

CLINICAL PREDICTORS OF MORTALITY AND FUNCTIONAL OUTCOMES FOLLOWING MODERATE-TO-SEVERE TRAUMATIC BRAIN INJURY: A SYSTEMATIC REVIEW AND META-ANALYSIS

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DOI: <https://doi.org/10.5281/zenodo.23058125>

Received	Accepted	Published
01 January 2026	17 March 2026	31 March 2026

ABSTRACT

Background

Early reliable prognosis following moderate to severe traumatic brain injury (TBI) can guide clinical decision-making and family counselling. This systematic review and meta-analysis aimed to review predictors of mortality and functional outcomes and assess existing prognostic models.

Objective

To identify predictors of mortality and functional outcomes and to determine the discriminatory ability of existing prognostic models in moderate-to-severe TBI patients.

Methods

PubMed and Europe PMC were searched from inception to 10 September 2026 along with the ClinicalTrials.gov registry for original prognostic studies of patients with moderate-to-severe TBI. Restricted maximum-likelihood random-effects models with modified Hartung–Knapp–Sidik–Jonkman confidence intervals were used to synthesize adjusted predictor estimates and model-discrimination measures separately. Risk of bias was assessed using QUIPS or PROBAST, as appropriate.

Results

Twenty-three studies were included, 10 of which were unique studies and led to seven quantitative syntheses. Higher age was associated with increased mortality (OR per year 1.046, 95% CI 1.034–1.059; $I^2=32\%$) and higher admission Glasgow Coma Scale scores predicted lower mortality (OR per point 0.811, 95% CI 0.786–0.838; $I^2=0\%$). There was no clear association between GCS and

unfavorable functional outcome (OR 0.881, 95% CI 0.678–1.144) or decreasing platelet count with mortality (OR 1.105, 95% CI 0.795–1.538). Any abnormal pupillary findings resulted in a very rough estimate. The pooled discrimination was 0.805 for IMPACT and 0.822 for CRASH. Overall, six studies had low, 13 moderate, and four high risk of bias.

Conclusions

Age and admission GCS were common predictors of mortality. The general discrimination of IMPACT and CRASH was good with some uncertainty. The prognosis should be based on clinical, neurological, radiological, and laboratory data.

Keywords:

Glasgow Coma Scale; mortality; prognostic factors; prognostic models; traumatic brain injury; systematic review

INTRODUCTION

Traumatic brain injury (TBI) is a leading cause of death and long-term neurologic disability, especially for those with moderate-to-severe injury. The clinical trajectories are highly variable, with some patients regaining a good level of independence, while others die early, develop a persistent disorders of consciousness, or become highly dependent with post-traumatic epilepsy [26]. This variability makes it difficult to make early decisions about intensive care, neurosurgical intervention, planning for rehabilitation, and communicating with families. The ability to make accurate prognostication is therefore important, but predictions made during the acute phase are still subject to uncertainty due to sedation, extracranial injuries, physiological instability and differences in treatment settings.

Neurological examination continues to be the key to early prognosis. The Glasgow Outcome Scale-Extended (GOSE) is a standardized assessment of impaired consciousness and remains a common method of injury classification and clinical monitoring [34]. Functional outcome is generally measured by the Glasgow Outcome Scale (GOS) and the extended Glasgow Outcome Scale (eGOS), which categorize outcome as death, severe disability, moderate disability, and good recovery [11,38]. Abnormal pupillary responses and older age have been consistently linked to mortality and poor functional outcomes as have lower admission GCS scores [13,15,35]. Their predictive value might vary, however, depending on the time of assessment, prehospital care, sedation, definition of outcome, and length of follow-up.

Multivariable prognostic models were developed to improve prognostic accuracy beyond that provided by individual clinical indicators. The International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) models incorporate demographic, neurological, radiological, and laboratory data, and the Corticosteroid Randomization After Significant Head Injury (CRASH) models predict mortality and functional outcome based on routinely collected admission data [23,33]. Model performance has been generally found to be acceptable in external validation studies, but there are differences in model performance across countries, healthcare systems, and patient subgroups [19,21,30]. Complex monitoring has not been consistently demonstrated to have added value, but may be beneficial in specific intensive-care populations when physiological cerebral parameters are added [2]. Likewise, frailty, comorbidity and perioperative risk classifications can offer prognostic information which is not fully captured by traditional models of TBI [10,13].

There has been an increasing number of studies that have investigated laboratory and physiological predictors. Several laboratory and physiological parameters have been associated with poor outcomes, including: thrombocytopenia, platelet-related indices, hyponatremia, lactate, inflammatory biomarkers, and nutritional status [16–18,20,32,36,37]. The systemic immune-inflammation index, neutrophil-to-lymphocyte ratio, glucose-to-lymphocyte ratio and C-reactive protein-to-albumin ratio are other readily available biomarkers that have been studied recently

[1,5,8,37]. Other radiological parameters such as intracranial haemorrhage, computed tomography severity and vascular abnormalities may be useful in providing further prognostic information [4,31]. However, the different thresholds, timing of measurement, adjustment variables and definitions of outcomes make it difficult to make direct comparisons between studies.

Machine-learning methods have also broadened the scope of prognostic studies by modelling the complex relationships between many clinical parameters that are nonlinear. There are some internally developed models that report high discriminatory performance, but they may be optimistic due to small samples and data-driven predictor selection and lack of external validation [6,29,40]. Participant-selection bias, missing data, inconsistent measurement of predictors, and inadequate control of confounding factors are also potential sources of bias in prognosis studies. Structured assessment of these associations and/or model performance estimates, using tools like QUIPS and PROBAST, is therefore important when assessing the clinical trustworthiness of reported associations or model performance estimates [9,39].

While numerous prognostic factors have been studied, there is still some confusion about which factors are consistently associated with the model across studies and the reliability of the models in other clinical settings. Evidence has been previously gathered and presented as a mix of different severities of injuries, definitions of outcome, and/or follow-up periods, or has been based on individual biomarkers and prediction tools. A synthesis that would disentangle mortality from functional outcomes and that would differentiate predictor associations from model discrimination is thus required.

The aim of this systematic review and meta-analysis was to assess the clinical, neurological, radiological and laboratory predictors of mortality and unfavorable functional outcomes in patients with moderate-to-severe TBI. The review also evaluated the discriminatory performance of the IMPACT and CRASH models and examined heterogeneity, risk of bias and certainty of the available evidence.

Methods

Review design and reporting

This systematic review and meta-analysis was performed and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement [25]. The review assessed predictors of mortality and poor functional outcomes, and the discriminatory ability of existing prognostic models in patients with moderate to severe TBI. There was no prospective registration of the review protocol.

