

Systematic Review of Multivariable Prognostic Models for Mild Traumatic Brain Injury

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Abstract

Prognostic models can guide clinical management and increase statistical power in clinical trials. The availability and adequacy of prognostic models for mild traumatic brain injury (MTBI) is uncertain. The present study aimed to (1) identify and evaluate multivariable prognostic models for MTBI, and (2) determine which pre-, peri-, and early post-injury variables have independent prognostic value in the context of multivariable models. An electronic search of MEDLINE, PsycINFO, PubMed, EMBASE, and CINAHL databases for English-language MTBI cohort studies from 1970–2013 was supplemented by Web of Science citation and hand searching. This search strategy identified 7789 articles after removing duplicates. Of 182 full-text articles reviewed, 26 met eligibility criteria including (1) prospective inception cohort design, (2) prognostic information collected within 1 month post-injury, and (3) 2+ variables combined to predict clinical outcome (e.g., post-concussion syndrome) at least 1 month later. Independent reviewers extracted sample characteristics, study design features, clinical outcome variables, predictor selection methods, and prognostic model discrimination, calibration, and cross-validation. These data elements were synthesized qualitatively. The present review found no multivariable prognostic model that adequately predicts individual patient outcomes from MTBI. Suboptimal methodology limits their reproducibility and clinical usefulness. The most robust prognostic factors in the context of multivariable models were pre-injury mental health and early post-injury neuropsychological functioning. Women and adults with early post-injury anxiety also have worse prognoses. Relative to these factors, the severity of MTBI had little long-term prognostic value. Future prognostic studies should consider a broad range of biopsychosocial predictors in large inception cohorts.

Key words: concussion; prognosis; systematic review; traumatic brain injury

Introduction

MILD TRAUMATIC BRAIN INJURIES (MTBIs) are very common. They account for at least 80% of all TBIs and have an annual incidence of more than 500 per 100,000.^{1–3} There is a large and compelling literature on the clinical course of MTBI in civilian trauma patients, athletes, active duty military service members, and veterans, summarized in several recent systematic reviews.^{4–11} It is now well-established that patients with MTBI typically recover within days to weeks, but a minority (of debated size) experience protracted or incomplete recovery. Persistent symptoms are associated with disability and high health service use.^{12–15} Identifying persons on a trajectory of poor outcome soon after MTBI is therefore essential.

As with other health conditions, flagging patients who are likely to have a good or poor outcome enables identification of those who need monitoring or who can benefit from early therapeutic interventions. Prognostic models can also enhance statistical power in randomized controlled trials through risk stratification and covariate adjustment.^{16,17} A single predictive variable is rarely sufficient, but multiple predictors can be combined into a multivariable prognostic model to accurately gauge risk for a clinical outcome of interest.¹⁸ By evaluating multiple predictor variables in the same sample, prognostic models can also clarify the relative importance of each and suggest causal links to good or poor outcome.¹⁹

A systematic review of multivariable prognostic models for moderate-to-severe TBI identified the Glasgow Coma Scale, pupil reactivity, and CT findings as the best predictors of outcome.²⁰

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These crude indicators lose their prognostic power when applied to patients with MTBI.^{21,22} MTBI is by definition associated with a ceiling or near ceiling score on the Glasgow Coma Scale.^{23,24} Pupil and CT abnormalities are typically absent. Clearly, more sensitive biomarkers will be necessary to improve prognostics for MTBI, and several (e.g., advanced neuroimaging techniques) appear promising in exploratory studies.²⁵ Psychosocial factors such as early post-injury anxiety also appear to influence outcome from MTBI.^{9,26} The relative importance of these biopsychosocial factors, however, and their joint ability to predict outcome from MTBI is not yet clear.

The primary aim of the present study is to identify and evaluate existing multivariable prognostic models appropriate for clinical and research applications. To the authors' knowledge, this is the first systematic review of multivariable prognostic models for MTBI. A further aim is to clarify which individual factors independently predict MTBI outcome. Other recent systematic reviews extracted information about correlates of MTBI outcome,^{19,27} most notably those performed by the International Collaboration on MTBI Prognosis and reported in a special issue of the Archives of Physical Medicine and Rehabilitation.¹⁹ By focusing on multivariable models derived from inception cohorts, the present study adds knowledge about the unique and relative prognostic value of each factor.

Methods

The protocol for the present study was registered with PROSPERO and can be accessed here: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42013003631.

