

Does tranexamic acid reduce risk of mortality on patients with hemoptysis?

A protocol for systematic review and meta-analysis

Liang-Fu Chen, MD^{a,b}, Ting-Cheng Wang, MD^{a,b}, Ting-Yi Lin, MD^{a,b}, Po-Jia Pao, MD^{a,b}, Karen Chia-Wen Chu, MD^{a,b}, Chih-Hao Yang, MD^{a,b}, Jer-Hwa Chang, MD^{c,d,e}, Chin-Wang Hsu, MD^{a,b}, Chyi-Huey Bai, PhD^f, Yuan-Pin Hsu, MD^{a,b,g,*}

Abstract

Background: Although tranexamic acid (TXA), a readily accessible antifibrinolytic agent, is widely adopted in hemorrhage scenarios, its role on mortality in patients with hemoptysis remains uncertain. New evidence is yet to be generated to evaluate the risk of mortality after using TXA in patients with hemoptysis.

Methods: PubMed, EMBASE, Cochrane Library, Web of Science, and Scopus databases were searched from inception to May 2020. Randomized controlled trials and observational studies that evaluated the effect of TXA on patients with hemoptysis were included. Data were independently extracted by 2 reviewers and synthesized using a random-effects model.

Main results: Five studies with a total of 20,047 patients were analyzed. When compared with the control, administration of TXA was associated with a reduction in short-term mortality (risk ratio = 0.78, 95% confidence interval [CI] 0.72–0.85; $I^2 = 0$), shorter bleeding time (mean difference = –24.61 hours, 95% CI –35.96 to –13.26, $I^2 = 0$), shorter length of hospital stay (mean difference = –1.94 days, 95% CI –2.48 to –1.40, $I^2 = 0$), and lower need for intervention (risk ratio = 0.38, 95% CI 0.16–0.87, $I^2 = 0$) in patients with hemoptysis. Compared with control, administration of TXA did not cause increased major or minor adverse effects.

Conclusions: TXA provided benefits in terms of a lower short-term mortality rate, less bleeding time, shorter length of hospital stays, and less need for intervention in patients with hemoptysis. Use of TXA was not associated with increased adverse effects.

Abbreviations: CI = confidence interval, IV= intravenous, MD = mean difference, RCT = randomized controlled trial, RR = risk ratio, TXA = tranexamic acid.

Keywords: hemoptysis, mortality, tranexamic acid

1. Introduction

Hemoptysis, which can result from various etiologies, with malignancy, pulmonary infection, and bronchiectasis listed as the 3 leading causes, remains a challenging condition for physicians.^[1] The clinical manifestations range from a nonalarming bloody expectoration to a life-threatening bleeding condition. Approximately 5% to 14% of patients presenting with

hemoptysis will have life-threatening hemoptysis,^[2] with a reported mortality rate between 9% and 38%.^[3] The amount of blood expectorated may be associated with in-hospital mortality.^[4] Additionally, a recent French nationwide study indicated that 9.0% of patients who were hospitalized for hemoptysis required admission to the intensive care unit.^[5] The reported average length of hospital stay among these patients is

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^aEmergency Department, Wan Fang Hospital, ^bDepartment of Emergency Medicine, School of Medicine, ^cSchool of Respiratory Therapy, College of Medicine,

^dDivision of Pulmonary Medicine, Department of Internal Medicine, ^ePulmonary Research Center, Wan Fang Hospital, ^fDepartment of Public Health, School of Medicine, College of Medicine, ^gResearch Center of Big Data and Meta-Analysis, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan.

* Correspondence: Yuan-Pin Hsu, Emergency Department, Wan Fang Hospital, Taipei Medical University, No. 111, Sec. 3, Xinglong Rd., Taipei 11696, Taiwan (e-mail: koakoahsu@gmail.com)

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approximately 8 days.^[5] Furthermore, Petersen and Weinreich^[6] reported a recurrence rate of 8.7% within 5 years of follow-up in patients with hemoptysis.

A guideline recommends that prompt intervention, including bronchial artery embolization, bronchoscopy, and surgical lung resection, is imperative in patients with massive hemoptysis.^[7] Meanwhile, in patients with mild hemoptysis, the course is mostly self-limited under adequate infection control.^[7] However, evidence regarding conservative and medical treatment in patients with submassive hemoptysis is lacking.