Information sources and search strategy

The databases PubMed, Europe PMC and ClinicalTrials.gov were searched from the database inception to 10th September, 2026. The search was conducted using controlled vocabulary and free text terms related to “traumatic brain injury,” “moderate traumatic brain injury,” “severe traumatic brain injury,” “mortality,” “functional outcome,” “prognosis,” “Glasgow Coma Scale,” “pupillary response,” “biomarkers,” “IMPACT” and “CRASH.” Eligible studies and relevant publications were also reviewed in reference lists for further original studies. The detailed search strategies for each database are included in Supplementary Table S1. The searches found 15,281 records, and after removing 1,588 duplicate records, 13,693 records remained.

Eligibility criteria

Studies were included if they involved patients with moderate-to-severe or severe TBI, or if a clearly defined majority of the study population had moderate-to-severe or severe TBI; if the study was conducted in a tertiary hospital, teaching hospital, intensive-care unit, or trauma center; and if the study compared an admission or early clinical, neurological, radiological, physiological, or laboratory predictor with mortality or functional outcome. Studies that developed a prognostic model and performed external validation with discrimination measures were also included.

Cohort studies (prospective and retrospective), registry studies, and studies using prognostic models were included. Studies that included predominantly mild TBI, lacked a relevant prognostic association or model-performance measure, lacked quantitative information, were secondary publications of an included study, or were reviews, editorials, case reports, or conference abstracts without usable information were excluded.

Study selection and data extraction

After deduplication, titles and abstracts were reviewed for eligibility. Full texts of potentially eligible reports were subsequently assessed. Multiple reports from the same cohort were connected and the most complete report was used for the relevant analysis. The reasons for exclusion at the full-text stage were noted.

The data extracted consisted of the author, year of publication, country, study design, number of patients, severity of TBI, definition of the predictor, definition of the outcome, follow-up period, adjusted effect estimate, confidence interval, and adjustment variables and prognostic-model performance. Unadjusted estimates were not used, but were replaced by adjusted estimates. Mortality and unfavourable functional outcome were analysed independently. Functional outcomes were based on the Glasgow Outcome Scale or Glasgow Outcome Scale-Extended [11,38]. Screening and data extraction were performed independently by two reviewers, and disagreements were resolved through discussion or consultation with a third reviewer.

Risk-of-bias assessment

Prognostic-factor studies were evaluated with the Quality in Prognosis Studies tool, which included the following criteria: participation, attrition, predictor measurement, outcome measurement, confounding, and statistical analysis [9]. The development and validation studies of prognostic models were evaluated based on the PROBAST criteria [39], focusing on participants, predictors, outcomes, and analysis. QUIPS assessments were categorized as low, moderate or high risk of bias.

PROBAST domain and overall judgements were categorized as low, high or unclear risk of bias in accordance with the original tool. The small sample size, lack of adequate handling of missing data, data-driven predictor selection, lack of adequate confounder adjustment, and lack of external validation were identified as important sources of concern.

Data synthesis and statistical analysis

Only when the predictors, outcomes, effect measures, and exposure increments were reported in at least two studies that were compatible was quantitative synthesis performed. The odds ratios were analyzed on the logarithmic scale, and the standard errors were calculated from reported confidence intervals. The estimates were then converted back to their original scale.

The effects of age, admission GCS and platelets were standardized to a 1-year increase, a 1-point increase in admission GCS and a $10 \times 10^9/L$ decrease in platelets, respectively. Pupillary abnormalities were only combined when studies reported adjusted associations with unfavorable functional outcome. Predictor associations were not analyzed with discrimination estimates for IMPACT and CRASH. The areas under the curves were transformed to the logit scale, pooled, and then back-transformed for presentation.

Random-effects models were employed because there was expected to be clinical and methodological heterogeneity. The variance between studies was estimated by restricted maximum likelihood and modified Hartung-Knapp-Sidik-Jonkman confidence intervals were computed, which take into account uncertainty in meta-analysis with small numbers of studies. I^2 was used to measure the statistical heterogeneity. Two-study synthesis results were considered exploratory, especially if the confidence intervals were large or the definitions of the predictors varied.

Age and mortality, admission GCS and mortality, admission GCS and unfavorable functional outcome, platelet decrease and mortality, abnormal pupillary findings and unfavorable functional outcome, IMPACT discrimination and

CRASH discrimination were analyzed separately. Studies that used incompatible coding, outcomes, or follow-up periods or effect measures were summarized narratively.

Formal funnel-plot asymmetry tests were not performed due to the low number of studies in each of the syntheses (less than 10 studies). All statistical analyses were conducted in R (R Foundation for Statistical Computing, Vienna, Austria) using the metafor package. Forest plots were generated in R, and statistical significance was evaluated using two-sided tests with $P < 0.05$, while interpretation prioritized effect estimates and 95% confidence intervals. Study design, risk of bias, inconsistency, indirectness, and imprecision were taken into account when

assessing certainty. The larger mortality syntheses provided low-certainty evidence, and estimates from only two heterogeneous studies were of very low certainty.

Results

Study selection and characteristics

Prior to deduplication, the supplied search set had 15,281 records, and 13,693 unique records. Full-text eligibility screening resulted in 23 original studies of patients with moderate to severe TBI, severe TBI, or in which the majority of patients had severe TBI. Between 2022 and 2025, 15 studies (65.2%) were published. The 23 studies were included in the qualitative synthesis, and 10 unique studies provided at least one compatible estimate for seven quantitative syntheses.

PRISMA 2020 Flow Diagram

Clinical predictors of mortality and functional outcomes in moderate-to-severe traumatic brain injury