Eligibility criteria

Studies with participants who sustained an MTBI according to the most widely used diagnostic criteria^{23,24} or a compatible definition of MTBI were included. Studies could have included patients with MTBI exclusively or reported separate analyses for an MTBI subgroup. Studies that analyzed a combined sample of MTBI and nonhead injury controls were also eligible, if diagnosis (MTBI vs. nonhead injury) was included as a covariate. Eligible studies must have reported on a global clinical outcome (e.g., symptomatic status). Narrow "outcomes" such as a medical complication (e.g., seizures) or specific symptom (e.g., fatigue) were excluded.

To maximize internal validity, only studies that had a prospective inception cohort design, recruiting patients from an acute care setting (e.g., emergency department), and whose cohort had at least 30 participants were included. Studies could have focused on school-aged children, adolescents, and/or adults for inclusion, enabling a comparison of similarities and differences in prognostic factors across the age span. Eligible studies must have combined at least two variables collected in the acute to subacute phase (< 1 month post-injury) in the prediction of clinical outcome at least 1 month later.

Note that the retrospective assessments of participants' pre-injury functioning were exempt from meeting these time interval criteria. For example, McNally and associates²⁸ had children and their parents retrospectively assess participants' pre-injury functioning at 1–2 weeks post-injury and predicted clinical outcome only 2–3 weeks later (as well as at subsequent time points). Studies using statistical techniques that modeled multiple time points (rather than a single discrete time point) were included if time post-injury was included as a covariate. Prognostic modeling need not have been a study's primary or even secondary aim. Only original full-text research manuscripts published in English in peer-reviewed journals were eligible (published abstracts do not present sufficient information to fulfill our study aims). Resources for translating articles from languages other than English were not available.

Data sources

The electronic search strategy (see Appendix 1) was adapted from the International Collaboration on Mild Traumatic Brain Injury Prognosis²⁹ by our multidisciplinary research team with expertise in neuropsychology and emergency medicine, in collaboration with a librarian (F.S.) who is experienced with systematic reviews. Because the present study was part of a systematic review series, the search strategy was designed to identify all observational and intervention studies involving patients with MTBI. That is, no search criteria specific to prognostic modeling was included. We set limits to English language studies published since 1970. The search was performed on Medline (June 12, 2013), EMBASE (June 25, 2013), PsychINFO (June 26, 2013), and CINAHL (June 26, 2013). RefWorks software was used to merge these search results and remove duplicates.

To supplement the electronic search, we hand-searched the reference lists in a series of recent MTBI systematic reviews by the International Collaboration on Mild Traumatic Brain Injury Prognosis¹⁹ and another focused on children.²⁷ We also searched for articles that cited any of the eligible studies in the present review using the Web of Science Citation Index (May 14, 2014). This latter search was primarily undertaken to find any external cross-validations of the prognostic models identified in our review, but also to update our search for new prognostic models.

Quantitative and qualitative synthesis

No quantitative synthesis was planned for the primary objective, which was to evaluate each multivariate prognostic model with respect to the strength of the methodology used for its development and its accuracy in predicting clinical outcome. Creating summary statistics for the prognostic value of individual predictors (our secondary objective) was considered. Marked heterogeneity in the measurement of predictors and outcomes, as well as the coding of each (e.g., continuous, ordinal, or dichotomous), precluded their quantitative synthesis, however.

Study selection

Study selection was undertaken in a multistage process, outlined in Figure 1. First, a single reviewer screened study titles and excluded articles that were clearly not relevant to MTBI. Second, a pair of reviewers independently screened study abstracts for general eligibility criteria. Next, two authors (NS and AG) independently reviewed the remaining abstracts for additional eligibility criteria specific to the present study—i.e., (1) prognostic variables collected within 1 month of injury, (2) longitudinal design with follow-up (time 2) assessment at least 1 month after initial (time 1) assessment, and (3) two or more time 1 variables combined to predict outcome at time 2. After this stage, one author (NS) performed a full-text review to check for eligibility. Articles identified as eligible at this stage were confirmed by a second author (AG), with a consensus discussion for discrepancies.

Data extraction

Data extraction was performed by a team of three authors (NS, AG, and WP) such that each data element was extracted independently by two reviewers. Data extraction forms were used to enhance standardization. In addition to the data elements presented in the supplementary on-line table (see online supplementary material at ftp.liebertpub.com), we extracted information about calibration, cross-validation, and assessor blinding. We extracted the full exclusion criteria set for each study, but reported in the table only whether studies excluded participants with previous MTBI, pre-injury psychiatric conditions, and comorbid extracranial injuries to facilitate between-study comparisons and because these are most associated with clinical outcome from MTBI.^{7,9,30}