Tranexamic acid (TXA), a synthetic lysine analog, is a commonly used antifibrinolytic agent that controls bleeding by inhibiting the conversion of plasminogen to plasmin. TXA has been widely used in the last two decades to reduce bleeding. Previous studies have indicated that TXA reduces mortality in patients with postpartum hemorrhage^[8] or major trauma.^[9] In addition, the administration of TXA shortened the duration of epistaxis in patients with hereditary hemorrhagic telangiectasia.^[10] However, the role of TXA in patients with hemoptysis is uncertain. A Cochrane review in 2013 and another meta-analysis in 2016 have found that systemic TXA is efficient in shortening the bleeding period.^[11,12] A latest systemic review and meta-analysis reported that TXA reduced bleeding volume, further intervention risk, and length of hospital stay in patients with hemoptysis.^[13] However, the effect of TXA on mortality is not examined in that study. Through this study, we aimed to synthesize the evidence on the risk of mortality after using TXA in patients with hemoptysis.

2. Methods

Our meta-analysis followed the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA)^[14] guidelines. The analysis was registered at PROSPERO (PROSPERO ID: CRD42020185062). Ethical approval or patient consent was not required because the present study was a review of published articles.

2.1. Search strategy and study design

To identify relevant evidence, 2 authors (LFC and YPH) independently searched PubMed, EMBASE, Cochrane Library, Web of Science, and Scopus from their first record to May 2020. The key search text words and MeSH terms were as follows: tranexamic acid, antifibrinolytic agents, and hemoptysis. The details of the search are provided in Supplementary Table 1, <http://links.lww.com/MD/G75>. No language restrictions were imposed. The reference sections of the identified studies and previous systematic reviews were manually examined for additional potential studies. The ClinicalTrials.gov registry (<http://clinicaltrials.gov/>) was also searched for unpublished studies.

2.2. Inclusion and exclusion criteria

All published human randomized controlled trials (RCTs) or observational studies with an adequate control group were included. The participants were either adult or pediatric patients presenting with hemoptysis of any etiology and severity. The intervention was administration of TXA via any route and any regimen. Patients in the control group were treated with a placebo or were provided no treatment. Case reports, case series, abstracts, and animal studies were excluded. Our primary outcome of interest was the mortality rate. The secondary outcomes were cessation of the bleeding rate, duration of

bleeding, amount of blood loss, need for intervention, length of hospital stay, and recurrence rate. Safety outcomes were major adverse events, such as venous thromboembolism, coronary artery occlusion, and stroke, which were attributable to the mechanism of action of TXA, and minor adverse events, such as nausea, dizziness, vomiting, abdominal pain, and diarrhea.

2.3. Data extraction and management

Two reviewers (LFC and CHY) independently extracted the data. The following information was extracted: first author, publication year, country, study design, sample sizes, inclusion and exclusion criteria, baseline characteristic, regimens of each intervention, and data of the outcome interest. Any controversies regarding recorded data were resolved through discussion between the authors or by consulting a third reviewer (YPH).

2.4. Assessment of risk of bias

Two investigators (TYL and PJP) independently assessed the methodological qualities of the included studies. The Cochrane risk of bias tool 2.0 for RCTs was used.^[15] This tool includes 6 domains: selection bias due to the inadequate generation of a randomized sequence or concealment of allocation before the assignment, performance bias due to the knowledge of allocated interventions by participants and personnel, detection bias due to the knowledge of allocated interventions by outcome assessors, reporting bias due to selective outcome reporting, and other biases. The Newcastle–Ottawa scale tool was applied to assess the quality of observational studies.^[16] Studies were evaluated by selection with a maximum of four stars, comparability with a maximum of 2 stars, and outcome with a maximum of three stars. Studies with cumulative stars ≥ 7 were considered to be of high quality. If no agreement could be reached, a third investigator (YPH) determined the rating.

