Treatment, outcome and prediction after mild traumatic brain injury

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Treatment, Outcome and Prediction after Mild Traumatic Brain Injury

Behandeling, uitkomsten en predictie na mild traumatisch hersenletsel

Thesis

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Festina lente.

To my mother, Tamara

Content

Chapter 1

General Introduction

Traumatic brain injury (TBI) is a sudden change in brain function or damage to the brain, caused by an external force, for instance in a motor vehicle or sports accident, fall or a violent incident.[1] It is estimated that each year TBI occurs in more than 60 million people worldwide and 2.5 million people in Europe.[2, 3] Often called a "silent epidemic",[4] TBI represents a global public health problem and an important cause of mortality and morbidity.[5, 6] The majority of patients (75-90%) present with "mild" TBI[7] and according to recent estimations more than 55 million people sustain a mild TBI each year.[2]

Economic, demographic and societal trends influence TBI epidemiology. Particularly in high-income countries, road traffic accidents are decreased due to better safety, and life expectancy is rising thanks to improved health care.[6] In Europe, TBIs are therefore most prevalent in children and young people (<25 years) and in older adults, with the majority caused by falls.[8, 9] Furthermore, although men are more likely to sustain a TBI through their lifetime, the proportion of women with TBI has been increasing. Fall-related injuries at the older age, more engagement of women in professional sport and the military, and better awareness of intimate partner violence, contribute to the increase in the reported number of TBIs.[10-12]

The categorization into mild, moderate and severe TBI is commonly based on the Glasgow Coma Scale score (GCS), which assesses the ability to speak (maximum 5 points) and to perform eye (max. 4 points) and bodily movements (max. 6 points). In that way, GCS score between 13 and 15 indicates "mild", score between 9 and 12 "moderate" and lower than 9 "severe" TBI. Health care and outcome following TBI partly depend on the initial TBI severity. They are also influenced by other injury-related and clinical information, and can also vary based on hospital policies and resources, and pre-injury and personal characteristics such as medical history, age, sex and gender (Figure 1).[13, 14] The needs for acute and post-acute care are, however, not always adequately met.[15, 16]

From the moment of a TBI and the involvement of medical professionals, numerous medical decisions and interventions can follow (Figure 1). Transportation to a specialized trauma center may be considered necessary, and urgent interventions may be required in prehospital setting in case of lowered oxygen level or blood pressure.[17] Upon the arrival at a medical center, it is important to decide on (other) emergency interventions, the performance of computed tomography (CT) and surgical procedures. Some patients are discharged home from the Emergency Department, whereas some are admitted to a hospital ward or to an intensive care unit. After a varying length of hospital stay, a percentage of patients may receive rehabilitation for physical, cognitive, speech, or mental health impairments.

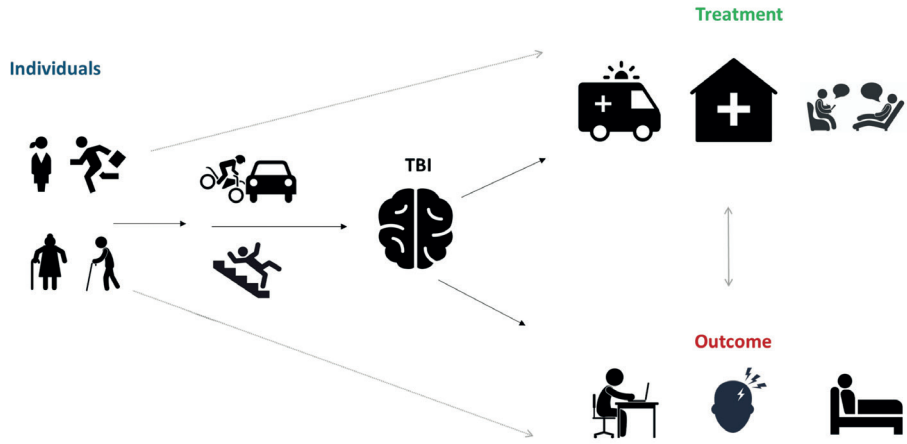

Figure 1. Treatment (prehospital, hospital and posthospital) and outcome (e.g. return to work, headache, tiredness) following traumatic brain injury (TBI) depend on TBI-related (e.g. injury severity and mechanism) and personal characteristics (e.g. age, sex/gender).

A substantial proportion of TBI patients suffer long term consequences in terms of physical disability, and incomplete return to the preinjury level of functioning, including work, social and everyday activities (Figure 1).[18, 19] A considerable proportion of these patients is classified as "mild", which shows that the initial TBI severity is not the only factor influencing outcomes. Mild TBI patients often experience cognitive, somatic and/or psychological symptoms, such as headache, fatigue, forgetfulness and depressive symptoms ("post-concussion symptoms").[20] Even after several months, these symptoms appear to be severe in approximately a quarter of mild TBI patients.[21-23] In addition to post-concussion symptoms, the symptoms of mental health disorders, such as posttraumatic stress disorder, can (co)occur after sustaining a mild TBI.[24] Experiencing different types of symptoms can lead to poorer outcomes and lower quality of life [25, 26] and potentially complicate treatment. A high burden of TBI, including its most frequent form: "mild", calls for improvement of care and outcome.

In this thesis, we aim to provide a better insight into the treatment and outcome of (mild) TBI and relations with sex/gender, age and comorbidity (**PART 1**), and to improve the identification of mild TBI patients with a higher risk of suboptimal short-term and longer-term outcomes (**PART 2**).

PART 1: Treatment and outcome of mild TBI: relations with sex/gender, age and comorbidity

Sex/gender, age and comorbidity can impact health care and outcomes following TBI. We use "sex/gender" and "men" and "women" to emphasize that biological and sociocultural components highly interact in health (TBI) outcomes. Knowledge from other medical

fields suggests that neglecting sex/gender in the context of access to health care, care pathways, treatment effects, and expected outcomes can have severe consequences.[27] Moreover, studies from critical care and cardiovascular medicine show that women have a lower likelihood of being admitted to intensive care and receiving diagnostic and therapeutic procedures.[28, 29] In addition, previous studies have suggested that men and women differ in outcomes following TBI, but that the size and direction of differences depend on the TBI severity and the type and timing of the outcome measured.[30] When outcome differences between men and women were observed, the hypothesized explanations mostly included hormonal biological factors and sociocultural differences, but were not tested.[31]

With aging population, the patients who present with a TBI are on average older.[32] These patients often have comorbid health issues and other frailty factors, whose impact on the outcomes is rarely studied.[12] Instead, these factors often represent exclusion criteria for participation in TBI trials. Furthermore, although age is associated with the unfavorable outcome after TBI and a mortality rate is substantial,[33, 34] some studies show that a considerable percentage of older TBI patients show comparable outcomes as younger patients with similarly severe injuries, at least in some domains of functioning.[35, 36] That suggests that the pessimism regarding the treatment choices and outcomes in older adults may often be unjustified. Importantly, that bias can also lead to differentiating older adults into different health care pathways when being admitted to a hospital and offering them less invasive treatments.[37] The patterns of health care and outcomes after TBI in older adults are, however, still inconclusive. In addition to frailty associated with age, some clinicians have concerns that co-occurring TBI and a psychiatric disorder can negatively affect treatments.[38] For instance, it remains unclear whether therapies for PTSD can be safely and effectively delivered in patients with both PTSD and TBI, which is relevant for a high number of civilian and military patients.[39]

Nonetheless, sex/gender, age and psychiatric comorbidity are only a few factors that can influence outcomes after TBI. The patients at higher risk of worse outcomes may require direct interventions or follow up care. Therefore, it is important to predict which patients are likely to develop acute or chronic complications.

Part II. Prediction: improving diagnosis and prognosis following mild TBI

Acute management of mild TBI patients

A computed tomography (CT) is a reference standard for diagnosing intracranial abnormalities. One of the challenges in the acute management of mild TBI patients is to correctly identify patients with an increased risk of intracranial pathology, who therefore need a CT. The simplest solution would be to scan none or all. However,

scanning all patients would lead to overcrowding of the ER, unnecessary radiation and high costs. If no one would be scanned, potentially important lesions would be missed, leading to insufficient treatment, poor recovery or death.[40] To optimize decision making in the acute management of mild TBI patients, various clinical decision rules have been developed.[41-43] They aim to identify patients who need to obtain a CT scan based on readily available clinical characteristics, such as age, GCS score, posttraumatic amnesia and symptoms of skull fracture at admission. The performance ("diagnostic accuracy") of those clinical decision rules is examined in terms of sensitivity and specificity. Sensitivity refers to the proportion (percentage) of CT scans with intracranial abnormalities for which the decision rule correctly indicates the need for CT. Specificity refers to the proportion (percentage) of CT scans without intracranial abnormalities for which the decision rule correctly indicates no need for CT. Compared to scanning all patients, these rules can increase specificity, with a small decrease in sensitivity for detecting intracranial lesions (Table 1).[40, 42]

Table 1. Sensitivity and specificity for detection of any intracranial lesion: three strategies.

Strategy	Sensitivity	Specificity
Scan all patients	100%	0%
CHIP rule	95%	25%
Scan no patients	0%	100%

CHIP= CT in head injury patients, Smits et al., 2007[44]

The clinical rules need to be further optimized- so that the number of unnecessary CT scans is further reduced (improved specificity) and/or the number of correctly identified lesions is increased (improved sensitivity). TBI-related blood-based biomarkers are promising candidates for improving the current clinical rules. Biomarker S100 calcium-binding protein B (S100B) has been already included in the Scandinavian CT guidelines in the decision making in the "low risk" mild TBI group.[45] Recent studies show that there are also other biomarkers whose associations with the abnormalities on CT may be utilized in identifying patients at risk of intracranial abnormalities and that they outperform S100B, such as glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase-L1 (UCHL-L1).[46-48]

Prognosis of longer-term outcomes following mild TBI

Months after a mild TBI, individuals often do not return to work and other usual activities and/or experience persistent symptoms.[22, 49] Accurately predicting which patients will have a suboptimal recovery would improve clinical decision making and care. These patients could be offered an intervention, scheduled more frequent follow up appointments and be provided with information about their probable trajectory of recovery. Prognostic models are used to predict outcome (e.g. incomplete recovery)

based on one or more predictor variables (e.g. age, GCS).

Currently, there are two sets of robust prognostic models based on admission characteristics following TBI of baseline GCS 3-12 (IMPACT)[50, 51] and GCS 3-14 (CRASH).[33] For instance, the CRASH models were developed to predict mortality and unfavorable outcome based on age, GCS, pupillary reactivity and major extra-cranial injury, and in the extended version also including the intracranial lesions on CT.[33] Traditionally, these injury-related characteristics- "what the injury brings to the patient" -are considered crucial for the prediction of outcome in the more severe TBI spectrum, whereas "what the patient brings to the injury" is seen as more important for the prediction of outcome in the milder end.[52] Such patient-related characteristics, e.g. psychiatric history and education, are predictive of the long-term outcome following mild TBI,[53, 54] in addition to clinical variables [33, 51, 52]. The predictive value of CT abnormalities for prediction of outcomes following mild TBI, however, varies in both children and adults, based on the population, types of lesions and outcome definition.[54-56] Moreover, recent studies have highlighted that symptoms measured days or weeks after a mild TBI are strong predictors of longer-term outcomes.[53, 54, 57] Nevertheless, there are still no robust prognostic models for the prediction of outcome following mild TBI.

Prognostic models: development and validation

Developing a prognostic model for the prediction of outcome following mild TBI is challenging. Firstly, selecting the endpoint (outcome) is not always straightforward. In the field of TBI, Glasgow Outcome Scale Extended (GOSE)[58] is the most frequently used measure of outcome and categorizes the global functional outcome from 1 (death) to 8 (complete return to preinjury functioning). In mild TBI, predicting an incomplete return to preinjury level (GOSE<8) could be more relevant than predicting severe disability or death (GOSE<5). Nonetheless, dichotomization of the endpoint is statistically [59] and clinically suboptimal.[60] Analyzing the GOSE as ordinal can increase the statistical power and provide insight in overall predictor effects.[60] Apart from the GOSE, it is also relevant to predict specific deficits following mild TBI, such as post-concussion and mental health symptoms.

Secondly, it is difficult to select predictors from many potential candidate predictors. Statistically, the most robust approach is to pre-specify the model structure based on the knowledge in the field and clinical experience.[61] Selecting final predictors solely based on p-values of univariable or multivariable associations among a large number of candidate predictors has various disadvantages, including instability of the selection, overestimation of predictor effects, and invalid statistical inference.[62] The most important consequence of data-driven selection strategies is overfitting. The effects of the selected predictors and the discriminative ability of the model are then overly optimistic: they

may describe the development cohort well, but effects are typically smaller in other cohorts. Moreover, it is important to determine how the predictor will be defined. One of the common pitfalls is the categorization of continuous predictors, which leads to the loss of information.[62] Finally, it is important to perform internal validation to assess the validity of a prognostic model and to avoid overoptimistic performance estimates that will not be achieved in other, "plausibly related populations" [63]- at external validation.[62]

External validity refers to the generalizability of a model to another context such as more recently diagnosed patients, or a different medical institution / country.[61] The performance of a prognostic model at external validation typically is examined in terms of the discriminative ability and calibration. Discrimination refers to the ability of a model to correctly distinguish between patients who would develop an outcome (e.g. die, incompletely recover, have a recurrence of the subdural hematoma, or experience severe post-concussion symptoms) and those who would not. Calibration refers to the agreement between the observed and predicted values. It relates to the difference between the average predicted probability and the observed outcome - for instance, predicting that 70% of mild TBI patients would completely recover by six months, while 50% actually does. Another aspect is the validity of regression coefficients, which describes the differences in the effects of predictors between the development and validation cohort. Different (usually poorer) performance of a prognostic model in an external validation study may be obtained due to differences in study population predictors and definitions of the variables, but also due to (suboptimal) modelling strategies in the development study (Figure 2).

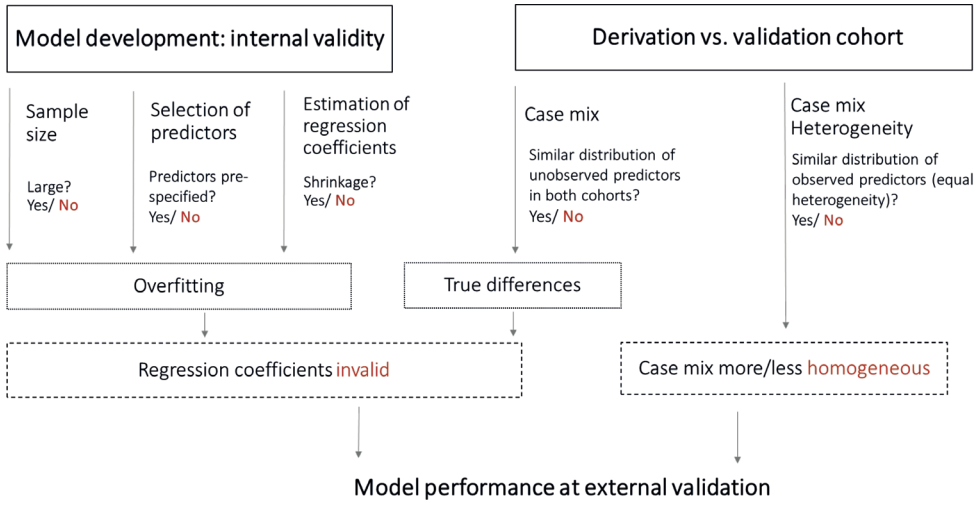

Figure 2. Common reasons for different (poor) model performance at external validation.

Models such as IMPACT[34] and CRASH[33], developed for prediction of outcome following more severe TBI, have been developed in quite large cohorts and have been extensively externally validated.[64, 65] However, the performance of models for prediction of outcome in mild TBI patients, including the models for specific subgroups such as patients with chronic subdural hematoma, has been insufficiently examined in external validation studies.[52] Before the implementation of a model in clinical context can be considered- and before new efforts in developing a "better" model, external validation studies should be performed.

CENTER-TBI study

As a response to the disease burden of TBI and the need for the improvement of characterization of TBI and clinical care, the Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) was established.[3] CENTER-TBI is a Europe-based multicenter, longitudinal, prospective, observational trial conducted in over 60 hospital centers in more than 20 countries and patients were included between December 2014 and December 2017.[3, 32] In order to meet the study aims - better disease characterization and clinical care- detailed data was collected on sociodemographic, injury-related and care pathway characteristics, and advanced imaging and TBI- related blood-based biomarkers. As outcomes, multiple domains of functioning were assessed covering global functioning, health-related quality of life and mental health. A particular strength was a collection of longitudinal clinical and outcome data and comprehensive data on processes of care. The richness of CENTER-TBI outcome data allows describing and analyzing differences between men and women and the factors contributing to these differences. Congruent with the changing epidemiology of TBI, around a quarter of CENTER- patients is aged 65 or older,[32] which enables examining patterns of care and outcome in this population. This large contemporary TBI cohort, containing a broad range of data from different sources and longitudinally assessed questionnaires, provides exceptional opportunities for improving prediction in mild TBI by examining performance of the current models and developing new models.

Thesis: aims and outline

The overarching aims of this thesis and specific research questions are listed below.

Aim 1. To describe treatment and outcome of (mild) TBI in relation with sex/gender, age and comorbidity

a) Do men and women differ in treatment and outcomes following TBI?
b) How can we explain outcome differences between men and women following mild TBI?
c) What are the care pathways, outcomes and determinants of the outcomes in older adults?
d) Are treatments for PTSD effective for patients with a history of TBI?

Aim 2. To improve prediction following mild TBI

a) Can blood-based biomarkers improve current clinical decision rules for selecting mild TBI patients for CT scanning?
b) How do existing prognostic models for outcome following mild TBI, including chronic subdural hematoma, perform in other contemporary TBI cohorts?
c) What is the relationship between methodological quality of prognostic model studies in TBI and model performance?
d) Can we improve predictions of functioning and post-concussion symptoms following mild TBI based on personal and clinical variables, CT results, blood-based biomarkers, and questionnaires?
e) Do intracranial traumatic lesions predict outcome following mild TBI in young people?

In **PART 1**, we compare treatments, care pathways, and six-month functional, health-related quality of life and mental health outcomes between men and women with TBI **(Chapter 2)**. In case of outcome differences, we explore if they can be explained by psychiatric history, care pathways, or sociodemographic variables **(Chapter 3)**. Moreover, we describe health utilization and six-month functional, health-related quality of life, and mental health outcomes in older adults, and explore possible determinants of these outcomes **(Chapter 4)**. Finally, we analyze existing studies investigating treatments for PTSD in patients with (a history of) TBI in terms of the methodological quality, appropriateness and effectiveness (**Chapter 5)**.

In **PART 2**, we compare the diagnostic accuracy for predicting intracranial abnormalities on CT of six biomarkers with four commonly used clinical decisions rules **(Chapter 6)**. We identify existing models for prediction of outcome following mild TBI **(Chapter 7)** and chronic subdural hematoma **(Chapter 8)**, and examine their performance in another cohort (CENTER-TBI/ Dutch Chronic Subdural Hematoma Dataset). We study the relationship between the model quality and the performance in external validation **(Chapter 9**). We develop prognostic models for functional outcome and post-concussion symptoms following mild TBI: first, the models containing readily available predictors; further, extended models with additional categories of predictors: early symptoms, CT imaging results and blood-based biomarkers, and symptoms measured weeks after injury **(Chapter 10)**. For children and young people, we explore the associations between intracranial pathology and global functional outcome following mild TBI (**Chapter 11)**.

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PART I

Treatment and outcome of mild traumatic brain injury: relations with sex/gender, age and comorbidity

Chapter 2

Differences between men and women in treatment and outcome after traumatic brain injury

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Abstract

Traumatic brain injury (TBI) is a significant cause of disability, but little is known about sex and gender differences following TBI. We aimed to analyze the association between sex/gender, and the broad range of care pathways, treatment characteristics, and outcomes following mild and moderate/severe TBI.

We performed mixed-effects regression analyses in the prospective multi-center Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study, stratified for injury severity and age, and adjusted for baseline characteristics. Outcomes were various care pathway and treatment variables, and 6-month measures of functional outcome, health-related quality of life (HRQoL), post-concussion (PCS) and mental health symptoms.

The study included 2862 adults (36% women) with mild (mTBI) (Glasgow Coma Score (GCS) 13-15), and 1333 adults (26% women) with moderate/severe TBI (GCS 3-12). Women were less likely to be admitted to the Intensive Care Unit (odds ratios [OR] 0.6, 95% confidence interval [CI] [0.4-0.8]) following mTBI. Following moderate/severe TBI, women had a shorter median hospital stay (OR 0.7, [0.5-1.0]).

Following mTBI, women had poorer outcomes; lower Glasgow Outcome Scale Extended (GOSE)) (OR 1.4, [1.2-1.6]), lower generic and disease-specific HRQoL, and more severe symptoms of post-concussion, depression and anxiety. Among them, women under 45 and above 65 years showed worse 6- month outcomes compared to men of the same age. Following moderate/severe TBI, there was no difference in GOSE (OR 0.9, CI [0.7-1.2], but women reported more severe post-concussion symptoms (OR 1.7, CI [1.1-2.6]).

Men and women differ in care pathways and outcomes following TBI. Women generally report worse 6-month outcomes, but the size of differences depends on TBI severity and age. Future studies should examine factors that explain these differences.

Key words: sex differences, traumatic brain injury, outcomes, treatment, care pathway.

Introduction

Traumatic brain injury (TBI) is a major public health concern and a leading cause of mortality and disability. [1] Many persons who have experienced a TBI show long-term disturbances in physical, cognitive, emotional, and overall functioning. [1-5] Nevertheless, sex and gender differences in health care and outcomes following TBI are still insufficiently investigated.

Sex refers to biological characteristics and it can be defined according to genetics, and morphology, whereas gender refers to sociocultural behaviors and attitudes. Although the terms are distinct, "sex" and "gender" are usually used interchangeably in the field of neurotrauma. [6-8] Nevertheless, they highly interact in humans, and differences in the context of health outcomes in humans are rarely the product of exclusively sex or gender. [9, 10]To emphasize that it is difficult to disentangle biological and sociocultural components in TBI, and that sex and gender probably have a combined impact, we will use the term "sex/ gender" to refer to differences between men and women.

TBI was traditionally considered a "male problem" and associated with risk-taking behaviors and men- dominated professions. [7, 11] Generally, men have more than a two-fold risk for sustaining a TBI and tend to acquire TBIs at a younger age. [12] Women, however, catch up in older age with a high proportion of fall-related TBIs. [13, 14] In addition, increased participation of women in military and contact sports has led to higher TBI rates among women. [1, 13, 15, 16] Moreover, a substantial percentage of women experience repetitive TBIs as a result of intimate partner violence. [17-20]

Current scientific guidelines strongly advise considering sex and gender in analyzing and reporting outcomes and treatment effects. [21-23] Some studies showed that women have less access and lower rates of direct transfers to trauma centers [6, 24] and fewer admissions to intensive care [25] after traumatic injuries. Following TBI, adherence to guidelines for performing computed tomography (CT) seem to be lower for women. [26, 27] Furthermore, there is evidence from other medical fields that can potentially be translated to the field of neurotrauma, such as men being provided with more aggressive treatments in cardiovascular medicine. [28] However, studies on differences in care specifically for TBI patients remain limited, and TBI researchers are encouraged to investigate sex/gender difference in admission and referral from the Emergency Department, and in outcome measures. [29]

Sex/gender differences in outcomes following TBI have been investigated more frequently, but often with inconsistent results, [29] even for important outcomes such as mortality. [6, 7, 30] Generally, systematic reviews and syntheses of studies found worse

outcomes in women, [8, 30, 31]particularly following mild TBI and when cognitive and psychological symptoms after several months were analyzed as outcomes. [8] In the moderate to severe spectrum of TBI, in which functional outcome and mortality were mostly analyzed as outcomes, a larger proportion of studies showed similar[32 33] outcomes in men and women, or better outcomes [8] in women.

Besides outcome measures and TBI severity, there are other personal and clinical factors that could impact the results of sex/gender based analyses such as extra-cranial injuries or medical history, but these are often not included. [8, 31]For instance, stratified analyses on both age and sex has shown that certain subgroups are at higher risk for developing poor outcomes following TBI, such as young women for PTSD, [34] women in "child-bearing years" for post-concussive symptoms, [35] and older women for mortality after isolated TBI. [36]

Nevertheless, sex/gender differences in treatment and outcomes following TBI remain inconclusive. Therefore, the aim of the current study is to determine the association between sex/gender and a broad range of care pathway and treatment characteristics, and outcomes following mild and moderate/severe TBI.

Methods

Patient population

The study population consisted of patients from the prospective multi-center longitudinal observational study Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI). [1] For this manuscript, the CENTER-TBI Core dataset, [37] version 2.0 was used. Data were collected from December 2014 to December 2017 in 63 European centers and in accordance with all relevant laws and regulations. Patients were included if they had a clinical diagnosis of TBI and were presented to study center within 24 hours of injury either to emergency room (ER), admission ward (ADM), or intensive care unit (ICU), had an indication for CT scanning, and provided informed consent. Participants were excluded if they had any severe preexisting neurological disorder that could confound outcome assessments.

Participants with baseline Glasgow Coma Score (GCS) between 13 and 15 were classified as mild, and with baseline GCS between 3 and 12 as moderate/severe. Sex/gender was defined based on medical records. Sociodemographic variables, medical history, clinical and injury characteristics were assessed at admission. CT scanning was performed within 24 hours after injury. The 6-month outcomes were measured 6 months post-injury (range 5-8 months).

Treatment: Care pathway and treatment characteristics

We analyzed the following care pathway variables:

Secondary referral was defined as transfer from another hospital to the study center (versus primary referral = direct transfer to the study hospital). **Time to study center** was defined as the time from injury to arrival to study center. It was dichotomized at the group median and analyzed only for patients with primary referral.

Discharge home after the Emergency Room (ER) versus discharge to other facility, hospital, high care unit and ICU was analyzed only for mild TBI patients. **Admission to ICU** after the Emergency Room (ER) versus discharge home, discharge to other facility, admission to hospital or high care unit, and it was analyzed for all patients and separately for hospitalized mild TBI patients.

Discharge to high care unit or other ICU, versus discharge to general ward, other hospital, rehabilitation, home, and nursing home, after being admitted to ICU, and it was analyzed only for moderate/severe patients.

Length of stay (LOS) was dichotomized at the group median of hospital stay, and it was analyzed for all patients and for patients who survived until the discharge. **Final discharge home** as final discharge location was based on discharge from ER, ICU and hospital (versus rehabilitation, nursing home, other hospital). **Final discharge to rehabilitation** as final discharge location was based on discharge from ER, ICU, and hospital (versus home, nursing home, other hospital). Final discharge was analyzed for patients who survived until the discharge.

As treatment characteristics, we analyzed:

Prehospital intubation, which was defined as intubated airway upon arrival to the study hospital and analyzed for patients with moderate/severe TBI.

Time to CT was defined as time from injury to first CT scanning and was dichotomized at the group median.

Intracranial pressure (ICP) monitoring was analyzed only for patients with moderate/severe TBI. **Cranial** and **extra-cranial surgery** performed during stay in the study hospital.

In-hospital outcome measures

In-hospital mortality was based on registered death at ER, hospital, and ICU discharge.

Functional outcome measures at 6-month

Glasgow Outcome Scale Extended (GOSE). The GOSE [38] is a structured interview which measures global outcome following TBI. It provides eight ordinal categories of outcome: dead (1); vegetative state; lower severe disability; upper severe disability; lower moderate disability; upper moderate disability; lower good recovery; and upper good recovery (8). GOSE was measured at 6 months by either a postal questionnaire or a telephone interview. Around 7% was responded by a proxy alone, and 9% by a patient and proxy together. The categories 'vegetative state (GOSE 2)' and 'lower severe disability (GOSE 3)' were combined, resulting in a seven-point ordinal scale.

Return to work. Return to work is assessed by a follow-up questionnaire. Return to work represented post-injury return to the previous job or school activity at the same or increased level or hours. Not returning to work represented return to the previous job or school activity at reduced level, sheltered employment, or inability to work/go to school. Answers reflecting changing or searching a job/school or being retired were not included.

Post-concussion and mental health symptoms at 6-month

Rivermead Postconcussion Symptoms Questionnaire (RPQ). The RPQ[39] measures cognitive, somatic, and emotional symptoms that are compared with the preinjury level. It contains 16 items that can be answered with 0=not experienced, 1=no more of a problem (than before the injury), 2=mild problem, 3=moderate problem, or 4=severe problem. Total score of >=12 (treating ratings "no more of a problem" as 0) [40] was considered indicative of having increased post-concussive symptoms.

Patient Health Questionnaire (PHQ-9). PHQ-9 [41] measures depression severity**.** It contains nine items using a four-point Likert scale (from 0=not at all to 3=nearly every day), and it can have a range 0-27. Cutoffs of 5, 10, and 15 indicate mild, moderate, and moderately severe to severe depressive symptoms, respectively. [42] The score was analyzed as an ordinal variable with four levels: none, mild, moderate, moderately severe/severe.

Generalized Anxiety Disorder 7-item scale (GAD-7). GAD-7 [43]measures severity of anxiety. It comprises seven items that can be answered form 0=not at all to 3=nearly every day, and it can have a range 0-21. Cutoffs 5, 10 and 15 indicate mild, moderate, and severe anxiety, respectively. [43] The score was analyzed as an ordinal variable with four levels: none, mild, moderate, severe.

Post-traumatic stress disorder (PTSD) Checklist for DSM-5 (PCL-5). [44]PCL-5 measures symptoms of PTSD according to DSM-5 criteria. [45] It consists of 20 items that can be answered with 0= not at all to 5= extremely and it can have a range 0- 80. The score >=33 was considered indicative of clinically relevant PSTD. [46, 47]

Health Related Quality of Life (HRQoL) measures at 6-month

Quality of life after brain injury - Overall Scale (QOLIBRI-OS). QOLIBRI- OS [48] is a brief TBI-specific index of HRQoL, which has a scale range of 0-100. Around 3% of questionnaires were filled by a proxy alone, and 10% by a patient and proxy together. Score <52 on QOLIBRI-OS was considered indicative of impaired disease-specific quality of life. [37, 49]

Short form health surveys (SF-12v2; SF-36v2). SF-12v2 [50] with 12 items and SF-36v2 with 36 items are self-reported and generic measures of HRQoL. The results can be summarized as mental and physical component scores ranging from 0 to 100. Mental and physical scores were based on SF-12v2 score, and when there was no available SF-12v2 score, the score was derived using SF-36v2 (when available). [37] Around 3% of questionnaires were filled by a proxy alone, and 10% by a patient and proxy together. Mental and physical scores <40 were considered indicative for impaired mental and physical HRQoL, respectively. [37, 49]

Statistical analyses

Descriptive statistics. Descriptive statistics for TBI characteristics, and treatment and outcome variables were presented separately for men and women using percentages for categorical variables and median with interquartile range for continuous outcomes. Differences were tested using non-parametric tests (e.g. Chi- square and Mann-Whitney U Test). All analyses were performed separately for mild and moderate/severe TBI.

Mixed effects regression analyses. The association with multiple treatment characteristics and outcomes following TBI was analyzed with univariable and multivariable mixed effects regression analyses with a random intercept for study center. In multivariable analyses, we adjusted for age, baseline GCS, pupillary reactivity, hypotension and hypoxia before arrival/ at admission, CT abnormalities (CT Marshall Classification); traumatic subarachnoid hemorrhage (tSAH), epidural hematoma; Injury Severity Score (ISS), preinjury medical situation (ASAPS classification), preinjury psychiatric disorder, and cause of injury (fall/motor vehicle accident (MVA) /violence/other) which represent important predictors of outcome in TBI and/ or can be associated with sex/ gender. [3, 46, 51-53] Analyses of prehospital and early hospital measures (secondary referral, time to study center, prehospital intubation, time to CT) were not adjusted for CT Marshall Classification, tSah and epidural hematoma.

The multivariable regression analyses were performed in a completed dataset, in which missing values in potential confounders were imputed based on an imputation model with all baseline characteristics, all outcomes, and auxiliary variables (sociodemographic variables, other indicators of medical history and CT abnormalities). The percentage of imputed missing values (Table 1) ranged from <1% (age, GCS, ISS) to 16% (Marshall CT for moderate/severe). Furthermore, when the outcome GOSE was assessed outside the time window (range 5-8 months), it was imputed based on GOSE measurements at other time points.[37] Other outcome variables were not imputed.

Logistic mixed effects regression models were fitted for dichotomized outcomes (e.g. treatment variables and mortality), whereas ordinal mixed effects regression models were fitted for ordinal outcomes (GOSE, depression and anxiety severity). The results were presented in forest plots of odds ratios for women versus men. For mild TBI, forest plots were also stratified by different age groups: 16-45 years, 45-65 years, and 65 and older (when there were ≥ 100 outcome events in logistic regression). For moderate/severe TBI, stratified plots were only shown for GOSE because of smaller subsamples.

To check the sensitivity of the results to imputation of missing values, and dichotomization of continuous 6-month outcomes, we performed complete-case and linear regression analyses, respectively (Supplementary Table S2 and S3).

Analyses were carried out in R version 5.3 (R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria) using lme4,[54] ordinal,[55] mice,[56] tableone,[57] and forest plot[58] packages.

Results

Patient characteristics in men and women in the CENTER-TBI study

The study included 2862 adults (36% women) categorized as having mild TBI, and 1333 adults (26% women) categorized as having moderate to severe TBI (Table 1).

Men were younger than women when they suffered a TBI ($p < 0.001$). Falls were the most common cause of mild TBI for both men and women, but the proportion of falls was higher in women ($p < 0.001$). The most frequent cause of moderate/severe TBI was a motor vehicle accident in men and women, but women had more moderate/severe TBIs due to falls, and men due to violence and other reasons ($p < 0.05$). Men with mild TBI had higher ISS ($p < 0.001$), lower GCS ($p < 0.05$) and higher percentage of epidural hematoma ($p < 0.001$). There were more women who sustained a moderate TBI, and men who sustained a severe TBI ($p < 0.05$). Women had higher proportion of psychiatric disorders prior to mild and moderate/severe TBI ($p < 0.001$), and worse physical health prior to mild TBI ($p < 0.001$; Table 1).

Table 1. Baseline characteristics of men and women with traumatic brain injury in the CENTER-TBI data

	Mild TBI				Moderate/ severe TBI			
	Men	**Women**	**p**	**Missing (%)**	**Men**	**Women**	**p**	**Missing (%)**
n	1842	1020			980	353		
GCS Baseline (%)	/	/	0.04	0			0.01	0
3-8 (%)	/	/			726 (74.1)	236 (66.9)		
9-13 (%)	128 (6.9)	63 (6.2)			254 (25.9)	117 (33.1)		
13	340 (18.5)	154 (15.1)			/	/		
14	1374 (74.6)	803 (78.7)			/	/		
15					/	/		
Age	50 [32, 65]	58 [37,73]	<0.001	0	47 [29, 64]	53 [30,69]	0.02	0
Cause of injury (%)			<0.001	1.6			0.01	3.6
Incidental Fall	824 (45.7)	570 (56.4)			358 (37.9)	151 (44.3)		
MVA	647 (35.8)	330 (32.7)			436 (46.2)	159 (46.6)		
other	173 (9.6)	70 (6.9)			85 (9.0)	17 (5.0)		
violence	161 (8.9)	40 (4.0)			65 (6.9)	14 (4.1)		
Total ISS	13 [8, 19]	9.00 [4, 16]	<0.00	0.8	34.00 [25, 48]	33.00 [25, 43]	0.28	0.8
Pupils Reactivity (%)*			0.23	4.3			0.44	4.1
Both reactive	1699 (96.9)	964 (98.0)			691 (73.9)	242 (70.3)		
One reactive	35 (2.0)	12 (1.2)			77 (8.2)	33 (9.6)		
Both non-reactive	20 (1.1)	8 (0.8)			167 (17.9)	69 (20.1)		
Hypoxia (%)	42 (2.4)	15 (1.5)	0.17	3.9	164 (17.8)	50 (15.1)	0.29	6.2
Hypotension(%)	47 (2.6)	24 (2.4)	0.84	3.0	159 (17.3)	43 (12.8)	0.07	6.0
Marshall CT Classification (%) *			0.09	9.8			0.36	16.4
No visible pathology	884 (53.3)	531 (57.5)			67 (8.2)	21 (7.1)		
Cisterns present	615 (37.1)	321 (34.7)			339 (41.3)	116 (39.5)		
Cisterns compressed	23 (1.4)	6 (0.6)			87 (10.6)	32 (10.9)		
Midline shift	2 (0.1)	3 (0.3)			22 (2.7)	2 (0.7)		
Evacuated and non-evacuated lesion	133 (8.0)	63 (6.8)			305 (37.1)	123 (41.8)		
Subarachnoid hemorrhage (%)	524 (30.9)	279 (29.5)	0.46	8.3	652 (76.5)	224 (72.0)	0.13	13.2
Epidural hematoma (%)	159 (9.4)	46 (4.9)	<0.00	7.9	144 (16.9)	51 (16.4)	0.91	13.0
Preinjury Psychiatric condition (%)	210 (11.6)	183 (18.0)	<0.00	1.0	120 (13.3)	64 (19.1)	0.01	7.1
Preinjury physical health- ASAPS Classification (%)			0.23	1.0			0.23	5.6
healthy patients	1063 (58.5)	505 (49.8)			532 (57.5)	177 (53.2)		
mild systemic disease	567 (31.2)	388 (38.2)			283 (30.6)	122 (36.6)		
severe systemic disease/ threat to life	188 (10.4)	122 (12.0)			110 (11.9)	34 (10.2)		

Note: CT= Computed Tomography; GCS= Glasgow Coma Scale; MVA= Motor vehicle accident; *Small subcategories merged for regression analyses. ASA PS, American Society of Anesthesiologists Physical Status; CT, computed tomography; GCS, Glasgow Coma Scale; ISS, Injury Severity Score; MVA, motor vehicle accident; TBI, traumatic brain injury.

The association between sex/ gender and care pathway and treatment characteristics

Following mild TBI, women had different care pathways, with lower proportion of referrals from another hospital (12% vs. 16%) and admissions to ICU (14% vs. 23%), more discharge home (34% vs. 25%), and shorter hospital stay (46% vs. 52% higher than median stay). Regarding treatment characteristics, women had longer time to CT scan (53% vs. 48% higher than median; Table 2; Supplementary Fig S1).

Following moderate/severe TBI, men and women had similar care pathway and treatment characteristics. Women, however, stayed shorter in hospital (44% vs. 52% for all, 34% vs. 43% above the median of length of stay), and had less prehospital intubations (51% vs. 58%, Table 2; Supplementary Fig S2).

Table 2. Descriptive statistics for care pathway and treatment characteristics for men and women with traumatic brain injury (TBI)

	Mild TBI			Moderate/ severe TBI		
	Men	**Women**	**p**	**Men**	**Women**	**p**
n	1842	1020		980	353	
Secondary referral (%)	287 (15.6)	120 (11.8)	0.006	189 (19.3)	67 (19.0)	0.963
Discharge home (%)	459 (25.0)	343 (33.9)	<0.001			
ICU admission (%)	428 (23.3)	146 (14.4)	<0.001	687 (70.6)	233 (66.6)	0.181
Discharge to high care (%)				189 (25.4)	69 (24.8)	0.921
Longer LOS (median)(%)	949 (52.4)	460 (46.0)	0.001	495 (52.2)	150 (44.0)	0.012
Longer LOS(median)- survivors (%)				412 (43.4)	117 (34.3)	0.004
Final Discharge Location (%) survivors			0.077			0.987
Home	1410 (80.1)	797 (82.1)	0.220	182 (25.2)	63 (24.2)	0.811
Rehabilitation	109 (6.2)	58 (6.0)	0.887	240 (33.3)	88 (33.8)	0.931
Prehospital intubation (%)				561 (58.0)	180 (51.4)	0.039
Longer time to CT (median) (%)	823 (48.2)	509 (53.4)	0.012	438 (50.8)	152(48.9)	0.616
ICP monitoring (%)				539 (58.5)	180 (54.9)	0.288
Cranial Surgery(%)	163 (11.6)	63 (9.3)	0.135	428 (44.0)	150 (43.2)	0.844
Extra-cranial Surgery(%)	218 (15.6)	87 (12.9)	0.123	288 (29.6)	86 (24.8)	0.099

Note: CT= Computed tomography, ICP=Intracranial pressure monitoring; ICU= Intensive care unit; LOS= Length of stay.

In mixed-effect multivariable analyses (Figure 1), there were no significant differences between men and women with mild TBI in the majority of care pathway and treatment characteristics. Women who sustained a mild TBI were less likely to have a secondary referral (odds ratio (OR) 0.7, 95% confidence interval [CI]: 0.6-0.95). Moreover, women were more likely to be discharged home after ER (OR, 1.4 95% CI:1.0-1.8; and less likely to be admitted to ICU (OR, 0.6 95% CI: 0.4-0.8), in the total mild TBI sample and among hospitalized mild TBI patients.

Men and women with moderate or severe TBI did not differ in the majority of care pathway and treatment characteristics (Figure 2). Among patients with primary referral (direct transfer to study hospital), women were somewhat less likely to have longer time to study hospital (OR 0.8, 95% CI: 0.6-1.1). Furthermore, women were more likely to have a rehabilitation as the final discharge location (OR 1.5, 95% CI: 1.0-2.1), but less likely to stay in hospital longer than median of 22 days (patients who survived until discharge OR 0.7, 95% CI: 0.5-1.0), and to have prehospital intubation (OR 0.8, 95% CI: 0.6-1.1).

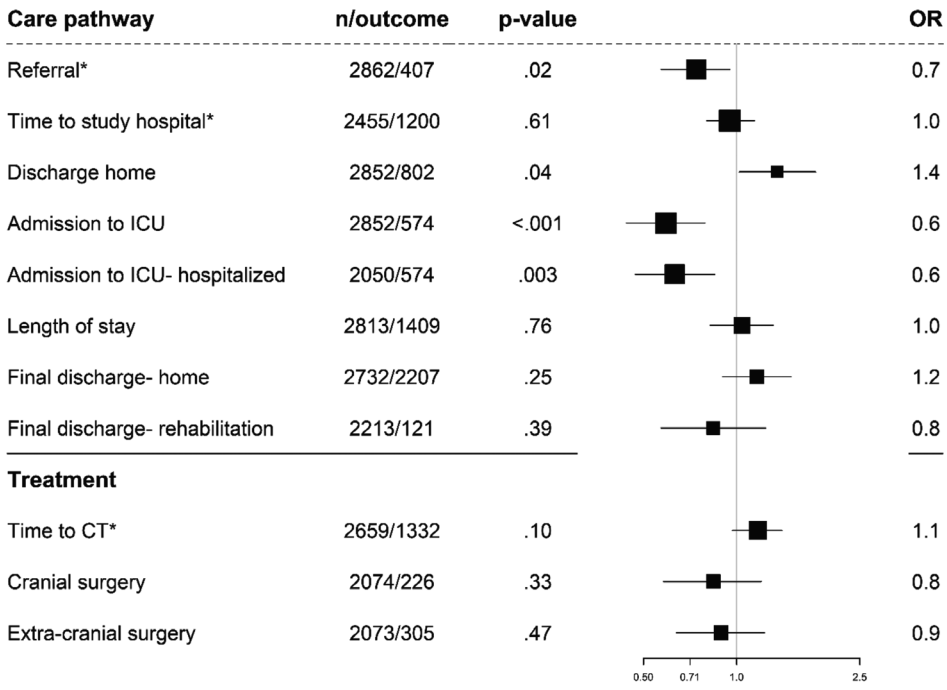

Figure 1. Forest plot with adjusted odds ratios (ORs) for women with mild traumatic brain injury: care pathway and treatment characteristics.
The ORs are adjusted for age, baseline Glasgow Coma Scale score, pupillary reactivity, hypotension and hypoxia before arrival/at admission, Marshall Classification, traumatic subarachnoid hemorrhage (tSAH), epidural hematoma; Injury Severity Score (ISS), pre-injury medical situation (ASA PS Classification), pre-injury psychiatric disorder, and cause of injury. *Not adjusted for CT Marshall Classification, tSAH, and epidural hematoma. ASA PS, American Society of Anesthesiologists Physical Status; CT, computed tomography; ICU, intensive care unit; n/outcome, number of patients/number of patients with outcome.

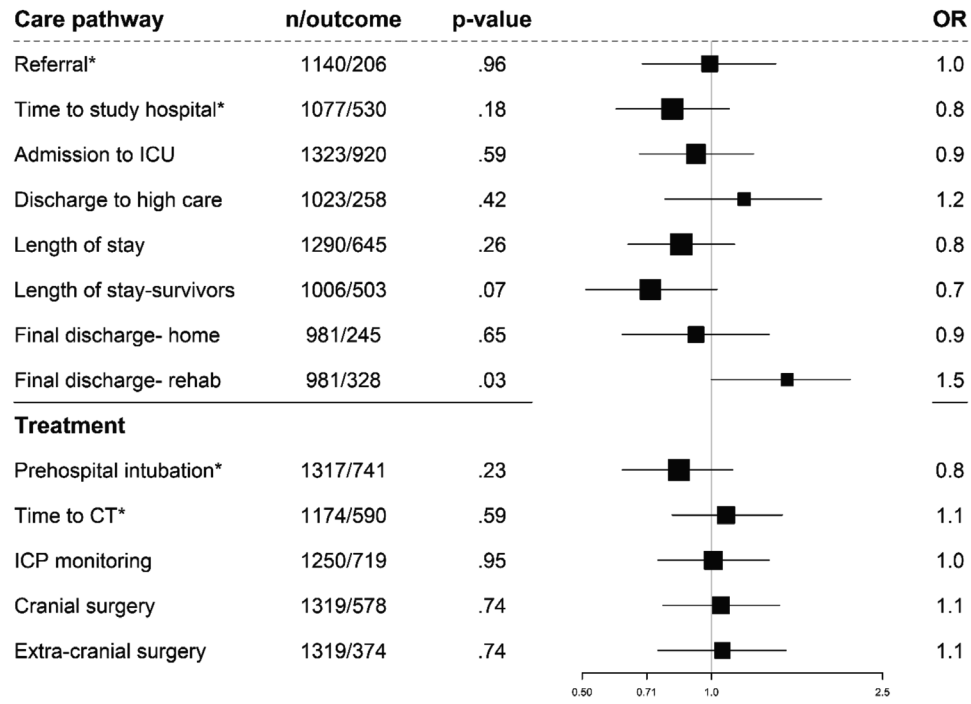

Figure 2. Forest plot with adjusted odds ratios (ORs) for women with moderate/severe traumatic brain injury: care pathway and treatment characteristics.
The ORs are adjusted for age, baseline Glasgow Coma Scale score, pupillary reactivity, hypotension and hypoxia before arrival/at admission, Marshall Classification, traumatic subarachnoid hemorrhage (tSAH), epidural hematoma, Injury Severity Score (ISS), pre-injury medical situation (ASA PS Classification), pre-injury psychiatric disorder, and cause of injury. ASA PS, American Society of Anesthesiologists Physical Status; CT, computed tomography; ICP, intracranial pressure; ICU, intensive care unit; n/outcome, number of patients/number of patients with outcome.

The association between sex/ gender, and in-hospital mortality and 6-month outcomes

For mild TBI, the proportion of missing values in 6-month outcomes varied from 17% for GOSE to 40-45% for other outcomes. For moderate or severe TBI, the proportion of missing values varied from 1% for in-hospital mortality, 13% for GOSE to about 60% for other outcomes (Supplement-Table 1). However, 26% of patients with moderate/severe did not survive until 6 months.

Following mild TBI, women had higher percentage of unfavorable outcomes (lower GOSE), lower generic and disease-specific HRQoL, and more severe symptoms of post-concussion, depression, anxiety, and post-traumatic stress disorder (Table 3; Supplement-Table 1; Supplementary Figure 3). There was no difference in probable PTSD diagnosis. Following moderate/severe TBI, women had more severe symptoms of post-concussion (Table 3; Supplement-Table 1; Supplementary Figure 4). Mental health measures were somewhat poorer in men, but the differences were insignificant (Table 3; Supplement- Table 1, Figure 4).

Table 3. Distributions of outcome variables for men and women with mild and moderate or severe traumatic brain injury (TBI)

	Mild TBI			Moderate or severe TBI		
	Men	**Women**	**p**	**Men**	**Women**	**p**
n	1842	1020		980	353	
In-hospital mortality (%)	28 (2.0)	15 (2.2)	0.863	213 (22.0)	73 (20.9)	0.717
Functional outcomes at 6 months						
GOSE (%)			0.005			0.464
1	56 (3.7)	33 (3.9)		258 (30.6)	89 (28.3)	
3	59 (3.9)	37 (4.3)		148 (17.5)	53 (16.8)	
4	43 (2.8)	40 (4.7)		53 (6.3)	29 (9.2)	
5	110 (7.2)	61 (7.1)		113 (13.4)	43 (13.7)	
6	158 (10.4)	90 (10.5)		98 (11.6)	29 (9.2)	
7	310 (20.4)	218 (25.5)		80 (9.5)	37 (11.7)	
8	783 (51.5)	376 (44.0)		94 (11.1)	35 (11.1)	
Return to work (%)			<0.001			0.005
job change	48 (4.3)	26 (4.2)		26 (5.4)	5 (2.9)	
not returned	203 (18.1)	110 (17.8)		295 (61.7)	96 (55.5)	
retired	260 (23.2)	206 (33.3)		52 (10.9)	37 (21.4)	
returned	610 (54.4)	277 (44.7)		105 (22.0)	35 (20.2)	
Post-concussion and mental health symptoms at 6 months						
Post-concussion (RPQ>11) (%)	320 (31.4)	246 (41.9)	<0.001	154 (43.3)	83 (56.5)	0.009
Depression (PHQ-9) (%)			<0.001			0.599
none	637 (64.1)	302 (52.7)		188 (53.6)	69 (47.6)	
mild	213 (21.4)	151 (26.4)		91 (25.9)	40 (27.6)	
moderate	85 (8.6)	73 (12.7)		43 (12.3)	20 (13.8)	
severe	59 (5.9)	47 (8.2)		29 (8.3)	16 (11.0)	
Anxiety-GAD-7 (%)			0.001			0.513
none	734 (74.0)	368 (64.7)		244 (68.9)	91 (63.2)	
mild	168 (16.9)	125 (22.0)		67 (18.9)	31 (21.5)	
moderate	58 (5.8)	48 (8.4)		25 (7.1)	15 (10.4)	
severe	32 (3.2)	28 (4.9)		18 (5.1)	7 (4.9)	
PTSD- PCL-5>32 (%)	96 (9.6)	57 (9.9)	0.926	30 (8.8)	14 (9.6)	0.930
Health Related Quality of Life (HRQoL) at 6 months						
Qolibri- OS <52 (%)	175 (16.9)	158 (26.6)	<0.001	103 (27.5)	51 (33.1)	0.232
SF12 Mental Score <40 (%)	211 (20.3)	177 (29.5)	<0.001	92 (25.3)	48 (31.4)	0.188
SF12 Physical Score <40 (%)	235 (22.6)	206 (34.3)	<0.001	129 (35.4)	59 (38.6)	0.566

Note: GAD-7=Generalized Anxiety Disorder 7-item; GOSE=Glasgow Outcome Scale Extended; PCL-5= Post-Traumatic Stress Disorder Checklist for DSM-5; PCS=Post-concussive symptoms; PHQ-9: Patient Health Questionnaire 9-item; RPQ=Rivermead Postconcussion Symptoms Questionnaire; QOLIBRI-OS= Quality of life after brain injury - Overall.

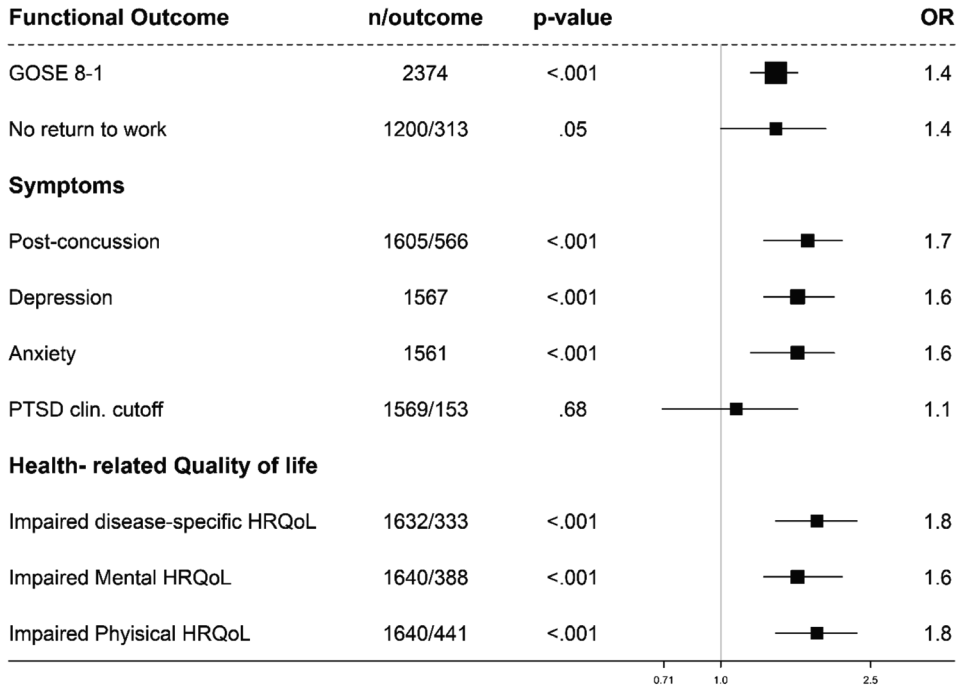

Figure 3. Forest plot with adjusted odds ratios (ORs) for women with mild traumatic brain injury: 6-month outcomes.
The ORs are adjusted for age, baseline Glasgow Coma Scale score, pupillary reactivity, hypotension and hypoxia before arrival/at admission, Marshall Classification, traumatic subarachnoid hemorrhage (tSAH), epidural hematoma, Injury Severity Score (ISS), pre-injury medical situation (ASA PS Classification), pre-injury psychiatric disorder, and cause of injury. ASA PS, American Society of Anesthesiologists Physical Status; GOSE, Glasgow Outcome Scale Extended; PTSD, post-traumatic stress disorder; n/outcome, number of patients/number of patients with outcome.

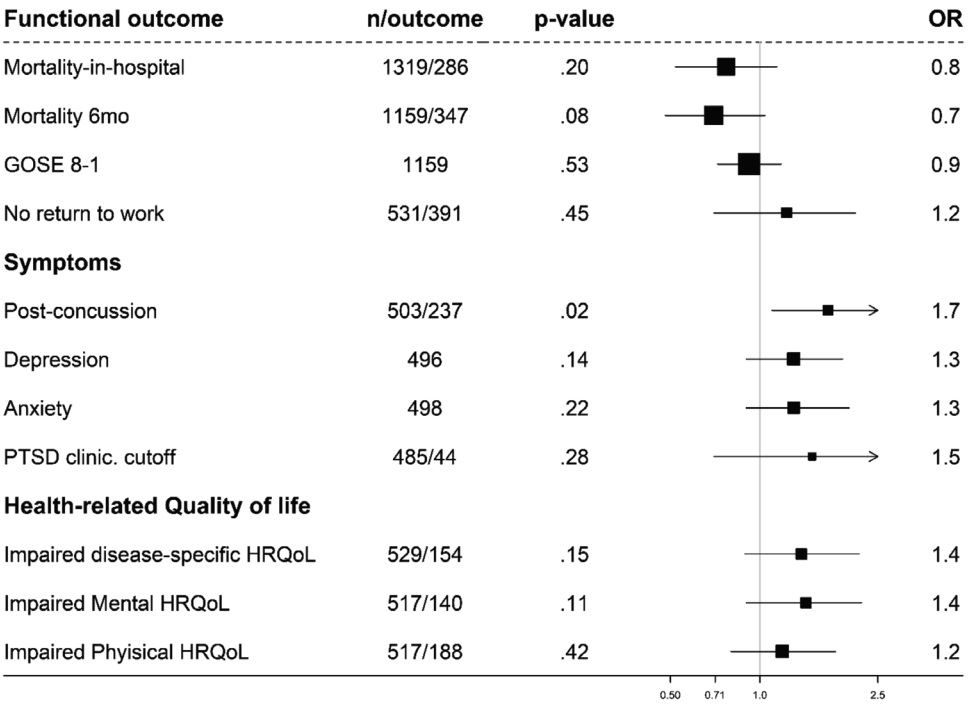

Figure 4. Forest plot with adjusted odds ratios (ORs) for women with moderate/severe traumatic brain injury: in-hospital mortality and 6-month outcomes.
The ORs are adjusted for age, baseline Glasgow Coma Scale score, pupillary reactivity, hypotension and hypoxia before arrival/at admission, Marshall Classification, traumatic subarachnoid hemorrhage (tSAH), epidural hematoma, Injury Severity Score (ISS), pre-injury medical situation (ASA PS Classification), pre-injury psychiatric disorder, and cause of injury. ASA PS, American Society of Anesthesiologists Physical Status; GOSE, Glasgow Outcome Scale Extended; PTSD, post-traumatic stress disorder; n/outcome, number of patients/number of patients with outcome.

In multivariable analyses of mild TBI patients (Figure 3), women were more likely to have a poor global outcome (OR 1.4, 95% CI: 1.2-1.6 for ordinal GOSE), and not to return to work (OR 1.4, 95% CI: 1.0-1.9). Moreover, women were more likely to experience more severe symptoms of post-concussion (OR 1.7, 95% CI: 1.3-2.1), depression (OR 1.6, 95% CI: 1.3-2.0), anxiety (OR 1.6, 95% CI: 1.2-2.0), and to report impaired disease-specific (OR 1.8, 95%CI: 1.4-2.3), mental (OR 1.6, 95%CI: 1.3-2.1) and physical (OR 1.8, 95% CI: 1.4-2.3) generic HRQoL. There was no association between sex/gender and probable PTSD diagnosis (OR 1.1, 95%CI: 0.7-1.6) present in smaller percentage of patients, but women showed higher PTSD symptoms in linear analysis (beta = 1.88, p = 0.01; Supplementary Table S3).

Following moderate or severe TBI, multivariable analyses (Figure 4) showed somewhat lower, but insignificant, odds ratios for women for in-hospital mortality OR 0.8, 95% CI: 0.5-1.2) and mortality at 6 months (OR 0.7, 95% CI: 0.5-1.0). No (substantial)

differences were found in 6-month ordinal GOSE (OR 0.9, 95% CI: 0.7-1.2), return to work (OR 1.2, 95% CI: 0.7-2.1), or impaired physical HRQoL (OR 1.2, 95% CI: 0.7-1.2). Adjusted linear analyses showed no differences in brain-injury-specific and physical HRQoL (Supplementary Table S3). However, women were more likely to experience more severe PCS (OR 1.7, 95% CI: 1.1-3.0). The likelihood for depression severity (OR 1.3, 95% CI: 0.9-1.9), anxiety severity (OR 1.3, 95% CI: 0.9-2.0), probable PTSD diagnosis (OR 1.5, 95% CI: 0.7-3.3), impaired mental (OR 1.4, 95% CI: 0.9-2.2) and impaired disease specific HRQoL (OR 1.4, 95% CI: 0.9-2.1) assessed with the QOLIBRI-OS was somewhat higher in women, but precision was limited and CIs included the null.

The association between sex/gender and 6-month outcomes in different age groups

Sex/gender differences in different age groups of mild TBI patients varied between outcomes (Figure 5). There was, however, no outcome or age group where men had worse outcomes, only the lack of differences or worse functioning of women were observed. The biggest sex/gender difference for GOSE (OR 1.9, 95% CI: 1.4-2.5), not returning to work (OR 1.6, 95% CI: 0.9-2.8), and PCS (OR 2.5, 95% CI: 1.5-3.8) were found in patients younger than age 45 years.

The difference was most pronounced in patients younger than age 45 years and older than 65 years for mental health and HRQoL: depression (OR 2.2, 95% CI: 1.5-3.2; OR 2.1, 95% CI: 1.3-3.2, respectively); anxiety (OR 1.9, 95% CI: 1.3-2.9; OR 1.7, 95% CI: 1.0-2.7), impaired mental (OR 2.4, 95% CI: 1.5-3.8; OR 2.0, 95% CI: 1.2-3.4), physical (OR 1.9, 95% CI: 1.1-3.3; OR 2.3, 95% CI: 1.5-3.5), and disease-specific HRQoL (OR 2.2, 95% CI: 1.3-3.6; OR 2.3, 95% CI: 1.3-3.8).Following moderate/severe TBI (Figure 6), women over 65 years had lower likelihood of poor functional outcome (GOSE) than men (0.6[0.3-0.96]), whereas women under 65 had similar (or slightly worse) global functioning as men (1.2[0.8-1.7] under 45; 1.0[0.6-1.5] 45-65).

