BMC Emergency Medicine

SYSTEMATIC REVIEW

Open Access

Effectiveness and safety of prehospital tranexamic acid in patients with trauma: an updated systematic review and meta-analysis with trial sequential analysis

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Abstract

Background The use of prehospital tranexamic acid (TXA) in patients with trauma has attracted considerable attention. This systematic review and meta-analysis aimed to provide the best evidence for clinicians.

Methods All related literature in PubMed, Embase, and the Cochrane Central Register of Controlled Trials (Central) databases were searched systematically from their establishment to July 1, 2023. The outcome measures included 24-hour and 28–30-day mortality and adverse events (multiple organ dysfunction syndrome, acute respiratory distress syndrome, thrombotic events, and infection events). The Revised Cochrane Risk of Bias Tool for Randomized Trials was used to evaluate the quality of the randomized controlled trials (RCTs). The Methodological Index for Nonrandomized Studies (MINORS) was used to evaluate the risk of bias in non-RCTs. The required information size was estimated using trial sequential analysis. The Grading of Recommendations, Assessment, Development, and Evaluation approach was used to evaluate the evidence quality.

Results Eleven studies (comprising 11,259 patients) were included; two of these were RCTs. The overall risks of bias were low in the RCTs. ROBINS-I risk of bias was Moderate in 3 studies, serious in 5 studies, and critical in 1 study. A significant reduction in 24-hour mortality was observed (odds ratio [OR], 0.82; 95% confidence interval [CI], 0.71–0.94). A subgroup analysis that included only RCTs revealed that prehospital TXA was associated with reduced 28–30-day mortality (OR, 0.80; 95% CI, 0.66–0.97) and increased risks of thromboembolism (OR, 1.22; 95% CI, 1.03–1.44) and infection (OR, 1.13; 95% CI, 1.00–1.28) events. The blood products for transfusion decreased by 2.3 units on average (weighted mean difference [WMD], − 2.30; 95%CI, − 3.59 to − 1.01).

Conclusions This updated systematic review showed that prehospital TXA reduced the 24-hour and 28–38-day mortality and blood transfusion but increased the risks of infection and thromboembolism in patients with trauma. Future RCTs with larger and more homogeneous samples will help verify our results.

Keywords Tranexamic acid, Prehospital, Trauma, Meta-analysis, Trial sequential analysis

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Introduction

Trauma is a leading cause of death and disability worldwide, accounting for 10% of all deaths [1]. Traumatic hemorrhage is the most common cause of early death in injured individuals [2, 3]. Approximately 25% of trauma victims have immediate coagulative malfunction and up to 40% die from hemorrhagic shock [4, 5]. Early treatment of coagulopathy consequently and hemorrhagic shock significantly decreases posttraumatic death [6]. Approximately 7% of patients with trauma have high fibrinolysis, which is a key component of trauma-induced coagulopathy and is associated with bleeding-related mortality, making it a potential therapeutic target [7–9]. Tranexamic acid (TXA) is an antifiber solvent that can improve clot stability by inhibiting plasminogen activation and fibrinolysis; thus, it may be an effective treatment [10].

Two major multicenter randomized controlled trials (RCTs) examined TXA in patients with trauma in the hospital [11, 12]. The results showed that TXA administered within 3 h of injury lowered the 28-day mortality in patients with suspected bleeding (CRASH-2 trial [12]) and mild and severe traumatic brain injury (CRASH-3 trial [11]). Despite ongoing concerns regarding the efficacy, dose, and indications of TXA, its low cost and risk make it commonly used in mature healthcare systems [6, 13]. However, developed countries still lack evidence regarding the beneficial effects of prehospital usage of TXA. The meta-analysis by Almuwallad et al. [14], including four trials with 2347 patients, suggested that prehospital TXA significantly reduced early (24-h) mortality, with no associated increase in the risk of venous thromboembolism. However, the authors reported no significant reduction in 28–30-day mortality.

Nevertheless, the enthusiasm of researchers for exploring the effects of prehospital TXA has not diminished. Many experiments on prehospital TXA have been published since the meta-analysis by Almuwallad et al., and the cumulative sample size has increased approximately five-fold. Therefore, this systematic review and meta-analysis were conducted to update the existing medical evidence.

Methods

We completed the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42023418399) registration before the start of the study and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15] throughout the study. Two authors independently agreed on each assessment during the study, and a third author arbitrated any disagreements.

Eligibility criteria

Studies that met the inclusion criteria were included according to the Participant-Intervention-Comparator-Outcomes-Study (PICOS) principles (Participant [P]: patients suspected or diagnosed with traumatic bleeding [including internal and external bleeding] or traumatic brain injury; Intervention (I): prehospital TXA administration; Comparator (C): no prehospital TXA; Outcomes (O): at least one of the following should be reported: mortality, adverse events, consumption of blood products, or quantity of supplementary fluids; and Study (S): RCT or cohort study).

The exclusion criteria were: (1) secondary analysis of RCTs, 2) previously published cohort studies involving the same population, and 3) protocols and meeting abstracts.

Search strategy and selection

We conducted the search using a combination of subject words and free words and constructed search expressions using logical symbols, wildcards, and Boolean logic operators. “Tranexamic acid” and “prehospital” were the two subjects for which a thorough literature search was conducted to determine all keywords and search terms. The retrieval databases included PubMed, Embase, and the Cochrane Central Register of Controlled Trials (Central). The retrieval time was limited from database inception to July 1, 2023. We placed no restrictions on the publication year, language, or region.

References were managed using EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA). After removing duplicate records, the titles and abstracts were initially screened by two independent investigators, and full-text publications were evaluated for all potentially relevant articles.

Data collection

To synthesize the evidence, a standardized, prepiloted Microsoft Excel (Microsoft Corp., Redmond, WA, USA) form was used to tabulate and extract data from the included studies. Separately, two authors extracted the following data: study design, number of patients, first author, year of publication, baseline characteristics of patients, duration of follow-up, Injury Severity Score (ISS), systolic blood pressure (SBP) upon emergency room arrival, number of patients with SBP < 90 mmHg, duration of the prehospital phase, adverse events (multiple organ dysfunction syndrome [MODS], acute respiratory distress syndrome [ARDS], thrombotic events, infection events), mortality (at 24 h and 28–30 days), blood product consumption, and crystalloid fluid input.

Risk of bias assessment

We used the Revised Cochrane Risk of Bias Tool for Randomized Trials (RoB 2.0) to evaluate bias from areas such as reporter (selective reporting), attrition (incomplete outcome data), detection (blinding of outcome assessment), performance (blinding of participants and personnel), selection (random sequence, allocation concealment), and others. Each domain was categorized as low, unclear, or high risk according to the risk classification system. For a cohort study, the ROBINS-I tool was used in accordance with Cochrane and GRADE guidelines. Each of the seven domains of the ROBINS-I tool were rated as being at low, moderate, serious or critical risk of bias (RoB), or no information. Additionally, if at least 10 trials were found, Egger's test was used to examine publication bias.

Quantitative data synthesis

The data in these studies were presented in various ways. To calculate the standard deviation (SD) of the mean from the standard error, 95% confidence interval (CI), and P value, we followed the recommendations of the Cochrane Handbook [16]. When data were presented as median and interquartile range or median and range, the mean and SD were calculated using the method described by Wan et al. [17].

