Incidence and mortality related risk factors in patients with severe traumatic brain injury: A meta-analysis

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Abstract. The present study aimed to clarify the onset of traumatic brain injury (TBI) and identify mortality-related risk factors in patients with severe TBI, to enable the early identification of high-risk individuals and timely implementation of prevention and treatment strategies to minimize mortality rates. Comprehensive database searches were conducted across Web of Science, PubMed, CINAHL and EMBASE, covering publications from database inception until October 17, 2023. Search terms in English included 'head trauma', 'brain trauma', 'mortality', 'death' and 'risk factor'. In total, two independent researchers screened and extracted the data on mortality onset and associated risk factors in patients with severe TBI. Meta-analysis was performed using R 4.2.2. A total of 33 cohort studies, including 71,718 patients with severe TBI, were selected for meta-analysis. The data indicated an overall mortality rate of 27.8% (95%CI: 22.5-33.2%) from database inception until October 17, 2023. Subgroup analysis revealed a mortality rate of 25.2% (95%CI: 20.2-30.1%) in developed countries, compared with 38.0% (95%CI: 21.4-54.7%) in developing countries. Additionally, the mean age of deceased patients was significantly higher compared with that of survivors (41.53±16.47). Key risk factors found to be associated with mortality included anemia [relative risk (RR), 1.42; 95%CI, 1.04-1.93], diabetes mellitus (RR, 1.40; 95%CI, 1.00-1.96), coagulopathy (RR, 4.31; 95%CI, 2.31-8.05), shock (RR, 3.41; 95%CI, 2.31-5.04) and systolic blood pressure≤90 mmHg (RR, 2.32; 95%CI, 1.65-3.27). Furthermore, pre-hospital intubation (RR, 1.48; 95%CI, 1.13-1.92),hypotension (RR, 2.04; 95%CI: 1.58, 2.63), hypoxemia (RR, 1.42; 95%CI: 1.13, 1.79), subdural hemorrhage (RR, 1.99; 95%CI: 1.50, 2.62), subarachnoid hemorrhage (RR, 1.64; 95%CI: 1.09, 2.47) and subdural hematoma (SDH; RR, 1.50; 95%CI: 1.04, 2.17). was identified to be a significant risk factor during hospitalization treatment. These results suggest that various factors, such as age, anemia, diabetes, shock, hypotension, hypoxemia, trauma scores and brain injury types, can all contribute to mortality risk in patients with severe TBI. Addressing these risk factors will likely be important for reducing mortality in this patient population.

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Introduction

Traumatic brain injury (TBI) is a critical medical condition that defined by structural damage and/or functional impairment of the brain due to excessive external force (1).The yearly incidence of TBI is estimated at 50 million cases worldwide; thus, ~50% of the global population will have an episode of TBI in their life (2). Severe TBI, typically indicated by a Glasgow Coma Scale score of 3-8, reflects a state where patients are typically unconscious or progressively losing awareness post-injury (3). The condition is associated with a high mortality rate, with ~30% of patients not surviving, while ~50% will experience moderate to severe disability within 1year, although a minority (10-20%) exhibit clear recovery (4). Due to its high risk of disability and mortality, severe TBI has been garnering attention. In data from 2014, the Centers for Disease Control and Prevention in the United States noted 2.53 million emergency

patients hospitalized due to brain injuries. 288,000 patients admitted to the hospital due to traumatic brain injury, and 56,800 patients succumbed to TBI (5). Between December 22, 2014 and August 1, 2017, 13,138 patients from 52 hospitals in 22 provinces of China were analyzed. Most patients were male [9,782 (74%)], with a median age of 48 years [interquartile range (IQR) 33-61]. Overall, 637 (5%) patients succumbed to TBI, including 552 (20%) with severe TBI. The expected 14-day mortality was 1,116 (13%), but 544 (7%) mortalities within 14 days were observed (observed to expected ratio 0·49) (6). Globally, in 2019, TBI had 27.16 million new cases, 48.99 million prevalent cases and 7.08 million years of life lived with disability. The global age-standardized incidence rate of TBI decreased significantly by -5.5% [95% confidence interval (CI) -8.9% to -3.0%] from 1990-2019. Regionally, in 2019, Eastern Europe and high-income North America had the highest burden of TBI. In 2019, Slovenia and Afghanistan had the highest age-standardized incidence rates of TBI. Falls were the leading cause of TBI in 74% (150/204) of countries/territories, followed by pedestrian road injuries (14%; 29/204), motor vehicle road injuries (5%; 11/204), and conflicts and terrorism (2%; 4/204) (6). In Canada ~160,000 individuals suffer from brain injuries each year, resulting in 11.000 deaths and over 6.000 permanent disabilities (7). Nearly half of the TBI cases in Canada are caused by falls and motor vehicle collisions, with an estimated direct and indirect cost of approximately $3 billion annually associated with TBI (8). Therefore, the incidence, disability and mortality rates of TBI are high in different countries and for different sexes and ages. Studying the risk factors that lead to increased incidence and mortality rates of TBI may help reduce the incidence and mortality rates of TBI.

With continuous advancements in diagnosis and treatment, patients with mild TBI are now more frequently discharged without significant long-term neurological effects (9). However, these improvements have not sufficiently impacted the persistently high mortality rates in patients with moderate to severe cranial-cerebral injuries. A previous study has indicated that 60% patients with TBI are vulnerable to emotional, cognitive, behavioral and physical impairments of varying severity (10). The mortality rate for severe TBI remains high, reaching 30-40% (11) and is frequently accompanied with multiple complications. Survivors frequently experience cognitive, motor, speech and psychological deficits, severely diminishing their quality of life (12). This deterioration imposes substantial economic costs and emotional strain on both families and society (10). Therefore, developing novel effective treatment strategies, improving prognostic accuracy and enhancing post-treatment quality of life for patients with severe TBI remain to be pressing challenges in the current clinical landscape. As a result, research into the prognostic factors for severe TBI is gaining increasing focus (9-12). Research shows that country, income level, pre hospital treatment, age, sex, anemia, diabetes, shock, hypotension, hypoxemia, trauma score, GCS, coagulation characteristics, and cerebral hemorrhage types are all incidence- and mobility-related risk factors in patients with severe TBI (13,14). However, these studies are relatively few and some of them are inconsistent, leading to ongoing controversies, such as coagulation characteristics, diffuse axonal injury (DAI), prehospital intubation, and cerebral hemorrhage types (15).Comprehensive meta-analyses and systematic reviews are beneficial tools for identifying mortality risk factors, enabling early recognition, heightened clinical vigilance and timely intervention. These measures are vital for reducing the severe TBI mortality rates.

Materials and methods

Review design. The present study followed the Preferred Reporting Items standards for both Systematic Reviews and Network Meta-Analyses guidelines (16) for conducting systematic reviews and meta-analyses, ensuring compliance with the standards (16). The present systematic review and meta-analysis were also conducted according to the Meta-analyses of Observational Studies in Epidemiology criteria for observational studies (17). The protocol was registered athttps://inplasy.com/, with a registration number ofINPLASY202440111.

Literature search. Relevant data were systematically retrieved from PubMed (https://pubmed.ncbi.nlm.nih.gov), Web of Science (https://webofscience.clarivate.cn), CINAHL (www.lib.cgu.edu.tw) and EMBASE (www.embase.com), encompassing studies from database inception until October 17, 2023. The search focused on English-language keywords, such as 'head trauma', 'brain trauma', 'mortality', 'death', and 'risk factor' (Table I). To minimize potential omissions, manual searches of references from selected studies and relevant reviews were conducted to identify additional literature. Only English-language studies were included.

Study selection and criteria for consideration of studies. Based on the PICOS framework (18) and established grading criteria for TBI (2,19), inclusion criteria were: i) Study subjects comprise patients with severe TBI (3≤GCS≤8); ii) cohort studies; iii) research content focuses on factors related to mortality in patients with severe TBI; iv) relevant data was extractable. Outcomes were drawn from studies reporting potential risk factors associated with incidence and mortality in severe TBI, including country, income level, pre-admission treatments, age, sex, anemia, diabetes, shock, hypotension, hypoxemia, trauma scores, GCS, coagulation profiles, cerebral hemorrhage types, locations and DAI. The study design focused on observational cohort studies with extractable data, excluding the following: i) Review articles, conference papers and case reports; ii) studies involving patients with mild (GCS ≥13) or moderate (8≤GCS≤12) TBI or mixed cohorts of moderate-to-severe TBI; iii) non-cohort studies; and iv) duplicate studies. In total, two independent reviewers, MWL and WMC, conducted thorough screening of titles and abstracts, retrieving full texts for studies that met the inclusion criteria. Discrepancies were resolved through discussions, with third-party arbitration by MYL when necessary.

Data collection, extraction, and outcomes of interest. Information was independently extracted by two researchers (BRZ and QJZ) from the selected studies, including the lead author, year of publication, country of origin, study design, sample size, subject age, criteria for severe TBI and reported mortality rates. Discrepancies in data extraction were resolved

Table I. Search strategy.

Database	Search strategy	Results
PubMed	(((Death (Title/Abstract)) OR mortality (Title/Abstract))) AND (((((((craniocerebral injuries (MeSH Terms)) OR brain injuries (MeSH Terms)) OR head injur* (Title/Abstract)) OR brain injur* (Title/Abstract)) OR head trauma (Title/Abstract)) OR brain trauma (Title/Abstract)) OR cerebral injur*) AND (risk factor (MeSH Terms)) Searches were limited to English language papers and human population.	2,171
Web of Science	(((((TS=('brain injur*')) OR TS=('head injur*')) OR TS=('brain trauma')) OR TS=('head trauma'))) AND (((TS=(death)) OR TS=(mortality))) AND (TS=('risk factor')) Searches were limited to English language. Refined by: * (excluding): review, conferenceabstractsand editorial material.	583
CINAHL	S1 TI mortality OR AB mortality OR TI death OR AB death S2 (MH 'Brain Injuries') S3 (MH 'Head Injuries') S4SU head injur* OR AB head injur* S5SU brain injur* OR AB brain injur* S6SU head trauma OR AB head trauma S7SU brain trauma OR AB brain trauma S8 S2 OR S3 ORS4 OR S5 OR S6 OR S7 S9 TX risk factor S9 S1 AND S8 AND S9	1,020
EMBASE	((((((('head injur*') OR ('brain injur*')) OR ('head trauma')) OR ('brain trauma')) OR ('cerebral injur*'))):ti,ab,kw AND ('risk factor') AND ((((mortality) OR (death))):ti,ab,kw)	2,614

through either consensus or consultation with a third party (MWL). The primary outcomes assessed were incidence and mortality-associated risk factors in patients with severe TBI, including age, anemia, diabetes, shock, hypotension, hypoxemia, trauma scores, GCS and coagulation disorders. Secondary outcomes focused on protective factors against mortality in these patients, such as diffuse axonal injury, EDH and the use of intracranial pressure monitors.