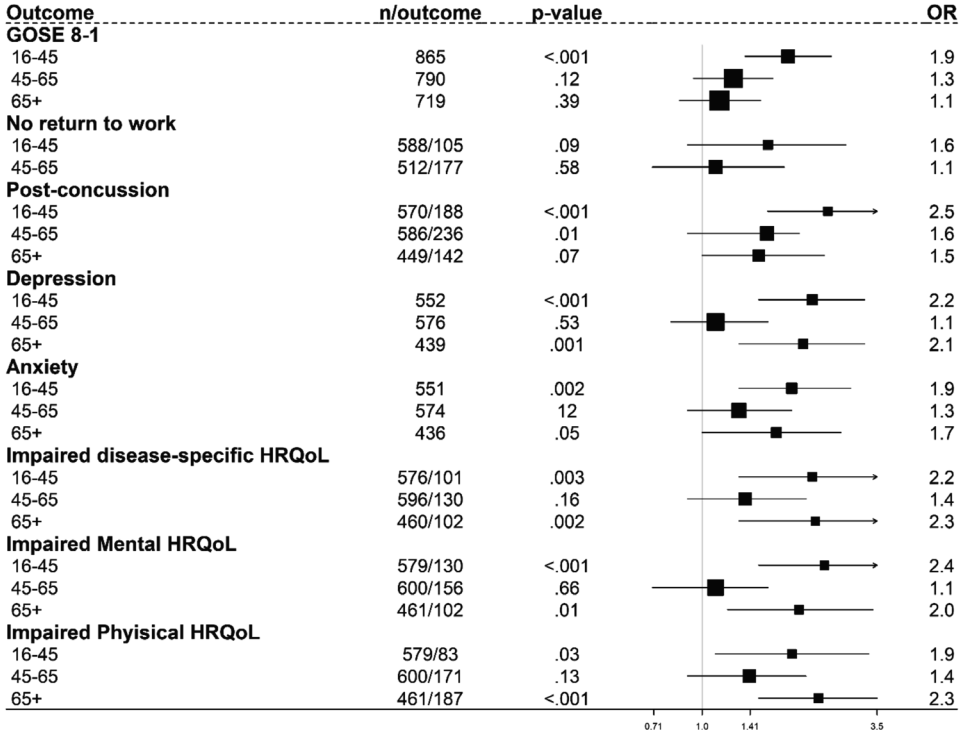

Figure 5. Forest plot with adjusted odds ratios (ORs) for women in different age groups: outcomes following mild traumatic brain injury.
The ORs are adjusted for age, baseline Glasgow Coma Scale score, pupillary reactivity, hypotension and hypoxia before arrival/at admission, Marshall Classification, traumatic subarachnoid hemorrhage (tSAH), epidural hematoma, Injury Severity Score (ISS), pre-injury medical situation (ASA PS Classification), pre-injury psychiatric disorder, and cause of injury. ASA PS, American Society of Anesthesiologists Physical Status; GOSE, Glasgow Outcome Scale Extended ;n/outcome, number of patients/number of patients with outcome.

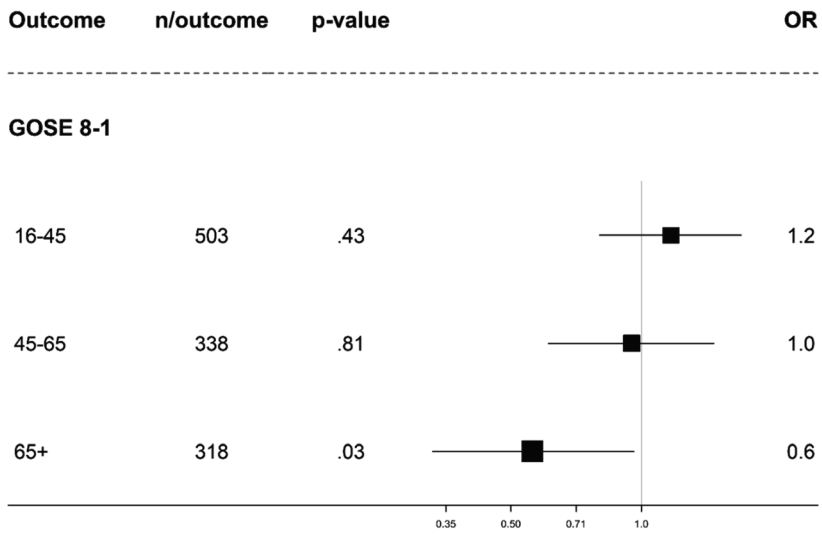

Figure 6. Forest plot with adjusted odds ratios (ORs) for women in different age groups: Glasgow Coma Scale Extended score following moderate to severe traumatic brain injury.
The ORs are adjusted for age, baseline Glasgow Coma Scale score, pupillary reactivity, hypotension and hypoxia before arrival/at admission, Marshall Classification traumatic subarachnoid hemorrhage (tSAH), epidural hematoma, Injury Severity Score (ISS), pre-injury medical situation (ASA PS Classification), pre-injury psychiatric disorder, and cause of injury. ASA PS, American Society of Anesthesiologists Physical Status; GOSE, Glasgow Outcome Scale Extended; n/outcome, number of patients/number of patients with outcome.

Discussion

We examined sex/gender differences in various care-pathway and treatment characteristics and outcomes following mild and moderate/ severe TBI. Men and women did not substantially differ in treatment characteristics, but some differences in care pathway, particularly discharge destinations following mild TBI, were found. Women generally reported worse 6- month outcomes, but the differences with men depended on TBI severity and age. Sex/gender differences were more pronounced following mild TBI, particularly under 45 and above 65 years of age.

We did not find strong association between sex/gender and most of the care pathway and treatment variables. Following mild TBI, women were less likely to be referred from another hospital to a study center, and to be admitted to ICU, and more likely to be discharged home. Apart from that, some differences were observed with limited precision: men had longer hospital stay and less discharge to rehabilitation following moderate/ severe TBI. Similar studies are limited in the field of TBI, and observed differences are partially consistent with other studies in trauma and critical care.

Contrary to our results of women's more direct transfers and thus decreased time to study

center, some previous studies have identified less access for women in general trauma care. [6, 59] For example, in a large Canadian retrospective cohort study, women had lower likelihood of direct transfer to trauma centers by both emergency service triage and the physicians. [24] Consistent with our result of less ICU admissions following mild TBI (but not moderate/severe), some other studies have found less access to intensive care following traumatic injuries in women. [60-63] [25] Similarly, women are shown to receive fewer aggressive treatments in other medical fields.[28, 64]

Lower rates of intensive care in women, as well as their shorter hospital stay, are usually attributed to women's lower injury severity, different injury mechanisms, and better recovery. [33, 60] [25] Even though we adjusted for baseline characteristics in our analyses, residual confounding remains possible. Therefore, the observed differences can be also the result of insufficient adjustment for differences in clinical needs. [58] [59] Nevertheless, obtaining differences in trauma care pathway after adjustment for relevant variables cannot completely rule out gender bias as a possible explanation. [30, 61, 65, 66] For better insight in patterns of care pathways, more studies on sex/gender differences in health care are necessary in the field of neurotrauma. In any case, discussing the importance of gender in context of health, and potential bias related to gender (and other aspects of identity) should be universally and systematically incorporated in training of health-care providers.

The study results are in line with some previous findings of worse outcomes in women several months after injury. [8, 30] Women reported more severe mental health and post-concussion symptoms compared to men, particularly following mild TBI, where women reported worse outcomes across all domains. Differences following moderate/severe TBI were generally smaller and less precise. The differences in self-report, particularly in the mental domain, might not be specifically related to the experience of TBI. Women generally tend to self-report more symptoms, and to seek medical help when needed. [67-69]Mental health disturbances from depressive and anxiety spectrum are generally higher in women than men, particularly in the young age. [70-73]

In addition, biological factors can interact with the general gender differences and contribute to more symptoms in women. For instance, disruption in hypothalamic-pituitary axis (HPA) and hypopituitarism seem to occur in more than a quarter of patients following TBI, and even in 15 % of (complicated) mild TBI patients,[74] which may affect outcomes and stress levels in a sex-specific manner. A recent study found differential dysregulation of HPA and, consequently, stress response, following mild TBI in female compared to male mice.[75]

Conversely, a neuroprotective role of hormones estrogen and progesterone following

TBI was found in animal studies and speculated in human studies, but the findings in human studies have been mixed.[8, 76, 77] Thus, differences in mortality after TBI were inconsistent in previous studies, [6, 7, 30, 78] and they stayed unclear in our study with an insignificant lower likelihood of women to die in hospital or by 6 months. Furthermore, we found a pattern of more disadvantage of women (versus men) in global functioning in reproductive age than other age groups, which is not in line with explanations based on neuroprotection of sex steroids. [77] Some authors explain this pattern by post-TBI disruption in production of sex steroids in pre-menopausal women, which results in the reduction of the neuroprotection. [35, 79]

In this study, women under 45 years of age, and over 65 years for some outcomes, showed particularly worse 6-month outcomes following mild TBI compared to men of the same age. Besides hormonal differences, men and women under 45 years may face different challenges in everyday life. Women report struggling with expectations of managing the household, and balancing domestic duties and childcare with rehabilitation when recovering from acquired brain injury.[80] [81] A substantial number of young adult women have to combine the role of the primary caregiver of underage children with the work role. In that way, gender norms can create extra burden for women under 45 years, and negatively impact their quality of life and mental health following TBI. [35, 82] In contrast, men may have the pressure to return to work and normal functioning more quickly, because they still prevail as primary wage earners, [35, 82]which could lead to better global functional outcome. At older age, women tend to outlive their partners, and they are more likely to live alone following TBI. [83] In addition, generally lower economic resources and power in the society can reduce (older) women's ability to adequately cope with a condition such as brain injury. [7, 69, 84, 85]

Sex/gender differences in subjective measures were, however, more pronounced in mild versus moderate/severe group. Difference in functioning following moderate or severe injuries may be more closely related to injury-related, physical and neurological disabilities. [34] [3]In contrast, functioning after milder injuries may be under greater influence of differences in self-report, perceived stress, and socio-economic factors, which are associated with sex and gender. Thus, taking sex/gender into account could be particularly beneficial in scheduling follow-up appointments and organizing rehabilitation following mild TBI. Furthermore, treatment differences could also impact outcomes after several months. For instance, direct transfer and short time to trauma care generally contribute to better outcomes. The potential impact of the admission to ICU following mild TBI is unclear. Substantial proportion of ICU admissions following mild TBIs seem to be unnecessary[86] and admission can be associated with negative psychological consequences, [87] but some patients do benefit from intensive monitoring.

This study has some limitations. Firstly, the proportion of missing values was high for some 6-month outcomes, particularly in the moderate/severe group. Men had larger proportions of missing values in 6-month mental health and quality of life outcomes; however, the proportions were comparable between men and women who survived until 6- months. Furthermore, due to testing for multiple endpoints, which can increase the probability of false-positive findings, it is possible that some differences were found due to chance. On the other hand, analyses of moderate/severe patients and age groups could be underpowered to find sex/gender differences. Moreover, although we adjusted the analyses with numerous relevant variables, we might have missed some important confounders for specific analyses. Additionally, sex was based on medical records and therefore may be incorrect for some patients, or not correctly matched to the gender identity (being a woman or a man). We recognize that there is a notable minority of both intersex and cisgender persons, who were not adequately captured by this dichotomy. Future TBI studies could profit from including more detailed measures of gender.

Further, this study included hospital centers across Europe (and Israel), with the majority being academic hospitals located in urban areas, and West and North Europe.[37, 88] Between and within European countries, there is a variability of health care and care pathways following TBI,[37, 88, 89] but also of gender inequalities in access to health care and unmet medical needs. [90] Generally, the areas with more traditional and restrictive gender norms, and with less implemented strategies to reduce gender bias in health systems, tend to have larger gender inequalities in health care[91, 92] Following TBI, we hypothesize that in those areas men are offered more aggressive treatments, and women have less access to care, particularly in case of violence. In addition, differences in intention to self-report symptoms following TBI may be larger in the contexts with more traditional gender norms.[93] A reliable sex/gender analyses stratified by country or region would require higher sample and better representation of East and South Europe, and smaller hospital centers. Moreover, the ability to generalize the findings of a European study to other geo-political and cultural settings is limited.

Strength of the study is the use of a large dataset of representative contemporary patients from different countries and with different injury severity. Importantly, there is a lack of studies on treatment and care pathway in the context of sex/gender and TBI, and this study provides an overview of a range of important characteristics. For 6-month functioning, a broad battery of different outcomes was used to cover various domains. The analyses were adjusted for study center and important personal and injury characteristics, which was a limitation of many previous studies.

In conclusion, men and women differ in care pathways and outcomes, depending on injury severity and age group. Future studies should continue investigating sex and gender

differences in health-care following TBI. In addition, underlying factors of the differences in outcomes, particularly following mild TBI, should be explored by disentangling the influence of socioeconomic, biological and treatment differences. Finally, differences should also be discussed in the context of provision and organization of care, such as incorporating gender considerations into training of health-care providers, and monitoring and rehabilitation of patients at risk of poorer outcomes following TBI.

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Author Disclosure Statement

All authors: No competing financial interests exist.

Ethical approval

The CENTER-TBI study (EC grant 602150) has been conducted in accordance with all relevant laws of the EU if directly applicable or of direct effect and all relevant laws of the country where the Recruiting sites were located, including but not limited to, the relevant privacy and data protection laws and regulations (the "Privacy Law"), the relevant laws and regulations on the use of human materials, and all relevant guidance relating to clinical studies from time to time in force including, but not limited to, the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) ("ICH GCP") and the World Medical Association Declaration of Helsinki entitled "Ethical Principles for Medical Research Involving Human Subjects". Informed Consent by the patients and/or the legal representative/next of kin was obtained, accordingly to the local legislations, for all patients recruited in the Core Dataset of CENTER-TBI and documented in the e-CRF. Ethical approval was obtained for each recruiting site. The list of sites, Ethical Committees, approval numbers and approval dates can be found on the website: https://www.centertbi.eu/project/ethical-approval

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Supplementary material

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Chapter 3

Explaining outcome differences between men and women following mild traumatic brain injury

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Abstract

Men and women differ in outcomes following mild traumatic brain injury (TBI). In the CENTER-TBI study, we previously found that women had worse 6-month functional outcome (Glasgow Outcome Score Extended (GOSE)), health-related quality of life (HRQoL), and mental health following mild TBI. The aim of this study was to investigate whether those differences were mediated by psychiatric history, gender- related sociodemographic variables, or by care pathways. We analyzed sex/gender differences in 6-month GOSE, generic and TBI-specific HRQoL, post-concussion and mental health symptoms using three sets of mediators: psychiatric history, sociodemographic variables (living alone, living with children, education and employment status/job category), and care-pathways (referral to study hospital and discharge destination after Emergency Room); while controlling for a substantial number of potential confounders (pre-injury health, and injury-related characteristics). We included 1842 men and 1022 women (16+) with a Glasgow Coma Score 13-15, amongst whom 83% had GOSE available and about 60% other 6-month outcomes. We used natural effects models to decompose the total effect of sex/gender on the outcomes into indirect effects that passed through the specified mediators, and the remaining direct effects. In our study population, women had worse outcomes and these were only partly explained by psychiatric history, and not considerably explained by sociodemographic variables nor by care pathways. Other factors than differences in specified variables seem to underlie observed differences between men and women in outcomes after mild TBI. Future studies should explore more aspects of gender roles and identity, and biological factors underpinning sex and gender differences in TBI outcomes.

Key words: sex differences, traumatic brain injury, mediation, outcomes, sociodemographic factors, care pathways.

Introduction

Traumatic brain injury (TBI) is a global health problem and a significant cause of disability.[1] Men and women differ in TBI epidemiology: men have a higher likelihood of sustaining a TBI, they experience it at younger age, and have a higher percentage of TBIs due to motor-vehicle and work-related accidents, while women more often sustain TBI due to falls and intimate partner and domestic violence. [2-4] Apart from TBI characteristics, differences in outcomes following TBI have also been described. [5]

Biological ("sex") and sociocultural ("gender") aspects strongly interact in humans, and differences in the context of health outcomes in humans are rarely the product of exclusively sex or gender, but rather their combined effect.[6] To emphasize that it is difficult to disentangle biological and sociocultural components, we will use the term "sex/gender" and "men" and "women".

The existence and the extent of the differences in outcomes after TBI varies between studies and depends on TBI severity,[7-9] age,[10, 11] and type of outcomes.[7, 12] Studies exploring sex/gender differences in outcomes following TBIs classified as moderate/severe mainly showed absence of differences or better outcomes in women. [7, 8, 13] Following mild TBI, the majority of studies indicate worse psychological and global functioning outcomes in women. [7, 9, 10] In a European cohort of TBI patients (Collaborative European Neurotrauma Effectiveness Research in TBI (CENTER-TBI)), we found worse functional outcomes, generic and specific health-related quality of life (HRQoL), and more severe post- concussion, depression, anxiety and post-traumatic stress symptoms in women 6- months after mild TBI, particularly in the age group younger than 45 and for some outcomes in the age group 65+. [14]The differences remained significant after controlling for pre-injury health and injury-related characteristics.

Injury characteristics do not seem probable mechanisms of the observed differences, since men generally sustain more severe mild TBIs, more extracranial injuries and show more pathology on CT than women. Nevertheless, there is a difference in prevalence rates of psychiatric disorders,[15] with women having higher rates of anxiety and mood disorders,[16]which are the most prevalent disorders worldwide.[17] Preinjury psychiatric history is the strongest risk factor for post-injury disorders,[18] and therefore can represent vulnerability for appearance of symptoms and lower health-related quality of life after a TBI.[12] Differences in brain morphology, cerebral blood flow, and levels and role of sex steroids may also impact the processes after TBI in a sex-specific manner.[10, 19]

Apart from biological differences, sociocultural expectations and roles can produce gender- specific stressors, thus interfering with the recovery after TBI.[20] [10, 21, 22] In many

societies women are expected to take over the role of primary homemaker and caregiver for children, and men of primary wage earner. In Europe, women are more likely to suffer from poverty, [23] to live alone, to take care of children, to be highly educated, and to be unemployed.[24] Sociodemographic factors are relevant, because they have been shown to be associated with health outcomes and HRQoL in different populations.[25-27] These factors can have an age-dependent impact due to hormonal variations and changes in roles, responsibilities and stressors over life-time. [10, 28] Lastly, differential trauma triage and management of TBI can also play a role in functioning following TBI. In the CENTER-TBI study, we found that women with mild TBI had higher likelihood of direct admission to hospital (trauma center), and lower likelihood of admission to intensive care in analyses adjusted for preinjury and injury characteristics. [14] However, the impact of differences in care pathways on the long-term outcomes following mild TBI is unclear.

Possible explanations of differences in post-TBI outcomes between men and women have rarely been tested. Mediation analysis is used to quantify the extent to which the relationship between two variables, for instance association between sex/gender and outcomes, can be explained by one or more intermediate variables, while controlling for other relevant factors. We hypothesized that the observed sex/gender differences in outcomes following mild TBI could be partly explained by psychiatric history, by sociocultural and gender- role related factors, and by acute management of mild TBI. In addition, the importance of these mechanisms may differ across age groups.

Therefore, we aimed to study whether the differences in outcomes after mild TBI, overall and in different age groups, were mediated by 1) psychiatric history, 2) sociodemographic variables (living alone, living with children, education, and employment status/job category), and/or 3) differences in care-pathways (referral to study hospital and discharge destination after Emergency Room (ER)).

Methods

Study population

The study population consisted of patients from the prospective multicenter observational CENTER-TBI study (Core data, version 2.1). Data were collected from December 2014 to December 2017 in 63 centers across Europe and Israel. The study was registered with Clinical-Trials.gov (NCT02210221). Ethical approval was granted for each recruiting site and informed consent was obtained for all patients by the patients and/or the legal representative/next of kin.

Inclusion criteria for the core study were a clinical diagnosis of TBI, presentation within

24 h after injury, and an indication for computed tomography (CT) scanning. [29]The core dataset included 3 strata that are differentiated according to care path: patients seen in the ER and then discharged; patients primarily admitted to the intensive care unit (ICU), and patients primarily admitted to the hospital ward (ADM).[30]

For this study, we selected patients aged 16 years or older, and classified as having mild TBI based on baseline Glasgow Coma Score (GCS) 13 to 15. Sex was recorded on medical forms at admission. Sociodemographic variables, medical history, and clinical and injury characteristics were assessed at admission. The results of first CT scanning reviewed centrally by CENTER-TBI researchers were selected for the analyses.

Ethical approval

The CENTER-TBI study (European Commission [EC] grant 602150) has been conducted in accordance with all relevant laws of the European Union (EU) if directly applicable or of direct effect and all relevant laws of the country where the recruiting sites were located, including but not limited to, the relevant privacy and data protection laws and regulations (the "Privacy Law"), the relevant laws and regulations on the use of human materials, and all relevant guidance relating to clinical studies from time to time in force including, but not limited to, the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95; "ICH GCP") and the World Medical Association Declaration of Helsinki entitled "Ethical Principles for Medical Research Involving Human Subjects." Informed consent by the patients and/or the legal representative/next of kin was obtained, accordingly to the local legislations, for all patients recruited in the core data set of CENTER-TBI and documented in the e-CRF. Ethical approval was obtained for each recruiting site. The list of sites, ethical committees, approval numbers, and approval dates can be found on the study website (https:// www.center-tbi.eu/project/ethical-approval).

Outcomes at 6 months

Glasgow Outcome Scale Extended (GOSE).[31] The GOSE assesses global functional outcome following TBI. It provides eight ordinal categories of outcome: dead (1); vegetative state (2); lower severe disability (3); upper severe disability (4); lower moderate disability (5); upper moderate disability (6); lower good recovery (7); and upper good recovery (8). GOSE was assessed at 6 months by either a questionnaire or a (telephone) interview. When it was assessed outside the time window (range 5–8 months), it was imputed based on all GOSE measurements available.[32] For the analyses, GOSE was dichotomized to incomplete (GOSE<8) and complete (GOSE=8) return to pre-injury level of functioning.

Short Form Health Surveys (SF-12v2; SF-36v2).[33] SF-12v2 with 12 items and SF-36v2 with 36 items are self-reported and generic measures of HRQoL. The results can be summarized as mental (MCS) and physical (PCS) component scores ranging from 0 to 100. MCS and PCS were based on a SF-12v2 score, and when there was no SF-12v2 score, the score was derived using corresponding items from available SF-36v2 questionnaires.

Quality of Life after Brain Injury-Overall Scale (QOLIBRI-OS).[34] The QOLIBRI-OS is a brief TBI-specific index of health-related quality of life (HRQoL) that covers physical condition, cognition, emotions, daily life, personal/social aspects, and current situation/ future prospects. The total score is on a scale that ranges 0–100.

Rivermead Post-Concussion Symptoms Questionnaire (RPQ).[35] The RPQ measures cognitive, somatic, and emotional symptoms that are compared with the pre-injury level. It contains 16 items that can be answered with 0 = not experienced, 1 = no more of a problem (than before the injury), 2 = mild problem, 3 = moderate problem, or 4 = severe problem. When calculating the total score, the category "no more of a problem (than before)" is treated as 0, and it has a score range of 0-64.

Patient Health Questionnaire (PHQ-9).[36] The PHQ-9 measures symptoms of depression. It contains nine items using a four- point Likert scale (from 0 = not at all to 3 = nearly every day), and it has a score range of 0–27.

Generalized Anxiety Disorder 7-item scale (GAD-7).[37] GAD-7 measures symptoms of anxiety. It comprises seven items that can be answered from 0 = not at all to 3 = nearly every day, and it can have a score range of 0–21.

Post-Traumatic Stress Disorder (PTSD) Checklist for DSM-5 (PCL-5).[38] PCL-5 measures symptoms of PTSD according to DSM-5 criteria. It consists of 20 items that can be answered with 0 = not at all to 4 = extremely, and it has a score range of 0–80.
For QOLIBRI-OS and SF-12v2 higher values indicate better quality of life/ more favorable outcomes, and for RPQ, PHQ-9, GAD-7, and PCL-5 higher values indicate more severe symptoms/ less favorable outcomes.

Exposure, baseline covariates and mediator variables

Figure 1 shows the examined mediation model for 6-month outcomes. Sex/gender was considered as the "exposure" (i.e., a variable associated with outcome) and it was coded as binary variable (men versus women).

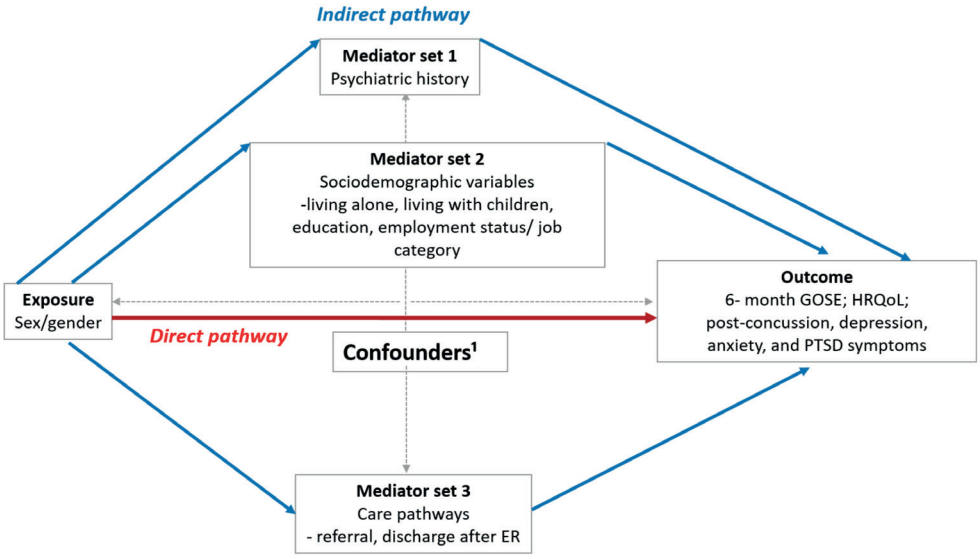

Figure 1. The proposed mediation model with direct and indirect (via psychiatric history, sociodemographic variables and care pathways). [1] age, preinjury physical health, cause of injury, baseline Glasgow Coma Score (GCS; 13-15), baseline pupillary reactivity; hypoxia; hypotension, Injury Severity Score (ISS), Marshall CT score, subarachnoid hemorrhage, epidural hematoma. GOSE= Glasgow Outcome Scale Extended; HRQoL= Health-related quality of life; PTSD= Posttraumatic stress disorder.

Psychiatric history included self-reported medical history of anxiety, depression, sleep problems, schizophrenia, substance abuse or other disorders at admission. Care pathway mediators were selected based on previous analyses of differences between men and women. [14] Referral was categorized to primary (direct transfer to the study hospital) and secondary (transfer from another hospital to the study hospital). Discharge destination from the Emergency Room was defined based on discharge home, admission to intensive care unit (ICU) or operating room, and other admission (hospital ward, other hospital) after ER. Gender-related sociodemographic mediator variables were assessed at admission: living alone (yes/no); living with children (yes/no); education (in years); and employment status/job category (unemployed; student; retired; professional/manager; associate professional/technician; clerk/sales and service worker; skilled manual worker or machine operator; other manual worker). Jobs indicated in the category "other" were classified into existing categories using European Skills/Competences, qualifications and Occupations (ESCO),[39] and service workers were categorized with clerk/sales workers, and machine operators with skilled manual workers. Sheltered/ special employments was categorized under other manual worker. For age analyses, smaller categories were merged: for age group 16-45 "retired" was merged with "unemployed"; for 45-65 "student" was merged with "unemployed"; for >65 all working categories were merged together, and "unemployed" was merged with "retired".

To control for confounding between exposure and outcome, exposure and mediator, and mediator and outcome, we conditioned on: age; preinjury physical health (no systemic disease; mild systemic disease; severe of life-threatening systemic disease); cause of injury (fall or other unintentional injury; motor vehicle accident; violence, suicide attempt or other); baseline GCS (range 13-15); baseline pupillary reactivity (both reactive/ one or both unreactive); hypoxia (yes/no); hypotension(yes/no); Injury Severity Score (ISS); first Marshall CT score (no visible pathology; cisterns present with 0-5 mm midline shift, cisterns compressed or absent with 0-5 mm midline shift; midline shift>5mm, evacuated lesion, non-evacuated mass lesion); subarachnoid hemorrhage on CT (yes/no); and epidural hematoma on CT (yes/no).

Statistical analyses

Descriptive statistics for TBI characteristics, mediators, treatment, and outcome variables were presented separately for men and women using percentages for categorical variables and median with interquartile range for continuous outcomes. Differences were tested using non-parametric tests (e.g., chi-square and Mann-Whitney U test) (Table 1, Supplementary Table 1).

We performed mediation analyses by fitting natural effect models for nested counterfactuals using the *medflex* [40]package in R. This method decomposes the total effect of an exposure on an outcome into 1) the natural indirect effect, i.e. the effect of the exposure on the outcome that is due to its effect on the mediator(s); and 2) natural direct effect, i.e. the effect of the exposure on the outcome that is not due to its effect on the mediator(s).[40] We chose this method because the decomposition method is valid even in the presence of an interaction effect between the exposure and the mediator(s) on the outcome (which can be explicitly modelled), and it allows consideration of multiple mediators simultaneously [40, 41]. The models were fitted using the "imputation-based approach" implemented in the medflex package, which requires fitting a model for the outcome mean.[40] Robust standard errors with sandwich estimator were used to account for the uncertainty inherent to the imputation model.

For each outcome, three joint mediation analyses were performed: one with psychiatric history, one with all sociodemographic variables, and one with all care pathways as specified mediators (*Figure 1*). We analyzed the following 6-month outcomes: GOSE, disease-specific HRQoL (QOLIBRI-OS), generic (SF12) mental and physical HRQoL, post-concussion symptoms (RPQ), depression (PHQ-9), anxiety (GAD-7), and PTSD (PCL-5). For each analysis, we reported estimates (regression coefficients) of direct and indirect effect of sex/gender. For models with significant indirect effect, we calculated the mediated proportion by dividing the indirect effect by the total effect, and multiplying by 100. We also performed separate analyses in different age groups: 16-45, 45-65, 65+

years (Supplementary Figures 1-3).

In addition, we performed sensitivity analyses where we also modelled interactions between exposure and mediators in their effect on the outcomes. Results from these analyses were similar and are reported in the Supplementary Materials. Because these models included interaction effect, we reported pure direct effect, pure indirect effect, and mediated interaction (estimate for exposure-mediator interaction).

Mediation analyses were performed in multiple imputed datasets with missing information in covariates and mediators imputed based on an imputation model with sex/gender, and all confounder, mediator, outcome, and auxiliary variables, using the R package *mice*.[42] Exposure values did not have missing values, and unobserved outcome values were not imputed. The results of the mediation analyses were pooled over 10 imputed datasets using the *mitools*[43] package.

Estimates (regression coefficients) for direct and indirect effects of sex/gender for continuous outcomes are presented in forest plots. Direct and indirect effects for dichotomized complete return to pre-injury functioning (GOSE=8), obtained in logistic regressions, are reported for women (men as reference category) on a scale of odds ratios.

Results

About two third of patients (64%) with mild TBI were men. Women with mild TBI were older (median 58 years vs. 50 [Q1 32, Q3 65]), had higher Glasgow Coma Score (79 % vs. 75% with GCS 15), lower percentage of abnormalities on CT (42.5% vs. 47%), and epidural hematoma (5% vs 10 %), and lower total body injury severity (ISS; 9 [4, 16] vs. 13 [8, 19.]) than men (*Table 1; Supplementary Table 1*). They sustained more TBIs due to falls (61% vs. 52%), and fewer due to motor vehicle accidents (33% vs. 36%) and violence (6% vs. 12.5%); and had worse preinjury physical (50% vs. 58.5% with no systemic disease) and psychiatric health (18% vs. 12% with history of psychiatric disorders; *Table 1, Supplementary Table 1*).

Fewer women were admitted to ICU or operating room (17% vs. 27%), and more were discharged home (34% vs. 25%). Women had slightly lower years of education (13 [10, 16] vs. 13 [11, 16], p=0.015), were more often retired (37% vs. 25%), less often had job occupation of skilled manual worker (4% vs. 13%) or other manual worker (7% vs. 12%), and slightly more often of professional/manager (15% vs. 13%). Women more frequently lived alone (27% vs. 20.5%; *Table 1*). Characteristics of men and women in different age groups are presented in Supplementary Table 2.

Table 1. Men and women with mild TBI (GCS 13-15): baseline characteristics, psychiatric history, sociodemographic and care pathway variables, and 6- month outcomes.

	Men	Women	p	Missing (%)
N	*1842*	*1022*		
Age (median [IQR])	50 [32, 65]	58 [37, 73]	<0.001	0
Cause of injury (%)			<0.001	1.7
Motor vehicle accident	647 (35.8)	331 (32.7)		
Fall or other unintentional injury	932 (51.6)	617 (61.0)		
Suicide attempt, violence	226 (12.5)	63 (6.2)		
Glasgow Coma Score (GCS) (%)			0.039	0
13	128 (6.9)	63 (6.2)		
14	340 (18.5)	154 (15.1)		
15	1374 (74.6)	805 (78.8)		
Total ISS (median [IQR])	13 [8, 19.]	9 [4, 16]	<0.001	0.8
Psychiatric history (%)	210 (11.6)	183 (18.0)	<0.001	1.1
Sociodemographic variables				
Living alone = yes (%)	377 (20.5)	279 (27.3)	<0.001	0
Living with children (%)	383 (20.8)	236 (23.1)	0.166	0
Education (years) (median [IQR])	13 [11, 16]	13 [10, 16]	0.015	19.9
Employment status / job category (%)			<0.001	7.7
professional/ manager	224 (13.3)	146 (15.3)		
associate professional/ technician	163 (9.6)	163 (9.6)		
clerk/sales/service	167 (9.9)	105 (11.0)		
skilled manual worker/ machine operator	223 (13.2)	41 (4.3)		
manual worker	203 (12.0)	70 (7.3)		
not employed	167 (9.9)	105 (11.0)		
retired	435 (25.7)	355 (37.2)		
student	161 (9.5)	86 (9.0)		
Care pathway variables				
Destination after ER (%)			<0.001	0.3
Home	459 (24.9)	344 (33.9)		
ICU or operating room	502 (27.3)	180 (17.8)		
Hospital ward, other hospital	879 (47.8)	490 (48.3)		
Referral= secondary (%)	287 (15.6)	120 (11.8)	0.006	0
Outcomes at 6 months				
Complete return to pre-injury functioning (GOSE=8) (%)	783 (51.5)	378 (44.1)	0.001	17
QoLIBRI- OS Total Score	75 [62, 88]	71 [50, 83]	<0.001	43
SF12 MCS	51.5 [42.6, 57.2]	48.2 [38.4, 56.5]	<0.001	42.7
SF12 PCS	50.2[41.4, 55.5]	45.7[36.6, 54.3]	<0.001	42.7
RPQ Total Score	4 [0, 15]	9 [1.5, 20]	<0.001	43.9
PCL- 5 Total Score	6 [2, 15]	8 [3, 18]	0.004	45.2
PHQ -9 Total Score	3 [0, 7]	4 [1, 8]	<0.001	45.3
GAD-7 Total Score	1[0, 5]	3 [0, 6]	<0.001	45.5

GAD-7, Generalized Anxiety Disorder 7-item scale; GCS, Glasgow Coma Scale; GOSE, Glasgow Outcome Scale Extended; ISS, Injury Severity Score; MCS= Mental Composite Score; PCL-5, Post-Traumatic Stress Disorder Checklist for DSM-5; PCS= Physical Composite score; PHQ-9, Patient Health Questionnaire 9-item; QOLIBRI-OS, Quality of Life after Brain Injury-Overall Scale; RPQ, Rivermead Post-Concussion Symptoms Questionnaire; SF12v2, Short Form Health Survey 12 item; TBI, traumatic brain injury.

Mediation analyses

Mediation via psychiatric history

There was a significant indirect effect of sex/gender mediated by psychiatric history (indirect effect, *Figure 2)* for all outcomes except physical HRQoL (SF-12v2 PCS -0.06 [-0.16, 0.05])*:* disease specific HRQoL (QOLIBRI-OS; -0.75 [-1.20, -0.30], proportion mediated 16%); generic mental HRQoL (SF-12v2 MCS -0.47[-0.75, -0.19], proportion mediated 17%), post-concussion (RPQ; 0.36[0.12, 0.60], proportion mediated 9%), depression (PHQ-9; 0.22 [0.09, 0.36], proportion mediated 16%), anxiety (GAD-7; 0.17 [0.06, 0.27], proportion mediated 14%), and post-traumatic stress symptoms (PCL-5; 0.39 [0.13, 0.65], proportion mediated 18%). Differences in outcomes were partly explained by psychiatric history, but to a small extent compared to other factors (proportion mediated 9% -18%).

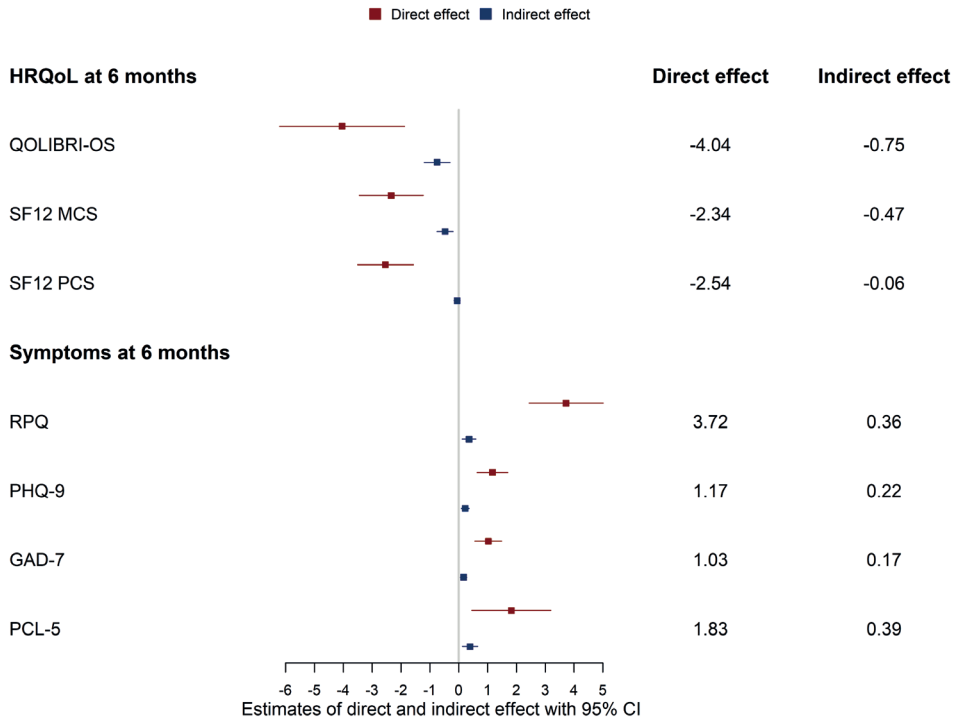

Figure 2. Mediation analyses: Estimates (regression coefficients with 95% Confidence Intervals) of direct effect of sex/gender and indirect effect via psychiatric history on outcomes following mild TBI: specific (QOLIBRI-OS; n=1633) and generic (SF12V2; n=1614) health-related quality of life, and post-concussion (RPQ; n=1606), depression (PHQ-9; n=1568), anxiety (GAD-7, n=1562), and post-traumatic stress (PCL-5, n= 1570) symptoms. QOLIBRI-OS, SF-12v2: higher values better HRQoL; RPQ, PHQ-9, GAD-7, PCL-5: higher values more severe symptoms. QOLIBRI-OS, Quality of Life after Brain Injury-Overall Scale; SF12V2, generic short form health survey; RPQ, Rivermead Post-Concussion Symptoms Questionnaire; PHQ-9, Patient Health Questionnaire; GAD-7, Generalized Anxiety Disorder 7-item scale; PCL-5, Post- Traumatic Stress Disorder Checklist for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

The effect of sex/gender not mediated by mental health problems ("direct effect"; *Figure 2*) was significant for all outcomes: disease-specific HRQoL (QOLIBRI-OS, -4.04 [-6.21,-1.88]]), mental HRQoL (SF-12v2 MCS; -2.34[-3.45, -1.24]), physical HRQoL (SF-12v2 PCS; -2.54[-3.50, -1.58]]), and post-concussion (RPQ; 3.72 [2.44, 5.01]), depression (PHQ-9 1.17 [0.64, 1.70]); anxiety (GAD-7 1.03 [0.56, 1.49]); and post-traumatic stress symptoms (PCL-5; 1.83 [0.46, 3.20]).

Logistic regression showed a small indirect effect of sex/gender mediated by psychiatric history (0.96 [0.94-0.99], proportion mediated 9%), and a substantial direct effect of sex/gender (0.65 [0.54-0.99], indicating lower likelihood of women for having better functional outcomes due to other factors.

Analyses in different age groups showed the largest significant indirect effect of sex/gender via psychiatric history in the age group 65 and older, indicating that worse outcomes in older women compared to men were to a considerable degree mediated by psychiatric history: proportion mediated 29% for post-concussion symptoms, 27% for post-traumatic stress symptoms, 25% for anxiety, 24% for depression, 20% for disease-specific and mental HRQoL , 19% for GOSE; Supplementary Figures 4-6, Supplementary Table 3).

Joint mediation via gender-related sociodemographic variables

The mediation analyses showed a negligible indirect effect of sex/gender jointly mediated by gender- related sociodemographic variables ("indirect effect"; *Figure 3*) for disease specific HRQoL (QOLIBRI-OS; -0.11 [-0.74, 0.51]); generic HRQoL (SF-12v2 MCS -0.06[-0.34, 0.21]; SF-12v2 PCS -0.05[-0.31, 0.21]]), post-concussion (RPQ; 0.07 [-0.24, 0.38]), depression (PHQ-9; 0.04[-0.11, 0.18]), anxiety (GAD-7; -0.01 [-0.14, 0.11]), and post-traumatic stress symptoms (PCL-5; -0.01[-0.36, 0.33]). Therefore, the differences between men and women in 6-month outcomes following mild TBI were not explained by gender- related sociodemographic variables.

The effect of sex/gender that was not mediated by sociodemographic variables ("direct effect"; *Figure 3*) was significant for all outcomes: disease-specific HRQoL (QOLIBRI-OS, -4.68 [-6.84, -2.52]), mental HRQoL (SF-12v2 MCS; -2.75 [-3.88, -1.61]), physical HRQoL (SF-12v2 PCS; -2.55 [-3.51, -1.59]), and post-concussion (RPQ; 4.01 [2.72, 5.30]), depression (PHQ-9; 1.36 [0.82, 1.90]), anxiety (GAD-7; 1.21 [0.74, 1.68], and post-traumatic stress symptoms (PCL-5; 2.23 [0.86, 3.60]).

Logistic regressions showed no indirect effect of sex/gender on complete return to pre-injury level of functioning (GOSE=8; n=1161/2376) mediated via sociodemographic variables (OR 1.02[0.98, 1.06] for indirect effect). The effect of sex/gender not mediated

by these characteristics was significant (GOSE=8; OR 0.61 [0.51, 0.74] for direct effect), indicating lower likelihood of complete return to pre-injury level of functioning for women due to other factors than the sociodemographic variables specified.

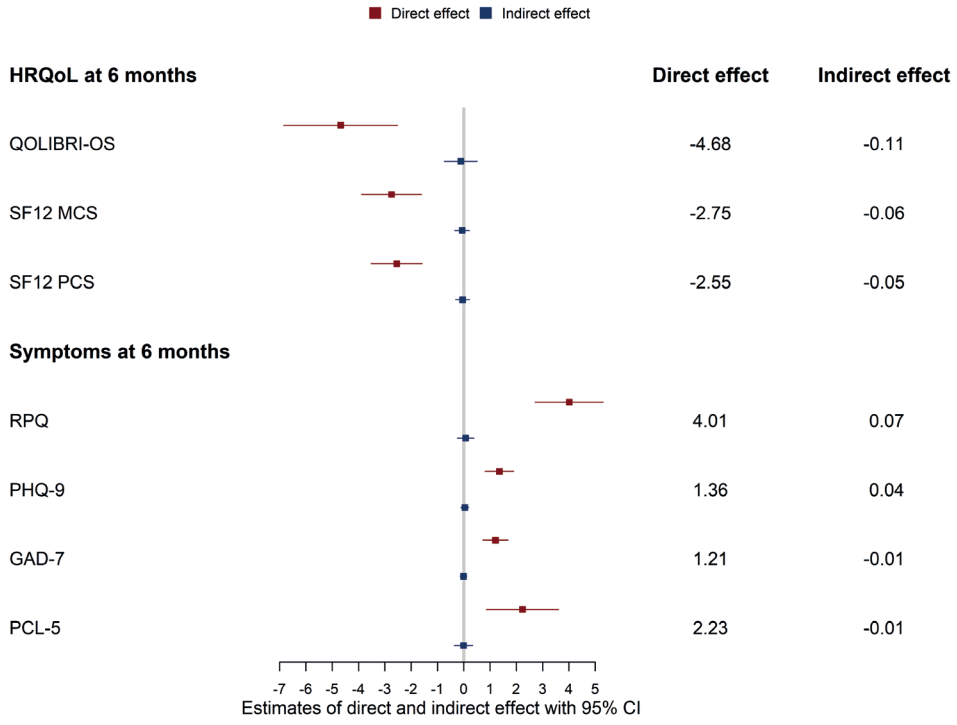

Figure 3. Mediation analyses: Estimates (regression coefficients with 95% Confidence Intervals) of direct effect of sex/gender and indirect effect via sociodemographic variables on outcomes following mild TBI: specific (QOLIBRI-OS; n=1633) and generic (SF12V2; n=1614) health-related quality of life, and post-concussion(RPQ; n=1606), depression (PHQ-9; n=1568), anxiety (GAD-7, n=1562), and post-traumatic stress (PCL-5, n= 1570) symptoms. QOLIBRI-OS, SF-12v2: higher values better HRQoL; RPQ, PHQ-9, GAD-7, PCL-5: higher values more severe symptoms. QOLIBRI-OS, Quality of Life after Brain Injury-Overall Scale; SF12V2, generic short form health survey; RPQ, Rivermead Post-Concussion Symptoms Questionnaire; PHQ-9, Patient Health Questionnaire; GAD-7, Generalized Anxiety Disorder 7-item scale; PCL-5, Post-Traumatic Stress Disorder Checklist for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

Subgroup age analyses showed the largest (albeit not statistically significant) indirect effect of sex/gender via sociodemographic factors in the group 65 and older, suggesting that worse outcomes among older women were partially mediated by sociodemographic factors. In contrast, in the age groups 16-45 and 45-65, there was a small (insignificant) indirect effect of sex/gender via sociodemographic factors in the opposite direction (Supplementary Figures 7-9).

Joint mediation via care pathways

The mediation analyses showed no indirect effect of sex/gender jointly mediated by care pathways ("indirect effect"; Figure 4) for disease- specific HRQoL (QOLIBRI-OS, 0.07 [-0.12, 0.26]), generic HRQoL (SF12 MCS; 0.06 [-0.05, 0.17]; SF12 PCS -0.02[-0.11, 0.08]), and post-concussion (RPQ; -0.07[-0.19, 0.04]), depression (PHQ-9; -0.01[-0.06, 0.03), anxiety (GAD-7;-0.02 [-0.06,0.03]), and post-traumatic stress symptoms (PCL-5; -0.06 [-0.18,0.06]). Thus, the differences between men and women in 6-month outcomes following mild TBI could not be explained by different care pathways.

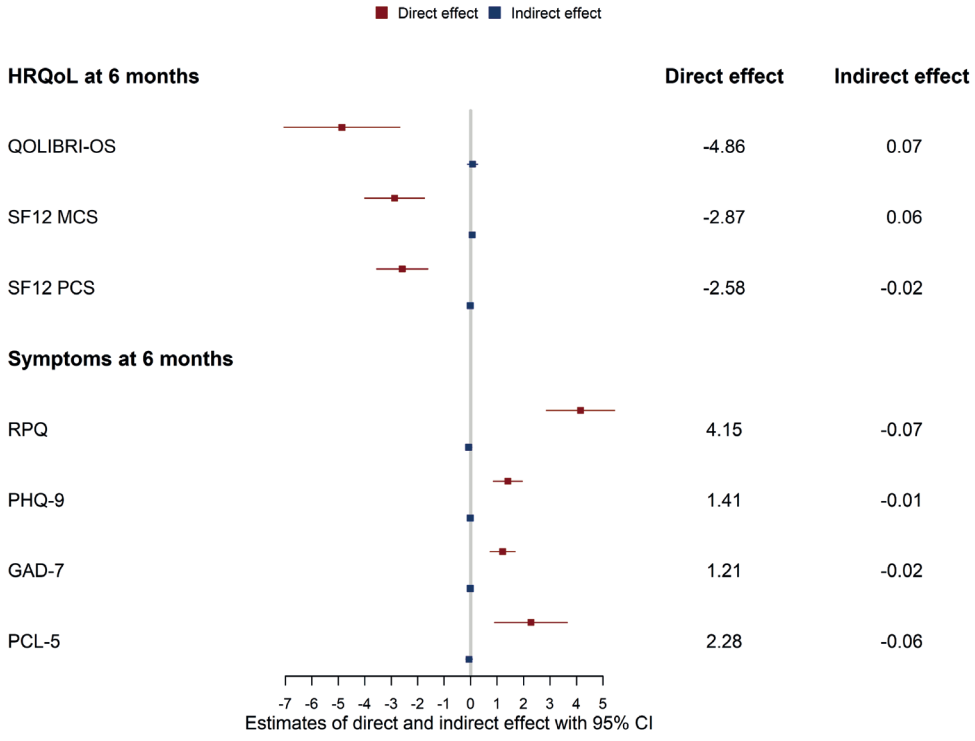

Figure 4. Estimates (regression coefficients with 95% Confidence Intervals) of direct effect of sex/gender and indirect effect via care pathways on outcomes following mild TBI: specific (QOLIBRI-OS; n=1633) and generic (SF12; n=1614) health-related quality of life, and post-concussion(RPQ; n=1606), depression (PHQ-9; n=1568), anxiety (GAD-7, n=1562), and post-traumatic stress (PCL-5, n= 1570) symptoms. QOLIBRI-OS, SF-12v2: higher values indicate better HRQoL; RPQ, PHQ-9, GAD-7, PCL-5: higher values indicate more severe symptoms. QOLIBRI-OS, Quality of Life after Brain Injury-Overall Scale; SF12V2, generic short form health survey; RPQ, Rivermead Post-Concussion Symptoms Questionnaire; PHQ-9, Patient Health Questionnaire; GAD-7, Generalized Anxiety Disorder 7-item scale; PCL-5, Post-Traumatic Stress Disorder Checklist for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

The effect of sex/gender not mediated by care pathways ("direct effect"; *Figure 4*) was significant for all outcomes: disease-specific HRQoL (-4.86 [-7.05, -2.68), mental HRQoL (SF-12 MCS; -2.87 [-4.00, -1.74]), physical HRQoL (SF-12 PCS; -2.58

[-3.55, -1.62]), and post-concussion (RPQ; 4.15 [2.87, 5.44), depression (PHQ-9; 1.41 [0.87, 1.95), anxiety (GAD-7; 1.21 [0.74, 1.68], and post-traumatic stress symptoms (PCL-5; 2.28 [0.91, 3.65]).

Logistic regressions showed that a small proportion of the effect of sex/gender was mediated by care pathways, very slightly increasing likelihood of complete return to pre-injury level of functioning (GOSE=8, 1161/2376) for women (1.03 [1.00- 1.06]). The direct effect of sex/gender was significant, indicating lower likelihood of complete return to pre-injury level of functioning for women (0.60 [0.50-0.73]) due to other factors than care pathways.

In all age groups, the indirect effect of sex/gender via care pathways was negligible (Supplementary Figures 10-12).

Discussion

Women show worse functional, health-related quality of life and mental health outcomes following mild TBI.[14] We explored whether these differences were mediated by psychiatric history, gender-related sociodemographic variables, and care pathways. Our results showed that differences in 6-month outcomes were not mediated by gender-related sociodemographic variables (i.e. living alone, living with children, education and employment status/job category), nor by specified care pathways (i.e. hospital referral and discharge destination after ER). Differences in all outcomes except for physical HRQoL were partly mediated by psychiatric history, but the proportion mediated was small. Therefore, other factors than differences in the sociodemographic and care pathway variables explored in this study seem to underlie differences between men and women in outcomes after mild TBI.

History of mental health problems is a risk factor for poor outcome after mild TBI.[44, 45, 46] Generally, women and men have comparable prevalence of psychiatric disorders, however, prevalence of the most frequent mood and anxiety disorders is higher in women. Recent studies suggest that rates of common mental health disorders have increased in women and remained stable in men in the last decades, with younger women at particular risk. [47, 48]We found that psychiatric history partly explained worse outcomes in women in all domains except physical health-related quality of life; nevertheless, the sex/gender differences still largely remained unexplained by this factor. In the age group 65 years and older, psychiatric history explained a higher proportion of the women's worse outcomes compared to other age groups. These results, together with the recent finding of sex differences in symptoms after mild TBI but not after orthopedic injury,[12] suggest that symptoms after TBI are not (completely) the result of differences in mental health history.

We selected sociodemographic variables that differed between men and women, and that can be associated with gender roles, and with health outcomes. In Europe, women are less likely to be employed, and more likely to take care of children, to live alone, and to finish tertiary education.[24] Overall, these mediators did not substantially explain differences in outcomes between men and women. Only worse outcomes of older women, compared to men of the same age, were to some extent explained by these sociodemographic variables. In contrast to other groups, in the age group 65+, women had lower education and more frequently lived alone.

We had information on employment status and broad job category. In our data, slightly more women were professionals/managers, while more men were manual workers. Because all manager and professional occupations were in the same category, differentiation between higher-status jobs was not possible. That is relevant because women have less access to the highest decision-making positions and higher tertiary education, and are underrepresented on corporate boards in management positions.[49-52] In addition, women are more likely to be paid less for the same job, and to perform domestic and care giver duties.[53] [54]However, we did not have information on salary, hours worked in household, role of a primary wage-earner, and role of a primary caregiver for children/ elderly family members, which can be particularly relevant for younger and middle-age women. [54] Therefore, we could capture gender roles and gender-specific stressors only to a limited extent [53], which could explain why worse outcomes in women were less explained by specified mediators in age groups 16-65 compared to the 65 years and older. Fulfilling family, household and work-related duties, and being paid less can represent a burden in recovery from a TBI, particularly in young and middle adulthood. [22, 55]

The role of primary wage earner, and masculine norms such as stoicism, self-reliance and restrictive emotionality can influence return to work and participation in rehabilitation after a TBI.[56, 57] As a consequence, gender identity can impact recovery.[53, 58]A qualitative study with men who experienced a TBI demonstrated that gender identity, and in particular masculine norms, motivated men to return to work more quickly and speed up discharge and recovery, which was beneficial for some and detrimental for others.[59] In addition, masculine traits can reduce the likelihood of recognizing and self-reporting health complaints,[60, 61]particularly in the domain of psychological functioning.[56] In the general European population, men perceive (or report) better health than women.[24] More detailed measurement of gender identity would contribute to better understanding the underlying mechanisms that cause gender differences in health-related outcomes.

Studies on sex and gender differences in care pathways and their impact on long-term functioning after TBI are scarce. Large retrospective studies of cardiovascular, trauma and critical care patients found that women were less likely to receive ICU treatment.[62-64]

In our data, more women had direct referral to study hospital, and were less triaged to ICU. In studies of treatment and care pathway, it is difficult to completely avoid residual confounding related to medical needs, [64] which could explain observed difference in care pathways. Triage of mild TBI patients to different care pathways is not clearly associated with outcome.[65, 66] Because there is no evidence of worse functional outcomes of patients triaged to other destinations,[67] admissions to ICU following mild TBI could often be unnecessary.[66] Additionally, some studies associate ICU admission with increased risk for PTSD one year after injury. [68] For some mild TBI patients, however, monitoring in hospital and intensive care can be beneficial to promptly identify any deterioration and to initiate surgery or critical care intervention if necessary.[66] For the functional, HRQoL and mental health outcomes we analyzed, care pathways did not explain differences between men and women.

Biological differences and particularly sex steroids represent another pathway that can mediate sex differences in outcomes.[69] For instance, animal models suggest that the hypothalamic–pituitary–adrenal axis (HPA) axis, which modulates the stress response,[70] and microglia,[71] which influence cerebral inflammation, have sex-specific responses. After TBI, female rodents have shown stronger inflammatory response ,[19] greater anxiety and reduction of sociability, [72] and differential stress response[70] than males. Hormonal differences can be of particular importance in explanation of symptoms in pre-menopausal women.[10] Moreover, genetic factors can interact with sex and/or gender on their impact of outcome after TBI. For example, being carrier of an APOE4 allele had negative impact on the GOSE measured 1-5 years after TBI, and the effect was stronger in women compared to men .[73]

To our knowledge, this is the first study that explores underlying mechanisms of differences in outcomes after TBI between men and women using a mediation framework. We explored three possible explanatory pathways: one via psychiatric history, one via gender-related sociodemographic variables, and one via care pathways. The method allowed studying joint mediation for both pathways, and including interaction between sex/gender and mediators in their impact on outcomes. We used a large multicenter European cohort of TBI patients and included different domains of functioning after six months.

Implications of this study involve informing clinicians and patients about different risks of poorer outcomes following mild TBI in context of sex, gender and mental health. If supported by future evidence, the results of our and other recent studies [11, 12] could be utilized for organizing follow up care, for instance scheduling earlier or more frequent appointments for women and persons with (history of) psychiatric difficulties. Further, other potential sociocultural and biological mechanisms of sex/gender differences should be measured and explored in upcoming TBI research.

This study also has some limitations. Mediation analyses assume complete control for confounding between exposure and mediators, mediators and outcome, and exposure and outcome. We controlled for a substantial number of pre-injury, clinical and injury characteristics. In addition, for each set of mediators, we performed joint mediation with mediators included simultaneously, thus providing additional control for confounding. However, unmeasured confounding remains possible, which might have biased the observed associations. Moreover, some relationships may be non-linear, which can complicate adjustment.[44] We only had information on self-reported medical history of psychiatric disorders, but not a measure of mental health symptoms before/ at the time of injury. We did not adjust for or analyze the impact of interventions and therapies after hospital admission and discharge. Furthermore, as frequently occurs in longitudinal TBI studies, 6-month outcomes were not available in a considerable number of patients, which can compromise validity. [74] The subgroup age analyses had lower power. Additionally, age groups (16-45, 45-65, 65+) were rather broad and possibly included persons in different life stages, characterized by different roles, stressors and biological processes. For instance, some previous studies found increased risk of PTSD following mild TBI for women aged 30-39 versus 18-29,[11] and of post-concussion symptoms for women aged 35-49 versus 17-34.[7, 12] In our study, the group aged 45-65 likely included both females in premenopause and menopause, and groups 45-65 and 65+ included both retired and (un)employed persons. The results are obtained in an European study with a substantial proportion of large trauma centers in urban areas in North-Western Europe.[30, 75] Therefore, the generalizability of findings to other areas is limited. Important indicators of gender roles and identity were not measured in this study. Sex was based on medical forms and will not always correspond to gender (identifying as a woman or a man). We recognize that there is a notable minority of intersex, transgender and non-binary persons, who are not captured by this dichotomy. We recommend inclusion of self-reports and more measures of gender where practical in future TBI studies.

In conclusion, men and women differ in outcomes following mild TBI, and those differences are only partly explained by psychiatric history, and not explained by gender-related sociodemographic and care pathway differences. Future studies should explore further aspects of gender roles and identity, and biological factors as underpinnings of sex and gender differences in TBI outcomes.

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Author Disclosure Statement

No competing financial interests exist.

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Supplementary material

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Chapter 4

Health care utilization and outcomes in older adults after Traumatic Brain Injury: a CENTER-TBI study

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Abstract

Introduction: The incidence of traumatic brain injury (TBI) is increasingly common in older adults aged ≥65 years, forming a growing public health problem. However, older adults are underrepresented in TBI research. Therefore, we aimed to provide an overview of health-care utilization, and of six-month outcomes after TBI and their determinants in older adults who sustained a TBI.

Methods: We used data from the prospective multi-center Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study. In-hospital and post-hospital health care utilization and outcomes were described for patients aged ≥65 years. Ordinal and linear regression analyses were performed to identify determinants of the Glasgow Outcome Scale Extended (GOSE), health-related quality of life (HRQoL), and mental health symptoms six-months post-injury.

Results: Of 1254 older patients, 45% were admitted to an ICU with a mean length of stay of 9 days. Nearly 30% of the patients received inpatient rehabilitation. In total, 554/1254 older patients completed the six-month follow-up questionnaires. The mortality rate was 9% after mild and 60% after moderate/severe TBI, and full recovery based on GOSE was reported for 44% of patients after mild and 6% after moderate/severe TBI. Higher age and increased injury severity were primarily associated with functional impairment, while pre-injury systemic disease, psychiatric conditions and lower educational level were associated with functional impairment, lower generic and disease-specific HRQoL and mental health symptoms.