STATA Version 12 (STATA Corp., College Station, TX, USA) was used for all statistical analyses. The continuity of variables was expressed as the weighted mean difference (WMD) and 95% CI. Dichotomous data were reported as odds ratios (ORs) and 95% CI. The results are graphically represented using forest plots. $P<0.05$ was regarded as statistically significant in each study. To assess the statistical heterogeneity of the combined studies, we also produced I^2 statistics. In studies with significant heterogeneity ($I^2>50\%$), the sources of heterogeneity were further examined. The meta-analysis employed a random-effects model after removing overt clinical heterogeneity. If the methods utilized in several studies varied significantly, a random-effects model was also applied. Conversely, the fixed-effects model was used when $I^2<50\%$, indicating nonexistent or little heterogeneity. A sensitivity analysis was performed to estimate the stability of the results by individually removing each study from the analysis. Subgroup analysis was conducted according to the study design (RCT or cohort study).

Trial sequential analysis

As the results of a meta-analysis may be biased by the presence of systematic errors (bias) or random errors (play of chance) owing to sparse data and repeated significance testing [18], we performed trial sequential analysis (TSA) using TSA software (version 0.9.5.10; Copenhagen Trial Unit, Copenhagen, Denmark). The optimal information size was set to a two-sided alpha of 0.05, beta of 0.80, and relative risk reduction of 30% using a DerSimonian–Laird random-effects model. TSA allows for the evaluation of the reliability of the statistical results of meta-analyses. TSA can be used to determine whether the CI and P values in the meta-analysis are sufficient to show the expected effects [19]. The required information size (RIS) and trial sequence monitoring boundary (TSMB) were adjusted for the meta-analysis. TSMB determines whether the evidence in a meta-analysis is reliable and conclusive [20]. If the cumulative Z-curve enters the futility boundaries or crosses TSMB, the expected intervention effect shows conclusive evidence. Otherwise, the evidence is deemed absent. For dichotomous data, we calculated RIS according to the average incidence of all the included RCTs. For continuous data, we estimated RIS based on a D^2 of 50% and the average difference and variance according to empirical assumptions, which were automatically generated by the software.

Quality of the evidence

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach was used to evaluate evidence quality [21]. Five factors contributed to reduced grades: limitation of the study design (more than a quarter of the studies were considered to have a serious risk of bias), inconsistency (substantial heterogeneity, $I^2>50\%$), indirectness (dissimilar populations, interventions, outcomes, and time points), imprecision (pooled sample size<300), and potential publication bias (funnel plot assessment and Egger's test two-tailed $P<0.1$, or study quantity<10). The quality of evidence was categorized as high, moderate, low, or very low.

Results

Study selection and characteristics

Overall, 568 articles were identified. After removing duplicates, 485 articles remained. The title- and abstract-eligibility checks resulted in the exclusion of 462 studies. After screening the entire texts of 23 potentially pertinent publications, 12 additional studies were excluded. Finally, 11 studies that met the inclusion criteria were included in the meta-analysis. The studies included two RCTs [22, 23] and nine cohort studies [24–32] (Fig. 1).

The characteristics of the included studies are shown in Table 1. The 11 studies included in this meta-analysis involved 5304 cases and 5955 controls. All patients were diagnosed with or suspected of having a hemorrhagic injury or traumatic brain injury. Blunt injury was the dominant mechanism. Only one study [26] included more than half of the patients with penetrating injuries. The mean ISS ranged 16–41. Most studies only include

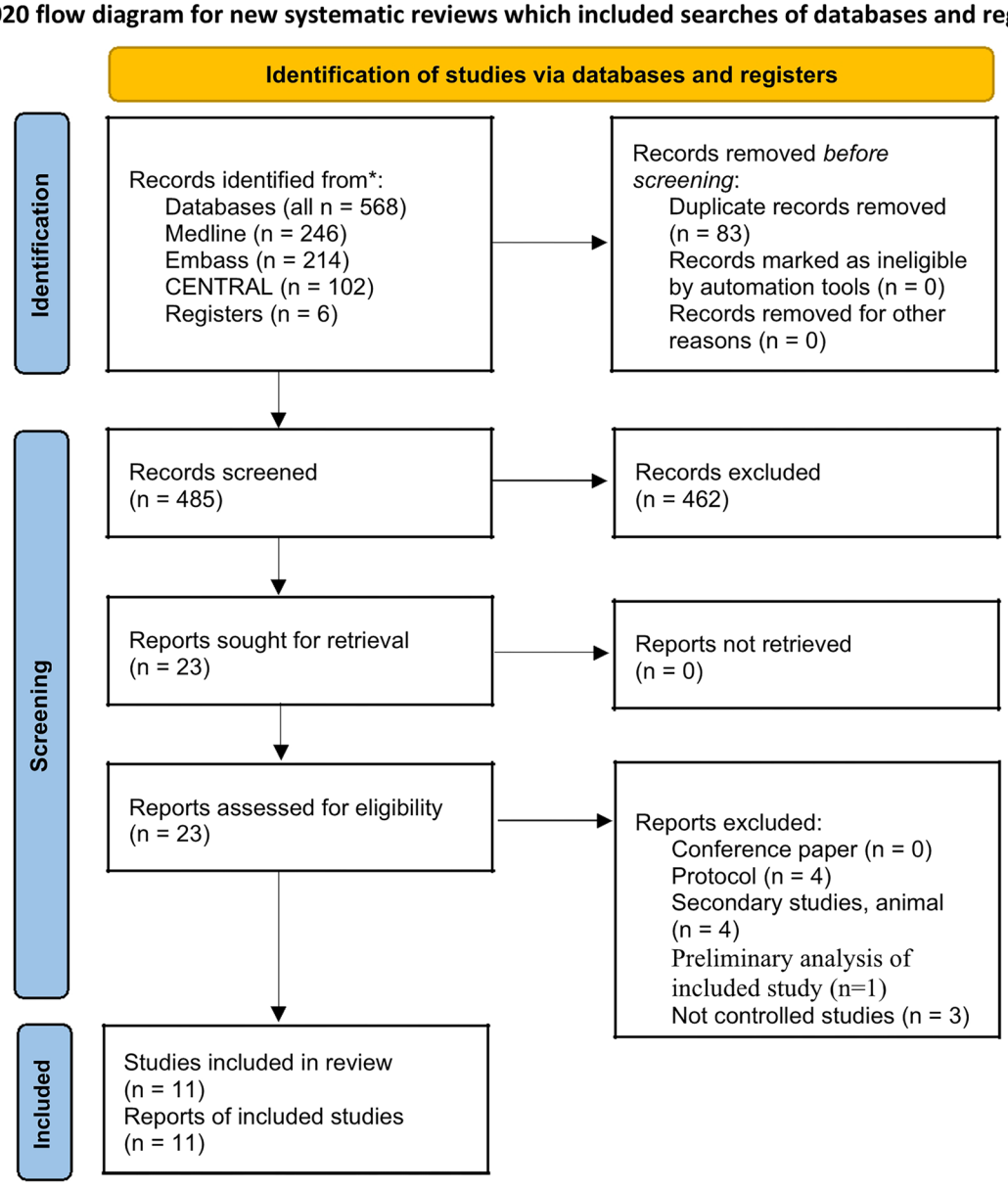

Fig. 1 Preferred reporting items for systematic reviews and meta-analysis (PRISMA) flowchart showing the search and selection process

patients who reach the emergency department or trauma center and intensive care unit. Two studies [30, 31] only excluded patients who died at the scene. The pre-hospital TXA dose of 9 included literatures was 1 g. In-hospital TXA was based on the decision of clinicians. The dosage of TXA was not clear in two studies [25, 32]. It is worth noting that Bossers et al.' s research [32] focused on patients with severe traumatic brain injury.

