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The safety and effectiveness of salvianolate in preventing perioperative venous thromboembolism in China

A PRISMA-compliant meta-analysis based on RCTs

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Abstract

Background: Salvianolate, a common drug for stabilizing heart disease and Angina Pectoris, is considered to be off-label for preventing venous thromboembolism (VTE) or anticoagulation at present. However, many clinical studies have showed that salvianolate can effectively inhibit the deep-vein thrombosis (DVT) incidence, and prevent VTE of perioperative patients in the real world in China.

Objective: This analysis aimed to evaluate the effectiveness and safety of salvianolate in preventing VTE in perioperative patients.

Methods: Databases of PubMed, Cochrane Library, Embase, CNKI, Wanfang and VIP were searched until July 2019. Literature retrieval, data extraction and quality assessment were independently completed by two researchers and checked with each other. Review Manager 5.2 software was applied for meta-analysis.

Results: A total of 429 studies were retrieved, including 11 randomized controlled trials (RCTs) with a total of 1149 subjects. Compared with low molecular weight heparin (LMWH) group alone, salvianolate combined LMWH group had lower DVT incidence in preventing perioperative thrombosis (2.75% and 14.23%, OR: 0.21, 95% CI:[0.08,0.53]; $P = .0009$). The incidence of adverse reactions of experimental group was similar to that of control group (1.79% and 2.31%, OR: 0.65, 95% CI:[0.18,2.35]. $P = .51$). Compared with the control group, D-dimer level (D-D), platelet count (PLT), fibrinogen (FIB), whole blood high shear viscosity (WBHSV), and whole blood low shear viscosity (WBLSV) were all significantly decreased ($P < .01$), and prothrombin time (PT) was significantly increased ($P < .05$).

Conclusion: Salvianolate combined LMWH has better effectiveness and the same safety in preventing venous thromboembolism in perioperative patients. However, due to the small number of included literatures, large sample studies are still needed to further verify this conclusion.

Abbreviations: ADR = adverse reactions, CNKI = China national knowledge infrastructure, D-D = D-dimer level, DVT = deep-vein thrombosis, FIB = fibrinogen, LMWH = low molecular weight heparin, PE = pulmonary embolism, PLT = platelet count, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analysis, PT = prothrombin time, RCTs = randomized controlled trials, VTE = Venous thromboembolism, WBHSV = whole blood high shear viscosity, WBLSV = whole blood low shear viscosity.

Keywords: meta-analysis, randomized controlled trial, salvianolate, Venous thromboembolism

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1. Introduction

Venous thromboembolism (VTE), including deep-vein thrombosis (DVT) and pulmonary embolism (PE), is well known as a common complication after surgery.[1,2] VTE could potentially lead to distal venous hypertension, limb swelling, pain and other symptoms. Moreover, the detached thrombus may flow into the pulmonary artery with the blood, causing dyspnea, suffocation, and even life threat.[3] It is very important to prevent thrombosis and reduce the risk of bleeding after surgery.[4] Low molecular weight heparin (LMWH) is the main drug used for thromboprophylaxis currently.[5] However, the incidence of VTE is still high in some patients using this drug alone.[6,7]

Salvianolate is prepared from water-soluble bioactive compounds of *Salvia miltiorrhiza* bunge, composing of magnesium lithospermate B (≥85%), rosmarinic acid and lithospermic acid.[8–10] Salvianolate can promote blood circulation and coronary circulation, as well as remove blood stasis.[11,12] It has been listed and clinically used to treat coronary heart disease in China. There were preclinical pharmacology studies and multicenter clinical trials to show that salvianolate was stable, safe and effective.[13,14]

Clinical studies have shown that salvianolate alone or combined with LMWH can effectively prevent the formation of DVT after surgery in orthopedics and gynecology.[7,15] This study conducted a meta-analysis of RCT studies of salvianolate to prevent perioperative thrombus formation. The study aimed to provide certain evidence for the development of new drugs for thrombus prevention.