Quality assessment of literature. The quality of cohort studies was evaluated by YLZ and SJG using the Newcastle-Ottawa Scale (NOS), which assessed critical factors, such as population selection, group comparability and outcome assessment. According to previous descriptions (20), the NOS assigned scores ranging from 0 to 9, where a score of ≥7 would suggest high study quality, 4-6 stars suggesting moderate quality and <4 suggesting low quality.

Statistical methods. Statistical analyses were performed using R version 4.2.2 (https://www.r-project.org; R Foundation) to assess the incidence and mortality-related risk factors among patients with severe TBI (21). Dichotomous outcomes were evaluated using risk ratios (RR) (22), whilst continuous outcomes were presented as mean differences (MD). Meta-analyses were performed to synthesize outcome data and pooled odds ratios (ORs) with corresponding 95%CIs were calculated (23). Given that the present meta-analyses incorporate data from patients who underwent various surgical procedures from diverse geographic regions, all outcomes were analyzed using the DerSimonian-Laird (DL) random-effects model (24). According to the recommendations provided by the Cochrane Handbook for Systematic Reviews of Interventions (https://training.cochrane.org/handbook/current/chapter-10#section-10-10-4-1) (25), a random-effects model was utilized for all of our meta-analyses. Subgroup analyses were performed based on country and varying definitions of severe TBI.

Sensitivity analysis. Sensitivity analysis assessed the stability and reliability of research outcomes by systematically removing individual studies to identify potential sources of heterogeneity, followed by an examination of the underlying causes. In the present study, leave-one-out sensitivity analysis was performed to evaluate mortality rates (26), using random-effects model to assess risk factors associated mortality (27).

Publication bias. Publication bias, driven by the study's inherent characteristics and the direction of its findings, influences decisions on whether to publish or disseminate the research, potentially resulting in unreported negative outcomes. Publication bias was evaluated using the Begg's test and funnel plots. $P<0.05$ was considered to indicate a statistically significant difference (28).

Results

Literature search results. A total of 6,388 articles were retrieved through database searches. After removing duplicates, 1,608 articles were excluded, resulting in 4,783 articles for title and abstract screening. Of these, 4,439 were excluded for the following reasons: 1,249 were reviews or conference papers, 23 were non-English publications and 3,167 were

unrelated to the research focus. Following this, 344 articles were subjected to full-text review, leading to the exclusion of additional studies, with 33 articles ultimately included in the meta-analysis (Fig. 1) (29-61). The median sample size was 439 cases, with a range of 77-34,175 cases, totaling 71,718 cases. The median mortality rate across the studies was 30.57%, ranging 5.83-78.72%. Of the selected articles, eight originated from developing countries with lower levels of economy, technology and living standards, including medical standards and 25 were from developed countries with higher levels of economic and social development, as well as higher living standards, including medical standards. Table II summarized the key characteristics of the studies included in the present meta-analysis.

Quality assessment of included studies. Table III presented the NOS ratings for the cohort studies, which yielded either 7 or 8 points, with 20 studies achieving a score of 7 and 13 studies receiving a score of 8. A detailed assessment of the overall quality of these studies was provided in Table III.

Meta-analysis results. The pooled analysis of patient mortality yielded a rate of 28.2% (95%CI, 22.8-33.6%; Figs. 2 and 3). Subgroup analysis indicated a mortality rate of 25.1% (95%CI,19.9-30.2%) in developed countries, compared with 38.3% (95%CI,23.8-52.7%) in developing countries (Fig. 2). Regarding clinical scoring, mortality was 35.4% (95%CI, 26.7-44.0%) for the GCS score, 19.9% (95%CI, 14.2-25.5%) for the Abbreviated Injury Scale (AIS) score and 35.2% (95%CI,19.8-50.5%) for both scores combined (Fig. 3).

Among the general demographic characteristics, deceased patients with severe TBI were significantly older compared with survivors (49.02±20.09). Female sex (RR, 1.14; 95%CI, 1.08-1.20) and comorbidities such as anemia (RR, 1.42; 95%CI, 1.04-1.93) and diabetes mellitus (RR, 1.40; 95%CI, 1.00-1.96) were identified as significant risk factors for mortality from severe TBI in this cohort. In terms of clinical symptoms, coagulopathy (RR, 4.31; 95%CI, 2.31-8.05), shock (RR, 3.41; 95%CI, 2.31-5.04), systolic blood pressure (SBP) ≤90 mmHg(RR, 2.32; 95%CI, 1.65-3.27), hypotension (RR, 2.04; 95%CI, 1.58-2.63), and hypoxemia (RR,1.42; 95%CI, 1.13-1.79) were all associated with an increased risk of mortality. Furthermore, negative ethanol status (RR, 1.54; 95%CI, 1.13-2.13) and penetrating injury (RR, 4.00; 95%CI, 3.33-4.76) were also significantly associated with increased mortality risk. Injury severity scores further highlighted risk factors for mortality, including GCS 3-5 (RR, 3.54; 95%CI, 1.33-9.43), Injury Severity Score (ISS)≥16 (RR, 3.34; 95%CI, 2.32-4.82) and AIS head ≥4 (RR, 3.00; 95%CI, 2.20-4.09; Fig. 4 and Table III). Neurological injury type also contributed to mortality risk, with subdural hemorrhage (RR, 1.99; 95%CI, 1.50-2.62), subarachnoid hemorrhage (RR, 1.64; 95%CI, 1.09-2.47), and subdural hematoma (SDH) (RR, 1.50; 95%CI, 1.04-2.17) being notable risk factors. Additionally, absence of epidural hemorrhage (EDH; RR, 1.54; 95%CI, 1.09-2.17) was significantly associated with an increased risk of mortality. Regarding treatment interventions, prehospital intubation (RR, 1.48;95%CI, 1.13-1.92) was associated with an increased risk of mortality, whereas intracranial pressure monitoring (RR, 0.84;95%CI, 0.62-1.14) did not show a statistically significant effect (Fig. 4 and Table III).

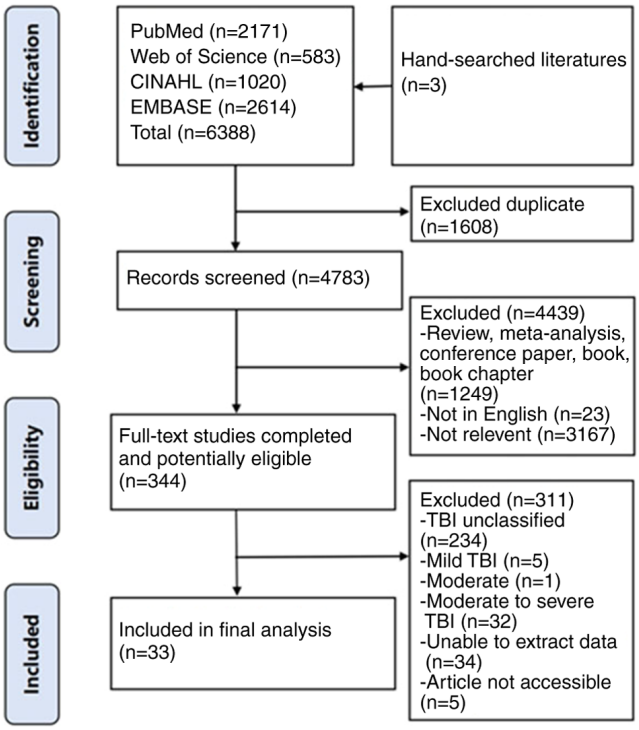

Figure 1. Schematic overview of the literature search and selection process. TBI, traumatic brain injury.

Table IV presented the results of the subgroup analysis, identifying several factors associated with an elevated mortality risk in patients with severe TBI across different countries. These factors included age (MD=14.28; 95%CI, 10.45-18.10), anemia (RR, 2.20; 95%CI, 1.20-4.04), diabetes mellitus (RR, 1.70; 95%CI, 1.01-2.88), SBP ≤90 mmHg (RR, 2.58; 95%CI, 1.85-3.59), hypotension (RR, 2.03; 95%CI, 1.40-2.94), hypoxemia (RR, 1.58; 95%CI, 1.21-2.07), subdural hemorrhage (RR, 2.46; 95%CI, 2.33-2.60), and subarachnoid hemorrhage (RR, 1.97; 95%CI, 1.27-3.04) in developed countries. GCS scores of 3-5 (RR, 3.17; 95%CI, 0.82-12.28) and subdural hemorrhage (RR, 2.46; 95%CI, 2.33-2.60) were also found to be significant mortality risk factors in developed countries. Additionally, female sex (RR, 1.10; 95%CI, 0.91-1.25) and absence of EDH (RR, 2.08; 95%CI, 0.81-5.26) demonstrated a positive association with mortality. Under GCS criteria (8≥GCS≥3) (2), age (MD, 10.41; 95%CI, 5.06-15.77), diabetes mellitus (RR, 1.70; 95%CI, 1.01-2.88), coagulopathy (RR, 4.86; 95%CI, 2.16-10.91) and subdural hemorrhage (RR, 1.98; 95%CI, 1.34-2.92) posed heightened mortality risks. SBP ≤90 mmHg (RR, 2.58; 95%CI, 1.85-3.59) was a key risk factor under AIS criteria (AIS≥3) (62). The two criteria identified hypotension (RR, 2.74; 95%CI, 2.26-3.33), hypoxemia (RR, 1.45; 95%CI, 1.14-1.83), subarachnoid hemorrhage (RR, 2.31; 95%CI, 1.90-2.81) and prehospital intubation (RR, 2.28; 95%CI, 1.84-2.84) as significant mortality risks. Additionally, protective effects were observed for female sex (RR, 1.35; 95%CI, 1.00-1.82) and absence of intracranial pressure monitoring (RR, 1.59; 95%CI, 1.12-2.22) under both criteria. Furthermore, absence of diffuse axonal injury (RR, 2.63; 95%CI, 1.47-4.76) and absence of EDH (RR, 2.27; 95%CI, 0.84-5.88) were more strongly associated with increased mortality in cases with GCS scores (8≥GCS≥3).