Risk of bias

The two RCTs showed low risks of bias [22, 23] in different domains (Fig. 2). The non-RCTs (n=9) were evaluated using ROBINS-I. Table 2 shows the quality checklist for the risk of bias for each cohort study. A low RoB was not found in any of this articles; three (33.3%) had moderate RoB, five (55.6%) serious RoB, and one (11.1%) critical RoB. Confounding bias, participant selection bias, and bias due to intervention classification are the most important ROBINS-I domains that contribute to moderate, serious, or critical RoB.

Meta-analysis

Mortality

All 11 included studies reported 28–30-day mortality. The TXA and non-TXA groups included 5,303 and 5,957 patients, respectively. Comprehensive analysis showed

Table 1 Main characteristics of all included studies

Source	Study Design	Intervention	Sample size	Age*	Gender (Male/female)	ISS*	SBP* (mmHg)	SBP≤90 mmHg (*n*)	Duration of prehospital phase* (min)	Follow-up
Leenen 2021	Prospective cohort study	Prehospital TXA	207	40	152/55	29	120	45	NA	28 days
		No prehospital TXA	215	49	146/69	29	120	41	NA	
Gulickx 2023	Prospective cohort study	Prehospital TXA	124	36.1	97/27	28	NA	24	50.4	30 days
		No prehospital TXA	353	42.7	238/115	18	NA	31	42.0	
Neeki 2018	Prospective cohort study	Prehospital TXA	362	37.96	293/69	16.08	78.42	NA	NA	28 days
		No prehospital TXA	362	37.64	293/69	17.15	83.66	NA	NA	
Imach 2021	Prospective cohort study	Prehospital TXA	2275	47.6	1679/596	32.4	113	539	77	30 days
		No prehospital TXA	2275	47.5	1688/587	32	111	571	77	
Menyar 2019	Retrospective cohort study	Prehospital TXA	102	31.4	98/4	22	107.3	55	74	30 days
		No prehospital TXA	102	31.5	91/11	22	102.4	74	62	
Wafaisade 2016	Prospective cohort study	Prehospital TXA	258	43	187/71	24	114	51	77.2	30 days
		No prehospital TXA	258	41	187/71	24	117	50	74.2	
Boudreau 2018	Retrospective cohort study	Prehospital TXA	62	44.5	45/17	22	126	NA	NA	NA
		No prehospital TXA	54	33	45/9	26	110	NA	NA	
Wessem 2021	Prospective cohort study	Prehospital TXA	120	42	80/40	34	120	23	61	28 days
		No prehospital TXA	114	53	77/37	29	127	15	61	
Guyette 2020	Randomized controlled trial	Prehospital TXA	447	41	327/120	12	123	NA	39	30 days
		Placebo	456	42	341/115	12	126	NA	39	
Russell 2023	Randomized controlled trial	Prehospital TXA	657	44.1	459/198	29	NA	464	NA	6 months
		Placebo	643	44.2	459/184	29	NA	445	NA	
Bossers 2020	Prospective cohort study	Prehospital TXA	693	47	486/207	27	142	NA	NA	12 months
		No prehospital TXA	1134	45	797/337	26	143	NA	NA	

TXA, tranexamic acid; ISS, Injury Severity Score; SBP, systolic blood pressure

* Data are expressed as means

that prehospital TXA had no advantage in reducing 28–30-day mortality in patients with trauma (P=0.710; OR, 0.97; 95% CI, 0.83–1.14; I^2=67.1%; Fig. 3). The sensitivity analysis showed that when one study was excluded at a time, the combined results did not change (OR, 1.01; 95% CI, 0.80–1.22). TSA showed that the cumulative Z-curve did not cross TSMB but crossed the futility boundary (Table 3). TSA of the pooled meta-analysis showed no evidence of the anticipated intervention effect. Publication bias was not evident in Egger's test (P=0.878). Subgroup analyses were conducted according to the study design. Meta-analysis of the RCTs showed that prehospital TXA reduced 28–30-day mortality (P=0.024; OR, 0.80; 95% CI, 0.66–0.97; I^2=0%; Fig. 3). TSA showed that the cumulative Z-curve did not cross TSMB and did not reach RIS (the cumulative information size was 2190). We observed no significant difference in the pooled analysis of cohort studies (P=0.815; OR, 1.02; 95% CI, 0.86–1.22; I^2=66.4%; Fig. 3).

Six studies [22, 23, 25, 26, 30, 31] calculated the mortality in patients with trauma 24 h after admission. The TXA and non-TXA groups included 4,123 and 4,341 patients, respectively. The results of the meta-analysis showed that prehospital TXA was associated with reduced 24-hour mortality (P=0.004; OR, 0.82; 95% CI, 0.71–0.94; I^2=46.3%; Fig. 4). The sensitivity analysis showed that the results were unstable (OR, 0.84; 95% CI, 0.51–1.02). TSA revealed strong evidence (Table 3); however, subgroup analysis suggested similar results between RCTs (P=0.027; OR, 0.71; 95% CI, 0.52–0.96; I^2=0%; Fig. 4) and cohort studies (P=0.035; OR, 0.85; 95% CI, 0.72–0.99; I^2=59.2%; Fig. 4).

Thromboembolic events

Thromboembolic events include deep vein thrombosis, pulmonary embolism, myocardial infarction, and ischemic stroke. Data on thromboembolism events were available from nine studies [22–24, 26–31]. The total

