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ORIGINAL ARTICLE

The efficacy and safety of tranexamic acid in lumbar surgery: A meta-analysis of randomized-controlled trials

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ABSTRACT

Objectives: This meta-analysis aims to assess tranexamic acid (TXA) effectiveness and safety in lumbar surgery.

Patients and methods: Renewals of randomized-controlled trials (RCTs) were conducted utilizing databases of medical literature such as PubMed, China Science and Technology Journal Database, Cochrane Library, China National Knowledge Infrastructure (CNKI), and EMBASE to compare principal and safety endpoints. The risk ratio (RR), standard mean difference (SMD), and 95% confidence intervals (CIs) were calculated. For the evaluation of the quality of the included studies, the Cochrane risk of bias criteria were utilized by two authors.

Results: In total, 49 articles were enrolled that included 4,822 patients. Of the patients, 2,653 were administered TXA and 2,169 were in the control group. The findings indicated that TXA was capable of significantly lowering postoperative blood loss (PBL), transfusion rate, transfusion volume, total blood loss (TBL), intraoperative blood loss (IBL), and drainage compared to the control group. Besides, hemoglobin (Hb) and hematocrit (Hct) values were higher in the TXA group compared to the control group. As the safety endpoints, TXA significantly reduced D-dimer levels compared to the control group; however, both TXA and control groups had no significant variations in deep venous thrombosis (DVT). Subgroup analysis was administrated according to the administration method of TXA and the operation type and intravenous and topical TXA were combined in the meta-analysis.

Conclusion: This meta-analysis showed that TXA had the potential to significantly lower PBL, transfusion rate, transfusion volume, TBL, IBL, and drainage compared to the control group. Besides, Hb and Hct values were higher in the TXA group compared to the control group. Its hemostatic potential after lumbar spine surgery is trustworthy. It is still controversial in safety endpoints that TXA can significantly reduce D-dimer compared to the control group, without no significant variations in DVT in both the TXA and control groups.

Keywords: Lumbar surgery; meta-analysis, tranexamic acid.

With the improvement of human life expectancy and changes in lifestyle, the number of patients undergoing lumbar surgery for lumbar diseases is increasing.[1] In lumbar surgery, extensive muscle tissue stripping can lead to spinal canal decompression, bone graft fusion, a large wound, and internal fixation may injure the long segment of the intraspinal venous plexus, and these factors are expected to cause more postoperative bleeding.[2] The amount of pre- and postoperative bleeding is closely related to the complexity of the operation and is directly related to the time of the drainage tube removal and the need for postoperative blood transfusion.[3] Reducing the exudation of incision blood and removing the drainage tube as soon as possible is not only necessary for postoperative rehabilitation, but it is also essential to minimize the risk of lower-extremity deep venous thrombosis (DVT).[4] Concurrently, minimizing quantity of blood loss from the wound following the surgery may help to eliminate the necessity for a blood transfusion.[5] Therefore, reducing perioperative blood loss is important to ensure the safety of surgery.[6]

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To minimize perioperative blood loss, physicians have utilized a variety of techniques, such as controlled hypotension, blood dilution, autologous blood transfusion, and application of hemostatic drugs.[7] Currently, in orthopedic surgery, hemostatic medications with various hemostatic routes have been widely utilized, but due to the need for immobilization, DVT risk exists and, therefore, the application of hemostatic drugs is still controversial.[8] As a common hemostatic drug, tranexamic acid (TXA) is a lysine synthetic derivative and an antifibrinolytic agent.[9] Its pharmacological action is to bind competitively to the lysine binding sites on the source of fibrinolytic enzyme, tissue type plasminogen activator, and plasmin to prevent the dissolution of thrombi.[10-12] Numerous studies have reported that TXA has no effect on enhancing the incidence of DVT, but most of them are routinely used for chemical thromboprophylaxis and, thus, the risk of thrombosis is still not clear.[13-16]

The application of TXA in lumbar surgery is relatively common, but it is still controversial and ambiguous about its safety and effectiveness.[17] Therefore, our study aimed to discover the safety and effectiveness of TXA in lumbar surgery to reinforce the hemostatic medicines clinical application.

PATIENTS AND METHODS

Search strategy

A literature search utilizing the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were carried out by two authors[18] for papers assessing the safety and effectiveness of TXA in lumbar operation. We searched in PubMed, the Cochrane Library, EMBASE, the China National Knowledge Infrastructure (CNKI), and the China Science and Technology Journal Database (commonly known as "VIP") comprehensively for randomized-controlled trials (RCTs). The language choice is restricted to English or Chinese, and the date of publication was set to begin on January 1st, 2003 to June 30th, 2021. "Tranexamic Acid" and "Lumbar" were utilized as key words, Other meta-analyses and reviews were used to retrieve additional relevant literature. For incomplete or missing data, we contacted the original research authors through electronic mail. Two authors reviewed the retrieved literature. In case of disagreements, a third author was invited to review the paper and render a final decision. No written consent or ethical approval was required, as all data in this meta-analysis were derived from previously published research.

Inclusion and exclusion criteria

Inclusion criteria:

1. The study was an RCT;
2. Evaluated TXA effectiveness and safety in lumbar surgery;
3. The subjects of study were patients who underwent lumbar surgery;
4. On basis of TXA, at least one of groups were assessed;
5. TXA had no dosage or use restrictions;
6. Language options were restricted to English or Chinese;
7. The papers included give sufficient data for analysis.

Exclusion criteria:

1. Animal experiments;
2. Non-randomized trials or semi-randomized controlled trials;
3. Case reports, non-clinical trials, or series;
4. Papers containing wrong or missing data or articles from which data could not be collected.

Endpoints

Total blood loss (TBL) and transfusion rate were the initial endpoints of the study. Secondary endpoints were postoperative drainage, transfusion volume, intraoperative blood loss (IBL), postoperative blood loss (PBL), hemoglobin (Hb) and hematocrit (Hct). Safety endpoints were DVT, and D-dimer (a fibrin degradation product that is traditionally used as a biomarker of DVT).[19,20]

Data extraction

The retrieved studies contents were reviewed by two authors independently. A third author validated the primary endpoints derived by the two authors. The following information were included in extracted data: author's first name, publication year, country conducted in, body mass index (BMI), the size of the sample, sex ratio, intervention, average age, operation type, follow-up time and the endpoints computed in each study. If the study's contents required clarifying, the study's primary author was called up. Conflicts were resolved via prevailing opinion or by calling up a third author who ultimately took the decision.

TABLE I
Guidance to assess study limitations (risk of bias) in Cochrane Reviews and corresponding GRADE assessment of quality of evidence

Risk of bias	Across studies	Interpretation	Considerations	GRADE assessment of study limitations
Low	Most information is from studies at low risk of bias.	Plausible bias unlikely to seriously alter the results.	No apparent limitations.	No serious limitations, do not downgrade.
Unclear	Most information is from studies at low or unclear risk of bias.	Plausible bias that about the results.	Potential limitations are unlikely to lower confidence in the estimate of effect.	No serious limitations, do not downgrade.
			Potential limitations are likely to lower confidence in the estimate of effect.	Serious limitations, downgrade one level.
High	The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results.	Plausible bias that seriously weakens confidence in the results.	Crucial limitation for one criterion, or some limitations for multiple criteria, sufficient to lower confidence in the estimate of effect.	Serious limitations, downgrade one level.
			Crucial limitation for one or more criteria sufficient to substantially lower confidence in the estimate of effect.	Very serious limitations, downgrade two levels.

Risk of bias assessments

Two authors independently appraised the studies' methodological quality using the Cochrane risk of bias criteria. Each item was classified as having a low risk, a high risk, or no obvious risk. The guideline for detecting limitations of this study (risk of bias) in Cochrane Reviews is shown in Table I, along with the corresponding GRADE evaluation of the quality of evidence. Every trial's bias assessment checklist involved seven items: randomization sequence generation, allocation concealment, blinding of participants and personnel, findings appraisal blinding, inadequate data findings, selective reporting, as

TABLE II
Study limitations in randomized-controlled trials: Explanation

	Explanation
Lack of allocation concealment	Those enrolling patients are aware of the group (or period in a crossover trial) to which the next enrolled patient will be allocated (a major problem in “pseudo” or “quasi randomized trials with allocation by day of week, birth date, chart number, etc.).
Lack of blinding	Patient, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated (or the medication currently being received in a crossover trial).
Incomplete accounting of patients and outcome events	Loss to follow-up and failure to adhere to the intention-to-treat principle in superiority trials; or in noninferiority trials, loss to follow-up, and failure to conduct both analyses considering only those who adhered to treatment, and all patients for whom outcome data are available.
	The significance of particular rates of loss to follow-up, however, varies widely and is dependent on the relation between loss to follow-up and number of events. The higher the proportion lost to follow-up in relation to intervention and control group event rates, and differences between intervention and control groups, the greater the threat of bias.
Selective outcome reporting	Incomplete or absent reporting of some outcomes and not others on the basis of the results.
Other limitations	Stopping trial early for benefit. Substantial overestimates are likely in trials with fewer than 500 events and that large overestimates are likely in trials with fewer than 200 events. Empirical evidence suggests that formal stopping rules do not reduce this bias.

well as additional biases. We evaluated publication bias according to the guidance shown in Table II.

Statistical analysis

The individual study results were analyzed and pooled using the Stata version 12.0 software (Stata Corp., College Station, TX, USA). Risk ratios (RRs), standardized mean differences (SMDs), and 95% confidence intervals (CIs) with two-sided p values were estimated in the pooled results. A *p* value of <0.05 was considered statistically significant. The I^2 test was utilized to assess heterogeneity. In case of I^2<50%, heterogeneity was deemed to be minor; but, in case of I^2>50%, heterogeneity was deemed to be substantial. If the I^2 was <50%, the fixed-effects model was utilized; when the I^2 was >50%, the random-effects model was utilized. If more than 10 studies were involved in the analysis of this endpoint, a funnel plot was constituted to scrutinize publication bias, as well as discovering the heterogeneity sources. We conducted a subgroup analysis of the indicators including the patients' TBL, transfusion rates, DVT, and D-dimer level. Subgroup analyses were performed on the basis of administration and operation type.

RESULTS

Studies retrieved and characteristics

Relying on the (PRISMA) guideline, a total of 2,963 studies were registered. The research titles and abstracts were reviewed to preclude studies that were not pertinent. Then, we excluded research that were not suitable by scanning articles full text. Ultimately, relying on the inclusion and exclusion criteria, 49 studies[21-69] including a total of 4,822 patients were enrolled (Figure 1).[70] At length, 2,653 patients (55.0%) and 2,169 patients (45.0%) were allotted to the experimental and the control groups, respectively. The researches involved were all RCTs in the meta-analysis. The participants' baseline characteristics in the RCTs are fully revealed in Table III.

Literature quality evaluation

Since studies included were all RCTs, two authors were saddled with the responsibility of assessing the retrieved studies quality relying on the Cochrane risk of bias criteria. In 49 studies, random sequence generation and allocation concealment were performed. Twenty-four studies verified

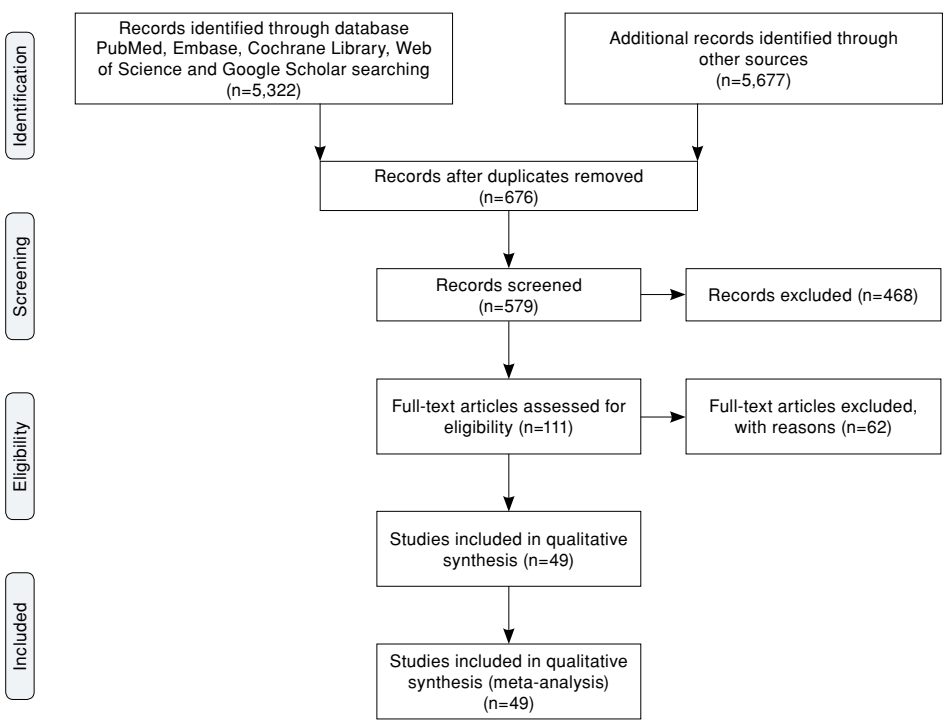

FIGURE 1. Flow diagram of the study selection process.[70]