Conclusion: The rate of impairment and disability following TBI in older adults is substantial, and poorer outcomes across domains are associated with worse preinjury health. Nonetheless, a considerable number of patients fully or partially returns to their preinjury functioning. There should not be pessimism about outcomes in older adults who survive.

Keywords: Traumatic brain injury, older adults, outcomes, health care utilization, health-related quality of life, mental health

Introduction

Traumatic brain injury (TBI) is a growing public health problem and a major cause of death and disability worldwide [1]. TBI can cause long-term impairment in physical, cognitive and emotional functioning [2-4]. In recent decades, there is a shift in the TBI population towards older age groups (≥65 years), especially in high-income countries where falls represent the primary cause of TBI [5]. This can be explained by a combination of improved traffic safety regulations, resulting in a decrease in road traffic injuries, and increased life expectancy with greater mobility in older people [5].

Compared to younger TBI patients, older patients have longer hospital stays [6,7], a slower recovery [8-10] and are more likely to die due to their TBI. [11] Recovery after TBI in older adults may be hampered by the presence of comorbidity, the presence of physical and mental health problems prior to injury, and the use of medication, which could complicate the treatment of TBI. Prior studies suggest that measures of pre-injury functioning and frailty are stronger predictors of outcome than age [12]. Nevertheless, previous TBI studies have often excluded older adults, especially those with pre-existing psychiatric and neurological problems [13]. While results from younger adult studies suggest a strong relationship between pre-injury characteristics and outcome after TBI, evidence from older adult cohorts is needed [14]. Chronic health complaints are also associated with increased healthcare utilization and costs [15]. In the general injury population, older patients have a higher health care utilization after discharge [16,17]. A prior study found that older patients (75-84 years) had significantly higher rates of rehospitalisation, home visits and informal care, and significantly lower rates of out-patient rehabilitation care compared to younger patients (55-74 years) [18].

Research on both health-related quality of life (HRQoL) and psychological outcomes in older adults after TBI is scarce. Previous HRQoL studies included small sample sizes and few studies included both generic and disease-specific measures of HRQoL [19]. In some studies, individuals showed a higher risk for emergence of psychiatric disorders including depression, anxiety and post-traumatic stress disorder (PTSD) after TBI [20], whereas in other studies older adults reported less psychological distress and less symptoms of depression and anxiety than younger adults [14]. Nonetheless, a systematic review on psychiatric assessments after TBI, concluded that psychological outcomes were insufficiently addressed in the emerging group of older TBI patients [20].

Since the number of older adults with TBI is substantial and has been increasing, it is important to investigate characteristics and outcomes in the older TBI population [21]. A recent systematic review on outcomes following mild TBI in older adults suggested "cautious optimism" in terms of long-term functional recovery and psychological health [14].

Better understanding of health care utilization and health outcomes of older people after TBI might help clinicians to set treatment goals. Furthermore, insight into patient characteristics related to poor outcomes in older patients may support the development of prognostic models for the older TBI population. Therefore, the aims of this study were to: 1) describe health care utilization following TBI in older adults, 2) assess six-month functional outcome, generic and disease-specific HRQoL, PTSD, anxiety and depression symptoms following TBI in older adults, and 3) identify determinants of six-month outcomes in the older TBI population.

Methods

Study design and population

We analyzed data from the prospective multi-center longitudinal observational Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) core study (version 3.0; registered at clinicaltrials.gov NCT02210221) [22]. Patients from 63 centers were invited to participate in the study from December 2014 to December 2017. Data was collected for patients with a clinical diagnosis of TBI, an indication for computed tomography (CT), who presented to a hospital within 24 hours after injury. Patients with a severe pre-existing neurological disorder, which could confound outcome assessments, were excluded. In CENTER-TBI core study, data from 4509 participants were available for analysis. For an overview of baseline characteristics, all adult (≥16 years) patients were included in this study. In all further analyses, only patients aged ≥65 years were included: 1254 patients recruited from 59 participating centres .

Informed consent was obtained according to local regulations and the Medical Ethics Committees approved the CENTER-TBI study in all participating centers (https://www.centertbi.eu/project/ethical-approval).

Measures

Demographics, pre-injury characteristics

Sociodemographic characteristics (including sex, age, living situation, education level), medical history and clinical and injury characteristics were assessed at the time of enrolment in the study. Age was categorized into three groups: 65 to 74 years, 75 to 84 years, and 85 years or older for descriptive analyses, and used as a continuous variable in regression analyses.

Living situation was categorized as living alone or not. Level of education was divided into primary school, secondary school, post-high school training and college/university.

Pre-injury health status was assessed with the American Society of Anaesthesiologists - physical status classification system (ASA-PS) and categorized as healthy, mild systemic disease and severe systemic disease/threat to life. Medication use included anticoagulants/ platelets aggregation inhibitor use and beta-blocker use. Pre-injury psychiatric conditions included depression, anxiety, sleep disorder, schizophrenia, substance abuse disorder and other.

Early computed tomography (CT) assessed the presence of intracranial traumatic abnormalities. TBI severity was rated using the Glasgow Coma Scale (GCS) [23]. TBI was considered mild in patients with GCS 13-15, moderate in patients with GCS 9-12, and severe in patients with GCS of 3-8. The injury severity score (ISS), which ranges from 0-75, indicates overall injury severity. It is calculated as the sum of square of the three highest values of the Abbreviated Injury Scale Score (AIS) from different body regions [24]. Injury mechanism was categorized as falls, road traffic incident, and other.

Health care utilization

Data on hospital admission, ICU admission, and inpatient and outpatient rehabilitation were collected. Length of stay at the ward and ICU were collected using several sources of CENTER-TBI forms. For rehabilitation, the transitions of care forms were consulted. In addition to collecting information on post-injury pathways of care from providers, information on inpatient and outpatient rehabilitation were reported by a patient or proxy in questionnaires assessed at six-month follow-up. Inpatient rehabilitation included admission to a general, geriatric, psychiatric or specialized TBI rehabilitation unit, or nursing home unit. Outpatient rehabilitation included physical therapy, occupational therapy, speech therapy, therapeutic recreation, cognitive remediation, vocational services, psychological services, nursing services, comprehensive day treatment, peer mentoring, social work, independent living, and home health.

Functional outcome at six months

Functional outcome was assessed at 6 months with the Glasgow Outcome Scale Extended (GOSE). When performed outside the time window (5-8 months), it was imputed based on GOSE measurements at other time points using a multi-state model [25]. The GOSE has eight ordinal categories: dead (1); vegetative state (2); lower severe disability (3); upper severe disability (4); lower moderate disability (5); upper moderate disability (6); lower good recovery (7); and upper good recovery (8). In this study, the categories 'vegetative state' and 'lower severe disability' were combined, as these could not be differentiated for GOSE ratings based on postal questionnaires because patients in a vegetative state require specialized tests for responsiveness, and this cannot be assessed by a questionnaire [26].

We gave centres flexibility in outcome assessment to help maximize follow-up rates and to tailor approaches to patients. The GOSE was assessed by a postal questionnaire or a structured interview by a trained assessor (telephone or face to face). Answers to GOSE questionnaires could be given by patients alone, and if that was not possible by patients with the help of a relative/ caregiver, or by a relative/caregiver alone. The ratings from interviews and questionnaires showed good agreement [27]. Interviews and questionnaires were scored centrally, and when both had been carried out, the rating was based on the interview.

Generic and disease-specific HRQoL at six months

Generic HRQoL was assessed using the 12-item short form health survey (SF-12v2) [28]. The HRQoL is summarized as a mental (MCS) and a physical component score (PCS). If there was no available SF-12v2 score, the score was derived using SF-36v2 if available [25]. The raw PCS-12 and MCS-12 scores were transposed as norm-based t-scores with a mean of 50 and a standard deviation of 10. Scores <40 were classified as impaired HRQoL [29].

The six-item Quality of Life after Brain Injury Overall Scale (QOLIBRI-OS) is a disease specific instrument and provides a profile of HRQoL in domains affected by TBI [30]. The instrument assesses the overall satisfaction with different domains of life. The total score scale ranges from 0-100 and scores <52 were classified as impaired HRQoL [1].

The measures of HRQoL were completed by patients alone, and for a small subset of patients by a relative/caregiver/friend. [32]

Psychological symptoms at six months

Post-traumatic stress

PTSD symptoms were assessed with the PCL-5 [33]. The PCL-5 includes 20 items reflecting the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) diagnostic criteria of PTSD. Items are scored on a five-point Likert scale ranging from 0 (not at all) to 4 (extremely) and the sum of scores ranges from 0 to 80. A total score ≥33 was considered clinically relevant [34].

Depression

Depression symptoms were assessed with The Patient Health Questionnaire (PHQ-9) [35]. It contains nine items, which are scored on a four-point Likert scale ranging from 0 (not at all) to 3 (nearly every day). The sum score ranges from 0-27. A score of 5-9 indicated mild depressive symptoms and a score of ≥10 indicate moderate to severe depressive symptoms.

Anxiety

Anxiety symptoms were assessed with the Generalized Anxiety Disorder questionnaire (GAD-7) [36], a seven-item instrument with a four-point Likert scale ranging from 0 (not at all) to 3 (nearly every day). The sum score ranges from 0-21 with a score from 5 to 9 indicating mild and a score of ≥10 indicating moderate to severe anxiety symptoms.

The measures of psychological symptoms were completed by patients alone.
All questionnaires that were not available in local languages of participating centres were translated and linguistically validated [37]. The questionnaires were scored centrally.

Statistical Analysis

Descriptive statistics for baseline characteristics, health care utilization, and health outcomes were presented with percentages for categorical variables and median and inter quartile range (IQR) for continuous variables. Differences in baseline characteristics were compared between three types of responders: those that completed at least one questionnaire (SF-12v2, QOLIBRI-OS, PCL-5, PHQ-9, GAD-7) at six months post-injury; non-responders; and those who died within six months post TBI, making use of chi-square and Mann-Whitney U tests. Health care utilization was reported for all patients with available data. Health outcomes were reported separately by age group (65–74, 75–84 and ≥85 years of age). Differences by age group were tested using the Kruskal-Wallis test. The association of possible determinants with multiple outcomes following TBI was analyzed with univariable and multivariable ordinal and linear regression analyses, and quantified with odds ratios (ordinal regression) and regression coefficients (linear regression

For the regression analyses, missing baseline characteristics were imputed using Multivariate Imputation by Chained Equation (MICE) approach based on an imputation model including all baseline characteristics, auxiliary variables (years of education) and all six-month outcomes, using the *mice* package in R [38]. For ordinal logistic regression, the model performance was assessed with the area under the receiver operating curve, which corresponds to the c statistic. The c statistic was used to quantify the ability of the model to discriminate between patients with different outcome levels . The c statistic ranges between 0.50 (no discrimination) and 1.0 (perfect discrimination). For linear regression, model performance was quantified with the adjusted coefficient of determination (R^2).

Analyses were performed in SPSS V.25 (statistical package for social sciences, Chicago, Illinois, USA) and R (version 4.0.4) (R foundational for statistical computing, Vienna, Austria) [39].

Results

Baseline characteristics

The study included 1254 older adults (59% male) with a median age of 74 (IQR: 69-80) (**Table 1**). There were 355 (28%) patients categorized as having moderate/severe TBI, and the median ISS was 16 (IQR: 9-25). Most patients had pre-injury systemic disease (77%) and 13% had a pre-injury psychiatric condition. Falls were the primary cause of TBI (67%). In total, 554 of 1254 (44%) patients completed at least one survey on outcome after injury at six-month (**Table 1**). The median ISS was twice as high for deceased patients (26, IQR 20-43) compared to responders (13, IQR 8-21) and non-responders (13, IQR 8-25). Of responders, 14% were classified as moderate/severe TBI patients, while 69% of deceased patients were classified as moderate/severe TBI patients.

Compared to younger adult (16-64) patients, older patients were more often female, more often lived alone, reported more pre-injury psychical and psychiatric conditions and more often used anticoagulant, platelet aggregation inhibitors and beta-blockers (Table 1). The mortality at discharge was 19% in the older age group, compared to 6% in the younger population.

Table 1. Characteristics of the older adult TBI population in the CENTER-TBI study by response status at six months.

Variable	Total population	Responders*	Non-responders	Deceased	Responders vs. Non-responders	Responders vs. deceased
N	N=1254	N=554	N=423	N=277	p-value	p-value
Age, median (IQR)	74 (69-80)	73 (68-78)	75 (69-81)	76 (71-82)	<0.001	<0.001
65-74 years	634 (50.6%)	318 (57.4%)	209 (49.4%)	107 (38.6%)		
75-84 years	479 (38.2%)	193 (34.8%)	158 (37.4%)	128 (46.2%)		
≥85 years	141 (11.2%)	43 (7.8%)	56 (13.2%)	42 (15.2%)		
Sex, male, n (%)	741 (59.1%)	320 (57.8%)	234 (55.3%)	187 (67.5%)	0.445	0.007
Living alone, n (%)	364 (29.0%)	157 (28.3%)	150 (35.5%)	57 (20.6%)	0.016	0.016
Missing, n (%)	4 (0.3%)	1 (0.2%)	2 (0.5%)	1 (0.4%)		
Highest educational level					<0.001	0.006
Primary school	254 (20.3%)	120 (21.7%)	96 (22.7%)	38 (13.7%)		
Secondary school	272 (21.7%)	128 (23.1%)	105 (24.8%)	39 (14.1%)		
Post-high school training	172 (13.7%)	96 (17.3%)	60 (14.2%)	16 (5.8%)		
College/university	173 (13.8%)	118 (21.3%)	41 (9.7%)	14 (5.1%)		
Missing, n (%)	383 (30.5%)	92 (16.6%)	121 (28.6%)	170 (61.4%)		
Pre-injury ASA-PS class, n (%)					0.034	<0.001
Healthy	256 (20.4%)	142 (25.6%)	78 (18.4%)	36 (13.0%)		
Mild systemic disease	659 (52.6%)	287 (51.8%)	234 (55.3%)	138 (49.8%)		
Severe systemic disease/threat to life	300 (23.9%)	118 (21.3%)	101 (23.9%)	81 (29.2%)		
Missing, n (%)	39 (3.1%)	7 (1.3%)	10 (2.4%)	22 (7.9%)		
Pre-injury physical conditions, n (%)					0.245	0.276
None	133 (10.6%)	66 (11.9%)	44 (10.4%)	23 (8.3%)		
1	275 (21.9%)	130 (23.5%)	91 (21.5%)	54 (19.5%)		
2	296 (23.6%)	140 (25.3%)	92 (21.7%)	64 (23.1%)		
3	236 (18.8%)	99 (17.9%)	78 (18.4%)	59 (21.3%)		
4 or more	299 (23.8%)	119 (21.5%)	115 (27.2%)	65 (23.5%)		
Missing, n (%)	15 (1.2%)	0 (0%)	3 (0.7%)	12 (4.3%)		
Pre-injury psychiatric condition, n (%)	164 (13.1%)	60 (10.8%)	63 (14.9%)	41 (14.8%)	0.034	0.034
Missing, n (%)	47 (3.7%)	4 (0.7%)	18 (4.3%)	25 (9.0%)		
Prior TBI, n (%)	107 (8.5%)	50 (9.0%)	40 (9.5%)	17 (6.1%)	0.694	0.444
Missing, n (%)	122 (9.7%)	29 (5.2%)	35 (8.3%)	58 (20.9%)		
Intracranial traumatic abnormality, n (%)	647 (51.6%)	287 (51.8%)	185 (43.7%)	175 (63.2%)	0.110	<0.001
Missing, n (%)	196 (15.6%)	56 (10.1%)	68 (16.1%)	72 (26.0%)		

Table 1. Continued.

Variable	Total population	Responders*	Non-responders	Deceased	Responders vs. Non-responders	Responders vs. deceased
Anticoagulants and platelets aggregation inhibitor use, n (%)					0.741	<0.001
Anticoagulant	225 (17.9%)	87 (15.7%)	77 (18.2%)	61 (22.0%)		
Platelet aggregation inhibitor	325 (25.9%)	148 (26.7%)	96 (22.7%)	81 (29.2%)		
Both	25 (2.0%)	8 (1.4%)	8 (1.9%)	9 (3.2%)		
No	618 (49.3%)	303 (54.7%)	216 (51.1%)	99 (35.7%)		
Missing, n (%)		8 (1.4%)	26 (6.1%)	27 (9.7%)		
Beta blocker use, n (%)	314 (25.0%)	131 (23.6%)	105 (24.8%)	78 (28.2%)	0.362	<0.001
Missing, n (%)	93 (7.4%)	16 (2.9%)	34 (8.0%)	43 (15.5%)		
Care pathway, n (%)					0.015	<0.001
ER	209 (16.7%)	127 (22.9%)	76 (18.0%)	6 (2.2%)		
Hospital ward	493 (39.3%)	254 (45.8%)	176 (42.3%)	60 (21.7%)		
ICU	552 (44.0%)	173 (31.2%)	168 (39.7%)	211 (76.2%)		
TBI Severity, n (%)					0.005	<0.001
Mild (GCS 13-15)	862 (68.7%)	468 (84.5%)	326 (78.9%)	68 (24.5%)		
Moderate/Severe (GCS 3-12)	355 (28.3%)	77 (13.9%)	87 (21.1%)	191 (69.0%)		
Missing, n (%)	37 (3.0%)	9 (1.6%)	10 (2.4%)	18 (6.5%)		
Injury mechanism					0.080	0.729
Falls	837 (66.7%)	358 (64.6%)	302 (71.4%)	177 (63.9%)		
Road traffic accident	284 (22.6%)	136 (24.5%)	83 (19.6%)	65 (23.5%)		
Other	133 (10.6%)	60 (10.8%)	38 (9.0%)	38 (9.0%)		
ISS, median (IQR)	16 (9-25)	13 (8-21)	13 (8-25)	26 (20-43)	0.079	<0.001

IQR: inter quartile range, ASA-PS class: American Society of Anesthesiologists Physical Status classification, TBI: Traumatic Brain Injury, GCS = Glasgow Coma Scale, ISS= Injury Severity Score, MVA: motor vehicle accident

*patients who completed at least one questionnaire (SF-12v2, QOLIBRI-OS, PCL-5, PHQ-9, GAD-7) at six months post-injury

[a] response vs non-response

[b] response vs deceased

Health care utilization of older patients after TBI

Of 1254 patients, 84% (1046) were admitted to a hospital ward and/or ICU. (**Table 2)**. There were 566 (45%) patients admitted to an ICU with mean LOS of 9.0 (SD=10.5) days. Discharge to an in-patient rehabilitation unit occurred in 22% of patients after mild TBI and in 61% of patients after moderate/severe TBI. About half of patients age 65-74 years (49%) and age 75-84 years (48%) were admitted to an ICU with a mean of respectively 10 (SD=11) and 8 (SD=10) days and 20% of persons aged ≥85 years were admitted to an ICU with a mean of 6 days (SD=6). Of males, 51% were admitted to an ICU with the LOS of 10 days (SD=11) and of females, 37% with a LOS of 8 days (SD=9). Of patients who survived discharge (n=1056), 30% of older adults received in-patient rehabilitation care and 12% received out-patient rehabilitation care. Of patients after mild TBI, 22% and of patients after moderate/severe TBI, 61% received in-patient rehabilitation care in the first six months after injury

Table 2. Hospital admission and in- and out-patient rehabilitation services for older adults in CENTER-TBI study.

	Ward		ICU		six-month in-patient rehabilitation[a]	six-month out-patient rehabilitation[a]
	Patients admitted to a ward, N (%)[b]	Mean number of days (SD)*	Patients admitted to an ICU, N (%)[c]	Mean number of days (SD)*	N (%)[d]	N (%)[e]
Total	817 (65.4)	9.6 (15.0)	566 (45.3)	9.0 (10.5)	285 (29.3)	117 (12.2)
Age						
65-74 years	408 (64.7)	9.3 (11.4)	306 (48.5)	10.0 (10.9)	139 (26.4)	73 (14.0)
75-84 years	322 (67.2)	10.4 (19.0)	231 (48.2)	8.2 (10.1)	124 (35.3)	42 (12.1)
≥85 years	87 (62.6)	8.0 (12.0)	29 (20.9)	5.7 (6.1)	22 (23.2)	2 (2.2)
Sex						
Male	490 (66.4)	10.2 (13.9)	375 (50.8)	9.8 (10.9)	165 (29.4)	61 (10.9)
Female	327 (64.0)	8.6 (16.4)	191 (37.4)	7.5 (9.4)	120 (29.3)	56 (14.0)
Injury mechanism						
Fall	547 (65.6)	8.6 (15.1)	319 (38.2)	8.2 (10.0)	174 (26.4)	70 (10.8)
Road traffic incident	199 (70.3)	10.8 (11.7)	171 (60.4)	9.4 (10.5)	84 (38.9)	39 (18.1)
Other	71 (53.8)	13.4 (20.5)	76 (57.6)	11.5 (11.9)	27 (27.6)	8 (8.2)
Pre-injury ASA-PS class, n (%)						
Healthy	182 (71.7)	8.0 (10.6)	114 (44.9)	10.0 (11.8)	51 (23.4)	38 (17.5)
Mild systemic disease	429 (65.1)	9.6 (13.0)	292 (44.3)	8.8 (10.3)	155 (29.8)	57 (11.1)
Severe systemic disease/threat to life	192 (64.6)	10.5 (21.0)	127 (42.8)	8.8 (10.0)	70 (32.3)	22 (10.4)
TBI Severity, n (%)						
Mild (GCS 13-15)	858 (70.2)	8.3 (15.0)	222 (25.9)	7.6 (10.2)	170 (22.0)	86 (11.3)
Moderate/Severe (GCS 3-12)	197 (55.6)	13.4 (14.4)	318 (89.8)	9.9 (10.4)	112 (60.9)	29 (15.8)

*Length of hospital stay for those patients admitted to a ward/ICU
[a] Based on patients who survived discharge (n=1056)[b]5 (0.4%) missing values [c]5 (0.4%) missing values
[d]84 (8.0%) missing values [e]97 (9.2%) missing values

Outcomes of older patients after TBI

Of 722 patients with mild TBI, 9% died within six months compared to 60% of 320 patients with moderate/severe TBI (**Table 3**). Around 30% of patients with mild and 83% of patients with moderate/severe TBI had a poor functional outcome (GOSE ≤ 4).

Of patients with mild or moderate/severe TBI, respectively 41% and 42% had impaired physical HRQoL scores and 22% and 21% had impaired mental HRQoL scores. Elevated symptoms of PTSD, depression and anxiety were present in respectively 5%, 15% and 9% of patients with mild TBI and 6%, 11% and 9% of patients after moderate/severe TBI.

Table 3. Distribution of outcome variables for the total population of older adults after TBI and by TBI severity.

	Total	TBI severity*		p-value
		Mild	Moderate/ Severe	
Functional outcome at 6 months				
GOSE	**n=1073/1254**	***n=722/862***	***n=320/355***	<0.001
1 (dead)	277 (25.8%)	68 (9.4%)	191 (59.7%)	
3 (vegetative state/lower severe disability)	120 (11.2%)	65 (9.0%)	54 (16.9%)	
4 (upper severe disability)	56 (5.2%)	43 (6.0%)	12 (3.8%)	
5 (lower moderate disability)	47 (4.4%)	37 (5.1%)	10 (2.8%)	
6 (upper moderate disability)	57 (5.3%)	48 (5.6%)	9 (2.8%)	
7 (lower good recovery)	175 (16.3%)	147 (20.4%)	26 (8.1%)	
8 (upper good recovery)	341 (27.2%)	314 (43.5%)	18 (5.6%)	
HRQoL at 6 months				
SF-12v2 PCS	***(n=541/1254)***	***n=461/862***	***n=71/355***	
Impaired SF-12v2 physical score (<40)	218 (40.3%)	187 (40.6%)	30 (42.3%)	0.787
Median (IQR)	43.3 (34.1-50.5)	43.3 (34.6-50.8)	42.3 (31.8-49.8)	0.315
SF-12v2 MCS	***(n=541/1254)***	***n=461/862***	***n=71/355***	
Impaired SF-12v2 mental score (<40)	117 (21.6%)	102 (22.1%)	15 (21.1%)	0.850
Median (IQR)	50.8 (42.1-58.3)	51.2 (42.0-58.3)	49.3 (41.8-58.2)	0.680
QOLIBRI-OS	***(n=544/1254)***	***n=460/862***	***n=75/355***	
Impaired QOLIBRI-OS (<52)	121 (22.2%)	102 (22.2%)	18 (24.0%)	0.725
Median (IQR)	71.0 (54.0-79.0)	71.0 (54.0-82.0)	67 (54.0-79.0)	0.253
Mental health symptoms at 6 months				
PTSD, PCL-5	***(n=515/1254)***	***n=439/862***	***n=68/355***	
PTSD, PCL-5 ≥33	24 (4.7%)	20 (4.6%)	4 (5.9%)	0.632
Median (IQR)	5.0 (1.0-12.0)	5.0 (2.0-12.0)	6.0 (1.0-13.8)	0.406
Depression, PHQ-9	***(n=519/1254)***	***n=439/862***	***n=71/355***	0.077
None	331 (63.8%)	283 (64.5%)	40 (56.3%)	
Mild	114 (22.0%)	90 (20.5%)	23 (32.4%)	
Moderate/Severe	74 (14.3%)	66 (15.0%)	8 (11.3%)	
Median (IQR)	3.0 (1.0-7.0)	3.0 (1.0-6.0)	3.0 (1.0-7.0)	0.650
Anxiety, GAD-7	***(n=515/1254)***	***n=436/862***	***n=70/355***	0.944
None	392 (76.1%)	329 (75.5%)	54 (77.1%)	
Mild	79 (15.3%)	69 (15.8%)	10 (14.3%)	
Moderate/Severe	44 (8.5%)	38 (8.7%)	6 (8.6%)	
Median (IQR)	1.0 (0.0-4.0)	1.0 (0.0-4.0)	1.0 (0.0-4.0)	0.897

Cut-off values: SF-12v2 PCS and SF-12v2 MCS < 40, QOLIBRI < 52, PCL-5 ≥ 33, PHQ-9 ≥ 10, GAD-7 ≥ 10; SF-12 PCS = Short Form (12) Health Survey (physical component score); SF-MCS = Short Form (12) Health Survey (mental component score); QOLIBRI = Quality of Life after Brain Injury
*Glasgow Coma Score (GCS) is missing for 37 (3.0%) patient

Of patients aged 65-74 years, 75-85, and ≥85 years, respectively 19%, 31% and 37% died within six months post-injury. For all outcomes, the differences in outcome between 65-74 years and ≥85 years were statistically significant, with lower GOSE and HRQoL (SF-12v2 PCS, SF-12v2 MCS, QOLIBRI-OS) scores and higher PCL-5, PHQ-9, and GAD-7 scores for patients aged 85 years and older (Supplementary Figure

1; post-hoc pairwise comparison: **Supplementary Table 2**). The largest difference by age was observed for SF-12v2 PCS with median scores of 46.7 (37.1-52.4) for patients aged 65-74 years, 40.2 (30.6-46.7) for patients aged 75-84 years and 34.7 (24.9-43.6) for patients ≥85 years (p<0.001).

Determinants of outcomes of older patients after TBI

For six-month outcomes, missing values varied from 14% for GOSE to 57%-59% for other outcomes (**Supplementary Table 3**)**.** In multi-variable analyses, lower educational level and pre-injury psychiatric conditions were associated with worse functional outcome, HRQoL and psychological problems (**Table 4, univariable: Supplementary Tables 4-6)**. Severe systemic disease was associated with all outcomes except for GAD-7 scores. Higher age was associated with poorer functional outcome (OR (25%:75%) = 0.54, $CI_{95\%}$ [0.44, 0.67] for ordinal GOSE), and SF-12v2 PCS (B (25%:75%) = -3.22, $CI_{95\%}$ [-4.83,-1.62]) but was not significantly associated with other outcomes (Table 4) . Female sex was associated with lower SF-12v2 PCS (B = -2.03, $CI_{95\%}$ [-3.84,-0.01]) and SF-12v2 MCS (B = -2.11, $CI_{95\%}$ [4.05, -0.18]) and higher PHQ-9 (B = 1.12, $CI_{95\%}$ [0.21,2.04]) and GAD-7 (B = 0.99, $CI_{95\%}$ [0.25,1.72]) scores (Table 4). Patients with a higher GCS were more likely to have a higher GOSE (OR (11:15) 2.31, $CI_{95\%}$ [1.95,2.73] for ordinal GOSE; Table 4). There was no significant association between living situation, prior TBI and beta-blocker use with any of the outcomes. The c-statistic of the GOSE ordinal logistic regression model was 0.79. The R^2 for the linear regression models ranged from 0.08 to 0.19 (**Table 4**).

Table 4. Multivariable regression analyses: Odds ratios (OR) for global functional outcome (GOSE), and regression coefficients (B) for generic HRQoL (SF-12v2), disease-specific HRQoL (QOLIBRI-OS), and post-traumatic stress (PCL-5), depression (PHQ-9) and anxiety (GAD-7) symptoms.

	Global functional outcome *	Health-related quality of life *			Psychological symptoms**		
Predictor	**GOSE (1-8) (OR, CI 95%)**	**SF-12 PCS (B, CI 95%)**	**SF-12 MCS (B, CI 95%)**	**QOLIBRI-OS (B, CI 95%)**	**PCL-5 (B, CI 95%)**	**PHQ-9 (B, CI 95%)**	**GAD-7 (B, CI 95%)**
Age [1]	**0.54 [0.44;0.67]**	**-3.22 [-4.83;-1.62]**	-0.44 [-2.17;1.29]	-2.34 [-5.71;1.03]	-0.04 [-1.86;1.77]	0.42 [-0.39;1.23]	0.01 [-0.66;0.68]
Female sex	1.08 [0.84;1.39]	-2.03 [-3.84;-0.01]	-2.11 [-4.05;-0.18]	-3.15 [-6.88;0.59]	1.75 [-0.27;3.78]	1.12 [0.21;2.04]	**0.99 [0.25;1.72]**
High school vs. Primary school	1.18 [0.82;1.71]	2.50 [-0.01;5.01]	**3.69 [1.02;6.37]**	**7.74 [2.59;12.89]**	-3.41 [-6.19;-0.63]	**-1.86 [-3.17;-0.55]**	**-2.12 [-3.20;-1.04]**
Post-high school vs. Primary s.	1.18 [0.81;1.73]	0.96 [-1.65;3.56]	1.02 [-2.12;4.16]	2.49 [-3.66;8.64]	0.05 [-3.13;3.23]	-0.21 [-1.56;1.14]	-1.25 [-2.50;0.01]
College/University vs. Primary s.	1.49 [1.00;2.21]	**4.90 [2.32;7.47]**	3.33 [0.53;6.12]	**6.87 [1.03;12.71]**	-3.15 [-6.20;-0.11]	**-1.81 [-3.14;-0.47]**	**-1.84 [-3.09;-0.59]**
Living alone	1.15 [0.88;1.52]	-0.17 [-2.16;1.81]	-0.73 [-2.83;1.37]	-1.74 [-5.75;2.28]	-1.24 [-3.41;0.94]	0.33 [-0.65;1.31]	-0.65 [-1.44;0.14]
Mild disease vs. Healthy	0.75 [0.55;1.04]	-2.52 [-4.70;-0.35]	-2.51 [-4.82;-0.21]	-5.59 [-10.03;-1.14]	2.14 [-0.24;4.52]	0.77 [-0.30;1.84]	-0.22 [-1.08;0.64]
Severe disease vs. Healthy	**0.53 [0.36;0.79]**	**-5.30 [-8.16;-2.44]**	**-6.13 [-9.15;-3.10]**	**-15.9 [-21.66;-10.14]**	**4.14 [0.95;7.32]**	**2.06 [0.63;3.49]**	0.50 [-0.64;1.64]
Pre-injury psychiatric conditions	**0.54 [0.38;0.76]**	-3.19 [-5.98;-0.40]	**-7.73 [-10.70;-4.75]**	**-11.93 [-17.62;-6.25]**	**5.38 [2.25;8.52]**	**3.80 [2.37;5.23]**	**2.44 [1.29;3.58]**
Prior TBI	1.27 [0.82;1.98]	1.30 [-1.83;4.44]	2.93 [-0.37;6.23]	0.54 [-5.91;6.98]	-2.82 [-6.18;0.54]	-0.45 [-1.98;1.08]	-0.99 [-2.17;0.19]
Anticoagulants/PAI use	0.76 [0.57;1.00]	-2.26 [-4.25;-0.26]	1.48 [-0.64;3.60]	-0.65 [-4.68;3.38]	-0.18 [-2.39;2.03]	-0.02 [-1.02;0.97]	0.43 [-0.36;1.23]
Beta blocker use	0.80 [0.60;1.07)	-1.68 [-3.90;0.54]	0.73 [-1.57;3.04]	-0.39 [-4.85;4.07]	-0.95 [-3.34;1.44]	-0.49 [-1.59;0.60]	-0.31 [-1.18;0.55]
Intracranial abnormalities	**0.55 (0.42;0.72)**	-0.80 [-2.68;1.08]	0.33 [-1.67;2.33]	-3.99 [-7.81;-0.18]	-0.25 [-2.36;1.86]	0.37 [-0.59;1.33]	0.17 [-0.63;0.97]
Road traffic incident vs. Falls	0.97 [0.72;1.30]	-0.49 [-2.57;1.60]	-1.22 [-3.44;0.99]	-1.61 [-5.86;2.64]	2.20 [-0.11;4.51]	0.28 [-0.76;1.31]	0.32 [-0.52;1.15]
Other vs. Falls	0.81 [0.54;1.23]	-0.47 [-3.29;2.36]	-1.84 [-4.87;1.18]	-2.73 [-8.52;3.05]	3.22 [0.01;6.42]	0.43 [-1.01;1.88]	0.61 [-0.54;1.76]
Glasgow Coma Score (GCS) [1]	**2.31 [1.95;2.73]**	0.55 [-0.83;1.92]	-0.39 [-1.86;1.08]	2.45 [-0.31;5.20]	0.48 [-1.11;2.06]	-0.03 [-0.72;0.67]	0.15 [-0.43;0.73]
Injury severity score (ISS) [1]	**0.50 [0.41;0.60]**	-1.43 [-2.84;-0.01]	**-2.49 [-4.00;-0.99]**	-1.32 [-4.17;1.53]	**2.43 [0.85;4.01]**	0.71 [0.00;1.42]	0.52 [-0.04;1.08]
Measure of performance	C-statistic 0.79	Adjusted R^2 0.19	Adjusted R^2 0.12	Adjusted R^2 0.15	Adjusted R^2 0.08	Adjusted R^2 0.12	Adjusted R2 0.10

[1]Continuous predictors scaled by interquartile range that compares the 1st quartile and the 3rd quartile. * Higher score=better outcome. ** Higher score= worse outcome.
A p-value <0.05 and a p-value **<0.01**.
GAD-7 = Generalized Anxiety Disorder questionnaire; GOSE = Glasgow Outcome Scale—Extended; PAI=platelets aggregation inhibitor PCL-5 = Posttraumatic Stress Disorder Checklist; PHQ-9 = Patient Health Questionnaire; SF-12 PCS = Short Form (12) Health Survey (physical component score); SF-MCS = Short Form (12) Health Survey (mental component score); QOLIBRI = Quality of Life after Brain Injury

Discussion

We aimed to describe the health care utilization and six-month functional, physical, and mental health of patients aged 65 years and older after TBI. Approximately a third of the TBI patients, consisting mostly of moderate and severe TBI patients, received in-patient rehabilitation. Furthermore, the majority of patients reported remaining disability after 6 months, especially in the functional and physical domain. However, of patients who survived, a substantial number of older patients recovered fully or partially to pre-injury health. HRQoL and mental health symptoms were comparable between patients with mild or moderate/severe TBI. Age and measures of injury severity were primarily associated with functional outcome and physical HRQoL. Systemic disease, pre-injury psychiatric conditions, and lower educational level were predictors of functional impairment, lower HRQoL and mental health 6 months post-injury.

Notably, nearly half of all patients aged ≥ 65 years were admitted to an ICU. An explanation for this relatively high percentage could be inclusion of the entire spectrum of TBI severities and recruitment from large university hospitals and specialized trauma referral centres in the CENTER-TBI study [25]. The mortality rate in older adults (≥65 years) was more than three times as high compared to the younger TBI population (<65 years), which is supported by other studies which found that TBI-related deaths are more likely in older age groups [11,40,41]. The mortality rate was especially high after moderate/severe TBI (60%), which may be explained by complications, chronic disease, restricted surgical treatment, extra-cranial injuries or biological ageing [42].

The rehabilitation needs in the older TBI population are high and there is a high prevalence of unmet rehabilitation needs [43,44]. Our study showed that just over 60% of the patients after moderate/severe TBI and 22% of patients after mild TBI received inpatient rehabilitation. Previous research reported that older adults received less intensive rehabilitation services than younger patients [21]. However, multiple studies have shown that (aggressive) treatment and rehabilitation benefits older adults, resulting in functional gain and a higher change of being able to return home [45-47]. It is suggested that a presumed poor outcome in older adults leads to reduced management intensity, which subsequently leads to a higher mortality risk [48].

While the mortality and morbidity rates were high, nearly half of older adults with mild TBI still returned to pre-injury functioning and 20% of older adults after moderate/severe TBI did not report severe disability or death. Additionally, health-related quality of life and mental health symptoms were comparable between older patients with mild or moderate/severe TBI.

Impaired mental and disease specific HRQoL were seen in nearly a quarter of older patients, which is comparable to the general TBI population [25]. Impaired physical HRQoL were found in 40% of older TBI patients which is considerably higher than the 29% found in the general TBI population [25]. This could be explained by a higher occurrence of pre-existing comorbidities, a worse pre-injury functional status and physical frailty in older adults. In CENTER-TBI, older adults do not seem to have higher proportions of depression and anxiety than TBI adults in general [49]. This is consistent to previous studies, which found that older adults report less psychological distress than younger adults [14]. However, the proportion of patients with severe depression and anxiety symptoms is higher than in the general population without TBI [50,51]. These long-term impairments in a considerable proportion of older TBI patients underline the importance of appropriate follow-up and treatment of older patients with disability after TBI.

Research on outcome following TBI in older adults has predominantly focused on subgroups of TBI severity and functional outcome [14]. In CENTER-TBI, we found that age and injury characteristics were associated with lower functional outcome but were not significant predictors of mental HRQoL and psychological symptoms when controlled for other important factors. This indicates that older age alone is not sufficient when we want to predict and understand outcomes in older TBI patients, which is in line with previous research suggesting that measures of pre-injury functioning and frailty are more strongly associated with the outcome than the age [12]. One previous study on prognostic factors of poor recovery after TBI in older adults suggested that recovery may be associated more with psychosocial than with biomedical or injury factors [52]. Additionally, previous studies in the adult mild TBI population and the older adult general injury population, showed that those with pre-injury morbidity recovered more slowly [53,54], which is consistent with our findings. These results can eventually be used for targeted rehabilitation programs and prognostic models in order to improve patient outcome. Detailed assessment, inclusion of socio-economic characteristics and pre-injury physical and mental health factors would help to identify older adults with a higher risk of poor outcomes after TBI, who should be monitored and provided early interventions.

This study included a large data sample from multiple European countries in which long-term outcome after TBI in older adults were examined. A variety of both health outcomes and predictors were assessed, including medical history and pharmacotherapy. We also recognize several limitations of our study. First, there are several unmeasured factors including pre- and post-injury frailty, pre-injury HRQoL, mental health at the time of injury, social support and type and frequency of interventions which could be of importance for prediction of outcome in the older population. Moreover, it could explain why the models for mental health domain do not have a high proportion of

explained variance.

Second, for several outcome measures at six-months the proportion of missing values was high. Non-responders were older, reported higher pre-injury morbidity, ISS, and GCS and were more likely to be admitted to the ICU. Non-response could therefore be related to the inability to complete the questionnaire due to generally worse pre-injury health, cognitive impairment, or language difficulties. In addition, patients with severe pre-existing neurological disorder were not included.[25] Thus, a subgroup of older patients with profound disabilities was potentially underrepresented, which may be particularly relevant for the moderate/ severe group with a very low response rate. This highlights the importance of adapting the assessments to older patients and patients with disabilities to facilitate their response. Third, this study only included patients with an indication for CT and who presented to university hospitals and specialized trauma centers, which could limit generalizability to older patients with minor TBIs. Finally, the recruitment of patients was not consecutive but influenced by logistic considerations, which might introduced some bias [25].

Conclusions

With an ageing population, the number of older patients who sustain TBI through incidental falls or road traffic incidents will increase, resulting in rising health care utilization and costs, functional impairment, and physical and mental health problems among older adults. There is a need to study TBI in older adults and to develop consensus on management guidelines for this population. This study reported a high mortality rate and a substantial rate of impairments and disabilities following TBI, especially in the functional and physical domain. Nonetheless, a substantial number of older patients recovers to pre-injury health or reports symptoms rates comparable to the general TBI population. The older patients who survive after TBI should receive the treatment and rehabilitation care to help them regain pre-injury health. Moreover, our study found that patient characteristics, including pre-injury systemic disease, pre-injury psychiatric conditions, and lower educational level are important predictors of poorer outcomes. These results underline the importance of a health care assessment in which these predictors are measured. An important overall implication for management of TBI patients in the acute stage is that there should not be pessimism about outcomes in older adults who survive, among which a substantial number fully or partially return to their preinjury functioning.

Supplementary Material

Supplementary material is available at: https://www.sciencedirect.com/science/article/pii/S0020138322003291?via%3Dihub

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Chapter 5

Treatment for posttraumatic stress disorder in patients with a history of traumatic brain injury: A systematic review

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Abstract

Posttraumatic stress disorder (PTSD) frequently co-occurs with traumatic brain injury (TBI). We conducted a systematic review to evaluate the appropriateness and effectiveness of treatments for PTSD in adult patients with a history of TBI. We searched for longitudinal studies aimed at treatments for PTSD patients who sustained a TBI, published in English between 1980 and February 2019. Twenty-three studies were found eligible, and 26 case studies were included for a separate overview. The quality of eligible studies was assessed using the Research Triangle Institute item bank. The majority of studies included types of cognitive-behavioral therapy (CBT) in male service members and veterans with a history of mild TBI in the United States. Studies using prolonged exposure (PE), cognitive-processing therapy (CPT) or other types of CBT, usually in combination with additional treatments, showed favorable outcomes. A smaller number of studies described complementary and novel therapies, which showed promising results. Overall, the quality of studies was considered low. We concluded that CBT seem appropriate for the patient population with history of TBI. The evidence is less strong for other therapies. We recommend controlled studies of PTSD treatments including more female patients and those with a history of moderate to severe TBIs in civilian and military populations.

Keywords: posttraumatic stress disorder; traumatic brain injury; psychotherapy; treatment effectiveness; systematic review.

Introduction

Posttraumatic stress disorder (PTSD) can develop after exposure to a traumatic event, and in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)[1] it is characterized by trauma-related intrusion and avoidance responses, changes in cognition, mood, arousal and reactivity, and functional impairment. The lifetime prevalence of PTSD varies between countries and populations. For the general population it typically ranges from 0.5 to 10%, however, higher rates have been found in post-conflict areas and in service members and veterans.[2, 3] PTSD can have a strong negative impact on overall functioning due to elevated risk of other health conditions,[4, 5] lower work productivity[6] and impaired social relationships.[7]

Clinical practice guidelines[8] recommend or suggest several therapies for the treatment of PTSD, with the strongest support for cognitive- behavioral therapy (CBT), such as trauma-focused psychotherapy. Nevertheless, previous research has shown that PTSD treatments have a significant dropout rate of approximately 20%[9, 10] and high nonresponse rates of 20 to 60% of patients.[9, 11] Thus, it is questionable whether all groups of patients can equally benefit from PTSD treatments.[12, 13]

One of the characteristics that could potentially influence the course of PTSD treatment, is a history of traumatic brain injury (TBI). TBI can be defined as "an alteration in brain function or other evidence of brain pathology, caused by an external force".[14] Approximately 70 to 80% of TBI cases can be classified as mild TBI,[15] which can be defined by "loss of consciousness (LOC) of approximately 30 minutes or less; an initial Glasgow Coma Scale (GCS) of 13–15 (after 30 minutes); and posttraumatic amnesia (PTA) not greater than 24 hours".[16] The remainder of cases, which are characterized by longer LOC and/or PTA and lower GCS, represent moderate and severe injuries. Moderate and severe TBIs can be associated with post-injury neurocognitive deficits lasting six months or longer, while in most cases mild TBIs result in a complete recovery.[17]

Nevertheless, 5 to 30% of patients who sustained a mild TBI experience persistent cognitive, emotional and physical symptoms, called post concussive symptoms (PCS), and do not fully return to their pre-injury level of functioning.[18-21]

The relationship between TBI and PTSD is strong and bidirectional, and still largely controversial.[22, 23] Individuals with a history of TBI have a higher prevalence of PTSD compared to the general population in both civilian[24-26] and in military samples.[27-30] TBI seems to be a risk factor for developing PTSD,[31] while pre-injury and post-injury PTSD predict persistent symptoms following TBI.[32] Moreover, symptoms of TBI and PTSD can overlap and both groups of patients can demonstrate symptoms such as

irritability, depressed mood and sleep problems, as well as memory and concentration difficulties.[33, 34] Notably, patients with PTSD alone can show long-term impairments across different domains of neurocognitive functioning.[35] Furthermore, the symptoms can also mutually aggravate each other.[36, 37]As a result, individuals with both conditions can exhibit poorer neuropsychological and overall functioning and higher PTSD and PCS severity, compared to individuals with only one condition.[26, 38-40]

Some clinicians have concerns that deficits associated with TBI and/or PTSD can influence the effectiveness of evidence-based PTSD treatments. It has been suggested that cognitive impairments, PTA, problems with emotion regulation and impulse control, higher symptom severity, and experiencing physical pain may limit patients' ability to engage in PTSD treatments, or benefit from them.[33, 41-43] For instance, some clinical providers emphasize cognitive limitations that they attribute to TBI as a reason of not using CPT for treating PTSD. [44] Thus, it is of high clinical interest to investigate whether recommended PTSD treatments are appropriate and effective in this population. Moreover, the effectiveness of other available treatments aimed at relieving PTSD is still largely unknown for the population with a history of TBI, such as complementary and alternative treatments that accompany or replace conventional therapies.

Neurological conditions and brain injuries are often represented as exclusion criteria in PTSD trials[45, 46] and, to date, only a few systematic reviews of treatments for PTSD in patients who sustained TBI have been conducted.[25, 47] The latest systematic review investigated studies on evidence-based treatments for individuals with mild TBI and PTSD published until 2009.[48]Although the authors did not find any eligible studies, they did discuss two case reports[49, 50] and a study on prevention of PTSD in patients with acute stress disorder (ASD) and TBI by Bryant, Moulds, Guthrie, and Nixon.[51] In addition, a literature review from Tanev et al.[42] focused on psychotherapy and pharmacotherapy in patients with comorbid PTSD and TBI. Based on three uncontrolled studies in military samples[52-54] and the study by Bryant et al.,[51] they concluded that CBT might be an effective PTSD treatment in patients who sustained a TBI, but that the impact of TBI "had not been elucidated" yet. Vasterling, Jacob and Rasmunsson[40] recently reviewed several successful applications of psychosocial interventions in patients with PTSD and TBI. [35, 51, 55-59] They suggested no barriers in using recommended CBT treatments in the context of TBI, but emphasized that the research is still in its early stages.

In summary, the effectiveness and appropriateness of PTSD treatments in patients who sustained TBI are unclear. It is therefore of great relevance to systematically gather the most recent evidence on PTSD treatments in individuals with a history of TBI and to utilize this to report on the various available treatments for the entire spectrum of TBI severity. Thus, the aims of the current systematic review are the following: 1) to provide

an overview of treatments for PTSD in adult patients with a history of TBI; 2) to evaluate the appropriateness of PTSD treatments, defined by treatment attendance, dropout and adverse effects, and effectiveness, defined by reductions in PTSD symptoms; and 3) to explore the impact of methodological quality and assessment methods on obtained treatment outcomes.

Methods

Search Strategy

To identify the maximum number of relevant studies, an extensive search strategy was developed in consultation with a medical librarian (Appendix A), encompassing treatments aimed at PTSD and broader categories of related mental disorders (e.g. anxiety, depression and ASD). The literature search was conducted via databases EMBASE, Medline Ovid, Web of science, Cochrane CENTRAL, PsycINFO Ovid and Google scholar and was restricted to papers involving human participants published in the English language until February 20th 2018. To include the most recent articles, a narrower version of this search, encompassing treatments for PTSD (Appendix A), was conducted for the period until February 21st 2019. Additionally, to encompass gray literature, such as unpublished articles, theses and reports, Google scholar and a database of clinical trials (clinicaltrials.gov) were searched.

Study Selection

Study design. The review included longitudinal studies (e.g. randomized controlled trials (RCTs), prospective cohort studies, retrospective cohort studies, case-control studies, pre-post studies) involving a treatment aimed at PTSD. Reviews, editorials, and cross-sectional studies were excluded. Descriptive studies of one or more patients were included for a separate overview. These case studies, reports and series aimed to complement the findings, because only a small number of eligible studies was expected based on previous reviews.[25, 42]

Participants. Studies were included if they involved adult (16+) civilian or military participants diagnosed with both TBI and PTSD and provided with treatment for PTSD, or diagnosed with TBI and provided with preventive intervention and/or early treatment for PTSD. Diagnosis of PTSD had to have been confirmed by a clinician, with a structured diagnostic interview, such as Clinician-Administered PTSD Scale for DSM (CAPS)[60, 61] and Structured Clinical Interview; PTSD Module (SCID PTSD Module)[62] or a medical record. There were no restrictions on TBI diagnosis or severity. TBI and PTSD could originate from the same or from a different traumatic event.

Treatment. The review included all types of interventions aimed at treatment of PTSD or PTSD symptoms: psychological, pharmacological, complementary, alternative and novel medical therapies. Early treatment was also included if an intervention was provided with the aim of preventing PTSD in participants who were diagnosed with ASD or considered at risk of long-term posttraumatic disturbances.

Outcome. Studies were selected when they measured at least one of the following outcomes after treatment aimed at PTSD: 1) changes in PTSD symptoms measured by a valid self-report e.g. Impact of Event Scale (IES)[63], PTSD Checklist for DSM (PCL),[64, 65] PTSD Symptom Scale Self-Report Version (PSS-SR)[66] or clinician-rated instrument (e.g. CAPS, SCID, etc.); 2) changes in diagnosis of PTSD in accordance with DSM or International Classification of Diseases (ICD) classification systems; 3) treatment adherence and retention in PTSD treatment; and lastly, 4) side effects and harms associated with PTSD treatment. In studies examining a change in PTSD symptoms, pre- and post- treatment level of these symptoms had to be clearly stated and statistically compared. The inclusion of case reports was not restricted to use of quantitative measures of PTSD symptoms.

Year of publication. Studies were included if they were published after 1980, when PTSD was officially included in DSM.

Multiple publications. When several publications used the same or overlapping data, a study was selected according to the following criteria: 1) largest sample and 2) largest percentage of patients who sustained a TBI and had PTSD. When the overlapping study contained any new outcome(s), only the new information was extracted and included in the results.

Data Extraction and Risk of Bias Assessment

The first reviewer (AM) screened all citations by titles and abstracts and subsequently screened the selected articles by full-text. The second reviewer (IRH) first screened a sample of titles and abstracts. Agreement in screening a sample of studies was above 80%;[67] therefore the second reviewer screened a random 10% of titles and abstracts, and a random 10% of full-texts. In case of discrepancies and doubts, a third reviewer (MC) was consulted. Moreover, reference lists of included articles and detected literature reviews were inspected to identify potentially missed relevant articles.

Data extraction included information on study design; setting; sample size; population; inclusion and exclusion criteria; TBI characteristics (definition, severity, mechanism, number, timing and diagnosis), PTSD characteristics (diagnosis, type, timing); comorbid psychopathology; treatment characteristics (type, dose, modifications for TBI,

concurrent therapies), PTSD-related and other outcomes; and attrition rates. Analyses for baseline differences, PTSD and other main outcomes, and associated effects were also extracted. Data extraction was performed by one reviewer (AM) and checked by a second reviewer (IRH).

Risk of bias was assessed using the Research Triangle Institute (RTI) item bank[68] by both reviewers and differences were discussed until consensus was reached. The instrument was selected because of its applicability for assessing methodological issues of different types of study designs, including the pre-post study without a comparison group, which prevailed in this review. Moreover, it includes an assessment of the validity of relevant domains, namely selection, information, performance, reporting, detection and attrition bias. For this review, 23 items were considered applicable (Appendix B). A domain was rated as low risk when all associated items were considered low risk of bias, as a moderate risk when up to 50% of corresponding items were assessed as having risk of bias, and a high risk if more than 50% of items were assessed as high or unknown risk of bias.[34]

Results

Literature Search

The literature search resulted in the detection of 9246 unique articles until February 2018 and additional 300 unique articles until February 2019 (Figure 1). They were screened by title and abstract, and subsequently, 439 publications were screened by full-text. The main reasons for excluding articles for full-text screening were involving patients who did not fully meet the diagnosis of PTSD or TBI (n=229), or an irrelevant study design or type of article (n=115). Some studies met most of the criteria, but were still excluded for the following reasons: treatments aimed at TBI/PCS and not at PTSD (n=6); analysis which was only focused on prediction of outcome by TBI status without stating and comparing pre- and post- treatment results in patients with history of TBI (n=4); subsample with TBI/PTSD not clearly separated from the complete sample (n=6) (Appendix C). Five articles were excluded as multiple publications from the articles which completely met the inclusion criteria. Therefore, the review was based on a total of 22 publications (23 studies; Figure 1). Furthermore, a complementary overview consisted of 20 publications (26 case studies/reports) describing a treatment outcome in a single patient.

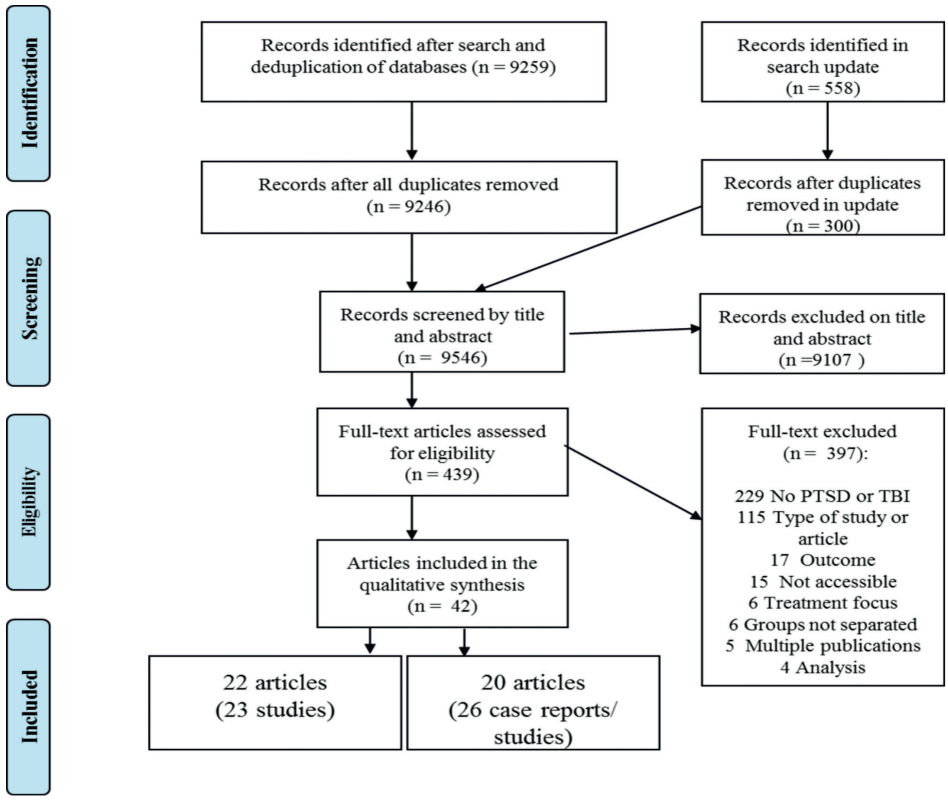

Figure 1. Prisma Flow Diagram (Moher, Liberati, Tetzlaff, & Altman, 2009).

Study Characteristics

Study characteristics of the included 23 studies from 22 publications are presented in Table 1. The majority of studies were conducted in the United States (US) (n=21) and two in Australia.[51, 69] All but two studies were carried out in samples of service members and veterans (n=21) in military/veteran affairs (VA) medical centers, whereas the two Australian studies were performed in hospitals with civilian samples. Four included studies[51, 69-71] were RCTs . Single arm pre-post studies represented the most common study design (n=12).

Participant characteristics. One study included a majority of females,[51] while in all other studies which reported sex, males were either overrepresented (n=10) or the only participants (n=11).

TBI characteristics. Studies involved exclusively (n=7) or predominantly (n= 11) mild TBI; and in the remainder of studies the severity was unclear. If reported, TBI was sustained at least 9-12 months or more prior to the treatment (n=11). Studies aimed

at PTSD prevention included patients within the first two[51] or four[69] weeks following trauma. History of TBI was typically determined based on military medical records or screening, and confirmed by a clinical assessment (n=15). In the remaining studies, diagnosis relied on hospital referrals (n=2); solely self-report or a screening instrument, or the source was unclear (n=6). Six studies described neurocognitive functioning or assessed PCS in addition to TBI status. [53, 70-74]

PTSD characteristics. Initial PTSD diagnosis was based on CAPS (n=17), or confirmed by a clinician/ hospital and a standardized questionnaire such as PCL (n= 5) and PSS (n=1). Trauma type was commonly unspecified. When explicitly stated, the highest share of service members and veterans was diagnosed with a combat-related PTSD (n=6), and a smaller percentage experienced other types of trauma, e.g. sexual or physical assault. Psychiatric comorbidities were reported in the majority of samples (n=14), which mostly included depression and history of suicidality.

Treatment. Types of treatment are listed in Table 1. CBT (n=2), and specific types of CBT, PE (n=6) and/or CPT (n=7), were the most commonly reported. One study described a type of exposure therapy called Trauma Management Therapy (TMT), which combines virtual reality and in vivo exposures. For some therapies, it was clear that they were either part of a larger intervention that included various therapies, such as cognitive and speech rehabilitation and psychoeducation (n= 5), or involved some modifications to reduce the impact of deficits associated with TBI and/or PTSD, like memory enhancing-strategies and compensatory devices (n=3). Concurrent pharmacotherapy was reported in ten studies.

Table 1. Characteristics of included studies presented by type of treatment.