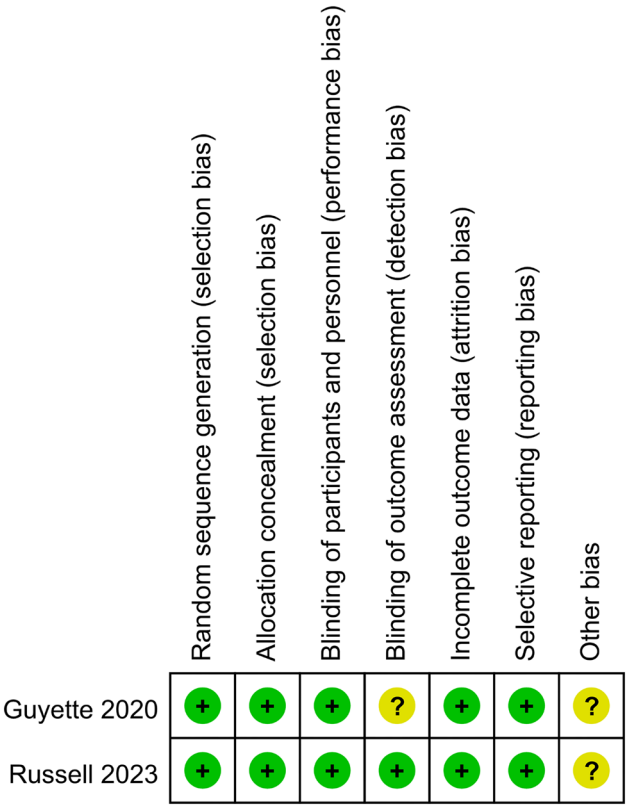

Fig. 2 Summary of risk of bias assessment of the randomized controlled trials

numbers of patients in the TXA and non-TXA groups were 4,303 and 4,337, respectively. The TXA group showed a 19% higher thromboembolism rate compared to the non-TXA group (P=0.019; OR, 1.22; 95% CI, 1.03–1.44; I^2=30.9%; Fig. 5). The sensitivity analysis showed that the results were stable (odds ratio [OR], 1.27; 95% CI, 1.00–1.49). TSA revealed strong evidence (Table 3). Subgroup analysis showed that only the aggregate analysis of RCTs was statistically significant (P=0.022; OR, 1.33; 95% CI, 1.04–1.70; I^2=10.1%; Fig. 5) and a RIS of 3978 (cumulative information size, 2198).

Infection events

Seven studies reported on infection events [22–24, 28–31]. The meta-analysis included 3,835 and 3,871 patients with and without TXA treatment, respectively. The infection rate was 9.8% higher in the TXA group (P=0.046; OR, 1.13; 95% CI, 1.00–1.28; I^2=0%; Fig. 6). Sensitivity analysis showed that the results were unstable (OR, 1.14; 95% CI, 0.97–1.31). TSA revealed an absence of evidence (Table 3). Subgroup analysis showed that the summary analysis of RCTs (P=0.024; OR, 1.25; 95% CI, 1.03–1.52; I^2=0%; Fig. 6) was statistically significant, while that in the cohort studies was not (P=0.453; OR, 1.06; 95% CI, 0.91–1.24; I^2=0%; Fig. 6).

ARDS and MODS

Four studies reported data on ARDS [23, 24, 28, 29]. The results of the meta-analysis showed no significant difference between the TXA and non-TXA groups (P=0.804; OR, 0.95; 95% CI, 0.64–1.42; I^2=21.2%; Fig. 7). The pooled analysis of five studies [23, 24, 29–31] showed no significant difference in the incidence of MODS between the two groups (P=0.351; OR, 0.95; 95% CI, 0.85–1.06; I^2=0%; Fig. 7).

Total blood products transfused and crystalloid infusion volume

Four studies [26–28, 31] reported on the total blood products transfused. Compared with the group without TXA, the blood products for transfusion by TXA decreased by an average of 2.3 units (P=0.000; WMD, −2.30; 95% CI, −3.59 to −1.01; I^2=81.8%; Fig. 8). Data from five studies [23, 24, 29–31] showed that the crystalloid infusion volume in the TXA group increased by an average of 620 mL (P=0.001; WMD, 620.68; 95% CI, 265.37–976.00; I^2=71.8%; Fig. 8).

Quality of the evidence

The grade evaluations of the quality of the evidence are shown in Table 4. Overall, the quality of the evidence was

Table 2 ROBINS-I assessment of study bias for included studies

Bias domain	Boudreau et al.	Wessem et al.	Leenen et al.	Gulickx et al.	Neeki et al.	Imach et al.	Menyar et al.	Wafaisade et al.	Bossers et al.
Due to confounding	Critical	Serious	Serious	Serious	Moderate	Serious	Moderate	Moderate	Moderate
Selection of participants	Serious	Low	Low	Low	Low	Moderate	Low	Low	Low
Classification of interventions	Moderate	Low	Moderate	Serious	Low	Low	Low	Low	Serious
Deviation from intended	Low	Low	Low	Low	Low	Low	Low	Low	Low
Missing data	Low	Low	Low	Low	Low	Moderate	Low	Low	Low
Measurement of outcomes	Moderate	Low	Low	Low	Low	Low	Low	Low	Low
Selection of the reported result	Low	Low	Low	Low	Low	Low	Low	Low	Low
Overall risk of bias	Critical	Serious	Serious	Serious	Moderate	Serious	Moderate	Moderate	Serious

