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Title

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ABSTRACT

Objective: Mild traumatic brain injury (mTBI) has been insufficiently researched and its definition remains elusive. Investigators are confronted by heterogeneity in patients, mechanism of injury and outcomes. Findings are thus often limited in generalizability and clinical application. A systematic review was performed to describe the adult populations included and enrolled in studies that evaluated the prognostic value of biomarkers to predict post-concussion symptoms following a mTBI. **Data sources**: Searches of MEDLINE, EMBASE, CENTRAL, CINAHL, Web of Knowledge, PsycBITE, and PsycINFO up to October 2016. **Data selection and extraction**: Two reviewers independently screened for potentially eligible studies, extracted data and assessed the overall quality of evidence by outcome using the Grading of Recommendations Assessment, Development and Evaluation approach. **Results:** A total of 23,298 citations were obtained from which 166 manuscripts were reviewed. Thirty-six cohort studies (2,812 patients) having enrolled between 7 and 311 patients (median 89) fulfilled our inclusion criteria. Most studies excluded patients based on advanced age (n=10 (28%)), neurologic disorders (n=20 (56%)), psychiatric disorders (n=17 (47%)), substance abuse disorders (n=13 (36%)) or previous TBI (n=10 (28%)). Twenty-one studies (58%) used at least two of these exclusion criteria. The pooled mean age of included patients was 39.3 (SD 4.6) years old (34 studies). The criteria used to define a mTBI were inconsistent. The most frequently reported outcome was post-concussion syndrome (PCS) using the Rivermead Post-Concussion Symptoms Questionnaire (n=18 (50%)) with follow-ups ranging from 7 days to 5 years after the mTBI. **Conclusions:** Most studies have recruited samples that are not representative and generalizable to the mTBI population. These exclusion criteria limit the potential use and translation of promising serum biomarkers to predict post-concussion symptoms.

Strengths and limitations of this study

- This systematic review and meta-analysis on the characteristics of patients included and enrolled in studies on the prognostic value of biomarkers for prediction of post-concussion symptoms reports important findings for researchers planning their study and for clinicians interpreting the available data.
- Strengths of this systematic review include the exhaustive search strategy performed using seven databases, the selection and data extraction conducted independently by two researchers and the registration beforehand in the Prospero database of the study protocol.
- This study is limited by the quality of the included studies as well as the unavailability of some relevant data such as some studies inclusion criteria, exclusion criteria and clear patient demographic data.

INTRODUCTION

Mild traumatic brain injury (mTBI) is frequently encountered by neurologists, primary care, emergency, sport medicine and rehabilitation health providers[1] and accounts for approximately 80% of all TBI.[2] The incidence of mTBI exceeds that of dementia, epilepsy and stroke, giving it the status of the most common brain disorder.[3] However, there is still an incomplete understanding of mTBI pathophysiology that leads to suboptimal diagnosis, treatment and prognostication.[4] With increasing attendance to Emergency Departments (ED) following mTBI by complex patients such as elderly,[5] intoxicated patients[6 7] and patients with psychiatric disorders,[8] there is an urgent need to optimise the care of mTBI patients.

Once considered benign, there has been increased awareness of the potential adverse consequences of mTBI.[9] While 80% of patients will report at least one early post-concussion symptom,[10] between 10% and 56% will exhibit persistent symptoms 3 months after a mTBI.[11-15] Physical, cognitive, and emotional symptoms, often described as post-concussion syndrome (PCS), that exceed the expected window of recovery have deleterious impacts on quality of life and daily functional outcome.[16-18] Prognostic markers have been highlighted for cognitive, psychiatric, and mortality outcomes.[19] However, the authors acknowledged that evidence regarding psychiatric and mortality outcomes is limited, and that little evidence exist concerning the role of biological markers in predicting the persistence of cognitive impairment after mTBI.[19] Under these conditions, there is still a need to develop objective assessment and prognostication tools. Novel brain specific serum biomarkers have been studied to assist the prognostic evaluation after mTBI but the translation of biomarker research into clinical practice is still pending.

Unfortunately, research in mTBI is beset with methodological challenges. Researchers are confronted with substantial heterogeneity of patients, various mechanisms of injury and a wide range of potential outcomes.[20 21] Therefore, many researchers choose to apply strict inclusion and exclusion criteria to minimize confounding by such factors and to decrease the inherent population heterogeneity.[20] This approach results in improved internal validity but also inevitably limits recruitment and generalizability of results. Some populations are therefore often excluded or less likely to be enrolled in TBI studies.[22] Furthermore, many methodological concerns regarding mTBI studies such as the inconsistency in mTBI definitions and the frequent inadequacy of outcome measures were highlighted in the recent synthesis performed by the International Collaboration on mTBI prognosis.[23] All these methodological issues further limit the translation to bedside care and might be applicable to research in the field of brain specific biomarkers following a mTBI. Identifying which patients are not enrolled and how often they are excluded from these studies will allow to underline the generalisability of this literature and highlight gaps that future researches should aim to fill.

This systematic review aims to describe populations included or enrolled in studies on the prognostic value of biomarkers for prediction of post-concussion symptoms following a mTBI. The secondary objectives are to describe the mTBI definition applied in these studies as well as the outcomes evaluated.

METHODS

Search strategy

A systematic review was performed to determine the prognostic value of biomarkers to predict the occurrence of post-concussion symptoms following a mTBI (International Prospective Register of Systematic Reviews (PROSPERO) registration CRD42016032578). In summary, a general search strategy aiming to identify articles which assessed the association between biomarkers and post-concussion symptoms in TBI was created for seven databases (from their inception to October 4, 2016): MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials, Web of Knowledge, PsycBITE and PsycINFO using MeSH terms, EMTREE terms and keywords for their respective database. This research used a general strategy with an additional focus on seven of the most studied and promising biomarkers (S-100β protein, neuron-specific enolase (NSE), glial fibrillary acidic protein (GFAP), ubiquitin carboxy-terminal hydrolase L1 (UCHL-1), cleaved tau (c-tau), microRNA, and brain-derived neurotrophic factor (BDNF)).[24-28] No language, type of study or date restriction were applied in the initial search strategy. The detailed EMBASE search strategy is available in Appendix 1. References from the included studies and narrative reviews were also scrutinized and relevant abstracts from congress and conferences were reviewed to identify potential peer-reviewed published studies.(Appendix 2) Authors of potentially relevant abstracts were contacted to identify potentially published studies not identified with our search strategies.

Study selection

Using EndNote (Thomson Reuters, version X7), all the citations obtained with our search strategies on the seven databases were combined. Duplicates were removed. Independently, two reviewers (EM, PAT) then scrutinized all citations and consecutively excluded studies using the title and abstract. Manuscripts of all potentially included studies were obtained. Studies in other language than English or French were translated into English. A third researcher (NL) was involved in case of disagreement and was responsible for the final decision regarding the inclusion of a study.

Studies were considered eligible for inclusion when they reported the association between at least one serum biomarker level and at least one post-concussion symptom evaluated ≥ 7 days following a mTBI. This delay was chosen to ensure that the outcomes represented a prognostic measure instead of a diagnostic evaluation. This study was limited to the adult (> 16 years old) population. Studies were excluded if they were animal studies, case-report, specific to a paediatric population, reporting on moderate or severe TBI unless specific data for mTBI patients could be extracted from the manuscript or by contacting the authors, post-concussion symptom evaluation was performed less < 7 days after the mTBI or the study was not published in a peer-reviewed journal.

Data extraction

Using a data collection form, two reviewers (EM, PAT) independently collected the relevant data from every included study. Therefore, data on the manuscript (journal, publication date, authors), study characteristics (period and methods of recruitment, country(ies), type of study, number of patients included and followed, number of hospitals involved, setting, inclusion and exclusion criteria, mTBI definition), biomarker (assays used and characteristics, detection limits, thresholds, timing of sampling, type of sampling (venous, capillary or arterial), number of samples), patient characteristics (age, gender, trauma mechanism, TBI severity) and the outcomes (outcome type, assessment timing, method of outcome assessment) were collected. When clarification or

additional information was needed, the corresponding author of the included study was contacted via email (up to three attempts).

Statistical analysis and quality assessment

Descriptive statistics were used to describe the population included and enrolled in the studies. Measures of central tendency (means and medians) and dispersion (standard deviation (SD)) were calculated using Statistical Analysis System software (SAS Institute, Cary, North Carolina, v. 9.4). Main data are also presented as proportions. In 14 studies where sufficient data was available, we calculated the pooled mean age of enrolled patients and its heterogeneity (I^2).[29] To be more inclusive, a pooled mean age was also calculated using a weighted average based on study sample size for 34 studies. Where possible, age mean and SD were estimated using formulae proposed by Hozo et al.[30]

The quality of the evidence of the three main outcomes was evaluated using the GRADE approach (post-concussion symptoms, GOS-E & GOS and return to work)[31]. Given the high heterogeneity of the outcomes evaluated and the scales used, no quality of evidence assessment was performed for the neuropsychological outcomes. This study is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (see Appendix 3).[32]

RESULTS

Characteristics of the included studies

After removal of duplicates, the search strategy yielded 23,298 unique citations. Following the assessment of titles and abstracts using our inclusion and exclusion criteria, a total of 166 manuscripts were reviewed (Figure 1). Thirty-six manuscripts fulfilled our criteria and were included in the present study (Table 1). Only one disagreement between the reviewers required the third researcher (NL) to make the final decision. A total of 2,812 patients were included in those studies, which individually included from seven to 311 patients (mean 104 (SD 62), median 89). Twenty-one studies were conducted in Europe while eight were from North America, six from Asia and one was from South America. Two studies were in German and were fully translated in English. Only eight studies (22%) evaluated patients from multiple centres. The most frequent biomarker studied was the S-100β protein (29 studies) followed by NSE (10 studies), C-tau (four studies), GFAP (four studies), UCHL-1 (three studies), BDNF (one study) and microRNA (one study).

Inclusion and exclusion criteria in the included studies

Age limits criteria and the age of the patients enrolled in the studies are illustrated in the eFigure 1. Regarding the inclusion criteria, an upper age limit was used in 10 studies (28%). Therefore, patients ≥ 65 years old were excluded in seven studies (19%) while those aged ≥ 85 years old were excluded in three more studies (total 10 studies, 28%). Across studies, the oldest patient enrolled ranged from 40 to 94 years old. The pooled mean age in the 14 studies with data on SD was 38.7 (SD 5.3) years old (18 studies) and was highly heterogeneous (I^2 97%). In 34 studies, the pooled mean age was 39.3 (SD 4.6) years old.

The most frequent exclusion criteria were neurologic disorders, psychiatric disorders, trauma to another body region, substance abuse disorders and previous TBI (Table 2). Twenty-one studies (58%) used at least two of these exclusion criteria. Medical comorbidities were infrequently used as exclusion criteria. Ten studies (28%) did not report any exclusion criteria and were therefore considered as having no exclusion criteria.

Mild traumatic brain injury definitions in the included studies

The mTBI definitions used were not standardised (Table 3). The Glasgow Coma Scale (GCS) was a criterion in 31 studies (86%) using either GCS 13-15 (23 studies (64%)), GCS 14-15 (seven studies (19%)) or GCS 15 only (one study (3%)). Other criteria such as loss of consciousness (LOC), post-traumatic amnesia (PTA) and focal neurologic deficit were inconsistently used to define mTBI. Three (8.3%), six (16.7%), and one (2.8%) studies used definitions promoted by the American College of Emergency Physician/Centers for Disease Control and Prevention,[33] the American Congress of Rehabilitation Medicine,[34] and the European Federation of Neurological Societies,[35] respectively.

Outcomes presented in the included studies

Table 4 presents the outcomes evaluated. The most frequently evaluated outcome was post-concussion syndrome (PCS) in 18 studies (50%). The Rivermead Post-Concussion Symptoms Questionnaire was the most used scale. Table 5 presents the number of symptoms required to define the presence of a PCS in the different studies. The number of symptoms used to define a positive PCS ranged between one and five with only 10 studies (28%) using ≥ 3 criteria. Among the 36 studies, there were 48 outcome evaluations and the delay between the mTBI and the outcome assessment was > 3 months in only 22 (46%) of them. Six studies used outcomes that were unlikely to detect subtle impairment after a mTBI such as the Glasgow Outcome Scale (GOS) or the GOS-Extended (GOS-E).[36]

Quality of the evidence

Using the GRADE approach, the quality of evidence was evaluated as low or insufficient for the most frequently studied outcomes (Table 6). Various neuropsychological assessments were grouped together in Table 4 but given the heterogeneity of the neuropsychological tests used and the analytic methods, no GRADE assessment was performed for this outcome.

DISCUSSION

Our systematic review highlights the selected patient populations in previously published reports. Most studies have restricted the inclusion of patients based on advanced age (28%), neurologic disorders (56%), psychiatric disorders (47%), substance abuse disorders (36%) or previous TBI (28%). The mean age of enrolled patients was only 38.7 years old. There are also important variations in the definitions of mTBI and in outcomes evaluated. The criteria used to define the occurrence of a positive PCS using the Rivermead Post-Concussion Symptoms Questionnaire ranged between one and five symptoms. These results impact on the generalizability and clinical applicability of the study findings on biomarkers and other prognostic tools following mTBI.

In comparison with moderate or severe TBI, mTBI remains relatively understudied and difficult to define through imaging and other investigative modalities.[20 21 37] Selection bias is common and strict enrolment criteria have been associated with exclusion of up to 95% of the general mTBI population.[20 22] Therefore, patients with pre-morbid conditions remain poorly studied despite their unfavourable prognosis and increased risk of disabilities.[38 39] The association between the biomarker and the outcome in patients with pre-morbid conditions might differ from the association with healthier patients therefore limiting the potential to draw clinical conclusions.

The epidemiology of TBI has evolved with increasing numbers of complex patients consulting for their injury, such as elderly[40] and patients with substance abuse, psychiatric or neurologic disorders.[6 8] Intoxicated patients also often present with altered conscious state raising the possibility of TBI and complicating initial clinical assessment.[41 42] Patients with previous TBI are also of concern given the complications of repetitive TBI.[43] All these patients pose a challenge to the clinician in terms of assessment of injury severity and prognosis. Moreover, these pre-injury factors are known to predispose to the development of persistent post-concussion symptoms leading to poorer functional outcomes.[38 39 44-46] In a large retrospective cohort study of patients with suspected TBI, the prevalence of these confounding factors was highlighted. Patients were frequently intoxicated with alcohol (20%) or had a psychiatric (25%) or neurologic disorders (25%).[22] Unfortunately, these same patients were frequently excluded from the studies included in our systematic review. Therefore, the study populations are often small non-representative subgroups of patients with fewer risk factors to develop post-concussion symptoms. Future studies should aim to maximize the recruitment of these clinically relevant patients.