First author; Country, Setting	Study Design/ Groups	Inclusion (Incl.)/ Exclusion (Excl.) criteria	TBI diagnosis	Pre-treatment; Post-treatment sample	Patients: population, % male, M age (SD), TBI severity	Primary treatment -Dosage
Types of cognitive and/or behavioral therapies (CBT)						
Browne et al., 2013 Australia, hospital	RCT: Usual care (UC) vs. Multidisciplinary Intervention (MI)	**Incl.**: 18–80 yo, within 4 weeks post- TBI, admitted for > 24hours. **Excl.**: moderate to severe TBI; current suicidality or intoxication.	hospital referral	n=142 (MI=69, UC=73); 1 mo: MI=33; 3 mos: MI=36; 6 mos: MI=31, UC=35	Civilian (mostly MVA); **MI** 74% male, M=38 (13.3); **UC** = 75% male; M=36 (14.6); Mild 100%	MI (incl. trauma- focused and CBT) -individually tailored
Bryant et al., 2003 Australia, hospital	RCT: CBT vs. Supportive counselling (SC)	**Incl.:** 18- 60 yo, MVA or nonsexual assaults within 2 weeks; Acute Stress Disorder; English proficiency; mild TBI.	hospital referral	n=24: n=24	Civilian; 34% male CBT & SC; **CBT** M=29 (13.9); **SC** M=33 (14.4); Mild 100%	CBT (incl. exposure) vs. SC -Individual, 5 sessions x 90 min (8 sessions), 5 wks
Davis et al., 2013 US, VA medical center (outpatient)	Retrospective cohort - TBI status cross-sectionally (with/ without TBI) - retrospective chart review	**Incl.:** OEF/OIF veterans with combat-related PTSD, outpatient program, initiated CPT. **Excl.:** ongoing treatment, subthreshold PTSD, moderate/ severe TBI.	VA medical record / self-report	n=136 (PTSD+ TBI=44)	Veterans; **PTSD** M=30 (7.6); **PTSD+ TBI** M= 30 (8.2); Mild 100%	CPT - Individual, 12 sessions (or less if sign. symptom reduction)
Gros et al., 2017 US, VA medical center (outpatient)	Pre-post study - TBI status cross-sectionally (with/ without TBI)	**Incl.:** veteran, reservist, or National Guard, 18– 65 yo, current SUD (DSM-IV) and PTSD; English proficiency. **Excl.:** psychosis [1], current suicidality or homicidality; eating /dissociative identity disorder; ongoing PTSD or SUD treatment; severe cognitive impairment.	screening (SAFE-TBI)	n=51 (PTSD+ TBI=30); n=51	Veterans; **PTSD** 86% male, M= 39 (10.4); **PTSD+ TBI** 97% male, M = 41 (11.1); Mild 93% to moderate-severe	PE+ relapse prevention - Individual, 12 wks x 90-min sessions
Jak et al., 2019 US, VA medical center	RCT (CPT vs. CPT enhanced with Cognitive Symptom Management and Rehabilitation Therapy (CogSMART)	**Incl.:** written consent, OEF/OIF veterans, PTSD, mild to moderate TBI, cognitive complaints; none or stable psychopharmacology. **Excl.**: SUD, suicidality, psychosis, dementia, non- English speaking, other interventions, prior sessions.	medical record and WARCAT	n= 100 (CPT=49, SMART CPT=50); PT: CPT=23; SMART CPT=27; 3 mos: CPT=16, SMART CPT=22	Veterans, **CPT** 88% male, M=34 (7.3); **SMART-CPT** 90% male, M=35 (8.5); Mild 94% to moderate	CPT, SMART CPT -Individual, 12 wks x 60-75 min sessions

Ragsdale & Voss Horrell, 2016 US, VA medical center (outpatient)	Pre-post - TBI status cross-sectionally (with/ without TBI)	**Incl.:** veterans with PTSD receiving individual CPT or PE.	screening and neuropsychological evaluation, TBI designation	n=41 (PTSD+TBI=19; CPT=20, PE=21); n=41	Veterans; 87.8% male; M=33 (8.2), range = 23–57); severity unknown	CPT or PE -CPT 12 sessions, PE 10–15
Ragsdale et al., 2018; US, VA medical center (outpatient)	Retrospective cohort – TBI status cross-sectionally (with/ without TBI)	**Incl:** OIF/OEF/OND veterans with combat-related PTSD participating in a trial	self-report and telephone interview with TBI criteria (VA/DoD)	n=88 (PTSD = 43; PTSD+TBI = 45)	Veterans, **PTSD** 93% male, M=39 (9.7); **PTSD + TBI** 96% male, M=36 (8.7); Severity unknown	TMT -14 individual and group sessions (or less if not necessary) x 90 min
Speicher et al., 2014; US, VA Clinic (residential)	Uncontrolled pre-post - retrospective chart review	**Incl.:** male veterans, PTSD, history of TBI; received occupational therapy and CPT. **Excl.:** current SUD; unmanaged psychosis[1]; serious medical condition; suicidality or homicidality (intent).	medical record and neuropsychological interview	n=26; n=26.	Veterans; 100% male; M=39 (11.9); Mild (81%) to severe	CPT -14 individual sessions and 14 group sessions x 60-90 min
Sripada et al., 2013 (Study 1) VA medical center (outpatient)	Observational cohort - TBI status cross-sectionally (with/ without) - retrospective chart review	**Incl.:** all patients with PTSD and PE treatment. **Excl.:** no criteria in place.	TBI designation in the patient record: positive screen and TBI consultation; service connected for TBI/PCS, or current TBI-related issues	n=51 (TBI=11); n=51 (ITT)/40 (TBI=8)	Veterans; 100% male; M=49; Mild 100%	PE -Individual 8–15 sessions x 90-min
Sripada et al., 2013 (Study 2) VA medical center (outpatient)	Observational cohort - TBI cross-sectionally (with/ without TBI) and type of treatment RCT (PE/ PCT)	**Incl.:** all patients with PTSD and receiving treatment.		n=22 (TBI=8); n=22 (TBI=8)	Veterans; 91% male; M= 33(6.9); Mostly mild	PE and PCT - Individual 10-12 sessions
Walter, Barnes et al., 2012 VA medical center (residential)	Uncontrolled pre-post	**Incl.:** male veterans, completed treatment, current PTSD (CAPS), history of TBI >1 year.	medical record and neuropsychological interview	n=53; n=47	Veterans; 100% male; M=35 (9.5); Mild (68%) to severe	CPT-C -14 individual sessions and 14 group sessions x 60-90 min, 8 wks
Walter, Kiefer et al, 2012 VA medical center (residential)	Uncontrolled pre-post	**Incl.:** male veterans, completed treatment, current PTSD (CAPS), history of TBI >1 year.	medical record and neuropsychological interview	n=28; n=28	Veterans; 100% male; M=36 (9.59); Mild 86% to moderate	CPT-C -14 individual sessions and 14 group sessions x 60-90 min, 8 wks
Walter et al., 2014 VA medical center (residential)/	Pre-post study - CPT vs. CPT-C	**Incl.:** PTSD, TBI > 1 year; able to complete activities of daily living, no ongoing medical issues that require external care.	medical record and neuropsychological interview	n=86 (CPT-C =46, CPT =40); n=71 (CPT-C =39; CPT =32)	Veterans: 100% male; **CPT** Mild 79% to severe, **CPT-C** Mild 71% to severe	CPT or CPT-C -14 individual and 14 group sessions x 60-90 min, 8 wks
Chard, 2011[M]				n=42; n=42	M= 36, Mild 67% to severe	

Table 1. Continued.

First author; Country, Setting	Study Design/ Groups	Inclusion (Incl.)/ Exclusion (Excl.) criteria	TBI diagnosis	Pre-treatment; Post-treatment sample	Patients: population, % male, M age (SD), TBI severity	Primary treatment -Dosage
Wolf et al., 2012 US, VA multicenter (outpatient, inpatient/ residential)	Uncontrolled pre-post	**Incl.:** OEF/OIF veterans, PTSD, documented TBI and lapsed window of expected recovery; ongoing cognitive deficits; **Excl.:** active psychosis[1]; suicidality or homicidality, self-harm; severe SUD.	screening - self-report and medical assessment	n=10; n=10	Veterans; 100% male; M=33(10.7), 24-52; Mild (60%) to moderate	PE -Individual 8 to 18 sessions (M =13.4)
Wolf et al., 2015 US, VA multicenter (outpatient, inpatient/ residential) / *Wolf et al., 2017[M]*	Uncontrolled pre-post	**Incl.:** veterans and military members completed at least 1 PE session. **Excl.:** psychosis[1], suicidality or homicidality, recent aggressive behavior or self-harm; severe SUD.	screening -self-report and medical assessment	n=69; n=69/ 44 n=44; n=44/ 31	Veterans and Active duty military; 94% male; M=34(8.0); Mild (75%) to severe 93% male; M=33(7.3); Mild 66% to severe	PE -Individual 1 to 8+ sessions (M=9.5)
Other therapies						
Carrick, McLellan et al., 2015a US, Brain Rehabilitation Center	Uncontrolled pre-post	**Incl.:** 18 + yo combat veterans (OEF, OIF) with TBI and chronic PTSD (CAPS) ; unsuccessful treatments for PTSD; consent. **Excl**.: psychosis [1] ; SUD[2]; suicidality.	assessment unclear	n=98; 1 wk: n= 98; 3 mos: n=14	Veterans; 100% male; M=39 (20-60); Severity unclear	Brain and vestibular rehabilitation - Individual, 3 per day for 2 wks (5 days per wk)
Carrick, Pagnacco, et al., 2015b US, Brain Rehabilitation Center	Uncontrolled pre-post	**Incl.:** 18 + yo combat veterans (OEF, OIF) with TBI and chronic PTSD (CAPS) ; unsuccessful treatments for PTSD. **Excl.:** psychosis[1]; current substance dependence[2]; suicidality.	assessment unclear	n=26; n=26.	Veterans; 100% male; M= 38.5 (25-58) Severity unclear	Brain and vestibular rehabilitation - Individual, 3 per day for 2 wks (5 days per wk)
Cole et al., 2015 US, VA medical center	Uncontrolled pre-post	**Incl.:** mild TBI (self-report) and continued cognitive symptoms; PTSD diagnosis **Excl.:** neurologic disease; learning/ attention / hyperactivity disorder; current SUD; history of psychosis [1]; moderate to severe TBI, TBI ≤ 12 mo, current exposure therapy.	self-report	n=10; n=9; 3 mos: n=8	Veterans; 100% male; M=46 (11.6); Mild 100%	Mindfulness-based Stress Reduction Treatment -Group; 8 sessions + 1 day retreat, 8 wks

Davis et al., 2016 US, military center (outpatient)	Uncontrolled pre-post	**Incl.:** accepted, but not yet received treatment, chronic PTSD; TBI (positive screen and self-report) at least 2 years prior. **Excl.:** shrapnel or prosthetics (spine or cranium); brain surgery; fever; acute systemic infection; intolerant to pressure on scalp or body: lactating or pregnant.	self-report and medical record	n=10; n=9	Active duty military; 100 % male; 27-45; severity not reported.	LTMT (light touch manual therapy) -Individual, 2 x 60 min (one wk apart)
Harch et al., 2017 US, Hyperbaric Center/ *Harch, 2012*[M]	Uncontrolled pre-post - case control study for SPECT analysis	**Incl.:** 18–65 yo, mild to moderate TBIs => 1 year old; chronic TBI/PCS or TBI/PCS/PTSD, no acute cardiac arrest or hemorrhagic shock, 0-3 DRS, negative screen for drugs/ pregnancy, good health, <90% on PBNRS. **Excl.:** contraindicated medical conditions, severe confinement anxiety, active intervention, not likely to complete, previous HBOT, history of hospitalization.	medical record, interview and neuropsychological testing	n=30; n=29	Veterans and Active duty military; 93% male; M=30 (21–51): Mild 83% to moderate	HBOT (hyperbaric oxygen therapy) -Individual, 40 sessions, Total dive= 60 min x 2 per day, 5 days per wk
Nelson & Esty, 2012; US, Brain Center	Uncontrolled pre-post	**Incl.:** veterans, persistent symptoms of TBI and PTSD, not progressing on standard treatments. **Excl.:** seizure disorder, sleep apnea, or ongoing substance abuse.	assessment unclear	n=7; n=5 (+2 reductions in shorter period)	Veterans; 60% male; age 23-42; Severity unclear	FNS (Flexyx Neurotherapy System) -Individual 22-25 sessions, 2-3 per wk, Total stimulation=4 sec
Ruff et al., 2012 US, VA medical center (polytrauma) /*Ruff et al., 2009*[M]	Uncontrolled pre-post observational	**Incl.:** at least one episode of mild TBI with LOC in combat setting, neurological deficits (incl. impaired olfaction), and PTSD.	interview, neurological and cognitive assessment	n=63; Prazosin =61, sleep hygiene =63	Veterans; 90% male; M=29 ± 0.92, 20-60; Mild 100%	Sleep hygiene counselling and prazosin -Prazosin targeted dose 7 mg at bedtime; 5 Sleep hygiene sessions, 9 wks
Weaver et al., 2018 US, army hospital (central assessment)	RCT (HBOT vs. sham) – analyses for subgroups with and without PTSD	**Incl.:**active duty or veterans, 18-65 yo**,** mild TBI and at least 3 persistent PCS; **Exc**l. moderate/ severe TBI, non-traumatic and penetrating injury, confounds of outcome measures or blinding.	medical record and structured interview (OSU TBI-ID)	n=71(PTSD+TBI HBOT=18:, sham=17; TBI HBOT=18, sham=18); n=71(ITT)	Military, 99% male, M=33 (21-53) (entire sample); Mild 100%	HBOT 99% oxygen, 1.5 ATA; vs. sham (air, 1.2 ATA) ; -Individual 40 sessions, 60 min x 5 days , 12wks

Note:[a]; [1]including psychotic/ bipolar disorder/ mania/ major depression with psychotic features; [2] alcohol or drugs; [M] Multiple publication; ASD= Acute Stress Disorder; CAPS= Clinician-Administered PTSD Scale; CPT- Cognitive Processing Therapy; CPT-C= Cognitive processing therapy, cognitive version; DoD= Department of Defense; DRS= Disability Rating Scale; DSM= Diagnostic and Statistical Manual of Mental Disorders; LOC= Loss of Consciousness; M= Mean; MVA= Motor Vehicle Accident; OEF= Operation Enduring Freedom; OIF= Operation Iraqi Freedom; OND= Operation New Dawn; PBNRS = Percent-Back-to-Normal' Rating Scale; PCL= PTSD Checklist for DSM (C-Civilian, M-Military, S- Specific); OSU TBI-ID = OhioState University TBI Identification Method; PCS= Post-concussive Symptoms; PCT=Person Centered Therapy; PE= Prolonged Exposure; PTSD= Posttraumatic Stress Disorder; RCT= Randomized Controlled Trial; SD= Standard Deviation; SPECT= Single Photon Emission Computed Tomography; SUD= Substance Use Disorder; TBI=Traumatic Brain Injury, TMT=Trauma Management Therapy; US=United States; VA= Veteran Affairs; mo(s)=month(s); wk(s)= week(s); WARCAT=Warrior Administered Retrospective Casualty Assessment Tool; yo= years old.

Risk of bias included studies.

There were four RCTs included in this study. Two of them represented early treatments in civilian samples, and two treatments for existing PTSD in veterans. Other studies were single-arms or lacking a control group balanced through stratification, matching or randomization, thus showing a selection bias. The performance bias represented a serious threat to validity in the majority of included studies; the concurrent therapies were frequently 1) unknown/ unclear or 2) mentioned, but their effects on outcomes were impossible to control for and distinguish from a primary treatment. The high detection bias arose from unblinded/ unreported assessors, while a not-treating clinician as an assessor was considered an indicator for a moderate risk of detection bias. In addition, valid self-report instruments have a lower reliability than structured clinical interviews (e.g. CAPS), which represent a gold standard for diagnosing PTSD.[61] Therefore, assessing PTSD diagnosis using only a self-reported measure was considered indicative of information bias. Moreover, certain bias was related to the assessment of TBI in the included military studies. While the lack of standardization and consistency in diagnosing TBI represents a general problem,[75, 76] military TBI is a particular challenge. It was typically based on self-report and retrospective medical assessment several months after the incident.[77] Furthermore, attrition was considered a source of bias in studies including only treatment completers or with attrition rate greater than 20% within a year. In addition, only a minority of studies reported an additional follow-up after three, six or more months after finalizing treatment. Although the sufficient time frame for follow-up of PTSD treatment is not specified in the guidelines (APA, 2017), it could have led to biased conclusions on efficacy. Finally, only two RCTs[51, 71] were assessed as having a low risk of bias in most assessed domains (Appendix D).

Narrative Synthesis of Treatment Outcomes

This synthesis is based on 23 studies (Table 1). Two studies represented an early intervention to prevent PTSD, while the other studies were treatments of existing PTSD. With the exception of one study[78] that observed increases in PTSD symptoms and mostly insignificant changes in other measures following Light Touch Manual Therapy (LTMT), all included studies found at least some positive consequences and implications of PTSD treatment. Three studies showed mixed findings.[69, 71, 77] More detailed results, categorized by type of treatment, are presented in continuation.

Cognitive and/or behavioral psychotherapies. Exposure and cognitive-processing therapies (CPT) in service members and veterans with PTSD and predominantly history of mild TBI, resulted in a significant reduction of PTSD symptoms in all studies (n=12), with no major differences in treatment adherence, measured by attendance and dropout.[43, 77] However, when patients with and without history of TBI, or with varying TBI severity were compared directly, results were inconsistent. For instance, Chard

et al.[79] observed greater improvements with greater TBI severity, but an overlapping study with greater sample size did not confirm the interaction between TBI severity and outcome.[57]

Furthermore, on the one hand, several other studies did not find TBI history or severity to be predictive of treatment outcomes.[55, 57, 80, 81] On the other hand, one study found smaller treatment effects when TBI was present,[82] and one found more rapid improvements with greater TBI severity.[83] Comparing standard CPT to CPT augmented with cognitive rehabilitation and modifications for cognitive deficits (SMART-CPT) showed equivalent PTSD reductions in patients with history of predominantly mild TBI and persistent cognitive complaints. SMART-CPT was, however, beneficial for cognitive functioning, and it resulted in improved attention, memory and problem solving.[70] Comparing standard CPT to Cognitive-only CPT (CPT-C) without written trauma account in patients with history of mild to severe TBI revealed similar PTSD reductions, and greater depression reduction following CPT.[57]

In civilian samples with history of mild TBI, early treatment with CBT aimed at PTSD obtained favorable or mixed results.[51, 69] Following early CBT, less patients developed PTSD following treatment and after six months compared to supportive counselling. The CBT group showed lower levels of posttraumatic and anxiety symptoms, but similar level of depression. A comprehensive multidisciplinary intervention (MI), which also included CBT, showed favorable outcomes in patients at lower risk of PTSD compared to the usual care: no one, compared to 24% in usual care, was diagnosed with PTSD at 6-month follow-up. Nevertheless, an equal percentage of high risk patients was diagnosed with PTSD at follow-up, and there were no differences in the level of PTSD, pain levels and depressive symptoms between the two groups.[69] Individuals at risk of PTSD and depression in the MI group had, however, lower general practitioner (GP) attendance.

Regarding treatment attendance, in the study of Davis et al.[77], PTSD patients with history of mild TBI showed comparable dropout rates from PTSD treatment but attended a lower number of sessions than patients without. In the study of Ragsdale et al.,[43] number of attended sessions, as well as sessions necessary to achieve fear extinction and habituation, did not differ between the two groups. Patients who sustained TBI attended six minutes shorter sessions than patients without TBI history, which was not considered clinically significant.

Other therapies for PTSD. In summary, other treatments for PTSD showed promising results in patients with history of TBI. However, only one study conducted a RCT and some adverse effects were also reported.

Pharmacotherapy. Only one study included medication (prazosin) in combination with psychoeducation as the main therapy, which showed reductions in PTSD symptoms and medication intake in patients with history of mild TBI.[74] Medications were used together with other therapies, but they were not indicated as the main treatment, and their independent effects on PTSD were not reported.[56, 57, 69, 84]

Complementary and alternative medicine (CAM) treatments. Mindfulness-based stress reduction (MBSR) showed a reduction in symptoms and improvement in attention in a small sample (n=9) of veterans with history of TBI.[72]

Novel therapies. Two studies from the same group of authors[85, 86] used brain and vestibular rehabilitation (VR), an exercise- based therapy focused on resolving vestibular symptoms. They reported short- and long- term reduction in PTSD symptoms after strategies for gaze stabilization in patients who did not react to other PTSD treatments. Moreover, two studies[71, 73] applied hyperbaric oxygen therapy (HBOT), which involved exposure to 100% oxygen in a pressurized chamber. Following HBOT in an uncontrolled study,[73] described clinically significant reductions in PTSD and improvements in neurocognitive functioning in patients with chronic complaints, which persisted after six months. However, one withdrawal and middle-ear barotrauma, bronchospasm, anxiety associated with aggravation of PTSD and temporary worsening of symptoms were also reported. In a RCT[71] that compared HBOT to sham-control with air, observed post-treatment reductions in PTSD regressed over six and 12 months. Similarly, there were some improvements in sleep, emotional and neuropsychological measures, but they diminished by six months.

Furthermore, Nelson & Esty[87] applied Flexyx Neurotherapy System (FNS) to a small sample with persistent symptoms. According to the authors, this novel variant of electroencephalograph biofeedback, resulted in beneficial PTSD outcomes. After a medical massage treatment called LTMT, that preceded the full-program in patients with chronic PTSD, contrary findings were observed: an increase in PTSD, maintenance of depression and anxiety, and improvement in immediate headache and anxiety.[78]

Table 2. Treatment outcomes of included studies by type of treatment.

Study ID, Primary treatment	PTSD- related outcome	Other outcomes measured	Timing of post-treatment measures	PTSD change and effect size*	Other outcomes effect : depression, PCS, anxiety and harms
Types of cognitive and/or behavioral therapies (CBT)					
Browne, 2013, MI (incl. CBT) vs. UC	MINI [1], PCL-C [2]	depression (MINI), disability (FIM), depression (CES- D), pain (BPI, painDETECT), alcohol use (AUDIT), exercise (6MW), balance (BBS)	1 mo (only MI) 3 mos (only MI) 6 mos	6 mo: sig. lower % diagnosed with PTSD or depression in MI group (0% vs. 24%); equal % "at risk" diagnosed with PTSD, depression or both (57% vs. 58%); non- sig. diff in PTSD symptom severity	6 mo: non sig. difference in depressive symptoms and depressive symptom severity
Bryant, 2003, CBT vs, supportive counselling	% diagnosis, CAPS [1], Impact of Event Scale[2]	anxiety (BAI), depression (BDI)	1 wk 6 mos	1 wk: sig. lower % met criteria for PTSD in the CBT group (8% vs. 58% (d=1.16); sig. lower score on Avoidance (d=2.45) and Intrusion (d=1.83) in the CBT group; 6 mo: sig. lower % met criteria for PTSD in the CBT group (17% vs. 58%) (d=0.87); lower score on Avoidance (d=1.65) and Intrusion (d=1.93)	1 wk and 6 mo: non sig. difference in depressive symptoms (BDI), sig. reductions in anxiety (BAI)
Davis, 2013, CPT	treatment completion and number of sessions	Not reported	retrospective	similar drop-out rates; PTSD group attended almost 2 sessions more than PTSD+TBI group (d=0.17); trend-pattern of PTSD+TBI group to slightly greater early drop-out rates than PTSD (non-sig., ϕ = .05)	/
Gros, 2017, PE	PCL-M [2]	substance use (MINI), depression (BDI)	weekly	sig. decrease in PTSD, but effect smaller for group with TBI (d=0.85) than without TBI (d=1.61)	sig. decrease in depressive symptoms, bigger effect in group without TBI
Jak, 2019 CPT or SMART-CPT	PCL-S [2]	PCS (NSI), quality of life (QOLI-B), satisfaction (CSQ) (CSQ); various neuropsychological outcomes	weekly post-treatment (PT) 3mo	clinically sig. decrease in PTSD in both groups (r=0.57), no difference between groups	sig. decrease in PCS (r=0.46), no difference between groups
Ragsdale, 2016, CPT or PE	PCL-S [2]	depression (BDI)	PT	sig. decrease in PTSD (combined PCL and BDI) , no sig. difference between PTSD+TBI and PTSD group (partial $\eta 2$ = .00), greater reduction in symptoms with PE than CPT in overall sample	sig. decrease in depressive symptoms
Ragsdale, 2018, TMT	treatment attendance and exposure process variables (EXP): fear activation, extinction rate, habituation	Influence of perceived executive functions (BRIEF-A)	retrospective	no difference in number of attended sessions (r=.08), sig. shorter sessions in PTSD+TBI group (6 min); no sig. difference in EXP (r=.08-.37); when controlling for PTSD severity sig. difference in overall fear activation (p=.047)	self-reported executive dysfunction did not sig. impact any of the exposure process variables
Speicher, 2014; CPT	CAPS [1], PCL-S [2]	occupational performance (COPM), depression (BDI)	PT	sig. and clinically significant decrease in PTSD: CAPS (d=2.01), PCL (d=1.37)	sig. decrease in depressive symptoms

Table 2. Continued.

Study ID, Primary treatment	PTSD- related outcome	Other outcomes measured	Timing of post-treatment measures	PTSD change and effect size*	Other outcomes effect : depression, PCS, anxiety and harms
Types of cognitive and/or behavioral therapies (CBT)					
Sripada, 2013a; PE	PCL-S [2]	Not reported	PT	sig. decrease in PTSD in PTSD+TBI subsample (d = 1.81, completers 2.22); TBI status did not sig. predict slope of the scores over time	/
Sripada, 2013b; PE and PCT	CAPS [1]	Not reported	PT	sig. decrease in PTSD in PTSD+TBI subsample (d = 1.51); change in outcomes not influenced by TBI history	/
Walter, Barnes, 2012; CPT-C	CAPS [1], PCL-S [2]	depression (BDI)	PT (incl. mid-treatment at week 4)	sig. decrease in PTSD (d = 1.0)	sig. decrease in depressive symptoms; subsample with MDD- sig. greater symptoms at each assessment
Walter, Kiefer, 2012; CPT-C	CAPS [1], PCL-S [2]	PCS (NSI)	PT	sig. decrease in PTSD: CAPS (d=1.43) and PCL (d=1.21)	sig. improvements on NSI; reduction in PTSD associated with a reduction in PCS
Walter, 2014; CPT or CPT-C *Chard et al, 2011*[M]	CAPS [1], PCL-S [2]	depression (BDI)	PT (incl. mid-treatment at week 4)	sig. decrease in PTSD, PCL dropped below one cutoff : TBI severity not a predictor of treatment outcome CAPS: partial η2=0.79, PCL: partial η2=0.67, more improvement in the moderate/severe than mild TBI group	sig. decrease in depressive symptoms, greater decrease with CPT than with CPT-C
Wolf, 2012; PE	PCL [2]	depression (BDI)	PT	100% reliable reduction in PTSD ; 90% clinically significant change and no longer met criteria for PTSD (d = 3.64)	sig. decrease in depressive symptoms, 90% reliable reduction in depression; 40% clinically sig. reduction in depression
Wolf, 2015; PE *Wolf, 2017*[M]	PCL [2]	depression (BDI PCS (NSI), behavioral outcomes (KBCI) and self-efficacy (Sesx)	weekly/PT	all: 75% reliable reduction in PTSD, 61% of participants clinically sig. change; completers: 96% reliable reduction, 86% clinically sig. change; non-completers: 40% reliable reduction, 16% clinically sig. change, n=4 worsening of PTSD symptoms (PCL), n=2 reliable change; moderate to severe TBI more rapid gains than mild TBI PCL: d = 1.80, TBI severity not a predictor of treatment outcome	sig. decrease in depressive symptoms sig. decrease in PCS (NSI)
Other therapies					
Carrick, McLellan 2015; BVH	CAPS [1]	Not reported	1 wk 3 mos (not reported)	1 wk: sig. decrease in PTSD symptoms (d=0.73); % of most severe PTSD (extreme+ severe) decreased from 77% to 49%	/

Carrick, Pagnacco 2015; BVH	CAPS [1]	Not reported	1 wk 3 mos	1 wk: sig. decrease in PTSD severity (d=0.92); 3 mos: (d=1.20)	/
Cole., 2015; MBSRT	PCL-C [2]	Attention (Cogstate); ratings of safety, feasibility, and acceptability of treatment	2 wks 3 mos	2 wks; sig. decrease in PTSD (d =1.56), 6/9 reliable change, 3 mos: d = 0.93, 3/8 reliable change	sig. improved attention; rated as acceptable and enjoyable (100%) and feasible (M=8.3/10)
Davis, 2016; LTMT	PCL-M [2]	patient-reported outcomes (PROMIS), quality of life (Neuro-QoL), medical outcome profile (MYMOP2)	4-7 days after	sig. increase in PTSD (d=1.21)	non. sig. change in depression and anxiety (Neuro-QoL Bank), sig. decrease in anxiety intensity (one item)
Harch, 2017; HBOT	PCL-M [2]	SPECT imaging, depression (PHQ-9), anxiety (GAD-7), quality of Life, PCS (RPQ), various neuropsychological outcomes	PT 6 mos	PT and 6 mo: sig. decrease in PTSD and around 50% below cutoff	sig. decrease in depression and anxiety, sig. improvements in PCS; 1 withdrew (ear infection, bronchospasm, and middle ear barotrauma), n=11 protocol breaks due primarily to adverse events but 10/ 11 finished the protocol.
Nelson, 2012; FNS	PSS [2]	neurobehavioral functioning (NFI), current levels of symptoms on separate 0–10 scales	PT	sig. decrease in PTSD (d= 0.79)	sig. decreases on four NFI dimensions, decrease in medication intake; minimal transient increases in symptoms
Ruff 2012; Sleep hygiene, prazosin	PCL-M [2]	olfaction testing score, number of headaches per month, severity of headache pain, cognitive function (MOCA), impaired nocturnal sleep (ESS).	PT(9 wks from start of treatment) 6 mos	9 wks and 6 mos: sig. decrease in PTSD, progressive reduction- sig. reduction from 9 wks to 6 mos	/
Weaver, 2018; HBOT	PCL-C[2]	PCS (NSI, RPQ), depression (CES-D), various quality of life scales , neuropsychological, neurological and sleep measures	PT (13 wks from baseline) 6 mos 12 mos	13 wks: sig. decrease in PTSD compared to sham, bigger change in PTSD+TBI subgroup; confirmed by longitudinal modelling only in total sample 6 mos: non sig. decrease in PTSD; 12 mos: non sig. worsening of PTSD	13 wks: sig. improvement in PCS (NSI, RPQ-3), bigger in PTSD+TBI subgroup; non sig. change in RPQ-13; 6 mos and 12 mos: non sig. change no serious adverse effects, minor barotrauma n=25

Note: [1]Clinician-rated; [2]Self-rated; * if reported; in case of multiple indicators, Cohen's d presented; reliable change >=5 points PCL; clinically significant change >=15 CAPS, >=10 PCL; [M] Multiple publication,:AUDIT= Alcohol Use Disorders Identification Test; BAI= Beck Anxiety Inventory; BBS= Berg Balance Scale; BDI=Beck Depression Inventory; BPI = Brief Pain Inventory; CAPS= Clinician-Administered PTSD Scale for DSM; BVR= Brain and vestibular rehabilitation; BRIEF-A=Behavior Rating Inventory of Executive Function–Adult Version; CES-D= Center for Epidemiological Studies Depression Scale; COPM= Canadian Occupational Performance Measure; CPT= Cognitive processing therapy; CSQ= Client Satisfaction Questionnaire; d= Cohen's effect size; FIM= Functional Independence Measure; FNS= Flexyx Neurotherapy System; ESS= Epworth Sleepiness Scale; FNS= Flex Neurotherapy; GAD-7: General Anxiety Disorder Scale-7; HBOT= Hyperbaric oxygen therapy; KBCI= Key Behaviors Change Inventory; LTMT= Light touch manual therapy; MDD= Major Depressive Disorder; MINI= Mini-International Neuropsychiatric Interview; MBSR= Mindfulness based stress reduction; MI=Multidisciplinary Intervention; MOCA= Montreal Cognitive Assessment; mo=months; NSI=Neurobehavioral Symptom Inventory; NF= Neurobehavioral Functioning Inventory; PCL= PTSD Checklist for DSM (C-Civilian, M-Military, S- Specific); PCS= Post-concussive symptoms; PE= Prolonged exposure; PHQ-9: Personal Health Questionnaire-9;PSS= PTSD Symptom Scale; PTSD= Posttraumatic Stress Disorder; r= Pearson r effect size; QOLI-B= Quality of Life Inventory; RPQ= Rivermead Post Concussion Symptoms Questionnaire; Sesx= TBI Self-efficacy Questionnaire; TBI=Traumatic Brain Injury; UC= Usual Care; VRR= Brain and Vestibular Rehabilitation; 6MW= 6-min Walk Test; mo(s)=month(s); wk(s)= week(s); η2= eta squared effect size; ϕ= phi effect size.

Case Reports/Studies

Case reports/studies are summarized in Appendix E. Most reports/studies originated from the US and involved male service members and veterans, and only two studies included civilian patients.[88, 89] The remaining studies were from the United Kingdom (UK) and Italy, which involved civilian patients (n=7).[50, 90-93] In accordance with other studies, case reports/ studies reported predominately positive effects of treatments, resulting in a reduction of PTSD symptoms in military and civilian patients with a history of TBI of different severities. However, some disturbances usually persisted. More detailed results of different treatments are presented below.

CBT. Treatments usually integrated complementary therapies aimed at enhancement of neurocognitive functioning, psychoeducation, and psychological strategies for TBI-related cognitions, such as changing negative beliefs about cognitive decline after TBI or learning memory strategies. Moreover, smaller modifications and adjustments of treatments were introduced in order to facilitate treatment adherence and effectiveness in patients who sustained TBI, such as reminder calls, backup appointments and decreased workload.

Predominately positive main outcomes of CBT were reported in civilian patients who sustained mild to severe TBIs.[88, 91, 93] Two case studies reported improvements in some, but not all psychiatric symptoms after applying CBT in civilian patients with a history of mild TBI.[50, 90] A significant adverse effect was reported in a patient who sustained an open head injury and had mild executive impairment. He responded to CBT with perseverations, in the form of continuously re-experiencing the most disturbing traumatic details for over a week.[90] PE, CPT and CPT-C reduced PTSD symptoms in service members and veterans who sustained mild and severe TBIs (n=6)[49, 94-97] and a civilian with a history of mild TBI.[89] Positive changes were also reported after a brief psychodynamic therapy[98] and Dialectical Behavior Therapy in combination with PE.[97] Pagani et al.[92] described two patients with chronic PTSD and a history of severe TBI, who showed reductions of PTSD symptoms and improvements in neuropsychological symptoms after eight sessions of Eye Movements Desensitization and Reprocessing (EMDR).

Pharmacotherapy. The absence of PTSD-related nightmares was reported after treatment with clonidine.[99] Citalopram in combination with group therapy and several other medications demonstrated stabilization of symptoms in a patient who sustained severe TBI.[100]

Complementary and alternative medicine (CAM). A case series described the successful usage of transcendental meditation (after PE or CPT) and its high acceptance

by military patients with mild blast-related TBI.[101] Furthermore, scalp and body acupuncture[102] and a combination of acupuncture and art therapy[103] were successfully used in military patients.

Novel treatments. The absence of PTSD symptoms was reported after HBOT[104] in a patient with mild blast-related injury; and a reduction of persistent symptoms following neurotherapy in veterans with multiple TBIs and chronic PTSD.[105]

Discussion

This extensive systematic review indicated that recommended psychotherapies for PTSD seem appropriate for the treatment of PTSD symptoms in population with history of TBI, while there is less evidence for other treatments aimed at PTSD symptoms. More precisely, all studies using PE, CPT or other CBT, commonly in combination with additional treatments, resulted in a reduction of PTSD symptoms among service members and veterans, with adverse effects rarely reported. A small number of studies and case studies which involved pharmacotherapy (prazosin, clonidine, citalopram), complementary (mindfulness, meditation, massage, acupuncture) and novel therapies (HBOT, neurotherapy, brain and vestibular rehabilitation) mainly showed promising results in patients with chronic PTSD symptoms. Almost all studies and case reports/studies reported positive PTSD outcomes, however, their quality was mainly low.

Methodological limitations arose from weak study designs, as in case reports/studies and single- arm studies, or from the lack of control in group allocation. Furthermore, in several studies, the main treatment was part of an integrative program, or the effects were not separated from concurrent therapies: pharmacotherapy; cognitive and speech therapies and modifications of treatments aimed at compensation of neurocognitive deficits. Thus, it was not clear whether the treatments would be equally appropriate and effective, or too demanding, without those adjuncts and adjustments. Furthermore, in order to obtain non-biased measures of treatment outcomes, a blinded assessment with gold standard techniques and longer follow-up is required. Lastly, TBI assessment significantly varied between studies, and included direct hospital referrals in civilian studies, and in the military context self-report, military records and clinical examination were used. Prompt, corroborated and accurate assessment of TBI is difficult in combat conditions, and records frequently rely on self-reports.[77] Nonetheless, to reduce bias, future studies could profit from usage of structured instruments for assessment of TBI.

Regarding generalizability, the evidence of treatment effectiveness remains unclear in context of severe injuries. Positive changes in PTSD symptoms were reported across levels of TBI severity. However, patients who sustained a moderate to severe TBI were

outnumbered or excluded. In addition, the majority of studies were conducted after a minimum of one year following a traumatic incident. Although two civilian studies suggested that an early intervention was not harmful but beneficial, it still cannot be concluded when it is optimal for interventions to be implemented after a trauma occurs, particularly involving severe TBIs, related pain and greater cognitive deficits.

Furthermore, the majority of studies involved male service members and veterans with high prevalence of multiple and blast-related injuries.[106] Thus, it is unclear whether the results can be generalized to female and civilian patients. Nevertheless, the study with a low risk of bias[51] and several case studies involving civilians provided results similar to results in the military population. In addition, there are some similarities between military and civilian populations. Although in lower percentages, other types of trauma than combat were present among service members and veterans, and unfortunately, blast-related injuries have recently become more common in civilians.[107] There is some evidence that there are no major differences between blast and non-blast-related injuries,[28, 108-110] but the issue remains under examination. Finally, the majority of studies involved comprehensive multidisciplinary treatments involving multiple types of therapies. While these might be common in military/VA and hospital settings, they could be less accessible for civilians who were not in residential care or for the veterans from countries other than the US. Based on the included studies, the efficacy of psychotherapies outside of integrative and multidisciplinary programs is unclear.

Studies of greater rigor are particularly needed for treatments that are not well-investigated in PTSD patients, with or without a history of TBI, namely HBOT,[71, 73] neurotherapy,[87, 105] LTMT,[78] and vestibular and brain rehabilitation.[85] A small number of included studies and case studies suggested some improvements in patients with chronic PTSD symptoms. However, increases in symptoms (LTMT),[78] and transient side-effects (HBOT)[73] are also reported. For instance, HBOT remains a controversial treatment with insufficient evidence for effectiveness in the context of TBI.[111] Uncontrolled studies typically found some improvements in TBI and PTSD-related symptoms, whereas there was no difference in effectiveness of HBOT compared to inactive treatment.[111, 112] In this review, an uncontrolled study found short- and long-term improvements of PTSD following HBOT,[73, 104] whereas in a RCT the post- treatment improvements did not persist[71] Moreover, evidence for the brain and vestibular rehabilitation and neurotherapy was particularly scarce and based on uncontrolled studies of a single groups of authors.[85, 86]

This review included only one study and two case studies targeting pharmacotherapy. Additionally, there was a relevant RCT (not completely meeting inclusion criteria regarding the sample and therefore excluded) of methylphenidate and galantamine in patients with PTSD, TBI or both by McAllister et al. [113]It observed improvements

in PTSD symptoms in association with methylphenidate. Available literature reviews suggest that medication targeting overlapping symptoms (e.g. selective serotonin reuptake inhibitors) can improve outcomes of both conditions, but many pharmacological treatments for one condition can aggravate the symptoms of the other.[45] Therefore, further research on psychopharmacology in this population is of pivotal importance.

Some important issues are beginning to be elucidated. It seems that CPT augmented with cognitive rehabilitation, compared to standard CPT, results in similar PTSD reductions, but substantial improvements in different cognitive domains.[70] Nevertheless, the findings were obtained in patients who sustained mild to moderate TBIs a few years before the therapy, and it therefore remains unclear how important those adjuncts are for reducing symptoms in patients with more severe and more recent TBIs.

Some researchers emphasize the importance of neurocognitive disturbances and not historical TBI status when considering differential treatment outcomes. In a recent study by Scott et al. (2017), response to CBT for PTSD-related sleep difficulties was related to verbal memory but not to TBI status. Similarly, early dropout and response to CPT in patients with PTSD and a history of TBI was associated with poorer executive functioning, and not TBI characteristics.[114] However, in the majority of included studies, objective neuropsychological functioning was not measured, and it should be included in future studies as an important confounder. In addition, other TBI characteristics, such as presence and duration of PTA and LOC, could also influence the treatment process and effects beyond TBI severity.[115]

Finally, this review has some limitations. Literature search was restricted to English and articles were only partly screened by two researchers. However, in case of doubts in screening, articles were discussed with a second and third researcher. In addition, reference lists of included articles and a base of clinical trials were also inspected.

Conclusion

TBI history should not discourage the application of PTSD treatments, particularly PE, CPT and other CBT, which seem to result in reductions of symptoms and have no serious adverse effects. However, the quality of evidence is limited. Therefore, future studies should conduct controlled PTSD trials to obtain more conclusive evidence regarding the treatment effectiveness in this population. In recent years, there has been a growing number of articles discussing functioning and treatment of patients with PTSD and a history of TBI, as well as announced trials that respond to some of the challenges in the field. Nevertheless, this review highlights the importance of improving several aspects of future studies: controlling for concurrent therapies; involving more female and civilian

patients; investigating the impact of TBI severity and other TBI characteristics; using valid and reliable instruments for TBI and PTSD, and assessing neurocognitive deficits using objective measures. Finally, the same therapies may be appropriate and effective in this subgroup of PTSD patients, but the needs and limitations of individuals should be taken into account in the treatment process.

Supplementary material

Supplementary material is available at: https://www.sciencedirect.com/science/article/pii/S0272735819302880?via%3Dihub#bb0020.

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PART II

Prediction: Improving diagnosis and prognosis following mild traumatic brain injury

Chapter 6

Biomarkers compared to clinical decision rules for selecting patients with mild traumatic brain injury for Computed Tomography: A prospective multicentre cohort study

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Under review

Abstract

Background: Clinical decision rules (CDR) have been implemented into clinical practice to select patients with mild traumatic brain injury (mTBI) for computed tomography (CT) scanning of the head.

Objective: To assess the value of blood-based biomarkers compared to CDRs to optimize the detection of intracranial abnormalities on CT.

Design: Prospective, multicentre cohort study.

Setting: 63 trauma centres across Europe.

Participants: 1889 patients (≥16 years of age) from the Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) study who presented with a Glasgow Coma Score (GCS) 13 to 15 and had biomarkers sampled within 24h.

Measurements: Outcomes were any intracranial traumatic abnormality (primary) and potential neurosurgical lesions on CT. We compared diagnostic accuracy of six biomarkers (GFAP, NFL, NSE, S100B, T-tau, UCH-L1) to four established CDRs (CT in Head injury Patients (CHIP); New Orleans criteria (NOC); Canadian CT head rule (CCHR); National Institute for Health and Care Excellence (NICE) guideline), and their combinations, in terms of sensitivity and specificity.

Results: With the biomarker threshold set to obtain the same sensitivity as each of the CDRs, GFAP was substantially more specific (19 to 35% percentage points (pp)) than any of the CDRs. With the same specificity as the CDRs, GFAP was more sensitive (2 to 21% pp). Compared to CDRs, UCH-L1, NFL and T-tau also showed increased diagnostic accuracy. Combining each biomarker – using a sensitivity threshold of 90% – with each CDR increased specificity with minor decrease in sensitivity, particularly for GFAP.

Limitation: Studies in broader mTBI populations and using robust point of care clinical assay platforms are warranted.

Conclusion: Measuring GFAP may reduce unnecessary CT scanning and should be considered for optimization of existing CDRs.

Key words: mild traumatic brain injury, clinical decision rules, computed tomography, biomarkers, GFAP

Introduction

Traumatic brain injury (TBI) can be defined as an "alteration in brain function, or other evidence of brain pathology, caused by an external force".[1] It affects over 50 million people each year globally.[2] Approximately 70-90% of patients who sustain a TBI are classified as mild (mTBI) according to the Glasgow Coma Score (GCS:13-15),[3] causing a great public health burden. In this group, efficient assessment to determine which patients require a head CT scan is important for timely identification of patients with intracranial abnormalities, whilst avoiding unnecessary radiation exposure, reducing costs, and decreasing Emergency Room (ER) crowding for those with a very low risk for intracranial injury.[4]

Clinical decision rules (CDRs) have been developed to facilitate decision-making for CT scanning. Those in widespread use include: the New Orleans criteria (NOC),[5] Canadian CT head rule (CCHR),[4] the National Institute for Health and Care Excellence (NICE)[6] guideline for head injury and CT in Head injury Patients (CHIP).[7] When compared to an "image all patients with head injury strategy" application of these CDRs can substantially reduce the number of CT scans, with a limited decrease in sensitivity for detecting all intracranial lesions and comparable ability to identify neurosurgical lesions.[8-10] However these strategies are still inefficient with 90-95% of scan's performed typically showing no intracranial injury. [7]

Blood-based protein biomarkers have the potential to improve the performance of CDRs. The Scandinavian guidelines incorporate the biomarker S100 calcium-binding protein B (S100B) to decide on CT in the "low risk" mTBI group, but the level of this astrocyte-related protein may be affected by extra-cranial injuries and sampling time.[11] Glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase-L1 (UCH-L1)[12,13] were recently approved by the US Food and Drug Administration for evaluation of mTBI.[14] We previously demonstrated that GFAP measured within 24h after injury was associated with CT abnormalities above and beyond clinical characteristics and other biomarkers.[15]

Routine assessment of biomarkers may reduce the number of unnecessary CT scans, while keeping the ability to detect intracranial abnormalities constant, or the number of detected additional intracranial lesions may be increased with the same ability to exclude truly negative CT scans. Robust evidence of the clinical utility of biomarkers beyond that obtained by established CDRs is essential for the broad integration and adoption in clinical practice.

We aimed to assess the diagnostic accuracy of six biomarkers (GFAP, NFL, NSE, S100B, T-tau, UCH-L1), relative to four CDRs (CHIP, NICE, NOC and CCHR), and the combinations of the biomarkers and the CDRs to inform the need for CT scanning in patients with mTBI.

Methods

The study is reported in accordance with the STARD statement.[16]

Participants

The study population consisted of patients from the prospective multicentre observational Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) study (Core data, version 3.0).[17] Data were collected from December 2014 to December 2017 in 63 centres across Europe and Israel. The study was registered with ClinicalTrials.gov (NCT02210221). Ethical approval was granted for each recruiting site and informed consent obtained from all patients and/or their legal representative/next of kin (https://www.center-tbi.eu/project/ethical-approval).

The inclusion criteria for the core study were a clinical diagnosis of TBI, presentation within 24h of injury, and a clinical indication for CT scanning.[17] The inclusion was not consecutive but influenced by logistic considerations.[17] For this study, we selected mTBI patients (GCS 13-15) 16 years of age or older, with an interpretable CT scan and with all six blood-based biomarkers measured within 24h post-injury (Appendix Figure 1).

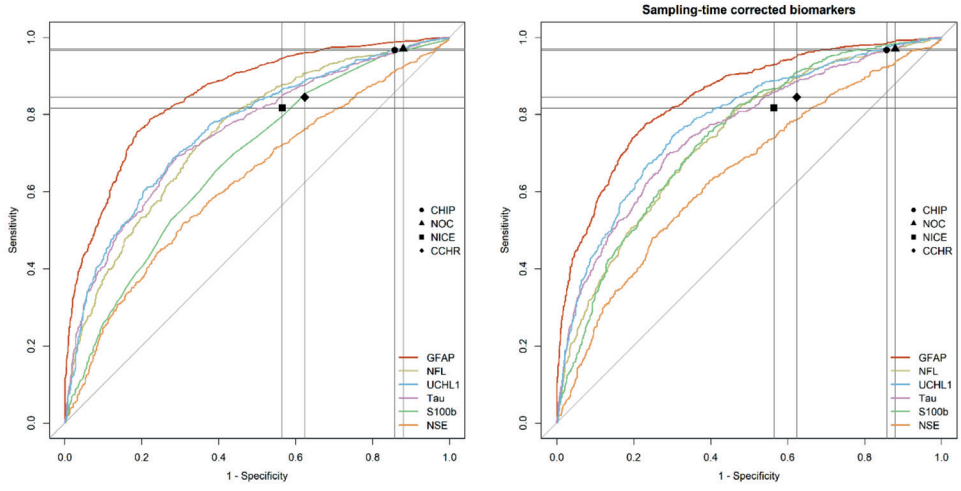

Figure 1. Receiver operating characteristic (ROC) curves for detecting any intracranial abnormality on CT of six biomarkers (GFAP, NFL, NSE, S100B, t-Tau, UCHL1), and of six sampling-time corrected biomarker values (right). Sensitivity and specificity for commonly used clinical decision rules are presented with symbols: CT in Head Injury Patients (CHIP); New Orleans criteria (NOC); National Institute for Health and Care Excellence (NICE); and Canadian CT head rule (CCHR) (N=1889, 874 CT+)

Outcome

The primary outcome was any (intra)cranial traumatic abnormality on the first CT scan defined by the presence of at least one of the following: hematoma (epidural, subdural, extra-axial), haemorrhage (subarachnoid, intraventricular), mixed density subdural collection, contusion, traumatic axonal injury, midline shift, cisternal compression, and/or depressed skull fracture. A linear skull fracture or skull base fracture in isolation was not considered as a traumatic intracranial abnormality (Appendix Table 1).

The secondary outcome was defined as a potential neurosurgical lesion: epidural hematoma, mass subdural hematoma (>25mL), mass contusion (>25mL), midline shift (>5mm), herniation, or depressed skull fracture (Appendix Table 1). Imaging data was extracted from central review of CT scans, conducted according to the National Institute of Neurological Disorders and Stroke (NINDS) Common Data Elements.[18] The central review panel (trained reviewers) were blinded to clinical information except for sex, age and care path stratum.

Clinical decision rules (CDR)s and biomarkers

Risk factors for CT abnormalities used in the CHIP, NOC, NICE and CCHR were prospectively collected (Table 1; Appendix Table 1). CHIP, NICE and CCHR consist of major/high risk criteria and minor/medium risk criteria. When CDRs had exclusion criteria, these were considered as additional risk factors: the NOC is not intended for patients with a GCS <15 and with neurological deficit, and the CCHR for patients with neurological deficit, post-traumatic seizures, or anticoagulant therapy. Consequently, when such risk factors were present, the patient was classified as being indicated CT by the respective CDR. When CDRs had additional inclusion criteria, these were combined with risk factors. In that way, loss or alteration of consciousness (LOC) and/or posttraumatic amnesia (PTA) were added to risk factors of NOC and CCHR. As sensitivity analysis, we also calculated NOC and CCHR without incorporating the LOC/PTA criterion (Appendix Table 1).

Major extra-cranial injury (MEI) was defined as an Abbreviated Injury Scale (AIS) score ≥ 3 for the face, thorax/chest, abdomen/pelvis, extremities, external and spine regions.
The following biomarkers were analysed in serum: GFAP, NFL, NSE, S100B, T-tau, UCH-L1. Collection and processing of biomarker assays, and the limits of detection have been described in detail in previous publications.[15,19] S100B and NSE were measured with a clinical-use automated system, using an electrochemiluminescence immunoassay kit (ECLIA) (Elecsys S100 and Elecsys NSE assays) run on the e602 module of Cobas 8000 modular analyzer (Roche Diagnostics, Mannheim, Germany) at the University of Pecs (Pecs, Hungary). GFAP, UCH-L1, NFL and t-tau were analyzed with an ultrasensitive immunoassay using digital array technology (Single Molecule

Arrays, SiMoA)-based Human Neurology 4-Plex B assay (N4PB) run on the SR-X benchtop assay platform (Quanterix Corp., Lexington, MA) at the University of Florida (Gainesville, Florida).

Data analysis

The study population is described in terms of clinical characteristics, positivity of CDRs and biomarker values using median and interquartile range for continuous variables and frequencies and percentages for categorical variables. Missing data in clinical characteristics ranged from 0% to 15% (LOC, PTA). Values were imputed 10 times assuming a missing at random mechanism and based on a model containing all components of CDRs (including age), log-transformed biomarkers, sampling time, outcomes (CT abnormalities), strata, and auxiliary variables pupillary reactivity, hypoxia, hypotension, sex, and neurosurgical interventions. Predictive mean matching was used for continuous, logistic regression for binary, proportional odds logistic regression for ordinal, and polytomous regression for categorical data.[20] Sensitivities, specificities and standard errors were pooled over imputed datasets and combined by Rubin's rules.

Comparison of the CDRs and biomarkers for detecting CT abnormalities

We calculated sensitivity and specificity for each CDR and biomarker in predicting CT abnormalities. Sensitivity was defined as the proportion of CDR positive patients among those with a positive CT scan (CT abnormalities present). Specificity was defined as the proportion of CDR negative patients among those with a negative CT scans (CT abnormalities absent). To compare biomarkers with the CDRs, we applied biomarker thresholds that either resulted in a) the same sensitivity as a CDR or b) the same specificity as a CDR (Appendix Table 2). Receiver operating characteristic (ROC) curves were created for graphical illustration with diagnostic accuracies of the CDRs indicated. Differences between each biomarker and each CDR were tested using McNemar's test.

Sensitivity analyses were performed to adjust for differences in sampling time of the biomarkers. A "sampling-time corrected" biomarker value was modelled for every biomarker. As longitudinal sampling had not been performed, we estimated 2 hour biomarker values based on a multivariable regression model (Appendix Figure 2).

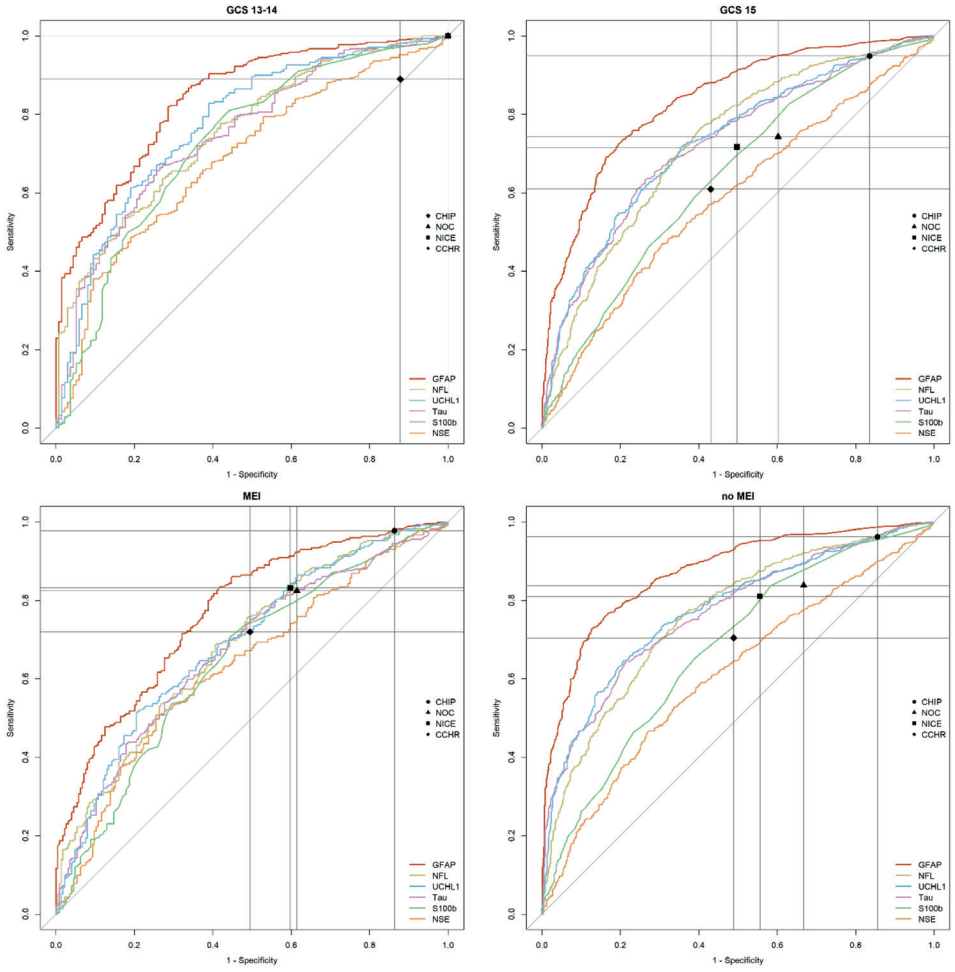

Figure 2. Receiver operating characteristic (ROC) curves for detecting any intracranial abnormality on CT of six biomarkers (GFAP, NFL, NSE, S100B, t-Tau, UCHL1) in patients with GCS 13-14 (446, 310 CT+) and GCS 15 (1443, 564 CT+), and with (498, 274 CT+) and without major extra-cranial injury (1391, 600 CT+). Sensitivity and specificity for commonly used specificity for commonly used clinical decision rules are presented with symbols: CT in Head Injury Patients (CHIP); New Orleans criteria (NOC); National Institute for Health and Care Excellence (NICE); and Canadian CT head rule (CCHR).

Subgroups and secondary endpoint

Subgroup analyses were performed by GCS [13-14,15], presence of MEI, and by sampling time intervals of biomarkers (0-6, 6-12, 12-18, 18-24 hours post-injury). Analyses were also performed with the endpoint: potential neurosurgical lesion.

Combinations of the CDRs, and biomarkers with sensitivity of 90% for detecting CT abnormalities

We calculated sensitivity and specificity for combinations of each CDR and each

biomarker in predicting any CT abnormality and potential neurosurgical lesion. For each biomarker, we applied the biomarker threshold that resulted in a sensitivity of 90% (Appendix Table 3). A biomarker was called "positive" if its value was above this threshold.

In a first scenario, we indicated a combination of a CDR and a biomarker as positive if the exclusion criteria were positive (for NOC and CCHR) or if the high risk/major criteria were positive. If only medium risk/minor criteria were positive, we indicated the combination as positive if a biomarker was also positive. In a second scenario, we indicated a combination of a CDR and a biomarker as positive only if both a CDR and a biomarker were positive. In a third scenario, we indicated a combination of a CDR and biomarker as positive if any of them - a CDR or a biomarker (or both)- was positive.

All analyses were performed in R (version 3.6) using packages *mice*,[20] *Hmisc* [21] *and pROC.*[22]

Results

Participants

In total, 1889 patients were included with 874 having any intracranial abnormality (46%), and 277 a potential neurosurgical lesion (15%; Appendix Table 1). The majority of included patients were male (66%) and the median age was 52 years. The majority had a GCS of 15 (76%) and MEI was present in 498 (26%, Table 1). Falls were the most common cause of injury, and dangerous mechanisms such as fall from elevation, being pedestrian or cyclist or ejected from vehicle was reported in 705 (39%). No PTA was reported in half of the patients (911, 57%).

The CHIP rule was positive in the large majority of patients (1616, 92%) while the CCHR adjusted with inclusion and exclusion criteria was the most conservative (1167 positive, 67%). Without inclusion criterion of LOC/PTA incorporated for NOC and CCHR (Appendix Table 1), NICE was the most conservative (1212 positive, 70%) and NOC the most liberal (1723 positive, 93%). The median sampling time of biomarkers was 12 [Quartile 1,Quartile 3: 5.4, 18.6] hours, and median time to CT was 2 [1.4, 3.6] hours after injury (Table 1). Most of the patients (1789, 95%) had a CT before biomarkers were sampled.

The 874 patients with intracranial abnormalities were older, with lower GCS and more often MEI, and had later sampling time and higher levels of biomarkers. As expected, patients with intracranial abnormalities had higher proportions of CDR positivity (Table 1).

Table 1. Characteristics, positivity of CDRs, and biomarker values of mild traumatic brain injury (TBI) patients with and without any intracranial abnormality on CT

	Overall	Missing (%)	Any intracranial abnormality	
			No	Yes
N	1889		1015	874
Sex = male (%)	1240 (65.6)	0	646 (63.6)	594 (68.0)
Age (median [Q1-Q3])	52 [33, 68]	0	48 [30, 64]	56.50 [37, 70]
Use of anticoagulants	137 (7.3)	1.1	62 (6.2)	75 (8.7)
Baseline Glasgow Coma Score		0		
13	113 (6.0)		15 (1.5)	98 (11.2)
14	333 (17.6)		121 (11.9)	212 (24.3)
15	1443 (76.4)		879 (86.6)	564 (64.5)
Major extra-cranial injury (%)	498 (26.4)	0	224 (22.1)	274 (31.4)
Injury cause		1.4		
Fall	911 (48.9)		484 (48.0)	427 (50.0)
Road traffic accident	661 (35.5)		169 (16.8)	121 (14.2)
Other	290 (15.6)		355 (35.2)	306 (35.8)
Dangerous mechanism[1] (%)	705 (38.9)	4.1	335 (34.5)	370 (44.0)
PTA duration		14.9		
No PTA	911 (56.7)		575 (61.8)	336 (49.6)
<2	443 (27.5)		248 (26.6)	195 (28.8)
2-4	59 (3.7)		29 (3.1)	30 (4.4)
>4	195 (12.1)		79 (8.5)	116 (17.1)
CDRs: indication for CT (%)				
CHIP (%)	1616 (92.1)	7.1	810 (87.1)	806 (97.8)
NOC* (%)	1344 (75.0)	5.1	641 (66.2)	703 (85.2)
NICE (%)	1212 (69.8)	8.0	536 (58.0)	676 (83.s1)
CCHR*(%)	1053 (61.4)	9.2	472 (51.0)	581 (73.5)
Time (hours)				
Time to CT	2.0 [1.4, 3.6]	0	2.1 [1.4, 3.4]	2.0 [1.4, 3.8]
Sampling time of biomarker	11.8 [5.4, 18.6]	0	8.6 [4.3, 16.8]	14.6 [7.6, 19.8]
Biomarkers (median [Q1-Q3])				
GFAP g/ml	1.3 [0.3, 5.7]	0	0.4 [0.1, 1.3]	4.9 [1.8, 14.4]
NFL pg/ml	12.7 [6.9, 27.2]	0	8.8 [5.3, 16.4]	21.2 [11.3, 47.6]
NSE ng/ml	14.8 [11.6, 20.4]	0	13.8 [11.1, 18.0]	16.8 [12.6 24.1]
S100B ng/ml	0.1 [0.1, 0.2]	0	0.1 [0.1, 0.2]	0.1 [0.1, 0.3]
Tau pg/ml	1.8 [1.0, 3.9]	0	1.3 [0.8, 2.2]	3.1[1.6, 6.8]
UCHL1 pg/ml	57.5 [27.4, 145.8]	0	36.3 [18.8, 71.7]	108.4 [50.9, 270.3]

CCHR= Canadian CT head rule; CHIP= CT in Head Injury Patients; NICE=National Institute for Health and Care Excellence; NOC= New Orleans criteria; [1] cyclist, pedestrian, ejected from a vehicle, fall from elevation >1m/5 stairs. *with exclusion and inclusion criteria added as additional risk factors.

