of the included prediction models are presented in the Online Supplements B and C.

Table 1. **Eligibility criteria for the external validation of existing prediction models in the curent study**

- Data:
  - Prospectively collected
- Patients:
  - Patients with mild TBI (GCS 13-15)
  - Adult patients (age ≥ 16 years)
- Outcome:
  - Examined at ≥ 6 months post-injury
  - Outcome measurement: HISC or another self-reported measurement in which the prevalence of post-concussion symptoms was broadly dichotomized into 'PCS according to the ICD-10 criteria' and 'no PCS according to the ICD-10 criteria'
- Predictors:
  - ≥ 80% of the predictors in the model should be measured in the current study
- Quality Requirements model:
  - Multivariable model of at least two predictors
  - At least one out of three quality criteria reported by Mushkuadini et al.21
    1. Large sample size (N > 500)
    2. > 10 cases (patients with PCS) for each candidate predictor considered
    3. The use of shrinkage and/or internal validation

Abbreviations: GCS = Glasgow Coma Scale; HISC = head injury severity scale; ICD = international classification of diseases; PCS = post-concussion symptoms; TBI = traumatic brain injury

Statistical analyses

Patient characteristics were reported by medians and interquartile ranges (IQR) for continuous variables and frequencies and percentages for categorical variables. To assess the possible influence of loss to follow-up, we compared characteristics of patients who completed the six-month outcome assessment and patients who were lost to follow-up using Chi-Square and Mann-Whitney *U* tests, since all continuous variables had a skewed distribution. Missing data on candidate predictors were subsequently imputed using multiple imputation.

The external validity of two existing models was assessed in terms of calibration and discrimination. Calibration refers to the agreement between observed and predicted outcomes. Calibration was graphically assessed and expressed as calibration-in-the-large, indicating whether predictions are systematically too low (calibration-in-the-large > 0) or too high (calibration-in-the-large < 0) and calibration slope (indicating the average strength of predictor effects and ideally equal to 1). Discrimination refers to the ability of a model to distinguish between patients who will develop PPCS and patients who will not develop PPCS and was expressed as the AUC. An AUC of 1 implies perfect discrimination and an AUC of 0.5 indicates that the model is no better than random chance. All variables from the Stulemeijer et al.[31] and Cnossen et al.[19] models were available in the UPFRONT data. However, education was measured as a continuous variable in study by Cnossen et al.[19] but as a categorical variable in the UPFRONT dataset. Therefore, for the external

validation we used the mean years of education for each category (low education: 8 years, middle education: 12 years, higher education: 15 years).

To examine the role of complaints at the ED (headache, nausea or vomiting, neck pain) we developed a new model with all predictors from the Stulemeijer et al.[31] and Cnossen et al.[19] models in a backwards selection procedure ($p < .157$).[32] We subsequently assessed whether the addition of complaints at the ED significantly improved this model by comparing goodness-of-fit of a model with and without complaints at the ED. To correct for optimism of the new model, we used bootstrap validation with 100 samples, where all modeling steps were repeated. Analyses were performed using SPSS statistics version 21.0 and R (version 3.2.2) using the *rms, foreign, pROC and mice* packages.

Results

Patient population

A total of 1,151 patients were included in the UPFRONT study, of whom 591 (51%) completed the six-month outcome assessment. Included patients had a median age of 51 years (Interquartile range 32 to 64) and 41% (n = 241) were female. Sixteen per cent (n = 94) had intracranial traumatic abnormalities on the initial head computed tomography (CT) scan. Patients included in the study were significantly older ($p < 0.01$), more often female ($p = 0.03$) and showed more CT abnormalities ($p = 0.01$) than patients lost to follow-up. In addition, patients included in the study less often reported pre-injury psychiatric disorders ($p = 0.04$) and more often reported pre-injury physical disorders ($p = 0 .04$, Table 2).

Persisting post-concussion symptoms

At six months post-injury, 370 patients (63%) reported at least one out of eight symptoms. A total of 241 patients (41%) reported three or more symptoms, indicating PPCS according to our criteria. Fatigue (38%), concentration problems (36%) and memory problems (35%) were most frequently reported (Figure 1).

External validation of existing models

Both existing models performed poorly; with an AUC of 0.64 (95% CI 0.60-0.68) for the Stulemeijer et al. model[31] and an AUC of 0.57 (95% CI 0.52-0.62) for the Cnossen et al. model[19] (Figure 2). Both models systematically underestimated the proportion of patients with PPCS (calibration-in-the-large > 0) and average effects of the set of predictors were too low (calibration slopes < 1).

Table 2. **Characteristics of 591 subjects included in the study and 560 subjects lost to follow-up**

	Included subjects (n = 591)		Subjects lost to follow-up (n = 560)		
Variable	**Missing**	**N (%)**	**Missing**	**N (%)**	***p*-value**
Demographic and preinjury characteristics					
Age (median, IQR range)	-	51 (32-64)	-	34 (22-53)	< .01
Sex (Female)	-	241 (41%)		194 (35%)	.03
Education†	31		249		.07
– Low		105 (19%)		66 (21%)	
– Middle		210 (37%)		134 (43%)	
– High		245 (44%)		111 (36%)	
Preinjury psychiatric disorders£	30	58 (10%)	238	58 (18%)	< .01
Preinjury physical disorders‡	-	185 (31%)	-	145 (26%)	.04
Preinjury headache or migraine	57	156 (29%)	279	87 (31%)	.60
Prior TBI	131	15 (3%)	113	27 (6%)	.05
ED characteristics					
CT abnormalities£	13	94 (16%)	8	61 (11%)	.01
LOC	3	494 (84%)	3	483 (87%)	.20
PTA	37	490 (88%)	41	440 (85%)	.08
Headache	87	263 (52%)	63	259 (52%)	.98
Nausea or vomiting	92	173 (35%)	78	174 (36%)	.64
Neck pain	120	71 (15%)	97	91 (20%)	.07
Early postinjury symptoms					
2-week PCS¥	160	240 (56%)	348	108 (51%)	.26
2-week posttraumatic stress£	117	114 (22%)	287	69 (25%)	.20

†Low education = less than 11 year of formal education; middle education = 11-14 years of formal education; high education = 15 or more years of formal education

£Includes any psychiatric disorder necessitating treatment by a psychologist or psychiatrists or use of psychotropic medication, or both

‡Includes cerebrovascular accident, heart diseases, hypertension, diabetes, asthma or other respiratory diseases, epilepsy or any malignant disorder

£Any lesions, compressed cisterns or midline shifts

¥Meeting the ICD-10 criteria for post-concussion symptoms, 2 weeks postinjury.

£Score on the Impact of Events Scale above 26, 2 weeks postinjury

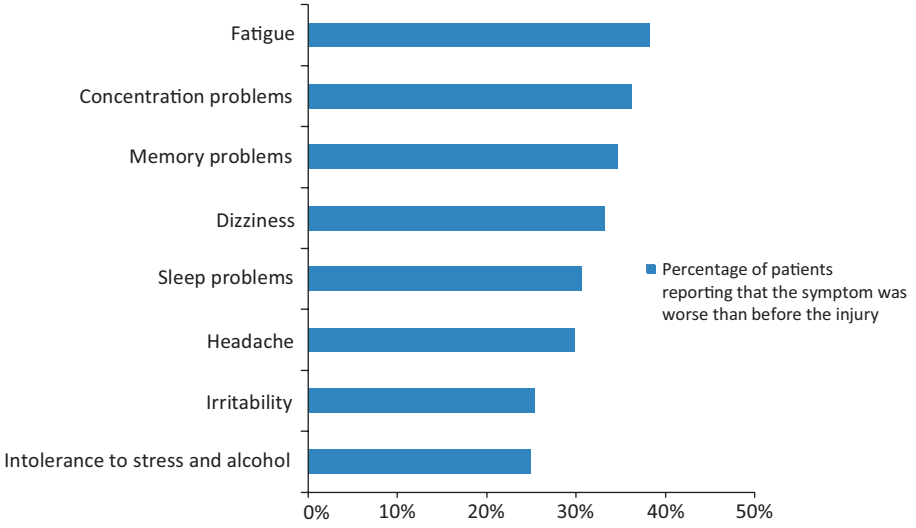
Abbreviations: ED = emergency department; CT = computed tomography; IQR = interquartile range; LOC = loss of consciousness; PCS = post-concussion symptoms; PTA = posttraumatic amnesia; TBI = traumatic brain injury

Development of the UPFRONT-PPCS model

Backward selection (p < 0.157) with all variables from the Stulemeijer et al. and Cnossen et al. models[19,31] resulted in the inclusion of three variables: female sex (OR 1.48, 95% CI 1.01-2.18), two-week PCS (OR 4.89, 95%CI 3.19-7.49) and two-week posttraumatic stress (OR 2.98, 95% CI 1.88-4.73; Table 3). PCS after two weeks was the strongest predictor: among the 241 patients with six-month PPCS, 192 (80%) already reported three or more symptoms after two weeks and almost all patients (n = 233, 97%) reported at least one symptom after two weeks.

However, among the patients reporting three or more symptoms after two weeks (n = 333), only half (n = 192) still reported three or more symptoms after six months. In the other half, early PCS resolved over time.

Figure 1. **Frequency of post-concussion symptoms six months post-injury**



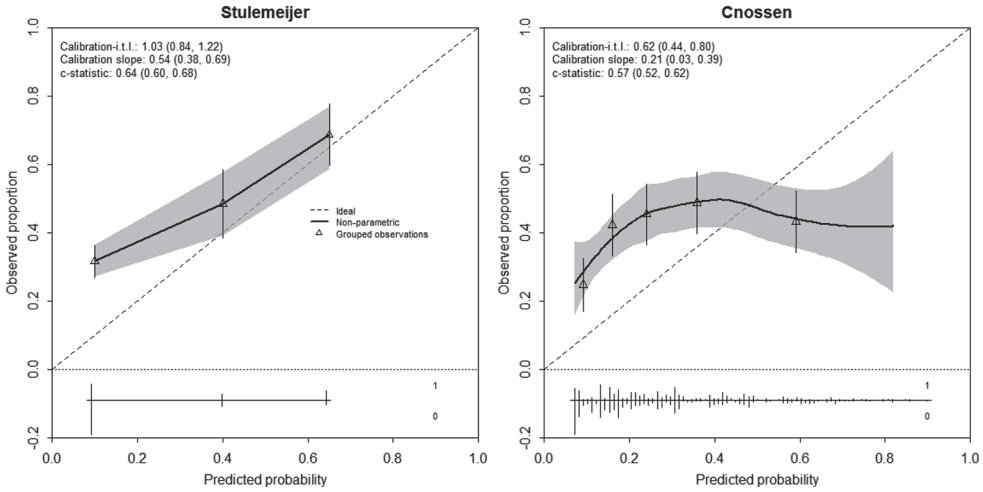
The addition of complaints at the ED (headache, nausea or vomiting and neck pain) significantly improved the model ($p < 0.01$). Of these complaints, only neck pain was statistically significantly associated with six-month PPCS (OR 2.58, 95% CI 1.39-4.78). The AUC of the final prediction model was 0.77 and decreased to 0.75 after bootstrap validation (Table 3). An overview of all uni- and multivariable associations of predictors is shown in Table 4.

Table 3. **Prediction model for six-month PPCS based on existing models and the role of ED symptoms**

Variable	OR (95% CI)
Female sex	1.48 (1.01-2.18)
Nausea or vomiting	0.88 (0.54-1.43)
Headache	0.94 (0.61-1.47)
Neck Pain	2.58 (1.39-4.78)
2-week PCS	4.89 (3.19-7.49)
2-week posttraumatic stress	2.98 (1.88-4.73)
AUC	**0.77**
AUC after bootstrap validation	**0.75**

Intercept: B = -2.241
Abbreviations: AUC = area under the curve; PCS = post-concussion symptoms

Figure 2. **Calibration plots for external validation Stulemeijer et al. and Cnossen et al. models**



X-axis shows predicted probabilities by the model in quantiles of patients and Y-axis shows observed proportion. The dotted diagonal lines represent perfect predictions. The triangles indicate the observed outcome frequency in quantiles of predicted probabilities, with 95% confidence interval. Calibration -i.t.l= Calibration-in-the-large.

Table 4. **Univariable and Multivariable Associations of all predictors in this study and 6-month PPCS**

Variable	Univariable association OR (95% CI)	Multivariable association OR (95% CI)
Age†	0.99 (0.99-1.00)	0.99 (0.98-1.01)
Female gender†	2.40 (1.60-3.14)	1.56 (1.05-2.32)
Education†		
– Low vs medium / high	1.10 (0.69-1.73)	0.87 (0.54-1.72)
– Medium vs low/high	1.26 (0.87-1.83)	1.39 (0.91-2.13)
Preinjury physical comorbidities†‡	1.05 (0.74-1.50)	1.20 (0.73-1.95)
Preinjury migraine or headache†	1.06 (0.74-1.51)	0.96 (0.63-1.47)
Preinjury psychiatric disorders†	1.63 (0.92-2.86)	1.18 (0.64-2.18)
Prior TBI†	1.22 (0.46-3.27)	1.25 (0.34-4.62)
PTA†	1.41 (0.82-2.40)	1.06 (0.55-2.03)
LOC†	0.92 (0.59-1.44)	0.89 (0.53-1.50)
2-week PCS‡	5.82 (3.94-8.60)	5.18 (3.39-7.91)
2-week posttraumatic stress‡	3.22 (2.12-4.50)	3.15 (1.93-5.16)
ED symptoms		
Headache	1.46 (1.03-2.07)	1.15 (0.73-1.75)
Nausea or vomiting	1.31 (0.85-2.01)	1.13 (0.73-1.76)
Neck pain	3.66 (2.23-6.01)	3.44 (2.05-5.78)

In the multivariable model, all variables are included. Therefore, the effect estimates might diverge slightly from the effect estimates in Table 3

‡Variable derived from Stulemeijer et al. model

†Variable derived from Cnossen et al. model

Discussion

Two existing prognostic models for persistent post-concussion symptoms (PPCS) performed poorly in the UPFRONT data. A new model including female sex, complaints at the ED and two-week PCS and posttraumatic stress as predictors for six-month PPCS, performed reasonably.

This is the first study that externally validated prognostic models specifically for PPCS following mTBI. Strengths of our study include the comprehensive search strategy for existing models and the large sample size, which is a requirement for external validation of logistic regression models.[33,34] In addition, our final prediction model was developed according to methodological recommendations for prediction modeling.[11,21,22,35] Limitations include the high percentage of patients lost to follow-up. Although follow-up rates were similar to other prospective studies in patients with mTBI,[6,36] selection bias cannot be excluded, which could have influenced the significance of predictors.[19] For example, our sample has a relatively large proportion of females and patients with intracranial CT abnormalities. In addition, our outcome measurement (HISC) differed from the outcome measurement used in both development studies (RPQ). The HISC includes eight symptoms from the ICD-10 criteria for post-concussion syndrome, whereas the RPQ includes only seven out of eight symptoms. In addition, using the HISC, patients rated symptoms for both their current and pre-injury situation and symptoms were only included if there was evidence of deterioration. In comparison, using the RPQ, patients had to provide one rating in which they were asked to compare current symptoms with symptoms before the injury. The difference in outcome measurement may have contributed to the poor model performance. For example, poor calibration-in-the-large of both models may have resulted from differences in outcome measurement and subsequent differences in prevalence rates of PPCS among studies.

Another potential source for unsatisfactory model performance in external validation is poor modeling methodology in the development studies.[22,37] In the model by Stulemeijer et al.[31] the relatively small sample size, the consideration of a large number of candidate predictors and data-driven selection methods, may have resulted in statistical overfitting.[22,37] Statistical overfitting means that a model appears to predict outcome well in the development population, but performs poorly in new patients.[37] An example is the extreme, and potentially imprecise effect estimate for early posttraumatic stress (OR = 10.0) in the development data, which was based on only 16 patients scoring above the cut-off point.[31] This may have contributed to the low calibration slope found in external validation. In the Cnossen et al.[19] study, modeling methodology was in line with recommendations.[21,22,35] Differences in the operationalization and coding of predictors might however have contributed towards poor external validity.[37] For example, pre-injury mental health and prior TBI were no relevant predictors in the current study. In the study by Cnossen et al.[19] these variables were based on self-report without a threshold for severity. In the current study, however, the presence of a prior TBI required documentation from medical records and pre-injury mental problems necessitated that a patient received treatment.

This difference in assessment may have caused the large differences in baseline prevalence (pre-injury mental health problems: 32% vs. 10%; prior TBI: 54% vs. 3%) between the Cnossen et al. study[19] and the current study, influencing performance in external validation. Next to model-related and measurement-related factors, differences in patient characteristics might further have contributed towards the poor model performance of both models. The sample from the UPFRONT study diverges substantially from both development samples in terms of demographics, TBI severity and pre-injury characteristics, which might have affected the discriminative ability of the models.

Predictors from both models, as well as complaints at the ED, were used to develop a new model. This model had a reasonable discrimination and can therefore be potentially valuable for clinical practice. Yet, external validation in a new and independent set of patients with mTBI is necessary to demonstrate its validity and applicability. In our newly developed model, we found that female sex, early PCS and early posttraumatic stress were associated with six-month PPCS, which is congruent with a systematic review on prognosis following mTBI.[10] In addition, we found that neck pain was a predictor. Although the influence of neck pain on PPCS has not been studied in large-scale prospective studies before, our findings are in line with the emerging view that concomitant cervical soft tissue injury may contribute to prolonged sequelae following mTBI.[38]

Among the predictors in our final model, early PCS was the strongest predictor and showed high sensitivity; i.e. 80% of the patients with PPCS already reported three or more symptoms after 2 weeks. This was in line with a 2015 study stating that 82% of the patients experiencing PPCS one year after mTBI already reported symptoms one month post-injury.[18] Specificity was however much lower with approximately half of the patients reporting three or more symptoms after two weeks developing PPCS. The feasibility of early PCS as predictor for PPCS is nevertheless hampered by the practical constraint that patients with mTBI are rarely followed-up routinely.[39]

In line with previous work,[10,18] our study demonstrates the complexity in developing a prognostic model for PPCS that is both valid and applicable for clinical practice. Given the heterogeneity of mTBI,[2] the multifactorial and complex nature of PPCS[18,40] and the lack of unity for definitions and assessment of PPCS,[20] improvement in consensus on definitions and standardization of data collection might be necessary before advances in prediction modeling can be accomplished. A recent initiative to standardize data collection in TBI are the Common Data Elements (CDEs), which have specific recommendations for the measurement of socio-demographic, pre-injury and clinical variables,[41] and thereby have the potential to enhance the comparability of future prognostic studies. For outcome assessment, the CDEs recommend the RPQ to assess PPCS. However, no guidance is provided on how the RPQ should be analyzed, while this varies widely in clinical practice.[14-18] More detailed recommendations are therefore warranted.

Conclusion

Existing prognostic models for persistent post-concussion symptoms perform poorly in an independent set of patients with mTBI. A new model, including female sex, complaints at the emergency department and two-week post-concussion and posttraumatic symptoms, performs reasonably. External validation is however necessary before this model can be considered for clinical practice. In addition, improvement in definition of post-concussion symptoms and standardization of data collection may further aid to future advances in this area.

Supplemental material is available at www.marysecnossen.nl

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8

Comparing health-related quality of life of Dutch and Chinese patients with traumatic brain injury: Do cultural differences play a role?

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Abstract

Background: There is growing interest in health related quality of life (HRQoL) as an outcome measure in international trials. However, there might be differences in the conceptualization of HRQoL across different socio-cultural groups. The objectives of current study were: (I) to compare HRQoL, measured with the short form (SF)-36 of Dutch and Chinese traumatic brain injury (TBI) patients one year after injury and; (II) to assess whether differences in SF-36 profiles could be explained by cultural differences in HRQoL conceptualization. TBI patients are of particular interest because this is an important cause of diverse impairments and disabilities in functional, physical, emotional, cognitive, and social domains that may drastically reduce HRQoL

Methods: A prospective cohort study on adult TBI patients in the Netherlands (RUBICS) and a retrospective cohort study in China were used to compare HRQoL one year post-injury. Differences on subscales were assessed with the Mann-Whitney *U*-test. The internal consistency, interscale correlations, item-internal consistency and item-discriminate validity of Dutch and Chinese SF-36 profiles were examined. Confirmatory factor analysis was performed to assess whether Dutch and Chinese data fitted the SF-36 two factor-model (physical and mental construct).

Results: 447 Dutch and 173 Chinese TBI patients were included. Dutch patients obtained significantly higher scores on role limitations due to emotional problems ($p < .001$) and general health ($p < .001$), while Chinese patients obtained significantly higher scores on physical functioning ($p < .001$) and bodily pain ($p = .001$). Scores on these subscales were not explained by cultural differences in conceptualization, since item- and scale statistics were all sufficient. However, differences among Dutch and Chinese patients were found in the conceptualization of the domains vitality, mental health and social functioning.

Conclusions: One year after TBI, Dutch and Chinese patients reported a different pattern of HRQoL. Further, there might be cultural differences in the conceptualization of some of the SF-36 subscales, which has implications for outcome evaluation in multi-national trials.

Background

Health-related quality of life (HRQoL) reflects an individual's perception of how an illness and its treatment affect physical, mental and social aspects of his/her life.[1] Because it provides well-standardized information on recovery patterns, frequency, nature, and predictors of disabilities, HRQoL has been recognized as an important outcome in many medical fields, including injury.[2] Similarly, there is growing interest in international HRQoL assessment as a result of the increasing number of international trials.[3]

Traumatic brain injury (TBI) is a major public health concern with a rising incidence all over the globe. In Europe, the annual number of hospital admissions is estimated at 262 per 100,000 population.[4] In other parts of the world, data on TBI incidence is less often collected systematically. Nevertheless, a 2004 epidemiological study in Eastern China found that the incidence of TBI among 77 hospitals was substantial.[5] TBI is an important cause of impairments and disability in functional, physical, emotional, cognitive, and social domains that may drastically reduce HRQoL.[6,7] As a consequence, HRQoL has been emerged as an important outcome measurement following TBI.[8]

Previous literature has indicated that there might be differences in the experience and conceptualization of HRQoL across different socio-cultural groups.[9-14] For example, in Western countries body and mind are usually regarded as two different entities, whereas Asian cultures have a more holistic sense among body and mind.[15] Therefore, the strict dichotomization of physical versus mental health, which is often included in HRQoL assessment, might not be applicable to Asian cultures.[9,12] Also, previous evaluations of the short form (SF)-36 among Asians have shown that they conceptualize social role functioning differently from Western populations.[9,10,12,16,17] For example, Asians are more directed towards others and the use of "sickness" as an excuse for avoiding social and labour responsibilities is considered unacceptable in the Asian culture.[10,15] Furthermore, while Western populations associate energy level strongly with physical health, Asians associate energy more strongly with mental health.[10-13,18]

To our knowledge, there is no previous study that directly compared HRQoL between Western and Asian patients after injury. The purpose of this study was to compare HRQoL, measured with the SF-36, of Dutch and Chinese TBI patients one year after the injury. Secondly, we aimed to assess whether potential differences in SF-36 profiles between these patients could be explained by cultural differences in HRQoL conceptualization.

Methods

This study was conducted and reported according to the 'Strengthening the Reporting of Observational Based Studies' (STROBE) statement version 4.[19]

Participants

Data for the current study were obtained from two cohort studies performed in the Netherlands and China. The Radboud University Brain Injury Cohort Study (RUBICS) includes patients aged 16 years and older with mild, moderate and severe TBI presenting at the emergency department (ED) of a level I trauma center in Nijmegen, the Netherlands. Patient demographics, clinical characteristics as well as outcome measurements after twelve months follow-up were prospectively collected between June 2003 and June 2010. More information on data collection and included patients can be found in previous publications.[20-24] Data on Chinese patients were obtained from a retrospective study on injury patients admitted to one of three national injury surveillance hospitals in Zhuhai, Guangdong Province, China between January and December 2006. Patients were 15 years or older and were examined at twelve months post-injury. Data on age, gender and injury severity were collected from the hospital database. No other baseline and injury characteristics that might be relevant in the current study (e.g. education, Glasgow Coma Scale) were measured. More information about this study can be found in a previous publication.[25]

To warrant comparability of patient groups, the following inclusion criteria to determine eligibility for current study were used: age ≥ 16 years, admitted to the hospital with a clinical diagnosis of TBI, provision of informed consent and completion of at least all items of one SF-36 subscale after twelve months follow-up. Patients referred home after the ED visit and patients who died within the first year post-injury were excluded.

TBI definition and classification

In the Dutch dataset, all patients sustained a TBI. Consequently, all patients meeting the inclusion criteria for the current study were included in the analyses. The Chinese dataset was not restricted to patients with TBI, but contained patients with various injuries. The TBI patients were selected by including all patients with an International Classification of Diseases and Related Health Problems (ICD-10) code of S06, referring to traumatic intracranial injury.

Severity of TBI was determined by the Abbreviated Injury Scale – Head (AISH). The AISH is, together with the Glasgow Coma Scale (GCS), the most commonly used index of severity in TBI.[26] Severity of TBI is ranked on a scale from 1 to 6 in which 1 being mild, 2 being moderate and 6 being unsurvivable.[27] Patients were classified into mild/moderate and severe TBI according to their AISH score (1-2 versus > 2).

The Chinese dataset did not report data on AISH. However, ICD-10 codes can be translated into AISH scores by using the ICD/AIS MAP.[28,29] Consequently, those patients with ICD-10 codes of S06.0, S06.1, S06.2 and S06.9 were classified as having mild or moderate TBI and those with ICD-10 codes of S06.3, S06.4, S06.5, S06.6, S06.7 and S06.8 were classified as having severe TBI.

Measurement of HRQoL

The SF-36 was used to measure 12-month HRQoL. The SF-36 is the most frequently used generic instrument for HRQoL[30] and has adequate internal consistency and validity in TBI patients.[31,32] The questionnaire has been translated and tested in more than 50 languages,[30] including Dutch[33] and Cantonese.[30] The SF-36 has two versions (version 1 and version 2) that differ slightly in wording, lay-out and the fact that the role questions have a dichotomous answer category in version 1 and a 5-point scale in version 2.

The SF-36 yields a profile of the following eight concepts: physical functioning (PF), role limitations related to physical health problems (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social role functioning (SF), role limitations related to emotional health problems (RE) and mental health (MH). The raw scores for each concept were transformed into a 0-100 scale in which higher scores indicated better HRQoL.

In the Dutch dataset, the 12-month SF-36 version 1 was administered by a postal questionnaire that was sent to all patients. In the Chinese dataset, the 12-month SF-36 version 1 was administered by a telephone interview. Patients were interviewed by a hospital nurse who received specific interview training.[25]

Statistical analyses

Differences between patients included in the study and those lost to follow-up were calculated using the non-parametric Mann-Whitney *U* test for continuous data and Chi square test for categorical data. Similarly, Dutch and Chinese patients included in this study were compared using these statistical tests on age, gender and TBI severity.

Means, standard deviations, medians, interquartile ranges and the percentage of patients with the highest ("ceiling") and lowest ("floor") scores on the SF-36 subscales were calculated for Dutch and Chinese patients classified by TBI severity. Since the number of severe TBI patients in the Chinese dataset was small (n = 20), the analyses were continued with mild and moderate TBI only.

Differences in SF-36 subscales between the Dutch and Chinese patients were calculated with the Mann-Whitney *U* test, since all subscales had a skewed distribution. To allow for multiple testing, a stringent *p*-value of 0.0065 (0.05 divided by 8 subscales) was considered statistically significant. To assess whether differences between Dutch and Chinese patients could be explained by age differences between both populations, the sample was stratified into three equal age groups based on percentiles (33th and 66th) in the total population and the analyses were repeated accordingly. Since sample sizes of the age cohorts were small, statistically significance was assessed on both the stringent *p*-value ($p < .0065$) and the standard *p*-value ($p < .05$).

To examine whether there were differences in cultural conceptualization of HRQoL among Dutch and Chinese patients, the psychometric assumptions underlying the construction of the SF-36 were assessed for both Dutch and Chinese patients. Therefore, the reliability coefficient ("Cronbach's alpha") for each subscale was estimated. Adequate internal consistency was defined as a reliability coefficient ≥ 0.70.[34] Additionally, the reliability coefficient of each subscale should be larger than the subscale's interscale correlations with all other subscales.[35]

Item-internal consistency and item-discriminate validity of the 35 items in both datasets were subsequently assessed. One item ("health change") was excluded since this provides an indication of perceived change in health rather than the health status one year post-injury. The correlation between each item and its hypothesized subscale ("corrected item-to-scale correlation") should be at least 0.40 for adequate item-internal consistency.[35,36] Item-discriminate validity was considered adequate if the correlation between an item and its hypothesized scale was larger than the correlations between that item and all other subscales.[35]

To examine whether Dutch and Chinese SF-36 subscales reflected the same underlying dimensions, i.e. a physical and mental dimension,[30,37] confirmatory factor analysis (CFA) with two latent constructs was performed. Based on theory and research in Western populations, it was hypothesized that the PF, RP and BP subscales were associated with the physical construct, whereas the MH, RE and SF subscales were associated with the mental construct.[30,37] For VT and GH it was expected that they load equally on both components.[30,37] To achieve model identification, for every latent variable, one factor loading was fixed to one (PH for physical construct; MH for mental construct; Online Supplement A). Maximum likelihood methods were used to estimate the associations between subscales and latent factors. The Tucker-Lewis Index (TLI; recommended > 0.95), Comparative Fit Index (CFI; recommended > 0.95) and the Root mean Square Error of Approximation (RMSE; recommended < 0.08) were used to examine model fit, as recommended by previous research.[38] The CFA analyses were performed using the Analysis of Moment Structures (AMOS) version 4 statistical software package. All other analyses were performed using Statistical Package for the Social Sciences (SPSS) version 21.

Results

Study population

The Dutch dataset consists of 2286 TBI patients. Of these patients, 223 were excluded because they were younger than 16 years and 804 patients were subsequently excluded because they did not receive the follow-up questionnaires because of various reasons (e.g. dementia, unknown address). 360 patients were further excluded because they were not admitted to the hospital after the ED visit. This results in 899 eligible patients of whom 447 completed all items of at least one of the SF-36 subscales after 12-month follow-up. Patients with a missing 12-month SF-36 did not differ from those included in this study on age and gender. Those lost to follow-up were

however less often diagnosed with severe TBI ($p < .01$). Of the included patients, 64% was male and the median age was 46 years (interquartile range 27-58). Half of the patients had an AISH of 1-2, indicating mild and moderate TBI.

The Chinese dataset comprises information on 3664 injury patients of whom 695 patients were diagnosed with TBI according to their ICD-10 codes. Forty-five patients were removed since they were younger than 16 years of age. Of the 650 eligible patients, 173 (27%) completed the 12-month follow-up assessment. The main reason for non-inclusion in the study was that the telephone number was not available in the hospital database.[25] Respondents were significantly older (median age respondents = 36; median age non-respondents = 32, $p = .01$) and less often diagnosed with severe TBI (respondents: 12% severe TBI, non-respondents: 18% severe TBI, $p = 0.04$). Median age of the included patients (n = 173) was 35 years (interquartile range 24-50) and 67% of the study population was male. The large majority (88%) had an AISH of 1 or 2 (mild or moderate TBI).

Dutch and Chinese patients did not differ in terms of gender. Dutch patients were however significantly older than Chinese patients ($p < .001$) and were significantly more often diagnosed with severe TBI ($p < .001$). Comparison of other demographic and clinical characteristics between patient groups was not possible since these were not measured in the Chinese data.

SF-36 scores of Dutch and Chinese patients

Scores on SF-36 subscales for Dutch and Chinese patients, stratified by TBI severity, are presented in Table 1. Generally, severe TBI patients seemed to report more problems with HRQoL than mild and moderate TBI patients. Ceiling effects were prominent for both Dutch and Chinese patients; more than half of the patients obtained a maximum score for role limitations due to physical problems. In the Dutch dataset, the strong ceiling effect was also shown for role limitations due to emotional problems, while in the Chinese dataset more than half of the patients obtained a maximum score for physical functioning. Since the Chinese dataset included 20 patients with severe TBI, all subsequent analyses were performed for only those patients with mild and moderate TBI.

When using the stringent *p*-value ($p < .0065$), Chinese patients obtained significantly higher scores on the subscales PF ($p < .001$) and BP ($p = .001$), while Dutch patients obtained higher scores on RE ($p < .001$) and GH ($p < .001$; see Figure 1 and Online Supplement B). Chinese patients also obtained higher scores on SF ($p = .026$), but this was not statistically significant using the stringent *p*-value.

Age differences between Dutch and Chinese patients did not explain the differences in the PF and RE scale scores, since differences remained statistically significant in the different age cohorts ($p < .0065$ in two age cohorts; $p < .05$ in one age cohort, see Online Supplement B).

***Table 1*. Short Form (SF)-36 scores of Dutch and Chinese traumatic brain injury patients 12 months post-injury**

Nijmegen, the Netherlands												
	Abbreviated Injury Score Head 1-2						**Abbreviated Injury Score Head > 2**					
	N	**Range**	**Mean (SD)**	**Median (IQR)**	**Floor (%)***	**Ceiling* (%)**	**N**	**Range**	**Mean (SD)**	**Median (IQR)**	**Floor (%)***	**Ceiling (%)***
PF	200	0-100	81.2 (24.6)	95 (70-100)	0.5%	38.0%	207	0-100	77.5 (28.5)	90 (70-100)	4.8%	30.0%
RP	211	0-100	68.1 (40.7)	100 (25-100)	19.9%	55.5%	214	0-100	56.7 (43.9)	75 (0-100)	29.9%	44.4%
BP	217	0-100	73.9 (26.2)	80 (52-100)	0.9%	38.2%	216	0-100	75.9 (25.2)	82 (62-100)	1.4%	40.7%
GH	213	0-100	68.5 (22.8)	72 (52-87)	0.5%	3.8%	216	10-100	70.2 (20.0)	72 (60-87)	0%	4.2%
VT	215	5-100	65.0 (21.3)	65 (50-80)	0%	5.6%	218	5-100	64.6 (20.3)	65 (50-80)	0%	4.6%
SF	217	13-100	81.5 (22.2)	88 (63-100)	0%	44.2%	220	13-100	78.3 (22.5)	88 (63-100)	0%	37.3%
RE	214	0-100	81.5 (34.2)	100 (67-100)	11.7%	72.9%	217	0-100	75.6 (38.1)	100 (67-100)	16.1%	65.9%
MH	216	0-100	74.5 (20.2)	80 (64-88)	0.5%	6.9%	218	20-100	73.8 (20.1)	80 (63-88)	0%	6.0%
Zhuhai, China												
	Abbreviated Injury Score Head 1-2						**Abbreviated Injury Score Head > 2**					
	N	**Range**	**Mean (SD)**	**Median (IQR)**	**Floor (%)***	**Ceiling (%)***	**N**	**Range**	**Mean (SD)**	**Median (IQR)**	**Floor (%)***	**Ceiling (%)***
PF	153	5-100	93.0 (16.8)	100 (95-100)	0%	64.7%	20	0-100	82.3 (26.2)	95 (75-100)	5.0%	45%
RP	153	0-100	68.8 (40.6)	100 (25-100)	19.6%	56.2%	20	0-100	60.0 (44.7)	88 (6-100)	25.0%	50%
BP	153	0-100	81.7 (26.4)	100 (67-100)	1.3%	56.9%	20	10-100	70.8 (27.8)	79 (52-97)	0%	25%
GH	153	5-100	58.0 (23.9)	60 (40-75)	0%	2.6%	20	15-85	51.5 (19.5)	53 (40-65)	0%	0%
VT	153	0-100	66.6 (23.8)	70 (50-85)	1.3%	7.8%	20	15-100	67.5 (24.8)	78 (46-85)	0%	10%
SF	153	11-100	85.0 (21.7)	89 (78-100)	0%	49.7%	20	33-100	80.6 (23.9)	89 (58-100)	0%	45%
RE	153	0-100	55.3 (41.0)	67 (0-100)	26.8%	37.3%	20	0-100	60.0 (44.1)	67 (0-100)	30.0%	45%
MH	153	4-100	75.6 (20.4)	80 (64-90)	0%	11.8%	20	48-100	81.0 (14.0)	82 (72-92)	0%	10%

Scale scores range from 0-100, with 100 representing optimal functioning.

*Floor (%) refers to the percentage of patients with the lowest score on a subscale (score 0); Ceiling (%) refers to the percentage of patients with the highest score on a subscale (score 100)

Abbreviations: SD = standard deviation; IQR = interquartile range; PF = physical functioning; RP = role physical; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role-emotional; MH = mental health

Table 2. **Reliability coefficients (in diagonals) and Pearson's correlation coefficients between Short Form (SF)-36 subscales in patients with mild and moderate traumatic brain injury**

Nijmegen, the Netherlands								
	PF	**RP**	**BP**	**GH**	**VT**	**SF**	**RE**	**MH**
PF	(.94)							
RP	.73**	(.90)						
BP	.64**	.71**	(.88)					
GH	.54**	.68**	.56**	(.83)				
VT	.41**	.60**	.50**	.66**	(.75)			
SF	.54**	.67**	.54**	.63**	.73**	(.83)		
RE	.38**	.59**	.37**	.47**	.55**	.66**	(.86)	
MH	.31**	.50**	.35**	.61**	.78**	.72**	.61**	(.89)
Zhuhai, China								
	PF	**RP**	**BP**	**GH**	**VT**	**SF**	**RE**	**MH**
PF	(.93)							
RP	.53**	(.90)						
BP	.47**	.68**	(.90)					
GH	.44**	.69**	.61**	(.76)				
VT	.30**	.50**	.43**	.51**	(.66)			
SF	.53**	.64**	.61**	.59**	.50**	(.49)		
RE	.26**	.56**	.41**	.49**	.47**	.45**	(.78)	
MH	.28**	.47**	.40**	.47**	.63**	.51**	.47**	(.70)

Table shows reliability coefficients and Pearson's correlation coefficients between SF-36 subscales in patients with mild and moderate traumatic brain injury 12 months post-injury

Abbreviations: PF = physical functioning; RP = role physical; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role-emotional; MH = mental health

For BP, however, the statistically significant differences between Dutch and Chinese patients did not withstand after stratification for age (no significant differences between Dutch and Chinese patients in 2 out of 3 age strata, see Online Supplement B). With regard to GH, Dutch patients obtained significantly higher scores in two out of three age cohorts ($p < .0065$). In the youngest age cohort, however, no statistically significant differences were found between Dutch and Chinese patients.

Cultural conceptualization of HRQoL

In the Dutch dataset, all SF-36 subscales had an adequate internal consistency and none of the intercorrelations between subscales were larger than the values of Cronbach's alpha (see Table 2). Item-internal consistency and item-discriminate validity were also adequate for all items. One of the items of the vitality scale (VT1), nevertheless, correlated higher with the MH scale ($r = 0.55$) than with the VT scale itself ($r = 0.49$; see Online Supplement C).

In the Chinese dataset, internal consistency was insufficient for two subscales (VT and SF). Also, the intercorrelations between SF and six other subscales were larger than the value of Cronbach's alpha for the SF scale. Item-internal consistency and item-discriminate validity were adequate for the large majority of items. However, four items (VT2, SF1, SF2 and MH3) obtained a corrected item-to-scale correlation below 0.40. Furthermore, some items from the GH, VT, SF and MH subscales correlated higher with other subscales than with their own hypothesized subscales (see Online Supplement C).

Figure 1. **Short Form (SF)-36 score profiles of Dutch and Chinese patients**

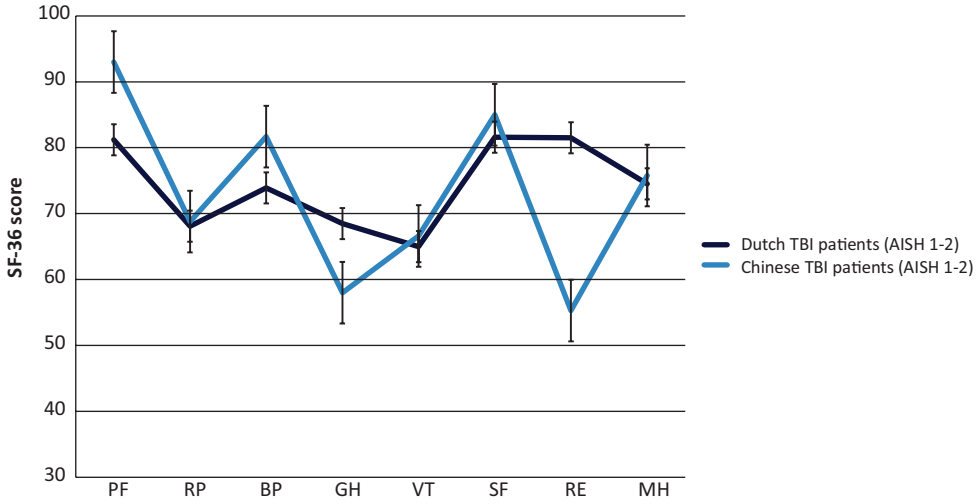

Figure shows SF-36 score profiles of Dutch and Chinese patients with mild and moderate traumatic brain injury 12 months post-injury. Scale scores range from 0-100, with 100 representing optimal functioning.
Abbreviations: PF = physical functioning; RP = role physical; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role-emotional; MH = mental health; AISH = Abbreviated Injury Scale Head

CFA with a two-factor model in the Dutch population resulted in a TLI of 0.88, a CFI of 0.95 and an RMSEA of 0.13, indicating a mixed pattern of model fit. The associations between the SF-36 subscales and the two latent constructs was as hypothesized for seven subscales. The VT subscale, however, was strongly associated with the mental component ($\beta = 1.08$, $p < .01$) but not with the physical component ($\beta = 0.01$, $p = 0.94$). The association between the physical and mental health construct was strong in the Dutch data ($r = 0.70$).

CFA with a two-factor model in the Chinese population had an adequate model fit (TLI: 0.95, CFI: 0.97 and RMSE: 0.08). However, the VT scale was negatively associated with the physical construct ($\beta = -2.31$, $p = .18$) and the association between the mental construct and VT ($\beta = 2.87$) was larger than its correlation with MH ($\beta = 1.00$). In addition, the association between GH and the physical construct ($\beta = 1.25$, $p = .01$) was larger than the association between GH and the

mental construct (β = 0.49, p = .14). The correlation between the physical and mental health construct was very strong (*r* = 0.92) in the Chinese data.

Table 3. **Confirmatory Factor Analysis of the Short Form (SF)-36 subscales**

		Nijmegen, the Netherlands			Zhuhai, China		
Observed variable	**Latent construct**	**β**	**B**	***p*-value**	**β**	**B**	***p*-value**
PF	Physical	1.00†	0.78	NA	1.00†	0.60	NA
RP	Physical	2.02	0.94	< .01	3.58	0.88	< .01
BP	Physical	1.04	0.76	< .01	2.04	0.77	< .01
GH	Physical	0.48	0.45	< .01	1.25	0.52	.01
VT	Physical	0.01	0.01	.94	-2.31	-0.97	.18
GH	Mental	0.59	0.45	< .01	0.49	0.28	.14
VT	Mental	1.06	0.86	< .01	2.87	1.65	.03
SF	Mental	1.13	0.88	< .01	1.19	0.75	< .01
RE	Mental	1.39	0.70	< .01	1.89	0.63	< .01
MH	Mental	1.00†	0.86	NA	1.00†	0.67	NA

Table represents unstandardized (β) and standardized (B) regression weights between subscales and the physical and mental component for both the Dutch and the Chinese mild and moderate traumatic brain injury patients 12 months post-injury. *Statistically significant (p < .05) association

†Regression weight was set to 1.00

Abbreviations: PF = physical functioning; RP = role physical; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role-emotional; MH = mental health

Discussion

Dutch and Chinese patients with mild and moderate TBI showed a different HRQoL pattern one year post-injury. Dutch patients reported less role limitations due to emotional problems and a better general health, whereas Chinese patients reported better physical functioning and less bodily pain. Differences in these subscales cannot be explained by variation in cultural conceptualization. However, there were differences in the conceptualization of some of the other subscales (vitality, mental health and social functioning).

Differences in SF-36 profiles among Dutch and Chinese patients were also recently found in cardiac patients.[39,40] There are various hypotheses that may explain these differences. Firstly, Dutch and Chinese patients might value similar symptoms and limitations differently. In China, health is usually described as a balance between “yin and yang” and the appreciation of one’s health is largely influenced by spirituality.[15] In the Dutch culture, on the opposite, HRQoL might be more related to the number and severity of symptoms. In addition, because cultural values emphasize harmony in Asian cultures, Asians might be more optimistic when experiencing similar symptoms and less likely to report negative and extreme feelings.[41] Related, coping strategies of Dutch and Chinese patients might vary, since these are largely influenced by cultural systems.[9]

Another hypothesis might be that the differences between Dutch and Chinese patients, especially in the physical health dimension, reflect the variation in acute and rehabilitation treatment between countries. In China, a part of the TBI related care is not reimbursed[42] and therefore, it is possible that some of the Chinese patients included in this study did not receive adequate acute or rehabilitative care, influencing their HRQoL one year post-injury. Lastly, the differences between Dutch and Chinese patients might also be explained by a lack of comparability of the included patients (e.g. there might have been baseline differences between patients) and study designs (prospective study with postal questionnaire versus retrospective study with telephone interview).