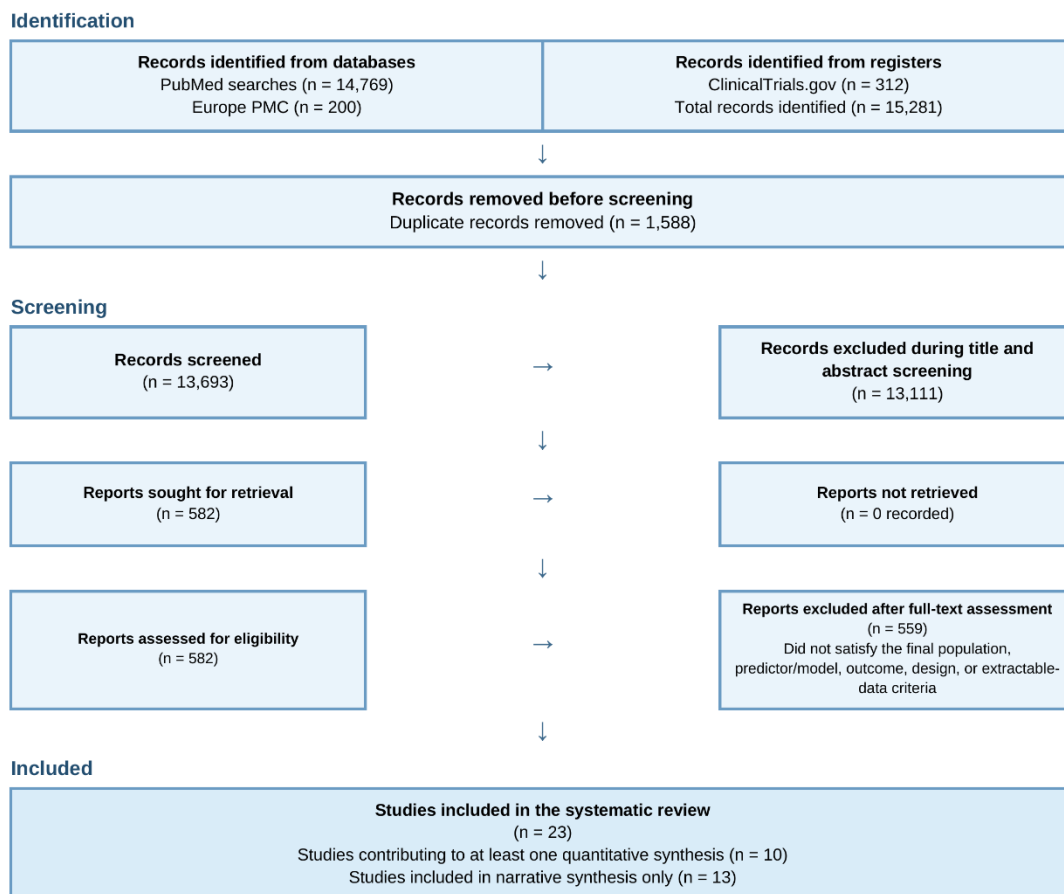


Figure 1. PRISMA 2020 flow diagram showing study identification, screening, eligibility assessment and inclusion.

The evidence included prospective and retrospective cohort studies, registry studies, development of prognostic models and external validation in tertiary hospitals, teaching hospitals, intensive care units, and trauma centers. Adults, children, surgical patients and patients with major

extracranial injury were included in the populations. Clinical diversity was addressed by conducting analyses separately for each outcome and by not pooling when the coding of the predictor, the effect measure, follow-up or population was incompatible.

Table 1 Characteristics of included studies

Study	Year	N	Population	Outcome	Design
Rostami et al.	2022	635	Adult severe TBI	Mortality; 6-12-month GOSE	Model validation
Wang et al.	2022	192	ICU TBI; 72.9% severe	Discharge GOS	Retrospective cohort
Maeda et al.	2019	635	Severe TBI	Hospital mortality; 6-month GOS	Registry validation
Rau et al.	2018	2059	Isolated moderate/severe TBI	Hospital mortality	Registry/ML
Bennis et al.	2020	45	Severe TBI	6-month outcome	Physiological cohort
Tohme et al.	2014	589	Adult severe TBI	14-day mortality	Prospective multicentre
Ogunlade et al.	2018	50	Surgical severe TBI	30-day GOS	Surgical cohort
Majdan et al.	2014	778	GCS 3-12	6-month mortality/GOS	External validation
Maggiore et al.	2009	130	Ventilated severe TBI	ICU mortality	ICU cohort
Leitgeb et al.	2013	538	Severe-TBI ICU survivors	1-year GOS	European multicentre
Chen et al.	2023	1266	Severe TBI	6-month GOS	Multicentre cohort
Li et al.	2022	170	Moderate/severe TBI	30-day mortality	Retrospective cohort
Lillemoe et al.	2022	4419	ICU-treated TBI	Hospital/12-month mortality	Multicentre registry
Jung et al.	2025	160	Severe TBI plus abdominal injury	Hospital mortality/GOS	Level-I cohort
Kiwanka et al.	2025	720	Adult moderate/severe TBI	90-day mortality; 1-year GOS	Single-centre cohort
Chen et al.	2024	358	Severe TBI undergoing CTA	Functional prognosis	Retrospective cohort

Study	Year	N	Population	Outcome	Design
Fatahi an et al.	2025	424	Paediatric moderate/severe TBI	Discharge GOS	Retrospective cohort
Shank ar et al.	2025	195	Adult severe TBI	Hospital mortality	Prospective cohort
Kokeg uchi et al.	2025	42375	Isolated severe TBI	Hospital mortality	Nationwide validation
Pineir o et al.	2024	134	Severe TBI plus extracranial trauma	Mortality	Trauma cohort
Aghad oost et al.	2025	195	Admission GCS ≤8	6-month outcome	Retrospective cohort
Marta et al.	2025	301	Adult severe TBI	28-day mortality	Multicentre/ML
Sharm a et al.	2024	1,125	Severe TBI	Mortality/poor outcome	Retrospective cohort

Quantitative synthesis of mortality predictors

Four studies provided compatible adjusted odds ratios for age and mortality. After converting the ACT-TBI estimate from a 10-year to a 1-year increment, each additional year of age was

associated with higher mortality (pooled adjusted OR 1.046, 95% CI 1.034-1.059; $I^2=32.0\%$). This corresponds to an approximate 4.6% increase in the adjusted odds of death per year.

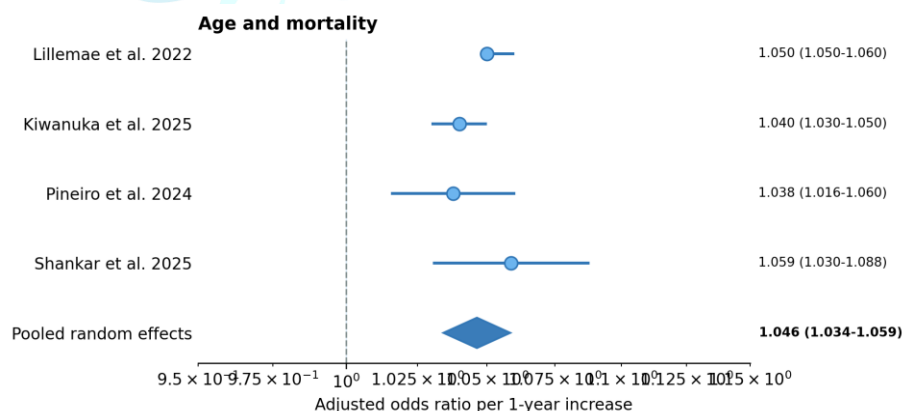


Figure 2. Forest plot of the association between increasing age and mortality.

Five studies reported comparable adjusted odds ratios for admission GCS and mortality. Each 1-point increase in GCS was associated with lower mortality (pooled adjusted OR 0.811, 95% CI

0.786-0.838; $I^2=0\%$). This corresponds to an approximate 18.9% reduction in the adjusted odds of death per additional GCS point.