Table II. Characteristics of studies included in the meta-analysis.

First author/s, year	Country	Patients type	Cohort design	Sample size	Age, years	Sex, male/female	Severe traumatic brain injury definition	Incidence (%)	(Refs.)
Jeremitsky *et al*, 2005	USA	NR	Retrospective	77	Survival, 39.8 ±19.6; death, 55.9±19.0	51/26	GCS≤8	27/77 (31.17)	(29)
van Wessem *etal*, 2022	Netherlands	NR	Prospective	234	Survival, 46 (28-59); death, 56 (32-73)	157/77	AIS head≥3	57/234 (24.36)	(30)
Shen *et al*, 2023	China	NR	Retrospective	269	Median, 72.8 (60-89)	209/60	GCS≤8	98/269 (36.43)	(31)
Failla *et al*, 2015	USA	NR	Prospective	244	Survival, 32.72±13.54; death, 42.69±17.30	199/45	GCS≤8	33/244 (13.52)	(32)
Tsai *et al*, 2022	China	NR	Retrospective	1,347	Survival, 56.0±19.3; death,62.4±18.7	910/437	AIS head≥3	134/1,347 (9.48)	(33)
Tang *et al*, 2021	China	NR	Retrospective	94	Median, 44.5 (31-57)	80/14	GCS<5	74/94 (78.72)	(34)
Rodríguez *et al*, 2019	Colombia	NR	Retrospective	83	Survival, 37.8±17.0; death, 81.7±18.7	76/7	Total AIS≥3; GCS≤8	26/83 (31.33)	(35)
Choffat *et al*, 2019	Switzerland	NR	Prospective	832	Median, 54.3 (32.2-71.3)	612/220	AIS head>3	255/832 (30.65)	(36)
Hartl *et al*, 2008	USA	NR	Prospective	797	Range, ≥16	-	GCS≤8	79/797 (9.91)	(37)
Kumar *et al*, 2019	USA	NR	Prospective	157	Survival, 33.54±1.35; death, 51.08±2.29	127/30	GCS≤8	48/157 (30.57)	(38)
Lele *et al*, 2019	India	NR	Prospective	200	Mean, 36.9±13.0	168/32	AIS head≥3; GCS<8	48/200 (24.00)	(39)
Dawes *et al*, 2015	USA	NR	Prospective	822	-	603/219	GCS≤8	319/822 (38.81)	(40)
Boto *et al*, 2014	Spain	NR	Prospective	652	Range, ≥15	-	GCS≤8	114/652 (17.48)	(41)
Shibahashi *et al*, 2021	Japan	NR	Retrospective	34,175	Survival, 60 (40-74); death, 70 (54-81)	23,607/10568	AIS head≥3	4,513/34,175 (13.21)	(42)
Emami *et al*, 2019	Germany	Isolated	Prospective	21,242	-	15,044/6198	AIS head≥3	8,691/21,242(40.91)	(43)
Corral *et al*, 2012	Spain	NR	Retrospective	224	Median, 35.6 (23-55)	189/35	GCS≤8	74/224 (33.04)	(44)
Catapano *et al*, 2019	USA	Isolated	Retrospective	600	Mean, 59.8±13.4	-	AIS head≥3	35/600 (5.83)	(45)
Franschman *et al*, 2011	Netherlands	NR	Retrospective	274	Survival, 36±7; death, 52±3	-	GCS≤8	121/274 (44.16)	(46)
Cai *et al*, 2016	USA	NR	Retrospective	580	Survival, 49.4±19.7; death, 63.3±20.2	410/169	AIS head≥3; GCS≤8	287/580 (49.48)	(47)
Lanzillo *et al*, 2019	Italy	NR	Prospective	457	Survival, 49.7±17.8; death, 61.9±13.6	290/167	GCS≤8	107/457 (23.41)	(48)
Rahimi *et al*, 2014	Iran	NR	Retrospective	108	Survival, 12.32±5.24; death, 12.55±4.90	81/27	GCS≤8	34/108 (31.48)	(49)
Yang *et al*, 2011	China	NR	Retrospective	234	Survival, 47.6±16.9; death, 55.6±18.0	-	GCS≤8	129/234 (55.13)	(50)
Talving *et al*, 2011	USA	Isolated	Retrospective	320	Mean, 10.7±5.1	234/86	AIS head≥3	25/320 (7.81)	(51)

Table II. Continued.

First author/s, year	Country	Patients type	Cohort design	Sample size	Age, years	Sex, male/female	Severe traumatic brain injury definition	Incidence (%)	(Refs.)
Catapano *et al*, 2016	USA	Isolated	Retrospective	698	Range, ≥40	475/223	AIS head≥3	42/698 (6.02)	(52)
Mohseni *et al*, 2014	Sweden	NR	Retrospective	622	Mean, 64±13	423/199	AIS head≥3	121/622 (19.45)	(53)
Talving *et al*, 2010	USA	Isolated	Retrospective	815	Range, 18-64	692/123	AIS head≥3	111/815 (13.62)	(54)
Talving *et al*, 2009	USA	All	Retrospective	436	Mean, 37±20	339/97	AIS head≥3	93/414 (22.46)	(55)
Wafaisade *et al*, 2010	Germany	Isolated	Retrospective	3,114	Range ≥16	2,150/964	AIS head≥3	773/3,114 (24.82)	(56)
Davis *et al*, 2003	USA	NR	Prospective	836	Range ≥18	677/159	GCS:3~8	378/836 (45.22)	(57)
Lustenberger *et al*, 2010	USA	Isolated	Retrospective	132	Mean,34.9±1.6	106/26	AIS head≥3	43/132 (32.58)	(58)
Saadat *et al*, 2012	Iran	NR	Retrospective	122	Median, 13 (7.75-17)	91/31	GCS≤8	49/122 (40.16)	(59)
Lustenberger *et al*, 2011	USA	Isolated	Retrospective	439	Mean,37.7±16.4	369/70	AIS head≥3	59/439 (13.44)	(60)
Salim *et al*, 2009	USA	NR	Retrospective	482	Mean,38.6±16.9	400/82	AIS head≥3	168/482 (35.06)	(61)

NR, not reported; -, notmentioned; GCS, Glasgow Coma Score; AIS, abbreviated injury scale.

Publication bias. Fig. 5 illustrated the results of the Begg's test for studies with a sample size of ≥10, indicating significant publication bias for incidence (t=2.46; P=0.0138), however, no significant publication bias for incidence of sex was found (t=1.01; P=0.331).

Sensitivity analysis. Table V presented the sensitivity analysis performed using the leave-one-out method, confirming the stability of the mortality rate results. For mortality-related risk factors, aside from sex, epidural hematoma and intracranial pressure monitoring, all other factors remained consistent following the application of the random-effects model (Fig. 6).

Discussion

A total of 33 articles were included in the present meta-analysis to examine the mortality incidence and risk factors associated with severe TBI. The NOS scores for cohort studies varied between 7 and 8, with 20 studies receiving a score of 7 and 13 studies scoring 8. According to previous literature (20), this reflects a considerable amount of literature analyzed, contributing to a relatively robust set of research outcomes. TBI is a non-degenerative, non-reproductive brain injury that is typically caused by excessive external force. It can lead to impaired or altered consciousness and resulting in temporary or permanent cognitive and physical disabilities (63). In the USA, TBI contributes to ~40% of injury-related fatalities (64). According to the Centers for Disease Control and Prevention, ~1.72 million individuals in the USA sustain TBIs annually, with 275,000 requiring hospitalization (65). These injuries lead to 50,000 deaths and 70,000 cases of long-term disability each year, with 5.3 million individuals living with these disabilities, creating significant emotional and socio-economic impact on society and corresponding families (66). A previous study has indicated that TBI is prevalent, which frequently results in neurological deficits, behavioral changes and cognitive decline, particularly among survivors of sports-related injuries (67). The broader public health implications of TBI are considerable (4,5,6,66). Severe TBI is associated with high rates of mortality and disability, with a small proportion of patients remaining in a vegetative state for extended periods (68). Previous studies have reported a median mortality rate of 30.57%, ranging from 5.83 to 78.72% (69-71). In the present analysis, the pooled mortality rate was 27.8% (95%CI: 22.5-33.2%), with subgroup analysis revealing 25.2% (95%CI: 20.2-30.1%) in developed countries and 38.0% (95%CI: 21.4-54.7%) in developing nations, aligning with previous studies (72,73). The significantly lower mortality rate in developed countries is likely attributed to superior economic resources, advanced emergency systems and timely medical interventions, which corroborates earlier findings (74,75). By contrast, in developing countries, such as China, due to insufficient investment in medical equipment, emergency medical systems and training of medical personnel, patients with TBI tended to have a higher mortality rate (76). To change this situation, trauma centers have been established in hospitals at different levels. Concurrently, manpower, material resources and funding have all been increased, which is coupled with the drive of purchasing various advanced medical equipment related to trauma and training medical personnel to enable

Table III. Risk of bias assessment according to the NOS score.