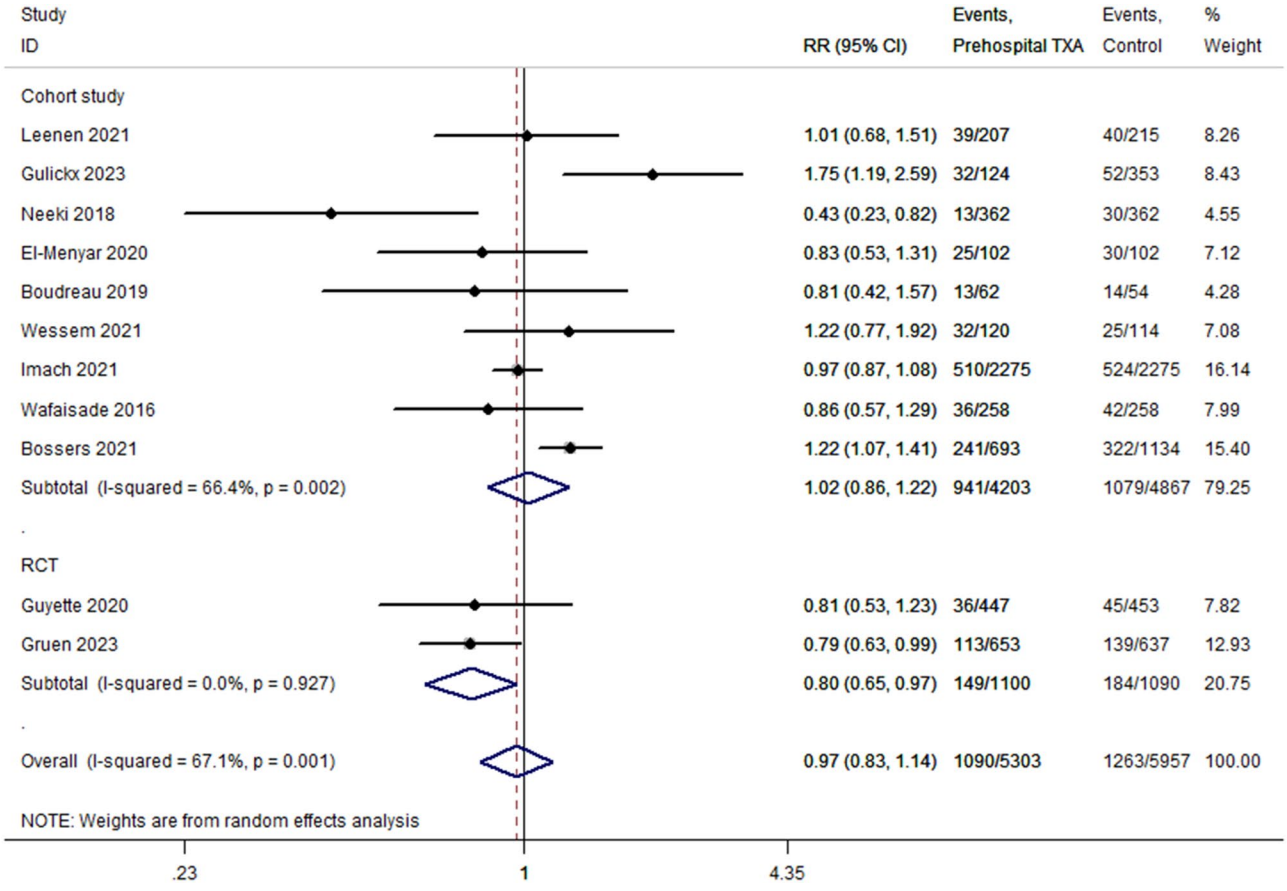

Fig. 3 Pooled and subgroup analyses of 28–30-day mortality

very low or low, mostly due to study limitations, inconsistencies, and potential publication bias.

Discussion

This meta-analysis of the curative effect of prehospital TXA in patients with trauma showed that compared to no TXA, prehospital TXA reduced 24-hour mortality. However, this effect did not persist for 28–30-day mortality. These results were consistent with those reported by Almuwallad et al. [14], although our study had a larger sample size. Notably, prehospital TXA reduced the 28–30-day mortality in the RCT subgroup. Compared to those of cohort studies, the results of the RCTs were more accurate and reliable. Selective bias may have contributed to the insignificant results of the cohort studies. While TSA showed that more RCTs are needed to verify the effects of prehospital TXA on 28–30-day mortality, the present study is the first to report the effect of prehospital TXA in this regard.

Previous studies showed the benefits of TXA in treating polytrauma [33–35]. These benefits include bleeding control, hemostasis, and resuscitation, which reduce mortality in patients with trauma. TSA in the current meta-analysis identified the early (within 24 h) benefits of TXA. Prehospital TXA reduced blood product consumption. Conversely, the infusion of crystalloids increased. However, the largest clinical trial (CRASH-2) [36] so far has not found any substantial reduction in the amount of blood transfusion or transfusion received by trauma patients treated by TXA. There are several possible reasons for this difference. First, the main measure of traumatic bleeding was surgical hemostasis, and the difference of procedures was conceivable. Second, Prehospital TXA enables patients to receive antifibrinolytic treatment earlier, resulting in less bleeding. Finally, the meta-analysis data showed statistical heterogeneity after conversion. In their meta-analysis of 129 trials involving more than 10,000 patients, Ker et al. [37] showed

Table 3 Meta- and trial sequential analyses of the outcomes

	Meta-analysis				TSA								
Outcomes	**OR**	**95%CI**	**P**	**I^2%**	**RRR%**	**IIA%**	**ICA%**	**D^2%**	**CIS**	**RIS**	**Cross TSMB**	**Cross FB**	**Evidence**
Mortality (at 28–30 days)	0.97	0.83, 1.14	0.71	67.4	19.25	13.63	16.88	78	11,260	17,841	NO	YES	AE
Mortality (at 24 h)	0.82	0.71, 0.94	0.004	46.3	25.94	7.25	9.79	71	8464	13,282	YES	NO	FE
Thromboembolism events	1.22	1.03, 1.44	0.019	30.9	-27.34	16.3	12.8	0	8964	9823	YES	NO	FE
Infection events	1.13	1.00, 1.28	0.046	0	-17.86	28.44	24.13	0	7706	3275	NO	NO	AE

AE, absent evidence; CI, confidence intervals; D2, diversity; FB, futility boundary; FE, firm evidence; ICA, incidence in control arm; CIS, cumulative information size, RIS, required information size; IIA, incidence in intervention arm; OR, odds ratio; RRR, relative risk reduction; TSMB, trial sequential monitoring boundary; TSA, trial sequential analysis

that TXA use was associated with a 38% reduction in the number of allogeneic blood transfusions. In summary, a reduction in blood transfusion by prehospital TXA was initially observed, which warrants further exploration.

TXA should be used with caution as antifibrinolytic therapy may be associated with increased risks of seizures [38, 39], myocardial infarction [40] and other thrombotic complications [41, 42]. However, the relationship between TXA and vascular occlusion remains controversial. Robert et al. [43] conducted an RCT to explore the effect of high-dose TXA and the influence of thromboembolic events in patients with acute gastrointestinal bleeding. The authors found increased venous thromboembolism events (deep venous thrombosis or pulmonary embolism) in the TXA group than in the placebo group (risk ratio [RR], 1.85; 95% CI, 1.15–2.98). Xie et al. [44] suggested that TXA was associated with the total incidence of vascular occlusion after total knee arthroplasty ($P<0.001$). However, a meta-analysis [45] of 216 studies involving 125,550 patients by Taeuber et al. reported no association between TXA levels and the overall risk of thromboembolic events. Previous meta-analyses [14] also reported similar conclusions. However, our study found that prehospital TXA increased the risk of vascular occlusion (OR 1.22; 95% CI, 1.03–1.44). Further investigation revealed that this discrepancy solely affected RCTs. TSA suggested that this result requires further verification. In view of the fact that the current research has not found the benefit of pre-hospital TXA on the overall mortality of trauma patients, and it will lead to an increase in the risk of thromboembolic events, TXA provided in hospital according to coagulation parameters may be a better choice. Interestingly, prehospital TXA administration increased the incidence of nosocomial infections. This may be because the suppression of plasminogen activation by TXA exacerbates staphylococcal infectious arthritis and sepsis [46].

Previous researches suggested that TXA should be administered as soon as possible after arriving at a trauma treatment location [11, 12, 36]. Most deaths due to bleeding in patients with trauma occur within hours of arrival at the trauma center, emphasizing the need for early prehospital assistance to provide helpful treatment [47–49]. Consequently, guidelines for early treatment have recently been developed, including the use of prehospital TXA after trauma [28, 34, 50]. The results of this study suggest that pre-hospital TXA may be beneficial to the early survival of trauma patients. However, stratified studies of the dosage and timing of drug administration are scarce. Further studies should not only focus on

