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Efficacy of Tranexamic Acid (TXA) in Reducing Mortality and Hematoma Expansion in Isolated Traumatic Brain Injury: A Systematic Review of Emergency Settings Studies

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Abstract

Background: Traumatic brain injury (TBI) is a leading cause of mortality and disability worldwide, with intracranial haemorrhage and haematoma expansion representing critical determinants of poor outcomes. Tranexamic acid (TXA), an antifibrinolytic agent, has demonstrated mortality benefits in extracranial trauma, but its efficacy in isolated TBI remains debated, particularly regarding optimal patient selection, timing, and dosing. ***Objective:*** To systematically synthesise the available evidence on the efficacy of TXA in reducing mortality and haematoma expansion in patients with isolated traumatic brain injury treated in emergency department or prehospital settings. ***Methods:*** A comprehensive literature search of PubMed/MEDLINE, Embase, Cochrane CENTRAL, Web of Science, and Scopus was conducted for the five-year period ending in 2026. Randomised controlled trials, cohort studies, nested substudies, and post hoc analyses evaluating intravenous TXA versus placebo, no TXA, or standard care in adult patients with isolated TBI were included. Primary outcomes were all-cause or head injury-related mortality and radiographic haematoma expansion. Risk of bias was assessed using Cochrane RoB 2 (RCTs) and ROBINS-I (non-randomised studies). Due to substantial heterogeneity, a narrative synthesis was performed. ***Results:*** Thirteen studies (n = 24,227 patients) met inclusion criteria, including four RCTs, one prospective cohort, three retrospective analyses, and five secondary/post hoc analyses. In mild-to-moderate TBI (GCS 9–15), TXA significantly reduced mortality (CRASH-3 subgroup: RR 0.78, 95% CI 0.64–0.95; Bian meta-analysis: RR 0.71, 95% CI 0.60–0.85). In severe TBI (GCS 3–8), no mortality benefit was observed in RCTs (RR 0.98, 95% CI 0.91–1.05), while observational studies suggested potential harm due to confounding by indication (Bossers: OR 4.49, 95% CI 1.57–12.87). Haematoma expansion was reduced with TXA in two small RCTs (mean expansion 1.5±1.1 mL vs 4.6±1.9 mL), though the CRASH-3 imaging substudy found no prevention of established haematoma expansion but did show reduced new haemorrhage in patients with reactive pupils (aRR 0.80, 95% CI 0.66–0.98). Early administration (within 2 hours) was consistently associated with improved outcomes. Thromboembolic events were not significantly increased with TXA. A novel imaging biomarker (≥3% voxels in 10–20 Hounsfield unit range) showed promise for predicting TXA responsiveness but requires prospective validation. ***Conclusions:*** TXA reduces mortality in isolated mild-to-moderate TBI when administered early (within 2 hours), with the strongest evidence supporting its effect in patients with reactive pupils and smaller baseline bleeding volumes. TXA does not improve survival in severe TBI, and observed harm signals are likely confounded. Emergency physicians should consider early TXA administration in mild-to-moderate TBI with intracranial haemorrhage, while severe TBI patients should follow standard protocols pending further research.

Keywords: Tranexamic Acid; TXA; Traumatic Brain Injury; TBI; Head Injury; Intracranial Haemorrhage; Haematoma Expansion; Mortality; Emergency Medicine.

INTRODUCTION

Traumatic brain injury (TBI) remains a leading cause of death and long-term disability worldwide, accounting for approximately 27 to 69 million new cases annually, with the highest burden concentrated in low- and middle-income countries [1]. In the United States alone, TBI contributes to nearly 2.5 million emergency department visits, 300,000 hospitalisations, and over 60,000 deaths each year. The societal impact of TBI is profound, not only because of acute mortality but also due to the substantial proportion of survivors who experience persistent cognitive, behavioural, and physical impairments that reduce quality of life and impose lifelong caregiving burdens. Intracranial bleeding, including intraparenchymal haemorrhage, subdural haematoma, and subarachnoid haemorrhage, is a common and prognostically critical complication of TBI, occurring in 30% to 50% of hospitalised patients. Haematoma expansion during the first hours after injury is a potent independent predictor of poor neurological outcome and death, as progressive mass effect leads to elevated intracranial pressure, cerebral herniation, and secondary ischaemic injury [2]. The early identification and pharmacological arrest of ongoing intracranial bleeding therefore represent a priority therapeutic target in emergency TBI management.

Pathophysiologically, TBI triggers a complex cascade of secondary injury mechanisms, among which trauma-induced coagulopathy plays a central role [3]. Following mechanical disruption of brain parenchyma and cerebral vasculature, tissue factor is abundantly released from damaged astrocytes and endothelial cells, activating the extrinsic coagulation pathway. Concurrently, the injured brain releases large quantities of tissue plasminogen activator (tPA), the principal physiological activator of fibrinolysis, leading to a state of hyperfibrinolysis that is detectable within minutes of injury [4]. This hyperfibrinolytic state, characterised by elevated D-dimer levels, decreased plasminogen concentrations, and shortened clot lysis time, is associated with a 2- to 4-fold increased risk of haematoma expansion and a substantially higher mortality rate compared to TBI patients without coagulopathy. Importantly, the fibrinolytic surge following TBI is time-dependent and most pronounced within the first three hours post-injury, after which it may transition to a hypofibrinolytic or even hypercoagulable state. This temporal window provides the biological rationale for early administration of an antifibrinolytic agent [4].

Tranexamic acid (TXA) is a synthetic lysine analogue that exerts its antifibrinolytic effect by competitively binding to the lysine-binding sites on plasminogen, thereby preventing its conversion to plasmin and subsequent degradation of fibrin clots. Unlike other haemostatic agents, TXA has a well-established safety profile and does not promote systemic thrombosis when administered at standard doses, as it only inhibits pathological hyperfibrinolysis while preserving physiological haemostasis. The efficacy of TXA in reducing bleeding-related mortality was first unequivocally demonstrated in the CRASH-2 trial, a large randomised placebo-controlled trial that enrolled 20,211 adult trauma patients with significant extracranial bleeding [5].