TABLE III
Characteristics of studies included in meta-analysis

			Sample size		Female, No (%)		Average age (years)		BMI		Intervention				
Authors	Year	Country	E	C	E	C	E	C	E	C	E	C	Follow-up	Operative type	Endpoints
Elmose et al.[21]	2019	Denmark	117	116	58 (0.49)	39 (0.36)	48.9±15.4	51.1±14.9	26.4±3.8	26.2±3.7	TXA, 10 mg/kg, IV	Equivalent normal saline (0.9%), IV	28 days	Minor lumbar spine surgery	Total blood loss, Intraoperative blood loss, postoperative blood loss
Kim et al.[22]	2017	South Korea	24	24	16 (0.67)	9 (0.375)	63.3±7.6	65.2±7.0	NA	NA	TXA, 5 mg/kg, IV, preoperation; A maintenance dosage of 1 mg/kg/h, until 5 h after surgery	100 mL normal saline (0.9%), IV	7 days	PLIF	Total blood loss, Intraoperative blood loss, postoperative blood loss, postoperative drainage, Hb, Hct
Kim et al.[22]	2017	South Korea	24	24	12 (0.50)	9 (0.375)	61.0±9.0	65.2±7.0	NA	NA	TXA, 10 mg/kg, IV, preoperation; A maintenance dosage of 2 mg/kg/h, until 5 h after surgery	100 mL normal saline (0.9%), IV	7 days	PLIF	Total blood loss, Intraoperative blood loss, postoperative blood loss, postoperative drainage, Hb, Hct
Liang et al.[23]	2016	China	30	30	15 (0.50)	12 (0.40)	51.1±10.7	53.8±11.2	26.2±4.1	24.9±5.3	Gelfoam was soaked in TXA (2,000 mg: 20 mL), topical, intraopration	Gelfoam	3 days	Lumbar spine surgery	Transfusion volume, postoperative drainage, Hb, Hct
Mu et al.[24]	2019	China	45	42	18 (0.40)	19 (0.45)	54.2±7.4	52.6±6.7	24.8±2.0	23.9±1.4	TXA, 15 mg/kg, IV, preoperation; A maintenance dose of 1 mg/kg, intraoperation	Normal saline (0.9%), 100 mL, IV; gelatin sponges soaked in normal saline, topical	84 days	PLIF	Transfusion rate, Intraoperative blood loss, postoperative blood loss, postoperative drainage, Hb, Hct
Mu et al.[24]	2019	China	39	42	17 (0.44)	19 (0.45)	51.8±8.1	52.6±6.7	24.7±1.8	23.9±1.4	Gelfoam was soaked in TXA (1 g: 50 mL), intraoperation	Normal saline (0.9%), 100 mL, IV, preoperation; gelatin sponges soaked in normal saline, topical, intraoperation	84 days	PLIF	Transfusion rate, Intraoperative blood loss, postoperative blood loss, postoperative drainage, Hb, Hct
Nagabhushan et al.[25]	2017	India	25	25	16 (0.64)	14 (0.56)	49.6±9.8	51.7±9.7	NA	NA	TXA, 10 mg/kg, IV preopration; A maintenance dosage of 1 mg/kg/h, until closure	10 mL normal saline (0.9%), IV	NA	Lumbar Spinal Fusion Surgery	Intraoperative blood loss, postoperative drainage, Hb
Ou et al.[26]	2018	China	59	59	28 (0.47)	29 (0.49)	64.2±4.6	64.0±5.1	22.6±3.3	22.6±3.2	Gelfoam was soaked in TXA (1 g: 10 mL), topical, intraoperation	Gelfoam was soaked in normal saline, topical	30 days	Lumbar decompression and fusion surgery	Total blood loss, transfusion volume, transfusion rate, postoperative drainage, Hb, Hct, D-dimer

TABLE III
Continued

Authors	Year	Country	Sample size		Female, No (%)		Average age (years)		BMI		Intervention		Follow-up	Operative type	Endpoints
			E	C	E	C	E	C	E	C	E	C			
Shi et al.[27]	2017	China	50	46	25 (0.50)	24 (0.48)	53.8±12.1	55.8±13.1	NA	NA	TXA, 30mg/kg, IV, preoperation; A maintenance dosage of 2 mg/kg/h, until the end of the operation	Equivalent normal saline (0.9%), IV	35 days	Posterior lumbar surgery for stenosis or spondylolisthesis	Total blood loss, transfusion rate, Intraoperative blood loss, postoperative drainage, Hb, Hct
Wang et al.[28]	2013	China	30	30	14 (0.47)	12 (0.4)	63.1±4.0	62.0±4.6	21.7±1.9	22.2±1.9	TXA, 15 mg/kg, IV, preoperation	Equivalent normal saline (0.9%), IV drip	2 days	Posterior approach lumbar surgery	Total blood loss, intraoperative blood loss, postoperative blood loss
Wong et al.[29]	2008	Canada	73	74	52 (0.71)	48 (0.64)	56.8±16.2	50.0±16.2	NA	NA	TXA, 10 mg/kg, IV; A maintenance dosage of 1 mg/kg/h	Equivalent normal saline (0.9%), IV	90 days	PLIF/PTIF	Transfusion rate, Hb, D-dimer,
Xu et al.[30]	2017	China	40	40	21 (0.525)	27 (0.675)	53.1±12	57.4±10.7	25.6±2.8	24.9±3.9	TXA (1g:100ml), topical, intraoperation	Gelfoam	30 days	Posterior spinal fusion surgery	Total blood loss, transfusion rate, postoperative drainage, Hct
Shi[59]	2016	China	55	53	24 (0.44)	25 (0.47)	54.6±12.2	52.3±12.1	24.7±4.2	72.2±3.9	TXA, 30 mg/kg, IV, preoperation; The maintenance dose of 2 mg/kg/h, until the end of the operation	Equivalent normal saline (0.9%), IV	3 days	PLIF	Total blood loss, transfusion rate, intraoperative blood loss, postoperative drainage, Hb, Hct, D-dimer
Shi[59]	2016	China	54	53	26 (0.48)	25 (0.47)	55.6±11.8	52.3±12.1	23.2±3.5	72.2±3.9	TXA, 20 mg/kg, IV, preoperation; the maintenance dose of 1 mg/kg/h, until the end of the operation	Equivalent normal saline (0.9%), IV	3 days	PLIF	Total blood loss, transfusion rate, intraoperative blood loss, postoperative drainage, Hb, Hct, D-dimer
Shi[59]	2016	China	55	53	32 (0.58)	25 (0.47)	54.5±11.2	52.3±12.1	23.5±3.7	72.2±3.9	TXA, 10 mg/kg, IV, preoperation; the maintenance dose of 0.5 mg/kg/h, until the end of the operation	Equivalent normal saline (0.9%), IV	3 days	PLIF	Total blood loss, transfusion rate, intraoperative blood loss, postoperative drainage, Hb, Hct, D-dimer
Huang and Yang[57]	2011	China	34	34	20 (0.59)	22 (0.65)	75.8±3.4	73.6±4.2	24.5±3.2	23.6±2.6	TXA, 1 g, IV; the same dosage of TXA, 2 h after the first administration	Equivalent normal saline (0.9%), IV	7 days	Multi-level lumbar spinal stenosis surgery	Transfusion rate, Intraoperative blood loss, postoperative drainage, Hb
Bu et al.[51]	2014	China	133	134	31 (0.23)	25 (0.19)	54.2±13.1	52.6±16.3	23.85±4.4	23.7±4.8	TXA, 1 g, topical, after the deep fascia was closed	Equivalent normal saline (0.9%), topical	90 days	PLIF	Transfusion volume, transfusion rate, postoperative drainage, Hb

TABLE III
Continued

Authors	Year	Country	Sample size		Female, No (%)		Average age (years)		BMI		Intervention		Follow-up	Operative type	Endpoints
			E	C	E	C	E	C	E	C	E	C			
Zhang et al.[54]	2015	China	35	38	20 (0.57)	21 (0.55)	52.3±9.7	51.6±10.4	23.1±2.8	23.8±3.2	Gelfoam was soaked in TXA (5 mL: 0.5 g), topical, intraoperation	NA	30 days	Two-segment lumbar posterior decompression and intervertebral fusion	Total blood loss, transfusion volume, transfusion rate, intraoperative blood loss, postoperative drainage
Zhang et al.[55]	2015	China	46	46	21 (0.46)	20 (0.43)	NA	NA	NA	NA	TXA, 2 g, topical, after laminotomy; TXA, 1 g, topical, intraoperation	Equivalent normal saline (0.9%), topical	15 days	PLIF with cage	Transfusion volume, intraoperative blood loss, postoperative blood loss, D-dimer
Yan[50]	2015	China	35	33	15 (0.43)	13 (0.39)	58.4±6.6	56.6±9.4	20.6±3.2	22.8±4.1	TXA, 15 mg/kg, IV, preoperation	Equivalent normal saline (0.9%), IV	2 days	PLIF/TLIF	Total blood loss, intraoperative blood loss, postoperative blood loss, Hb, Hct
Huang et al.[56]	2015	China	30	30	5 (0.17)	7 (0.23)	56.1±4.9	56.9±4.8	NA	NA	TXA, 30 mg/kg, IV, before operation; The maintenance dose of 1 mg/kg, intraoperation	Equivalent normal saline (0.9%), IV	3 days	PLIF	Transfusion volume, intraoperative blood loss, Hb, DVT
Feng[52]	2016	China	60	60	24 (0.4)	26 (0.43)	74.5±16.2	76.3±14.8	NA	NA	TXA (100 mL: 1 g), 15 mg/kg, IV, preoperation	Equivalent normal saline (0.9%), IV	90 days	lumbar spinal stenosis surgery	Intraoperative blood loss, postoperative drainage, Hb, D-dimer, DVT
Nian, et al.[58]	2016	China	30	30	13 (0.43)	11 (0.37)	54.6±10.9	52.1±11.0	24.6±3.2	25.7±3.3	TXA (100 mL: 1g), topical, intraoperation	Equivalent normal saline (0.9%), topical	7 days	PLIF	Total blood loss, transfusion rate, postoperative drainage, Hb, D-dimer
Wang et al.[66]	2016	China	25	25	10 (0.4)	12 (0.48)	64.7±8.0	66.3±9.8	23.5±4.0	21.8±3.5	TXA,100 mg/kg, IV, preoperation; The maintenance dose is 10 mg/kg/h, until the end of the operation	Equivalent normal saline (0.9%), IV	NA	ALSS	Transfusion volume, Intraoperative blood loss, postoperative drainage
Jia et al.[53]	2016	China	30	30	14 (0.47)	12 (0.40)	63.1±4.0	62.0±4.6	21.7±1.9	22.2±1.9	TXA, 15 mg/kg, IV, preoperation	Equivalent normal saline (0.9%), IV	2 days	Posterior approach lumbar surgery	Total blood loss, intraoperative blood loss
Meng et al.[67]	2017	China	40	40	16 (0.4)	20 (0.2)	61.1±5.8	62.7±6.1	27.5±4.7	26.1±4.9	TXA, topical	No use of TXA or other antifibrinolytic drugs	2 days	Lumbar spine surgery	Transfusion volume, transfusion rate, intraoperative blood loss, postoperative blood loss, DVT
Meng et al.[67]	2017	China	40	40	17 (0.425)	20 (0.2)	62.3±5.4	62.7±6.1	25.2±5.3	26.1±4.9	TXA, 15 mg/kg, IV, preopration	No use of TXA and other antifibrinolytic drugs	7 days	Lumbar spine surgery	Transfusion volume, transfusion rate, intraoperative blood loss, postoperative blood loss, DVT

TABLE III
Continued

Authors	Year	Country	Sample size		Female, No (%)		Average age (years)		BMI		Intervention		Follow-up	Operative type	Endpoints
			E	C	E	C	E	C	E	C	E	C			
Song et al.[64]	2017	China	16	16	NA	NA	18~65	18~65	NA	NA	TXA, 1g, IV, preoperation; A maintenance dosage of 10 mg/kg/h, until the end of the operation	Equivalent normal saline (0.9%), IV	1 day	Transpedicular vertebral osteotomy	Total blood loss, transfusion volume, postoperative drainage
Chang et al.[65]	2017	China	29	29	15 (0.52)	17 (0.59)	51.1±13.7	52.8±14.6	NA	NA	Gelfoam was soaked in TXA, 500 mg	Gelfoam	7 days	PLIF	Intraoperative blood loss, postoperative drainage, Hb, Hct
Zhang et al.[69]	2017	China	41	41	18 (0.44)	22 (0.54)	49.6±8.7	46.8±10.7	NA	NA	TXA, 10 mg/kg, IV, preoperation	Equivalent normal saline (0.9%), IV	7 days	PLIF	Total blood loss, Intraoperative blood loss, postoperative drainage, Hb, DVT
Zhang et al.[69]	2017	China	41	41	22 (0.54)	22 (0.54)	49.0±9.1	46.8±10.7	NA	NA	TXA, 15 mg/kg, IV, preoperation	Equivalent normal saline (0.9%), IV	7 days	PLIF	Total blood loss, Intraoperative blood loss, postoperative drainage, Hb, DVT
Liu and Liu[62]	2018	China	39	39	15 (0.38)	18 (0.46)	66.3±5.6	64.2±4.8	25.4±3.1	24.7±2.6	TXA, 1g, topical, intraoperation	Equivalent normal saline (0.9%), topical	3 days	PLIF	Intraoperative blood loss, postoperative drainage, Hb, Hct, D-dimer
Zhang et al.[60]	2018	China	54	50	32 (0.59)	20 (0.4)	45.8±10.6	44.1±9.9	22.2±2.4	22.3±2.7	TXA, 15 mg/kg, IV, preoperation	Equivalent normal saline (0.9%), IV	3 days	Percutaneous pedicle screw fixation for thoracolumbar fractures	Total blood loss, intraoperative blood loss, D-dimer
Hu et al.[61]	2018	China	40	40	NA	NA	67.0±10.5	64.5±10.1	NA	NA	TXA, 10 mg/kg, IV, preoperation; A maintain dose of 2 mg/kg/h, until the end of the operation	Equivalent normal saline (0.9%), IV	3 days	Surgery for spinal metastatic tumors	Transfusion rate, intraoperative blood loss, postoperative drainage, Hb
Chen et al.[63]	2018	China	100	100	35 (0.43)	43 (0.43)	55.7±15.8	53.9±13.6	23.80±4.7	23.7±5.1	TXA (5 mL: 0.5g), 1 g, IV, preoperation; A maintenance dose of 10 mg/kg/h	Equivalent normal saline (0.9%), IV	2 days	Multilevel lumbar inter-body fusion	Total blood loss, intraoperative blood loss, postoperative blood loss, Hb, Hct, DVT
Liu et al.[68]	2019	China	35	35	19 (0.54)	20 (0.57)	76.8±4.3	77.4±4.2	25.4±2.8	25.3±3.9	TXA, 10 mg/kg, IV, preoperation; A maintenance dose of 1 mg/kg/h, intraoperation	Equivalent normal saline (0.9%), IV	90 days	Posterior lumbar surgery of 3 segments	Transfusion rate, intraoperative blood loss, postoperative drainage, Hb
Wang et al.[33]	2017	China	39	41	18 (0.46)	19 (0.46)	41.2±10.3	42.5±9.5	NA	NA	TXA, 10 mg/kg, IV; The maintenance dose of 1 mg/kg/h, until the end of the operation	Equivalent normal saline (0.9%), IV	12 weeks	Transforaminal thoracic inter-body fusion (TTIF)	Total blood loss, intraoperative blood loss, postoperative drainage, D-dimer, DVT

