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Tranexamic acid for gastrointestinal bleeding: A systematic review with meta-analysis of randomized clinical trials

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ABSTRACT

Background: Acute gastrointestinal bleeding is a common life-threatening emergent condition. Immediate tranexamic acid is useful for reducing hemorrhage following operation and bleeding trauma, but evidence on the effects of tranexamic acid in patients with gastrointestinal bleeding is limited or highly heterogeneous. It is still unclear about using tranexamic acid in the emergent condition of gastrointestinal bleeding. This study, therefore, aimed to determine whether or not tranexamic acid should be used in gastrointestinal bleeding management through systematic review and meta-analysis.

Methods: We searched three biomedical databases for relevant randomized controlled trials on this topic. Two authors independently selected studies and extracted data for bias assessment and meta-analysis of bleeding, further intervention, mortality, transfusion, and intensive care unit admission. Available data were pooled using a random-effects model, and the results were presented as risk ratios (RRs) with 95% confidence intervals (CIs). Heterogeneity and small study effects were also assessed.

Results: Thirteen randomized controlled trials (n = 2271) were included in the present synthesis. Our meta-analysis revealed that tranexamic acid significantly reduced the rates of continued bleeding (RR = 0.60; 95%CI, 0.43–0.84), urgent endoscopic intervention (RR = 0.35; 95%CI, 0.24–0.50), and mortality (RR = 0.60; 95%CI, 0.45–0.80) compared with the placebo.

Conclusion: According to the available evidence, the present synthesis confirms that tranexamic acid is an effective medication for patients with upper gastrointestinal bleeding. Early administration of tranexamic acid may be worth to be recommended for treating upper gastrointestinal bleeding in the emergency department. However, the effects of tranexamic acid on lower gastrointestinal bleeding warrant further clarification.

1. Introduction

Acute gastrointestinal bleeding is a common life-threatening emergent condition with a reported mortality of 2%–10%. The overall annual incidence of upper gastrointestinal bleeding ranges from 39 to 172 per 100,000 [1-3]. The causes of upper gastrointestinal bleeding can be classified into several broad categories on the basis of anatomical and pathophysiological factors. The most common causes of upper gastrointestinal bleeding include peptic ulcer disease, esophagogastric varices, and erosive esophagitis [4]. In the emergency department, the initial evaluation of patients with acute gastrointestinal bleeding involves an assessment of hemodynamic stability, and resuscitation and blood transfusion may be provided, if necessary. In hemodynamically unstable patients, urgent intervention is usually required (e.g., endoscopic, colonoscopic, surgical, or transcatheter arterial embolization or transfusion). Endoscopy is currently considered an effective method for achieving therapeutic and diagnostic modalities in the treatment of both upper and lower gastrointestinal bleeding. Pharmacological treatment also plays an important role, and proton pump inhibitors are recommended for all patients with peptic ulcer bleeding.

Tranexamic acid (TXA), an antifibrinolytic pharmacological agent, is useful for alleviating hemorrhage after operation and bleeding trauma

Abbreviations: CI, confidence interval; RR, risk ratio; WMD, weighted mean difference.

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[5-7]. The Clinical Randomization of an Antifibrinolytic in Significant Head injury-2 trial showed that TXA reduces mortality in patients with bleeding trauma if given within an hour [8]. Because the trial recruited trauma patients, endoscopy was not performed in the trial. Early administration of TXA safely reduced mortality risk in patients with bleeding trauma and is highly cost-effective [9]. Physicians may administer TXA for trauma patients at the first encounter in the emergency department, and TXA has been widely discussed in the field of emergency medicine over the past decade [10-15]. Although the use of TXA for treating gastrointestinal bleeding is an important clinical topic in emergency medicine [16], no clear relevant recommendations are available. Accordingly, a series of studies have reported the possible effectiveness of TXA in the treatment of acute gastrointestinal bleeding. Barer et al. found that TXA may reduce the mortality rate; however, it was not associated with decreased rates of bleeding or surgical intervention [17]. Hawkey et al. noted that TXA significantly reduced the amount of blood in the stomach at endoscopy [18]. A 2014 meta-analysis revealed that TXA reduced the mortality and surgery rates but did not produce any difference in bleeding or reduction in the need for transfusion [19]. Some randomized controlled trials (RCTs) have subsequently been reported. Tavakoli et al. reported that time to endoscopy was significantly shorter in patients receiving TXA, but no significant differences were found in mortality, rebleeding, blood transfusion, or endoscopic or surgical intervention rates [20]. In a trial by Saidi et al., transfusion, rebleeding, and emergency endoscopy rates were all significantly lower in the TXA –treated group, but the mortality rate was nonsignificantly lower [21]. Thus, the effectiveness of TXA in reducing mortality, rebleeding, and intervention rates remains unclear, and it is not routinely used for treating gastrointestinal bleeding in emergency departments. In this systematic review, we aimed to determine whether TXA should be used in the treatment of gastrointestinal bleeding.

2. Materials and methods

The study protocol for this prospective systematic review and meta-analysis can be found in PROSPERO (CRD42020150730). According to the aim of this study we mentioned above, our research question in PICO form is

P: Patients with gastrointestinal bleeding

I: Tranexamic acid

C: Placebo/no treatment

O: Bleeding, further intervention, mortality, transfusion, and intensive care unit admission rate.

In brief, we collected and analyzed RCTs to compare the efficacy of TXA treatment with that of placebo, non-TXA agent, or no treatment in patients with gastrointestinal bleeding, and the primary and secondary outcomes were rebleeding rate, continued bleeding rate, mortality, and further surgical or endoscopic intervention.

The study inclusion criteria were as follows: (a) all patients with upper and lower gastrointestinal bleeding without limitation of disease and age; (b) tranexamic acid with all routes of administration, different dosages, and intervention times; and (c) every trial should have a prospective randomized controlled design.

2.1. Databases, search strategy, and study selection

We searched the Embase, PubMed, and Cochrane Library databases for randomized clinical trials by using the search term “gastrointestinal hemorrhage,” with ‘OR’ coordination synonyms of “gastrointestinal bleeding,” “lower gastrointestinal tract hemorrhage,” “upper gastrointestinal bleeding,” “duodenal ulcer bleeding,” “gastric ulcer bleeding,”; and also with the term “tranexamic acid” with ‘OR’ coordination synonyms of “transamine” and “aminotransferase.” We used ‘AND’ to combine the two concepts without restriction on publication language or date before June, 2020. We reviewed reference lists of other systematic reviews on this topic to retrieve additional studies. Subsequently, two of our review team members (P.L.L. and K.S.Y.) independently reviewed titles and abstracts of potential references, retrieving full texts for further review and eligibility judgment. The final decision on study selection was made through discussion by all team members.