Geriatric patients represent a constantly growing proportion of the trauma population as the world is ageing.[47 48] The absolute incidence of TBI among the geriatric patients is rising as a result of the increased life expectancy and mobility.[5] Advanced age was an exclusion criteria in 10 studies (28%) but the patients enrolled were mostly young with a mean age of only 38.7 (SD 5.3) years old. Recent large TBI epidemiologic studies[49 50] showed that more than 40% of the mTBI population are older than 50 years and the median age of patients is at least 44 years.[5 51] Geriatric patients seems therefore underrepresented in our included studies despite the fact that they have a poorer functional outcome with an increased occurrence of post-concussion symptoms.[52] The effect of age on the circulating blood-based biomarker is controversial.[53] Geriatric patients often have medical comorbidities that can potentially impact the biomarker's production, metabolism and clearance thus altering its baseline circulating serum level and its release following a mTBI. Interestingly, patients with renal impairment were excluded in only three studies (8%) even though medical comorbidities might represent a more robust exclusion criteria than age alone.

The definition of mTBI was widely variable between the studies often limiting the comparability of studies. While GCS was almost universally included as a criterion, other criteria such as PTA, LOC and neuroimaging results were inconsistently used. Mild TBI is a heterogeneous group with a wide range of "severity". The symptom-based GCS classification often fails to demonstrate the whole spectrum of severity. The diagnostic criteria can be unreliable and overlap many conditions such as dementia, delirium or intoxication and the presence of confounding factors during the initial assessment are frequent.[8]

One major limitation to our understanding of mTBI is the lack of universal definition of the outcomes evaluated.[54] Most patients recover completely but for those affected by persistent symptoms, there are controversies about the nomenclature and definitions associated with post-concussion symptoms and PCS.[55] This is particularly noticeable in our systematic review as the diagnosis criteria of PCS was highly variable ranging from one to more than five criteria on the Rivermead Post-Concussion Symptoms Questionnaire to determine the presence or the absence of PCS. The timing of outcome evaluation was also variable ranging from seven days to more than five years. PCS is a complex constellation of symptoms with a significant variability between individuals. Since most symptoms are subjective, there is a high risk of misdiagnosis[56] and we are still unable to predict the occurrence of PCS. Biomarkers are promising to help predict the recovery and the risk of persistent PCS but well-designed confirmatory studies that address the methodological limitations are needed to enhance our knowledge of mTBI consequences.[19] The

lack of standardisation in the definition of the outcomes undoubtedly contributes to impede the translation from research to daily bedside care in the field of brain specific biomarkers. Another shortcoming that might partly explain the difficulty of using serum biomarkers to predict post-concussion symptoms are that these symptoms are not specific to mild TBI and are prevalent both in the general population and after non-head injuries.[57]

There are numerous other potential benefits to study biomarkers after a mTBI.[37] In addition to improving the initial prognostication, the use of biomarkers could help making the diagnosis, determine more accurately the need for neuroimaging, evaluating the disease progression, determining the safe moment to return to sport or activities and might be used as a surrogate assessment tool for investigational treatments.[26 27] As mTBI diagnostic criteria are subjective, nonspecific and overlap other conditions, a biomarker level could alleviate the paucity around the initial presentation and represent an objective assessment tool.

Strengths and limitations

Our study has several limitations. We looked both at the characteristics of the inclusion/exclusion criteria and the patients enrolled. The absence of exclusion criteria does not mean that some subgroups of patient will be enrolled and often studies failed to present the number of patients screened and approached to be enrolled. Therefore, we can expect that our review underestimates the poor representation of subgroups such as patients with substance abuse, psychiatric and neurologic disorders. Ten studies did not report any exclusion criteria and were considered as having no exclusion criteria but this might be a misinterpretation thus making the underestimation even more likely. We have however used high methodological standards to perform our systematic review. We have completed an exhaustive unrestrictive search strategy using seven databases and screened 23,298 citations. Studies were researched and data were extracted independently by two reviewers. This study is reported in accordance with the recommended PRISMA Statement.

CONCLUSION

The patients included and enrolled in studies on the prognostic value of biomarkers following mTBI are not representative of the mTBI population. Subgroups such as elderly, patients with neurologic, psychiatric and substance abuse disorders and patients with previous TBI are often excluded and poorly represented even though they are at high risk of post-concussion symptoms and associated disabilities. The lack of standardisation of definitions further impedes the translation from research to everyday patient care. Broader inclusion criteria and standardised definitions, particularly mTBI and PCS, are required to maximise the generalizability and the translation to bedside care of the promising brain specific biomarkers.

Contributors EM has had the original idea for this study. EM, PAT and NL conceived the study's design and protocol with support, input and oversight from ME, MCO, EDG, BM and PAC. EM and PAT elaborated the original database search strategy. EM and PAT performed the study selection and data extraction with oversight from ME, MCO, EDG, PAC and NL. PAT prepared the data for statistical analysis. Statistical analysis plan was elaborated by ME, BM and NL. EM and PAT wrote the manuscript first draft. All authors contributed to the manuscript revision and they all approved the final submitted version. All authors are accountable for all aspects of this study.

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Competing interests None declared.

Data sharing statement: No additional data are available.

Tables

Table 1. Characteristics of included studies

First author	Year of study publication	Countries	Number of hospitals	Number of patients included	Biomarkers assessed
Ingebrigtsen[58]	1995	Norway	1	50	S-100β
Waterloo[59]	1997	Norway	1	7	S-100β
Ingebrigtsen[60]	1999	Norway	1	50	S-100β
Ingebrigtsen[61]	2000	Norway, Sweden, Denmark	3	182	S-100β
Herrmann[62]	2001	Germany	1	69	S-100β, NSE
de Kruijk[63]	2002	Netherlands	1	107	S-100β, NSE
Townend[64]	2002	United Kingdom	4	148	S-100β
de Kruijk[65]	2003	Netherlands	1	111	S-100β, NSE
Savola[66]	2003	Finland	1	199	S-100β
Stranjalis[67]	2004	Greece	1	100	S-100β
de Boussard[68]	2005	Sweden	3	122	S-100β
Stålnacke[69]	2005	Sweden	1	88	S-100β, NSE
Stapert[70]	2005	Netherlands	1	50	S-100β
Bazarian[71]	2006 (BI)	USA	1	35	S-100β, C-Tau
Bazarian[72]	2006 (RNN)	USA	1	96	S-100β
Bulut[73]	2006	Turkey	1	60	C-Tau
Naeimi[74]	2006	Austria	1	45	S-100β, NSE
Sojka[75]	2006	Sweden	1	98	S-100β, NSE
Jakola[76]	2007	Norway	3	89	S-100β
Stålnacke[77]	2007	Sweden	1	69	S-100β, NSE
Lima[78]	2008	Brazil	1	50	S-100β
Ma[79]	2008	USA	1	50	C-Tau
Schütze[80]	2008	Germany	1	74	S-100β, NSE
Müller[81]	2009	Norway	1	93	S-100β
Kleinert[82]	2010	Germany	1	73	S-100β
Meric[83]	2010	Turkey	1	80	NSE
Topolovec-Vranic[84]	2011	Canada	1	141	S-100β, NSE
Metting[85]	2012	Netherlands	1	94	S-100β, GFAP
Okonkwo[86]	2013	USA	3	215	GFAP
Abbasi[87]	2014	Iran	2	109	S-100β
Diaz-Arrastia[88]	2014	USA	3	206	GFAP, UCHL-1
Ryb[89]	2014	USA	1	150	S-100β
Heidari[90]	2015	Iran	1	176	S-100β
Dey[91]	2016	India	1	20	S-100β, UCHL-1
Korley[28]	2016	USA	2	311	C-Tau, GFAP, UCHL-1
Yang[92]	2016	China	1	76	miR-93, miR-191, miR-499

BI: Brain Injury; C-Tau: cleaved tau; BDNF: brain-derived neurotrophic factor; GFAP: glial fibrillary acidic protein; miR: micro ribonucleic acid; NSE: neuron specific enolase; RNN: Restorative Neurology and Neuroscience; UCHL-1: ubiquitin carboxy-terminal hydrolase L1; USA: United States of America.

Table 2. Exclusion criteria used in the included studies

Exclusion criteria	Number of studies (n, %)
Neurologic disorder	20 (55.6)
Psychiatric disorder	17 (47.2)
Significant trauma to another body region than the head	17 (47.2)
Substance abuse (drug or alcohol)	14 (38.8)
Previous traumatic brain injury	10 (27.8)
Alcohol intoxication	9 (25)
Renal impairment	3 (8.3)
Cardiac disease	2 (5.6)

Table 3. Criteria used to define mild traumatic brain injury (mTBI) in the included studies

Criteria		Number of studies (n, %)
Glasgow Coma Scale (GCS)	13-15	23[§] (63.8)
	14-15	7 (19.4)
	15	1 (2.8)
	NR	5[∂] (13.9)
Loss of consciousness (LOC)	< 10 minutes	4 (11.1)
	< 15 minutes	5 (13.9)
	< 30 minutes	9[§] (25)
	No duration	8[∂] (22.2)
	No use of LOC	10 (27.8)
Post-traumatic amnesia (PTA)	< 15 minutes	1 (2.8)
	< 30 minutes	0 (0)
	< 60 minutes	4[§] (11.1)
	< 24 hours	3 (8.3)
	No duration	7[∂] (19.4)
	No use of PTA	21 (58.3)
Initial altered mental state	Yes	3 (8.3)
Absence of focal neurology deficit	Yes	14 (38.9)
Triaged to non-contrast head CT using the (ACEP/CDC) evidence-based joint practice guideline		3[∂] (8.3)
Use of the American Congress of Rehabilitation Medicine definition (1993)		6 (16.7)
Use of European Federation of Neurological Societies (EFNS) definition (2002)		1[§] (2.8)

* ACEP: American College of Emergency Physicians; CDC: Centre for Disease Control; CT: Computed Tomography; TBI: Traumatic Brain Injury.
[§] Heidari et al. (2015)[90] used the following mTBI definition: (1) a GCS score of 13–14; (2) a GCS score of 15 with loss of consciousness (LOC) < 30 minutes, post-traumatic amnesia (PTA) < 1 hour; or (3) a GCS score of 15 without LOC or PTA.
[∂] Korley et al. (2016)[28] presented 3 different cohorts with different inclusion criteria. Only the mTBI definition of the case cohort is presented in the table.

Table 4. Outcome evaluated in the included studies

Outcome evaluated	**Number of studies (n, %)**
Post-concussion syndrome	18 (50)
Neuropsychological evaluation	9 (25)
GOS-E; GOS	5 (13.8); 4 (11.1)
Return to work	4 (11.1)
Headache	3 (8.3)
Life satisfaction	2 (5.6)
RHFUQ	2 (5.6)
Anxiety or depression	1 (2.7)
Daily activity functioning	1 (2.7)
Olfactory function	1 (2.7)
Post-traumatic related stress	1 (2.7)
Quality of life	1 (2.7)
SF-36	1 (2.7)
Delay of outcome assessment after TBI	**Assessments (n=48 outcomes) (n, %)**
7 days	3 (6.3)
14 days	6 (12.5)
1 month	6 (12.5)
1.1-3 months	11 (23)
3.1-6 months	11 (23)
6.1-12 months	6 (12.5)
12.1-18 months	4 (8.2)
> 18.1 months	1 (2)

GOS: Glasgow Outcome Scale; GOS-E: Glasgow Outcome Scale-Extended; RHFUQ: Rivermead Head Injury Follow-up Questionnaire; SF-36: Acute Medical Outcomes F6-36v2 Health Survey; TBI: traumatic brain injury.

Table 5. Definition of post-concussion syndrome (PCS)

Scale used	Number of positive symptoms to define the presence of a PCS	Number of studies (n, %)
Rivermead Post-Concussion Symptoms Questionnaire	≥ 1	3 (17)
	≥ 2	1 (5.5)
	≥ 3	5 (28)
	≥ 4	1 (5.5)
	≥ 5	2 (11)
	Not specified	6 (33)

Table 6. Outcomes quality of evidence according to the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach

Outcomes	Number of studies (number of patients)	Design	Findings and direction	GRADE
Post-concussion symptoms	18 studies (n=2048)	Observational	Important heterogeneity in populations enrolled, definitions of outcome variables, and evaluation delay. Only four associations between post-concussion symptoms and a biomarker were statistically significant. Only eight studies used multivariate regression analyses and confidence intervals were often large.	Low
GOS-E & GOS	9 studies (n=1235)	Observational	Slight discrepancies in definitions, wide differences in populations enrolled, methods quality as well as in evaluation delay, and inconsistencies in associations (only 3 were significant), their direction and strength.	Insufficient
Return to work	4 studies (n=432)	Observational	Slight discrepancies in definitions and reporting but considerable differences in evaluation delay (one week to one year). Only one study showed a significant association with increased S-100β protein serum level.	Insufficient

GOS: Glasgow Outcome Scale; GOS-E: Glasgow Outcome Scale (GOS) Extended

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Figure legend

Figure 1. PRISMA flow diagram of included studies

Supplementary files legend

eFigure 1. Age of patients enrolled in the included studies

eTable 1. Search strategy for the Excerpta Medica dataBASE (EMBASE)
eTable 2. List of congresses and conferences screened
eTable 3. PRISMA Checklist

