

# BMJ Open Characteristics of patients included and enrolled in studies on the prognostic value of serum biomarkers for prediction of postconcussion 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 generalisability 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 postconcussion symptoms following an 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 (2812 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%)), neurological disorders (n=20 (56%)), psychiatric disorders (n=17 (47%)), substance abuse disorders (n=13 (36%)) or previous traumatic brain injury (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 postconcussion syndrome 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 generalisable to the mTBI population. These exclusion criteria limit the potential use

## 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 postconcussion 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.

and translation of promising serum protein biomarkers to predict postconcussion symptoms.

## INTRODUCTION

Mild traumatic brain injury (mTBI) is frequently encountered by neurologists, primary care, emergency, sport medicine and rehabilitation health providers<sup>1</sup> and accounts for approximately 80% of all TBI.<sup>2</sup> The incidence of mTBI exceeds that of dementia, epilepsy and stroke, giving it the status of the most common brain disorder.<sup>3</sup> However, there is still an incomplete understanding of mTBI pathophysiology that leads to suboptimal diagnosis, treatment and prognostication.<sup>4</sup> With increasing attendance to emergency departments following

mTBI by complex patients such as elderly,<sup>5</sup> intoxicated patients<sup>6,7</sup> and patients with psychiatric disorders,<sup>8</sup> there is an urgent need to optimise the care of patients with mTBI.

Once considered benign, there has been increased awareness of the potential adverse consequences of mTBI.<sup>9</sup> While 80% of patients will report at least one early postconcussion symptom,<sup>10</sup> between 10% and 56% will exhibit persistent symptoms 3 months after an mTBI.<sup>11–15</sup> Physical, cognitive and emotional symptoms, often described as postconcussion syndrome (PCS), that exceed the expected window of recovery have deleterious impacts on quality of life and daily functional outcome.<sup>16–18</sup> Prognostic markers have been highlighted for cognitive, psychiatric and mortality outcomes.<sup>19</sup> 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.<sup>19</sup> 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.<sup>20, 21</sup> Therefore, many researchers choose to apply strict inclusion and exclusion criteria to minimise confounding by such factors and to decrease the inherent population heterogeneity.<sup>20</sup> This approach results in improved internal validity but also inevitably limits recruitment and generalisability of results. Some populations are therefore often excluded or less likely to be enrolled in TBI studies.<sup>22</sup> 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 Mild Traumatic Brain Injury Prognosis.<sup>23</sup> 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 an 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 postconcussion symptoms following an 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 postconcussion symptoms following an mTBI (International Prospective Register of Systematic Reviews (PROSPERO) registration CRD42016032578). In summary, a general search strategy aiming to identify articles that assessed the association between protein biomarkers and postconcussion symptoms in traumatic brain injury (TBI) was created for seven databases (from their inception to 4 October 2016): MEDLINE, Embase, CINAHL, Cochrane Central Register of Controlled Trials, Web of Science, PsycBITE and PsycINFO using Medical Subject Headings (MeSH terms), Embase Subject Headings (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-100 $\beta$  protein, neuron-specific enolase (NSE), glial fibrillar acidic protein (GFAP), ubiquitin carboxy-terminal hydrolase L1 (UCHL-1), cleaved tau (c-tau), microRNA and brain-derived neurotrophic factor (BDNF)).<sup>24–28</sup> No language, type of study or date restriction were applied in the initial search strategy. The detailed Embase search strategy is available in online supplementary table 1. References from the included studies and narrative reviews were also scrutinised, and relevant abstracts from congress and conferences were reviewed to identify potential peer-reviewed published studies (online supplementary table 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, V.X7), all the citations obtained with our search strategies on the seven databases were combined. Duplicates were removed. Independently, two reviewers (EM and P-AT) then scrutinised 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 (NLS) 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 postconcussion symptom evaluated  $\geq 7$  days following an 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, specific to a paediatric population, reporting on moderate or severe TBI or if the postconcussion symptom evaluation was performed  $<7$  days after the mTBI or the study was not published in a peer-reviewed journal. Case reports were also excluded.

## Data extraction

Using a data collection form, two reviewers (EM and P-AT) independently collected the relevant data from every included study. Therefore, data on the manuscript (journal, publication date and 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 and mTBI definition), protein biomarker (assays used and characteristics, detection limits, thresholds, timing of sampling, type of sampling (venous, capillary or arterial) and number of samples), patient characteristics (age, gender, trauma mechanism and TBI severity) and the outcomes (outcome type, assessment timing and 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 (SD) were calculated using Statistical Analysis System software (V.9.4). Main data are also presented as proportions. In 14 studies where sufficient data were available, we calculated the pooled mean age of enrolled patients and its heterogeneity ( $I^2$ ).<sup>29</sup> 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.*<sup>30</sup>

The quality of the evidence of the three main outcomes was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (postconcussion symptoms, Glasgow Outcome Scale (GOS-E) and GOS-Extended (GOS-E) and return to work).<sup>31</sup> 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 (online supplementary table 3).<sup>32</sup>

## 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 (NLS) to make the final decision. A total of

2812 patients were included in those studies, which individually included from 7 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-100 $\beta$  protein (29 studies) followed by NSE (10 studies), c-tau (4 studies), GFAP (4 studies), UCHL-1 (3 studies), BDNF (1 study) and microRNA (1 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 online supplementary figure 1. Regarding the inclusion criteria, an upper age limit was used in 10 studies (28%). Therefore, patients  $\geq 65$  years old were excluded in seven studies (19%), while those aged  $\geq 85$  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.