TABLE III
Continued

Authors	Year	Country	Sample size		Female, No (%)		Average age (years)		BMI		Intervention		Follow-up	Operative type	Endpoints
			E	C	E	C	E	C	E	C	E	C			
Wang et al.[32]	2019	China	30	28	14 (0.47)	13 (0.46)	60.5±6.3	62.1±4.2	24.7±2.6	25.2±1.9	TXA, 15 mg/kg, IV; The maintenance dose of 15 mg/kg	Equivalent normal saline (0.9%), IV	12 months	PLIF	Total blood loss, Intraoperative blood loss, postoperative drainage, Hb, Hct, D-dimer, DVT
Deng et al.[31]	2019	China	50	49	24 (0.48)	25 (0.51)	62±2.0	61±2.5	NA	NA	TXA, IV	Equivalent normal saline (0.9%), IV	3 months	TLIF	Intraoperative blood loss, postoperative drainage, Hb
Xia[37]	2019	China	20	21	10 (0.5)	12 (0.57)	50.2±12.5	54.0±12.8	NA	NA	TXA saline, 800 mL, topical	Equivalent normal saline (0.9%), topical	NA	TLIF	Postoperative drainage, Hb, D-dimer
Xia[37]	2019	China	4	4	1 (0.25)	2 (0.5)	60.3±12.5	63.0±9.3	NA	NA	TXA saline, 803 mL, topical	Equivalent normal saline (0.9%), topical	NA	TLIF	Postoperative drainage, Hb, D-dimer
Xu et al.[34]	2019	China	30	30	17 (0.57)	16 (0.53)	49.6±12.8	50.6±16.2	25.3±3.0	25.7±3.0	TXA saline, 1 g in 100 mL, topical	Equivalent normal saline, applied	72 hours	PLIF	Total blood loss, transfusion rate, intraoperative blood loss
Yang et al.[35]	2019	China	18	16	8 (0.44)	8 (0.5)	72.5±6.3	73.7±6.1	23.5±2.2	23.2±2.4	TXA, 1 g in 100 mL, IV; TXA saline, 1 g in 100 mL, topical	Equivalent normal saline (0.9%)	3 days	PLIF	Total blood loss, transfusion volume, transfusion rate, postoperative drainage, Hb, Hct
Zhao et al.[36]	2019	China	43	43	21 (0.49)	23 (0.53)	71.3±4.4	71.1±4.3	NA	NA	TXA, 30 mg/kg, IV; TXA saline, 0.5 g in 10 mL, topical	Equivalent normal saline (0.9%)	4 days	Other	Intraoperative blood loss, postoperative drainage, Hb, D-dimer
Zhu[38]	2019	China	39	39	22 (0.56)	20 (0.51)	64.4±3.6	64.1±4.1	24.76±4.11	25.0±4.2	TXA, 20 mg/kg, IV; The maintenance dose of 2 mg/kg/h, until the end of the operation	Equivalent normal saline (0.9%)	12 weeks	PLIF/TLIF	Total blood loss, transfusion rate, postoperative drainage, intraoperative blood loss
Zhu[38]	2019	China	40	39	22 (0.55)	20 (0.51)	63.9±4.0	64.1±4.1	24.2±3.8	25.0±4.2	TXA saline, 0.1 g/mL, topical	Equivalent normal saline (0.9%)	12 weeks	PLIF/TLIF	Total blood loss, transfusion rate, postoperative drainage, intraoperative blood loss
Ding et al.[47]	2020	China	15	15	NA	NA	64.3±5.6	66.2±5.0	27.2±3.1	26.1±2.3	TXA, 5 mg/kg, IV; The maintenance dose of 2 mg/kg/h, until the end of the operation	Equivalent normal saline (0.9%)	1 week	PLIF	Total blood loss, postoperative drainage, intraoperative blood loss, postoperative blood loss, Hb, Hct

TABLE III
Continued

Authors	Year	Country	Sample size		Female, No (%)		Average age (years)		BMI		Intervention		Follow-up	Operative type	Endpoints
			E	C	E	C	E	C	E	C	E	C			
Ding et al.[47]	2020	China	15	15	NA	NA	62.0±7.0	66.2±5.0	26.5±2.8	26.1±2.3	TXA, 10 mg/kg, IV; The maintenance dose of 2 mg/kg/h, until the end of the operation	Equivalent normal saline (0.9%)	1 week	PLIF	Total blood loss, postoperative drainage, intraoperative blood loss, postoperative blood loss, Hb, Hct
He et al.[46]	2020	China	20	20	12 (0.6)	9 (0.45)	58.0±12.4	57.9±11.8	25.0±5.2	24.8±4.4	TXA, 10 mg/kg, IV; 6-8 mg/kg/h up to a total dose of 15 mg/kg during the surgery	Equivalent normal saline (0.9%), IV	NA	TLIF	Transfusion rate, intraoperative blood loss, postoperative blood loss, postoperative drainage, Hb
Li et al.[49]	2020	China	70	70	46 (0.66)	47 (0.67)	66.7±3.3	65.6±3.2	24.0±3.3	22.8±2.4	TXA, 15 mg/kg, IV	100 mL IV saline (0.9%)	3 months	Other	Total blood loss, intraoperative blood loss, Hb, DVT
Li et al.[49]	2020	China	70	70	45 (0.64)	47 (0.67)	65.6±4.8	65.6±3.2	22.2±2.8	22.8±2.4	TXA saline, 2 g in 20 mL, injected into the incision	100 mL IV saline (0.9%)	3 months	Other	Total blood loss, intraoperative blood loss, Hb, DVT
Xia et al.[43]	2020	China	46	44	26 (0.57)	20 (0.45)	51.2±10.4	56.3±13.9	NA	NA	TXA, 1 g in 100 mL, topical	Equivalent normal saline (0.9%)	7 days	Other	Transfusion volume, transfusion rate, D-dimer, postoperative drainage
Yang et al.[42]	2020	China	33	32	13 (0.39)	14 (0.44)	62.9±5.3	65.6±7.2	30.3±6.5	24.4±3.6	TXA, 15 mg/kg, IV	Equivalent normal saline (0.11%)	72 hours	Other	Intraoperative blood loss, postoperative drainage, Hb, D-dimer
Yang et al.[42]	2020	China	32	32	15 (0.47)	14 (0.44)	65.6±7.5	65.6±7.2	28.2±5.9	24.4±3.6	TXA, 15 mg/kg, IV; TXA 1.0 g in 10 mL, topical; the maintenance dose of 15 mg/kg/h, until the end of the operation	Equivalent normal saline (0.11%)	72 hours	Other	Intraoperative blood loss, postoperative drainage, Hb, D-dimer
Yang et al.[48]	2020	China	30	30	17 (0.57)	15 (0.5)	66.8±5.3	67.6±7.0	25.8±2.1	25.4±1.1	TXA, 10 mg/kg, IV; The maintenance dose of 2 mg/kg/h, until the end of the operation	Equivalent normal saline (0.9%), IV	72 hours	Other	Total blood loss, transfusion volume, intraoperative blood loss, postoperative drainage, Hct, Hb, D-dimer
Zhang et al.[39]	2020	China	151	138	94 (0.62)	91 (0.66)	54.7±9.9	57.0±10.2	25.8±3.3	25.2±3.5	TXA, 1 g, IV	Equivalent normal saline (0.9%), IV	35 days	PLIF	Total blood loss, transfusion rate, postoperative blood loss, intraoperative blood loss, Hb, Hct
Liu et al.[40]	2021	China	40	40	23 (0.58)	21 (0.53)	50.2±12.2	49.3±11.6	24.9±1.7	25.2±1.6	TXA, 1 g in 100 mL, IV	Equivalent normal saline (0.9%), IV	1 week	PLIF	Total blood loss, intraoperative blood loss, postoperative blood loss, D-dimer

TABLE III
Continued

Authors	Year	Country	Sample size		Female, No (%)		Average age (years)		BMI		Intervention		Follow-up	Operative type	Endpoints
			E	C	E	C	E	C	E	C	E	C			
Mi et al.[44]	2021	China	50	50	24 (0.48)	22 (0.44)	56.5±16.8	55.6±17.6	NA	NA	TXA, 1 g in 20 mL, topical	100 mL IV saline (0.9%)	7 days	TLIF	Transfusion rate, intraoperative blood loss, postoperative drainage, D-dimer, DVT
Yuan et al.[41]	2021	China	39	30	22 (0.56)	17 (0.57)	64.1±6.7	63.9±7.3	24.3±2.6	23.6±2.3	TXA saline, 2 g in 100 mL, IV before surgery	NA	3 months	PLIF	Hb, Hct, total blood loss, intraoperative blood loss, D-dimer, transfusion rate, postoperative drainage
Yuan et al.[41]	2021	China	36	30	20 (0.56)	17 (0.57)	65.5±6.8	63.9±7.3	24.6±2.6	23.6±2.3	TXA saline, 2 g in 100 mL, IV; the maintenance dose of 10 mg/kg/h, until the end of the operation	NA	3 months	PLIF	Hb, Hct, total blood loss, intraoperative blood loss, D-dimer, transfusion rate, postoperative drainage
Zhang et al.[45]	2021	China	40	40	NA	NA	NA	NA	NA	NA	TXA, 1-2 g, IV; TXA, 1 g, topical	100 mL IV saline (0.9%)	NA	Other	Total blood loss, transfusion volume, transfusion rate, intraoperative blood loss, postoperative drainage, Hb, Hct, D-dimer

BMI: Body mass index; PTIF: Posterior thoracicinterbody fusion; TLIF: Transforaminal lumbar interbody fusion; DVT: Deep venous thrombosis; E: Experimental group; C: Control group; TXA: Tranexamic acid; PLIF: Posterior lumbar interbody fusion; PTIF: Posterior thoracic interbody fusion; TLIF: Transforminal lumbar interbody fusion; ALSS: Adult lumbar spine scoliosis; TBL: Total blood loss; IBL: Intraoperative blood loss; PBL: Postoperative blood loss; Hb: Hemoglobin; Hct: Hematocrit; IV: Intravenous; Htc: Hematocrit.