Comparison of CDRs and biomarkers for CT abnormalities

With the biomarker threshold for positivity set to obtain comparable sensitivity as the four respective CDRs, GFAP was substantially more specific (19-35 percentage points (pp)) than any of the CDRs (p<.001;Table 2; Figure 1, Appendix Table 4). When translating the increased specificity into number of CT scans, using GFAP rather than the most sensitive CDR (CHIP) would avoid 194 unnecessary CT scans among the 1015 CT negative patients. Compared to the other CDRs, this reduction was even larger, ranging from 293 to 352 (Table 3).

Table 2. Specificity [95% CI] of biomarkers for detection of any intracranial lesion on CT at biomarker thresholds with comparable sensitivity to respective Clinical Decision Rules (CDR)s (upper rows) and sensitivity [95% CI] at specificity comparable to respective CDRs (bottom rows) in patients with Glasgow Coma Score 13-15 (N=1889; 874 CT+)
Differences between the sensitivity and specificity of each CDR and each biomarker were tested using McNemar's test. Statistical significance is indicated by asterisks.

	CHIP	**NOC**	**NICE**	**CCHR**
Sensitivity selected %	**97**	**83**	**82**	**71**
CDR	14 [12-16]	34 [31-37]	44 [40-47]	51 [48-54]
GFAP	33 [30-36]***	69 [66-72]***	72 [70-75]***	84 [81-86]***
NFL	14 [12-17]	51 [48-54]***	53 [50-57]***	66 [63-69]***
UCH-L1	15 [12-17]	50 [47-53]***	53 [50-56]***	69 [66-72]***
Tau	12 [10-14]	45 [42-48]***	48 [45-52]*	68 [65-71]***
S100B	8 [7-10]***	37 [34-40]	37 [34-40]**	50 [47-53]
NSE	4 [3-05]***	26 [23-29]***	29 [26-32]***	46 [43-49]*
	CHIP	**NOC**	**NICE**	**CCHR**
Specificity selected %	**14**	**34**	**44**	**51**
CDR	97 [95-98]	83 [81-86]	82 [79-84]	71 [68-74]
GFAP	99 [98-99]**	96 [95-98]***	95 [93-96]***	92 [90-94]***
NFL	97 [95-98]	91 [90-93]***	87 [85-90]***	83 [81-86]***
UCH-L1	97 [95-98]	90 [88-92]***	86 [84-89]**	83 [81-86]***
Tau	96 [95-97]	89 [87-92]***	84 [82-86]	81 [78-83]***
S100B	95 [94-97]	86 [83-88]	74 [71-77]***	70 [67-73]
NSE	91 [89-93]***	79 [77-82]*	72 [69-75]***	66 [63-70]

CCHR= Canadian CT head rule; CHIP= CT in Head Injury Patients; CI= Confidence Intervals; NICE=National Institute for Health and Care Excellence; NOC= New Orleans criteria. *p<0.05;**p<0.01; ***p<.001 with McNemar's test.

With the threshold of biomarkers set to obtain comparable specificity as the four CDRs, GFAP was more sensitive (2-21 pp) than all CDRs (p<.01;Table 2; Figure 1, Appendix Table 5). Using GFAP rather than the CDRs would result in 17 additional CT abnormalities detected among 874 CT positive patients compared to CHIP, and considerably more compared to the other CDRs, ranging from 112 to 183 (Table 3).

NFL, UCH-L1 and T-tau were also more specific and more sensitive than the CDRs NOC, NICE and CCHR, but to a lesser degree than GFAP (Table 2, Figure 1, Appendix Tables 4 and 5). NSE had poorer specificity and sensitivity compared to all CDRs, and S100B had similar or poorer specificity and sensitivity compared to the CDRs (Table 2, Figure 1, Appendix Tables 4 and 5).

Table 3. Relationship between indication for CT based on Clinical Decision Rule (CDR) (CHIP, NOC, NICE, CCHR) and on dichotomized GFAP for patients without (CT-) and with (CT+) any intracranial abnormality on CT
*GFAP is dichotomized based on thresholds that result in the same sensitivity as a CDR (a) or in the same specificity as a CDR (b). The percentage of avoided CT scans among CT- equals the difference in specificity, and the percentage of additional abnormalities detected among CT+ equals the difference in sensitivity.**

	a) CT - (N=1015)			b) CT + (N=874)		
	GFAP -	**GFAP +**	**Avoided CT- scans**	**GFAP -**	**GFAP +**	**Additional CT abnormalities detected**
CHIP -	88	57	251-57=194	4	25	25-8=17
CHIP +	251	619		8	837	
NOC -	290	60	410-60=350	10	135	135-22=113
NOC +	410	255		22	707	
NICE -	360	81	374-81=293	14	146	146-34=112
NICE +	374	199		34	680	
CCHR -	456	61	393-61=332	31	223	223-40=183
CCHR +	393	105		40	580	

SE= sensitivity of CDR; SP= Specificity of CDR; CCHR= Canadian CT head rule; CHIP= CT in Head Injury Patients; NICE=National Institute for Health and Care Excellence; NOC= New Orleans criteria. *Due to rounding, not always completely equal.

Table 4. Sensitivity [95% CI] and specificity [95% CI] of combinations of Clinical Decision Rules (CDR) s and biomarkers for any intracranial lesion in patients with Glasgow Coma Score 13-15 (N=1889; 874 CT+): CT indicated if major risk factors of CDRs are positive, or if minor/medium risk factors of CDRs are positive and a biomarker is positive**.**
A biomarker is called "positive" if its value is above the threshold that resulted in a sensitivity of 90%.

		CHIP	**NOC**	**NICE**	**CCHR**
Sensitivity %	**CDRs**	97 [95-98]	83 [81-86]	82 [79-84]	71 [68-74]
Specificity %		14 [12-16]	34 [31-37]	44 [40-47]	51 [48-54]
Sensitivity %	**GFAP + CDR**	95 [94-97]	80 [77-82]	79 [77-82]	70 [67-73]
Specificity %		27 [24-29]	60 [57-63]	59 [56-62]	58 [55-61]
Sensitivity %	**NFL + CDR**	95 [94-97]	79 [76-82]	80 [77-83]	70 [66-73]
Specificity %		24 [22-27]	54 [51-57]	52 [49-55]	58 [55-61]
Sensitivity %	**UCH-L1 + CDR**	96 [94-97]	79 [76-82]	80 [77-82]	70 [67-73]
Specificity %		21 [19-24]	50 [47-53]	52 [49-55]	55 [52-59]
Sensitivity %	**Tau + CDR**	96 [94-97]	79 [76-81]	79 [77-82]	70 [67-73]
Specificity %		21 [19-24]	50 [47-53]	52 [48-55]	56 [53-59]
Sensitivity %	**S100B + CDR**	95 [94-97]	78 [76-81]	79 [76-82]	70 [67-73]
Specificity %		20 [17-22]	48 [45-51]	50 [47-53]	54 [51-57]
Sensitivity %	**NSE + CDR**	96 [95-97]	78 [75-81]	77 [75-8]	70 [67-73]
Specificity %		17 [15-19]	41 [38-44]	47 [44-50]	52 [49-56]

CCHR= Canadian CT head rule; CHIP= CT in Head Injury Patients; CI= Confidence Intervals; NICE=National Institute for Health and Care Excellence; NOC= New Orleans criteria.

When biomarker values were corrected to a sampling time of 2 hours post-injury, GFAP and NFL showed similar or slightly lower specificities and sensitivities, while S100B and UCH-L1 showed higher specificities and sensitivities than found with the observed measurements (Appendix Table 6). The most prominent difference was for S100B that had considerably better diagnostic accuracy when corrected to earlier sampling time e.g. 9-16 pp higher specificity and 1-12 pp higher sensitivity compared to the CDRs (Figure 1, Appendix Table 6).

Subgroups and secondary outcome

In patients with GCS 13-14, the CDRs CHIP, NOC and NICE were positive in all patients, and therefore had perfect sensitivity (1) and no specificity (0) (Figure 2). Using biomarkers, specificity could only be enhanced by accepting lower sensitivity (e.g. for sensitivity of 95%, specificity of GFAP was 43%[35-52]). In patients with GCS 15, GFAP showed superior diagnostic accuracy than all CDRs (p<.001; Figure 2, Appendix Table 7).

The diagnostic accuracy in patients without MEI was consistent with the overall results (Figure 2, Appendix Table 8). In patients with MEI, GFAP had better specificity and sensitivity than NOC, NICE and CCHR (p<.001), but the difference was smaller than in patients without MEI. None of the biomarkers had both higher specificity and sensitivity than CHIP in patients with MEI.

GFAP had high diagnostic accuracy relative to the CDRs and other biomarkers in each six-hour sampling time interval since the injury (Appendix Table 9 and Figure 3). Consistent with the sampling-time corrected results, the diagnostic accuracy of UCH-L1 was better in earlier sampling time intervals than in the latest interval, and NFL showed the opposite pattern (Appendix Figure 3). For the outcome potential neurosurgical lesion, GFAP had the best diagnostic accuracy relative to the CDRs and other biomarkers, followed by NFL (Appendix Table 10, Appendix Figure 4).

Combinations of the CDRs, and biomarkers with sensitivity 90% for detecting CT abnormalities

When medium/ minor risk factors of a CDR were only considered positive if a biomarker was positive, respective combinations of the CDRs and biomarkers had slightly lower sensitivity and substantially higher specificity than the CDRs alone for any CT abnormality (Table 4). The improvement in specificity was the largest for GFAP (7-26 pp) and the smallest for NSE (1-7 pp; Table 4). For the outcome potential neurosurgical lesion, the improvement in specificity was the largest for GFAP (5-20 pp) and NFL (6-18 pp; Appendix Table 11).

When the combinations of a CDR and a biomarker were considered positive only if both the CDRs and the biomarker were positive, respective combinations had lower sensitivity and much higher specificity than the CDRs alone, particularly for GFAP (increase 24-46 pp; Appendix Table 12). When the combinations were considered positive if the CDR or biomarker was positive (or both), respective combinations had higher sensitivity (increase 2-24 pp for GFAP) but lower specificity than the CDRs (decrease 3-17 pp for GFAP; Appendix Table 13).

Discussion

We compared the diagnostic accuracy of six biomarkers and four commonly used CDRs, and their combinations, for detecting intracranial abnormalities on CT in mTBI patients. With the threshold set to obtain the same sensitivity as the CDRs, GFAP was substantially more specific than the CDRs. With the same specificity, GFAP was more sensitive. Consistent patterns of GFAP superiority over other biomarkers were observed across GCS levels, sampling time intervals, using sampling-time corrected biomarker values, for absence or presence of major extra-cranial injuries (MEI), and when detecting neurosurgical lesions. Compared to CDRs, the difference was most pronounced in the patients with GCS 15, without MEI, and with later sampling-time intervals. Combining medium/minor CDR risk factors with biomarkers (using a sensitivity threshold of 90% for each biomarker) resulted in improved specificity with minor loss of sensitivity.

Our findings are consistent with the results of the ALERT-TBI study.[13] In that study, GFAP alone and GFAP and UCH-L1 combined, dichotomized based on pre-specified cut-offs, had sensitivities of 96% and 98% respectively in predicting intracranial abnormalities. Furthermore, previous work from the TRACK-TBI [23] group suggested that after adjustment for traditional clinical covariates (age, pupillary exam, GCS, and ISS) GFAP provided a diagnostic benefit for the diagnosis of intracranial injury and was also superior to the American College of Emergency Physicians (ACEP) Guidelines. However, this study included the entire injury spectrum (mild to severe) and did not examine contemporary CDRs. More recently another CENTER-TBI study has demonstrated a robust incremental discriminative ability of blood biomarkers, particularly GFAP, to predict CT positivity compared to clinical parameters, but did not assess the performance against current diagnostic CDRs.[15] A recent US-based study compared the performance of GFAP and UCHL1 with three CDRs, and their combinations, in 349 mild TBI patients (23 with intracranial lesions on CT).[24] The CCHR had the highest specificity, but the combination of CCHR and GFAP had the best diagnostic performance for detecting abnormalities. The authors concluded that the addition of biomarkers to CDRs could improve current practice and should be further investigated.[24]

Based on analyses in CENTER-TBI, GFAP is the best candidate for predicting intracranial injury in mTBI patients with indications for CT, followed by NFL and UCH-L1. S100B, UCH-L1 and t-Tau have relatively high discriminative ability within 0-6 hours post-injury[12,25,26] and lower diagnostic accuracy in later time intervals. Considering the short half-life of S100B,[27] it is not surprising that its diagnostic accuracy was better in the sensitivity analysis corrected to the 2 hour value. Of note, GFAP was still superior, consistent with the comparisons of S100B and GFAP in the

TRACK-TBI study.[23] NFL has a long half-life [27] and showed good diagnostic accuracy and discriminative ability in later sampling-time intervals. Moreover, GFAP was less affected by extra-cranial injuries, in line with other studies:[27] although GFAP had better diagnostic accuracy in the group without MEI than with MEI, it was still superior to other biomarkers in the MEI subgroup.

Our analyses suggested that the commonly used CDRs could be optimized with biomarkers and tailored for specific contexts. Where sensitive rules are used (e.g. CHIP), unnecessary CT scanning could be reduced with minimal loss in sensitivity. In contexts with more conservative CDRs (e.g. NICE and CCHR), detection of more abnormalities could be achieved with similar specificity. Furthermore, differences in diagnostic accuracy of biomarkers over time can be clinically important because some mildly injured patients present after a delay, or may only be seen after longer waiting times at the ER. It may be useful to consider one biomarker such as GFAP that is predictive across sampling times, or to have a panel of biomarkers that covers multiple time intervals when improving upon current CDRs.

Rather than replacing CDRs, it might be preferable to combine GFAP with readily available clinical characteristics. For instance, for the high- risk patients according to the commonly used CDRs, a CT scan would always be indicated, whereas for medium risk patients biomarkers could be the decisive factor. Additionally, using different biomarker sensitivity thresholds in combination with CDRs would allow the selection of alternative trade-offs in specificity and sensitivity improvements, to suit clinical aims and management strategies. This approach to integration of biomarkers with clinical characteristics could make the adoption of biomarkers more attractive to clinicians than replacing the CDRs with biomarkers. For the optimal combinations of the CDRs and biomarkers, CDRs should be updated with re-estimated coefficients for risk factors and biomarkers, and continuous variables (e.g. age and biomarkers) should be considered as such to optimally exploit their diagnostic value. Furthermore, before GFAP can be incorporated in decision making for CT scanning in mTBI, results between different laboratories should be cross-mapped and robust clinical use assay platforms are needed. Moreover, biomarker levels and performance in predicting intracranial lesions should be explored using more diverse samples of patients in terms of race and ethnicity, sex and age.[28]

This study also has limitations. First, in CENTER-TBI, one of the inclusion criteria was a clinical indication for CT, and large trauma centres were overrepresented.[17] This could have contributed to the high percentage of intracranial and potential neurosurgical lesions compared to other mTBI studies. The diagnostic accuracy of CDRs and of biomarkers may differ in mTBI patients presenting to ERs of smaller hospitals. Studies in broader mTBI patient populations are necessary to determine if the gains in

diagnostic accuracy are consistent. Second, most patients had undergone CT scanning before sampling of biomarkers and the sampling time differed between patients with and without CT abnormality. We addressed this issue in subgroup analyses, differentiated by time interval and in a sensitivity analysis in which all biomarker values were modelled towards a 2 hour interval post-injury. Third, a research-use only platform was used for assays of biomarkers GFAP, UCH-L1, NFL, T-tau, for which diagnostic thresholds have not (yet) been established, and coefficients of variation in replicate samples were relatively high.[15] Nevertheless, in order to avoid using artificial biomarker thresholds, we compared diagnostic performance of biomarkers to CDRs based on sensitivity and specificity thresholds of CDRs. Fourth, the diagnostic analyses were not restricted to patients with specific inclusion/exclusion criteria of the CDRs; nonetheless, they were explored in the entire patient group considered relevant (GCS 13-15).[29] Fifth, our study used any intracranial injury on CT as the reference standard, while modern CT scanners can detect small intracranial injuries that are of relatively minor acute clinical consequence. (30) Importantly, our findings were replicated when solely considering lesions that might benefit from neurosurgical intervention.

In conclusion, GFAP outperforms existing CDRs in terms of diagnostic accuracy for predicting any intracranial abnormality or lesions possibly requiring neurosurgery on CT scan. When validated with robust clinical assay platforms, GFAP is a good candidate for updating commonly used CDRs and improving clinical decision making on CT scanning in patients with mTBI.

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Contributors

AM, DvK, EWS, FL, HFL, AIRM, VFLN, DKM designed the study. KW, EC, AB, VFLN and KF substantially contributed to data acquisition. AM performed data analysis under supervision of DvK and EWS. FL, AIRM, DKM substantially contributed to interpretation of data in clinical context. SM performed the literature search and drafted the results of the search. AM drafted the manuscript and DvK, EWS, FL, HFL, AIRM, VFLN, DKM, KW, EC, AB, KF critically revised the manuscript. All authors approved the final version of the manuscript.

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Competing interests

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Supplementary material

Supplementary material is available at https://figshare.com/s/75d2fa065efe0bcb1961

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Chapter 7

Prediction of global functional outcome and post-concussive symptoms after mild traumatic brain injury: external validation of prognostic models in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study

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Abstract

The majority of patients with traumatic brain injury (TBI) are categorized as mild according to a baseline Glasgow Coma Scale (GCS) score of 13 to 15. Prognostic models that were developed to predict functional outcome and persistent post-concussive symptoms (PPCS) after mild TBI have rarely been externally validated. We aimed to validate existing models predicting 3 to 12-month Glasgow Outcome Scale Extended (GOSE) or PPCS in adults with mild TBI.

We analyzed data from the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) project, which included 2862 adults with mild TBI, with 6-month GOSE available for 2374, and the Rivermead Post-concussion Symptoms Questionnaire (RPQ) for 1605 participants. Model performance was evaluated based on calibration (graphically and characterized by slope and intercept) and discrimination (c-index).

We validated five published models for 6-month GOSE and three for 6-month PPCS scores. The models used different cutoffs for outcome and some included symptoms measured 2 weeks post-injury. Discriminative ability varied substantially (C- index between 0.58 and 0.79). The models developed in the CRASH trial for prediction of GOSE<5 discriminated best (C- index 0.78 and 0.79), but were poorly calibrated. The best performing models for PPCS included 2-week symptoms (C- index 0.75 and 0.76).

In conclusion, none of the prognostic models for early prediction of GOSE and PPCS has both good calibration and discrimination in persons with mild TBI. In future studies prognostic models should be tailored to the population of mild TBI, predicting relevant endpoints based on readily available predictors.

Key words: external validation, mild traumatic brain injury, prognostic model, Glasgow Outcome Scale Extended, post-concussive symptoms._

Introduction

Traumatic brain injury (TBI) is a major health concern with over 50 million new cases reported globally every year. [1, 2] Approximately 70- 90% of patients with TBI present with a Glasgow Coma Score (GCS) of 13-15, which falls in the mild TBI category. [3] Although the majority of these patients recover shortly after the incident, a notable percentage continue to have persistent complaints. These complaints can interfere with daily life, social, and work activities, [4, 5] and about 50% of persons with mild TBI do not return to their pre-injury level of functioning 6-months after injury. [6-8]

The most prominent post-injury disturbances are cognitive, emotional, somatic and behavioral symptoms, often referred to as the post-concussive symptoms, [9] or if the sequel of symptoms persist over time, post-concussion syndrome (PCS). The concept of PCS has been questioned in recent years, [10] and therefore some authors refer to the multiple concurrent post-concussive symptoms several months after TBI as persistent post-concussive/post-concussion symptoms (PPCS). [11-14] The prevalence of 6-month PPCS after mild TBI varies substantially between studies, partly because of differences in diagnostic criteria, and is typically between 10 and 40% in civilian samples presenting to hospital. [4, 15-18]

Considering the high percentage of functionally-impaired persons with mild TBI, the economic burden of prolonged treatment and decreased productivity, [19] it is important to promptly identify persons who are at high risk of long-term consequences. Therefore, a well-performing prognostic model for outcome prediction after mild TBI is important to assist patients and health-care providers in making well-informed treatment decisions. Before implementation of a model for decision-making in clinical practice can be considered, it is crucial to assess its performance in an external validation study. In recent years, there have been initiatives towards external validation of prognostic models for mild TBI, [6, 20] but validation studies are still scarce. The CENTER-TBI project provides an excellent opportunity for external validation of existing models in a large prospective cohort of contemporary TBI patients from 18 countries across Europe, and Israel. [21]

The aim of this study was to examine the performance of existing models for prediction of outcome following mild TBI. We searched for published predictors and prognostic models for functional outcome (Glasgow Outcome Scale Extended (GOSE)) and PPCS for mild TBI and validated these prognostic models using the CENTER-TBI database.

Methods

study population

The study population consisted of patients from the prospective longitudinal observational CENTER-TBI study (Core data, version 2.0). Data were collected from December 2014 to December 2017 in 58 centers across Europe and Israel. Ethical approval was granted for each recruiting site and informed consent was obtained for all patients by the patients and/or the legal representative/next of kin. Inclusion criteria for the core study were a clinical diagnosis of TBI, presentation within 24 h after injury, and an indication for CT scanning. [21] The core dataset included 3 strata that are differentiated according to care path: patients seen in the Emergency Room (ER); patients primarily admitted to the intensive care unit (ICU), and patients primarily admitted to the hospital ward (non-ICU).

For this study, 2862 (age 16+) adults with mild TBI, as defined by a baseline GCS of 13-15, were included. 2374 persons had information on 6-month GOSE and 1605 had information on some or all 6- month Rivermead Postconcussion Symptoms Questionnaire (RPQ)[22] items, measuring PPCS.

Measurements

Predictors. Sociodemographic, preinjury and injury characteristics were based on hospital charts. Imaging, blood sampling, and neurological assessment were performed at the ER. Post-concussive and psychological symptoms were assessed at 2-3 weeks post-injury (range 10-27 days) in patients admitted to the ER, and in some centers (participating in an additional imaging sub-study) also in patients admitted to a hospital ward other than the ICU. The following instruments were used: RPQ for post-concussive symptoms, PTSD Checklist for DSM- 5 (PCL-5)[23] to screen for post-traumatic stress disorder (PTSD), Patient Health Questionnaire (PHQ -9)[24] for depression, and Generalized Anxiety Disorder (GAD-7)[25] for anxiety.

Outcome. The GOSE is widely used as a primary outcome in TBI studies. [26] The GOSE provides eight categories of outcome: dead (1); vegetative state (2); lower severe disability (3); upper severe disability (4); lower moderate disability (5); upper moderate disability (6); lower good recovery (7); and upper good recovery (8). The highest score (8) represents a complete return to a preinjury level of functioning. [27]The GOSE was assessed 6 months post–injury, and when outside the time window (range 5-8 months), it was imputed based on GOSE measurements at other time points (approximately 30%).[2, 26] The RPQ is the most frequently employed self-reported symptom inventory measuring PPCS. [28] RPQ consists of 16 cognitive, somatic and emotional symptoms that can be assessed from ''not experienced at all" (0) to ''severe problem" (4), and it was

administered 6 months post-injury.

The self-report instruments were addressed in 18 languages. Prior to the data collection, instruments existing only in English were translated and linguistically validated in the respective languages according to the guidelines of Acquadro. [29] The linguistic validation procedure consisted of multiple steps, including forward translation, cognitive debriefing, backward translation, harmonization, and finalization of translated versions. A manuscript dedicated to the linguistic validations is currently in preparation. Psychometric properties of the instruments have been investigated using criteria of the classical test and item response theory (other publications in preparation).[30-32]

Selection of prognostic models

Eligible prognostic models were selected based on a review with predefined search strategy and predefined inclusion criteria. Existing prognostic models and predictors of GOSE or PPCS were identified by a search in MEDLINE, EMBASE, and the Cochrane Library, that included studies published until May 2019 [Supplement, Table 1], and reference lists of systematic reviews. [33-35] Prognostic models were included if they were developed to predict GOSE or PPCS at 3 -12 months post-injury in patients with GCS 13-15 at baseline. Models that were developed in populations which included other TBI severities were also selected if at least a proportion of patients had a GCS in the range between 13 and 15.Moreover, models had to fulfill at least one of the following quality criteria to be considered eligible: 1) large sample size (N > 500); 2) > 10 outcome events for each candidate predictor considered; 3) the use of shrinkage and/ or some form of internal validation. [36] We extracted predictors of outcome from eligible models and from all studies that explored prediction of 3-12- month GOSE and PPCS in persons with mild TBI.

Statistical analyses

The external validity of the models was assessed with measures of calibration and discrimination. Calibration is the agreement between predicted and observed outcome values and was measured by the calibration intercept, the calibration slope and visualized by a calibration plot. The calibration intercept expresses calibration-in-the-large: if the outcomes are systematically underestimated (intercept <0) or overestimated (intercept>0), and the calibration slope indicates if the strength of the associations between predictors and outcomes is underestimated (slope>1; "underfit") or overestimated (slope <1; "overfit") . A calibration plot graphically compares mean observed with mean predicted outcomes. In a perfect scenario, the calibration intercept and slope would be 0 and 1, respectively, and combinations of predicted and observed outcomes would be on the 45° line. Discrimination refers to the ability to classify patients with a poor versus good outcome based on a prognostic model, and was assessed by the area under the

Operator Receiver Characteristic curve (AUC), which is equal to the concordance (C) index in logistic regression models. The AUC or C- index ranges between 0.50 (no discrimination, equals to chance) and 1.0 (perfect discrimination).

The C- index obtained in validation studies is influenced by differences in both the regression coefficients (slope) and the case-mix heterogeneity. To disentangle their influence on the discriminative ability of logistic regression models, we used the model-based concordance (mbc), which is only influenced by differences in case-mix heterogeneity. [37]

All models were validated using patients with GCS 13-15 with all information on the relevant predictors available in the CENTER-TBI dataset ("complete case analysis"). When predictors were not registered in CENTER- TBI, and therefore were completely unavailable, their predictor effect were set to 0, and only discrimination and calibration slope were assessed. As a sensitivity analysis, models were also validated in all patients with GCS 13-15, using imputation to complete missing data in predictors ("imputation analysis" in one complete dataset).

All analyses were performed in R (3.5.3, R Foundation for Statistical Computing, Vienna, Austria, 2019) using the rms package for model validation[38] and the mice package for imputation of missing values. [39] The calibration plot was created using val. prob.ci.2 function.[40] The 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. [41]

Results

Model selection

Based on the literature search criteria (Supplement- Table 1), 417 abstracts were screened. Based on the full-text screen, forty-three articles described predictors of 3 to 12-month PPCS (n=29), GOSE (n=11) or both (n=3), and 5 articles presented prognostic models for prediction of the GOSE (n=9) and PPCS (n=3) (Table 1; Supplement- Table 2 and Table 3). The most frequent predictors in prognostic models were age, GCS, extra-cranial injuries and alcohol intoxication (Table 1). Other frequent predictors of outcome were: sex/gender [8, 20, 42-46], education [6, 8, 20, 46-51], pre-injury mental health [6, 8, 42, 43, 46, 47, 50, 52-54], cause of injury [6, 42, 45, 47], neuroimaging markers [49, 51, 55-57] and post-injury symptoms [8, 20, 54, 55, 58-60] (Table 1; Supplement- Tables 4 and 5).

Table 1. Predictors of Glasgow Outcome Scale Extended (GOSE) and persistent post-concussive symptoms (PPCS) from the models validated in the CENTER-TBI data

Predictor	GOSE					PPCS		
	CRASH		Nijmegen, RUBICS		UPFRONT	TRACK-TBI Pilot	UPFRONT	Nijmegen, RUBICS
	Basic	CT	Clinical all	Clinical -isolated TBI	ED+			
Preinjury and sociodemographic characteristics								
Age	XX	XX	XX	XX	X	XX	X	X
Sex or Gender	X	X	X	X	X	XX	XX	X
Education		XX			XX	XX	X	X
Country income	XX							
Mental health					XX	XX		X
Physical health							X	XX
Previous TBI					X	XX	X	X
Headache/migraine						XX	X	
Seizures						X		
Injury and peri-injury characteristics								
GCS	XX	XX	X	X	XX	X		X
Abnormal pupillary response	XX	XX	X	X				
Injury severity			XX	XX				
Hypotension			X	X				
Hypoxia			X	X				
CT abnormalities [1]		XX	X	X	X	X		X
Cause of injury	X	X						
Extra-cranial injury	XX	XX	XX			X	X	X
Facial fractures				X				
PTA			X	X	XX	XX	X	X
LOC			X	X		XX	X	X
Time from injury	X	X						
Alcohol intoxication			XX	XX	XX	X		
Anticoagulants			X	X	XX			
Neck pain					X		XX	
Early symptoms [2]							XX	
Post-injury symptoms at 2 weeks								
Depression					XX			
Anxiety					XX			
Post-concussive symptoms					XX		XX	XX
Posttraumatic stress					X		XX	XX
Coping styles					XX			
Fatigue								X
Self-efficacy								X

Note: XX =final model; X= candidate predictor; CT= Computed Tomography; ED= Emergency Department; GCS= Glasgow Coma Score; LOC= Loss of Consciousness; PTA= Post-traumatic amnesia. [1] hemorrhagic contusion, petechial hemorrhage, ventricle and cisterns obliteration, subarachnoid hemorrhage, mid-line shift, non-evacuated hematoma; [2]headache, nausea, dizziness.

We validated five models predicting GOSE and three models predicting PPCS (Tables 2 and 3). Additional three models were deemed unsuitable for validation because more than 70% of predictor variables were not available (CT and Combined Nijmegen model[7]) or because the model equation was not available (ED UPFRONT model [8]).

Eligible models predicting GOSE

Models for predicting 6-month GOSE were the Basic and CT models from the CRASH trial; [61]Clinical models for mild TBI and isolated TBI the Nijmegen Radboud University Brain Injury Cohort Study (RUBICS) study; [57] and the ED+ model from the UPFRONT study [8] (Table 2). All models predicted dichotomized GOSE, but with differently defined endpoints: severe disability or death (GOSE<5), disability or death (GOSE<7) or complete/upper good recovery (GOSE=8), respectively (Table 2). They contained different predictors, but all models included a measure of injury severity (GCS, ISS or major extra-cranial injury), and most models also included age and alcohol intoxication. In addition to admission characteristics, the UPFRONT model included 2- week symptoms (Table 2), which were assessed with different instruments than in the CENTER-TBI study (and therefore rescaled in validation). The predictors neck pain at the ER and coping styles from the UPFRONT model were not assessed in the CENTER-TBI study. The CRASH models were developed in an adult population with GCS 3-14, which partly includes mild TBI. In our study, they were validated in adults with GCS 13-15 and GCS 13-14. Other models were developed only in the population with GCS 13-15. The UPFRONT model was developed in patients with loss of consciousness (LOC) <30 min and posttraumatic amnesia (PTA) <24h, and no major psychiatric disorders (Table 2). These inclusion criteria were not used in our validation, but were applicable to the majority of the validation population and therefore were not expected to impact the results.

Table 2. Models for predicting Glasgow Outcome Scale Extended (GOSE) validated in the CENTER-TBI data.

Study	Model	Population; Setting	Outcome	Predictors	Reported performance (AUC)
CRASH, 2008	Basic model	Adult GCS 3-14	GOS<4 (GOSE<5) at 6 months	-Age (after 40 years) -GCS -Pupillary reactivity -Extra-cranial injury	0.81*
	CT model			Basic model plus -Petechial hemorrhage -Obliteration of third ventricle and cisterns -Subarachnoid hemorrhage -Mid-line shift -Non-evacuated hematoma	0.83*
Nijmegen-RUBICS, 2010	Clinical	Adult GCS 13-15 Neuro-logical/surgical consultation; Level 1 trauma center, the Netherlands, 1998-2005	GOSE <7 at 6 months	-Age -Injury Severity Score Total -Alcohol intoxication	0.71
		GCS 13-15 No polytrauma (isolated TBI)		-Age -Injury Severity Score-Head - Alcohol intoxication	0.69
UPFRONT, 2017	ED+	Adult GCS 13-15 LOC <30 min; PTA<24h, no major psychiatric disorder; three level-1 trauma centers, the Netherlands, 2013-2015	GOSE=8 at 6 months	-Education -Mental health history -Alcohol intoxication -Neck pain -GCS -PTA duration -Depression (2 weeks) -Anxiety (2 weeks) -Complaints (2 weeks) -Passive coping style -Avoidant coping style	0.77**

Note: C=Concordance; AUC= Area under the Curve; CT= Computed Tomography; ED= Emergency Department; GCS= Glasgow Coma Score; PTA= Post-traumatic amnesia.*for high-income countries;**after internal validation.

Eligible models predicting PPCS

Models predicting 6-month PPCS were developed in the TRACK-TBI pilot study, UPFRONT and Nijmegen studies (Table 3). The endpoint was differently defined or measured by different instruments (Table 3). In the TRACK-TBI pilot [46], PPCS were assessed with the RPQ and dichotomized according to International Classification of Diseases (ICD) criteria for PCS; that is, a score ≥2 on at least three of the following symptoms: headache, dizziness, fatigue, irritability, sleep disturbances, poor concentration, forgetfulness, poor memory, frustration, or depression.. [46] In the UPFRONT study, dichotomization of PPCS was done in a similar way, but measured using the Head Injury Severity Checklist (HISC). The Nijmegen study defined high PPCS as a score ≥2 on 13 out of all 16 RPQ items. The TRACK-TBI Pilot model only included admission characteristics as predictors, whereas the other models also included symptoms measured approximately 2 weeks post-injury (Table 3). These symptoms were assessed by different instruments (Supplement- Table 6). In addition, there were

some differences between development and validation studies in the definition and measurement of preinjury mental, physical health, headache and nausea (Supplement-Table 6). The TRACK-TBI Pilot study excluded patients with major psychiatric, neurological or life-threatening diseases; UPFRONT included patients who sustained LOC or PTA, and without substance addiction; and Nijmegen included patients with age 18-60 and LOC<30 min (Table 3). The validation population was not restricted based on age, psychiatric disorder, LOC or PTA. Substance addiction and LOC>30min were reported for only a small number of patients in the validation population. As sensitivity analyses, the validation population for the UPFRONT model was restricted to sustained LOC and/or PTA, and the validation population for the Nijmegen model to age group 18-60 (Supplement- Table 9).

Table 3. Models for predicting persisting post-concussive symptoms (PPCS) validated in the CENTER-TBI study.

Model	Population; Setting	Outcome	Predictors	Reported performance (AUC)
TRACK TBI Pilot, 2017	Adult GCS 13-15; 3 level I trauma centers, US, 2010-2012	score ≥2 on 3 out of 8 symptoms[1] (ICD) measured by RPQ at 6 months	-Age -Female sex -Years of education -Preinjury migraine or headache -Preinjury psychiatric disorders -Prior TBI -PTA -LOC	0.74
UPFRONT, 2018	Adult GCS 13-15; sustained LOC or PTA, no substance addiction, dementia; 3 level I trauma centers, the Netherlands, 2013-2015	3 out of 8 symptoms (ICD) measured by HISC at 6 months	-Female sex -Neck pain -Nausea -Headache -Post-concussive symptoms (2 weeks) -Post-traumatic symptoms (2 weeks)	0.75*
Nijmegen, RUBICS, 2008	GCS 13-15; LOC<30 min, 18-60 years old; 1 level I trauma center, the Netherlands, 2004-2006	score ≤ 2 on 13 out of 16 RPQ items at 6 months	- Preinjury physical health - Post-concussive symptoms (0-37 days) - Post-traumatic symptoms (0-37 days)	0.73*

Note: AUC= Area under the Curve; GCS= Glasgow Coma Score; HISC= Head Injury Severity Checklist; ICD= International Classification of Diseases; LOC= Loss of consciousness; PTS= Post-traumatic symptoms; RPQ=Rivermead Post-concussion symptoms Questionnaire.[1] headache; dizziness; fatigue; irritability; sleep disturbances; poor concentration; forgetfulness, poor memory; frustration or depression *after internal validation.

CENTER-TBI data

In total 2862 adults with mild TBI were included in CENTER-TBI. The majority were male (64%) and around half were admitted to a non-ICU hospital ward (47%). The mean age was 53 years (IQR 33-68) and the mean years of education 13 [11-16]. The majority of patients had a GCS of 15 (71%).More than a quarter had a major extra-cranial injury (27%) and almost half CT abnormalities (45%) [Supplement- Table 7].

Subsamples without available 6-month outcomes did not differ from the overall cohort in the majority of baseline characteristics, but patients with completed 6-month RPQ were somewhat more educated, had more CT abnormalities at baseline, a higher proportion of PTA and LOC, and a slightly lower percentage of psychiatric disorders (Supplement-Table 7).

Sample with available both 2-3 week symptoms and 6-month outcomes differed from the total cohort: patients were mostly discharged after ER, had a median age of 51 years (35-63), a higher proportion of females, more patients with GCS 15; and a smaller proportion of patients with major extra-cranial injuries, and with CT abnormalities [Supplement- Table 7].

More than 70% of persons achieved good recovery (GOSE>=7), with 49% of persons completely returning to their preinjury level of functioning (GOSE=8). Nevertheless, 11% experienced severe disability or had died (GOSE<5) at 6 months. 43% of persons had mild to severe PPCS (ICD classification for PCS), and 22% moderate to severe PPCS (ICD classification for PCS). Distributions of some predictors and outcomes differed in the CENTER-TBI compared to the development studies, particularly for models from the CRASH trial [Supplement- Table 6].

Model performance in CENTER-TBI study

Models predicting GOSE

The CRASH models showed poor calibration and good discrimination for the outcome GOSE<5, which was observed in only 11 % of patients. Percentage of death/unfavorable outcome was overestimated (Basic model: 20% vs. 11%, calibration intercept=-0.82; Table 4), particularly for the CT model (27% vs 11%; calibration intercept=-1.38; Table 4). In population with GCS 13-14, i.e. the patient selection that was used in the development study, calibration-in-the-large was better (calibration intercept=-0.26 for Basic, -1.13 for CT, Table 4). The calibration slope was close to 1 indicating similar effects of predictors compared to the CRASH trial. Models showed good discriminative ability, especially the CT model (c- index=0.79; Table 4). The discriminative ability of the CRASH models was somewhat reduced by the more homogeneous patient population of CENTER-TBI compared to the development population, as expressed by the expected C- index if the model was correct (mbc=0.79-80 versus c-index of 0.81-0.83 in the development data, Table 4).

The Nijmegen Clinical models showed relatively good calibration, with slight underestimation of proportions of unfavorable outcome (GOSE<7; 26% vs. 28%; 22% vs. 26%; Table 4). The slopes suggested smaller effects of predictors (slope=0.82-0.83; Table 4) and slightly worse discriminative ability in CENTER-TBI than in the Nijmegen

study (C index= 0.66.-0.69). The mbc indicated a somewhat more heterogeneous patient case-mix in the CENTER-TBI study compared to the Nijmegen study (mbc=0.72-0.70 versus C-index 0.71-0.69; Table 4), which increased the ability to correctly discriminate between patients with GOSE <7 and GOSE ≥7.

For the ED plus model calibration- in- the- large was not assessed because several predictors were not registered in CENTER-TBI. Discrimination was assessed, but it was expected to be lower due to absence of several predictors in the CENTER-TBI data. The ability to discriminate patients with complete recovery (GOSE=8) was lower than in the development study (C index=0.70; Table 4). Analyses of C indices and slope suggested smaller effects of predictors in CENTER-TBI and substantial overfitting (slope=0.5; Table 4). If the regression coefficients were valid for the CENTER-TBI sample, the model would have a good discriminative ability (mbc=0.80; Table 4), and even slightly better than in the development study (c=0.77, Table 4) because of the more heterogeneous case-mix in the CENTER-TBI study.

Table 4. Results of external validation of models predicting 6-month Glasgow Outcome Score Extended (GOSE) in patients with mild traumatic injury (TBI) - complete case analyses in the CENTER-TBI study (n=2269).

Models for 6- month GOSE	Development	Validation					
	C	Sample/ outcome events	Intercept [95% CI]	Predicted vs. Observed Outcome	mbc	C [95% CI]	Slope [95% CI]
CRASH, Basic	0.81	2269/259	-0.82 [-0.96, -0.68]	20%; 11%	0.79	0.78 [0.74, 0.81]	0.96 [0.83, 1.09]
		558/111	-0.26 [-0.49,-0.03]	23%; 20%	0.79	0.76 [0.76, 0.77]	0.95 [0.73,1.16]
CRASH, CT	0.83	2064/233	-1.38 [-1.53,-1.22]	27%; 11%	0.80	0.79 [0.75,0.82]	0.90 [0.78,1.02]
		492/93	-1.13 [-1.39,-0.87]	34%; 19%	0.82	0.78 [0.73,0.84]	0.82 [0.63,1.01]
Nijmegen Clinical -in all mild TBI	0.71	2248/635	0.13 [0.02,0.23]	26% ; 28%	0.72	0.69 [0.66,0.71]	0.82 [0.71,0.94]
Nijmegen Clinical -in Isolated TBI (no polytrauma)	0.69	1098/284	0.24[0.1,0.38]	22% ; 26%	0.70	0.66 [0.59,0.74]	0.83 [0.64,1.02]
UPFRONT ED +	0.77	548/352**	/	/	0.80	0.70 [0.66,0.75]	0.49 [0.36-0.62]

***subset with GCS 13-14. ****predicting positive outcome.** C= concordance; CI= Confidence Interval; ED= Emergency Department; mbc=model based concordance.

Models predicting PPCS

The TRACK -TBI Pilot model correctly estimated the proportion of patients with PPCS, defined as having 3 or more mild to severe symptoms at 6 months (42% vs. 42%; Table 5), but showed overfitting (slope<0.5; Table 5) and poor discriminative ability (C index=0.58; Table 5). The mbc was substantially higher than the observed C index (mbc=0.74 vs. 0.58, Table 5) and equivalent to the C in the development study (C=0.74, Table 5). This pattern suggested that predictor effects (regression coefficients) differed between studies, whereas case-mix heterogeneity was comparable.

Models for prediction of PPCS which included 2-week post-injury symptoms were validated in a smaller sample of CENTER-TBI patients, for whom that information was available, and they performed well (C index 0.75-0.76). For the UPFRONT model, calibration in the large was not assessed due to an unmeasured predictor (neck pain) in the CENTER-TBI study. The discrimination ability (C index= 0.75; Table 5) and the effects of predictors were equivalent to UPFRONT (slope=1.0; Table 5). The Nijmegen model was well- calibrated; but it slightly overestimated the proportion of persons with high PPCS at 6 months (19% vs. 15%; Table 5). The calibration slope was close to 1 indicating similar effects of predictors. Discrimination was even slightly higher than in the development study (C index =0.76; Table 5) because of the somewhat more heterogeneous patient case-mix of the CENTER-TBI study compared to Nijmegen.

Table 5. Results of external validation of models predicting persisting post-concussive symptoms (PPCS) in patients with mild traumatic injury (TBI) - complete case analyses in the CENTER- TBI study (n=1292).

Model for PCS	Development	Validation					
	C	Sample/ outcome events	Intercept [95% CI]	Predicted vs. Observed Outcome	mbc	C [95% CI]	Slope [95% CI]
TRACK TBI Pilot; 2017	0.74	1292/544	-0.02 [-0.14,0.10]	42%; 42%	0.74	0.58 [0.55,0.61]	0.32 [0.20,0.43]
UPFRONT; 2018	0.75	408/147	/	/	0.75	0.75 [0.71,0.80]	1.02 [0.78,1.27]
Nijmegen; 2008 **	0.73	403/61	-0.32 [-0.62,-0.01]	19%; 15%	0.74	0.76 [0.69,0.82]	1.03 [0.77,1.28]

****to be comparable with other models, high PCS were set as endpoint instead of low PCS.**
C= concordance; CI= Confidence Intervals; ED= Emergency Department; mbc=model based concordance.

Calibration plots are shown in a Supplement[Figures 1-7]. The performance of models was consistent in analyses after imputation of missing values, except for models containing 2- week post-injury symptoms, which showed lower performance [Supplement- Table 8]. The sensitivity analyses with the additional inclusion criteria used in the development study showed somewhat better performance of UPFRONT and Nijmegen models for PPCS (Supplement- Table 9).

Discussion

This study identified predictors and prognostic models for 3-12 months GOSE and PPCS in persons with mild TBI; and examined the performance of five models for predicting 6- month GOSE outcome and three models for predicting 6-month PPCS in an independent dataset of mild TBI patients from the CENTER-TBI study. Overall, the definitions of unfavorable outcome differed between studies, and the ability of the models to distinguish between favorable and unfavorable outcome varied substantially (c-index 0.58-0.79). The CRASH models predicting severe disability or death discriminated best, but they were poorly calibrated to the population of mild TBI patients. For prediction of PPCS, the models which included 2-week post-injury symptoms showed the best discriminative ability and were well calibrated. In models with reasonable discriminative ability, the most frequent predictors were age, GCS and extra-cranial injuries for GOSE, and preinjury health and post-injury symptoms for PPCS.

CRASH models discriminated well but they largely overestimated the percentage of persons with poor outcome, and used the endpoint (GOSE<5) that may not be appropriate for the mild TBI population. It was developed for mostly moderately to severely injured patients whereas the validation population consisted of mildly injured patients. In the previous external validation in persons with mild TBI, [6] CRASH models showed good discriminative ability and miscalibration in the population GCS 13-14, consistent with this study, but discriminated poorly in the total mild TBI population. The Nijmegen model (2008) for GOSE showed somewhat lower discriminative ability and some overfitting in our study, and low performance in the previous external validation, [6] which could be partly due to high number of candidate predictors and lack of internal validation in the model development. The performance of the UPFRONT model could not completely be assessed in the CENTER-TBI data.

The model for PPCS based on admission characteristics (TRACK-TBI, 2008) showed poor performance, consistent with the previous external validation. [20]A relatively small sample size for the development of the prognostic model, particularly effective sample size for binary outcome, might have led to unstable regression coefficients, and consequently, differences in performance between development and validation studies. [46] In addition, true differences in populations might also have contributed to the differences in effects of predictors between studies. The performance of models containing post-injury symptoms (UPFRONT 2017; Nijmegen, 2008) were in line with their performance in the development studies. Nevertheless, the CENTER-TBI sample in which these models have been validated (both 2-3 weeks post-injury symptoms and 6- months PCS scores available) had lower injury severity, younger age, lower percentage of CT abnormalities and higher GOSE than the overall mild TBI population in the

CENTER-TBI. Therefore, the performance of the models may have been different in the total mild CENTER-TBI population.

Although post-injury symptoms substantially improve prediction of outcomes, they are measured several days or weeks post-injury, which does not routinely happen across hospital centers and for all persons with mild TBI. The majority of centers only follow persons that were admitted to hospital, and frequently schedule appointments a month or later following injury, [62] when symptoms are already persisting. The clinical applicability of a model containing predictors measured after discharge is therefore debatable for some hospital settings, and when the intention is to make predictions at the time of presentation/admission. Symptoms measured weeks after injury may be particularly helpful for making decisions about rehabilitation and specialized care. A model based on measures of medical history, injury characteristics and early symptoms, which are easily obtainable and have shown associations with outcomes following TBI in previous studies, may be more universally useful for the early prediction of outcome. For instance, protein biomarkers are currently considered to have potential for diagnosis and prediction in the context of TBI. [63-65] However, their prognostic value for longer-term outcomes following mild TBI is yet to be established.

Beside difficulties in the selection of appropriate predictors, problematic practices and lack of agreement in assessment and definition of outcomes hinder development of prognostic models for both GOSE and PPCS. The models for functional outcome used different cut-offs of GOSE to define the endpoint, which could partly explain the variability in performance between them. It may be more difficult to discriminate between persons with mild TBI with incomplete and complete return to pre-injury functioning (e.g. GOSE <8) than between persons with and without disability (GOSE<7 or even GOSE<5), [6] and different predictors may be relevant for predicting upper good overall recovery (GOSE=8) versus disability/ death (GOSE<5). In addition, using GOSE as an ordinal outcome seems to have added value over dichotomization. [66] Of note, the overall utility of using GOSE as an outcome measure in persons with mild TBI has been disputed, because the measure may not be sensitive enough to capture different health disturbances despite good overall functioning. Usage of a broad battery of different measures in CENTER-TBI and TRACK-TBI studies, which cover health-related generic and disease-specific quality of life, return to work and daily activities, and cognitive and psychological functioning, provide new opportunities for prognostic modelling of outcome following mild TBI. [65, 67, 68] Moreover, composite measures based on several instruments, and encompassing different symptoms together with global functioning have been proposed as an alternative to GOSE. [55] Nevertheless, our study confirms that a significant percentage of persons with mild TBI do not return to baseline global functioning 6 months post-injury. [6, 8]

Similarly, there is no agreement regarding the clinical criteria or operational definition of PCS or PPCS. [17].The Common Data Elements (CDEs) initiative, which aims to standardize data collection in TBI, recommends the RPQ for assessing post-concussive symptoms, but does not provide further guidance. [69] For instance, PCS can be mapped to ICD-10 based on several RPQ items, [17, 20, 46, 70] thereby using different scoring criteria (mild or worse and moderate or worse symptoms); composed from all RPQ items, [58] or based on a cutoff of the total RPQ score. [71] According to the classification methods and criteria in use, associations with predictors and other outcome measures (such as GOSE) vary substantially. [17] In our study, models for PPCS used different definitions of outcome and/or different instruments for measuring post-concussive symptoms. Therefore, a sensible and uniform definition of the PCS or PPCS endpoint is a prerequisite of a good model.

A limitation regarding this study is that some of the predictors from validated models were not assessed in the CENTER-TBI study (e.g. early neck pain and coping styles), which prevented assessment of calibration intercepts and could have influenced other performance indices. Moreover, some predictors and outcomes were measured by different tools and instruments (e.g. medical history, psychological symptoms). The differences emphasize the importance of incorporating newly discovered predictors into the CDEs and using uniform instruments in TBI research. Additionally, the prognostic models we validated were selected based on our search strategy and eligibility criteria, and do not necessarily represent all existing prognostic models for mild TBI.

Furthermore, a substantial percentage of CENTER-TBI patients did not have an assessment of 2-3 week post-injury symptoms and 6- month outcomes ; therefore, the models which included 2-3 week symptoms were validated in a smaller and more favorable subsample. The response rate at 6-months was, however, in line with other observational studies in the field and comparable with the response rate in the development studies. Patients with and without 6-month RPQ differed in some baseline characteristics, but without a clear pattern that would suggest a substantial systematic influence on the validation results. Further, recruitment in CENTER-TBI study was not consecutive and referral centers for neurotrauma were overrepresented. The self-report instruments were administered in several languages and in several European countries, but the linguistic and cultural comparability was good (unpublished data). A major strength of this study is the use of a large and representative sample of contemporary patients from different countries and numerous medical centers. In addition, all important indices relevant for external validation studies are reported. [72]

In conclusion, we assessed the performance of several prognostic models for GOSE and

PPCS. None of the models predicting GOSE have both good discriminative ability and good calibration in persons with mild TBI. Models for PPCS based on admission characteristics perform poorly, whereas models that included post-injury symptoms perform better in terms of discrimination and calibration. TBI-related and psychological symptoms collected at 2 weeks improve prediction and should be collected when possible. Novel predictors obtainable at admission, such as biomarkers, could be incorporated in future model developments. Future studies should improve prediction following mild TBI by developing models that 1) distinguish well between persons who will have longer- term negative outcomes and who will not; 2) are calibrated to the population of mild TBI; 3) use relevant cutoffs and endpoints for persons with mild TBI, such as return to normal life without TBI-related symptoms; 4) use predictors available at admission or before discharge, which are feasible to collect in clinical practice for early detection of persons with longer-term consequences. These models could be extended with symptoms collected at 2-3 weeks for later stage outcome prediction.

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Author Disclosure Statement

All authors: No competing financial interests exist.

Ethical approval

The CENTER-TBI study (EC grant 602150) has been conducted in accordance with all relevant laws of the EU if directly applicable or of direct effect and all relevant laws of the country where the Recruiting sites were located, including but not limited to, the relevant privacy and data protection laws and regulations (the "Privacy Law"), the relevant laws and regulations on the use of human materials, and all relevant guidance relating to clinical studies from time to time in force including, but not limited to, the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) ("ICH GCP") and the World Medical Association Declaration of Helsinki entitled "Ethical Principles for Medical Research Involving Human Subjects". Informed Consent by the patients and/or the legal representative/next of kin was obtained, accordingly to the local legislations, for all patients recruited in the Core Dataset of CENTER-TBI and documented in the e-CRF. Ethical approval was obtained for each recruiting site. The list of sites, Ethical Committees, approval numbers and approval dates can be found on

the website: https://www.centertbi.eu/project/ethical-approval

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Supplementary material

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Chapter 8

External validation of prognostic models predicting outcome after chronic subdural hematoma

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Abstract

Background: Several prognostic models for outcome after chronic subdural hematoma (CSDH) treatment have been published in recent years. However, these models are not sufficiently validated for use in daily clinical practice. We aimed to assess the performance of existing prediction models for outcome in patients diagnosed with CSDH.

Methods: We systematically searched relevant literature databases up to February 2021 to identify prognostic models for outcome prediction in patients diagnosed with CSDH. For the external validation of prognostic models, we used a retrospective database, containing data of 2384 patients from three Dutch regions. Prognostic models were included if they predicted either mortality, hematoma recurrence, functional outcome, or quality of life. Models were excluded when predictors were absent in our database or available for <150 patients in our database. We assessed calibration, and discrimination (quantified by the concordance index C) of the included prognostic models in our retrospective database.

Results: We identified 1680 original publications of which 1656 were excluded based on title or abstract, mostly because they did not concern CSDH or did not define a prognostic model. Out of 18 identified models, three could be externally validated in our retrospective database: a model for 30-day mortality in 1656 patients, a model for 2-month, and another for 3-month hematoma recurrence both in 1733 patients. The models overestimated the proportion of patients with these outcomes by 11% (15% predicted vs. 4% observed), 1% (10% vs. 9%) and 2%, (11% vs. 9%); respectively. Their discriminative ability was poor to modest (C of 0.70[0.63-0.77]; 0.46[0.35-0.56]; 0.59[0.51-0.66]; respectively).

Conclusions: None of the examined models showed good predictive performance for outcome after CSDH treatment in our dataset. This study confirms the difficulty in predicting outcome after CSDH and emphasizes the heterogeneity of CSDH patients. The importance of developing high-quality models by using unified predictors and relevant outcome measures and appropriate modeling strategies is warranted.

Keywords: Chronic subdural hematoma, prognostic models, external validation, recurrence, mortality

Introduction

Chronic subdural hematoma (CSDH) is a common condition in neurosurgical practice. CSDH is mainly diagnosed in older adults with an overall reported incidence ranging from 20.6-79.6 per 100,000 persons per year.[2,6,24,33] Burr-hole craniostomy is the most commonly performed and worldwide most accepted treatment option in symptomatic CSDH[41,26], most often with the insertion of closed-system drainage.[17,7,4,8,36] In CSDH, the multiplicity of (peri)operative options may influence the outcome after surgical treatment, in addition to the variety of outcome measures such as recurrence, mortality, functional outcome, and quality of life. However, the outcome of CSDH is not only influenced by treatment choices. Outcome can also be related to baseline characteristics such as age, sex, comorbidity, severity of symptoms, the use of medication, and the severity of abnormalities seen on baseline imaging. The contribution of various (peri) operative features to outcome is still under investigation in multiple randomized controlled trials.[15]

Multivariable prognostic models are developed to predict outcome based on baseline patient characteristics. Model-based outcome predictions can inform clinicians and patients and improve decision-making.[29] For instance, models can be used to predict the probability that a hematoma will require re-operation, and hence inform the patients and their next-of-kin on what outcome to expect and which treatment option may be optimal.[45] Even if the same treatment strategy is implemented for all patients, a prognostic model can improve their management. For example, a patient with higher probability of poor outcome can be invited for an earlier appointment or additional rehabilitation. Apart from clinical practice, prognostic models can be used for covariate adjustment in clinical trials and for standardized outcome comparisons between studies, countries or centers.[52,29]

However, prognostic models are developed in a specific patient population and do not have to be equally successful in making predictions in another setting. Before considering the implementation of a model in clinical practice, the model should show good performance in an independent population in a different place or time.[13]

Over the years, several CSDH prognostic models[56,48,46,42,37,34,31,20,12,11,5,54,23,58,57,40,30,10,25,3,55,27,22,16,1,38] have been published. The developers of CSDH prognostic models aim to predict and stratify patients' risk of mortality, recurrence, and/or functional outcome after surgical CSDH treatment. These models are developed in a specific patient population and have not been externally validated. External validation – assessing the performance of a model in a sufficiently large cohort of patients in a different place or time – is essential before these prognostic models can be considered for guiding clinical decisions.

Moreover, external validation and updating of existing models are preferred before starting developing new models.

This study aims to identify existing prognostic models for outcome after CSDH treatment and to assess the performance in a large dataset of CSDH patients.

Material and methods

Literature search

Medline Ovid, Embase, Web of Science, Cochrane Central, and Google Scholar were systematically searched from their starting dates to February 2021 (See Supplemental Table 1 for search string). Titles and abstracts of these studies were screened by the first author (DCH) to identify all CSDH prognostic models after which the full text was screened. Any discrepancies were discussed (authors DCH, AM, RD, and HL) and resolved through consensus.

Selection of studies: Inclusion and exclusion criteria

Studies were included if they contained at least one predictor of one of the outcomes of interest in patients with CSDH, that is mortality, recurrence, and functional status. Studies only describing possible predictors of outcome, without the development and presentation of a prediction model, were excluded. In addition, when predictors were absent in our data or were available for only a small number of patients (pre-specified minimum: 150 patients), these models were also excluded. We did not set specific quality criteria that the development studies needed to satisfy to be included.

Data extraction

From each paper, we extracted: the number of patients, inclusion criteria, predictors, outcomes, the prediction model, and its discriminative ability in the development study (area under the curve (AUC).

Study population of the validation cohort

Independently from each other, three regions of the Netherlands (Amsterdam (AM), Rotterdam (RO), and North-East (NE)) collected retrospective data from 2384 consecutive patients who were treated for a CSDH in different time frames between 1991 and 2019. Amsterdam included 288 patients diagnosed between 2012 to 2018. In Rotterdam, two cohorts of patients were included: 509 patients diagnosed between 1991 to 2008 and 280 patients diagnosed between 2010 to 2015. North-East Netherlands included 1307 patients in this database, diagnosed between 2004 to 2019. Data were completely anonymized, all potentially identifying information was removed by the treating hospital, and merged into a large retrospective database, which became the

validation cohort for this external validation study.

Measurement of predictors and outcomes in the validation cohort

Patient characteristics were extracted from clinical records.

The CSDH preoperative volume was measured with different methods. Researchers in Amsterdam used Brainlab AG (Munich, Germany) and researchers in North-East Netherlands used the ABC/2 volume formula. This formula can be used fast and easily with good accuracy.[53]

One of the prognostic models used the occurrence of septations within the CSDH.

The presence or absence of septations was not always available in our database. Only if a patient was diagnosed with a 'trabecular' or 'membranous' CSDH, information on septations was present. In other hematoma types, we could not deduce the presence of septations from the name of the hematoma type only and therefore hematoma types other than 'trabecular' or 'membranous' were scored as not containing septations.

Mortality within 30 days (yes/no) was determined based on the time of death.

Hematoma recurrence was defined as receiving medical treatment (reoperation or retreatment with dexamethasone) for CSDH.

Statistical analyses

The performance of prediction models was evaluated in terms of calibration and discrimination. Calibration refers to the agreement between predicted and observed risk and it was visualized by a calibration plot, and quantified by calibration in the large (agreement between average observed and predicted outcomes and calibration intercept) and a calibration slope.[50] The calibration intercept expresses the difference between the average predicted risk and the average observed risk. An intercept >0 indicates that predictions were on average too low, and an intercept <0 indicates that predictions were on average too high. The calibration slope indicates if the average strength of the association between predictors and outcomes was correctly estimated. A slope <1 indicates overfitting (overestimated associations), whereas a slope >1 indicates underfitting (underestimated associations).

Discrimination describes the ability of a model to correctly separate patients with the outcome and without, and it was quantified by the concordance (C) index. The C-index estimates the probability that the risk prediction of randomly selected patients with the outcome (e.g. with CSDH recurrence at three months) was higher than the risk

prediction of a randomly selected patient without that outcome (e.g. without CSDH recurrence at three months).

To understand the influence of the slope and case-mix heterogeneity on the discriminative ability of a model, we calculated the model-based concordance (mbc).[51] The mbc is only influenced by the case-mix heterogeneity, and not by the validity of regression coefficients.