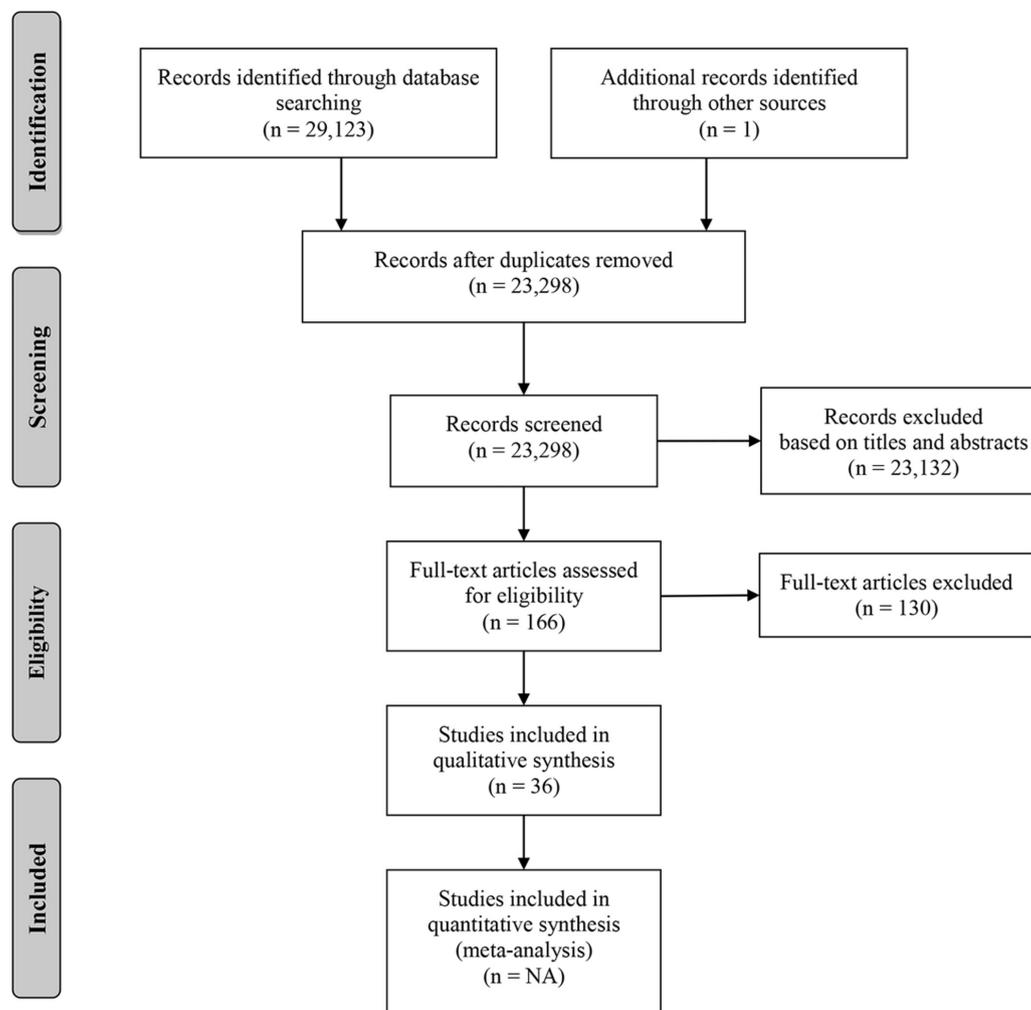
The most frequent exclusion criteria were neurological disorders, psychiatric disorders, trauma to another body region, substance abuse disorders and previous TBI (table 2). Twenty-one studies (58%) used at least two of these exclusion criteria. Medical comorbidities were infrequently used as exclusion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

### mTBI 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 (7 studies (19%)) or GCS 15 only (1 study (3%)). Other criteria such as loss of consciousness (LOC), post-traumatic amnesia (PTA) and focal neurological 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,<sup>33</sup> the American Congress of Rehabilitation Medicine<sup>34</sup> and the European Federation of Neurological Societies,<sup>35</sup> respectively.

### Outcomes presented in the included studies

Table 4 presents the outcomes evaluated. The most frequently evaluated outcome was 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  $\geq 3$  criteria. Among



**Figure 1** PRISMA flow diagram of included studies. Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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 an mTBI such as the GOS or the GOS-E.<sup>36</sup>

#### 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 area under the receiver operating characteristic curve (AUROC) analyses to assess the potential prognostic value of biomarkers to predict the occurrence of outcomes in patients with an mTBI. Among these, only one compared the area under the curve 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%), neurological 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 generalisability 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<sup>37</sup> and patients with substance

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

\*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). BI, brain injury; C-tau, cleaved tau; GFAP, glial fibrillar acidic protein; miR, microRNA; NSE, neuron-specific enolase; RNN, restorative neurology and neuroscience; UCHL-1, ubiquitin carboxy-terminal hydrolase L1.