Our finding that social functioning is conceptualized differently among Dutch and Chinese mild and moderate TBI patients is consistent with previous research about psychometrics of the SF-36 in Asian cultures.[9,10,14,16-18] It has been suggested that the concept of social functioning is more Westernized and less clear for Asian people.[14] The strong association between vitality and mental health in our Chinese sample was also consistent with previous literature of the general population.[11,13,14,18] In traditional Chinese medicine a mental disorder is referred to as "the loss of a vital substance of spirit",[17] which could explain this strong association. Notwithstanding, we also found that vitality was strongly associated with mental health but not with physical health in the Dutch population, suggesting that this association could also be related to the TBI rather than to cultural conceptualization. The sequelae of mild and moderate TBI often includes mental health problems as well as fatigue or lack of energy,[43,44] whereas physical problems, such as headache, usually resolve within a few months.[45] Since this is the first study that performed CFA with the SF-36 in a TBI population, current findings should be confirmed by future studies with larger numbers of patients. The high correlation between mental and physical health in Chinese patients may indicate that these patients have a more holistic sense among body and mind.[15] As a consequence, one latent factor rather than two (physical and mental health) might have been more appropriate for the Chinese patients. This should also be confirmed in studies with larger sample sizes.

This is the first study that directly compared HRQoL between Asian and Western patients after injury. A strength of current study is that we did not only assess differences on the SF-36 subscales between Dutch and Chinese patients, but also examined whether these differences could be explained by cultural differences in the conceptualization of quality of life. In addition, we stratified our analyses for age and severity and included an adequate sample size.

Results should however be interpreted in the light of the following limitations. First, response rates were relatively low (50% for the Netherlands and 27% for China) for both datasets. Although low response rates do not necessarily result in bias,[46] we cannot exclude that the patients in our study comprise an a-select sample. A second limitation concerns the comparability of Dutch and Chinese patients. Although patients were similar in terms of gender, and were stratified based

on TBI severity and age, we cannot exclude that the patient groups differed on demographic and clinical variables (e.g. education, Glasgow Coma Scale) that were not measured in the Chinese dataset. Related, comorbidity was not assessed in both cohorts, while it is common in TBI patients[47,48] and could also influence HRQoL.[49] Moreover, the Dutch study administered the SF-36 by a postal questionnaire while the Chinese study used telephone interviews, which might not be comparable. For example, in a telephone interview, social desirability bias is relatively likely to occur,[50,51] which might have resulted in more optimistic results among Chinese patients. Also, a postal questionnaire, especially in patients with severe TBI, might not be reliable because of memory and concentration problems experienced by these patients.[52] Comparability of Dutch and Chinese patients is further hampered by differences in study design; the Dutch database was a prospective cohort study whereas the Chinese dataset was retrospectively collected.

The time between injury and follow-up can also be considered a limitation in this study. Although it is known that a subset of mild and moderate TBI patients experience long-lasting symptoms,[44,49,53] the majority is expected to be recovered one year post-injury.[54] This might have caused the strong ceiling effects in our study. Ceiling effects are considered to be present if the highest score on a subscale is obtained in more than 15% of the respondents,[55,56] which was the case in the majority of subscales for Dutch and Chinese mild and moderate patients. Ceiling effects may reduce reliability and validity of subscales[56] and might indicate that the SF-36 lacks sensitivity to examine differences in TBI patient groups one year after the injury. In addition, the skewed distribution might have influenced the validity of the CFA analyses because normality is one of the assumptions of the maximum likelihood method. However, in small sample sizes ($N < 200$) the maximum likelihood method outperformed other analytical methods such as diagonally weighted least squares.[57]

Given these limitations, the findings of current study should be interpreted as preliminary and hypothesis generating. We therefore recommend future studies to use highly comparable patient groups in terms of demographics and clinical variables and a detailed registration of the acute and rehabilitative care provided. Additionally, the inclusion of more objective outcome measurements (e.g. Glasgow Outcome Scale Extended) might provide insight on whether Western and Asian patients experience other symptoms or interpret/cope differently with similar symptoms following injury. Related, next to the SF-36, which is a measurement of general HRQoL, a disease-specific measurement such as the QOLIBRI[58] is recommended to measure the full impact of TBI on HRQoL.[59] In addition, qualitative studies, such as interviews or focus groups might also be suitable to study cultural differences in HRQoL after injury.

Our finding that Chinese mild and moderate TBI patients conceptualize some of the subscales differently, poses a challenge for multi-national trials with HRQoL as outcome measurement. A prerequisite in multi-national trials measuring health status is that the same underlying dimensions are measured and that these dimensions are culturally meaningful in all participating

countries.[13] Our research shows that this can be doubted in a TBI population, which was in line with findings in the general population.[9,11] We therefore recommend multi-national trials including both Asian and Western countries to be cautious in their interpretation of health outcome.

Conclusions

One year after TBI, Dutch and Chinese patients reported a different pattern of HRQoL. Further, we found cultural differences in the conceptualization of some of the SF-36 subscales, which has implication for outcome evaluation in multi-national trials.

Supplemental material is available at www.marysecnossen.nl

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PART

Comparative effectiveness research in traumatic brain injury

9

Adherence to guidelines in adult patients with traumatic brain injury: A living systematic review

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Abstract

Guidelines aim to improve the quality of medical care and reduce treatment variation. The extent to which guidelines are adhered to in the field of traumatic brain injury (TBI) is unknown. The objectives of this systematic review were to (1) quantify adherence to guidelines in adult patients with TBI, (2) examine factors influencing adherence, and (3) study associations of adherence to clinical guidelines and outcome.

We searched EMBASE, MEDLINE, Cochrane Central, Pubmed, Web of Science, PsycINFO, SCOPUS, CINAHL, and grey literature in October 2014. We included studies of evidence-based (inter) national guidelines that examined the acute treatment of adult TBI patients. Methodological quality was assessed using the Research Triangle Institute item bank and Quality in Prognostic Studies Risk of Bias Assessment Instrument.

Twenty-two retrospective and prospective observational cohort studies, reported in 25 publications, were included, describing adherence to 13 guideline recommendations. Guideline adherence varied considerably between studies (range 18%-100%) and was higher in guideline recommendations based on strong evidence compared to those based on lower evidence, and lower in recommendations of relatively more invasive procedures such as craniotomy. A number of patient-related factors, including age, Glasgow Coma Scale and intracranial pathology, were associated with greater guideline adherence. Guideline adherence to Brain Trauma Foundation guidelines seemed to be associated with lower mortality.

Guideline adherence in TBI is suboptimal and wide variation exists between studies. Guideline adherence may be improved through the development of strong evidence for guidelines. Further research specifying hospital and management characteristics that explain variation in guideline adherence is warranted.

Introduction

Traumatic brain injury (TBI) is a major public health concern affecting approximately 150-300 per 100,000 people annually in Europe.[1] The World Health Organization has predicted that TBI will be one of the leading causes of death and disability worldwide by the year 2020.[2]

The care for TBI patients is often complex and multidisciplinary. Guidelines, protocols and care pathways have been developed to improve quality of care, to reduce variation in practice and to ensure that evidence-based care is optimally implemented.[3]

A 2013 systematic review[4] found that the use of protocols in the management of severe TBI in the intensive care unit (ICU) led to improved patient outcomes. However, the findings were based on observational studies that did not report on adherence rates. Without an understanding of adherence rates, the improved outcomes stated in the review cannot be directly attributed to the use of protocols.

Guideline adherence can be defined as the proportion of patients treated according to a guideline recommendation, which often represents evidence-based or best practice care. Previous studies have found that guideline adherence in medicine is generally low[5-7] and varies widely across centers,[7,8] medical condition,[9] types of guideline,[10,11] and time period.[8,10] As a result, many patients do not receive evidence-based care, while others receive unnecessary care that may even be harmful.[5] To date, no systematic review of the literature about guideline adherence in TBI has been conducted.

The aim of this systematic review was to provide a comprehensive overview of professionals' adherence to guidelines in adult TBI patients. The objectives were threefold:

1. To quantify adherence to guidelines in adult patients with TBI;
2. To explore factors influencing adherence to TBI guidelines in those studies reporting on adherence;
3. To examine the association between adherence to guidelines and outcome in patients with TBI in those studies reporting on adherence.

Material and methods

This review was conducted and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.[12] Details of the protocol for this systematic review were registered on PROSPERO (registration number CRD42014012863) and can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014012863.

This review is being prepared as a "*living systematic review"* as part of the CENTER-TBI project[13] (www.center-tbi.eu). A living systematic review is a high quality, up-to-date, online summary of health research that is updated as new research becomes available.[14] This means that the searches will be re-run frequently and new studies will be incorporated into the review, with revisions to recommendations as appropriate. We will seek to publish regular updates.

Information sources

A comprehensive literature search was conducted on October 22th, 2014. Search strategies were developed in consultation with search experts using a combination of subheadings and text words (Online Supplement A). The databases EMBASE, MEDLINE (via Ovid SP), Cochrane Central, Pubmed as supplied by publisher, Web of Science, PsycINFO, SCOPUS and CINAHL were searched. In addition, grey literature was examined via Google Scholar, opengrey.eu and dissertation databases (openthesis.org, dissertation.com). Reference lists and citation indices of the included papers and relevant reviews were inspected to identify additional relevant citations. All selected studies were downloaded to the reference management database Endnote X5[15] and duplicates were removed. We restricted the search to original articles published in English. There was no date restriction.

Inclusion and exclusion criteria and study selection

We used the following inclusion and exclusion criteria to select studies:

Study designs: We included retrospective and prospective cohort studies, cross-sectional studies, time series and controlled clinical trials. Reviews, qualitative studies, case reports and editorials were excluded.

Participants: Studies were included if they were conducted in adult patients with suspected or confirmed TBI. Studies including a mixed population (e.g. all trauma patients) were only included if they presented their results for TBI patients separately. Studies solely about children were excluded as other factors, such as radiation, might play a role in guideline adherence in this group. If studies presented results for children and adults separately, only the information on adults was extracted.

Guidelines: Evidence-based international and national clinical TBI guidelines were included. Evidence-based guidelines were defined as guidelines for which evidence was found in quantitative research. We included studies analyzing adherence to a complete guideline or protocol as well as studies analysing adherence to one or more single guideline recommendations. Local and regional guidelines, and guidelines based on expert opinion were excluded. Studies were further excluded if they assessed adherence to guidelines not published or implemented during the study period.

Adherence: Adherence or compliance was conceptualized as the percentage of patients who were treated according to a guideline, a subset of guidelines or an individual recommendation of a guideline. This definition was chosen to enable comparison of adherence to different guidelines or guideline recommendations. Studies using self-reported adherence were excluded due to the risk of overestimation.[16]

Setting: Studies were included if they examined the acute curative care of TBI patients, in the pre-hospital setting, emergency department (ED), hospital ward care and intensive care unit (ICU).
The first review author (MC) screened all titles and abstracts and deleted obviously irrelevant citations. After the initial selection, two independent reviewers (MC and ACS) screened the remaining citations on title and abstract and obtained those selected in full text. Results were compared and any disagreement was resolved by discussion or consulting a third author (SP). The search process was documented according to the PRISMA flowchart.[12]

Data collection and assessment of methodological quality

Two reviewers (MC and ACS) independently extracted data and assessed the risk of bias of included studies. Any discrepancies were resolved by discussion or consulting a third author (SP). A data extraction form was developed based on the Effective Practice and Organization of Care Cochrane Review Group (EPOC) data collection checklist,[17] and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[18] In addition, topic-relevant criteria about guidelines, adherence, and influencing factors were extracted. Guideline recommendations were classified as strong or weak/moderate recommendations. Strong recommendations were defined as being based on good quality randomized controlled trials (RCTs). Weak or moderate recommendations were defined as being based on moderate- or poor quality RCTs, cohort studies, case control studies or case series.

We developed three risk of bias forms to rate the risk of bias in quantifying adherence (objective 1), exploring factors influencing adherence (objective 2) and examining the association between adherence and outcome (objective 3). Risk of bias forms were based on items from the Research Triangle Institute (RTI) Item Bank for observational studies[19,20] (Objective 1 and 3) and the Quality in Prognostic Studies (QUIPS) risk of bias tool[21] (Objective 2). The risk of bias was assessed for each of the three objectives separately as different risks are relevant in the three objectives. Moreover, it was possible that studies assessing more than one review objective had a low risk of bias for one objective but a high risk for another.

Risk of bias items were subdivided into six categories for every objective: selection bias/ confounding, performance bias, attrition bias, detection bias, reporting bias and information bias[19,22] (see Online Supplement B). For every category, individual items were scored as high, low or unclear risk of bias.

If at least one item in a bias category was scored as high, the risk of bias within this category was scored as moderate risk. If at least 50% of the items in a bias category were scored as high, the risk of bias category was scored as high risk. Every study received a total risk of bias score for every objective that was equal to the highest score obtained in all risk of bias criteria.

Risk of bias was presented with a table stratified by objective. Attrition and detection bias were not reported for objective 1 because these were considered irrelevant for the percentage adherence obtained. We accounted for risk of bias by narratively describing studies with a low (none of the criteria was rated as high risk of bias) and moderate (< 50% of the criteria was rated as high risk of bias) risk of bias separately for the three objectives.

In order to enhance inter-rater reliability, data extraction and risk of bias forms were pilot-tested on three studies that were likely to be included in the review. Inter-rater reliability was assessed by calculating concordance rates between the two independent reviewers in data screening, data extraction and risk of bias assessment.

Data synthesis

Due to heterogeneity in settings, guidelines, populations, statistical methods and outcomes, meta-analytic techniques were not used. Instead, we conducted a narrative synthesis of results stratified by objective.

For every guideline recommendation that was examined in at least two studies, mean guideline adherence was calculated by adding up the total number of patients treated according to the guideline recommendation and subsequently dividing them by the total number of patients eligible for the guideline. In addition, the percentage adherence was presented separately for strong and moderate/weak recommendations. We also compared the differences in percentage adherence for relatively more invasive (e.g. intracranial pressure monitoring and intracranial operation) and less invasive (e.g. computer tomography scanning and anti-seizure prophylaxis) procedures separately. A total percentage adherence was not calculated, as there was considerable variation in guidelines and patient severity.

An overview of factors influencing adherence was conducted. We examined whether associations between predictive factors and adherence were positively or negatively directed and whether they were statistically significant ($p < 0.05$). Additionally, we conducted an overview of the association between adherence and outcome and reported whether associations were positively or negatively directed and statistically significant.

All eligible studies were used for objective 1. Those that also reported factors influencing adherence and/or outcome were further analyzed for objective 2 and/or objective 3. There were

no further specific inclusion criteria for these objectives. All results are presented before and after the exclusion of studies that were judged as high risk of bias.

Treatment of studies with multiple publications

Multiple publications refer to the situation where more than one article has been written based on the same dataset.[23] Multiple publications assessing the same guideline in an overlapping time period and setting were dealt with by extracting information from the study that could be used for the most study objectives. If the number of objectives was similar across studies with multiple publications, the article that included the largest number of patients was chosen. Articles from the same dataset that assessed different guidelines or that were conducted during a different study period or in a different setting, were analyzed separately.

Results

Study selection

A total of 1,903 citations were identified through the extensive search strategy (Figure 1). After removing duplicates, 912 were screened on citation and 518 obviously irrelevant records (determined on title) were removed. We screened 394 citations on title and abstract and excluded 310. We obtained 84 citations in full text of which 62 were excluded. Three additional citations were found via reference lists and citation indices. For an overview of related studies excluded at the full text stage, see Online Supplement C.

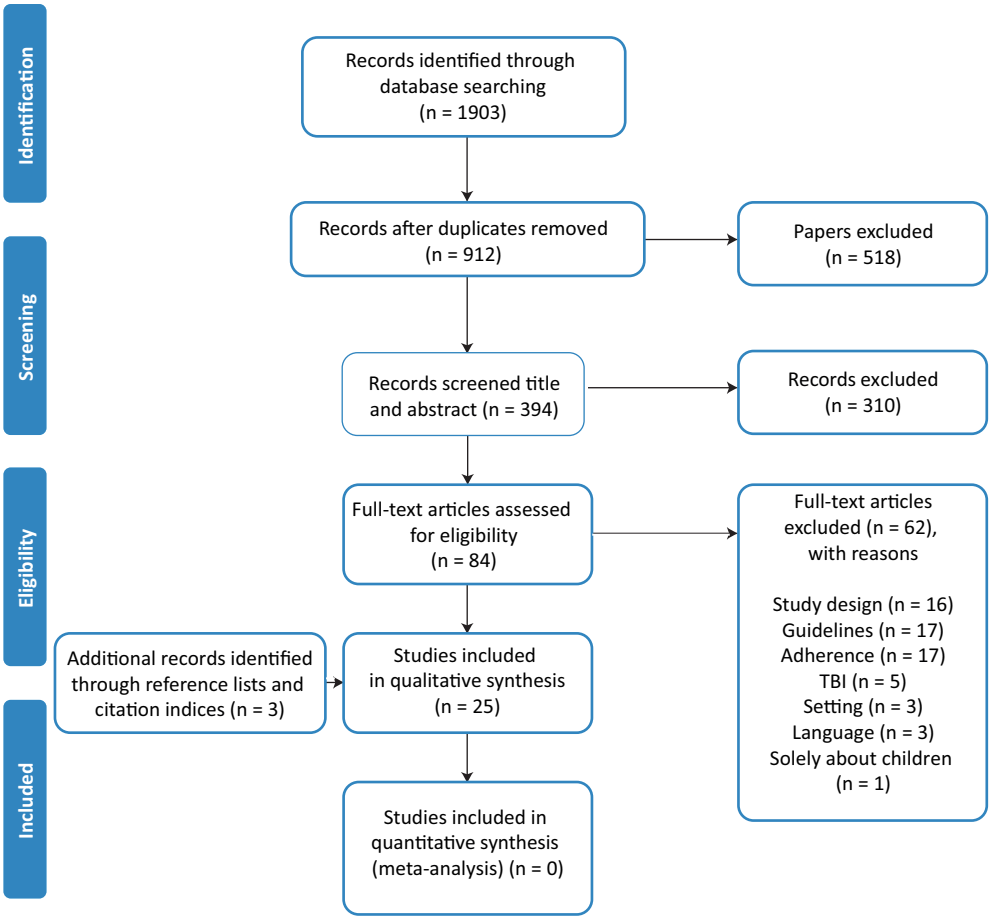
The concordance rates between the two independent reviewers were generally high in screening of title and abstract (91%), screening of full text (81%), and data extraction (93%).

Study characteristics

We included 22 studies, reported in 25 publications (Table 1). Three articles were removed from the analyses because of multiple publications.[10,24,25] Two more studies were based on the same dataset,[26,27] but the study describing the least number of objectives[26] was still included for extracting the amount of adherence to another guideline recommendation.

All included studies used an observational cohort design with fourteen being retrospective [28-41] and eight being prospective.[26,27,42-47] Twelve studies described multicenter studies[26-31,34,36,40,41,44,46] with a median of eight (range 2-155) hospitals included. All studies were conducted in North America (n = 9) or Europe (n = 13) and were published between 2002 and 2014. Six of the included studies[33,40,41,43,44,46] examined adherence to more than one guideline recommendation (mean number of guideline recommendations in studies describing more than one guideline recommendation: 3.6; range 2-6). The sample size in the included studies ranged from n = 27[38] to n = 10,628[28] patients.

Figure 1. **PRISMA flowchart of the selection process**



Reasons for exclusion full text: Study design: the study was no prospective or retrospective cohort study, RCT, clinical trial, cross-sectional study or time series; Guideline: the study did not describe a guideline, the guideline was local or not evidence-based, the guideline was not implemented or disseminated before the study period; Adherence: the study did not measure adherence per patient, adherence was self-reported; TBI: the study was not about TBI patients; Setting: the study was not conducted during the hospital and prehospital setting; Language: the study was not published in English; Solely about children: the study did not include adults.
Abbreviation: TBI = traumatic brain injury
Adapted From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Adherence to a total of thirteen guideline recommendations was assessed, including those from the Brain Trauma Foundation (BTF),[48] National Institute of Health and Clinical Excellence (NICE)[49] and Scandinavian guidelines for the initial management of minimal, mild and moderate head injury.[50] The most frequently studied guideline recommendation was the BTF guideline for Intracranial Pressure (ICP) monitoring (n = 9). Other guidelines that were studied in more than one study were the NICE guidelines for CT scanning (n = 5), the BTF guidelines for pre-hospital

intubation (n = 7), transport (n = 2), steroids (n=2) and resuscitation (n = 2), and the Scandinavian guidelines for computer tomography (CT) scanning and hospital admission (n = 2).

Six studies were performed during ICU admission, seven during an emergency department (ED) visit and three during the pre-hospital phase. The remainder (six studies) reported on a combination of these settings. The majority of studies reported on guideline recommendations that were judged as weak/moderate. Only seven studies included strong recommendations. The majority of studies were funded by government organizations. One study[29] was funded by the BTF.

Methodological quality

Overall, the methodological quality of studies was good, with the majority of studies judged at low risk of bias in most domains (Table 2). For studies measuring the amount of adherence to guidelines (objective 1, n = 22), 19 had an overall low risk of bias. The remainder (n = 3)[34,36,38] received a high risk of bias score, due to high scores on selection bias / confounding.

For studies exploring factors influencing adherence to guidelines (objective 2, n = 10), respectively three and four studies received a low and moderate overall risk of bias score. Three studies[34,43,44] were judged as being at high risk of bias due to selection bias / confounding.

None of the studies examining the association between adherence to guidelines and outcome (objective 3, n = 11) had an overall low risk of bias. Nine studies received a moderate risk of bias score and two studies[42,46] a high risk of bias score. This was due to selection bias / confounding, performance bias and information bias. None of the studies sufficiently isolated the impact of the guideline studied from concurrent interventions. In addition, some studies used inappropriate control groups or did not adjust for confounders while others calculated adherence- or quality scores that were based on non-validated scoring mechanisms or partly based on guideline recommendations that were not evidence-based or (inter)national. Concordance rates between independent reviewers in assessing risk of bias was high (92%), and any discrepancies were resolved by discussion or consulting a third author.

Amount of adherence to guidelines

The amount of guideline adherence was reported in all included studies (Table 1) and varied considerably between (range 18%-100%) and within (range 0%-100%) studies. Excluding studies with a high risk of bias[34,36,38] did not influence this variation.

Table 1. **Characteristics of the included studies (n = 22)**

Study ID	Objective	Study Design & Setting	Patients	Guideline & topic	Strength of recommendation*	Adherence operationalization	Adherence (% (n adherent / n total))
Alali (2013)	1,2,3	Retrospective cohort (US, Canada) in 155 centers	Severe TBI , age ≥ 16	BTF (2007) – ICP monitoring	M/W	ICP monitor inserted	18% (1874/10628)
Andriessen (2011)	1[A]	Same dataset as Biersteker (2012)	Severe TBI , age ≥ 16	BTF (2007) – Pre-hospital intubation	M/W	Pre-hospital intubation performed	69% (234 /339)
Biersteker (2012)	1,2,3	Prospective cohort (The Netherlands) in 5 centers	Severe TBI , age ≥ 16, intracranial pathology or 2/3 criteria: age> 40, ED motor score ≤ 3 or systolic blood pressure < 90mmHg	BTF (2007) – ICP monitoring	M/W	ICP monitor inserted	46% (123/265)
Bulger (2002)	1,3	Retrospective cohort (US) in 33 centers	Severe TBI, multitrauma, age ≥ 18. ICP monitoring: abnormal head CT	BTF (1995) – Pre-hospital intubation and ICP monitoring	M/W	Pre-hospital intubation performed	43% (79/182)
						ICP monitor inserted	58% (105/182)
Fakhry (2004)	1,3	Prospective cohort with historical control group (US)	Severe TBI, age>14	BTF (1995) – ICU management of severe TBI patients [B]	M/W	Following ICU protocol***	76% (466/611)
Farahvar (2012) *Gerber (2013)*	1,2,3	Retrospective analysis of prospectively collected database (US) in 22 centers	Severe TBI, intracranial pathology or 2/3 criteria: age > 40, hypotension or GCS motor score ≤ 3; ICP lowering treatment on first 2 days	BTF (2000) – ICP monitoring	M/W	ICP monitor inserted	83% (1084/1307)
Franschman (2012) *Franschman (2009)*	1	Retrospective cohort (The Netherlands) in 3 centers	Severe, CT scan confirmed TBI, age > 10	BTF (2000) – pre-hospital intubation	M/W	Pre-hospital intubation performed	88% (NR/372)
Griesdale (2010)	1,2,3	Retrospective cohort (Canada)	Severe TBI, intracranial pathology	BTF (2000) – CP monitoring	M/W	ICP monitoring with EVD inserted	61% (98 / 161)[C]

Table 1. **Continued**

Study ID	Objective	Study Design & Setting	Patients	Guideline & topic	Strength of recommendation*	Adherence operationalization	Adherence (% (n adherent / n total))
Harr (2011) *Heskestad (2012)*	1,2	Retrospective cohort (Norway)	ICD-10 diagnosis head injury, age ≥ 15 years	Scandinavian guidelines (2000) – CT scanning & hospital admission	M/W	CT scanning and hospital admission according to algorithm	61% (520/860)
Härtl (2006)	1,2,3	Same dataset as Farahvar (2012)	Severe TBI	BTF (2000) – Direct transport	M/W	Direct transfer to trauma center	77% (864 / 1118)
Haydon (2013)	1	Retrospective cohort (UK)	Head injury, age ≥ 16, received a CT scan	NICE CG 56 (2007) – CT scanning	S	Documentation of ≥1 CT scan requirements	84% (129/153)
						Performing CT scan ≤ 1 hour of request for all but three of indications	86% (93/108)
						Performing CT scan ≤ 8 hours in three other risk factors	100% (21/21)
Heskestad (2008)	1,2	Prospective cohort (Norway)	ICD-10 diagnosis head injury	Scandinavian guidelines (2000) – CT scanning & hospital admission	M/W	CT scanning and hospital admission according to algorithm	51% (259/ 508)
Mauritz (2008)	1,2,3	Prospective cohort in 13 tertiary care centers (Austria, Slovakia, Bosnia and Macedonia)	Severe TBI	BTF (1995) – Pre-hospital intubation, direct transport, s teroid use	M/W	Following BTF guidelines for:	
					M/W	Pre-hospital intubation	58% (673/1172)
					M/W	Direct transfer	72 (534/746)
					S	Steroids not used	83% (468/564)
Mooney (2011)	1	Retrospective cohort (UK) in 2 centers	Head injury	NICE CG56 (2007) – T scanning	S	CT performed according to criteria	97 (741/762)
Prowse (2009)	1	Retrospective cohort (UK)	Isolated head injury	NICE CG56 (2007) – CT scanning	S	NICE criteria reported in patients that had a CT scan performed	70% (23/33)

Table 1. **Continued**

Study ID	Objective	Study Design & Setting	Patients	Guideline & topic	Strength of recommendation*	Adherence operationalization	Adherence (% (n adherent / n total))
Ravindran (2007)	1	Retrospective cohort (UK)	Head injury	NICE CG4 (2003) – CT scanning	S	NICE criteria reported in patients that had a CT scan performed out of hours	100% (27/27)
Rognas (2013)	1	Prospective cohort (Denmark)	Severe TBI	BTF (2007) and Scandinavian Guidelines on pre-hospital management of TBI (2008) – pre-hospital intubation	M/W	Pre-hospital intubation performed	93% (50/54)
Rusnak (2007)	1,3	Prospective cohort (Austria) in 5 centers	Severe TBI	BTF (1995) – Various recommendations		Following BTF guidelines (see Rusnak (2007) table 2) for:	
					M/W	Resuscitation of BP & O2	79% (217/274)
					M/W	Indications for ICP monitoring	68% (283/415)
					M/W	Hyperventilation	92% (363/393)
					M/W	Barbiturates	83% (269/326)
					S	Steroids	89% (362/409)
					M/W	Anti-seizure prophylaxis	89% (360/407)
Shafi (2014)	1,2,3	Retrospective cohort (US) in 11 centers	Severe TBI patients, age<99, intracranial pathology	BTF (2007) – various recommendations		Following BTF guidelines (see Shafi (2014) table 1):	
					M/W	Endotracheal intubation	92% (1890/2056)
					M/W	Resuscitation	75% (48/64)
					M/W	ICP monitoring	52% (818/1569)
					M/W	ICP directed therapy	76% (742/978)

Table 1. **Continued**

Study ID	Objective	Study Design & Setting	Patients	Guideline & topic	Strength of recommendation*	Adherence operationalization	Adherence (% (n adherent / n total))
Shafi (2014b)	1	Retrospective cohort (US) in 5 hospitals	Severe TBI, age ≥ 16	BTF – various recommendations	M/W	Pre-hospital intubation performed	94% (468/497)
					M/W	Intracranial pressure monitoring in trauma patients with a GCS ≤ 8 and intracranial bleed on head CT and endotracheal intubation	39% (100/257)
					M/W	Craniotomy in patients with GCS ≤ 8 and intracranial bleed on head CT	20% (66/326)
Shravat (2006)	1	Retrospective cohort (UK)	Head injury	NICE CG56 (2007) – CT scanning	S	Whether CT had been requested within existing NICE criteria	100% (472/472)
Talving (2013)	1,2,3	Prospective cohort (US)	Severe TBI, age> 18, meeting BTF criteria for ICP monitoring	BTF (2007) – ICP monitoring	M/W	ICP monitor inserted	47% (101/216)

*S = strong recommendation, the guideline recommendation was based on good quality randomized controlled trials; M/W = strong/weak recommendation, the guideline recommendation was based on lower level evidence

[A]= Due to multiple publications, only the amount of intubation adherence is assessed from Andriessen. For ICP monitoring see Biersteker (2012).

[B]= See appendix Fakhry (2004) for the ICU protocol

[C]= Authors stated that 98 out of 171 patients got an ICP monitor placed. They also stated that 10 of the patients that got no ICP monitor placed, did not had an indication. We therefore recalculated the percentage adherence without those 10 patients.

Abbreviations: TBI = Traumatic Brain Injury; NR = not reported; AIS = Abbreviated Injury Scale; BTF = Brain Trauma Foundation; ICP = Intracranial Pressure; LOS = Length of Stay; GCS = Glasgow Coma Scale; ED = Emergency Department; GOSE = Glasgow Outcome Scale Extended; US = United States of America; CT = Computed Tomography; ICU = Intensive Care Unit; RLAS = Rancho Los Amigos Scale; ISS = Injury Severity Score; EVD = External Ventricular Drainage; ICD = International Classification of Diseases; HI = Head Injury; NICE = National Institute of health and Clinical Excellence; HIC = High Income Country; UMIC = Upper Middle Income Country; LMIC = Lower Middle Income Country; BP = Blood Pressure; O_2 = Oxygen; RBC = Red Blood Cell; SBP = Systolic Blood Pressure; CPP = Cerebral Perfusion Pressure

Definitions: severe TBI = GCS < 9.

Among the guidelines that were examined by more than one study, adherence was the highest in NICE CT-scan guidelines[35-39] (mean 87%, range 70-100%) and the lowest in BTF Intracranial Pressure (ICP) monitoring guidelines[10,26,28-30,32,40,41,46,47] (mean 31%, range 18-83%). Studies about the NICE CT scan guidelines were all performed at the ED in the United Kingdom and included patients with head injury. The majority had a single-center design. Studies about ICP monitoring were performed in Europe and North America and performed during ICU admission. Most studies used a multi-center design. The studies with the lowest and highest percentage adherence to ICP monitoring guidelines were comparable multi-center studies performed in North America. The study with the highest percentage adherence was based on the TBI-Trac database, which is a database from the BTF aiming to track and improve adherence, while the study with the lowest percentage was based on general trauma databases. A visual display of adherence per guideline is provided in Figure 2. After removing studies with a high risk of bias (n = 3), adherence to the NICE guidelines was 75%. Adherence to other guidelines did not differ substantially.

Figure 2. **Percentage Guideline Adherence for various guideline recommendations**

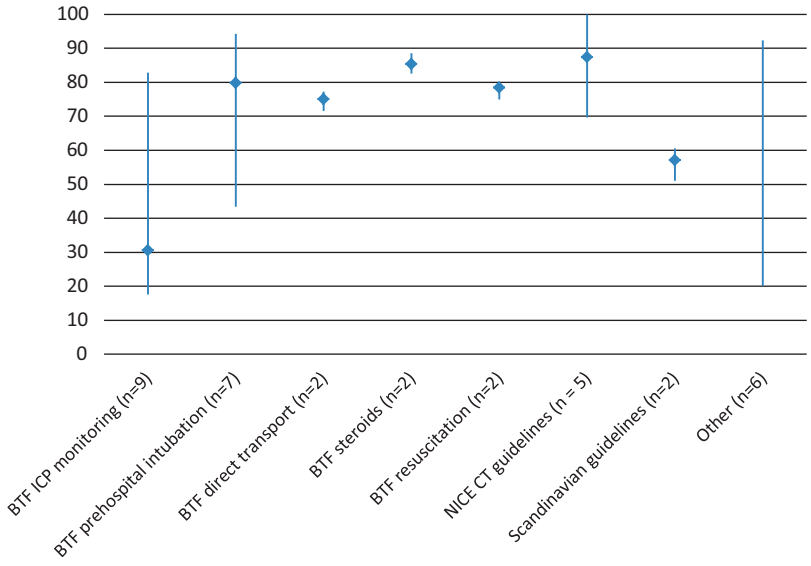


Figure displays lowest, highest and mean percentages adherence for various guideline recommendations. Numbers correspond with number of guideline recommendation and not to individual studies since some studies reported on multiple guideline recommendations. "Other" is a summary measure of following: BTF ICU protocol for patients with severe TBI42, BTF hyperventilation46, BTF barbiturates46 BTF anti-seizure prophylaxis46, BTF ICP directed therapy40 and BTF craniotomy41.
Abbreviations: BTF = Brain Trauma Foundation; ICP = Intracranial Pressure; NICE = National Institute for Health and Care Excellence; CT = Computer Tomography

To assess whether strength of recommendation was related to guideline adherence, we divided guidelines into strong, and moderate/weak recommendations. Strong recommendations consisted of NICE CT scan guidelines, reported in five studies, and BTF steroids guidelines, reported in two studies. All other guideline recommendations were based on low levels of evidence. Mean

adherence to strong recommendations was 93% (range 70-100%) while adherence to moderate/weak recommendations was considerable lower (mean 49%, range 18-94%). Percentages did not differ substantially after removing studies that were found to be at high risk of bias. One study[42] was excluded from this analysis as it reported adherence to an ICU protocol that was based on both strong and moderate/weak recommendations.

In addition, we considered whether the invasiveness of the intervention was related to adherence. Across studies, relatively invasive interventions such as ICP monitoring and intracranial operations obtained a mean adherence rate of 30% (range: 8-83%), while less invasive interventions such as CT scanning and anti-seizure prophylaxis obtained a much higher adherence rate (mean: 79%, range 51-100%).

Factors influencing guideline adherence

Ten studies identified factors influencing adherence (Table 3). Most studies assessed patient demographics and clinical characteristics. Three studies assessed treatment, hospital or country characteristics. Taking the results together, the BTF guidelines, in particular the ICP monitoring recommendations, were consistently more often adhered to in younger patients with extra-cranial injury and more severe TBI (indicated by Glasgow Coma Scale (GCS), Head Abbreviated Injury Scale (HAIS), abnormal pupillary reactions and intracranial pathology). The Scandinavian guidelines were more often adhered to in older patients with moderate head injury in comparison with mild and minimal head injuries.

Among studies with a relatively low risk of bias that assessed factors influencing adherence using multivariable analyses, age was significantly associated with adherence in all studies (younger age is associated with greater adherence in severe TBI patients; older age is associated with greater adherence in minimal, mild and moderate TBI patients). Studies about ICP monitoring further reported that adherence was more often accomplished in patients with a lower GCS and the occurrence of intracranial pathology.

Factors that were studied but not significantly associated with adherence included race, [28,40] certain severity indices (GCS motor score[28]; Acute Physiology and Chronic Health Evaluation (APACHE) II score[32]), certain laboratory values (international normalized ratio and prothrombin time[47]; blood alcohol level[33]) certain complications (tachycardia[47]; hypoxia[47]), referral status[27] and structural hospital characteristics (hospital type[28]; number of beds[28]; trauma center designation[28]). For an overview of factors significantly associated with adherence in at least one study see Table 3. For a complete overview of all factors studied, see Online Supplement D.

Table 2. **Risk of Bias Assessment**

Study ID	Selection Bias / Confounding			Performance Bias			Attrition Bias		Detection Bias		Reporting Bias			Information Bias			Highest score OB1	Highest score OB2	Highest score OB3
	OB1	OB2	OB3	OB1	OB2	OB3	OB2	OB3	OB2	OB3	OB1	OB2	OB3	OB1	OB2	OB3			
Alali (2013)	L	M	L	L	L	M	L	L	L	L	L	L	L	L	L	L	L	M	M
Andriessen (2011)	L	-	-	L	-	-	-	-	-	-	L	-	-	L	-	-	L	-	-
Biersteker (2012)	L	L	L	L	L	M	L	L	L	L	L	L	L	L	L	L	L	L	M
Bulger (2002)	L	-	L	L	L	M	-	L	-	L	L	-	L	L	-	L	L	-	M
Fakhry (2004)	L	-	H	L	-	H	-	L	-	L	L	-	L	L	-	L	L	-	H
Farahvar (2012)	L	M	L	L	L	M	L	L	L	L	L	L	L	L	L	L	L	M	M
Franschman (2012)	L	-	-	L	-	-	-	-	-	-	L	-	-	L	-	-	L	-	-
Griesdale (2010)	L	M	M	L	L	M	L	L	L	L	L	L	L	L	L	L	L	M	M
Harr (2011)	L	M	-	L	L	-	L	-	L	-	L	L	-	L	L	-	L	M	-
Härtl (2006)	H	H	L	L	L	M	L	L	L	L	L	L	L	L	L	L	H	H	M
Haydon (2013)	L	-	-	L	-	-	-	-	-	-	L	-	-	L	-	-	L	-	-
Heskestad (2008)	L	H	-	L	L	-	L	-	L	-	L	L	-	L	L	-	L	H	-
Mauritz (2008)	L	H	L	L	L	M	L	L	L	L	L	L	L	L	L	M	L	H	M
Mooney (2011)	H	-	-	L	-	-	-	-	-	-	L	-	-	L	-	-	H	-	-
Prowse (2009)	L	-	-	L	-	-	-	-	-	-	L	-	-	L	-	-	L	-	-
Ravindran (2007)	H	-	-	L	-	-	-	-	-	-	L	-	-	L	-	-	H	-	-
Rognas (2013)	L	-	-	L	-	-	-	-	-	-	L	-	-	L	-	-	L	-	-
Rusnak (2007)	L	-	L	L	-	M	-	H	-	L	L	-	L	L	-	M	L	-	H
Shafi (2014)	L	L	L	L	L	M	L	L	L	L	L	L	L	L	L	M	L	L	M
Shafi-b (2014)	L	-	-	L	-	-	-	-	-	-	L	-	-	L	-	-	L	-	-
Shravat (2006)	L	-	-	L	-	-	-	-	-	-	L	-	-	L	-	-	L	-	-
Talving (2013)	L	L	L	L	L	M	L	L	L	L	L	L	L	L	L	L	L	L	M

Table represents the risk of bias for the three objectives.

Abbreviations: OB1 = objective 1 (assessing the amount of adherence); OB2 = objective 2 (assessing factors influencing adherence); OB3 = objective 3 (assessing the association between adherence and outcome); L = Low Risk of Bias; M = Moderate Risk of Bias; H = High Risk of Bias

Table 3. **Factors significantly associated with adherence to guidelines in at least one study**

	BTF – ICP monitoring					BTF – direct transport	BTF – various recommendations		Scandinavian guidelines	
	Alali (2013)	**Biersteker (2012)**	**Farahvar (2012)**	**Griesdale (2010)**	**Talving (2013)**	**Härtl (2006)**	**Mauritz (2008)**	**Shafi (2014)**	**Harr (2011)**	**Heskestad (2008)**
Patient and Clinical characteristics										
Age	--[A]	--	--[A]	--[A]	--	+		--	++	+/-[A]
Male Gender	--[A]	+	+[A]	+[A]	+[A]			++	+	+/-[A]
Insurance status	++[A*]							+/-		
Injury mechanism	++/--[A]	+/-[A]								
GCS	-[A]	--	-[A]	--[A]	--**			+/-[A]		
HISS									++	++[A]
HAIS	+[A]				+			++		
Comorbidity	--[A]							+/-[A]		
Extracranial injury		+[B]			++			+/-[A]		
Abnormal pupillary reactions		++	++[A]		-[A]					
Hypotension	--[A]	-[A]	-[A]	+[A]	--			--****		
Intracranial pathology	++[A]	++	+[A]	++[A]	++			++		
PTT					--					
Process, hospital and country characteristics										
Decompressive craniotomy/ craniectomy				++[A]	++***					
Teaching status	++[A]									
Gross national product							++[A]			

+ = Positive, non-significant effect; - = negative, non-significant effect; ++ = positive, significant effect; -- = negative, significant effect; +/- = direction or statistical significance unknown

[A] = predictor is solely univariately assessed; [B] = predictor is significant in univariate analyses, but not in multivariable analyses

*Commercial insurance vs noncommercial insurance (United States)

**Lowest GCS within 24 hours is statistically associated with adherence; median GCS was not statistically associated

***Decompressive craniotomy within 4 hours is associated with adherence in univariate and multivariable analysis, decompressive craniotomy within 24 hours is only associated in univariate analysis

****Authors measured systolic blood pressure. Higher systolic blood pressure is associated with more adherence

Abbreviations: GCS = Glasgow Coma Scale; HISS = Head Injury Severity Scale; HAIS = Head Abbreviated Injury Scale; PTT = Partial Thromboplasting Time

The association between guideline adherence and outcome

Eleven studies examined the association between guideline adherence and outcome (Table 4). All studies examined the BTF guidelines with six studies investigating ICP monitoring guidelines, one study examining direct transfer, and the remainder combining various BTF recommendations into a compliance or quality score.

Outcome measurements included in-hospital mortality,[28,29,42] [29,32,40,47] two-week mortality,[30,34] 28-day mortality,[32] six-month mortality,[27] Glasgow Outcome Scale (GOS) and Rancho Los Amigos

Table 4. **The association between adherence to guidelines and patient outcome**

Study ID	Outcome variables	Direction of association
Alali (2013)	In-hospital mortality	--
Biersteker (2012)	6 month mortality	-
	6 month unfavorable outcome	+
	ICU LOS	++[c]
	Hospital LOS	++[c]
Bulger (2002)	In-hospital mortality	--
	Hospital LOS	-
Fakhry (2004)	Mortality	--[c]
	ICU LOS	--[c]
	Hospital LOS	--[c]
	Unfavorable outcome (GOSE) at discharge	--[c]
	Lower RLAS at discharge	--[c]
Farahvar (2012) Gerber (2013)	2-weeks mortality	--
Griesdale (2010)	In-hospital mortality	++
	28-days mortality	+
	ICU LOS	++[c]
Härtl (2006)	2-weeks mortality	--
Mauritz (2008)	ICU mortality	-/--
Rusnak (2007)	ICU mortality	-
	90 days unfavorable outcome (GOS)	-
	ICU LOS	+[c]
	Hospital LOS	-[c]
Shafi (2014)	In-hospital mortality	--
Talving (2013)	In-hospital mortality	--
	ICU LOS	++
	Hospital LOS	++

**+ = Positive, non-significant effect; - = negative, non-significant effect; ++ = positive, significant effect; -- = negative, significant effect. The direction of the multivariable analyses were noted. If there was no multivariable analysis performed, the univariate analysis was reported and a [c] was noted.

[c]= Univariate association adherence – outcome

Scale (RLAS) at discharge,[42] 90-day Extended Glasgow Outcome Scale (GOSE),[46] six-month GOSE,[27] ICU survival,[44,46] and ICU and hospital length of stay (LOS).[27,29,42,47]

The majority of studies (n = 8) analyzed the adherence-outcome association with multiple regression adjusted for relevant confounders[30,34,40,44,46] or for propensity scores.[27,32,47] Two multi-center studies analyzed the association on hospital level by dividing hospitals into quartiles based on their percentage adherence[28] or by dividing hospitals into having an aggressive or nonaggressive approach.[29] One study assessed the association in univariable analyses.[42]

Eight out of eleven studies reported a statistically significant association between adherence and a reduction in mortality with odds ratios ranging from 0.15 to 0.96[28-30,34,40,42,44,47] One study additionally described an association between adherence and higher scores on GOSE and RLAS.[42] One study reported increased in-hospital mortality in those treated according to the guideline but no significant differences between groups in 28-day mortality.[32] For ICU and hospital LOS, three studies[27,32,47] reported an association with longer LOS and one study reported an association with shorter LOS.[42] All other associations were non-significant.

After adjusting for the risk of bias by removing studies with a high risk of bias on at least one of the criteria and outcomes that have been assessed in univariable analyses, all but one of the nine remaining studies[32] reported an association between adherence and a reduction in mortality. Functional outcome was assessed in one study,[27] showing non-significant results. The association with LOS was assessed with multivariable analyses in two studies[29,47] showing contradictory results. Statistical methods and results can be found in Online Supplement E.

