An independently validated nomogram for individualised estimation of short-term mortality risk among patients with severe traumatic brain injury: a modelling analysis of the CENTER-TBI China Registry Study

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Summary

Background Severe traumatic brain injury (sTBI) is extremely disabling and associated with high mortality. Early detection of patients at risk of short-term (≤14 days after injury) death and provision of timely treatment is critical. This study aimed to establish and independently validate a nomogram to estimate individualised short-term mortality for sTBI based on large-scale data from China.

Methods The data were from the Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) China registry (between Dec 22, 2014, and Aug 1, 2017; registered at ClinicalTrials.gov, NCT02210221). This analysis included information of eligible patients with diagnosed sTBI from 52 centres (2631 cases). 1808 cases from 36 centres were enrolled in the training group (used to construct the nomogram) and 823 cases from 16 centres were enrolled in the validation group. Multivariate logistic regression was used to identify independent predictors of short-term mortality and establish the nomogram. The discrimination of the nomogram was evaluated using area under the receiver operating characteristic curves (AUC) and concordance indexes (C-index), the calibration was evaluated using calibration curves and Hosmer–Lemeshow tests (H-L tests). Decision curve analysis (DCA) was used to evaluate the net benefit of the model for patients.

Findings In the training group, multivariate logistic regression demonstrated that age (odds ratio [OR] 1.013, 95% confidence interval [CI] 1.003–1.022), Glasgow Coma Scale score (OR 33.997, 95% CI 14.657–78.856), Injury Severity Score (OR 1.020, 95% CI 1.009–1.032), abnormal pupil status (OR 1.738, 95% CI 1.178–2.565), midline shift (OR 2.266, 95% CI 1.378–3.727), and pre-hospital intubation (OR 2.059, 95% CI 1.472–2.879) were independent predictors for short-term death in patients with sTBI. A nomogram was built using the logistic regression prediction model. The AUC and C-index were 0.859 (95% CI 0.837–0.880). The calibration curve of the nomogram was close to the ideal reference line, and the H-L test p value was 0.504. DCA curve demonstrated significantly better net benefit with the model. Application of the nomogram in external validation group still showed good discrimination (AUC and C-index were 0.856, 95% CI 0.827–0.886), calibration, and clinical usefulness.

Interpretation A nomogram was developed for predicting the occurrence of short-term (≤14 days after injury) death in patients with sTBI. This can provide clinicians with an effective and accurate tool for the early prediction and timely management of sTBI, as well as support clinical decision-making around the withdrawal of life-sustaining therapy. This nomogram is based on Chinese large-scale data and is especially relevant to low- and middle-income countries.

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Research in context

Evidence before this study

We searched PubMed and Google Scholar without any language restrictions for articles published before April 1, 2023, using the search terms "(severe traumatic brain injury) AND (prediction model OR nomogram)". Most of the prediction models were established for patients with TBI and only five models were for patients with sTBI. These models were built based on relatively small sample sizes or on databases established about 20 years ago, which undoubtedly differs from today's TBI in terms of epidemiology and treatment levels and may lead to inaccurate predictions. In addition, pre-hospital intubation, a real and objective factor that can be recorded at the time of admission was not included in these models. Further, many existing prognostic models for TBI were developed based on data from high-income countries (HICs), which limits the applicability of the model in low- and middle-income countries (LMICs). Therefore, a more comprehensive risk model practical for LMICs for predicting the occurrence of short-term death in patients with sTBI is needed.

Added value of this study

In this study, we established a novel nomogram based on a large-scale data from China for predicting individualised short-term (≤14 days after injury) mortality in patients with sTBI. Our purpose was to provide a short-term mortality risk prediction model for patients with sTBI in the form of a visual and personalised nomogram, where all predictors are common tests for patients with sTBI and are easy to obtain clinically and convenient to use. The risk factors were as follows: older age, lower Glasgow Coma Scale score, higher Injury Severity Score, abnormal pupil status, brain midline shift, and pre-hospital intubation.

Implications of all the available evidence

The nomogram may provide clinicians with a simple and intuitive tool for the early detection and identification of patients at high risk of short-term death, which may be of significance in the clinical management, treatment, and consideration of withdrawal of life-sustaining therapy for sTBI in LMICs.

Introduction

With more than 50 million people suffering from traumatic brain injury (TBI) annually, TBI is a major global public health problem, causing a global economic loss of about $400 billion.[1] The incidence of TBI in China is higher than that of other countries, thus forming a serious challenge for the Chinese healthcare system.[2] There are different types of TBI, among which severe traumatic brain injury (sTBI) is particularly disabling and lethal, having a mortality rate of approximately 23.0%–38.8%,[2–4] which is of great concern to clinicians. Accurately predicting the prognosis of each patient with sTBI can facilitate early clinical decision-making and doctor-patient communication.[5]

In the era of precision medicine, prediction models are increasingly used and their value is becoming more essential in diagnostic and treatment decisions, prognosis management, and public health resource allocation.[6] Nomograms are widely used prediction models in medicine, especially in oncology.[7] Even in patients with COVID-19, a nomogram has been used to identify patients at risk of non-invasive respiratory strategies failure.[8] The nomogram integrates multiple factors into the quantitative model, including demographic and clinicopathological characteristics, to provide an individual probability of a specific outcome.[9] The model does not produce risk grades, but rather combines all proven prognostic factors and quantifies risk as precisely as possible, and previous studies have shown the improved predictive accuracy of nomograms compared to risk grades.[10]