TABLE IV
Assessment of methodological quality of included studies

Study	Random allocation	Hidden distribution	Blind method	Incomplete outcome data	Selective reporting of results	Other bias	Quality grade
Wong et al.[29]	Randomized	No clear	Double-blind	Low	Low	Low	A
Huang and Yang[57]	Randomized	No clear	No clear	Low	Low	Low	C
Wang et al.[28]	Randomized	No clear	Double-blind	Low	Low	Low	B
Bu et al.[51]	Randomized	No clear	Single-blind	Low	Low	Low	B
Huang et al.[56]	Randomized	No clear	No clear	Low	Low	Low	C
Yan[50]	Randomized	No clear	No clear	Low	Low	Low	C
Zhang et al.[55]	Randomized	No clear	No clear	Low	Low	Low	C
Zhang et al.[54]	Randomized	No clear	No clear	Low	Low	Low	C
Liang et al.[23]	Randomized	No clear	No clear	Low	Low	Low	B
Feng[52]	Randomized	No clear	No clear	Low	Low	Low	C
Jia et al.[53]	Randomized	No clear	Double-blind	Low	Low	Low	B
Nian et al.[58]	Randomized	No clear	No clear	Low	Low	Low	C
Shi et al.[27]	Randomized	No clear	Triple-blind	Low	Low	Low	B
Wang et al.[66]	Randomized	No clear	No clear	Low	Low	Low	C
Chang et al.[65]	Randomized	No clear	No clear	Low	Low	Low	C
Kim et al.[22]	Randomized	No clear	Double-blind	Low	Low	Low	B
Nagabhushan et al.[25]	Randomized	No clear	Double-blind	Low	Low	Low	A
Shi[59]	Randomized	No clear	Double-blind	Low	Low	Low	B
Song et al.[64]	Randomized	No clear	No clear	Low	Low	Low	C
Xu et al.[30]	Randomized	No clear	No clear	Low	Low	Low	A
Meng et al.[67]	Randomized	No clear	No clear	Low	Low	Low	C
Zhang and Yang[69]	Randomized	No clear	Double-blind	Low	Low	Low	B
Chen et al.[63]	Randomized	No clear	No clear	Low	Low	Low	C
Hu et al.[61]	Randomized	No clear	No clear	Low	Low	Low	C
Liu and Liu[62]	Randomized	No clear	No clear	Low	Low	Low	C
Mua et al.[24]	Randomized	No clear	No clear	Low	Low	Low	A
Ou et al.[26]	Randomized	No clear	No clear	Low	Low	Low	A
Zhang et al.[60]	Randomized	No clear	Single-blind	Low	Low	Low	B
Elmose et al.[21]	Randomized	No clear	Double-blind	Low	Low	Low	A
Liu et al.[68]	Randomized	No clear	No clear	Low	Low	Low	C
Wang et al.[33]	Randomized	No clear	Double-blind	Low	Low	Low	A
Wang et al.[32]	Randomized	No clear	No clear	Low	Low	Low	C
Deng et al.[31]	Randomized	No clear	Single-blind	Low	Low	Low	B
Xia[37]	Randomized	No clear	Single-blind	Low	Low	Low	B
Xu et al.[34]	Randomized	No clear	Double-blind	Low	Low	Low	A
Yang et al.[35]	Randomized	No clear	Double-blind	Low	Low	Low	A
Zhao et al.[36]	Randomized	No clear	No clear	Low	Low	Low	C
Zhu[38]	Randomized	No clear	Double-blind	Low	Low	Low	A
Ding et al.[47]	Randomized	No clear	Double-blind	Low	Low	Low	A
He et al.[46]	Randomized	No clear	Double-blind	Low	Low	Low	A
Jianjiang et al.[49]	Randomized	No clear	No clear	Low	Low	Low	C
Xia et al.[43]	Randomized	No clear	Double-blind	Low	Low	Low	A
Yang et al.[42]	Randomized	No clear	No clear	Low	Low	Low	C
Yang et al.[48]	Randomized	No clear	No clear	Low	Low	Low	C
Zhang et al.[39]	Randomized	No clear	Single-blind	Low	Low	Low	B
Liu et al.[40]	Randomized	No clear	No clear	Low	Low	Low	C
Mi et al.[44]	Randomized	No clear	No clear	Low	Low	Low	C
Yuan et al.[41]	Randomized	No clear	No clear	Low	Low	Low	C
Zhang et al.[45]	Randomized	No clear	No clear	Low	Low	Low	C

participant and personnel blinding, while 24 studies demonstrated outcome assessment blinding. Other biases were not mentioned in any of the studies. Table IV summarizes the quality score of the literature.

Primary effective endpoints

Total blood loss (mL)

Total blood loss was reported in 27 studies (35 trial comparisons). In all, 2,841 patients were assessed for TBL, with 1,623 and 1,218 allotted to the experimental and the control groups, respectively. The results demonstrated that the control group's TBL were significantly higher than that of the experimental group (SMD: -1.15, 95% CI: -1.37 to -0.92, I^2=87.9%, p=0.000) (Figure 2). We utilized the random-effects model.

Transfusion rate (%)

There were 14 studies (18 trial comparisons) covered the transfusion rate. In all, 172 of 1,366 individuals in the experimental group required blood transfusion, and 337 of 1,039 individuals in the control group required concurrently. The results indicated that TXA significantly reduced blood transfusions incidence compared to the control group (12.6% *vs.* 31.4%) (RR: 0.41, 95% CI: 0.34 to 0.49 I^2=1.7%, p=0.434) (Figure 3). The fixed-effects model was done.

Secondary effective endpoints

Transfusion volume (mL)

Thirteen studies (14 trial comparisons) reported the transfusion volume. In the aggregate, 1,136 patients were contained to evaluate the transfusion

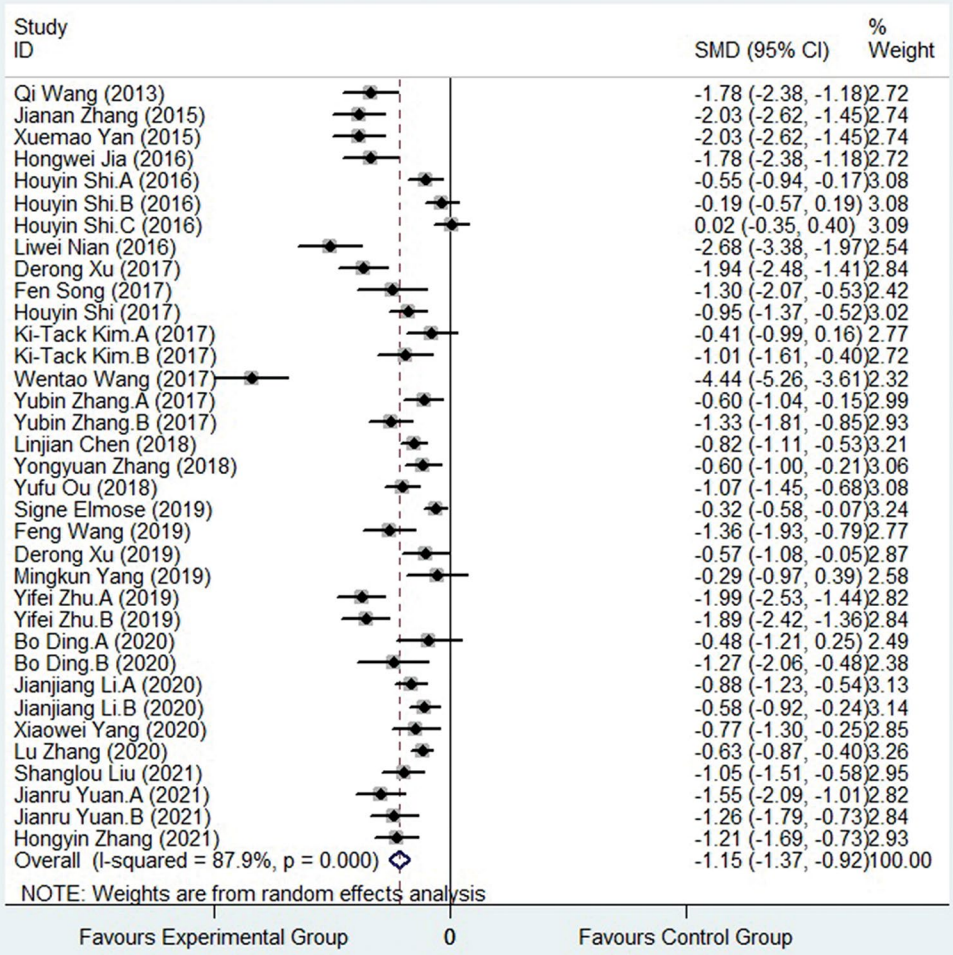

FIGURE 2. Comparison of TBL between the TXA group and the control group.
SMD: Standardized mean difference; TBL: Total blood loss; TXA: Tranexamic acid.

rate, 588 and 548 in the experimental and control groups, respectively. Based on findings, compared to the control group, transfusion volume seems to be significantly lower in the experimental group's transfusion volume (SMD: -2.42, 95% CI: -3.24 to -1.60, I^2=96.9%, p=0.000) as illustrated in Supplementary Figure 1. The random-effects model was done.

Intraoperative blood loss (mL)

Thirty-nine studies (51 trial comparisons) reported IBL. The number of patients was 3,881, with 2,180 allotted to the experimental group and 1,701 to the control group. The statistical findings revealed that, compared to the control group, the experimental group's IBL was significantly lower (SMD: -0.83, 95% CI: -1.05 to -0.61, I^2=91.3%, p=0.000) as illustrated in Supplementary Figure 2. The random-effects model was done.

Postoperative blood loss (mL)

Eleven studies (15 trial comparisons) reported PBL. A total of 1,385 patients were evaluated for PBL. Of them, 761 and 624 were allotted to the experimental and control groups, respectively. Compared to the control group, the experimental PBL was significantly lower (SMD: -2.13, 95% CI: -2.68 to -1.57, I^2=94.9%, p=0.000) as illustrated in Supplementary Figure 3. The random-effects model was done.

Postoperative drainage (mL)

Thirty-five studies (44 trial comparisons) reported postoperative drainage. In all, 3,109 patients were assessed for postoperative drainage, with 1,704 and 1,405 allotted to the experimental and control groups, respectively. The findings revealed that the experimental had significantly lower postoperative drainage than the control group (SMD: -1.55, 95% CI: -1.83 to -1.26, I^2=92.2%, p=0.000) as illustrated in Supplementary Figure 4. The random-effects model was done.

Hemoglobin (g/dL)

Thirty-two studies (42 trial comparisons) reported Hb content. A total of 3,326 patients were involved to evaluate Hb content, of whom 1,863 were in the experimental group and 1,463 in the control group. The findings indicated that the experimental group's Hb content was significantly higher than the control group (SMD: 0.53, 95% CI: 0.36 to 0.71, I^2=83.9%, p=0.000) as illustrated in Supplementary Figure 5. The random-effects model was done.

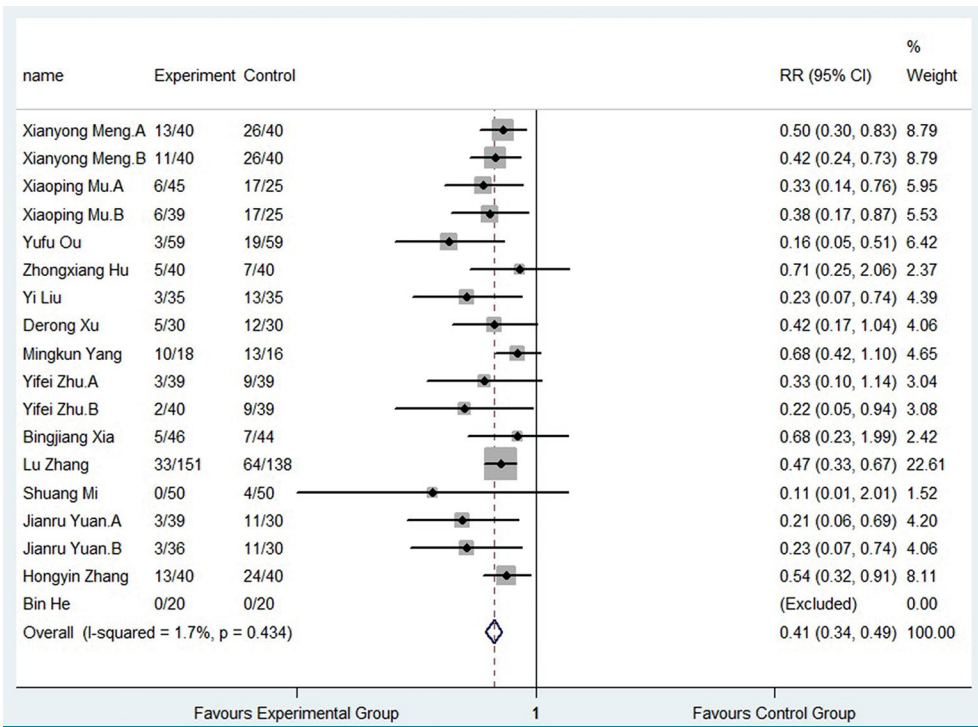

FIGURE 3. Comparison of Transfusion rate between the TXA group and the control group.
RR: Risk ratio; TXA: Tranexamic acid.

Hematocrit (%)

Eighteen studies (24 trial comparisons) reported Hct. A total of 1,844 patients were evaluated for Hct, of whom 1,052 and 792 in the experimental and control groups, respectively. The results demonstrated that the TXA group had a greater level of Hct than the control group (SMD: 0.39, 95% CI: 0.08 to 0.70, I^2=91.0%, p=0.000) as illustrated in Supplementary Figure 6. The random-effects model was done.

Safety endpoints

Deep venous thrombosis

Eight studies (11 trial comparisons) covered DVT, of which 19 out of 581 in the experimental group and 23 out of 432 in the control group experienced DVT. There was no significant variation among the TXA and control groups (3.2% *vs.* 5.3%) (RR: 0.78, 95% CI: 0.48 to 1.28, I^2=0.0%, p=0.926) as illustrated in Figure 4. The fixed-effects model was done.

D-dimer (mg/L)

The concentration of D-dimer can be used in blood tests to help to diagnose thrombosis. Negative results can rule out thrombosis, while positive results suggest thrombosis probability, even so other potential reasons were not excluded. Therefore, its fundamental usage is to exclude thromboembolic diseases with a low probability. D-dimer was evaluated in 19 studies (24 trial comparisons), enrolling 1,837 participants for D-dimer assessment. The experimental group composed of 1,014 participants, whereas the control group composed of 823 participants. The results revealed that, compared to the control group, the experimental group's D-dimer levels were significantly lower (SMD: -0.35, 95% CI: -0.70 to -0.01, I^2=92.5%, p=0.000) as illustrated in Figure 5. The random-effects model was done.

