Wang *et al.*
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REVIEW

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Red blood cell transfusion strategy in traumatic brain injury patients: a systematic review and meta-analysis

Jing Wang[1], Xiang-Hui Li[2], Jiang-Quan Yu[2*] and Rui-Qiang Zheng[2*]

Abstract

Background The optimal red blood cell transfusion (RBCT) strategy for traumatic brain injury (TBI) patients remains a topic of debate. This systematic review and meta-analysis aimed to compare the outcomes of a liberal transfusion strategy versus a restrictive strategy in critically ill patients with TBI.

Methods PubMed, Web of Science, Embase, and Cochrane Library were searched from inception to November 17, 2024. We included randomized controlled trials (RCTs) of critically ill adult patients with TBI, reporting data on RBCT strategies. The outcomes included intensive care unit (ICU) mortality, long-term mortality, unfavorable functional outcomes, and the incidence of adverse events, such as transfused acute respiratory distress syndrome (TARDS) and venous thromboembolism. We also performed subgroup analyses comparing the association between disease severity and long-term mortality. This review was submitted to PROSPERO (Registration number: CRD42024558797).

Results In the results, our analysis revealed that compared to a restrictive transfusion strategy, a liberal strategy did not significantly reduce the risk of ICU mortality (RR: 0.74; 95% CI 0.28–1.91; $P=0.53$) and long-term mortality (RR: 1.02; 95% CI 0.83–1.25; $P=0.87$), but it was able to reduce the risk of unfavorable functional outcomes (RR: 0.90; 95% CI 0.82–0.98; $P=0.01$), although there may be a false positive error. In addition, the liberal transfusion strategy was associated with a higher incidence of Transfused Acute Respiratory Distress Syndrome (TARDS) (RR: 1.78; 95% CI 1.06–2.98; $P=0.03$).

Conclusions In critically ill patients with TBI, a liberal RBCT strategy appears to improve functional outcomes but carries the risk of false positive errors. In addition, this strategy does not seem to improve survival and may increase the risk of TARDS. Despite this, there remains insufficient evidence to recommend either strategy in this population.

Keywords Traumatic brain injury, Red blood cell transfusion, Mortality, Transfused acute respiratory distress syndrome, Meta-analysis

*Correspondence:
Jiang-Quan Yu
yujiangquan2021@163.com
Rui-Qiang Zheng
zhengruiqiang2021@163.com
Full list of author information is available at the end of the article

Introduction

Traumatic brain injury (TBI), a head injury caused by mechanical force, affects over 50 million people annually worldwide and is a leading cause of mortality among young individuals [1]. The brain is highly vulnerable to oxygen deprivation [2]. In TBI patients, anemia can contribute to secondary brain injury by reducing arterial oxygen content and limiting cerebral oxygen supply [3]. Impaired autoregulation of cerebral blood flow in TBI further reduces cerebrovascular reserve, heightening the risk of brain hypoxia, even in cases of mild anemia [4]. Red blood cell transfusion (RBCT) might benefit TBI patients by improving oxygen delivery and reducing brain tissue hypoxia [5]. Transfusion strategies generally follow liberal or restrictive approaches, with Hb thresholds of 10 g/dL and 7 g/dL, respectively [6].

The optimal red cell transfusion strategies for TBI patients remain controversial. Although maintaining higher hemoglobin (Hb) levels has been established not to improve mortality [7, 8], this notion may not necessarily apply to TBI patients. Numerous studies have indicated that a liberal transfusion strategy could favorably impact mortality and prognosis in TBI patients [9–11]. However, Robertson CS et al., in a Randomized Controlled Trial (RCT), revealed that maintaining Hb concentration at > 10 g/dL not only failed to improve neurological outcomes at six months in patients with a closed head injury but may also increase the risk of thromboembolic events [8]. Furthermore, Turgeon et al., through a multicenter RCT, reported that a liberal red cell transfusion strategy did not lower the risk of unfavorable functional outcomes for TBI patients at 6 months [6]. In addition, a previous meta-analysis offered more proof supporting restrictive instead of liberal transfusion strategies in TBI patients [12]. This systematic review and meta-analysis aim to synthesize conflicting literature to define the optimal transfusion Hb threshold for TBI patients.

Methods

This meta-analysis adhered to the PRISMA guidelines [13] [the PRISMA checklist can be found in the Supplementary Materials section (Table S1)], and was submitted to PROSPERO (Registration number: CRD42024558797).

Eligibility criteria

The inclusion criteria were as follows: (1) studies involving adult (age ≥ 18) patients diagnosed with TBI who require transfusion treatment; (2) studies in which the liberal and restrictive transfusion strategies are the primary interventions; (3) studies with mortality [intensive care units (ICU) and long-term mortality (60 days to 180 days mortality)] and unfavorable functional outcomes [assessed using the Glasgow Outcome Scale (GOS) or Glasgow Outcome Scale-Extended (GOS-E)] as the endpoint results; (4) clinical RCTs; (5) studies with transfusion data; and (6) studies published in English.