Author, year	Selection	Comparability	Outcome	NOS score	(Refs.)
Jeremitsky *et al*, 2005	4	1	2	7	(29)
van Wessem *et al*, 2022	4	1	3	8	(30)
Shen *et al*, 2023	4	1	3	8	(31)
Failla *et al*, 2015	4	1	3	8	(32)
Tsai *et al*, 2022	4	1	2	7	(33)
Tang *et al*, 2021	4	1	3	8	(34)
Rodríguez *et al*, 2019	4	1	2	7	(35)
Choffat *et al*, 2019	4	1	3	8	(36)
Hartl *et al*, 2008	4	1	3	8	(37)
Kumar *et al*, 2019	4	1	3	8	(38)
Lele *et al*, 2019	4	1	3	8	(39)
Dawes *et al*, 2015	4	1	2	7	(40)
Boto *et al*, 2014	4	1	3	8	(41)
Shibahashi *et al*, 2021	4	1	3	8	(42)
Emami *et al*, 2019	4	1	2	7	(43)
Corral *et al*, 2012	4	1	2	7	(44)
Catapano *et al*, 2019	4	1	2	7	(45)
Franschman *et al*, 2011	4	1	2	7	(46)
Cai *et al*, 2016	4	1	2	7	(47)
Lanzillo *et al*, 2019	4	1	3	8	(48)
Rahimi *et al*, 2014	4	1	2	7	(49)
Yang *et al*, 2011	4	1	2	7	(50)
Talving *et al*, 2011	4	1	3	8	(51)
Catapano *et al*, 2016	4	1	2	7	(52)
Mohseni *et al*, 2014	4	1	2	7	(53)
Talving *et al*, 2010	4	1	2	7	(54)
Talving *et al*, 2009	4	1	2	7	(55)
Wafaisade *et al*, 2010	4	1	2	7	(56)
Davis *et al*, 2003	4	1	2	7	(57)
Lustenberger *et al*, 2010	4	1	2	7	(58)
Saadat *et al*, 2012	4	1	2	7	(59)
Lustenberger *et al*, 2011	4	1	2	7	(60)
Salim *et al*, 2009	4	1	2	7	(61)

Each asterisk represents one point. NOS, Newcastle-Ottawa scale.

patients with TBI to receive timely and effective treatment in turn improving prognosis (77,78).

The overall incidence and mortality rates of moderate and severe TBI in Central Norway have remained low, but are significantly increased from the age of 70 years onwards, with the majority of individuals aged ≥80 years succumbing to severe TBI (79,80). These estimates are heavily influenced by the elevated rates in the elderly population (79), aligning with the present findings. This trend is largely attributed to age-related degenerative organ conditions, diminished compensatory mechanisms, reduced physiological resilience and the presence of comorbidities, such as heart and lung failure (81). Additionally, poor regulatory function, coupled with frequent complications, further compounds the risk (81). Elderly patients with intracranial hemorrhage will typically struggle to endure the combined stress of trauma and surgery, worsening pre-existing conditions, lowering the body's tolerance to brain injury and in turn heightening the likelihood of complications, sequelae and mortality (82). These elements critically affect prognosis. Studies (83,84) previously

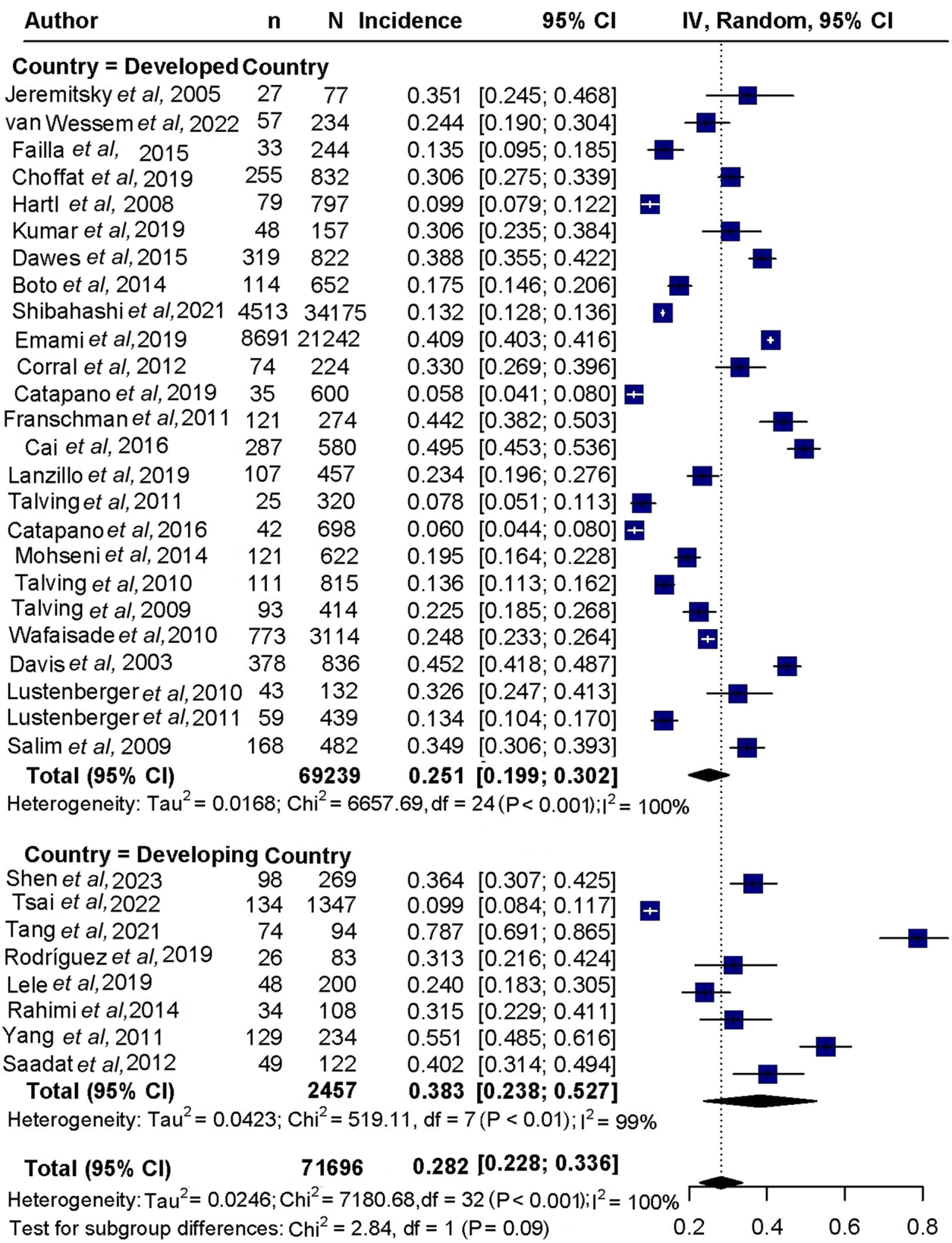

Figure 2. Forest plot illustrating the incidence of severe traumatic brain injury across different countries (developed and developing countries). IV,I nverse variance.

highlighted that patients aged ≥65 years had a higher mortality rate and poorer neurological recovery compared with those in younger patients with TBI. Anemia (RR, 1.42; 95%CI, 1.04-1.93) and diabetes mellitus (RR, 1.41; 95%CI, 1.07-1.84) have been identified as significant mortality risk factors in severe TBI. Hemoglobin, essential for oxygen transport, becomes compromised during anemia, leading to reduced cerebral oxygenation and secondary brain injury (85). A

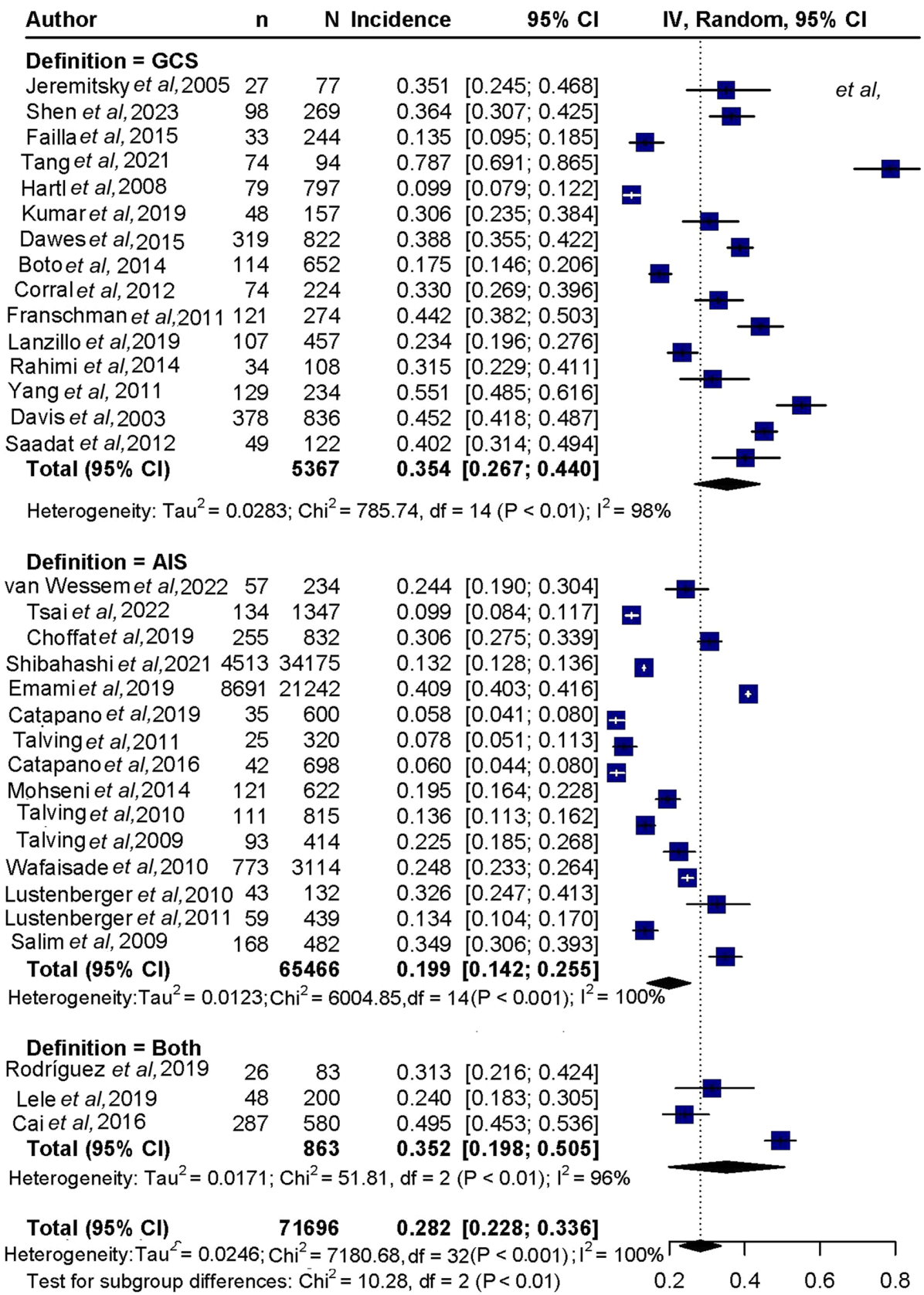

Figure 3. Forest plot comparing incidence rates of severe traumatic brain injury usingvarying definitions. GCS, Glasgow coma scale; AIS, abbreviated injury scale; IV, inverse variance.