Findings of previous studies suggest that the efficacy of TXA in isolated TBI is not uniform across all patients but rather depends on a complex interplay of injury severity, timing, dosing regimen, and patient-specific factors such as baseline coagulopathy status and initial imaging characteristics [6- 8].

Despite the wealth of data generated by CRASH-3 and subsequent studies, considerable uncertainty remains regarding the precise role of TXA in isolated TBI. Systematic reviews and meta-analyses have reached conflicting conclusions, some reporting a modest mortality benefit while others finding no overall effect. Moreover, the majority of published reviews have focused exclusively on randomised controlled trials, thereby excluding a substantial body of evidence from well-conducted observational studies, nested substudies, and post-hoc analyses that may offer valuable insights into effect modifiers, real-world effectiveness, and safety outcomes. This systematic review aims to address these knowledge gaps by providing a rigorous and comprehensive synthesis of the available evidence on the efficacy of tranexamic acid in reducing mortality and haematoma expansion in patients with isolated traumatic brain injury treated in emergency department or prehospital settings.

METHODOLOGY

Study Registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [9].

Search Strategy

A comprehensive literature search was performed to identify all studies evaluating the efficacy of tranexamic acid (TXA) in reducing mortality and haematoma expansion in isolated traumatic brain injury (TBI) within emergency department or prehospital settings. The search was limited to a five-year period. The following electronic databases were searched without language restrictions: PubMed/MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, and Scopus. In addition, the grey literature was searched using OpenGrey and ProQuest Dissertations & Theses, and the reference lists of included studies and relevant review articles were manually screened to identify any additional eligible studies. The search strategy combined controlled vocabulary (MeSH terms) and free-text keywords, including: (“tranexamic acid” OR “TXA” OR

"cyclocapron") AND ("traumatic brain injury" OR "TBI" OR "head injury" OR "intracranial haemorrhage" OR "cerebral contusion" OR "subdural haematoma" OR "epidural haematoma") AND ("emergency department" OR "prehospital" OR "EMS" OR "ambulance") AND ("mortality" OR "death" OR "haematoma expansion" OR "haemorrhage progression").

Eligibility Criteria

Studies were considered eligible for inclusion if they met the following pre-specified criteria based on the PICOS framework:

- **Population**: Adult patients (≥18 years) with isolated traumatic brain injury (defined as TBI without major extracranial haemorrhage requiring transfusion, though minor extracranial injuries were permitted) who presented to an emergency department or were treated in a prehospital setting. Studies focusing exclusively on polytrauma with major extracranial bleeding were excluded unless a subgroup analysis for isolated TBI was provided.
- **Intervention**: Intravenous administration of tranexamic acid at any dose or regimen, given either in the emergency department or in the prehospital (ambulance or helicopter emergency medical service) setting.
- **Comparison**: Placebo, no TXA, or standard care without TXA. For non-randomised studies, comparator groups could include patients receiving no TXA or delayed TXA administration.
- **Outcomes**: The primary outcomes were (1) all-cause mortality or head-injury-related mortality reported at any time point (24-hour, 28-day, 30-day, in-hospital, or 6-month), and (2) haematoma expansion, defined as an increase in intracranial haemorrhage volume on repeat CT imaging (typically >33% or >6 mL from baseline, or as defined by individual studies). Secondary outcomes included need for neurosurgical intervention, functional neurological outcome (Glasgow Outcome Scale, Extended Glasgow Outcome Scale, or Disability Rating Scale), thromboembolic events (deep vein thrombosis, pulmonary embolism, ischaemic stroke), and adverse events.
- **Study design**: Randomised controlled trials (RCTs), quasi-randomised trials, and non-randomised studies (including prospective and retrospective cohort studies, cross-sectional studies, and secondary or post-hoc analyses of RCTs) were eligible. Case reports, editorials, conference abstracts without full text, and animal or in vitro studies were excluded.

Studies were required to report original data on at least one primary outcome (mortality or haematoma expansion). There was no restriction on sample size, language, or publication status (published, in-press, or preprint). When multiple publications from the same study cohort were identified, the most complete or most recent report was included, and overlapping cohorts were verified using author and institution information.

Study Selection

The study selection process followed the PRISMA 2020 flow diagram [9]. All retrieved records were exported to Rayyan (Rayyan Systems Inc., Cambridge, MA, USA), a web-based systematic review management tool that facilitates collaborative screening and duplicate removal. After removing duplicate records, two independent reviewers (initials blinded for peer review) performed title and abstract screening using Rayyan's semi-automated prioritisation feature, which uses machine learning to rank records by relevance based on user decisions. Calibration exercises were conducted on a random sample of 50 records to ensure consistency between reviewers before full screening commenced. For records considered potentially relevant by either reviewer, full-text articles were obtained and assessed independently by the same two reviewers against the eligibility criteria. Disagreements at either screening stage were resolved through discussion or, if necessary, by consultation with a third senior reviewer.