Search strategy

Four databases (PubMed, Web of Science, Embase, and Cochrane Library) were comprehensively searched for studies on blood transfusion strategies employed in TBI patients, from inception to November 17, 2024. Two authors independently screened the included studies. Other relevant journals were also reviewed manually. The key search terms were "Traumatic Brain Injury", "TBI", "head trauma", "acute brain injury", "acute traumatic brain injury", "anemia", "transfusion", "blood transfusion", "hemoglobin transfusion", "Red Blood Cell Transfusion", and "randomized controlled trial". Supplementary Materials (Table S2) detail our digital search strategy.

Data extraction

Data were compiled using MS Excel. Two independent authors extracted the required information [J W and X–H L] via literature screening. A consensus was reached through discussion between the authors in instances of disagreement regarding a study, with a third author [J-Q Y] consulted to resolve the dispute through arbitration should no consensus be reached. The extracted data from each trial included first author, publication date, study setting and design, diagnosis, sample content, Glasgow Coma Score (GCS) upon admission, target Hb concentration, outcome measures, and follow-up duration.

Bias risk assessment

Bias risk assessment was conducted using the Cochrane Collaboration's risk of bias assessment tool and the Cochrane Risk of Bias version 2 (ROB2) [14]. Specifically, the Cochrane Collaboration's risk of bias assessment tool was used to evaluate random sequence generation, allocation concealment, participant and staff blinding, outcome assessment blinding, incomplete results data management, and selective outcome reporting, among other biases (Fig. S1). The entire ROB2 assessment was classified into three categories: low bias risk, moderate concerns, and high bias risk (Fig. S2). Furthermore, the adapted Jadad scoring system was employed to evaluate article quality (Table S3).

Outcomes

The primary outcomes were mortality and unfavorable functional outcomes. Unfavorable functional outcomes were assessed using the GOS or GOS-E. The GOS is the most widely utilized clinician-reported outcome in acute head injury, and the GOS-E is recommended as the

preferred outcome measure for major trauma and head injury [15]. Notably, GOS scores ranged from 1 to 5, with scores of 1, 2, and 3 indicating death, vegetative state, and severe disability, respectively [15, 16]. The GOS-E is an ordinal scale with scores ranging from 1 (death) to 8 (indicating a complete return to normal life). Adverse functional outcomes were defined as GOS-E ≤ 4 [17, 18]. The secondary outcomes were Transfused Acute Respiratory Distress Syndrome (TARDS) incidences and venous thromboembolic morbidity.

Statistical analysis

Statistical analyses for this meta-analysis were conducted using Review Manager 5.4. Considering clinical heterogeneity, risk ratios and 95% confidence intervals (CI) for dichotomous outcome data were determined using a random-effects model. Study heterogeneity was evaluated using the obtained *P* value and I^2 statistics, with the I^2 statistic indicating the proportion of total variation in effect estimates attributed to inter-study differences. Notably, an I^2 value > 75% indicated substantial heterogeneity and differences with $P < 0.05$ between the two groups were deemed statistically significant. We performed a subgroup analysis to explore the association between disease severity (moderate to severe TBI versus mild TBI) and long-term mortality. The *Z* value represented the overall statistical test result. Since only six studies were included in this meta-analysis, a funnel plot was not generated for qualitative assessment of publication or report bias. In addition, a sensitivity analysis was conducted to identify any individual study that might have exerted a disproportionate influence on the analysis (STATA 18).

Trial sequential analysis

To reduce the risk of type I errors, a Trial Sequential Analysis (TSA) was conducted to estimate the necessary information for such studies, potentially allowing for the timely termination of similar research and avoidance of medical resource wastage. A one-tailed testing strategy with a Type I error rate of 5% and 80% statistical power was used to pool and evaluate long-term mortality and functional outcome data from the included studies. The TSA was performed using the TSA software (version 0.9.5.10 Beta).

Evidence certainty

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system [19] was used to evaluate the certainty of evidence for the analyzed outcomes. Evidence quality was categorized as high, moderate, low, or very low, considering factors, such as risk of bias, inconsistency, indirectness, imprecision, and publication bias. The GRADEpro software was used to create the GRADE evidence profile table.

Results

Initially, a total of 304 records were obtained. Following deduplication, 235 records remained. Furthermore, 207 studies that did not meet the predetermined criteria were excluded after a thorough review of titles. The remaining full-text articles were then screened, after which only six studies were included in the final analysis (Fig. 1). The list of excluded studies and the reason for exclusion are presented in Table S4.