2.2. Data extraction and quality assessment

Two reviewers (P.L.L. and K.S.Y.) independently extracted and double-checked information on patients' sex, age, bleeding site, disease, TXA administration route, treatment timepoint and frequency, rebleeding, need for endoscopy or surgical intervention or transcatheter arterial embolization, continued bleeding, blood loss volume, blood transfusion, ICU admission rate, length of ICU or hospital stay, and readmission rate, as well as all causes of mortality. After data extraction, the two reviewers evaluated randomization generation, allocation concealment, investigators' blinding, participants' blinding, assessors' blinding, and participants' loss to follow-up using the Cochrane risk-of-bias tool [22]. All team members made a final decision on quality assessment when the two reviewers made conflicting judgments.

2.3. Analysis and statistics

We pooled mean and standard deviation for transfusion volume and presented the pooled results as weighted mean differences (WMDs) with their 95% confidence intervals (CIs). We subsequently pooled events and total samples for binary outcomes including continued bleeding rate, rebleeding, need for further interventions (such as transcatheter arterial embolization), need for surgical intervention, blood transfusion rate, ICU admission rate, and all causes of mortality. The pooled results of binary outcomes were presented as risk ratios (RRs) with their 95% CIs. These pooled estimates were made using a random-effects model. Furthermore, the I^2 test was used to examine heterogeneity. If a pooled estimate was contributed to by more than ten RCTs, we performed a funnel plot for detecting publication bias. Overall judgment of synthesized evidence was made according to the Grading of Recommendation, Assessment, Development, and Evaluations (GRADE) method [23]. There are four levels of evidence certainty in the GRADE scheme: Very Low (⊕◯◯◯), Low (⊕⊕◯◯), Moderate (⊕⊕⊕◯), and High (⊕⊕⊕⊕).

3. Results

Our search results provided 743 references from the Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials (127 references), Embase (394 references) and PubMed (222 references). One additional reference was identified by manual search after we reviewed the reference lists of the included trials and relevant systematic reviews. However, of these, 127 references were excluded due to duplications, and 599 references were excluded because they were irrelevant (396 references), did not address gastrointestinal bleeding (59 references), did not compare TXA with placebo (50 references), and were non–RCTs (94 references). Full article reviews were conducted for 20 references, 6 of which were removed for because they were conference abstracts without any other details (2 references) [24,25], compared TXA with other medications (1 reference) [26], and reported a trial protocol (1 reference) [27]. Finally, the remaining 14 references from 13 RCTs, which met all our eligibility criteria for this analysis (Fig. 1), were included in our qualitative and quantitative analyses [17,18,20,21,28-37].

3.1. Characteristics and quality of included studies

The 13 RCTs recruited 2271 patients with gastrointestinal bleeding and were performed in Australia [31,35], Iran [20,21], Russia [28],

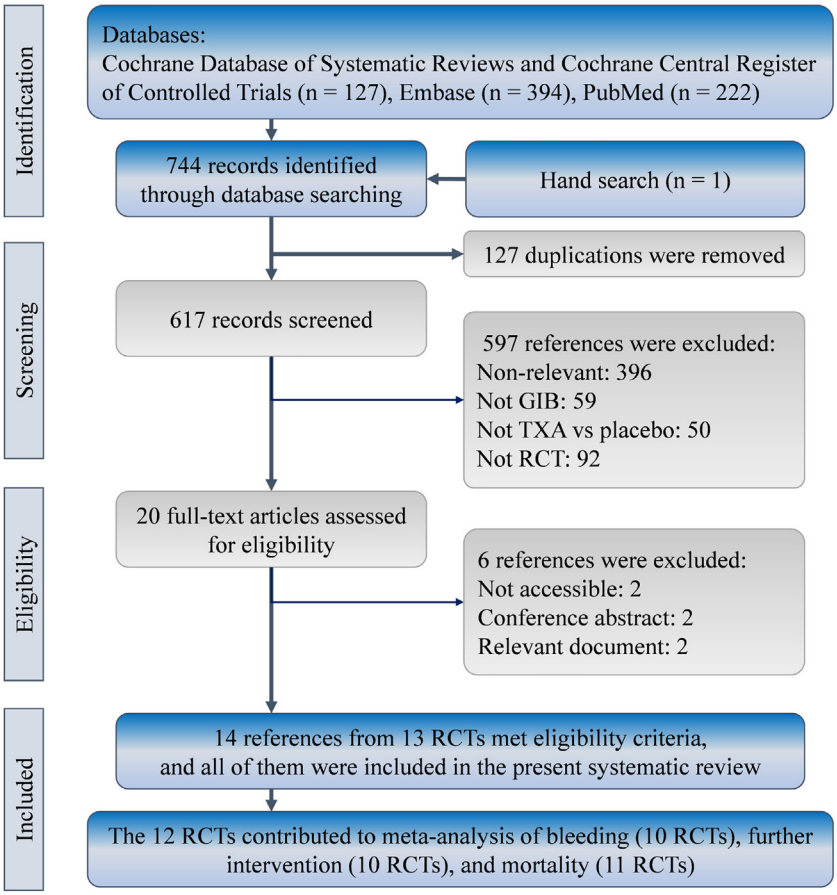

Fig. 1. Flow of evidence selection for the effect of tranexamic acid on gastrointestinal bleeding according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. GIB, gastrointestinal bleeding; RCT, randomized controlled trial; TXA, tranexamic acid.

Sweden [29,32,36,37], Turkey [34], and the United Kingdom [17,18,31,33] over 1967–2020. Most of them investigated the effects of TXA on upper gastrointestinal bleeding, with only two trials focused on lower gastrointestinal bleeding [33,35] and only one not separating upper and lower gastrointestinal bleeding [20]. The major diseases underlying gastrointestinal bleeding were ulcer and erosion. Only one RCT focused on colitis [33]. Other information on sex and mean age are presented in Table 1, and the quality analysis of the included RCTs is illustrated in Fig. 2. Most trials did not clearly present the allocation process details and raised some concerns about selection bias due to a lack of clarity regarding randomization generation and allocation concealment.