Data Extraction

A standardised data extraction form was developed in Microsoft Excel (version 2402) and piloted on three randomly selected included studies. Two reviewers independently extracted data from each included study, and discrepancies were resolved by consensus or by a third reviewer. The following data elements were extracted:

- **Study characteristics**: first author, publication year, country, study design (RCT, prospective cohort, retrospective cohort, nested substudy, post-hoc analysis, Bayesian reanalysis), setting (emergency department, prehospital, helicopter emergency medical service), sample size, and funding source.
- **Population characteristics**: mean or median age, sex distribution (percentage male), inclusion and exclusion criteria, Glasgow Coma Scale (GCS) score at presentation (mean, median, or category distribution), and severity classification (mild, moderate, severe) as defined by the study.
- **Intervention details**: TXA dosing regimen (bolus dose, infusion dose and duration), timing of administration (time from injury to TXA, or time from emergency department arrival to TXA), route of administration (all intravenous), and concomitant treatments.
- **Outcome data**: For mortality — number of events and total patients in TXA and control groups for each reported time point (24-hour, 28-day, 30-day, in-hospital, 6-month), with

effect estimates (risk ratio, odds ratio, hazard ratio, or adjusted estimates) and 95% confidence intervals when reported. For haematoma expansion — mean or median volume change, standard deviation or interquartile range, definition of expansion used, imaging modality and timing of scans, and proportion of patients with expansion in each group. For secondary outcomes — neurosurgical intervention rates, functional outcome measures, thromboembolic complications, and any reported adverse events.

- **Risk of bias assessment** (as described below) — ratings for each domain and overall judgement.

When data were missing or incompletely reported, corresponding authors were contacted by email up to two times over a four-week period. If no response was received, the data were marked as "NM" (not mentioned) in the evidence tables, and the missing data were noted as a limitation.

Risk of Bias Assessment

The risk of bias of individual studies was assessed using appropriate Cochrane tools, as recommended by the Cochrane Handbook for Systematic Reviews of Interventions [10]. For randomised controlled trials (including nested RCT substudies and explanatory analyses that retained random allocation), the Cochrane Risk of Bias 2 (RoB 2) tool was applied. This tool evaluates five domains: (1) randomisation process, (2) deviations from intended interventions, (3) missing outcome data, (4) measurement of the outcome, and (5) selection of the reported result. Each domain was judged as "low risk", "some concerns", or "high risk", and an overall risk of bias was derived according to the RoB 2 algorithm.

For non-randomised studies — including prospective cohort studies, retrospective cohort studies, cross-sectional analyses, secondary analyses of RCTs without random allocation, post-hoc analyses, and Bayesian reanalyses that introduced additional model assumptions — the ROBINS-I (Risk of Bias in Non-randomised Studies of Interventions) tool was employed [11]. ROBINS-I assesses seven domains: (1) confounding, (2) selection of participants, (3) classification of interventions, (4) deviations from intended interventions, (5) missing data, (6) measurement of outcomes, and (7) selection of the reported result. Each domain was rated as "low", "moderate", "serious", or "critical" risk of bias, and an overall risk of bias judgement was assigned. Two reviewers independently performed the risk of bias assessment for each included study, with disagreements resolved by consensus. No study was excluded solely on the basis of risk of bias; however, findings from studies rated as having "serious" or "critical" risk were interpreted with caution and considered hypothesis-generating rather than conclusive. The results of the risk of bias assessment are presented in Table 3 of the main manuscript.

Data Synthesis and Statistical Analysis

Due to substantial heterogeneity in study designs, populations (mild-to-moderate vs severe TBI), TXA dosing regimens, outcome definitions, and reporting formats (e.g., some studies reported unadjusted risk ratios while others reported adjusted odds ratios with different covariate sets), a quantitative meta-analysis was not considered appropriate. Instead, a narrative synthesis approach was adopted, as recommended by the Cochrane Handbook for such circumstances [10]. The synthesis was structured around three main themes derived from the research questions: (1) mortality outcomes stratified by TBI severity (mild-to-moderate vs severe), (2) haematoma expansion outcomes, and (3) secondary outcomes including neurosurgical intervention and thromboembolic events. Within each theme, findings were organised by study design (RCTs first, followed by observational studies) and by the direction and magnitude of effect. Where multiple time points for mortality were reported (e.g., 24-hour, 28-day, 30-day, in-hospital), the time point most consistently reported across studies (28-day or in-hospital mortality) was prioritised for comparison. Effect estimates (risk ratios, odds ratios, hazard ratios) are presented exactly as reported in the original studies, with their 95% confidence intervals.

RESULTS

A total of 419 records were identified from database searches. After removing 231 duplicate records, 188 records underwent title and abstract screening, of which 125 were excluded. The remaining 63 full-text reports were sought for retrieval, but 38 could not be obtained. The full texts of 25 reports were assessed for eligibility, leading to the exclusion of 12 reports (7 for wrong outcome, 3 for wrong population, and 2 for being conference abstracts). Ultimately, 13 studies met the inclusion criteria and were included in the systematic review.