Models were validated in a) patients who had relevant data available (complete case analysis); and b) in patients with missing predictor values imputed (imputation analysis). In imputation analysis, if a predictor variable was not assessed in a certain region, values for all patients on that variable were imputed based on available data from other hospitals. The model for multiple imputation included predictor and outcome variables, hospital regions, and auxiliary variables (e.g., hematoma thickness, aphasia, midline shift). The results were averaged over 10 imputed datasets using Rubin's rules.[35] Missing outcomes were not imputed.

If a model was developed for a specific population (e.g. older adults), the model was validated in all patients with CSDH, and in that specific subgroup (e.g. older adults). The performance of models was assessed and presented for the pooled data of all hospital centers and three separate regions in the Netherlands.

Analyses were performed in R (version 3.6.0)[32] using packages rms[18], and mice[49].

Results

Included publications

The initial search identified 3105 studies of which 1680 remained after the removal of double references (Figure 1).

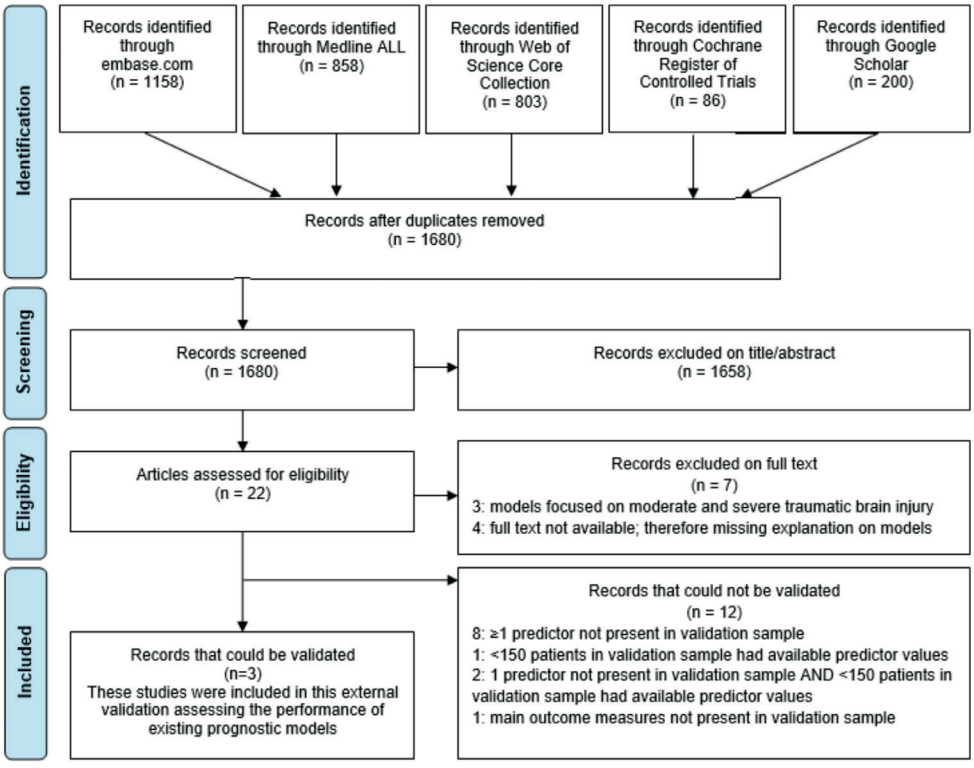

Figure 1. Flow Diagram on the article selection process.

Sixteen hundred fifty-eight records were excluded based on title/abstract because they did not concern CSDH and/or they only reported predictors of outcome, but did not develop a prognostic model. The remaining 22 articles were screened on full text of which 7 were excluded on full text; three articles were excluded because they did focus on moderate and severe traumatic brain injury and not on CSDH specifically. Four articles were excluded because the full text was not available and therefore no further explanation on the prognostic models could be found.

The remaining 15 articles were included but of these 12 could not be validated (Figure 1, Table 1).

Table 1. Papers presenting models that could not be validated in our data

Author, year	Model	N	Predictors	Outcome
Abouzari, 2009	-	300	Age, Glasgow Coma Scale, Hematoma density, Hematoma thickness, Midline shift, Sex, Brain atrophy, Intracranial air	Recurrence
Chen, 2010	**P-POSSUM**	531	Age, Glasgow Coma Scale, Respiratory history, Systolic blood pressure, Cardiac signs, Electrocardiogram, Laboratory results: haemoglobin, white cell count, urea, sodium, potassium, Pulse	Mortality
Chihi, 2021	**FLOP-score**	119	Age, Glasgow Coma Scale, Motor deficit, Brain Natriuretic peptide	Functional status (modified Rankin Scale; mRS)
Maldaner, 2019	**FIT-Score**	253	Age, Motor deficit, Orientation	Functional status (mRS) at 3 months
McIntyre, 2020	**iGCS versus CCI**	109	Charlson Comorbidity Index (CCI), Glasgow Coma Score, 5-and 11-factor modified Frailty Index (mFI-5 and mFI-11)	Discharge location and mortality
Riemann, 2020	-	755	Age, Comorbidities, Glasgow Coma Score, Haemoglobin	Unfavourable outcome
Sastry, 2020	-	1647	5-factor modified Frailty Index	Complications, discharge location, readmission and mortality
Shen, 2019	-	102	Use of antithrombotics, Brain atrophy, Pneumocephalus volume	Recurrence of bilateral CSDH
Stanisic, 2017	**Oslo CSDH Scale**	107	Density on CT-scan, Preoperative CSDH volume, Postoperative CSDH volume	Recurrence requiring reoperation
Won, 2019	**modified Oslo Grading System (mOGS)**	389	Density on CT-scan, Preoperative CSDH volume, Postoperative seizure, Postoperative air trapping, Postoperative CSDH volume	Postoperative recurrence
Yan, 2018	-	514	Age, Preoperative CSDH volume, CSDH classification, Postoperative CSDH volume	Postoperative recurrence
Kwon, 2018	**CSDH Scoring System**	154	Age, Glasgow Coma Scale, Hematoma thickness, Midline shift, Motor function, Orientation	Functional status (mRS) at 6 months

*GCS: Glasgow Coma Scale; **SDH=SubDural Hematoma; ǂTBI=Traumatic Brain Injury

For eight articles one or more predictors of the described models could not be found in our retrospective database (e.g., frailty scores, laboratory results, and pneumocephalus volume). For one article less than 150 patients in the validation cohort had available predictor values (e.g. postoperative volume), and for two articles one predictor could not be found in our retrospective database and another predictor had too many missing values. For one article the main outcome measure was missing in our retrospective database. Finally, three papers (4 models) were included in the external validation (Table 2).

Table 2. Papers included in the external validation

Author, year	Model	Population	Operative technique	Predictors	Outcome	AUC in the development study
Alford et al., 2020	Subdural Hematoma in the Elderly (SHE) score	Age >65 with an CSDH (N=89) Retrospective data	Unknown	Age (<80, ≥80), Admission GCS score* (3-4, 5-12, 13-15), SDH** volume in mL (<50, ≥50)	30-day mortality	0.80
Andersen et al., 2018	Model A-postoperative Model B-preoperative (in nomograms)	Unilateral CSDH, diagnosed 2010-2012 (N=763). Retrospective data	Burr-hole craniostomy or craniotomy	SDH**volume, Type, Drainage time, Subgaleal drain, Surgical complications, History of hypertension	3-month recurrence requiring reoperation	optimism-corrected c index of 0.63 for model A; 0.60 for model B
Jack et al., 2014	Risk factor scoring system for CSDH	CSDH, diagnosed 2005-2009 (N=331). Retrospective data	Burr-hole craniostomy or craniotomy	Age (≤80, >80), SDH**volume in mL (≤160, >160), Septations in SDH**	2-month recurrence requiring reoperation	Not reported

*GCS: Glasgow Coma Scale; **SDH=SubDural Hematoma; ǂTBI=Traumatic Brain Injury

Models selected for validation

All selected models were developed for patients with unilateral hematoma. The Subdural Hematoma in the Elderly (SHE)-scoring model by Alford, 2020 [3] was developed to predict 30-day mortality in older patients (>65 years) based on age, admission Glasgow Coma Scale (GCS) score, and hematoma volume. The model by Jack, 2014 [23] was developed to predict 2-month hematoma recurrence based on age, hematoma volume, and septations on CT. The preoperative prognostic model (Model B) proposed by Andersen, 2019 [5] aimed to predict 3-month recurrence based on hematoma volume, hematoma density, and history of hypertension. Andersen's postoperative model (Model A) additionally included drainage time, drain type, and surgical complications (Table 1). The Andersen models, developed with Fine-Gray regression, were validated based on predictions derived from their nomograms (Supplemental Table 2).

Population

1760 patients with a unilateral hematoma were included (55% from NE, 35% from RO, 11% from AM; Table 2). Four primary treatment modalities were used; 47% received surgery, 43% surgery with additional dexamethasone, 3% dexamethasone, and 7% a wait and see policy. The mean (SD) age was 73.0 years (12.4), 1293 male (74%), and mean hematoma volume was 112 mL (cc) (54.5). 4% of patients died within 30 days, 9% had a recurrence of CSDH requiring retreatment at 2 months, and 10% at 3 months (Table 3).

Table 3. Baseline characteristics, predictors and outcomes of patients with chronic subdural hematoma

	Overall	Missing	Available 30-day mortality (Alford)	Missing	Available 2-month recurrence (Jack)	Missing	Available 3-month recurrence (Andersen)	Missing
Sample size	1760		1656		1733		1733	
Sex =male (%)	1293 (73.5)	0	1232 (74.4)	0	1276 (73.6)	0	1276 (73.6)	0
Hospital (%)		0		0		0	159 (9.2)	0
Amsterdam	186 (10.6)		87 (5.3)		159 (9.2)		963 (55.6)	
North-East	963 (54.7)		963 (58.2)		963 (55.6)		611 (35.3)	
Rotterdam	611 (34.7)		606 (36.6)		611 (35.3)			
Treatment (%)		0		0		0		0
Wait and see	129 (7.3)		129 (7.8)		129 (7.4)		129 (7.4)	
Surgery	830 (47.2)		731 (44.1)		803 (46.3)		803 (46.3)	
Surgery + dexamethasone	754 (42.8)		749 (45.2)		754 (43.5)		754 (43.5)	
Dexamethasone	47 (2.7)		47 (2.8)		47 (2.7)		47 (2.7)	
Predictors								
Age (mean [SD])	73.0 (12.4)	0	73.0 (12.4)	0	72.9 (12.4)	0	72.9 (12.4)	0
Hypertension (%)	218 (16.1)	22.9	X		X		X	
Baseline Glasgow Coma Scale score (%)		6.5		6.4	X		X	
<5	4 (0.2)		4 (0.3)					
5-12	195 (11.8)		192 (12.4)					
13-15	1447 (87.9)		1354 (87.4)					
Baseline total volume [mL] (mean [SD])	112.6 (54.5)	46.6	111.3 (54.8)	47.8	112.8 (54.7)	46.9	112.8 (54.7)	46.9
Baseline septations (%)	335 (37.2)	48.8	X		328 (37.1)	49	X	
Density (%)		45.4	X		X			46
Homogenous	503 (52.3)						487 (52.0)	
Membranous	331 (34.4)						325 (34.7)	
Mixed	4 (0.4)						3 (0.3)	
Separated	123 (12.8)						121 (12.9)	
Drainage time (%)		56.9	X		X			57.2
No drain	100(13.2)						98 (13.2)	
1-24 hours	385 (50.7)						373 (50.3)	
24-48 hours	205 (27.0)						202 (27.2)	
>48 hours	69 (9.1)						69 (9.3)	
Surgery drain type (%)		74.9	X		X			75.7
No drain	100 (22.6)						98 (23.3)	
Subdural	163 (36.9)						147 (34.9)	
Subgaleal/subperiosteal	179 (40.5)						176 (41.8)	
Postoperative surgical complications (%)	99 (7.2)	22.4	X		X		95 (7.1)	22.7
Outcomes								
Mortality 30 days (%)	65 (3.9)	5.9	65 (3.9)	0	X		X	
Recurrence within two months (%)	155 (8.9)	1.5	X		155 (8.9)	0	X	
Recurrence within three months = 1 (%)	164 (9.5)	1.5	X			X	164 (9.5)	0

X= not in the model; SD=Standard Deviation; mL=milliliters.

Performance of models in the retrospective database

Sixteen hundred fifty-six patients with available information on 30-day mortality were selected for validation of Alford's model and 1733 patients with available information on 2-month and 3-month hematoma recurrence were selected for validation of Jack's model and Andersen's models, respectively.

The prognostic model of Alford predicted that 15% of patients would die within 30 days, whereas the observed proportion in our data was 4%. Thus, it overestimated the proportion of patients dying within 30 days by 11 percentage points (intercept= -1.51 [-1.77,-1.26]; Figure 2a, Table 4).

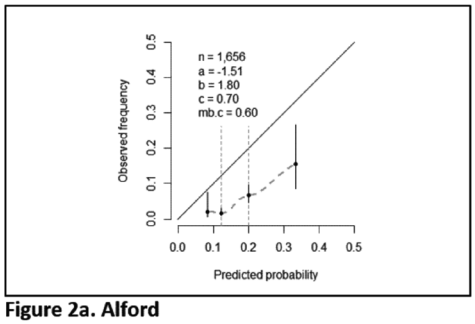

Figure 2a. Alford

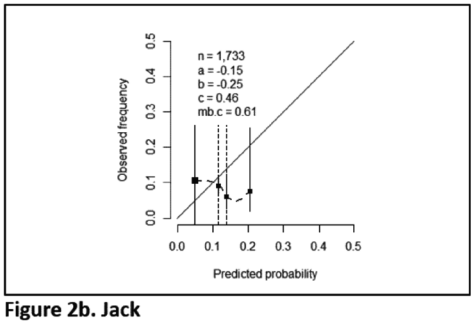

Figure 2b. Jack

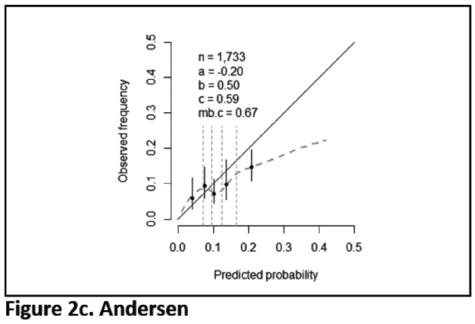

Figure 2c. Andersen

n=number of patients included
a=intercept
b=slope
c=concordance index
mbc=model based concordance

Figure 2. Performance of models in the retrospective database; **Figure 2a.** Alford.

Table 4. Performance of models (Alford, Jack and Andersen) in external validation: complete case and imputation analyses

	Alford model	Jack model	Andersen model	
			Model A	Model B
Original C	0.80	x	0.63*	0.60*
Mbc	0.60	0.61	0.72	0.67
Complete case analysis				
N/ event number	823/ 23	852/79	22/3	782/77
M predicted; M observed (%)	15%; 2.8%	15%; 2.8%	15%; 2.8%	15%; 2.8%
Intercept	-1.84[-2.25,-1.42]	-0.04[-0.27,0.19]	-0.63[-1.90,0.65]	-0.25[-0.49,-0.01]
C	0.70[0.59-0.82]	0.48[0.43-0.54]	0.67[0.31-1.02]	0.60[0.54-0.67]
Slope	1.92[0.99,2.85]	-0.02[-0.47,0.43]	0.69[-0.85, 2.22]	0.63[0.25,1.02]
Imputation analysis				
N/ event number	1656/65	1733/155	1733/164	1733/164
M predicted-, M observed (%)	15.4%, 3.9%	10.2%, 8.9%	13.9%, 9.5%	11.3%, 9.5%
Intercept	-1.51[-1.77,-1.26]	-0.15[-0.33,0.02]	-0.46[-0.73,-0.19]	-0.20[-0.44,0.05]
C	0.70[0.63-0.77]	0.46[0.35-0.56]	0.65[0.57-0.73]	0.59[0.51-0.66]
Slope	1.80[1.17,2.43]	-0.25[-1.05,-0.56]	0.64[0.18,1.11]	0.50[0.01,1.00]

*corrected for optimism. C= concordance index; M= Mean; Mbc= Model based concordance; N= sample size.

The overestimation of the 30-day mortality rate was consistent for the patient selection (>65 years) that was used for model development (16% predicted vs. 5% observed; intercept= -1.38[-1.65, -1.12]); Supplemental Table 2). The slope (1.92[0.99, 2.85]) indicated a stronger association between the predictors and the outcome in our data. Nevertheless, the discriminative ability (C=0.70[0.63-0.77]) was reduced by the more homogeneous case-mix in our study (mbc= 0.60 versus C= 0.80 in the development study).

The prognostic model by Jack (2-month hematoma recurrence) showed a negative calibration slope, indicating reverse predictor effects (-0.25[-1.05,-0.56]). This indicated that higher predicted probabilities of recurrence by the model were in our data associated with lower observed rates. Additional analyses showed, for instance, that, in contrast with the model, age above 80 was associated with a lower likelihood of recurrence at 2 months in our data (Supplemental Figure 1).

The proportion of patients with recurrent hematoma by 3 months was estimated accurately (10% predicted vs. 9 % observed; intercept= -0.15[-0.33, 0.02]), but the discriminative ability of the prognostic model was extremely poor (C<0.50; Table 4; Figure 2b).

Andersen's preoperative model (3-month hematoma recurrence) (B) slightly overestimated the proportion of patients with a recurrence within 3 months (11% predicted vs. 9% observed; intercept= -0.20[-0.44, 0.05]). The calibration slope indicated that the effect of the predictors on outcomes in the validation data was much weaker than in the model (calibration slope=0.50[0.01, 1.00]; Table 4). The discriminative ability of model B

(C= 0.59[0.51-0.66]), corresponded to the development study (C=0.60), but also reflected the more heterogeneous case-mix in the validation study (mbc=0.67; Figure 2c).

The performance of Andersen's postoperative model (3-month hematoma recurrence) (A) was assessed with great uncertainty due to a large amount of missing data in postoperative variables (e.g. type of drain). The effects of predictors were weaker in the validation study (calibration slope=0.64[0.18, 1.11]) and the model overestimated the proportion of patients with 3-month recurrence (14% predicted vs. 9% observed; intercept= -0.46 [-0.73,-0.19]). It showed a slightly higher discriminative ability (0.65[0.57-0.73]) than in the development study (C=0.63), lifted by a more heterogeneous case-mix than in the development study.

The results of complete case analyses were consistent with imputation analyses (Table 4). In addition, analyses per hospital region generally showed consistent results (Supplemental Table 3).

Discussion

We examined the performance of three published prognostic models for the prediction of outcome in patients with unilateral CSDH using a retrospective database, which contains data from three regions in the Netherlands. None of the models showed both good discriminative ability and calibration in our data. The most likely explanations of the predictive performance of the models in our data concern suboptimal modeling strategies and differences in study populations.

The differences in the population (case-mix) and differences in the distribution of predictors (case-mix heterogeneity) between the development and validation study can affect model performance in the validation setting. The prognostic model by Alford [3] largely overestimated the percentage of patients who died within 30 days, which could be associated with the substantially different mortality rate between the development study and validation study. It is possible that the patient population was more severely affected in the development study, which was not captured by the predictors in the model; for instance, patients might have had more comorbidities. In addition, although this model was able to discriminate reasonably well between patients who died and did not die within 30 days based on age, hematoma volume, and GCS score, the discrimination ability was decreased by the more homogeneous case-mix in our data. The case-mix and case-mix heterogeneity of the validation data also differed compared to the study of Andersen; for instance, patients had a higher GCS score, a smaller hematoma volume, a lower percentage of drain placement, and a different distribution of hematoma density.[5] In our retrospective validation cohort dataset almost half of the patients were treated

with dexamethasone; 43% of patients were operated with additional dexamethasone and 3% received primary dexamethasone. In these patients the recurrence rate might be lower, but also favorable outcome is expected to be worse and patients in the validation cohort might suffer from more adverse events and higher mortality in comparison the cohorts used for model development.[21]

Moreover, the effects of predictors differed between our study and development studies. For instance, whereas older age was predictive of 2-month recurrence in the model of Jack[23], in our dataset age above 80 was associated with a lower recurrence rate. It is possible that older patients were more likely to die or to receive no treatment at all, in case of hematoma recurrence or in case of comorbidity or greater frailty scores in the validation study. However, frailty scores were not included in the retrospective database. In addition, different definitions of predictors could have contributed to observed differences in the effects of predictors. For example, the inter-rater variability concerning the classification of hematoma types is considered low,[47] but assessing septations on a CT scan is prone to inter-rater variability because membranes cannot always be clearly recognized on CT scans.[39] If the predictor 'septations' was not specifically scored in patients, trabecular hematomas were marked as 'septations present'. All other hematoma types (homogenous, mixed, and separated) were marked as 'septations absent'. This restraint in detecting septations in the validation cohort is expected to lead to an underestimation of septations in our population, because septations can also occur in homogenous, mixed, and separated hematoma types.

Finally, suboptimal modeling strategies have likely negatively affected the effects of predictors and model performance in a new setting (our data). A very small sample size of older adults with CSDH was used for the development of the Alford model[31]. In addition, in the models of Alford[31] and Jack[23], continuous predictors were dichotomized/categorized (e.g., age, hematoma volume). Although categorization can make a model seem appealing and easier to use, it leads to a loss of information and usually poor performance in other cohorts.[28,43]. Furthermore, the predictors were selected based on p-values and there was no internal validation, which lead to overfitting; meaning that predictor effects are overestimated, model performance in the development sample is overoptimistic, and performance in external validation is poor(er).[44] The authors of the Andersen[5] model did apply shrinkage in the model development, an approach to prevent overfitting, but the models still showed weaker effects of predictors in our study, probably due to differences in case-mix. In addition, the discriminative ability of this model was also modest in the development study (C=0.60). The generally limited discriminative ability obtained in both the development study and validation cohort suggests that other variables could be considered for the prediction of this outcome in future studies.

Besides considering other predictors, the strategies for developing models for predicting outcome after CSDH should therefore be improved. Future studies should comprise large samples and collaborative efforts. The predictors should not be primarily selected by p-values but based on level I evidence and clinical expertise. Also, internal validation should be applied in model development. In that way, the effects of predictors are less likely to be exaggerated leading to optimistic model performance.[44]The categorization of continuous variables should be avoided and missing values should be imputed using single or multiple imputation techniques.[28,43] Unified definitions of baseline data elements (predictors) and a unified core outcome set would also facilitate a more reliable establishment, validation, and clinical usefulness of models. In addition, when proposing a new prognostic model, all relevant information that indicates model performance and enables future external validation studies should be reported, such as full model equation and discriminative ability.

Furthermore, the results also suggest that it is difficult to predict the outcome after CSDH. It is known that "there is significant heterogeneity in the data elements that are collected and reported as part of clinical studies examining outcomes for CSDH".[9] Moreover, the disease CSDH itself is also heterogeneous. CSDH patients have in common that they are generally older and that most have a high GCS score on admission, but many other characteristics differ such as frailty and overall clinical status. From our experience, a more voluminous CSDH does not necessarily indicate a larger midline shift or more severe clinical symptoms. Also, a less voluminous hematoma does not always result in a rapid recovery without the occurrence of a recurrence. Moreover, the use of anticoagulants is not necessarily related to a more voluminous CSDH, and more severe symptoms at admission are not necessarily related to a poorer functional outcome. This heterogeneity in the data of CSDH patients makes prediction inherently challenging.

Limitations and future directions

In this study, we systematically searched for published models for the prediction of outcome after CSDH and validated eligible models in our multicenter database. However, we did not perform a systematic review nor assessed the quality of published studies, since we considered the validation as 'proof' of validity. However, since our retrospective database was originally not built to validate these prognostic models, a substantial number of models could not be validated in our data due to unmeasured predictors and outcomes, and due to a large number of missing values. We nevertheless describe these models and encourage other studies with available data to validate all models identified by our search. Also, for the models we did validate there was a significant percentage of missing data. Although complete case and imputation analyses point in the same direction, this should be noted as a limitation. Moreover, although

we systematically searched the literature to identify existing models. Finally, we did not consider the number of outcomes and our data-quality insufficient to develop a new model.

Even if we would have used a prospective database, there are no well-established predictors and outcomes derived from level-I evidence. Currently, there is no consensus on the definition of CSDH and no consensus on baseline data elements nor a core outcome set. The CODE-CSDH group established a Delphi survey to reach consensus on a core outcome set and baseline data elements to be used in future CSDH studies.[19] Results of this survey are expected in the spring of 2022. It is expected that these results will be a first step in decreasing the heterogeneity and with that improving the quality of available CSDH data. The Dutch Subdural Hematoma Research group (DSHR)[14] is planning to establish a prospective, observational, multicenter registry. Once consensus is reached on the Delphi survey, the DSHR will incorporate the baseline data elements and core outcome set in their prospective database. In the future, this prospective registry can be used for the development of a new prognostic model. This future model should predict endpoints that are relevant for clinical practice. These endpoints will correspond to the core outcome set, as to be determined at the consensus meeting of the CODE-CSDH group.

Conclusion

Published models for the prediction of outcome following CSDH did not perform well in our retrospective database. The study confirms the complexity of predicting outcome in patients with CSDH and the need for the collection of standard baseline variables and a core outcome set and for improved modeling strategies, which will improve current prognostic models. This should be part of the focus of future large-scale data collections.

Compliance with Ethical Standards

Conflict of Interest: All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval: This article does not contain any studies with human participants performed by any of the authors.

Informed consent: For this type of study formal consent is not required.

Supplementary material

Supplementary material is available at: https://link.springer.com/article/10.1007/s00701-022-05216-8#Sec17

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Chapter 9

Does poor methodological quality of prediction modeling studies translate to poor model performance? An illustration in traumatic brain injury

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Abstract

Background: Prediction modeling studies often have methodological limitations, which may compromise model performance in new patients and settings. We aimed to examine the relation between methodological quality of model development studies and their performance at external validation.

Methods: We systematically searched for externally validated multivariable prediction models that predict functional outcome following moderate or severe traumatic brain injury. Risk of bias and applicability of development studies was assessed with the Prediction model Risk Of Bias Assessment Tool (PROBAST). Each model was rated for its presentation with sufficient detail to be used in practice. Model performance was described in terms of discrimination (AUC), and calibration. Delta AUC (dAUC) was calculated to quantify the percentage change in discrimination between development and validation for all models. Generalized estimation equations (GEE) were used to examine the relation between methodological quality and dAUC while controlling for clustering.

Results: We included 54 publications, presenting ten development studies of 18 prediction models, and 52 external validation studies, including 245 unique validations. Two development studies (four models) were found to have low risk of bias (RoB). The other eight publications (14 models) showed high or unclear RoB. The median dAUC was positive in low RoB models (dAUC 8%, [IQR -4% to 21%]) and negative in high RoB models (dAUC -18%, [IQR -43% to 2%]). The GEE showed a larger average negative change in discrimination for high RoB models (-32% (95% CI: -48 to -15) and unclear RoB models (-13% (95% CI: -16 to -10)) compared to that seen in low RoB models.

Conclusion: Lower methodological quality at model development associates with poorer model performance at external validation. Our findings emphasize the importance of adherence to methodological principles and reporting guidelines in prediction modeling studies.

Keywords: Prognostic model studies, Traumatic Brain Injury, PROBAST

Introduction

Prediction models estimate an individual's risk of a certain outcome based on a combination of (clinical) characteristics. Despite numerous efforts to provide guidelines and recommendations for the reporting and analyses of prediction modeling studies[1,2], these studies often suffer from methodological limitations. Prior reviews have judged the methodological quality of prediction modeling studies generally as poor[3-5], due to the small sample size of the derivation cohort, and a lack of internal and external validation. Furthermore, prediction modeling studies often suffer from incomplete reporting, which could indicate that specific methodological aspects were not considered.

Prognostic models that predict functional outcome after moderate and severe TBI are abundant in the literature; 67 prognostic models for moderate and severe TBI have been developed, of which 31 were externally validated over the past decades[6]. The ability to accurately predict patient outcome after traumatic brain injury (TBI) has an important role in clinical practice and research. Outcome prognostication may support clinicians in providing reliable information to patients and relatives, and guide clinical management and study design.

Satisfactory methodological quality of prediction modeling studies is considered a prerequisite before implementation of the model in clinical practice should be advocated. Usability of a prediction model, which could be determined by whether sufficient information is provided about the model to enable use in practice, is expected to stimulate its implementation. The reporting of the full model equation enables validation, whereas the development of an online calculator might facilitate use in clinical practice. Assessing the quality of included studies and model usability are therefore important steps in systematic reviews of prediction models.

Recently, the PROBAST tool has become available to assess the risk of bias and concerns regarding applicability of studies that develop and/or validate a multivariable prediction model in systematic reviews[7]. Risk of bias indicates that shortcomings in the study design, conduct, or analysis may lead to systematically distorted estimates of model predictive performance. Methodological quality of prediction modeling studies might therefore be related to model performance, with lower methodological quality resulting in poor performance, especially in new patients and settings.

The aim of our study was to empirically examine the relation between the methodological quality of a model development study and model performance at external validation.

Methods

Systematic Search

We used data from a recent systematic review of multivariable prediction models based on admission characteristics (first 24 hours after injury), for patients after moderate and severe TBI (Glasgow Coma Scale ≤ 12) that were published between 2006-2018[6] (Supplementary Table 1 and 2). The protocol of this systematic review has been registered on PROSPERO (registration number 2016: CRD42016052100). Studies were eligible for inclusion if they reported on the development, validation or extension of multivariable prognostic models for functional outcome in patients aged ≥ 14 years with moderate and severe TBI. There were no limitations concerning outcome measurement, provided that functional outcome was measured between 14 days and 24 months after injury.

We updated the systematic search for 2019-2021 (December 2018-June 2021). One investigator (IRH) independently screened records for possibly relevant studies based on title and abstract. Subsequently, full texts of potentially relevant articles were assessed for eligibility. In case of doubt, a second investigator (AM) was consulted.

Study Selection

We selected externally validated prediction models for moderate and severe TBI (Supplements Table 1) as previously identified by Dijkland et al., (2019) or identified through the updated search. To be included, the model development study had to report model performance in terms of discriminative ability. The external validation could be described in the same publication that described model development, or in a separate publication.

Table 1. Methodological quality of model development studies for outcome following moderate and severe traumatic brain injury in terms of Applicability and Risk of Bias assessed with the original PROBAST and models' usability in research and clinical practice.

Study	Models	Applicability				Risk of bias					Usability	
		Participant selection	Predictors	Outcome	Overall applicability	Participant selection	Predictors	Outcome	Analysis	Overall RoB	Research	Practice
Knaus	APACHE II	H	L	L	H	L	L	L	H	H	y	y
Le Gall	SAPS II	H	L	L	H	L	L	L	H	H	n	y
Lemeshow	MPM II models	H	L	L	H	L	L	L	H	H	n	n
Signorini	Signorini	L	L	L	L	L	L	L	H	H	n	y
Hukkelhoven	Hukkelhoven model	L	L	L	L	L	L	L	L	L	y	y
Maas	Rotterdam CT score	L	L	L	L	L	L	L	U	U	n	y
Perel	CRASH models	L	L	L	L	L	L	L	U	U	n	y
Steyerberg	IMPACT models	L	L	L	L	L	L	L	L	L	y	y
Jacobs	Nijmegen models	L	L	L	L	L	L	L	H	H	y	y
Yuan	Yuan models	L	L	L	L	L	U	L	H	H	n	y

Risk of Bias: Low = L; High = H; Unclear = U
Usability: No = n; Yes = y
All models within the same publication were judged the same on applicability, risk of bias and usability and therefore results are reported per publication.

Table 2. Overview of risk of bias, applicability, usability and similarity in study design of development and validation studies.

Model development studies (N=10 development studies)		
Overall Risk of Bias of development studies		
High	6	60%
Low	2	20%
Unclear	2	20%
Applicability of development studies		
High	3	30%
Low	7	70%
Unclear	0	0%
Usability of models		
Research		
Yes	4	40%
No	6	60%
Clinical practice		
Yes	9	90%
No	1	10%
External validation studies (N=245)		
Similarity in study design between development and validation cohorts		
Similar	147	60%
Cohort to trial	26	11%
Trial to cohort	71	29%
NA	1	
Relatedness		
Related	35	14%
Moderately related	45	18%
Distantly related	164	67%
NA	1	

Risk of bias: Risk of bias was assessed with the original PROBAST (Supplementary Table 3).
Usability: The model was deemed usable in research if the full model equation or sufficient information to extract the baseline risk (intercept) and individual predictor effects was reported, and usable in clinical practice if an alternative presentation of the model was included (e.g. a nomogram, score chart or web calculator).
Relatedness: To judge relatedness we created a relatedness rubric, aiming to capture various levels or relatedness by dividing the validation studies into three categories: 'related', 'moderately related', and 'distantly related' (Supplementary Table 4).

Data Extraction

One investigator (IRH) extracted data from the included studies. A check for all included studies was performed by a second investigator (AM). For the development studies, the data extraction form was based on the Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modeling Studies (CHARMS) checklist[8], and included the source of data, participants, outcome, sample size, predictors, missing data, model development, performance measures, and presentation. For the validation studies, data was extracted on the study design, setting, inclusion criteria, sample size, and model performance. To ensure consistency of the data extraction, the form was tested on two studies by both investigators.

If one publication reported on multiple prediction models, data extraction was performed separately for each model. Prediction models were classified as separate if they included

a different set of predictors (e.g. IMPACT core, and IMPACT extended[9]). Models with identical set of predictors, but for different outcomes (e.g. mortality and unfavorable outcome) were not classified as separate models.

Risk of Bias and Applicability

Risk of bias and applicability of included development studies were assessed with the Prediction model Risk Of Bias Assessment Tool (PROBAST)[7]. Judgements on high, low, or unclear risk of bias for the model development studies were made for five key domains (participant selection, predictors, outcome, sample size and participant flow, and analysis) using 20 signaling questions (Supplementary Table 3). We also used a short form based on the PROBAST including 8/20 signaling questions, which was recently proposed and validated, and showed high sensitivity (98%) and perfect specificity to identify high RoB[10].

Table 3. The median AUC at development and external validation and the absolute and percentage change between development AUC and validation AUC stratified by Risk of Bias (RoB) of model development studies based on the original PROBAST.

	N	Median AUC at development (N=10) [IQR]	Median AUC at external validation (N=245) [IQR]	Median delta AUC [IQR]	Median AUC change in percentage [IQR]
Low RoB	139	0.78 [0.77, 0.79]	0.80 [0.76, 0.84]	0.02 [-0.01, 0.06]	8% [-4, 21]
High RoB	45	0.86 [0.84, 0.86]	0.79 [0.69, 0.84]	-0.06 [-0.16, -0.01]	-18% [-43, -2]
Unclear RoB	61	0.83 [0.81, 0.86]	0.83 [0.77, 0.88]	0.00 [-0.06, 0.04]	0.0% [-19, 10]

To determine if there was a reasonable number of outcome events in a logistic regression (PROBAST item 4.1), The lowest number of events in the smallest group of two outcome frequencies (patients with the outcome versus without the outcome) was divided by the total degrees of freedom used during the whole modeling process. The total degrees of freedom was based on the number of variables (continuous variables) or categories (categorical variables) in the model; henceforth referred to as Events Per Parameter (EPP). All candidate predictors were considered as part of the modeling process, including those not selected for the multivariable model based on univariable regression analysis or selection procedures. We assumed a reasonable number of outcome events when EPP ≥10.

Concerns regarding the applicability of an included study to the review question can arise when the population, predictors, or outcomes of the included study differ from those specified in the review question[7]. Applicability was judged based on three key domains (participant selection, predictors, and outcome).

Two reviewers (IRH and AM) independently completed the PROBAST checklist (Supplementary Table 3). A third independent reviewer (LW) scored two of the model development studies (17%). Discrepancies between reviewers were resolved through

discussion or by consultation with a senior member (DvK) of the review team. The RoB, applicability and usability were reported per study, in which we presented one assessment for models described in the same publication, but with a different set of predictors (e.g. IMPACT core, and IMPACT extended) and models with identical set of predictors, but for different outcomes (e.g. mortality and unfavorable outcome). An overall judgement about risk of bias and applicability of the prediction model study was reached based on a summative rating across all domains according to the PROBAST criteria (low, high, or unclear).

Usability

A model's usability in research and clinical practice was rated for its presentation with sufficient detail to be used in the intended context and target population. The model was deemed usable in research if the full model equation or sufficient information to extract the baseline risk (intercept) and individual predictor effects was reported, and usable in clinical practice if an alternative presentation of the model was included (e.g. a nomogram, score chart or web calculator).

Relatedness

For validation studies, we assessed the similarity between the derivation population and the validation population for each study, which we refer to as "relatedness". To judge relatedness we created a rubric, aiming to capture various levels or relatedness by dividing the validation studies into three categories: 'related', 'moderately related', and 'distantly related' [6] (Supplementary Table 4). The rubric contained three domains: I) setting (Intensive Care Unit, Emergency Department, Ward; Country; Not specified), II) inclusion criteria and III) outcome assessment and timing. Studies that did not meet the domain about setting were judged 'moderately related', whereas studies that did not meet the domains about inclusion criteria and/or outcome assessment and timing were judged 'distantly related'.

Table 4. Results of generalized estimated equations (GEE) for the percentage change in AUC between 10 development and 245 validation studies.

	Percentage change in AUC (95% CI)
Intercept	9.5% (5.5, 13.4)
Risk of bias (Low)	
High	-31.7% (-48.2, -15.2)
Unclear	-13.4% (-16.4, -10.3)
Study design (Similar)	
Cohort to trial	-18.5% (-26.2, -10.8)
Trial to cohort	0.19% (-3.7, 4.1)

The generalized estimated equations (GEE) model includes a random intercept on model level (N=18), Risk of Bias assessment (Low, High, Unclear based on the original PROBAST) and similarity in study design between the development and validation study (Similar, Cohort to trial, Trial to cohort) to estimate the percentage change in AUC between the development and validation studies. The intercept indicates the percentage change in AUC for low risk of bias models with a similar study design between the development and validation study.

Model Performance

Model performance was summarized in terms of discrimination and calibration. In prior studies, discrimination was assessed in terms of the c statistic or AUC, which ranges between 0.50 (no discrimination) and 1.0 (perfect discrimination). In prior studies, calibration was typically assessed with the calibration intercept *a*, which indicates whether predictions are systematically too low or too high, and should ideally be 0. Prior studies also reported the calibration slope *b* which indicates whether the overall prognostic effect of the linear predictor of the developed model is over- or underestimated, and should ideally be 1.

Relation between Methodological Quality and Model Performance

To quantify the relation between methodological quality at development and model performance at external validation, we first calculated the change in discriminative performance between the derivation cohort and the validation cohort. The percent change in discrimination was calculated as follows:

$$\%\ change\ in\ discrimination = \frac{(validation\ AUC - 0.5) - (derivation\ AUC - 0.5)}{(derivation\ AUC - 0.5)}\ x\ 100$$

For instance, when the AUC decreases from 0.70 in derivation to 0.60 in validation, this drop of 0.10 points represents a 50% loss in discriminative power (since 0.50 represents the lowest possible value). We calculated the median and interquartile range (IQR) of the change in discrimination for low, high and unclear RoB models.

We used generalized estimated equations (GEE) to estimate the effect of the RoB classification (Low; High; Unclear RoB based on the original PROBAST) on the observed change in discrimination, taking into account the correlation between validations of the same model and similarity in study design between the development and validation study (Similar; Cohort to trial; Trial to cohort).

Evidence synthesis

A synthesis was provided for the included development and external validation studies. Extracted data, RoB, applicability and usability were presented in summary tables and where appropriate in graphical representations. Figures were constructed with R software version 3.6 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study Selection

We included 54 publications comprising 18 multivariable regression models (Figure 1). The publications include ten (10/55) model development papers, describing 18 models, and 52 (52/54) validation papers, describing 245 external validations. These 18 models were previously described by Dijkland et al., (2020), and no additional models were included based on the updated search strategy.

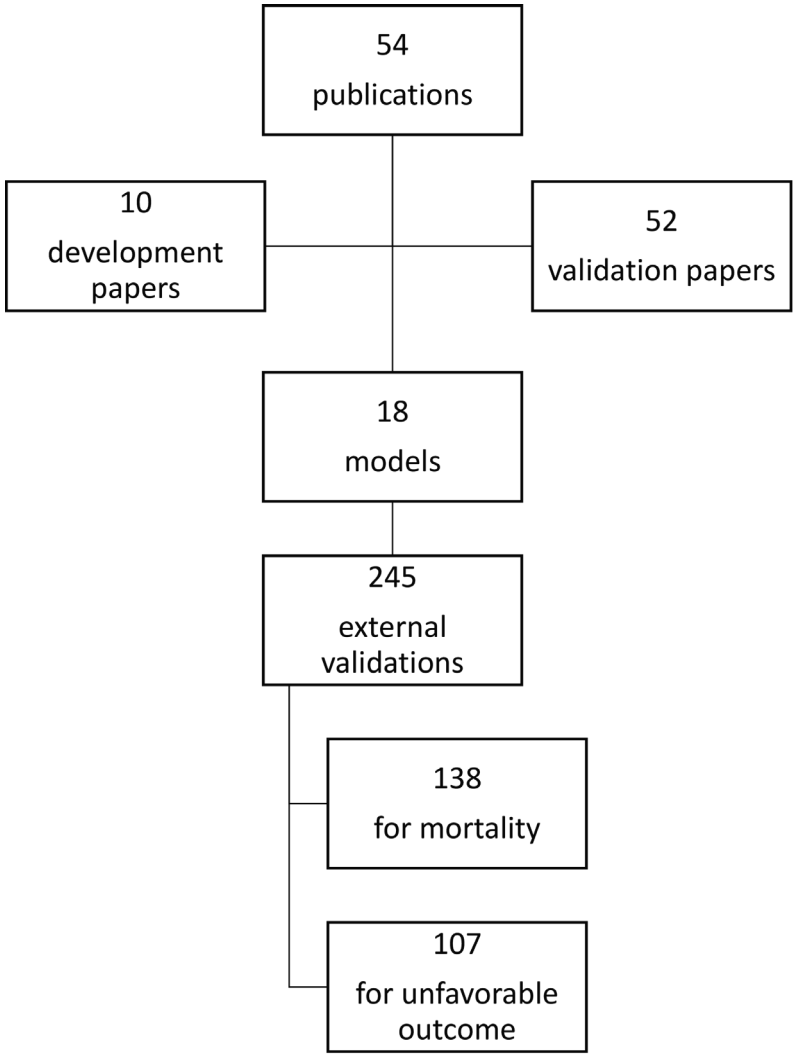

Figure 1. Flowdiagram of included studies based on the systematic search.

Study Characteristics

The 18 multivariable prognostic models predict mortality or unfavorable outcome at discharge or up to twelve months after hospital admission and were published between 1985 and 2021 (Supplementary Table 5). Four models (4/18; 22%) were developed in adult patients (aged > 14 years) who were admitted to the ICU (11-13), and fifteen models (14/18; 78%) were specifically developed in patients with TBI [9,14-19]. Data for model development were collected through single or multi-center observational cohort studies, randomized controlled trials (RCTs) or pooled data derived from both cohort studies and RCTs. All studies, except for Yuan et al.,[19] used prospective data.

Candidate predictors of outcome following TBI were collected at admission and typically included a combination of demographic, clinical and radiology characteristics. The number of missing predictor and outcome data was not reported in three studies (3/10; 30%) (Supplementary Table 5 continued). Three studies (3/10; 30%) applied imputation methods for handling missing data. Seven studies (7/10; 70%) used a selection procedure, for instance stepwise selection, to reduce the number of predictors that were included in the final model.

Five studies (5/10; 50%) used an internal validation procedure (e.g. bootstrap validation procedure or cross-validation), whereas in the other five studies (5/10; 50%) the internal validation procedure was lacking or inefficient (split-sample procedure).

The AUCs at development ranged between 0.71 to 0.90 for the prediction of mortality, and between 0.65 to 0.90 for the prediction of unfavorable outcome. Of the nine development studies that described model performance in terms of calibration, three studies (3/9; 33%) exclusively reported the Hosmer-Lemeshow goodness-of-fit test and one (1/9; 11%) exclusively showed calibration graphically using a calibration plot, whereas five studies (5/9; 55%) reported both the Hosmer-Lemeshow goodness-of-fit test and a calibration plot.

Methodological quality of model development studies

Methodological quality of model development studies was assessed in terms of applicability and Risk Of Bias (RoB) with the PROBAST checklist (Table 1). Of the ten model development studies, eight (8/10; 80%) were judged high RoB (Table 2). In each case (8/8), the statistical analysis (analysis domain) resulted in a high RoB, due to insufficient sample size, suboptimal handling of missing data and lack of or insufficient internal validation procedures (e.g. split-sample procedure). Four model development studies (4/10; 40%) were deemed high RoB in terms of applicability as these models were developed for patients admitted to the ICU and not strictly for patients following moderate and severe TBI. For most studies (9/10), the overall judgment on a short form based on the PROBAST, including 8/20 signaling questions, was consistent with the

original PROBAST (Supplementary Table 6). Based on the short form, one study was identified as low RoB, but unclear RoB (CRASH models) on the original PROBAST, due to key information that was not reported.

Usability

Just over half of the model development studies (6/10; 60%) provided the full model equations or sufficient information to extract the baseline risk (intercept) and individual predictor effects (regression coefficients). Most (8/10; 80%) studies included a presentation of the final prediction models, such as a nomogram or score chart, which makes implementation of the model in clinical practice more feasible (Table 2). Almost half of the studies (4/10; 40%) included insufficient information to externally validate the models (Table 2).

External validation

The 18 prognostic models were externally validated 245 times (Supplementary Table 7). The IMPACT prognostic models were externally validated most extensively (127 times), followed by the CRASH models (56 times). Most (164/245, 67%) of the validation studies were judged 'distantly related' (Table 2), indicating that the validation cohort substantially differed from the model development study in terms of inclusion criteria and/or outcome assessment. Furthermore, 45/245 (18%) of the validation studies were judged 'moderately related', as the models were validated in a different setting (e.g. country) than the model was originally developed in.

The discriminative ability of the models showed substantial variation (Supplementary Table 8; Figure 2). Overall, the AUCs at external validation ranged between 0.47 to 0.94 for the prediction of mortality, and between 0.61 to 1.00 for the prediction of unfavorable outcome.

There was substantial variation in the agreement between observed and predicted probabilities. The reported calibration intercept ranged between -1.27 to 0.93 for mortality, and between –0.51 to 2.39 for the prediction of unfavorable outcome. The reported calibration slopes ranged between 0.72 to 2.3 for mortality and between 0.71 to 2.5 for unfavorable outcome.

Relation between methodological quality and model performance

The difference between the AUC at development and validation was highly variable (Figure 2). The median change in the discriminative ability in low RoB models was positive (N=149 validation studies, dAUC 8%, [IQR -4% to 21%]) compared to a negative median dAUC in high ROB models (N=45 validation studies, dAUC -18%, [IQR -43% to -2%]) (Table 3).

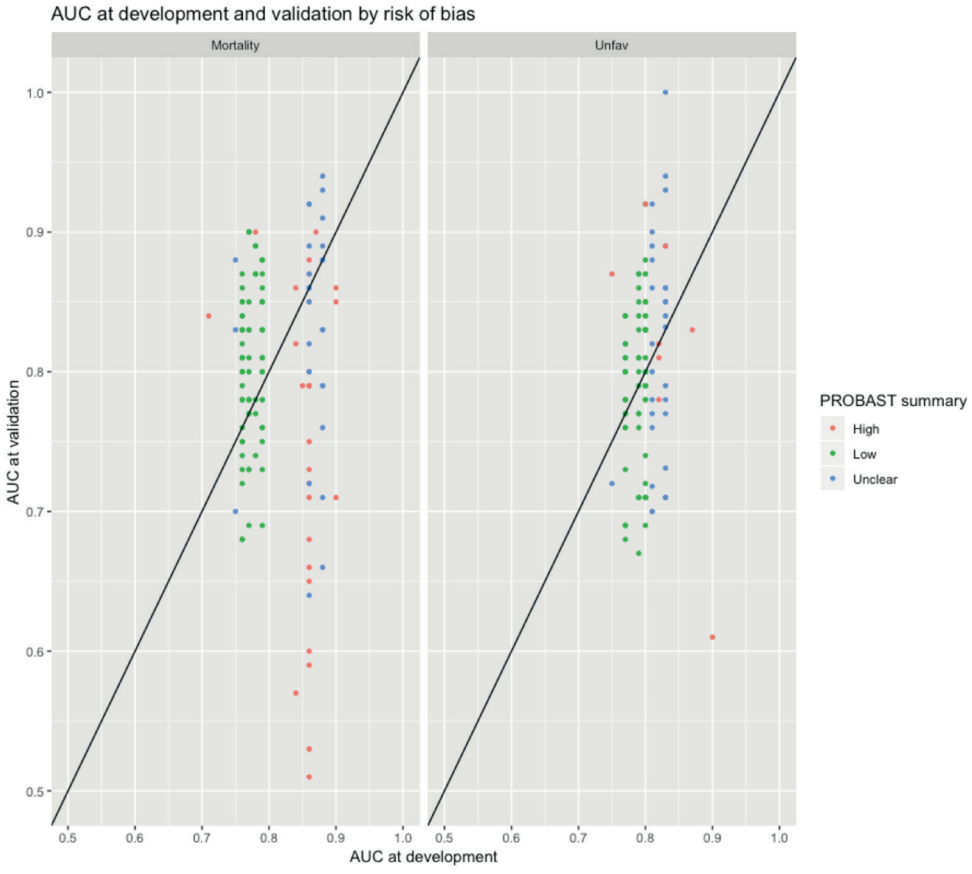

Figure 2. AUC of 18 models at development and in 242 validation studies by Risk of Bias assessed with the PROBAST.

Using the GEE, we found a larger average negative change in discrimination for high ROB models (-32% (95% CI: -48 to -15) and unclear RoB models (-13% (95% CI: -16 to -10)) compared to that seen in low RoB models (Table 4), while taking into account the correlation between validations of the same model and similarity in study design between the development and validation study. Models that were developed in a cohort and validated in a trial had an estimated change in discrimination of -18% (95% CI: -26 to -10), whereas models that were developed in a trial and validated in a cohort had an estimated change in AUC of 0.4% (95% CI: -3 to 4), compared to models that were developed and validated in data derived from a similar study design.

Discussion

We examined the relation between methodological quality of prediction model development studies and performance at external validation for prognostic models predicting outcome of patients after moderate or severe traumatic brain injury (TBI). Of the ten included model development studies, two studies (four models) were found to have low risk of bias (RoB) and were applicable for patients after moderate and severe TBI. The other eight publications (fourteen models) showed 'high' or 'unclear' RoB and had limited usability or applicability for patients after moderate and severe TBI. At external validation model performance is typically reduced[20]. However, our findings showed that, on average, the change in discriminative ability was positive in validations of 'low' RoB models meaning that the models performed better at external validation. Conversely, the change in discriminative ability was negative for 'high' RoB models, which means that the models performed worse at external validation. Methodological quality of model development studies was associated with discriminative ability at external validation, implying that poor methodological quality results in poorer model performance in new patients and settings. A recent large-scale validation study of a short form based on the PROBAST in the field of cardiovascular disease showed that high RoB was associated with poorer discrimination[10]. Our study confirms these findings for prognostic models in the field of TBI.

We critically appraised and assessed methodological quality of model development studies using the PROBAST[7]. Since its publication the PROBAST has, for instance, been applied in the field of rehabilitation[21], cardiology[10] and infectious diseases (COVID-19)[22]. Consistent with prior studies, the overall judgement on the 20 PROBAST questions was often 'unclear' or 'high' [21-24], due to key details that were not reported [5]. These findings emphasize the importance of adherence to reporting guidelines, such as the TRIPOD reporting guideline [25]. Additionally, the PROBAST checklist, which includes 20 items on participant selection, study design, predictors, outcome and statistical analysis, can inform investigators on what should be reported in prognostic model studies. A short form based on the PROBAST, consisting of 8/20 items, was recently validated and could distinguish well between high and low RoB [10]. In our study, the overall judgment on the short form was consistent with the original PROBAST for almost all studies.

A prior study reported that the majority of prediction studies in high impact journals did not follow methodological recommendations based on reporting statements, checklists and quality assessment tools [26]. Similarly, in most model development studies included in our study the statistical analyses were suboptimal due to insufficient sample size, suboptimal handling of missing data, stepwise selection procedures, and lack of or insufficient internal validation procedures, resulting in a high RoB. Consistent with prior studies that have critically appraised model development studies in TBI, internal

validation studies of models developed before 2005 were often lacking or inefficient [3,4]. In contrast, models that were developed more recently, between 2005 and 2021, did more often include an internal validation procedure. In recent years, the importance of internal validation has been stressed [27,28] and internal validation procedures are accessible through free statistical software such as R [29]. These developments may have resulted in a higher uptake of these practices.

External validation aims to examine how the model performs in new patients from different settings [30]. This may relate to model performance in patients from different regions or countries (geographical validation), or in patients that differ from the derivation cohort on a characteristic (domain validation) [2]. External validation, preferably across a range of settings, is required before clinical application of a model can be recommended. Varying levels of relatedness between the development and validation study are expected. We used a relatedness rubric to define the consistency between development and validation studies, using three categories: 'related', 'moderately related' and 'distantly related' [13]. Most of the validation studies differed substantially from the model development study in terms of inclusion criteria and/or outcome assessment, and were judged 'distantly related'.

Differences in case-mix (distribution of patient characteristics) might arise from various levels of relatedness between the development and validation study and differences in study design between the development and validation study. Case-mix differences typically affect the observed change in discrimination [31]. Differences in case-mix are expected between observational cohort studies and RCTs, with cohort studies being more heterogeneous. We found that similarity in study design between the development and validation study was associated with the observed change in discriminative ability. For instance, models that were developed in a cohort and validated in a trial had worse discriminative ability at external validation, whereas models that were developed in a trial and validated in a cohort had better discriminative ability at external validation, compared to models that were developed and validated in data derived from a similar study design. These findings reflect larger case-mix heterogeneity in cohorts versus trials. Differences in case-mix can be measured through the model based concordance (c) statistic (mbc) [32], which provides insight into the influence of case-mix heterogeneity on the discriminative ability. In our study, the mbc was reported in only two of the validation studies published after its introduction in 2016 [33,34].

Prior systematic reviews found that calibration, the agreement between observed and predicted outcomes, is described less often than discrimination [5,26,35]. Similarly, a number of the external validation studies did not assess model performance in terms of calibration. When reported, calibration was assessed with the Hosmer-Lemeshow

goodness-of-fit test [36] or shown graphically with a calibration plot. The Hosmer-Lemeshow statistic has poor power to detect various violations of model assumptions [37]. Although broadly used as a measure of calibration in validation studies, this statistic is not recommended for this purpose [38]. To be able to compare model performance between validation studies, reporting the calibration intercept and slope is preferred. Dijkland et al. [6] concluded that the calibration of models for moderate and severe TBI was highly variable, reflecting heterogeneity in reliability of predictions, which motivates continuous validation and updating if clinical implementation is pursued.

Strengths and Limitations

The key strength of this study is that a risk of bias assessment (PROBAST) was related to model performance in external validation studies. Although the 'Explanation and Elaboration' form provides extensive instructions for the scoring of PROBAST, many items are open for interpretation and the overall judgement is dependent on decisions that are made throughout the reviewing process. For instance, to determine if there was a reasonable number of outcome events relative to the number of predictors, we used EPP ≥ 10, which is widely adopted in prediction modeling studies as the minimal guideline criterion for binary logistic regression analysis. However, more recently, authors have suggested higher EPP's of at least 20 and criteria that consider the outcome prevalence, overall model performance, and predictor distributions to determine the sample size required (39). In our study, two of the twelve model development papers were assessed by a third independent reviewer (LW) (Cohen's kappa = 0.64). In each case the disagreement between the reviewers were 'no information' versus '(probably) yes', and they did not influence the overall RoB score.

We included 18 prognostic models for functional outcome following moderate and severe TBI that were externally validated at least once. Although the assessment of model performance in new patients and settings is crucial, external validation is often lacking [20]. Therefore, we could include only a limited number of models. In our study, we decided to examine the association between methodological quality and performance in terms of discrimination and not calibration for several reasons. First, calibration is less often described than discrimination. The calibration at external validation using the calibration intercept and slope was reported for only 8 of 18 models. Second, different measures (e.g. Hosmer-Lemeshow goodness-of-fit test, calibration plot, calibration intercept (calibration-in-the-large) and slope) are used to assess calibration, which makes it more difficult to compare calibration between validation studies. These different calibration measures, such as the calibration intercept and slope, are likely to be affected differently by methodological quality of the development study. Third, apart from methodological quality of the development study, calibration is likely influenced by relatedness between the development and validation study. Thus, calibration can

be highly variable between external validation studies because of differences in setting and patient characteristics. For instance, it can be strongly influenced by differences in outcome rates between development and validation, beyond what is predicted by the model. Furthermore, consistent with prior studies, there was low variability in the PROBAST overall judgements as well as the relatedness assessment. Because of the limited sample size and low variability additional variables that might have an effect on the observed change in discrimination (e.g. relatedness) were not included in the GEE. Other variables (e.g. usability and applicability) were not included in the GEE as they were not expected to have an effect on the observed change in discrimination. The models with low RoB, the Hukkelhoven model and IMPACT models [9,15], were externally validated more frequently than the models classified as high RoB. This implies that the number of external validations might be related to methodological quality of the model development study. Apart from low RoB, these models were also presented with sufficient information to be externally validated. Our results are limited in terms of number of models, but confirm findings from a larger study, which showed that most published prediction models are at high RoB and that high RoB is associated with poorer discrimination. A previous study by Venema et al., (2021) included 556 prediction models for cardiovascular disease, with 1147 validations from the Tufts Predictive Analytics and Comparative Effectiveness (PACE) CPM Registry [10]. Venema et al., also corrected for other factors that could be related to the difference in model performance between development and external validation, including overlap in authors between development and validation study, sample size at validation, and years between the development and validation study. In our study, we did not assess methodological quality of the validation studies, which could also influence the difference in model performance between the development and validation study. Future research should further explore the association between methodological quality of external validation studies and model performance.

Conclusion

Higher methodological quality of model development studies is associated with better model performance at external validation in the field of TBI. Our findings support the importance of adherence to methodological principles at model development and following guidelines for reporting of prediction modeling studies.

List of abbreviations

AUC:	Area Under the operating receiver Curve
GEE:	Generalized Estimation Equations
Mbc:	Model based concordance (c) statistic
PROBAST:	Prediction model Risk Of Bias Assessment Tool
RCT(s):	Randomized Controlled Trial(s)
RoB:	Risk of Bias
TBI:	Traumatic Brain Injury

Ethical approval and Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

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Competing interests

The authors declare that there is no conflict of interest.

Authors' contributions

IRH and AM extracted the data, and conducted the RoB assessment with help of LW. IRH took the lead in writing the manuscript. DvK supervised the project. All authors contributed to writing the manuscript, and they all read and approved the final manuscript.

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Supplementary material

Supplementary material is available at: https://diagnprognres.biomedcentral.com/articles/10.1186/s41512-022-00122-0#Sec22.

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Chapter 10

Prognostic models for global functional outcome and post-concussion symptoms following mild TBI: a CENTER TBI study

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Submitted

Abstract

After mild traumatic brain injury (mTBI), a substantial proportion of individuals do not fully recover on the Glasgow Outcome Scale Extended (GOSE) or experience persistent post-concussion symptoms (PPCS). We aimed to develop prognostic models for the GOSE and PPCS at 6 months after mTBI and to assess the prognostic value of different categories of predictors (clinical variables; questionnaires; CT; blood biomarkers). From the CENTER-TBI study, we included participants aged 16 or older with Glasgow Coma Score (GCS) 13-15. We used ordinal logistic regression to model the relationship between predictors and the GOSE, and linear regression to model the relationship between predictors and the Rivermead Post-concussion Symptoms Questionnaire (RPQ) total score. First, we studied a pre-specified Core model. Next, we extended the core model with clinical and sociodemographic variables available at presentation (Clinical model). The Clinical model was then extended with early post-concussion symptoms assessed at presentation, CT variables, biomarkers, or all three categories (extended models). In a subset of patients mostly discharged home from the Emergency Department, the Clinical model was extended with 2-3 week post-concussion and psychological symptoms. Predictors were selected based on Akaike's Information Criterion. Performance of ordinal models was expressed as a concordance index (C) and performance of linear models as proportion of variance explained (R2). Bootstrap validation was used to correct for optimism. We included 2376 mTBI patients with 6-month GOSE and 1605 patients with 6-month RPQ. The Core and Clinical models for GOSE showed moderate discrimination (C=0.68 95% CI 0.68 to 0.70 and C=0.70[0.69 to 0.71], respectively) and injury severity was the strongest predictor. The extended models had better discriminative ability (C= 0.71[0.69 to 0.72] with early symptoms; 0.71[0.70 to 0.72] with CT variables or with biomarkers; 0.72[0.71 to 0.73] with all three categories). The performance of models for RPQ was modest (R2=4% Core; R2=9% Clinical), and extensions with early symptoms increased the R2 to 12%. The 2-3-week models had better performance for both outcomes in the subset of participants with these symptoms measured (C=0.74 [0.71 to 0.78] vs. C=0.63[0.61 to 0.67] for GOSE; R2=37% vs. 6% for RPQ). In conclusion, the models based on variables available before discharge have moderate performance for the prediction of GOSE and poor performance for the prediction of PPCS. 2-3 week data are required for better predictive ability of both outcomes. The performance of the proposed models should be examined in independent cohorts.