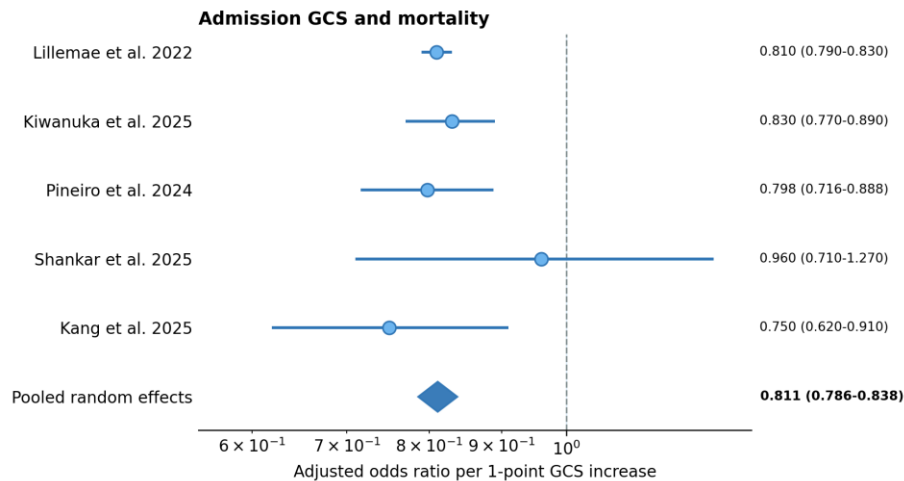


Figure 3. Forest plot of the association between admission Glasgow Coma Scale score and mortality.
Values below 1 indicate lower odds of mortality with increasing GCS.

Quantitative synthesis of functional outcome predictors

Two studies supplied compatible adjusted estimates for admission GCS and unfavorable functional outcome. The direction favored better

outcome with higher GCS, but the modified Hartung-Knapp interval included no association (pooled adjusted OR 0.881 per point, 95% CI 0.678-1.144; $I^2=0\%$). Because only two studies contributed, this result is exploratory.

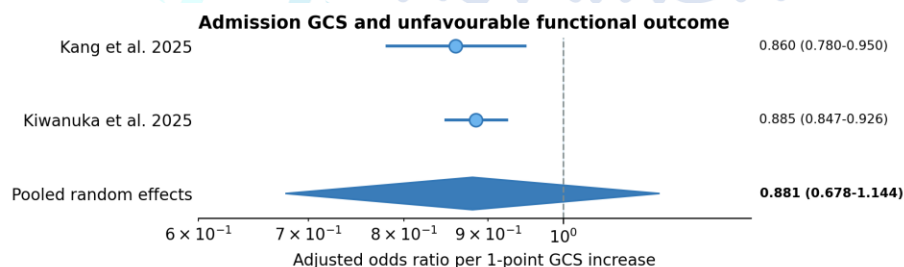


Figure 4. Forest plot of the association between admission Glasgow Coma Scale score and unfavorable functional outcome.

Two severe-TBI studies reported compatible continuous adjusted effects of platelet count on mortality. When harmonized to a decrease of $10 \times 10^9/L$, the pooled point estimate suggested higher mortality, but the conservative interval included no association (pooled adjusted OR 1.105, 95% CI 0.795-1.538; $I^2=0\%$). This result remained exploratory because of small-k

uncertainty and rounding of one source interval. Lillemae et al. also reported an association between early thrombocytopenia with mortality in moderate-to-severe TBI, but its subgroup estimate was not combined because a directly compatible continuous subgroup effect was unavailable in the supplied report.

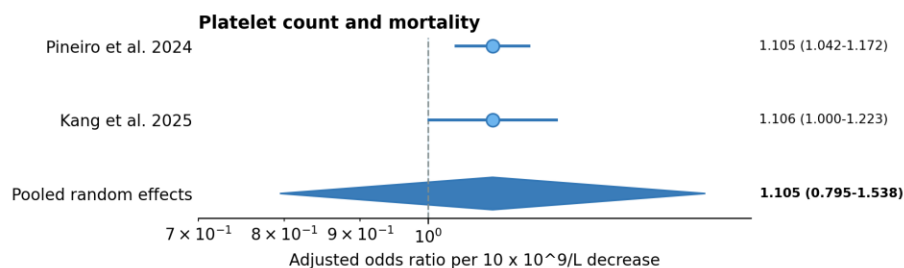


Figure 5. Forest plot of the association between decreasing platelet count and mortality. This two-study synthesis should be considered exploratory.

Quantitative synthesis of pupillary findings

Two studies reported adjusted odds ratios for abnormal pupillary findings and unfavorable functional outcome. The pooled point estimate suggested increased odds of an unfavorable outcome, but definitions differed (unequal pupils versus abnormal pupillary light reflex) and heterogeneity was substantial (pooled adjusted OR

3.219, 95% CI 0.005-2297.803; $I^2=91.4\%$). The extremely imprecise modified Hartung-Knapp interval reflects the combination of only two heterogeneous studies; this result is exploratory and should not be interpreted as evidence of a precise effect size. The pooled estimate should therefore be interpreted as inconclusive.

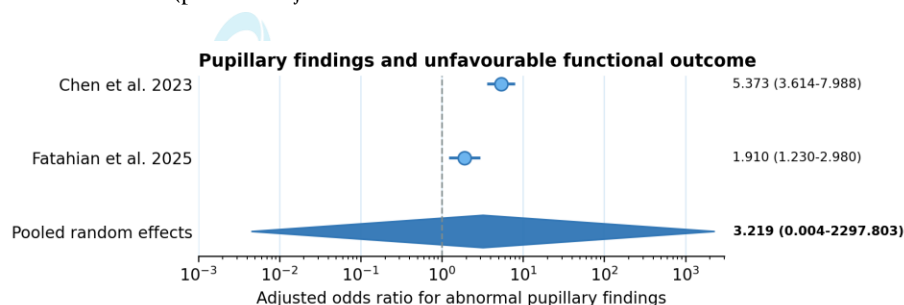


Figure 6. Forest plot of the association between abnormal pupillary findings and unfavorable functional outcome.

Quantitative synthesis of prognostic-model discrimination

Two external validation studies supplied compatible AUCs and confidence intervals for the IMPACT core model and 6-month unfavorable functional outcome. Random-effects pooling on the logit-AUC scale produced a pooled AUC of 0.805 (95% CI 0.559-0.931; $I^2=0\%$). Three studies

contributed CRASH-model discrimination estimates for 6-month unfavorable outcome, producing a pooled AUC of 0.822 (95% CI 0.677-0.911; $I^2=54.2\%$). These estimates indicate generally good discrimination, but the wide small-sample intervals and differences in validation settings require caution.