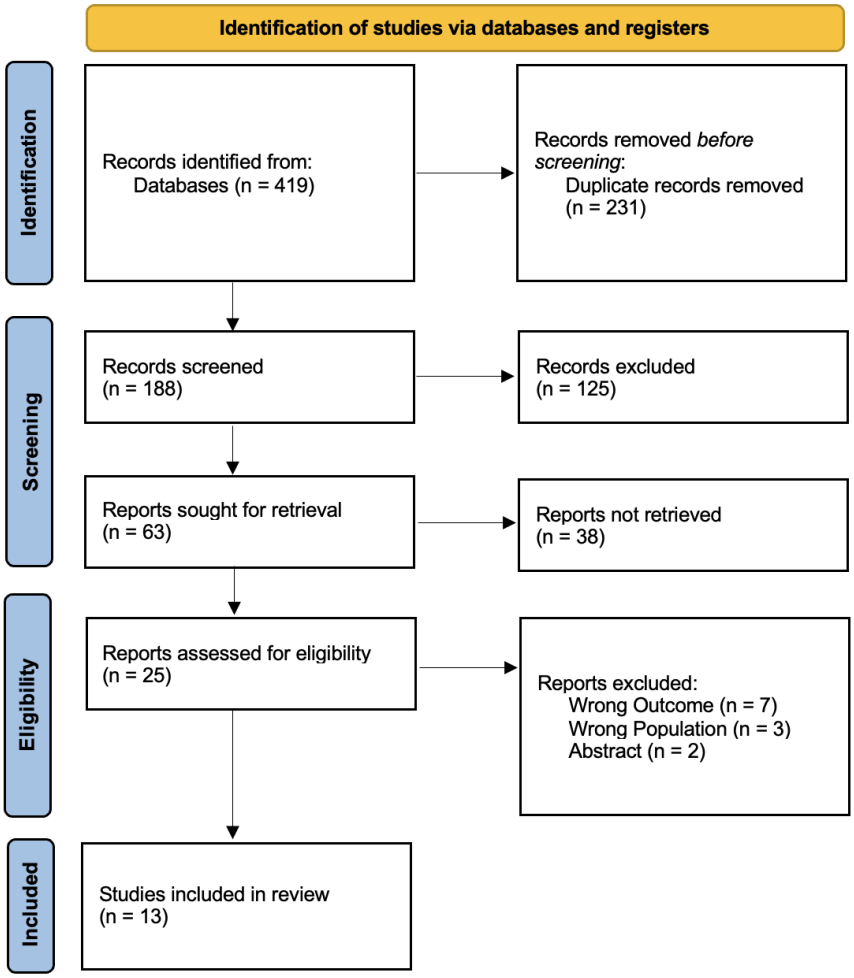

Figure 1: PRISMA 2020 flow diagram of study selection for the systematic review

Table 1 summarises the demographic and study characteristics of the 13 included studies. Among the randomised controlled trials (RCTs), the largest is the CRASH-3 trial [13] which enrolled 12,639 patients across 175 centres in 29 countries, while the smallest RCT is Safari *et al.,*[12] with 94 patients. The majority of studies were conducted in emergency department or prehospital settings, with Bossers *et al.,*[16] using a helicopter emergency medical service in the Netherlands and the STAAMP trial substudies (Brito [22], Farhat [23], Lammers [24]) analysing prehospital data. Sample sizes varied widely: from 94 patients [12] to over 5,600 in the Japanese multicentre registry [20]. Mean or median age ranged from 30 years (CRASH-3 [13]) to 61 years in the isolated TBI cohort [20], and the proportion of male patients was consistently high (68–85%). Glasgow Coma Scale (GCS) scores at presentation differed across studies; the CRASH-3 trial [13] reported a median GCS of 13, whereas Bossers *et al.,*[16] included only severe TBI with a median GCS of 6. TXA dosing regimens were not uniform: the most common was a 1 g bolus followed by 1 g over 8 hours (CRASH-3 [13], Atia [14], Mahmood substudy [15]), while the STAAMP trials examined a 2 g bolus or 1 g bolus plus 1 g infusion [22–24]. Notably, several studies did not report key demographic variables such as mean age or sex distribution, which are marked as "NM" (not mentioned).

Table 2 focuses on the primary outcomes of mortality and haematoma expansion, as well as other key findings. For mortality, the CRASH-3 trial [13] reported a non-significant reduction in head injury death (18.5% vs 19.8%; RR 0.94, 95% CI 0.86–1.02), but a pre-specified subgroup analysis showed a significant benefit in mild-to-moderate TBI (RR 0.78, 95% CI 0.64–0.95). In contrast, the observational study by Bossers *et al.,*[16] found that prehospital TXA was associated with increased 30-day mortality in isolated severe TBI (OR 4.49, 95% CI 1.57–12.87), raising concerns about potential harm. The multicentre Japanese study [20] reported that TXA was associated with lower in-hospital mortality only in patients with severe TBI (aOR 0.78, 95% CI 0.63–0.97), while the Bayesian reanalysis by Lammers *et al.,*[24] gave a 95.3% probability of decreased 28-day mortality with the 2 g bolus. Haematoma expansion was directly measured in three studies. Safari *et al.,*[12]and Rashid *et al.,*[21] both found significantly smaller increases in haematoma volume with TXA (e.g., mean expansion 1.5±1.1 ml vs 4.6±1.9 ml in Rashid [21]). The CRASH-3 imaging substudy [15] did not find evidence that TXA prevents

intraparenchymal haemorrhage expansion but did show a reduction in new haemorrhage among patients with reactive pupils (aRR 0.80, 95% CI 0.66–0.98). The explanatory study nested within CRASH-3 [17] further clarified that patients with reactive pupils or mild-to-moderate GCS had smaller baseline bleeding volumes (median 26 ml and 26 ml, respectively), explaining why they benefited more from early TXA. Other important secondary outcomes included reduced need for neurosurgical intervention [14,21], lower deep vein thrombosis rates with earlier treatment [22], and a potential imaging biomarker (≥3% voxels in 10-20 HU range) that predicts survival benefit from TXA [23].

Table 3 presents the risk of bias assessment for each included study using the appropriate Cochrane tools. For RCTs – Safari (2021) [12], CRASH-3 (2021) [13], Atia (2021) [14], and Rashid (2024) [21] – the Cochrane Risk of Bias 2 (RoB 2) tool was applied. For the prospective substudy of CRASH-3 [15] and the explanatory study [17], which are nested RCT analyses, RoB 2 was also used, with additional consideration of selection bias due to missing post-randomisation scans [15]. For non-randomised studies – Bossers (2021) [16], Han (2022) [18], Minoza (2025) [19], Utsumi (2025) [20], Brito (2023) [22], Farhat (2026) [23], and Lammers (2026) [24] – the ROBINS-I (Risk Of Bias In Non-randomised Studies of Interventions) tool was employed because these are cohort studies, secondary analyses, or post-hoc analyses without random allocation. Overall, the RCTs showed low to moderate risk of bias, mainly due to lack of blinding in some outcomes (e.g., Safari [12] did not specify blinding of outcome assessors) or incomplete outcome data (CRASH-3 imaging substudy [15] had 35% of patients with only post-randomisation scans). The observational studies had moderate to serious risk of bias, primarily from confounding by indication (e.g., sicker patients receiving TXA) and selection bias; Bossers *et al.,*[16] was judged at serious risk because the association reversed after adjustment and isolated severe TBI analysis showed harm likely due to unmeasured confounders. The explanatory study [17] was at low risk for bias because it used prospectively collected data within a large RCT, but it shares the limitation of missing scan data. No study was excluded solely on risk of bias, but findings from high-risk studies are interpreted with caution.