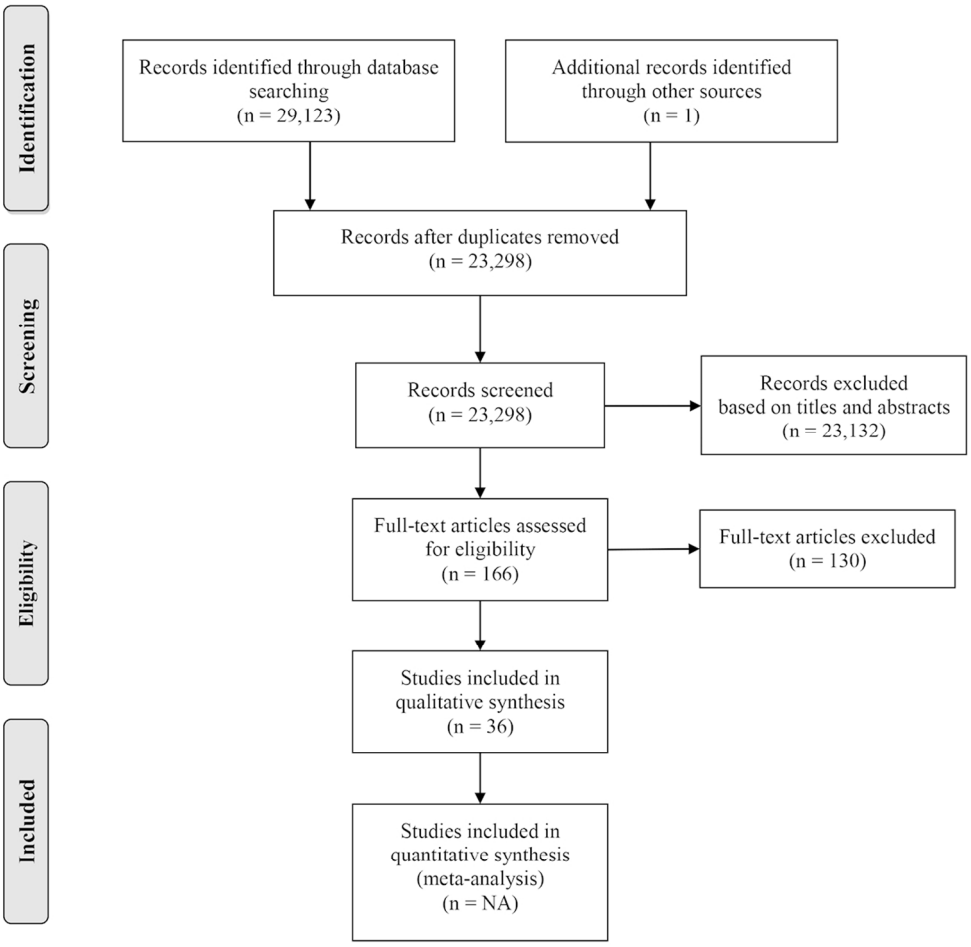

Figure 1. PRISMA flow diagram of included studies

112x119mm (300 x 300 DPI)

eTable 1. Search strategy for the Excerpta Medica dataBASE (EMBASE)

EMBASE SEARCH STRATEGY
Traumatic brain injury **1.** (('brain injury':ti,ab OR 'brain injuries':ti,ab OR 'brain injured':ti,ab OR 'brain injure':ti,ab OR 'brain injures':ti,ab OR 'brain trauma':ti,ab OR 'brain traumas':ti,ab OR 'brain traumatic':ti,ab OR brain:ti,ab OR brain:ti,ab OR 'mild traumatic brain injury':ti,ab OR 'mild traumatic brain injure':ti,ab OR 'mild traumatic brain injured':ti,ab OR 'mild traumatic brain injures':ti,ab OR 'mild traumatic brain injuries':ti,ab OR 'minor traumatic brain injury':ti,ab OR 'minor traumatic brain injure':ti,ab OR 'minor traumatic brain injured':ti,ab OR 'minor traumatic brain injures':ti,ab OR 'minor traumatic brain injuries':ti,ab OR 'minimal traumatic brain injury':ti,ab OR 'minimal traumatic brain injure':ti,ab OR 'minimal traumatic brain injured':ti,ab OR 'minimal traumatic brain injures':ti,ab OR 'minimal traumatic brain injuries':ti,ab OR mtbi:ti,ab OR 'minor head trauma':ti,ab OR 'minor head traumas':ti,ab OR 'minor head traumatic':ti,ab OR 'minimal head trauma':ti,ab OR 'minimal head traumas':ti,ab OR 'minimal head traumatic':ti,ab OR concussion*:ti,ab OR 'brain concussion'/exp OR 'brain concussions'/exp OR contusions:ti,ab OR contusions/exp OR 'brain contusion'/exp OR 'brains injury':ti,ab OR 'brains injuries':ti,ab OR 'brains injured':ti,ab OR 'brains injure':ti,ab OR 'brains injures':ti,ab OR 'brains trauma':ti,ab OR 'brains traumas':ti,ab OR 'brains traumatic':ti,ab OR brains:ti,ab OR brains:ti,ab OR 'brainstem injury':ti,ab OR 'brainstem injuries':ti,ab OR 'brainstem injured':ti,ab OR 'brainstem injure':ti,ab OR 'brainstem injures':ti,ab OR 'brainstem trauma':ti,ab OR 'brainstem traumas':ti,ab OR 'brainstem traumatic':ti,ab OR brainstem:ti,ab OR brainstem:ti,ab OR 'head injury':ti,ab OR 'head injuries':ti,ab OR 'head injured':ti,ab OR 'head injure':ti,ab OR 'head injures':ti,ab OR 'head trauma':ti,ab OR 'head traumas':ti,ab OR 'head traumatic':ti,ab OR head:ti,ab OR head/exp OR heads:ti,ab OR 'heads injuries':ti,ab OR 'heads injured':ti,ab OR 'heads injure':ti,ab OR 'heads injures':ti,ab OR 'heads trauma':ti,ab OR 'heads traumas':ti,ab OR 'heads traumatic':ti,ab OR 'heads':ti,ab OR heads:ti,ab OR 'Brain edema'/exp OR 'Brain edema':ti,ab OR 'Brain swelling':ti,ab OR 'cerebral edema':ti,ab OR 'intracranial edema':ti,ab OR 'Hematoma'/exp OR Hematoma:ti,ab OR Haematoma:ti,ab OR 'brain hematoma'/exp OR 'Hemorrhage'/exp OR Hemorrhage:ti,ab OR Haemorrhage:ti,ab OR 'subarachnoid hemorrahge'/exp OR 'brain hemorrhage'/exp OR 'brain ventricle hemorrhage'/exp OR 'craniocerebral injury':ti,ab OR 'craniocerebral injuries':ti,ab OR 'craniocerebral injured':ti,ab OR 'craniocerebral injure':ti,ab OR 'craniocerebral injures':ti,ab OR 'craniocerebral trauma':ti,ab OR 'craniocerebral traumas':ti,ab OR 'craniocerebral traumatic':ti,ab OR craniocerebral:ti,ab OR craniocerebral*:ti,ab OR 'intracranial injury':ti,ab OR 'intracranial injuries':ti,ab OR 'intracranial injured':ti,ab OR 'intracranial injure':ti,ab OR 'intracranial injures':ti,ab OR 'intracranial trauma':ti,ab OR 'intracranial traumas':ti,ab OR 'intracranial traumatic':ti,ab OR intracranial:ti,ab OR intracrani*:ti,ab OR 'intra-cranial injury':ti,ab OR 'intra-cranial injuries':ti,ab OR 'intra-cranial injured':ti,ab OR 'intra-cranial injure':ti,ab OR 'intra-cranial injures':ti,ab OR 'intra-cranial trauma':ti,ab OR 'intra-cranial traumas':ti,ab OR 'intra-cranial traumatic':ti,ab OR 'intra-cranial':ti,ab OR 'intra-crani':ti,ab OR 'intercranial injury':ti,ab OR 'intercranial injuries':ti,ab OR 'intercranial injured':ti,ab OR 'intercranial injure':ti,ab OR 'intercranial injures':ti,ab OR 'intercranial trauma':ti,ab OR 'intercranial traumas':ti,ab OR 'intercranial traumatic':ti,ab OR intercranial:ti,ab OR intercrani*:ti,ab OR 'inter cranial injury':ti,ab OR 'inter-cranial injuries':ti,ab OR 'inter-cranial injured':ti,ab OR 'inter-cranial injure':ti,ab OR 'inter-cranial injures':ti,ab OR 'inter-cranial trauma':ti,ab OR 'inter-cranial traumas':ti,ab OR 'inter-cranial traumatic':ti,ab OR 'inter-cranial':ti,ab OR

‘cerebral injury’:ti,ab OR ‘cerebral injuries’:ti,ab OR ‘cerebral injured’:ti,ab OR ‘cerebral injure’:ti,ab OR ‘cerebral injures’:ti,ab OR ‘cerebral trauma’:ti,ab OR ‘cerebral traumas’:ti,ab OR ‘cerebral traumatic’:ti,ab OR cerebral:ti,ab OR cerebr*:ti,ab OR ‘cerebellum injury’:ti,ab OR ‘cerebellum injuries’:ti,ab OR ‘cerebellum injured’:ti,ab OR ‘cerebellum injure’:ti,ab OR ‘cerebellum injures’:ti,ab OR ‘cerebellum trauma’:ti,ab OR ‘cerebellum traumas’:ti,ab OR ‘cerebellum traumatic’:ti,ab OR cerebellum:ti,ab OR cerebel*:ti,ab OR ‘forebrain injury’:ti,ab OR ‘forebrain injuries’:ti,ab OR ‘forebrain injured’:ti,ab OR ‘forebrain injure’:ti,ab OR ‘forebrain injures’:ti,ab OR ‘forebrain trauma’:ti,ab OR ‘forebrain traumas’:ti,ab OR ‘forebrain traumatic’:ti,ab OR forebrain:ti,ab OR forebrain*:ti,ab) AND (injury*:ti,ab OR injuries:ti,ab OR injured:ti,ab OR injure:ti,ab OR injures:ti,ab OR trauma:ti,ab OR traumas:ti,ab OR traumatic*:ti,ab OR traumato*:ti,ab OR damag*:ti,ab)) OR TBI:ti,ab OR Glasgow coma scale:ti,ab OR GCS:ti,ab OR ‘traumatic brain injury’:ti,ab OR ‘traumatic brain injure’:ti,ab OR ‘traumatic brain injured’:ti,ab OR ‘traumatic brain injures’:ti,ab OR ‘traumatic brain injuries’:ti,ab OR ‘Head injury’/de OR ‘brain injury’/de OR ‘brain hemorrhage’/de OR ‘diffuse axonal injury’/de OR ‘coma’/de OR ‘brain hemorrhage’/de OR ‘Glasgow coma scale’/de OR ‘blast injury’/exp OR ‘blast-induced brain injury’/exp OR ‘Blast exposition’:ti,ab OR ‘blast injuries’:ti,ab OR ‘blast injury’:ti,ab OR ‘blast injure’:ti,ab OR ‘blast injured’:ti,ab OR ‘sports-related concussion’:ti,ab OR ‘sport-related concussion’:ti,ab OR SRC:ti,ab
Biomarkers **2.** biomarker*:ab,ti OR 'biomarker'/exp OR 'biologic marker':ab,ti OR 'biologic markers':ab,ti OR 'biological marker':ab,ti OR 'biological markers':ab,ti OR 'biochemical marker':ab,ti OR 'biochemical markers':ab,ti OR 'laboratory marker':ab,ti OR 'laboratory markers':ab,ti OR 'immunological marker':ab,ti OR 'immunological markers':ab,ti OR 'immune marker':ab,ti OR 'immune markers':ab,ti OR 'serum marker':ab,ti OR 'serum markers':ab,ti OR 'clinical marker':ab,ti OR 'clinical markers':ab,ti OR 'surrogate end point':ab,ti OR 'surrogate end points':ab,ti OR 'surrogate endpoint':ab,ti OR 'surrogate endpoints':ab,ti OR ‘neuronal protein’/exp OR ‘neuronal proteins’:ti,ab OR ‘neuronal protein’:ti,ab OR ‘neuronal marker’:ti,ab OR ‘neuronal markers’:ti,ab OR ‘nerve tissue protein’:ti,ab OR ‘nerve tissue proteins’:ti,ab OR ‘nerve protein’/exp OR ‘nerve proteins’:ti,ab OR ‘neuronal calcium sensor’/exp OR ‘neuron specific nuclear protein’/exp OR ‘astrocyte protein’:ti,ab OR ‘astrocyte protein’/exp OR ‘S-100’:ti,ab OR S100*:ti,ab OR ‘S100B’:ti,ab OR ‘S-100B’:ti,ab OR ‘S100BB’:ti,ab OR ‘S-100BB’:ti,ab OR ‘S-100B protein’:ti,ab OR ‘S100-β’:ti,ab OR ‘S100β’:ti,ab OR ‘protein S100B’/exp OR GFAP:ti,ab OR ‘GFAP’/exp OR ‘glial protein’:ti,ab OR ‘glial proteins’:ti,ab OR ‘glial fibrillary acidic protein’:ti,ab OR ‘glial fibrillary acidic proteins’:ti,ab OR ‘glial intermediate filament protein’:ti,ab OR ‘glial intermediate filament proteins’:ti,ab OR astroprotein*:ti,ab OR ‘GFA-protein’:ti,ab OR ‘GFA-proteins’:ti,ab OR ‘Glial Fibrillary Acidic Protein’/exp OR ‘neuron specific enolase’/exp OR ‘Neuron specific nuclear protein’/exp OR NSE:ti,ab OR NSE/exp OR ‘neuron specific enolase’:ti,ab OR ‘neuron-specific enolase’:ti,ab OR ‘gamma-enolase’:ti,ab OR ‘nervous system specific enolase’:ti,ab OR ‘phosphopyruvate hydratase’:ti,ab OR ‘Phosphopyruvate Hydratase’:ti,ab OR ‘enolase’/exp OR ‘C-tau’:ti,ab OR ‘C-tau’ OR ‘cleaved-tau’:ti,ab OR ‘tau protein’:ti,ab OR ‘tau Proteins’:ti,ab OR ‘tau protein’/exp OR ‘UCH-L1’:ti,ab OR UCHL1:ti,ab OR ‘ubiquitin carboxyl-terminal hydrolase l-1’:ti,ab OR ‘ubiquitin c-terminal