previous study using animal models of TBI has demonstrated that anemia can aggravate brain injury (86). In another study using a rat TBI model, Hare *et al* (87) observed that anemia enlarged the contusion area and accelerated apoptotic neuron death in cerebral tissue injury following acute neurotrauma, thereby aggravating secondary damage. Decreased hematocrit

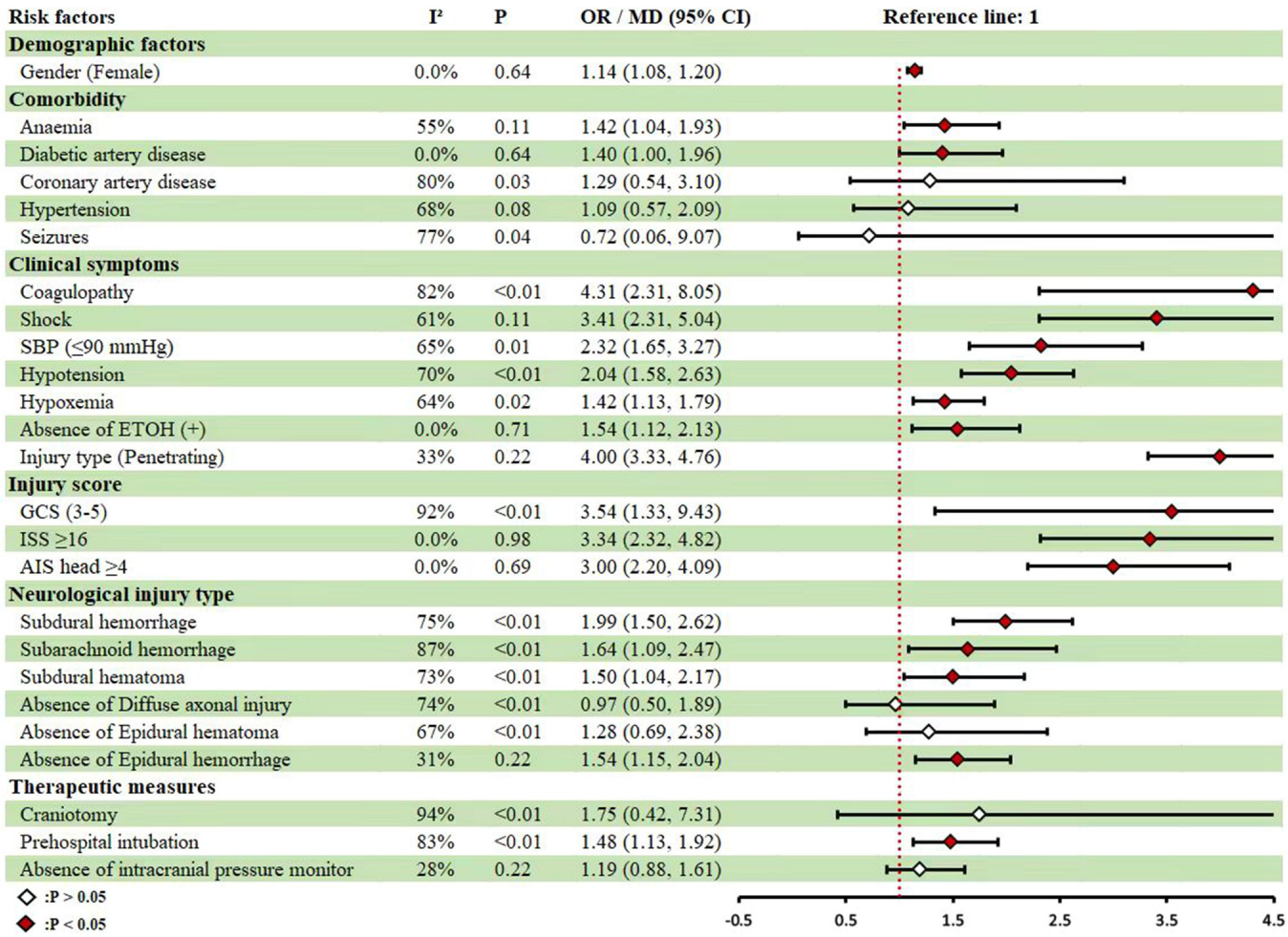

Figure 4. Forest plot showing risk factors associated with mortality in patients with severe traumatic brain injury. SBP, systolic blood pressure; GCS, Glasgow Coma scale; RR, risk ratio; ETOH, alcohol; AIS, abbreviated injury scale.

has been associated with poorer discharge prognosis scores in patients with TBI (88), while hemoglobin levels ≤10 g/dl are associated with reduced cerebral oxygenation and an increased risk of unfavorable outcomes (89). By contrast, transfusion of red blood cell suspension has been documented to enhance cerebral oxygen metabolism in patients with TBI (89). Blood glucose levels have also been implicated in patient prognosis (90-92), with previous studies identifying a relationship between elevated blood glucose upon admission and adverse outcomes in patients with severe cranial injuries the following morning. Post-trauma insulin resistance frequently emerges, impeding the biological efficacy of insulin and contributing to hyperglycemia (90). Ischemia and hypoxia following brain injury trigger anaerobic metabolism, leading to substrate production and the accumulation of acidic metabolites, which exacerbate the ischemia, edema and neuronal necrosis (93). This in turn increases the risk of mortality among patients with severe brain injury. Effective blood glucose regulation has been reported to improve patient outcomes (94). However, early blood sugar reduction alone is insufficient. Instead, sustained stabilization of blood glucose post-reduction creates optimal conditions for a positive prognosis. Zhu *et al* (95) report that intensive glycemic control (IGC) plays a protective role in improving neurological outcome, decreasing infection rate and reducing the length of stay in intensive care units (ICU). However, IGC therapy can also remarkably increase the risk of hypoglycemia, but it will not affect the mortality in TBI patients. Previous studies on the glucose lability index have indicated that blood glucose variability in patients with severe brain injury constitutes an independent mortality risk factor (96-98). In total, ~66% patients with severe TBI present with abnormal coagulation profiles upon emergency admission, whereas ~50% of those with coagulopathies experience early brain contusion exacerbation or progression of hemorrhage within 48 h post-injury (99). In addition, the severity of the initial brain injury is directly associated the onset of coagulation dysfunction, with more severe injuries precipitating earlier occurrences (100). Post-TBI coagulopathy is commonly associated with poor prognosis, a finding that aligns with the present study (100). Numerous studies have reported an association between coagulation function and patient prognosis (99,101,102). The more severe the TBI, the worse the coagulation function and the worse patient prognosis. The cause may be the abnormal coagulation function caused by the activation of endogenous coagulation pathways after acute trauma, leading to secondary TBI and worsening of patient condition (103). Therefore, timely supplementation of low-dose fresh frozen plasma may improve the coagulation function and prognosis of patients with severe TBI. Previous studies have shown that hypotension (defined as systolic

Table IV. Results of pooled analysis on for risk factors in patients with sTBI.

Risk factor	Country		sTBI definition			Total
	Developed	Developing	GCS	AIS	Both	
Demographic factors						
Age years, (mean ± SD)	Deaths: 55.78 (15.21) Alive: 41.53 (16.47)	Deaths: 55.78 (15.21) Alive: 53.04 (20.69)	Deaths: 51.83 (19.91) Alive: 39.88 (18.08)	Deaths: 62.40 (18.70) Alive: 56.00 (19.3)	-	Deaths: 54.59 (20.103) Alive: 49.02 (20.09)
Sex (Female) (female vs. male)	1.14 (1.09,1.22)	0.96 (0.73,1.25)	1.14 (1.06,1.20)	1.06 (0.97,1.37)	1.35 (1.00,1.82)	1.10 (0.97,1.25)
Comorbidity						
Anemia (yes vs. no)	2.20 (1.20,4.04)	1.29 (0.99,1.68)	-	-	-	1.42 (1.04,1.93)
Diabetic mellitus (yes vs. no)	1.70 (1.01,2.88)	1.22 (0.79,1.89)	1.70 (1.01,2.88)	1.22 (0.79,1.89)	-	1.40 (1.00,1.96)
Coronary artery disease (yes vs. no)	-	-	-	-	-	1.29 (0.54,3.10)
Hypertension (yes vs. no)	-	-	-	-	-	1.09 (0.57,2.09)
Seizures (yes vs. no)	-	-	-	-	-	0.72 (0.06,9.07)
Clinical symptoms						
Coagulopathy (yes vs. no)	-	-	4.86 (2.16,10.91)	4.49 (1.89,10.66)	-	4.31 (2.31,8.05)
Shock (yes vs. no)	-	-	-	-	-	3.41 (2.31,5.04)
Systolic blood pressure (≤90 mmHg) (yes vs. no)	2.58 (1.85,3.59)	1.39 (0.86,2.25)	1.39 (0.86,2.25)	2.58 (1.85,3.59)	-	2.32 (1.65,3.27)
Hypotension (yes vs. no)	2.03 (1.40,2.94)	1.94 (1.64,2.29)	1.90 (1.68,2.16)	-	2.74 (2.26,3.33)	2.04 (1.58,2.63)
Hypoxemia (yes vs. no)	1.58 (1.21,2.07)	1.15 (0.92,1.42)	1.40 (1.02,1.91)	-	1.45 (1.14,1.83)	1.42 (1.13,1.79)
ETOH (+) (yes vs. no)	-	-	-	-	-	0.65 (0.47,0.89)
Injury type (Blunt) (blunt vs. penetrating)	-	-	-	-	-	0.25 (0.21,0.30)
Injury score						
GCS (3-5)	3.17 (0.82,12.28)	5.02 (3.06,8.24)	-	-	-	3.54 (1.33,9.43)
ISS ≥16	-	-	-	-	-	3.34 (2.32,4.82)
AIS head ≥4	-	-	-	-	-	3.00 (2.20,4.09)
Neurological injury type						
Subdural hemorrhage (yes vs. no)	2.46 (2.33,2.60)	1.48 (1.10,1.97)	1.98 (1.34,2.92)	1.95 (1.16,3.27)	-	1.99 (1.50,2.62)
Subarachnoid hemorrhage (yes vs. no)	1.97 (1.27,3.04)	0.89 (0.68,1.17)	2.25 (0.96,5.29)	1.15 (0.75,1.76)	2.31 (1.90,2.81)	1.64 (1.09,2.47)
Subdural hematoma (yes vs. no)	1.53 (0.96,2.42)	1.48 (1.03,2.14)	1.50 (1.13,1.99)	1.59 (0.73,3.48)	-	1.50 (1.04,2.17)
Diffuse axonal injury (no vs.yes)	-	-	2.63 (1.47,4.76)	0.65 (0.38,1.11)	-	0.97 (0.50,1.89)
Epidural hematoma (no vs. yes)	-	-	1.61 (0.74,3.45)	0.93 (0.30,2.78)	-	1.54 (1.09,2.17)
Epidural hemorrhage (no vs. yes)	2.08 (0.81,5.26)	1.39 (0.89,2.17)	2.27 (0.92,5.88)	1.41 (1.27,1.56)	-	1.54 (1.15,2.04)

Table IV. Continued.