Characteristics of included research

The six studies [6, 8, 9, 20–22] included in this meta-analysis compared TBI patients who underwent the liberal transfusion strategy to those who received the restrictive transfusion strategy. Table 1 details the comprehensive characteristics of the included studies, which were published between 2006 and 2024. The sample sizes across the individual studies ranged between 44 and 734. Furthermore, among these six RCTs, four [6, 8, 20, 21] compared the effects of the liberal transfusion strategy (Hb ≥ 10 g/dL) to those of the restrictive transfusion strategy (Hb ≥ 7 g/dL). In two trials [9, 22], the target Hb concentration was ≥ 9 g/dL for the liberal transfusion strategy.

Mortality

Three studies [6, 9, 20] encompassing 847 patients reported ICU mortality. Nonetheless, there was no statistically significant difference in mortality between the groups subjected to liberal and restrictive transfusion strategies (RR: 0.74; 95% CI 0.28–1.91; $P = 0.53$), with moderate heterogeneity possibly present ($I^2 = 48\%$) (Fig. 2a). Moreover, long-term mortality, defined as mortality occurring after between 60 and 180 days, was reported in five studies [6, 8, 9, 20, 21], with no significant disparity found between the two groups (RR: 1.02; 95% CI 0.83–1.25; $P = 0.87$), as well as a possible low heterogeneity ($I^2 = 0\%$) (Fig. 2b). According to the TSA results, the Required Information Size (RIS) for these investigations was 3797 participants. Moreover, the Z-curve did not cross the conventional boundary, as well as the TSA and RIS lines, highlighting the need for additional research to corroborate the influence of different transfusion strategies on long-term mortality in TBI patients (Fig. S3).

Unfavorable functional outcomes

Three trials assessed the impact of various transfusion strategies on functional outcomes [6, 9, 22]. Notably, 371/621 (60%) patients who underwent the liberal transfusion strategy and 414/620 (67%) patients who

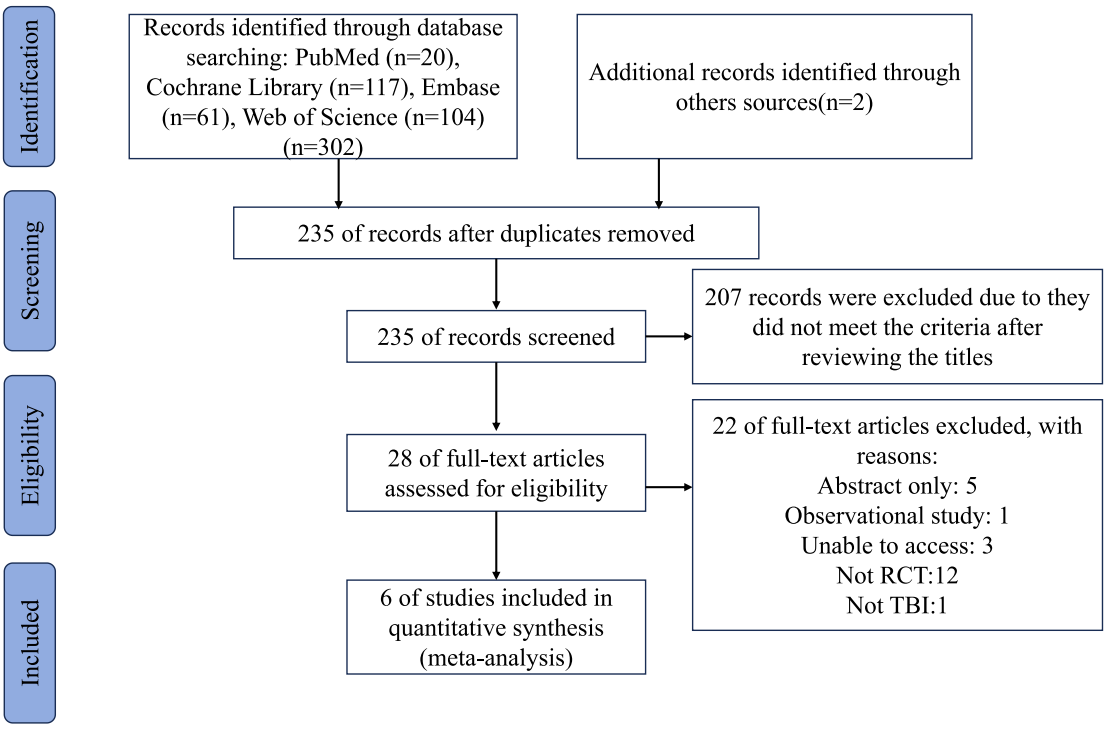


Fig. 1 Study flow diagram detailing the literature search

underwent the restrictive transfusion strategy experienced unfavorable outcomes. The results showed that the liberal transfusion strategy can reduce the risk of unfavorable outcomes compared to the restrictive strategy (RR: 0.90; 95%CI 0.82–0.98; $P=0.01$), with low heterogeneity possibly present ($I^2=0\%$) (Fig. 3). According to the TSA results, the RIS for these investigations was 6036 participants. The Z-curve crossed the traditional boundary but did not reach the TSA and RIS lines, which indicates that the results may be prone to false positives, and additional research is necessary for further validation (Fig. S4).