In previous studies, several sTBI mortality risk models were developed,[5,11–16] which contributed to a better understanding of the risk of mortality associated with sTBI. However, these models mostly were built based on a limited number of samples or without independent external validation. Furthermore, even for prognostic models of patients with TBI, the vast majority of models were based on populations from high-income countries (HICs).[11,17,18] In addition, pre-hospital intubation plays an important role in the prognosis of sTBI,[19,20] however, data on pre-hospital intubation in these established models were lacking. Therefore, a more comprehensive prediction model practical for low- and middle-income countries (LMICs) based on a large sample size and including more essential factors is

needed. The purpose of this study is to develop and then independently validate a nomogram that would be readily accessible for clinical use for the assessment of individualised short-term mortality probability of patients with sTBI.

Methods

Study population

The study population was from the Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) China registry (registered at ClinicalTrials.gov, NCT02210221), a prospective, multicentre, longitudinal, observational study. The study was modelled on the European CENTER-TBI registry,[21] with an identical format for data collection and coding. The study was approved by the Ethics Committee of Renji Hospital, Shanghai Jiao Tong University School of Medicine (no: Renji Lunshen [2014] 166K) and local institutional review boards of each participating site, and informed consent was obtained from all patients according to local regulations. A total of 13,627 patients who were admitted to the hospital with a clinical diagnosis of TBI and an indication for computed tomography (CT) from 56 neurosurgical centres and 22 provinces from Dec 22, 2014, to Aug 1, 2017, were enrolled. Then, patients with Glasgow Coma Scale (GCS) scores of ≤8 and complete information were selected for inclusion in our study to establish the prediction model for short-term mortality in patients with sTBI. Eligible cases were divided into a training group (which was used to construct the nomogram) and a validation group, by allocation of centres (grouping methods are detailed in the Supplementary Methods). The data in the two groups are completely independent and do not overlap.

Data collection and definition

According to the CENTER-TBI China Registry study protocol, the following clinical information was collected: patients' demographics, pre-injury factors such as usage of anticoagulants and antiplatelet agents, injury information on arrival at the hospital including GCS score, Injury Severity Score (ISS), clinical symptoms, vital signs, and imaging findings, information regarding treatment with intracranial surgery, survival status at discharge, and discharge destination. In the case of in-hospital death, the time and cause of death were recorded. The length of hospital stay was recorded for survivors.

Short-term mortality was defined as survival time ≤14 days after injury.[3,22,23] An abnormal pupil status was defined as one or both pupils being dilated, or an absence of the pupillary light reflex. Pre-injury physical status was scored according to the first four-level ordinal scale of the American Society of Anaesthesiologists Physical Status (ASA-PS) classification system: ASA-PS I (healthy), ASA-PS II (mild systemic disease), ASA-PS III (severe systemic disease), and ASA-PS IV (severe systemic disease that is a constant threat to life). Prehospital intubation was defined as the patient receiving endotracheal intubation prior to arrival at the hospital. Both the GCS score and the ISS were scored according to the corresponding criteria.[24,25] GCS was analysed as a categorical variable in our study.

Statistical analysis

All eligible cases of CENTER-TBI China registry were included in this analysis, and no additional sample-size calculation was performed. To identify demographic characteristics, descriptive statistics were reported as frequencies and proportions for categorical variables, and medians and interquartile ranges (IQRs) for continuous variables. Normality was assessed using the Kolmogorov–Smirnov test, Shapiro–Wilk test, and QQ plots. Equality of variance was assessed using Levene's test. Differences between medians were assessed with the Mann–Whitney U test and proportions with the χ^2 test or Fisher's exact test, as appropriate. In the model development stage, univariate analysis was used to identify the differences between patients who survived and those who died, the Mann–Whitney U test and the χ^2 test were used for univariate analyses, as appropriate. Variables screened by univariate analyses were included in the multivariate logistic analysis to determine independent predictors of short-term mortality. The nomogram was then established based on multivariable logistic regression results. The discrimination of the nomogram was evaluated using area under the receiver operating characteristic curves (AUC) and concordance indexes (C-index), the sensitivity analysis was performed by receiver operating characteristic (ROC) curves. The calibration was evaluated using calibration curves and Hosmer–Lemeshow tests (H-L test). Both discrimination and calibration were evaluated using bootstrapping methods with 1000 resamples. Furthermore, decision curve analysis (DCA) was used to evaluate the net benefit of the model for patients. In the model validation stage, the nomogram was externally validated in a validation group consisting of independent data from 16 centres. Univariate analyses and multivariable logistic regression analyses were performed using IBM SPSS (version 27.0.1). R statistical software (version 4.0.5) was used to plot the nomogram, ROC curves, calibration curves, and DCA curves.

Role of the funding source

The funder of the study had no role in study design, data collection, data analyses, data interpretation, or writing of the report.