2.5. Statistical analysis

Data were analyzed using Review Manager (version 5.3, Copenhagen, Denmark). Meta-analyses were performed using a random-effects model. For binary outcomes, the risk ratio (RR) was estimated with the 95% confidence interval (CI). The mean difference (MD) and 95% CI were used to estimate continuous outcomes. Significant differences between the groups were set at 2-sided P values $< .05$. Heterogeneities among the studies were estimated using the I^2 statistic. The statistical heterogeneity was categorized into low (25%–50%), moderate (50%–75%), or high ($>75\%$) according to the I^2 values.^[17] In case of substantial heterogeneity, factors that could potentially affect the magnitude of the treatment response were explored using prespecified subgroup analysis (route of administration). To test the robustness of our result of primary outcome, we performed a sensitivity analysis by restricting the meta-analysis of the evidence from only RCTs. If at least 10 studies were included, publication bias was assessed by detecting the asymmetry in funnel plots and using the Egger test.^[18]

3. Results

3.1. Study characteristics

The flow diagram of literature search is displayed in Figure 1. In total, 1871 studies were retrieved from different sources, including PubMed, EMBASE, Scopus, the Cochrane Library,

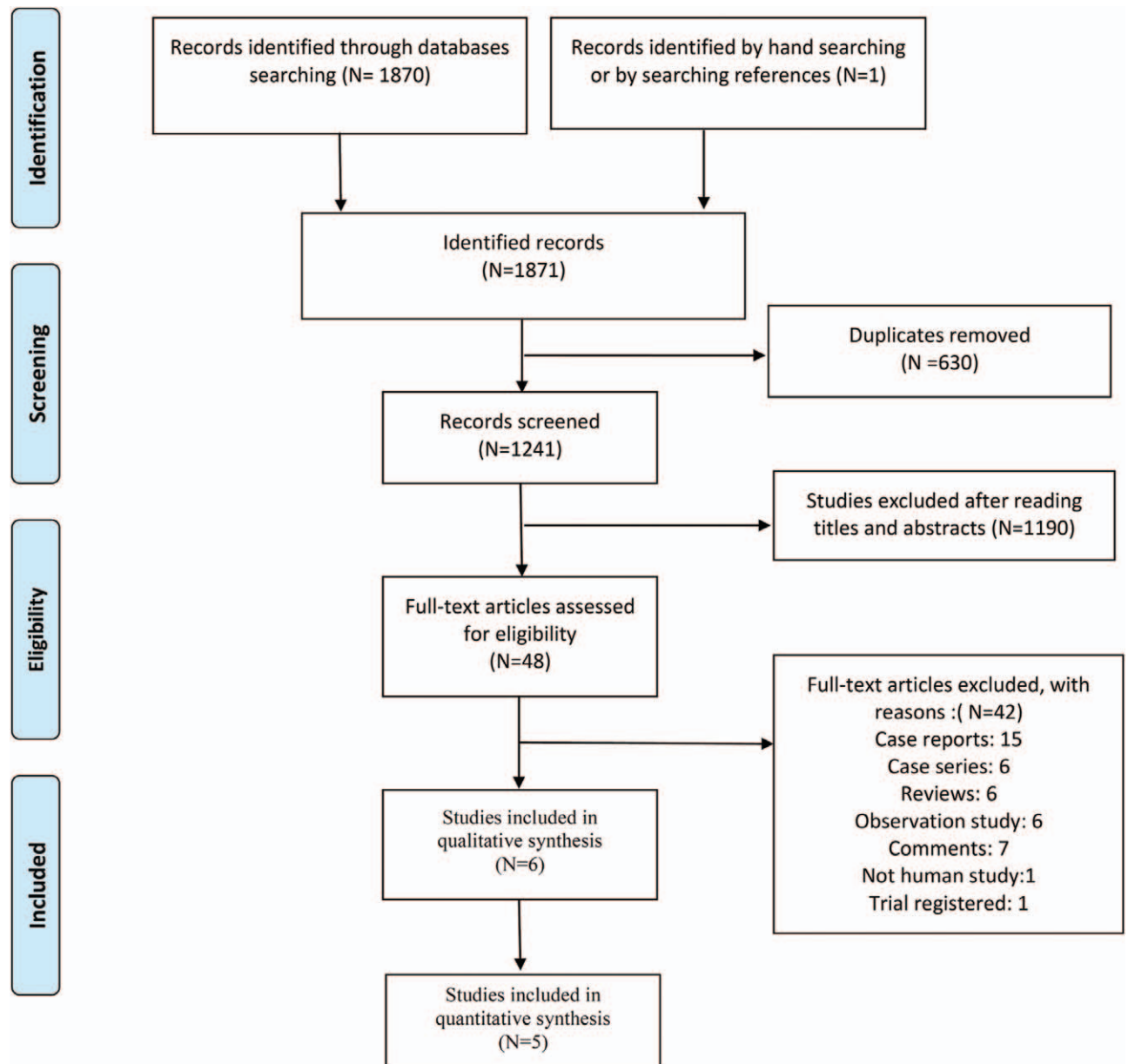


Figure 1. Flowchart of article selection process.