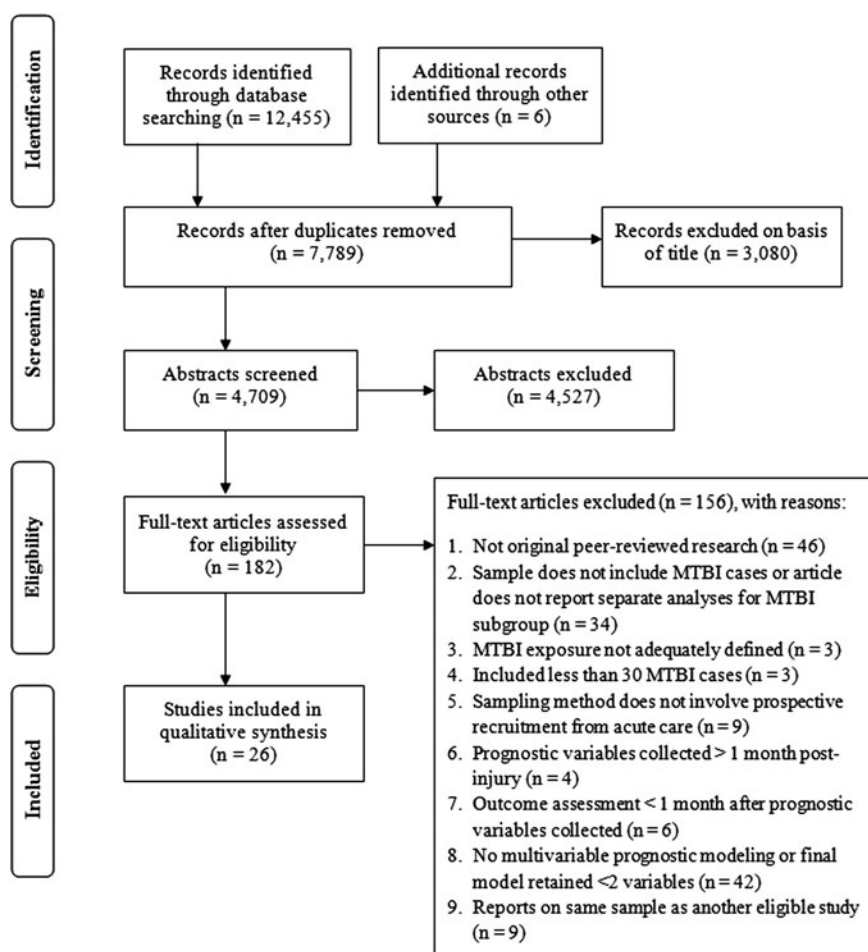


FIG. 1. Preferred reporting items of systematic reviews and meta-analyses flow diagram. MTBI, mild traumatic brain injury.

Contact with authors

Seven studies were found to be eligible but reported the strength of individual predictors (e.g., odds ratio) and not the overall performance of their multivariable prognostic model(s) (e.g., area under the curve). In these instances, the corresponding author was contacted to request this additional information.

Methodological quality

There is no widely used quality assessment tool for multivariable prognostic models. Elements that pertain to both methodological rigor (e.g., attrition and handling of missing data), model performance (e.g., calibration and discrimination), and clinical utility as recommended by reporting guidelines for observational studies³¹ and a systematic review of multivariable prognostic models for moderate-to-severe traumatic brain injury²⁰ were extracted.

Results

The search results are presented in Figure 1. The electronic search identified 30 eligible studies and the supplementary search strategies identified 2 additional studies.^{27,32} A number of studies reported on the same or overlapping samples. Faux and associates³³ incorporated the sample from Sheedy and colleagues,³⁴ so only the former was included. Bazarian and coworkers³⁵ and Bazarian and associates³⁶ analyzed the same sample; the former was included because it reported on longer term follow-up. Five eligible studies seemed to use the same cohort recruited from two emergency de-

partments in Ohio.^{28,37–40} McNally and associates²⁸ was chosen to represent this cohort because it included the broadest set of candidate predictors. This resulted in the inclusion of 26 eligible studies. Characteristics of the 26 studies are available in a supplementary on-line table (see online supplementary material at <ftp.liebertpub.com>). Several studies reported more than one prognostic model. The table includes 49 models (although note that one study reported a disproportionately large number ($n=14$) of models).⁴¹

Sample characteristics

The studies meeting eligibility criteria predominantly recruited adults ($n=19$; 73%) from emergency departments (100%) in North America ($n=10$; 39%), Europe ($n=10$; 39%), Australia ($n=5$; 19%), or multiple of these ($n=1$; 4%). Table 1 shows additional study sample characteristics. There was considerable heterogeneity across eligible studies in the definition of MTBI exposure and exclusion criteria. The American Congress of Rehabilitation Medicine diagnostic criteria²³ were used in seven (27%) of the studies, occasionally with modifications. The remainder used idiosyncratic MTBI definitions that biased the sample toward having less severe injuries (e.g., by imposing more narrow restrictions of loss of consciousness (LOC) duration and excluding patients with abnormal CT or neurological examination findings) or more severe injuries (e.g., requiring that participants were clinically triaged to CT). Summary statistics for injury severity are presented in Table 1.