Secondary outcomes

TARDS

Three studies [6, 8, 9] involving 980 patients reported 38 and 20 TARDS cases in the liberal and restrictive transfusion strategy groups, respectively. Furthermore, the liberal transfusion strategy group exhibited a significant increase in TARDS risk (RR 1.78, 95% CI 1.06–2.98, $P=0.03$), with low heterogeneity possibly present ($I^2=1\%$) (Fig. 4a).

Venous thromboembolism

Venous thromboembolism comprises deep vein thrombosis and pulmonary embolism. Three studies [6, 8, 9] reported venous thromboembolism incidence and pooled analysis revealed no significant difference in venous thromboembolism incidence between the two groups (RR:1.80; 95% CI 0.70–4.62; $P=0.22$), with a substantial heterogeneity possibly present ($I^2=68\%$) (Fig. 4b).

Subgroup analyses exploring the association between disease severity and long-term mortality

Patients were further stratified into two subgroups based on disease severity, with moderate to severe TBI defined as a GCS score ranging from 3 to 12. A comparison of the various transfusion strategies with long-term mortality was conducted within both subgroups. According to the results, transfusion strategy did not correlate significantly with long-term mortality in patients with moderate to severe TBI (RR: 0.86; 95% CI 0.52–1.42; $P=0.56$). In patients with mild TBI, no statistical differences between the liberal transfusion strategy versus the restrictive transfusion strategy (RR: 1.19; 95% CI 0.62–2.28; $P=0.60$). There appeared to be minimal variability observed between the two subgroups in terms of heterogeneity ($I^2=0\%$) (Fig. 5).

Sensitivity analysis

To ascertain the impact of individual trials on the overall results, the included studies were systematically and qualitatively assessed for sensitivity. There was no

Table 1 Characteristics of included studies

Study	Design	Diagnosis	Setting	Population		Age		GCS	Target Hemoglobin	Outcome measure	Definition of unfavourable outcome	Follow-up time
				LTS	RTS	LTS	RTS					
Gobatto et al. [8]	RCT	Moderate or severe TBI	Two ICUs	21	23	33 ± 11	36 ± 15	3–12	9 g/dL, 7 g/dL	ICU, hospital, 6-months mortality rates; adverse events; ICP; lengths of ICU and hosptial stay; lengths of MV; neurological status at hospital and 6 months discharge	GOS-3	6 months
Robertson et al. [7]	RCT	Closed head injury	Two traumu centers	101	99	21–48	22–44	3–15	10 g/dL, 7 g/dL	GOS; mortality; ARDS; infections; DRS	GOS 1–3	6 months
Yamal et al. [21]	post hoc analysis of RCT	Closed head injury	Two traumu centers	101	99	NM	NM	3–8	10 g/dL, 7 g/dL	ICP; MAP; CPP; PbtO2	NM	6 months
McIntyre et al. [20]	subgroup analysis of RCT	Moderate to severe head injury	22 tertiary-level and 3 community ICUs	38	29	39.8 ± 18.1	41.7 ± 20.4	NM	10-12 g/dL, 7-9 g/dL	ICU, hospital, 30-day and 60-day mortality rates; ICU and hospital length of stay; rates of organ failure	NM	2 months
Turgeon et al. [5]	RCT	Moderate or severe TBI	34 ICUs	369	367	48.9 ± 18.8	48.4 ± 19.0	3–12	10 g/dL, 7 g/dL	unfavorable outcome; mortality; FIM; infections;Length of MV; Length of ICU stay; Transfusion complications	GOS-E ≤ 3, 4, 5	6 months
Taccone et al. [22]	RCT	TBI	72 ICUs	240	246	NM	NM	≤ 13	9 g/dL, 7 g/dL	unfavorable neurological outcome; 28-day survival; GOS-E score at 180 days; ICU and hospital lengths of stay	GOS-E 1–5	6 months

RCT: Randomized Controlled Trial; ICU: intensive care unit; TBI: traumatic brain injury; LTS: Liberal Transfusion Strategy; RTS: Restrictive Transfusion Strategy; GCS: Glasgow Coma Scale; MV: mechanical ventilation; ICP: intracranial pressure; GOS: Glasgow Outcome Scale; GOS-E: Glasgow Outcome Scale Extended; ARDS: Adult Respiratory Distress Syndrome; DRS: Disability Rating Scale; NM: not mentioned; MAP: mean atrerial pressure; CPP: cerebral perfusion pressure; PbtO2: brain tissue oxygenation; FIM: Function Independence Measure