Key words: mild traumatic brain injury, Glasgow Outcome Scale Extended, post-concussion symptoms, prognostic model, predictors, biomarkers.

Introduction

The majority of patients with traumatic brain injury (TBI) present with a Glasgow Coma Score (GCS) of 13 to 15 and are classified as mild.[1] However, "mild" appears to be a misnomer since a substantial percentage of patients do not completely return to their pre-injury level of functioning and/or experience persistent post-concussion symptoms (PPCS) several months after sustaining a TBI.[2-4] Therefore, it would be beneficial to identify individuals early after injury, who are at higher risk of suboptimal functional outcome or PPCS as this would facilitate follow up for therapeutic intervention. Although high-quality evidence is still limited,[5,6] brief early psycho-educational and cognitive-behavioral interventions have the potential to improve functional outcome and reduce the likelihood of persistent symptoms after mild TBI.[7,8,9]

There are currently no satisfactory models for prediction of outcomes following mild TBI.[10,11] Our recent external validation study performed in a large European cohort of TBI patients[12] showed that none of the models for prediction of 6-month outcome after mild TBI based on variables available at presentation had both good agreement between observed and predicted values, and good ability to distinguish between patients with favorable and unfavorable outcome. The definition of unfavorable outcome, however, differed between prognostic studies. Predicting the full Glasgow Outcome Scale Extended (GOSE)[13] range compared to dichotomization by a cutoff would have greater statistical power and be more informative.[14]

Prognostic models that included 2-3 week symptoms had satisfactory performance at external validation.[12] Studies in mild TBI consistently show that symptoms measured weeks after injury improve prediction and therefore should be routinely collected. [3,11] Assessing 2-3 symptoms is, however, often clinically impractical and unsuitable for acute care of mild TBI patients. There is a need for a model that can predict outcome in the acute setting, in addition to a prediction model that incorporates measures assessed later after injury.

Patient-reported symptoms measured early after a TBI are associated with incomplete recovery and persistent symptoms after 1 month.[15,16] Imaging variables have shown inconsistent associations with the outcomes, depending on other characteristics of mild TBI patients, the exact type of lesion, and definition of the outcome.[3,17] Blood biomarkers have been associated with intracranial abnormalities on CT following mild TBI[18,19,20] but they have been insufficiently investigated for longer-term prognosis. If they turn out to be independent predictors of outcome, as some studies suggest,[21,22] biomarkers would represent a readily accessible asset in the acute care of mild TBI patients.[23]

We aimed to develop prognostic models for GOSE and PPCS 6 months after mild TBI based on characteristics available at presentation and suitable for early detection of high-risk patients. In addition, we explored if the performance of prognostic models improved by adding different categories of predictors available before discharge from hospital: biomarkers, symptoms, CT characteristics, or all the aforementioned. We also explored if 2-3 week symptoms improved the predictive performance of the models.

Methods

Study population

The study population consisted of patients from the prospective longitudinal observational Collaborative European NeuroTrauma Effectiveness. Research in Traumatic Brain Injury (CENTER-TBI) study (registration number: NCT02210221). The data version used for this study was Core 3.0.[24] Patients were enrolled from December 2014 to December 2017 in 63 centers across Europe and Israel. Ethical approval was obtained for each recruiting site and informed consent was obtained from all patients and/or their legal representative/next of kin: https://www.center-tbi.eu/project/ethical-approval. Inclusion criteria for the core study were a clinical diagnosis of TBI, presentation within 24 h after injury, and an indication for computed tomography (CT) scanning according to local rules. Patients were excluded if they had severe pre-existing neurological disorder that could confound outcome assessments.[2] In CENTER-TBI, patients were differentiated by care pathway and assigned to the ER stratum (patients who were discharged from an ER), admission stratum (patients who were admitted to a hospital ward), or intensive care unit (ICU) stratum (patients who were admitted to the ICU).[2]

We selected patients who were 16 years or older with a baseline GCS 13 to 15 and available outcome assessments. Missing predictor data were imputed to allow for fair comparison between model variants using Multivariate Imputation by Chained Equations assuming a missingness at random mechanism.[25] The imputation model contained all predictor and outcome variables, and predictive mean matching was used for continuous, logistic regression for binary, proportional odds logistic regression for ordinal, and polytomous regression for categorical data. For the development of models containing 2-3 week symptoms, we only selected patients for whom this assessment was obtained. By the CENTER-TBI study design, these assessments were performed in ER stratum and a subgroup of patients admitted to a hospital ward).[2]

Outcomes assessed at 6 months

We analyzed associations with 6-month GOSE and PPCS. The GOSE has the following categories: (1) dead, (2) vegetative state, (3) lower severe disability, (4) upper severe disability, (5) lower moderate disability, (6) upper moderate disability, (7) lower good recovery, and (8) upper good recovery. The GOSE was collected using structured interviews and patient/

caregiver questionnaires. The categories vegetative state and lower severe disability were combined in one group as these could not be differentiated in the postal questionnaire. We used GOSE ratings imputed to exactly 180 days based on the GOSE recorded at different time points (from 2 weeks to one year) based on a multistate model.[26]

PPCS were assessed by the Rivermead Post-concussion Symptoms Questionnaire (RPQ).[27] The RPQ consists of 16 common symptoms that can appear after mTBI/concussion. Patients are asked to rate how problematic symptoms were compared to the situation before the injury on a 5-point Likert scale (0–4). A score of 0 indicates 'not experienced at all; 1 indicates 'no more of a problem (than before)', 2 indicates 'a mild problem'; 3 indicates 'a moderate problem; 4 indicates 'a severe problem'. The total score is calculated as the sum of items, with a range from 0 (representing no change in symptoms since the injury) to 64 (most severe symptoms). When calculating the total score, '1' responses were rated as 0. The questionnaire was translated and linguistically validated in languages of the participating centers.[28] When using a binary endpoint, we dichotomized the RPQ Total score based on a cutoff >=16.[29]

Candidate predictors

Questionnaires

The RPQ was assessed in the hospital center (at presentation or during hospital stay, median 1 day [0-1]), and after 2-3 weeks in patients from ER stratum and in a subgroup of Admission stratum (median 20 days [15-28]). The Post-Traumatic Stress Disorder (PTSD) Checklist for DSM-5 (PCL-5),[30] Generalized Anxiety Disorder 7-item scale (GAD-7),[31] Patient Health Questionnaire (PHQ-9)[32] were assessed at 2-3 weeks, and were considered as predictors in "2-3 week" prognostic models. The PCL-5[30] measures symptoms of PTSD according to DSM-5 criteria. It consists of 20 items that can be answered with 0 = not at all to 5 = extremely, and it can have a score range of 0–80. The GAD-7[31] measures severity of anxiety. It comprises seven items that can be answered from 0 = not at all to 3 = nearly every day, and it can have a score range of 0–21. The PHQ-9[32] measures depression severity. It contains nine items using a 4-point Likert scale (from 0 = not at all to 3 = nearly every day), and it can have a score range of 0–27.

Clinical and sociodemographic characteristics.

Sociodemographic, pre-injury and injury-related variables were prospectively collected: age, GCS, total injury severity score (ISS), sex, psychiatric history, preinjury health American Society of Anesthesiologists Physical Status[ASA PS] Classification, prior TBI, history of migraines or headaches, education level, employment, living alone, cause of injury, alcohol intoxication, pupillary reactivity, posttraumatic amnesia, loss of consciousness, vomiting, headache (Suppl. Table 1). GCS is the total GCS at baseline. ISS can range from 0 to 75 (in brain-injured population from 1 to 75)[33] and is

calculated as the sum of the squares of the 3 body regions with the highest Abbreviated Injury Scale (AIS). If any AIS is scored 6, the ISS is automatically 75. Additionally, we calculated extra-cranial ISS (considering the AIS of the face, abdomen, chest, extremities and external injuries and excluding the head AIS) and head AIS (the highest AIS out of brain injury, head, neck and cervical spine).

Table 1. Characteristics of mild TBI patients with available 6-month Glasgow Outcome Scale Extended (GOSE) (N=2376) and Rivermead Post-concussion Symptoms Questionnaire (RPQ) (N=1605), and 2-week RPQ (N=640; N=476) in the CENTER- TBI study

	6-month GOSE	**Missing %**	**6-month RPQ**	**Missing %**	**6-month GOSE+ 2 -week RPQ**	**Missing %**	**6-month 2 -week RPQ**	**Missing %**
n	**2376**		**1605**		**640**		**476**	
Age median [Q1-Q4]	53 [34, 68]	0	53[35, 66]	0	49[31, 62]	0	51[34.75, 63]	0
Sex male (%)	1519 (63.9)	0	1018 (63.4)	0	378 (59.1)	0	279 (58.6)	0
Preinjury health ASAPS (%)		0.8		0.4		0		0
No systemic disease	1292 (54.8)		909 (56.9)		383 (59.8)		383 (59.8)	
Mild	803 (34.1)		538 (33.7)		2024 (31.9)		158 (33.2)	
Severe	261 (11.1)		151 (9.4)		53 (8.3)		39 (8.2)	
Psychiatric history (%)	312 (13.3)	1	202 (12.6)	0.5	86 (13.5)	0.2	62 (13.0)	0
Cause of injury (%)		1.8		1.6		1.1		1.3
fall and other	1353 (58.0)		888 (56.2)		373 (58.9)		268 (57.0)	
Traffic	846 (36.2)		613 (38.8)		226 (35.7)		185 (39.4)	
violence	135 (5.8)		78 (4.9)		34 (5.4)		17 (3.6)	
Glasgow Coma Score (%)		0		0		0		0
13	161 (6.8)		103 (6.4)		15 (2.3)		12 (2.5)	
14	421 (17.7)		269 (16.8)		56 (8.8)		39 (8.2)	
15	1794 (75.5)		1233 (76.8)		569 (88.9)		425 (89.3)	
Total Injury Severity Score (ISS) median Median[Q1-Q4]	10 [5, 18]	0.9	10[5, 18]	0.7	5 [2, 9]	0.2	5[2.75, 9]	0
ISS extra-cranial	3[0,9]	0%	4[0,9]	0%	1[0,4]	0%	1[0,4]	0%
Head AIS	3[2,3]	1%	3[2,3]	0.8%	2[1,2]	0.3%	2[1,2]	0.2%
Any intracranial abnormality (%)	1028 (46.3)	6.6	718 (47.4)	5.5	113 (18.6)	5.2	98 (21.4)	3.6
NFL <=48 h median[Q1-Q4]	13.5 [7.2, 28.5]	20.4	12.8 [7.3, 25.7]	18.2	8.4[5.2, 14.4]	16.4	8.8[5.6, 14.4]	13.7
RPQ Total Score at baseline median[Q1-Q4]	8 [2, 15]	29.4	8 [2.75, 15]	26.2	8 [2, 15.75]	10.9	8.50 [2, 16]	11.3
RPQ Total Score at 2 weeks median[Q1-Q4]	8 [0, 20]	73.1	8[2, 21]	70.3	8[0, 20]	0	8 [2, 21]	0
RPQ Total Score at 6 months median[Q1-Q4]	6 [0, 16]	32.5	6 [0, 16]	0	4 [0, 14]	25.6	4 [0, 14]	0
GOSE at 180 days		0		0.1		0		0
1	89 (3.7)		0		1 (0.2)		0	
3	99 (4.2)		42 (2.6)		8 (1.2)		4 (0.8)	
4	74 (3.1)		53 (3.3)		1 (0.2)		1 (0.2)	
5	174 (7.3)		119 (7.4)		27 (4.2)		21 (4.4)	
6	247 (10.4)		205 (12.8)		53 (8.3)		49 (10.3)	
7	517 (21.8)		410 (25.6)		133 (20.8)		118 (24.8)	
8	1176 (49.5)		775 (48.3)		417 (65.2)		283 (59.5)	

CT variables.

We included the following CT characteristics, scored upon central review of the CT scans obtained at presentation: traumatic axonal injury (TAI), cisternal compression, midline shift (>5mm), subarachnoid hemorrhage, contusion, (non-) evacuated hematoma, and a composite variable any abnormality on CT (Supp. Table 1).

Biomarkers.

We included the following biomarkers sampled <=48h after injury: glial fibrillary acidic protein (GFAP), serum neurofilament light (NFL), neuron-specific enolase (NSE), S100 calcium-binding protein B (S100B), total-Tau (t-tau), ubiquitin C-terminal hydrolase -L1 (UCHL1). The median sampling time was 14 h [Q1-Q3: 6-20h]. The sampling was within 24 h for the majority of patients (91%).

The sampling of blood-based biomarkers has been described in previous studies.[18] S100B and NSE were measured with a clinical-use automated system, using an electrochemiluminescence immunoassay kit (ECLIA) (Elecsys S100 and Elecsys NSE assays) run on the e602 module of Cobas 8000 modular analyzer (Roche Diagnostics, Mannheim, Germany) at the University of Pecs (Pecs, Hungary). Serum GFAP, UCHL1, NFL and t-tau were analyzed with an ultrasensitive immunoassay using digital array technology (Single Molecule Arrays, SiMoA)-based Human Neurology 4-Plex B assay (N4PB) run on the SR-X benchtop assay platform (Quanterix Corp., Lexington, MA) at the University of Florida (Gainesville, Florida).

Medians and interquartile ranges were shown for continuous variables and percentages for categorical variables (Table 1, Supp. Table 2).

Table 2. Prognostic models for 6-month Glasgow Outcome Scale Extended (GOSE) in mild TBI: model performance (N=2376)

	Core model	Clinical model	Clinical +early symptoms (RPQ)	Clinical +CT	Clinical +Biomarkers	Clinical+ early RPQ, CT, biomarkers	Clinical+2-3wk symptoms [subset N=640]
Ordinal GOSE (1-8)							
Nagelkerke R2 (optimism-corrected)	0.18	0.21	0.22	0.24	0.23	0.26	0.21
C (optimism- corrected)	0.68 [0.68-0.70]	0.70 [0.69-0.71]	0.71 [0.69-0.72]	0.71 [0.70-0.72]	0.71 [0.70 -0.72]	0.72 [0.71-0.73]	0.74 [0.71-0.78]
C (optimism-corrected) for different cutoffs							
GOSE=8	0.69	0.70	0.72	0.71	0.71	0.73	0.75
GOSE>=7	0.73	0.74	0.75	0.75	0.76	0.76	0.76
GOSE>=5	0.79	0.80	0.80	0.80	0.82	0.81	0.69**

C= concordance index; ** only 10 outcome events;

Model development

Based on a systematic review,[34] a recent review and validation study,[12] subsequent studies[16,35,36] and clinical expertise, we selected candidate predictors and easily obtainable core variables. For GOSE, the core model included age, GCS and ISS. For RPQ, the

core model included sex, psychiatric history and preinjury health. We extended the core models with a) clinical and sociodemographic variables available at presentation, b) RPQ total score measured at the hospital center early after injury, c) CT variables, d) blood-based biomarkers, e) RPQ total score, CT results and biomarkers (Figure 1). Finally, in the subgroup of patients in whom assessments were performed at 2-3 weeks, we extended the core model with f) 2-3 week symptoms.

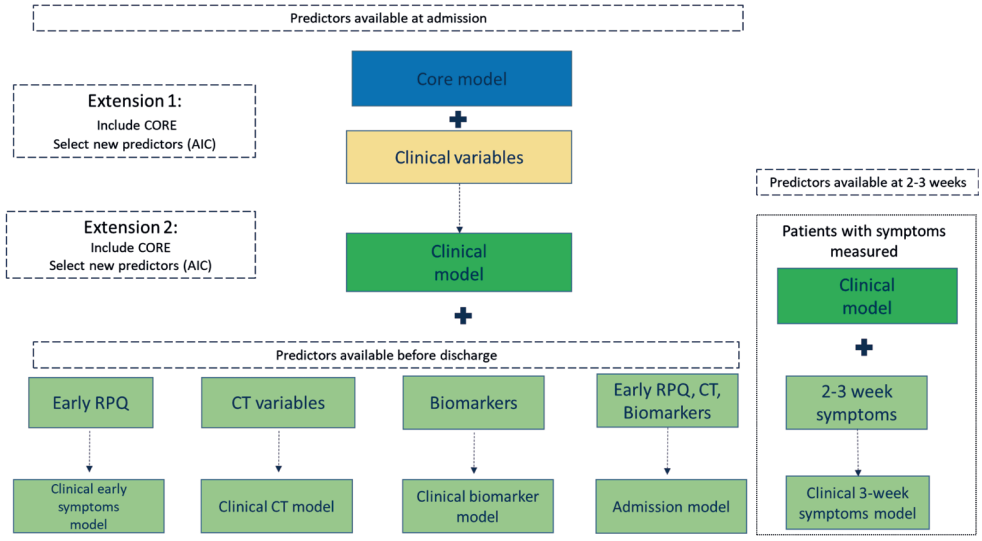

Figure 1. Two-phase modelling strategy

We used ordinal logistic regression to model the relationship between predictors and the GOSE, and linear regression to model the relationship between predictors and RPQ total score. We assessed nonlinear effects of age, ISS and biomarkers. We assessed non-linear transformations with polynomials of log-transformed ISS and log-transformed values of biomarkers for both outcomes, and non-linear transformations with polynomials of age and of log-transformed GFAP for prediction of RPQ. When we examined extra-cranial and head injury severities separately, we assessed nonlinear transformations with polynomials for head AIS for prediction of GOSE.

In the first model extension, the Core model was extended with other clinical variables. Core variables were included ("forced") into the model and clinical predictors were selected based on Akaike's Information Criterion (AIC) (Figure 1, Figure 2 A). The AIC was used to select the best model fit with the smallest number of parameters: a higher AIC indicates better predictive ability (how much a predictor adds to the model) penalizing for the complexity of the model (as expressed by the degrees of freedom). AIC strikes a balance between identifying predictors and preventing overfitting. In the

second phase, the Clinical model was extended with other categories of variables (b-f). The additional predictors were selected based on the AIC for individual factors, and core variables were always included ("forced") into the model (Figure 1). The AIC for candidate predictors in examined models was reported graphically.

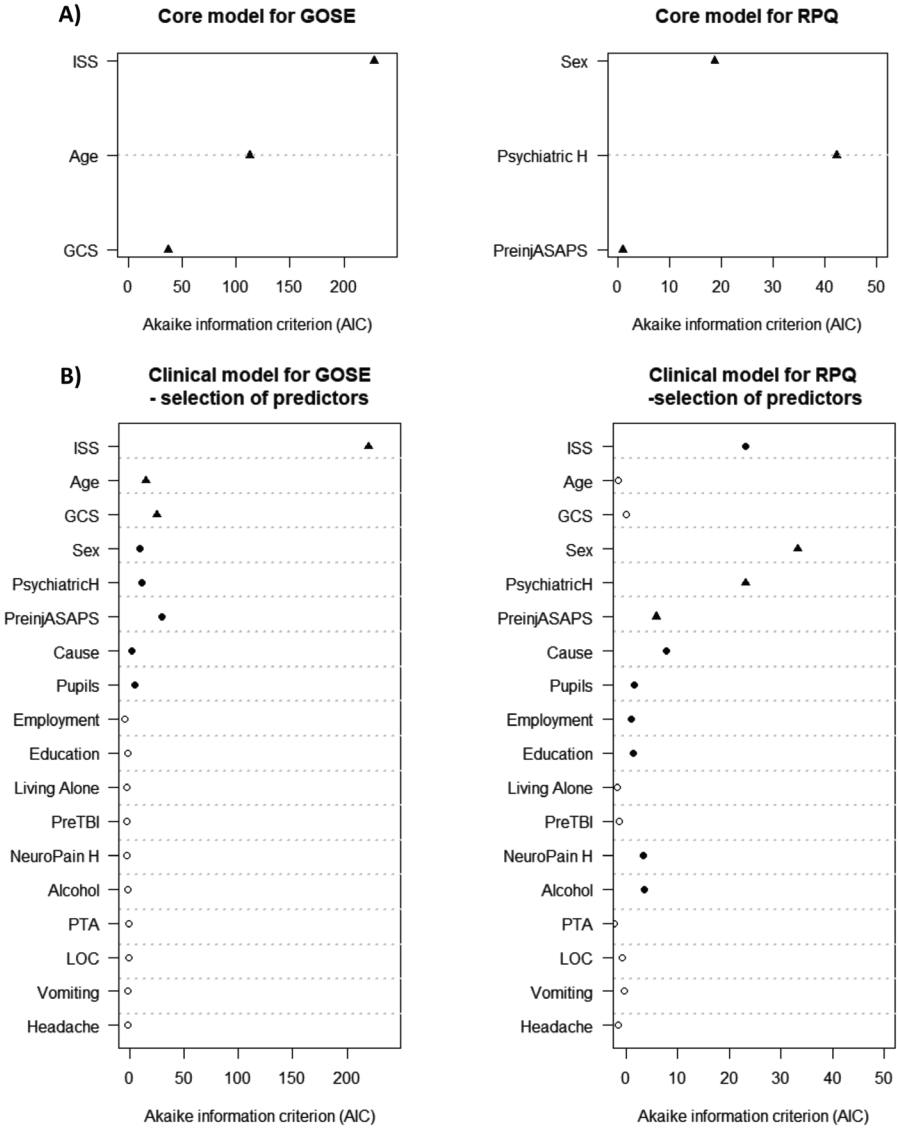

Figure 2. The Core and Clinical models for prediction of Glasgow Outcome Scale Extended (GOSE) and Rivermead Postconcussion Symptom Questionnaire (RPQ).
Black circles indicate selected predictors based on AIC. Black triangles indicate pre-specified core predictors.
Legend: ASA-PS= American Society of Anesthesiologists Physical Status; GCS= Glasgow Coma Scale; ISS=Injury Severity Score Total; Neuropain H=History of Migraines/ Headaches; PreTBI= Prior traumatic brain injury; PTA= Posttraumatic amnesia; LOC= Loss of consciousness.

Bootstrap validation with 500 repetitions was used to estimate a uniform shrinkage factor (corrected calibration slope) and optimism in performance. We report model equations for which the regression coefficients of the final models were multiplied by a shrinkage factor and the model intercept was re-estimated. We also report the equations of models that were refitted to a dichotomized GOSE (cutoff GOSE=8), using the same shrinkage factor. The performance of ordinal logistic regression models was quantified with the concordance index (C), which quantifies the ability of a model to discriminate between patients with different levels of outcome. Overall performance was quantified with partial Nagelkerke R^2, which represents the scaled difference in the log-likelihood of a model with and without the prognostic factor(s). The performance of the models was also reported for different cutoffs of the GOSE. The performance of linear regression models was quantified with the proportion of explained variance (R^2). For comparison with other studies, we also reported C obtained in logistic regression analysis that modelled the relationship between predictors and a dichotomized RPQ Total score. Performance was calculated across imputed datasets and confidence intervals were estimated using 200 bootstrap samples.

To examine calibration of the models for predicting complete recovery (GOSE 8) and significant post-concussion symptoms (RPQ>=16) in different European regions, we performed cross-validation with a leave-one-region-out approach: The regions West, North and South-East (Supp. Table 1) were consecutively left out for model fitting and were then used for model validation. The R-package rms[37] (Regression Modeling Strategies) was used for all regression analyses.

Results

Study population

We included 2376 patients with an imputed GOSE at 180 days. The imputed GOSE variable was made by the CENTER-TBI statisticians and directly extracted from the CENTER-TBI dataset.[26,38] For 1605 patients, RPQ was assessed at 6 month follow-up. The median age was 53 years and the majority of patients were male (64% and 63%) and with GCS 15 (76% and 77%; Table 1). The median ISS was 10 and almost half of the patients had intracranial abnormalities on CT (Table 1). The median RPQ Total score was 8 at baseline and 2-3 weeks, and 6 at 6 months (Table 1). About half of the patients did not completely return to their preinjury functioning according to the GOSE. As expected, patients who had symptoms measured at 2-3 weeks (N=640; N=476) were less severely injured (median ISS 5 and ISS extra-cranial 1; 89% GCS 15; 19% and 21% intracranial abnormalities), younger (median age 49 and 51), and somewhat less frequently male (59%; Table 1; Suppl. Table 2).

Prediction of 6-month GOSE

The pre-specified core model contained age, ISS (non-linear) and GCS (linear). It had a discriminative ability of C= 0.68 (CI 95% 0.68-0.70). All predictors contributed to the model, but ISS was by far the strongest predictor (Figure 2A). When the model was extended with sex, preinjury health (ASAPS), psychiatric history, cause of injury, and pupillary reactivity, the performance improved (C=0.70 (CI 95% [0.69-0.71], Nagelkerke R^2 increased from 18% to 21%; Table 2). The strongest predictor in this Clinical model was ISS, followed by preinjury health, GCS, and age (Figure 2B, Supp. Table 4). When we modelled extra-cranial injury severity (ISSe) and head injury severity (head AIS) separately, rather than the overall ISS, model performance was comparable (C=0.70 (CI 95% [0.68-0.71]). Both predictors, but especially head AIS, were strong (Supp. Figure 1).

When the Clinical model was extended with either early symptoms, CT variables, or biomarkers, the performance further improved to a similar degree for all models (early symptoms: C=0.71 [0.69-0.72], Nagelkerke R^2= 22%; CT variables: C=0.71[0.70 -0.72], Nagelkerke R^2= 24%; biomarkers: C=0.71[0.70 -0.72], Nagelkerke R2= 23%; Table 2, Supp. Table 4). In all these models, ISS was the strongest predictor, and preinjury health, age, GCS, psychiatric history and sex were also robust predictors. In addition, early RPQ had high predictive ability and was selected for the Clinical Early symptoms model (Suppl. Figure 2, Supp. Table 4). Any intracranial abnormality, tSAH, TAI, and non-evacuated hematoma were selected for the Clinical CT model (Suppl. Figure 3, Supp. Table 4). The final Clinical Biomarker model contained NFL, S100B and NSE, in addition to clinical variables (Suppl. Figure 4, Supp. Table 4).

When the Clinical model was simultaneously extended with all three types of variables (CT variables, biomarkers, early RPQ), the performance improved further (C=0.72[0.71-0.73], Nagelkerke R^2=26%; Table 2). The final model included all variables from the Clinical model; early RPQ; CT variables any intracranial abnormality, non-evacuated hematoma, and tSAH; and biomarkers NFL, s100B, GFAP and NSE. Consistent with other analyses, ISS, early RPQ and preinjury health showed the best predictive ability (Figure 3; Supp. Table 4). All described models discriminated better for the outcome good recovery (GOSE>=7; C=0.73-0.76; Table 2) and moderate disability/good recovery vs. severe disability/ death (GOSE>=5; C=0.79-0.82) than for upper good recovery (GOSE=8; C=0.69-0.73; Table 2).

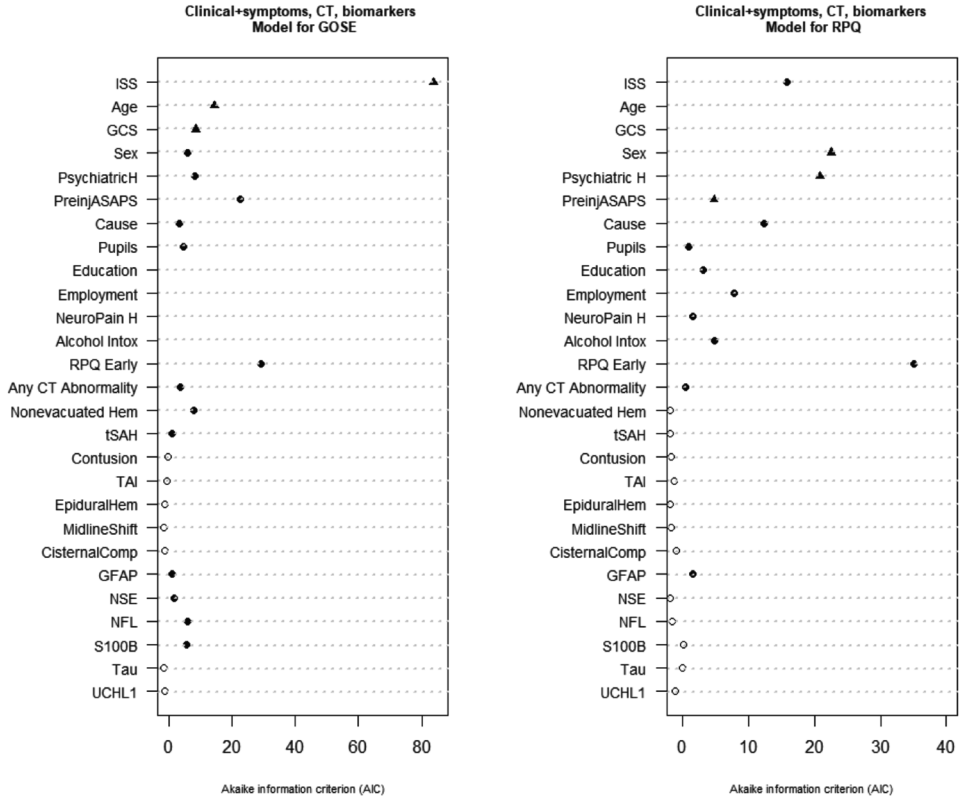

Figure 3. The Clinical+ symptoms, CT, biomarkers models for prediction of Glasgow Outcome Scale Extended (GOSE) and Rivermead Postconcussion Symptom Questionnaire (RPQ).
Black circles indicate selected predictors based on AIC. Black triangles indicate pre-specified core predictors.
Legend: ASA-PS= American Society of Anesthesiologists Physical Status; GCS= Glasgow Coma Scale; ISS=Injury Severity Score Total; Neuropain H=History of Migraines/ Headaches; RPQ= Rivermead Post-Concussion Symptoms Questionnaire; ; PCL-5= Post-Traumatic Stress Disorder (PTSD) Checklist for DSM-5; GAD-7= Generalized Anxiety Disorder 7-item scale (GAD-7); PHQ-9= Patient Health Questionnaire; TAI= Traumatic axonal injury; tSah= Traumatic subarachnoid hemorrhage.

The model developed in the subset of patients with 2-3 week symptoms available had substantially better discriminative ability (C=0.74 [0.71-0.78] compared to C=0.63[0.61-0.67] of the Clinical model without 2-3 week symptoms in the same subset, n=640) and overall performance (Nagelkerke R^2 21% vs. 7%). Apart from the core variables, this model included cause of injury, psychiatric history, post-concussion (RPQ) and post-traumatic stress disorder (PCl-5) symptoms. The strongest predictors were 2-3 week post-concussion symptoms (Fig 4). ISS (particularly of the head) and age were also important predictors of PPCS in this subset (Fig 4; Supp. Table 4, Supp. Figure 5).

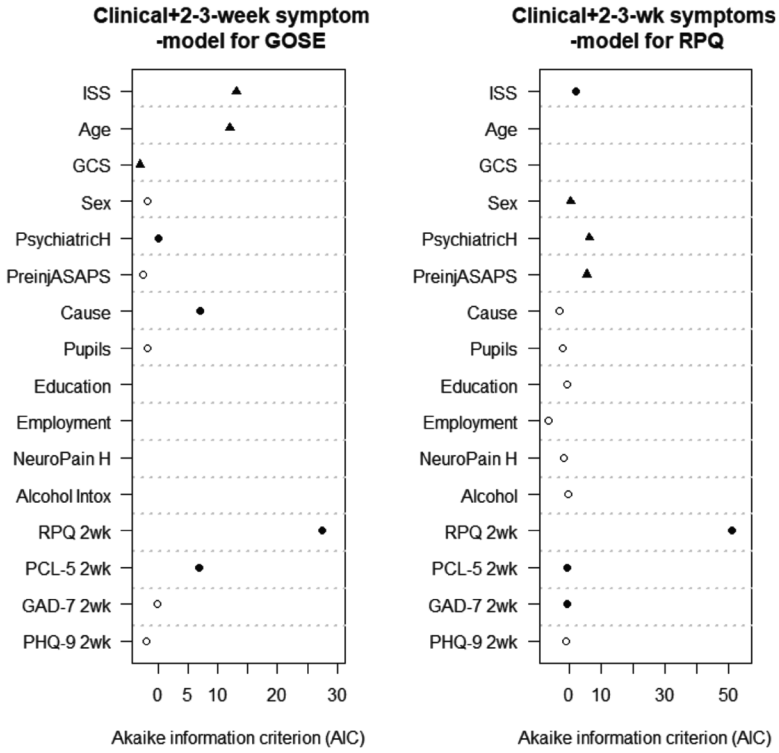

Figure 4. The Clinical+ 2-3 week symptoms models for prediction of Glasgow Outcome Scale Extended (GOSE) and Rivermead Postconcussion Symptom Questionnaire (RPQ).
Black circles indicate selected predictors based on AIC. Black triangles indicate pre-specified core predictors.
Legend: ASA-PS= American Society of Anesthesiologists Physical Status; GCS= Glasgow Coma Scale; ISS=Injury Severity Score Total; Neuropain H=History of Migraines/ Headaches; RPQ= Rivermead Post-Concussion Symptoms Questionnaire; ; PCL-5= Post-Traumatic Stress Disorder (PTSD) Checklist for DSM-5; GAD-7= Generalized Anxiety Disorder 7-item scale (GAD-7); PHQ-9= Patient Health Questionnaire.

The probability of 6-month outcome can be calculated based on model equations (Text box 1; Supp. Table 6 A and B).

Text Box 1. Predicting global functional outcome (GOSE) for two different patients based on the Clinical model

Patient 1: Woman, 44 years, mild systemic disease (mild obesity), psychiatric history (depression), TBI caused by motor vehicle accident (MVA), GCS 14, Total ISS 9, one nonreactive pupil.

Linear predictor (lp)= 0.965+(-0.010*44)+(-0.263*1)+(-0.533*1)+(0.269*1)+(0.169*1) + (0.099*log(9))+(-0.193*(log(9)^2))+(-0.502*1)

$1/(1+\exp^{-lp})$= 0.2=**20%** probability of complete return to preinjury functioning

Patient 2: Man, 32 years, no systemic disease, no psychiatric history, TBI caused by fall, GCS 15, Total ISS 2, reactive pupils.

lp= 0.965+(0.403*1)+(-0.010*32)+(0.549*1)+(0.099*log(2))+(-0.193*(log(2)^2))

$1/(1+\exp -lp$)=0.83=**83%** probability of complete recovery to preinjury functioning

Prediction of 6- month RPQ

The Core model for RPQ including sex, psychiatric history and preinjury health explained only 4% of the variance of the 6-month RPQ Total Score (Table 3, Figure 2A). For the Clinical model, apart from the core variables, ISS, cause of injury, pupillary reactivity, alcohol intoxication, history of headaches, education and employment were also selected. With the inclusion of new variables, the proportion of explained variance increased, but it remained modest (9%, Table 3). The strongest predictors of outcome were sex, psychiatric history and ISS (Figure 2B; Supp. Table 5). When we included ISS and head AIS separately, the model performance was similar (R^2=9%) and both predictors were selected, nevertheless, head AIS had a stronger predictive ability.

Table 3. Prognostic models for 6-month Rivermead Post-concussion Symptoms Questionnaire (RPQ) total score in mild TBI patients: model performance (N=1605)

Predictors of PPCS (RPQ Total Score) at 6 months	Core model	Clinical model -Selected	Clinical +early PCS (RPQ)	Clinical +CT	Clinical +Biomarker	Clinical+ early RPQ,CT, biomarkers	Clinical+2-3wk symptoms [subset N=476]
R2 (optimism-corrected)	0.04	0.09	0.12	0.09	0.09	0.12	0.37
C (optimism-corrected) for cutoff >=16	0.60	0.65	0.67	0.65	0.66	0.67	0.83

C= concordance index; R2= coefficient of determination

In the extensions of the Clinical model, the proportion of explained variance increased to 12% when early symptoms (RPQ) were added, and also and also when all three categories were added (Table 3, Supp. Figure 2). Extending the models only with CT variables and biomarkers did modestly improve the model performance (R^2=9%, Table 3). However, some predictors were selected in addition to the Clinical model: any intracranial abnormality for the Clinical CT model (Suppl. Figure 3, Supp. Table 5); and GFAP and Tau for the Clinical biomarker model (Suppl. Figure 4; Supp. Table 5).

For the model extended with all three types of variables, early RPQ, any intracranial abnormality on CT and GFAP were selected in addition to the Clinical model (Figure 3; Supp. Table 5). In all extended models, the strongest predictors were sex and psychiatric disorder, and other robust predictors, but to a lesser extent, were ISS, preinjury health and cause of injury. From additional categories, early RPQ had a particularly strong predictive ability (Figure 3; Suppl. Figure 2; Supp. Table 5).

The model developed in the subset of patients with symptoms reported at 2-3 week explained 37% of the variance (compared to 6% for the Clinical model in the same subset). It included, in addition to the core variables: ISS, 2-3 week post-concussion (RPQ), post-traumatic stress (PCL-5) and anxiety symptoms (GAD-7; Figure 4; Supp. Table 5). By far the strongest predictor was the 2-3 week RPQ (Figure 4). In contrast with previous analyses, male sex was associated with higher PPCS after the addition of 2-3 week symptoms (Supp. Table 5). When we included ISSe and head AIS separately, only extra-cranial ISS was selected for the Clinical model in the subset (Supp. Figure 5 A) and only head AIS for the Clinical + 2-3 week symptoms model (Supp. Figure 5 B).

The 6-month RPQ score can be estimated based on model equations (Text box 2; Supp. Table 7).

Text Box 2. Predicting post-concussion symptoms (RPQ score) for two different patients based on the Clinical model

Patient 1: Woman, mild systemic disease (mild obesity), history of headaches, psychiatric history (depression), secondary education, part-time employed, TBI caused by motor vehicle accident, not intoxicated, Total ISS 9, one nonreactive pupil.

Total RPQ score= 7.295 (intercept) -(1.098*1) +(3.323*1) +(4.460*1) +(1.524*1)+ (0.192*1)+ (0.709*log(9))+ (0.584*log(9)^2) +(3.910*1) =24

Patient 2: Man, no systemic disease, no psychiatric history, bachelor degree, full-time employed, TBI caused by fall, not intoxicated, Total ISS 2, reactive pupils.

Total RPQ score= 7.295+(-3.376*1)+(-0.709*log(2))+(0.584*(log(2)^2)=**4**

The logistic models predicting dichotomized 6-month RPQ (cutoff >=16) had a discriminative ability corrected for optimism between C=0.60 and 0.67 (Table 3). Only the Clinical model with 2-3 week symptoms, developed in the subset of patients, had much better discriminative ability (C=0.83; Table 3).

Discussion

We developed prognostic models for 6-month global functional outcome (GOSE) and persistent post-concussion symptoms (RPQ) in patients with GCS 13-15 and assessed the additional value of different categories of predictors. The Clinical model for GOSE, containing age, GCS, ISS, preinjury health, psychiatric history, cause of injury and pupillary reactivity had moderate discriminative ability (C=0.70), and ISS was the strongest predictor. The models extended with additional categories of predictors: early post-concussion symptoms, CT variables, biomarkers and all three categories of variables had slightly better discriminative ability (C=0.71-0.72). When the model was extended with symptoms measured at 2-3 weeks, the discriminative ability was substantially better (C=0.74 vs. 0.63 in a subset primarily discharged home from the ED), primarily based on the strong predictive ability of post-concussion symptoms. The Clinical model for 6-month PPCS including sex, preinjury health, psychiatric history, ISS, pupillary reactivity, alcohol intoxication, history of migraines, education and employment explained only 9% of the outcome variance. The extension with early post-concussion symptoms increased the proportion of explained variance (to 12%), whereas the addition of CT variables and biomarkers did not. The model with 2-3-week symptoms had substantially better performance (R2=37% vs. 6% in the subset of patients with the symptoms measured).

In the CENTER-TBI study, global functional outcome could be predicted moderately well based on readily available injury-related, preinjury and sociodemographic characteristics, and other categories of predictors that could be collected before discharge from hospital. However, our results support the view that, based on these variables, it is easier to differentiate mild TBI patients in the lower levels of 6-month GOSE than in the highest level.[10] Our models discriminated better for the endpoint severe disability/ death (GOSE<5) and disability/death (GOSE<7) than for incomplete recovery (GOSE<8), and performed better in CENTER-TBI data[12] than the existing models developed to predict these outcomes.[39,40] For the endpoint incomplete recovery, our clinical and extended models had somewhat better performance (C=0.70-0.73) than the UPFRONT ED model[3] in its derivation cohort (C=0.69) but the performance of the UPFRONT ED model could not be examined in CENTER-TBI data. In the UPFRONT study, for instance, injury severity score, one of the strongest predictors in our study, was not a candidate predictor, medical history only incorporated neurological domain, blood-based biomarkers were not assessed, and CT abnormalities were not found predicative of the outcome. An important predictor in UPFRONT "neck pain", was not separately assessed in the acute stage in CENTER-TBI.

Although it has been suggested that the outcome in mild TBI is primarily determined

by what "the patient brings to the injury",[10] our result suggest that the injury severity is essential for the prediction of outcome even in mild TBI, as quantified by the high AIC for ISS in all analyses. While both head and extra-cranial injury severities were important predictors, the robustness of injury severity score in prediction of both outcomes was primarily driven by the severity of head injury. In some other mild TBI studies, however, ISS was not a strong predictor of 6-month outcome.[10] This discrepancy could arise from differences in other candidate predictors, outcome assessment and study populations (e.g. in the variability of ISS). Furthermore, aspects of physical and psychiatric preinjury health also represent robust predictors of functioning after mild TBI, as shown by this and other studies.[10,41]

Early symptoms, CT variables and biomarkers further improved the performance of models for GOSE. In particular, higher early post-concussion symptoms were associated with a lower likelihood of a good functional outcome. That is in line with a recent prognostic model for 1-month GOSE that incorporated acute post-concussion symptoms, such as headache, concentration difficulty and photophobia.[16] (Non-) evacuated hematoma, although rare in this group of patients, had high predictive value, consistent with the CRASH model for prediction of outcome in patients with GCS <=14.[40] Some biomarkers showed multivariable associations with the outcomes, but the increase in discriminative ability was not substantial. Higher levels of biomarkers, particularly NFL ("chronic biomarker") and S100B ("acute"), were associated with a lower likelihood of a good functional outcome. In previous studies, correlations were found between NFL, t-Tau and occasionally GFAP, and return to sport, more severe symptoms and unfavorable outcome.[42-45] Our findings support further examination of biomarkers as predictors of outcome in mild TBI; nevertheless, they do not appear as central components of prognostic models for long-term prognosis in mild TBI. Still, they can be relevant for understanding the underlying mechanisms of outcome differences. Finally, 2-3 week symptoms were strong predictors of GOSE, which is consistent with the UPFRONT study showing improved model performance after inclusion of emotional distress and coping measured at 2 weeks (from C=0.69 to 0.77).[3]

Similarly as for the prediction of the incomplete recovery (GOSE=8), the proportion of explained variance was low in the models for PPCS that did not include early, and particularly 2-3-week symptoms. Due to our study design (assessment of 2-3 week symptoms only in a patient subgroup), we cannot draw strong conclusions, but it seems that it is not sufficient to assess symptoms only on presentation or early during hospital stay. The performance of these models (clinical and extended models) was in line with other studies.[34,46] Even though 6-month symptoms could not be predicted well based on characteristics available before discharge from hospital, the predictors sex, psychiatric history, preinjury health and ISS (particularly head injury severity) showed associations with this outcome. CT positivity and biomarkers (in particular GFAP) were associated

with PPCS, but neither CT variables nor biomarkers notably improved the performance of the models for PPCS. Interestingly, different biomarkers were selected in models for GOSE and PPCS. Generally, similar predictors were important for the prediction of both PPCS and GOSE, however, injury-related characteristics were more prominent predictors of the (ordinal) GOSE and personal/pre-injury characteristics of PPCS.

In the subset of patients primarily discharged from ED, the discriminative ability of the models containing only baseline characteristics had a lower discriminative ability. The performance of the model with 2-3 week symptoms was satisfactory and even higher than other published prognostic models for PPCS that include the symptoms[11,47] in CENTER TBI data (C=0.75- 0.76).[12] Therefore, in order to identify patients with PPCS (and with incomplete recovery), the post-concussion symptoms should be assessed at follow-up. Additionally, illness perceptions[48] and maladaptive coping[49] have been found predictive of PPCS. A brief assessment of the most predictive symptoms could be organized in person, by telephone or online after several weeks where feasible. Moreover, a recent model based on characteristics available at admission that showed a good discriminative ability included detailed assessments of personal factors (including personality and pre-injury status).[50] A more comprehensive assessment at presentation or discharge might represent a substitute or addition to a follow-up, however, it may not be practical in acute care.

Strengths and limitations

We developed prognostic models in a large sample of contemporary patients with mild TBI. These models have shown comparable or better discriminative ability than the existing published models for mild TBI. We added different categories of predictors, which could demonstrate the incremental value of different types of variables. Moreover, the model(s) can be selected for research and clinical purposes based on the available type of data. Different categories of predictors could make the models applicable for making predictions in different clinical contexts. To prevent overfitting, we pre-specified important variables based on the literature and clinical knowledge, used favorable event per variable ratio and internal validation procedures. Missing values were imputed using multiple imputation. To increase power and to cover all levels of the outcome, the GOSE was analyzed as an ordinal variable. We examined models' calibration in different regions.

The CENTER-TBI patients with GCS 13-15 had a high percentage of intracranial and extra-cranial injuries. One of the inclusion criteria was an indication for CT scanning and large trauma centers were over-represented. It is possible that injury-related characteristics and CT variables would be more homogeneous in a broader patient selection who present to the ED (majority with low injury severity and without CT abnormalities), and that the

models would therefore have a lower discriminative ability. That is also suggested by the poorer performance of the Clinical model in the subset of patients primarily discharged home after the ED and less severely injured. In addition, the 2-3-week symptoms were only assessed in that subset. The predictive ability of post-concussion and post-traumatic stress symptoms, important predictors of outcome, were therefore not determined in the entire spectrum of mild TBI patients. Further, we could not make a clear distinction between an evacuated and a non-evacuated hematoma, since the central review was blinded on the information on surgery. Importantly, whereas in CENTER-TBI the GOSE rating included assessments of the consequence of all injuries, including extra-cranial, in some contexts (e.g. trials in the United States), the GOSE typically includes an assessment of the consequences of TBI only.[51] That can impact the importance of some predictors, such as injury severity score and biomarkers. Biomarkers GFAP, NFL, UCHL1 and Tau were analyzed on a research platform, not commercially available, which impedes the validation and usage of the models in which they were included. Finally, these models have not yet been validated in an independent cohort.

Conclusion

We presented prognostic models for the prediction of ordinal GOSE and PPCS at 6 months in patients with GCS 13-15. The models for GOSE based on predictors available before discharge from the hospital have moderate performance and ISS is the strongest predictor. The models for PPCS without post-injury symptoms perform poorly. CT variables, biomarkers (NFL and S100B), and questionnaires assessing symptoms improve predictions of GOSE, and questionnaires assessing symptoms improve predictions of PPCS. For both outcomes, the models with symptoms assessed at 2-3 weeks performed well, which should encourage scheduling follow-up appointments. The examination of the performance of the proposed models in independent cohorts is warranted.

Ethical Approval

The CENTER-TBI study (EC grant 602150) has been conducted in accordance with all relevant laws of the European Union if directly applicable or of direct effect and all relevant laws of the country where the recruiting sites were located, including but not limited to, the relevant privacy and data protection laws and regulations (the "Privacy Law"), the relevant laws and regulations on the use of human materials, and all relevant guidance relating to clinical studies from time to time in force including, but not limited to, the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) ("ICH GCP") and the World Medical Association Declaration of Helsinki entitled "Ethical Principles for Medical Research Involving Human Subjects". Informed consent by the patients and/or the legal representative/ next of kin was obtained, according to the local legislations, for all patients recruited

in the core data set of CENTER-TBI and documented in the electronic case report form (e-CRF). Ethical approval was obtained for each recruiting site. The list of sites, ethical committees, approval numbers, and approval dates can be found on the Web site https://www.centertbi.eu/project/ethical-approval

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Chapter 11

Computed tomography lesions and their association with global outcome in young people with mild traumatic brain injury

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Abstract

Introduction: Mild traumatic brain injury (mTBI) can be accompanied by structural damage to the brain. Here, we investigated how CT abnormalities and patterns relate to long-term global functional outcome in young patients with mTBI.

Methods: All patients with mTBI (GCS 13-15) ≤24 years in the multi-center, prospective, observational CENTER-TBI study were included. Patient demographics, CT findings, and GOSE scores at 12 months follow-up were analyzed. The association between CT abnormalities and functional recovery was assessed using multivariable mixed ordinal and logistic regression models.

Results: A total of 462 patients with mTBI and initial brain CT from 46 study centers were included. The median age was 19 (17-22) years, and 322 (70%) were males. CT imaging showed a traumatic intracranial pathology in 171 patients (37%). Patients with a positive CT scan were less likely to achieve a complete recovery 12 months postinjury. The presence of any CT abnormality was associated with both lower GOSE scores and incomplete recovery (GOSE <8), also when adjusted for demographical and clinical baseline factors.

Conclusion: The presence of CT abnormalities was predictive of outcome 12 months after mTBI in young patients, which might help to identify patients who might benefit from early follow-up and additional care.

Introduction

Traumatic brain injury (TBI) is one of the most common injuries in young people, displaying an overall prevalence of ~30% among individuals ≤25 years.[1] The vast majority of those patients is classified as mild TBI (mTBI), clinically defined by a Glasgow Coma Scale (GCS) of 13-15.[2,3] Though termed "mild", increasing evidence from both pediatric and adult observational studies suggests that in a substantial proportion of patients with mTBI, the injury course is in fact not benign but associated with serious long-term sequalae such as diminished functional capacity and persistent post-concussive symptoms.[4–7]

Computed tomography (CT) scans are typically used to detect brain lesions in the acute care setting. However, harmful, potentially carcinogenic exposure to radiation poses a strong incentive to limit the use of CT imaging to a very selected group of high-risk patients, especially among young people. Still, a study of >43.000 pediatric and adolescent mTBI patients found that 19%-69% of patients undergo CT scanning across hospitals in the United States.[8] At the same time, according to the Center for Disease Control, intracranial injuries are only identified in 7.5% of pediatric and adolescent mTBI patients (<18 years) on brain CT.[9]

While the role of CT imaging to acutely diagnose intracranial brain lesions and guide treatment is widely acknowledged, it is decisively less clear whether the presence of intracranial pathologies on CT imaging can be used to make predictions on the long-term global outcome in young mTBI patients. Earlier studies found no additional value of CT findings compared to clinical predictors alone when predicting global outcome after mTBI in adult cohorts.[10,11] However, recent results from large, multicenter observational studies have challenged this view, finding a significant association between pathological CT scans and functional outcome.[4,12,13] Those studies were conducted in adults with mTBI.

In this study, we aimed to assess how intracranial findings on CT imaging relate to the long-term global outcome in a young cohort of mTBI patients 12 months after brain injury.

Methods

Study Design and Patient Selection

CENTER-TBI is a prospective, multicenter, observational cohort study of patients presenting with traumatic brain injury (TBI) of all severities and was conducted from December 2014 to December 2017 at 65 participating study centers in Europe and

Israel.[14] Patients were eligible for enrollment when presenting with a clinical diagnosis of TBI to a participating study center within 24 hours and when a CT scan was performed at presentation. The indication for CT imaging was made at the discretion of each participating study center/the treating physician. The study protocol was approved by the institutional review boards of each participating study center (https://www.center-tbi.eu/project/ethical-approval) and informed consent from each patient or their legally acceptable representatives was obtained prior to inclusion. The present study includes children, adolescents, and young adults aged ≤24 years at the time of enrollment who had an available initial brain CT scan and presented with a GCS score of 13-15. Data (CENTER Core version 3.0) were accessed via the clinical study data management tool Neurobot (RRID: SCR_ 017004).

CT imaging

CT scans were reviewed by a central review panel of three trained reviewers who evaluated the CT characteristics according to the National Institute of Neurological Disorders and Stroke (NINDS) TBI Common Data Elements (TBI-CDE). Reviewers were blinded to clinical information except for sex, age, and clinical care pathway (discharge, admission to the regular ward, ICU admission).[15] For the present study, we defined "CT Positive" as any trauma-related intracranial abnormality on initial brain CT (i.e., not including isolated skull fractures) while "CT Negative" indicated a non-pathological CT scan. CT findings coded as "indeterminate" by the central reviewers (4 findings) were counted as negative findings.

Outcome Measure

The primary outcome of this study was the global functional capacity at 12-months follow-up defined by the Glasgow Outcome Scale Extended (GOSE). Complete recovery was defined as a GOSE score of 8, while scores of 7 or lower were regarded as incomplete recoveries. We used the 12-month GOSE endpoint variable provided in the Neurobot database, which includes both observed ratings and, when GOSE ratings were missing at 12 months, but available at other time points, centrally imputed values using a multi-state model.[16]

Statistical Analysis

Group comparisons were performed using the Mann-Whitney *U* test for continuous variables and Fisher's exact test for categorical variables. Missing data was imputed using multilevel multiple imputation (100 datasets) that included the variables 12-months GOSE (outcome), sex, age, extracranial injury severity score (ISS), GCS <15, and intracranial CT abnormality (predictors) and study center (cluster variable). Missing data was assumed to be missing at random. The association between the presence of an intracranial CT lesion on the 12-month GOSE score was evaluated using mixed

ordinal regression models. We also assessed the association between those predictors and complete recovery at 12 months using mixed logistic regression models. Models were adjusted for age, sex, extracranial ISS, GCS score <15, and included a random intercept for study center. Covariables were selected based on previous literature and clinical reasoning.[17–20] Regressions were performed on the multiply-imputed datasets, and effect estimates were subsequently pooled according to Rubin's rules.[21] Odds ratios and their 95% confidence intervals are reported. The outcome analysis was repeated as a complete-case-analysis (n = 388). All analyses were conducted with the software R (version 4.1.1).[22]

Results

Patient characteristics

A total of 462 patients met the inclusion criteria for this study and were enrolled at 46 study centers across Europe. The median age was 19 (17-22) years and 70% were males. Road traffic incidents and incidental falls were the most common injury causes. Seventy-seven percent of individuals presented to the emergency room with a GCS score of 15 and the median extracranial injury severity score (ISS) was 10 (5-18). Admission to the regular ward was the most common clinical care pathway (49%). Twelve months after mTBI, a complete recovery was achieved by almost 70% of young patients. Only four patients were dead or had severe disability at 12 months follow-up. All analyzed patient characteristics are summarized in Table 2.

Indications for CT imaging

The most commonly reported reason to perform a brain CT scan in our study population was the presence of a risk factor in a patient with a GCS score of 15 (Supplement Table 2). The second most common reason was the presence of a head wound (27%), followed by a GCS score <15. In a minority of patients, exclusion of brain injuries prior to discharge (13%) or suspicion of maxillofacial injuries (9%) were given as the reason to perform CT imaging. However, multiple risk factors could be selected for an individual patient in the CENTER-TBI questionnaire by the treating physician.

CT pathologies

Intracranial traumatic pathology ("CT Positive") was detected in 171 of 462 patients (37%; Figure 1). Among those, the most common pathologies on brain CT were traumatic subarachnoid hemorrhages (48%), followed by contusions (40%), and epidural hematomas (37%). Acute subdural hematomas were identified in 29% of CT positive patients and traumatic axonal injuries in 14%. Intraventricular hemorrhages (4 patients) and subdural collection mixed densities (1 patient) were rare.

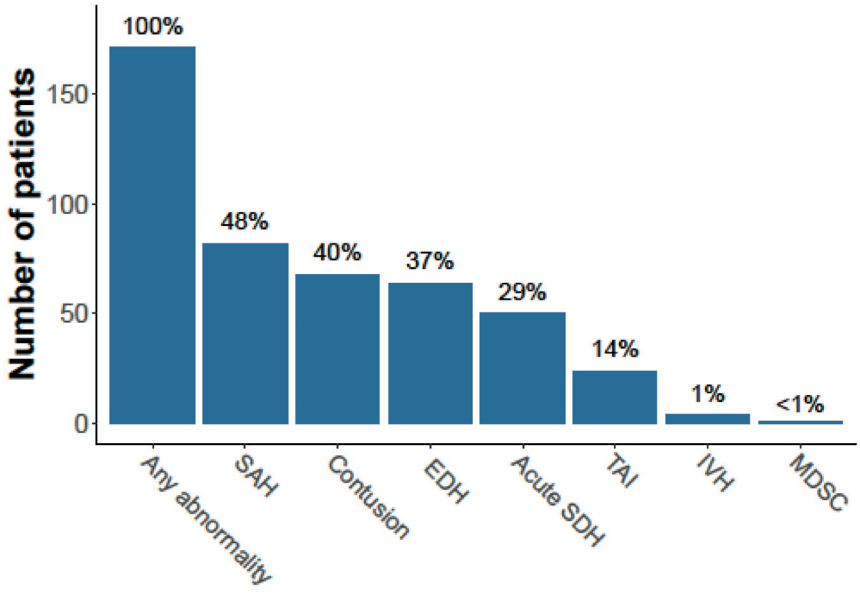

Figure 1. Occurrence of traumatic intracranial abnormalities on CT-imaging.

Comparison of "CT Positive" and "CT Negative" patients

The group of individuals with a positive CT scan displayed a higher proportion of male sex as well as differences regarding a history of alteration of consciousness and post-traumatic amnesia (Supplement Table 1). Individuals with a positive CT scan were more likely to present with a GCS score <15 (35% vs. 16%). While there was no significant difference in extracranial ISS, the median total ISS was significantly higher in individuals with a positive CT scan (16 [9-25] vs. 9 [4-13]). A difference between the two groups was also found regarding the clinical care pathway, where CT positive patients were much more frequently admitted to the ICU (45% vs. 10%). While 77% of patients with a negative CT scan achieved full recovery (GOSE=8) one-year after brain injury, this was only the case in 54% of patients with a positive CT scan (p <0.001).

Association of CT lesions and GOSE in multivariable analyses

Mixed ordinal regression models were used to assess the association between intracranial CT abnormalities and GOSE scores 12 months postinjury with adjustment for the demographical variables age and sex, and the clinical variables GCS <15 and extracranial ISS. The presence of an intracranial pathology on brain CT scan was associated with a lower likelihood of achieving higher 12-month GOSE scores (adjusted OR 0.387 [0.237 – 0.633]; Supplement Table 2). Similarly, the presence of any intracranial lesion was associated with a lower likelihood of full recovery one-year after mTBI (adjusted OR 0.409 [0.248 – 0.675]). The complete-case-analyses of the same models yielded similar results (Supplement Table 3).