**Table 2** Exclusion criteria used in the included studies

Exclusion criteria	Number of studies (n, %)
Neurological 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)

abuse, psychiatric or neurological disorders.<sup>6 8</sup> Intoxicated patients also often present with altered conscious state raising the possibility of TBI and complicating initial clinical assessment.<sup>38 39</sup> Patients with previous TBI are also of concern given the complications of repetitive TBI.<sup>40</sup> All these patients pose a challenge to the clinician in terms of assessment of injury severity and prognosis. Moreover, these preinjury factors are known to predispose to the development of persistent postconcussion symptoms leading to poorer functional outcomes.<sup>41–45</sup> In a large retrospective cohort study of patients with suspected TBI, patients were frequently intoxicated with alcohol (20%) or had a psychiatric (25%) or neurological disorders (25%).<sup>22</sup> 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.<sup>46 47</sup> The absolute incidence of TBI among the geriatric patients is rising as a result of the increased life expectancy and mobility.<sup>5</sup> 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 epidemiological studies<sup>48 49</sup> 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.<sup>5 50</sup> Geriatric patients therefore seem under-represented in our included studies despite the fact that they have a poorer functional outcome with an increased occurrence of post-concussion symptoms.<sup>51</sup> The effect of age on the circulating blood-based biomarker is controversial.<sup>52</sup> 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 an 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.<sup>20 22</sup> Therefore, patients

**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 min	4 (11.1)
<15 min	5 (13.9)
<30 min	9* (25)
No duration	8† (22.2)
No use of LOC	10 (27.8)
Post-traumatic amnesia (PTA)	
<15 min	1 (2.8)
<30 min	0 (0)
<60 min	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 definition (2002)	1* (2.8)

\*Heidari *et al*<sup>80 90</sup> used the following mTBI definition: (1) a GCS score of 13–14; (2) a GCS score of 15 with LOC <30 min, PTA <1 hour; or (3) a GCS score of 15 without LOC or PTA.

†Korley *et al*<sup>28 28</sup> presented three different cohorts with different inclusion criteria. Only the mTBI definition of the case cohort is presented in the table.

‡ACEP, American College of Emergency Physicians; CDC, Centers for Disease Control and Prevention.

with premorbid conditions remain poorly studied despite their unfavourable prognosis and increased risk of disabilities.<sup>41 42</sup> Also, the association between the protein biomarker and the outcome in patients with premorbid conditions might differ from the association with healthier patients, therefore limiting the potential to draw clinical conclusions. Future studies should aim to maximise 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 neurological disorder on

**Table 4** Outcome evaluated in the included studies

Outcome evaluated	Number of studies (n, %)
Postconcussion 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.

protein biomarker baseline level and the kinetic modelling of protein biomarker release in the serum following an mTBI 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. mTBI is a heterogeneous group with a wide range of ‘severity’. The symptom-based GCS

**Table 5** Definition of postconcussion 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)

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 is frequent.<sup>8</sup>

One major limitation to our understanding of mTBI is the lack of universal definition of the outcomes evaluated.<sup>53</sup> Most patients recover completely but for those affected by persistent symptoms, there are controversies about the nomenclature and definitions associated with postconcussion symptoms and PCS.<sup>54</sup> 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 7 days to more than 5 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,<sup>55</sup> 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.<sup>19</sup> 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 postconcussion symptoms are that these symptoms are not specific to mTBI and are prevalent both in the general population and after non-head injuries.<sup>56</sup>

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 an mTBI.<sup>57</sup> In addition to improving the initial prognostication, the use of

**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
Postconcussion symptoms	18 studies (n=2048)	Observational	Important heterogeneity in populations enrolled, definitions of outcome variables and evaluation duration. Only four associations between postconcussion symptoms and a biomarker were statistically significant. Only eight studies used multivariate regression analyses and CIs were often large.	Low
GOS-E and GOS	Nine 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 three were significant), their direction and strength.	Insufficient
Return to work	Four studies (n=432)	Observational	Slight discrepancies in definitions and reporting but considerable differences in evaluation duration (1 week–1 year). Only one study showed a significant association with increased S-100 $\beta$ protein serum level.	Insufficient

GOS, Glasgow Outcome Scale; GOS-E, Glasgow Outcome Scale-Extended.

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.<sup>26 27</sup> As mTBI diagnostic criteria are subjective, non-specific 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 neurological 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 unrestricted 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 neurological, psychiatric

and substance abuse disorders and patients with previous TBI are often excluded and poorly represented even though they are at high risk of postconcussion 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 generalisability and the translation to bedside care of the promising brain-specific biomarkers.

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