3.2. Bleeding

Continued bleeding and rebleeding data were available for five RCTs (n = 1005) [20,30-32,35] and eight RCTs (n = 1821), respectively (Fig. 3A) [17,18,20,21,28,30,34,36]. The pooled results indicated that TXA (65/575) led to a significantly lower continued bleeding rate than did placebo (93/430; RR = 0.60; 95% CI, 0.43–0.84). The pooled estimates also revealed that TXA could lead to a lower rebleeding rate (95/972) than placebo (110/849; RR = 0.84; 95% CI, 0.61–1.15). These pooled estimates were not highly heterogeneous ($I^2 = 26\%$, $P = 0.25$; $I^2 = 14\%$, $P = 0.32$ for continued bleeding and rebleeding, respectively).

3.3. Further intervention

Relevant data on further interventions concerning bleeding were reported for ten RCTs (Fig. 3B) [17,18,20,21,28-30,32,34,36]. All of them reported surgical intervention (n = 2025) [17,18,20,21,28-32,34,36]; moreover, four of them presented further endoscopic intervention (n = 904) [18,20,21,34], and two reported urgent endoscopic intervention [20,21]. The pooled results indicated that TXA treatment (further surgical intervention: 92/1076; any endoscopic intervention: 64/519) did not lead to a significantly lower rates of further surgical intervention (RR = 0.70; 95% CI, 0.44–1.10) or endoscopic intervention (RR = 0.91; 95% CI, 0.54–1.51) than did placebo (further surgical intervention: 116/949; any endoscopic intervention: 49/385), but pooled estimates showed that TXA (36/338) reduced urgent endoscopic intervention rates compared with placebo (60/203; RR = 0.35; 95% CI, 0.24–0.50). However, these pooled estimates were highly heterogeneous ($I^2 = 53\%$, $P = 0.03$ for surgical).

3.4. Mortality

In total, 11 RCTs (n = 2109) reported mortality (Fig. 3C) [17,18,20,21,28-30,32,34-36]. The pooled results clearly demonstrated that treatment with TXA (72/1118) led to a significantly lower mortality rate than did placebo (106/991; RR = 0.60; 95% CI, 0.45–0.80), with very low heterogeneity ($I^2 = 0\%$; $P = 0.92$). Only one RCT [35]

Table 1
Characteristics of the included randomized clinical trials.

Author	Location	Inclusion years	Bleeding site	Disease	Relevant outcome
Bagnenko 2011	Russia	NR	Upper GI	NR	Bleeding, further intervention, mortality, and transfusion
Barer 1983	UK	1980–1982	Upper GI	Ulcer Erosion Unclear	Bleeding, further intervention, mortality, and transfusion
Bergqvist 1980	Sweden	NR	Upper GI	Ulcer Erosion Varices	Further intervention and mortality
Biggs 1976	Australia	NR	Upper GI	Ulcer Erosion MWS Varices Unclear	Bleeding, further intervention, mortality, and transfusion
Cormack 1973	UK	1969–1971	Upper GI	NR NR	Bleeding and transfusion
Engqvist 1979	Sweden	1974–1975	Upper GI	Ulcer Erosion Varices Unclear	Bleeding, further intervention, mortality, and transfusion
Hawkey 2001	UK	NR	Upper GI	Ulcer Erosion MWS Varices Unclear	Bleeding, further intervention, mortality, transfusion, and ICU administration
Hollanders 1982	UK	NR	Lower GI	Colitis	Nil
Holstein 1987	Sweden	1982–1984	Upper GI	Ulcer Erosion MWS	Bleeding, further intervention, mortality, and transfusion
Karadaş 2020	Turkey	2016–2018	Upper GI	Ulcer Unclear	Bleeding, further intervention, mortality, and transfusion
Saidi 2017	Iran	NR	Upper GI	Unclear	Bleeding, further intervention, mortality, and transfusion
Smith 2018	Australia	2011–2014	Lower GI	Diverticulum Angiodysplasia	Bleeding, mortality, and transfusion
Tavakoli 2018	Iran	NR	Upper GI and Lower GI	Ulcer Erosion Unclear	Bleeding, further intervention, mortality, transfusion, and ICU administration

Author	Group	TXA main rout	Time point and frequency of TXA treatment	Number of cases	Sex (M/F	Age
Bagnenko 2011	TXA	IV or oral	Q8H for 3 days	22	14/8	62
	Placebo			25	5/10	64
Barer 1983	TXA	IV	Q6H for 48 h	256	177/79	60.4
	Placebo			260	155/105	62.9
Bergqvist 1980	TXA	Oral	Initial	21	14/7	60.8
	Placebo			22	20/2	57.6
Biggs 1976	TXA	IV	Q8H for 48 h	103	75/28	Unclear
	Placebo			97	80/17	Unclear
Cormack 1973	TXA	Oral	Q8H for 7 days	76	49/27	Unclear
	Placebo			74	51/23	Unclear
Engqvist 1979	TXA	IV + oral	IV Q4H for 3 days and oral Q6H for 4 days	76	55/21	58.8
	Placebo			73	61/12	56.4
Hawkey 2001	TXA	IV	Q6H for 4 days	103	80/23	60.3
	Placebo			103	80/23	56.2
Hollanders 1982	TXA			Overall	Overall	Overall
	Placebo			12	4/8	42.2
Holstein 1987	TXA	IV + oral	IV Q4H for 3 days and oral Q6H for 3 days	72	50/22	62.4
	Placebo			82	58/24	65.4
Karadaş 2020	TXA	NG	Initial	78	52/26	62.9
	Placebo			79	54/25	63.2
Saidi 2017	TXA	NG	Initial first 30 min	67	41/26	63.8
	Placebo			64	41/23	64.7
Smith 2018	TXA	Oral	Q6H for 4 days	49	32/17	68
	Placebo			47	31/16	68
Tavakoli 2018	TXA	IV/IV + oral	Q6H for 1 day	271	182/89	60.5
	Placebo			139	92/47	59.14

GI, gastrointestinal; ICU, intensive care unit; MWS, Mallory–Weiss Syndrome; NR, no report.
IV, intravenous; M/F, male / female; NG, nasogastric tube; NR, no report; Q4H, every four hours; Q6H, every six hours; Q8H, every eight hours; TXA, tranexamic acid.

reported a nonsignificantly higher mortality rate in the TXA group. This trial was also the only study that focused on a population with lower gastrointestinal bleeding [35]. Another RCT investigating TXA for lower gastrointestinal bleeding did not report mortality [33]. Funnel plots for the pooled mortality estimate did not show serious asymmetry (Fig. 4).