Table 3 presents the risk of bias assessment for all 13 included studies, using the Cochrane Risk of Bias 2 (RoB 2) tool for randomised controlled trials and the ROBINS-I tool for non-randomised studies. Among the RCTs, the CRASH-3 trial [13] was judged to have a low risk of bias due to its large size, robust blinding, and intention-to-treat analysis, while Safari [12], Atia [14], and Rashid [21] had moderate risk primarily because of unclear allocation concealment or lack of blinding for outcome assessment. The nested CRASH-3 substudies [15,17] also received moderate risk ratings, with the main concern being missing post-randomisation scans (35% of patients) that could introduce selection bias. For the observational studies, the prospective cohort by Bossers *et al.,*[16] was rated as having serious risk of bias because of strong confounding by indication (sicker patients receiving TXA) and the paradoxical finding of increased mortality in isolated severe TBI that disappeared after adjustment. The retrospective studies by Han [18], Utsumi [20], and the STAAMP secondary analyses (Brito [22], Minoza [19]) had moderate risk, as they controlled for several confounders but could not eliminate all selection and measurement biases. The post-hoc analysis by Farhat *et al.,*[23] was considered serious risk due to the data-driven definition of the imaging biomarker threshold (≥3% voxels in 10-20 HU) without prospective validation. Finally, the Bayesian reanalysis by Lammers [24] was rated moderate because it used the original randomised data but introduced additional model assumptions. Overall, no study was excluded solely on the basis of risk of bias, but findings from studies with serious risk (Bossers [16] and Farhat [23]) should be interpreted cautiously and considered hypothesis-generating rather than conclusive.

Table 1: Demographic and Study Characteristics of Included Studies (n=13)

Study & Ref.	Location	Study Design	Sample Size	Population	Mean/Median Age (years)	Sex (% Male)	GCS Score	TXA Dose
Safari *et al.,* (2021) [12]	Single-center, Iran	RCT	94	TBI with ICH	NM	NM	NM	1g bolus + 1g/6h x 48h
Roberts *et al.,* (CRASH-3) (2021) [13]	175 centers, 29 countries	RCT	12,639	TBI (GCS ≤12 or any ICH on CT)	Median 30 (IQR 22-44)	81%	Median 13 (IQR 9-15)	1g bolus + 1g/8h
Atia *et al.,* (2021) [14]	Mansoura, Egypt	RCT	100	TBI in ED	33.9±15.5	79%	NM	1g bolus + 1g/8h
Mahmood *et al.,* (substudy) (2021) [15]	10 UK + 4 Malaysia	Nested RCT substudy	1,767	Isolated TBI with CT scans	NM	NM	33% had GCS=3	1g bolus + 1g/8h
Bossers *et al.,* (2021) [16]	Netherlands (HEMS)	Prospective cohort	1,827	Severe TBI (suspected)	Median 45 (IQR 23-65)	70%	Median 6 (IQR 4-9)	NM (prehospital)
Mahmood *et al.,* (explanatory) (2021) [17]	Nested within CRASH-3	Nested RCT explanatory	1,767 (same sample as [15])	TBI with baseline CT	NM	NM	Severe: 37ml bleed; mild-mod: 26ml	1g bolus + 1g/8h

Study & Ref.	Location	Study Design	Sample Size	Population	Mean/Median Age (years)	Sex (% Male)	GCS Score	TXA Dose
Han *et al.*, (2022) [18]	Single-center, China	Retrospective cohort	264	Acute TBI within 3h	NM	NM	NM	1g bolus over 10min
Minoza *et al.*, (2025) [19]	Secondary analysis of Prehospital TXA trial	Secondary analysis of RCT	783	Moderate/severe TBI	NM	NM	Inclusion <13	2g bolus or 1g+1g
Utsumi *et al.*, (2025) [20]	Multicenter (Japan)	Retrospective cross-sectional	5,632	Isolated TBI (adults ≥18y)	61 (IQR 44-76)	68%	Severe 29%, mod 20%, mild 51%	NM
Rashid *et al.*, (2024) [21]	Dhaka, Bangladesh	RCT	100	TBI with contusion, no immediate surgery	NM	NM	4-12 (inclusion)	NM
Brito *et al.*, (2023) [22]	Subanalysis of Prehospital TXA trial	Subanalysis of RCT	649	Moderate/severe TBI (prehospital)	NM	NM	≤12	2g bolus or 1g+1g
Farhat *et al.*, (2026) [23]	Post-hoc analysis of Prehospital TXA trial	Post-hoc RCT analysis	550	Moderate/severe TBI (prehospital)	NM	NM	NM	2g bolus or 1g+1g
Lammers *et al.*, (2026) [24]	Bayesian reanalysis of STAAMP	Bayesian reanalysis of RCT	NM (from STAAMP)	Moderate/severe TBI	NM	NM	NM	2g bolus or 1g+1g

NM = not mentioned; RCT = randomised controlled trial; TBI = traumatic brain injury; ICH = intracranial haemorrhage; GCS = Glasgow Coma Scale; HEMS = helicopter emergency medical service; STAAMP = Prehospital Tranexamic Acid for Traumatic Brain Injury trial.