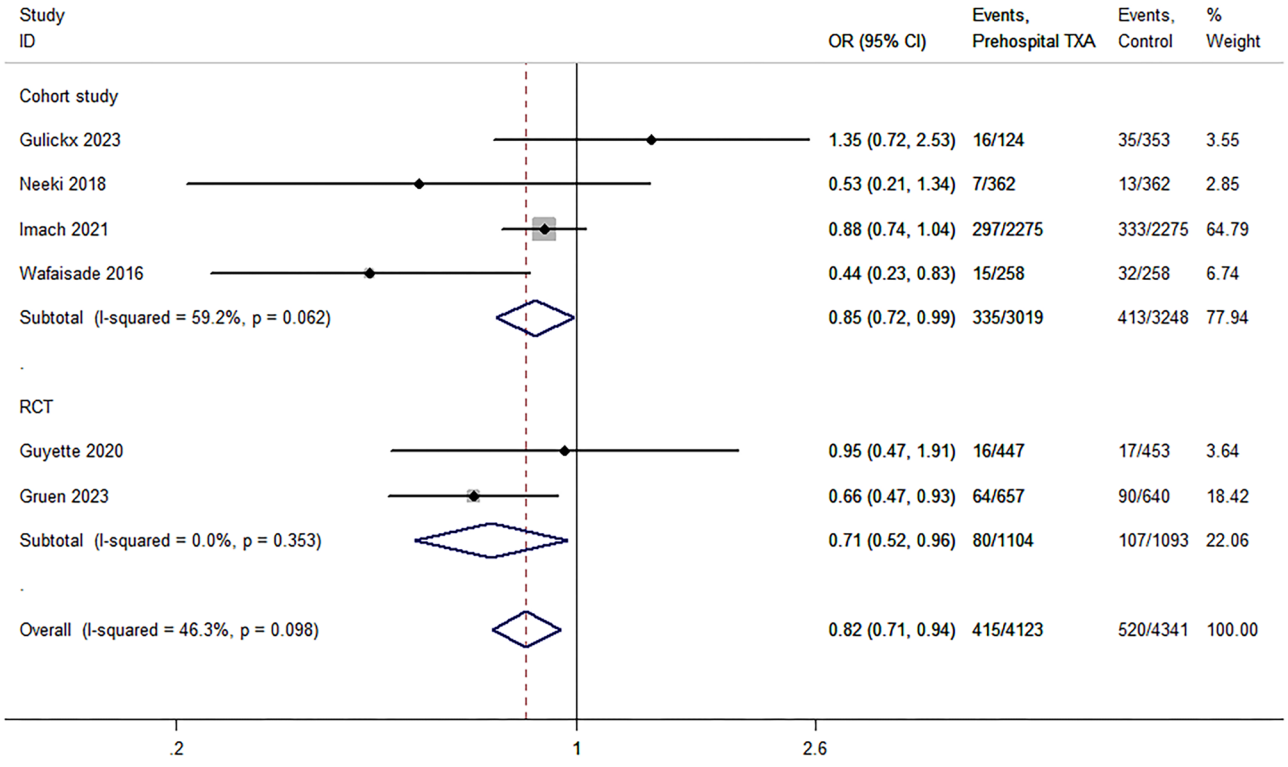

Fig. 4 Pooled and subgroup analyses of 24-hour mortality

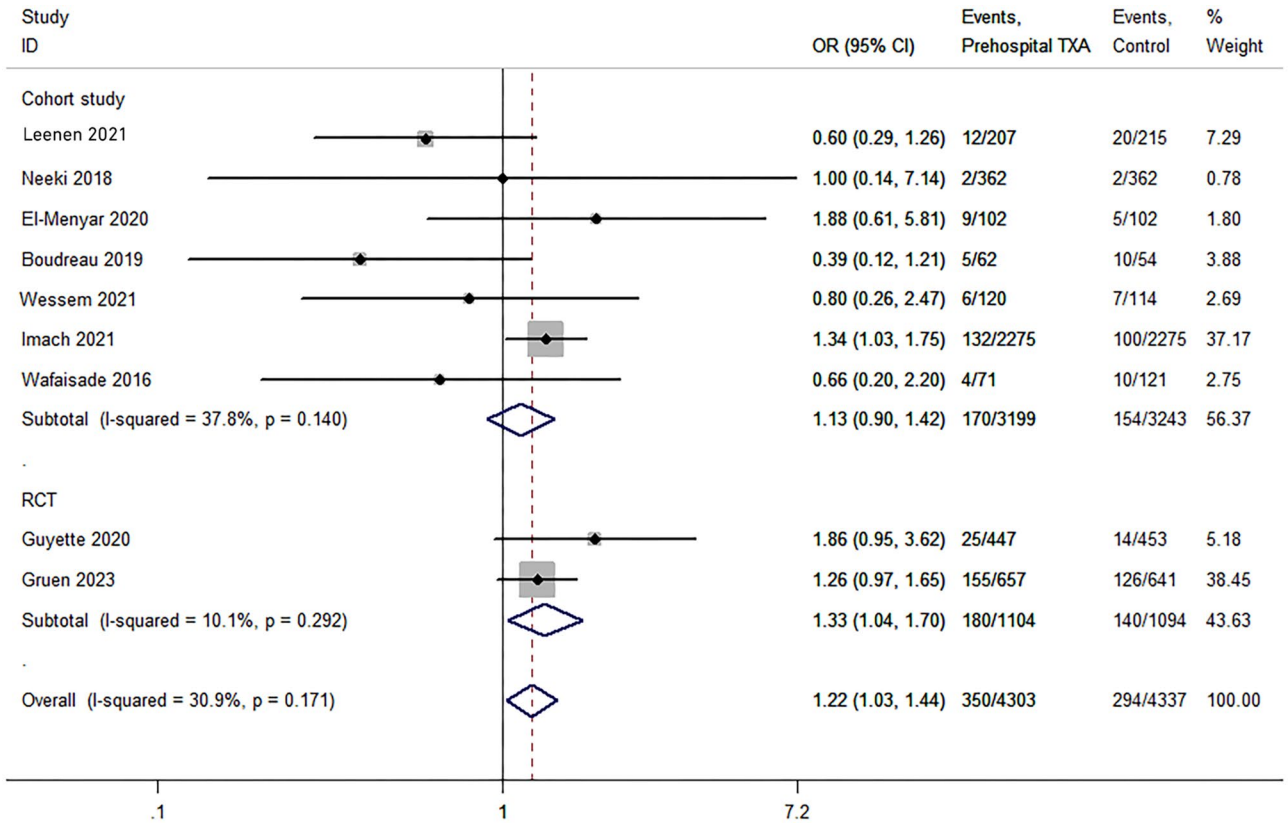

Fig. 5 Pooled and subgroup analyses of thromboembolic events

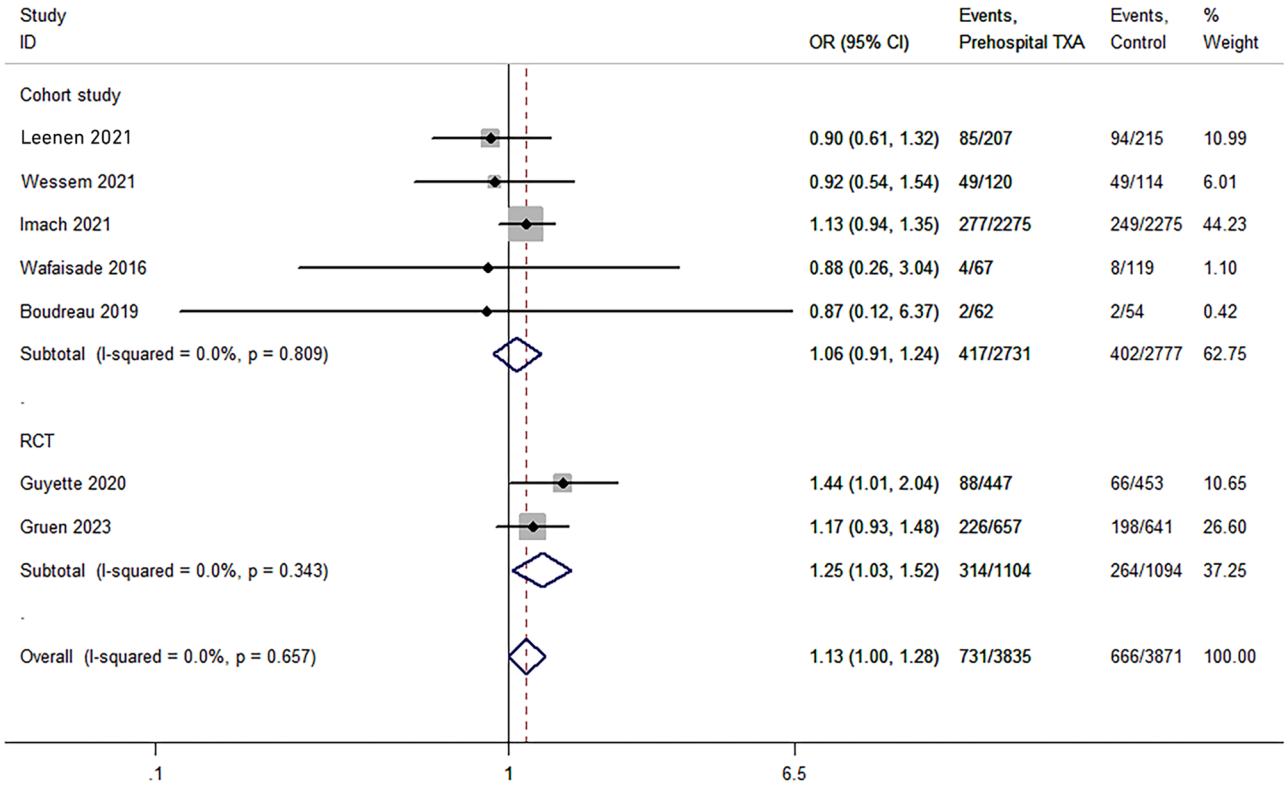

Fig. 6 Pooled and subgroup analyses of infection events

Table 4 Summary of the findings and assessment of the quality of the evidence

	Summary of findings				Quality of evidence assessment (GRADE)				
Overall	**Trials**	**Participants**	**I^2, %**	**WMD/OR (95% CI)**	**Study limitation**	**Inconsistency**	**Imprecision**	**Publication bias**	**Quality**
Mortality (at 28–30 days)	11	11,260	67.4	0.97 (0.83, 1.14)	-1	-1	None	None	Low
Mortality (at 24 h)	6	8464	46.3	0.82 (0.71, 0.94)	-1	None	None	-1	Low
Thromboembolism events	9	8964	30.9	1.22 (1.03, 1.44)	-1	None	None	-1	Low
Infection events	7	7706	0	1.13 (1.01, 1.28)	-1	None	None	-1	Low
MODS	5	6301	0	0.95 (0.85, 1.06)	-1	None	None	-1	Low
ARDS	4	1672	21.2	0.93 (0.63, 1.38)	-1	None	None	-1	Low
Total blood products transfused (in units)	4	1560	81.8	-2.30 (-3.59, -1.01)	-1	-1	None	-1	Very low