3.5. Secondary outcomes

We also performed a meta-analysis of the numbers of patients receiving transfusion, transfusion volumes, and numbers of patients moved to the ICU. Nine RCTs reported the transfusion rate, with a total of 1928 patients [17,18,20,28,30-32,35,36], and the pooled

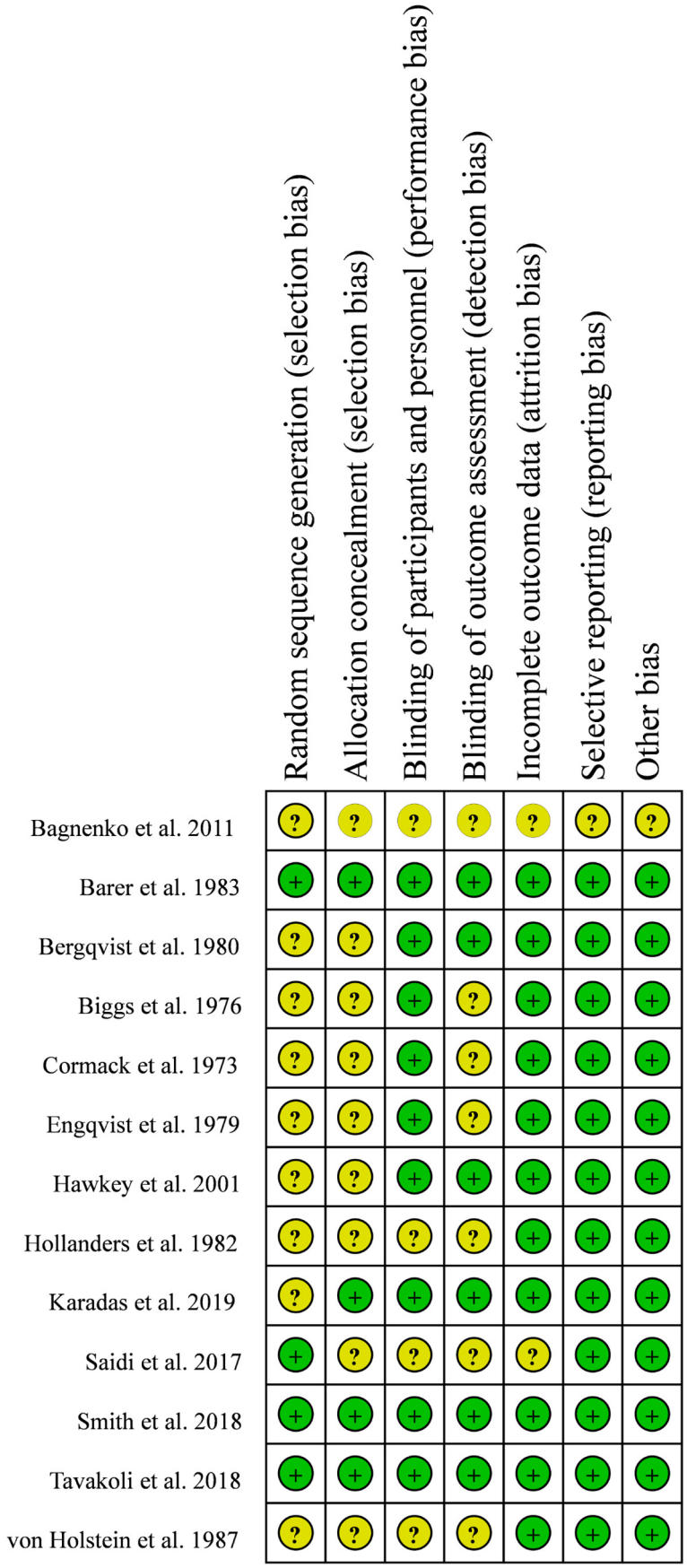

Fig. 2. Graph displaying risk of bias.