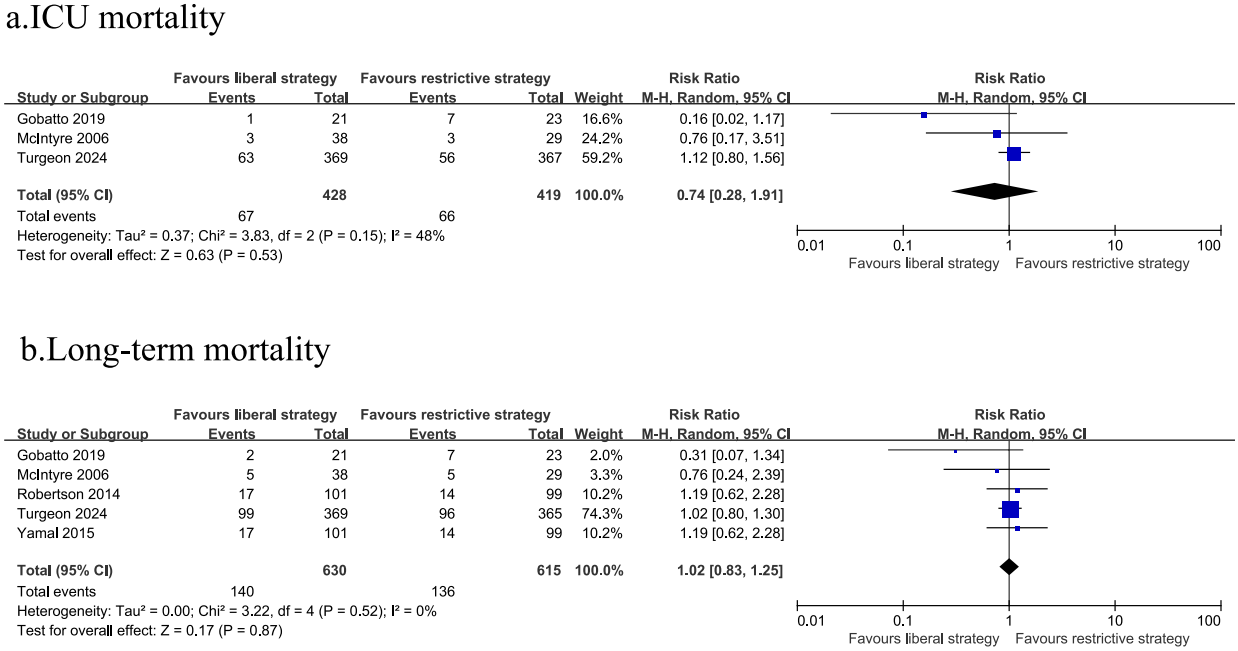


Fig. 2 Effects of different transfusion strategies on mortality. M–H, Mantel–Haenszel method; CI, confidence interval. **a** Effects of different transfusion strategies on ICU mortality. **b** Effects of different transfusion strategies on long-term mortality

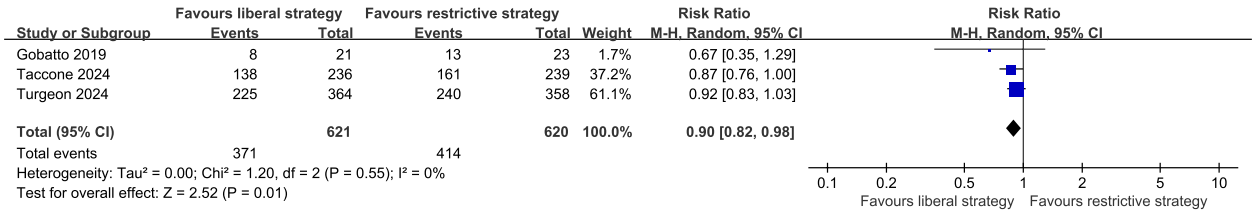


Fig. 3 Risk ratio of unfavorable functional outcomes in the LTS group versus the RTS group. M–H, Mantel–Haenszel method; CI, confidence interval

significant influence from any single study, confirming the consistency of the findings (Additional file: Figs. S5–S9).

GRADE certainty assessments

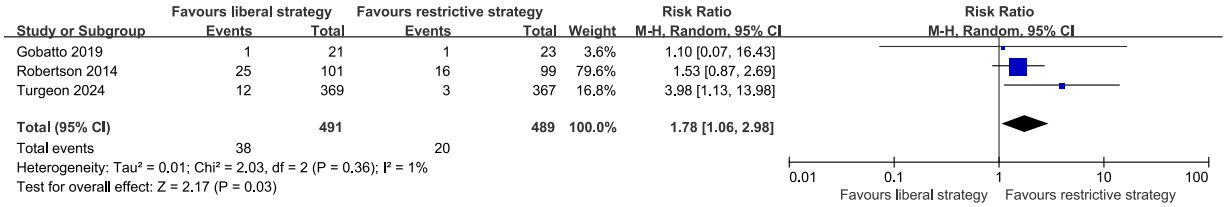
There was no significant difference in the impact of different transfusion strategies on ICU and long-term mortality in TBI patients (with low certainty of evidence). Furthermore, the certainty of evidence for the effects of liberal transfusion strategies on GOS/GOS-E, TARDS, and venous thromboembolism was low (Fig. S10).