Web of Science, clinicaltrials.gov, and manual search. Subsequently, 630 duplicated records were removed and 1190 articles were excluded after screening titles and abstracts. The full text was then extracted to assess the eligibility. Eventually, 6 and 5 studies were included for qualitative and quantitative analysis, respectively, because Alberto-Pasco and Soto reported the outcome of interest as a composite of mortality and requirement for blood transfusion.^[19–24]

3.2. Study characteristics

The characteristics of the included studies are summarized in Table 1. These studies were conducted in Peru, Thailand, Israel, India, and Japan. Four studies were RCTs, 1 was a retrospective cohort study, and 1 was a case–control study. Five studies enrolled inpatients and 1 study included both inpatients and

outpatients. Three studies excluded patients with massive hemoptysis, and the threshold for massive hemoptysis varied among studies. Additionally, 2 RCTs excluded patients with renal failure. Five studies comprised patients with hemoptysis due to all etiologies, and 1 study comprised patients with hemoptysis due to only tuberculosis. Sample sizes ranged from 24 to 19,866 patients, with mean patient ages ranging from 40.1 to 72 years. TXA was administered through inhalation in 1 study, oral route in 1 study, and intravenous (IV) route in 3 studies; 1 study did not provide information regarding the route of administration. The dosage of TXA varied among studies.

3.3. Risk of bias assessment

The assessment of risk of bias is shown in Supplementary Table 2, <http://links.lww.com/MD/G76>. Among RCTs, the study by

Table 1
Characteristics of the included studies.

Author, publication year	Country	Study design/setting	Inclusion criteria		Cause of hemoptysis	Sample size, N	Age, mean (SD)	Intervention	Control
			Exclusion criteria						
Ruiz, 1994 ^[19]	Peru	RCT/in-patient	N/A		Tuberculosis	TXA: 13	TXA: N/A	TXA IV 1000mg TID	Placebo
Tscheikuna et al, 2002 ^[20]	Thailand	RCT/in-patient and out-patient	Patient with hemoptysis		Any causes	TXA: 21	TXA: 45.38 (15.43)	TXA PO 500 mg TID/	Placebo
Bellam et al, 2016 ^[21]	India	RCT/in-patient	Bleeding \geq 500 mL/day Patient with acute-onset, ongoing hemoptysis		Any causes	TXA: 43	TXA: 42.63 (16.6)	TXA IV 1000 mg STAT + 1000 mg Q8H/	Placebo
Wand et al, 2018 ^[22]	Israel	RCT/in-patient	Bleeding \geq 600 mL/day Renal failure		Any causes	TXA: 25	TXA: 40.1 (13.6)	TXA nebulized 500mg TID	Nebulized NS
Kinoshita et al, 2019 ^[24]	Japan	OS/in-patient	Patient with hemoptysis in past 24 h		Any causes	TXA: 25	TXA: 68 (N/A)	TXA nebulized 500mg TID	Nebulized NS
Alberto-Pasco and Soto, 2013 ^[23]	Peru	CC/in-patient	Bleeding \geq 200 mL/day Respiratory and hemodynamic instability renal failure coagulopathy		Any causes	TXA: 22	TXA: 69 (N/A)	TXA IV of uncertain dose and frequency	No TXA
			Patient admitted due to hemoptysis		Any causes	TXA: 9933	TXA: 72 (14)	TXA IV of uncertain dose and frequency	No TXA
			Hemoptysis after admission		Any causes	Control: 9933	Control: 72 (13)	TXA of uncertain route, dose and frequency	No TXA
			Patient admitted due to hemoptysis		Any causes	TXA: 45	Median=35	TXA of uncertain route, dose and frequency	No TXA
			N/A		Any causes	Control: 35			

C=control group, CC=case-control study, IV=intravenous, N/A=not applicable, NS=normal saline, OS=observational study, PO=per Os, RCT= randomized control trial, TXA=tranexamic acid.