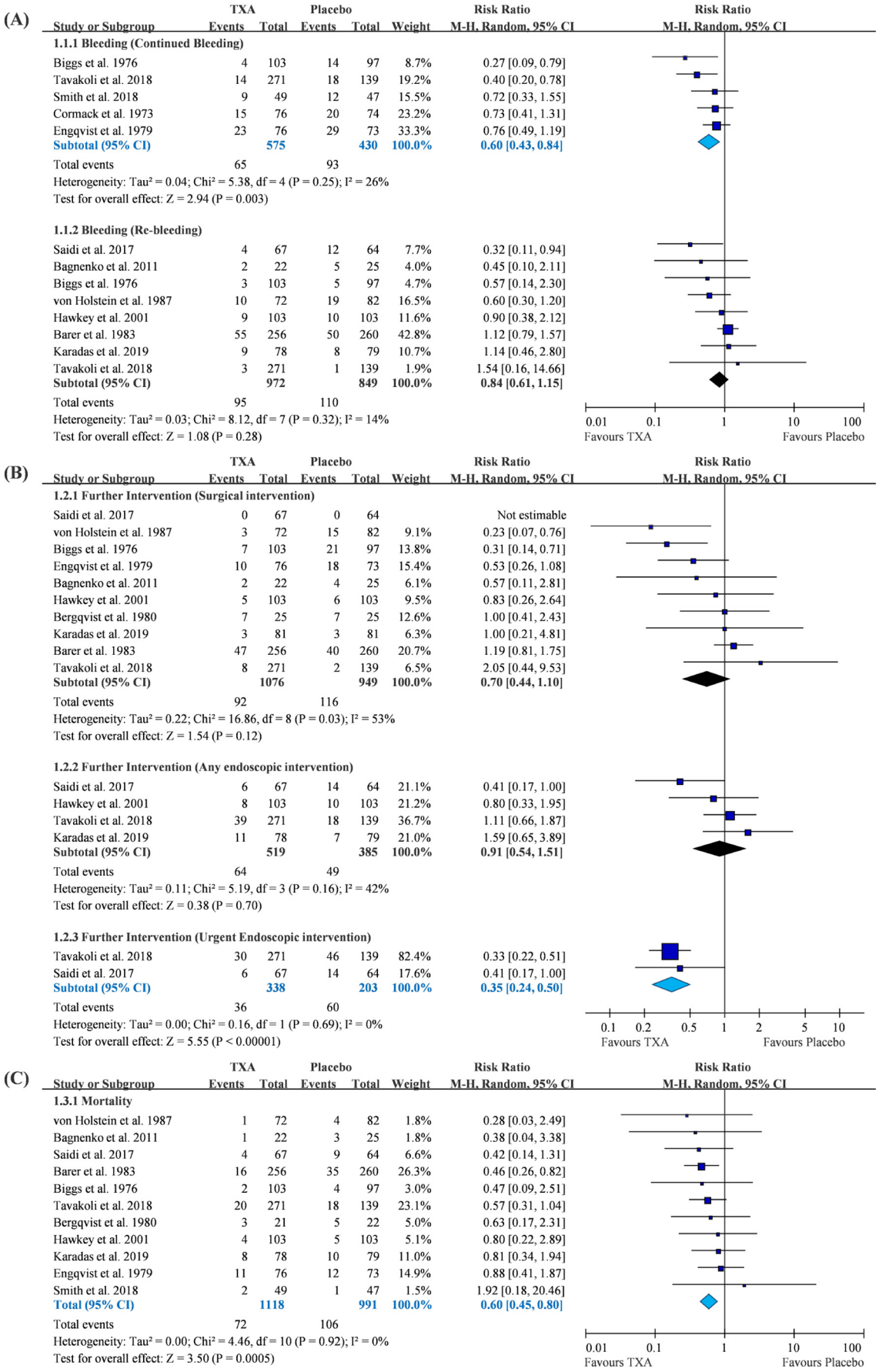

Fig. 3. Forest plots for (A) bleeding, (B) further intervention, and (C) mortality. CI, confidence interval; M–H, Mantel–Haenszel method; TXA, tranexamic acid.

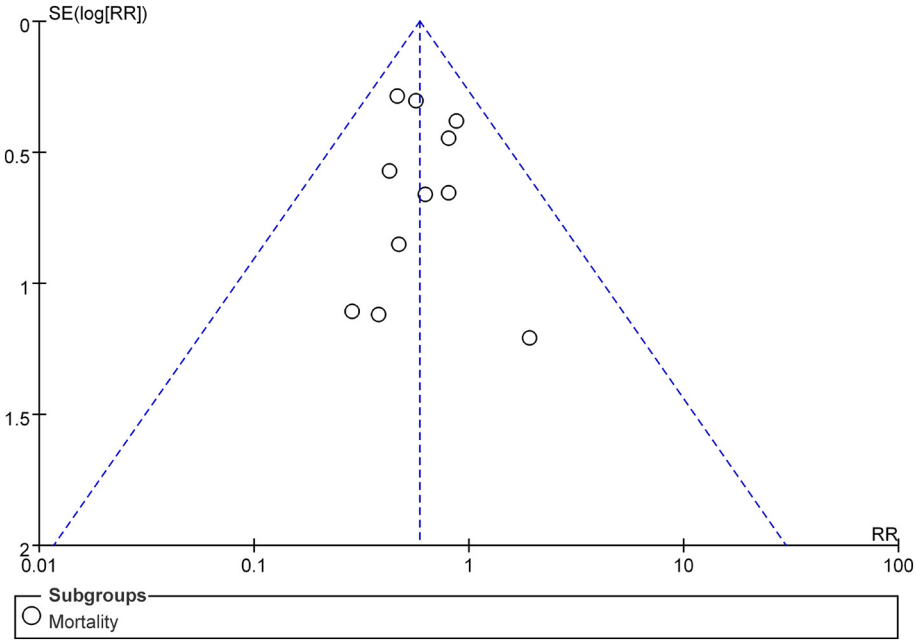

Fig. 4. Funnel plot for mortality. RR, risk ratio; SE, standard error.

estimates showed similar transfusion rates in the TXA and placebo groups (RR = 0.94; 95% CI, 0.76–1.16). Nonsignificant differences were found in the following subgroups of trials: upper gastrointestinal bleeding (RR = 0.95; 95% CI, 0.76–1.18), the single trial addressing lower gastrointestinal bleeding (RR = 0.78; 95% CI, 0.33–1.83), and no specific gastrointestinal bleeding (RR = 1.49; 95% CI, 0.19–11.92; Appendix 2). A similar trend was observed in the pooled results for transfusion volume (WMD = −0.56; 95% CI, −1.69–0.58; Appendix 3). Moreover, the pooled estimates revealed similar ICU admission rates for the TXA and placebo groups (RR = 1.22; 95% CI, 0.33–4.59; Appendix 4).

4. Discussion

In this systematic review and meta-analysis, we included 13 relevant RCTs, which recruited 2271 patients with gastrointestinal bleeding. Our review found that TXA may have a beneficial effect on mortality and continued bleeding and that it decreases the rate of further urgent endoscopic intervention. Although TXA appeared not to significantly reduce further surgical intervention, further endoscopic intervention, rebleeding rate, blood transfusion, or ICU admission rate, most of these outcomes are based on limited evidence (two to six RCTs). The certainty of these findings ranged from very low to moderate (Table 2).

A lower mortality rate was found with lowered rates of continued bleeding and urgent endoscopic intervention in the TXA group because most deaths in the population with gastrointestinal bleeding result from massive bleeding and hypovolemia. TXA has been demonstrated to prevent mortality in patients with major trauma bleeding or intracranial bleeding [8,38] and may increase blood clot formation and temporarily stop bleeding. In our analysis, however, only one trial investigated the effects of TXA in patients with lower gastrointestinal bleeding, with no demonstrable difference in mortality between the TXA and placebo groups [35]. In this trial, the most common diseases were colon diverticulitis and angiodysplasia, which are clearly different from upper gastrointestinal bleeding diseases. In the other trials included in our analysis, ulcer and erosion were the major diseases causing upper gastrointestinal bleeding. Because only two trials addressed lower gastrointestinal bleeding [20,35], the efficacy of TXA for treating lower gastrointestinal bleeding remains unclear.

Our findings also revealed that TXA reduces the rate of continued bleeding. This result confirms that TXA prevents fibrinolysis and directly reduces the fibrinolytic activity of pepsin. Continued bleeding is defined as active bleeding or oozing after medication, and rebleeding is defined as the recurrence of bleeding after more than 6 h with no bleeding, where the new onset is accompanied by a drop in hemoglobin concentration of 2 g/dL or more, or endoscopic evidence of fresh bleeding. TXA may increase blood clot formation and stop bleeding temporarily because inhibits fibrinolytic activity. However, if the underlying condition (ulcer or erosion) has not healed, rebleeding may occur in a short time. No significant differences were observed in the transfusion rates between groups, which were consistent with the rebleeding rates, initial hemoglobin, and vital signs. Patients with active bleeding and hypovolemia may require red blood cell transfusion despite an apparently normal hemoglobin level, particularly if the patient remains hemodynamically unstable despite appropriate fluid resuscitation. Among patients without active bleeding and who are hemodynamically stable because of fluid resuscitation, high-risk patients (i.e., those with cardiovascular disease) and low-risk patients should receive blood transfusions if their hemoglobin levels are <9 and <7 g/dL, respectively. The lack of a significant difference in the rebleeding rates between the groups is consistent with the nonsignificant difference obtained in transfusion.