Table 4 Important adjusted predictors not suitable for pooling

Predictor	Outcome	Adjusted estimate	Study
Abnormal pupil reaction	14-day mortality	HR 2.47 (1.72-3.54)	Tohme 2014
Bilateral abnormal pupils	90-day mortality	OR 8.66 (5.49-13.77)	Kiwanuka 2025
Unequal pupils	Unfavorable GOS	OR 5.37 (3.61-7.99)	Chen 2023

Predictor	Outcome	Adjusted estimate	Study
Hypotension	90-day mortality	OR 3.57 (1.61-7.70)	Kiwanuka 2025
Rotterdam CT score	30-day mortality	HR 1.57 (1.23-2.00)	Li 2022
Platelet-to-lymphocyte ratio	30-day mortality	HR 1.52 (1.11-2.09)	Li 2022
High glucose-to-lymphocyte ratio	Discharge unfavorable GOS	OR 1.63 (1.18-2.78)	Fatahian 2025
High SII	Unfavorable GOS	OR 6.70 (3.82-11.75)	Chen 2023
Intracranial hemorrhage	Hospital mortality	OR 20.25 (7.08-71.80)	Shankar 2025
Head AIS 5	Unfavorable GOS	OR 3.52 (1.32-9.40)	Kang 2025
Massive transfusion	Unfavorable GOS	OR 2.92 (1.23-6.95)	Kang 2025

Performance of prognostic models

External validation studies showed acceptable-to-good discrimination. The range of the AUCs for the IMPACT core assessments was from 0.79 to 0.85 for mortality and 0.79 to 0.86 for functional-outcome assessments, and the range of the CRASH AUCs was from 0.76 to 0.86 for mortality and 0.76 to 0.86 for functional-outcome

assessments. Sometimes physiological monitoring and/or ASA score or laboratory variables were added, and this led to better discrimination, but these increments were tested in heterogeneous populations. Internal machine-learning AUCs were 0.95-0.97, but these are subject to greater optimism bias and should not be considered as externally validated performance.

Table 5 Selected prognostic model performance

Study	Outcome	Model	AUC (95% CI)	Validation
Rostami 2022	Mortality	IMPACT core	0.85	External
Rostami 2022	Unfavorable outcome	IMPACT core	0.79	External
Wang 2022	Discharge GOS	GCSP plus lactate	0.866 (0.827-0.904)	Internal
Maeda 2019	Unfavorable outcome	CRASH basic	0.86 (0.82-0.90)	External
Maeda 2019	Unfavorable outcome	IMPACT core	0.81 (0.77-0.85)	External
Rau 2018	Hospital mortality	Artificial neural network	0.968	Internal
Majdan 2014	6-month mortality	IMPACT extended	0.85 (0.81-0.89)	External
Majdan 2014	6-month unfavorable	CRASH basic	0.80 (0.75-0.84)	External
Bennis 2020	Unfavorable outcome	CRASH plus physiology	0.90 (0.80-1.00)	LOOCV
Li 2022	30-day mortality	PLR	0.711 (0.618-0.803)	Internal

Study	Outcome	Model	AUC (95% CI)	Validation
Kiwanuka 2025	1-year unfavorable	IMPACT CT plus ASA	0.805	Model evaluation
Fatahi an 2025	Discharge unfavorable	GLR	0.71	Internal
Kokeguchi 2025	Hospital mortality	rSIG	0.655 (0.644-0.666)	Temporal
Aghadoost 2025	6-month unfavorable	NLR	0.925	Internal
Marta 2025	28-day mortality	Random forest	0.95	Internal

Risk of bias and certainty of evidence

Six studies were rated as low overall risk of bias, 13 were rated as moderate risk of bias and four were rated as high risk of bias. Retrospective designs, incomplete reporting of missing data, data-driven predictor selection, and limited adjustment for confounding, small event counts, and limited external validation were common concerns. Machine-learning models developed internally

were the most likely to be optimistic. The associations between age and GCS and mortality were not strongly supported by the certainty of the evidence, and the associations between the two studies functional-outcome and platelet syntheses were not strongly supported by the certainty of the evidence, due to the presence of clinical heterogeneity and all evidence being observational.

Table 6 Overall risk-of-bias assessment

Judgement	Studies	Principal concerns
Low	Rostami 2022; Maeda 2019; Tohme 2014; Majdan 2014; Shankar 2025; Kokeguchi 2025	External validation or clearly specified multivariable methods
Moderate	Bennis 2020; Maggiore 2009; Sanchez 2013; Chen 2023; Li 2022; Lillemoe 2022; Kang 2025; Kiwanuka 2025; Chen 2024; Fatahian 2025; Pineiro 2024; Aghadoost 2025; Sharma 2024	Selection, missing-data, measurement, confounding or validation concerns
High	Wang 2022; Rau 2018; Ogunlade 2018; Marta 2025	Small sample or internally developed model with substantial optimism/overfitting concerns

Table 7 Domain-level QUIPS and PROBAST risk-of-bias judgements

Study	Tool	Participation	Attrition	Predictor	Outcome	Confounding	Analysis	Overall
Rostami 2022	PROBAST	L	L	L	L	L	L	Low
Wang 2022	PROBAST	M	M	M	L	M	H	High

Study	Tool	Participa tion	Attriti on	Predict or	Outco me	Confoun ding	Analys is	Overall
Maeda 2019	PROB AST	L	L	L	L	L	L	Low
Rau 2018	PROB AST	M	M	M	L	M	H	High
Bennis 2020	PROB AST	M	M	L	L	M	H	Moderate
Tohme 2014	QUIPS	L	L	L	L	L	L	Low
Ogunlade 2018	QUIPS	M	M	M	L	H	H	High
Majdan 2014	PROB AST	L	L	L	L	L	L	Low
Maggiore 2009	QUIPS	M	M	M	L	M	M	Moderate
Sanchez 2013	QUIPS	M	M	L	L	M	M	Moderate
Chen 2023	QUIPS	M	M	M	L	M	M	Moderate
Li 2022	QUIPS	M	M	M	L	M	M	Moderate
Lillemae 2022	QUIPS	L	M	L	L	M	M	Moderate
Kang 2025	QUIPS	M	L	L	L	M	M	Moderate
Kiwanuka 2025	QUIPS	M	M	L	L	M	M	Moderate
Chen 2024	QUIPS	M	M	M	M	H	M	Moderate
Fatahian 2025	QUIPS	M	M	M	L	M	M	Moderate
Shankar 2025	QUIPS	L	L	L	L	M	M	Low
Kokeguchi 2025	PROB AST	L	L	L	L	L	L	Low
Pineiro 2024	QUIPS	M	L	L	L	M	M	Moderate
Aghadoost 2025	QUIPS	M	M	M	L	M	M	Moderate
Marta 2025	PROB AST	M	M	M	L	H	H	High
Sharma 2024	QUIPS	M	M	M	L	M	M	Moderate

L indicates low risk, M moderate or unclear risk, and H high risk. For PROBABST studies, the harmonized columns represent participants, predictors, outcome and analysis; attrition and

confounding columns record corresponding applicability or missing-data concerns where relevant.