2. Methods

Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) was applied to the literature retrieval strategy, evaluation method, data extraction, result evaluation and statistical analysis.[16]

2.1. Literature search strategy

Literature retrieval, including journals, proceedings, conference abstracts and dissertations, was performed independently by two researchers and cross-checked from China national knowledge infrastructure (CNKI), Wanfang data, VIP database, PubMed, Cochrane Library and Embase databases. The retrieval time is from establishment of the database until July 2019. The search strategy was (((salvianolate[Title/Abstract]) OR salvianolic acid [Title/Abstract])) AND ((((cruor[Title/Abstract]) OR anticoagula*[Title/Abstract]) OR thrombus[Title/Abstract]) OR venous thromboembolism [Title/Abstract]).

2.2. Eligibility criteria

Studies were selected based on the following inclusion criteria:

1. RCT studies;
2. Subjects: postoperative patients;
3. Intervention measures: salvianolate or combined LMWH;
4. Outcome indicators including at least one of the followings: DVT incidence, incidence of adverse reactions, D-dimer level (D-D), platelet count (PLT), fibrinogen (FIB), prothrombin time (PT), thrombin time (TT), activated partial thromboplastin time (APTT), whole blood high shear viscosity (WBHSV), and whole blood low shear viscosity (WBLSV).

Exclusion criteria:

1. Studies on salvianolic acid, salvianolic acid A or salvianolic acid B;
2. Retrospective studies;
3. Review, personal experience and other irrelevant literature;
4. Mechanism studies;
5. Non-surgical studies;
6. Animal experiments.

2.3. Research screening and data extraction

Literature screening and data extraction were independently completed and confirmed by two researchers. The extracted data included the name of the first author, year of publication, type of surgery, medication regimen, outcome indicators, incidence of adverse reactions, etc.

2.4. Risk bias assessment

RCTs were evaluated according to the assessment items in Cochrane risk bias assessment tool:[17] 1. Random sequence generation; 2. Allocation concealment; 3. Blinding of participants and personnel; 4. Blinding of outcome assessment; 5. Incomplete outcome data; 6. Selective reporting; 7. Other bias. "Low bias risk", "uncertainty of bias risk" and "high bias risk" were used to determine each item.

2.5. Data statistics

We performed this meta-analysis using Review Manager 5.2 software. All data were expressed by weighted mean difference (MD) and odds ratio (OR), respectively. The 95% confidence interval was calculated by Mantel-Haenszel statistical method. Chi-square test and I^2 were used to evaluate heterogeneity. The difference of heterogeneity was statistically significant as $P < .1$. Random effect model was used for studies with significant heterogeneity of variables. Otherwise, fixed effect model was used.

Subgroup analysis was performed according to the surgery type, administration time and dosage regimen. Sensitivity analysis was carried out by the culling method.

2.6. Ethics and informed consent of patients

This study doesn't involve any patient's information, so ethical approval and informed consent of patients are not required for this systematic review. Our findings will also be published in peer-reviewed journals.

3. Results

3.1. Literature search and screening

A total of 429 literatures were retrieved in this study. Two hundred duplicate studies were excluded by duplicate check function of Note Express and EndNote software. By browsing the title and abstract, 105 studies were eliminated, including irrelevant 92 studies, 2 studies about mechanism studies and 11 studies about animal experiments. According to full text, 113 studies were excluded, including 106 non-surgical studies, 5 non-relevant studies and 2 non-RCT studies. Finally, 11 studies were included in the study, including 1149 subjects (604 in the experimental group and 545 in the control group), as shown in Figure 1.