TABLE 1. DESCRIPTIVE STATISTICS FOR INJURY SEVERITY AND METHODOLOGICAL FEATURES

Variable	# studies reporting	Range	Central tendency
GCS = 15	13 (50%)	57% to 100% of sample	Median = 86%, IQR = 75% to 96% M = 84%, SD = 13%
Loss of consciousness	11 (42%)	10% to 86% of sample	Median = 43%, IQR = 35% to 61% M = 46%, SD = 22%
Computed tomography abnormal	16 (62%)	0% to 49% of sample	Median = 4%, IQR = 0% to 20% M = 10%, SD = 14%
Motor vehicle accident	18 (69%)	2% to 82% of sample	Median = 29%, IQR = 10% to 55% M = 33%, SD = 23%
Sample size	26 (100%)	37 to 1,999 participants	Median = 125, IQR = 85 to 205 M = 267, SD = 430
Last follow-up	26 (100%)	1 to 15 months	Median = 3, IQR = 3 to 6 months M = 5, SD = 4
Attrition rate	23 (89%)	0% to 47% of sample at initial assessment	Median = 16, IQR = 11% to 22% M = 18, SD = 11

GCS, Glasgow Coma Scale; IQR, interquartile range; SD, standard deviation.

Outcome assessment

The most common outcome was post-concussion symptom reporting, dichotomized as post-concussion syndrome (PCS) present or absent ($n = 13$), otherwise categorized ($n = 1$), or as a continuous variable ($n = 5$). Several studies measured functional outcome with the Glasgow Outcome Scale-Extended ($n = 3$), Rivermead Head Injury Follow-up Questionnaire ($n = 2$), return to work ($n = 1$), or other clinician rating ($n = 2$). Finally, quality of life ($n = 5$) or neuropsychological ($n = 2$) outcomes were analyzed in a minority of prognostic models. Assessor blinding was not applicable to most studies because they analyzed patient-reported outcomes. Of the studies reporting on the Glasgow Outcome Scale-Extended or another clinician-rated outcome, none stated that the assessor was blinded to all prognostic variables.

Prognostic model derivation and validation

Most studies considered a large number of candidate predictors and then used a data-driven method for selecting predictors into a final prognostic model, most commonly screening with bivariate correlations and/or stepwise regression ($n = 19$ of 25 reporting this information). The ratio of participants (for linear regression) or poor outcome cases (for logistic regression) to predictor variables in the final model was greater than 10:1 for 15 of 28 models from 24 studies, not including 1 study that had a very low participant:variable ratio for all 12 of the models reported.⁴¹ Very few studies reported model calibration via a goodness-of-fit test (e.g., the Hosmer–Lemeshow statistic) for agreement between predicted and observed predictions. Only one eligible study performed internal validation⁴² and found considerable shrinkage of model discrimination.

Not a single external cross-validation of an eligible study was identified, either in the same article or through a Web of Science citation search. Faux and coworkers³³ stated a purpose of “cross-validating” a multivariable prognostic model developed from a previous sample.³⁴ Rather than apply the original model to the new sample, they performed a regression analysis (using the same set of predictors), resulting in different predictor weights. More than 20% of the sample was lost to follow-up in 8 of the 24 eligible studies that documented it. At this attrition rate, outcome estimates likely contain major bias.⁴³

Prognostic model performance

Of the 11 models reported in five studies that had a dichotomous outcome and were evaluated with receiver operating characteristic curve analyses, only 2 achieved “good” discrimination (area under the curve > 0.80) by standard interpretive criteria. The model predicting PCS in Stujelmeir and colleagues⁴² fell to 0.70 after correcting for optimism with bootstrapping (an internal validation technique). The prognostic model reported by Topolovec-Vranic and associates⁴⁴ may have been artificially inflated because the physician classifying cases as normal or abnormal at follow-up appears to have been blinded to only one of the predictors in the model.

An additional four models with dichotomous outcomes in four studies reported total classification accuracy but not the area under the receiver operating characteristic curve.^{33,45–47} Total classification accuracy ranged from 66% to 85%. In addition, the logistic regression model predicting 1 month PCS outcome in Bazarian and colleagues³⁵ achieved 90% classification accuracy but only in the 42% of the sample that could be classified according to a subsequent publication.³⁶ A prognostic model is considered effective when its classification error rate is less than the base rate of the outcome of interest. There was only one study⁴⁷ (with high attrition and low event:predictor ratio) in which the prognostic model was more than 5% better than the default assumption that all participants will achieve a good outcome.