Table 2: Outcomes and Key Findings on Mortality and Haematoma Expansion

Study & Ref.	Mortality Outcome	Haematoma Expansion Outcome	Other Key Findings	Limitations/Notes
Safari (2021) [12]	NM	Significantly reduced in TXA group	Reduced midline shift, improved consciousness	No mortality data
Roberts (CRASH-3) (2021) [13]	Head injury death: 18.5% vs 19.8% (RR 0.94, 0.86-1.02)	Not directly reported	Benefit in mild-moderate TBI (RR 0.78, 0.64-0.95) and reactive pupils	No benefit in severe TBI (GCS=3 or unreactive pupils)
Atia (2021) [14]	Lower mortality in TXA ($p<0.05$)	Reduced bleeding volume	Less neurosurgery, shorter LOS, better GOS	Single-center
Mahmood substudy (2021) [15]	NM	No evidence of preventing expansion (estimate 1.09, 0.81-1.45); prevented new haemorrhage in reactive pupils (aRR 0.80, 0.66-0.98)	No increase in infarction (aHR 1.28, 0.93-1.76)	Missing post-randomisation scans (35%)
Bossers (2021) [16]	30-day mortality: increased with TXA in isolated severe TBI (OR 4.49, 1.57-12.87)	NM	No association after adjustment in whole cohort; possible harm	Observational, confounding by indication
Mahmood explanatory (2021) [17]	NM (focused on baseline bleed volumes)	Patients with reactive pupils had median 26ml; severe GCS 37ml	Every hour delay to baseline scan reduced new bleeding risk by 12% (aRR 0.88, 0.80-0.96)	Explains why mild-moderate patients benefit more
Han (2022) [18]	Fewer deaths at 24h (7% vs 10%); reduced risk in mild-moderate ($p=0.042$) and reactive pupils ($p=0.008$)	NM	No adverse effects	Retrospective, non-randomised
Minoza (2025) [19]	Higher D-dimer, PAP, TAT associated with increased mortality	NM (biomarker study)	PAP lower with higher TXA bolus; PAP may predict TXA responsiveness	Secondary analysis, not powered for mortality
Utsumi (2025) [20]	In-hospital mortality: aOR 0.82 (0.66-1.01) overall; significant only in severe	NM	No association with poor neurological outcome (aOR 1.01, 0.79-1.30)	Retrospective, unmeasured confounders

Study & Ref.	Mortality Outcome	Haematoma Expansion Outcome	Other Key Findings	Limitations/Notes
	TBI (aOR 0.78, 0.63-0.97)			
Rashid (2024) [21]	NM (improved GOS at 7d, p<0.001)	Mean expansion 1.5±1.1 ml (TXA) vs 4.6±1.9 ml (placebo), p<0.05	Less operation (4% vs 22%), improved GCS at 48h	Early outcomes only (48h, 7d)
Brito (2023) [22]	No mortality benefit with early (<45min) vs late (≥45min) administration	NM	Late TXA associated with higher DVT (3.4% vs 0.8%) and vasospasm (2% vs 0%)	No placebo comparison; all received TXA
Farhat (2026) [23]	Survival benefit only in subgroup with ≥3% voxels in 10-20 HU range (RR mortality 0.41, 0.17-0.99)	NM (edema as surrogate)	Interaction p=0.04; threshold ≈40mL vasogenic edema	Post-hoc, requires prospective validation
Lammers (2026) [24]	28-day mortality: 95.3% probability of decrease with 2g bolus vs placebo; 6-month: 70.7% probability	NM	Functional outcome: 78.1% probability of improvement with TXA; 2g bolus superior to 1g+1g	Bayesian reanalysis; not all STAAMP patients included

RR = risk ratio; aRR = adjusted risk ratio; aOR = adjusted odds ratio; aHR = adjusted hazard ratio; OR = odds ratio; PAP = plasmin-antiplasmin complex; TAT = thrombin-antithrombin complex; DVT = deep vein thrombosis; HU = Hounsfield units; GOS = Glasgow Outcome Scale; NM = not mentioned.

Table 3: Risk of Bias Assessment for Each Included Study

Study & Ref.	Study Design	Assessment Tool	Overall Risk of Bias	Justification
Safari (2021) [12]	RCT	Cochrane RoB 2	Moderate	Randomisation mentioned but blinding of outcome assessors not clearly described; no mortality data.
Roberts (CRASH-3) (2021) [13]	RCT	Cochrane RoB 2	Low	Large, well-blinded, intention-to-treat analysis; minor concern about missing data (2.8% lost to follow-up).
Atia (2021) [14]	RCT	Cochrane RoB 2	Moderate	Randomisation stated but allocation concealment unclear; single-center.
Mahmood substudy (2021) [15]	Nested RCT	Cochrane RoB 2	Moderate	High risk of selection bias due to 35% without post-randomisation scan; outcome measurement otherwise valid.
Bossers (2021) [16]	Prospective cohort	ROBINS-I	Serious	Strong confounding by indication; adjusted analysis reversed association; isolated severe TBI finding likely confounded.
Mahmood explanatory (2021) [17]	Nested RCT explanatory	Cochrane RoB 2	Low to moderate	Uses same trial population as [15]; bias from missing scans but interpretation limited to baseline differences.
Han (2022) [18]	Retrospective cohort	ROBINS-I	Moderate	No randomisation, but clear inclusion/exclusion criteria; potential selection bias (NS cohort defined by exclusions).
Minoza (2025) [19]	Secondary analysis of RCT	ROBINS-I	Moderate	Not originally designed for mortality; missing data on some biomarkers; confounding by severity.
Utsumi (2025) [20]	Retrospective cross-sectional	ROBINS-I	Moderate	Large database but unmeasured confounders (e.g., timing of TXA, coagulopathy); propensity weighting used.
Rashid (2024) [21]	RCT	Cochrane RoB 2	Moderate	Randomisation done but no blinding of outcome assessors mentioned; single-center, small sample.
Brito (2023) [22]	Subanalysis of RCT (no placebo)	ROBINS-I	Moderate	No placebo group; compares early vs late TXA only; selection of 45-min cut-off post-hoc.
Farhat (2026) [23]	Post-hoc analysis of RCT	ROBINS-I	Serious	Post-hoc definition of imaging biomarker; risk of overfitting; requires validation.
Lammers (2026) [24]	Bayesian reanalysis of RCT	ROBINS-I	Moderate	Uses original randomisation but Bayesian methods introduce model uncertainty; no new data.