Results

General characteristics

The clinical information of a total of 2824 patients with sTBI was obtained from the database. There were 193

patients that were excluded due to incomplete records, of these 5 had missing survival data, 15 had missing pupillary light reflex information, 19 had missing CT information, and 154 had incomplete ISS. Incomplete cases accounted for only 6.8% of all patients with sTBI in the study. Differences between eligible cases and incomplete cases for most variables were not statistically significant (Table S1). There were 2631 patients from 52 centres and 22 provinces enrolled in this study. The 52 centres were divided into two groups using a centre-based method. Finally, there were 36 participating centres including 1808 patients that comprised the training group and the remaining 16 centres including 823 patients comprised the validation group (Fig. 1, Table 1, Table S2).

In the training group, the data of 1808 patients from 36 centres were used to establish the nomogram. The median age was 48 (IQR 34, 59) years, with 82.5% being male. There were 82.0% of the patients that were healthy with an ASA-PS I. There were 36.1% of the patients that had abnormal pupil status. As for the GCS score, 21.7% of the patients scored 8, 22.8% scored 7, 18.9% scored 6, and 12.6%, 9.6%, and 14.4% scored 5, 4, and 3, respectively. The median ISS was 25 (IQR 17, 33). Endotracheal intubation was performed in 37.3% of patients before admission. Regarding CT information, 34.0% of patients had a brain midline shift ≥5 mm, 39.8% had a midline shift <5 mm, 61.2% had a compressed basal cistern, 85.9% had traumatic subarachnoid haemorrhage (tSAH), and 95.6% of patients had intracranial lesions. Surgery was performed in 63.8% of patients. The cause of injury in 61.0% of patients was traffic accidents, and accidental falls were the cause in 29.3% of patients. In terms of the outcome, 80.4% of the patients survived and 19.6% died (Table 1). The leading cause of death was primary brain injury, accounting for 66.8% of deaths, followed by secondary brain injury, accounting for 26.8% (Table S3).

In the validation group, the data of 823 patients from 16 centres were used for independent external validation. The median age was 53 (IQR 41, 64) years, with 72.3% being male. Of these patients, 48.1% had abnormal pupil status. A GCS score of 8 was found in 18.7% of patients, 20.2% of the patients had a score of 7, 17.3% had a score of 6, and 14.5%, 13.2%, and 16.2% had scores of 5, 4, and 3, respectively. The median ISS was 25 (IQR 17, 30). In this group, 78.3% of the patients survived and 21.8% died (Table 1). Similar to the training group, the leading cause of death in validation group was primary brain injury, accounting for 69.8% of deaths, followed by secondary brain injury, accounting for 24.6% (Table S3).

The training group was younger (median age 48 vs 53, $p < 0.0001$) and had more male patients (82.5% vs 72.3%, $p < 0.0001$). The training group was also in better pre-injury health with 82.0% of patients having ASA-PS I (82.0% vs 71.9%, $p < 0.0001$). The training group had better GCS scores than the validation group, detailed information is shown in Table 1. The training group had a higher rate of pre-hospital intubation (37.3% vs 16.7%, $p < 0.0001$). In the training group, there were fewer patients with a midline shift ≥5 mm (34.0% vs 41.3%, $p = 0.00041$), more patients had tSAH (85.9% vs 80.7%, $p = 0.00025$), fewer had intracranial lesions (95.6% vs 97.6%, $p = 0.019$), and fewer received surgical treatment (63.8% vs 70.7%, $p = 0.0012$). The mortality rate was also

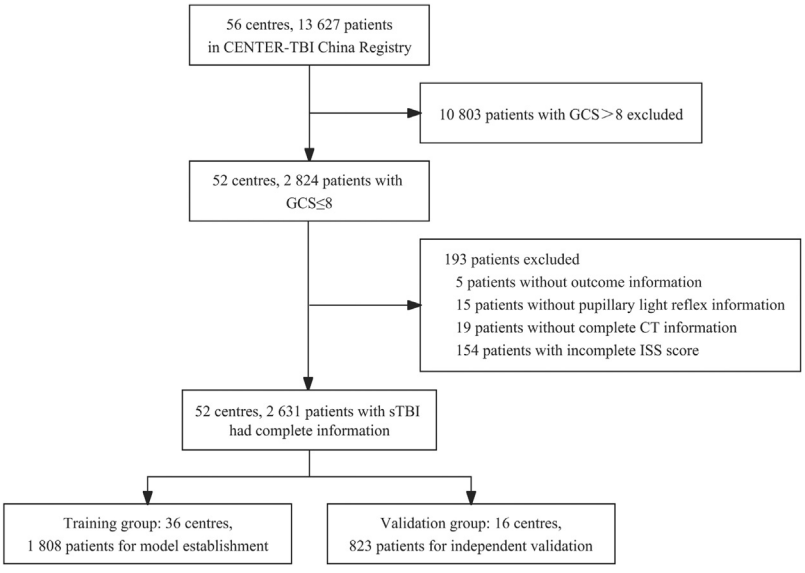

***Fig. 1:* Flow chart for patient selection.** CENTER-TBI = Collaborative European NeuroTrauma Effectiveness Research in TBI; GCS = Glasgow Coma Scale; ISS = Injury Severity Score.