Six studies analyzed a continuous outcome, and all reported total R^2 values for their final models, which ranged widely from 0.06 to 0.89. The only two studies achieving a total $R^2 > 0.40$ ^{41,48} shared several features: large number of predictors, small sample sizes (i.e., inadequate participant:variable ratio), stepwise predictor selection, and post-concussion symptom severity score as the outcome.

Creating clinician-friendly prediction rules from regression coefficients can facilitate translation of prognostic models into patient care.¹⁹ This was done in only one eligible study.⁴²

Independent prognostic value of predictors

Table 2 summarizes the pre-, peri-, and early post-injury prognostic variables considered across the eligible studies and their unique contributions to multivariable prediction. Many pre- (e.g.,

TABLE 2. INDIVIDUAL PREDICTORS AND THEIR SIGNIFICANCE IN MULTIVARIABLE PROGNOSTIC MODELS

Predictor	Findings
Pre-injury	
Age	Not selected* or nonsignificant in 9 ^{35,42,44,58-63} of 14 studies. Adolescents more ⁶⁴ or less ²⁸ likely to have high PCS symptoms. Younger age generally associated with lower risk of PCS and poor outcome (GOS-E <7) across the lifespan. ⁶⁵ Each year older in adulthood raised risk of poor outcome (GOS-E <7) by 2% ⁵⁴ and PCS by 5%. ⁶⁶
Sex	Not selected or nonsignificant in 6 of 12 studies. ^{42,46,54,61,63,64} All six studies finding an association reported worse symptomatic outcomes for women. ^{35,44,59,60,65,67} Sex association less clear in children and with functional outcomes.
Education	Adult education level not related to symptomatic ^{44,67} but possibly functional outcome. ^{42,63} Higher parental education level and child academic achievement associated with lower risk of short-term neuropsychological impairment. ⁵⁸
Intelligence	Not selected or nonsignificant in two of three studies. ^{28,32,60} Low IQ independently associated with higher post-concussion symptom severity in one pediatric study. ³²
Developmental disorder	In three pediatric studies, ^{46,58,68} history of learning disability or Attention Deficit Hyperactivity Disorder was considered as predictor but found to be nonsignificant.
Genetics	APOE-ε4 allele uniquely predicted neuropsychological outcome in a single study. ⁶⁹
Prior MTBI(s)	Not selected or nonsignificant in five of six studies. ^{42,44,63,64,66} Strongest predictor in one pediatric study, explaining 25% of variance in outcome. ⁴⁶
Post-concussion symptoms	Inconsistent findings across three pediatric studies. ^{28,32,58}
Physical health	Lower pre-injury physical health was associated with worse outcome in all three adults studies that considered it. ^{42,61,67} It did not contribute to a pediatric multivariable model that included pre-injury psychosocial health. ³²
Mental health	Uniquely related to outcome in seven studies. ^{32,46,60-62,67} In the two studies reporting no effect, post-injury mental health variables were highly significant predictors in the model. ^{42,59}
Peri-injury	
Diagnosis	Of four studies that included nonhead injury trauma controls, ^{28,58,60,67} MTBI group status was independently associated with outcome in only one. ²⁸ In that study, injury severity variables had relatively weak prognostic value compared with noninjury variables, and ceased to make a significant contribution beyond 3 months post-injury.
Glasgow Coma Scale	Not selected or nonsignificant in six of six studies. ^{42,47,54,63,64,69}
Loss of consciousness	Not selected or nonsignificant in six out of eight studies. ^{28,35,44,47,54,63,64,66} Strongest predictor in one study (odds ratio = 8.1), where the outcome assessor judging recovery status was seemingly not blinded to this variable. ⁴⁴
Amnesia	Not selected or nonsignificant in 8 of 10 studies. ^{35,46-48,54,61,63,64,66,70} Of the two studies reporting an association, one found a lower risk of PCS ³⁵ and the other found a higher risk of PCS. ⁴⁸
Intoxicated	Associated with better outcome in two adult studies ^{33,54} .
Computed tomography	Did not uniquely predict outcome in five of five studies that coded findings dichotomously (normal/abnormal). ^{42,62,64,65,69} Two studies that coded specific types of pathology both found that certain CT variables (number of hemorrhagic contusions ⁵⁴ and presence of subarachnoid hemorrhage ⁶³) uniquely contributed to a multivariable model; however, reduced models excluding CT variables had comparable discrimination.
Extracranial injury	Uniquely predicted functional outcome ^{42,54} but not symptomatic outcome ^{42,66} in adults. In one pediatric study, comorbid extracranial injury uniquely predicted symptomatic outcome only as reported by parents (not children) and only at 1 month (not later follow-up). ²⁸
Mechanism of injury	Not selected or nonsignificant in five of five studies. ^{28,35,42,44,64}
Early post-injury	
Symptoms	Total symptom severity scores predicted outcome in some studies ^{41,42,44,67} but not others ^{47,48,58,70} (four of eight). Specific symptoms such as headache ^{42,44,64,71} and body pain ^{33,42,60,61} were also inconsistent predictors.