Discussion

This systematic review provides an overview of adherence to guidelines, its determinants and association with outcomes in patients with TBI. We included 22 studies, reported in 25 publications. Guideline adherence in TBI was found to be suboptimal overall, and varied widely between studies (from 18%-100%) and within multi-center studies. Guideline recommendations based on strong evidence were more often adhered to in comparison with recommendations based on lower level evidence. Guideline adherence was also influenced by age and severity (indicated by intracranial pathology and lower GCS). Importantly, guideline adherence appears related to patient outcomes, as adherence to BTF (especially ICP monitoring) guidelines was associated with a reduction in mortality in all but one study after correction for risk of bias.

This systematic review included three objectives, and thereby provided an overview of the entire scope of adherence to guidelines in TBI. However, five important notes should be made regarding the completeness and applicability of the evidence. First, despite the existence of over 100 evidence-based guideline recommendations,[51] adherence was assessed for only thirteen

recommendations. Results can therefore not be generalized to all guideline recommendations. Second, the variability in adherence might have been confounded by the invasiveness of the recommended intervention. We found a lower adherence rate in studies about invasive interventions such as ICP monitoring and craniotomy in comparison to studies with less invasive interventions. Invasive interventions require more experience and skills within the institution and therefore may face greater barriers to be implemented than less invasive interventions.

Third, no definitive conclusion about the efficacy of guidelines can be drawn from this review as we did not include any cluster RCTs. These results should encourage the conduct of cluster RCTs to more rigorously examine the efficacy of guidelines for TBI.

Fourth, all included studies were conducted in Europe and North America. Hence, our findings are not generalizable to non-Western countries because lack of resources restricts the routine use of aggressive treatment strategies in these countries.[52] Related, our findings cannot be generalized to children as it is known that guideline adherence in children varies from guideline adherence in adults[36] and might also be influenced by other factors such as concern about radiation.

Last, the majority of current TBI guidelines are not based on high quality evidence. TBI is however emerging as an important topic in research with large-scaled, high-quality multicenter studies conducted all over the globe[13]. These are likely to result in revised guidelines based on more rigorous evidence.[13] The findings of this review might not be generalizable to a situation in which TBI guidelines are based on robust evidence, which underlines the importance of keeping this systematic review, as well as other systematic reviews in the field of TBI, 'living'.

Overall, the methodological quality of the studies was good. The association between adherence to guidelines and outcome was however highly suspect for performance bias, as none of the studies sufficiently isolated the impact of the guideline studied from concurrent interventions. It is, nevertheless, plausible that patients who had, for example, an ICP monitor inserted, also had a higher chance of receiving other relatively aggressive treatment, and that these treatments confounded the association with outcome.

Although selection bias/confounding did not seem a major threat to validity in the association between adherence and outcome, the risk of bias form we used did not account for confounding by indication. Observational studies in critical care may easily suffer from confounding by indication, i.e. a different *a priori* risk of unfavorable outcome between those treated and those not treated according to the guideline.[53,54] Although the majority of studies made attempts to reduce the risk of confounding by multivariable analysis or propensity score adjustment, these methods may still insufficiently resolve the problem of confounding by indication as they do not account for unmeasured confounders.[54-56] This is in contrast to an RCT, where comparability between groups is achieved on measured and unmeasured characteristics. In this review, two

studies defined guideline adherence at the level of the hospital, which is more likely to provide a valid estimate of the effect of adherence on outcome.

Suboptimal adherence and between center variation have been reported in other systematic reviews about guideline adherence in critical care.[6,57] Ebben and associates[6] reported a variation as large as 0 to 98% in a systematic review about guideline adherence in the pre-hospital and emergency care.

The large between-center variation suggests that guideline adherence is a management or structural characteristic, which is consistent with a qualitative study about guideline adherence in the ICU.[58] These authors reported that unit culture and communication were among the most important factors in guideline adherence. Furthermore, the availability of electronic protocols, education, reminders and an audit-feedback system were identified by participants as important determinants of guideline adherence. Surprisingly, only one of the included studies in this review assessed the association between hospital characteristics and adherence.[28]

In this review we found that strong recommendations were more often adhered to than recommendations based on lower level evidence. This is consistent with the findings of a study about oncology guidelines.[59] This may imply that clinicians are not convinced by the benefit of moderate and weak guideline recommendations, which is supported by our finding that intracranial pathology is associated with adherence to ICP monitoring guidelines. The recommendation to place an ICP monitor in patients without CT abnormalities but with additional risk factors stems from one prospective study published in 1982,[60] while the recommendation to place an ICP monitor in patients with an abnormal head CT is, albeit still controversial, based on more robust evidence.

Other clinical characteristics that were associated with guideline adherence were age and GCS. The negative association between age and adherence in severe TBI patients is conceivable as older age is associated with medical comorbidity and premorbid anticoagulant- or antiplatelet use.[61] It has been suggested that these patients should not be treated aggressively,[62] although the BTF guidelines do not specify any subgroups in their recommendations.

The positive association between lower GCS and adherence to BTF guidelines is in line with findings from methodological studies about confounding by indication in critical care, which describe that the most intensive treatments, such as ICP monitoring, are often reserved for the most ill.[53,63]

The association between adherence and a reduction in mortality is consistent with a systematic review of protocolized management of patients with TBI in the ICU[4] and a cost-benefit analysis about the effectiveness of the BTF guidelines.[64] Although these findings are consistent, they

should be interpreted with caution because of the high risk of confounding by indication and performance bias in these studies.

Strengths of this systematic review include the use of a comprehensive search strategy and independent screening, data extraction and quality assessment by two review authors. As there is no gold standard for risk of bias assessment in observational studies,[65] we developed and pilot-tested our own form. This could be considered a review limitation, however, we attempted to describe the six threats to validity as described by the Cochrane Collaboration and used two validated forms. In addition, concordance rates in assessing bias were high suggesting unambiguous items. Finally, despite an extensive search strategy, we found no unpublished studies. Although the performance of audits to test and improve guideline adherence is well practiced,[66] these reports are seldom published in international journals. Combined with the fact that we excluded non-English language studies, it is likely that some publication bias exists within this review.

The results of this review imply that guideline adherence in TBI is suboptimal. Certain subgroups, such as older patients or severe TBI patients with a relatively high GCS are even less likely to be treated according to the guidelines. One solution may be for guideline developers to take into account specific subgroups of patients and tailor their recommendations accordingly.

The fact that strong guideline recommendations were more often followed than those based on less robust evidence, speaks to the need for adequate investment in high-quality research to evaluate treatment efficacy and effectiveness, and for this research to be incorporated rapidly into guidelines. We would recommend high quality RCTs and large-scale comparative effectiveness studies using robust methods to adjust for confounding by indication for this purpose.

The large variation found in this systematic review highlights the importance of hospital characteristics and/or management strategies in guideline adherence. Although this has been reported in qualitative studies, further quantitative research may shed greater light on its importance and elucidate which characteristics inhibit clinicians from adhering to guidelines.

In this systematic review, we found an association between adherence to current guidelines and reduced mortality. These results should be interpreted as preliminary because only two studies accounted for confounding by indication and none could eliminate the effect of concurrent interventions. It is important that future studies investigating guideline adherence or treatment effectiveness use robust methods to adjust for confounding by indication and concurrent treatment interventions to estimate effectiveness.

Supplemental material is available at www.marysecnossen.nl

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Adherence to guidelines in adult patients with traumatic brain injury, Living Systematic Review Update 3

About this LSR

This Living Systematic Review will be updated at approximately a three to six month intervals (Table 1), at which time this online supplementary material will be updated accordingly.

Table 1. **Living Systematic Review History**

Version	Search date*	Number of new included studies	Implications for conclusions
Update 3	June 2017	This update: 5 Cumulative for updates: 13	As update 1. Adherence to the anti-seizure prophylaxis guidelines is 90% in one study. Adherence to BTF mannitol recommendation was 72% in one study. Guideline adherence ranges from 0-100%.
Update 2	January 2017	This update: 1 Cumulative for updates: 8	As update 1
Update 1	September 2016	This update: 7 Cumulative for updates: 7	Adherence to ICP monitoring guidelines was higher in studies published in 2015 and 2016 than reported in the original review. The association between guideline adherence and clinical outcome became more uncertain due to the inclusion of a high-quality study that did not find an association between adherence and outcome.
Original	October 2014	22	Guideline adherence is suboptimal and varies widely (18-100%). Guideline adherence is associated with age and TBI severity and the quality and invasiveness of the guideline recommendation. Adherence to BTF guidelines might be associated with a reduction in mortality.

*Date at which the search was run

Key information from new included studies

The update search in June 2017 identified seven new studies,[1-7] of which three were based on the same data.[4-6] Therefore, data from five studies were extracted.[1-4,7] The cumulative number of studies since the publication of the original review is 13 (see Table 2). In this update we describe the 13 studies that have been included since the original review.

CT guidelines

One study examined adherence to the NICE head CT guidelines in a hospital in Czech Republic and found that adherence decreased from 72% in 2000 to 20% in 2015.[8] The adherence rate of 20% is significantly lower than adherence to NICE head CT guidelines in the original review (Median 97%). Authors elaborate that the decrease in adherence might be related to a decrease in number of hospital beds. One study examined adherence to the most recent version of the Scandinavian head CT guidelines for patients with mild TBI that also incorporated S100B as a biomarker in a level II trauma center in Sweden.[9] Adherence was 85%. Among the patients with normal S100B (n = 229), 73 (32%) received a CT scan while there was no indication. Furthermore, a total of 39 (7%) patients did not receive a CT scan while they had an elevated S100B value (n = 497) and thus an indication according to the guidelines. One study examined adherence to the Canadian head CT rule in a tertiary care hospital in Singapore.[2] Adherence was 71%. A total of 20% of the patients did not receive a CT scan while they had an indication according to the Canadian head CT rule, whereas 9% of the patients received a CT scan without an indication. In this study, guideline adherence was higher among patients with retrograde amnesia, patients injured in motor vehicle accidents and patients presenting with headache (Table 3).

Anti-seizure prophylaxis guidelines

One study examined adherence to the anti-seizure prophylaxis guidelines from the AANS in a level I trauma center in the US.[1] They found that in 90% of the patients, anti-seizure prophylaxis was stopped > 7 days from injury, in line with the guideline recommendations.

Brain Trauma Foundation guidelines

The other studies examined adherence to the BTF guidelines.[3,4,10-15] Two studies examined adherence to a set of BTF criteria, resulting in adherence rates of 70 and 74%.[12,13] One study examined mannitol administration in a center in Canada and found that 72% of the patients that received mannitol had an appropriate indication.[11] One study examined guideline adherence in a tertiary care hospital in Tanzania and reported adherence rates in the range 0-36%.[7] The remainder of studies, including the two studies that examined a total set of BTF guidelines and the study from Tanzania, examined guideline adherence to ICP monitoring guidelines.[3,4,7,10,12-15] Mean adherence was 53% (range 0-100%), which is higher than the percentage reported in the original review (31%).

One study examined predictors of adherence to ICP monitoring guidelines.[14] None of their predictors (including age, gender, GCS, hypotension and CT abnormalities) was statistically significant associated with guideline adherence (Table 3).

The association between guideline adherence and patient outcome was studied in five studies using the BTF guidelines (Table 4).[4,10,12-14] Higher adherence was associated with lower in-hospital mortality in two studies analysing the guideline-adherence association on the patient level.[13,14] One study assessed the adherence-outcome association in both India and in the US. They found that higher adherence resulted in lower mortality in India but not in the US.[12] Two studies did not find a statistically significant association between guideline adherence to ICP monitoring guidelines and patient outcome.[4,10] One of these however did report an association between ICP monitoring, complications and worse functional independence.[4]

We note that the BTF guidelines have been revised in 2016.[16] Therefore, a new cycle of audits of compliance will need to be undertaken with regard to the BTF guidelines.

Table 2. **Characteristics of studies included since the publication of the original systematic review (n = 13)**

Study ID	Objective†	Study Design & Setting	Patients	Guideline & topic	Adherence operationalization	Adherence (% (n adherent / n total))
Aiolfi (2017)	1,3	Retrospective analysis of US trauma database (2013-2015)	Severe TBI, age ≥ 16y, meeting BTF criteria for ICP monitoring	BTF (2007) – ICP monitoring	% of patients that had an ICP monitor placed	12% (1519/13,188)
Calcagnile (2016)		Prospective cohort, 1 center in Sweden	Mild TBI (GCS 14-15), LOC < 5 min, no neurological deficits nor additional risk factors	Scandinavian guidelines (2013) – CT guidelines	Head CT scan performed in patients with risk factors and elevated S100B	85% (614/726)
Dawes (2015)	1,3	Prospective cohort, 14 centers in the US	Severe TBI patients with blunt trauma to the head, GCS <9 on arrival and abnormal head CT	BTF (2007) – ICP monitoring and craniotomy	% ICP monitoring in all pt	46% (338/734)
					% craniotomy in pt with epidural hematoma, subdural hematoma, midline shift, mass lesion or intraparenchymal contusion	40% (134/335)
Elliot (2015)	1	Retrospective cohort, 1 center in Canada	Severe TBI patients that received mannitol	BTF (2007) - mannitol	% of patients that received mannitol according to documented appropriate indication	72% (86/120)
Gomez (2017)	1	Retrospective analysis of database (1987 – 2012)	Severe TBI patients, meeting BTF criteria for ICP monitoring	BTF (2007) – ICP monitoring	% of patients that had an ICP monitor placed	65% (1049/1622)
Gupta (2016)	1,3	Retrospective cohort, level I trauma center in Seattle and India	Severe TBI patients (HAIS ≥ 3, GCS <9), alive with tracheal intubation in the ICU>48h from time of admission	BTF (2007) – 17 guideline recommendations	% of patients with indication that is treated according to the guidelines	India: overall 74%, SD 11.0, ICP monitor 63%, range 2.5-100% Seattle: overall 71.6%, ICP monitor 84%, range 1.5-100%
Lambert (2016)	1	Retrospective cohort, 1 center in Czech Republic	Head injury, age ≥ 18, cranial CT performed during duty hours	NICE (2014) – CT guidelines	Head CT performed in patients in case of risk factors‡	72% (36/50) in 2000 20% (10/50) in 2015

Table 2. **Continued**

Study ID	Objective†	Study Design & Setting	Patients	Guideline & topic	Adherence operationalization	Adherence (% (n adherent / n total))
Lee (2015)	1,3	Prospective cohort study, 1 center in US	Severe TBI	BTF (2007) – 15 guideline recommendations	% of patients with indication that is treated according to the guidelines	Overall: 71% (range 28.6-94.4%) ICP monitoring: 41% (50/123)
Smart (2017)	1	Prospective cohort study, 1 tertiary care hospital in Tanzania	Severe TBI	BTF (2007) – ICP monitoring, continuous arterial blood pressure monitoring, hyperosmolar therapy, craniotomy	% of severe TBI patients that was treated with the specific treatment	ICP monitoring: 0% (0 / 115) Arterial blood pressure monitoring: 0% (0 / 115) Hyperosmolar therapy: 36% (41 / 115) Craniotomy: 36% (41 / 115)
Tan (2017)	1,2	Retrospective cohort, 1 center in Singapore	GCS 13-15, age ≥ 16y,	Canadian CT head rule – CT scanning	% of head CTs according to the criteria	71% (248 / 349)
Tang (2015)	1,2,3	Retrospective cohort, 1 center in US	Patients meeting the BTF criteria for ICP monitoring	BTF (2007) – ICP monitoring	% of patients that had an ICP monitor placed	36% (71/194)
Tarapore (2016)	1	Retrospective cohort, 1 center in US	TBI, age>12	BTF (2007) – ICP monitoring	% of patients with severe TBI that had an ICP monitor placed	100% (n = 832)
Zaman (2017)		Retrospective cohort, 1 level I trauma center, US	Not specified	AANS & AAPM&R – anti-seizure prophylaxis	% of patients in which anti-seizure prophylaxis was stopped > 7 days from injury	90% (156 / 173)

† Objective 1 = assessing the amount of adherence to guidelines; Objective 2 = assessing factors influencing adherence to guidelines; Objective 3 = assessing the association between guideline adherence and patient outcome

*S = strong recommendation, the guideline recommendation was based on good quality randomized controlled trials; M/W = medium/weak recommendation, the guideline recommendation was based on lower level evidence

‡ Risk factors: (1) GCS less than 13, (2) GCS less than 15 after 2h, (3) suspected open or depressed skull fracture, (4) any sign of basal skull fracture, (5) posttraumatic seizure, (6) focal neurological deficit, (7) more than 1 episode of vomiting, (8) age ≥ 65y, (9) any history of bleeding or clotting disorders, (10) dangerous mechanism of injury, (11) more than 30 min retrograde amnesia

Table 3. **Factors significantly associated with adherence to guidelines**

Study ID	Significant predictors
Tan (2017)	Motor vehicle crashes, headache, retrograde amnesia
Tang (2015)	No significant predictors

Table 4. **The association between adherence to guidelines and patient outcome**

Study ID	Outcome variables	Direction of association
Aiolfi (2017)	30-day mortality	+
	Complications	++
	Functional independence	--
Dawes (2015)	In-hospital mortality	+/- ‡
Gupta (2015)	In-hospital mortality India	--
	In-hospital mortality Seattle	-
Lee (2015)	In-hospital mortality	-/-- †
Tang (2015)	In-hospital mortally	--

**+ = Positive, non-significant association between adherence and outcome; - = negative, non-significant association between adherence and outcome; ++ = positive, significant association between adherence and outcome (e.g. guideline adherence is associated with an increase in in-hospital mortality); -- = negative, significant association between adherence and outcome (e.g. guideline adherence is associated with a decrease in in-hospital mortality). The direction of the multivariable analyses were noted. If there was no multivariable analysis performed, the univariate analysis was reported and a [c] was noted.

‡ Risk adjusted mortality for ICP monitoring was 41.8% in the lowest tercile, 33.8% in the middle tercile and 42.0% in the highest tercile. Risk adjusted mortality for craniotomy was 55.8% in the lowest tercile, 47.1% in the middle tercile and 56.0% in the highest tercile.

†Patients in the lowest compliance group (< 55%) had a higher odds on mortaility, while patients in the moderate and high compliance groups (55-75% and > 75%) were indisguishable.

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10

Variation in structure and process of care in traumatic brain injury: Provider profiles of European neurotrauma centers participating in the CENTER-TBI study

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Abstract

Introduction: The strength of evidence underpinning care and treatment recommendations in traumatic brain injury (TBI) is low. Comparative effectiveness research (CER) has been proposed as a framework to provide evidence for optimal care for TBI patients. The first step in CER is to map the existing variation. The aim of current study is to quantify variation in general structural and process characteristics among centers participating in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study.

Methods: We designed a set of 11 provider profiling questionnaires with 321 questions about various aspects of TBI care, chosen based on literature and expert opinion. After pilot testing, questionnaires were disseminated to 71 centers from 20 countries participating in the CENTER-TBI study. Reliability of questionnaires was estimated by calculating a concordance rate among 5% duplicate questions.

Results: All 71 centers completed the questionnaires. Median concordance rate among duplicate questions was 0.85. The majority of centers were academic hospitals (n = 65, 92%), designated as a level I trauma center (n = 48, 68%) and situated in an urban location (n = 70, 99%). The availability of facilities for neurotrauma care varied across centers; e.g. 40 (57%) had a dedicated neuro-intensive care unit (ICU), 36 (51%) had an in-hospital rehabilitation unit and the organization of the ICU was closed in 64% (n = 45) of the centers. In addition, we found wide variation in processes of care, such as the ICU admission policy and intracranial pressure monitoring policy among centers.

Conclusion: Even among high-volume, specialized neurotrauma centers there is substantial variation in structures and processes of TBI care. This variation provides an opportunity to study effectiveness of specific aspects of TBI care and to identify best practices with CER approaches.

Introduction

Traumatic Brain Injury (TBI) is an important threat to public health with a crude incidence rate of up to 849 per 100,000 people in European countries.[1,2] TBI is emerging as one of the leading causes of death and disability worldwide resulting in huge personal suffering and far-reaching socioeconomic consequences.[3,4]

Different perspectives on various aspects of care exist, and the evidence underpinning guideline recommendations for treatment of patients with TBI is weak.[3,5] There is growing realization that randomized clinical trials alone will not be able to provide the evidence base that is needed to address these knowledge gaps.[6] Comparative effectiveness research (CER) has been proposed as a good complementary approach to strengthen the evidence base. CER has been defined as "the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care".[7] CER exploits between-center differences in patient management by comparing centers that perform a certain intervention routinely to others that do not. This approach is expected to be particularly suitable for TBI since large between-center differences in both patient management and outcomes have been previously reported.[8,9]

The Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study is a large-scale observational multicenter study focusing on characterization and CER in TBI. The first step for CER is to provide an overview of variation in structures and processes of care in the participating centers ('provider profiling'). Such an overview can be used to identify areas where large between-center variation exists, to guide future CER analyses. But it can also directly be used for CER. For example, treatment effectiveness of a certain intervention can be studied by comparing outcome in patients from centers that routinely perform the intervention to outcome in patients from centers that do not routinely perform the intervention. Therefore, the objective of the current study is to quantify variation in general structure and process characteristics among centers participating in the CENTER-TBI study and to identify topics for CER.

Material and methods

CENTER-TBI study

CENTER-TBI is a prospective longitudinal observational study conducted in 72 centers from 20 countries across Europe and Israel.[3] One of the global aims is to "identify the most effective clinical care and provide high-quality evidence in support of treatment recommendations and guidelines".[3] This will be pursued by CER approaches. For more information, see also www.center-tbi.eu. Before the patient inclusion started, a detailed inventory of center characteristics was performed by distributing a set of questionnaires on structures and process of TBI care: The

Provider Profiling (PP) questionnaires (see Online Supplement A). This set of questionnaires was distributed among 71 centers, since two CENTER-TBI centers represented different departments from the same hospital with similar structures and processes.

Development process of the Provider Profiling Questionnaires

The PP questionnaires went through a comprehensive developing process to warrant completeness and relevance of topics and face validity of questions. The neurotrauma evidencemap (http://neurotrauma.evidencemap.org/) was searched for gaps and inconsistencies in knowledge of optimal treatment and organization of TBI care, and used to define topics of interest. We included topics relevant for CER as well as topics relevant for descriptive analyses. Initial questions were formulated based on literature and suggestions from experts in the field. Available surveys and questionnaires in the field of TBI or critical care[10,11] were searched for and used for the (re) formulation of (additional) questions.

Questions related either to structures or processes of general or TBI-specific care. Structure refers to the conditions under which patient care is provided (e.g. the number of beds, trauma center designation, hospital facilities), and process refers to activities that constitute patient care (e.g. general hospital or department policies).[12] Structural information could be extracted from hospital databases, annual reports and local registries. Process information refers to general policies rather than individual treatment preferences of responsible physicians. General policy was defined as 'the way the large majority of patients (> 75%) with a certain indication would be treated', recognizing that there might be exceptions. We included open questions and multiple-choice questions. All questions were presented with text boxes that contained definitions and a short explanation about the interpretation and completion of the question. The definitions used in this paper are summarized in Online Supplement B.

Experts in the field provided feedback on the initial formulated questions and proposed new questions and topics in three subsequent phases. Consulted experts included neurosurgeons, (neuro)intensivists, neurologists, emergency department (ED) physicians, rehabilitation physicians, medical ethicists, health care economists and epidemiologists. Some of the consulted experts had previous experience with the design and conduct of surveys in the field of TBI or critical care. In a first phase, a small group of experts discussed the questionnaires during an email conversation and a group discussion. In a second phase, an international expert panel, consisting of 25 experts from 9 countries, was consulted per email. These experts provided feedback on one or more of the questionnaires. Decisions on proposed content and formulation were then made during a group discussion with a small group of experts. These draft PP questionnaires were then pilot-tested in 16 of the participating CENTER-TBI centers. Each center completed two or three questionnaires, such that each questionnaire was pilot-tested at least three times. All answers were checked for unexpected or missing values and ambiguous questions were subsequently reformulated or deleted. Pilot-testers additionally completed a form in which they were asked to

provide feedback, which was incorporated accordingly. All these processes resulted in a final set of eleven questionnaires related to different phases of TBI care (see Table 1). In total, there were 321 questions included in the PP.

Table 1. **Characteristics of the Provider Profiling questionnaires**

Questionnaire	No. of questions	Topics
1. General	41	Structural characteristics of the hospital, catchment area, volume, facilities, staffing characteristics, payment, equipment, costs
2. Medical ethics	17	Department of medical ethics, IRB approval, informed consent procedures
3. Prehospital trauma care	28	First aid initiatives, dispatch systems, emergency services, hospital reception and initial treatment
4. Emergency department	50	Structural characteristics of the ED, imaging, guidelines, ED overcrowding, treatment, admission policy, discharge policy, withdrawal of life support
5. Admission	22	Structural characteristics of the ward, admission policy, guidelines, observations, treatment policy, step down beds, discharge policy
6. Structural and organizational aspects of the ICU	27	Structural characteristics of the ICU(s), staffing characteristics, admission policy, ICU decision making
7. Treatment at the ICU	70	Protocol use, ICP- and CPP monitoring, sedation, non-surgical treatment of severe TBI patients, seizure prophylaxis, treatment of fever, DVT prophylaxis, mechanical ventilation
8. Ethical aspects of the ICU	20	Withdrawal of life support, age and ICU admission
9. Neurosurgery	21	Volume, staffing characteristics, decision making, protocols, surgical management of mass lesions
10. Rehabilitation	14	In-hospital rehabilitation facilities, referral to post-acute care
11. Country	11	Health care policy, dispatch systems, insurance

The provider profiling questionnaires consist of 11 separate questionnaires. Table shows number of questions and topics for each of the questionnaires.
Abbreviations: IRB = institutional review board, ED = emergency department, ICU = intensive care unit, ICP = intracranial pressure, CPP = cerebral perfusion pressure, TBI = traumatic brain injury, DVT = deep venous thrombosis prophylaxis

Distribution of the questionnaires

During presentations and workshops at two consecutive CENTER-TBI investigators meetings, information on the PP questionnaires was provided. Local investigators, as the senior persons supervising the CENTER-TBI study in the centers, were extensively informed in person and per email about the aim of the study and we emphasized the confidentiality of their responses. Additionally, to achieve unequivocal responses, we instructed them on how to respond to the process questions. We emphasized that we were asking for general policies, rather than individual treatment preferences and stimulated discussions with colleagues to identify the general policy of their department/center. Questionnaires were completed using a web-based system (Quesgen Systems Inc.) An instruction video was made available and any questions from local investigators were answered per email.

The local investigators in each center were responsible for the completion process in their center. Staff members with the appropriate expertise and knowledge needed to complete one or more questions or questionnaires. The local investigators were responsible for monitoring progress and checking face validity of all answers. The first author (MC) reminded local investigators regularly and answered any questions by email.

We aimed to receive completed questionnaires before centers started recruiting patients. As CENTER-TBI had a phased start of the inclusion period, PP questionnaires were completed between December 2014 and April 2016.

Questionnaire completion and data cleaning

A questionnaire was considered completed by a center if > 90% of the questions had been answered. Data from participating centers were included in the current paper if the center had completed the first PP questionnaire ('general'), since the first questionnaire provides the general structure information necessary for provider profiles. The first author (MC) screened the completed questionnaires for missing values and contacted local investigators if any missing data were present. They were asked to complete the missing data if possible or provide a reason for missingness. Data were further screened for outliers and local investigators were contacted to confirm values that were considered out of range.

Statistical analyses

To estimate reliability of the questionnaires, we included 17 (5%) duplicate questions, including all question formats. We equally included structure and process questions in the duplicate questions. Concordance rates were estimated by calculating the percentage of overlap between duplicate questions, and presented as mean, median and range. For open questions (e.g. what is the number of intensivist in your center), a maximum difference of 10% was considered concordant. For all hospital characteristics in this paper, frequencies and percentages were presented for categorical variables and medians and interquartile ranges (IQR) were presented for continuous variables. For a more in-depth understanding of the variation among centers, we checked whether there were differences between relatively high- and middle-income countries versus relatively lower-income countries, and also if there were differences between countries from different geographic locations (North and West Europe versus South and East Europe and Israel). We used the Chi-square test, and if appropriate, Fisher's exact test to examine whether differences between groups were statistically significant ($p < .05$). The designation into relatively lower-income countries was based on a 2007 report by the European Commission.[13] Bosnia Herzegovina, Bulgaria, Hungary, Latvia, Lithuania, Romania and Serbia were subsequently classified as relatively lower-income countries. The subdivision into geographic location was based on the classification by the United Nations. Austria, Belgium, Denmark, Finland, France, Germany, Lithuania, the Netherlands, Norway, Sweden and the United Kingdom (UK) were subsequently classified as countries from West and North Europe, while all other countries were

classified as countries from South and East Europe and Israel. Analyses were performed using the Statistical Package for Social Sciences (SPSS) version 21.

Results

Completion process

All 71 eligible centers completed the provider profiling questionnaire about general structural and process information. Questionnaires were completed by multiple persons per center, including neurologists, neurosurgeons, trauma surgeons, intensivists, research nurses and administrative staff members. The 71 centers were from 20 European countries (see Figure 1). Each country had 1 to 9 participating centers (median = 2.5). The United Kingdom (UK) had most centers participating (n = 9), while Serbia and Switzerland both had one participating center. Thirteen of the included centers were from relatively lower-income countries and 25 centers were from countries in South and East Europe (including Israel).

Reliability of the questionnaires

The median concordance rate between duplicate questions was 0.85 (mean: 0.81; range 0.44-0.97), meaning that 85% of the responses were similar. Concordance rates were lowest for questions about treatment policy (e.g. on what indications would you admit a patient with mild TBI to the ward) and for open questions (e.g. what is the number of intensivists working at your center). Most multiple-choice questions about structure had concordance rates above 0.90.

General structural characteristics

The participating centers were predominately academic centers (n = 65, 92%), designated as a level I or II trauma center (n = 54, n = 74%) and situated in an urban location (n = 70, 99%, see Table 2). The majority of participants indicated that they had access to a helicopter platform (n = 57, 80%) and an acute trauma team (n = 63, 89%). Around half of the centers (n = 40, 57%) had a dedicated neuro ICU. Centers from relatively high- and middle-income countries more often indicated that they have a dedicated neuro ICU (n = 35, 61%) than centers from relatively lower-income countries (n = 5, 39%, p = .13, see Online Supplement C). The large majority of centers had participated previously in research about acute cerebral disorders. Fifty-one (72%) centers were involved in more than five neurotrauma research applications over the past five years (see Table 2).

Figure 1. **Centers and countries included in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study**

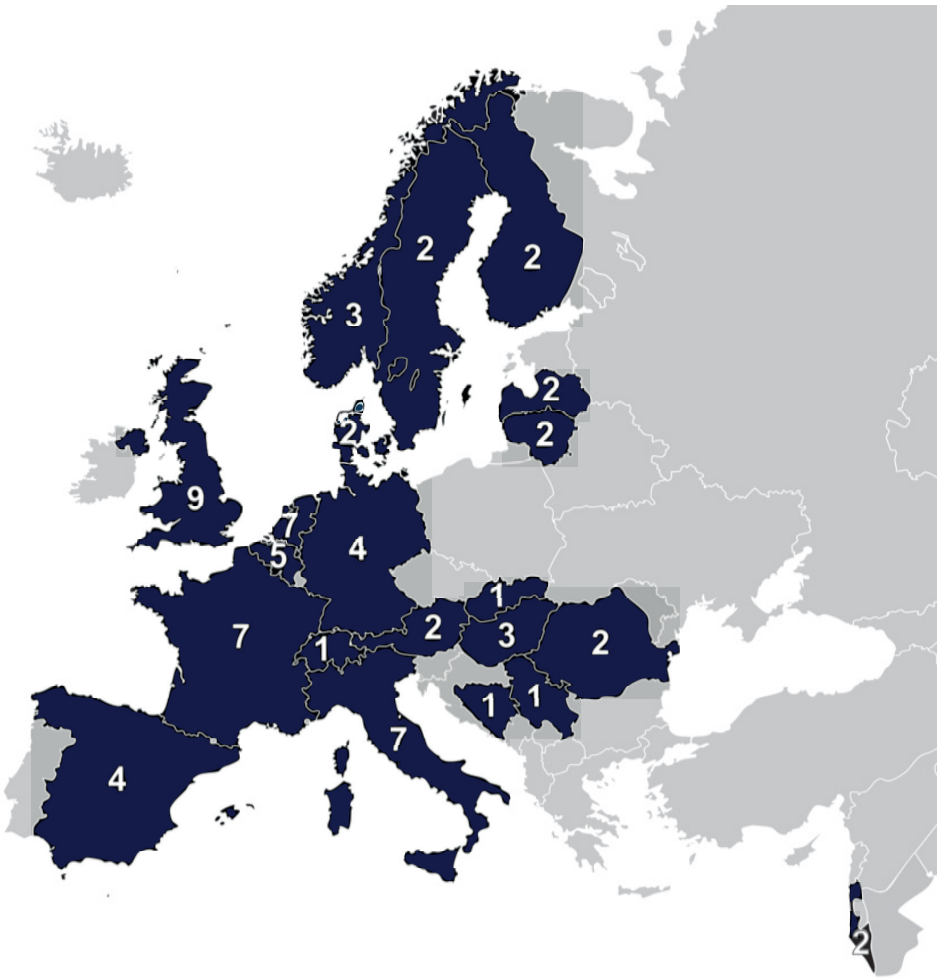

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Table 2. **General structural characteristics of the participating centers (n = 71)**

Characteristic	N completed	N (%)*
Academic hospital (vs. non-Academic)	71	65 (92%)
Trauma center designation	71	
– Level I		48 (68%)
– Level II		4 (6%)
– Level III		1 (1%)
No designation / NA		18 (25%)
Urban location (vs. suburban and rural location)	71	70 (99%)
Helicopter platform	71	57 (80%)
Acute trauma team	71	63 (89%)
The availability of a dedicated neuro ICU	70	40 (57%)
Number of ICUs (median, IQR)	69	3 (2-5)
The availability of an in-hospital rehabilitation unit	70	36 (51%)
Neurotrauma research applications in the past 5 y	71	
– > 5		51 (72%)
– 3-5		13 (18%)
– 1-2		4 (6%)
– 0 or unknown		3 (4%)
Distance nearest trauma center that receives patients with severe TBI (km, median, IQR)	52	56 (17-100)

***** Table presents number and percentage of centers unless otherwise specified
Abbreviations: ICU = Intensive care unit; IQR = Interquartile Range

The median number of beds in the participating centers was 1000 (IQR 682-1395) of which 31 (IQR 22-44) were ICU beds (see Table 3 and Online Supplement D). Centers had a median of 3 (IQR 2-6) resuscitation rooms at the ED and 24 (IQR 16-39) operating rooms. Three (IQR 2-4) of these were potentially available for TBI patients. The median number of annual ED visits was 53,428 (IQR 30,002-90,268). The median number of annual ICU admission was 1240 (IRQ 560-2019), of which 91 (IQR 52-160) were TBI patients.

Seventy-five per cent (n = 53) of the centers had separate 24/7 emergency operation rooms. The majority of centers indicated that they had an electronic patient system at the ward (n = 57, 80%) and the ICU (n = 56, 79%). There was variation in the organization of the ICU in the participating centers; i.e. 45 (64%) centers had a closed ICU organization, 3 (4%) an open ICU organization and the remainder (n = 22, 32%) a mixed ICU organization. Centers from relatively high- and middle-income countries more often reported that they had a closed ICU structure (n = 40, 70%) compared to centers from relatively lower-income countries (n = 5, 39%). Step down beds were available in 71% (n = 50) of the centers. Centers from North and West Europe more often reported that they had a step down bed facility than centers from South and East Europe and Israel (n = 36, 80% vs. n = 14, 56%, p = .03, see Online Supplement C). Maximum laboratory

turnaround times, the possibility for in-hospital coma stimulation and the location of TBI relevant facilities also varied widely among the included centers (see Table 4).

Table 3. **Volume characteristics of the participating centers (n = 71)**

Characteristic	N completed	Median (IQR)
Number of beds		
Number of ED observational beds	69	16 (7-32)
Number of hospital beds	69	1000 (682-1395)
Number of ICU beds	71	31 (22-44)
Number of resuscitation and operating rooms		
Number of resuscitating rooms	69	3 (2-6)
Number of operating rooms	70	24 (16-39)
Number of operating rooms potentially available for TBI patients[A]	69	3 (2-4)
Number of patients		
Annual ED visits	63	53,428 (30,002-90,268)
Annual ICU admissions	65	1240 (560-2019)
Number of TBI patients		
Annual number of TBI patients at the ICU	63	91 (52-160)
Annual neurosurgical procedures to evacuate contusion	59	9 (4-21)
Annual decompressive craniectomies	56	13 (8-22)

[A] Operating rooms potentially available for TBI patients are the operating rooms that can be used for emergency and non-emergency TBI patients (e.g. trauma operating rooms, neurosurgical operating rooms). Rooms that are used for non-TBI surgery in TBI patients (e.g. orthopedic surgery in patients with multiple trauma) should be excluded here.

Abbreviations: IQR = interquartile range; ED = emergency department; ICU = intensive care unit; TBI = traumatic brain injury; SAH = subarachnoid hemorrhage

Table 4. **Hospital facilities of the participating centers (n = 71)**

Characteristic	N completed	N (%)
General		
Separate 24/7 emergency operation rooms	71	53 (75%)
Electronic patient system		
– Ward	71	57 (80%)
– ICU	71	56 (79%)
Facility for overnight observation	69	54 (78%)
Lab turnaround time[A]	68	
– 0-30minutes		25 (36%)
– > 30 minutes		26 (38%)
NA. No lab SOP at the ED		17 (25%)
Organization of the ICU	70	
– Closed		45 (64%)
– Open		3 (4%)
– Mixed		22 (32%)
Step down beds	70	50 (71%)
In-hospital coma stimulation	70	34 (49%)
TBI related		
Location TBI facilities	71	
– Different buildings		20 (28%)
– Same building, different floors		45 (63%)
– Same building, same floors		6 (9%)

[A] The laboratory turnaround times that are record in the lab Standard Operating Procedures (SOP) at the emergency department for severely injured patients

Abbreviations: ICU = intensive care unit; NA = not applicable; SOP = Standard Operating Procedures; TBI = traumatic brain injury

On average 14 neurologists, 10 neurosurgeons, 17 intensivists, 4 trauma surgeons and 10 ED physicians were working in the centers (see Table 5). Nearly all centers (n = 69, 97%) had at least one residency program for trainees towards becoming a specialist. The specialist most often in charge of TBI patients at respectively the ED, ward and ICU were predominately ED physicians, neurosurgeons and intensivists. Most centers had 24/7 in-house availability of OR personnel (n = 62, 87%) and CT technicians (n = 66, 93%). Median intensivist-to-patient ratio, and ICU nurse-to-patient ratio were 1: 5 (IQR 1:3 to 1:8) and 1:2 (IQR 1:1 to 1:3). Night coverage at the ICU was performed by a certified intensivist in two-third of the centers (n = 44, 65%) and by a trainee or fellow in the remainder of centers. Almost all centers from the relatively lower-income countries (n = 12, 92%) reported that night coverage was performed by a certified intensivist, in comparison to 58% of the centers from the relatively high- and middle-income countries. Also, more centers from South and East Europe (n = 22, 88%) had night coverage by a certified intensivist, compared to centers from North and West Europe (n = 22, 51%, see Online Supplement C).

Table 5. **Staffing characteristics of the participating centers (n = 71)**

Characteristic	N completed	N (%)*
Number of specialists (median, IQR)		
– Neurologist	71	14 (8-21)
– Neurosurgeon	68	10 (7-13)
– Intensivist	68	17 (10-28)
– Trauma surgeon	68	4 (0-10)
– ED physician	69	10 (3-19)
Residency programs		
– Neurologist	70	65 (93%)
– Neurosurgeon	71	67 (94%)
– Intensivist	71	64 (90%)
– Trauma surgeon	71	36 (51%)
Availability OR personnel	71	
– 24/7 in-house availability		62 (87%)
– On call within 30 minutes		9 (13%)
Availability CT technicians	71	
– 24/7 in-house availability		66 (93%)
– On call within 30 minutes		5 (7%)
Intensivist-to-patient ratio (median, IQR)	69	1: 5 (1: 3- 1: 8)
ICU nurse-to-patient ratio (median, IQR)	69	1: 2 (1: 1- 1: 3)
Night coverage ICU	68	
– Certified intensivist/ ICU physician		44 (65%)
– Trainee (in residency training)		20 (29%)
– Fellow in training for ICU		4 (6%)

***** Table presents number and percentage of centers unless otherwise specified

[A] Number of specialists is displayed per 40-hour workweek.

Abbreviations: IQR = interquartile range; ED = emergency department; OR = operating rooms; CT = computed tomography

General process characteristics

With regard to computed tomography (CT) scanning in patients with mild TBI at the ED, 79% of the centers (n = 54) indicated to use CT guidelines (see Table 6). In addition, seven centers (10%) from Austria, Denmark, France, Spain and Sweden routinely determine S100B as a prognostic biomarker for neurological deterioration at the ED. There was variation among centers in their ICU admission policy; i.e. 44 (64%) centers generally admit patients with moderate TBI (Glasgow Coma Scale (GCS) 9-12) and CT abnormalities to the ICU, while 25 (36%) centers only admit these patients to the ICU in the presence of other risk factors. This variation was also shown for moderate TBI patients without CT abnormalities and patients with mild TBI on anti-coagulant therapy. There was a trend towards a higher ICU admission rate in centers from relatively high- and middle-income countries than in centers from relatively lower-income countries (see Online Supplement C).

The large majority of participants (n = 61, 91%) indicated that their general policy is to insert intracranial pressure (ICP) monitors in patients with GCS < 9 and CT abnormalities. However, centers vary in whether they would place an ICP monitor in patients with GCS < 9 without CT abnormalities and patients with intraventricular haemorrhages. Variation in ICP monitoring is also reported within the centers, since half of the centers indicated that there is structural variation between (neuro)surgeons in their center with regard to the decision to place an ICP monitor. The threshold for medical management of elevated ICP was 20 mmHg in the large majority of centers (n = 57, 87%). However, centers varied widely in their threshold for decompressive craniotomy; i.e. in 12% (n = 7) the threshold was 20 mmHg, in 57% (n = 35) the threshold was 25 mmHg and in 31% (n = 19) the threshold was 30 mmHg.

Table 6. **General process information of the participating centers (n = 71)**

Characteristic	N Completed	N (%)
Emergency department		
Use of CT scan guidelines at the ED	68	54 (79%)
Routine use of S100B as prognostic biomarker at the ED	71	7 (10%)
ICU admission policy		
Patients with moderate TBI (GCS 9-12) without CT abnormalities are admitted to the ICU	69	
– No or only in the presence of other risk factors		50 (72%)
– General policy		19 (28%)
Patients with moderate TBI (GCS 9-12) with CT abnormalities are admitted to the ICU	69	
– No or only in the presence of other risk factors		25 (36%)
– General policy		44 (64%)
Patients with mild TBI (GCS 13-15) using anti-coagulant therapy are admitted to the ICU	69	
– No or only in the presence of other risk factors		53 (77%)
– General policy		16 (23%)
ICP monitoring		
ICP monitoring is performed in patients with GCS<9 and CT abnormalities	67	
– No or only in the presence of other risk factors		6 (9%)
– General policy		61 (91%)
ICP monitoring is performed in patients with GCS<9 without CT abnormalities	67	
– No or only in the presence of other risk factors		52 (78%)
– General policy		15 (22%)
ICP monitoring is performed in patients with intraventricular hemorrhages	67	
– No or only in the presence of other risk factors		46 (69%)
– General policy		21 (31%)
ICP sensors that are used at the ICU:	67	
– Parenchymal		21 (31%)
– Ventricular		6 (9%)
– Both		40 (60%)

Table 6. **Continued**

Characteristic	N Completed	N (%)
ICP monitoring is performed in patients with intraventricular hemorrhages	67	
– No or only in the presence of other risk factors		46 (69%)
– General policy		21 (31%)
ICP sensors that are used at the ICU:	67	
– Parenchymal		21 (31%)
– Ventricular		6 (9%)
– Both		40 (60%)
Management of elevated ICP		
Threshold for medical management of elevated ICP	66	
– > 15mmHg		3 (5%)
– > 20mmHg		57 (86%)
– > 25mmHg		6 (9%)
Threshold for decompressive craniotomy in elevated ICP	61	
– > 20mmHg		7 (12%)
– > 25mmHg		35 (57%)
– > 30mmHg		19 (31%)
ICU policies		
Structural variation between (neuro)surgeons with regard to their decision to place an ICP sensor	69	33 (48%)
General policy with regard to the management of extremity fractures in patients with sTBI	68	
– Damage control		58 (85%)
– Definitive care		10 (15%)

Abbreviations: CT = computed tomography; ED = emergency department; ICU = intensive care unit; ICP = intracranial pressure; BTF = Brain Trauma Foundation; GCS = Glasgow Coma Scale; sTBI = severe traumatic brain injury

Insurance and payment systems

In the majority of countries (n = 16, 80%), a health care insurance was compulsory for all inhabitants. In 45% of the countries (n = 9), patients nevertheless had to pay a part of the delivered care themselves via either a co-payment (5 countries) or a deductible (4 countries). Most centers were funded by the government (n = 60; 85%). Centers typically got reimbursed by all-in amounts per patient rather than by payment for individual interventions. Most doctors received a fixed monthly salary (n = 58, 82%). In 11% (n = 8) of the centers, doctors received an additional fee for services. Twenty-three (32%) centers received additional payment for the treatment of privately insured patients.