hydrolase':ti,ab OR 'ubiquitin carboxy terminal esterase':ti,ab OR 'ubiquitin thiolesterase':ti,ab OR 'ubiquitin'/exp OR 'ubiquitin protein ligase'/exp OR 'ubiquitin tholesterase'/exp OR SBDP:ti,ab OR SBDP150:ti,ab OR SBDP145:ti,ab OR SBDP120:ti,ab OR 'SBDP'/exp OR 'Spectrin'/exp OR 'fodrin'/exp OR 'spectrin breakdown product'/exp OR 'NF-H':ti,ab OR NFH:ti,ab OR 'NFP-200':ti,ab OR NFP200:ti,ab OR 'hyperphosphorylated neurofilament':ti,ab OR 'neurofilament protein':ti,ab OR 'neurofilament proteins':ti,ab OR 'neurofilament H protein':ti,ab OR 'neurofilament H proteins':ti,ab OR 'neurofilament triplet protein':ti,ab OR 'neurofilament triplet proteins':ti,ab OR 'neurofilament M protein'/exp OR 'neurofilament'/exp OR 'microRNA'/exp OR 'MicroRNAs'/exp OR 'BDNF':ti,ab OR 'BDNF'/exp OR 'brain derived neurotrophic factor'/exp OR 'brain derived neurotrophic factor receptor'
Outcomes (post-concussion symptoms related terms) **3.** 'post-concussion syndrome'/exp OR 'post-concussion syndrome':ti,ab OR 'postconcussion':ti,ab OR 'post-concussion symptom':ti,ab OR 'postconcussion symptoms':ti,ab OR 'postconcussion syndrom':ti,ab OR 'post concussion syndrom':ti,ab OR 'post-concussive symptom':ti,ab OR 'postconcussive symptom':ti,ab OR 'post concussive symptom':ti,ab OR 'post-concussive syndrom':ti,ab OR 'postconcussive syndrom':ti,ab OR 'post concussive syndrom':ti,ab OR 'post-concussion recovery':ti,ab OR 'postconcussion recovery':ti,ab OR 'post concussion recovery':ti,ab OR 'post-traumatic symptom':ti,ab OR 'posttraumatic symptom':ti,ab OR 'post traumatic symptom':ti,ab OR 'persistent':ti,ab OR 'persistent concussive syndrome':ti,ab OR 'postconcussion syndrome'/exp OR 'postconcussion syndrome':ti,ab OR 'long term':ti,ab OR 'permanent':ti,ab OR 'prolonged':ti,ab OR 'late recovery':ti,ab OR 'recovery':ti,ab OR 'poor outcome':ti,ab OR 'outcome':ti,ab OR 'disability'/exp OR 'disability':ti,ab OR 'sick leave':ti,ab OR 'medical leave'/exp OR 'glasgow outcome scale'/exp OR 'glasgow outcome scale':ti,ab OR 'assessment':ti,ab OR 'patient outcome assessment':ti,ab OR 'outcome assessment'/exp OR 'outcome assessment':ti,ab OR 'symptom assessment'/exp OR 'symptom assessment':ti,ab OR 'neurologic symptom':ti,ab OR 'neurologic symptoms':ti,ab OR 'neurologic manifestation':ti,ab OR 'Neurologic Manifestations':ti,ab OR 'neurological problem':ti,ab OR 'neurological problems':ti,ab OR 'neurologic disease':ti,ab OR 'cognitive symptom':ti,ab OR 'cognitive symptoms':ti,ab OR 'mild cognitive impairment':ti,ab OR 'cognitive impairment':ti,ab OR 'cognitive defect':ti,ab OR 'cognition':ti,ab OR 'Neurobehavioral manifestations':ti,ab OR 'neuropsychological symptom':ti,ab OR 'neuropsychological symptoms':ti,ab OR 'behavioral symptom':ti,ab OR 'behavioral symptoms':ti,ab OR 'behavioural symptom':ti,ab OR 'behavioural symptoms':ti,ab OR 'rivermead post-concussion symptoms questionnaire':ti,ab OR 'rivermead post-concussion questionnaire':ti,ab OR 'rivermead post concussion symptoms questionnaire':ti,ab OR 'rivermead post concussion questionnaire':ti,ab OR 'prognosis'/exp OR 'prognosis':ti,ab OR 'predictive value'/exp OR 'predictive value':ti,ab OR 'predictive values':ti,ab OR 'predictive validity'/exp OR 'predictive validity':ti,ab OR 'clinical course'/exp OR 'clinical course':ti,ab OR 'disease course'/exp OR 'disease course':ti,ab OR 'incidence':ti,ab OR 'mortality':ti,ab OR 'Quality of life'/exp OR 'quality of life':ti,ab OR 'quality of life assessment'/exp OR 'quality of working life'/exp OR 'return to work'/exp OR 'return to work' OR 'follow up'/exp OR 'follow up studies':ti,ab OR 'follow up study':ti,ab OR 'follow-up studies':ti,ab OR 'follow-up study':ti,ab OR 'comparative study'/exp OR 'comparative study':ti,ab OR 'cohort studies':ti,ab OR 'cohort study':ti,ab OR 'cohort analysis'/exp OR 'cohort analysis':ti,ab OR 'longitudinal study'/exp OR 'longitudinal study':ti,ab OR 'longitudinal studies':ti,ab OR 'randomized controlled trial'/exp OR 'randomized controlled trial':ti,ab OR 'controlled clinical trial'/exp OR 'controlled clinical trial':ti,ab OR 'clinical trial'/exp OR 'clinical

trial':ti,ab OR headache/exp OR 'headache':ti,ab OR 'Posttraumatic headache'/exp OR 'posttraumatic headache':ti,ab OR 'primary headache'/exp OR 'secondary headache'/exp OR 'dizziness'/exp OR 'dizziness':ti,ab OR 'vertigo'/exp OR 'vertigo':ti,ab OR 'nausea'/exp OR 'nausea':ti,ab OR 'nausea and vomiting'/exp OR 'nausea and vomiting':ti,ab OR 'vomiting'/exp OR 'vomiting':ti,ab OR 'hyperacusis':ti,ab OR 'loudness recruitment'/exp OR 'loudness recruitment':ti,ab OR 'noise sensitivity':ti,ab OR 'sleep disturbance':ti,ab OR 'sleep disorder'/exp OR 'sleep disorder':ti,ab OR 'sleep arousal disorder'/exp OR 'sleep arousal disorder':ti,ab OR 'dyssomnia':ti,ab OR 'insomnia':ti,ab OR fatigue/exp OR 'fatigue':ti,ab OR 'mental fatigue':ti,ab OR 'dysthymia'/exp OR 'dysthymia':ti,ab OR 'chronic fatigue syndrome'/exp OR 'chronic fatigue syndrome':ti,ab OR 'irritable mood':ti,ab OR 'irritable':ti,ab OR 'irritability'/exp OR 'annoyance':ti,ab OR 'impatience':ti,ab OR 'anger'/exp OR 'anger':ti,ab OR 'despresion'/exp OR 'depression':ti,ab OR 'depressive disorder':ti,ab OR 'long term depression'/exp OR 'long-term synaptic depression':ti,ab OR 'frustration'/exp OR 'frustration':ti,ab OR 'frustrated':ti,ab OR 'Impatient':ti,ab OR 'forgetfulness':ti,ab OR 'memory disorder'/exp OR 'memory disorder':ti,ab OR 'memory disorders':ti,ab OR 'poor memory':ti,ab OR 'information processing speed':ti,ab OR 'deceleration in information processing':ti,ab OR 'impede processing speed':ti,ab OR 'speed of processing':ti,ab OR 'processing speed':ti,ab OR 'speed of information processing':ti,ab OR 'information processing'/exp OR 'working memory'/exp OR 'working memory':ti,ab OR 'short term memory'/exp OR 'short term memory':ti,ab OR 'vision disorder':ti,ab OR 'vision disorders':ti,ab OR 'visual disorder'/exp OR 'visual disorder':ti,ab OR 'visual impairment'/exp OR 'visual impairment':ti,ab OR 'visual impairments':ti,ab OR 'vision disability':ti,ab OR 'vision disabilities':ti,ab OR 'blurred vision'/exp OR 'blurred vision':ti,ab OR 'visual acuity'/exp OR 'visual acuity':ti,ab OR 'visual consequences':ti,ab OR 'visual deficit':ti,ab OR 'visual deficits':ti,ab OR 'vision loss':ti,ab OR 'visual function':ti,ab OR 'visual system function'/exp OR 'vision'/exp OR 'visual quality of life':ti,ab OR 'photophobia'/exp OR 'photophobia':ti,ab OR 'light sensitivity':ti,ab OR 'light sensitivities':ti,ab OR 'diplopia'/exp OR 'diplopia':ti,ab OR 'double vision':ti,ab OR 'Psychomotor agigation':ti,ab OR 'restlessness'/exp OR 'restlessness':ti,ab OR 'psychomotor hyperactivity':ti,ab OR 'psychomotor excitement':ti,ab OR 'Anxiety'/exp OR 'Anxiety':ti,ab OR 'Anxieties':ti,ab OR 'Nervousness':ti,ab OR 'Hypervigilance':ti,ab OR 'Anxiety Assessment':ti,ab OR 'Anxiety Disorders':ti,ab OR 'Loss of concentration':ti,ab OR 'Loss of attention':ti,ab OR 'Drowsiness':ti,ab
Finalization **4.** #1 AND #2 AND #3

eTable 2. List of congresses and conferences screened

1) American Academy of Emergency Medicine (AAEM)
2) American Academy of Neurology (AAN)
3) American Association of Neurological Surgeons (AANS)
4) American Association for the Surgery of Trauma (AAST)
5) American College of Emergency Physicians (ACEP)
6) Australasian College for Emergency Medicine (ACEM)
7) American College of Sports Medicine (ACSM)
8) American Medical Society for Sports Medicine (AMSSM)
9) American Neurological Association (ANA)
10) Australian and New Zealand Association of Neurologists (ANZAN)
11) Canadian Association of Emergency Physicians (CAEP)
12) Congress of Neurological Surgeons (CNS)
13) European Neurological Society (ENS)
14) International Brain Injury Association (IBIA)
15) International Symposium on Intensive Care and Emergency Medicine (ISICEM)
16) Society for Academic Emergency Medicine (SAEM)
17) Société de Neuropsychologie de Langue Française (SNLF)
18) World Congress on Brain Injury
19) World Congress of Neurology (WCN)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5 – eTable 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	—
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	—
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	—
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6-7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6-7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	—
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	—
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	10

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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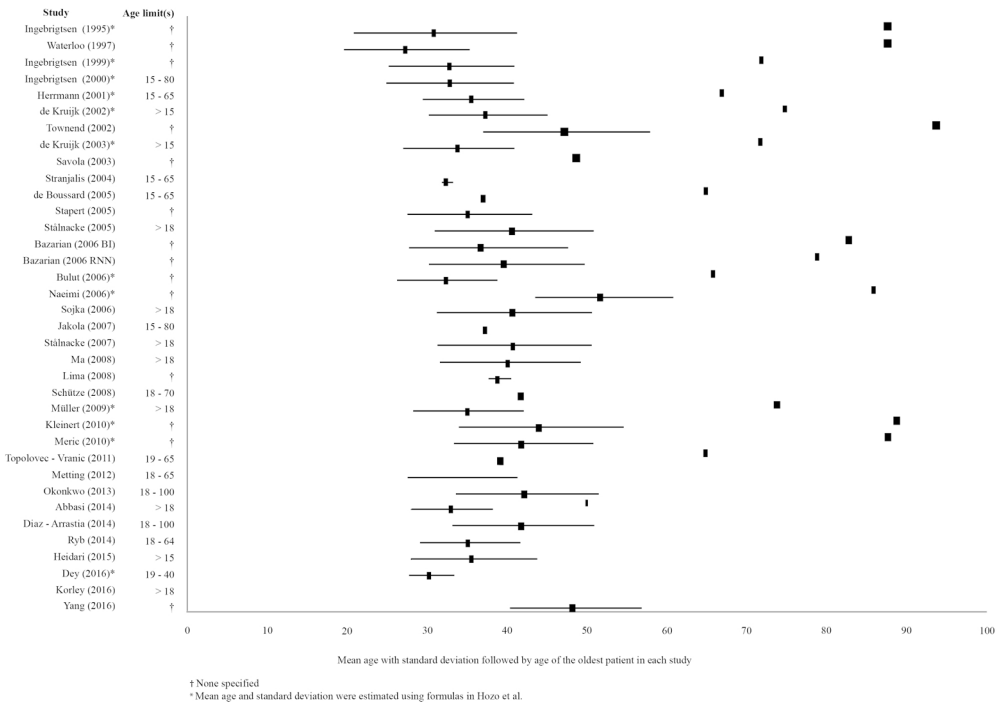

† None specified
* Mean age and standard deviation were estimated using formulas in Hozo et al.

170x118mm (300 x 300 DPI)

BMJ Open

Characteristics of patients included and enrolled in studies on the prognostic value of serum biomarkers for prediction of post-concussion symptoms following a mild traumatic brain injury: A systematic review

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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Diagnostics, Emergency medicine
Keywords:	Traumatic brain injury, post-concussion symptoms, post-concussion syndrome, biomarkers, systematic review

Title

Characteristics of patients included and enrolled in studies on the prognostic value of serum biomarkers for prediction of post-concussion symptoms following a mild traumatic brain injury: A systematic review

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ABSTRACT

Objective: Mild traumatic brain injury (mTBI) has been insufficiently researched and its definition remains elusive. Investigators are confronted by heterogeneity in patients, mechanism of injury and outcomes. Findings are thus often limited in generalizability and clinical application. Serum protein biomarkers are increasingly assessed to enhance prognostication of outcomes but their translation into clinical practice has yet to be achieved. A systematic review was performed to describe the adult populations included and enrolled in studies that evaluated the prognostic value of protein biomarkers to predict post-concussion symptoms following a mTBI. **Data sources**: Searches of MEDLINE, EMBASE, CENTRAL, CINAHL, Web of Science, PsycBITE, and PsycINFO up to October 2016. **Data selection and extraction**: Two reviewers independently screened for potentially eligible studies, extracted data and assessed the overall quality of evidence by outcome using the Grading of Recommendations Assessment, Development and Evaluation approach. **Results:** A total of 23,298 citations were obtained from which 166 manuscripts were reviewed. Thirty-six cohort studies (2,812 patients) having enrolled between 7 and 311 patients (median 89) fulfilled our inclusion criteria. Most studies excluded patients based on advanced age (n=10 (28%)), neurologic disorders (n=20 (56%)), psychiatric disorders (n=17 (47%)), substance abuse disorders (n=13 (36%)) or previous TBI (n=10 (28%)). Twenty-one studies (58%) used at least two of these exclusion criteria. The pooled mean age of included patients was 39.3 (SD 4.6) years old (34 studies). The criteria used to define a mTBI were inconsistent. The most frequently reported outcome was post-concussion syndrome (PCS) using the Rivermead Post-Concussion Symptoms Questionnaire (n=18 (50%)) with follow-ups ranging from 7 days to 5 years after the mTBI. **Conclusions:** Most studies have recruited samples that are not representative and generalizable to the mTBI population. These exclusion criteria limit the potential use and translation of promising serum protein biomarkers to predict post-concussion symptoms.