(continued)

TABLE 2. (CONTINUED)

Predictor	Findings
Anxiety	Uniquely associated with outcome in four of five adult studies ^{45,48,59,61,70} and in all four was the strongest predictor in the multivariable model. This relationship was limited to women in the one study that examined sex interactions. ⁵⁹ Parental anxiety in the emergency department did not predict parent-reported symptomatic outcome in a pediatric sample. ⁶⁸ Acute post-traumatic stress uniquely predicted outcome in two of three studies ^{42,47,60} and negative beliefs about MTBI in two of two. ^{45,47}
Sensory-motor tests	Assessed in a single study, ⁴¹ but demonstrated promising prognostic power.
Cognitive tests	Objective cognitive/neuropsychological tests predicted symptomatic ^{33,35,41,48} and neuropsychological ^{58,69} outcome in six studies but not in three others. ^{60,61,70} It is noteworthy that for predicting late neuropsychological outcome, early neuropsychological testing was by far the strongest predictor. ^{58,69}
Neuroimaging	MRI performed within 48 h post-injury did not uniquely predict neuropsychological recovery in one study. ⁶⁹ In another, MRI conducted at 12 days (SD=4) post-injury uniquely contributed to predicting functional outcome at 3 months post-injury, over and above clinical, demographic, and CT variables. ⁶³
Serum biomarkers	S-100B uniquely predicted outcome in two of four studies ^{44,66,69,71} and neuron-specific enolase in one of two studies. ^{44,71} Two of these studies examined both biomarkers; one found S-100B but not neuron-specific enolase to be prognostic ⁷¹ while the other study found the opposite pattern. ⁴⁴

PCS, post-concussion syndrome; GOS-E, Glasgow Outcome Scale-Extended; MTBI, mild traumatic brain injury; CT, computed tomography; MRI, magnetic resonance imaging; SD, standard deviation.

*“Not selected” refers to a predictor variable that was considered in a study’s analyses but not included in the final multivariable model, typically because of multicollinearity or failure to improve overall model discrimination to a statistically significant degree.

age, sex, previous MTBIs), peri- (e.g., LOC, CT findings, mechanism of injury), and post-injury variables (e.g., anxiety, neuropsychological testing, serum biomarkers) were considered. The most consistent independent predictors of poor outcome were female sex, pre-injury mental health, post-injury anxiety and traumatic stress, and post-injury cognitive functioning.

Discussion

The present study systematically reviewed the literature for multivariable prognostic models for MTBI. The primary aim was to identify models that can be used in clinical practice (e.g., triaging patients at risk for poor outcome) and research (e.g., risk stratification in clinical trials). The review focused on inception cohort designs to provide the strongest level evidence and because using information collected soon after the injury to predict long-term outcome is most clinically relevant. Although we identified 26 eligible studies involving 6939 participants aged 5 to 80+ from three continents, the methodology used to develop them was largely suboptimal and their predictive accuracy was low. In line with our secondary aim, we identified several pre-, peri-, and early post-injury prognostic factors that independently predicted MTBI outcome in multivariable models.

Multivariable prognostic models

Eligible studies almost universally used bivariate screening and stepwise regression approaches to select variables into a prognostic model from a larger set of candidate predictors. These methods result in unstable predictor selection and bias in the covariate coefficients, especially at lower subject per predictor ratios.^{49,50} Subject per predictor ratios were low (<10:1) for many studies—i.e., the sample size was inadequate for the number of predictor variables. Calibration was not reported for most models. Models derived on one sample produce inflated estimates of discrimination.

Correcting for this optimism with internal validation techniques such as bootstrapping was performed in only one eligible study.⁴² No model has been externally validated in a new sample.

The fact that multivariable prognostic modeling was not a primary objective of most eligible studies helps explain these significant methodological shortcomings. Many of the concerns outlined by Kristman and coworkers⁵¹ that pertain to MTBI cohort studies generally, including variable definitions of MTBI, selection bias, psychometrically weak end points, and high attrition, were also present among most eligible studies, however.