Depending on the source of bleeding, different medications and interventions may provide better outcomes. Surgical, radiological, and endoscopic interventions are usually performed for gastrointestinal bleeding diagnosis and treatment. In particular, endoscopic interventions have both therapeutic and diagnostic roles. Therefore, endoscopic intervention may be more common as a diagnostic procedure than as a surgical intervention. Tavakoli et al. found that early administration of TXA could apparently decrease the urgent endoscopy rate and prolong the time needed to execute the procedure in patients with acute significant gastrointestinal bleeding [20]. Our findings indicated only nonsignificant differences in endoscopic intervention rates between the TXA and placebo groups. However, TXA may reduce the rate of urgent endoscopic intervention as compared with placebo.

Table 2
Summary of findings.

No. of participants (studies)	Certainty of the evidence	Relative effects (95% CI)	Anticipated risk with Placebo	Risk with TXA	Comments
Bleeding (continued bleeding)					
1005 (5 RCTs)	⊕⊕⊕◯[a] MODERATE	**RR 0.60** (0.43 to 0.84)	216 per 1000	86 fewer per 1000 (from 123 fewer to 34 fewer)	TXA reduces continued GI bleeding
Bleeding (rebleeding)					
1821 (8 RCTs)	⊕⊕⊕◯[a] MODERATE	**RR 0.84** (0.61 to 1.15)	130 per 1000	20 fewer per 1000 (from 50 fewer to 20 more)	TXA does not alleviate GI rebleeding
Further intervention (surgical intervention)					
2025 (10 RCTs)	⊕◯◯◯[a,b,c] VERY LOW	**RR 0.70** (0.44 to 1.10)	122 per 1000	36 fewer per 1000 (from 68 fewer to 13 more)	TXA does not reduce further surgical intervention risk
Further intervention (any endoscopic intervention)					
904 (4 RCTs)	⊕◯◯◯[a,b,c] VERY LOW	**RR 0.91** (0.54 to 1.51)	127 per 1000	11 fewer per 1000 (from 58 fewer to 65 more)	TXA does not reduce endoscopic intervention risk in general
Further intervention (urgent endoscopic intervention)					
541 (2 RCTs)	⊕⊕⊕◯[a] MODERATE	**RR 0.35** (0.24 to 0.50)	296 per 1000	192 fewer per 1000 (from 224 fewer to 148 fewer)	TXA reduces urgent endoscopic intervention risk
Mortality					
2109 (11 RCTs)	⊕⊕⊕◯[a] MODERATE	**RR 0.60** (0.45 to 0.80)	107 per 1000	42 fewer per 1000 (from 58 fewer to 21 fewer)	TXA reduces risk of all causes of mortality

CI, confidence interval; RCT, randomized controlled trial; RR, risk ratio; TXA, tranexamic acid.
[a] Downgraded one level due to unclear risk of bias in many trials.
[b] Downgraded one level due to wide range of confidence interval and relatively small sample size.
[c] Downgraded one level due to high heterogeneity ($I^2 > 50\%$).

4.1. Comparison with previous evidence

There is a systematic review and meta-analysis on this topic in the Cochrane review by Bennett et al., and their analysis includes eight RCTs (n = 1701) on TXA for upper gastrointestinal bleeding [19]. The study shows the beneficial effects of TXA for mortality, but no differences in rebleeding rate, transfusion rate, surgery rate, or the side effect of thromboembolic event. The authors indicated that additional studies are still needed. In our study, we found an additional five RCTs on this topic, and further covered use of TXA in lower gastrointestinal bleeding. Consequently, in the present analysis, we included 13 RCTs with 2271 gastrointestinal bleeding patients and clearly demonstrated a significantly lower mortality, continued bleeding, and urgent endoscopic intervention rates than for placebo. However, these findings are uncertain as evaluated using the GRADE method.

4.2. Implications for emergency practice

In emergency medicine, the relevant guidelines do not recommend TXA in patients with upper gastrointestinal bleeding because outcomes such as bleeding, surgery, and transfusion rates were not reduced [39,40]. Most of these guidelines are based on the aforementioned Cochrane review [19]. However, there is also no clear time frame for using TXA in the relevant guidelines.

The present systematic review and meta-analysis may further the understanding of using TXA for gastrointestinal bleeding in emergency department by encouraging RCTs on this topic. On the basis of previous trials, TXA could be administered initially with topical route via a nasogastric tube [21,29,34], intravenous route [17,18,20,30], oral route [31,35], or a combination of oral and intravenous routes for 4–6 h per day for 3–7 days [20,29,32,33]. Early administration of TXA per 6 h may be beneficial in emergency medicine practice, although it is unclear how different administration routes may have different effects. Our findings and recommendations are similar to a meta-analysis on TXA for severe traumatic or postpartum bleeding. Immediate TXA is recommended for treating acute severe traumatic or postpartum bleeding due to increased survival rate. Nevertheless, survival rate may decrease by 10% with every 15-min delay, with no benefits after 3 h [9]. In the emergency department, early-administered TXA may be recommendable for treating patients with gastrointestinal bleeding.

4.3. Limitations

Our analysis has several key limitations that may restrict the generalizability of our conclusions. Among the different studies we analyzed, there were different definitions of rebleeding and continued bleeding, and different criteria for endoscopy or surgical intervention. In addition, because proton pump inhibitors are the prevailing treatment for gastric ulcers, some trials combined TXA and proton pump inhibitors or H_2 blockers, whereas other trials treated patients with TXA alone. Hence, our evidence cannot clearly distinguish the effects of TXA administered alone and in combination of other drugs. The dosage and administration route of TXA are additional complicating factors; the routes in particular can differ among intravenous, oral, and endoscopic injections. Thus, further trials are in progress: the proposed Hemorrhage Alleviation with Tranexamic Acid–Intestinal System trial intends to recruit 12,000 patients to verify whether TXA has beneficial effects on upper gastrointestinal bleeding [41]. However, only two trials investigated the effects of TXA in patients with lower gastrointestinal bleeding, with nonsignificant differences in mortality reported between the TXA and placebo groups. Because of insufficient data, our findings for the efficacy of TXA on lower gastrointestinal bleeding may be underpowered.

5. Conclusions

According to the available evidence, the present synthesis confirmed that TXA is an effective medication for treating upper gastrointestinal bleeding, and that early-administered TXA may be worth recommending for the treatment of patients with gastrointestinal bleeding in the emergency department. However, the effect of TXA on lower gastrointestinal bleeding remains unclear.