Sensitivity and reporting considerations

Modified Hartung-Knapp-Sidik-Jonkman intervals were used for all random-effects syntheses. The AUCs were analyzed on the logit scale and then back transformed for presentation. The two-study GCS-functional-outcome, platelet, pupillary and IMPACT analyses were considered exploratory. Funnel plots and asymmetry tests were not created as there were fewer than 10 studies in each synthesis, which would make the tests underpowered and potentially misleading.

Mortality follow-up was in-hospital to 12 months, and clinical heterogeneity is still present even with low I^2 . One 2025 multicenter study reported 307 participants in the abstract but presented outcome data for 301 participants; it was therefore excluded from the pooled predictor analyses.

Overall interpretation

Older age and lower admission GCS were independently associated with mortality in the expanded moderate to severe TBI evidence base. The platelet-mortality and pupillary-outcome pools were directionally plausible, but inconclusive following small-sample correction, and the GCS-functional-outcome pool was inconclusive. The generally good discrimination of unfavorable functional outcome of IMPACT and CRASH was not narrowed by pooling. In individual cohorts, the presence of pupillary abnormalities, hypotension, CT severity, and coagulopathy and inflammatory biomarkers were prognostically important. The results are in favor of early multidimensional prognostic assessment instead of using a single biomarker or an internally developed model.

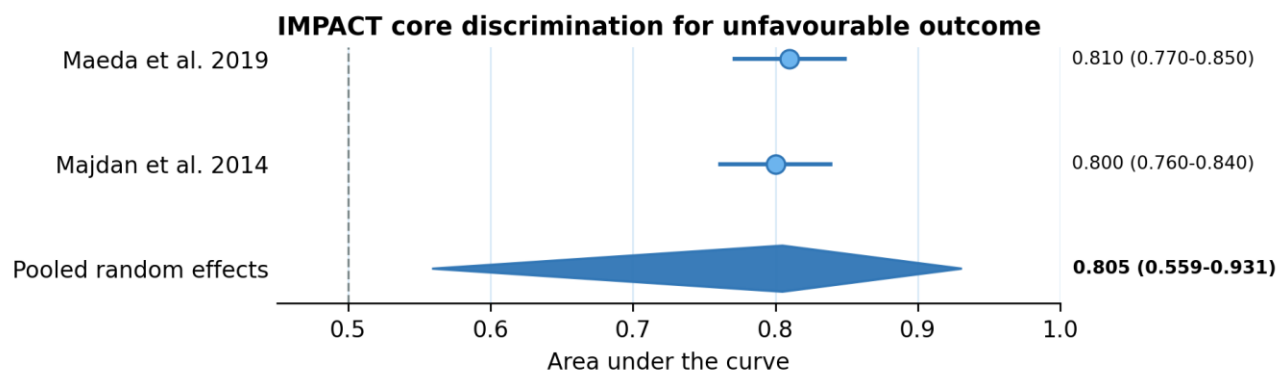


Figure 7. Forest plot of IMPACT core-model discrimination for 6-month unfavorable functional outcome.

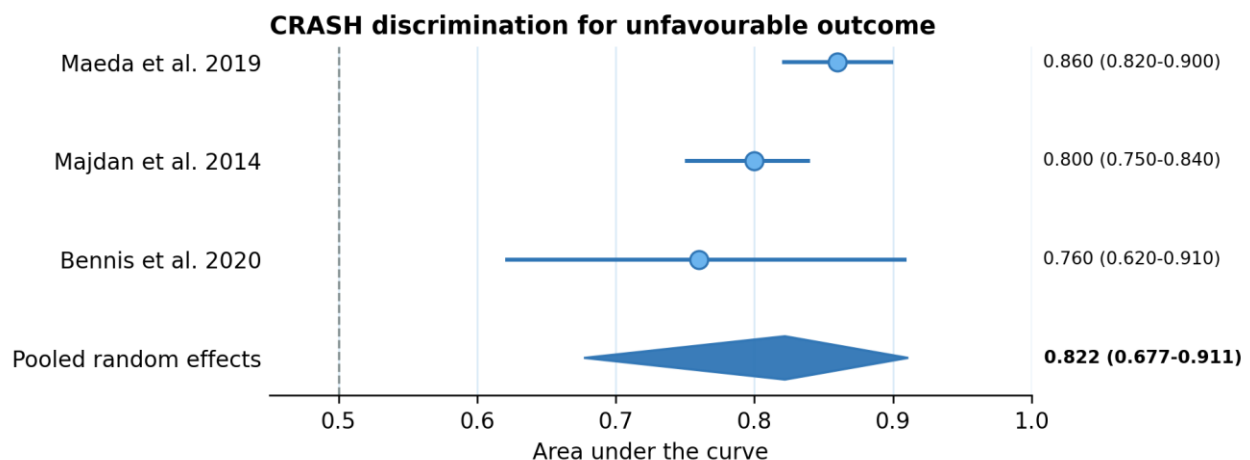


Figure 8. Forest plot of CRASH-model discrimination for 6-month unfavourable functional outcome.

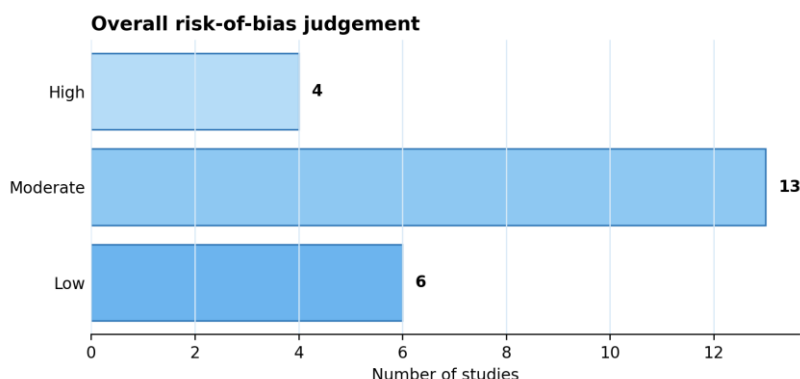


Figure 9. Distribution of overall study-level risk-of-bias judgements.