Tscheikuna et al had an unclear selection bias because the randomization protocol was not mentioned. Ruiz found a high risk of attrition bias because they did not perform the intention-to-treat analysis; the reporting bias was evaluated as unclear owing to the lack of protocol disclosed. The remaining 2 RCTs were rated as low-risk bias. For observational studies, 1 study was rated as a high-quality study (scored 8 stars); the study by Alberto-Pasco and Soto was rated as a low-quality study because of limited information regarding population selection, comparability, and exposure details.

3.4. Primary outcome: overall mortality

Three studies (n=19,937) reported the comparison between the mortality rate when TXA and control were used for the treatment of hemoptysis. TXA was administered through the IV or inhalation route. One study investigated the effect of TXA on in-hospital mortality, 1 on short-term mortality, and 1 on 30-day mortality rate. We regarded these reported outcomes as sharing a similar property of short-term mortality rate. The pooled result indicated that using TXA was associated with reduction in the short-term mortality rate (RR=0.78, 95% CI 0.72–0.85; Fig. 2). There was no significant heterogeneity

between the groups ($I^2=0\%$). A subgroup analysis for patients receiving IV TXA (n=19890) also indicated a reduction in short-term mortality (RR=0.78, 95% CI 0.72–0.85; Fig. 3). Wand et al reported the effect of TXA on long-term mortality. The result showed that using nebulized TXA significantly reduced the 1-year mortality rate compared with the control (n=47, 16% vs 18%, $P<.01$). In the sensitivity analysis by excluding evidence from the observational study, the result indicated that TXA led to a lower short-term mortality rate (RR=0.38, 95% CI 0.10–1.39; Supplementary Figure 1, <http://links.lww.com/MD/G71>). However, this finding did not reach statistically significant.

3.5. Secondary outcome

3.5.1. Cessation of bleeding. Two studies (n=93) reported on the cessation of bleeding rate following TXA administration compared with the control. One study evaluated the bleeding status 7 days after oral TXA treatment, and another study evaluated the rate of bleeding resolution 5 days after TXA treatment through nebulization. A total of 41 of 46 (89.1%) patients who received TXA achieved cessation of bleeding, compared with 29 of 47 (61.7%) patients who received the

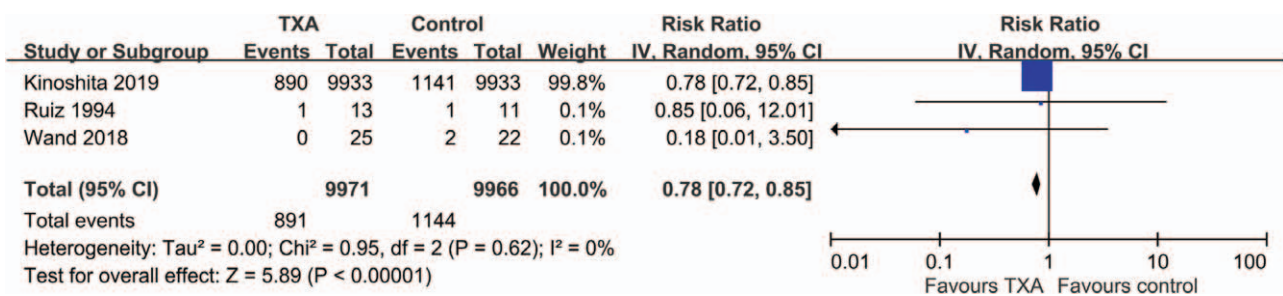


Figure 2. Meta-analysis evaluating the short-term mortality rate after tranexamic acid administration.

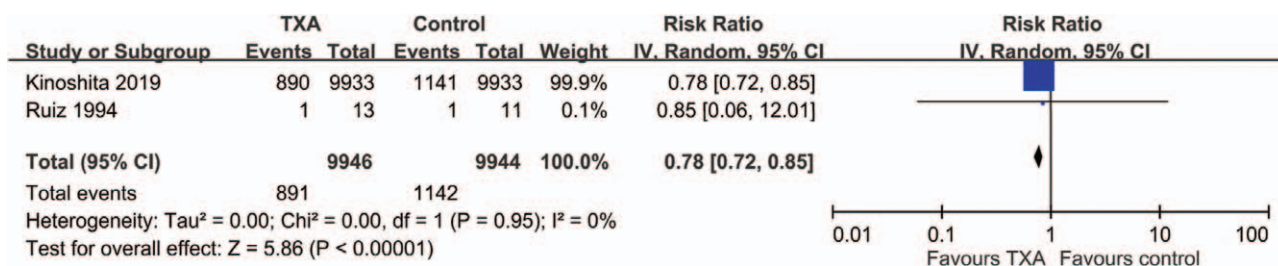


Figure 3. Meta-analysis evaluating short-term mortality rate of the intravenous tranexamic acid subgroup.