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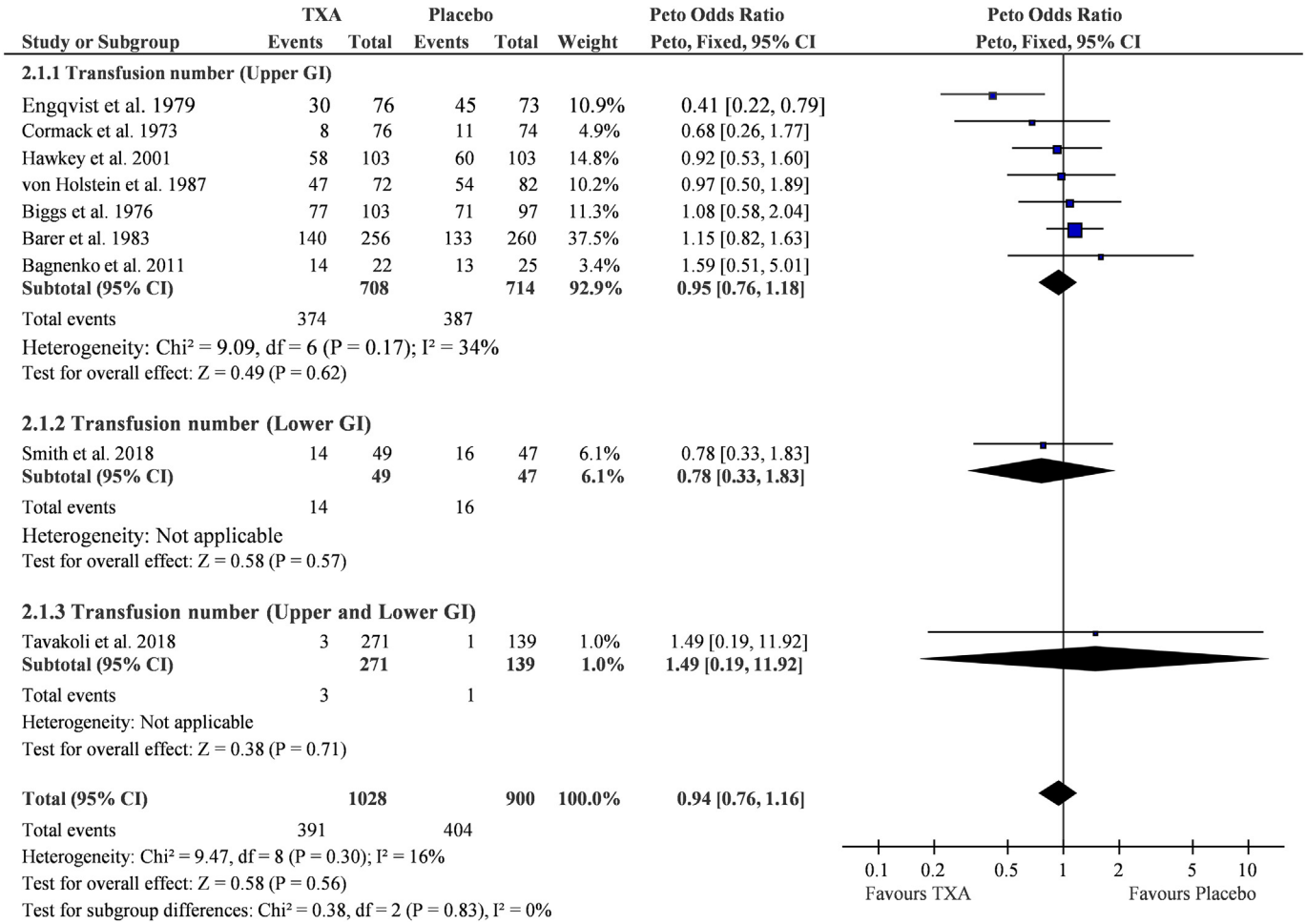
Declaration of Competing Interest

Po-Lin Lee, M.D., Kai-Suan Yang, M.D., Hong-Wei Tsai, M.D., Sen-Kuang Hou, M.D., pH.D., Director, Yi-No Kang, Consultant, M.A., and Chun-Chao Chang, M.D., Professor declare that they have nothing to disclose regarding financial or nonfinancial conflicts of interest with respect to this manuscript.

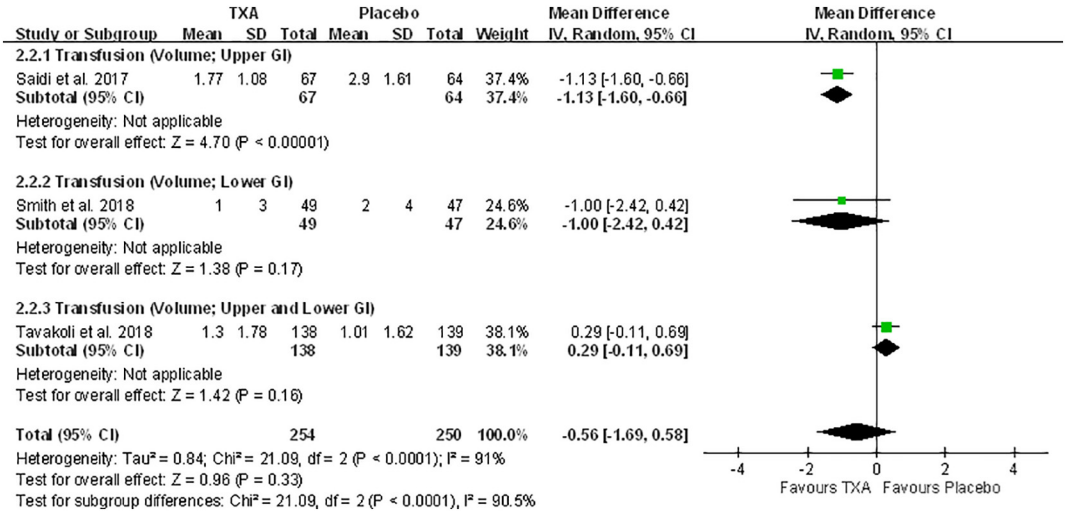
Appendix 1. Database and search strategy