Discussion

We found considerable variation in general structure and process characteristics among 71 specialized neurotrauma centers participating in the CENTER-TBI study. Most of these centers were high-volume academic level I trauma centers situated in an urban location. Centers varied widely in their ICU organization, hospital facilities and admission- and treatment policies. The effectiveness of these structures and interventions can therefore adequately be studied with CER.

Our provider profiling questionnaires have strengths and limitations. One of the strengths is the comprehensive development process, which consisted of several stages and involved many experts. As a consequence, the questionnaires address all aspects relevant to TBI care. Secondly, local investigators were extensively informed about the aim, procedures and practical issues during presentations, workshops and emails. This might explain the 100% response rate. The length of our questionnaires can be regarded as a limitation. Long questionnaires have been associated with lower data quality,[14,15] an effect that is often due to fatigue and boredom.[15] Since the questionnaires could be spread over time and over different persons, the negative effect of length was however confined.

Another limitation of our study concerns the generalizability of our findings. The included centers comprise a group of neurotrauma centers participating in a European multicenter study. Our findings therefore cannot be generalized to all centers caring for neurotrauma patients in Europe. Furthermore, our study provides information on what centers reported rather than characteristics that were directly observed. Therefore, we cannot exclude that some of our findings provide a too optimistic picture. For example, almost all centers indicated that they would insert an ICP monitor in patients with severe TBI and CT abnormalities, which is recommended by Brain Trauma Foundation guidelines. However, a systematic review about guideline adherence reported that ICP monitoring guidelines were only followed in one-third of the patients.[5] Later, results from the ongoing CENTER-TBI study will provide insight into discrepancies between reported and actual policies in the participating centers.

The concordance rate between duplicate questions (median: 0.85), indicates a certain degree of subjectivity in the responses. The concordance rate was especially low for process questions, which indicates that there might be differences in policy among wards and doctors, no clear policy at all or difficulties in understanding and interpreting the questions. It might also indicate that some of the doctors that completed the questionnaire might not be representative of their department or center. Although our concordance rate was very similar to a 2001 survey study among European countries,[11] results on process characteristics should be interpreted with caution. The reported concordance rate does not account for chance concordance since no statistical measures are available that do account for chance and can also provide one figure for

different outcomes (dichotomous, categorical and continuous) that we had in our questionnaire. When interpreting the concordance rate, it should however be acknowledged that some answers might be similar by chance.

Finally, there were only 13 centers from a relatively lower-income country and 25 centers from South and East Europe (including Israel). We therefore had limited power to detect differences between centers from relatively high-and middle-income countries versus centers from relatively lower-income countries and centers from different geographic locations.

Although we studied a sample of highly specialized centers, we found substantial differences in important structural and process characteristics. Largest differences were seen in the specialization and organization of the ICU, i.e. half of the centers indicated to have a dedicated neuro ICU and 64% indicated to have a closed ICU organization. Additionally, rehabilitation facilities varied widely, with half of the centers having an in-hospital rehabilitation unit and the possibility for coma stimulation. We also found large differences in the reported policies regarding ICU admission and ICP monitoring across centers. The variation in structure and process among specialized neurotrauma centers was in line with previous survey studies.[11,12] Enblad and associates[11] included European centers with a particular interest in neuro ICU and brain monitoring in their survey study. They also found large between-center differences in structures of care (e.g. 76% had a separate NICU, 50% had a neurosurgeon as ICU director). Checkley and associates[12] reported similar findings. They conducted a survey in 69 centers participating in the United States critical illness and injury outcome study. The majority of their centers were teaching hospitals with critical care training. However, 58% of their centers had a closed ICU organization and their annual hospital admission rate ranged from 1,170 to 56,330, indicating large between-center differences in volume. Also there were large differences in the protocols available at their surveyed ICUs.

Although in this study we only reported on general structure and process characteristics, it is clear that the between-center variation is substantial and provides an opportunity for CER. Variation among centers and countries comprises an important prerequisite for CER and enables between-center and between-country comparisons of effective structures and processes of care. We can for example study the influence of a dedicated neuro ICU on outcome in severe TBI patients by studying patients' outcome in the 40 centers with a dedicated neuro ICU and in the 30 centers without a dedicated neuro ICU. This requires outcome data on patient level, which are currently collected in the CENTER-TBI study. In such a comparison it is important to correct for differences in other structural and process characteristics between these centers, which can potentially be accomplished with advanced statistical modeling. Other potential interesting topics for CER based on the current study include the effectiveness of an in-hospital rehabilitation unit, the effectiveness of high-volume vs. low-volume hospitals, the effectiveness of closed vs. mixed ICU organization, and the effectiveness of admission- and ICP monitoring policies.

Conclusion

Even among high-volume, specialized neurotrauma centers there is substantial variation in structures and processes of TBI care. This variation provides an opportunity to study effectiveness of specific aspects of TBI care and to identify best practices with CER approaches.

Supplemental material is available at www.marysecnossen.nl

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Management of mild traumatic brain injury at the emergency department and hospital admission in Europe: A survey of 71 neurotrauma centers participating in the CENTER-TBI study

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Abstract

Previous studies have indicated that there is no consensus about management of mild traumatic brain injury (mTBI) at the emergency department (ED) and during hospital admission. We aim to study variability between management policies for TBI patients at the ED and hospital ward across Europe.

Centers participating in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study received questionnaires about different phases of TBI care. These questionnaires included 71 questions about TBI management at the ED and at the hospital ward.

We found differences in how centers defined mTBI. For example, 40 centers (59%) defined mTBI as a Glasgow Coma Scale (GCS) score between 13-15 and 26 (38%) as a GCS score between 14-15. At the ED various guidelines for the use of head CT in mTBI patients were used; 32 centers (49%) used national guidelines, 10 centers (15%) local guidelines and 14 centers (21%) used no guidelines at all. Also differences in indication for admission between centers were found. After ED discharge, 7 centers (10%) scheduled a routine follow-up appointment, while 38 (54%) did so only after ward admission.

In conclusion, large between-center variation exists in policies for diagnostics, admission and discharge decisions in patients with mTBI at the ED and during hospital admission. Guidelines are not always operational in centers, and reported policies systematically diverge from what is recommended in those guidelines. The results of this study may be useful in the understanding of mTBI care in Europe and show the need for further studies on the effectiveness of different policies on outcome.

Introduction

Traumatic brain injury (TBI) is a common reason for presentation at the emergency department (ED) and hospital admission in Europe.[1] A recent systematic review estimated the number of annual hospital admissions at 262 per 100,000 persons.[2] However, many more patients are seen at the Emergency Department (ED) each year. TBI is associated with significant long-term disability and has become a major socioeconomic and health burden throughout the world.

Among the TBI patients presenting at the ED, the large majority (75-90%) are classified as 'mild' TBI. The most frequently used definition of mild TBI is a GCS score between 13-15 and loss of consciousness of less than 30 minutes or amnesia not extending beyond 24 hours after blunt head injury.[3,4] Because of the low risk of intracranial damage, a computed tomography (CT) scan of the head or hospital admission is not always necessary in these patients. To estimate the risk of intracranial abnormalities in mild TBI, various prediction rules and guidelines have been developed, for example the Canadian CT head rule, National Institute for Health and Care Excellence (NICE) guidelines for head injury and CT in Head Injury Patients (CHIP) rule.[5-8] Based on a set of minor and major risk factors, these prediction rules recommend whether a CT scan of the head should be performed. The results of the CT scan subsequently influence the decision on whether a patient should be admitted to the hospital or could be safely discharged home.

After mild TBI, patients may experience post-traumatic symptoms such as headaches, dizziness and memory or concentration problems, resulting in significant disability. In many cases these symptoms dissolve over time, however a group of patients (estimated between 5% and 30%) may suffer from prolonged symptoms.[9] Studies showed that handing out discharge information and scheduling routinely follow-up sessions could reduce these post-traumatic symptoms.[10,11]

However, still little is known about the optimal treatment of mTBI and there is no consensus about management of these patients.[12] Therefore, variation in structure and process of mTBI care is expected, which may result in variation in outcome. In this study, we aim to describe the current management of mild TBI at the emergency departments and hospital wards in Europe. Specifically, we aim to provide insight in the use of diagnostics, admission policy and discharge policy at the ED and hospital ward.

Methods

Questionnaires

Between 2014 and 2016, we approached the principal investigators of 71 centers from 19 European countries and Israel, participating in the CENTER-TBI (Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury) study, a multicenter prospective observational study on TBI,[13] with the request to complete a set of 11 questionnaires about structure and

process of care for TBI patients: The Provider Profiling (PP) questionnaires. The questionnaires were developed based on literature and expert validation and were subsequently pilot-tested. Questionnaires were discussed during presentations, workshops and email conversations. Reliability, which was assessed by calculating concordance rates between duplicate questions (5% of the questions) in all 11 questionnaires, was adequate (median concordance rate of 0.85). More detailed information about the development, administration and content of the total set of provider profiling questionnaires is available in a previous publication.[14]

For this study, we analyzed the results of a questionnaire about ED and a questionnaire about hospital admission policy, for a total of 71 questions (Online Supplement A). Topics included structural characteristics of hospital and ED, imaging, guidelines, treatment, admission policy, observation and discharge policy at the ED and in hospital ward.

Question formats and definitions

Most questions had a multiple choice format where one or more answers could be selected. Two questions had an open format. Questions addressed structures (e.g. "is overnight observation at the ED available for patients with TBI") and processes (e.g. "are guidelines or protocols used to decide when mild TBI patients are discharged from the ED"). The questions about processes refer to general policies rather than individual treatment preferences. General policy was defined as the way the majority of patients with a certain indication would be treated (> 75%).

Statistical analysis

We used standard descriptive statistics. Categorical variables were presented as frequencies and percentages and continuous variables were presented as medians and interquartile ranges (IQR). Analysis was performed using IBM Statistical Package for Social Sciences (SPSS) version 21.

Results

All 71 centers completed the 'Hospital admission' questionnaire and 68 centers completed the 'ED' questionnaire (response rates 100% and 96% respectively). Among the centers that did not complete the ED questionnaire, three centers (4%) indicated that their center had no ED since they were specialized in severe neurotrauma or collaborated with the ED of another hospital. The questionnaires were answered by ED physicians, neurosurgeons, neurologists, intensivists and administrative staff members. The majority of participating centers were academic (n = 65; 92%), level 1 trauma centers (n = 48; 68%) situated at an urban location (n = 70; 99%).

Classification of TBI

It appeared that different definitions of severity levels for TBI were used (Table 1). Forty centers (59%) defined mild TBI as a patient with a GCS score between 13-15 and 26 centers (38%) as a GCS score between 14-15. Moderate TBI was considered a GCS score between 9-12 in 38 centers

(56%) and 9-13 in 22 (32%). The majority of the centers considered severe TBI as a GCS score between 3-8 (n = 62; 91%).

Table 1. **GCS scores that are considered as mild, moderate and severe TBI**

GCS score	N (%)
Mild TBI	
11-14	1 (1.5%)
12-15	1 (1.5%)
13-15	40 (59%)
14-15	26 (38%)
Moderate TBI	
8-11	1 (1.5%)
8-12	2 (3%)
9-12	38 (56%)
9-13	22 (32%)
9-14	1 (1.5%)
10-13	1 (1.5%)
11-13	1 (1.5%)
11-14	1 (1.5%)
12-13	1 (1.5%)
Severe TBI	
3-7	1 (1.5%)
3-8	62 (91%)
3-9	2 (3%)
3-10	2 (3%)
3-11	1 (1.5%)

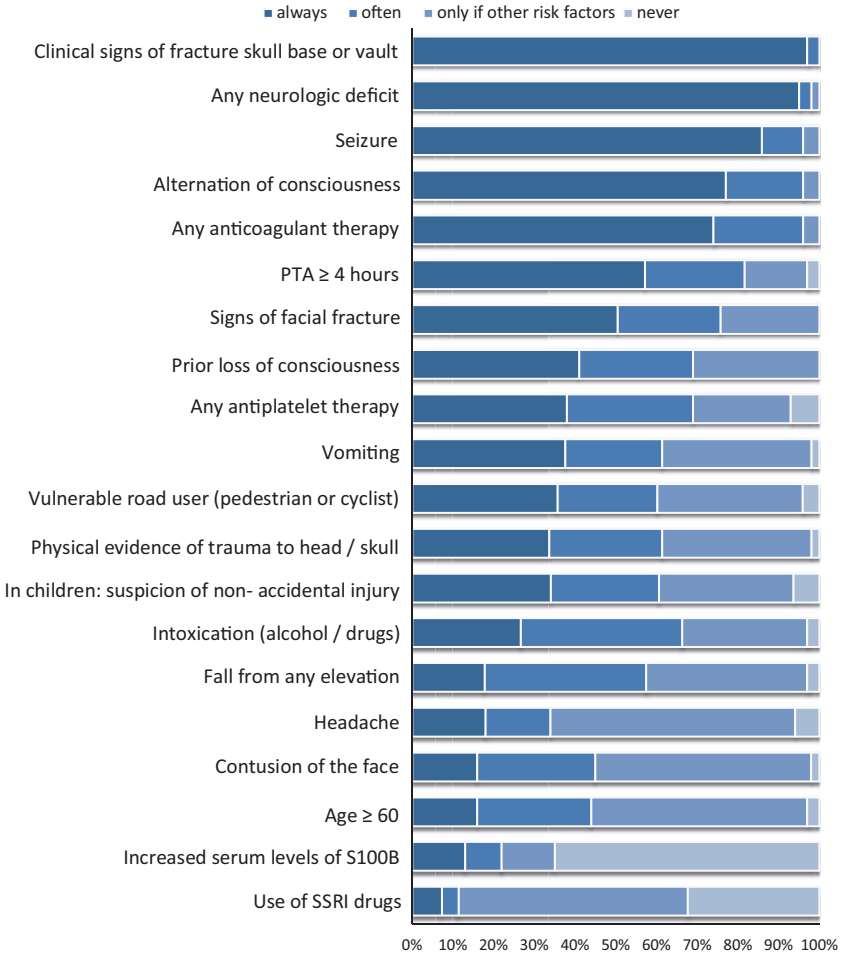
The responders were asked to enter the lowest and highest GCS score per TBI group, the bold GCS range represents the range most common in the literature.

Diagnostics at the ED

ED physicians (n = 35; 49%) and neurosurgeons (n = 15; 21%) were most often in charge for the treatment of TBI patients at the ED. At the ED various rules or guidelines for the use of head CT in patients with mild TBI were used: more than half of the centers used (multi)national guidelines, such as NICE-guidelines (n = 16; 24%), Scandinavian guidelines (n = 7; 10%), other (inter)national guidelines (n = 12; 17%). Only few of the centers use prediction rules such as the Canadian CT Head rule (n = 4; 6%), New Orleans criteria (n = 1; 1.5%) and CHIP rule (n = 4; 6%). In addition 10 centers (15%) used other local guidelines and 14 centers (20.5%) used no guidelines at all. More than 90% (n = 62) of the centers considered their CT scanning policy liberal. Most centers (n = 45; 66%) stated to be more restrictive in the use of a CT scan in children compared to adults. CT scans at the ED were mostly ordered by ED physicians (n = 37; 54%) and neurosurgeons (n = 16; 24%). Only in 7% of the centers (n = 5, including 4 centers from the Netherlands) neurologists order the CT scans. Most centers standardly perform a CT scan in patients with clinical signs of skull base fracture, any neurologic deficit or a seizure (Figure 1). In some situations the indication for CT differs among centers. For example, 50 centers (74%) standardly use a CT scan in patients on

anticoagulant therapy, while 15 (22%) indicated that they would do this often. The CT scanning guidelines were mainly implemented by written protocols and algorithms (n = 38; 56%) or via verbal direction from senior doctors in 22 centers (32%, Online Supplement B). In half of the centers guideline development and maintenance is overseen by multidisciplinary groups (Online Supplement B). The majority of centers have not performed audits to check for adherence to guideline at ED (n = 27; 40%, Online Supplement B)

Figure 1. **Frequency of ordering head CT scan in patients with mild TBI, by clinical indication**



Per situation the responders had to choose the correct policy for their center: *Always/general policy:* if the situation is, in general, a reason for ward admission in your hospital. This must represent a general consensus among colleagues, rather than individual preference; *Often/partial:* the situation is often seen as a reason for ward admission in your hospital. However, it is not general practice, because not everyone in your hospital agrees or admission is only general policy in a subset of the patients; *Only in the presence of other risk factors:* if the situation is never solely a reason for ward admission, but it might be a reason in combination with one or more other risk factors; *Never*: if the situation is never the only reason for ward admission.

Magnetic Resonance Imaging (MRI) was used in addition to the CT scan if there was discrepancy between clinical symptomatology and presence of CT abnormalities in mild TBI patients (75% of the centers). In six centers (9%) from Austria, Denmark, Spain, Sweden and United Kingdom, s100B is routinely determined as a prognostic biomarker for neurologic deterioration. Many centers had the availability of overnight observation at the ED for TBI patients before they were discharged (n = 54; 79%).

Admission at the ward

At the hospital ward, neurosurgeons (n = 56; 79%) were most often in charge for the treatment of TBI patients. Forty-four (65%) centers indicated to use guidelines in the decision on whether mild TBI patients should be admitted to the hospital ward. Most centers admitted TBI patients to the neurosurgical ward (n = 53; 75%). In addition, TBI patients were routinely admitted to the neurology (n = 16; 23%) or surgery ward (n = 15; 21%). Patients with cerebrospinal fluid (CSF) leak, CT progression, new CT abnormalities and shock were standardly admitted to the ward. For other admission indications, the policy was more diverse. For example 25 centers (37%) indicated that patients with pre-injury anticoagulation were routinely admitted to the ward, while 27 centers (39%) indicated that they would only admit these patients to the ward if other risk factors are present (Figure 2).

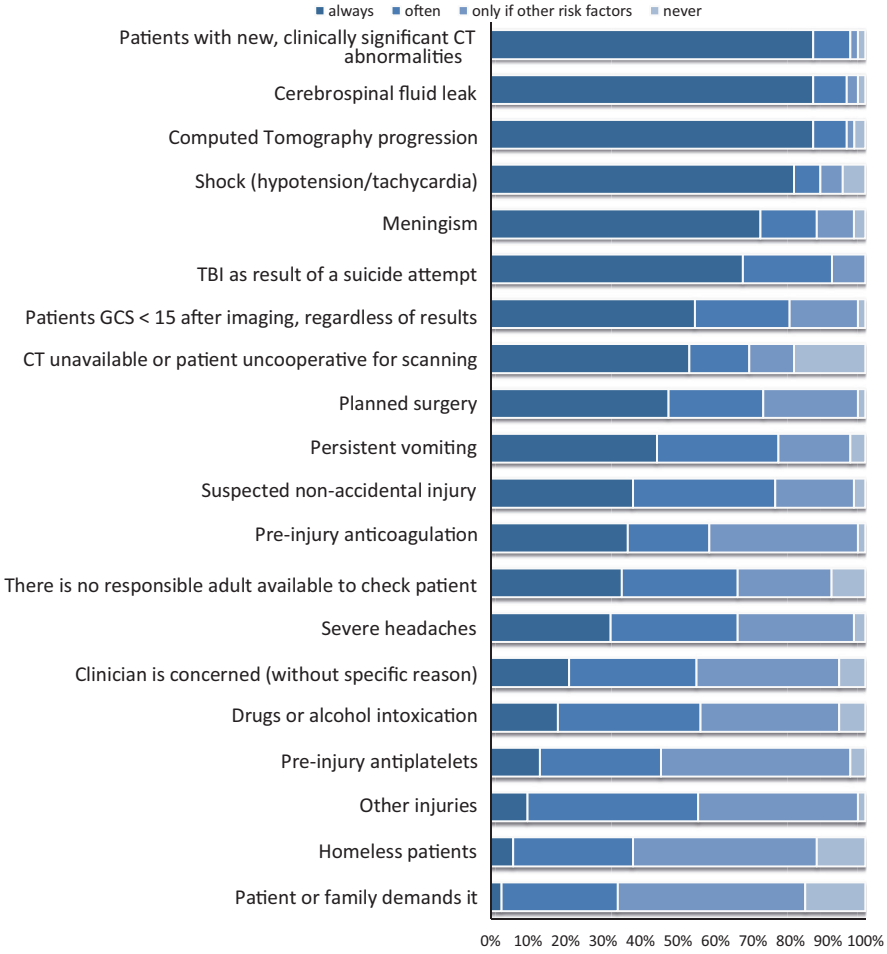
When patients are admitted at the ward, GCS is assessed systematically to detect neurological deterioration. About half of the centers (n = 37; 52%) used the scheme 'half-hour for 2 hours, then 1-hourly for 4 hours, then 2-hourly', thus in accordance with the NICE guidelines. The other half of the centers had another frequency of GCS assessment, ranging from hourly to every 24 hours. In 11 centers (16%) the Galveston Orientation and Amnesia Test (GOAT), a test for PTA, is systematically used at the ward and 12 centers (17%) use another form of PTA assessment.

Fifty-three centers (75%) have step down beds for patients who no longer need ICU care but are also not well enough for a routine hospital ward. At these high care wards, neurosurgeons (n = 32; 60%) and intensivists (n = 13; 25%) were most often in charge of the patients. Reasons for admission to the high care wards in isolated TBI patients included decreased consciousness level (n = 48; 68%), to monitor vital functions (n = 45; 63%), frequent GCS assessments (n = 38; 54%), confusion (n = 35; 49%) and intracranial complications (n = 32; 45%).

Treatment

Fifty-four centers (79%) state that they reverse pre-injury oral anticoagulation use if CT abnormalities are present, 46 (68%) do so if surgery was considered and 2 (3%) centers reverse anticoagulation in all patients admitted to the ward. Anticoagulation was commonly reversed with vitamin K (n = 62; 91%) or prothrombin complex concentrate (n = 55; 81%). Other treatments mentioned in this context were: FFP (n = 47; 69%), platelets (n = 40; 59%), fibrinogen (n = 20; 29%) or recombinant factor VII (n = 11; 16%).

***Figure 2*. Frequency of ward admission of patients with mild TBI, by clinical indication**



Per situation the responders had to choose the correct policy for their center: *Always/general policy:* if the situation is, in general, a reason for ward admission in your hospital. This must represent a general consensus among colleagues, rather than individual preference; *Often/partial:* the situation is often seen as a reason for ward admission in your hospital. However, it is not general practice, because not everyone in your hospital agrees or admission is only general policy in a subset of the patients; *Only in the presence of other risk factors:* if the situation is never solely a reason for ward admission, but it might be a reason in combination with one or more other risk factors; *Never*: if the situation is never the only reason for ward admission.

If TBI patients have a cerebrospinal fluid leak (with possibly an increased risk of infections), 34 of the centers (48%) would employ a strategy of watchful waiting before they start treatment with antibiotics. In contrast, 26 centers (37%) start antibiotics immediately and 9 (13%) start antibiotics only if patients have a fever.

TBI patients with an early seizure (a posttraumatic seizure occurring within 7 days of the trauma) receive anti-epileptic drugs (AED) immediately in 39 centers (55%). About one third (n = 22) start AED only in patients with CT abnormalities and an early seizure and 7 centers (10%) never start

AED in TBI patients with early seizure. Additionally, there are differences in the use of anti-seizure prophylaxis in patients with specific characteristics (Online Supplement C).

Discharge information

In 38 centers (56%) guidelines are used to decide whether patients with mild TBI could be discharged from the ED. In 54 centers (79%) printed discharge information is available in the ED and hospital ward to hand out to patients who are discharged home. After discharge from the ED, 42 centers (62%) provide information about post-traumatic symptoms verbally, while 55 centers (78%) do so after discharge from the hospital ward. Overall, more information is provided verbally than in written form (Table 2).

Table 2. **General discharge information provided at discharge from the ED and hospital ward**

Information	ED		Hospital ward	
	Verbally n (%)	Written n (%)	Verbally n (%)	Written n (%)
Details of nature and severity of injury	49 (72%)	40 (59%)	51 (72%)	47 (66%)
Symptoms that prompt patients to return for consultation	42 (62%)	58 (85%)	52 (73%)	44 (62%)
Details about the recovery process, including the fact some patients may appear to make quick recovery but later experience difficulties or complication	51 (75%)	38 (56%)	58 (82%)	30 (42%)
Contact details of community and hospital services in case of delayed complication	37 (54%)	50 (74%)	40 (56%)	45 (63%)
Information about return to everyday activities, including school/work/sports/driving	44 (65%)	37 (54%)	52 (73%)	39 (55%)
Information about post-concussion syndrome/ persisting symptoms and what to do in this situation	42 (62%)	38 (56%)	55 (78%)	22 (31%)
Information about use of pain killers and other medication	45 (66%)	45 (66%)	46 (65%)	45 (63%)
Details of support organization	39 (57%)	8 (12%)	39 (55%)	22 (31%)

Follow-up policy

A routine follow-up appointment at the outpatient clinic is scheduled in 7 centers (10%) after discharge from the ED, at a median period of 4 weeks after discharge (IQR 2.5-6). After discharge from the hospital ward, 38 centers (54%) routinely schedule a follow-up appointment at a median period of 6 weeks (IQR4-7.8). In 16 centers (24%) patients are referred to the general practitioner, regardless of persisting symptoms. In case of persisting symptoms, the patients are advised to go back to the general practitioner (ED n = 30; 44% and ward n = 17; 24%) or hospital (ED n = 34; 50% and ward n = 24; 34%).

Discussion

This study provides a broad overview of the current care for mild TBI patients in Europe and shows that there are wide between-center variations in diagnostic, admission and discharge policies. The most striking findings are the large variation in; GCS scores that are considered a specific TBI severity, the use of CT guidelines, and policies for patients on anticoagulants. We also found large variation in follow-up policy after discharge, where the majority of patients is not receiving routinely follow-up, despite the existing evidence and guidelines for TBI.

Our findings are in line with previous research. For example, in 2001 de Kruijk et al.[15] performed a survey study in 67 European centers. They also reported a lack of consensus of mild TBI management (e.g. definitions, guidelines) in Europe at ED and hospital admission. Pulhorn et al.[16] investigated management of mild TBI at 19 hospital wards in Britain and also found variation in the assessment of GCS at the ward and discharge recommendations. Our study confirms results of Stern at al.[17], they performed a survey study at the ED in 72 centers in New England and found significant variability in the use of guidelines and management of mild TBI care as well.

What this study adds to previous research is that it shows that not only guidelines are not always operational in centers, but also that actual policies systematically diverge from what is recommended in those guidelines. Audits to check for adherence to the guidelines could give more insight in this, but the majority of the centers have not perform audits in the last five years. Moreover, our survey pinpoints areas of clinical controversy that could do well with more clinical research.

In recent years the use of prognostic biomarkers such as s100B has been studied extensively.[18,19] The Scandinavian guideline for mild TBI even incorporated s100B in their CT scan recommendations.[20] However, in our study we observed that S100B is used as a prognostic biomarker in only 6 centers, of which 3 centers are Scandinavian.

Future research is needed to investigate whether the variation in guideline use and policies is associated with outcome. Currently, all the participating centers are collecting patient outcome data for the CENTER-TBI study.[13] By combining current data with data on patient outcomes, we will be able to investigate whether between-center differences in policy are associated with patient outcomes, and subsequently explore the effectiveness of different policy strategies in comparative effectiveness research (CER). CER requires variation to study effectiveness of treatments or policies by comparing centers who routinely perform an intervention to centers who do not, or at least less frequently.[12] In our study we found large between-center differences that enable further study with CER approaches. For example, we can compare centers that routinely perform follow-up at the outpatient clinic, with centers that do not routinely perform follow-up and analyze the relation with outcome. And we can compare the effects of routinely

giving platelets to patients on antiplatelet drugs, a procedure which has been associated with poor outcome in spontaneous ICH, but has not been studied in TBI. Thus, in the CER context, we are actually satisfied with the observed variation in care because this provides the opportunity to compare outcomes between centers with different treatment policies.

This study has some limitations that should be taken into account when interpreting the data. The reliability of the results depends on the interpretation and willingness of the investigators to be truthful and transparent in their answers. We tried to enhance this by explicitly asking for general policy rather than individual preferences and explained all answer options carefully. Furthermore, because the majority of participating centers were academic level 1 trauma centers, the findings might not be generalizable to centers with a lower trauma center designation. However, we believe the variation in policies will only increase when also lower trauma center designations would be included.

In conclusion, large between-center variations exist in policies for diagnostics, admission and discharge decisions in patients with TBI at the emergency department and hospital ward. The results of this study may be useful in the understanding of TBI care in Europe and show the need for further studies on the effect of different policies on patient outcome.

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Variation in monitoring and treatment policies for intracranial hypertension in traumatic brain injury: A survey in 66 neurotrauma centers participating in the CENTER TBI study

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Abstract

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

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

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

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

Background

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

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

A novel and promising approach in estimating treatment effectiveness is to exploit the existing variation by comparing standard practices between different centers or countries which is referred to as comparative effectiveness research (CER).[10,11] The Collaborative European Neurotrauma Effectiveness Research in TBI (CENTER-TBI) study (grant: 602150) is currently recruiting and will use CER methodology to study treatment effectiveness of ICP management.[10] As a first step, we examined self-perceived practices of ICP monitoring and associated treatment policies, by sending a survey to the centers participating in the CENTER-TBI study. Since previous European survey studies that addressed ICP management have been published more than ten years ago,[12,13] this study will provide an up-to-date overview of ICP management in Europe. Topics identified as showing substantial between-center variation that are plausibly associated with patient outcome will be selected for CER, and their treatment effectiveness can be studied once the CENTER-TBI patient-level data becomes available.

Methods

Study sample

All centers participating in the prospective longitudinal observational CENTER-TBI study (https://www.center-tbi.eu) were asked to complete a set of questionnaires on structures and processes of care for patients with TBI. Questionnaires were sent to 71 centers from 20 countries between 2014 and 2015.[14] Three centers dropped-out from the CENTER-TBI study, resulting in 68 eligible centers from Austria (n = 2), Belgium (n = 4), Bosnia Herzegovina (n = 2), Denmark (n = 2), Finland (n = 2), France (n = 7), Germany (n = 4), Hungary (n = 2), Israel (n = 2), Italy (n = 9), Lithuania (n = 2), Latvia (n = 3), the Netherlands (n = 7), Norway (n = 2), Romania

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

Questionnaire development and administration

A set of questionnaires to measure structure and process of TBI care was developed based on available literature and expert opinion, and has been comprehensively described in a previous publication.[14] Pilot-testing was undertaken in 16 of the participating centers and feedback was incorporated into the final questionnaire design.

One of the questionnaires contained 29 questions on ICP monitoring and treatment at the ICU (Online Supplement A). In most questions, we explicitly asked for the 'general policy', which was defined as the treatment or monitoring modality estimated to be used in more than 75% of patients, recognizing that there might be exceptions. In some questions, we asked for quantitative estimations. The representatives of the centers could indicate how often they used a particular monitoring or treatment strategy (never 0-10%, rarely 10-30%, sometimes 30-70%, frequently 70-90%, always 90-100%). The options 'frequently' and 'always' were interpreted as representing the general policy, in line with a previous report.[15] All definitions used in the questionnaire are described in Online Supplement B.

Analyses

We calculated frequencies and percentages for all variables related to the number of responders for that variable. We examined factors associated with a relatively aggressive ICP monitoring and treatment strategy with the Chi-squared or Fisher's exact test as appropriate. Centers were classified as being relatively aggressive if they: (a) place an ICP monitor in patients with a Glasgow Coma Scale (GCS) score ≤ 8 and an abnormal head computed tomography (CT) scan, and (b) if they generally perform at least one out of three second-tier treatments that represented a maximum therapy intensity (barbiturates, decompressive craniectomy and hypothermia < 35° Celsius).[16]

We examined whether there were differences between and within geographic regions in the use of first and second-tier treatments. Countries were divided into seven geographic regions (Northern Europe, Western Europe, UK, Southern Europe, Eastern Europe, Baltic States and Israel). Within each region, we examined the percentage of centers that indicated that the particular treatment was their general policy. In addition, we assessed the influence of geographic region on treatment decision by performing logistic regression analysis with treatment as dependent variable (general policy yes / no) and geographic region (categorical variable) as independent variable. The Nagelkerke R^2 was reported, representing the proportion of variation in treatment that can be explained by geographic region. Analyses were performed using the Statistical Package for Social Sciences (SPSS) version 21.[17]

Results

Participating centers

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

Indications for ICP monitoring

The majority of participants (n = 58, 91%) indicated that they would generally place an ICP monitor in patients with GCS ≤ 8 and CT abnormalities (Figure 1). ICP monitors were less often considered for other indications, e.g. GCS ≤ 8 without CT abnormalities (n = 15, 23%), inability to assess a patient with CT abnormalities clinically (e.g. due to sedatives; n = 11, 17%), and intraventricular hemorrhage (n = 21, 33%). Around one-third of the participants would place an ICP monitor in polytrauma patients (GCS > 8) who require extracranial surgery or mechanical ventilation but would not otherwise have an indication for ICP monitoring. Patient-specific reasons for not monitoring ICP included: the risk of raised ICP was considered low (n = 40, 62%), patients were considered unsalvageable (n = 37, 57%) or GCS was above 8 (n = 37, 57%; Online Supplement B).

Variability in monitoring and treatment of intracranial hypertension

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

Figure 1. **Indications for ICP monitoring placement**

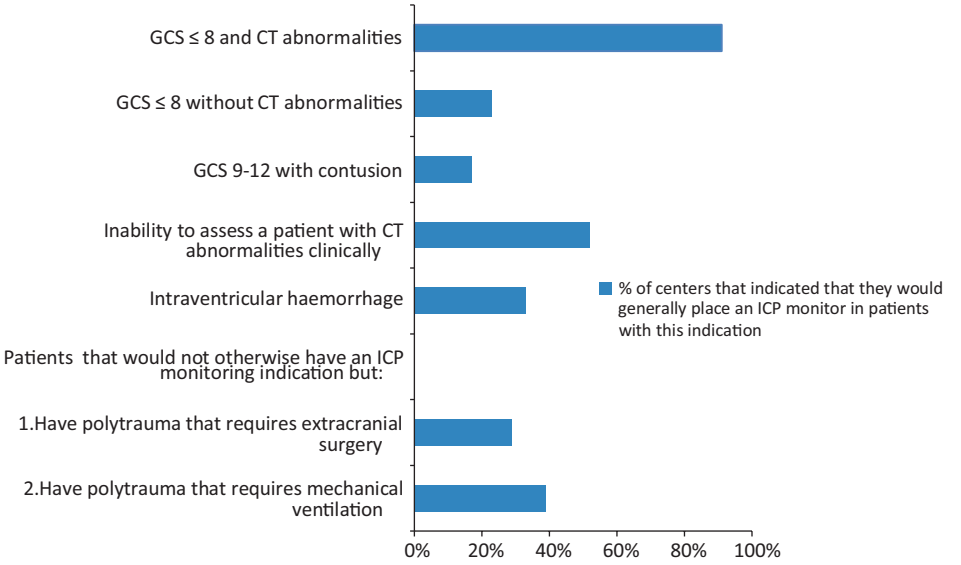


Figure presents percentage of centers that indicated that they would generally place an ICP monitor in patients with the described characteristics.
Question is completed by 64/66 centers.
Abbreviations: CT = Computed Tomography; GCS = Glasgow Coma Scale; ICP = Intracranial Pressure

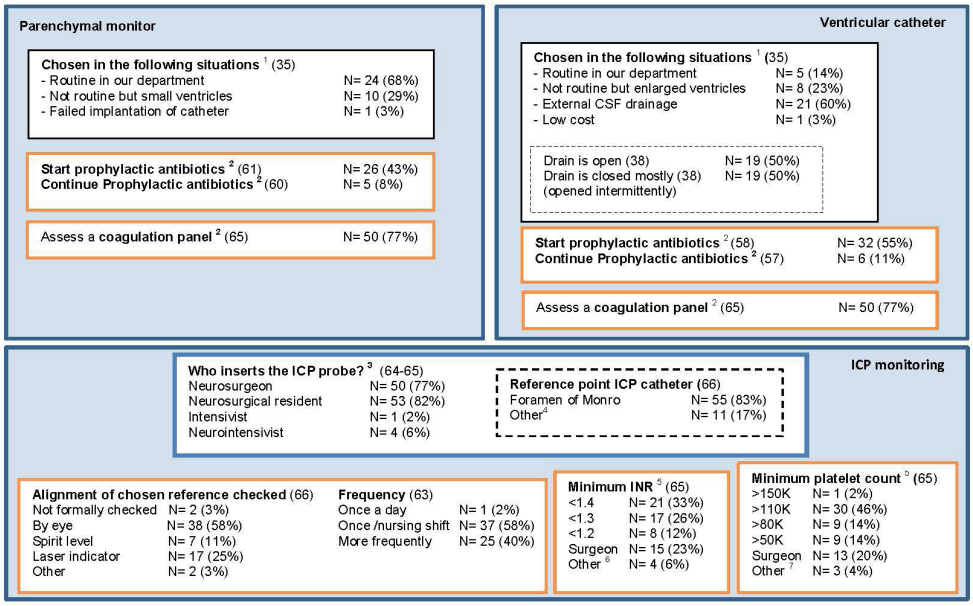
Parenchymal and ventricular ICP devices

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

Precautions with ICP monitor placement

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

Figure 2a. **Algorithm for ICP management: ICP monitoring**



The blue box represents ICP monitoring with the policy for parenchymal monitor on the left and ventricular catheter on the right. Orange boxes are checkpoints during the ICP monitoring process. The N represents the number of centers that indicated this answer as general policy with a corresponding percentage (%). The number in parenthesis after the titles represents the number of centers that completed this question.

Abbreviations. CSF: cerebrospinal fluid, ICP: intracranial pressure, INR: International Normalized Ratio

1) Centers that indicated these situations as top 1 of the top 3 reasons for choosing a ventricular or parenchymal catheter **2)** Frequently and always summed **3)** Arterial blood pressure, midauricular level, ventrix motor, NA (we only use parenchymal monitors), room air, calibrated by device and meatus externa **4)** Prior to insertion ventricular catheter for ICP monitoring **5)** Depending on other factors such as the use of platelet aggregation inhibitors **6)** Multiplate and rotem analysis prior to surgery if concerns

Additional neuromonitoring

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

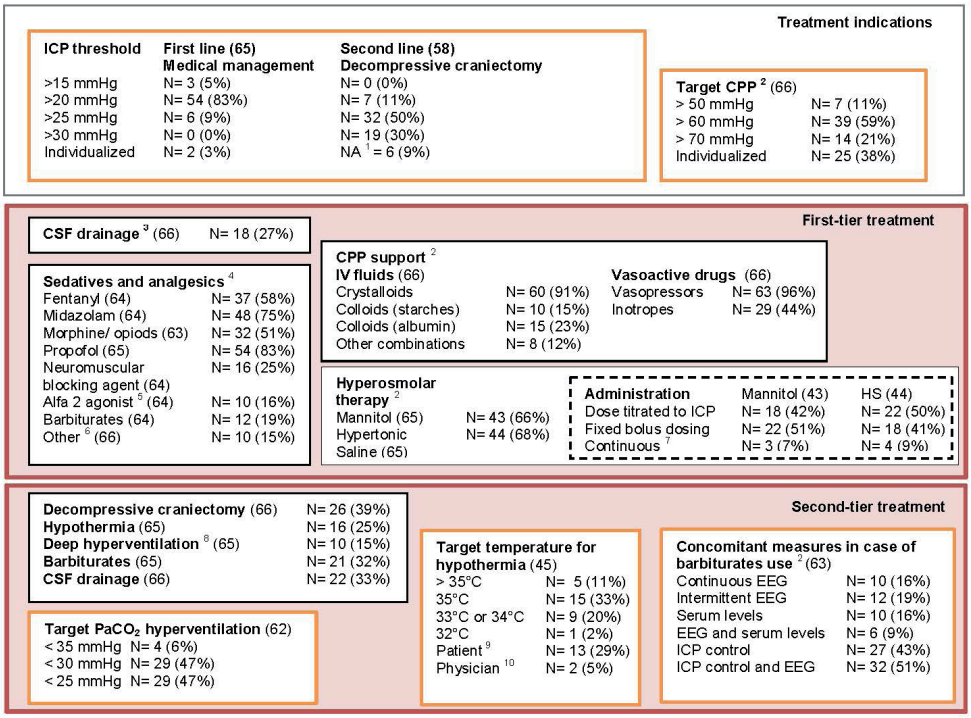
First-tier treatment of elevated ICP

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

Propofol (n = 54, 83%), midazolam (n = 48, 75%), fentanyl (n = 37, 58%) and morphine (n = 32, 51%) were generally used as part of first-tier treatment in patients with elevated ICP, whereas the use of alpha 2 agonists (n = 10, 16%) and barbiturates (n = 12, 19%) was less frequent (Figure 2B; Online Supplement B). Neuromuscular blocking agents were generally used in

16 (25%) centers. Participants typically preferred a specific combination of sedatives and analgesics as part of first-tier treatments; i.e. 50 participants (76%) indicated they used 2-4 out of 8 sedatives and analgesics as general policy and the other interventions only infrequently (Online Supplement B).

Figure 2b. **Algorithm for ICP management: treatment indications, first- and second- tier treatment**



The red box represents ICP treatment with first-tier treatment on top and second-tier treatment at the bottom. Orange boxes are checkpoints during the ICP treatment process. The N represents the number of centers that indicated this answer as general policy with a corresponding percentage (%). The number in parenthesis after the titles represents the number of centers that completed this question.

Abbreviations: CSF: cerebrospinal fluid, CPP: cerebral perfusion pressure, EEG: electro-encephalogram, HS: hypertonic saline, ICP: intracranial pressure, IV: intravenous

1) Decompressive craniectomy is (almost) never performed in our hospital **2)** Multiple answers were possible **3)** Only if ventricles are enlarged **4)** Frequently and always summed **5)** Clonidine or dexmedetomidine **6)** Sufentanil (4), reminfentanyl (2), beta blockers (1), alfentanil (2), esketamine (1) **7)** Standard continuous infusion **8)** PaCO2 < 30 mmHg **9)** Variable, depends on patient **10)** Variable, depends on physician

Regarding the use of osmotic therapy, two-thirds of the participants indicated generally using mannitol (n = 43, 65%) and/or hypertonic saline (n = 44, 67%). Seventeen participants indicated the use of mannitol, but not hypertonic saline, as their general policy, whereas 18 participants indicated the opposite. Fourteen (22%) participants indicated to generally using hypertonic saline in conjunction with mannitol (Figure 2B). Crystalloids were the most commonly used intravenous (IV) fluids to augment CPP (n = 60, 91%), while other fluids (starches, albumin

and other combinations) were less often used (12-23%). Vasopressors were generally used in almost all centers to support CPP (n = 63, 96%). Among the parameters that are used to titrate vasoactive drugs, mean arterial pressure targets (n = 51, 77%) and transpulmonary thermodilution monitoring by means of pulse contour cardiac output (n = 35, 53%) were most often used (Online Supplement B).

Second-tier treatments for refractory intracranial hypertension

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

Factors associated with aggressive monitoring and treatment policies

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

The influence of geographic region on treatment decisions

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

Table 1. **Factors associated with an aggressive ICP management style**

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

£ BTF guidelines or institutional guidelines that were broadly based on the Brain Trauma Foundation (BTF) guidelines

†Relatively high volume (number of severe TBI patients admitted to the ICU higher than the median number of severe TBI patients admitted to the ICU (n = 92)) vs. relatively low volume (number of severe TBI patients admitted to the ICU lower than or equal to the median number of severe TBI patients admitted to the ICU.

‡ The division into relatively high and low income was based on a 2007 report by the European Union.[18] High-income = Austria, Belgium, Denmark, Finland, France, Germany, Israel, Italy, the Netherlands, Norway, Spain, Sweden, United Kingdom and Switzerland; Relatively low-income = Bosnia Herzegovina, Bulgaria, Hungary, Latvia, Lithuania, Romania and Serbia.

£Northern Europe = Norway, Sweden, Finland and Denmark; Western Europe = Austria, Belgium, France, Germany, Switzerland and the Netherlands; Southern Europe = Italy and Spain; Eastern Europe = Hungary, Romania, Serbia and Bosnia Herzegovina; Baltic States = Latvia and Lithuania

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

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

Table presents the percentage of participants within each geographic region that indicated that the first- or second-tier treatment was their general policy. Nagelkerke R2 was derived from a logistic regression analysis with treatment (general policy yes / no) as dependent variable and geographic region (categorical variable) as independent variable. Nagelkerke R2 represents the proportion of variance of the treatment variable that is accounted for by geographic region.

Northern Europe = Norway, Sweden, Finland and Denmark; Western Europe = Austria, Belgium, France, Germany, Switzerland and the Netherlands; Southern Europe = Italy and Spain; Eastern Europe = Hungary, Romania, Serbia and Bosnia Herzegovina; Baltic States = Latvia and Lithuania.