Risk factor	Country		sTBI definition			Total
	Developed	Developing	GCS	AIS	Both	
Therapeutic measures						
Craniotomy (yes vs. no)	-	-	-	-	-	1.75 (0.42,7.31)
Prehospital intubation (yes vs. no)	-	-	1.20 (0.91,1.58)	1.41 (1.32,1.50)	2.28 (1.84,2.84)	1.48 (1.13,1.92)
Intracranial pressure monitor (no vs. yes)	0.97 (0.58,1.61)	1.49 (0.93,2.44)	1.25 (0.91,1.69)	0.45 (0.15,1.30)	1.59 (0.89,2.78)	1.19 (0.88,1.61)

Only one article included [Age, Tsai *et al*, 2022 (30); Anaemia, Boto *et al*, 2014 (38); Diabetic mellitus, Tsai *et al*, 2022 (30); Coagulopathy, Boto *et al*, 2014 (38); SBP, Saadat *et al*, 2012 (56); Hypotension, Yang *et al*, 2011 (Country) (47), Choffat *et al*, 2019 (sTBI Definition) (33); Hypoxemia, Choffat *et al*, 2019 (33); GCS, Shen *et al*, 2023 (28); Subarachnoid hemorrhage, Cai *et al*, 2016 (44); Subdural hematoma, Shen *et al*, 2023 (28); Prehospital intubation, Choffat *et al*, 2019 (33); Intracranial pressure monitor, Lele *et al*, 2017 (36)]; -, Not mentioned; sTBI, severe traumatic brain injury; GCS, Glasgow Coma Score; AIS, Abbreviated Injury Scale; ETOH, ethanol; ISS, injury severity score.

pressure <90 mmHg) and hypoxia (PaO_2≤60 mmHg) can double the mortality risk in patients with craniocerebral injuries (104,105). Studies from the 1970s have identified 'systemic injury', involving hypotension, hypoxia and hypercapnia, to be predictors of increased mortality (106-109), consistent with the present study. In the present study, diffuse axonal injury (RR, 0.38; 95%CI, 0.21-0.68) and EDH (RR, 0.45; 95%CI, 0.30-0.69) exhibited a more pronounced protective effect against mortality in patients with severe TBI, as measured using the GCS. However, clinical evidence of diffuse axonal injury on MRI appears to be primarily beneficial for predicting short-term functional outcomes during hospitalization, without a clear association with long-term prognosis (110,111).EDH is less likely to cause brain herniation and coagulation dysfunction, which may explain why the mortality rate of EDH is also lower (112).

Previous studies have indicated that EDH is associated with favorable outcomes, defined as a Glasgow Outcome Scale (GOS) of 4 or 5 (good recovery or moderate disability) at discharge or follow-up, with rates ranging from 69 to 95% (mean, 84.3±14.6%; median 88.9%) (113,114). By contrast, the outcomes for subdural hematoma (SDH) during the perioperative period vary significantly, with rates between 9 and 76% (mean 32.1±13.6%, median 26.5%) (115,116). In the present study, subdural hemorrhage (RR, 1.99; 95%CI, 1.50-2.62), subarachnoid hemorrhage (RR, 1.64; 95%CI, 1.09-2.47) and SDH (RR, 1.50; 95%CI, 1.04-2.17) were identified to be mortality risk predictors in patients with severe TBI, whilst epidural hemorrhage (RR, 0.69; 95%CI, 0.63-0.76) was observed to be protective, being associated with improved prognosis and lower mortality rate of episodic hemorrhage. Subdural hemorrhage, subarachnoid hemorrhage and subdural subatoma can not only lead to progressive hemorrhagic injury (PHI), but also to brain herniation and coagulation dysfunction, which can increase the mortality rate of patients with TBI (117). PHI following TBI represents a key secondary injury mechanism that significantly contributes to both disability and mortality in affected patients (118). In total, ~20% patients with TBI patients require surgical intervention due to PHI, with a notably poorer prognosis observed in those who develop PHI compared with those who do not (119). The rate of in-hospital mortality for patients with TBI with adverse outcomes stands at 29%, with mortality rates of 17% for patients without PHI and 44% for those with PHI (119). Stein *et al* (120) previously identified SDH as having the highest likelihood of PHI among various TBI types. Further analysis of 782 TBI cases revealed a significant association between SDH and the occurrence of PHI (121). Di *et al* (122) previously identified a significantly higher risk of PHI in patients with EDH compared with those with other types of TBI lesions, with the risk of PHI in patients with EDH being ~4X greater compared with that of patients. The requirement for prehospital intubation (RR, 1.48; 95%CI, 1.13-1.92) found in the present study suggests a severe clinical condition, frequently involving impaired consciousness or respiratory failure, thereby contributing to increased mortality. Despite previous studies reporting that prehospital intubation does not reduce mortality in patients with severe TBI (123,124), the skill level of medical personnel has emerged as a critical factor. Poorly executed intubation by inadequately trained personnel significantly elevates the risk of mortality,

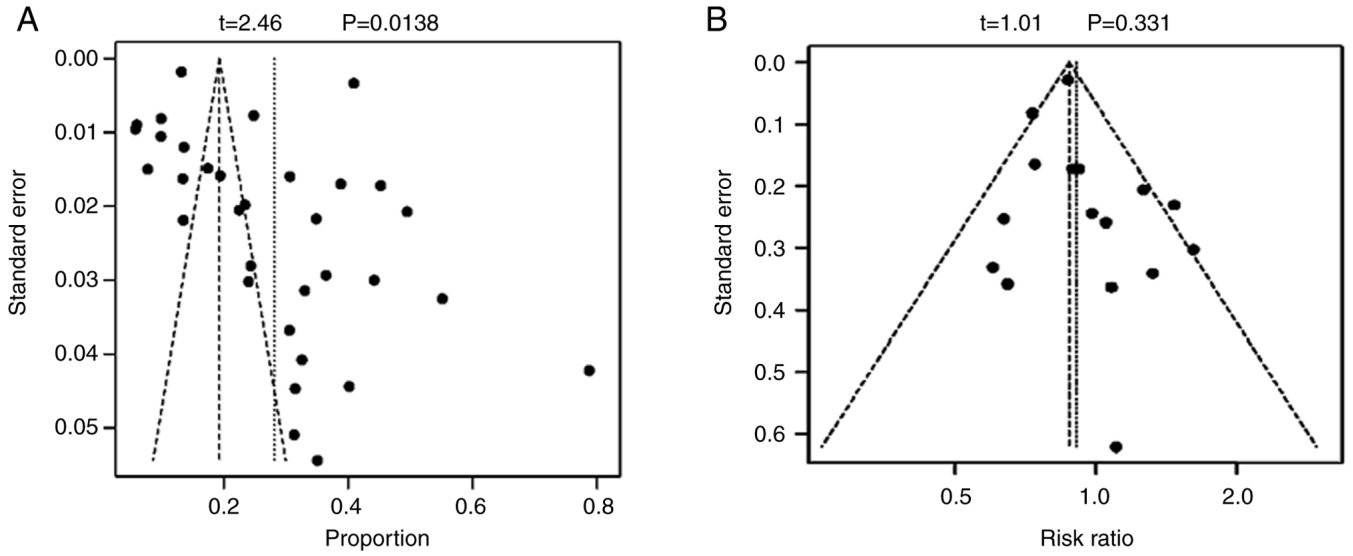

Figure 5. Funnel plot assessing potential publication bias. Publication bias was evaluated using the Begg's test and funnel plots. (A) Funnel plot of risk factors leading to increased mortality in severe TBI patients. (B) Funnel plot of sex.

suggesting that in the absence of properly trained providers, routine prehospital intubation should be reconsidered for patients with TBI (125). Conversely, recent data indicate that when performed by experienced and well-trained practitioners following current TBI guidelines, prehospital endotracheal intubation can be beneficial (126). However, prehospital intubation remains to be a risk factor for mortality in patients with severe TBI in the present study, whilst the use of intracranial pressure monitors (RR, 0.75; 95%CI, 0.65-0.86) has been shown to be protective.