Publication bias and sensitivity analysis and subgroup analysis

According to the TXA administration method and the type of operation, subgroup analysis was done. Subgroup analysis results are listed in Supplementary Figures 7-14. The patients' TBL in the posterior lumbar surgery (PLS) group, posterior lumbar interbody fusion (PLIF) group, other operative type group and PLIF/transforaminal lumbar interbody fusion (TLIF) group was significantly lower compared to the control group (SMD: -0.84, 95% CI: -1.39 to -0.28, I^2=89.4%, p=0.000; SMD: -1.14, 95% CI: -1.42 to -0.86, I^2=79.9%, p=0.000; SMD: -1.21, 95% CI: -1.67 to -0.75, I^2=92.0%, p=0.000; SMD: -1.94, 95% CI: -2.32 to -1.56, I^2=87.9%, p=0.799) as illustrated in Supplementary Figure 7. The findings revealed that patients' TBL in the intravenous administration group, topical application group, and intravenous administration before the operation group was significantly lower compared to the control

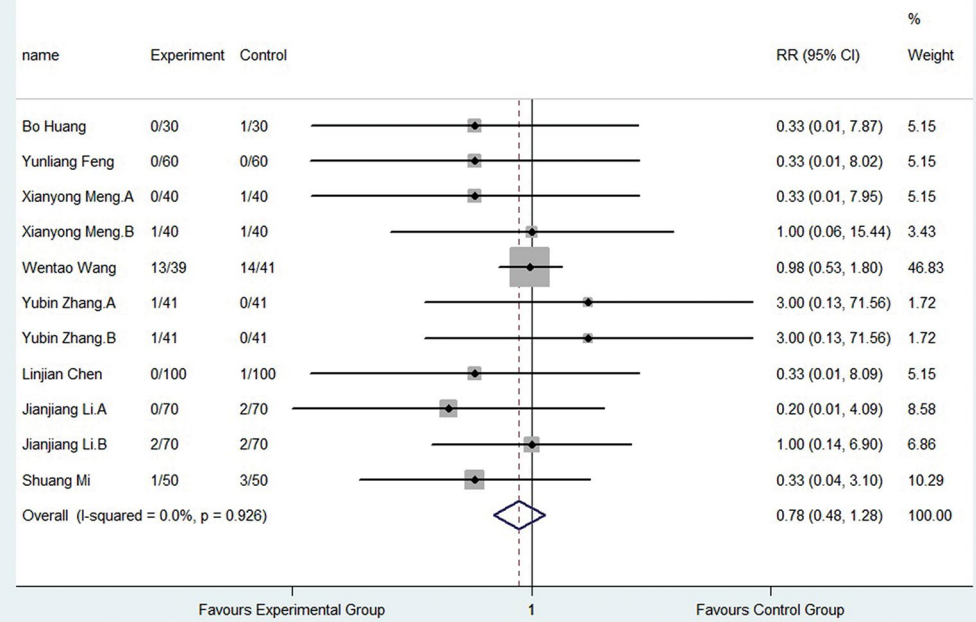

FIGURE 4. Comparison of DVT between the TXA group and the control group.
RR: Risk ratio; DVT: Deep venous thrombosis; TXA: Tranexamic acid.

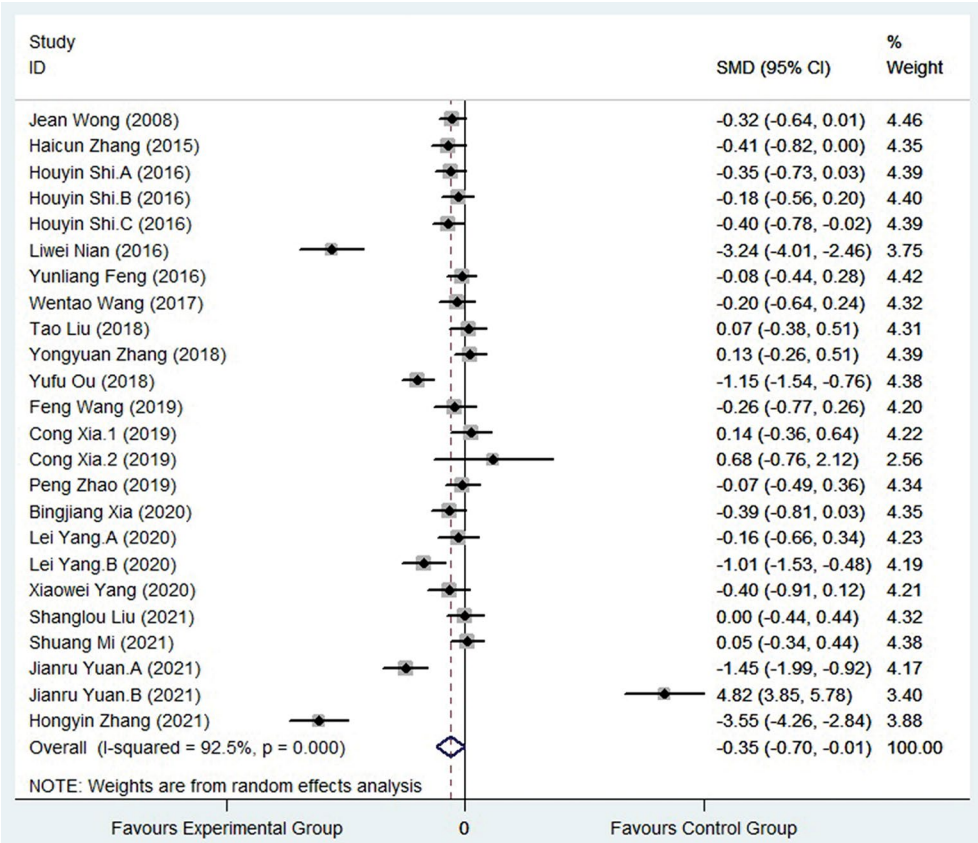

FIGURE 5. Comparison of D-dimer between the TXA group and the control group.
SMD: Standardized mean difference; TXA: Tranexamic acid.

group, whereas there were no significant variations in the intravenous administration group + topical application group (SMD: -1.06, 95% CI: -1.32 to -0.81, I^2=87.7%, p=0.000; SMD: -1.46, 95% CI: -1.95 to -0.97, I^2=87.8%, p=0.000; SMD: -1.55, 95% CI: -2.09 to -1.01; SMD: -0.29, 95% CI: -0.97 to 0.39) as illustrated in Supplementary Figure 8. The transfusion rates in the PLIF group, the other operational type group, as well as the PLIF/TLIF group were all significantly lower compared to the control group. There were no significant variations between the TLIF group and the control group (RR: 0.40, 95% CI: 0.33 to 0.48, I^2=18.3%, p=0.269; RR: 0.60, 95% CI: 0.39 to 0.92, I^2=0.0%, p=0.855; RR: 0.27, 95% CI: 0.11 to 0.70, I^2=0.0%, p=0.658; RR: 0.11, 95% CI: 0.01 to 2.01) as illustrated in Supplementary Figure 9. The transfusion rates in the topical application group, intravenous administration group, and intravenous administration before the operation group were all significantly lower compared to the control group, whereas there were no significant variations while comparing intravenous administration with topical application (RR: 0.40, 95% CI: 0.30 to 0.54, I^2=0.0%, p=0.440; RR: 0.41, 95% CI: 0.32 to 0.53, I^2=0.0%, p=0.684; RR: 0.21, 95% CI: 0.06 to 0.69) as illustrated in Supplementary Figure 10 There were no significant variations in DVT in the PLIF group patients, other operative type group, transforaminal thoracic interbody fusion (TTIF), TLIF, and the control group (RR: 1.00, 95% CI: 0.29 to 3.41, I^2=0.0%, p=0.764; RR: 0.47, 95% CI: 0.13 to 1.64, I^2=0.0%, p=0.805; RR: 0.98, 95% CI: 0.53 to 1.80; RR: 0.33, 95% CI: 0.04 to 3.10) as illustrated in Supplementary Figure 11. There were no significant variations in the intravenous administration group's DVT patients, topical application group, and control group (RR: 0.85, 95% CI: 0.50 to 1.46, I^2=0.0%, p=0.856; RR: 0.54, 95% CI: 0.15 to 1.94, I^2=0.0%, p=0.719) as illustrated in Supplementary Figure 12. Patients in the PLS group had significantly lower D-dimer levels compared to the control group (SMD: -0.31, 95% CI: -0.53 to -0.09, I^2=0.0%, p=0.698) as illustrated in Supplementary Figure 13; however, there were no significant variations in the patients' D-dimer levels in the PLIF group, other operative type group, TLIF

group, and control group (SMD: -0.26, 95% CI: -1.05 to 0.53, I^2=96.0%, p=0.000; SMD: -0.55, 95% CI: -1.11 to 0.02, I^2=92.1%, p=0.000; SMD: 0.11, 95% CI: -0.19 to 0.41, I^2=0.0%, p=0.703). The findings revealed that the patients' D-dimer levels in the topical application group and intravenous administration before the operation were all significantly lower than those in the control group (SMD: -0.88, 95% CI: -1.61 to -0.15, I^2=94.7%; SMD: -1.45, 95% CI: -1.99 to -0.92, p=0.000), but there were no significant differences among the intravenous administration group, intravenous administration + topical application group and control group (SMD: 0.10, 95% CI: -0.29 to 0.49, I^2=89.9%, p=0.000; SMD: -0.07, 95% CI: -0.49 to 0.36) as illustrated in Supplementary Figure 14.

As demonstrated in Supplementary Figures 15-24, the funnel plot revealed that the retrieved articles had a publication bias. The sensitivity analysis findings are illustrated in Supplementary Figures 25-30.

DISCUSSION

This meta-analysis demonstrated that TXA had a significant impact on lowering the TBL, transfusion rate, transfusion volume, IBL, PBL, drainage and D-dimer compared to the control group and it did not increase the occurrence of DVT; therefore, its effectiveness and safety were proven to be well established.

Recently, with the maturity of lumbar surgical techniques and the improvement of surgical equipment, bleeding during lumbar surgery has been effectively controlled.[71] However, lumbar surgery is still one of the surgical procedures that causes extensive blood loss and, thus, surgeons are concerned about how to reduce perioperative blood loss.[72] The TXA has been approved by the United States Food and Drug Administration (FDA) for more than 30 years and was added to the World Health Organization (WHO) Essential Drugs List in 2011.[73] It shows excellent tolerance, with only rare dose-dependent adverse reactions, including nausea, vomiting, diarrhea, headache, upright reaction, blurred vision, and vertigo.[74] Many original studies and reviews have suggested that TXA is safer than placebo and does not increase the incidence of DVT or pulmonary embolism.[75] Additionally, clinical findings indicate that TXA usage in cardiac valve replacement and total hip arthroplasty can significantly minimize intraoperative blood transfusion volumes without enhancing the risk of thrombosis.[76] Even so, TXA's effectiveness and safety in lumbar surgery still remain controversial.

Currently, there are many articles studying TXA in lumbar surgery. In terms of its efficacy, Du and Feng[77] conducted a meta-analysis to show that TXA had an important ability to minimize IBL and length of hospital stay following lumbar spinal fusion surgery. According to Lu et al.,[78] TXA usage significantly decreased perioperative blood loss and the needs of red blood cell transfusions, but other surgical and clinical outcomes were not significantly different. On the other hand, some scholars put an opposed opinion that TXA might be incapable to reduce blood transfusion rate. Gong et al.[79] performed a meta-analysis and concluded that intravenous TXA had the ability to significantly minimize surgical blood loss. However, TXA treatment did not result in a significant reduction in the transfusion rates in treated patients. Endres et al.[80] performed a retrospective, case-control study and suggested that, when TXA was used in PLS, the Hb concentration was higher and the amount of blood loss was reduced. It lacked the capability to demonstrate a variation in transfusion rates. Furthermore, the safety of the TXA is also under study and some have offered the opinion that it has not any effect on enhancing thrombotic events risk. Bai et al.[81] performed a meta-analysis and proposed that TXA can minimize Hb loss, TBL, intraoperative and PBL, and it does not enhance thrombotic events risk following posterior lumbar fusion. However, there was no significant variation in blood transfusion rates. A retrospective, non-randomized, case-cohort study was performed by Sun et al.[82] and reported that TXA efficiently lowered perioperative blood loss, tube drainage durations, and length of hospitalization and it had no impact on increasing the risk of complications. Ren et al.[83] also carried out a retrospective, case-control study and concluded that TXA significantly minimized PBL, shortened the time to withdrawal of drainage tubes and the length of hospitalization in patients receiving PLS fusion surgery, although it did not increase the complication incidence. In contrast, Baldus et al.[84] conducted a comparative study with controls and found that the TXA group had less blood loss and received fewer blood transfusions than the aprotinin treatment group without any significant differences in the intraoperative or postoperative complications. As a result, it is yet unclear if TXA is safe and effective enough to be utilized in the clinic.

Our results revealed that TXA might significantly reduce TBL, transfusion rate, transfusion volume, IBL, PBL, drainage, and D-dimer compared to the control group. While comparing to the control group, TXA could significantly improve Hb and Hct and there

were no significant variations in DVT among the TXA group and the control group. We did subgroup and sensitivity analyses after assessing that the endpoints had a high degree of heterogeneity. There were no restrictions on the usages or dose of TXA in our inclusion criteria and, therefore, we performed a subgroup analysis according to the method of administration of TXA (intravenous injection or local injection) and compared their postoperative drainage. Both routes could significantly reduce the patients' TBL postoperative drainage compared to the control group. Nonetheless, there were no significant variations in postoperative drainage among the two subgroups, and these results cannot explain the heterogeneity. We speculated that this might be because the articles we included had a limited sample size and the patients were relatively heterogeneous. The disunity of the control group and the different dosages used in the TXA group might be also causes of heterogeneity.