Discussion

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

Strengths of this study include the high response rate (97%), the extensive development process of the questionnaire, and the comprehensive examination of both monitoring and treatment. In addition, since our survey was completed by centers that are currently collecting patient-level data for the CENTER-TBI study, the results of this study can directly be used as input for the CER analyses, once the patient-level data becomes available. A limitation of our study is that the included centers represent a selected group of European neurotrauma centers that are prominent in the field of neurotrauma care and research. Consequently, the picture obtained might be skewed. In addition, this study is dependent on perceived practices rather than on clinical data. Although we repeatedly emphasized confidentiality of results, we cannot exclude that some physicians presented (even subconsciously) a more favorable image or presented individual treatment preferences rather than the general policy in a center. This can be explored when individual patient-level data are available. A further limitation is that we asked for isolated general treatments but did not assess specific combinations. In clinical practice, however, different treatments are used simultaneously and outcome might be determined by the combination of treatments provided rather than by one particular intervention.

The substantial variation in strategies for ICP management in our study was in line with previous survey studies in Europe[12,13] and the United States.[15] For example, Hesdorffer et al.[15] found that mannitol, hypertonic saline and hyperventilation were generally used in half of their centers. Guidelines have been proposed to reduce treatment variation in medicine.[19] Although there has been an increase in protocolisation of medicine and awareness of guidelines during the last decade, variation in ICP management may not have reduced.[12,13] Moreover, some participants claimed using treatments that are discouraged in the BTF guidelines. For example, one-fifth of the participants specified to use barbiturates as first-tier treatment, while this is a second-tier treatment in the BTF guidelines.[20] The discrepancy between BTF guidelines and reported policies indicates that there is little consensus among neurotrauma centers with respect to ICP management. This might be due to the relatively small evidence-base underpinning the guidelines.[3]

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

Based on current findings, we would recommend prioritizing the following topics for CER because of feasibility of the center-level approach:

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

Conclusion

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

Supplemental material is available at www.marysecnossen.nl

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13

Rehabilitation after traumatic brain injury: A survey in 70 neurotrauma centers participating in the CENTER TBI study

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Abstract

Objective: To describe variation in structural and process characteristics of acute in-hospital rehabilitation and referral to post-acute care for patients with traumatic brain injury (TBI) across Europe.

Methods: A 14-item survey about in-hospital rehabilitation and referral to post-acute care was sent to 71 neurotrauma centers participating in a European multicenter study (CENTER-TBI). The questionnaire was developed based on literature and expert opinion and was pilot-tested before sending out to the centers.

Results: 70 (99%) centers in 20 countries completed the survey. The included centers were predominately were academic level I trauma centers. Among the 70 centers, a multidisciplinary rehabilitation team can be consulted at 41% (n = 29) of the ICUs and 49% (n = 34) of the wards. Only 13 (19%) centers used rehabilitation guideline in patients with TBI. Age was reported as a major determinant of referral decisions in 32 (46%) centers, with younger patients usually referred to specialized rehabilitation centers, and patients ≥ 65 years also referred to nursing homes or local hospitals.

Conclusion: Substantial variation exists in structural and process characteristics of in-hospital acute rehabilitation and referral to post-acute rehabilitation facilities among neurotrauma centers across Europe.

Introduction

Moderate and severe traumatic brain injuries (TBI) are a growing public health problem and often lead to substantial physical and psychological burden for patients and relatives. Since TBI is not a single event, but a life-long disorder with differential needs over time, it is recognized as one of the most challenging areas in modern rehabilitation medicine.[1]

Patients with moderate or severe TBI are usually referred to level I trauma centers where the process of rehabilitation starts with an emphasis on issues such as swallowing, contractures, pressure sores and neurobehavioral disorders. From the acute care setting patients may be referred to specialized in- or outpatient rehabilitation settings, nursing facilities or for example neuropsychiatric wards in psychiatric hospitals. A patient out of post-traumatic amnesia with an attention span and physical condition that allows for two or three therapy sessions of about 10-15 minutes a day, is usually referred to an inpatient rehabilitation setting. Patients with disorders in consciousness, who recover slowly or suffer from severe neurobehavioral problems, may be referred to nursing facilities or psychiatric hospitals. However, well accepted algorithms to support the choice of follow-up treatment do not exist.[2]

Although there is growing evidence that both acute and post-acute rehabilitation interventions are beneficial for patients with acquired brain injury, including TBI,[3-5] their specific ingredients, mechanism of action and efficacy is still referred to as a 'black box'.[6] As a consequence, large variations in structure and process characteristics of TBI rehabilitation may exist. Structures refer to conditions under which rehabilitation care is provided (e.g. availability of an in-hospital rehabilitation unit, personnel, facilities),[7] and processes refer to treatment- and referral policies.[7] As they may be related to differences in patient outcomes, exploring the variations in structure and process characteristics of TBI rehabilitation might provide directions for the identification of effective interventions.

The objective of this study is to provide a broad overview of structural and process characteristics of TBI rehabilitation among European neurotrauma centers, with a focus on acute in-hospital rehabilitation and referral to post-acute inpatient or outpatient care.

Methods

Study sample

This study is part of the Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) study, which is a prospective longitudinal observational study conducted in 72 centers from Austria, Belgium, Bosnia Herzegovina, Denmark, Finland, France, Germany, Hungary, Israel, Italy, Lithuania, Latvia, the Netherlands, Norway, Romania, Serbia, Spain, Sweden, the United Kingdom and Switzerland.8 The included centers predominately were academic hospitals

(n = 65, 92%), situated in an urban location (n = 70, 99%), with a level I or II trauma center designation (n = 52, 74%). Centers had a median of 1000 (Interquartile range 682-1395) hospital beds and treat approximately 91 (interquartile range 52-160) patients with moderate and severe TBI annually. For more information about the participating centers, see our previous publication.[9]

Questionnaire development and administration

Between 2014 and 2016, the local investigators, who are the senior persons supervising the CENTER-TBI study in each center, were approached to complete a set of 11 questionnaires, containing 321 questions: The Provider Profiling (PP) questionnaires. Questions concerned structures and processes of TBI care. For questions about process, we specifically asked for the 'general policy' in a particular center, which was defined as the way the large majority of patients (> 75%) with a certain indication would be treated, recognizing that there might be exceptions. We also explicitly mentioned that we were interested in the general policy at the department or hospital rather than individual treatment preferences.

The set of questionnaires was distributed among 71 out of 72 centers, since two CENTER-TBI centers represented different departments from the same hospital with similar structures and processes. The questionnaires were developed based on literature (e.g. the neurotrauma evidencemap: http://neurotrauma.evidencemap.org) and expert opinion and were subsequently pilot-tested in 16 of the participating centers. All answers were checked for unexpected or missing values, and ambiguous questions were subsequently reformulated or deleted. Pilot-testers additionally completed a form in which they were asked to provide feedback, which was incorporated accordingly in the final questionnaires. Local investigators were informed about the PP questionnaires by presentations, workshops and emails. To be able to assess the reliability of the questionnaires, 17 (5%) questions were duplicated and asked twice in different parts of the questionnaires. We assessed the percentage of overlap between duplicate questions and calculated the median concordance rate over these 17 questions. The concordance rate was adequate, with a median of 0.85, meaning that 85% of the responses were similar. For more information about the development, administration and content of the total set of PP questionnaires, see our previous publication.[9]

The questionnaire about rehabilitation addressed both in-hospital rehabilitation and referral to post-acute rehabilitation facilities (Online Supplement A). This questionnaire included fourteen multiple-choice questions about structures (e.g. "what rehabilitation facilities are available at your institution") and processes (e.g. "where are TBI patients with the following clinical characteristics generally referred to") of rehabilitation care.

Statistical analyses

Frequencies and percentages of all categorical variables were reported. We subsequently calculated differences between relatively high- and middle-income countries versus relatively

lower-income countries using Chi-Square, and if appropriate, Fisher's exact test. The designation into relatively lower-income countries was based on a 2007 report by the European Commission10 and the countries Bosnia-Herzegovina, Bulgaria, Hungary, Latvia, Lithuania, Romania and Serbia were subsequently classified as relatively lower-income countries. Analyses were performed using the Statistical Package for Social Sciences (SPSS) version 21.

Results

Participating centers

The questionnaire about rehabilitation was completed by 99% (n = 70) of the participating centers. In the majority of centers, the questionnaire was completed by a rehabilitation physician (n = 28, 40%) or a neurosurgeon (n = 22, 31%). Other specialists that completed the questionnaire included neurologists, intensivists, heads of in-hospital rehabilitation units and study nurses.

Rehabilitation specialists

The majority of participants indicated that rehabilitation physicians could be consulted for patients with TBI at the Intensive Care Unit (ICU; n = 48, 70%) and the ward (n = 54, 78%; Table 1). Of the centers that indicated that they could consult rehabilitation physicians at the ICU (n = 48) and ward (n = 54), around one third reported that rehabilitation physicians were consulted in all patients with TBI. The remainder indicated that rehabilitation physicians were asked for a consult on indication.

The large majority of centers could consult physical therapists, occupational therapists, speech therapists, dieticians, social workers and/or rehabilitation nurses in both the ICU and ward. Neuropsychologists were available in half of the centers (ICU: n = 36, 52%; ward: n = 45, 65%).

In around half of the centers, a multidisciplinary rehabilitation team could be consulted for patients with TBI at the ICU (n = 29, 41%) and ward (n = 34, 49%). A multidisciplinary team was here defined as a full multidisciplinary rehabilitation service and not as isolated physiotherapy provision. There were no differences between high/middle-income and relatively lower-income countries on any of the described characteristics (Table 1).

Guidelines

In only 13 (19%) centers, rehabilitation guidelines or protocols were used when treating patients with TBI. Most of these guidelines were developed based on expert opinion within the center and not based on evidence-based guidelines.

Table 1. **In-hospital rehabilitation in 70 European neurotrauma centers participating in the CENTER-TBI study**

Characteristic	All centers (n = 70)	Centers in high- and middle-income countriesŁ (n = 57)	Centers in relatively lower-income countriesł (n = 13)	*P*-value
Rehabilitation specialists that can be consulted for TBI patients at the ICU				
Rehabilitation physician	48 (70%)	38 (67%)	10 (83%)	.32*
Neuropsychologist	36 (52%)	31 (54%)	5 (42%)	.42
Physical therapist, occupational therapist or speech therapist	67 (96%)	55 (97%)	12 (92%)	.47*
Dietician, social worker or rehab nurse	63 (90%)	51 (99%)	12 (93%)	.61*
Multidisciplinary rehabilitation team	29 (41%)	21 (37%)	8 (62%)	.10
Rehabilitation specialists that can be consulted for TBI patients at the ward				
Rehabilitation physician	54 (78%)	43 (75%)	11 (92%)	.44*
Neuropsychologist	45 (65%)	37 (65%)	8 (67%)	.59*
Physical therapist, occupational therapist or speech therapist	68 (97%)	56 (98%)	12 (92%)	.34*
Dietician, social worker or rehab nurse	65 (93%)	53 (93%)	12 (92%)	.65*
Multidisciplinary rehabilitation team	34 (49%)	56 (44%)	9 (69%)	.10
Structural characteristics				
TBI specific rehabilitation guidelines	13 (19%)	12 (22%)	1 (8%)	.44*
In-hospital coma stimulation	34 (49%)	27 (47%)	7 (54%)	.67
In-hospital rehabilitation unit	36 (51%)	28 (49%)	8 (62%)	.45
Outpatient rehabilitation facility	25 (36%)	21 (37%)	4 (31%)	.76*
Structural connection with rehabilitation facilities	57 (81%)	47 (83%)	10 (77%)	.64*

Table presents characteristics of in-hospital rehabilitation in 70 neurotrauma centers across Europe. *P*-values represent differences between high- and middle-income versus lower-income countries calculated by Chi Square test or Fisher's exact test (*).
ŁHigh / middle income: Austria, Belgium, Denmark, Finland, France, Germany, Israel, Italy, the Netherlands, Norway, Spain, Sweden and the United Kingdom; Relatively low income: Bosnia Herzegovina, Bulgaria, Hungary, Latvia, Lithuania, Romania and Serbia
ł North and West Europe: Austria, Belgium, Denmark, Finland, France, Germany, Lithuania, the Netherlands, Norway, Sweden and the United Kingdom; South and East Europe and Israel: Bosnia Herzegovina, Hungary, Israel, Italy, Latvia, Romania, Serbia, Spain and Switzerland

Coma stimulation

Half of the participants (n = 34) reported that they use coma stimulation in their center. In these centers, mobility stimulation (n= 29, 85%) was used most often, followed by sensory stimulation (n = 25, 74%) and pharmacological stimulation (n= 19, 56%, Online Supplement B).

Rehabilitation facilities

Half of the participants (n = 37) reported to have an in-hospital rehabilitation unit, while one third had an outpatient rehabilitation facility (n = 25). In addition, 57 (81%) participants indicated to have structural connections with rehabilitation facilities in the area. There were no differences

between relatively high- and middle-income and lower-income countries on any of these characteristics (Table 1).

Referral to post-acute rehabilitation facilities

To assess referral patterns to post-acute rehabilitation facilities, participants were presented four cases and they were requested to indicate which referral institutions they would consider. They were allowed to provide more than one answer, as long as it reflected their 'general policy'. The cases included (1) patients < 65 years and (2) elderly patients > 65 years; both age groups with the following characteristics: (A) not obeying commands and (B) obeying commands but still in posttraumatic amnesia (PTA) and with severe behavioral problems.

The large majority indicated that the young patients would be referred to rehabilitation centers (Figure 1). Young patients not obeying commands could also be referred to nursing homes (n = 17), local hospitals (n = 19) or coma care facilities (n = 16). For young patients obeying commands but still in PTA and with severe behavioral problems, psychiatric hospitals (n = 17), local hospitals (n = 20) or outpatient facilities (n = 15) were also reported as referral possibilities.

Figure 1. **Referral to rehabilitation facilities in 70 neurotrauma centers participating in the CENTER-TBI study**

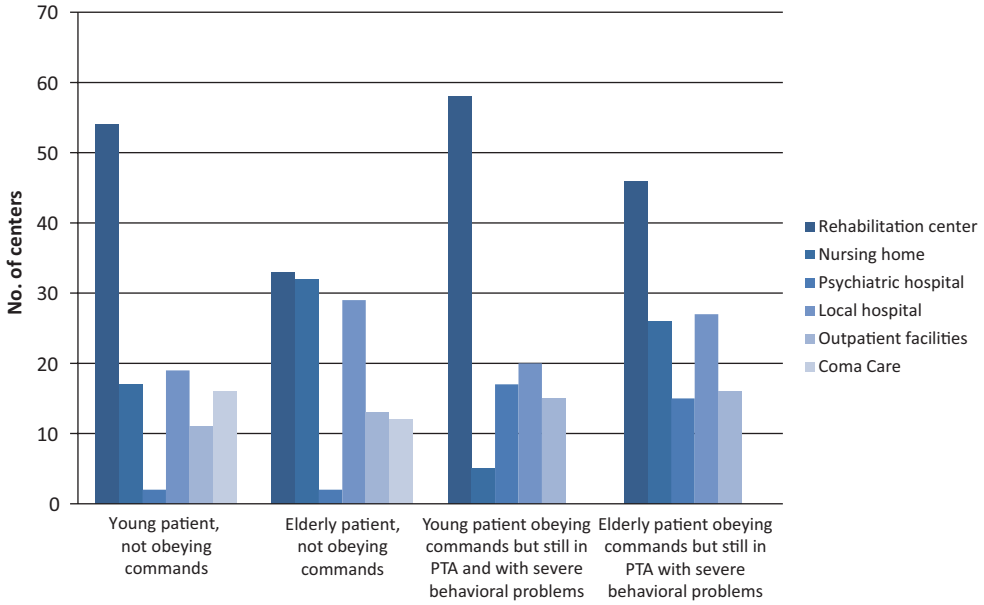


Figure shows which rehabilitation facilities a center would consider in patients with certain characteristics. Centers were allowed to select more than one facility as long as it reflected their general policy. Elderly patient: age ≥ 65year

For elderly patients, a more mixed image appeared. Elderly patients not obeying commands could be referred to either rehabilitation centers (n = 33), nursing homes (n = 32) or local hospitals (n = 29). For elderly patients obeying commands but still in PTA and with severe behavioral problems, rehabilitation centers (n = 46) were most often considered, followed by nursing homes (n = 26) and local hospitals (n = 27).

Influence of age on referral decisions

Participants were asked explicitly whether patient's age has a major influence on referral decisions. Forty-six per cent (n = 32) indicated that this was the case. Participants declared that rehabilitation programs have age limits or selection favoring younger patients. Also, the rehabilitation potential of older patients is regarded lower, and as a consequence, older patients are more often referred to non-specialized rehabilitation programs or nursing homes (Online Supplement C).

We elaborated whether the influence of age on referral decisions was dependent on income, geographic location (North and West Europe vs. South and East Europe and Israel), the completer of the questionnaire (rehabilitation physician vs. other completer), personnel characteristics (availability of a rehabilitation physician and neuropsychologist) and the availability of an in-hospital multidisciplinary team and an in-hospital rehabilitation unit (Online Supplement D). We found that high- and middle-income countries more often indicated that age has a major influence on referral in comparison to relatively lower-income countries ($p < .01$). There were however no differences between high- and middle and relatively lower-income countries in whether they would generally refer elderly patients to nursing homes. We additionally found a trend toward higher referral to nursing homes in elderly patients with PTA and behavioral problems in North and West Europe in comparison in South and East Europe and Israel ($p = .09$). In addition, we found that centers in which a rehabilitation physician was available more often indicated that age has a major influence on referral decisions in comparison to centers in which a rehabilitation physician was not available ($p = .05$).

Waiting time for rehabilitation facilities

We asked for the average waiting time for rehabilitation facilities, which was defined as the time between the moment that the patient is ready to be discharged from the center and the time of admission or first visit at the referral institute. The average waiting time was usually no longer than one month (Table 2). For specialized rehabilitation centers, patients could be admitted within a few days in seven (10%) centers, within one week in 26 (38%) centers and within one month in 27 (40%) centers. The waiting time for nursing homes and coma care facilities was slightly longer.

Table 2. **Waiting time for rehabilitation facilities among 70 European neurotrauma centers participating in the CENTER-TBI study**

Waiting time	Rehabilitation center (n = 68)	Nursing home (n = 58)	Psychiatric hospital (n = 55)	Local hospital (n = 63)	Coma care facility (n = 53)
Within a few days	7 (10%)	8 (14%)	20 (36%)	31 (49%)	6 (11%)
Within one week	26 (38%)	15 (26%)	14 (25%)	20 (32%)	10 (19%)
Within one month	27 (40%)	21 (36%)	13 (24%)	10 (16%)	21 (40%)
> 1 month	8 (12%)	14 (24%)	8 (15%)	2 (3%)	16 (30%)

Table presents the waiting time for rehabilitation facilities among 70 neurotrauma centers across Europe.

Factors relevant for referral decision

Participants had to indicate how important certain factors were in their referral decision to rehabilitation facilities. They were asked to give a score of 1 (most important) to 5 (least important) to the following aspects: quality of care, distance to a patient's home, availability at short notice, specialized neuro-rehabilitation, and funding (Figure 2). Distance to a patient's home was rated as the most important factor for rehabilitation referral and funding/financial reason was rated as the least important factor.

Figure 2. **Factors considered important in the referral decision of 70 neurotrauma centers participating in the CENTER-TBI study**

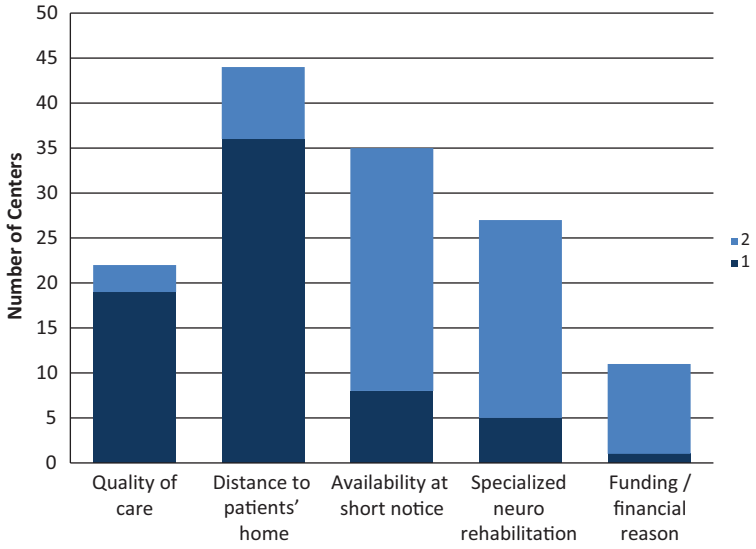
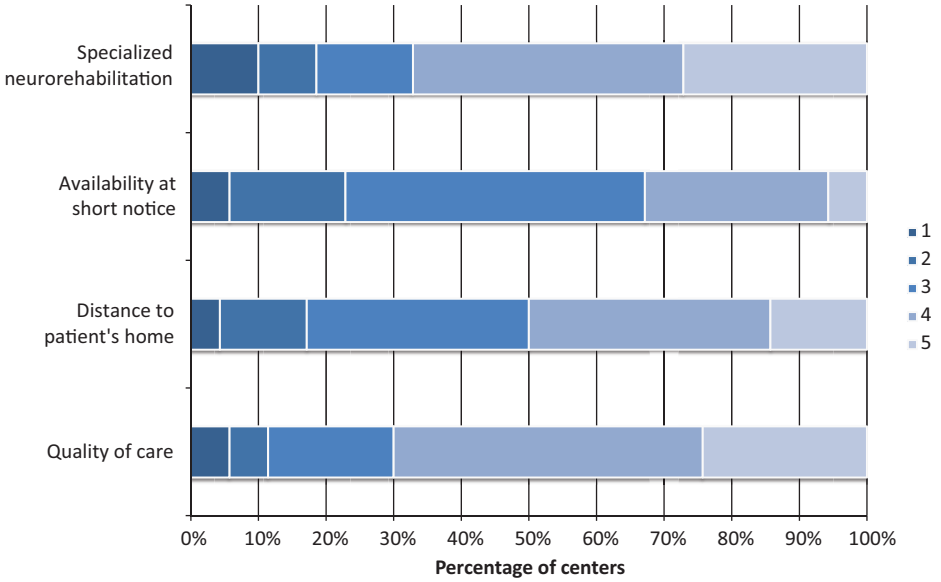


Figure shows the number of centers that responded with an 1 (most important) or 2 (second most important) to the five factors that could be considered relevant in decisions about referral to rehabilitation facilities.

Satisfaction with rehabilitation possibilities

We subsequently asked participants how satisfied they were with rehabilitation possibilities in their area, using the same criteria (except for funding/financial reason). Regarding quality of care and specialized neuro-rehabilitation possibilities, the majority of centers were satisfied (score 4 or 5 out of 5). However, for distance to a patient's home and availability at short notice, less than half of the centers gave a score of 4 or 5 (Figure 3). Three centers, from three different countries indicated that they were dissatisfied with all four items (score 1 or 2 on all items).

Figure 3. **Satisfaction with rehabilitation facilities in 70 neurotrauma centers participating in the CENTER-TBI study**



Centers were asked whether they were satisfied with the rehabilitation facilities in their region: 1 = not satisfied; 5 = completely satisfied

Discussion

We found marked variation in structure and process characteristics of early in-hospital TBI rehabilitation and referral to post-acute rehabilitation care among 70 centers participating in a European TBI research project.

The following limitations should be taken into account when interpreting the data. First and foremost, the included centers comprise a selected group of neurotrauma centers participating in a European multicenter study. The centers are all active in the field of neurotrauma care and research, and therefore, it may be that the picture obtained is better than the real overall situation in Europe. The differences in structures and processes may be even larger when considering non-specialized centers. Our findings therefore cannot be generalized and should

be interpreted with caution. Secondly, our study provides information on what centers reported rather than characteristics that were directly observed. Lack of concordance between reported and observed characteristics is common in survey studies. For example, a 2007 survey study about intracranial pressure (ICP) monitoring reported that 77% of the patients were treated according to the guidelines,11 while a recent systematic review found that the mean percentage adherence to ICP monitoring guidelines was only 31%.[12] We cannot exclude that the centers in our study also provided a more favorable image of their structural and process characteristics. This would again result in a more favorable picture. Related, questionnaires were completed by only a few physicians in every center rather than by all physicians that treat patients with TBI in a particular center. Although we asked for their general policy, we cannot exclude that some of the answers display personal opinions rather than the department or hospital policy. Results from the ongoing CENTER-TBI study will provide insight into possible discrepancies between these policy opinion statements and actual practice. Another limitation is that the question on referral preferences did not take into account patients' and proxies' preferences and needs. It should be acknowledged that referral decisions in clinical practice often incorporate patients' and proxies' preferences and might be based on shared decision-making. Therefore, the results on referral preferences should be interpreted as the participant's rating of relative importance of five factors rather than displaying actual referral patterns. The PP questionnaires themselves also have some limitations. For example, the length (321 questions) may have resulted in lower data quality.[9]

The observed variation in structure and process is consistent with other surveys about rehabilitation after TBI.[13-16] Large variation in rehabilitation practices might be partly explained by the limited use of guidelines. Only one-fifth of the centers in our survey indicated that they use TBI-specific rehabilitation guidelines during the acute treatment phase. These guidelines were based on expert opinion and developed within the center, rather than based on national/ international evidence-based guidelines. This reflects an absence of evidence-based guidelines on this topic. For instance, the Brain Trauma Foundation guidelines, which are probably the most often used guidelines for the treatment of patients with severe TBI, have not included recommendations regarding in-hospital rehabilitation.[17] We would therefore recommend guideline developers to include recommendations about early rehabilitation in their guidelines.

Another interesting finding is the influence of age on referral decisions. In our survey, patients above age 65 are less often referred to specialized rehabilitation centers than younger patients and around half of the centers indicated that age has a major influence on referral decisions. This shows a clear disparity in access to care, and is against the Article 21 of the Fundamental Rights of EU. Inequality in access to rehabilitation care after brain injury has been widely shown for racial and ethnic minorities[18-21] and uninsured patients[19,21] and our study implies that patients with an older age are also at risk. Notwithstanding, it has been shown that elderly patients can make substantial improvements during inpatient rehabilitation and could often be discharged home.[22,23] Since the prevalence of elderly TBI patients is increasing,[24] physicians and policy

makers should be aware of the age disparity, and the influence of age on rehabilitation potential should be studied further in future studies. The concept of inferior rehabilitation potential in the elderly may be a consequence of a self-fulfilling prophecy in earlier practices and studies. In addition, further qualitative research might unravel why age is an important factor in referral to rehabilitation facilities for some doctors and centers and not for others.

Another implication of our work is that the effectiveness of rehabilitation interventions could be studied with comparative effectiveness research (CER). Knowledge about effectiveness and best practices of TBI rehabilitation is critically important since recent research has suggested that differences in outcome between developed and developing countries are mainly due to differences in rehabilitation care, rather than differences in acute care.[25] CER refers to the use of existing differences in policy between centers to analyze treatment effectiveness. A prerequisite for CER is that there is considerable variation in policy among centers, which is shown in our study. We therefore think that CER is an adequate framework to enhance knowledge about effectiveness of rehabilitation interventions in TBI and inform patients, clinicians and guideline developers directly about this information. CER within the CENTER-TBI project can be studied by comparing patients in centers that perform a certain intervention as the general policy to patients in centers that do not generally use this intervention. For example, we can compare the outcome of comatose patients from the 34 centers that use in-hospital coma stimulation to comatose patients from the 36 centers that do not use in-hospital coma stimulation, after correcting for case mix and other differences among centers. Other potential interesting topics for CER based on the current results include the availability of an in-hospital multidisciplinary team, the treatment of elderly patients in specialized rehabilitation centers vs. in nursing homes and the impact of waiting time on outcome.

Conclusion

Marked variation in structure and process of in-hospital rehabilitation and referral to rehabilitation facilities exists between European neurotrauma centers. This variation provides the possibility to study effectiveness of specific rehabilitation interventions in comparative effectiveness research, but also indicates that there is likely room for improvement in quality of care, long-term outcome and cost-effectiveness of TBI rehabilitation. In addition, this study found a disparity in access to specialized rehabilitation care for elderly patients. Future research is warranted to study referral decision-making processes and further investigate the rehabilitation potential of elderly patients.

Supplemental material is available at www.marysecnossen.nl

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14

Causes and consequences of treatment variation in moderate and severe traumatic brain injury: A multicenter study

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Abstract

Objectives: Although guidelines have been developed to standardize care in traumatic brain injury (TBI), between-center variation in treatment approach has been frequently reported. We examined variation in treatment for TBI by assessing factors influencing treatment and the association between treatment and patient outcome.

Design: Secondary analysis of prospectively collected data.

Setting: Five level-I trauma centers in the Netherlands (2008-2009).

Patients: 503 patients with moderate or severe TBI (Glasgow Coma Scale: 3-13).

Interventions: We examined variation in seven treatment parameters: direct transfer, involvement of mobile medical team, mechanical ventilation, intracranial pressure (ICP) monitoring, vasopressors, acute neurosurgical intervention and extracranial operation.

Measurements and Main Results: Data were collected on patient characteristics, treatment and six-month Glasgow Outcome Scale Extended (GOSE). Multivariable logistic regression models were used to assess the extent to which treatment was determined by patient characteristics. To examine whether there were between-center differences in treatment, we used unadjusted and adjusted random effect models with the seven treatment parameters as dependent variables. The influence of treatment approach in a center (defined as aggressive and nonaggressive based on the frequency ICP monitoring) on outcome was assessed using multivariable random effect proportional odds regression models in those patients with an indication for ICP monitoring. Sensitivity analyses were performed to test alternative definitions of aggressiveness.

Treatment was modestly related to patient characteristics (Nagelkerke R^2 range 0.12-0.52) and varied widely among centers, even after case-mix correction. Outcome was more favorable in patients treated in aggressive centers than those treated in nonaggressive centers (OR: 1.73; 95% CI 1.05-3.15). Sensitivity analyses, however, illustrated that the aggressiveness-outcome association was dependent on the definition used.

Conclusions: The considerable between-center variation in treatment for patients with brain injury can only partly be explained by differences in patient characteristics. An aggressive treatment approach may imply better outcome, although further confirmation is required.

Introduction

Although clinical guidelines have been developed to reduce variability in care of patients with traumatic brain injury (TBI), between-center variation in treatment approach has been frequently reported.[1-3] It is not fully understood to what extent differences in treatment approach among centers reflect differences in patient population ('case-mix') or differences in hospital policy. Clinical patients characteristics, such as age and Glasgow Coma Scale (GCS), are associated with treatment approach and guideline adherence in TBI.[4,5] However, it is also known that treatment approach is at least partly a hospital characteristic and is influenced by local routines[2] and health care policies.[6] Moreover, insufficient numbers of prospective, randomized controlled trials are available to underpin clinical TBI guidelines,[7] which vary widely in content,[8] thereby failing to sufficiently reduce treatment variation

Whether treatment variability among centers reflects variation in quality of care and subsequently influences patient outcome is unknown. For the majority of interventions for moderate- and severe TBI, effectiveness is not established yet.[7] Additionally, deviation from best practices could theoretically also reflect adequate, patient-tailored care.[9] Large between-center variation in outcome after TBI has however been described[10] and it has been suggested that differences in quality of care might at least partly explain this variation.

In this study, we therefore examined variation in treatment for moderate and severe TBI by assessing factors influencing treatment and the association between treatment and patient outcome.

Materials and methods

Design, setting and patients

We performed a secondary analysis of the Prospective Observational COhort Neurotrauma (POCON) study dataset, which contains prospectively collected data about 508 patients with moderate and severe TBI (GCS 3-13) presenting at five level I trauma centers in the Netherlands between June 1, 2008 and May 31, 2009. Patients were consecutively enrolled and extensive data checks were performed to warrant that all eligible patients were asked to participate in this study. All centers were Academic centers. Three centers were from urban areas and two from rural regions. In each center, protocols based on the Brain Trauma Foundation (BTF) guidelines (2007)[11] were available. Patients younger than 16 years old and those who were admitted to the hospital more than 72 hours post-injury were excluded.[12] We further excluded patients with gunshot injuries (n = 4) or a missing value on one of the seven treatment variables of interest (n = 1).

The institutional review board (IRB) of the coordinating hospital (Radboud University Nijmegen Medical Center) approved the study protocol and the other participating hospitals provided a feasibility statement.[12] Informed consent was obtained orally or written during outcome assessment after six months.[12] Further details on the development of the POCON database have been reported in a previous publication.[12]

Patient variables

Data from medical records were entered into a research database by trained research staff supervised by a physician.[12] Collected variables included age, gender, GCS, Abbreviated Injury Scale (AIS) scores for head, face, neck, skin, thorax, abdomen, spine and extremities, pupillary reactivity, hypoxic episode (at injury scene or emergency department (ED), yes = confirmed (SaO_2 < 90%) or suspected based on clinical grounds), hypotensive episode (at injury scene or ED, yes = confirmed (SBP < 90 mmHg) or suspected based on clinical ground), glucose (mmol/L) and hemoglobin (g/dL) levels. For all these variables (except for hypoxia and hypotension), the first score after arriving at the ED was used for analysis.

Severe and moderate TBI were defined as a GCS score at ED 3-8 and 9-13, respectively. Extracranial injury severity score (ISS) was calculated by adding the squared AIS scores of the three most severely injured body regions with exclusion of the AIS head. The initial computed tomography (CT) scan performed was assessed using the Traumatic Coma Data Bank (TCDB) score.[13] Additionally, the presence of subarachnoid hemorrhages (SAH, present/absent) and epidural hemorrhages (EDH, present/absent) were scored. In case of missing values, the second CT scan was taken on condition that the scan was made within six hours after the first scan and prior to any neurosurgical intervention.

Outcome was measured with the Glasgow Outcome Scale Extended (GOSE) six months post-injury by either a postal questionnaire or a telephone interview. The categories 'vegetative state' (GOSE = 2) and 'lower severe disability' (GOSE = 3) were combined, as there were only two patients with a vegetative state. The seven-point GOSE was subsequently used as an ordinal outcome variable.

Differences in case-mix according to observed patient characteristics were summarized as the probability on survival and favorable outcome (GOSE ≥ 5) for each patient, based on the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) lab model, including age, GCS motor score (first score after arriving at the ED), pupillary reaction (first score after arriving at the ED), hypoxia, hypotension, CT classification, SAH, EDH, glucose (first score after arriving at the ED) and hemoglobin (first score after arriving at the ED) as predictors.[14] These prognostic scores reflect the chances, respectively, of survival and favorable outcome given a patient's baseline- and clinical characteristics.

Treatment variables

The following acute treatment processes were considered based on the BTF and Dutch prehospital guidelines: transfer (direct/indirect); involvement of the mobile medical team (yes / no), endotracheal intubation (at the scene / during transport / during hospital stay / before operation), mechanical ventilation (yes / no), sedation (yes / no), ICP monitoring (yes / no), barbiturates (yes / no), cerebrospinal fluid (CSF) drainage (yes / no), vasopressors for cerebral perfusion pressure (CPP) support (yes / no), hyperventilation (yes / no), osmotherapy (mannitol, hypertonic saline and/or HyperHAES®: yes / no), induced hypothermia (< 35°C: yes / no), acute neurosurgical intervention (yes / no), delayed neurosurgical intervention (yes / no) and extracranial operation (yes / no).

We excluded endotracheal intubation for further analysis, as the BTF recommendation at the scene is not fully applicable to the Netherlands due to short travelling distances from scene to level I trauma center.[15] We also excluded sedation, CSF drainage, hyperventilation and osmotherapy as no reliable information was collected on treatment doses while different doses of these therapies are considered as representing different treatment intensity in the BTF guideline.[16] Barbiturates, hypothermia and delayed neurosurgical intervention were further excluded as they were conducted in less than 10% of the patients.

To examine the association between treatment approach and outcome, we divided centers into "aggressive" and "nonaggressive" based on the frequency of ICP monitor placement in patients with a BTF indication for ICP monitoring; i.e. patients with severe TBI and an abnormal head CT (TCDB score ≥ 2) or patients with severe TBI (GCS ≤ 8), a normal head CT (TCDB score = 1) and two out of the following three risk factors: (1) age > 40 years, (2) hypotensive episode (SBP < 90 mmHg), and (3) motor score ≤ 3 (unilateral or bilateral motor posturing).[16] Centers inserting an ICP monitor in ≥ 50% of patients meeting the criteria were defined as aggressive; the remainder was defined as nonaggressive. This subdivision has been reported in previous studies about treatment effectiveness.[1,17,18]

Statistical analyses

To calculate whether patient characteristics and treatment differed significantly among five centers, we used the chi-square test for dichotomous and ordinal variables and the non-parametric Kruskal-Wallis test for continuous variables, since these all had a skewed distribution.

To assess to what extent treatment was determined by patient characteristics, we used multivariable logistic regression models with treatment as dependent variable and the IMPACT prognostic variables and extracranial ISS as predictors. Backward elimination of predictors (at $p > .157$[19]) was used to select patient characteristics that were the strongest determinants of treatment. We calculated Nagelkerke R^2 to determine the variance in treatment that was determined by patient characteristics.

To explore the effect of center on treatment we subsequently used random effect logistic regression models with treatment as dependent variable and a random intercept for center as independent variable. Random effect models correct for between-center differences in treatment that are attributable to factors not in the model or differences that exist by chance. In a univariable model (with only a random intercept for center), crude differences between centers in treatment were estimated. Subsequently, the relevant patient characteristics were added as covariates to adjust for between-center differences in case-mix.

Differences between aggressive and nonaggressive centers in patient- and treatment characteristics were calculated using chi-square and Kruskall Wallis tests. Only those patients with an indication for ICP monitoring were selected. The effect of aggressiveness on outcome was subsequently analyzed with a random effects proportional odds regression model with aggressiveness (yes / no), a random intercept for center and the IMPACT probability score of favorable outcome as independent variables and the ordinal GOSE as dependent variable. This model estimates the effect of aggressiveness on outcome adjusted for patient characteristics and for other differences between centers than the treatment under study. The effect of aggressiveness was expressed as an odds ratio (OR). The corresponding 95% confidence interval (CI) was calculated using bootstrapping with 500 samples.

From the random effect models we derived the model parameter tau^2 [20] to quantify the between-center variation in respectively treatment and outcome that cannot be explained by factors in the model or chance. We expressed the between-center variation as an OR for the difference of a hospital at the 97.5th percentile versus the 2.5th percentile (Exp(3.92$\sqrt{T^2}$)), for better clinical interpretation. A value of 1 represents no unexplained differences in respectively treatment or outcome between centers with the most and least treatment or unfavorable outcomes.

Missing values in baseline- and clinical characteristics were imputed with multiple imputations with all patient baseline- and clinical characteristics and GOSE as covariates. The random effect analyses were performed in R (version 3.1.2) using the *ordinal*[21], *lme4*[22] and *graphics*[23] packages. All other analyses were performed using Statistical Package for the Social Sciences (SPSS) version 21. A *p*-value < 0.05 was considered statistically significant in all analyses.

Sensitivity analyses

As the definition of aggressiveness was arbitrary, we performed sensitivity analyses with alternative definitions. The following alternative definitions of aggressiveness were considered:

1. ICP monitor inserted in ≥ 45% of those with a BTF indication, as this would move one center from the less aggressive to the aggressive group.
2. Treatment with a Therapy Intensity Level (TIL)[24] ≥ 2 in ≥ 50% of the patients with a BTF indication for ICP monitoring. TIL ≥ 2 refers to mild to extreme ICP lowering therapy and

includes vasopressors for CPP support, osmotic therapy, hyperventilation, CSF drainage, hypothermia, barbiturates and neurosurgical interventions

3. Acute neurosurgical intervention performed in ≥ 50% of the patients with a mass lesion.
4. ICP monitoring, TIL ≥ 2 and intracranial operation performed in ≥ 50% of those indicated.

Results

Patient characteristics

The study population consisted of 503 patients with a median age of 46 years (Interquartile range 28-65). Patients were predominately male (n = 349; 69%) and 335 (67%) patients had a presenting GCS ≤ 8. There were 191 missing data points, which we imputed with multiple imputation techniques.

Patient characteristics varied considerably among the centers (Table 1). In the center with the most favorable case-mix, the probability of survival based on patient characteristics was 87% (95% CI: 49%-97%). In the center with the most severe patients this probability was 57% (24%-92%). Actual outcome (n=410) differed significantly among centers with the poorest outcome in the center with the most severe and oldest patients (center 3).

Effect of patient characteristics on treatment

Patient characteristics modestly predicted treatment (Table 2). The regression models based on patient characteristics explained 12% to 52% of the variance in treatment. The wide range indicates variation in how much a decision to treat is determined by observed patient characteristics.

The models included on average 6 (range 4-8) predictors with age, GCS motor score, pupillary reactivity, CT classification and extracranial ISS score being significant variables in the majority of models predicting treatment. More intensive treatments were generally more often performed in younger patients with more severe TBI.

Treatment variation among centers

Treatment varied substantially among centers (Figure 1). There was significant variation in six out of seven treatment interventions (mobile medical team, mechanical ventilation, ICP monitoring, vasopressors, acute neurosurgical intervention and extracranial operation). The greatest variability was seen in involvement of the mobile medical team (range 26%-54%) and the use of ICP monitoring (range 12%-40%).