Database	Search strategy	Hits
Cochrane database of systematic review	(GI bleeding OR gastrointestinal bleeding OR GI hemorrhage OR gastrointestinal hemorrhage OR rectal hemorrhage OR rectal bleeding OR rectum bleeding OR rectum hemorrhage OR duodenal ulcer bleeding OR gastric ulcer OR EV bleeding OR esophageal bleeding OR esophagus hemorrhage OR esophagus bleeding OR esophageal hemorrhage) AND (tranexamic acid OR transamin OR TXA OR transamine)	127
Embase	('gi bleeding' OR 'gi hemorrhage' OR 'gastro intestinal bleeding'/exp OR 'gastro intestinal bleeding' OR 'gastro intestinal haemorrhage''/exp OR 'gastro intestinal haemorrhage'' OR 'gastro intestinal hemorrhage'/exp OR 'gastro intestinal hemorrhage' OR 'gastroduodenal bleeding'/exp OR 'gastroduodenal bleeding' OR 'gastroduodenal haemorrhage''/exp OR 'gastroduodenal haemorrhage'' OR 'gastroduodenal hemorrhage'/exp OR 'gastroduodenal hemorrhage' OR 'gastrointestinal bleeding'/exp OR 'gastrointestinal bleeding' OR 'gastrointestinal bleeding recurrence'/exp OR 'gastrointestinal bleeding recurrence' OR 'gastrointestinal blood loss'/exp OR 'gastrointestinal blood loss' OR 'gastrointestinal canal bleeding'/exp OR 'gastrointestinal canal bleeding' OR 'gastrointestinal canal haemorrhage''/exp OR 'gastrointestinal canal haemorrhage'' OR 'gastrointestinal canal hemorrhage'/exp OR 'gastrointestinal canal hemorrhage' OR 'gastrointestinal haemorrhage''/exp OR 'gastrointestinal haemorrhage'' OR 'gastrointestinal hemorrhage'/exp OR 'gastrointestinal hemorrhage' OR 'gastrointestinal tract bleeding'/exp OR 'gastrointestinal tract bleeding' OR 'gastrointestinal tract haemorrhage''/exp OR 'gastrointestinal tract haemorrhage'' OR 'gastrointestinal tract hemorrhage'/exp. OR 'gastrointestinal tract hemorrhage' OR 'gastrointestine bleeding'/exp OR 'gastrointestine bleeding' OR 'gastrointestine haemorrhage''/exp OR 'gastrointestine haemorrhage'' OR 'gastrointestine hemorrhage'/exp OR 'gastrointestine hemorrhage' OR 'gastrointestine tract bleeding'/exp OR 'gastrointestine tract bleeding' OR 'gastrointestine tract haemorrhage''/exp OR 'gastrointestine tract haemorrhage'' OR 'gastrointestine tract hemorrhage'/exp OR 'gastrointestine tract hemorrhage' OR ''haemorrhage, gastrointestinal'/exp OR ''haemorrhage, gastrointestinal' OR 'hemorrhage, gastrointestinal'/exp OR 'hemorrhage, gastrointestinal' OR 'lower gastrointestinal tract haemorrhage''/exp OR 'lower gastrointestinal tract haemorrhage'' OR 'lower gastrointestinal tract hemorrhage'/exp OR 'lower gastrointestinal tract hemorrhage' OR 'upper gi bleeding' OR 'bleeding, upper gastrointestinal'/exp. OR 'bleeding, upper gastrointestinal' OR 'upper digestive haemorrhage''/exp OR 'upper digestive haemorrhage'' OR 'upper digestive hemorrhage'/exp OR 'upper digestive hemorrhage' OR 'upper digestive tract haemorrhage''/exp OR 'upper digestive tract haemorrhage'' OR 'upper digestive tract hemorrhage'/exp OR 'upper digestive tract hemorrhage' OR 'upper gastrointestinal bleeding'/exp OR 'upper gastrointestinal bleeding' OR 'upper gastrointestinal haemorrhage''/exp OR 'upper gastrointestinal haemorrhage'' OR 'upper gastrointestinal tract bleeding'/exp OR 'upper gastrointestinal tract bleeding' OR 'upper gi hemorrhage' OR 'upper gastrointestinal hemorrhage'/exp OR 'upper gastrointestinal hemorrhage' OR 'duodenal ulcer bleeding'/exp OR 'duodenal ulcer bleeding' OR 'duodenal ulcer haemorrhage''/exp OR 'duodenal ulcer haemorrhage'' OR 'duodenal ulcer hemorrhage'/exp OR 'duodenal ulcer hemorrhage' OR 'duodenum ulcer haemorrhage''/exp OR 'duodenum ulcer haemorrhage'' OR 'duodenum ulcer hemorrhage'/exp. OR 'duodenum ulcer hemorrhage' OR 'gastric ulcer'/exp OR 'gastric ulcer' OR 'ev bleeding') AND ('tranexamic acid'/exp OR 'tranexamic acid' OR 'transamine'/exp OR transamine OR 'alpha oxoglutarate transferase'/exp OR 'alpha oxoglutarate transferase' OR 'amino transferase'/exp OR 'amino transferase' OR 'aminotransferase'/exp OR 'aminotransferase' OR 'aminotransferases'/exp OR 'aminotransferases' OR 'd54.680'/exp OR 'd54.680' OR 'transaminase'/exp OR 'transaminase' OR 'transaminases'/exp OR 'transaminases' OR txa) AND ('randomized controlled trial'/exp OR 'randomized controlled trial')	394
PubMed	(GI bleeding OR gastrointestinal bleeding OR GI hemorrhage OR gastrointestinal hemorrhage OR rectal hemorrhage OR rectal bleeding OR rectum bleeding OR rectum hemorrhage OR duodenal ulcer bleeding OR gastric ulcer OR EV bleeding OR esophageal bleeding OR esophagus hemorrhage OR esophagus bleeding OR esophageal hemorrhage) AND (tranexamic acid OR transamin OR TXA OR transamine)	222

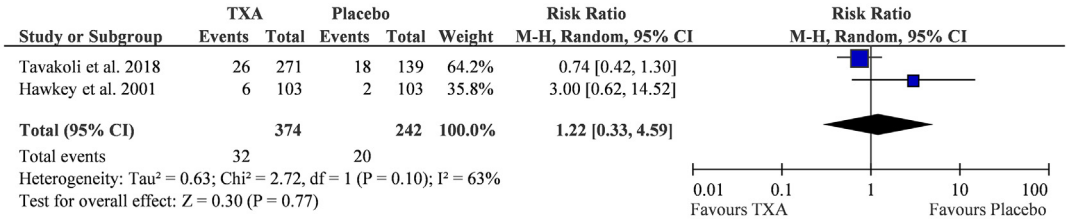
Appendix 2. Forest plot for transfusion rate



Appendix 3. Forest plot for transfusion volume



Appendix 4. Forest plot for intensive care unit administration rate



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