To the best of our knowledge, the safety of TXA has been a bigger issue than studies of its efficacy, on account of its hemostatic mechanism that through the abnormal hyperactive fibrinolytic enzyme, causing platelet agglutination and inhibiting the decomposition of coagulation factors, and playing a hemostatic role. Until now, several studies have found that TXA is not associated with the increasing risk of complications; but the patients enrolled in these studies are also routinely prophylaxis with antithrombotic drugs after surgery which may cover the potential increased risk of TXA in venous thromboembolism. Besides, these vast majority of studies also exclude patients with comorbidities and patients who may be at risk for thromboembolism. The result in the meta-analysis suggests that the level of D-dimer decreases in TXA group than the control group. After reviewing the included literatures, we found that, in some of them, the D-dimer levels in the experimental group were somewhat less than in the control group, and there were non-significant variations. Others showed that TXA attenuated the increase of D-dimer after surgery. We can speculate that it is related to its anti-fibrinolytic effect: fibrinolytic enzymes, plasminogen, and fibrin binding may be inhibited by TXA by blocking lysine binding sites on plasminogen molecules, thus inhibiting the fibrinolytic decomposition caused by fibrinolytic enzyme. Theoretically, the risk of thrombosis is low after TXA use.

The potential clinical implications are as follows: *(i)* Thirty RCTs were identified, which comprised 3,042 subjects, more than in previous meta-analyses. The larger, population-inclusive, evidence-based review we conducted summarized the data and might provide a theoretical basis for future clinical drug use; *(ii)* Subgroup analyses were carried out based on the type of operation and administration route to account for the impact of several parameters on the overall effect; *(iii)* To determine the source of heterogeneity, we performed a sensitivity analysis to indicate the impact of sample size on the overall effect; and *(iv)* Ten indicators were assessed including TBL, transfusion rate, transfusion volume, IBL, PBL, drainage Hb, Hct, D-dimer, and DVT, which seemed to be more comprehensive than previous articles. Nonetheless, this study has some limitations: *(i)* We did not examine the interactions among the subgroup analyses due to the inherent limitations of the enrolled studies; *(ii)* The impact of the baseline features on the results could not be determined, since the outcome events documented in the enrolled studies were utilized; *(iii)* As most of the included articles did not report this information, we could not extract relevant data for some baseline features, such as other drug use, hypertension, or diabetes, which may cause some mixed bias. In addition, subgroup analysis according to the dose of TXA, the age of the adults and the safety endpoints, such as the risk of cerebrovascular accident, heart disease, or pulmonary embolism could not be performed; *(iv)* The outcomes of the various interventions in the control group may show significant heterogeneity. Even so, for ethical issues, we realize that it is unrealistic to compel the original author to refrain from using any hemostatic or anticoagulant interventions; hence, we incorporated all of these articles; *(v)* Since the limitation of the number of safety events such as cardiac problems or pulmonary embolism in published RCTs, the more safety endpoints could not be included; and *(vi)* Since there were no obvious findings were found in sensitivity analysis we conducted, it was not detailed in the paper. Moreover, although the results from this meta-analysis did not find an increased risk for DVT, RCTs included almost all exclude patients with comorbidities for this reason and consisted of patients with a low risk. It is still not clear that the safety of TXA in patients with risk factors. Further comprehensive studies with more data are needed to confirm these findings.

In conclusion, this meta-analysis demonstrates that TXA has the potential to significantly minimize TBL, transfusion rate, transfusion volume, IBL, PBL, drainage compared to the control group. Besides, the Hb and Hct values were higher in the TXA group than the control group. Its hemostatic potential

after lumbar spine surgery is trustworthy. Besides, it is still controversial in safety endpoints that TXA can significantly reduce D-dimer compared to the control group, whereas there were no significant variations in DVT between the TXA and the control groups.

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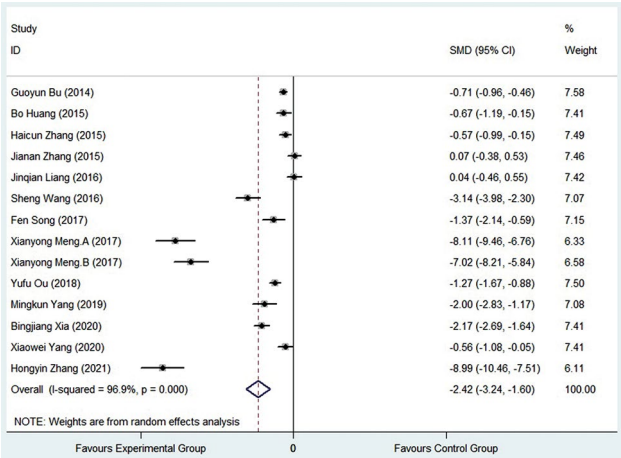
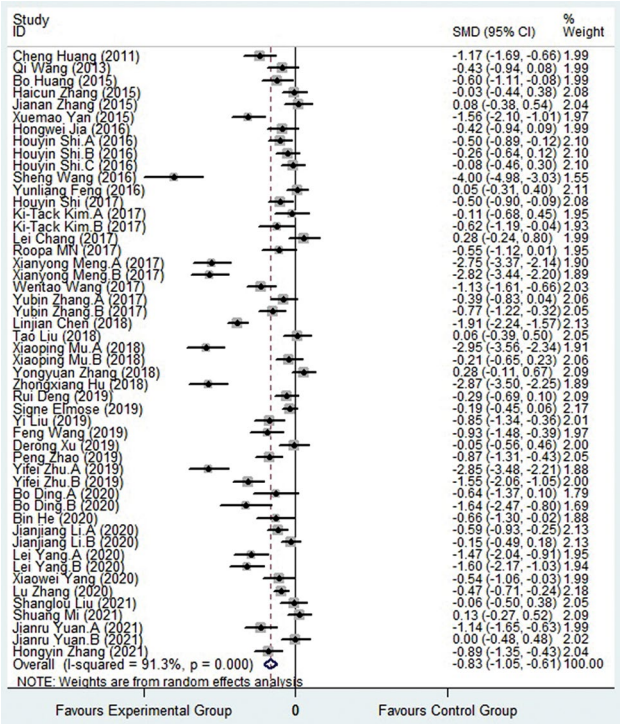
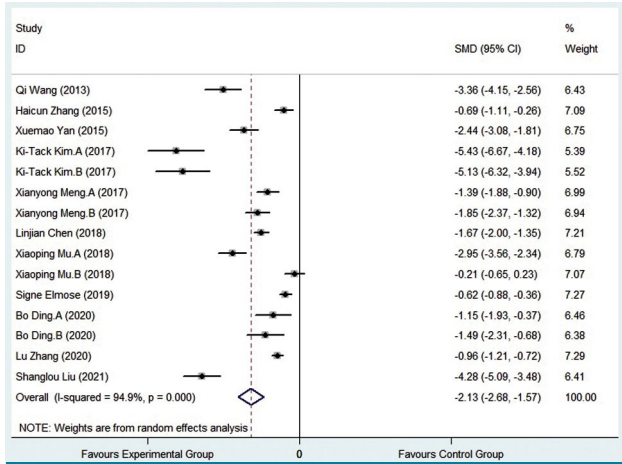


SUPPLEMENTARY FIGURE 1. Comparison of Transfusion volume between the tranexamic acid group and the control group.



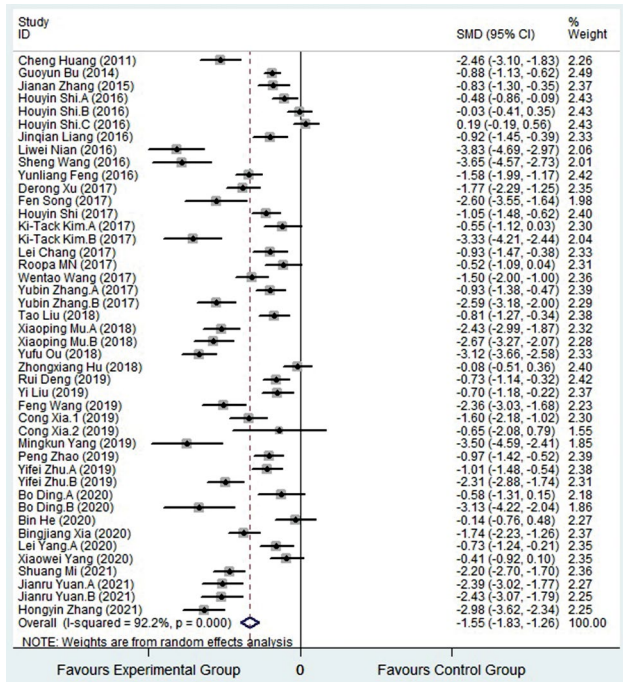
SUPPLEMENTARY FIGURE 2. Comparison of intraoperative blood loss between the tranexamic acid group and the control group.

SMD: Standardized mean difference.



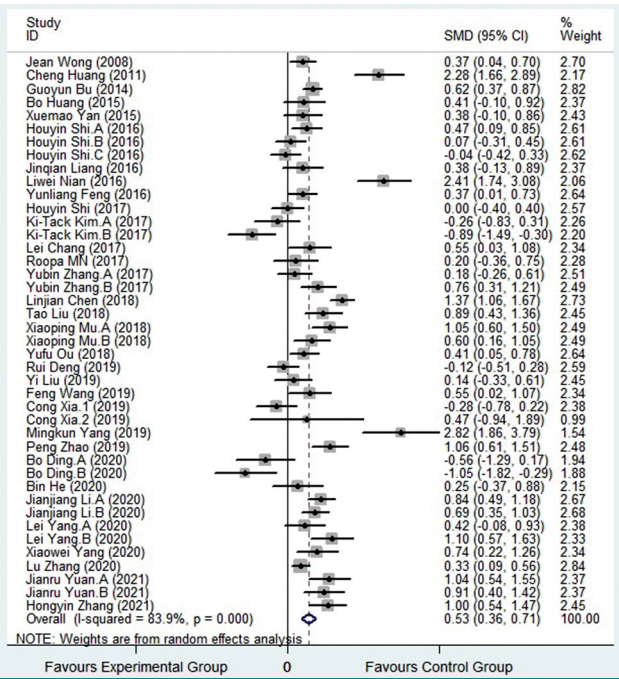
SUPPLEMENTARY FIGURE 3. Comparison of PBL between the TXA group and the control group.

SMD: Standardized mean difference. PBL: Postoperative blood loss; TXA: Tranexamic acid.



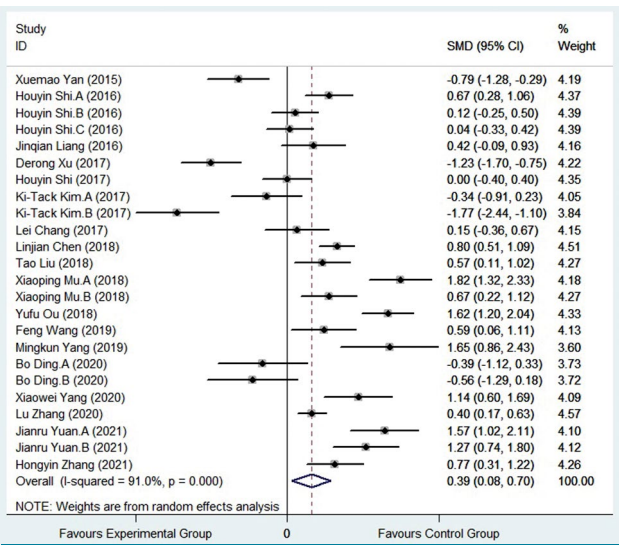
SUPPLEMENTARY FIGURE 4. Comparison of Postoperative drainage between the TXA group and the control group.

SMD: Standardized mean difference; CI: Confidence interval; TXA: Tranexamic acid.



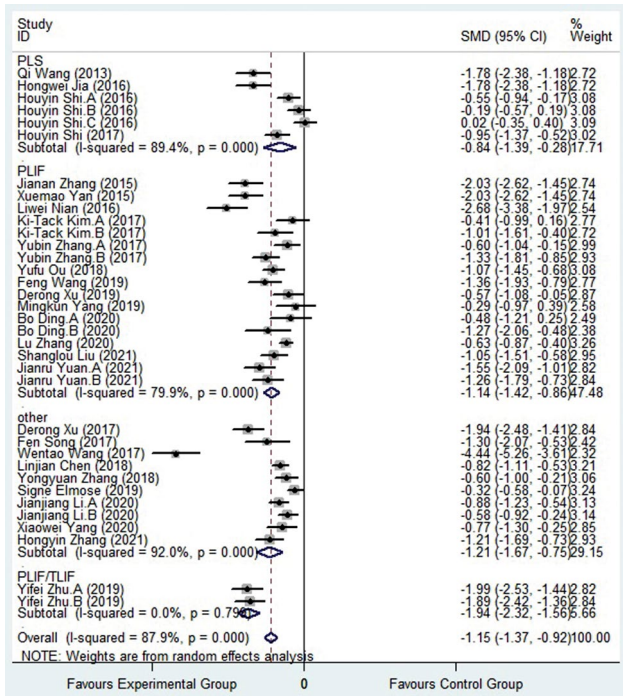
SUPPLEMENTARY FIGURE 5. Comparison of Hb between the TXA group and the control group.

SMD: Standardized mean difference; CI: Confidence interval; TXA: Tranexamic acid.