control (RR=1.44, Table 2, Supplementary figure 2-A, <http://links.lww.com/MD/G72>). However, the pooled results were not statistically different.

3.5.2. Time required to stop bleeding. Two studies (n=70) investigated the time in which bleeding stopped after the treatment. In both the studies, TXA was administered systemically; 1 intravenously and 1 orally. Forest plots indicated that compared with patients treated with the control, those treated with TXA had a significantly shorter bleeding time (MD=−24.61 hours, 95% CI −35.96 to −13.26, I²=0; Table 2, Supplementary figure 2-B, <http://links.lww.com/MD/G72>).

3.5.3. Bleeding volume. In 3 studies, the bleeding volume after treatment was measured between the groups. The method and time point of measurement varied among studies. Therefore, we did not pool the results. Ruiz did not provide information regarding measurement of the bleeding volume and the variance of the effect sizes. They reported a significant reduction of bleeding volume after treatment with IV TXA. In the study by Bellam et al, the bleeding volume was measured on Day 1 and Day 2. They found that compared with the control, treatment with IV TXA reduced the bleeding volume on Day 1 (84.3 vs 145 mL) and Day 2 (34.19 mL/day vs 90.4 mL). In the study by Wand et al, the bleeding volume was measured as milliliters per 24 hours. The daily bleeding volume significantly reduced since Day 2 when patients were treated with TXA through nebulization compared with the placebo.

3.5.4. Length of stay. Three studies (n=19977) provided information on the hospital length of stay. Two studies used intravenous TXA and 1 study used nebulized TXA. The result showed that the length of stay was significantly shorter in the TXA group than in the control group (MD=−1.94 days, 95% CI −2.48 to −1.40, I²=0; Table 2, Supplementary figure 2-C, <http://links.lww.com/MD/G72>). A subgroup analysis was performed on two studies (n=19930) using IV TXA. The result indicated

that patients receiving IV TXA had a significantly shorter length of stay compared with those receiving the control (MD=−1.93 days, 95% CI −2.49 to −1.37 days, I²=0; Table 2, Supplementary figure 3, <http://links.lww.com/MD/G73>).

3.5.5. Need for intervention. Two studies (n=111) investigated whether patients with hemoptysis still required the intervention for hemostasis after medication. The procedure included surgery, bronchoscopy, or bronchial artery embolization. The pooled result revealed that TXA administration significantly reduced the need for intervention, compared with the controls (RR=0.38, 95% CI 0.16–0.87, I²=0; Table 2, Supplementary figure 2-D, <http://links.lww.com/MD/G72>).

3.5.6. Recurrence. The recurrence of hemoptysis was assessed in 3 studies (n=135). In 2 of these studies, TXA was administered through the IV route, and in 1 study, it was administered through nebulization. Hemoptysis recurring within 1 month or during the hospitalization was termed as short-term hemoptysis recurrence. A total of 5 of 81 (6.2%) patients who received TXA had short-term recurrent hemoptysis compared with 8 of 55 (14.5%) patients who received the control (RR=0.40, Table 2, Supplementary figure 2-E, <http://links.lww.com/MD/G72>). However, the pooled results were not statistically different. Wand et al reported that patients administered TXA through nebulization had a significantly lower recurrence rate within 1 year compared with those administered the control (n=47, 4% vs 22.7%, P<.01).

3.5.7. Safety. No major complications, such as thromboembolic events, were observed in any of the clinical trials. In the large retrospective study, no significant difference was recorded in terms of thromboembolism (TXA 2.3% vs control 2.1%, P=.34) and seizure (TXA, 5/9933 cases vs control, 9/9933 cases). All clinical trials (n=191) documented minor adverse effects associated with TXA, including nausea, dizziness, and gastrointestinal upset. The pooled result showed no significant difference

Table 2
Meta-analysis of secondary outcome.