Demographics	All eligible patients (n = 2631)		p value
	Training group (n = 1808)	Validation group (n = 823)	
Age (Median and IQR)	48 (34, 59)	53 (41, 64)	<0.0001
Sex			<0.0001
Female	316 (17.5%)	228 (27.7%)	
Male	1492 (82.5%)	595 (72.3%)	
Pre-injury ASA-PS classification			<0.0001
ASA-PS I	1482 (82.0%)	592 (71.9%)	
ASA-PS II	242 (13.4%)	176 (21.4%)	
ASA-PS III	61 (3.4%)	42 (5.1%)	
ASA-PS IV	23 (1.3%)	13 (1.6%)	
Anticoagulant therapy	416 (23.0%)	17 (2.1%)	<0.0001
Antiplatelet therapy	431 (23.8%)	24 (2.9%)	<0.0001
Abnormal pupil status	653 (36.1%)	396 (48.1%)	<0.0001
GCS			0.010
3	260 (14.4%)	133 (16.2%)	
4	173 (9.6%)	109 (13.2%)	
5	227 (12.6%)	119 (14.5%)	
6	342 (18.9%)	142 (17.3%)	
7	413 (22.8%)	166 (20.2%)	
8	393 (21.7%)	154 (18.7%)	
ISS (Median and IQR)	25 (17, 33)	25 (17, 30)	<0.0001
Systemic hypotension (<90 mmHg)	75 (4.2%)	27 (3.3%)	0.188
Pre-hospital intubation	675 (37.3%)	137 (16.7%)	<0.0001
Midline shift			0.00041
No shift	474 (26.2%)	213 (25.9%)	
Shift <5 mm	720 (39.8%)	270 (32.8%)	
Shift ≥5 mm	614 (34.0%)	340 (41.3%)	
Compressed basal cistern	1106 (61.2%)	523 (63.6%)	0.272
tSAH	1553 (85.9%)	664 (80.7%)	0.00025
Intracranial lesions	1729 (95.6%)	803 (97.6%)	0.019
Surgery	1153 (63.8%)	582 (70.7%)	0.0012
Injury cause			<0.0001
Traffic accident	1103 (61.0%)	437 (53.1%)	
Accidental fall	529 (29.3%)	238 (28.9%)	
Other	176 (9.7%)	148 (18.0%)	
Outcome			0.185
Survival	1453 (80.4%)	644 (78.3%)	
Death	355 (19.6%)	179 (21.8%)	

sTBI = severe Traumatic Brain Injury; IQR = Interquartile Range; ASA-PS = The American Society of Anaesthesiologists Physical Status Classification System; GCS = Glasgow Coma Scale; ISS = Injury Severity Score; tSAH = Traumatic Subarachnoid Haemorrhage.

Table 1: **Demographics of training group and validation group.**

slightly lower in the training group, but there was no statistically significant difference (19.6% vs 21.8%, $p = 0.185$).

Screening for predictive factors

We used univariate analysis to screen variables, and variables with statistically significant differences ($p < 0.05$) were included in the multivariate logistic regression analysis to further identify independent predictors. Multivariate analysis showed that age (OR 1.013; 95% CI 1.003–1.022; $p = 0.0086$), GCS of 3 (OR 33.997; 95% CI 14.657–78.856; $p < 0.0001$), GCS of 4 (OR 22.241; 95% CI 9.471–52.228; $p < 0.0001$), GCS of 5 (OR 9.060; 95% CI 3.892–21.093; $p < 0.0001$), GCS of 6 (OR 5.573; 95% CI 2.422–12.821; $p < 0.0001$), GCS of 7 (OR 4.421; 95% CI 1.894–10.322; $p = 0.00059$), ISS (OR 1.020; 95% CI 1.009–1.032; $p = 0.00067$), abnormal pupil status (OR 1.738; 95% CI 1.178–2.565; $p = 0.0053$), midline shift ≥5 mm (OR 2.266; 95% CI 1.378–3.727; $p = 0.0013$), midline shift <5 mm (OR 1.761; 95% CI 1.076–2.883; $p = 0.024$), and pre-hospital intubation (OR 2.059; 95% CI 1.472–2.879; $p < 0.0001$)

were independent risk factors for short-term death (Table 2).

Risk prediction nomogram establishment

To inform the individual prediction of short-term mortality of patients with sTBI, a prediction nomogram (R^2 = 0.405, C-index = 0.859) was established based on the multivariate logistic regression analysis results (Fig. 2, Table 2, Table S4). The variables that increased the probability of short-term mortality included older age, lower GCS score, higher ISS, abnormal pupil status, midline shift, and pre-hospital intubation. To use the nomogram, first, locate a specific point of an individual patient on each variable axis; second, draw a vertical line upwards from the variable axis, each variable corresponds to a specific point on the Points scale (top); third, add together all the points from each variable, and locate the result on the Total Points scale (bottom); forth, draw a vertical line downwards from the Total Points scale, corresponding to the predicted short-term mortality axis to determine the short-term mortality risk. To make this nomogram easier to use, a free online prediction tool is provided here: https://rj2021.shinyapps.io/Prediction_model/.

Predictive accuracy and net benefit of model

The AUC and C-index were 0.859 (95% CI 0.837–0.880, Fig. 3A) in the training group and 0.856 (95% CI 0.827–0.886, Fig. 3B) in the validation group. The H-L test *p* value of the model was 0.504, and there was good agreement between the predicted and observed probability in the calibration curves of both groups (Fig. 4A and B). The DCA curves showed significant net benefit of the predictive model in both the training (Fig. 5A) and validation groups (Fig. 5B).