Table 2. Corrected random-effects meta-analysis results

Outcome	Predictor or model	k	Pooled estimate	95% CI	I ²	Status
Mortality	Age per 1-year increase	4	OR 1.046	1.034-1.059	32.0%	Conclusive
Mortality	GCS per 1-point increase	5	OR 0.811	0.786-0.838	0%	Conclusive
Unfavorable function	GCS per 1-point increase	2	OR 0.881	0.678-1.144	0%	Exploratory
Mortality	Platelets per 10 x 10 ⁹ /L decrease	2	OR 1.105	0.795-1.538	0%	Exploratory
Unfavorable function	Abnormal pupillary findings	2	OR 3.219	0.005-2297.803	91.4%	Exploratory
Unfavorable function	IMPACT core discrimination	2	AUC 0.805	0.559-0.931	0%	Exploratory
Unfavorable function	CRASH discrimination	3	AUC 0.822	0.677-0.911	54.2%	Exploratory

Table 3 Complete study-level inputs underlying the meta-analyses

Study	Predictor	N/events	Mortality	Beta	SE	OR	95% CI	Adjustment set	Source
Lillema 2022	Age per year	4419/NR	12 months	NR	Derived from CI	1.05	1.05-1.06	Age, sex, GCS, comorbidity, admission, SAPS II, year, platelets	eTable 4
Kiwana 2025	Age per year	720/137	90 days	NR	Derived from CI	1.04	1.03-1.05	Age, GCS, pupils, hypoxia, hypotension, CT findings, ASA	Multivariable model
Pineiro	Age	134/51	1 year	0.037	0.011	1.037	1.016-1.060	Age, GCS, platelets	Table 5, p.8

Study	Predictor	N/events	Mortality	Beta	SE	OR	95% CI	Adjustment set	Source
2024									
Shankar 2025	Age per 10 y	195/55	Hospital	NR	Derived from CI	1.77	1.37–2.36	Age, sex, GCS, eGFR, ISS, CT, ICH, GSW	Table 3, p.5
Lillema 2022	GCS point per	4419/NR	12 months	NR	Derived from CI	0.81	0.79-0.83	Age, sex, GCS, comorbidity, admission, SAPS II, year, platelets	eTable 4
Kiwana 2025	GCS point per	720/137	90 days	NR	Derived from CI	0.83	0.77-0.89	Age, GCS, pupils, hypoxia, hypotension, CT findings, ASA	Multivariable model
Pinheiro 2024	GCS point per	134/51	1 year	−0.226	0.055	0.797	0.716–0.889	Age, GCS, platelets	Table 5, p.8
Shankar 2025	GCS point per	195/55	Hospital	NR	Derived from CI	0.96	0.71–1.27	Age, sex, GCS, eGFR, ISS, CT, ICH, GSW	Table 3, p.5
Kang 2025	GCS point per	160/33	Hospital	NR	Derived from CI	0.75	0.62–0.91	MAP, base deficit, GCS, aPTT, platelets, fibrinogen	Table 4, p.8
Kang 2025	GCS point per	160/NR	Unfavorable GOS	NR	Derived from CI	0.86	0.78-0.95	Age, head AIS, GCS, transfusion and injury variables	Functional model
Kiwana 2025	GCS point per	720/NR	1-year unfavorable GOS	NR	Derived from CI	0.885	0.847-0.926	Age, GCS, pupils, hypoxia, hypotension, CT findings, ASA	Favourable estimate inverted
Pinheiro 2024	Platelets per unit	134/51	1 year	−0.010	0.003	0.990	0.984–0.996	Age, GCS, platelets	Table 5, p.8

Study	Predictor	N/events	Mortality	Beta	SE	OR	95% CI	Adjustment set	Source
Kang 2025	Platelets per unit	160/33	Hospital	NR	Derived from rounded CI	0.99	0.98-1.00	MAP, base deficit, GCS, aPTT, platelets, fibrinogen	Table 4, p.8
Chen 2023	Unequal pupils	1266/NR	6-month unfavorable GOS	NR	Derived from CI	5.373	3.614-7.988	Multivariable clinical and laboratory model	Article regression table
Fathahian 2025	Abnormal pupil reflex	424/NR	Discharge unfavorable GOS	NR	Derived from CI	1.91	1.23-2.98	GCS, Rotterdam CT score, pupil reflex, GLR	Article regression table
Maeda 2019	IMPACT core AUC	511/NR	6-month unfavorable GOS	NR	Logit-AUC SE from CI	0.81	0.77-0.85	External validation	Article model table
Majdan 2014	IMPACT core AUC	778/NR	6-month unfavorable GOS	NR	Logit-AUC SE from CI	0.80	0.76-0.84	External validation	Article model table
Maeda 2019	CRASH basic AUC	511/NR	6-month unfavorable GOS	NR	Logit-AUC SE from CI	0.86	0.82-0.90	External validation	Article model table
Majdan 2014	CRASH basic AUC	778/NR	6-month unfavorable GOS	NR	Logit-AUC SE from CI	0.80	0.75-0.84	External validation	Article model table
Benis 2020	CRASH AUC	45/NR	6-month unfavorable GOS	NR	Logit-AUC SE from CI	0.76	0.62-0.91	Leave-one-out validation	Article model table

Predictors reported in individual studies

Several predictors had strong adjusted associations but were not pooled due to incompatible definitions, effect measures, or time points of the outcomes. Abnormal pupils, both bilaterally and

unequal, were always linked to poor outcomes. Other individual cohorts showed prognostic value for hypotension, abnormal coagulation indices, inflammatory markers, intracranial hemorrhage and higher CT severity.

Discussion

Principal findings

Twenty-three studies were included in this systematic review, with seven quantitative syntheses provided by 10 of these studies. The most consistent independent predictors of mortality were older age and lower admission Glasgow Coma Scale (GCS) scores. The adjusted odds of death were approximately 4.6% greater for every additional year of age, and approximately 18.9% less for every 1-point increase in admission GCS. The associations between GCS and unfavorable functional outcome and decreasing platelet count and death were inconclusive when using small-sample conservative confidence intervals. Abnormal pupil findings yielded a directionally plausible, but highly imprecise estimate that was highly heterogeneous. The pooled confidence intervals for the IMPACT and CRASH models were generally wide but the models had good discrimination.

Interpretation of the findings

The correlation of age with mortality is similar to that observed in other studies that have demonstrated that physiological reserve, frailty, comorbidities and treatment tolerance are factors that affect recovery following severe TBI [7,10,13,28]. The age is included in both the IMPACT and CRASH models as it has a prognostic value which remains after adjustment for neurological and radiological severity [23,33]. However, chronological age should not be used as a stand-alone indicator. Its relationship with outcome could be modified by functional status prior to injury, systemic complications, and/or treatment intensity, especially for older or medically complex patients [7,10].