Methodology aside, the identified prognostic models had limited ability to predict clinical outcome after MTBI, based on standard interpretive criteria for clinical significance of area under the receiver operating characteristic curve and total classification accuracy statistics for models with dichotomous outcomes. The only studies explaining more than 40% of variance in a continuous outcome had a serious risk of bias (e.g., because of attrition) and overfitting. No model created decision rules and externally validated them in new patients. For these reasons, none of the multivariable prognostic models identified in the present review can be recommended for clinical use. Further, none of the existing models can be endorsed for enriching a clinical trial sample or stratifying randomization. Including key covariates (see below) in clinical trial analyses, however, may be a reasonable interim solution.

Independent predictors of MTBI outcome

The most robust prognostic factors, when considered alongside others in multivariable models, were pre-injury mental health and acute post-injury neuropsychological functioning. Sex and early post-injury anxiety were also strong independent prognostic factors in adults, at least for symptomatic outcome. When included in a multivariable model, early post-injury anxiety tended to be the strongest independent predictor. There was positive but limited evidence that worse pre-injury physical health and comorbid

extracranial injury are independently associated with worse outcome in all age groups. In addition, there was limited evidence, based on a small number of studies, that APOE-4 carrier status, being sober (versus intoxicated with alcohol) in the emergency department, maladaptive beliefs about MTBI, and contusions and diffuse axonal injury on magnetic resonance imaging uniquely contribute to prediction of poor outcome in adults. Recent evidence suggests that measures of white matter integrity from diffusion tensor imaging may complement conventional magnetic resonance imaging in MTBI outcome prediction.⁵²

Age effects through adulthood were equivocal, perhaps because the effect is nonlinear and older adults were excluded from most studies. Few and mixed results for age effects were observed within pediatric samples. In the sport-related concussion literature, adolescents appear to be at higher risk for protracted recovery than younger children²⁷ and college-aged adults.¹¹ At present, evidence suggests that adolescents and older adults may be vulnerable to poor outcome.

Findings related to two serum protein biomarkers (S-100B and neuron-specific enolase) were equivocal. Other candidate prognostic factors were repeatedly shown to have poor unique prognostic value in eligible studies. Consistent with previous reviews,²¹ clinical indicators of MTBI severity (e.g., LOC or amnesia) did not predict outcome, especially at longer follow-ups. Mechanism of injury was not prognostic. Previous MTBI, typically assessed by self-report and coded dichotomously, did not predict outcome, but modifying factors might include the number and recency of previous MTBI(s).⁵³ This finding also appears to differ from the sport setting,¹¹ where athletes may have more frequent and more recent previous injuries.

These findings contribute over and above recent systematic reviews of MTBI cohort studies by highlighting the independent prognostic value of pre-, peri-, and early post-injury factors in the context of multivariable models. Our findings were also based on largely different studies, likely because of differences in eligibility criteria and the timing of the search—only 6 of the 26 eligible studies were included in any other contemporary systematic review of MTBI cohort studies.^{7,9,10,27} Of note, a recent and relevant study using the large-scale Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) database²² was published after completing the above literature search and synthesis. One of the prognostic models identified in our review⁵⁴ performed poorly in this external sample. The TRACK-TBI team explored additional possible predictors. Consistent with the present review, age and psychiatric history were the strongest independent predictors of functional outcome at 3 and 6 months post-MTBI. The full multivariable prognostic model achieved modest discrimination (area under the curve = 0.68 to 0.69).

In summary, several biopsychosocial prognostic factors other than MTBI severity appear uniquely related to outcome, highlighting opportunities for early intervention. For example, early cognitive-behavioral therapy could modify psychological risk factors.⁵⁵ Known prognostic factors can be included as covariates in clinical trials and incorporated into future prognostic studies, perhaps supplemented by advanced assessment methods (e.g., genetic polymorphisms and magnetic resonance spectroscopy) to improve model discrimination.

Limitations

The patients in our eligible studies are likely not representative of the MTBI population. All patients presented to an emergency department, which is not the first point of care for many persons with MTBI.² Diverse recruitment methods and eligibility criteria

(e.g., triaged to CT) yielded samples with variable injury severity, but likely biased toward the more severe end of the MTBI spectrum. For example, while it is widely thought that fewer than 10% of MTBIs involve an LOC,⁵⁶ about half of participants in our eligible studies had LOC (Table 1). The prognostic factors identified in the present study may differ in sport and military settings.

By limiting our search to English language articles, we may have missed relevant studies published in other languages. Other recent systematic reviews of MTBI cohort studies, however, found no eligible studies in other languages.^{7,9,10,27} We accepted diverse clinical end points, which may have masked important differences. For example, extracranial injury tended to predict functional but not symptomatic outcome, while sex was more consistently related to symptomatic than functional outcome.