Table 1. Patient characteristics, clinical baseline status, and outcome in mTBI patients ≤24 years in the CENTER-TBI study

Variable	Total (n= 462)	CT Positive (n= 171)	CT Negative (n= 291)	P value	Missing/ Unknown
Age	19 (17-22)	19 (16-22)	19 (17-22)	0.433	0 (0%)
Sex				<0.001	0 (0%)
Female	140 (30%)	35(21%)	104 (36%)		
Male	322 (70%)	136 (80%)	186 (64%)		
Care Pathway				<0.001	0 (0%)
ER discharge	132 (29%)	10 (6%)	122 (42%)		
Ward admission	225 (49%)	84 (49%)	141 (49%)		
ICU admission	105 (23%)	77 (45%)	28 (10%)		
Prior TBI	53 (12%)	15 (9%)	38 (13%)	0.126	12 (3%)
Injury Cause				0.113	2 (<1%)
Road-traffic incident	191 (41%)	79 (46%)	112 (39%)		
Incidental fall	165 (36%)	49 (29%)	116 (40%)		
Other non-intentional injury	39 (8%)	13 (8%)	26 (9%)		
Violence/assault	46 (10%)	20 (12%)	26 (9%)		
Suicide attempt	2 (<1%)	0 (0%)	2 (<1%)		
Other	17 (4%)	9 (5%)	8 (3%)		
Alcohol				0.095	21 (5%)
Definite	68 (15%)	20 (13%)	48 (17%)		
Suspected	21 (5%)	10 (6%)	11(4%)		
Drugs				0.297	38 (8%)
Definite	10 (2%)	6 (4%)	4 (1%)		
Suspected	5 (1%)	2 (1%)	3 (1%)		
GCS				<0.001	0 (%)
13	24 (5%)	15 (9%)	9 (3%)		
14	83 (18%)	45 (26%)	38 (13%)		
15	355 (77%)	111 (65%)	244 (84%)		
LOC				0.699	44 (10%)
Yes	201 (48%)	79 (50%)	122 (47%)		
Suspected	55 (13%)	17 (11%)	38 (15%)		
PTA				0.010	51 (11%)
Ongoing	65 (16%)	28 (20%)	37 (14%)		
Resolved	140 (34%)	47 (33%)	93 (34%)		
Suspected	12 (3%)	4 (3%)	8 (3%)		
Alteration of Consciousness				<0.001	54 (12%)
Yes, immediate	77 (19%)	29 (19%)	48 (19%)		
Not tested (LOC)	53 (13%)	22 (15%)	31 (12%)		
Suspected	11 (3%)	8 (5%)	3 (1%)		
Delayed onset	12 (3%)	9 (6%)	3 (1%)		
Extracranial ISS (median)	1 (0-9)	4 (0-9)	1 (0-8)	0.170	0 (0%)
Total ISS (median)	10 (5-18)	16 (9-25)	9 (4-13)	<0.001	1 (<1%)
GOSE at 12 months					74 (16%)
Full recovery	268 (69%)	80 (54%)	188 (77%)	<0.001	
Incomplete recovery	120 (31%)	68 (46%)	52 (21%)	<0.001	
Unfavorable outcome	4 (<1%)	0 (%)	4 (2%)	0.302	

CT = Computed tomography, ER = Emergency Room, GCS = Glasgow Coma Scale, GOSE = Glasgow Outcome Scale Extended, ICU = Intensive Care Unit, ISS = Injury severity score, LOC = Loss of consciousness, TBI = Traumatic Brain Injury

Discussion

Adolescents and young adults ≤24 years have high incidence rates of TBI.[23,24] With approximately 80-90%, the vast majority of TBI is thereby classified as mTBI and this number might even be higher as many young patients with mTBI do not seek medical care.[1,2,25] Although the term mTBI implies a favourable and benign clinical course, increasing evidence suggests that this is not the case in a substantial fraction of patients.[4,7,26,27] The present study emphasizes this aspect in a mTBI cohort of young patients ≤24 years, of whom almost one third did not achieve a complete recovery 12 months after the injury.

While the value of CT imaging for diagnosis and direction of treatment is well-established, its role in predicting long-term outcome remains controversial. On one hand, some studies showed no additional value compared to clinical factors alone; on the other hand, recent multicenter studies demonstrated a significant association with poorer outcome.[4,11,12,28] Those studies were conducted in adult TBI patients and data in younger cohorts, especially regarding long-term outcome, is scarce. Levin et al. described a significant relation between CT abnormalities and diminished neuropsychological recovery in children with mTBI over the first year.[29,30]

The median age of 19 years in our study was distinctively lower than in previous (adult) studies. As CT scans are performed in a considerable proportion of patients even in the young population, those patients form a large and clinically important group of TBI patients.[8] We found a significant relation between the presence of an intracranial pathology and the GOSE score at 12 months. This is a clinically important finding, because identifying patients at risk for an incomplete recovery is an essential aim in the management of mTBI. Firstly, providing an accurate prognosis is important for patients and their relatives. Secondly, despite a general lack of high-quality studies, there is evidence that interventions such as patient education as well as psychological and rehabilitative measures can be effective to treat mTBI symptoms in both young and adult patients.[31–33] The findings of this study indicate that the presence of intracranial CT findings should be considered when estimating the long-term outcome of young patients with mTBI.

We acknowledge several limitations of this study. While CENTER-TBI was open for patients of all ages, pediatric patients were underrepresented, as most centers were general hospitals which often had separate pediatric units for children with TBI. Therefore, our sample size was limited compared to the overall CENTER-TBI core study population. Another implication is that our cohort of young patients ≤24 years consists mostly of adolescents and young adults with relatively few children. Therefore, our results are

not generalizable to young children and more studies are needed in this even younger age group. It has also to be mentioned that the term "CT abnormality" encompasses a broad range of intracranial pathologies which might have different implications for the outcome. Also, interventions and treatments were not analyzed. While we did not perform further analyses with subclassifications into single lesions due to limited patient numbers, further studies are needed to address this important question.

In conclusion, we found that intracranial CT abnormalities were significantly associated with an increased likelihood of lower global outcome 12 months after mTBI in individuals ≤24 years in the CENTER-TBI study. This information might be used to develop protocols that aim to identify young patients with mTBI at risk for an incomplete recovery who might benefit from closely-monitored follow-up and early treatment interventions.

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Ethics statement

Ethical approval was obtained for each recruiting site. A complete list is given on https://www.center-tbi.eu/project/ethical-approval. All patients had to give their informed consent prior to enrollment in CENTER-TBI.

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Chapter 12

General Discussion

Treatment and outcome following traumatic brain injury (TBI) are not only determined by the baseline TBI severity. They can vary by patient characteristics but are largely unexplored in this context. In addition, the most frequent form of TBI: "mild" is associated with a considerable long-term impairment, personal suffering and societal costs. This thesis aimed to describe treatment and outcome in relation with sex and gender, age and comorbidity (**PART 1**) and to improve the prediction of outcome following mild TBI (**PART 2**). In this chapter, we discuss the main findings and recommendations for future research and practice.

PART 1: Treatment and outcome of mild TBI: relations with sex/gender, age and comorbidity

Differences between men and women in outcomes following TBI are inconsistently observed and their explanations are rarely tested. Mental health and physical comorbidity can also impact TBI-related treatment and outcome. In particular, comorbidities may be relevant for outcome in older adults, a growing TBI population. In **PART 1**, we aimed to describe treatment and outcome following TBI in relation to sex/gender, age and comorbidity (Main findings in ***Text box 1***).

Text box 1. Treatment and outcome (PART 1): Main findings

- Do men and women differ in treatment and outcomes following TBI?

We did not find notable differences in treatment (e.g. rates of surgeries), however, women were less likely to have a secondary referral and to be admitted to an intensive care unit (ICU) after mild TBI. Women had worse 6-month functional outcomes following mild (but not moderate/severe) TBI and reported worse 6-month health-related quality of life (HRQoL), and more severe mental health and post-concussion symptoms. Differences in outcomes were most prominent following mild TBI and at younger age (16-45 years).

- How can we explain outcome differences between men and women following mild TBI?

Psychiatric history could only partly explain sex/gender differences in symptoms, functioning and mental HRQoL, and care pathways and sociodemographic characteristics could not explain differences in outcomes. More studies are needed.

- What are the care pathways, outcomes and determinants of the outcomes in older adults following TBI?

Almost half of older adults were admitted to an ICU, around a third received inpatient and 12% outpatient rehabilitation at 6 months. The mortality rate was high (9% after mild, 60% after moderate/severe TBI), but nearly half of older adults with mild and 6% with moderate/severe TBI returned to the preinjury functioning within 6 months. Increased age and injury severity were associated with worse functioning. Pre-injury systemic disease, psychiatric history and lower education were associated with worse functioning, lower HRQoL and more severe mental health symptoms.

- Are treatments for PTSD effective for patients with a history of TBI?

Cognitive and behavioral therapies seem effective for the reduction of PTSD in patients with a history of traumatic brain injury, and for other types of therapies evidence is less strong. However, studies were generally assessed as having low quality.

Treatment of mild TBI: relations with sex/gender, age and comorbidity

We did not observe substantial differences in care pathways and treatment between men and women after adjusting for age, preinjury and injury-related factors (**Chapter 2**). However, women did have a lower likelihood of secondary referral to a study hospital (OR 0.7, 95% 0.6-0.95) and of admission to an ICU (OR 0.6, 95% 0.4-0.8) after sustaining a mild TBI. Our results are partly consistent with other studies from the field of trauma and critical care, in which women had a lower likelihood of direct transfers [1, 2] and less access to intensive care.[3-6] In CENTER-TBI, the secondary referral was more frequent in ICU patients,[7] which may explain the lower likelihood of women having indirect transfers. The studies finding lower rates of intensive care for women have been accumulating, although analyzing patients with various conditions and severe injuries, and not specifically (mild) TBI.[3-6] Following moderate/severe TBI, however, we did not observe sex/gender differences in admission to an ICU. The explanations and the implications of the sex/gender differences after mild TBI are unclear. Potential confounder variables were included in our analyses of differences and in some other studies with lower rates of ICU admissions for women.[5] Nevertheless, it is difficult to adjust for all relevant aspects of injury and medical history.

We cannot confirm or completely disregard the possibility of a bias in triaging patients to trauma centers and the ICU, speculated or analyzed in recent publications. [1, 5, 8, 9] Importantly, a study in the CENTER-TBI registry found that patients whose TBIs were caused by low-energy falls were less likely to receive critical care, although they had comparable rates of intracranial abnormalities and mortality.[10] While we did adjust for

the cause of injury, we did not specifically adjust for low/high energy. Considering that low-energy falls were more frequent in women and older people, these characteristics could also lead to presumptions of lower risk of complications and play a role in medical decisions on care pathways. Another question is if the differences in care pathways and treatment affect the outcome. Recently, a CENTER-TBI study showed that primary and secondary transfers were associated with comparable outcomes following moderate/severe TBI.[11] Admission to ICU after a mild TBI is highly variable between hospital centres[12] and often considered unnecessary,[13] however in some cases can contribute to better outcome.[14] We could not explain outcome differences between men and women by care pathways (**Chapter 3**).

Among older adults, 45% were admitted to an ICU. Consistent with the sex/gender difference found in **Chapter 2,** that percentage was higher for older men (51%) than for older women (37%) (**Chapter 4**). About a third of older patients had inpatient rehabilitation (general, geriatric, psychiatric or specialized TBI rehabilitation; nursing home) within 6 months, which is in line with the total adult population in CENTER-TBI.[15] However, only 12% of older patients received outpatient rehabilitation (physical, occupational, speech therapy; therapeutic recreation; cognitive remediation; vocational, psychological, nursing services), which is lower than in the total population.[15] This relatively low percentage of rehabilitation after TBI is congruent with other studies reporting unmet needs of TBI patients, particularly in the psychological and cognitive domains.[15-17] Of note, age has shown to be a factor in deciding on the type of rehabilitation: some studies found a higher likelihood to receive inpatient rehabilitation/nursing homes for older adults, but less intensive services (e.g. fewer hours of therapy)[18] and lower likelihood to receive specialized rehabilitation.[19-21] Rehabilitation after TBI in older adults is generally considered beneficial. [21-23]

In **Chapter 5**, we reviewed studies on treatments for PTSD for patients with (a history of) TBI. The majority of included studies involved patients with mild TBIs sustained years before the intervention in military/veteran samples and examined the effects of cognitive and/or behavioral therapies. These therapies (e.g. exposure, cognitive-processing)[24-27] were associated with the reduction of PTSD symptoms with no reported adverse effects. Complementary (e.g. mindfulness-based)[28] and novel therapies (e.g. brain and vestibular rehabilitation, hyperbaric oxygen)[29, 30] showed promising results. However, the majority of studies were assessed as having a moderate or high risk of bias. Therefore, we concluded that the (history of) mild TBI should not discourage the application of therapies, but that more high-quality studies should be conducted.

Outcome of mild TBI: relations with sex/gender, age and comorbidity

We found that women had a higher likelihood of worse functional outcome 6 months

following mild TBI (OR=1.4, 95% CI: 1.2-1.6), but not following moderate/severe TBI (0.9, 95% CI: 0.7-1.2) (**Chapters 2, 3, 10**). Women also reported more severe post-concussion (OR 1.7, 95% CI: 1.1-2.6) mental health symptoms and impaired health-related quality of life (HRQoL), with the most notable differences following mild TBI. The largest outcome differences between men and women were found at younger age (16-45 years) and for some mental health outcomes at older age (>65 years). Although there are inconsistencies, studies generally suggest that women report worse outcomes following mild TBI and for psychological and symptomatic outcomes,[31] particularly post-concussion symptoms.[32, 33] To overcome the limitations of previous studies,[31, 34] we used a large sample, adjusted for a large number of potential confounders and analyzed different domains of the outcome.

Different biological and sociocultural explanations have been proposed for outcome differences, often driven by the obtained age patterns. [32, 33, 35] For instance, more pronounced worse outcomes of women in premenopausal age could indicate hormonal mechanisms.[33] Furthermore, a combination of work-related, child-caring and household responsibilities and stressors for women in young and middle adulthood could contribute to the more severe symptoms and functional impairments.[35, 36] Observed outcome differences could also be explained by general differences between men and women in self-reporting; however, a recent study found differences in post-concussion symptoms following mild TBI, but no differences following orthopedic injuries.[32] Moreover, the reasons why women self-report poorer health have not been elucidated, and multiple societal and biological factors could be involved, such as gaps in education, employment and prevalence of depression.[37] However, the hypothesized explanations of differences had been rarely explored.[38] Using a mediation framework, we found that the differences in outcomes following mild TBI were partly explained by psychiatric history, but not by care pathways (referral and admission to ICU) and gender-related sociodemographic variables (employment/job category, education, living alone, living with children) (**Chapter 3**). In the group of patients over 65 years of age, psychiatric history and sociodemographic variables explained the largest percentage of variation in outcomes between men and women compared to younger age groups.

A substantial proportion of older adults died within 6 months (60% after moderate/severe, 9% after mild; **Chapter 4)**. Among patients who survived, a substantial proportion completely returned to the preinjury level of functioning (6% after moderate/severe, 44% after mild TBI). The proportion of patients with impaired physical HRQoL was substantial. However, the rates of impaired mental and brain-specific HRQL and increased mental health symptoms were comparable to the general TBI population[7, 39, 40] In multivariable analyses of 6-month outcomes, increased age and TBI severity (CT abnormalities, GCS) were associated with the poorer functional outcome, but not with

worse mental health outcomes. Older women had a higher likelihood of worse HRQoL and mental health (**Chapters 2**, **3**, **4**). After mild TBI, older women had similar functional outcome as older men, and after moderate/severe TBI, women had lower likelihood of worse functional outcome (**Chapter 2**). Psychiatric history and education were strongly related to all outcomes: functional; physical, mental and brain-injury specific HRQoL; symptoms of depression, PTSD and anxiety (**Chapter 4**). In addition, a more frequent history of psychiatric disorders and sociodemographic variables (e.g. lower educational level) could partly explain worse HRQoL and mental health reported by older women compared to older men (**Chapter 3**). Furthermore, a pre-existing systemic disease that influences other organs or the entire body was associated with all outcomes except anxiety symptoms. Our findings emphasize the importance of preinjury comorbidity for both mental and physical health after a TBI in older adults, and probably explain the high mortality rate and a substantial percentage of impaired physical HRQoL (**Chapter 4**).

PART 2: Prediction: Improving diagnosis and prognosis following mild TBI

Although the most common TBI severity is called "mild", about a half of mild TBI patients did not completely return to their preinjury level of functioning in the CENTER-TBI study.[7] Moreover, intracranial abnormalities were detected on CT scan in almost half of mild TBI patients in CENTER-TBI, and the most common pathology was subarachnoid hemorrhage. Chronic subdural hematoma is also a frequent intracranial pathology, developed in a large percentage of older adults after a mild head trauma.[41] Predicting who has developed intracranial pathology after a mild TBI and who will experience persistent post-concussion symptoms or functional impairments is challenging. In **Part 2** of this thesis, we aimed to improve prediction following mild TBI (Main findings in ***Text box 3***).

Text box 3. Prediction: Main findings associated with research questions

- Can blood-based biomarkers improve current clinical decision rules (CDRs) for selecting mild TBI patients for CT scanning?

Yes, particularly GFAP is a promising candidate. Using GFAP may reduce the number of unnecessary CT scans in comparison with commonly used CDRs, with a comparable ability to detect intracranial injuries.

- How do existing prognostic models for outcome following mild TBI, including chronic subdural hematoma (CSDH), perform in other contemporary TBI cohorts?

Models for the prediction of outcome following mild TBI based on admission characteristics and models for the prediction of outcome following CSDH did not perform well in terms of calibration and/or discrimination. Models for mild TBI that included 2-3 week symptoms had satisfactory performance.

- What is the relationship between methodological quality of prognostic model studies in TBI and model performance?

Poorer methodological quality (higher risk of bias) is associated with poorer performance (worse discriminative ability) at external validation.

- Can we improve predictions of functioning (GOSE) and persistent post-concussion symptoms (PPCS) following mild TBI based on personal and clinical variables, CT results, blood-based biomarkers, and questionnaires?

Prognostic models for GOSE based on variables available at presentation before discharge have moderate discriminative ability, and models for PPCS perform poorly. Injury severity has greater importance for GOSE and personal characteristics have greater relative importance for PPCS. CT variables, biomarkers, and questionnaires assessing symptoms improve predictions of GOSE, and questionnaires assessing symptoms improve predictions of PPCS.

- Do intracranial traumatic lesions predict outcome following mild TBI in young people?

Yes, intracranial traumatic lesions are associated with the functional outcome a year after mild TBI in young people.

Improving diagnosis following mild TBI

We found that the diagnostic accuracy of serum biomarkers for detecting intracranial abnormalities on CT, including the potential neurosurgical lesions, was higher than the diagnostic accuracy of commonly used clinical decision rules (CDRs). Particularly GFAP, followed by UCHL1, NFL and Tau had higher diagnostic accuracy (**Chapter 6**). However, combining currently used CDRs with biomarkers may be more sensible approach: for instance, indicating a CT scan for the high- risk patients according to

the commonly used CDRs and using biomarker as decisive factor for the medium risk patients. As such, the number of unnecessary CT scans can be reduced with minor loss of sensitivity. GFAP showed the best sensitivity and the best specificity across GCS levels, sampling time intervals and with/without extra-cranial injuries. Although rarely directly compared with actual clinical practice, the superiority of GFAP in identifying intracranial lesions has been shown in other recent studies.[42-44] In addition, this study confirms that the sampling time of biomarkers also plays a role in the ability of a biomarker to detect intracranial lesions: biomarkers with a shorter half-life, such as S100B and UCHL1, have better diagnostic accuracy in earlier time intervals since the injury, whereas biomarkers with a longer half-life, such as GFAP and particularly NFL, have better diagnostic accuracy later after injury.[45, 46]

Improving prognosis following mild TBI

We identified existing models for the prediction of outcome after mild TBI for validation in CENTER-TBI data (**Chapter 7**) and of outcome after subdural hematoma (CSDH) for validation in retrospective data from three regions in the Netherlands (**Chapter 8**). Importantly, only a few models we identified could be fully validated due to unmeasured variables in validation cohorts, or due to deficient reporting of the full model equation in development studies. The models for mild TBI predicted different endpoints of the Glasgow Outcome Scale Extended (GOSE) and differently defined persistent post-concussion symptoms endpoint; the models specifically for CSDH predicted mortality and hematoma recurrence. The models for mild TB based on admission characteristics and models for CSDH did not perform well in terms of calibration or discrimination, or both (**Chapters 7 and 8**). The CRASH models, developed for TBI patients with GCS<= 14 for the prediction of severe disability or death (GOSE<5) had the best discriminative ability (C=0.78-79), however, they largely overestimated the percentage of patients with this outcome. Models for prediction of 6-month post-concussion symptoms following mild TBI containing 2- week symptoms performed well in terms of discrimination (C=0.75-76) and calibration (slope=1.0, intercept= -0.3).

Some differences in performance may be due to differences in study populations that are not (completely) reflected in the model predictors. For instance, compared to some development cohorts, the CENTER-TBI population has a relatively high percentage of intracranial abnormalities, major extra-cranial injuries and admissions to the ICU, and a relatively high median age. This can be related to the inclusion of large university hospitals and trauma centers, indication for CT as an inclusion criterion, no exclusion criterion related to age, and population aging. Other important aspects are differences in collection and definitions of the TBI-related variables, which we can relate to the common data elements. Although tremendous effort has been done in recent years-reflected in European-based CENTER-TBI and US-based Transforming Research and

Clinical Knowledge in TBI (TRACK –TBI) studies,[47] some variables are not consistently collected in research, such as assessments of (neck) pain and coping after injury. Moreover, some variables are not consistently defined. For chronic subdural hematoma, there are still no common data elements and core outcomes defined. For instance, the definition of one of the most common outcomes: "recurrence" varies between studies or is not reported.[48] Although one of the most important outcomes following mild TBI, several questionnaires are used for assessing post-concussion symptoms and there is no consensus on the definition of the severe symptoms.[49, 50] The main outcome measure in traumatic brain injury Glasgow Outcome Scale Extended, is assessed in different ways across trials: sometimes the consequences of all injuries are considered (including polytrauma, like in CENTER-TBI) and sometimes the consequences of TBI only (excluding polytrauma, like in US-based TRACK-TBI).[51] In addition, the GOSE is dichotomized in different ways in modelling studies.

Some prognostic models that we examined were developed using suboptimal modelling strategies, such as selecting predictors based on statistical significance and using a small effective sample, inefficient use of data (no imputation strategy for missing values), and omitting internal validation procedures, particularly for CSDH (**Chapter 8**). In **Chapter 9,** we confirmed that the quality of the development study influenced the performance at external validation. We found that model development studies from the field of TBI with - according to Prediction model Risk Of Bias ASsessment Tool (PROBAST)[52] -a higher risk of bias had worse performance (discriminative ability) at external validation. Consistent with reviews from other medical fields, [53] this study emphasized the importance of following methodological and reporting guidelines and supported the usage of risk of bias instruments such as Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD)[54] and PROBAST[52] in model development and validation.

We developed and presented new prognostic models for GOSE and post-concussion symptoms following mild TBI (**Chapter 10**). We avoided common pitfalls of previous studies (**Chapter 7 and 9**) related to the dichotomization of predictors and outcomes, selection of predictors, imputation of missing values and internal validation. As models for mild TBI based on admission characteristics usually show a modest discriminative ability [55, 56](**Chapter 7**), the Core and Clinical models included variables available at admission but were extended with different categories of predictors available before discharge: CT variables, biomarkers and questionnaires (symptoms), and finally with questionnaires (symptoms) assessed at 2-3 weeks. The models for GOSE that included variables available at admission or before discharge had moderate discriminative ability (C=0.69-0.72), which was comparable to, or better than the existing models based on admission characteristics (**Chapter 7**). For post-concussion symptoms, the models based only on variables available

at presentation or before discharge had a relatively low proportion of variance explained (R2=4-12%). For both outcomes, the inclusion of post-injury symptoms – particularly at 2-3 weeks – improved the discriminative ability, which is consistent with the results of our external validation of models for mild TBI (**Chapter 7**).

We confirmed that "what the patient brings to the injury" is important for the prognosis of outcome after mild TBI:[57] medical history, including psychiatric history and history of headaches, and personal characteristics, such as age, sex/gender, employment and education (**Chapters 2, 3, 4 and 10**). However, we also showed that "what the injury brings to the patient" has predictive value for outcome following mild TBI- above all for the functional outcome (**Chapters 4, 10 and 11**). Injury severity score was a prominent predictor of both GOSE and persistent symptoms, and the strongest baseline predictor of GOSE. In addition, cause of injury, and pupillary reactivity were predictors of both outcomes. CT variables and biomarkers, such as NFL, were also associated with the global outcome and improved model performance. However, the incremental value was relatively modest for prediction of GOSE and even smaller for prediction of PPCS. Although biomarkers seem to largely improve the ability to detect intracranial abnormalities (**Chapter 6**), they only slightly improve the ability to predict 6-month outcomes (**Chapter 10**). Interestingly, different biomarkers were selected in models for GOSE and for PPCS: NFL and S100B for GOSE, and GFAP for PPCS. In patients younger than 25 years (**Chapter 11**), CT abnormalities showed associations with the functional outcome a year after mild TBI. This is in line with other large contemporary studies, such as TRACK-TBI, showing that lesions on CT are associated with the outcome after mild TBI. [58] Nevertheless, not all studies found a strong association between the CT abnormalities and outcome after mild TBI.[55, 59] It is important to mention that both CENTER-TBI and TRACK-TBI included large trauma centers and on average, relatively "severely" injured mild TBI patients, and therefore injury-related characteristics may be more prominent predictors than in some other mild TBI studies including patients only seen at the ED or general practitioner.

In conclusion, both "what the injury brings to the patient" and "what the patient brings to the injury" are important for the prediction of outcome after mild TBI. Nevertheless, the importance of the injury-related characteristics seems to be greater for the prediction of global functioning (and physical HRQoL),[60], while the relative importance of personal characteristics seem to be greater for the prediction of symptoms (and mental HRQoL). Finally, we showed that it is easier to predict lower levels of GOSE (severe disability/death, good recovery/death) than higher levels of GOSE (complete recovery) or persistent symptoms based on the personal, clinical and injury-related characteristics available at presentation and before discharge. For explaining more variance in the complete return to preinjury functioning and persistent symptoms, it seems crucial to assess post- symptoms and coping after injury, or more detailed personality and psychological health around the time of injury, in line with findings from other studies

in the field.[55, 61-64] For instance, perceiving TBI as a serious condition and expecting cognitive deficits,[64-66] having a passive and avoidant coping style instead of problem-focused,[55, 67] and being afraid to involve in the usual activities[68] can be associated with a higher risk of incomplete recovery and persistent symptoms.

Recommendations for future research and practice

PART I: Treatment and outcome of mild TBI: relations with sex/gender, age and comorbidity

Text box 2. Treatment and outcome: Recommendations for future research and practice

- Further explore sex/gender differences after TBI:
  - in other geographical areas in addition to North-West Europe
  - using other endpoints
  - using other methods of confounding adjustment.
- Discuss with health care providers and students a potential bias in TBI triage, diagnosis and treatment related to:
  - gender
  - age
  - other patient characteristics e.g. ethnicity, injury mechanism.
- Examine if sex/gender differences may be explained by other variables:
  - sociocultural (gender roles, identity and inequality)
  - biological (hormones, neuropathology, genes).
- Give more attention to TBI caused by intimate partner violence in research and practice.
- For older adults, examine whether to update existing prognostic models for functional outcome with information on physical and mental health comorbidities.
- Adapt outcome assessments to people with increased age and disabilities.
- Tailor follow-up appointments to patient differences (gender, age, mental health).
- Provide cognitive-behavioral treatments to patients with PTSD and a history of mild TBI, when needed.
- Examine the effectiveness of PTSD treatments in civilians, women, and patients with more recent TBIs, particularly complementary and novel treatments.

Our findings complement the insights from other medical fields[69] and also show the importance of incorporating potential confounder variables in the analyses. Future TBI studies should continue to examine sex/gender differences in various aspects of health care and in other geographical areas than European, predominantly Western and high-income countries. The lower rates of admission to the ICU for women seem particularly robust and call for exploring the mechanisms and impacts by adjusting for additional relevant variables, conducting qualitative and quantitative research with healthcare providers, and using other statistical methods. For instance, in the case of unobserved confounding and practice variation, instrumental variable analysis can be superior to covariate adjustment.[70]

In older adults, we focused on care pathways upon admission, and inpatient and outpatient rehabilitation at 6-months. Future studies should examine the intensity of specific types of rehabilitation and types of treatments in this group. Moreover, the access to rehabilitation could potentially be increased for older, but also younger TBI patients.[15, 16] Furthermore, possible biases in medical decision making related to patient characteristics such as gender, age, ethnicity, medical history and injury mechanisms[71, 72] should be more often discussed with healthcare providers and students. The effects of treatments for PTSD should be estimated using randomized control trials or better controlling for relevant factors (e.g. neurocognitive functioning) and including more civilians, women, and patients with recent mild TBIs and severe TBIs. Based on our systematic review, the usage of cognitive-behavioral treatments for PTSD is recommended for patients with a history of mild TBI.

The observed outcome differences between men and women after mild TBI could not be explained by the variables that we examined: psychiatric history, sociodemographic variables and care pathways. However, the available sociodemographic variables could probably not adequately capture socioeconomic inequalities and gender roles: we could not include information on primary wage earner, primary caregiver for children, and salary, or differentiation between higher status jobs. Additionally, these variables can have different implications across geocultural areas within and outside Europe, and therefore should be further examined. We did not have a measure of gender identity, for instance masculine norms and self-reliance, which could affect self-report of symptoms and return to work.[73, 74] In addition to conducting qualitative studies,[74-76] the collection of more in-depth information on gender roles and identity could help to explain some of the observed patterns. Moreover, a possible biological pathway via hormonal,[77, 78] genetic[79] and/ or neuropathological[38, 80] differences, which we did not examine, should be addressed in the future. Furthermore, TBIs resulting from intimate partner violence (IPV), although often unreported as such, are more prevalent in women and associated with worse outcomes.[65] Because of the high personal suffering and high occurrence, they require more attention in research, diagnosis and treatment.

Our studies showed a high rate of mortality and disability in older adults. Nevertheless, the percentage of favorable outcomes was also considerable, which suggests that rehabilitation should not be discouraged only because of increased age. Although age was clearly related to functional and physical outcomes, we showed that physical and psychiatric medical history and education were strongly associated with all analyzed domains of recovery: functional, HRQoL and mental health. These aspects are, however, not included in the existing prognostic models for the prediction of outcome following TBI.[81, 82] It is worth exploring if prognostic models should be updated for this group of patients. Moreover, our studies indicate that personal characteristics and medical history should be assessed in clinical practice in addition to injury-related variables and could be relevant for scheduling follow up care.

In our studies, the percentage of missing values in 6-month outcomes was substantial, which could have influenced some observed patterns: men, older persons and patients with more severe injuries are usually less likely to respond. In the CENTER-TBI study, different efforts were made for optimizing the response rates, such as organizing assessments by telephone in addition to in-person appointments, using questionnaires in addition to interviews, and including patient caregivers' responses for some outcomes.[83] However, the non-response rate was particularly high in older adults, who often have cognitive deficits, physical disabilities and other obstacles to respond to questionnaires. The assessments of outcomes in research and practice should be better tailored to people with increased age and more disabilities.

PART 2: Prediction: Improving diagnosis and prognosis following mild TBI

Text box 4. Prediction: Recommendations for future research and practice

- Consider GFAP for updating clinical decision rules for selecting mild TBI patients for CT:
  - Develop and validate platforms for rapid analyses of GFAP
  - Conduct health economic analysis.
- Follow methodological guidelines to reduce risk of bias in model development.
- To improve prediction after chronic subdural hematoma (CSDH):
  - Develop common data elements (harmonize what to measure and how)
  - Use checklists (e.g. TRIPOD and PROBAST).
- For prediction of outcome following mild TBI consider both:
  - patient-related (e.g. medical history, age, sex/gender)
  - injury-related (e.g. injury severity score) characteristics.

- Validate prognostic models for mild TBI developed in CENTER-TBI in independent cohorts.
- Assess post-injury symptoms, particularly post-concussion symptoms, for dynamic prognosis of outcome following mild TBI.
- Invite mild TBI patients for follow up appointments when possible.
- Clarify which types of intervention to offer to which mild TBI patients.

GFAP should be considered for updating current clinical decision rules for the selection of mild TBI patients for CT. Nevertheless, the large cohorts- CENTER-TBI and TRACK-TBI- have a relatively high median sampling time (around 12 hours) which can contribute to the good performance of GFAP, but it is often too late for usage at the ED. Although sensitivity analyses in different sampling time intervals[84, 85] and using sampling time-corrected values point in the same direction, caution is necessary. In clinical practice, it would be useful to have a biomarker that is diagnostically superior both shortly (for rapid medical decisions at the ED) and later after injury (for patients presenting with delay). Moreover, clinical adoption requires a rapid test that will provide results quickly, similar to the assessment of clinical variables. Available findings using the point-of-care (POC) platform (Abbott Laboratories)[86] that delivered the results within 15 min supported the usage of GFAP, however, they used frozen samples.[44] Further development and validation of rapid platforms for analyzing GFAP (or other promising biomarkers) are warranted and expected in the future.

Of note, we defined artificial cutoffs for biomarkers to mimic either the sensitivity or the specificity of a clinical decision rule. However, for usage in clinical practice, a new rule incorporating a validated cutoff of GFAP, or a new prediction model incorporating GFAP in a continuous manner is necessary. In the end, a biomarker analysis is expected to have a lower price than a CT scan,[87] nonetheless, health economic analyses should be conducted to confirm that the usage of GFAP is truly cost-effective in different clinical contexts and long-term. [61]

In the prognostic studies, we confirmed the importance of the Common Data Elements[88] for improving the prediction of outcome by enabling external validation and establishing the importance of predictors. Whereas they have been largely developed for TBI in general,[89, 90] they can be further improved by agreement on the definitions of the endpoints (e.g. severe post-concussion symptoms and GOSE) and on important variables that should be collected in the context of mild TBI. For CSDH, common data elements still need to be developed: with the aim of identifying Data Elements and standardizing reporting in future CSDH studies, there is an ongoing study that involves a Delphi process with healthcare professionals, researchers, patients and

carers.[91] Furthermore, our studies confirm the importance of following methodological guidelines[92] in the development studies, because they impact the performance of models in other cohorts. In that process, checklists and instruments such as TRIPOD[93] and PROBAST[52] can be useful.

Easily obtainable injury characteristics such as injury severity score and presence of extracranial injury should be assessed for the prognosis of functional outcome (and physical aspects of quality of life)[60] and to a lesser extent for symptomatic and mental health outcomes. CT variables or blood-based biomarkers can be used to slightly improve the prognosis of functional outcome. Further, we found similar incremental value of CT variables and biomarkers: therefore, if blood-based biomarkers are used for the diagnosis of intracranial abnormalities, these can also be used for the prognosis. Considering some inconsistency related to CT variables and a small number of studies involving biomarkers, future systematic reviews and meta-analyses can clarify in which contexts/patients these types of variables are most useful. Furthermore, our studies suggest that sociodemographic characteristics (e.g. education, employment) and information on medical history (e.g. healthy patient vs. with systemic disease; history of migraines and headaches, psychiatric disorders) should be collected, particularly when predicting symptomatic and mental health outcomes. Obtaining better insight into the mental health preceding the injury when there is no official diagnosis is probably valuable, but challenging. Patients can have difficulties describing or admitting their mental health difficulties, and the extensive assessment can be impractical upon admission.

Post-concussion symptoms assessed through questionnaires at presentation or during hospital stay can be a practical and rapid way to improve predictions. Although their predictive value seems smaller than the predictive value of symptoms that persist for weeks after injury, they are rarely analyzed at both time-points (hours/days vs. weeks after injury) in the same study. Early assessment can be more meaningful for some symptoms (e.g. headache) than for some others (e.g. sleep difficulties). In the CENTER-TBI study, it is difficult to draw clear conclusions because 2-3 week symptoms were only assessed in a subset of mild TBI patients. It would be useful to examine if there are benefits of using these early measures for scheduling follow up assessments or if all mild TBI should be invited for a follow-up. The value of assessing post-concussion and posttraumatic symptoms after several weeks, consistently found in different studies (including Chapters 7 and 10), should motivate organizing follow-up appointments for improving prognosis and care. [55, 94] Besides in-person appointments, they could also be organized by telephone (e.g. for older patients) or online (for younger patients).

Nevertheless, current findings suggest that follow up appointments are not easily accessible for mild TBI patients. In Europe, there seems to be a large variation in follow

up appointments, with a minority of centers scheduling routine appointments after ED and around half after hospital admission. [95] One study in the Netherlands showed that a quarter of non-hospitalized mild TBI patients returned to the clinic within several months because of complaints.[96] In the US, less than half of mild TBI patients and about a half of patients who experienced increased symptoms had a follow-up appointment with a medical practitioner.[17] Among patients who did have some follow-up care, a large majority found it useful. [17] Moreover, in addition to post-concussion symptoms, these follow-up appointments could involve brief assessment of other important predictors, such as pain and passive/avoidant coping, [55, 62, 97] which could improve predictions, but also serve as treatment targets. One of the reasons why it is important to improve identification of at-risk mild TBI patients at risk is to timely offer treatment, such as brief telephone counselling,[67, 97] graded exposure therapy,[62] multidimensional psycho-educational intervention[98] and generally, cognitive-behavioral therapy. [67, 97, 99] Improving treatments should go in line with improving prognosis: future studies should continue exploring the effectiveness of interventions and tailoring them to specific patients' needs, symptoms and underlying mechanisms.

General Conclusion

In the first part of this thesis, we aimed to describe care pathways, treatment and outcome in relation to sex/gender, age and comorbidity. We did not find substantial sex/gender differences in treatment. Following mild TBI, we observed differences between men and women in some care pathways and in all examined outcomes: functional, post-concussion and mental health symptoms, and health-related quality of life. The outcome differences should be further investigated by assessing more biological and gender-related variables. In older adults, the rate of poor outcome was substantial, but also of the complete return to preinjury functioning. It is important to assess preinjury physical and mental health of older adults because of strong associations to different types of outcomes. Older age should not discourage treatment and rehabilitation, and a history of TBI should not discourage treatments for posttraumatic stress disorder.

In the second part of this thesis, we aimed to improve prediction following mild TBI. The blood-based biomarker GFAP is promising for updating current clinical decision rules for the selection of mild TBI patients for computed tomography (CT). To improve prediction, model development studies should follow methodological guidelines that foster internal validity and reporting quality. In addition, the efforts in improving common data elements in TBI and chronic subdural hematoma research should be continued. Both "what patient brings to the injury" and "what the injury brings to the patient" should be included for the prognosis of outcome following mild TBI. Baseline injury-related characteristics are particularly important for the prediction of

functional outcome and pre-injury/ personal variables for the prediction of persistent symptoms. Incorporating CT variables and biomarkers can lead to minor improvements in predictive ability, however, 2-3 week assessments of symptoms are required for a substantial improvement of predictions. These findings may support researchers in conducting prediction studies, and clinicians in making decisions on CT scanning, additional medical appointments and treatments, and in informing mild TBI patients about their trajectory of recovery.

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Appendices

Summary

Traumatic brain injury (TBI) is a sudden change in brain function or damage to the brain, caused by an external force. TBI represents a global public health problem and an important cause of morbidity. According to the most often used severity classification (Glasgow Coma Score), the majority of patients present with a mild TBI. A substantial proportion of "mild" TBI patients do not completely return to their preinjury functioning, such as work, social and leisure activities, months after injury. They frequently experience persistent cognitive (e.g. forgetfulness), somatic (e.g. headache) and emotional (e.g. irritability) symptoms called post-concussion symptoms, and symptoms of mental health disorders often (co-)occur. The initial TBI severity is not the only factor impacting clinical decisions and patient outcomes following TBI. Treatment and outcome can vary based on other clinical and personal characteristics. TBI studies suggest outcome differences between men and women, but the direction and size of differences vary. Because of an aging population, older adults represent a growing TBI population. Increased age and the presence of mental and physical comorbidities can influence treatment and outcome.

Complex associations between different types of personal and clinical variables challenge the prediction of outcome after mild TBI. Clinical decision rules based on clinical variables have been developed for selecting mild TBI patients for computed tomography (CT) but need further optimization. Models for the prognosis of long-term outcomes following mild TBI have been rarely examined in new cohorts (externally validated) and robust prognostic models are currently unavailable. It is important to improve the identification of mild TBI patients at risk of acute (e.g. intracranial pathology) and persistent complications (e.g. recurrence of lesions, post-concussion symptoms and incomplete recovery) to inform patients and provide adequate treatment.

The overall aims of this thesis were to describe the treatment and outcome of (mild) TBI in relation to sex/gender, age and comorbidity (**Part 1**) and to improve diagnosis and prognosis following mild TBI (**Part 2**). To achieve our aims, we mainly used the Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) Core study, which is a Europe-based multicenter, longitudinal, prospective, observational trial that included 4509 TBI patients- including 2864 patients categorized as mild.

Part I: Treatment and outcome of mild TBI: relations with sex/gender, age and comorbidity

Main findings

In **Chapter 2**, we described care pathways, treatment and outcome in relation to sex/

gender. Men and women did not substantially differ in care pathways and treatments following mild and moderate/severe TBI after adjusting for relevant injury-related and clinical variables. However, some differences were observed, such as a lower likelihood of women to have a secondary referral (OR 0.7, 95% 0.6-0.95) and to be admitted to intensive care (OR 0.6, 95% 0.4-0.8) after mild TBI. Women had worse functional outcome (OR 1.4, 95% CI: 1.2-1.6), and reported more severe post-concussion and mental health symptoms and lower health-related quality of life (HRQoL) after mild TBI. The differences were most prominent in mild TBI patients aged 16-45 years and for some outcomes in older adults (65+). In **Chapter 3,** we hypothesized that the observed outcome differences could be explained by differences in care pathways (Chapter 2), gender-related sociodemographic variables (education, employment/ job category, living with children, living alone) and differences in mental health before the injury (psychiatric history). We examined these 3 pathways using a mediation framework. The worse outcomes in women following mild TBI were only partly explained by psychiatric history, and could not be explained by care pathways and sociodemographic variables. In **Chapter 4**, we described care pathways, 6-month outcomes and the factors associated with the outcomes in older adults. Almost half of older adults were admitted to an ICU, and around a third received inpatient rehabilitation and 12% outpatient rehabilitation 6 months after TBI. The 6-month mortality rate was high, particularly after moderate/ severe TBI (60%). The proportion of patients with mild TBI who completely returned to their preinjury functioning was substantial (44%). Worse functional outcome was associated with increased age and injury severity. All types of outcomes (worse functioning, lower HRQoL and more severe mental health symptoms) were associated with worse pre-injury health, psychiatric history and lower education. In **Chapter 5**, we systematically reviewed studies on treatment for PTSD for individuals with a (history of) TBI. Based on 23 studies and 26 case studies, we concluded that cognitive-behavioral interventions were effective for patients with a history of mild TBI and that the evidence was less strong for other interventions and patients with more severe and more recent TBIs.

Discussion

We mostly analyzed sex/gender differences in large university hospitals in North-West Europe and used covariate adjustment. We recommend further examination of the differences in treatment and outcome by analyzing other geocultural areas and using other methods of confounding adjustment. Sex/gender differences and age patterns in outcomes could not be adequately explained by the analyzed pathways (psychiatric history, sociodemographic variables, care pathways), therefore we recommend collecting biological characteristics and more detailed aspects of gender roles and identity. There should not be pessimism about the outcomes of older adults who survive. When treating older TBI patients and making predictions about their outcome, it is important to

incorporate medical history (overall and mental health). When examining the effects of interventions for PTSD in patients with TBI, we recommend randomized controlled trials or better control for confounding, and including more women, civilians and patients with more recent TBIs. In TBI research, special attention should be focused on data collection in patients with vulnerabilities, such as cognitive, mental and physical disabilities, and injuries sustained due to violence. In clinical practice, a possibility of bias related to personal characteristics (e.g. age, sex and gender, ethnicity, medical history) in triage, diagnosis and treatment should be discussed with health care providers and students.

Part 2: Prediction: Improving diagnosis and prognosis following mild TBI

Main findings

In **Chapter 6**, we compared the diagnostic accuracy of six blood-based biomarkers and four clinical decision rules (CDRs) for detecting abnormalities on CT in mild TBI patients. We found that biomarkers, particularly glial fibrillary acidic protein GFAP, had superior diagnostic accuracy: with the biomarker threshold set to obtain the same sensitivity as each of the four CDRs, GFAP was substantially more specific (19 to 35% percentage points) than any of the CDRs. Biomarkers ubiquitin C-terminal hydrolase-L1 (UCH-L1), neurofilament light chain protein (NFL) and T-tau also showed good diagnostic accuracy. Combining GFAP with the components of the current CDRs improved specificity for detecting abnormalities on CT with a minor loss of sensitivity. To improve prediction of future outcomes, we first examined the performance of the existing prognostic models. In **Chapter 7,** we validated models for the prediction of 6-month outcome after mild TBI in the CENTER-TBI study: 5 models for the prediction of global functional outcome and 3 models for the prediction of persistent post-concussion symptoms. The outcome definitions varied between models. The models including predictors available at admission did not have satisfactory performance in terms of discrimination and calibration. The models for the prediction of outcome after mild TBI that included 2-3 week symptoms performed well (C-statistic 0.75-76; intercept=-0.3, slope=1.0). In **Chapter 8,** we validated models for the prediction of after chronic subdural hematoma: a model for the prediction of 30-day mortality and models for 2-month and 3-month hematoma recurrence. They overestimated the outcome rate (11%, 1%, 2%, respectively) or they had poor discriminative ability (C-statistic 0.70, 0.46, 0.59, respectively). In **Chapter 9**, we examined the relation between methodological quality of model development studies in the field of TBI and the performance at external validation. We found that a higher risk of bias in the model development, assessed by the Prediction model Risk Of Bias Assessment Tool (PROBAST), was associated with worse performance at external validation. In

Chapter 10, we developed prognostic models for the prediction of 6-month global functional outcome and persistent post-concussion symptoms following mild TBI and assessed the prognostic value of different categories of predictors. Both injury-related and personal characteristics were important for the prognosis of functional outcome at baseline, and injury severity was the strongest predictor. CT variables, biomarkers, and questionnaires assessing symptoms improved predictions of global functional outcome and questionnaires assessing symptoms improved predictions of persistent post-concussion symptoms. For both outcomes, the inclusion of 2-3 week symptoms substantially improved model performance. In **Chapter 11**, we found that intracranial abnormalities were associated with 1-year functional outcome in young persons with mild TBI.

Discussion

For improving diagnosis after mild TBI and reducing unnecessary CT scans, we recommend using GFAP for updating current clinical decision rules. Our findings should be validated with the robust point of care assays and confirmed in a health-economic analysis. For improving prognosis following mild TBI, including chronic subdural hematoma, methodological guidelines should be followed and the quality of reporting and risk of bias should be assessed in model development and validation. In addition, we recommend further harmonization of data elements in data collection. Both injury-related (e.g. injury severity, CT abnormalities) and patient-related (e.g. mental and physical medical history, sociodemographic variables) characteristics should be considered for the prognosis of outcome after mild TBI, particularly for the prognosis of global functioning. We recommend scheduling follow-up appointments for mild TBI patients when possible, as the importance of assessing 2-3 post-injury symptoms was consistently found in previous studies and confirmed in our studies. The prognostic models for functional outcome and persistent post-concussion symptoms developed in CENTER-TBI should be validated in independent cohorts. Our findings related to diagnosis and prognosis should be corroborated in a broader group of mild TBI patients who present to smaller clinics and hospitals, as CENTER-TBI included patients with indications for CT and recruited from large hospital centers.

Samenvatting

Traumatisch hersenletsel is een plotselinge verandering in het functioneren van het brein of letsel aan het brein veroorzaakt door een externe kracht. Het is een ernstig volksgezondheidsprobleem en een belangrijke overlijdensoorzaak. Volgens de meest gebruikte ernstclassificatie (Glasgow-comaschaal), vertoont het merendeel van de patiënten een milde vorm van traumatisch hersenletsel. Een aanzienlijk deel van patiënten met een "milde" vorm van traumatisch hersenletsel maakt geen terugkeer naar normaal functioneren, waardoor ze op het gebied van werk, hun sociale leven en vrije tijd maanden na het incident nog negatieve consequenties ervaren. Zo hebben patiënten vaak last van aanhoudende cognitieve (bv. vergeetachtigheid), somatische (bv. hoofdpijn) en emotionele (bv. prikkelbaarheid) symptomen genaamd 'post-concussion symptoms (PCS)' (symptomen die kunnen worden ervaren na een milde vorm van traumatisch hersenletsel). Daarnaast doen geestelijke gezondheidsklachten zich ook vaak voor na mild traumatisch hersenletsel. De oorspronkelijke ernst van het hersenletsel is niet de enige factor die van invloed is op klinische beslissingen en patiëntenzorg na traumatisch hersenletsel.

De behandeling en de uitkomst na traumatisch hersenletsel kunnen variëren op basis van andere klinische en persoonlijke kenmerken. Onderzoek naar traumatisch hersenletsel wijzen bijvoorbeeld op verschillen in uitkomsten tussen mannen en vrouwen, maar waar de verschillen liggen en hoe groot deze verschillen zijn varieert. Als gevolg van de vergrijzende samenleving vertegenwoordigen ouderen een toenemend aandeel van mensen met traumatisch hersenletsel. Oplopende leeftijd en de aanwezigheid van geestelijke of fysieke comorbiditeiten kan van invloed zijn op de behandeling en diens uitkomst. Complexe verbanden tussen verschillende vormen van persoonlijke en klinische variabelen bemoeilijken het voorspellen van een uitkomst na mild traumatisch hersenletsel. Klinische beslisregels op basis van klinische variabelen zijn ontwikkeld met als doel het selecteren van patiënten met een milde vorm van traumatisch hersenletsel voor computertomografie scan (CT scan), maar deze beslisregels moeten verder worden uitgewerkt. Modellen voor het voorspellen van langdurige uitkomsten na een milde vorm van traumatisch hersenletsel zijn zelden bestudeerd in nieuwe patiënten (ofwel, extern gevalideerd) en accurate en betrouwbare voorspelmodellen zijn momenteel niet beschikbaar. Het is belangrijk om het herkennen van patiënten met een milde vorm van hersenletsel die risico op acute en langdurige complicaties lopen te verbeteren om patiënten beter te kunnen informeren en behandelen.

De algemene doelstellingen van deze scriptie waren om de behandeling en uitkomst van (mild) traumatisch hersenletsel in betrekking tot (biologische) sekse/gender, leeftijd en comorbiditeit te omschrijven (**Deel 1**), en om diagnose en prognose na afloop van een

milde vorm van traumatisch hersenletsel te verbeteren (**Deel 2**). Zodoende, hebben we grotendeels gebruik gemaakt van de *Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury* (CENTER-TBI) Core study, een Europees onderzoek dat multicenter, longitudinaal, prospectief en observationeel was ingericht en waarbij 4509 patiënten met traumatisch hersenletsel, waaronder 2864 met een milde vorm, onderdeel van waren.

Deel I: Behandeling en uitkomst na mild traumatisch hersenletsel: Het verband met sekse/gender, leeftijd en comorbiditeiten

Belangrijkste bevindingen

In **Hoofdstuk 2** omschrijven we zorgtrajecten, behandelingen en uitkomsten in verhouding tot sekse/gender. Er was geen belangrijk onderscheid tussen mannen en vrouwen als het gaat om de zorgtrajecten en behandelingen bij patiënten met milde vormen of matig tot ernstige vormen van traumatisch hersenletsel. Hierbij is gecorrigeerd voor relevante klinische of letsel-gerelateerde variabelen. Echter, enkele verschillen zijn geconstateerd, zoals een geringere kans dat vrouwen secundair worden doorverwezen (OR 0.7, 95% 0.6-0.95) en dat ze worden opgenomen op de intensive care (OR 0.6, 95% 0.4-0.8) na milde vormen van traumatisch hersenletsel. Vrouwen hadden een minder goede globale functionele uitkomst (OR 0.7, 95% 0.6-0.95) en meldden ernstigere PCS en geestelijke gezondheidsklachten en gezondheids-gerelateerde kwaliteit van leven (GKvL) na milde vormen van traumatisch hersenletsel. De verschillen waren het grootst bij patiënten met mild traumatisch hersenletsel tussen 16 en 45 jaar oud en voor sommige uitkomsten ook bij vijfenzestigplussers. In **Hoofdstuk 3** presenteren wij de hypothese dat de waargenomen verschillen in uitkomst verklaard kunnen worden aan de hand van afwijkende zorgtrajecten, gender-gerelateerde sociodemografische variabelen (onderwijsniveau, arbeidsstatus, wonen met kinderen, alleenstaand zijn) en verschillen in geestelijke gezondheid voorafgaand aan het letsel (psychiatrische geschiedenis). Deze drie trajecten hebben we aan de hand van een 'mediation analysis' onderzocht. De meest ongunstige uitkomsten bij vrouwen konden slechts gedeeltelijk door psychiatrische geschiedenis worden verklaard, en konden niet aan de hand van zorgtrajecten of sociodemografische variabelen verklaard worden. In **Hoofdstuk 4** omschrijven we zorgtrajecten, uitkomsten na zes maanden en de factoren die gerelateerd zijn aan de uitkomsten die bij ouderen (vijfenzestigplussers) worden waargenomen. Bijna de helft van de ouderen werd opgenomen op de intensive care, ongeveer één derde ontving klinische rehabilitatie en 12% ontving poliklinische rehabilitatie zes maanden na het traumatisch hersenletsel. Het sterftecijfer na zes maanden was hoog, vooral na matig tot ernstige hersenletsel (60%). De proportie patiënten met milde vormen van traumatisch hersenletsel die een volledige terugkeer maakten tot normaal functioneren was aanzienlijk (44%). Slechtere uitkomsten konden in verband worden gebracht met

een hogere leeftijd en de ernst van het letsel. Alle uitkomsten (slechter functioneren, een lager GKvL en ernstigere vormen van geestelijke gezondheidsproblematiek) konden met een slechtere gezondheid voor het ontstaan van het letsel, psychiatrische gezondheid en een lager onderwijsniveau in verband worden gebracht. In **Hoofdstuk 5** hebben we op systematische wijze onderzoek gedaan naar de behandeling van een posttraumatische stressstoornis bij individuen met een (voorgeschiedenis van) traumatisch hersenletsel. Op basis van 23 onderzoeken en 26 casestudies zijn we tot de conclusie gekomen dat cognitieve gedragsinterventies effectief waren voor patiënten met een voorgeschiedenis van milde vormen van traumatisch hersenletsel en dat het bewijs minder overtuigend was als het ging om andere vormen van interventies of patiënten met een ernstigere en een meer recente vorm van traumatisch hersenletsel.

Discussie

We hebben grotendeels verschillen in sekse/gender in grote universitaire ziekenhuizen in Noord-West Europa onderzocht en daarbij gecorrigeerd voor potentiële confounders (relevante klinische of letsel-gerelateerde variabelen). Wij raden aan om verder onderzoek te doen naar de verschillen in behandelingen en uitkomst door middel van het analyseren van andere geoculturele gebieden en het gebruik van andere methoden om te corrigeren voor confounding. Verschillen in uitkomsten tussen de sekse/genders en leeftijdspatronen konden niet voldoende verklaard worden aan de hand van de bestudeerde trajecten (psychiatrische geschiedenis, sociodemografische variabelen, en zorgtrajecten). Daarom raden wij het verzamelen van biologische kenmerken en meer gedetailleerde aspecten van genderrollen en –identiteit aan. Er is geen aanleiding tot pessimisme als het gaat om de uitkomsten voor oudere volwassenen die een traumatisch hersenletsel overleven. Bij het behandelen van oudere patiënten met traumatisch hersenletsel en bij het voorspellen van uitkomsten is het van belang om hun medische geschiedenis (zowel in het algemeen als geestelijke gezondheid) mee te nemen. Bij het onderzoek naar de effecten van interventies na posttraumatische stressstoornis (PTSS) bij patiënten met traumatisch hersenletsel raden wij gerandomiseerde studie met controlegroep (randomized controlled trials) aan of betere controle van confounding. Daarnaast moet onderzoek gedaan worden naar de effectiviteit van interventies voor PTSS bij vrouwen, burgers en patiënten met meer recente vormen traumatisch hersenletsel. Bij onderzoek naar traumatisch hersenletsel zou er in het bijzonder aandacht gevestigd moeten worden op dataverzameling bij patiënten met kwetsbaarheden, waaronder cognitieve, geestelijke en fysieke beperkingen, en letsel wat is opgelopen als gevolg van geweld. In de klinische praktijk moeten mogelijke vooroordelen als het gaat om persoonlijke kenmerken (bv. leeftijd, sekse en gender, etniciteit, medische geschiedenis) in triage, diagnose en behandelingen bespreekbaar worden gemaakt met zorgaanbieders en studenten.

Deel 2: Predictie: Verbetering van de diagnose en prognose na milde vormen van traumatisch hersenletsel

Belangrijkste bevindingen

In **Hoofdstuk 6** vergeleken we de diagnostische nauwkeurigheid van zes bloed-gebaseerde biomarkers en vier klinische beslisregels voor het detecteren van afwijkingen op CT-scans bij patiënten na milde vormen van traumatisch hersenletsel. Wij vonden dat biomarkers, met name glial fibrillary acidic protein (GFAP), superieure diagnostische nauwkeurigheid hadden: met de drempelwaarde ingesteld om dezelfde gevoeligheid te verkrijgen als elk van de vier klinische beslisregels, was GFAP substantieel specifieker (19 tot 35% procentpunten) dan elk van de klinische beslisregels. De biomarkers ubiquitine C-terminal hydrolase-L1 (UCH-L1), neurofilament light chain protein (NFL) en T-tau vertoonden ook een goede diagnostische nauwkeurigheid. Het combineren van GFAP met de componenten van de huidige klinische beslisregels verbeterde de specificiteit voor het detecteren van afwijkingen op de CT-scan met een gering verlies aan sensitiviteit. Om de prognose te verbeteren, hebben we eerst de prestatie van de bestaande prognostische modellen onderzocht. In **Hoofdstuk 7** hebben wij modellen gevalideerd voor het voorspellen van 6-maanden uitkomst na milde vormen van traumatisch hersenletsel in de CENTER-TBI studie: 5 modellen voor het voorspellen van de globale functionele uitkomst en 3 modellen voor het voorspellen van persisterende PCS. De uitkomstdefinities varieerden tussen de modellen. De modellen met bij opname beschikbare voorspellers presteerden niet bevredigend in termen van discriminatie en kalibratie. De modellen voor de voorspelling van de uitkomst na milde vormen van traumatisch hersenletsel die 2-3 weken symptomen bevatten presteerden goed (C-statistic 0.75-76; intercept=-0.3, slope=1.0). In **Hoofdstuk 8** valideerden wij modellen voor de voorspelling van een chronisch subduraal hematoom: een model voor de voorspelling van 30-dagen mortaliteit en modellen voor 2-maanden en 3-maanden hematoomrecidief. Zij overschatten de uitkomst (respectievelijk 11%, 1%, 2%) of hadden een slecht discriminerend vermogen (C-statistic 0.70, 0.46, 0.59, respectievelijk). In **Hoofdstuk 9** onderzochten wij de relatie tussen de methodologische kwaliteit van modelontwikkelingsstudies op het gebied van traumatisch hersenletsel en de prestaties van de modellen bij externe validatie. Wij vonden dat een hoger risico op bias in de modelontwikkeling, beoordeeld met de Prediction model Risk Of Bias Assessment Tool (PROBAST), geassocieerd was met slechtere prestaties bij externe validatie. In **Hoofdstuk 10** ontwikkelden wij prognostische modellen voor het voorspellen van 6-maanden globaal functioneren en persisterende *PCS* na milde vormen van traumatisch hersenletsel. Daarnaast beoordeelden we de prognostische waarde van verschillende categorieën van voorspellers. Zowel letsel-gerelateerde als persoonlijke kenmerken waren belangrijk voor de prognose van de functionele uitkomst bij opname, en de letselernst was de sterkste voorspeller. CT variabelen, biomarkers, en vragenlijsten

die symptomen evalueerden verbeterden de voorspellingen van de globale functionele uitkomst. Vragenlijsten die symptomen evalueerden verbeterden de voorspellingen van persisterende *PCS*. Voor beide uitkomsten geldt dat het meenemen van symptomen op 2-3 weken de prestaties van het model aanzienlijk verbeterde. In **Hoofdstuk 11** vonden we dat intracraniële afwijkingen geassocieerd waren met functionele uitkomsten na 1 jaar bij jonge mensen met milde vormen van traumatisch hersenletsel.

Discussie

Voor het verbeteren van de diagnose na milde vormen van traumatisch hersenletsel en het verminderen van onnodige CT-scans, bevelen wij het gebruik van GFAP aan voor het updaten van de huidige klinische beslisregels. Onze bevindingen moeten worden gevalideerd en de kosteneffectiviteit moet worden bevestigd. Voor het verbeteren van de prognose na milde vormen van traumatisch hersenletsel, inclusief chronisch subduraal hematoom, moeten methodologische richtlijnen worden gevolgd en moet de kwaliteit van de rapportage en het risico op bias worden beoordeeld bij de ontwikkeling en validatie van modellen. Bovendien bevelen wij verdere harmonisatie van gegevenselementen bij de gegevensverzameling aan. Zowel letsel-gerelateerde (b.v. ernst van het letsel, CT-afwijkingen) als patiënt-gerelateerde (b.v. mentale en fysieke medische geschiedenis, sociodemografische variabelen) kenmerken moeten worden overwogen voor de prognose van de uitkomst na mild TBI, met name voor de prognose van het globaal functioneren. Wij bevelen aan om, indien mogelijk, vervolgafspraken in te plannen voor patiënten met milde vormen van traumatisch hersenletsel, aangezien het belang van het beoordelen van symptomen na 2-3 weken na het letsel consistent werd gevonden in eerdere studies en werd bevestigd in onze studies. De prognostische modellen voor functionele uitkomsten en persisterende PCS ontwikkeld in de CENTER-TBI studie moeten gevalideerd worden in onafhankelijke cohorten. Onze bevindingen met betrekking tot diagnose en prognose zouden bevestigd moeten worden in een bredere groep van milde vormen van traumatisch hersenletsel die zich presenteren in kleinere klinieken en ziekenhuizen, aangezien patiënten in de CENTER-TBI studie werden geïncludeerd bij een indicatie voor een CT-scan en gerekruteerd in grote ziekenhuizen.

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