In the current analysis, the most consistent neurological predictor was admission GCS. The scale is still important in the classification and early assessment of impaired consciousness [34] and lower scores have been correlated with mortality and functional dependence [15,22,35] many times. The pooled mortality association was not influenced by the differences in setting and

length of follow-up, suggesting clinical relevance of early GCS assessment. Sedation, intubation, intoxication, seizures and extracranial injuries may, however, affect GCS. Thus, the use of models that incorporate GCS with pupil response, lactate or physiological measures might give more prognostic information than GCS alone [2,14,22,36].

However, the combined association of GCS with unfavourable functional outcome was not statistically significant following small sample adjustment. This should not be taken as an indication that GCS is not a useful functional test. Two studies provided compatible adjusted estimates and functional recovery is influenced by rehabilitation, complications, social support, and time of assessment. There are two standardized outcome categories: the Glasgow Outcome Scale and Glasgow Outcome Scale-Extended [11,38] but there can be comparability issues due to differences in dichotomization and follow-up. Post-traumatic epilepsy can also have a negative impact on long-term independence following survival from the acute injury [26].

For abnormal pupillary findings, the point estimate was higher for unfavourable outcome, but the confidence interval was very wide and there was a high degree of heterogeneity. Unequal pupils, bilateral non-reactivity and abnormal pupillary light reflexes can be various manifestations of brainstem dysfunction, intracranial mass effect or raised ICP. They have been shown to be useful in clinical cohorts and prediction models have been developed [13,22,23,33]. The radiological severity, intracranial hemorrhage and vascular injury are important complementary data [4,31]. The results of decompressive surgery or patients with major extracranial injuries may also differ from those of isolated TBI patients [12,24] and so a single pooled estimate may not be valid.

The platelet synthesis suggested that there was an association with increasing mortality at decreasing platelet count, but this was inconclusive. Thrombocytopenia in early stage has been linked to hospital and long-term mortality [18,27] and platelet inflammatory markers could also be a

reflection of the severity of systemic injury [16]. These relationships may be complicated by coagulation abnormalities, hemorrhage, transfusion, renal dysfunction and by extracranial trauma [7,12]. Therefore, platelets should be evaluated in the context of a comprehensive physiological and haematological evaluation, and not as a single cut-off for prognosis.

Biomarkers that are easily accessible at admission and inexpensive have been recently assessed. Neutrophil-to-lymphocyte ratio, systemic immune-inflammation index, glucose-to-lymphocyte ratio and C-reactive protein-to-albumin ratio have been found to be associated with mortality or poor functional outcome [1,5,8,37]. Patients with systemic physiological stress can also be identified by lactate, nutritional indices, hypernatremia and related metabolic abnormalities [17,20,32,36]. Due to the differences in sampling time, cut-off selection and adjustment models, however, quantitative pooling was not possible. These markers need to be validated externally prior to being used routinely for prognosis.

The discrimination estimates from the pooled IMPACT and CRASH were similar to good, but not perfect, prognostic performance. The two models have been developed and validated internationally [19,21,23,30,33]. They may not perform as well when used in populations other than those in which they were originally developed, where the injury mechanism, age, available treatment resources, and/or the frequency of outcomes differ. In some patients, physiological monitoring may help to predict better [2] and in others, the context of the patient's experience may be added by the clinician that is not captured by formal scores [3]. However, validated models should be used in conjunction with rather than in place of, subjective judgement. Machine-learning studies have been reported to have high areas under the curve such as clinical and imaging and physiological based models [6,29,40]. This type of performance can be over-optimistic if the models are built and tested on the same set of data. The present risk-of-bias assessment revealed some common issues: data-driven predictor selection, small event counts, and

incomplete reporting and inadequate external validation. The use of internally validated models should thus be avoided as a substitute for the use of the established prognostic models until they are prospectively tested in other populations.

Clinical implications

The results corroborate a multi-dimensional approach to prognosis. Age and admission GCS are helpful early parameters, but other parameters such as pupillary response, computed tomography findings, physiological instability, extracranial injury, coagulation status and relevant laboratory markers should also be taken into account in making decisions. Combined with GCS, the reverse shock index can help in early triage [14] and model-based estimates can help to increase consistency when used in conjunction with the clinical situation.

The prognosis estimates should not be used as stand-alone cut-off points for restricting treatment. Initial predictions may change due to resuscitation, surgery, complications and rehabilitation. Assessment should be repeated when there is sedation or systemic instability that affects neurological examination. Communication with families should recognize that there is uncertainty, and that the prediction of death does not mean that there is not a possibility of long-term functional recovery.

Strengths and limitations

One of the strengths of this review was the ability to separate out mortality, functional outcomes and model discrimination. Where possible, predictor increments were harmonized, and estimates adjusted to give priority to the adjusted estimates, and clinically incompatible results were not combined. Restricted maximum-likelihood random-effects models and modified Hartung-Knapp-Sidik-Jonkman confidence intervals were used to account for uncertainty in small meta-analyses. Appropriate tools for assessing risk of bias were used for prognostic-factor and prediction-model studies [9,39] and reporting was guided by PRISMA 2020 [25].

There are a number of constraints to be taken into account. The majority of studies included were observational and therefore were open to residual confounding. Mortality follow-up varied from hospitalisation to 12 months, and functional outcome varied in terms of time and type. Clinical heterogeneity was achieved by including the following populations: adult, paediatric, surgical, isolated-TBI and combined-injury. Four syntheses had only two studies, and had wide confidence intervals and low or very low certainty. Funnel plots were not used for formal assessment of funnel plot asymmetry as there were less than 10 studies in each synthesis. Some potentially important biomarkers were also not pooled due to differences in the definitions of the predictors and reporting scales and adjustment variables.

Implications for future research

Prospective, multicentre studies with a prespecified set of predictors and a standardized outcome assessment should be used in future prognostic studies. Mortality should be reported at well-defined time points and functional outcome should be measured preferably by structured GOS or GOSE interviews [11,38]. Clinically interpretable and consistent increments should be used to report continuous predictors, not data-derived cut-offs.

Prediction models need to be validated outside of the healthcare system, age groups and injury mechanism. AUC should not be the only measure reported in studies; calibration, discrimination and clinical usefulness should also be reported. Adequate sample size, handling missing data transparently, internal validation and independent external data sets should be used in machine-learning investigations [29,40]. Individual-participant-data meta-analysis could be useful to identify if there are interactions between age, GCS, pupil, laboratory markers and radiological findings, and if the effects of these factors vary between clinically relevant subgroups.

Conclusion

Age and admission GCS were independent predictors of mortality after moderate to severe

TBI. The discrimination of unfavorable functional outcome was generally good for IMPACT and CRASH, although there was some uncertainty due to the limited number of studies that were included in the pooled analyses. Evidence of platelet count, pupillary abnormalities and functional-outcome predictors was inconclusive or very imprecise. Prognostication should be based on validated clinical models and neurological examination, imaging, physiological status and laboratory results, and not on a single predictor.

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