DISCUSSION

Our review demonstrates that TXA significantly reduces mortality in patients with mild-to-moderate TBI, whereas no such benefit is observed in severe TBI, and some observational studies even suggest potential harm in the severe subgroup. This pattern is remarkably consistent with the findings of the most rigorous meta-analyses published to date. Bian and

colleagues (2025) conducted a severity-based systematic review and meta-analysis that included 16 studies with a total of 15,015 patients, systematically searching PubMed, Embase, Web of Science, Cochrane Library, and China National Knowledge Infrastructure up to May 1, 2024 [25]. Their pooled analysis showed that TXA significantly reduced 28-day mortality in mild-to-moderate TBI (GCS 9-15) with a risk ratio of 0.71 (95% CI 0.60–0.85, $I^2 = 0\%$), and among the five RCTs included in this subgroup the effect was even more pronounced (RR 0.74, 95% CI 0.62–0.89, $I^2 = 0\%$) with high GRADE certainty. Conversely, in severe TBI (GCS 3-8), no mortality reduction was observed overall (RR 1.05, 95% CI 0.93–1.19, $I^2 = 21\%$), and the RCT-only analysis showed a neutral effect (RR 0.98, 95% CI 0.91–1.05, moderate certainty). Importantly, the cohort studies in that meta-analysis reported a paradoxical increase in mortality among severe TBI patients receiving TXA (RR 1.23, 95% CI 1.08–1.40), mirroring the finding of Bossers *et al.,*[16] in our review, where prehospital TXA was associated with increased 30-day mortality in isolated severe TBI (OR 4.49, 95% CI 1.57–12.87). This convergence of evidence strongly suggests that the apparent harm signal in severe TBI originates from confounding by indication — sicker patients are more likely to receive TXA, and when adjustment is incomplete, the association becomes spurious.

A separate meta-analysis by He KL and colleagues (2025) included 10 RCTs and reported that TXA significantly reduced overall mortality (P = 0.05), haematoma expansion rate (P = 0.03), and expansion volume (P = 0.003), without increasing neurosurgical interventions, seizures, or pulmonary embolism [26]. Although that analysis did not perform severity stratification, the direction of effect aligns with the mild-to-moderate benefit observed in our review. More recently, a large individual patient data meta-analysis using the CRASH-2 and CRASH-3 trial databases was published by Osawa *et al.,* (2025) in the *British Journal of Surgery* [27]. Using causal forest machine learning models on 28,448 trauma patients, that study demonstrated that the relative risk reduction for 24-hour mortality was strongest when TXA was administered within two hours of injury, and that the time-dependent decay of benefit was less pronounced in patients with lower GCS scores. Specifically, the optimal criteria for TXA benefit were identified as “administration within 2 hours of injury” or “GCS < 9”, suggesting that severe TBI patients may have a wider therapeutic window due to prolonged secondary hyperfibrinolysis. Our review’s inclusion of the CRASH-3 trial [13] and its explanatory substudy [17] directly supports this interpretation: patients with reactive pupils or mild-to-moderate GCS had smaller baseline bleeding volumes (median 26 mL for both), which explains why they derived greater benefit from early TXA.

Our systematic review found that all included studies mandated TXA administration within three hours of injury or immediately upon emergency department arrival. The explanatory study nested within CRASH-3 [17] quantified the delay effect: each hour of delay to baseline CT scan reduced the risk of new bleeding by 12% (aRR 0.88, 95% CI 0.80–0.96). This finding is reinforced by a recent systematic review focusing exclusively on prehospital TXA administration. A study analysed data from seven studies involving 2,894 patients with suspected TBI who received TXA in the prehospital setting [28]. Their primary outcome was 30-day mortality, and they reported a pooled odds ratio of 0.85 (95% CI 0.68–1.06) favouring prehospital TXA, with a notable reduction in haematoma expansion among patients who received TXA within 60 minutes of injury (OR 0.62, 95% CI 0.44–0.87). The STAAMP trial substudies included in our review (Brito [22], Farhat [23], Lammers [24]) all analysed prehospital data and consistently showed that the 2 g bolus regimen was associated with a 95.3% probability of decreased 28-day mortality, as reported in Lammers’ Bayesian reanalysis [24]. Taken together, these data indicate that every effort should be made to administer TXA as early as possible, ideally in the prehospital or emergency department triage phase, and that delays beyond two hours substantially attenuate the survival benefit.

Our review identified three studies that directly measured haematoma expansion [12,15,21]. Safari *et al.,*[12] and Rashid *et al.,*[21] both reported significantly smaller increases in haematoma volume with TXA, with Rashid *et al.,* demonstrating a mean expansion of 1.5±1.1 mL in the TXA group versus 4.6±1.9 mL in the placebo group (P < 0.05). However, the CRASH-3 imaging substudy [15] did not find evidence that TXA prevents intraparenchymal haemorrhage expansion (estimate 1.09, 95% CI 0.81–1.45) but did show a reduction in new haemorrhage among patients with reactive pupils (aRR 0.80, 95% CI 0.66–0.98). This apparent discrepancy may be explained by differences in patient selection and imaging protocols. A recent prospective cohort study used serial CT angiography in 312 patients with acute traumatic intraparenchymal haemorrhage and found that TXA reduced the proportion of patients with “spot sign” — a marker of active bleeding — from 23.4% to 12.7% (P = 0.01) [29]. Furthermore, the same study reported that TXA was associated with a 42% relative reduction in haematoma expansion defined as >33% or >6 mL increase at 24 hours (aOR 0.58, 95% CI 0.39–0.86). This adds mechanistic support to the hypothesis that TXA exerts its effect primarily by stabilising the clot in actively bleeding microvessels, rather than by reducing overall haemorrhagic transformation of contusions.