Strengths and limitations of this study

- This systematic review on the characteristics of patients included and enrolled in studies on the prognostic value of serum protein biomarkers for prediction of post-concussion symptoms reports important findings for researchers planning their study and for clinicians interpreting the available data.
- Strengths of this systematic review include the exhaustive search strategy performed using seven databases, the selection and data extraction conducted independently by two researchers and the registration beforehand in the Prospero database of the study protocol.
- This study is limited by the quality of the included studies as well as the unavailability of some relevant data such as some studies inclusion criteria, exclusion criteria and clear patient demographic data.

INTRODUCTION

Mild traumatic brain injury (mTBI) is frequently encountered by neurologists, primary care, emergency, sport medicine and rehabilitation health providers[1] and accounts for approximately 80% of all TBI.[2] The incidence of mTBI exceeds that of dementia, epilepsy and stroke, giving it the status of the most common brain disorder.[3] However, there is still an incomplete understanding of mTBI pathophysiology that leads to suboptimal diagnosis, treatment and prognostication.[4] With increasing attendance to Emergency Departments (ED) following mTBI by complex patients such as elderly,[5] intoxicated patients[6 7] and patients with psychiatric disorders,[8] there is an urgent need to optimise the care of mTBI patients.

Once considered benign, there has been increased awareness of the potential adverse consequences of mTBI.[9] While 80% of patients will report at least one early post-concussion symptom,[10] between 10% and 56% will exhibit persistent symptoms 3 months after a mTBI.[11-15] Physical, cognitive, and emotional symptoms, often described as post-concussion syndrome (PCS), that exceed the expected window of recovery have deleterious impacts on quality of life and daily functional outcome.[16-18] Prognostic markers have been highlighted for cognitive, psychiatric, and mortality outcomes.[19] However, the authors acknowledged that evidence regarding psychiatric and mortality outcomes is limited, and that little evidence exist concerning the role of biological markers in predicting the persistence of cognitive impairment after mTBI.[19] Under these conditions, there is still a need to develop objective assessment and prognostication tools. Novel brain specific serum protein biomarkers have been studied to assist the prognostic evaluation after mTBI but the translation of protein biomarker research into clinical practice to predict PCS is still pending.

Unfortunately, research in mTBI is beset with methodological challenges. Researchers are confronted with substantial heterogeneity of patients, various mechanisms of injury and a wide range of potential outcomes.[20 21] Therefore, many researchers choose to apply strict inclusion and exclusion criteria to minimize confounding by such factors and to decrease the inherent population heterogeneity.[20] This approach results in improved internal validity but also inevitably limits recruitment and generalizability of results. Some populations are therefore often excluded or less likely to be enrolled in TBI studies.[22] Furthermore, many methodological concerns regarding mTBI studies such as the inconsistency in mTBI definitions and the frequent inadequacy of outcome measures were highlighted in the recent synthesis performed by the International Collaboration on mTBI prognosis.[23] All these methodological issues further limit the translation to bedside care and might be applicable to research in the field of brain specific biomarkers following a mTBI. Identifying which patients are not enrolled and how often they are excluded from these studies will allow to underline the generalisability of this literature and highlight gaps that future researches should aim to fill.

This systematic review aims to describe populations included or enrolled in studies on the prognostic value of protein biomarkers for prediction of post-concussion symptoms following a mTBI. The secondary objectives are to describe the mTBI definition applied in these studies as well as the outcomes evaluated.

METHODS

Search strategy

A systematic review was performed to determine the prognostic value of protein biomarkers to predict the occurrence of post-concussion symptoms following a mTBI (International Prospective Register of Systematic Reviews (PROSPERO) registration CRD42016032578). In summary, a general search strategy aiming to identify articles which assessed the association between protein biomarkers and post-concussion symptoms in TBI was created for seven databases (from their inception to October 4, 2016): MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials, Web of Science, PsycBITE and PsycINFO using MeSH terms, EMTREE terms and keywords for their respective database. This research used a general strategy with an additional focus on seven of the most studied and promising protein biomarkers (S-100β protein, neuron-specific enolase (NSE), glial fibrillary acidic protein (GFAP), ubiquitin carboxy-terminal hydrolase L1 (UCHL-1), cleaved tau (c-tau), microRNA, and brain-derived neurotrophic factor (BDNF)).[24-28] No language, type of study or date restriction were applied in the initial search strategy. The detailed EMBASE search strategy is available in Appendix 1. References from the included studies and narrative reviews were also scrutinized and relevant abstracts from congress and conferences were reviewed to identify potential peer-reviewed published studies.(Appendix 2) Authors of potentially relevant abstracts were contacted to identify potentially published studies not identified with our search strategies.

Study selection

Using EndNote (Thomson Reuters, version X7), all the citations obtained with our search strategies on the seven databases were combined. Duplicates were removed. Independently, two reviewers (EM, PAT) then scrutinized all citations and consecutively excluded studies using the title and abstract. Manuscripts of all potentially included studies were obtained. Studies in other language than English or French were translated into English. A third researcher (NL) was involved in case of disagreement and was responsible for the final decision regarding the inclusion of a study.

Studies were considered eligible for inclusion when they reported the association between at least one serum protein biomarker level and at least one post-concussion symptom evaluated ≥ 7 days following a mTBI. This duration was chosen to ensure that the outcomes represented a prognostic measure instead of a diagnostic evaluation. This study was limited to the adult (> 16 years old) population. Studies were excluded if they were animal studies, case-report, specific to a paediatric population, reporting on moderate or severe TBI unless specific data for mTBI patients could be extracted from the manuscript or by contacting the authors, post-concussion symptom evaluation was performed less < 7 days after the mTBI or the study was not published in a peer-reviewed journal.

Data extraction

Using a data collection form, two reviewers (EM, PAT) independently collected the relevant data from every included study. Therefore, data on the manuscript (journal, publication date, authors), study characteristics (period and methods of recruitment, country(ies), type of study, number of patients included and followed, number of hospitals involved, setting, inclusion and exclusion criteria, mTBI definition), protein biomarker (assays used and characteristics, detection limits, thresholds, timing of sampling, type of sampling (venous, capillary or arterial), number of samples), patient characteristics (age, gender, trauma mechanism, TBI severity) and the outcomes (outcome type, assessment timing, method of outcome assessment, including statistical analyses used to assess the association between protein biomarkers and outcomes)

were collected. When clarification or additional information was needed, the corresponding author of the included study was contacted via email (up to three attempts).

Statistical analysis and quality assessment

Descriptive statistics were used to describe the population included and enrolled in the studies. Measures of central tendency (means and medians) and dispersion (standard deviation (SD)) were calculated using Statistical Analysis System software (SAS Institute, Cary, North Carolina, v. 9.4). Main data are also presented as proportions. In 14 studies where sufficient data was available, we calculated the pooled mean age of enrolled patients and its heterogeneity (I^2).[29] To be more inclusive, a pooled mean age was also calculated using a weighted average based on study sample size for 34 studies. Where possible, age mean and SD were estimated using formulae proposed by Hozo et al.[30]

The quality of the evidence of the three main outcomes was evaluated using the GRADE approach (post-concussion symptoms, GOS-E & GOS and return to work)[31]. Given the high heterogeneity of the outcomes evaluated and the scales used, no quality of evidence assessment was performed for the neuropsychological outcomes. This study is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (see Appendix 3).[32]

RESULTS

Characteristics of the included studies

After removal of duplicates, the search strategy yielded 23,298 unique citations. Following the assessment of titles and abstracts using our inclusion and exclusion criteria, a total of 166 manuscripts were reviewed (Figure 1). Thirty-six manuscripts fulfilled our criteria and were included in the present study (Table 1). Only one disagreement between the reviewers required the third researcher (NL) to make the final decision. A total of 2,812 patients were included in those studies, which individually included from seven to 311 patients (mean 104 (SD 62), median 89). Twenty-one studies were conducted in Europe while eight were from North America, six from Asia and one was from South America. Two studies were in German and were fully translated in English. Only eight studies (22%) evaluated patients from multiple centres. The most frequent protein biomarker studied was the S-100β protein (29 studies) followed by NSE (10 studies), C-tau (four studies), GFAP (four studies), UCHL-1 (three studies), BDNF (one study) and microRNA (one study).

Inclusion and exclusion criteria in the included studies

Age limits criteria and the age of the patients enrolled in the studies are illustrated in the eFigure 1. Regarding the inclusion criteria, an upper age limit was used in 10 studies (28%). Therefore, patients ≥ 65 years old were excluded in seven studies (19%) while those aged ≥ 85 years old were excluded in three more studies (total 10 studies, 28%). Across studies, the oldest patient enrolled ranged from 40 to 94 years old. The pooled mean age in the 14 studies with data on SD was 38.7 (SD 5.3) years old (18 studies) and was highly heterogeneous (I^2 97%). In 34 studies, the pooled mean age was 39.3 (SD 4.6) years old.

The most frequent exclusion criteria were neurologic disorders, psychiatric disorders, trauma to another body region, substance abuse disorders and previous TBI (Table 2). Twenty-one studies (58%) used at least two of these exclusion criteria. Medical comorbidities were infrequently used as exclusion criteria. Ten studies (28%) did not report any exclusion criteria and were therefore considered as having no exclusion criteria.

Mild traumatic brain injury definitions in the included studies

The mTBI definitions used were not standardised (Table 3). The Glasgow Coma Scale (GCS) was a criterion in 31 studies (86%) using either GCS 13-15 (23 studies (64%)), GCS 14-15 (seven studies (19%)) or GCS 15 only (one study (3%)). Other criteria such as loss of consciousness (LOC), post-traumatic amnesia (PTA) and focal neurologic deficit were inconsistently used to define mTBI. Three (8.3%), six (16.7%), and one (2.8%) studies used definitions promoted by the American College of Emergency Physician/Centers for Disease Control and Prevention,[33] the American Congress of Rehabilitation Medicine,[34] and the European Federation of Neurological Societies,[35] respectively.

Outcomes presented in the included studies

Table 4 presents the outcomes evaluated. The most frequently evaluated outcome was post-concussion syndrome (PCS) in 18 studies (50%). The Rivermead Post-Concussion Symptoms Questionnaire was the most used scale. Table 5 presents the number of symptoms required to define the presence of a PCS in the different studies. The number of symptoms used to define a positive PCS ranged between one and five with only 10 studies (28%) using ≥ 3 criteria. Among the 36 studies, there were 48 outcome evaluations and the duration between the mTBI and the outcome assessment was > 3 months in only 22 (46%) of them. Six studies used outcomes that were unlikely to detect subtle impairment after a mTBI such as the Glasgow Outcome Scale (GOS) or the GOS-Extended (GOS-E).[36]

Assessment of outcomes in the included studies

Half of studies used multivariate regression models to assess the association between protein biomarkers at the initial visit and the presence of outcomes at follow-up. Eleven studies (30.5%) used AUROC (Area Under the Receiver Operating Characteristic curve) analyses to assess the potential prognostic value of biomarkers to predict the occurrence of outcomes in patients with a mTBI. Among these, only one compared the AUC obtained using the protein biomarker alone to that obtained with a multivariate model including clinical factors.

Quality of the evidence

Using the GRADE approach, the quality of evidence was evaluated as low or insufficient for the most frequently studied outcomes (Table 6). Various neuropsychological assessments were grouped together in Table 4 but given the heterogeneity of the neuropsychological tests used and the analytic methods, no GRADE assessment was performed for this outcome.

DISCUSSION

Our systematic review highlights the selected patient populations in previously published reports. Most studies have restricted the inclusion of patients based on advanced age (28%), neurologic disorders (56%), psychiatric disorders (47%), substance abuse disorders (36%) or previous TBI (28%). The mean age of enrolled patients was only 38.7 years old. There are also important variations in the definitions of mTBI and in outcomes evaluated. The criteria used to define the occurrence of a positive PCS using the Rivermead Post-Concussion Symptoms Questionnaire ranged between one and five symptoms. These results impact on the generalizability and clinical applicability of the study findings on protein biomarkers and other prognostic tools following mTBI.

The epidemiology of TBI has evolved with increasing numbers of complex patients consulting for their injury, such as elderly[37] and patients with substance abuse, psychiatric or neurologic disorders.[6 8] Intoxicated patients also often present with altered conscious state raising the possibility of TBI and complicating initial clinical assessment.[38 39] Patients with previous TBI are also of concern given the complications of repetitive TBI.[40] All these patients pose a challenge to the clinician in terms of assessment of injury severity and prognosis. Moreover, these pre-injury factors are known to predispose to the development of persistent post-concussion symptoms leading to poorer functional outcomes.[41-45] In a large retrospective cohort study of patients with suspected TBI, patients were frequently intoxicated with alcohol (20%) or had a psychiatric (25%) or neurologic disorders (25%).[22] These patients were excluded in respectively 25%, 47% and 56% of the studies included in our systematic review. Moreover, geriatric patients represent a constantly growing proportion of the trauma population as the world is ageing.[46 47] The absolute incidence of TBI among the geriatric patients is rising as a result of the increased life expectancy and mobility.[5] Advanced age was an exclusion criteria in 10 studies (28%) but the patients enrolled were mostly young with a mean age of only 38.7 (SD 5.3) years old. Recent large TBI epidemiologic studies[48 49] showed that more than 40% of the mTBI population are older than 50 years and the median age of patients is at least 44 years.[5 50] Geriatric patients seems therefore underrepresented in our included studies despite the fact that they have a poorer functional outcome with an increased occurrence of post-concussion symptoms.[51] The effect of age on the circulating blood-based biomarker is controversial.[52] Geriatric patients often have medical comorbidities that can potentially impact the biomarker's production, metabolism and clearance thus altering its baseline circulating serum level and its release following a mTBI. Interestingly, patients with renal impairment were excluded in only three studies (8%) even though some medical comorbidities might represent a more robust exclusion criteria than age alone.