Discussion

Our results show that the liberal transfusion strategy may improve functional outcomes in TBI patients, although there is a potential for false-positive results. In addition, this strategy does not reduce ICU mortality or long-term mortality and may increase the risk of TARDS. Furthermore, the subgroup analysis results indicate that regardless of the severity of TBI, a liberal transfusion strategy does not improve the mortality in patients with TBI. Nonetheless, this study had limited data, necessitating additional research to establish the most appropriate transfusion approach for TBI patients.

Multiple studies have reported anemia as a common occurrence among TBI patients. Several observational studies implied an association between Hb < 9 g/dL and unfavorable outcomes in TBI patients [23, 24]. In addition, anemia was reported as a significant etiological factor contributing to secondary injury in TBI patients [8]. Anemia has been recognized as an independent risk factor for unfavorable outcomes in critically ill neurological patients [24].

a. TARDS



b. Venous thromboembolism

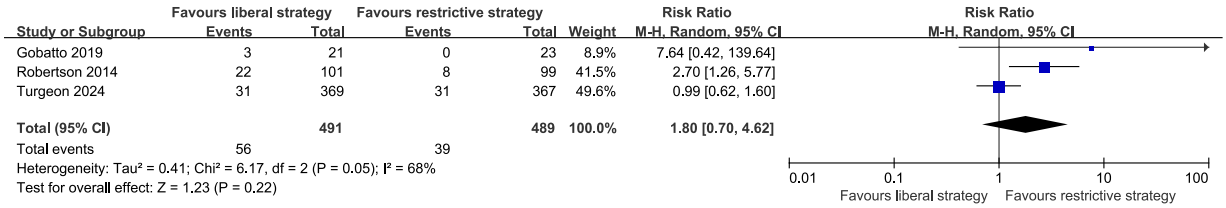


Fig. 4 Effects of different transfusion strategies on secondary outcome. M–H, Mantel–Haenszel method; CI, confidence interval. **a** Risk ratio of ARDS in the LTS group versus the RTS group. **b** Risk ratio of venous thromboembolic in the LTS group versus the RTS group

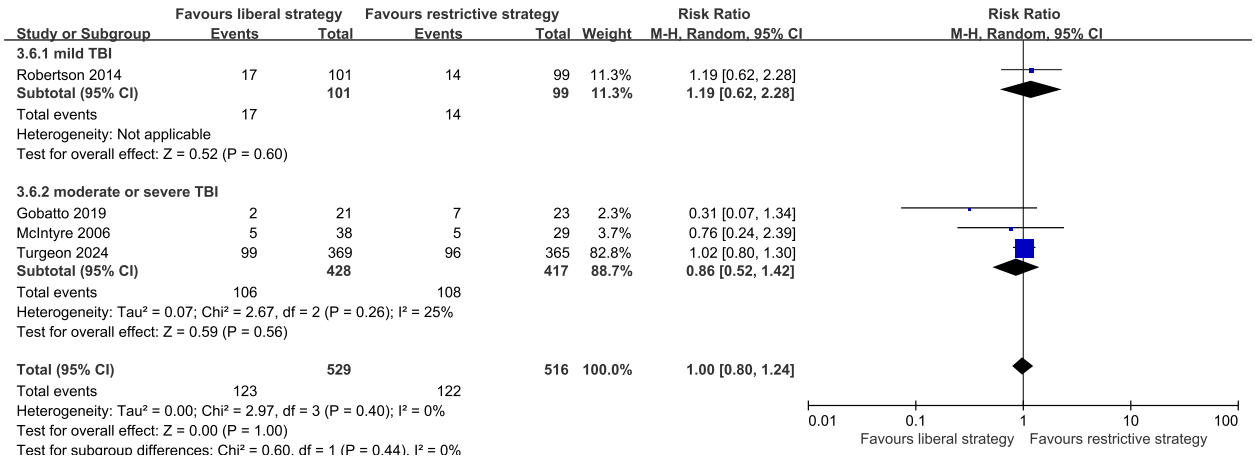


Fig. 5 Forest plot of the relationship between disease severity and long-term mortality