Crystalloid infusion volume (mL)	5	6434	71.8	620.68 (265.37, 976.00)	-1	-1	None	-1	Very low

MODS, multiple organ dysfunction syndrome; ARDS, acute respiratory distress syndrome; WMD, weighted mean difference; OR, odds ratio

improving the survival of trauma patients but also on the relationship between thromboembolic events, infectious complications, and early mortality.

The present study had some limitations. First, only two of the 11 included studies were RCTs, and the lack of randomization created a risk of confusion and bias. We attempted to explain these hazards using a subgroup analysis. The two RCTs demonstrated differing significance and homogeneity from cohort studies. Second, the different TXA doses and administration times may have resulted in heterogeneity. Third, the ISS varied considerably between studies and within some studies, which

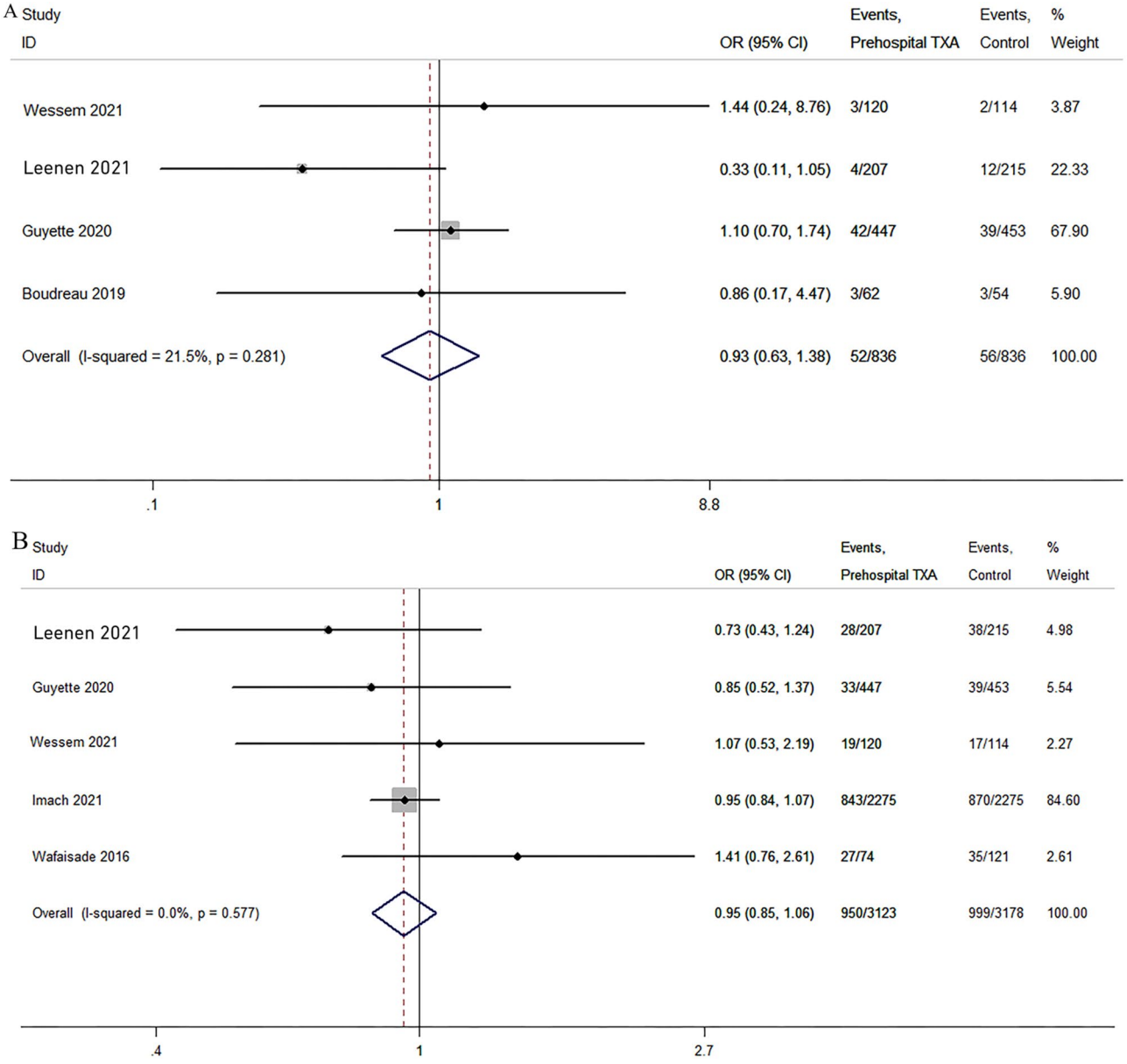

Fig. 7 Pooled analyses of acute respiratory distress syndrome (ARDS) (**A**) and multiple organ dysfunction syndrome (MODS) (**B**)