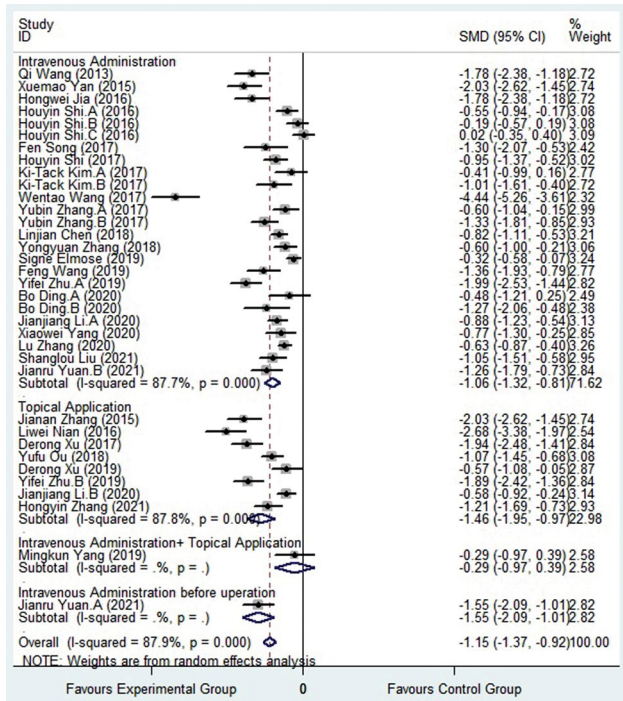
SUPPLEMENTARY FIGURE 6. Comparison of Hct between the TXA group and the control group.

SMD: Standardized mean difference; CI: Confidence interval; TXA: Tranexamic acid.



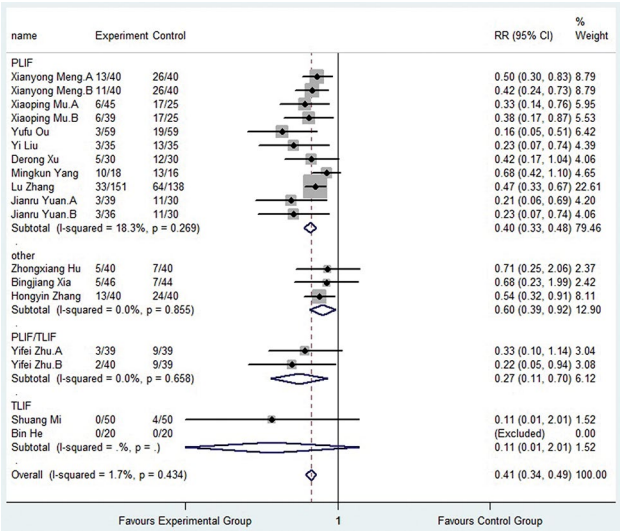
SUPPLEMENTARY FIGURE 7. Comparison of TBL between the TXA group and the control group. (Subgroup analysis according to operative type).

SMD: Standardized mean difference; CI: Confidence interval; TBL: Total blood loss; TXA: Tranexamic acid.



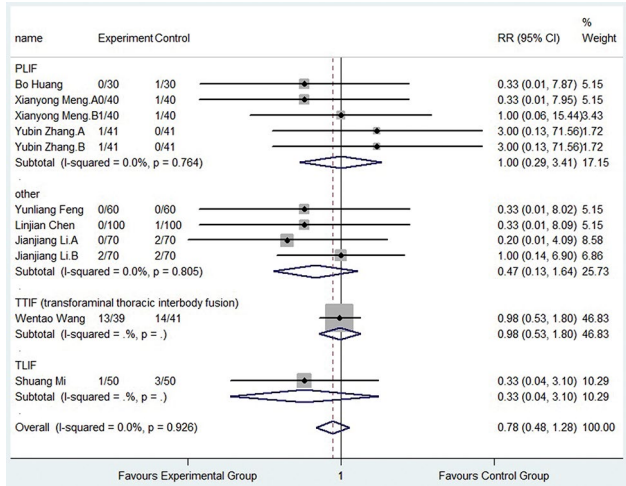
SUPPLEMENTARY FIGURE 8. Comparison of TBL between the TXA group and the control group. (Subgroup analysis according to administration).

SMD: Standardized mean difference; CI: Confidence interval; TBL: Total blood loss; TXA: Tranexamic acid.



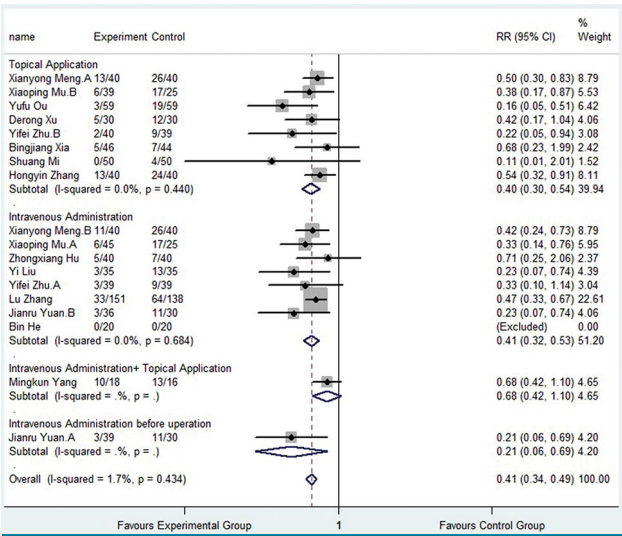
SUPPLEMENTARY FIGURE 9. Comparison of Transfusion rate between the TXA group and the control group. (Subgroup analysis according to operative type).

RR: Risk ratio; CI: Confidence interval; TXA: Tranexamic acid.



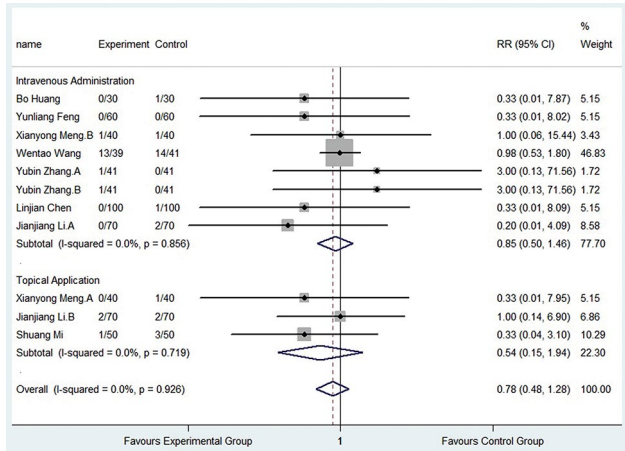
SUPPLEMENTARY FIGURE 11. Comparison of DVT between the TXA group and the control group. (Subgroup analysis according to operative type).

RR: Risk ratio; CI: Confidence interval; TXA: Tranexamic acid; DVT: Deep venous thrombosis.



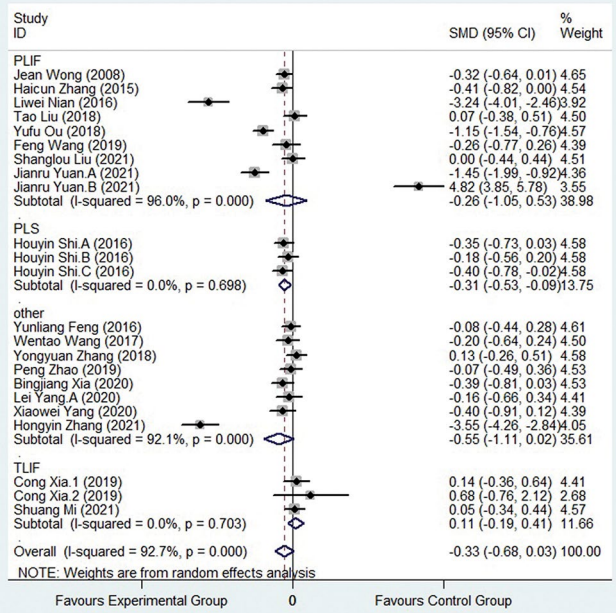
SUPPLEMENTARY FIGURE 10. Comparison of Transfusion rate between the TXA group and the control group. (Subgroup analysis according to administration).

RR: Risk ratio; CI: Confidence interval; TXA: Tranexamic acid.



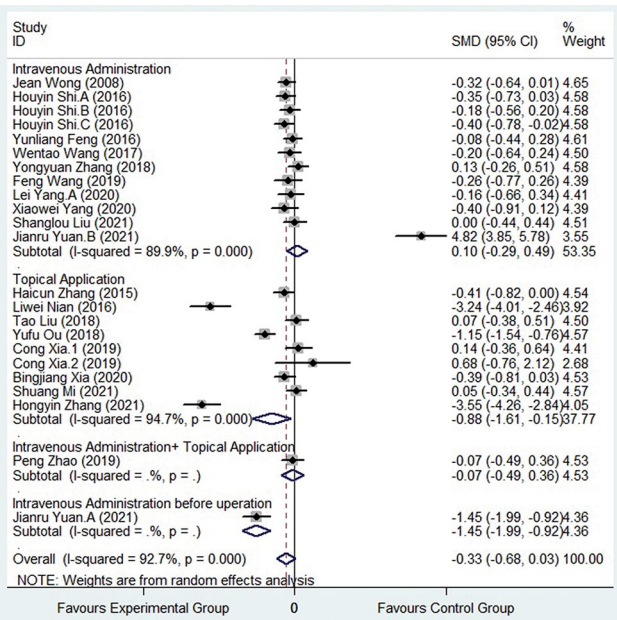
SUPPLEMENTARY FIGURE 12. Comparison of DVT between the TXA group and the control group. (Subgroup analysis according to administration).

RR: Risk ratio; CI: Confidence interval; DVT: Deep venous thrombosis; TXA: Tranexamic acid.



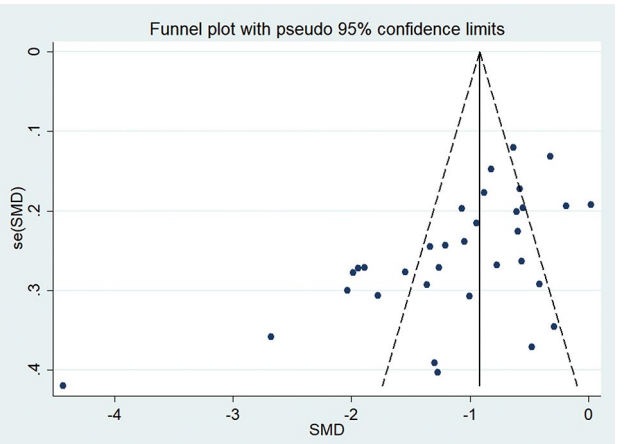
SUPPLEMENTARY FIGURE 13. Comparison of D-dimer between the TXA group and the control group. (Subgroup analysis according to operative type).

SMD: Standardized mean difference; CI: Confidence interval; TXA: Tranexamic acid.



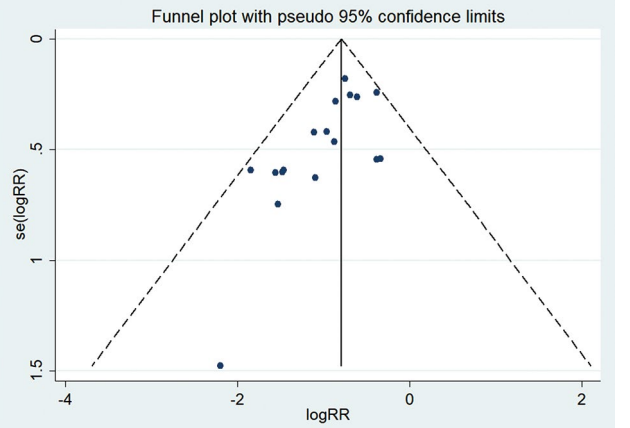
SUPPLEMENTARY FIGURE 14. Comparison of D-dimer between the TXA group and the control group. (Subgroup analysis according to administration).

SMD: Standardized mean difference; CI: Confidence interval; TXA: Tranexamic acid.



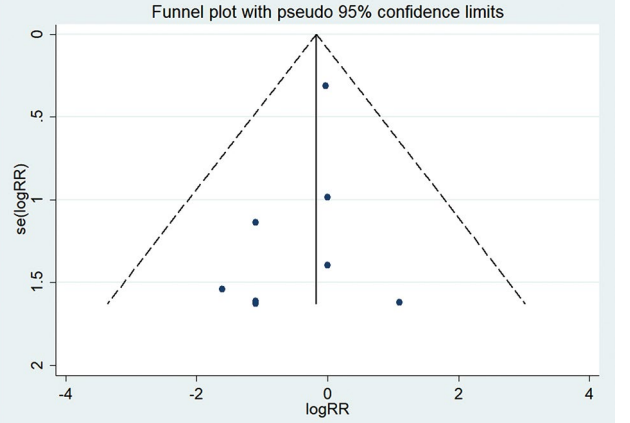
SUPPLEMENTARY FIGURE 15. Comparison of TBL between the TXA group and the control group. (Funnel plot)

SMD: Standardized mean difference; TBL: Total blood loss; TXA: Tranexamic acid.



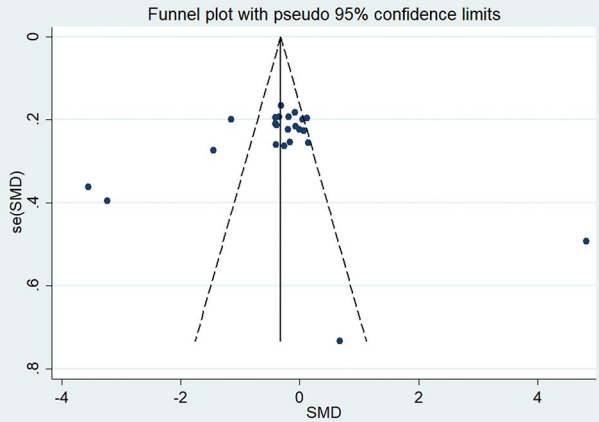
SUPPLEMENTARY FIGURE 16. Comparison of Transfusion rate between the TXA group and the control group (Funnel plot).

RR= Risk ratio; TXA: Tranexamic acid.