Outcome of interest	No. of studies	No. of patients	Effect sizes (95% CI)	P	I ² (%)
Cessation of bleeding	2	70	RR, 1.44 (0.85 to 2.43)	.17	74
Time required to stop bleeding, h	2	70	MD, −24.61 (−35.96 to −13.26)	<.05*	0
Length of stay, days	3	19977	MD, −1.93 (−2.49 to −1.37)	<.05*	0
Length of stay (days), IV TXA subgroup	2	19930	MD, −1.93 (−2.49 to −1.39)	<.05*	0
Need for intervention	2	111	RR, 0.38 (0.16 to 0.87)	<.05*	0
Recurrence	3	135	RR, 0.40 (0.12 to 1.28)	.12	0

IV=intravenous, MD=mean difference, RR=risk ratio, TXA=tranexamic acid.
* Statistically significant.

between TXA and control groups with regard to minor adverse effects (Supplementary Figure 4, <http://links.lww.com/MD/G74>).

4. Discussion

The principal finding of our study is that administration of TXA was associated with a reduction of the short-term mortality rate. IV administration of TXA also reduced short-term mortality in that subset of patients. Of noted, the pooled evidence driven from only RCTs also indicated that using TXA reduced the short-term mortality rate but this finding was statistically non-significant. Moreover, TXA use led to a shorter bleeding time, lower bleeding volume, shorter length of hospital stay, and less requirements for intervention compared with the control. Administration of TXA was not associated with the recurrence of hemoptysis or increase in major or minor adverse effects.

Expectoration of large amounts of blood is associated with high morbidity and mortality. Advances in medical imaging, fiberscope technology, and interventional radiology have led to improved outcomes, with the reporting mortality rates ranging from 7% to 30% since 2000.^[25-27] However, a strong recommendation regarding pharmacological treatment, such as antifibrinolytic agents for hemoptysis, does not exist.^[28-30] TXA is an antifibrinolytic agent that is commonly used to control bleeding, and it has recently been proven a promising strategy to reduce mortality from hemoptysis.^[22] Our study provided a comprehensive search from five databases and involved manual checking of the relative reviews and references to identify eligible studies. In total, 19,943 patients were included, a number that was significantly larger than that of patients in the latest systematic review ($n=617$).^[13] We found that TXA administration consistently led to a 22% reduction in shorter-term mortality. Moreover, a consistent reduction in short-term mortality by 22% was observed in a subset of patients receiving IV TXA. Additionally, according to the study by Wand et al, treatment with TXA through inhalation reduced the long-term mortality by 2%. In accordance with our findings, previous large-scale clinical trials have demonstrated that administration of TXA reduced the mortality of patients during uncontrolled post-partum hemorrhage and traumatic bleeding.^[8,9] Of noted, the weight of the observational study was far larger than other RCTs in the current meta-analysis. The evidence based on only RCTs was not powerful to show the reduction on the short-term mortality. Therefore, more large-scale RCTs were warranted to clarify the issue.

Mild hemoptysis tends to stop spontaneously in some cases.^[20] For hemoptysis $\geq 1\text{L}$ per 24 hours, a mortality rate up to 58% was reported.^[31] Among cases of fatal hemoptysis, the inciting cause of death is asphyxiation from inability to oxygenate or ventilate because of the hemorrhage flooding the airways.^[32] The volume of the conducting airway is approximately 150 mL,^[33] and a nonsignificant amount of pulmonary bleeding may hinder oxygenation before hemodynamics becomes unstable.^[34] Therefore, it is critical to reduce the bleeding volume and foster bleeding cessation. Our study showed that patients in the TXA group showed earlier bleeding cessation by 24.3 hours compared with those in the control group. In addition, the results from three RCTs indicated that the administration of TXA reduced the bleeding volume. However, we did not observe any benefit of TXA in terms of the hemoptysis cessation rate. This could be attributed to the small number of the included studies with small sample sizes. Additional large clinical trials should be conducted to prove or disapprove our hypothesis.