Trauma scoring quantifies injury severity through objective criteria, serving a fundamental role in trauma management (127). The GCS score remains a widely accepted tool for assessing both the severity and prognosis of patients with TBI. It mainly evaluates three parameters, eye, verbal and motor responses, with the total score reflecting the patient's level of consciousness. A score of 15 represents normal consciousness, whilst lower scores correspond to increasing levels of impairment (128). TBI severity can be categorized into three levels based on GCS scores: Mild (13≤GCS<15); moderate (9≤GCS<12); and severe (3≤GCS<8) (129). Nevertheless, the GCS has its limitations, particularly in its subjectivity and inability to accurately evaluate patients requiring endotracheal intubation or those unable to communicate verbally (128). Studies have demonstrated that the GCS-Full Outline of Unresponsiveness (FOUR) score are comparable in predicting TBI outcomes, including mortality, length of hospital stay and morbidity (130,131). The FOUR score, however, offers a more comprehensive neurological assessment with higher specificity and positive predictive value, making it a valuable clinical tool (130). In patients with TBI, the FOUR score has been reported to surpass GCS in predicting hospital stay duration and morbidity (132). Additionally, injury severity, low GCS and polytrauma are key predictors of early in-hospital mortality, while surgical interventions such as head, chest, abdomen, limb, blood vessels and other surgical procedures are associated with extended hospitalizations (133). The AIS divides the body into nine compartments, which are then reclassified into six regions for calculating the ISS. The AIS code consists of 6 'front points' for injury location and 1 'rear point' for injury severity. Severity is rated from 1 to 5, with a score of 6 indicating a non-survivable injury (134). A previous study has shown that patients with severe TBI in the unfavorable outcome group have an average AIS score of 4.39±0.82 and a higher frequency of AIS scores of 5. Therefore, an AIS head score of five significantly raises the likelihood of an unfavorable prognosis (135). In the present study, GCS scoring contributed 35.0% (95%CI: 25.8-44.3%) and AIS scoring contributed 19.9% (95%CI: 14.2-25.5%), whereas their combined use accounted for 33.4% (95%CI: 21.8-45.0%), indicating that GCS remains a widely employed tool for assessing patients with severe TBI. The present study identified several factors that were significantly associated with increased mortality risk in patients with TBI with GCS scores: Age (MD, 10.41; 95%CI, 5.06-15.77), diabetes mellitus (RR, 1.70; 95%CI, 1.18-2.45), coagulopathy (RR, 4.86; 95%CI, 2.16-10.91) and subdural hemorrhage (RR, 1.98; 95%CI, 1.34-2.92). In severe TBI cases with AIS scores, SBP ≤90 mmHg (RR, 2.58; 95%CI, 1.85-3.59) was associated with a higher mortality risk. Additionally, for severe TBI cases evaluated using both GCS and AIS scores, hypotension (RR, 2.74; 95%CI, 2.26-3.33), hypoxemia (RR, 1.42; 95%CI, 1.13-1.79), subarachnoid hemorrhage (RR, 2.31; 95%CI, 1.90-2.81) and prehospital intubation (RR, 2.28; 95%CI, 1.84-2.84) were associated with an elevated risk of mortality. These results indicated that GCS provides a more accurate prediction of mortality risk in elderly patients and those with diabetes, coagulopathy or subdural hemorrhage, whereas AIS demonstrates greater predictive value in cases involving SBP ≤90 mmHg. In patients experiencing hypotension, hypoxemia, subarachnoid hemorrhage or requiring prehospital intubation, both GCS and AIS offer improved predictive capabilities for assessing mortality risk in severe TBI. Furthermore, diffuse axonal injury (DAI; RR, 0.38; 95%CI, 0.21-0.68) was found to have a notable protective effect against mortality in severe TBI cases with GCS scores, which may be related to the relatively small effect of TBI combined with DAI on the mortality rate

Table V. Sensitivity analysis for risk factors in patients with sTBI.

Risk factor	Country		sTBI Definition			Total
	Developed	Developing	GCS	AIS	Both	
Demographic factors						
Age years, (mean ± SD)	Deaths: 56.82 (17.8) Alive: 43.26 (16.9)	Deaths: 51.06 (19.48) Alive: 52.31 (23.6)	Deaths: 52.42 (21.61) Alive: 40.35 (18.75)	Deaths: 59.71 (23.12) Alive: 55.39 (21.04)	-	Deaths: 53.81 (18.93) Alive: 50.69 (23.27)
Sex (Female) (female vs. male)	1.19 (1.08, 1.32)	0.93 (0.75, 1.15)	1.08 (0.83, 1.33)	1.14 (1.08, 1.20)	1.35 (1.15,1.59)	1.10 (0.97,1.25)
Comorbidity						
Anemia (yes vs. no)	2.20 (1.20,4.04)	1.35 (1.09,1.66)	-	-	-	1.64 (1.25,2.14)
Diabetic mellitus (yes vs. no)	1.70 (1.18,2.44)	1.22 (0.83,1.80)	1.70 (1.18,2.44)	1.22 (0.83,1.80)	-	1.46 (1.09,1.94)
Coronary artery disease (yes vs. no)	-	-	-	-	-	1.34 (0.39,1.95)
Hypertension (yes vs. no)	-	-	-	-	-	1.26 (0.95,1.69)
Seizures	-	-	-	-	-	0.50 (0.16,1.51)
Clinical symptoms (yes vs. no)						
Coagulopathy (yes vs. no)	-	-	4.86 (2.16,10.91)	3.21 (2.88,3.57)	-	3.27 (2.93,3.65)
Shock (yes vs. no)	-	-	-	-	-	3.90 (2.87,5.31)
SBP (≤90 mmHg)	2.34 (2.18,2.51)	1.39 (0.86,2.25)	1.39 (0.86,2.25)	2.34 (2.18,2.51)	-	2.32 (2.16,2.48)
Hypotension (yes vs. no)	2.06 (1.75,2.43)	1.94 (1.64,2.29)	1.88 (1.60,2.20)	-	2.74 (2.26,3.33)	2.03 (1.78,2.32)
Hypoxemia (yes vs. no)	1.62 (1.39,1.89)	1.15 (0.90,1.46)	1.53 (1.31,1.79)	-	1.45 (1.14,1.83)[a]	1.51 (1.32,1.72)
ETOH (+) (yes vs. no)	-	-	-	-	-	0.65 (0.51,0.83)
Injury type (blunt) (blunt vs. penetrating)	-	-	-	-	-	0.26 (0.21,0.33)
Injury score						
GCS (3-5)	3.06 (2.30,4.07)	5.02 (3.06,8.24)	-	-	-	3.47 (2.71,4.43)
ISS ≥16	-	-	-	-	-	3.34 (2.31,4.81)
AIS head ≥4	-	-	-	-	-	2.98 (2.19,4.06)
Neurological injury type						
Subdural hemorrhage (yes vs. no)	2.46 (2.33,2.60)	1.47 (1.09,1.98)	2.12 (1.59,2.82)	2.43 (2.30,2.57)	-	2.42 (2.29,2.56)
Subarachnoid hemorrhage (yes vs. no)	2.15 (1.87,2.47)	0.83 (0.62,1.10)	2.47 (1.95,3.13)	1.03 (0.38,1.29)	2.31 (1.90,2.81)	1.75 (1.55,1.98)
Subdural hematoma (yes vs. no)	1.28 (1.03,1.59)	1.48 (1.03,2.14)	1.50 (1.13,1.99)	1.20 (0.93,1.54)	-	1.32 (1.10,1.59)
DDiffuse axonal injury (no vs. yes)	-	-	2.63 (1.47,4.76)	0.97 (0.85,1.11)	-	1.03 (0.91,1.18)
Epidural hematoma (no vs. yes)	-	-	1.72 (1.14,2.70)	1.20 (0.67,2.13)	-	1.54 (1.09,2.17)
Epidural hemorrhage (no vs. yes)	2.08 (0.81,5.56)	1.43 (1.06,1.96)	2.17 (0.88,5.26)	1.41 (1.28,1.56)	-	1.43 (1.30,1.56)
Therapeutic measures						
Craniotomy (yes vs. no)	-	-	-	-	-	0.94 (0.67,1.31)
Prehospital intubation (yes vs. no)	-	-	1.23 (1.02,1.48)	1.41 (1.32,1.50)	2.28 (1.84,2.84)	1.44 (1.36,1.53)

Table V. Continued.

Risk factor	Country		sTBI Definition			Total
	Developed	Developing	GCS	AIS	Both	
Therapeutic measures						
Craniotomy (yes vs. no)	-	-	-	-	-	0.94 (0.67,1.31)
Prehospital intubation (yes vs. no)	-	-	1.23 (1.02,1.48)	1.41 (1.32,1.50)	2.28 (1.84,2.84)	1.44 (1.36,1.53)
Intracranial pressure monitor (no vs. yes)	0.92 (0.53,1.59)	1.52 (1.12,2.04)	1.23 (0.90,1.69)	0.45 (0.17,1.14)	1.59 (1.12,2.22)	1.22 (0.92,1.59)

Only one article included (Age, Tsai *et al*, 2022 (33); Anaemia, Boto *et al*, 2014 (41); Diabetic mellitus, Tsai *et al*, 2022 (33); Coagulopathy, Boto *et al*, 2014 (41); SBP, Saadat *et al*, 2012 (59); Hypotension, Yang *et al*, 2011 (Country) (50), Choffat *et al*, 2019 (sTBI Definition) (36); Hypoxemia, Choffat *et al*, 2019 (36); GCS, Shen *et al*, 2023 (28); Subarachnoid hemorrhage, Cai *et al*, 2016 (44); Subdural hematoma, Shen *et al*, 2023 (28); Prehospital intubation, Choffat *et al*, 2019 (33); Intracranial pressure monitor, Lele *et al*, 2017 (36); -, Not mentioned; sTBI, severe traumatic brain injury; GCS, Glasgow Coma Score; AIS, Abbreviated Injury Scale; ETOH, ethanol; ISS, injury severity score.

of TBI patients and clinical evidence of DAI on MRI may only be useful for predicting short-term in-hospital functional outcome (136). However, a previous study has indicated that neither clinical nor anatomic DAI associates with survival, Glasgow Outcome Scale-Extended or Quality of Life after Brain Injury-Overall Scale outcomes (136). A single-point reduction in GCS score nearly doubles the risk of in-hospital mortality, whilst coagulopathy increases the risk of in-hospital mortality ~6 times (137).

In the general population across all age groups (0-65 years), TBI incidence is typically higher in male compared with female patients (138). However, certain studies have suggested that female patients tend to exhibit a greater frequency and longer duration of post-TBI symptoms, such as headaches, anxiety and depression, compared with those in male patients (139,140), which is consistent with the results of the present study. Additionally, in the present study, male sex and intracranial pressure monitoring appear to be protective factors in severe TBI cases. This association may result from the early detection of intracranial pressure changes and timely therapeutic interventions. Psychological resilience may also serve a role, with male patients exhibiting greater resilience during TBI recovery (141,142), whilst female patients may face higher risks of anemia, hypotension and immune disorders (141,143).