Discussion

Using independent, recent, and non-overlapping data from 36 centres, the objective of this study was to develop a nomogram for predicting short-term (≤14 days after injury) mortality in patients with sTBI. The factors increasing short-term mortality included older age, lower GCS score, higher ISS, abnormal pupil status, midline shift, and pre-hospital intubation. This model was then independently externally validated using data from another 16 centres.

Age was a strong predictor of mortality, with older age being associated with higher mortality in patients with TBI.[26] The reason for this may be that older patients have a higher prevalence of chronic comorbidities, such as cardiovascular and cerebrovascular diseases, which could lead to more complications during the treatment phase, thus increasing the risk of death. In addition, the treatment plan is often more conservative in older patients than in younger patients.[27] Further, the prevalence of brain injury rises with the increase of the elderly population,[1,28] which thus increases the public health burden. Accurately predicting the risk of death in elderly patients has positive benefits for guiding clinical treatment.

The GCS score is the simplest and most reliable way to evaluate the severity and prognosis of patients with TBI. Various studies have shown that a lower GCS indicates poor prognosis,[29] and GCS has been found to be an indispensable predictor in various model studies,[11,18] which is consistent with the results from our analyses. Pupil status is also a common and objective independent factor for death in patients with sTBI.[30] Abnormal pupillary response or pupillary dilation, signs of oculomotor nerve compression or brainstem damage, often suggest the impending development of brain herniation, which increases the risk of death. Study results have shown that even when patients have the same GCS score, their mortality risk varies greatly depending on pupil size and response status.[30] Both GCS score and pupillary response are readily available information in the early stages after trauma, and the combined evaluation of these two variables can increase accuracy in assessing the prognosis of patients.

The rate of comorbidities involving injuries to other regions of the body in patients with TBI is approximately 23%–41%.[31] Severe extracranial trauma may cause blood loss, vascular embolism, coagulation disorders, and vital organ dysfunction, which further aggravates secondary injuries after brain injury. Extracranial injury is also an independent factor for death in patients with TBI.[31,32] The ISS is a commonly used method to assess the severity of trauma. Our results showed that a higher ISS score was suggestive of higher mortality in patients with sTBI, which was in accordance with the findings of previous studies.[31,32]

Computed tomography (CT) is essential to objectively assess structural brain damage after TBI.[33,34] In our study, brain midline shift was a strong predictor of short-term death. Midline shift, suggesting elevated intracranial pressure, is one of the signs of disease aggravation, and when the midline shift is ≥5 mm, it suggests that the patient needs immediate surgical treatment to prevent brain herniation.

As patients with sTBI have a high incidence of airway obstruction and hypoxia at the accident scene, appropriate pre-hospital airway management is essential to prevent secondary injuries.[35] However, several studies as well as our analysis found that pre-hospital intubation was associated with increased mortality in patients with sTBI.[19,36] In Espen Fevang et al.'s systematic review, they summarised 21 studies and found a median mortality rate of 48% (range 8–94%) for patients that underwent pre-hospital intubation, and 29% (range 6–67%) for patients intubated in the emergency department.[20] The possible mechanism for this finding is that patients undergoing pre-hospital endotracheal intubation often have severe and life-threatening injuries, and death is

Variables	Survival (n = 1453)	Death (n = 355)	p[a] Value	OR	Lower 0.95	Upper 0.95	p[b] Value
Age (Median and IQR)	47 (34, 58)	50 (37, 63)	0.00028	1.013	1.003	1.022	0.0086
Sex			0.121				
Female	244 (16.8%)	72 (20.3%)		–	–	–	–
Male	1209 (83.2%)	283 (79.7%)		–	–	–	–
Pre-injury ASA-PS classification			0.0023				
ASA-PS I	1202 (82.7%)	280 (78.9%)		1.000	–	–	–
ASA-PS II	196 (13.5%)	46 (13.0%)		1.001	0.620	1.616	0.996
ASA-PS III	42 (2.9%)	19 (5.4%)		2.693	1.265	5.735	0.010
ASA-PS IV	13 (0.9%)	10 (2.8%)		1.180	0.386	3.612	0.771
Anticoagulant therapy			<0.0001				
No	1090 (75.0%)	302 (85.1%)		1.000	–	–	–
Yes	363 (25.0%)	53 (14.9%)		1.921	0.752	4.911	0.173
Antiplatelet therapy			0.00010				
No	1078 (74.2%)	299 (84.2%)		1.000	–	–	–
Yes	375 (25.8%)	56 (15.8%)		0.644	0.270	1.538	0.322
Abnormal pupil status			<0.0001				
No	1035 (71.2%)	120 (33.8%)		1.000	–	–	–
Yes	418 (28.8%)	235 (66.2%)		1.738	1.178	2.565	0.0053
GCS			<0.0001				
3	105 (7.2%)	155 (43.7%)		33.997	14.657	78.856	<0.0001
4	96 (6.6%)	77 (21.7%)		22.241	9.471	52.228	<0.0001
5	182 (12.5%)	45 (12.7%)		9.060	3.892	21.093	<0.0001
6	302 (20.8%)	40 (11.3%)		5.573	2.422	12.821	<0.0001
7	382 (26.3%)	31 (8.7%)		4.421	1.894	10.322	0.00059
8	386 (26.6%)	7 (2.0%)		1.000	–	–	–
ISS	25 (17, 29)	29 (25, 38)	<0.0001	1.020	1.009	1.032	0.00067
Pre-hospital intubation			<0.0001				
No	979 (67.4%)	154 (43.4%)		1.000	–	–	–
Yes	474 (32.6%)	201 (56.6%)		2.059	1.472	2.879	<0.0001
Systemic hypotension (<90 mmHg)			<0.0001				
No	1412 (97.2%)	321 (90.4%)		1.000	–	–	–
Yes	41 (2.8%)	34 (9.6%)		1.386	0.725	2.648	0.323
Midline shift			<0.0001				
No shift	432 (29.7%)	42 (11.8%)		1.000	–	–	–
Shift <5 mm	617 (42.5%)	103 (29.0%)		1.761	1.076	2.883	0.024
Shift ≥5 mm	404 (27.8%)	210 (59.2%)		2.266	1.378	3.727	0.0013
Compressed basal cistern			<0.0001				
No	619 (42.6%)	83 (23.4%)		1.000	–	–	–
Yes	834 (57.4%)	272 (76.6%)		1.161	0.790	1.706	0.447
tSAH			0.0043				
No	219 (15.1%)	36 (10.1%)		1.000	–	–	–
Yes	1234 (84.9%)	319 (89.9%)		1.502	0.909	2.482	0.112
Intracranial lesions			0.157				
No	67 (4.6%)	12 (3.4%)		–	–	–	–
Yes	1386 (95.4%)	343 (96.6%)		–	–	–	–
Surgery			0.130				
No	512 (35.2%)	143 (40.3%)		–	–	–	–
Yes	941 (64.8%)	212 (59.7%)		–	–	–	–
Injury cause			0.250				
Traffic accident	868 (59.7%)	235 (66.2%)		–	–	–	–
Accidental fall	434 (29.9%)	95 (26.8%)		–	–	–	–
Other	151 (10.4%)	25 (7.0%)		–	–	–	–