Besides increasing arterial oxygen saturation, improving Hb levels is the other crucial strategy for enhancing tissue oxygen delivery [24]. While evidence indicates that maintaining higher Hb concentrations has been reported to not necessarily confer an advantage to the most critically ill patients [7, 25]. However, a restrictive transfusion strategy may worsen the condition of patients with moderate to severe brain injuries [20]. In TBI patients, maintaining elevated Hb levels can improve cerebral oxygenation, mitigate the anemia-induced increase in intracranial pressure [26], and contribute to a higher blood pressure (BP), thus ensuring cerebral perfusion pressure (CPP) [8]. Preliminary research findings have linked the liberal transfusion strategy to a better prognosis in TBI patients [10, 11]. For instance, a single-center RCT involving 44 patients revealed that patients in the liberal transfusion strategy group had a lower ICU mortality rate and better neurological functional outcomes at six months [9]. A recent large-scale multicenter RCT also suggested that those who received a liberal transfusion

strategy were less likely to have an unfavorable functional outcome than those who received a restrictive strategy [22]. Our meta-analysis results also indicated that a liberal transfusion strategy might have lowered the risk of unfavorable functional outcomes in TBI patients ($P=0.01$), these findings are in contrast with those of Florez-Perdomo et al., a meta-analysis that reviewed four studies and found no significant difference in mortality rates between the liberal and restrictive transfusion groups [27]. Furthermore, the analysis of TSA results demonstrated the possibility of false positive errors in this conclusion, suggesting the necessity for further research to validate these findings. A.F. Turgeon et al. found no significant difference in mortality or neurological outcomes at 6 months between patients receiving a liberal transfusion strategy and those receiving a restrictive strategy in a randomized controlled trial involving 742 participants [6]. Herein (a meta-analysis comprising 847 and 1245 patients for the ICU and long-term mortality analyses, respectively), we found no statistically significant differences in ICU and long-term mortality between the two transfusion intervention groups.

Moreover, research evidence suggests that liberal transfusion strategies may have detrimental effects. Specifically, the risks of transfusion-associated adverse events increase with the volume of blood products administered. It is noteworthy that a previous RCT linked Hb levels maintained at 10 g/dL with a higher incidence of thromboembolic events [8]. Transfusion-induced alterations in rheological parameters and the infusion of pro-inflammatory and pro-thrombotic microparticles may contribute to thrombosis [28]. In addition, a previous meta-analysis that involved 30 RCTs revealed that compared to liberal transfusion approaches, restrictive blood transfusion strategies may effectively decrease the risk of venous thrombosis (RR: 0.65; 95% CI 0.44–0.94; $p=0.02$) [29]. Nevertheless, our findings indicated that implementing restrictive transfusion strategies does not necessarily reduce thromboembolism occurrence in TBI patients ($P=0.22$).

Analysis of data from several RCTs revealed that the liberal transfusion strategy group exhibited a notably higher TARDS incidence compared to the restrictive transfusion strategy group ($P=0.03$), which contradicts previous studies [6, 8]. However, this does not imply that the restrictive strategy reduces the incidence of TARDS. This difference could be attributed to transfusion-associated circulatory overload (TACO) and transfusion-related acute lung injury (TRALI). Both TACO and TRALI manifest as acute respiratory distress within 6 h of blood transfusion and exhibit pulmonary edema on chest radiographs [30]. Notably, the pathogenesis of TACO and TRALI remains incompletely understood. Research indicates that the incidence of TACO increases with blood transfusion volume and total fluid administered during the perioperative period of non-cardiac surgery [31]. TRALI depends on patient-related factors and blood product-related factors [32]. Despite distinct pathophysiological mechanisms, both TACO and TRALI could exacerbate pulmonary edema, ultimately leading to unfavorable outcomes for patients [30].

Establishing clearer thresholds for blood transfusion based on individual physiological responses could be crucial in reducing the occurrence of transfusion-related complications, alleviating anemia-induced secondary brain injury, and striking a balance between the potential risks of transfusion and anemia for patients [33]. Brain tissue oxygenation ($PbtO_2$) has recently garnered significant research attention, with 23 ± 7 mmHg suggested as the normal threshold [34]. Okonkwo et al. conducted a phase II RCT revealing that compared to ICP-only treatment, multimodal Intracranial Pressure (ICP) monitoring along with $PbtO_2$ assessment could more effectively alleviate brain tissue hypoxia in TBI patients [35]. Furthermore, cerebral microdialysis (CMD) could be employed as an invasive monitoring approach, enabling continuous tracking of brain metabolism in individuals with severe TBI [36, 37]. Moreover, CMD could reduce the risk of metabolic crises at specific Hb levels, thus guiding transfusion strategies and facilitating individualized treatments for TBI patients [38]. Clinically, personalized transfusion protocols could be developed based on Hb levels and multimodality neuromonitoring to improve patient outcomes and reduce transfusion-related complications.

Considering the possible sources of heterogeneity, we further conducted a sensitivity analysis. The results showed that heterogeneity may have originated from the study of Robertson et al. [8] in the unfavorable functional outcomes, where the heterogeneity decreased from 47 to 0% after removing this study. This study did not emphasize the presence of anemia in patients at baseline but rather maintained Hb levels through different strategies, which could introduce some bias. Therefore, we excluded this study when evaluating the functional outcomes. Furthermore, we conducted a subgroup analysis to explore the sources of heterogeneity, and the results indicated that disease severity is not a source of heterogeneity. However, only one study was included in the mild TBI group, which may introduce a certain degree of bias in the results.