Neuroinflammation and neurodegeneration triggered by TBI can disrupt intestinal function through the bidirectional brain-gut axis, leading to motility disorders and increased mucosal permeability (144,145). Alterations in microbiota composition, along with activation of resident and recruited immune cells, intensify both systemic and neuroinflammation, further aggravating brain damage. Children with TBI commonly experience gastrointestinal dysfunction, which can be evaluated using the gastrointestinal failure (GIF) score. This score provides a critical assessment of gastrointestinal function, where its average over the first 3 days holds significant prognostic value for predicting ICU mortality in surgical intensive care units (146). As such, gastrointestinal dysfunction and the GIF score may represent potential risk factors for mortality in patients with severe brain injury, though further research is required. Previous studies have also indicated that patients with severe TBI exhibit fluid overload in brain tissue (147,148). However, fluid overload has not been significantly associated with mortality, prolonged ventilator use, increased risk of acute kidney injury or extended pediatric intensive care unit stay (147), suggesting it may not be a major determinant of mortality in this context. In moderate to severe TBI cases, hypocalcemia occurs most frequently, followed by hypomagnesemia, hypokalemia, hypernatremia, hyponatremia and hypermagnesemia (149). Hypocalcemia, hypomagnesemia and hypokalemia generally present early after TBI, whereas hypernatremia typically arises during the intracranial pressure (ICP) phase and hyponatremia appears predominantly after ICP reduction (149). The concurrent presence of hypernatremia and hypocalcemia has been associated with prognostic outcomes (150). Furthermore, early post-traumatic seizures have been associated with extended ICU and hospital stays, prolonged mechanical ventilation and worse 24-month outcomes, including mortality and the development of post-traumatic epilepsy (151).

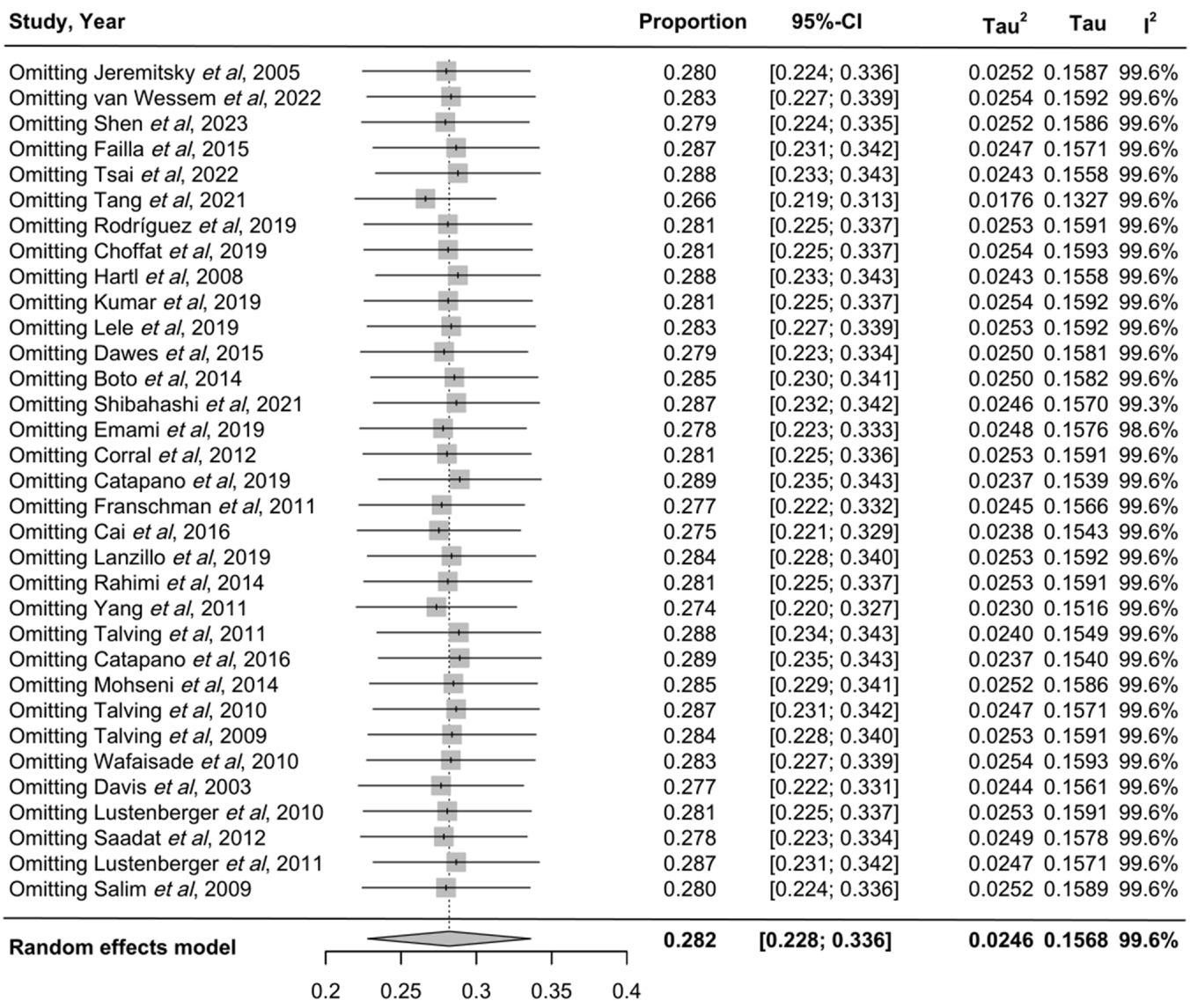

Figure 6. Sensitivity analysis evaluating incidence rates in severe traumatic brain injury cases.

The present meta-analysis examined risk factors possibly contributing to the incidence and mortality of patients with severe TBI, encompassing variables, such as age, geographic region, income level, anemia, diabetes, shock, hypotension, hypoxemia, trauma severity scores and specific types of brain injury. The cohort studies included were of high quality, as reflected by NOS scores ranging from 7 to 8, with 20 studies scoring 7 and 13 studies scoring 8.

However, limitations in the present study must be acknowledged. Evaluation standards for TBI vary significantly among hospitals and countries, which may have affected the uniformity of assessment criteria. In addition, the prognosis of severe TBI is shaped by medical expertise, economic resources, available emergency systems and medical infrastructure, which can lead to disparities between developed and developing nations. The type, location and presence of associated organ damage in brain injuries can further contribute to outcome variability. Furthermore, it should also be noted that GCS scores in patients with TBI may be skewed by confounding factors, such as hypoxia, hypotension and shock. Publication bias in the Begg test for the incidence of severe brain trauma may be due to the heterogeneity in the study population included in the meta-analysis. In the included studies, there may be significant differences in basic diseases (such as anemia and diabetes), physiological status (such as shock, hypotension and hypoxemia), trauma scores, and brain injury types in each patient. These factors may have varying degrees of effect on the incidence of severe brain trauma, leading to biased results. In addition, there may be differences in the criteria for defining and grading brain injury among different studies, which may also increase heterogeneity between studies and affect the results of the meta-analysis.

The present study identified age, anemia, diabetes, shock, hypotension, hypoxemia, trauma score, brain injury type and coagulation dysfunction as significant risk factors for both the onset of TBI and mortality in severe TBI. Immediate correction of anemia, diabetes, shock, hypotension, hypoxemia and coagulation dysfunction in patients with severe TBI is therefore recommended to improve prognosis.

TBI with a GCS score of <8 associated with a poor outcome (2). Prognosis can vary depending on the specific nature of the TBI (152). Additionally, various factors, such

as anemia, hypoxemia and shock, may influence GCS scores, potentially leading to inaccurate assessments. Nevertheless, recent advances in comprehensive treatment have resulted in improved outcomes for some patients.

The present study found that the GCS and AIS have their own advantages and disadvantages in evaluating severe TBI. GCS provides a more accurate prediction of mortality risk in elderly patients and those with diabetes, coagulopathy or subdural hemorrhage, whereas AIS demonstrates a greater predictive value in cases involving SBP ≤90 mmHg. In patients experiencing hypotension, hypoxemia, subarachnoid hemorrhage or requiring prehospital intubation, both GCS and AIS offer improved predictive capabilities for assessing the mortality risk in severe TBI (153).

In the present study, prehospital intubation was identified to be a risk factor for mortality in severe TBI, though its role in treatment remains a subject of debate. Despite this, prehospital intubation is recommended for patients in deep coma or with respiratory and circulatory instability (154). In such cases, intubation by trained and experienced practitioners is essential to manage ventilation, optimize oxygenation and secure the airway, providing critical time for more advanced interventions upon hospital admission.

The present study also identified ICP as a protective factor in severe TBI, though it remains widely recognized that ICP is strongly associated with both preoperative and postoperative mortality (155,156). Consequently, continuous monitoring of ICP in patients with severe TBI, both before and after surgery, is essential to ensure prompt and effective intervention.

Previous studies have indicated that neither clinical nor anatomical DAI significantly influenced survival, Glasgow Outcome Scale-Extended or Quality of Life after Brain Injury-Overall Scale outcomes (135,157). However, EDH was associated with a higher survival rate (113). In the present analysis, both DAI and EDH demonstrated a stronger protective effect against mortality in severe TBI cases compared with that with lower GCS scores, which is inconsistent with previous studies and requires further research to confirm. While prior studies did not identify sex as an independent predictor of poor outcomes in severe TBI (158), the present results suggest that male sex exhibits a more pronounced mortality-preventing effect in such cases.

Future iterations of the present study are anticipated to include a broader range of high-quality literature. Whilst the present study has examined the risk factors influencing both the incidence and mortality in severe TBI patients, more robust trial designs and high-quality clinical studies are needed to generate more comprehensive and higher-tier evidence. Such advancements will deepen the understanding of factors contributing to the occurrence and mortality of severe TBI. Effective management of various factors that can be effectively treated outside the hospital by the ambulance team, such as diabetes, shock, hypotension, hypoxemia and prehospital intubation, can eventually result in a decreased mortality rate. By contrast, coagulopathy, subdermal hemorrhage, subarachnoid hemorrhage and subatoma can only be effectively treated in a hospital setting. Therefore, prompt transportation to the hospital is of paramount importance because the treatment for coagulopathy, coagulopathy, subdermal hemorrhage, subarachnoid hemorrhage and subatoma should be introduced as soon as possible. With the continuous improvement in the economy, medical system, medical level, and medical equipment, whether in developed countries or not, the level of treatment and prevention of TBI brain injury is also constantly improving, and the mortality and disability rates of severe TBI will further decrease.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

MWL, BRZ, RLL and WMC had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. ZQM, BRZ, RLL, YEC and QJZ contributed to the conceptualization, data curation, formal analysis and writing original draft. YEC, SJG, YLZ and MWL contributed to the methodological design, writing reviewing and editing. MWL, YLZ and SJG verified research data. MWL, RLL, WC, ZQM and YLZ contributed to the investigation (data collection). MWL and YEC confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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