IQR = Interquartile Range; ASA-PS = the American Society of Anaesthesiologists (ASA) Physical Status Classification System; GCS = Glasgow Coma Scale; ISS = Injury Severity Score; tSAH = Traumatic Subarachnoid Haemorrhage. [a]Test by Mann–Whitney U test or $\chi 2$ test. [b]Test by multivariate logistic regression analysis.

Table 2: **Univariate and multivariate analysis for training group.**

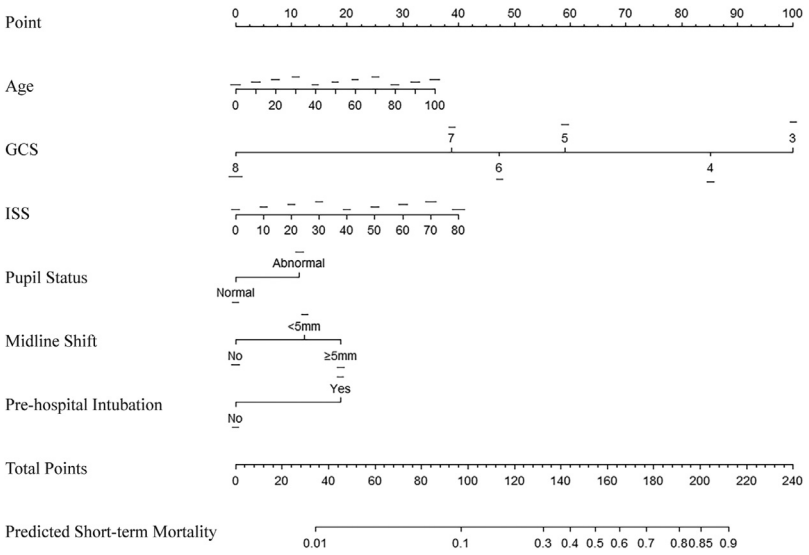

***Fig. 2:* Nomogram of short-term mortality for sTBI patients.** GCS = Glasgow Coma Scale; ISS = Injury Severity Score. To use the nomogram, (1) locate a specific point of an individual patient on each variable axis; (2) draw a vertical line upwards from the variable axis, each variable corresponding to a specific point on the points scale (top); (3) add all of the points from each variable together, and locate the result on the Total Points scale (bottom); (4) draw a vertical line downwards, corresponding to the predicted short-term mortality axis to determine the short-term mortality risk. To make this nomogram easier to use, a free online prediction tool is provided: https://rj2021.shinyapps.io/Prediction_model/.

often unavoidable in these patients, even with timely tracheal intubation.

For patients with sTBI, we hope to accurately predict the patient's mortality with some quick and easily accessible information when the patient arrives at the emergency department. Our nomogram provides clinicians with an accurate and effective tool for the early prediction and timely management of sTBI to improve the prognosis of patients. Some prognostic models have been published in the field of TBI, the CRASH and IMPACT models are well-known,[11,18] they were developed based on large populations and have been