Table 1. **Baseline and clinical characteristics, prognostic scores and six-month outcome of 503 adult patients with moderate and severe traumatic brain injury**

Characteristics	Total (n = 503)	Center 1 (n = 73)	Center 2 (n = 117)	Center 3 (n = 82)	Center 4 (n = 76)	Center 5 (n = 155)	P-value
Baseline and clinical characteristics							
Age (median, IQR)	46 (28-65)	39 (26-65)	47 (26-66)	54 (32-71)	51 (34-68)	45 (27-59)	.02
Male gender	349 (69%)	49 (67%)	84 (72%)	55 (67%)	54 (71%)	107 (69%)	.94
Severe TBI (GCS ≤8)	335 (67%)	51 (70%)	67 (57%)	63 (77%)	53 (70%)	101 (65%)	.06
GCS motor score (median, IQR)*	2 (1-5)	1 (1-5)	4 (1-6)	1 (1-5)	4 (1-5)	1 (1-5)	.02
Pupillary reactivity*							.01
– Both pupils reactive	334 (71%)	40 (65%)	94 (85%)	50 (63%)	47 (67%)	103 (69%)	
– One pupil reactive	30 (6%)	3 (4%)	4 (3%)	10 (13%)	4 (6%)	9 (6%)	
– No pupil reactive	107 (23%)	19 (31%)	13 (12%)	19 (24%)	19 (27%)	37 (25%)	
Hypoxia (confirmed or suspected)	97 (21%)	8 (12%)	23 (20%)	30 (44%)	6 (9%)	30 (20%)	.00
Hypotension (confirmed or suspected)	99 (20%)	15 (22%)	27 (24%)	16 (20%)	5 (7%)	36 (23%)	.04
CT classification ^							.00
– Normal	130 (27%)	14 (20%)	47 (43%)	5 (6%)	13 (17%)	51 (34%)	
– Diffuse II	151 (31%)	19 (27%)	28 (25%)	30 (37%)	28 (38%)	46 (31%)	
– Diffuse III/IV	44 (9%)	5 (7%)	10 (9%)	6 (7%)	7 (10%)	16 (11%)	
– Mass lesion	160 (33%)	33 (46%)	25 (23%)	40 (50%)	26 (35%)	36 (24%)	
SAH	201 (42%)	32 (45%)	37 (34%)	45 (56%)	27 (38%)	60 (40%)	.03
EDH	52 (11%)	11 (16%)	12 (11%)	12 (15%)	6 (8%)	11 (7%)	.25
Extracranial ISS (median, IQR)	5 (1-16)	4 (0-13)	5 (1-16)	5 (1-13)	4 (0-13)	9 (1-20)	.01
Glucose (mmol/L; median, IQR)*	7.9 (6.4-10.3)	8.4 (6.6-10.3)	7.8 (6.2-10.4)	8.4 (6.7-9.9)	7.8 (6.2-10.3)	7.9 (6.6-10.3)	.77
Hemoglobin (g/dL; mean, SD)*	7.9 (7.0-8.6)	8.0 (7.4-8.6)	7.9 (6.6-8.8)	7.9 (7.4-8.7)	7.8 (6.7-8.9)	7.7 (6.9-8.5)	.31

Table 1. **Continued**

Characteristics	Total (n = 503)	Center 1 (n = 73)	Center 2 (n = 117)	Center 3 (n = 82)	Center 4 (n = 76)	Center 5 (n = 155)	*P*-value
IMPACT prognostic scores							
$P_{Survival}$ (median, IQR)[B]	.78 (.36-.96)	.80 (.37-.95)	.87 (.49-.97)	.57 (.24-.92)	.74 (.37-.96)	.81 (.34-.97)	.02
$P_{Favorable\ outcome}$ (median, IQR)[B]	.48 (.15-.85)	.48 (.18-.81)	.66 (.28-.88)	.31 (.11-.74)	.45 (.13-.82)	.50 (.12-.87)	.01
Outcome							
6-month GOSE							.04
1. Death	164 (40%)	22 (38%)	33 (35%)	34 (50%)	26 (39%)	49 (39%)	
2. Vegetative state	2 (1%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	
3. Lower severe disability	28 (7%)	3 (5%)	7 (7%)	9 (13%)	5 (8%)	4 (3%)	
4. Upper severe disability	29 (7%)	4 (7%)	9 (10%)	3 (5%)	7 (11%)	6 (5%)	
5. Lower moderate disability	39 (9%)	7 (12%)	14 (15%)	5 (7%)	5 (8%)	8 (6%)	
6. Upper moderate disability	44 (11%)	1 (2%)	7 (7%)	8 (12%)	5 (8%)	23 (19%)	
7. Lower good recovery	44 (11%)	10 (17%)	9 (10%)	5 (7%)	9 (13%)	11 (9%)	
8. Upper good recovery	60 (14%)	10 (17%)	15 (16%)	4 (6%)	9 (13%)	22 (18%)	

Values are presented as n (%) unless otherwise specified. *P*-values represent Kruskall Wallis or Chi Square results between the five centers.
Abbreviations: IQR = Interquartile range; TBI = Traumatic Brain Injury; GCS = Glasgow Coma Scale; CT = Computed Tomography; SAH = Subarachnoid Hematoma; EDH = Extradural Hematoma; ISS = Injury Severity Score; IMPACT = International Mission for Prognosis and Analysis of Clinical Trials; GOSE = Glasgow Outcome Scale Extended.
[A]CT classification is based on the Traumatic Coma Databank.[13]. Diffuse II refers to CT abnormalities without swelling or shift; Diffuse III refers to CT abnormalities with swelling (compressed cisterns); Diffuse IV refers to CT abnormalities with a shift.
[B]$P_{survival}$ is the probability of six-month survival; $P_{favorable\ outcome}$ is the probability of six-month favorable outcome (GOSE > 4). The prognostic scores are based on the variables in the IMPACT lab model[14]: age, GCS motor score, pupillary reaction, hypoxia, hypotension, CT classification, SAH, EDH, Glucose and Hemoglobin. They were calculated after data imputation.
Missing values: Pupillary reactivity: n = 32; hypoxia: n = 29; hypotension: n = 9; CT classification n = 18; SAH = 23; EDH = 23; ISS extracranial n = 7; Glucose n = 30; HB n = 20; GOSE: n = 93.
*the first value after arriving at the emergency department was displayed here

Table 2. **Baseline- and clinical patient characteristics influencing treatment**

Baseline or clinical characteristic	Direct transfer	Mobile Medical Team	Mechanical Ventilation	ICP monitoring	Vasopressors for CPP	Acute Neurosurgical intervention [A]	Extracranial operation
Age (per 10 yr)	0.87 (0.76-0.99)*	0.85 (0.77-0.95)**	0.83 (0.72-0.95)**	0.76 (0.66-0.86)**	0.78 (0.68-0.89)**		0.84 (0.74-0.95)*
GCS motor score	-	0.58 (0.52-0.66)**	0.53 (0.45-0.63)**	0.72 (0.63-0.83)**	0.75 (0.65-0.88)**	0.80 (0.66-0.96)*	-
Pupillary reaction							
– One versus both	1.76 (0.56-5.50)	0.48 (0.20-1.16)	1.43 (0.38-5.38)	-	1.37 (0.55-3.42)		2.45 (1.24-4.84)*
– None versus both	2.54 (1.27-5.07)*	0.62 (0.36-1.09)	0.35 (0.15-0.84)*	-	0.48 (0.25-0.91)*		0.43 (0.15-1.26)
Hypoxia	-	0.54 (0.31-0.94)**	-	-	-	0.37 (0.16-0.83)*	0.41 (0.21-0.81)*
Hypotension	-	-	-	0.62 (0.33-1.17)	-		-
CT classification							
– Diffuse II vs normal	0.50 (0.20-1.25)	-	3.58 (1.90-6.76)**	7.40 (2.62-20.90)**	3.72 (1.37-10.08)**	NA	-
– Diffuse III/IV vs normal	0.32 (0.10-1.07)	-	2.13 (0.77-5.88)	14.04 (4.25-46.36)**	16.42 (5.42-49.74)**	NA	-
– Mass lesion vs normal	0.10 (0.04-0.24)**	-	8.45 (4.03-17.73)**	26.97 (9.10-79.92)**	40.95 (14.78-113.48)**	NA	-
SAH	-	-	-	1.85 (1.08-3.16)*	-		-
EDH	2.96 (1.14-7.66)*	-	-	1.69 (0.84-3.37)	-	2.59 (1.10-6.06)*	-
Extracranial ISS	-	1.03 (1.01-1.05)**	1.04 (1.00-1.07)*	1.03 (1.01-1.05)**	1.03 (1.00-1.05)*		1.09 (1.06-1.11)**
Glucose	-	-	1.14 (1.02-1.27)*	1.08 (0.99-1.18)	1.11 (1.02-1.20)*		1.09 (0.99-1.18)
Hemoglobin	-	0.76 (0.64-0.91)**	0.82 (0.64-1.04)	-	-	1.28 (0.96-1.71)	0.77 (0.63-0.94)*
Nagelkerke R^2	**0.19**	**0.40**	**0.52**	**0.43**	**0.42**	**0.12**	**0.34**

Table presents adjusted odds ratio (OR) and 95% confidence interval (CI) of baseline and clinical characteristics influencing treatment.

Abbreviations: ICP = Intracranial Pressure; CPP = Cerebral Perfusion Pressure; GCS = Glasgow Coma Scale; CT = Computer Tomography; SAH = Subarachnoid Hematoma; EDH = Extradural Hematoma; ISS = Injury Severity Score.

*P < .05; ** p < .01

[A] Analyses performed in 160 patients with mass lesions as acute intracranial operations were not performed in patients without mass lesion

Figure 1. **Treatment characteristics by center (n = 503)**

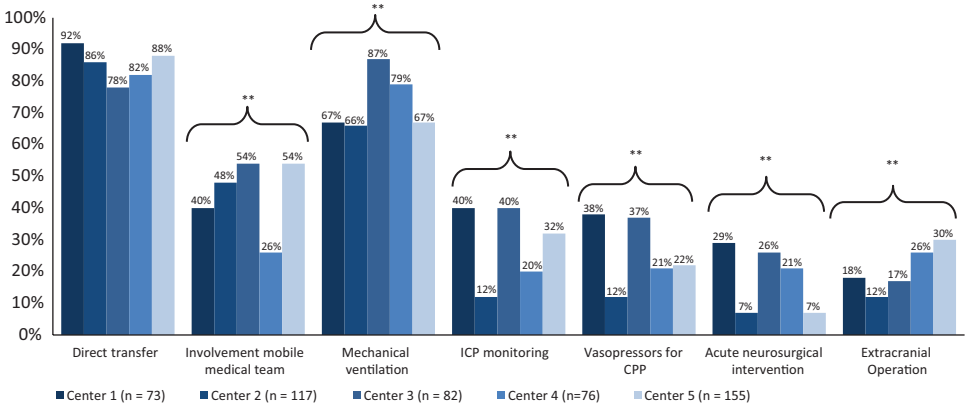

Figure shows the percentage of patients that receive treatment per center.
*P < 0.05; ** p < 0.01
Abbreviations: ICP = Intracranial Pressure; CPP = Cerebral Perfusion Pressure

Unadjusted random effect models confirmed the wide between-center variation in treatment (Figure 2). For example, an average patient had a 9.06 higher odds of having an ICP monitor placed in the hospital that performed most ICP monitoring (97.5th percentile) compared to the hospital that performed least ICP monitoring (2.5th percentile). Substantial differences were also reported for mobile medical team (OR = 4.30), mechanical ventilation (OR = 4.26), vasopressors (OR = 7.02), acute neurosurgical intervention (OR = 5.92) and extracranial operation (OR = 4.08).

Between-center variation generally became smaller after case-mix correction (correction for relevant predictors from Table 2), indicating that patient characteristics explained some of the variation. However, for the majority of treatments the between-center differences remained remarkable with differences in odds of receiving treatment up to 5.21 between centers that performed most and least treatment ($OR_{adjusted}$ Mechanical ventilation: 3.51; ICP monitoring: 5.21; Vasopressors: 3.20).

Exceptions were transfer, for which between-center differences were completely explained by differences in case-mix among centers ($OR_{adjusted}$ = 1.00), and mobile medical team, acute neurosurgical intervention and extracranial operation, for which the difference in odds of receiving treatment increased after case-mix correction ($OR_{adjusted}$ Mobile medical team: 6.61, Acute neurosurgical intervention: 7.32; Extracranial operation: 5.13). This indicates that there is even more variation among centers after correction for demographic and clinical patient characteristics.

Figure 2. **Between-center differences in treatment characteristics in unadjusted and adjusted random effect models**

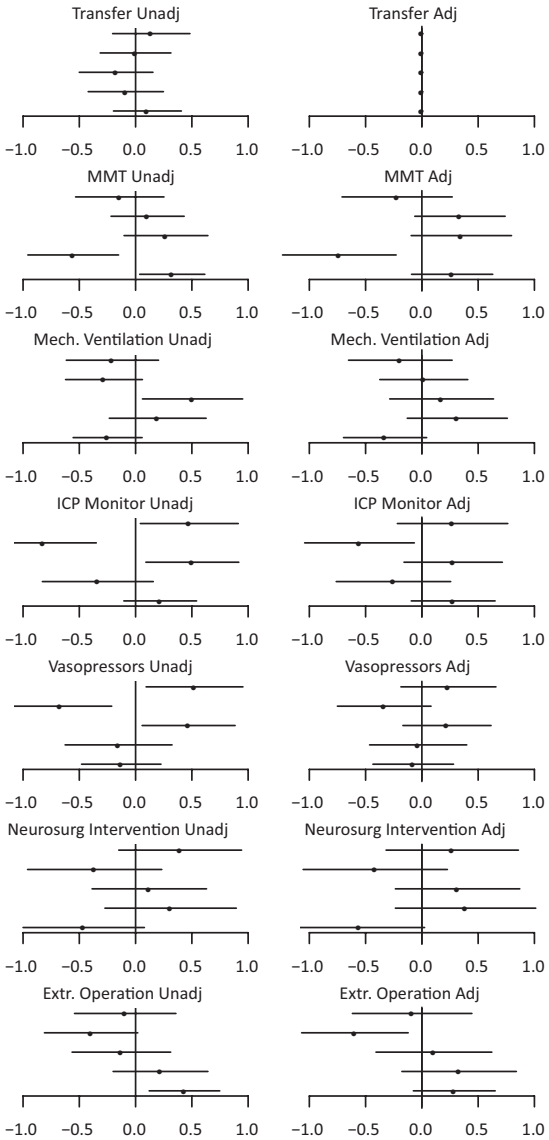

Figure presents the random intercepts for center based on random effect models with treatment as dependent variable. Model 1 (unadjusted) includes only a random intercept for hospital, and model 2 (adjusted) includes a random intercept for hospital and all relevant patient characteristics as covariates. The random hospital coefficients and 95% Confidence Intervals are shown.

Model parameter tau2 was derived to quantify the between-center variation in treatment, not explained by factors in the model or by chance. Tau2 was expressed as the OR for the difference of a hospital at the 97.5th percentile vs the 2.5th percentile (Exp(3.92√T2)) for better clinical interpretation.

Tau2: Direct transfer unadjusted = 2.21; Direct transfer adjusted = 1.00; Mobile medical team unadjusted = 4.30; Mobile medical team adjusted = 6.61; Mechanical ventilation unadjusted = 4.26; Mechanical ventilation adjusted = 3.51; Intracranial pressure monitoring unadjusted = 9.06; Intracranial pressure monitoring adjusted = 5.21; Vasopressors unadjusted = 7.02; Vasopressors adjusted = 3.20; Acute neurosurgical intervention unadjusted = 5.92; Acute neurosurgical intervention adjusted = 7.32; Extracranial operation unadjusted = 4.08; Extracranial operation adjusted = 5.13.

Abbreviations: Unadj = unadjusted model; Adj = adjusted model; MMT = Mobile Medical Team; ICP = Intracranial Pressure; Neurosurg Intervention = Acute neurosurgical intervention

Effect of treatment variation on patient outcome

Since ICP monitoring is indicated in patients with severe TBI and CT abnormalities or two out of three risk factors (age > 40, SBP < 90mmHg, unilateral/bilateral motor posturing) we omitted patients who did not fulfill these criteria from the aggressiveness-outcome analyses. This resulted in 300 eligible patients, of whom 266 completed the 6-month follow-up assessment. Patients with a follow-up assessment were generally older (median age 49 vs. 43), were more often female (33% vs. 15%) and had more often a SAH at the CT-scan (55 vs. 32%). There were no other statistically significant differences between patients with and without an outcome assessment.

Two centers were classified as having an aggressive approach towards ICP monitoring (center 1: 55% and center 5: 54%) and three as having a nonaggressive approach (center 2: 19%; center 3: 47%; center 4: 26%). Baseline- and clinical characteristics, summarized as the predicted probability of survival and favorable outcome, did not differ among aggressive and nonaggressive centers (Online Supplement A). Aggressive and nonaggressive centers did not differ on general procedures except for direct transfer (88% vs. 79%, p = .04) and mechanical ventilation (86% vs. 96%, p < .01). As expected, aggressive centers used more vasopressors for the treatment of patients with elevated ICP (43% vs. 29%, p = .02). Adjusted for case-mix, patients treated in aggressive centers had a more favorable outcome than patients treated in nonaggressive centers (OR: 1.73; 95% CI 1.05-3.15, Table 3). Additionally, treatment approach explained the between-center differences in outcome among centers. In the reference model adjusted for case-mix, the center with the best outcome (97.5th percentile) had a two-times higher odds on favorable outcome compared to the center with the worst outcome (2.5th percentile) that was not explained by factors in the model or chance. After the addition of aggressiveness, this value decreased to one, indicating that differences in outcome among centers can be attributed to the extent to which centers maintain an aggressive treatment approach. Alternative definitions of aggressiveness resulted in non-significant effects (Table 3). However, combining all definition into one 'aggressiveness' score resulted in a statistically significant positive association between aggressiveness and patient outcome (OR: 2.11, 95%CI 1.12-3.99)

Table 3. **Estimates of treatment effect (odds ratio (OR) and 95% confidence interval (CI) and between-center differences in six-month outcome (Glasgow outcome scale extended) in 266 patients with an indication for Intracranial Pressure (ICP) monitoring**

Model	OR (95% CI)	Exp(3.92√T²)
Reference		
Adjusted for probability of favorable outcome	-	1.93
Analysis aggressiveness		
ICP monitor in ≥ 50%, adjusted for probability favorable outcome[A]	1.73 (1.05-3.15)	1.00
Sensitivity analyses		
I: ICP monitor in ≥ 45%, adjusted for probability favorable outcome[B]	1.24 (0.73-2.11)	1.71
II: TIL2+ in ≥ 50% adjusted for probability favorable outcome[B]	1.24 (0.73-2.11)	1.71
III: Acute neurosurgical intervention in ≥ 50% of patients with CT score ≥ 5 (mass lesion) adjusted for probability favorable outcome (160 patients)[C]	0.72 (0.34-1.41)	1.00
IV: ICP monitor, acute neurosurgical intervention and TIL2 in ≥ 50%, adjusted for probability favorable outcome[D]	2.11 (1.12-3.99)	1.00

Table presents Odds Ratio (OR) and 95% Confidence Interval (CI) of random effect proportional odds analyses with aggressiveness and the probability of favorable outcome as dependent variables and six-month Glasgow Outcome Scale Extended (ordinal scale) as outcome.

Parameter Tau2 (T2) represents between-center variation not explained by factors in the model or by chance. The value of T2 was expressed as the OR for the difference between the hospital with the most favorable outcome (97.5th) percentile versus the hospital with the most unfavorable outcome (2.5th percentile (Exp(3.92√T^2)))

CT score is based on the Traumatic Coma Databank 13.

Abbreviations: ICP = Intracranial Pressure; GCS = Glasgow Coma Scale; CT = computer tomography; TIL2+ = therapy intensity level 2 (any of the following: vasopressors for CPP support, osmotic therapy, hyperventilation, cerebrospinal fluid drainage, hypothermia, barbiturates and neurosurgical intervention).

[A] Center 1 and 5 are classified as aggressive

[B] Center 1,3 and 5 are classified as aggressive

[C] Center 1, 3 and 4 are classified as aggressive

[D] Center 1 is classified as aggressive

Discussion

We found considerable variation in patient population, treatment and outcome among five level I trauma centers treating moderate and severe TBI patients. Treatment was modestly related to patient characteristics, and varied substantially between centers, even after correcting for case-mix. Treatment approach was significantly related to six-month outcome after case-mix correction, with a more favorable outcome in patients treated in centers maintaining an aggressive approach with respect to ICP management. Yet, these results depended on the definition of aggressiveness and should therefore be interpreted with caution.

Variation in treatment approach is commonly reported in the field of TBI.[1,4,25] A multicenter study in the United States reported that the use of ICP monitors in severe TBI patients even ranged from zero to 100% among centers.[1] Differences in treatment approach might be explained by differences in policies and guidelines among centers.[2,6,8] It remains, nevertheless, surprising that five level I trauma centers from the same country with similar structures, policies and guidelines, show substantial treatment variation.

One of our hypotheses was that treatment variation at least partly reflected variation in case-mix, as we found major differences in patient characteristics between centers. The *a priori* chances on survival and favorable outcome based on patient characteristics were almost twice as high in the center with the least severe patients compared to the center with the most severe patients. This could reflect differences in admission policy, dispatch decisions and population served. Further, recruiters were neurologists in some centers (center 2 and 5) and neurosurgeons and intensivists in others. Although the inclusion was consecutive and extensive data checks have been performed in all centers, we cannot exclude the possibility that less severe patients were missed in centers where a neurosurgeon or intensivist included patients.

Despite extensive variation, patient characteristics only modestly predicted treatment in our study. This was consistent with a previous study about factors influencing ICP monitoring.[5] Similar findings were also reported in a study about adherence to various BTF recommendations.[26] A possible explanation is that the associations between patient characteristics and treatment interventions are not linear but instead follow an inverse U curve, i.e. intensive treatment is considered in those with a poor prognosis, and not in those with an extremely poor prognosis (no treatment benefit expected) or those with a good prognosis (treatment is not necessary). The findings from our study suggest a new alternative explanation; treatment is merely a center characteristic. We found large differences in the odds of receiving certain treatments among centers, even after case-mix correction; i.e. similar patients had an over five times higher odds of having an ICP monitor placed in the center that used most ICP monitors (97.5th percentile) compared to the center that used least ICP monitors (2.5th percentile).

We found a more favorable outcome in patients treated in centers maintaining an aggressive treatment approach. This was previously shown in a multicenter study in the United States.[1] Authors divided centers as being aggressive and nonaggressive based on a cut-off of 50% adherence to ICP monitoring guidelines and found lower mortality in patients treated in aggressive centers. One other multi-center study divided centers into quartiles based on their percentage ICP monitoring.[4] They also found that patients in centers in the higher ICP quartiles had a more favorable outcome. These studies did not assess to what extent treatment approach explained differences between centers in outcome. We did and we found that treatment approach in terms of ICP monitoring did explain between-center differences in outcome. This finding is important, as unexplained differences in outcome between centers have been frequently reported in the field of TBI.[10]

Analyzing treatment effectiveness by comparing outcome in aggressive and nonaggressive centers has strengths and limitations. A major strength is that this method may better avoid biases related to confounding by indication, which is a threat in observational studies examining treatment effectiveness on patient level.[27,28] A limitation is however that the subdivision results in an artificial difference between centers with no relevance for clinical practice. Related, the

cut-off point of aggressiveness is arbitrary; our sensitivity analyses showed that shifting the cut-off point with 5% already resulted in non-significant findings. Also, we defined centers as aggressive if they placed an ICP monitor in ≥ 50% of the patients with a BTF indication, consistent with previous investigations.[1,17,18] It might however be argued that 50% adherence to standards is still rather low and that a cut-off of 80-90% would comprise a more appropriate definition for aggressiveness. This was however not possible in our dataset, since the highest percentage patients treated with ICP monitoring in our sample was 55%, congruent with a systematic review on guideline adherence in TBI.[29]

Another limitation of our study is that the number of patients available was modest for the number of treatment variables examined, which may result in false positive findings. However, our sensitivity analyses all showed consistent results. A last limitation concerns the generalizability of our study. Our data was collected between 2008 and 2009 in five level I trauma centers within the same country. However, all participating centers implemented the 2007 BTF guidelines,[11] which makes them comparable to other level I trauma centers in Western countries that have implemented these guidelines. The BTF guidelines have recently been updated[16] but the ICP monitoring indications have not been changed, further improving the generalizability of our study.

Our study has implications for clinical practice and future research in the field. Observational studies analyzing the effectiveness of ICP monitoring on patient level have resulted in contradictory findings,[30] which might be due to confounding by indication. Our study adds to the increasing evidence that ICP monitoring might be an effective treatment strategy for patients with TBI, as suggested by previous studies with a relatively low risk of confounding by indication.[1,4] More research is however needed to further strengthen the evidence, especially since the significance of the effect depended on the definition of aggressiveness. In future studies, ideally, treatment approach should be defined in advance, independently from the data with for example a questionnaire about treatment policy or former registry data. We further recommend (observational) treatment effectiveness studies in the field of TBI to analyze effectiveness on the hospital level. Although this method is statistically inefficient, especially in case of large within-center variation, it may better adjust for unobserved confounding by indication. Rather than dividing centers into aggressive and nonaggressive, there should be enough centers included to divide them into for example deciles based on the percentage treated.

We would further recommend examining what structure, process and physician-related factors underlie center differences in treatment approach. This will give insight in decision-making processes around TBI treatment and additionally can provide policy makers targets for quality improvement interventions.

We also recommend to further assess patient characteristics that determine TBI treatment. The variables used in this study were all commonly reported confounders for which treatment effectiveness studies usually correct in their analyses. The finding that they only modestly relate to treatment might imply two things. There might either be additional unobserved patient characteristics influencing treatment decision-making or treatment is relatively independent from patient characteristics. The first situation would be problematic as these unobserved patient characteristics could confound the association between treatment and outcome. The second situation would be favorable as treatment allocation is relatively random and consequently, the influence of patient-level confounders would be minimal.

Conclusion

In conclusion, the considerable between-center variation in treatment for patients with brain injury is only partly explained by differences in patient characteristics. Although many patient- and center factors may be relevant for treatment decision-making, patients treated in more aggressive centers may have a more favorable outcome. Future studies with treatment approach defined at center level are needed to validate our findings.

Supplemental material is available at www.marysecnossen.nl

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Estimating treatment effectiveness of intracranial pressure monitoring in traumatic brain injury

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With great interest we read the study by Yuan *et al.*[1] in a recent issue of *Critical Care Medicine.* In this retrospective observational multicenter study the authors aimed to assess the effectiveness of intracranial pressure (ICP) monitoring in patients with moderate and severe traumatic brain injury (TBI). They found a favorable effect of ICP monitoring on mortality in three subgroups.

There are two drawbacks that we would like to address concerning this study. First, although knowledge about differential treatment effects in subgroups is valuable for individualized patient care, subgroups in this study were not predefined. Testing multiple subgroups within the same patient population is not recommended, since there is a high risk of spurious findings.[2] For example, when testing 20 subgroups, one of these will be statistically significant just by chance when using $p < 0.05$. The subgroup results should therefore be interpreted as explorative. Further confirmation in large-scale observational studies is required before starting randomized controlled trials in the suggested subgroups.

Second, the adjustment for confounding by indication has likely been incomplete. As expected, patients with ICP monitoring differed from those not monitored in several aspects. Authors aimed to adjust for confounding by indication by estimating propensity scores of receiving treatment and corrected their analyses accordingly. Propensity scores can however only correct for *observed* confounders[3] while treatment decisions may also be based on factors that are not captured in the data. As an alternative approach, we would suggest instrumental variable (IV) analyses to estimate treatment effects in observational studies in TBI. IV analysis is a relatively new method that can adjust for unobserved confounders. The instrument should be highly correlated with the treatment under study but not with the observed and unobserved confounders. Since between-center variation in treatment is large in TBI, center might be a suitable instrument. To our knowledge, two studies estimated effectiveness of ICP monitoring using this IV-like approach.[4,5] In both studies, patients treated in centers that more often performed ICP monitoring, had a lower mortality and a more favorable outcome. This approach is expected to provide a less bias estimate of treatment effects.

In sum, the results of Yuan et al.[1] should be interpreted with caution. We recommend future studies with IV-like methods to validate their subgroups findings.

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Adjusting for confounding by indication in observational studies in traumatic brain injury

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Abstract

Background: Observational studies are at risk for confounding by indication, referring to a situation where the indication for a particular intervention is a confounder in the association between the intervention and outcome. The objective of the current study was to define the circumstances for the validity of methods to adjust for confounding by indication in observational studies.

Methods and findings: As a case-study, we performed post-hoc analyses of data prospectively collected from three European and North-American TBI studies including a total of 1,725 patients with moderate and severe TBI. The effects of three interventions (intracranial pressure (ICP) monitoring, intracranial operation and primary referral) were estimated in a proportional odds regression model with the Glasgow Outcome Scale as ordinal outcome variable. Three analytical methods were compared: classical covariate adjustment; propensity score adjustment; and instrumental variable (IV) analysis in which the percentage exposed to an intervention in each hospital was added as an independent variable, together with a random intercept for each hospital. In addition, a simulation study was performed in which a hypothetical beneficial intervention (OR = 1.65) was simulated for scenarios with and without unmeasured confounders.

For all three interventions, covariate adjustment and propensity score adjustment resulted in non-significant estimates of the effect (OR range 0.80-0.92), whereas the IV approach indicated that ICP monitoring was beneficial (OR per 10% change: 1.17; 95% CI 1.01-1.42).

In our simulation study, we found that covariate adjustment and propensity score adjustment provided estimates in line with the simulated effect if all confounders were adjusted for (OR range: 1.37-1.67). However, the estimates became invalid in case of unmeasured confounders (OR range: 0.98-1.03). The IV approach provided an estimate with a similar direction as the simulated effect (OR per 10% change 1.04-1.05), but was statistically inefficient.

Conclusions: The effect estimation of interventions in observational TBI studies strongly depends on the analytical method used. When unobserved confounding and practice variation are expected, instrumental variable analysis should be considered to estimate effectiveness of interventions in large-scale observational multicenter studies.

Introduction

Randomized controlled trials (RCTs) are considered the cornerstone of evidence-based medicine. They are however not always feasible due financial, ethical and practical constraints.[1] Observational studies constitute the main alternative. A key challenge in observational studies is confounding by indication, referring to a situation where the indication is a confounder in the association between the intervention and outcome.[2] As a consequence, patients exposed and not exposed to a particular intervention might not be exchangeable, hampering causal inference.

The epidemiological and statistical literature describes several analytical methods to account for confounding, among which covariate- and propensity score adjustment are probably the most commonly applied. In covariate adjustment, measured confounders are added as independent variables to the analytical model. This results in a risk-adjusted effect estimate.[3,4] In propensity score adjustment, the chance ('propensity') of being exposed to the intervention, based on measured patient characteristics, is added as a covariate to the model or used to match patients exposed and not exposed.[4] Propensity score adjustment aims to balance factors influencing management decisions[3,5,6] and is especially to be considered when there are few outcome events.[4] These commonly applied methods however cannot adequately correct for unmeasured confounders. For example, a surgeon may decide to perform an operation because of his clinical intuition. Clinical intuition might be related to the patient's prognosis but may not be adequately captured in the clinical data and thereby may leave residual confounding.[2,7,8] A relatively new method to adjust for confounding is instrumental variable (IV) analysis. In IV, a substitute variable, 'the instrument' (e.g. hospital), is used as level of analysis. IV is becoming more popular in comparative effectiveness research (CER) and can theoretically adjust for unmeasured confounders.[3,4,9] However, its validity depends on the degree to which the following three assumptions are met: The instrument should be strongly associated with the intervention under study (assumption 1), not related to the confounders (assumption 2) and not independently associated with the outcome under study (assumption 3).[3,4,9]

Clinical practice in patients with traumatic brain injury (TBI) is generally hypothesized to be prone to confounding by indication because treatment choice and outcome are highly dependent on injury severity. In addition, the combination of a low evidence-base and strong (cultural or eminence based) beliefs of best practice leads to large practice variation between hospitals.[10] This combination makes IV analysis of observational studies in TBI a promising approach. For the purpose of the current study, we selected three interventions that have shown to be effective according to best available evidence and expert consensus meetings, [11-15] with guidelines advocating these strategies,[16-21] but also have shown extensive practice variation: ICP placement for ICP directed therapies versus serial clinical and radiological assessment,[22] to operate or not in mass lesions,[23] and primary versus secondary referral to specialized care.[21]

The objective of the current study was to define the circumstances for the validity of methods to adjust for confounding by indication using three selected interventions in TBI patients and a simulation study.

Methods

Study populations and interventions

Three TBI datasets were used. The Prospective Observational Cohort Neurotrauma (POCON) dataset consists of 557 consecutive patients with moderate and severe TBI (Glasgow Coma Scale (GCS) score 3-13) from five level I trauma centers in the Netherlands between 2008-2009. Detailed information on data collection, procedures and patients has been described previously.[24] From the POCON dataset, we extracted 266 patients with an indication for intracranial pressure (ICP) monitoring according to the 2007 Brain Trauma Foundation (BTF) guidelines;[25] that is, patients with a GCS ≤ 8 and a Computed Tomography (CT) Marshall score ≥ 2, or patients with a GCS score ≤ 8, CT Marshall score < 2 and at least one of the following risk factors: 1) age > 40 years; 2) hypotensive episode (SBP < 90 mmHg); and 3) motor score ≤ 3 (unilateral of bilateral motor posturing).

We further used the International Mission for Prognosis and Analysis of Clinical Trials (IMPACT) dataset, which consists of data from prospective studies and phase III trials in patients with moderate and severe TBI.[26] The International and North American Tirilazad trial (86 hospitals between 1992 and 1994) was selected from the IMPACT dataset to estimate the effectiveness of intracranial operations (craniotomy or craniectomy). From the 2159 patients included in these trials, data of 677 patients with severe TBI, a mass lesion and a six-month outcome assessment were extracted.

We additionally selected the European Brain Injury Consortium (EBIC) study (67 hospitals, in 1995) from the IMPACT dataset, which contains information on 822 patients. Referral and outcome were assessed in 782 patients, who were subsequently extracted. Detailed information on the IMPACT dataset has been comprehensively described in previous publications.[26-28]

Data collection

Collected patient variables in all datasets included age, gender, GCS (motor) score, pupillary reactivity (both pupils reactive, one pupil reactive, no pupil reactivity), hypoxic episode (at injury scene or emergency department), hypotensive episode (at injury scene or emergency department), admission glucose level (mmol/L) and admission hemoglobin level (hb, g/L). In all datasets, the initial CT scan was assessed using the Marshall score,[29] and the presence of traumatic subarachnoid hemorrhages (tSAH) and epidural hemorrhages (EDH) were scored.

To summarize patient characteristics, we calculated the probability of survival and favorable outcome (Glasgow Outcome Scale (GOS) score ≥ 4) for each patient based on the IMPACT laboratory model[30] with all above-mentioned demographic and clinical factors as predictors. These prognostic scores reflect chances on respectively survival and favorable outcome based on baseline characteristics.

Six-month outcome was assessed using the Glasgow Outcome Scale Extended (GOS-E) in the POCON dataset and the GOS in the EBIC and Tirilazad trial datasets. Both scales were collapsed into a four-point ordinal scale: 1= death or persistent vegetative state; 2 = severe disability; 3 = moderate disability; 4 = good recovery.

Statistical analyses

Missing values in patient characteristics were imputed using single imputation. To assess differences in patient characteristics between patients exposed and not exposed to the interventions in the imputed datasets, we used Chi-Square tests for dichotomous and ordinal variables and non-parametric Mann-Whitney *U* tests for continuous variables since they all had a skewed distribution.

To examine the effectiveness of interventions, we used proportional odds logistic regression models with the 4-point ordinal GOS as outcome variable. A proportional odds model increases statistical power in comparison to a conventional logistic regression model with a binary outcome.[31] The odds ratios (OR) derived from a proportional odds regression model could be interpreted as the average shift over the GOS caused by the intervention under study.[31]

As a reference, we estimated unadjusted effects of the interventions with patient (exposed to the intervention yes / no) as the unit of analysis. To adjust for confounders, we performed covariate adjustment, propensity score adjustment and IV analysis. In the covariate-adjusted model, the variables from the IMPACT prognostic model[30] (age, GCS motor score, pupillary reaction, hypoxia, hypotension, CT classification, tSAH, EDH, glucose and Hb) were added as independent variables. In a propensity score adjusted model, the propensity of being exposed to the intervention was computed using multivariable logistic regression with the intervention under study as dependent variable and all IMPACT variables as predictors. The linear predictor of the propensity score model was added as a covariate to the proportional odds regression models. We used fixed effect models for all the patient-level analyses. The ORs and 95% confidence intervals (CIs) were obtained from the models and the ORs indicated the odds of a more favorable outcome for patients who were exposed to the intervention compared to patients not exposed.

For the IV analyses, we entered the percentage exposed to the intervention in each hospital (the instrument) as an independent variable to the analyses, together with a random intercept for hospital to correct for other between-hospital differences than the intervention under study

or between-hospital differences that existed by chance. All IMPACT prognostic variables were added as covariates to increase statistical power.[32] To minimize the influence of chance, we only included hospitals with data on at least 20 patients in the IV analyses. The ORs were obtained from the models and the corresponding 95% CIs were calculated using bootstrapping with 500 samples. The ORs indicated an odds of a more favorable outcome for a 10% increase in exposure to the intervention. Assumptions of the IV approach were checked by calculating the partial F statistic, in line with recommendations.[33] In addition, we checked associations with measured confounders by calculating Spearman's correlation coefficients between the instrumental variables and the prognostic scores of survival and favorable outcome. The third assumption (the instrumental variable is not independently associated with outcome) cannot be empirically verified, but is captured in the random effect model that we used.

The proportional odds analyses were performed in R (version 3.1.2) using the *ordinal* package.[34] Other analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 21. A p-value < 0.05 was considered statistically significant.

Sensitivity analyses

As sensitivity analyses we explored alternative methods related to propensity score adjustment and IV. Propensity score matching was used to match patients who were exposed to the intervention to patients who were not exposed to the intervention with a maximum difference of 0.10 between propensity scores. An advantage of propensity score matching is that patients with non-overlapping propensity scores are omitted from the analyses, increasing the comparability of those exposed and not exposed.[3,5] This however may also result in a non-representative sample[3] and a loss of statistical power.[35] We further used inverse probability weighting (IPW) as an alternative propensity score method. In IPW, the outcome of patients exposed to the intervention is extrapolated to the non-exposed patients with similar propensity scores; i.e. for every patient exposed with a probability of 0.20, there are four patients with the same probability who were not exposed. The outcome of the exposed patient is subsequently extrapolated to all other four patients with the same propensity score.[36] We used standardized weights in which we divided the unadjusted chance of receiving the intervention in the total study population by the propensity score.[37] Since this still resulted in large standard errors, we winsorized our cohort by 95%; i.e. patients below the 2.5th and above the 97.5th percentile received the scores belonging to the 2.5th and 97.5th quartile, respectively.

As an alternative to the IV approach used in this study, we divided hospitals into two groups based on their preference for the intervention. The mean percentage exposed to each intervention was calculated and hospitals scoring above these means were classified as having a high preference, whereas hospitals scoring below the means were classified as having a low preference.

Since the percentage patients exposed to the intervention in each hospital can still be based on case-mix (e.g. in a hospital with more severely injured patients, the percentage patients receiving aggressive interventions might be higher) and could also exist by chance, we estimated a random intercept for hospital from a model predicting exposure to the intervention yes / no adjusted for the IMPACT variables. This random intercept for exposure represents the chance of receiving the intervention in a specific hospital corrected for case-mix and was subsequently used instead of the percentage exposed in the IV analyses. A disadvantage of this method is that the estimate obtained is hard to interpret and very uncertain due to the shrinkage of the between-hospital variation by the random effects model.

Simulation study

In empirical data, 'true' effects are never known and as a consequence, estimating the validity of analytical methods remains difficult. Therefore, we performed a simulation study in which a true treatment effect was simulated in the data. The simulation study was built around the POCON dataset, which was inflated to 133,000 patients from 20 hospitals. We simulated a hypothetical intervention with a beneficial effect of OR = 1.65. For the association between the hypothetical intervention and confounders, we used the observed associations between ICP monitoring and confounders in the POCON dataset. We used six-month survival (yes / no) as outcome variable, which was generated based on a combination of the prognostic effect of the confounders and the effect of the hypothetical intervention.

We simulated four different scenarios and estimated the treatment effect using covariate adjustment, propensity score adjustment and IV analysis. In the first scenario, there were only measured confounders. We used motor score and pupillary reactivity as representing the measured confounders. In the second scenario, both measured and unmeasured characteristics comprised confounders. Marshall CT scores and the presence of a tSAH were used as unmeasured confounders. For both the first and second scenario, no between-hospital variation existed, which is comparable to a single-center study. The third and fourth scenarios were similar to the first and the second, but included between-hospital variation in how often the hypothetical intervention was performed. Since the observed variation of ICP monitoring among hospitals ranged from 17 to 58%, every hospital received a random percentage within this range. The simulations were performed in R statistical software using the *rms*[38] and *lme4*[39] packages.

Results

Patient characteristics

In the POCON dataset, used for exploring the effects of ICP monitoring, patients who received an ICP monitor (n = 110) had a worse *a priori* prognosis than patients who did not receive an ICP monitor (n = 156; chance on survival 39% and 58% respectively, p = .03). Also, observed outcome was less favorable in patients who received an ICP monitor (p < .01).

In the Tirilazad dataset, used for exploring the effects of intracranial surgery, patients who did (n = 579) and did not (n = 98) receive an intracranial operation did not differ on baseline characteristics except for hypotension (14% vs. 21%, p = .05) and the presence of an EDH (31% vs 10%, p < .01), nor did the observed outcome differ (p = .22).

In the EBIC dataset, used for exploring the effects of referral policy, patients who were primary referred (n = 334) had higher blood glucose levels (8.1 vs. 7.9 mmol/L, p = .01) and more often a tSAH (47% vs. 38%, p = .01) compared to patients who were secondary referred (n = 448). There were no other differences between groups (Table 1).

Covariate and propensity score adjustment

Univariable analyses showed that patients receiving an ICP monitor in the POCON dataset had a worse outcome than patients not receiving an ICP monitor (OR 0.51; 95%CI 0.32-0.81; Table 2). For intracranial operation and primary referral, as analyzed in the Tirilazad and EBIC datasets respectively, no statistically significant differences between treated and non-treated patients were found. Adjusting the effect for demographic and clinical covariates or for the propensity score resulted in non-significant estimates below one for all three interventions (OR range 0.80-0.92), indicating that exposure to the interventions might be associated with unfavorable outcome.

Instrumental variable analysis

In the POCON dataset, the percentage of patients that received an ICP monitor ranged from 17-58% between participating hospitals. All five hospitals included at least 20 patients (range 37-51 patients). For intracranial operation, only seven hospitals from the Tirilazad dataset included more than 20 patients, encompassing 172 patients. The percentage of patients receiving an intracranial operation ranged from 67 to 100% between hospitals. For primary referral, 12 hospitals from the EBIC dataset included more than 20 patients, reducing the sample size to 350 patients. The percentage primary referrals ranged from 17 to 83% between hospitals.

The instruments (percentage of patients exposed to the intervention in each hospital) were associated with the interventions under study (Partial F statistic 6.96 to 65,9, all p < .01). In addition, correlations between the instruments and confounders were small and generally non-significant (Online Supplement A). However, the percentage treated with an intracranial operation in each center in the Tirilazad dataset was significantly associated with the prognostic score on survival (r = .17, p = .03).

Table 1. **Baseline, clinical and outcome characteristics of patients exposed and not exposed to three interventions**

Characteristic	POCON dataset			Tirilazad dataset			EBIC dataset		
	ICP+ (n = 110)	ICP- (n = 156)	*P*	Intr. Operation+ (n = 579)	Intr. Operation- (n = 98)	*P*	Primary Ref. (n = 448)	Secondary Ref. (n = 334)	*P*
Age (median, IQR)	45 (27-57)	58 (35-70)	*< .01*	35 (24-47)	33 (25-47)	*.83*	33 (22-53)	41 (26-60)	*.53*
Male gender	79 (72%)	99 (64%)	*.15*	463 (80%)	78 (80%)	*.93*	245 (73%)	337 (75%)	*.52*
GCS motor score (median, IQR)	1 (1-1)	1 (1-3)	*.01*	4 (3-5)	4 (3-5)	*.71*	5 (2-6)	5 (2-6)	*.95*
Pupillary reactivity			.04			.94			.51
– Both pupils reactive	48 (44%)	93 (60%)		346 (60%)	57 (58%)		213 (64%)	298 (66%)	
– One pupil reactive	13 (12%)	14 (9%)		106 (18%)	18 (18%)		30 (9%)	44 (10%)	
– No pupil reactive	49 (44%)	49 (31%)		127 (22%)	23 (24%)		91 (27%)	106 (24%)	
Hypoxia (yes or suspected)	24 (22%)	50 (32%)	*.07*	115 (20%)	25 (26%)	*.20*	93 (28%)	132 (30%)	*.62*
Hypotension (yes or suspected)	22 (20%)	55 (35%)	*.01*	80 (14%)	21 (21%)	*.05*	87 (26%)	104 (23%)	*.36*
CT classification†			< .01			NA			.06
– Normal	2 (2%)	26 (16%)		NA	NA		49 (15%)	46 (10%)	
– Diffuse II	25 (23%)	64 (41%)		NA	NA		102 (31%)	125 (28%)	
– Diffuse III/IV	19 (17%)	15 (10%)		NA	NA		45 (14%)	52 (12%)	
– Mass lesion	64 (58%)	51 (33%)		579 (100%)	98 (100%)		138 (41%)	225 (50%)	
tSAH	70 (64%)	77 (49%)	*.02*	319 (55%)	56 (57%)	*.71*	156 (47%)	168 (38%)	.01
EDH	19 (17%)	10 (6%)	*.01*	178 (31%)	10 (10%)	*<. 01*	30 (%)	44 (10%)	*.69*
Glucose (mmol/L) (median, IQR)	9.0 (7.3-11.1)	8.3 (6.7-11.0)	*.21*	8.4 (6.9-10.8)	8.4 (6.5-10.8)	*.78*	8.1 (6.8-10.9)	7.9 (6.4-9.6)	.01
Hemoglobin (g/dL) (mean, IQR)	7.5 (6.3-8.3)	7.6 (6.6-8.5)	*.34*	12.8 (11.0-14.3)	13.2 (11.1-14.8)	*.32*	12.7 (11.0–14.4)	12.9 (11.3–14.3)	*.56*
$P_{survival6}$ ‡	.39 (.15-.77)	.58 (.12-.92)	*.03*	.74 (.52-.86)	.75 (.47-.85)	*.25*	.75 (.38-.92)	.79 (.44-.93)	.40
P_{fav6} ‡	.16 (.06-.41)	.40 (.05-.78)	*< .01*	.49 (.23-.72)	.53 (.19-.71)	*.52*	.49 (.19 - .76)	.53 (.22-.78)	*.42*

Table 1. **Continued**

Characteristic	POCON dataset			Tirilazad dataset			EBIC dataset		
	ICP+ (n = 110)	**ICP- (n = 156)**	***P***	**Intr. Operation+ (n = 579)**	**Intr. Operation- (n = 98)**	***P***	**Primary Ref. (n = 448)**	**Secondary Ref. (n = 334)**	***P***
GOS			< .01			.22			.32
– Death	60 (54%)	73 (47%)		190 (33%)	37 (38%)		116 (35%)	146 (32%)	
– Persistent vegetative state	2 (2%)	0 (0%)		36 (6%)	3 (3%)		11 (3%)	7 (2%)	
– Severe disability	20 (18%)	16 (10%)		77 (13%)	8 (8%)		46 (14%)	68 (15%)	
– Moderate disability	22 (20%)	26 (17%)		85 (15%)	20 (20%)		70 (21%)	85 (19%)	
– Good recovery	6 (6%)	41 (26%)		191 (33%)	30 (31%)		91 (27%)	142 (32%)	

Table presents values after data imputation. Values are presented as n (%) unless otherwise specified. *P*-values represent the differences between patients receiving and not receiving the intervention.

† CT classification is based on the Marshall classification. Diffuse II refers to CT abnormalities without swelling or shift; Diffuse III refers to CT abnormalities with swelling (compressed cisterns); Diffuse IV refers to CT abnormalities with a shift.

‡ P(survival6) is the probability of 6-month survival; P(fav6) is the probability of 6-month favorable outcome (GOS ≥ 4). The probabilities are based on the variables in the IMPACT lab model[30]; age, GCS motor score, pupillary reaction, hypoxia, hypotension, CT classification, SAH, EDH, Glucose and Hemoglobin.

Abbreviations: CT = Computed Tomography; EBIC = European Brain Injury Consortium; ED = Emergency Department; EDH = Extradural Hematoma; GOS = Glasgow Outcome Scale; GCS = Glasgow Coma Scale; ICP+ = patients receiving Intracranial Pressure monitoring; ICP- = patients not receiving Intracranial Pressure monitoring; IMPACT = International Mission for Prognosis and Analysis of Clinical Trials in TBI; Intr. Operation+ = patients receiving intracranial operation (Craniotomy or craniectomy); Intr. Operation- = patients not receiving intracranial operation (Craniotomy or craniectomy); ISS = Injury Severity Score; IQR = Interquartile range; POCON = Prospective Observational Cohort Neurotrauma Study; Ref = referral; tSAH = traumatic Subarachnoid Hematoma.