Selection bias is common and strict enrolment criteria have been associated with exclusion of up to 95% of the general mTBI population.[20 22] Therefore, patients with pre-morbid conditions remain poorly studied despite their unfavourable prognosis and increased risk of disabilities.[41 42] Also, the association between the protein biomarker and the outcome in patients with pre-morbid conditions might differ from the association with healthier patients therefore limiting the potential to draw clinical conclusions. Future studies should aim to maximize the inclusion and the recruitment of these clinically relevant patients. To facilitate the inclusion of these patients, studies addressing the influence of age, intoxication and previous neurologic disorder on protein biomarker baseline level and the kinetic modelling of protein biomarker release in the serum following a mild TBI are required.

The definition of mTBI was widely variable between the studies often limiting the comparability of studies. While GCS was almost universally included as a criterion, other criteria such as PTA, LOC and neuroimaging results were inconsistently used. Mild TBI is a heterogeneous group with a wide range of "severity". The symptom-based GCS classification often fails to demonstrate the whole spectrum of severity. The diagnostic criteria can be unreliable and overlap many conditions such as dementia, delirium or intoxication and the presence of confounding factors during the initial assessment are frequent.[8]

One major limitation to our understanding of mTBI is the lack of universal definition of the outcomes evaluated.[53] Most patients recover completely but for those affected by persistent symptoms, there are controversies about the nomenclature and definitions associated with post-concussion symptoms and PCS.[54] This is particularly noticeable in our systematic review as the diagnosis criteria of PCS was highly variable ranging from one to more than five criteria on the Rivermead Post-Concussion Symptoms Questionnaire to determine the presence or the absence

of PCS. The timing of outcome evaluation was also variable ranging from seven days to more than five years. PCS is a complex constellation of symptoms with a significant variability between individuals. Since most symptoms are subjective, there is a high risk of misdiagnosis[55] and we are still unable to predict the occurrence of PCS. Biomarkers are promising to help predict the recovery and the risk of persistent PCS but well-designed confirmatory studies that address the methodological limitations are needed to enhance our knowledge of mTBI consequences.[19] The lack of standardisation in the definition of the outcomes contributes to impede the translation from research to daily bedside care in the field of brain specific biomarkers. Another shortcoming that might partly explain the difficulty of using protein biomarkers to predict post-concussion symptoms are that these symptoms are not specific to mild TBI and are prevalent both in the general population and after non-head injuries.[56]

In addition to the aforementioned shortcomings, a methodological issue that possibly limits the translation of protein biomarkers from research to everyday care is the statistical methods used to assess the value of these biomarkers. Showing that a given protein biomarker sampled at the initial admission is correlated with outcomes at follow-up is certainly valuable, but this result in itself remains insufficient to inform patient management. Guidelines and clinical decision rules aiming to rule out unnecessary neuroimaging or to identify patients who are at high risk of experiencing persistent symptoms following their mTBI require operational tools. To this end, practicable information on the prognostic (discriminative) value of protein biomarkers is necessary. In our systematic review, only 30% of studies performed AUROC analyses and only one study compared the AUC obtained using the protein biomarker alone with that obtain with a multivariable model. Unless protein biomarkers are shown to add significant prognostic value over and above clinical factors readily available in clinical settings, they are unlikely to be integrated into daily clinical practice. However, there are numerous other potential benefits to study protein biomarkers after a mTBI.[57] In addition to improving the initial prognostication, the use of biomarkers could help making the diagnosis, determine more accurately the need for neuroimaging, evaluating the disease progression, determining the safe moment to return to sport or activities and might be used as a surrogate assessment tool for investigational treatments.[26 27] As mTBI diagnostic criteria are subjective, nonspecific and overlap other conditions, a biomarker level could alleviate the paucity around the initial presentation and represent an objective assessment tool.

Strengths and limitations

Our study has several limitations. We looked both at the characteristics of the inclusion/exclusion criteria and the patients enrolled. The absence of exclusion criteria does not mean that some subgroups of patient will be enrolled and often studies failed to present the number of patients screened and approached to be enrolled. Therefore, we can expect that our review underestimates the poor representation of subgroups such as patients with substance abuse, psychiatric and neurologic disorders. Ten studies did not report any exclusion criteria and were considered as having no exclusion criteria but this might be a misinterpretation thus making the underestimation even more likely. We have however used high methodological standards to perform our systematic review. We have completed an exhaustive unrestrictive search strategy using seven databases and screened 23,298 citations. Studies were researched and data were extracted independently by two reviewers. This study is reported in accordance with the recommended PRISMA Statement.

CONCLUSION

The patients included and enrolled in studies on the prognostic value of protein biomarkers following mTBI are not representative of the mTBI population. Subgroups such as elderly, patients with neurologic, psychiatric and substance abuse disorders and patients with previous TBI are often excluded and poorly represented even though they are at high risk of post-concussion symptoms and associated disabilities. The lack of standardisation of definitions further impedes the translation from research to everyday patient care. Broader inclusion criteria and standardised definitions, particularly mTBI and PCS, are required to maximise the generalizability and the translation to bedside care of the promising brain specific biomarkers.

Contributors EM has had the original idea for this study. EM, PAT and NL conceived the study's design and protocol with support, input and oversight from ME, MCO, EDG, BM and PAC. EM and PAT elaborated the original database search strategy. EM and PAT performed the study selection and data extraction with oversight from ME, MCO, EDG, PAC and NL. PAT prepared the data for statistical analysis. Statistical analysis plan was elaborated by ME, BM and NL. EM and PAT wrote the manuscript first draft. All authors contributed to the manuscript revision and they all approved the final submitted version. All authors are accountable for all aspects of this study.

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Competing interests None declared.

Data sharing statement: No additional data are available.

Tables

Table 1. Characteristics of included studies

First author	Year of study publication	Countries	Number of hospitals	Number of patients included	Biomarkers assessed	Multivariate* AUROC†
Ingebrigtsen[58]	1995	Norway	1	50	S-100β	×/×
Waterloo[59]	1997	Norway	1	7	S-100β	×/×
Ingebrigtsen[60]	1999	Norway	1	50	S-100β	×/×
Ingebrigtsen[61]	2000	Norway, Sweden, Denmark	3	182	S-100β	×/×
Herrmann[62]	2001	Germany	1	69	S-100β, NSE	✓/✓
de Kruijk[63]	2002	Netherlands	1	107	S-100β, NSE	✓/×
Townend[64]	2002	United Kingdom	4	148	S-100β	✓/✓
de Kruijk[65]	2003	Netherlands	1	111	S-100β, NSE	✓/×
Savola[66]	2003	Finland	1	199	S-100β	✓/✓
Stranjalis[67]	2004	Greece	1	100	S-100β	✓/✓
de Boussard[68]	2005	Sweden	3	122	S-100β	×/×
Stålnacke[69]	2005	Sweden	1	88	S-100β, NSE	✓/×
Stapert[70]	2005	Netherlands	1	50	S-100β	×/×
Bazarian[71]	2006 (BI)	USA	1	35	S-100β, C-Tau	×/✓
Bazarian[72]	2006 (RNN)	USA	1	96	S-100β	×/✓
Bulut[73]	2006	Turkey	1	60	C-Tau	×/×
Naeimi[74]	2006	Austria	1	45	S-100β, NSE	×/×
Sojka[75]	2006	Sweden	1	98	S-100β, NSE	✓/×
Jakola[76]	2007	Norway	3	89	S-100β	✓/×
Stålnacke[77]	2007	Sweden	1	69	S-100β, NSE	✓/×
Lima[78]	2008	Brazil	1	50	S-100β	×/×
Ma[79]	2008	USA	1	50	C-Tau	×/×
Schütze[80]	2008	Germany	1	74	S-100β, NSE	✓/×
Müller[81]	2009	Norway	1	93	S-100β	✓/×
Kleinert[82]	2010	Germany	1	73	S-100β	×/×
Meric[83]	2010	Turkey	1	80	NSE	×/✓
Topolovec-Vranic[84]	2011	Canada	1	141	S-100β, NSE	✓/✓
Metting[85]	2012	Netherlands	1	94	S-100β, GFAP	✓/×
Okonkwo[86]	2013	USA	3	215	GFAP	✓/✓
Abbasi[87]	2014	Iran	2	109	S-100β	×/×
Diaz-Arrastia[88]	2014	USA	3	206	GFAP, UCHL-1	×/✓
Ryb[89]	2014	USA	1	150	S-100β	✓/✓
Heidari[90]	2015	Iran	1	176	S-100β	✓/×
Dey[91]	2016	India	1	20	S-100β, UCHL-1	×/×
Korley[28]	2016	USA	2	311	C-Tau, GFAP, UCHL-1	✓/✓
Yang[92]	2016	China	1	76	miR-93, miR-191, miR-499	×/×

BI: Brain Injury; C-Tau: cleaved tau; BDNF: brain-derived neurotrophic factor; GFAP: glial fibrillary acidic protein; miR: micro ribonucleic acid; NSE: neuron specific enolase; RNN: Restorative Neurology and Neuroscience; UCHL-1: ubiquitin carboxy-terminal hydrolase L1; USA: United States of America.
*The association between protein biomarker(s) and outcome(s) was assessed using a multivariate regression model; †The prognostic value of protein biomarker(s) was assessed using an Area Under the Receiver Operating Characteristic curve (AUROC).

Table 2. Exclusion criteria used in the included studies

Exclusion criteria	Number of studies (n, %)
Neurologic disorder	20 (55.6)
Psychiatric disorder	17 (47.2)
Significant trauma to another body region than the head	17 (47.2)
Substance abuse (drug or alcohol)	14 (38.8)
Previous traumatic brain injury	10 (27.8)
Alcohol intoxication	9 (25)
Renal impairment	3 (8.3)
Cardiac disease	2 (5.6)

Table 3. Criteria used to define mild traumatic brain injury (mTBI) in the included studies

Criteria		Number of studies (n, %)
Glasgow Coma Scale (GCS)	13-15	23[§] (63.8)
	14-15	7 (19.4)
	15	1 (2.8)
	NR	5[∂] (13.9)
Loss of consciousness (LOC)	< 10 minutes	4 (11.1)
	< 15 minutes	5 (13.9)
	< 30 minutes	9[§] (25)
	No duration	8[∂] (22.2)
	No use of LOC	10 (27.8)
Post-traumatic amnesia (PTA)	< 15 minutes	1 (2.8)
	< 30 minutes	0 (0)
	< 60 minutes	4[§] (11.1)
	< 24 hours	3 (8.3)
	No duration	7[∂] (19.4)
	No use of PTA	21 (58.3)
Initial altered mental state	Yes	3 (8.3)
Absence of focal neurology deficit	Yes	14 (38.9)
Triaged to non-contrast head CT using the (ACEP/CDC) evidence-based joint practice guideline		3[∂] (8.3)
Use of the American Congress of Rehabilitation Medicine definition (1993)		6 (16.7)
Use of European Federation of Neurological Societies (EFNS) definition (2002)		1[§] (2.8)

* ACEP: American College of Emergency Physicians; CDC: Centre for Disease Control; CT: Computed Tomography; TBI: Traumatic Brain Injury.
[§] Heidari et al. (2015)[90] used the following mTBI definition: (1) a GCS score of 13–14; (2) a GCS score of 15 with loss of consciousness (LOC) < 30 minutes, post-traumatic amnesia (PTA) < 1 hour; or (3) a GCS score of 15 without LOC or PTA.
[∂] Korley et al. (2016)[28] presented 3 different cohorts with different inclusion criteria. Only the mTBI definition of the case cohort is presented in the table.

Table 4. Outcome evaluated in the included studies

Outcome evaluated	Number of studies (n, %)
Post-concussion syndrome	18 (50)
Neuropsychological evaluation	9 (25)
GOS-E; GOS	5 (13.8); 4 (11.1)
Return to work	4 (11.1)
Headache	3 (8.3)
Life satisfaction	2 (5.6)
RHFUQ	2 (5.6)
Anxiety or depression	1 (2.7)
Daily activity functioning	1 (2.7)
Olfactory function	1 (2.7)
Post-traumatic related stress	1 (2.7)
Quality of life	1 (2.7)
SF-36	1 (2.7)
Duration between mild TBI and outcome assessment	**Assessments (n=48 outcomes) (n, %)**
7 days	3 (6.3)
14 days	6 (12.5)
1 month	6 (12.5)
1.1-3 months	11 (23)
3.1-6 months	11 (23)
6.1-12 months	6 (12.5)
12.1-18 months	4 (8.2)
> 18.1 months	1 (2)

GOS: Glasgow Outcome Scale; GOS-E: Glasgow Outcome Scale-Extended; RHFUQ: Rivermead Head Injury Follow-up Questionnaire; SF-36: Acute Medical Outcomes F6-36v2 Health Survey; TBI: traumatic brain injury.