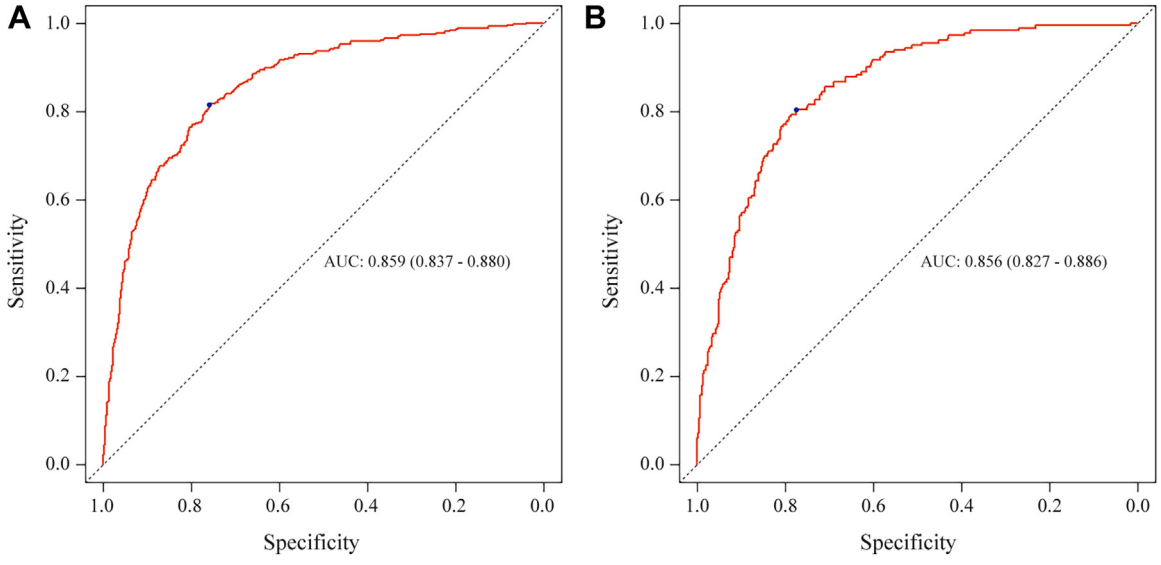

***Fig. 3:* ROC curves for the risk of short-term mortality.** (A) Training group. (B) Validation group. ROC = Receiver Operating Characteristic curve; AUC = Area Under the ROC Curve.

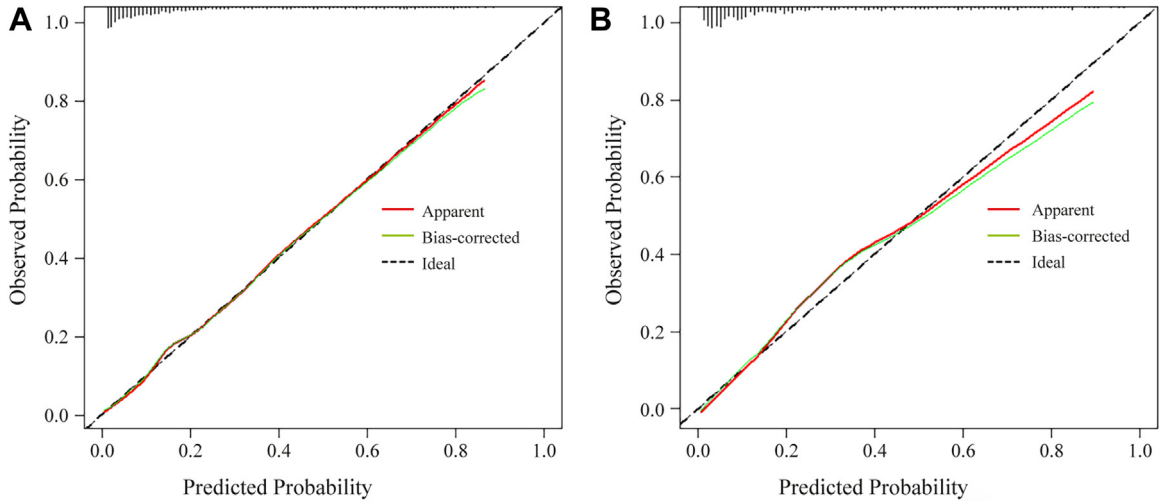

Fig. 4: **Calibration curves for short-term mortality prediction.** (A) Training group. (B) Validation group.

extensively externally validated, and both models have good performance in terms of discrimination and calibration. Given that the outcome of this study was 14-day mortality, we compared our model with the CRASH model. Our model performed comparably to the CRASH model, and even slightly better in low-income countries (C-index 0.859 vs 0.840). The CRASH model was not validated for 14-day mortality, due to a lack of validation data. However, since the establishment of the CRASH model, many external validations have been conducted by various research institutions around the world, and the reported external validity varies widely (C-index range 0.66–1.00).[17] In our previous study, we used the CRASH model to predict 14-day mortality in patients with TBI (GCS ≤14) from the CENTER-TBI China Registry database. The expected 14-day mortality was 1116 (13%), but 544 (7%) deaths within 14 days were observed (observed to expected ratio 0.49 [95% CI 0.45–0.53]),[37] suggesting that the CRASH model may be not applicable to China, or other LMICs. As for the CRASH/IMPACT models, they were developed based on databases established about 20 years ago, the epidemiology of TBI has changed, and approaches to pre-hospital care, diagnostic capabilities, and intensive-care monitoring and treatment are continually improving,[1,38] thus these two models may not be suitable for present healthcare and societal environments, leading to inaccurate predictions. In addition, the data used to establish these two models were sourced from clinical trials, which could limit their external validity. Consequently, the prognostic analysis of TBI should be seen as a continuous process that needs updating and validation in future research. Compared with the CRASH/IMPACT models, pre-hospital intubation, a real and objective factor that was recorded at the time of admission without being subject to the influence of hospital