Using IV analysis, we found that patients treated in hospitals that performed 10% more ICP monitors had an 1.17 (95% CI 1.01-1.42; Table 2) higher odds on favorable outcome, compared to patients treated in hospitals where ICP monitoring was less often employed. For intracranial operation a 10% increase resulted in a higher odds of favorable outcome, but this was not statistically significant (OR 1.42, 95% CI 0.95-1.96). For primary referral, centers admitting more primary referred patients and less secondary referred patients had a worse outcome (OR: 0.91, 95% CI 0.81-1.03), but this estimate was not statistically significant. More primary referrals and consequently less secondary referrals are indicative for less specialized neurocritical care, and therefore, an odds ratio below one was in line with expectations.

Table 2. **Comparing analytical methods to adjust for confounding by indication in proportional odds logistic regression models with the Glasgow Outcome Scale as outcome**

Approach	POCON dataset ICP monitoring OR (95% CI)	Tirilazad dataset Intracranial operation OR (95% CI)	EBIC dataset Primary referral OR (95% CI)
Univariable model	0.51 (0.32-0.81)	1.04 (0.70-1.54)	0.85 (0.66 – 1.10)
Covariate adjustment*	0.91 (0.48-1.74)	0.92 (0.59-1.42)	0.85 (0.64 – 1.15)
Propensity score adjustment**	0.80 (0.66-0.96)	0.86 (0.57-1.28)	0.92 (1.28 – 0.65)
Hospital-level approach†	1.17 (1.01-1.42)	1.42 (0.95-1.97)ǂ	0.91 (0.81 – 1.03)Ł

*Model was adjusted for the following confounders: Age, GCS motor score, pupillary reaction, hypoxia, hypotension, CT classification, tSAH, EDH, glucose and hemoglobin

**A propensity score was calculated based on the following variables: Age, GCS motor score, pupillary reaction, hypoxia, hypotension, CT classification, tSAH, EDH, glucose and hemoglobin. The natural logarithm of the propensity score was added the analytic model.

†Per 10% change; Model was adjusted for the following confounders: Age, GCS motor score, pupillary reaction, hypoxia, hypotension, CT classification, tSAH, EDH, glucose and hemoglobin

ǂAnalyses in 7 centers with a total of 172 patients

ŁAnalyses in 12 centers with a total of 350 patients

Abbreviations: POCON = Prospective Observational Cohort Neurotrauma; EBIC = European Brain Injury Consortium

Sensitivity analyses

Propensity score matching and IPW resulted in similar effect estimates compared to covariate adjustment and propensity score adjustment (Online Supplement B). The alternative hospital-level approaches resulted in effect estimates in the same direction as the instrumental variable analyses. Confidence intervals were however large, indicating an increase of statistically inefficiency.

Simulation study

The univariable analyses resulted in ORs ranging from 0.69 to 1.02 for the four different scenarios (Table 3). In the scenarios where the associations between intervention and outcome were influenced by measured confounders only (scenario 1 and 3), covariate- and propensity score adjustment resulted in ORs in the range of 1.37-1.67, broadly in line with the simulated effect (OR = 1.65). However, in the scenarios where unmeasured confounders also influenced the association between intervention and outcome (scenario 2 and 4), the adjusted ORs were all

non-significant and close to the point of no effect (OR range 0.98-1.03), implying no difference in outcome among patients exposed and not exposed to the hypothetical intervention. IV analysis resulted in a positive and statistically significant effect (OR 1.04-1.05 per 10% change), indicating that patients admitted to hospitals that more often performed the hypothetical intervention had better odds on survival than patients admitted to hospitals where the intervention was less often performed. The standard errors of the hospital-level analyses (SE = 0.07) were however far larger than the standard errors in the patient-level analyses (SE 0.01), indicating a substantial reduction in statistical efficiency. A summary of findings about validity and efficiency of analytical methods is presented in Table 4.

Table 3. **Comparing analytical methods to adjust for confounding by indication in a simulation study with 6-month survival as binary outcome**

Approach	Scenario 1* OR (95% CI)	Scenario 2* OR (95% CI)	Scenario 3* OR (95% CI)	Scenario 4* OR (95% CI)
Univariable model	1.02 (1.00-1.04)	0.69 (0.68-0.71)	0.96 (0.93-0.98)	0.72 (0.70-0.74)
Covariate adjustment	1.67 (1.63-1.71)	0.99 (0.97-1.02)	1.52 (1.47-1.56)	1.03 (1.00-1.06)
Propensity score adjustment	1.52 (1.48-1.55)	0.98 (0.98-1.01)	1.37 (1.34-1.41)	1.00 (0.97-1.03)
Hospital-level approach†	NA	NA	1.05 (1.04-1.07)	1.04 (1.02-1.05)

*Scenario 1 = observed confounders, no hospital variation; Scenario 2 = observed and unobserved confounders, no hospital variation; scenario 3 = observed confounders, hospital variation (17-58%), scenario 4 = observed and unobserved confounders, hospital variation (17-58%)
†Per 10% change

Table 4. **Characteristics of analytical methods to adjust for confounding by indication based on our simulation- and validation study**

Approach	Adjustment for measured confounders	Adjustment for unmeasured confounders	Statistical efficiency	Relying on strong assumptions	Interpretation
Univariable model	-	-	+	-	+
Covariate adjustment	+	-	+/- ǂ	-	+
Propensity score adjustment	+	-	+	-	+
Instrumental variable analysis	+	+*	-	+	-

ǂ Statistical efficiency depends on the number of covariates and the number of patients with the outcome of interest ('events').
*In theory, instrumental variable analysis can correct for unmeasured confounders.

Discussion

We compared analytical methods to adjust for confounding by indication in observational studies using three empirical case studies and a simulation study. The estimated effects strongly depended on the analytical method applied. As expected, the presence of unmeasured confounders, makes

covariate and propensity score adjustment invalid. Instrumental variable (IV) analysis, although statistically inefficient and relying on strong assumptions, may then provide more valid estimates of the effectiveness of interventions.

Covariate and propensity score adjustment

Covariate and propensity score adjustment are commonly used in observational studies. We found that these methods could provide an unbiased estimate of the effect of the intervention, on the condition that all relevant confounders are measured and adjusted for. Covariate and propensity score adjustment cannot adjust for unmeasured confounders.[2,3,7,8,35] In our simulation study, for example, the beneficial interventions appeared non-effective when analyzed with covariate or propensity score adjustment, due to residual confounding by indication.

Instrumental variable analysis

IV analysis resulted in better estimates of the effect of interventions in our simulation study; the direction of the effect was congruent with the simulated effect. In our empirical case studies, the directions of effects were in line with how patients should be treated according to guidelines for TBI[16-20] and best available evidence.[11,20,21,40]

IV analysis is becoming more popular in TBI research. Several recently published TBI studies analysed effectiveness at the hospital level[41-44] and a large European CER study is planning to use hospital-level analysis to assess effectiveness of many TBI interventions.[45] Previous studies typically divided hospitals into groups (e.g. tertiles[41] or quartiles[42]) based on the percentage of patients treated. The percentage treated in each hospital can also be used as a continuous variable, which increases statistical power.

Nevertheless, IV analysis also has limitations that warrant comment. First, IV analysis is statistically inefficient compared to conventional analytical methods. Since the analyses are performed at the level of the hospital, the effective sample size decreases. As a consequence, a large number of centers and patients and substantial variability in exposure to interventions across centers are needed to obtain statistically significant results in case of a true beneficial effect. The conduct of IV analysis might therefore be relatively expensive and resource-intensive. Second, the interpretation of the OR differs from the conventional analyses. Rather than providing information on the effect size of interventions in individual patients, IV provides information on whether patients' outcome will improve when hospitals change their policy with respect to a specific intervention.[3,5] The issue of interpretation is prominent for primary referral. Although primary referral on the patient-level might be associated with more specialized neurocritical care, at the hospital-level a larger number of secondary referrals are indicative for relatively more specialized neurocritical care. Therefore, for primary referral, a negative association between the instrument 'percentage primary referrals' and outcome was expected, which was indeed found in the EBIC data. Third, the success of IV analysis depends on whether the underlying

assumptions are met.[5,46,47] Thus, IV analysis might not always be defendable. For example, we found that for intracranial operation, the instrument was statistically significantly associated with patient-level confounders and therefore, the second assumption was violated. Between-hospital variation, caused by other variables than those in the model, could theoretically be captured by the random effect model. Nevertheless, when correlations are strong (e.g. centers that often perform a particular intervention are all from the same geographic region that differs from other regions in many aspects), the statistical model will be unable to separate the effect of the intervention from the effect of the confounder. In these situations, one should consider other analytical methods or conclude that it is not possible to analyze the effectiveness of the particular intervention in the dataset.

Strengths and limitations

A major strength of our study is that we included both empirical case studies and a simulation. The TBI examples show how the various analytical methods worked with actual patient data and demonstrated the influence of analytical method on effect estimate. The simulation study subsequently provided insight into the underlying mechanisms and thereby indicated which methods provided valid estimates of the treatment effect in different situations. A limitation of our simulation study is that we only examined four scenarios while there are many more possible interactions between treatment and confounders that might be of interest. A second limitation is that we used the observed range from one dataset (POCON), whereas the actual range might differ. Future simulation studies could address alternative scenarios and should further investigate how statistical power can be optimized when using IV analysis. Another limitation of the simulation study is that we included two variables as presenting the measured confounders and two variables as presenting the unmeasured confounders. As a consequence, the predictive value of our predictors is relatively modest which may have resulted in unstable estimates.

Our case studies also have several limitations. The data is relatively outdated (data was collected between 1992 and 2009) and analyzed post-hoc. Therefore, the current study cannot be used to draw conclusions about the effectiveness of interventions. In addition, each intervention was measured in only one dataset while it would be more interesting to demonstrate the different analytical methods for each intervention over different datasets. This was not possible in our study since not all interventions were measured in all three datasets. Furthermore, specific concerns exist in the data with regard to the three interventions. An ICP monitor is a diagnostic procedure and cannot influence outcome on itself, while it can cause complications. The actual comparison is between ICP driven therapies versus clinical/radiological driven therapies. With regard to the variable intracranial operation, the clinical applicability is unclear since the exposure and intervention in these data are not defined specifically (What kind of mass lesions? What intracranial operation?). More granular information on these interventions was unavailable inherent to the post-hoc setup. A final limitation is that all three datasets were relatively modest in terms of number of hospitals and number of patients. The POCON dataset had only five

hospitals, while the Tirilazad and EBIC datasets had only seven and 12 hospitals that included at least 20 patients, respectively. Therefore, differences among hospitals might also exist by chance, e.g. if a hospital included only 20 patients, these patients might not be representative for the general policy in the particular hospital. Therefore, we recommend future studies using IV analyses in TBI to include a larger number of hospitals and a large number of patients in each hospital. In addition, since the 'percentage treated' in each hospital is based on data of the included patients, it might still be subject to confounding by indication. We indeed found that the instrument 'percentage patients treated with intracranial operation' was associated with the patient-level confounders. Alternatively, policies with regard to an intervention might be identified by (former) registry data or by an independent survey study completed by all the participating hospitals. Such an approach will be used in an ongoing TBI study.[45]

Conclusion

Effect estimates of interventions in observational studies strongly depend on the analytical method used. Covariate- and propensity score adjustment could easily result in an invalid estimate due to confounding by indication. Instrumental variable analysis may provide a more valid estimate, but is statistically inefficient and its validity depends on whether underlying assumptions are met. When unobserved confounding and practice variation are expected, IV analysis should be considered to estimate effectiveness of interventions in large-scale observational multicenter studies.

Supplemental material is available at www.marysecnossen.nl

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17

General discussion

The aim of this thesis was to study outcome and opportunities for comparative effectiveness research (CER) in patients with traumatic brain injury (TBI) from a methodological perspective. This chapter describes the main findings of this thesis and highlights some important methodological considerations. The chapter ends with recommendations for research, policy, and clinical practice.

Part I – MAIN FINDINGS

Outcome following traumatic brain injury

Prevalence

We found substantial variation in prevalence rates for both post-concussion symptoms and psychiatric disorders. Prevalence rates may depend on timing and patient population, but were also largely influenced by diagnostic criteria and analysis strategy. Using the definition of three or more self-endorsed symptoms (any severity) from the ICD-10, approximately half of the mild TBI (mTBI) patients could be 'diagnosed' with post-concussion symptoms six months post-injury (Chapter 2, 3, 6, 7). Anxiety and major depressive disorder following TBI (all severities) were diagnosed during the first year post-injury in 21% and 17% of the patients, respectively (Chapter 4). Although these percentages were significantly higher than population base rates, they do not vary substantially from pre-injury prevalence rates (13-19%). Pooled prevalence rates for psychiatric disorders appeared to increase over time, with prevalence rates of more than 40% in studies using relatively long follow-up periods (3-10 years; Chapter 4). With regard to health-related quality of life (HRQoL), one year following mild and moderate TBI, the majority of patients scored in the upper levels (Chapter 8). Scores on the domain vitality, however, remained suboptimal, in line with the finding that fatigue was one of the most prevalent post-concussion symptoms (Chapter 2, 3, 7).

Predictors

The etiology of post-concussion symptoms following mTBI is complex and multidimensional and may include biological factors (e.g. diffuse axonal injury, repetitive TBI), psychological factors (e.g. pre-injury psychiatric disorders), social factors (e.g. social support) and personality factors (e.g. coping). In addition, post-concussion symptoms might be more often endorsed among females, those with a lower education, those reporting neck pain at the emergency department and those involved in litigation and compensation procedures. A large proportion of those reporting persistent post-concussion symptoms (e.g. after six months) already experienced symptoms in the first weeks post-injury (Chapter 2, 7). Psychiatric disorders following TBI were associated with pre-injury psychiatric disorders, TBI severity (moderate TBI vs. severe TBI), brain volume, post-injury unemployment, early post-injury psychiatric symptoms and a memory of the traumatic event (Chapter 5). These results should however be interpreted with caution since predictors were predominately assessed in underpowered studies using univariable analyses.

Prediction models for post-concussion symptoms

A prediction model based on age, sex, years of education, pre-injury migraine and headache, pre-injury psychiatric disorders, prior TBI, posttraumatic amnesia (PTA) and loss of consciousness (LOC) explained 21% of the variance in six-month post-concussion symptoms, which decreased to 14% after bootstrap validation (Chapter 6). This model performed poorly at external validation (Chapter 7). A new model based on sex, subjective complaints at the emergency department and early post-injury post-concussion symptoms and posttraumatic stress performed reasonably (Area Under the Curve (AUC) 0.77; AUC after bootstrap validation: 0.75; Chapter 7).

Comparative effectiveness research in traumatic brain injury

Variation in structures and processes of care

To assess variation in structures and processes of care, we developed a set of questionnaires 'The provider profiling questionnaires' in the context of the Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) study, a large observational cohort study in 68 European neurotrauma centers (see Chapter 1 and Chapter 10 for more information). We found considerable variation in structures and processes of TBI care across Europe. Although the large majority of centers were academic hospitals, designated level I trauma centers from urban areas with a research interest in TBI, there were major differences in organization of care, facilities and treatment policies (Chapter 10). In addition, computed tomography (CT) scan policy, ward admission, discharge policy, intracranial pressure (ICP) management, in-hospital rehabilitation and referral to rehabilitation institutes varied considerably (Chapter 11-13). The wide variation found in the provider profiling questionnaires was in line with an observational cohort study where we found large between-center variation in treatment decisions, even after correction for case-mix (Chapter 14). The existing treatment variation provides an opportunity to study treatment effectiveness with CER.

Guideline adherence

Although, the majority of European neurotrauma centers indicated to use TBI guidelines (Chapter 11, 12), guideline adherence for most interventions was low and ranged from 18% to 100% in a systematic review (Chapter 9). In addition, some European neurotrauma centers claimed to have a treatment policy that systematically diverges from guideline recommendations (Chapter 11, 12). For example, one-fifth of European neurotrauma centers claimed to use barbiturates as first tier therapy in the treatment of intracranial hypertension, while barbiturates are only recommended as second tier treatment.[1]

Analytical methods for observational CER studies

Estimates of treatment effects in observational CER studies are strongly dependent on the analytical method used. Covariate- and propensity score adjustment are by definition unable to correct for unobserved confounders and may therefore result in an invalid estimate of the

treatment effect (Chapter 15, 16). Instrumental variable analysis, using the percentage of patients exposed to an intervention in each hospital as substitute variable, may provide a more valid estimate. However, this method is statistically quite inefficient, relies on strong assumptions and is difficult to interpret. In addition, substantial between-center variation in the treatment of interest is required to make this approach feasible.

Part II – INTERPRETATION

Outcome following traumatic brain injury

Definitions and measurement

Although mild TBI (mTBI) is usually defined by a Glasgow Coma Scale (GCS) score 13-15 (Chapter 2), almost 40% of the European neurotrauma centers participating in the CENTER-TBI study indicated to use more restrictive criteria (GCS 14-15; Chapter 11). This may result in differences in prevalence rates and may also influence the importance of predictors. For example, clinical variables and CT abnormalities might be predictive of mTBI outcome in patients with GCS scores 13 and 14, but not in those scoring in the upper level (GCS score 15).[2]

In addition, there seems to be variation in the measurement of patient characteristics across different studies. For example, in Chapter 6, the presence of a prior TBI and pre-injury psychiatric disorders were based on self-report without a threshold for severity, resulting in rates of 54% and 32%, respectively. In Chapter 7, however, more stringent criteria were applied for prior TBI and pre-injury psychiatric disorders, resulting in rates of 3% and 10%, respectively. Therefore, it is not surprising that the model developed in Chapter 6 performed poorly in the external validation study in Chapter 7.

Improvements in consensus on definitions of mTBI and standardization of data collection are necessary to compare different studies examining prevalence and predictors of mTBI sequelae. This could be accomplished by studies adhering to data collection standards provided by the common data elements (CDE)[3,4] that were recently tested in the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) Pilot study.[5]

Role of misattribution

In Chapter 3, 6 and 7, we found that at six months post-injury a substantial proportion (39-53%) of mTBI patients reported three or more post-concussion symptoms of any severity. This high prevalence was in line with previous studies using similar criteria.[6,7] However, it can be debated whether patients 'diagnosed' with post-concussion symptoms in these studies truly reflect a subgroup with clinically significant symptomatology necessitating follow-up and treatment. It is known that post-concussion symptoms are also reported in non-brain injured trauma patients[8,9] and in healthy adults.[10] Consequently, a part of the patients 'diagnosed' with post-concussion

symptoms in this thesis likely consists of patients experiencing benign, everyday symptoms that were misattributed as being related to the sustained TBI.

To prevent potential misattribution, in Chapter 7 patients had to rate symptoms for both their current and pre-injury situation. Symptoms were only included if they deteriorated in comparison to the pre-injury level. It is nevertheless unlikely that such a strategy circumvents the problem of misattribution since patients might be tempted to report fewer pre-injury symptoms; referred to as the 'good-old-day' bias.[11-13] Misattribution could be prevented by using comprehensive multidisciplinary assessment and clinical evaluation of symptoms (Chapter 2). There are however no standards available on how and when this should be accomplished.

Next to misattribution of benign, everyday symptoms, it is also possible that psychiatric disorders following TBI are misattributed as being related to TBI. For example, in Chapter 4 we observed a trend towards a higher prevalence of psychiatric disorders over time. Late onset of psychiatric disorders is relatively common[14,15] and can be explained by ongoing stressors and problems experienced by TBI patients or because insight into social, cognitive and emotional disability might develop after physical recovery. However, it cannot be excluded that the onset of mental health problems years after TBI is related to independent stressors rather than to the sustained TBI and its consequences.

We further found a high pre-injury prevalence of psychiatric disorders and a strong association between pre- and post-injury disorders. Since recurrence of psychiatric disorders is common (up to 85%),[16] the causal role of TBI for the development of psychiatric disorders becomes uncertain. Since many studies only record *if* there is a psychiatric history and not *when* the patient suffered from psychiatric disorders, it cannot be excluded that some patients already had a psychiatric disorder during the injury, which continued over the follow-up period. Since psychiatric disorders are associated with an enhanced risk of sustaining a TBI,[17-19] the proportion of TBI patients with an existing psychiatric disorder might be relatively pronounced, increasing the post-injury prevalence rates.

It should nevertheless be noted that there is a subgroup of patients who develops novel psychiatric disorders following TBI. It might be particularly interesting to study which pre-injury, peri-injury, clinical, social and personality factors contribute to the onset of a psychiatric disorder following TBI in previously healthy adults.

Research setting

The research setting should be taken into account when analyzing prevalence rates and determining the relevance of predictors for outcome following TBI. Many studies about mTBI recruit patients seeking care at the emergency department. These patients are usually relatively severely injured, and have a higher incidence of LOC and intracranial hemorrhages. The outcome

of these patients might therefore not be comparable to outcome of patients sustaining sport-concussion or patients seeking medical care at the general practitioner.

Some studies included in the systematic reviews in Chapter 4 and 5 recruited patients from rehabilitation institutes and patients who self-enrolled. These patients might also diverge substantially from those recruited at the emergency department since they likely comprise a subgroup of patients experiencing sequelae, causing their rehabilitation needs or their interest in a TBI outcome study.

Notwithstanding, patients included in studies using similar inclusion criteria and settings are not necessarily comparable, since there are large between-country and between-center differences in admission and referral policies (Chapter 11). In addition, case-mix variation among hospitals can be substantial (Chapter 14), which may drastically influence outcome. Therefore, study-specific inclusion criteria and case-mix of included patients should always be described comprehensively and taken into account when comparing prevalence rates and predictors of sequelae following TBI.

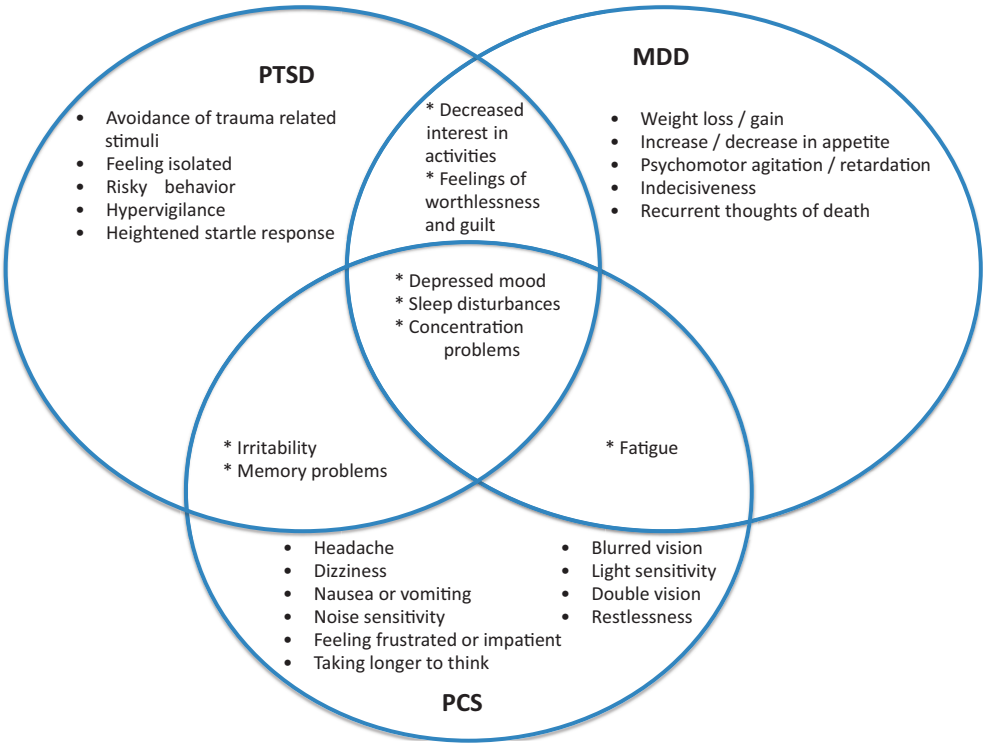
Attrition

Studies in mTBI generally have high attrition rates. In Chapter 6-8, outcome after six and twelve months was assessed in only 50-58% of the patients. This may imply selection bias, which could have important implications for the interpretation of both prevalence rates and predictors. Therefore, minimizing attrition should be a key objective in future prognostic studies and can potentially be accomplished by ongoing contacts with participants,[20] incentives for participation,[21] sending postcard and telephone reminders,[21] and using telephone interviews[21] or home visits.[22]

Overlap between post-concussion symptoms and psychiatric disorders

In this thesis, we either focused on post-concussion symptoms or on psychiatric disorders, whereas there is substantial overlap in symptoms; i.e. the post-concussion symptoms depressed mood, sleep disturbances, concentration problems, irritability, memory problems and fatigue are also symptoms of depression and posttraumatic stress disorder (PTSD; Figure. 1). Therefore, PTSD and depression should always be considered as differential diagnoses. In addition, it should be examined whether post-concussion syndrome (PCS) is a unique clinical syndrome or that post-concussion symptoms might be better interpreted as (prodromal) symptoms of psychiatric disorders.[9] The validity of PCS as a clinical diagnosis has been debated for decades,[23] and to prevent ongoing controversies, the following two research projects are recommended:

Figure 1. **Overlap in symptoms of PTSD (DSM-5), MDD (DSM-5) and PCS (Rivermead post-concussion questionnaire)**



Abbreviations: MDD = major depressive disorder; PCS = post-concussion symptoms; PTSD = posttraumatic stress disorder

- A qualitative study in which patients reporting post-concussion symptoms on the Rivermead Post-concussion questionnaire (RPQ) from a larger cohort study are invited for an interview. During this interview, the endorsed post-concussion symptoms can be assessed in-depth, for example by investigating how distressing the symptoms are, whether the symptoms influence daily life, how often the patient experiences the symptoms and whether the patient has treatment needs. In addition, a structured diagnostic interview can be used to assess the presence of a psychiatric disorder and to determine whether the reported post-concussion symptoms can be better explained by the psychiatric disorder. Such a study provides insight into the clinical relevance of post-concussion symptoms, treatment needs and overlap between psychiatric disorders and post-concussion symptoms.
- A prospective cohort study with a comprehensive outcome battery including post-concussion symptoms, psychiatric disorders and other relevant outcome measurements such as HRQoL, return to work and clinical outcome (e.g. Glasgow Outcome Scale Extended (GOSE). The association between post-concussion symptoms (using different cut-off points) and the other relevant outcome measurements (HRQoL, return to work, GOSE) can be assessed, controlled for psychiatric disorders. This study could provide insight into the overlap between post-

concussion symptoms and psychiatric disorders and the clinical relevance of post-concussion symptoms

Measuring outcome following TBI

In this thesis, we used clinical outcome, post-concussion symptoms, psychiatric disorders and HRQoL to assess outcome following TBI. All these outcome measurements have their strengths and limitations. Clinical outcome (e.g. measured with the GOSE) might be relatively objective but may not be sensitive in an mTBI population. Post-concussion symptoms might be common and distressing and are relatively easy to assess, but the diagnosis of PCS is controversial and there is lack of consensus on definitions and analysis strategy. Psychiatric disorders can be validly assessed but the causal role of TBI is difficult to ascertain due to high pre-injury rates. HRQoL might provide valuable information on recovery from a patient's perspective, but caution should be taken when using the physical and mental summary scores from the SF-36, since the two-factor structure has not been convincingly confirmed in patients with TBI (Chapter 8).

Given these strengths and limitations, multidimensional outcome assessment, including clinical outcome (GOSE), post-concussion symptoms (RPQ), psychiatric disorders (structured clinical interview for DSM-5 (SCID-5) and HRQoL (SF-36, Quality of life after brain injury (QOLIBRI) is highly recommended in studies on outcome following TBI. In addition, tests of neuropsychological functioning (e.g. Rey auditory verbal learning test, trail making test, Wechsler adult intelligence scale) should be used to measure impaired cognitive functions. Rather than using a large outcome battery, novel psychometric applications such as item response theory, in which the outcome assessment can be tailored to the severity of symptoms experienced by the patient, might be useful in capturing the full range of mTBI outcome while minimizing the response burden.[24]

For psychiatric disorders, there is generally consensus that the presence or absence of psychiatric disorders should be assessed by clinical examination, a structured diagnostic interview (e.g. the SCID-5), or both. Structured diagnostic interviews have shown to be reliable in a TBI population with interrater reliability ranging from 80 to 100% (Chapter 4). The use of structured diagnostic interviews in TBI outcome studies is however relatively expensive and labor-intense. As a consequence, many studies using structured diagnostic interviews have small sample sizes (Chapter 4, 5). However, since the prevalence of psychiatric disorders during the first year post-injury is approximately 20% (Chapter 4), a large sample size is necessary to reliably assess the effect of predictors for psychiatric disorders. For example, if 10 candidate predictors are considered, at least 100 patients with psychiatric disorders are needed to prevent statistical overfitting. A prognostic study with 100 patients with a psychiatric disorder, and thus 500 patients in total (prevalence 20%) using structured diagnostic interviews might not be feasible. Hence, many researchers may face the dilemma of either using a valid outcome measurement in a small sample or using self-reported questionnaires in a larger sample. This dilemma might be partially

solved by data sharing (e.g. combining smaller studies using structured diagnostic interviews) or meta-analyses of published studies (Chapter 5), when measurements are comparable.

Predicting post-concussion symptoms and psychiatric disorders

Despite a considerable number of publications on prognostic factors, currently no model can validly predict TBI sequelae in terms of post-concussion symptoms and psychiatric disorders.[8,25,26] It has been repeatedly reported that the predictive value of clinical factors, including CT abnormalities, GCS and pupillary reactivity is limited in mTBI patients.[11,25] Outcome following mTBI seems to be more determined by "what the patient brings to the injury" than by "what the injury brings to the patient". Among the factors that a patient can bring to the injury, socio-demographics, pre-injury psychiatric disorders, prior TBI and early symptoms have been repeatedly tested and comprise consistent predictors of mTBI sequelae. In addition, it has recently been shown that coping may predict poor outcome following mTBI.[27] Other patient-related factors including the appraisal of the trauma, emotional and behavioral response during the trauma, attributions of the traumatic event, social support and personality factors have been widely described,[11,28,29] but have not been examined in prospective studies with sufficient statistical power yet. The relevance of these factors are however in line with psychological theories, such as the cognitive model for PTSD by Ehlers and Clark,[30] Seligman's learned helplessness theory of depression,[31] and Iverson's conceptual model of the post-concussion syndrome,[11] and should be the target of future prognostic studies.

To increase our knowledge on relevant predictors for TBI sequelae it is also important that prediction-modeling studies use solid methodology[26,32-36] and are replicated. In Chapter 5, however, we found that a total of 171 predictors for psychiatric disorders were studied in the literature, among which only 24 (14%) were examined by at least two studies using comparable measurements. Similarly, there is no external validation study for prediction models of psychiatric disorders following TBI yet and we were the first to externally validate existing models for post-concussion symptoms (Chapter 7).

MTBI sequelae are complex and the strongest predictors (symptoms after two weeks) are impractical to include in a prediction model. Hence, it can be debated whether prediction modeling is the most valid, economic and practical way to identify risk-prone patients. Alternatively, post-concussion symptoms could be tracked with a mobile phone or web application during the first months post-injury. If a patient scores above a certain cut-off point (e.g. three or more symptoms), the symptom-track application could recommend the patient to visit the general practitioner. General practitioners can subsequently be trained to assess post-concussion symptoms, exclude or confirm concomitant diseases, reassure and inform the patient and refer to specialized treatment if necessary. The feasibility of such an approach and the comparative effectiveness of tracking patients versus predicting risk-prone patients should be the target of future studies.

Comparative effectiveness research in traumatic brain injury

Provider profiling

Provider profiling aims to profile structural and process characteristics of centers participating in a multicenter study. It provides information on treatment variation and potential relevant topics for CER analyses. We showed that a sound development process and regular contacts between local investigators and a researcher, resulted in a reliable questionnaire (concordance rate: 0.85) with a completion rate of 96 to 100%. Although provider profiling is highly recommended for future multicenter studies, it might be preferable to develop a shorter questionnaire focused on a subset of pre-specified research questions. In addition, to obtain additional insight into reliability of responses and within-center variation, it can be recommended to ask multiple clinicians in each center to complete the questionnaire.

Another recommendation for future provider profiling studies is to add vignettes of hypothetical patients to the questionnaire. In vignettes, multiple treatment interventions that are used simultaneously can be assessed. In addition, responses to vignettes are not influenced by differences in case-mix among centers. For the provider profiling questionnaires, however, the influence of case-mix cannot be excluded. For example, if some centers receive more severely injured patients than other centers (e.g. level I vs. level II/III trauma center), they might routinely use more aggressive treatment interventions. Therefore, case-mix should be taken into account when interpreting the results of the provider profiling questionnaires.

Treatment variation and guideline adherence

We found considerable variation in treatment and adherence to TBI guidelines. Guideline adherence was dependent on the invasiveness of the intervention (more adherence to less invasive interventions) and patient-related factors (age and TBI severity). Moreover, guideline adherence was associated with quality of the evidence underpinning the recommendations, with higher adherence to higher-quality guideline recommendations (Chapter 9). Consequently, to improve guideline adherence and reduce practice variation, there is an urgent need for high-quality evidence regarding treatment effectiveness in TBI. Observational CER studies might provide a promising framework to enhance our knowledge and to support guideline recommendations.

Comparative effectiveness research

Although observational CER studies are promising in enhancing our knowledge on treatment effectiveness, we found that the effect estimate obtained in such studies was largely dependent on the analytical method used (Chapter 16). Analytical methods can broadly be divided into patient-level approaches (e.g. covariate adjustment) and hospital-level approaches (e.g. instrumental variable analysis). Patient-level approaches are recommended in situations where patients exposed and not exposed to the intervention of interest are expected to be reasonably

exchangeable on both observed and unobserved characteristics. For example, when patients admitted during the night with certain indications routinely receive a particular treatment while patients admitted during the day with similar indications do not receive this treatment, and differences between patients admitted during day and night can be measured and controlled for.

For many interventions, however, patients exposed and not exposed are not expected to be exchangeable; i.e. they may differ on various factors of which some cannot be measured and adjusted for (e.g. factors related to clinical intuition). These factors may subsequently confound the association between intervention and outcome, resulting in an invalid estimate of the treatment effect. For instance in panel 1, it cannot be excluded that clinicians more often provide written discharge information to patients with a high risk of post-concussion symptoms than to patients with a lower risk, based on their clinical intuition. In such a situation, a hospital-level approach could be considered.

Panel 1. **Example of a CER research question**

Research question	Does written discharge information, compared to oral discharge information and no information, prevent the development of post-concussion symptoms six months after sustaining mild TBI?
Rationale	Persistent post-concussion symptoms are debilitating and may interfere with quality of life and functioning. Early information and reassurance may prevent the development of post-concussion symptoms, although findings from RCTs are inconclusive (Al Sayegh, 2010).
Patients	Mild TBI patients, GCS 13-15, referred home after emergency department admission. Exclude patients that received systematic follow-up visit by GP or specialist practitioner since it is uncertain if these professionals provided oral and written information
Interventions	Provision of written discharge information on TBI, its possible late consequences and where to consult in case of difficulties
Controls	Provision of oral information on TBI, its possible late consequences and where to consult in case of difficulties No discharge information provided
Outcome	Primary outcome: 6-month Rivermead Post-Concussion Questionnaire (linear scale) Secondary outcomes: Return to work / school / activities, functional outcome (GOSE), Health Related Quality of Life (SF-36, QOLIBRI), depression and posttraumatic stress (PCL-5 and PHQ-9)

The hospital-level approach is based on instrumental variable (IV) analysis. In IV, a substitute variable ('the instrument') is used as independent variable in the analyses with patient outcome as dependent variable. In multicenter observational CER studies, 'treatment preference' could be used as instrument and four different definitions can be considered (Table 1).

IV analysis can theoretically adjust for unobserved confounders.[38,39] The method however has several limitations warranting comment. First, IV analysis relies on strong assumptions, which are often violated.[38,40] Some assumptions (e.g. there is no association between the instrument and other factors influencing outcome) can be captured by using a random effect model (Chapter 14, 16), which is therefore recommended in multicenter observational CER studies. Nevertheless,

when correlations between the instrument and a confounding variable are strong, the statistical model might not be able to separate the effect of treatment from the effect of the confounder.

Another limitation of multicenter observational CER studies is that they are relatively expensive and resource intensive since a large number of centers and a large number of participants in each center are necessary to obtain sufficient statistical power (Chapter 16) Lastly, the interpretation of CER studies using IV analysis might diverge from RCTs and traditional analytical methods for observational studies. Rather than estimating effectiveness of a particular intervention on the patient-level, CER provides information on how a change in hospital policy would affect patient outcomes. Caution is needed when interpreting these estimates since they might be counter-intuitive. For example, in Chapter 16 we estimated the effectiveness of primary transfer to specialized neurocritical care. When we assume that neurocritical care is effective, we would expect a positive association between primary referral and favorable outcome on the patient level, but a negative association when using the percentage primary referred as an instrument; i.e. centers receiving predominately primary referrals are usually less specialized than centers also receiving secondary referrals.

Notwithstanding, all methods for causal inference in observational data have strengths and limitations and are based on underlying assumptions. Therefore, we agree with Greenland[41] that none of the methodologies should be regarded as 'correct' or 'absolute' and that data should be analyzed from multiple perspectives instead. For future observational CER studies, this implies that all statistical techniques that are reasonable for the research question of interest should be reported.

Researchers should determine, based on pre-specified criteria (e.g. are patients treated and not treated expected to be exchangeable? Is there between-center variation in treatment and case-mix?), which analytical methods are expected to provide a valid estimate of the treatment effect and clinical meaningful differences in effect estimates using these different analytical methods should be interpreted. In addition, if ethical, practical and financial feasible, high-quality, pragmatic RCTs are recommended to confirm the results of observational CER studies.

Table 1. **Different definitions of preference-based instruments in multicenter observational CER studies**

	Instrument	Operationalization	Case-mix adjustment	Statistical efficiency	Interpretation
Instruments based on actual patient data from the observational study	Observed percentage treated	For each hospital, the number of patients treated divided by the total number of patients with a treatment indication is calculated and used as an independent variable in the analyses	No	-	-
	Adjusted observed percentage treated	The random intercept for treatment, adjusted for case-mix is used as an independent variable in the analyses	Yes	- -	- -
Instruments based on other sources of information	Treatment preference according to provider profiling	Whether centers indicated to generally perform a certain treatment (1) or not (0) is used as an independent variable in the analyses	No	- -	-
	Treatment preference according to vignettes	Whether centers indicated to perform a certain treatment in hypothetical patients (1) or not (0) is used as an independent variable in the analyses	Yes	- -	-

Living systematic reviews

Systematic reviews aim to summarize and weight evidence and could directly inform clinicians and guideline developers on effectiveness of interventions. Systematic reviews are however often outdated[42] and therefore may not present the current state-of-the-knowledge for a particular topic. Living systematic reviews (LSRs) have been proposed as a possible solution.[43,44] Chapter 9 presents the first LSR in TBI. With the publication of this LSR we showed that LSRs are feasible. In addition, the results of the LSR highlight the necessity of regular updates; in less than three years, 13 additional studies were included, comprising 37% of the total evidence base and significantly changing the review conclusion. For example, two additional studies measuring the association between guideline adherence and outcome were included that did not report a statistically significant association.[45,46] One of these used hospital-level analyses and was therefore judged as having a relatively low risk of confounding. As a consequence, the original conclusion that guideline adherence results in better patient outcomes became more uncertain.

The future of LSRs might nevertheless depend on its organization and may also necessitate a change in research culture. The LSR in Chapter 9 was written in the context of the CENTER-TBI project.[47] Consequently, review authors were invited to participate in review courses, an expert panel was constituted, arrangements with a medical journal on the publication of updates were arranged and review authors were reminded regularly to conduct a new update. All these steps might be necessary for the success of LSRs and should therefore be continued. Rather than including these tasks in a work package of individual research projects, it might be preferable to constitute one organization (e.g. the Cochrane group) warranting quality and updates of LSRs in medicine.

Next, the conduct of LSRs may necessitate a change in research culture. At this moment, scientific researchers are rewarded by the number of publications and their citation records.[48] LSRs however do not result in multiple publications, and therefore it might be discouraging for researchers to get involved in conducting LSRs. A multidimensional incentive system such as the 'productivity, quality, reproducibility, sharing and translating potential (PQRST)' developed by Ioannidis and Khoury[49] might be promising in shifting the focus from number of publications towards clinical relevance.

PART III – 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

Research on outcome following TBI

- Standardize the definition for mild TBI
- Standardize data collection practices (e.g. by following the recommendations of the CDE[3,4])
- Include multidimensional outcome assessment, including the GOSE, SCID-5, RPQ, SF-36, QOLIBRI and neuropsychological tests
- Clearly describe research setting, inclusion criteria and case-mix
- Prevent attrition in prognostic studies
- In case a patient reports a pre-injury psychiatric disorder, examine if and when the patient has recovered
- Study overlap between post-concussion symptoms and psychiatric disorders and study whether post-concussion symptoms are unique and clinically relevant and which cut-off point on the RPQ is the most valid
- Study whether a mobile phone application to track symptoms following mTBI is feasible
- Examine the etiology of psychiatric disorders following TBI in patients without a history of psychiatric disorders
- Perform confirmatory factor analysis with a large sample of TBI patients to confirm the SF-36 two-factor structure

Research on prognostic models for mTBI outcome

- Consider predictors that are in line with psychological theories and focus on factors "that the patient brings to the injury"
- Prioritize replication of prediction modeling studies and external validation of prediction models, rather than testing new predictors and new models

- Use methodology in line with recommendations (e.g. prevent statistical overfitting by using an adequate sample size and a limited number of candidate predictors, use internal and external validation)
- Study the comparative effectiveness of tracking mild TBI patients versus predicting mild TBI patients at high risk for persistent post-concussion symptoms

Research on treatment effectiveness

- Use provider profiling in multicenter studies and consider the addition of vignettes
- Explore the use of large-scale multicenter CER studies to generate evidence on treatment effectiveness in TBI
- Consider instrumental variable analysis if patients exposed and not exposed to an intervention are not expected to be exchangeable
- Use a random effect model in hospital-level analyses
- Do not consider one particular analytical method as the most appropriate for the research question but report the results of all analytical methods that are considered reasonable for the research question of interest
- Summarize state-of-the-knowledge for each treatment intervention in LSRs

Recommendations for policy

- Inform the public about the potential consequences of mTBI
- Provide funding for research on studies about mTBI outcome.
- Provide funding for large-scale observational CER studies examining treatment effectiveness of interventions with large between-center variation
- Obligate reporting the results of all analytical methods that are considered reasonable in research proposals of observational studies
- Constitute an institution (e.g. Cochrane group) that could warrant the quality of LSRs in medicine
- Enable a change in research culture that values LSRs

Recommendations for clinical practice

- Inform and reassure mTBI patients about the potential sequelae
- Examine post-concussion symptoms and psychiatric disorders during follow-up of patients with TBI
- Use multidimensional comprehensive assessment of post-concussion symptoms rather than symptom checklists
- If available, consult LSRs as a source of evidence for treatment interventions

Part IV: OVERALL CONCLUSION

This thesis aimed to examine outcome and opportunities for CER in TBI from a methodological perspective. We first examined the prevalence and predictors of TBI sequelae. Prevalence rates appeared to vary widely and depended on pre-injury factors, patient population, assessment, analysis strategy and diagnostic criteria used. The etiology of TBI sequelae is complex and multifactorial and includes biological, psychological and social factors that might be difficult to capture in a prediction model. When studying prevalence and predictors of psychiatric disorders and post-concussion symptoms following TBI, the role of misattribution, research setting, selection bias and the overlap in symptomatology between post-concussion symptoms and psychiatric disorders should be taken into account.

Our second aim was to assess to what extent CER could contribute to evidence generation in TBI. Current evidence underpinning TBI guidelines is weak, and consequently, there is large variation in policy and guideline adherence among neurotrauma centers. This variation provides an opportunity for CER. However, the effect estimate obtained in observational CER studies may depend on the analytical method used. Since all analytical methods have their strengths and limitations and are based on untestable assumptions, it is important that researchers do not consider one particular analytical method as the most appropriate. Instead, different analytical methods that are reasonable for the research question of interest should be used as sensitivity analyses. To confirm the results of observational CER studies, high-quality pragmatic RCTs are recommended.

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Summary

Introduction

Traumatic brain injury (TBI) is one of the leading causes of death and disability worldwide. In Europe, approximately 75,000 patients die each year as a consequence of TBI and many more patients are challenged with a range of disabilities and symptoms as a consequence of TBI that may drastically reduce functioning and quality of life. Although TBI has emerged as an important topic in medical research, research endeavors have not yet resulted in major advances in our understanding of TBI, nor in an improvement of patient outcomes.

Research in TBI is hampered by the heterogeneity of the patient population, the lack of standardized outcome instruments and the fact that secondary insults and complications are common and may interact with the effects of a possibly beneficial treatment. More specific problems in prognostic studies are that they often include too many predictors and do not use internal or external validation approaches. As a consequence, the evidence derived from many TBI studies is modest.