Most prognostic factors and outcomes were measured similarly across pediatric and adult studies, enabling a lifespan approach to literature synthesis. Certain differences in instrumentation (e.g., parent vs. self-reported post-concussion symptoms) and relevance (e.g., alcohol intoxication as a prognostic factor and return to work as a functional outcome), however, limited the number of conclusions that apply to both groups. The effect size or strength of prognostic factors could be compared with others within studies but not across studies because of differences in variable measurement, coding, and analytic methods.

Conclusions

At present, there is no existing multivariable prognostic model that can adequately predict individual patient outcomes from MTBI. Recovery from MTBI depends on a diverse range of biopsychosocial factors. Female sex, pre-injury mental health problems, early post-injury cognitive impairment, and acute psychological distress are associated with the worst prognosis. In children, pre-injury vulnerability strongly influences outcome. Traditional clinical measures of MTBI severity and even the presence of MTBI (vs. nonhead injury) were relatively unimportant. Genetics, extracranial injury, serum biomarkers, subacute magnetic resonance imaging, and novel psychosocial variables (e.g., “boom and bust” pattern of activity resumption) may further account for the heterogeneity in MTBI outcomes, but there is as yet insufficient evidence for these factors.

It will be essential for future prognostic studies to consider a broad range of biopsychosocial predictors in large inception cohorts, use model selection methods that can maximize reproducibility,⁵⁰ and externally cross-validate a user-friendly version of the model so that it can be used in clinical practice. International collaboration using common data elements may be necessary. Prognostic models developed and cross-validated in the IMPACT moderate-to-severe TBI database⁵⁷ can serve as a blueprint for progress in MTBI prognostic research. Outcome measures more refined than the Glasgow Outcome Scale-Extended and more objective than post-concussion symptom checklists could further enhance MTBI prognostics.

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APPENDIX 1. OVID ONLINE SEARCH STRATEGY

1. exp Brain Edema/
2. exp Cerebrovascular Trauma/
3. exp Craniocerebral Trauma/
4. exp Coma/
5. exp Glasgow Coma Scale/
6. exp Glasgow Outcome Scale/
7. Rancho Los Amigos Scale.ti,ab.
8. ((brain* or capitis or cerebr* or crani* or hemispher* or inter-crani* or intra-crani* or skull* or head) adj4 (contusion* or damag* or fractur* or injur* or trauma* or wound*)) .ab,ti.
9. ((brain or crani* or cerebr* or head or inter-cran* or intra-cran*) adj4 (bleed* or haematoma* or haemorrhag* or hematoma* or hemorrhag* or pressure)) .ti,ab.
10. (Glasgow adj1 (coma or outcome) adj1 (scale* or score*)) .ab,ti.
11. diffuse axonal injur*.ti,ab.
12. ((brain or cerebral or intracranial) adj3 (edema or oedema or swell*)) .ab,ti.
13. ((coma* or concuss* or unconscious*) adj2 (damag* or fractur* or injur* or trauma* or wound*)) .ti,ab.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. (mild* or minor).ti,ab.
16. (mtbi or mhi).ti,ab.
17. (concuss* adj4 (symptoms or syndrome*)) .ti,ab.
18. (postconcuss* or post-concuss*) .ti,ab.
19. ((posttraum* or post-traum*) adj4 (symptom* or complaint*)) .ti,ab.
20. 15 or 16 or 17 or 18 or 19
21. 14 and 20
22. exp cohort studies/
23. exp case-control studies/
24. exp prognosis/
25. exp prevalence/
26. exp risk/
27. exp morbidity/
28. exp survival analysis/
29. exp survival analysis/
30. prognos*.ti,ab.
31. predict*.ti,ab.
32. (population-based adj3 (study or cohort or sample)) .ti,ab.
33. cohort*.ti,ab.
34. longitudinal*.ti,ab.
35. ((unselected or consecutive* or prospective*) adj3 (sample* or series or patients or participants)) .ti,ab.
36. natural history.ti,ab.
37. follow-up*.ti,ab.
38. exp “Outcome Assessment (Health Care)”/
39. (intervention* adj3 stud*) .ti,ab.
40. randomized controlled trial.pt.
41. Randomized controlled trial/
42. Randomized Controlled Trials as Topic/
43. clinical trial.pt.
44. Double-Blind Method/
45. double blind*.ti,ab.
46. Placebos/
47. placebo*.ti,ab.
48. randomi*.ti,ab.
49. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48
50. 21 and 49
51. limit 50 to (english language and yr= “1970 -Current”)
52. animals/ not (humans/ and animals/)
53. 51 not 52