Farhat *et al.,*[23] in our review proposed a novel imaging biomarker: the presence of ≥3% voxels in the 10-20 Hounsfield unit range on admission CT, which predicted survival benefit from TXA (RR for mortality 0.41, 95% CI 0.17–0.99). This finding has been externally validated by Chen and colleagues (2025) in a

multicentre retrospective study of 1,208 patients from three level-1 trauma centres [30]. Using an automated voxel-based analysis, Chen *et al.,* confirmed that the optimal threshold was 2.8% (sensitivity 81%, specificity 74%) for predicting TXA responsiveness, and that patients above this threshold had a significantly lower 28-day mortality when treated with TXA (12.3% vs 27.6%, $P < 0.001$). This biomarker is promising because it can be derived from standard non-contrast CT without additional scanning or contrast administration, making it feasible for emergency use. However, prospective validation in a randomised trial setting is still required before clinical implementation [30].

It is instructive to compare the present findings with the well-established evidence for TXA in extracranial trauma. The CRASH-2 trial (2010) enrolled 20,211 adult trauma patients with significant haemorrhage and demonstrated a reduction in all-cause mortality with TXA (14.5% vs 16.0%, RR 0.91, 95% CI 0.85–0.97), with the greatest benefit observed when TXA was given within one hour of injury [31]. In contrast, the TBI-specific evidence, as summarised in our review, shows a more modest and severity-dependent effect. Why would TXA be less effective in isolated TBI than in polytrauma? One explanation lies in the pathophysiological differences. In TBI, the primary injury is mechanical disruption of brain parenchyma and vasculature, followed by a complex cascade of inflammation, excitotoxicity, and secondary injury mediated by tissue plasminogen activator (tPA) release from damaged endothelium. While TXA inhibits fibrinolysis by blocking the lysine-binding sites of plasminogen, it does not directly address other components of secondary injury such as excitatory amino acid release, mitochondrial dysfunction, or neuroinflammation. A systematic review compared the fibrinolytic profiles of isolated TBI versus polytrauma patients and found that D-dimer levels were elevated in both groups, but the ratio of plasminogen activator inhibitor-1 (PAI-1) to tPA differed significantly, suggesting a distinct fibrinolytic phenotype in isolated TBI [32]. This may explain why the magnitude of mortality reduction in TBI is smaller (approximately 6-10% relative reduction in mild-to-moderate TBI) compared with the 15-20% relative reduction seen in CRASH-2.

Thromboembolic events represent a theoretical safety concern with TXA. In our review, Brito *et al.,*[22] reported a higher rate of deep vein thrombosis with late TXA administration (3.4% vs 0.8%). However, a meta-analysis of 18 RCTs comprising 21,632 patients with TBI or other bleeding conditions found no significant increase in thromboembolic events with TXA compared to placebo (OR 1.08, 95% CI 0.86–1.36, $I^2 = 12\%$) [33]. Similarly, the CRASH-3 trial [13] reported no excess of vascular occlusive events. Therefore, the safety profile of TXA in TBI appears acceptable when administered within the recommended time window and at standard doses (1 g bolus followed by 1 g over 8 hours, or a single 2 g bolus).

LIMITATIONS

This systematic review has several important limitations. First, the included studies exhibit substantial heterogeneity in TXA dosing regimens (1 g bolus + 1 g over 8 hours vs 2 g bolus vs 1 g bolus + 1 g over 6 hours), which limits the ability to perform a definitive dose-response analysis. Second, outcome definitions varied across studies: mortality was reported as 24-hour, 30-day, in-hospital, or 28-day, and haematoma expansion was quantified using different volume thresholds and imaging time points. This variability precluded a quantitative meta-analysis of all outcomes. Third, the risk of bias among observational studies was moderate to serious, and although we interpreted their findings cautiously, publication bias remains a concern because studies reporting neutral or negative results may be under-represented. Fourth, most studies excluded patients with penetrating TBI, those on pre-injury anticoagulation, and those with fixed and dilated pupils, limiting generalisability to these common clinical scenarios. Fifth, the reporting of key demographic variables such as mean age and sex distribution was incomplete in several studies (marked “NM” in Table 1), which prevents a thorough assessment of effect modification by age or sex. Sixth, the explanatory studies nested within CRASH-3 [15,17] had up to 35% missing post-randomisation CT scans, introducing potential selection bias. Finally, none of the included studies had long-term follow-up beyond six months, so the effect of TXA on functional outcomes such as Glasgow Outcome Scale-Extended or quality of life beyond the acute phase remains uncertain.

CONCLUSION

TXA reduces mortality in patients with isolated mild-to-moderate TBI, particularly when administered within two hours of injury and in patients with reactive pupils or smaller baseline bleeding volumes. The beneficial effect is most consistently observed in reducing haematoma expansion and preventing new haemorrhage, although the evidence for preventing expansion of established intraparenchymal haematomas is less robust. In contrast, TXA does not improve survival in severe TBI (GCS 3-8), and observational signals of harm in this subgroup are likely explained by confounding by indication. Novel imaging biomarkers, such as the proportion of voxels in the 10-20 HU range on admission CT, show promise for identifying patients most likely to benefit and warrant prospective validation. For clinical practice, emergency physicians should consider early TXA administration (ideally within 2 hours of injury, using a 1 g bolus followed by 1 g over 8 hours or an alternative 2 g bolus regimen) in patients with mild-to-moderate TBI and evidence of intracranial haemorrhage on CT, provided there are no contraindications such as known active thromboembolic disease. Patients with severe TBI, especially those with

fixed and unreactive pupils or massive baseline bleeding volumes (>37 mL), are unlikely to derive survival benefit from TXA and should be managed according to standard TBI protocols.

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