In this thesis we focused on two important topics in TBI research. In part I, we focused on outcome following TBI, including the prevalence and predictors of psychiatric disorders and post-concussion symptoms. In part II, we examined whether comparative effectiveness could contribute to evidence generation in TBI, with a focus on current guideline adherence, treatment variation and analytical methods. For both purposes, we followed a methodological perspective. The aims of this thesis were operationalized in the following two main research questions:

1. **What is the prevalence and what are predictors of outcome following TBI?**
    a. What is the prevalence of TBI outcome in terms of persistent post-concussion symptoms, psychiatric disorders and HRQoL?
    b. What are predictors of TBI outcome?
    c. Can we identify patients at greatest risk for suffering post-concussion symptoms?
2. **To what extent can CER contribute to evidence generation in TBI?**
    a. To what extent do clinicians adhere to current evidence from guidelines?
    b. To what extent does variation in structure and process characteristics exist among centers treating patients with TBI?
    c. What is the influence of analytical methods on the estimate of treatment effectiveness in observational studies? And which method may provide a valid estimate in case of confounding by indication?

PART I: Outcome following traumatic brain injury

In **Chapter 2** we summarized the literature on post-concussion symptoms with a focus on definitions, epidemiology, etiology, clinical assessment and treatment. Although post-concussion symptoms were frequently reported following mild TBI, it is uncertain whether they represent a clinically relevant syndrome (the post-concussion syndrome). Prevalence of post-concussion symptoms varied and depended on pre-injury characteristics, patient population, assessment, analysis strategy, and diagnostic criteria. The etiology of post-concussion symptoms is likely multifactorial and complex and may include biological factors (e.g. diffuse axonal injury, repetitive TBI), psychological factors (e.g. pre-injury psychiatric disorders), social factors (e.g. social support) and personality factors (e.g. coping). In addition, post-concussion symptoms are often reported among patients involved in litigation and compensation procedures. Comprehensive multidisciplinary assessment of post-concussion symptoms using standardized instruments is recommended to improve early identification of post-concussion symptoms.

In **Chapter 3** we compared different classification methods for post-concussion symptoms in a prospective cohort study of 731 mild TBI patients from the Netherlands. Post-concussion symptoms were assessed with the Rivermead Post-Concussion Questionnaire (RPQ) using the following analysis strategies: The RPQ mapped to the ICD-10/DSM-IV criteria, the RPQ total score, the RPQ-3 and the RPQ three-factor model. These divergent definitions resulted in prevalence rates of six-month post-concussion symptoms ranging from 11% to 39%. We additionally found that the effect of predictors varied for the different definitions, e.g. the predictors injury severity score, abbreviated injury score of the head, comorbidities and hospital admission were significantly associated with PCS using some of the classification methods for PCS but not when using others.

In **Chapter 4 and 5** we systematically reviewed the literature on prevalence and predictors of psychiatric disorders following TBI. In both reviews we focused on studies using structured diagnostic interviews for psychiatric disorders. In **Chapter 4**, a total of 34 studies were included. Prevalence rates of psychiatric disorders varied widely. Pooled estimates for anxiety and depressive disorders were 19% and 13% pre-injury and 21% and 17% in the first year post-injury. Pooled prevalence rates appeared to increase over time, with more than 40% of the patients diagnosed with a psychiatric disorders after 3-10 years. In **Chapter 5**, 26 studies were included. Major depressive disorder following TBI was associated with female gender, pre-injury depression, TBI severity (moderate TBI vs. severe TBI), early post-injury psychiatric symptoms, post-injury unemployment and a lower brain volume, whereas posttraumatic stress disorder (PTSD) was related to shorter posttraumatic amnesia, memory of the traumatic event and early post-traumatic symptoms. The results of this review should however be interpreted with caution since predictors were predominately assessed in underpowered studies using univariable analyses.

In **Chapter 6 and 7** we focused on prediction modeling following mild TBI. In **Chapter 6**, we used variables available at the emergency department (ED) to predict six-month post-concussion symptoms, using the RPQ linear scale in a prospective cohort study in the United States. A total of 277 mild TBI patients were included. A prediction model based on age, gender, years of education, pre-injury migraine and headache, pre-injury psychiatric disorders, prior TBI, posttraumatic amnesia and loss of consciousness explained 21% of the variance in outcome, which decreased to 14% after bootstrap validation. In **Chapter 7**, the model developed in **Chapter 6** was externally validated in 591 mild TBI patients participating in a prospective cohort study in the Netherlands. The model, as well as another existing prediction model, performed poorly in external validation (Area Under the Curve (AUC): 0.57-0.64). A new model, based on female sex, symptoms at the ED (neck pain, headache, nausea or vomiting) and two-week post-concussion symptoms and posttraumatic stress symptoms, performed reasonably (AUC: 0.77; AUC after bootstrap validation: 0.75).

In **Chapter 8,** we compared health-related quality of life (HRQoL) of Dutch and Chinese patients with mild and moderate TBI one year post-injury. For this purpose, we used a prospective cohort study from the Netherlands (447 patients) and a retrospective cohort study from Zhuhai, China (173 patients). There were differences among Dutch and Chinese patients on the dimensions general health, physical functioning, bodily pain and role limitations due to emotional problems. Scores on vitality were suboptimal for both patient groups. Using confirmatory factor analysis, we found that the vitality subscale was strongly associated with the mental health component and not with the physical component.

PART II: Comparative effectiveness research in traumatic brain injury

In **Chapter 9**, we systematically reviewed the literature on TBI guideline adherence. We included 22 studies describing adherence to 13 guideline recommendations. Guideline adherence varied considerably between studies (range 18-100%) and was dependent on the invasiveness of the intervention, patient-related factors (age and TBI severity) and the quality of the evidence underpinning the guideline recommendation. Guideline adherence seemed to be associated with lower mortality. The systematic review was published as a living systematic review, meaning that updates are published when new information becomes available. The most recent update from June 2017 (2 years and 8 months after the initial search) revealed a total of 13 new studies (37% of the total evidence base). In the more recent studies, guideline adherence to intracranial pressure (ICP) monitoring guidelines was higher but the association between guideline adherence and clinical outcome became more uncertain.

In **Chapter 10-13**, we presented the results of the provider profiling studies, which are part of the Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) study, a large observational cohort study among 68 European neurotrauma centers. In **Chapter 10**, we

introduced the provider profiling questionnaires and reported variation in general structural and process characteristics. We found that the majority of participating centers were academic hospitals, level I trauma centers and situated in an urban location. However, the availability of facilities for neurotrauma care and general processes of care varied considerably.

In **Chapter 11**, we describe the emergency department and hospital admission management across Europe. There were large differences in the definition of mild TBI across centers. In addition, many different guidelines were used to determine whether a patient should receive a computed tomography (CT) scan. Routine follow-up after ED admission was only scheduled in 10% of the centers. Written discharge information was routinely provided in approximately half of the centers.

In **Chapter 12** we described monitoring and treatment policies for intracranial hypertension. Although the majority of centers indicated to place an ICP monitor in patients with severe TBI and CT abnormalities, there was no consensus on other indications or on peri-insertion precautions. We additionally found wide variation in the use of first- and second-tier treatments for elevated intracranial pressure. Approximately half of the centers were classified as having a relatively aggressive approach to ICP monitoring and treatment, whereas the other half was relatively conservative. Although the majority of participants indicated to follow TBI guidelines, the reported policy at the ED, hospital ward and the intensive care unit (ICU) diverged substantially from what is stated in the guidelines. For example, one-fifth of European neurotrauma centers claimed to use barbiturates as first tier therapy, while barbiturates are only recommended as second tier therapy.

In **Chapter 13**, we examined rehabilitation policies for patients with severe TBI. An in-hospital multidisciplinary rehabilitation team was available in 41% of the ICUs and 49% of the wards. Coma stimulation was available in half of the centers and another half of the centers had an in-hospital rehabilitation unit. Age was reported as a major determinant of referral decisions in half of the centers, with younger patients usually referred to specialized rehabilitation centers, and patients ≥ 65 years also referred to nursing homes or local hospitals

In **Chapter 14**, we performed a secondary analysis of prospectively collected data from five level I trauma centers in the Netherlands to examine causes and consequences of treatment variation. We included 503 patients and found that patient characteristics explained 12-52% of the variation in treatment. Treatment varied substantially among centers, even after adjustment for case-mix. We found that outcome was more favorable in patients treated in centers maintaining an aggressive approach towards ICP monitoring than in centers maintaining a less aggressive approach.

The wide variation in structure and processes of care for TBI patients found in **Chapters 10-14** provides an opportunity to study treatment effectiveness with comparative effectiveness research (CER). The analytical method chosen for CER analyses may however drastically influence the effect estimate of the treatment, which is explained in **Chapter 15** and **16**. Covariate adjustment and propensity score adjustment cannot adjust for unmeasured confounders, and therefore, may result in an invalid estimate of the treatment effect. Instrumental variable analysis can theoretically adjust for unmeasured confounders but is statistically inefficient, dependent on strong assumptions and difficult to interpret.

Discussion

The aim of this thesis was to study outcome and opportunities for CER in patients with traumatic brain injury. We found that prevalence rates of post-concussion symptoms and psychiatric disorders varied widely and were dependent on pre-injury factors, patient population, assessment, analysis strategy and the diagnostic criteria used. Etiology of TBI sequelae is complex and multifactorial and includes biological, psychological and social factors that might be difficult to capture in a prediction model. When studying prevalence and predictors of psychiatric disorders and post-concussion symptoms following TBI, the role of misattribution, research setting, attrition and the overlap in symptomatology between post-concussion symptoms and psychiatric disorders should be taken into account.

Current evidence underpinning TBI guidelines is weak, and consequently, there is large variation in policy and guideline adherence among neurotrauma centers. This variation provides an opportunity for CER. However, the effect estimate obtained in observational CER studies largely depends on the analytical method used. Since all analytical methods have their strengths and limitations and are based on untestable assumptions, it is important that researchers do not consider one particular analytical method as the most appropriate. Different analytical methods that are reasonable for the research question under study should be used as sensitivity analyses and the results of observational CER studies should be confirmed by high-quality RCTs.

Based on the content of this thesis and its interpretation, we formulated specific recommendations for research, policy and clinical practice, including standardization of definitions for mild TBI and data collection practices and the prevention of attrition in prognostic studies. In addition, we recommend studying overlap between post-concussion symptoms and psychiatric disorders and examining whether a symptom track application is feasible to identify mTBI patients with prolonged sequelae. For research on treatment effectiveness, we recommend the use of provider profiling and comparative effectiveness research. Research findings on treatment effectiveness should subsequently be summarized into living systematic reviews. For clinical practice, we recommend to inform and reassure mTBI patients about the potential sequelae and to use multidimensional comprehensive assessment of post-concussion symptoms.

Samenvatting

Introductie

'Een dronken student loopt na een avond stappen tegen een deur aan. Ondanks dat zij niet direct klachten ervaart en zich alles kan herinneren heeft zij de eerste weken na het 'ongeluk' last van hoofdpijn, concentratieproblemen en vermoeidheid.'

'Een fanatieke hockeyster botst tijdens een wedstrijd tegen haar tegenspeelster aan. Zij raakt bewusteloos en moet op de spoedeisende hulp worden behandeld aan een hoofdwond. Zij kan zich niks meer herinneren van het ongeval en heeft nog maanden last van zware hoofdpijn, duizeligheid, misselijkheid en prikkelbaarheid.'

'Een automobilist raakt de macht over het stuur kwijt en rijdt tegen een boom aan. Naast een aantal botbreuken en kneuzingen heeft de klap op zijn hoofd geresulteerd in meerdere kleine bloedingen in de hersenen. Na langdurige behandeling op de intensive care volgen nog maanden van revalidatie. Na een jaar kan hij weer redelijk zelfstandig functioneren maar is hij als gevolg van concentratieproblemen, geheugenverlies en vermoeidheid niet meer in staat om zijn baan als docent weer op te pakken.'

Bovengenoemde drie patiënten hebben één ding gemeen: zij hebben allen een vorm van traumatisch hersenletsel doorgemaakt. Traumatisch hersenletsel is een vorm van niet-aangeboren hersenletsel waarbij een externe oorzaak, zoals een klap tegen het hoofd, resulteert in een verandering van de hersenfunctie. Traumatisch hersenletsel wordt vaak gecategoriseerd in licht (casus 1), matig-ernstig (casus 2) en ernstig (casus 3). Met name ernstig traumatisch hersenletsel is een van de belangrijke doodsoorzaken wereldwijd en vormt daarmee een groot probleem voor de volksgezondheid. Patiënten die een ernstig traumatisch hersenletsel overleefd hebben kunnen nog langdurige gevolgen ondervinden in het dagelijks leven (zie casus 3). Maar ook na een lichte vorm van traumatisch hersenletsel, ook wel hersenschudding genoemd (zie casus 1), zijn er patiënten die maanden, en soms jaren na het ongeval nog klachten ervaren. Deze klachten betreffen vaak cognitieve klachten (geheugenproblemen, concentratieproblemen), somatische klachten (hoofdpijn, duizeligheid) en emotionele klachten (rusteloosheid, depressie) en kunnen worden samengevat onder de term 'postcommotionele symptomen'. Naast postcommotionele symptomen, ontwikkelt een deel van de patiënten psychiatrische stoornissen. Met name posttraumatische stressstoornis (PTSS) en depressie komen relatief vaak voor.

Het is tot op heden onbekend waarom sommige patiënten na (licht) traumatisch hersenletsel klachten en psychiatrische stoornissen ontwikkelen en anderen binnen weken of maanden weer volledig herstellen. Voorgaande onderzoeken naar voorspellende factoren ('predictoren') hebben verschillende beperkingen, waardoor momenteel weinig bekend is over welke factoren wel en niet samenhangen met een hogere kans op langdurige klachten en psychiatrische stoornissen. In veel studies zijn de onderzoeksresultaten samengevat in een predictiemodel. Een predictiemodel

is een wiskundige formule op basis van verschillende factoren die in theorie gebruikt kan worden om de kans op langdurige klachten in te schatten bij patiënten met traumatisch hersenletsel. Een dergelijke risicoschatting kan gebruikt worden om artsen, patiënten en naasten te informeren over de prognose en om keuzes te maken omtrent de behandeling. Er zijn nog geen gevalideerde modellen die de uitkomst na licht traumatisch hersenletsel voorspellen, noch zijn er gevalideerde modellen voor psychiatrische stoornissen na licht, matig-ernstig en ernstig traumatisch hersenletsel.

Een ander belangrijk en actueel onderwerp binnen het onderzoeksveld van traumatisch hersenletsel is het meten van de effectiviteit van behandelingen. Gerandomiseerd onderzoek met een controlegroep wordt hiervoor gezien als de 'gouden standaard'. In gerandomiseerd onderzoek worden patiënten random toegewezen aan een behandelconditie en een controleconditie. Het verschil in uitkomst tussen behandelde en onbehandelde patiënten kan hierdoor met voldoende zekerheid worden toegeschreven aan de behandeling. Gerandomiseerde studies zijn echter niet altijd mogelijk om praktische, ethische en financiële redenen. Daarnaast hebben zij tot op heden niet geresulteerd in een verbetering van de zorg voor patiënten met traumatisch hersenletsel. Observationele studies vormen een alternatief voor gerandomiseerde studies. In observationele studies worden patiënten met traumatisch hersenletsel gevolgd en worden klinische gegevens en behandelinformatie genoteerd. De effectiviteit van behandeling kan in deze studies worden onderzocht door patiënten die een bepaalde behandeling hebben gekregen te vergelijken met patiënten die de behandeling niet hebben gekregen. Een probleem hierbij is echter dat deze patiënten niet altijd vergelijkbaar zijn. Of een patiënt wel of geen behandeling krijgt hangt in observationele studies namelijk af van allerlei factoren, zoals leeftijd en conditie van de patiënt, ernst van het letsel en de klinische intuïtie van de arts. Hierdoor is het onduidelijk of een verschil in uitkomst tussen behandelde en onbehandelde patiënten toe te schrijven is aan de behandeling of veroorzaakt wordt door andere factoren. Met sommige factoren, zoals bijvoorbeeld leeftijd, kan rekening gehouden worden in statistische analyses. Niet alle verschillen tussen patiënten kunnen echter gemeten worden, waardoor het onduidelijk blijft of een verschil in uitkomst tussen behandelde en onbehandelde patiënten veroorzaakt wordt door de behandeling of door andere factoren.

Een relatief nieuwe manier om met dit probleem om te gaan, is om de effectiviteit niet op patiënt-niveau maar op ziekenhuisniveau te analyseren. Deze methode kan worden gebruikt binnen de zogenoemde vergelijkende effectiviteitsstudies. Dit zijn vaak grootschalige internationale studies waar meerdere ziekenhuizen aan meewerken. Door uitkomsten van patiënten in ziekenhuizen die een bepaalde behandeling vaak uitvoeren te vergelijken met uitkomsten van patiënten in ziekenhuizen die de behandeling weinig uitvoeren, kunnen we een schatting krijgen van de effectiviteit van deze behandeling. Een voorwaarde hiervoor is echter dat er voldoende variatie is tussen ziekenhuizen in hoe vaak de behandeling wordt toegepast.

Onderzoeksvragen

Dit proefschrift heeft als doel om onze kennis te verdiepen met betrekking tot uitkomsten na traumatisch hersenletsel. Daarnaast hebben we mogelijkheden onderzocht voor vergelijkend effectiviteitsonderzoek. Deze doelen zijn geoperationaliseerd in de volgende hoofd- en deelvragen:

1. **Wat is de prevalentie van en wat zijn predictoren voor uitkomst na traumatisch hersenletsel?**
    a. Wat is de prevalentie van postcommotionele symptomen, psychiatrische stoornissen en een verminderde kwaliteit van leven?
    b. Wat zijn predictoren voor uitkomst na traumatisch hersenletsel?
    c. Kunnen we patiënten met het een hoog risico op postcommotionele symptomen identificeren?
2. **In welke mate kan vergelijkend effectiviteitsonderzoek bijdragen aan kennis over behandeleffectiviteit bij traumatisch hersenletsel?**
    a. In welke mate houden clinici zich aan de huidige richtlijnen voor traumatisch hersenletsel?
    b. In welke mate is er variatie tussen ziekenhuizen in de behandeling van patiënten met traumatisch hersenletsel?
    c. Wat is de invloed van analytische methoden op de schatting van behandeleffectiviteit in observationele studies? En welke methode resulteert in een valide schatting?

Dit proefschrift is geschreven in het kader van de 'Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) study: een grootschalige observationele studie naar traumatisch hersenletsel studie in 68 Europese ziekenhuizen.

Deel I: Uitkomst na traumatisch hersenletsel

In **hoofdstuk 2** hebben we de huidige literatuur met betrekking tot postcommotionele symptomen samengevat. We hebben hierbij gekeken naar definities, epidemiologie, etiologie, diagnostische instrumenten en behandeling. Alhoewel postcommotionele symptomen vaak werden genoemd na licht traumatisch hersenletsel, is het tot op heden onduidelijk of deze symptomen een klinisch relevant syndroom vormen. De prevalentie van postcommotionele symptomen varieerde sterk en was afhankelijk van de patiëntpopulatie, de diagnostische criteria en de analyse strategie. De etiologie van postcommotionele symptomen is complex en multifactorieel en bestaat onder andere uit biologische factoren (onder andere diffuse axonale beschadigingen), psychologische factoren (onder andere positieve psychiatrische voorgeschiedenis), sociale factoren (onder andere sociale steun) en persoonlijkheidsfactoren (onder andere coping). Uitgebreide diagnostiek en het gebruik van gestandaardiseerde meetinstrumenten is sterk aanbevolen om postcommotionele symptomen vroeg te identificeren.

In **hoofdstuk 3** van dit proefschrift hebben we verschillende analysestrategieën voor post-commotionele symptomen vergeleken bij 731 patiënten met licht traumatisch hersenletsel. Alhoewel postcommotionele symptomen vaak met een vragenlijst in kaart worden gebracht (bijvoorbeeld de Rivermead Post-Concussion Questionnaire, RPQ), is er geen consensus bereikt over hoe deze vragenlijst geanalyseerd dient te worden. Verschillende analysestrategieën kunnen echter tot verschillende prevalenties leiden waardoor het moeilijk is om onderzoeken met elkaar te vergelijken. De verschillende analysestrategieën in deze studie resulteerden in prevalenties in de range 11-39% Daarnaast bleek dat sommige predictoren voorspellend waren voor postcommotionele symptomen geanalyseerd met de ene analysestrategie maar niet met de andere. Uit deze studie blijkt dat het belangrijk is om de analysestrategie voor de RPQ te standaardiseren, zodat toekomstig wetenschappelijk onderzoek beter met elkaar vergeleken kan worden.

In **hoofdstuk 4** en **5** hebben we door middel van literatuurstudies gekeken naar de prevalentie en predictoren van psychiatrische stoornissen na traumatisch hersenletsel. In **hoofdstuk 4** hebben we 34 observationele studies geïncludeerd. De prevalenties voor angst en depressie waren 19% en 13% vóór het ongeval en 21% en 17% gedurende het eerste jaar na het ongeval. De prevalentie leek toe te nemen met de tijd: drie tot tien jaar na het ongeval werden meer dan 40% van de patiënten gediagnosticeerd met een psychiatrische stoornis. In **hoofdstuk 5** hebben we 26 observationele studies geïncludeerd waarbij we naar predictoren hebben gekeken. Depressie na traumatisch hersenletsel kwam vaker voor bij vrouwen, bij patiënten met een psychiatrische stoornis in de voorgeschiedenis, bij patiënten met een matig-ernstig traumatisch hersenletsel, bij patiënten die vlak na het ongeluk psychische klachten hadden of werkloos waren en bij patiënten met een kleiner hersenvolume. PTSS na traumatisch hersenletsel kwam vaker voor bij patiënten die zich het ongeval konden herinneren, korter geheugenverlies hadden en patiënten die al vroeg na het ongeval stress symptomen rapporteerden.

In **hoofdstuk 6** en **7** analyseerden we predictiemodellen voor uitkomst na licht traumatisch hersenletsel. In **hoofdstuk 6** gebruikten we variabelen beschikbaar op de spoedeisende hulp om te voorspellen welke patiënten een grotere kans hebben op postcommotionele symptomen na zes maanden. Hiervoor hebben we gebruik gemaakt van een observationele studie uit de Verenigde Staten met 277 patiënten. Een predictiemodel gebaseerd op de variabelen leeftijd, geslacht, opleiding, psychiatrische voorgeschiedenis, een eerder traumatisch hersenletsel, geheugenverlies na het ongeval en bewustzijnsverlies na het ongeval voorspelde 14% van de variatie in postcommotionele symptomen. In **hoofdstuk 7** hebben we dit model getest in een groep van 591 Nederlandse patiënten. Het model bleek slecht te functioneren. De ‘area under the curve (AUC)’ was 0.57, wat betekent dat het model nauwelijks beter was in het voorspellen van postcommotionele symptomen dan het opgooien van een munt (AUC = 0.50). Een nieuw model, gebaseerd op geslacht, het ervaren van klachten op de spoedeisende hulp (nekpijn, hoofdpijn, misselijkheid en overgeven) en symptomen na twee weken (postcommotionele symptomen en

stresssymptomen) was redelijk in staat om postcommotionele symptomen na zes maanden te voorspellen (AUC = 0.75).

In **hoofdstuk 8** hebben we onderzoek gedaan naar kwaliteit van leven bij patiënten met licht en matig-ernstig traumatisch hersenletsel uit Nederland (447 patiënten) en China (173 patiënten). Nederlandse en Chinese patiënten scoorden verschillend op de dimensies algemene gezondheid, fysiek functioneren, pijn en rolbeperkingen door emotionele problemen. Beide populaties scoorden slecht op de dimensie vitaliteit, wat inhoudt dat zij een jaar na het ongeval nog symptomen van vermoeidheid en futloosheid hadden.

Deel II: vergelijkend effectiviteitsonderzoek bij traumatisch hersenletsel

In **hoofdstuk 9** hebben we middels een literatuurstudie onderzocht in welke mate clinici zich aan de huidige richtlijnen voor traumatisch hersenletsel houden. We hebben hiervoor 22 studies geïncludeerd. Bij 18% tot 100% van de patiënten werden richtlijnen adequaat opgevolgd. Adherentie was geassocieerd met patiëntfactoren (leeftijd en ernst van het hersenletsel), de kwaliteit van de richtlijn en de invasiviteit van de behandeling. Patiënten die behandeld werden volgens de richtlijnen hadden een betere uitkomst dan patiënten die niet behandeld werden volgens de richtlijnen. Aangezien literatuurstudies vaak niet meer actueel zijn als ze gepubliceerd worden, hebben we er voor gekozen om de review regelmatig te updaten. Dit wordt ook wel een 'living systematic review' genoemd. **Hoofdstuk 9** is de eerste 'living systematic review' wereldwijd. De meest recente update (Juni 2017) liet zien dat er in nog geen drie jaar na de originele zoekstrategie 13 nieuwe studies geïncludeerd waren, welke bijna 40% van het totaal aantal studies representeerden. Het toevoegen van deze 13 studies resulteerde tevens in een aantal aanpassingen in de conclusies en laat daarmee het belang zien van het updaten van literatuurstudies.

In **hoofdstuk 10-13** presenteerden we de resultaten van de 'provider profiling' vragenlijst: een vragenlijst die door alle deelnemende ziekenhuizen aan de CENTER-TBI studie is ingevuld en tot doel had om de variatie tussen ziekenhuizen in kaart te brengen. In **hoofdstuk 10** introduceerden we de 'provider profiling' vragenlijst en lieten we een aantal algemene ziekenhuisverschillen zien. Ondanks dat bijna alle ziekenhuizen een Academische affiliatie hadden en over een level I trauma center beschikten, waren er grote verschillen in de faciliteiten voor patiënten met traumatisch hersenletsel. Ook waren er grote verschillen in behandelbeleid.

In **hoofdstuk 11** beschreven we verschillen in de zorg op de spoedeisende hulp en tijdens opname in het ziekenhuis tussen de Europese centra. We lieten onder andere zien dat er verschillen zijn in de definitie van licht traumatisch hersenletsel. Daarnaast vonden we grote verschillen in het CT scan beleid tussen ziekenhuizen, waarbij sommige centra een liberaal beleid hadden (bijna alle

patiënten met licht traumatisch hersenletsel krijgen een scan) en andere centra meer restrictief handelden (alleen patiënten met een grote kans op complicaties krijgen een scan). Na het bezoek aan de spoedeisende hulp, had tien procent van de ziekenhuizen het beleid om de patiënt terug te zien op de polikliniek. Ongeveer de helft van de centra gaf schriftelijke informatie mee aan patiënten na het doormaken van licht traumatisch hersenletsel.

In **hoofdstuk 12** beschreven we verschillen in het monitoren en behandelen van patiënten met een verhoogde intracraniële druk. Een verhoogde intracraniële druk kan ontstaan doordat een bloeding of zwelling in de hersenen ruimte inneemt. Aangezien de hersenen niet kunnen uitzetten zal de druk in de hersenen op zo'n moment toenemen wat levensbedreigend kan zijn. Behandelingen om de druk te verlagen, zoals medicatie of een operatie kunnen echter ook weer complicaties geven. Bijna alle deelnemende centra gaven aan de intracraniële druk standaard te meten bij patiënten met ernstig traumatisch hersenletsel. De behandeling verschilde echter sterk, waarbij ongeveer de helft van de ziekenhuizen een relatief agressieve benadering had en de andere helft meer conservatief handelde. Opvallend was ook dat een deel van de centra aangaf een behandelbeleid te hebben dat in tegenspraak is met internationale richtlijnen. Een-vijfde van de centra gaf bijvoorbeeld medicijnen om het centrale zenuwstelsel te dempen (barbituraten) als eerste middel om de druk te verlagen, terwijl dit in verband met een hoog risico op complicaties alleen wordt aangeraden als andere behandelingen niet aanslaan.

In **hoofdstuk 13** hebben we de Europe centra gevraagd naar hun revalidatiemogelijkheden en verwijsbeleid. Ook hier vonden we veel variatie. De helft van de centra beschikte over een revalidatieafdeling waar patiënten met ernstig traumatisch hersenletsel behandeld konden worden. Met betrekking tot verwijzing vonden we dat leeftijd een belangrijke rol bleek te spelen. Patiënten onder de 65 jaar werden meestal verwezen naar gespecialiseerde revalidatiecentra na hun ziekenhuisopname, terwijl oudere patiënten vaker werden verwezen naar verpleeghuizen en niet-gespecialiseerde ziekenhuizen.

In **hoofdstuk 14** hebben we gekeken naar oorzaken en gevolgen van behandelvariatie in een observationele studie met 503 patiënten afkomstig uit vijf Nederlandse Academische ziekenhuizen. We vonden dat variatie vooral werd bepaald door ziekenhuisfactoren en niet zozeer door verschil in patiëntkarakteristieken tussen ziekenhuizen. Patiënten met ernstig traumatisch hersenletsel die in ziekenhuizen behandeld werden met een agressieve benadering hadden een betere uitkomst dan patiënten die in meer conservatieve centra behandeld werden.

De substantiële variatie in **hoofdstuk 10** t/m **14** biedt kansen om behandeleffectiviteit te analyseren met vergelijkende effectiviteitsstudies. Het succes van zo'n vergelijkende effectiviteitsstudie is echter sterk afhankelijk van de statistische methode die hiervoor gebruikt wordt, wat uitgewerkt is in **hoofdstuk 15 en 16.** Conventionele methoden om te corrigeren voor patiëntkenmerken kunnen niet corrigeren voor factoren die niet gemeten zijn (bijvoorbeeld factoren die gerelateerd

zijn aan klinische intuïtie). Het analyseren van behandeleffecten op ziekenhuisniveau kan hier mogelijk wel voor corrigeren, maar is moeilijk te interpreteren en statistisch inefficiënt, wat betekent dat er veel patiënten nodig zijn om een effect aan te tonen als er een effect is. Verder is deze methode gebaseerd op een aantal aannames welke moeilijk te testen zijn.

Discussie

Het doel van dit proefschrift was om onze kennis met betrekking tot uitkomsten en mogelijkheden voor vergelijkend effectiviteitsonderzoek bij patiënten met traumatisch hersenletsel te vergroten. Om dit te bereiken hebben we meerdere literatuurstudies en observationele studies verricht.

We vonden dat de prevalentie van postcommotionele symptomen en psychiatrische stoornissen sterk varieerde en samenhing met de voorgeschiedenis van een patiënt, de patiëntenpopulatie, diagnostische criteria en analyse strategieën. De etiologie is complex en multifactorieel en bestaat onder andere uit biologische, psychologische en sociale factoren die moeilijk te integreren zijn in een predictiemodel. Bij het interpreteren van onderzoeken naar de prevalentie en predictoren van uitkomsten na traumatisch hersenletsel is het belangrijk om de volgende factoren in overweging te nemen:

- Er kan sprake zijn van misattributie waarbij symptomen na traumatisch hersenletsel worden toegeschreven aan het traumatisch hersenletsel terwijl ze eigenlijk een andere oorzaak hebben.
- De ernst van de symptomen kan samenhangen met de onderzoekssetting en hoeft dus niet generaliseerbaar te zijn naar alle patiënten met traumatisch hersenletsel. Het is aannemelijk dat patiënten met licht traumatisch hersenletsel op de spoedeisende hulp of in revalidatie instellingen ernstigere klachten hebben dan patiënten die zich bij de huisarts hebben gemeld of geen hulp hebben gezocht.
- Patiënten die deelnemen aan onderzoek kunnen verschillen van patiënten die niet willen deelnemen aan onderzoek of zijn uitgevallen.
- Er kan sprake zijn van overlap tussen postcommotionele symptomen en psychiatrische stoornissen.

Verder hebben we gevonden dat clinici zich matig aan de huidige richtlijnen voor traumatisch hersenletsel houden en dat er veel variatie is in het behandelbeleid in Europa. Aan de ene kant is dit zorgwekkend aangezien sommige patiënten mogelijk niet de meest effectieve zorg krijgen. Aan de andere kant vormt de huidige variatie een mogelijkheid om de behandeleffectiviteit te onderzoeken met vergelijkende effectiviteitsstudies. De statistische methode is hierbij erg belangrijk. Veel gebruikte methoden kunnen niet corrigeren voor alle verschillen tussen behandelde en onbehandelde patiënten, omdat sommige verschillen, zoals klinische intuïtie, niet meetbaar zijn. Analyses op het niveau van het ziekenhuis kunnen dit theoretisch gezien wel maar zijn statistisch inefficiënt, gebaseerd op een aantal sterke aannames en zijn moeilijk

te interpreteren. Aangezien alle methoden voor- en nadelen hebben, is het onmogelijk om te stellen welke methode 'het beste' is. Daarom is het belangrijk dat onderzoekers verschillende methoden naast elkaar gebruiken bij het analyseren van de behandeleffectiviteit. Tot slot is het belangrijk dat de resultaten van observationele studies bevestigd worden in kwalitatief hoogwaardige gerandomiseerde studies met een controlegroep.

Dankwoord

Beste lezer,

Na het lezen van dit proefschrift bent u waarschijnlijk meer te weten gekomen over traumatisch hersenletsel en onderzoek naar uitkomsten en vergelijkende effectiviteit. Nu het einde van dit proefschrift nadert, vraagt u zich misschien af waarom dit proefschrift begon met de beroemde spreuk van Forrest Gump (1994):

"Life is like a box of chocolates, you never know what you gonna get"

In dit proefschrift heeft u kunnen lezen dat het moeilijk te voorspellen is welke patiënten met traumatisch hersenletsel langdurige klachten ontwikkelen (so you never know what you gonna get). Daarnaast heb ik laten zien dat het als patiënt met traumatisch hersenletsel moeilijk te voorspellen is welke behandeling je kunt verwachten, aangezien er grote verschillen zijn tussen ziekenhuizen (again, you never know what you gonna get).

Naast de inhoudelijke link met mijn proefschrift en het feit dat ik een fervent chocoladeliefhebber ben (melkchocolade met hazelnoot voor wie nog cadeau inspiratie zoekt), staat deze spreuk voor hoe ik mijn baan als promovendus heb ervaren. Als wetenschapper in spé ben ik in maart 2014 gestart met het doen van onderzoek. Vele verwachtingen, of hypotheses zoals we dat in de wetenschap noemen, heb ik gehad. Sommige hypotheses bleken te kloppen, maar veelal bleken de resultaten verrassend. Als wetenschapper ben ik me er van bewust geworden dat je niet alles kunt voorspellen, maar dat je door te onderzoeken daadwerkelijk een bijdrage kunt leveren aan de kennis of de veronderstelde kennis. Daarom is de wetenschap voor mij net als 'a box of chocolates'; verrassend, uitdagend en je krijgt er niet snel genoeg van.

Chocolade eet je natuurlijk niet alleen (behalve tijdens het afronden van je proefschrift, daarom dank aan de AH to go in het Erasmus MC voor het op peil houden van de voorraad), noch schrijf je een proefschrift alleen. Daarom wil ik iedereen die heeft bijgedragen aan de totstandkoming van dit proefschrift hartelijk bedanken.

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I would then like to thank all CENTER TBI investigators and participants. It has been a huge opportunity to be involved in such an ambitious project and to collaborate with dedicated researchers and clinicians. Special thanks to Andrew and David, the principle investigators of this project. I have learned a lot from the both of you about project management and communication skills and I have appreciated your feedback on my papers, which resulted in major improvements. Also special thanks to Nicole, Nada, Ruben and all other colleagues involved in the narrative review in Chapter 2. It has been an immense task to write such a comprehensive review in only a two-month period, but it was great working with you and I have learned a lot from your dedication, experience and writing skills. Ook wil ik graag alle IMPACT, POCON, RUBICS, Zhuhai, TRACK-TBI en UPFRONT onderzoekers bedanken voor het verzamelen van de data en de mogelijkheid die jullie mij hebben gegeven om artikelen te schrijven op basis van de door jullie verzamelde data.

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Het was mij een groot genoegen om dit proefschrift te mogen schrijven. Alle mensen die ik niet bij naam heb kunnen noemen maar wel bijzondere ontmoetingen en gesprekken mee heb gehad of mee heb samengewerkt, wil ik bij deze ook nog van harte bedanken. Ik hoop dat dit proefschrift een kleine bijdrage heeft geleverd aan onze kennis over uitkomsten en vergelijkende effectiviteit bij patiënten met traumatisch hersenletsel. Daarnaast hoop ik dat dit proefschrift zal resulteren in uitgebreid vervolgonderzoek, zodat we op gegeven moment met enige zekerheid kunnen stellen: “you DO know what you gonna get”.

Maryse Cnossen, Rotterdam aug. 2017

List of Publications

1. Huijben JA, van der Jagt M, **Cnossen MC**, et al. Variation in blood transfusion and coagulation management in Traumatic Brain Injury at the Intensive Care Unit: A survey in 66 neurotrauma centers participating in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study. *J Neurotrauma* 2017.

2. Yue JK, Ngwenya LB, Upadhyayula PS, et al. Emergency department blood alcohol level associates with injury factors and six-month outcome after uncomplicated mild traumatic brain injury. *J Clin Neurosci* 2017.

3. Lingsma HF, **Cnossen MC**. Identification of patients at risk for poor outcome after mTBI. *Lancet Neurol* 2017; 16(7): 494-5.

4. **Cnossen MC,** Lingsma HF, Tenovuo O, et al. Rehabilitation after traumatic brain injury: A survey in 70 European neurotrauma centres participating in the CENTER-TBI study. *J Rehabil Med* 2017; 49(5): 395-401.

5. **Cnossen MC,** Polinder S, Vos PE, et al. Comparing health-related quality of life of Dutch and Chinese patients with traumatic brain injury: do cultural differences play a role? *Health Qual Life Outcomes* 2017; 15(1): 72.

6. Foks KA, **Cnossen MC,** Dippel DWJ, et al. Management of mild traumatic brain injury at the emergency department and hospital admission in Europe: A survey of 71 neurotrauma centers participating in the CENTER-TBI study. *J Neurotrauma* 2017.

7. **Cnossen MC**, Winkler EA, Yue JK, et al. Development of a Prediction Model for Post-Concussive Symptoms following Mild Traumatic Brain Injury: A TRACK-TBI Pilot Study. *J Neurotrauma* 2017.

8. **Cnossen MC,** Scholten AC, Lingsma HF, et al. Predictors of Major Depression and Posttraumatic Stress Disorder Following Traumatic Brain Injury: A Systematic Review and Meta-Analysis. *J Neuropsychiatry Clin Neurosci* 2017; 29(3): 206-24.

9. **Cnossen MC**, Polinder S, Andriessen TM, et al. Causes and Consequences of Treatment Variation in Moderate and Severe Traumatic Brain Injury: A Multicenter Study. *Crit Care Med* 2017; 45(4): 660-9.

10. de Munter L, Polinder S, Lansink KW, **Cnossen MC**, Steyerberg EW, de Jongh MA. Mortality prediction models in the general trauma population: A systematic review. *Injury* 2017; 48(2): 221-9.

11. **Cnossen MC,** Steyerberg EW, Lingsma HF. Methods for Prediction Research in Mild Traumatic Brain Injury. *J Neurotrauma* 2017; 34(2): 540.

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

13. **Cnossen MC**, Polinder S, Lingsma HF, et al. Variation in Structure and Process of Care in Traumatic Brain Injury: Provider Profiles of European Neurotrauma Centers Participating in the CENTER-TBI Study. *PLoS One* 2016; 11(8): e0161367.

14. Scholten AC, Haagsma JA, **Cnossen MC,** Olff M, van Beeck EF, Polinder S. Prevalence of and Risk Factors for Anxiety and Depressive Disorders after Traumatic Brain Injury: A Systematic Review. *J Neurotrauma* 2016; 33(22): 1969-94.

15. **Cnossen MC**, Scholten AC, Lingsma HF, et al. Adherence to Guidelines in Adult Patients with Traumatic Brain Injury: A Living Systematic Review. *J Neurotrauma* 2016.

16. **Cnossen MC,** Lingsma HF, Maas AI, Menon DK, Steyerberg EW. Estimating Treatment Effectiveness of Intracranial Pressure Monitoring in Traumatic Brain Injury. *Crit Care Med* 2015; 43(12): e599.

PhD Portfolio

Summary of PhD training and teaching activities

Name of PhD student:	Maryse Cnossen
Erasmus MC department:	Public Health
PhD period:	2014-2017
Promotor:	Prof.dr. E.W. Steyerberg
Copromotors:	Dr. H.F. Lingsma
	Dr. S. Polinder

	Year	Workload (ECTS)
1. PhD. training		
General academic skills		
Systematic searching in pubmed and other databases – W. Bramer	2014	0.6
Advanced medical writing and editing – P. Greenland	2014	0.7
Academic English C1.1. – A. Breemen	2014	2.3
Research integrity – S. van de Vathorst	2015	0.3
CPO course – Center for Patient Oriented Research	2015	0.3
Biomedical English writing and communication – D. Alexander	2015	3.0
Time management course – D. Schut	2016	0.2
Jonge Vrouwen in de Academie – Supervrouwen Academy / Erasmus MC	2017	1.2
Research skills		
Introduction to systematic reviews – A. Synnot	2014	1.0
Methods of public health research – L. Burdorf	2014	0.7
Methods of health services research – N. Klazinga	2014	0.7
Health economics – K. Rendekop	2014	0.7
Methodological topics in epidemiology – A. Deghan	2014	1.4
Advanced analysis of prognostic studies – E.W. Steyerberg	2015	0.7
Quality of life measurements – J. van Busschbach	2015	0.9
Logistic regression – S. Lemeshow	2015	1.4
Introduction to psychology of medical decision making – V. Shaffer	2015	0.2
Cursus GRADE rating – Nederlands huisartsen genoodschap	2015	0.3
Advanced systematic review course – A. Synnot	2015	0.3
Clinical outcome assessment in a multicultural context – M. Martin	2016	0.2

	Year	Workload (ECTS)
Seminars and workshops		
Seminars department of public health, Erasmus MC	2014-2017	2.0
Research meetings medical decision making, department of public health, Erasmus MC	2014-2017	1.0
Workshop transition of care – Oslo	2014	0.3
Symposium 'Quantitative methods for medical research', Erasmus MC	2015	0.1
Symposium 'The scientific basis for evaluation of quality of hospital care', Erasmus MC	2015	0.1
Symposium Cochrane Netherlands	2015	0.3
Presentations at national and international meetings and conferences		
Provider profiling CENTER TBI investigators training meeting, Antwerp	2014	1.0
Completing the provider profiling questionnaires CENTER TBI investigators training meeting, Antwerp (workshop)	2014	1.0
Provider profiling CENTER TBI investigators second training meeting, Antwerp	2015	1.0
Completing the provider profiling questionnaires CENTER TBI investigators second training meeting, Antwerp (workshop)	2015	1.0
Adjusting for confounding by indication in observational studies: An example in traumatic brain injury European conference of epidemiology, Maastricht	2015	1.0
Variation in treatment decisions in traumatic brain injury: Predictors and associations with outcome North American society for medical decision making, Saint Louis (poster)	2015	1.0
Predicting depression and PTSD after traumatic brain injury: A systematic review Department of public health, Erasmus MC (research meeting)	2016	1.0
Guideline adherence in traumatic brain injury: A systematic review, International brain injury association, The Hague	2016	1.0
Predicting depression and PTSD after traumatic brain injury: A systematic review International brain injury association, The Hague	2016	1.0
Rehabilitation after severe traumatic brain injury in Europe: A survey study in 68 centers International brain injury association, The Hague	2016	1.0

	Year	Workload (ECTS)
Comparing health related quality of life of Dutch and Chinese patients with traumatic brain injury: Do cultural factors play a role? International society for quality of life research, Copenhagen (poster)	2016	1.0
Outcome following traumatic brain injury: An integrative approach Department of public health, Erasmus MC (research meeting)	2017	1.0
Development of a prediction model for post-concussive symptoms following mild traumatic brain injury: A TRACK-TBI Pilot study International brain injury association, New Orleans	2017	1.0
Predicting post-concussive symptoms following mild traumatic brain injury: External validation and updating of an existing model International brain injury association, New Orleans (poster)	2017	1.0
2. Teaching activities		
Courses		
Coachen van toekomstige erasmusartsen (basis)	2015	0.2
Vaardigheidsonderwijs geven	2015	0.2
Teach the teacher basiscursus	2015	0.6
Workshop tentamenvragen maken	2016	0.2
Workshop Individuele begeleiding	2016	0.2
Lecturing		
Primary prevention	2015-2017	1.2
Supervising		
Supervising bachelor thesis	2014	3.0
Community project	2015-2017	1.2
Other teaching activities		
Tutor medical students	2015-2016	1.5
Coaching medical students	2014-2017	0.8
Coordinator of the teaching program primary prevention	2016-2017	1.0

About the Author

Maria (Maryse) Catharina Cnossen was born on March 8th, 1987 in Den Helder, the Netherlands. In 2006, she past her secondary school exams at the Rijnlands Lyceum in Oegstgeest and started studying Health Sciences at the VU University in Amsterdam. After obtaining a bachelor's degree, she started a pre-master and master in Clinical Psychology at Leiden University. She obtained her master's degree in 2012 *(Cum Laude)*. Her master thesis focused on the association between attachment style and therapeutic alliance in patients with personality disorders. From 2012 to 2014, Maryse worked as a psychologist and project associate at the Dutch child protection service and GGZ Centraal. In 2014 she started her PhD. project at the Department of Public Health of the Erasmus MC in Rotterdam, which resulted in this thesis. Maryse is planning to continue her scientific career as a postdoctoral researcher.