Table 5. Definition of post-concussion syndrome (PCS)

Scale used	Number of positive symptoms to define the presence of a PCS	Number of studies (n, %)
Rivermead Post-Concussion Symptoms Questionnaire	≥ 1	3 (17)
	≥ 2	1 (5.5)
	≥ 3	5 (28)
	≥ 4	1 (5.5)
	≥ 5	2 (11)
	Not specified	6 (33)

Table 6. Outcomes quality of evidence according to the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach

Outcomes	Number of studies (number of patients)	Design	Findings and direction	GRADE
Post-concussion symptoms	18 studies (n=2048)	Observational	Important heterogeneity in populations enrolled, definitions of outcome variables, and evaluation duration. Only four associations between post-concussion symptoms and a biomarker were statistically significant. Only eight studies used multivariate regression analyses and confidence intervals were often large.	Low
GOS-E & GOS	9 studies (n=1235)	Observational	Slight discrepancies in definitions, wide differences in populations enrolled, methods quality as well as in evaluation duration, and inconsistencies in associations (only 3 were significant), their direction and strength.	Insufficient
Return to work	4 studies (n=432)	Observational	Slight discrepancies in definitions and reporting but considerable differences in evaluation duration (one week to one year). Only one study showed a significant association with increased S-100β protein serum level.	Insufficient

GOS: Glasgow Outcome Scale; GOS-E: Glasgow Outcome Scale (GOS) Extended

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Figure legend

Figure 1. PRISMA flow diagram of included studies

Supplementary files legend

eFigure 1. Age of patients enrolled in the included studies

eTable 1. Search strategy for the Excerpta Medica dataBASE (EMBASE)
eTable 2. List of congresses and conferences screened
eTable 3. PRISMA Checklist

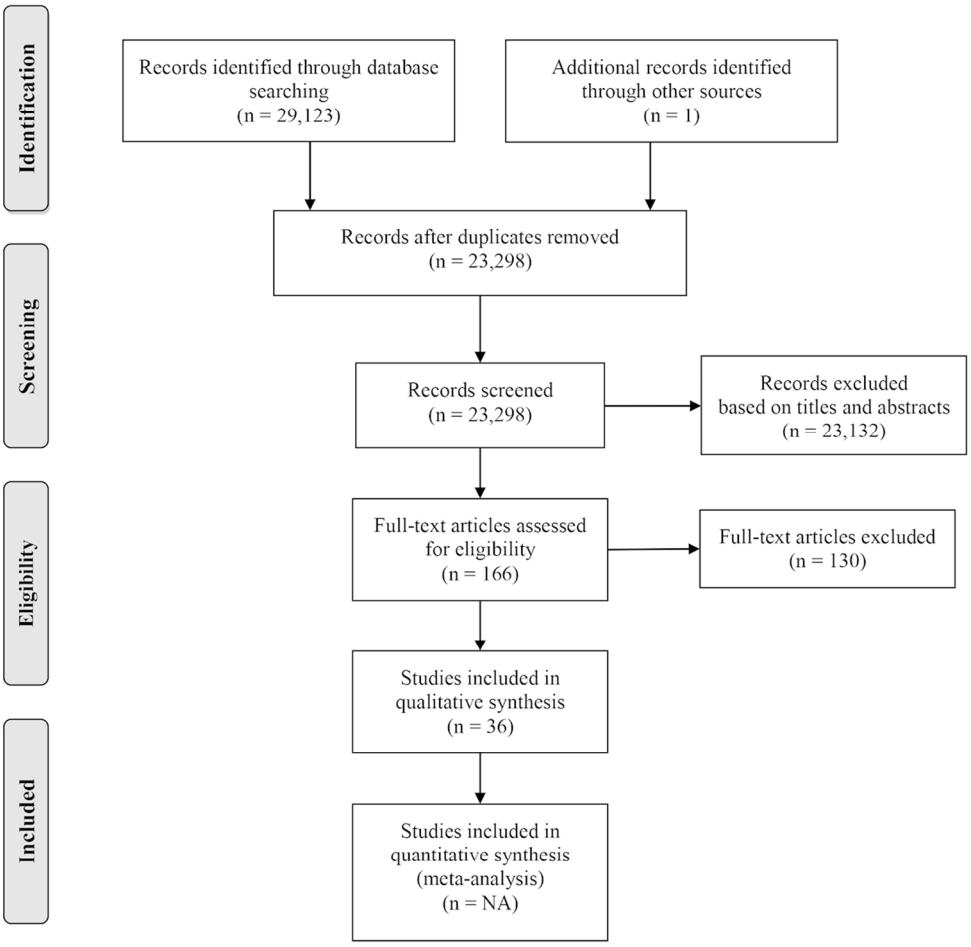
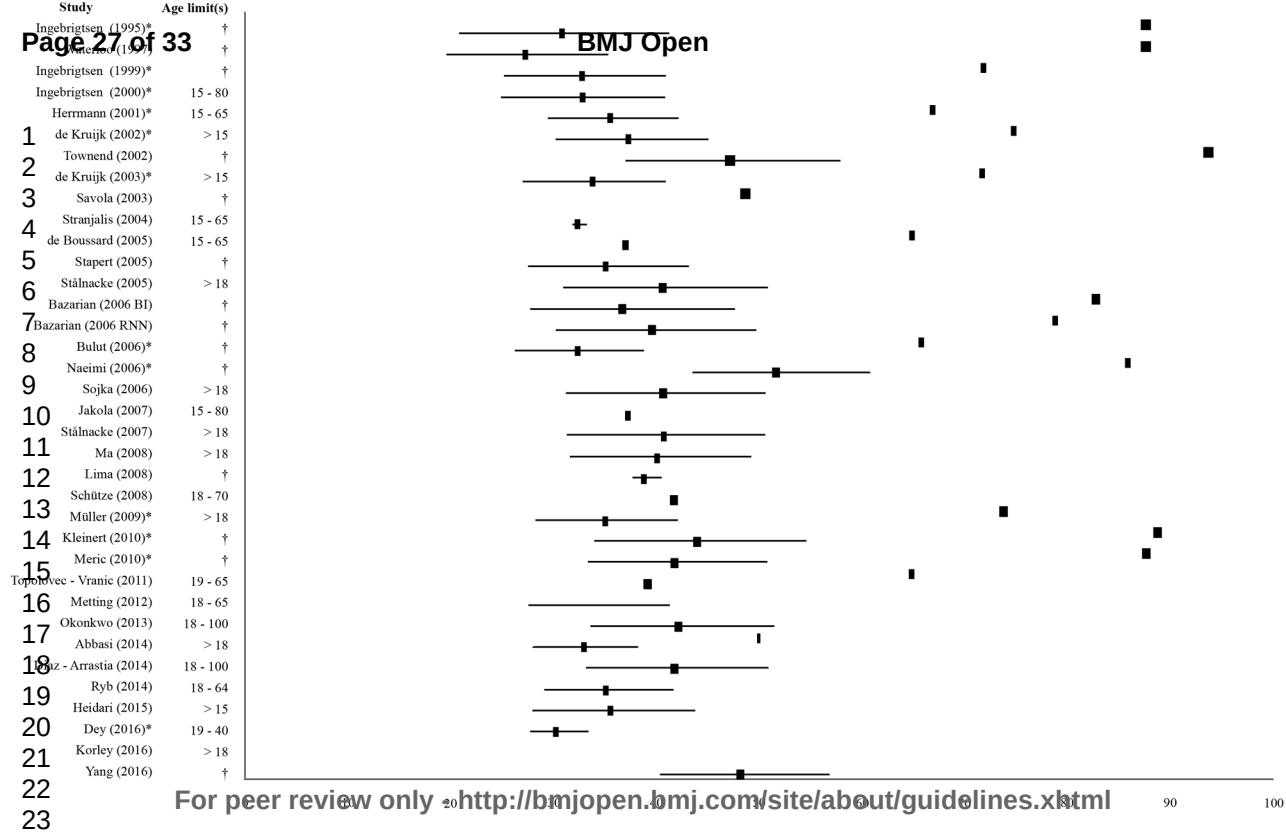


Figure 1. PRISMA flow diagram of included studies

112x119mm (300 x 300 DPI)



† None specified

* Mean age and standard deviation were estimated using formulas in Hozo et al.

eTable 1. Search strategy for the Excerpta Medica dataBASE (EMBASE)

EMBASE SEARCH STRATEGY
Traumatic brain injury **1.** (('brain injury':ti,ab OR 'brain injuries':ti,ab OR 'brain injured':ti,ab OR 'brain injure':ti,ab OR 'brain injures':ti,ab OR 'brain trauma':ti,ab OR 'brain traumas':ti,ab OR 'brain traumatic':ti,ab OR brain:ti,ab OR brain:ti,ab OR 'mild traumatic brain injury':ti,ab OR 'mild traumatic brain injure':ti,ab OR 'mild traumatic brain injured':ti,ab OR 'mild traumatic brain injures':ti,ab OR 'mild traumatic brain injuries':ti,ab OR 'minor traumatic brain injury':ti,ab OR 'minor traumatic brain injure':ti,ab OR 'minor traumatic brain injured':ti,ab OR 'minor traumatic brain injures':ti,ab OR 'minor traumatic brain injuries':ti,ab OR 'minimal traumatic brain injury':ti,ab OR 'minimal traumatic brain injure':ti,ab OR 'minimal traumatic brain injured':ti,ab OR 'minimal traumatic brain injures':ti,ab OR 'minimal traumatic brain injuries':ti,ab OR mtbi:ti,ab OR 'minor head trauma':ti,ab OR 'minor head traumas':ti,ab OR 'minor head traumatic':ti,ab OR 'minimal head trauma':ti,ab OR 'minimal head traumas':ti,ab OR 'minimal head traumatic':ti,ab OR concussion*:ti,ab OR 'brain concussion'/exp OR 'brain concussions'/exp OR contusions:ti,ab OR contusions/exp OR 'brain contusion'/exp OR 'brains injury':ti,ab OR 'brains injuries':ti,ab OR 'brains injured':ti,ab OR 'brains injure':ti,ab OR 'brains injures':ti,ab OR 'brains trauma':ti,ab OR 'brains traumas':ti,ab OR 'brains traumatic':ti,ab OR brains:ti,ab OR brains:ti,ab OR 'brainstem injury':ti,ab OR 'brainstem injuries':ti,ab OR 'brainstem injured':ti,ab OR 'brainstem injure':ti,ab OR 'brainstem injures':ti,ab OR 'brainstem trauma':ti,ab OR 'brainstem traumas':ti,ab OR 'brainstem traumatic':ti,ab OR brainstem:ti,ab OR brainstem:ti,ab OR 'head injury':ti,ab OR 'head injuries':ti,ab OR 'head injured':ti,ab OR 'head injure':ti,ab OR 'head injures':ti,ab OR 'head trauma':ti,ab OR 'head traumas':ti,ab OR 'head traumatic':ti,ab OR head:ti,ab OR head/exp OR heads:ti,ab OR 'heads injuries':ti,ab OR 'heads injured':ti,ab OR 'heads injure':ti,ab OR 'heads injures':ti,ab OR 'heads trauma':ti,ab OR 'heads traumas':ti,ab OR 'heads traumatic':ti,ab OR 'heads':ti,ab OR heads:ti,ab OR 'Brain edema'/exp OR 'Brain edema':ti,ab OR 'Brain swelling':ti,ab OR 'cerebral edema':ti,ab OR 'intracranial edema':ti,ab OR 'Hematoma'/exp OR Hematoma:ti,ab OR Haematoma:ti,ab OR 'brain hematoma'/exp OR 'Hemorrhage'/exp OR Hemorrhage:ti,ab OR Haemorrhage:ti,ab OR 'subarachnoid hemorrahge'/exp OR 'brain hemorrhage'/exp OR 'brain ventricle hemorrhage'/exp OR 'craniocerebral injury':ti,ab OR 'craniocerebral injuries':ti,ab OR 'craniocerebral injured':ti,ab OR 'craniocerebral injure':ti,ab OR 'craniocerebral injures':ti,ab OR 'craniocerebral trauma':ti,ab OR 'craniocerebral traumas':ti,ab OR 'craniocerebral traumatic':ti,ab OR craniocerebral:ti,ab OR craniocerebral*:ti,ab OR 'intracranial injury':ti,ab OR 'intracranial injuries':ti,ab OR 'intracranial injured':ti,ab OR 'intracranial injure':ti,ab OR 'intracranial injures':ti,ab OR 'intracranial trauma':ti,ab OR 'intracranial traumas':ti,ab OR 'intracranial traumatic':ti,ab OR intracranial:ti,ab OR intracrani*:ti,ab OR 'intra-cranial injury':ti,ab OR 'intra-cranial injuries':ti,ab OR 'intra-cranial injured':ti,ab OR 'intra-cranial injure':ti,ab OR 'intra-cranial injures':ti,ab OR 'intra-cranial trauma':ti,ab OR 'intra-cranial traumas':ti,ab OR 'intra-cranial traumatic':ti,ab OR 'intra-cranial':ti,ab OR 'intra-crani':ti,ab OR 'intercranial injury':ti,ab OR 'intercranial injuries':ti,ab OR 'intercranial injured':ti,ab OR 'intercranial injure':ti,ab OR 'intercranial injures':ti,ab OR 'intercranial trauma':ti,ab OR 'intercranial traumas':ti,ab OR 'intercranial traumatic':ti,ab OR intercranial:ti,ab OR intercrani*:ti,ab OR 'inter cranial injury':ti,ab OR 'inter-cranial injuries':ti,ab OR 'inter-cranial injured':ti,ab OR 'inter-cranial injure':ti,ab OR 'inter-cranial injures':ti,ab OR 'inter-cranial trauma':ti,ab OR 'inter-cranial traumas':ti,ab OR 'inter-cranial traumatic':ti,ab OR 'inter-cranial':ti,ab OR

‘cerebral injury’:ti,ab OR ‘cerebral injuries’:ti,ab OR ‘cerebral injured’:ti,ab OR ‘cerebral injure’:ti,ab OR ‘cerebral injures’:ti,ab OR ‘cerebral trauma’:ti,ab OR ‘cerebral traumas’:ti,ab OR ‘cerebral traumatic’:ti,ab OR cerebral:ti,ab OR cerebr*:ti,ab OR

‘cerebellum injury’:ti,ab OR ‘cerebellum injuries’:ti,ab OR ‘cerebellum injured’:ti,ab OR ‘cerebellum injure’:ti,ab OR ‘cerebellum injures’:ti,ab OR ‘cerebellum trauma’:ti,ab OR ‘cerebellum traumas’:ti,ab OR ‘cerebellum traumatic’:ti,ab OR cerebellum:ti,ab OR cerebel*:ti,ab OR

‘forebrain injury’:ti,ab OR ‘forebrain injuries’:ti,ab OR ‘forebrain injured’:ti,ab OR ‘forebrain injure’:ti,ab OR ‘forebrain injures’:ti,ab OR ‘forebrain trauma’:ti,ab OR ‘forebrain traumas’:ti,ab OR ‘forebrain traumatic’:ti,ab OR forebrain:ti,ab OR forebrain*:ti,ab) AND

(injury*:ti,ab OR injuries:ti,ab OR injured:ti,ab OR injure:ti,ab OR injures:ti,ab OR trauma:ti,ab OR traumas:ti,ab OR traumatic*:ti,ab OR traumato*:ti,ab OR damag*:ti,ab)) OR

TBI:ti,ab OR Glasgow coma scale:ti,ab OR GCS:ti,ab OR ‘traumatic brain injury’:ti,ab OR ‘traumatic brain injure’:ti,ab OR ‘traumatic brain injured’:ti,ab OR ‘traumatic brain injures’:ti,ab OR ‘traumatic brain injuries’:ti,ab OR