The length of hospital stay is an important indicator of the patient quality of care and functional evaluation. Decreased length of hospital stay was associated with decreased medical costs in patients with hemoptysis.^[24] Our study demonstrated that administration of TXA significantly reduced the length of stay by 1.94 days. In consistency with our observation, TXA administration to patients suffering from truncal and peripheral vascular trauma led to a 4-day shortening of hospital period, compared with placebo.^[35] The explanation of this finding was that TXA provided better bleeding control, which may cause less morbidity during a hemoptysis episode, resulting in early discharge.

The requirement of embolization or surgical intervention to treat hemoptysis indicates additional medical efforts, risk of surgery, and anesthesia complications. A recent large RCT showed that TXA administration failed to reduce the requirement of surgical, endoscopic, or radiological intervention in patients with acute gastrointestinal bleeding.^[36] In contrast, TXA reduced the requirement for Brace suture and laparotomy surgery in patients with postpartum hemorrhage.^[8] There is little evidence about the pharmacological effect of hemoptysis on the need for hemostasis intervention. In our study, we observed that TXA reduced the requirement of further interventions by 62%.

A major concern with the application of TXA was the increase of thromboembolic events. TXA is associated with more than 3-fold increased odds of venous thromboembolism in patients with trauma.^[37] Moreover, some studies showed that TXA administration led to a 6% to 11% increase in postoperative seizure among patients who underwent cardiac surgery.^[38,39] In addition, a case report had raised the concern that TXA administration led to pulmonary embolism in patients with chronic hemoptysis secondary to bronchiectasis.^[40] However, in our study, no increased major adverse events were observed in the included RCTs.^[19-22] Furthermore, TXA administration did not increase the incidence of thromboembolic events and seizure in a large-scale included observational study.^[24] Therefore, TXA seemed safe for hemoptysis control.

Although our meta-analysis demonstrated the benefit of TXA for hemoptysis, it has several limitations. First, limited studies were included and the case numbers of the RCTs involved were relatively small. Second, observational studies were also included, which could have introduced a selection bias. Third, the length of treatment, dosage, and form of TXA administration, and the definition of severity of hemoptysis varied among the studies, which may introduce clinical heterogeneities. However, significant statistical heterogeneities were observed only at the analysis of the hemoptysis cessation rate. Fourth, some factors, such as smoking, malignancy, pulmonary infection, and anti-coagulant drug use,^[41-43] were associated with increased rate of mortality and hemoptysis recurrence. These confounding factors were not fully disclosed in some studies (Supplementary Table 3, <http://links.lww.com/MD/G77>). Moreover, most of the studies included all etiologies of hemoptysis, except one study that specifically dealt with tuberculosis-related hemoptysis. Therefore, whether the results of our study could be generalized to a specific population warrants further investigation. Finally, a funnel plot for assessing publication bias was not depicted owing to the small number of studies included.

5. Conclusions

Our meta-analysis indicated that administration of TXA was associated with a reduction of short-term mortality rate, shorter time required to stop bleeding, shorter length of hospital stays,

and less requirement of intervention among patients with hemoptysis. TXA is considered a safe medication for hemoptysis.

Author contributions

Liang-Fu Chen, Ting-Cheng Wang, and Yuan-Pin Hsu had full access to all data in the study and take responsibility for data integrity and accuracy of data analysis.

Acquisition, analysis, or interpretation of data: Liang-Fu Chen, Ting-Cheng Wang, Chih-Hao Yang, Ting-Yi Lin, Po-Jia Pao, Karen Chia-Wen Chu, and Jer-Hwa Chang.

Concept and design: Liang-Fu Chen and Yuan-Pin Hsu.

Data curation: Liang-Fu Chen, Po-Jia Pao.

Drafting of manuscript: Liang-Fu Chen, Ting-Cheng Wang and Yuan-Pin Hsu.

Investigation: Liang-Fu Chen, Ting-Yi Lin, Po-Jia Pao, Karen Chia-Wen Chu, Chih-Hao Yang.

Resources: Ting-Cheng Wang, Chyi-Huey Bai.

Statistical analysis: Chin-Wang Hsu and Chyi-Huey Bai.

Study supervision: Ting-Cheng Wang and Yuan-Pin Hsu.

Supervision: Ting-Cheng Wang, Jer-Hwa Chang, Chin-Wang Hsu, Yuan-Pin Hsu.

Writing – original draft: Liang-Fu Chen, Ting-Cheng Wang, Karen Chia-Wen Chu.

Writing – review & editing: Yuan-Pin Hsu.

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