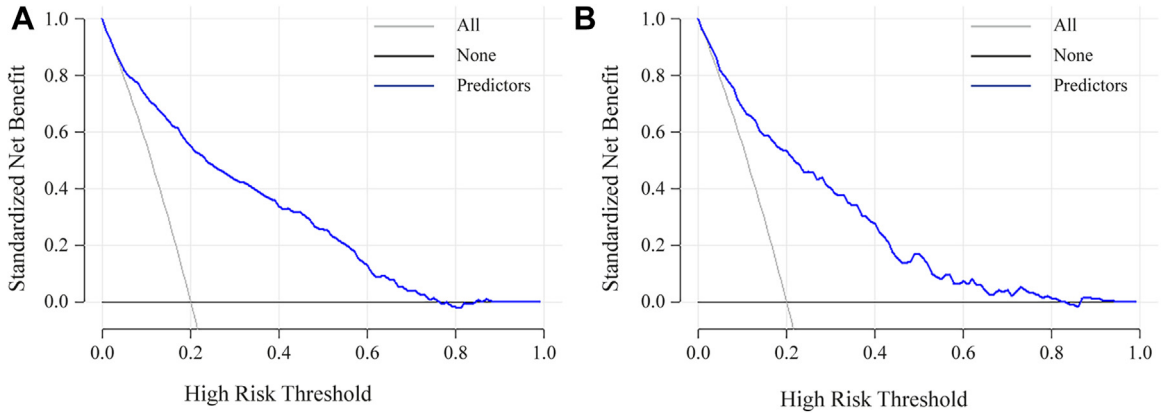

Fig. 5: **Decision curve analysis of short-term mortality prediction for sTBI.** (A) Training group. (B) Validation group.

doctors, was newly included in our model, which makes the prediction model more consistent with real clinical scenarios. Further, many existing prognostic models for TBI were developed based on data from HICs, however, it is very clear that the prevalence, causes of TBI, diagnoses, treatment, and prognosis vary largely between HICs and LMICs.[1,38,39] This is the first time, to our knowledge, that a model was developed based on a large multicentre observational cohort that is highly practical for LMICs.

The CENTER-TBI China Registry is currently the latest multicentre observational cohort in China, including patients from 56 centres and 22 provinces. The cohort does not set strict inclusion criteria, making these patients more representative of the general population and subsequent findings more relevant to clinical practice. According to TRIPOD Statement,[6] selecting patients randomly for validation across all participating centres will lead to lack of power during model development and validation, however centre-based selection is justified. Thus, when selecting the validation group, our selection was centre-based, and the data in the two groups are completely independent and do not overlap. The fact that there are differences between centres, which has also been objectively documented in our previous study,[37] explains the significant differences in demographics and injury characteristics between the two groups. From the perspective of developing a predictive model, these differences in the groups were actually beneficial to testing the external validity of the model. Additionally, to ensure the nomogram had external validity, the modelling stage should include data from as many provinces as possible. Thus, we adjusted the allocation of training and validation groups accordingly, as described in the Supplementary Method. Based on these principles, a short-term mortality prediction model for patients with sTBI was developed. All the predictors in our model are easily accessible for clinical use. After internal validation and independent external validation, we found that the model has good discrimination, calibration, and the decision curve analysis showed a significantly good net benefit for the predictive model.

Our model has some limitations. First, our model lacks predictors related to laboratory tests, whereas according to similar studies, some biological indicators, such as haemoglobin and glucose, are also independently associated with death.[18,40] However, it has also been shown that the addition of these factors does not have a significant effect on the enhancement of the model effect.[17,41] Second, our model focused on the short-term mortality of patients with sTBI, which is one of the most important and practical concerns in clinical practice. However, the long-term prognosis is also very important but was not assessed in this study.

In conclusion, we found that age, GCS score, ISS, abnormal pupil status, midline shift, and pre-hospital intubation were predictors of short-term (≤14 days after injury) death in patients with sTBI. A prediction nomogram for the early prediction of short-term death was developed, and external validation confirmed that the model was accurate. The personalised model may provide clinicians with a simple and intuitive tool for the early detection and identification of patients with sTBI at high risk of short-term death, which may be of help both in treatment management and in the consideration of withdrawal of life-sustaining therapy in LMICs.

Contributors

JF, GG, and JJ contributed to the study concept and design. LL, TW, and LX contributed to data acquisition and analysis. LL and TW drafted the manuscript and figures. JF, LL, and TW contributed to both data analysis and the manuscript's critical revision. CY and L.S–H contributed to the manuscript's critical revision. LL, TW, LX, and JF accessed and verified the underlying data. All authors reviewed and revised the manuscript and approved the final manuscript as submitted. JF was responsible for the decision to submit the manuscript.

Data sharing statement

Researchers who submit a methodologically sound study proposal that is approved by the author group can have access to the study protocol, individual participant data, data dictionary, analytic code, and analysis scripts. Proposals can be directed to corresponding author. A data access agreement is required, and all access must comply with regulatory restrictions imposed on the original study.

Declaration of interests

JF declare support from the Shanghai Academic Research Leader (21XD1422400) and Shanghai Medical and Health Development Foundation (20224Z0012). All other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.101975.

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