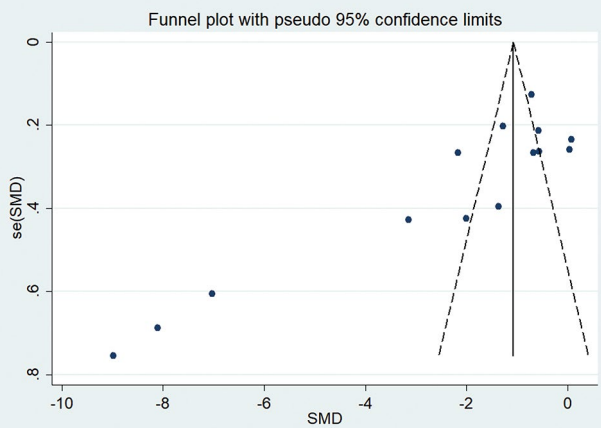


SUPPLEMENTARY FIGURE 17. Comparison of Transfusion volume between the TXA group and the control group. (Funnel plot)

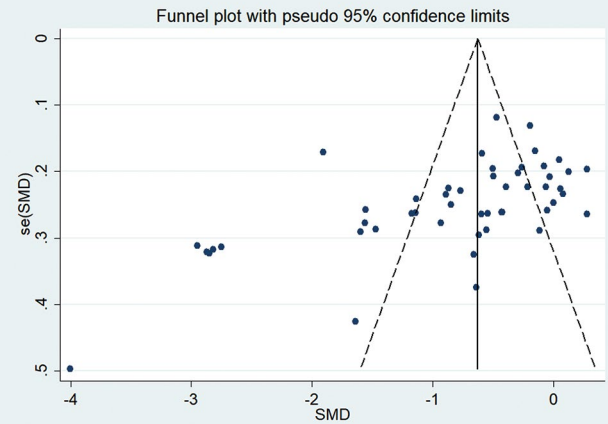
SMD: Standardized mean difference; TXA: Tranexamic acid.



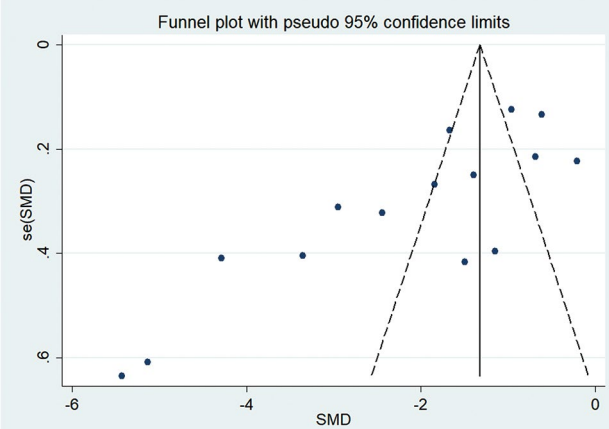
SUPPLEMENTARY FIGURE 18. Comparison of IBL between the TXA group and the control group. (Funnel plot)
SMD: Standardized mean difference; IBL: Intraoperative blood loss.



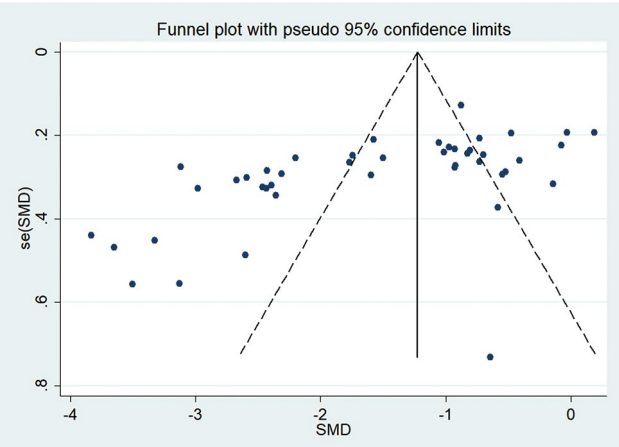
SUPPLEMENTARY FIGURE 19. Comparison of PBL between the TXA group and the control group. (Funnel plot)
SMD: Standardized mean difference; PBL: Postoperative blood loss.



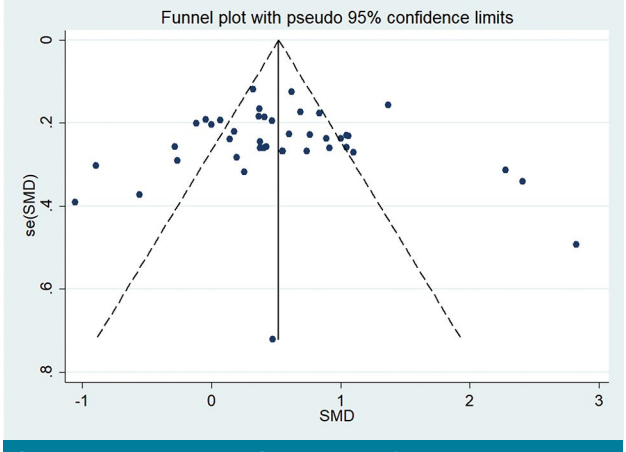
SUPPLEMENTARY FIGURE 20. Comparison of Postoperative Drainage between the TXA group and the control group. (Funnel plot)
SMD: Standardized mean difference; TXA: Tranexamic acid.



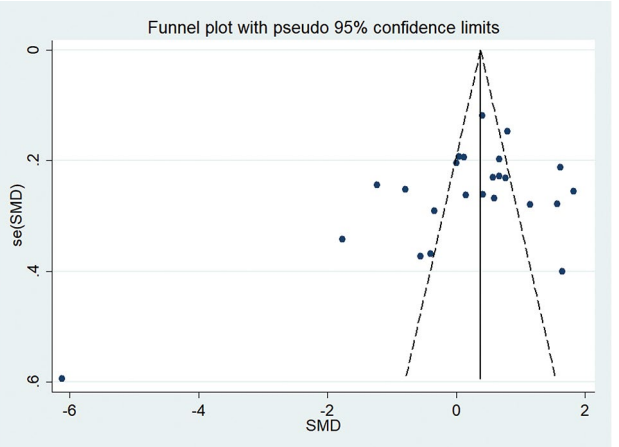
SUPPLEMENTARY FIGURE 21. Comparison of Hb between the TXA group and the control group. (Funnel plot)
SMD: Standardized mean difference; TXA: Tranexamic acid.



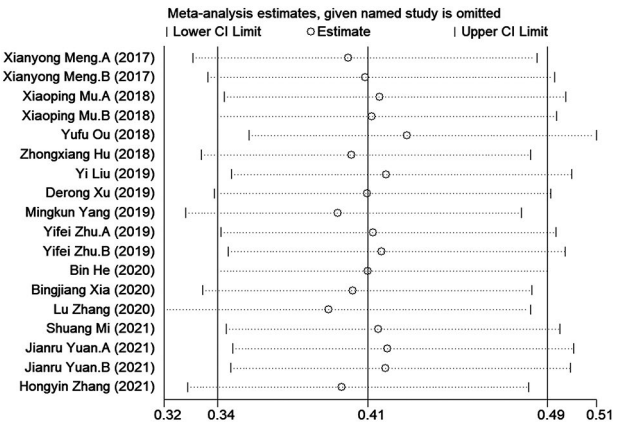
SUPPLEMENTARY FIGURE 22. Comparison of Hct between the TXA group and the control group. (Funnel plot)
SMD: Standardized mean difference; TXA: Tranexamic acid.



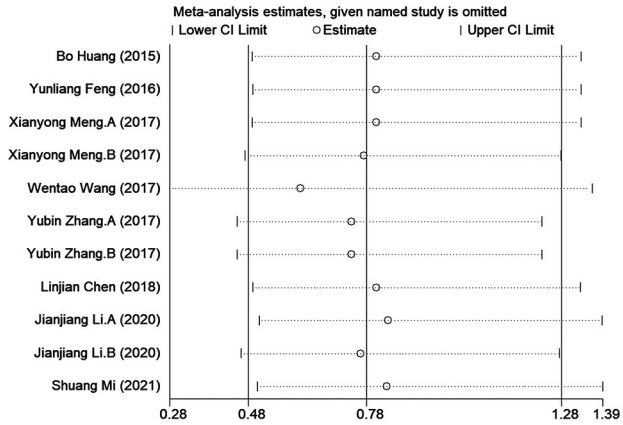
SUPPLEMENTARY FIGURE 23. Comparison of DVT between the TXA group and the control group. (Funnel plot)
SMD: Standardized mean difference; DVT: Deep venous thrombosis; TXA: Tranexamic acid.



SUPPLEMENTARY FIGURE 24. Comparison of D-dimer between the TXA group and the control group. (Funnel plot)
SMD: Standardized mean difference; TXA: Tranexamic acid.

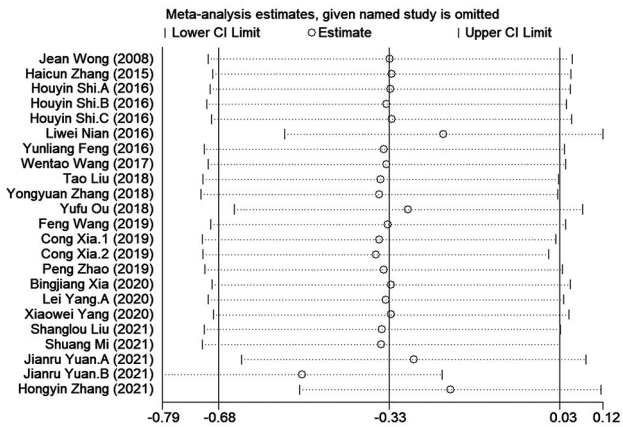


SUPPLEMENTARY FIGURE 26. Comparison of Transfusion rate between the TXA group and the control group. (Sensitivity analysis)
RR: Risk ratio; TXA: Tranexamic acid.



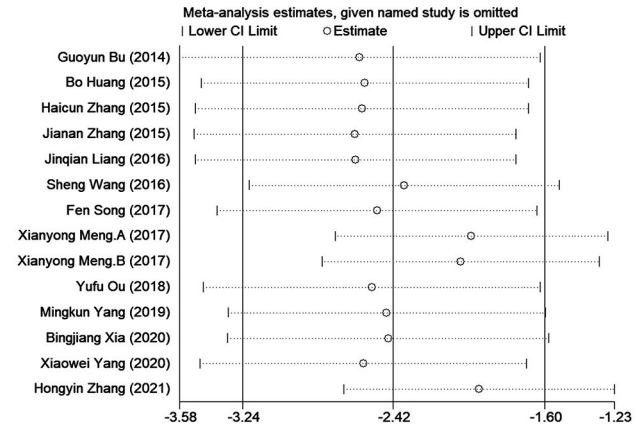
SUPPLEMENTARY FIGURE 26. Comparison of Transfusion volume between the TXA group and the control group. (Sensitivity analysis)

SMD: Standardized mean difference; TXA: Tranexamic acid.



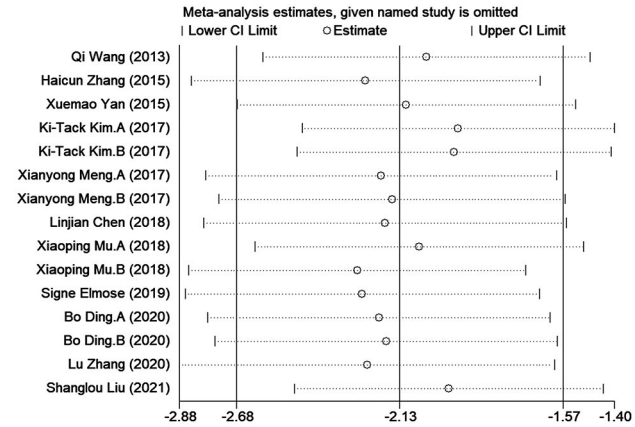
SUPPLEMENTARY FIGURE 27. Comparison of IBL between the TXA group and the control group. (Sensitivity analysis)

SMD: Standardized mean difference; IBL: Intraoperative blood loss; TXA: Tranexamic acid.



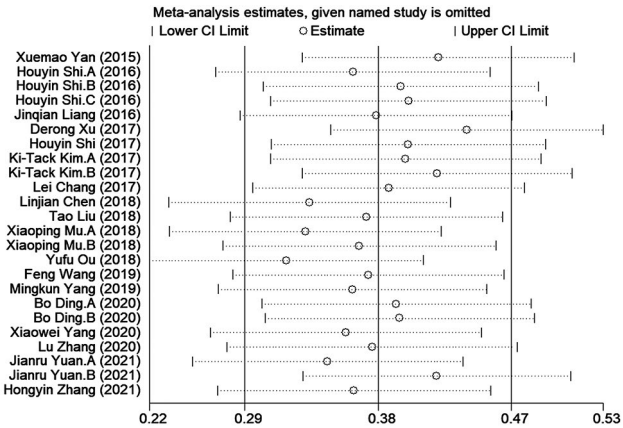
SUPPLEMENTARY FIGURE 28. Comparison of PBL between the TXA group and the control group. (Sensitivity analysis)

SMD: Standardized mean difference; PBL: Postoperative blood loss; TXA: Tranexamic acid.



SUPPLEMENTARY FIGURE 29. Comparison of Hct between the TXA group and the control group (Sensitivity analysis).

CI: Confidence interval; Hct: Hematocrit; TXA: Tranexamic acid.



SUPPLEMENTARY FIGURE 30. Comparison of D-dimer between the TXA group and the control group (Sensitivity analysis).

CI: Confidence interval; TXA: Tranexamic acid.