This study had some limitations. First, despite executing an exhaustive database search, we only included studies published in English and did not explore the gray

literature or reach out to authors to inquire about unpublished studies. Consequently, we cannot definitively exclude the risk of publication bias. Second, the definitions of liberal and restrictive transfusion thresholds differed across studies, introducing an element of heterogeneity. Third, due to the unavailability of relevant data, we were unable to compare the volume of blood transfusions between the two groups. Finally, we observed significant heterogeneity in certain outcomes. Consequently, we employed a random effects model to aggregate observations and reduce confounding biases, but this may have made it challenging to detect differences in conclusion. Furthermore, sensitivity analyses showed no studies that deviated significantly from the norm, suggesting that the results obtained were reasonably dependable. Herein, we aimed to establish more appropriate transfusion strategies for TBI patients through a meta-analysis of RCTs. Our findings revealed that liberal transfusion strategies are associated with an increased incidence of TARDS in TBI patients. This association may be linked to TACO and TRALI, although distinguishing between these conditions in clinical practice remains challenging. As diagnostic tools continue to evolve, future research should further explore the impact of different transfusion strategies on TBI patients.

Conclusions

Our meta-analysis revealed that the liberal transfusion strategy did not reduce mortality but may improve unfavorable outcomes in TBI patients. Furthermore, the liberal blood transfusion strategy could increase TARDS incidences in TBI patients. It is also noteworthy that this study had a limited sample size, necessitating additional research with larger sample sizes to delineate the appropriate transfusion threshold for TBI patients.

Abbreviations

BP	Blood pressure
CI	Confidence interval
CMD	Cerebral microdialysis
CPP	Cerebral perfusion pressure
CaO_2	Arterial oxygen content
GOS	Glasgow Outcome Scale
GOS-E	Glasgow Outcome Scale-Extended
GCS	Glasgow Coma Score
ICU	Intensive care unit
ICP	Multimodal intracranial pressure
GRADE	Grading of recommendations assessment, development, and evaluation
Hb	Hemoglobin
RCTs	Randomized controlled trials
RR	Risk ratio
RIS	Required information size
RBCT	Red blood cell translation
RBCs	Red blood cells
PMNs	Polymorphonuclear leukocytes
$PbtO_2$	Brain tissue oxygenation
TARDS	Transfused acute respiratory distress syndrome
TBI	Traumatic brain injury
TSA	Trial sequential analysis
TACO	Transfusion-associated circulatory overload
TRALI	Transfusion-related acute lung injury

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40001-025-02498-3.

Additional file 1: Figure S1. Risk of bias summary.

Additional file 2: Figure S2. ROB2 Traffic Light for the included RCTs.

Additional file 3: Figure S3. TSA for long-term mortality in randomized controlled trials: one-sided boundary, the incidence of 16.83% in the liberal strategy, the incidence of 14.14% in the restrictive strategy, α of 5%, and power of 80% were set.

Additional file 4: Figure S4. TSA for unfavorable functional outcomes in randomized controlled trials: one-sided boundary, the incidence of 61.8% in the liberal strategy, the incidence of 67% in the restrictive strategy, α of 5%, and power of 80% were set.

Additional file 5: Figure S5. Sensitivity analysis of ICU mortality. CI, confidence interval.

Additional file 6: Figure S6. Sensitivity analysis of long-term mortality. CI, confidence interval.

Additional file 7: Figure S7. Sensitivity analysis of unfavorable functional outcome. CI, confidence interval.

Additional file 8: Figure S8. Sensitivity analysis of ARDS. CI, confidence interval.

Additional file 9: Figure S9. Sensitivity analysis of thromboembolic. CI, confidence interval.

Additional file 10: Figure S10. GRADE certainty assessment.

Additional file 11: Table S1. PRISMA Checklist.

Additional file 12: Table S2. Digital content search strategies.

Additional file 13: Table S3. Modified Jadad scoring for the included RCTs.

Additional file 14: Table S4. List of excluded studies and reason for exclusion.

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Author contributions

JW, JY, and RZ contributed to the conception and design of the study. JW, XL, and JY performed the data extraction. JW performed statistical analyses and drafted the manuscript. JY helped to revise the manuscript and technical support. All authors contributed to approving the submitted version.

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Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Medical College, Yangzhou University, Department of Intensive Care Unit, Northern Jiangsu People's Hospital Affiliated to Yangzhou University, No. 98 Nantong West Road, Yangzhou 225001, Jiangsu, China. [2]Department of Intensive Care Unit, Northern Jiangsu People's Hospital Affiliated to Yangzhou University, No. 98 Nantong West Road, Yangzhou 225001, Jiangsu, China.

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