‘Head injury’/de OR ‘brain injury’/de OR ‘brain hemorrhage’/de OR ‘diffuse axonal injury’/de OR ‘coma’/de OR ‘brain hemorrhage’/de OR ‘Glasgow coma scale’/de OR

‘blast injury’/exp OR ‘blast-induced brain injury’/exp OR ‘Blast exposition’:ti,ab OR ‘blast injuries’:ti,ab OR ‘blast injury’:ti,ab OR ‘blast injure’:ti,ab OR ‘blast injured’:ti,ab OR ‘sports-related concussion’:ti,ab OR ‘sport-related concussion’:ti,ab OR SRC:ti,ab

Biomarkers

2. biomarker*:ab,ti OR 'biomarker'/exp OR 'biologic marker':ab,ti OR 'biologic markers':ab,ti OR 'biological marker':ab,ti OR 'biological markers':ab,ti OR 'biochemical marker':ab,ti OR 'biochemical markers':ab,ti OR 'laboratory marker':ab,ti OR 'laboratory markers':ab,ti OR 'immunological marker':ab,ti OR 'immunological markers':ab,ti OR 'immune marker':ab,ti OR 'immune markers':ab,ti OR 'serum marker':ab,ti OR 'serum markers':ab,ti OR 'clinical marker':ab,ti OR 'clinical markers':ab,ti OR 'surrogate end point':ab,ti OR 'surrogate end points':ab,ti OR 'surrogate endpoint':ab,ti OR 'surrogate endpoints':ab,ti OR

‘neuronal protein’/exp OR ‘neuronal proteins’:ti,ab OR ‘neuronal protein’:ti,ab OR ‘neuronal marker’:ti,ab OR ‘neuronal markers’:ti,ab OR ‘nerve tissue protein’:ti,ab OR ‘nerve tissue proteins’:ti,ab OR ‘nerve protein’/exp OR ‘nerve proteins’:ti,ab OR ‘neuronal calcium sensor’/exp OR ‘neuron specific nuclear protein’/exp OR

‘astrocyte protein’:ti,ab OR ‘astrocyte protein’/exp OR

‘S-100’:ti,ab OR S100*:ti,ab OR ‘S100B’:ti,ab OR ‘S-100B’:ti,ab OR ‘S100BB’:ti,ab OR ‘S-100BB’:ti,ab OR ‘S-100B protein’:ti,ab OR ‘S100-β’:ti,ab OR ‘S100β’:ti,ab OR ‘protein S100B’/exp OR

GFAP:ti,ab OR ‘GFAP’/exp OR ‘glial protein’:ti,ab OR ‘glial proteins’:ti,ab OR ‘glial fibrillary acidic protein’:ti,ab OR ‘glial fibrillary acidic proteins’:ti,ab OR ‘glial intermediate filament protein’:ti,ab OR ‘glial intermediate filament proteins’:ti,ab OR astroprotein*:ti,ab OR ‘GFA-protein’:ti,ab OR ‘GFA-proteins’:ti,ab OR ‘Glial Fibrillary Acidic Protein’/exp OR

‘neuron specific enolase’/exp OR ‘Neuron specific nuclear protein’/exp OR NSE:ti,ab OR NSE/exp OR ‘neuron specific enolase’:ti,ab OR ‘neuron-specific enolase’:ti,ab OR ‘gamma-enolase’:ti,ab OR ‘nervous system specific enolase’:ti,ab OR ‘phosphopyruvate hydratase’:ti,ab OR ‘Phosphopyruvate Hydratase’:ti,ab OR ‘enolase’/exp OR

‘C-tau’:ti,ab OR ‘C-tau’ OR ‘cleaved-tau’:ti,ab OR ‘tau protein’:ti,ab OR ‘tau Proteins’:ti,ab OR ‘tau protein’/exp OR

‘UCH-L1’:ti,ab OR UCHL1:ti,ab OR ‘ubiquitin carboxyl-terminal hydrolase l-1’:ti,ab OR ‘ubiquitin c-terminal

hydrolase':ti,ab OR 'ubiquitin carboxy terminal esterase':ti,ab OR 'ubiquitin thiolesterase':ti,ab OR 'ubiquitin'/exp OR 'ubiquitin protein ligase'/exp OR 'ubiquitin tholesterase'/exp OR

SBDP:ti,ab OR SBDP150:ti,ab OR SBDP145:ti,ab OR SBDP120:ti,ab OR 'SBDP'/exp OR 'Spectrin'/exp OR 'fodrin'/exp OR 'spectrin breakdown product'/exp OR

'NF-H':ti,ab OR NFH:ti,ab OR 'NFP-200':ti,ab OR NFP200:ti,ab OR 'hyperphosphorylated neurofilament':ti,ab OR 'neurofilament protein':ti,ab OR 'neurofilament proteins':ti,ab OR 'neurofilament H protein':ti,ab OR 'neurofilament H proteins':ti,ab OR 'neurofilament triplet protein':ti,ab OR 'neurofilament triplet proteins':ti,ab OR 'neurofilament M protein'/exp OR 'neurofilament'/exp OR

'microRNA'/exp OR 'MicroRNAs'/exp OR

'BDNF':ti,ab OR 'BDNF'/exp OR 'brain derived neurotrophic factor'/exp OR 'brain derived neurotrophic factor receptor'

Outcomes (post-concussion symptoms related terms)

3. 'post-concussion syndrome'/exp OR 'post-concussion syndrome':ti,ab OR 'postconcussion':ti,ab OR 'post-concussion symptom':ti,ab OR 'postconcussion symptoms':ti,ab OR 'postconcussion syndrom':ti,ab OR 'post concussion syndrom':ti,ab OR 'post-concussive symptom':ti,ab OR 'postconcussive symptom':ti,ab OR 'post concussive symptom':ti,ab OR 'post-concussive syndrom':ti,ab OR 'postconcussive syndrom':ti,ab OR 'post concussive syndrom':ti,ab OR 'post-concussion recovery':ti,ab OR 'postconcussion recovery':ti,ab OR 'post concussion recovery':ti,ab OR 'post-traumatic symptom':ti,ab OR 'posttraumatic symptom':ti,ab OR 'post traumatic symptom':ti,ab OR

'persistent':ti,ab OR 'persistent concussive syndrome':ti,ab OR 'postconcussion syndrome'/exp OR 'postconcussion syndrome':ti,ab OR 'long term':ti,ab OR 'permanent':ti,ab OR 'prolonged':ti,ab OR 'late recovery':ti,ab OR 'recovery':ti,ab OR 'poor outcome':ti,ab OR 'outcome':ti,ab OR 'disability'/exp OR 'disability':ti,ab OR 'sick leave':ti,ab OR 'medical leave'/exp OR 'glasgow outcome scale'/exp OR 'glasgow outcome scale':ti,ab OR 'assessment':ti,ab OR 'patient outcome assessment':ti,ab OR 'outcome assessment'/exp OR 'outcome assessment':ti,ab OR 'symptom assessment'/exp OR 'symptom assessment':ti,ab OR

'neurologic symptom':ti,ab OR 'neurologic symptoms':ti,ab OR 'neurologic manifestation':ti,ab OR 'Neurologic Manifestations':ti,ab OR 'neurological problem':ti,ab OR 'neurological problems':ti,ab OR

'neurologic disease':ti,ab OR 'cognitive symptom':ti,ab OR 'cognitive symptoms':ti,ab OR 'mild cognitive impairment':ti,ab OR 'cognitive impairment':ti,ab OR 'cognitive defect':ti,ab OR 'cognition':ti,ab OR 'Neurobehavioral manifestations':ti,ab OR 'neuropsychological symptom':ti,ab OR 'neuropsychological symptoms':ti,ab OR 'behavioral symptom':ti,ab OR 'behavioral symptoms':ti,ab OR 'behavioural symptom':ti,ab OR 'behavioural symptoms':ti,ab OR

'rivermead post-concussion symptoms questionnaire':ti,ab OR 'rivermead post-concussion questionnaire':ti,ab OR 'rivermead post concussion symptoms questionnaire':ti,ab OR 'rivermead post concussion questionnaire':ti,ab OR

'prognosis'/exp OR 'prognosis':ti,ab OR 'predictive value'/exp OR 'predictive value':ti,ab OR 'predictive values':ti,ab OR 'predictive validity'/exp OR 'predictive validity':ti,ab OR 'clinical course'/exp OR 'clinical course':ti,ab OR 'disease course'/exp OR 'disease course':ti,ab OR 'incidence':ti,ab OR 'mortality':ti,ab OR

'Quality of life'/exp OR 'quality of life':ti,ab OR 'quality of life assessment'/exp OR 'quality of working life'/exp OR 'return to work'/exp OR 'return to work' OR

'follow up'/exp OR 'follow up studies':ti,ab OR 'follow up study':ti,ab OR 'follow-up studies':ti,ab OR 'follow-up study':ti,ab OR 'comparative study'/exp OR 'comparative study':ti,ab OR 'cohort studies':ti,ab OR 'cohort study':ti,ab OR 'cohort analysis'/exp OR 'cohort analysis':ti,ab OR 'longitudinal study'/exp OR 'longitudinal study':ti,ab OR 'longitudinal studies':ti,ab OR 'randomized controlled trial'/exp OR 'randomized controlled trial':ti,ab OR 'controlled clinical trial'/exp OR 'controlled clinical trial':ti,ab OR 'clinical trial'/exp OR 'clinical trial':ti,ab OR

headache/exp OR 'headache':ti,ab OR 'Posttraumatic headache'/exp OR 'posttraumatic headache':ti,ab OR 'primary headache'/exp OR 'secondary headache'/exp OR 'dizziness'/exp OR 'dizziness':ti,ab OR 'vertigo'/exp OR 'vertigo':ti,ab OR 'nausea'/exp OR 'nausea':ti,ab OR 'nausea and vomiting'/exp OR 'nausea and vomiting':ti,ab OR 'vomiting'/exp OR 'vomiting':ti,ab OR 'hyperacusis':ti,ab OR 'loudness recruitment'/exp OR 'loudness recruitment':ti,ab OR 'noise sensitivity':ti,ab OR 'sleep disturbance':ti,ab OR 'sleep disorder'/exp OR 'sleep disorder':ti,ab OR 'sleep arousal disorder'/exp OR 'sleep arousal disorder':ti,ab OR 'dyssomnia':ti,ab OR 'insomnia':ti,ab OR fatigue/exp OR 'fatigue':ti,ab OR 'mental fatigue':ti,ab OR 'dysthymia'/exp OR 'dysthymia':ti,ab OR 'chronic fatigue syndrome'/exp OR 'chronic fatigue syndrome':ti,ab OR 'irritable mood':ti,ab OR 'irritable':ti,ab OR 'irritability'/exp OR 'annoyance':ti,ab OR 'impatience':ti,ab OR 'anger'/exp OR 'anger':ti,ab OR 'despresion'/exp OR 'depression':ti,ab OR 'depressive disorder':ti,ab OR 'long term depression'/exp OR 'long-term synaptic depression':ti,ab OR 'frustration'/exp OR 'frustration':ti,ab OR 'frustrated':ti,ab OR 'Impatient':ti,ab OR 'forgetfulness':ti,ab OR 'memory disorder'/exp OR 'memory disorder':ti,ab OR 'memory disorders':ti,ab OR 'poor memory':ti,ab OR 'information processing speed':ti,ab OR 'deceleration in information processing':ti,ab OR 'impede processing speed':ti,ab OR 'speed of processing':ti,ab OR 'processing speed':ti,ab OR 'speed of information processing':ti,ab OR 'information processing'/exp OR 'working memory'/exp OR 'working memory':ti,ab OR 'short term memory'/exp OR 'short term memory':ti,ab OR 'vision disorder':ti,ab OR 'vision disorders':ti,ab OR 'visual disorder'/exp OR 'visual disorder':ti,ab OR 'visual impairment'/exp OR 'visual impairment':ti,ab OR 'visual impairments':ti,ab OR 'vision disability':ti,ab OR 'vision disabilities':ti,ab OR 'blurred vision'/exp OR 'blurred vision':ti,ab OR 'visual acuity'/exp OR 'visual acuity':ti,ab OR 'visual consequences':ti,ab OR 'visual deficit':ti,ab OR 'visual deficits':ti,ab OR 'vision loss':ti,ab OR 'visual function':ti,ab OR 'visual system function'/exp OR 'vision'/exp OR 'visual quality of life':ti,ab OR 'photophobia'/exp OR 'photophobia':ti,ab OR 'light sensitivity':ti,ab OR 'light sensitivities':ti,ab OR 'diplopia'/exp OR 'diplopia':ti,ab OR 'double vision':ti,ab OR 'Psychomotor agigation':ti,ab OR 'restlessness'/exp OR 'restlessness':ti,ab OR 'psychomotor hyperactivity':ti,ab OR 'psychomotor excitement':ti,ab OR 'Anxiety'/exp OR 'Anxiety':ti,ab OR 'Anxieties':ti,ab OR 'Nervousness':ti,ab OR 'Hypervigilance':ti,ab OR 'Anxiety Assessment':ti,ab OR 'Anxiety Disorders':ti,ab OR 'Loss of concentration':ti,ab OR 'Loss of attention':ti,ab OR 'Drowsiness':ti,ab
Finalization **4.** #1 AND #2 AND #3

eTable 2. List of congresses and conferences screened

1) American Academy of Emergency Medicine (AAEM)
2) American Academy of Neurology (AAN)
3) American Association of Neurological Surgeons (AANS)
4) American Association for the Surgery of Trauma (AAST)
5) American College of Emergency Physicians (ACEP)
6) Australasian College for Emergency Medicine (ACEM)
7) American College of Sports Medicine (ACSM)
8) American Medical Society for Sports Medicine (AMSSM)
9) American Neurological Association (ANA)
10) Australian and New Zealand Association of Neurologists (ANZAN)
11) Canadian Association of Emergency Physicians (CAEP)
12) Congress of Neurological Surgeons (CNS)
13) European Neurological Society (ENS)
14) International Brain Injury Association (IBIA)
15) International Symposium on Intensive Care and Emergency Medicine (ISICEM)
16) Society for Academic Emergency Medicine (SAEM)
17) Société de Neuropsychologie de Langue Française (SNLF)
18) World Congress on Brain Injury
19) World Congress of Neurology (WCN)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5 – eTable 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	—
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	—
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	—
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6-7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6-7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	—
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	—
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	10

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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