may understate the efficacy of TXA in investigations with larger ISS values. Fourth, some studies lacked sufficient data to measure the dispersion for effect measurements (SD or SE). Data translated using this formula may have resulted in statistical heterogeneity. Finally, the differences in trauma investigation, including transport times, severity of injury, blunt/penetrating trauma, level 1/level 2 trauma center, civil/military study setting etc., are also factors are also factors that cause bias. Nevertheless, we evaluated the quality of evidence using a validated tool and considered the level of certainty of the evidence for each result.

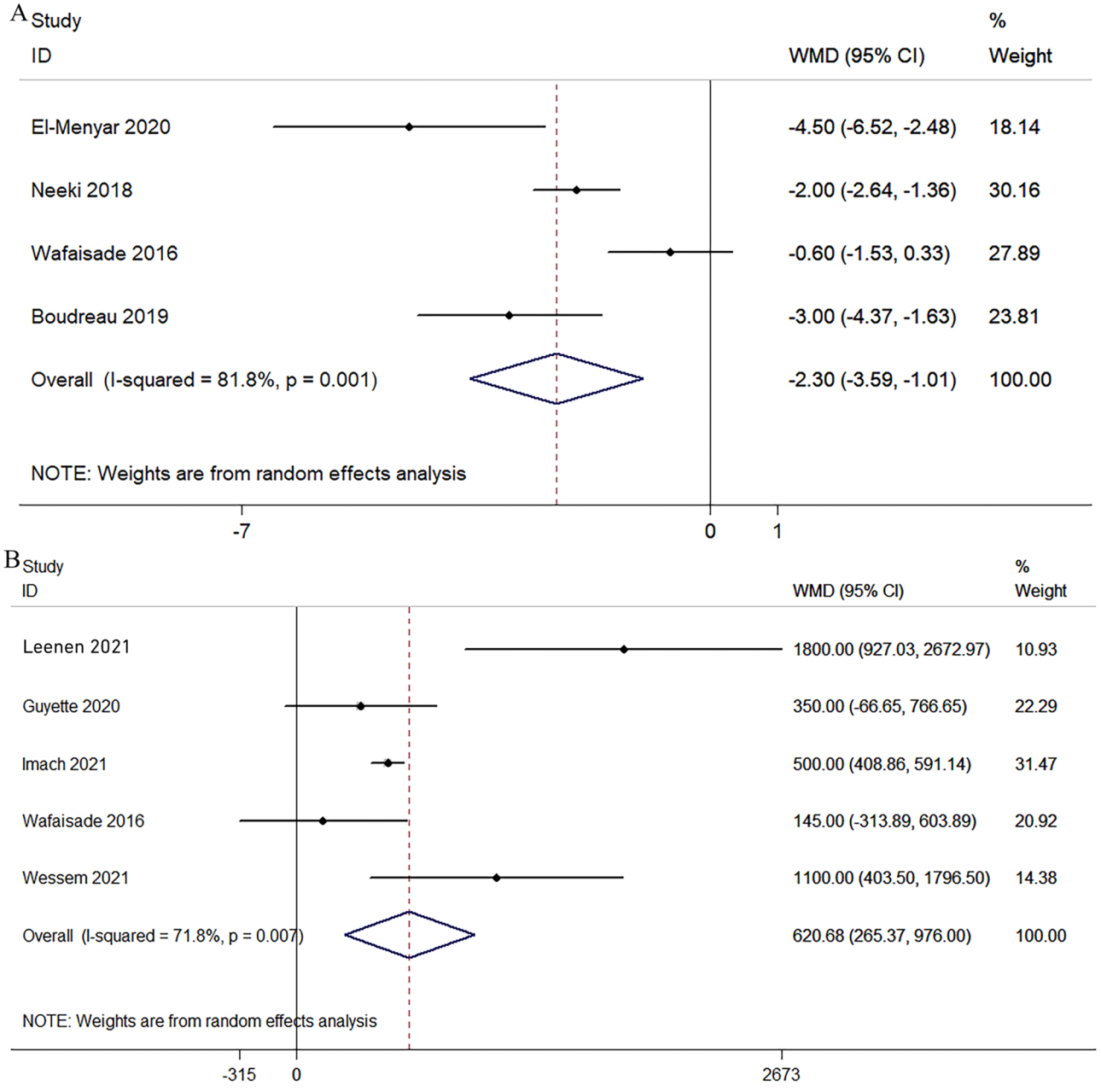

Fig. 8 Pooled and analyses of total blood products transfused (**A**) and crystalloid infusion volume (**B**)

Conclusions

The results of this meta-analysis of published studies showed that prehospital TXA significantly reduced the 24-hour mortality of patients with trauma. This effect was also observed for 28–30-day mortality in the RCT subgroup. Additionally, prehospital TXA was associated with increased risks of thromboembolism and infection. These findings suggest the need to reconsider the risk-benefit ratio of TXA in the prehospital setting.

Abbreviations

ARDS	Acute respiratory distress syndrome
CI	Confidence interval
GRADE	Grading of recommendations, assessment, development, and evaluation
ISS	Injury Severity Score
MINORS	Methodological Index for nonrandomized studies
MODS	Multiple organ dysfunction syndrome
OR	Odds ratio
PICOS	Participant-Intervention-Comparator-Outcomes-Study
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
RCT	randomized controlled trial
RR	Risk ratio
RIS	Required information size
RoB 2.0	Revised Cochrane Risk of Bias tool for randomized trials
SBP	Systolic blood pressure
SD	Standard deviation

TSA	Trial sequential analysis
TSMB	Trial sequence monitoring boundary
TXA	Tranexamic acid
WMD	Weighted mean difference

Acknowledgements
Not applicable.

Author contributions
Conceived and designed the study: H-Y C, W-T XPerformed the study: H-Y C, L-G W, C-C F, W Y, W-T XAnalyzed the data: H-Y C, L-G W, C-C FWrote the manuscript: H-Y C, W Y, W-T X.

Funding
No funding was disclosed by the author(s).

Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable. The study was waived by the Ethics Committee of the People's Hospital of Nanchuan District.

Consent for publication
Not applicable.

Conflict of interest
The authors, their immediate families, and any research foundation with which they are affiliated have not received any financial payments or other benefits from any commercial entity related to the subject of this article.

Received: 19 March 2024 / Accepted: 17 October 2024
Published online: 25 October 2024

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