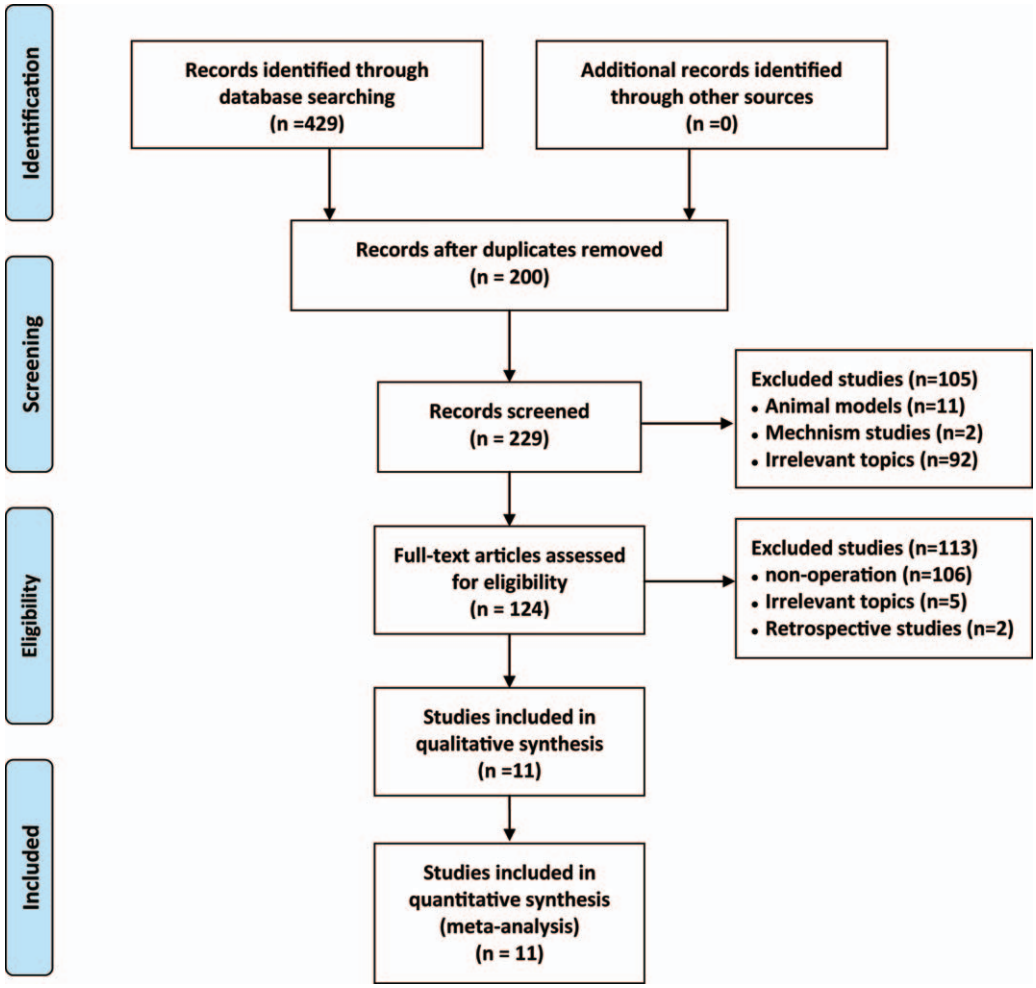

Figure 1. Flowchart of studies identified, included and excluded.

3.2. The basic features of included studies

The basic features of included studies were showed in Table 1. In the eleven included studies, there are five orthopedics studies, three gynecology studies, one liver transplantation study, one lower extremity trauma study, and one ophthalmology study. There are two main outcomes, DVT incidence and incidence of adverse reactions. Eight secondary outcomes, D-D level, PLT, PT, TT, APTT, FIB, WBHSV and WBLSV, were respectively replaced by numbers 1–8.

Table 1

Basic features of the study included.

		Intervention							
First author	year	experiment	control	Sample size (E/C)	Intervention duration	Surgery type	Outcomes	DVT (%, E/C)	ADR (%, E/C)
Song SH	2019	sal	NS	30/30	2w	liver transplantation	2,3,5,6	NA	NA
Hai SE	2012	sal	NS	113/87	1w	lower extremity trauma	1,2,4,5	NA	NA
Zheng K	2013	sal	NS	30/70	6d	gynecology	1,2,5	NA	0/0
Bao JW	2012	sal	LMWH	60/60	2w	orthopedics	NA	15/28.3	NA
Ni Y	2015	sal	LMWH	30/30	10d	orthopedics	3,4,6	6.7/13.3	NA
Li Y	2019	sal+LMWH	LMWH	48/48	3d	ophthalmology	1,2,3,5,7,8	0/8.3	NA
Li HJ	2012	sal+LMWH	LMWH	30/30	2w	orthopedics	2	NA	NA
Ye K	2015	sal+LMWH	LMWH	103/100	2w	orthopedics	1,2,3,5	4.8/11	2.9/4
Zhou HX	2015	sal+LMWH	LMWH	40/40	2w	orthopedics	1,2,3,5	5/12.5	0/0
Cheng J	2017	sal+LMWH	LMWH	50/50	2w	gynecology	1,2,3,5,6,7,8	2/30	2/4
Li HS	2018	sal+LMWH	LMWH	50/50	1w	gynecology	1,2,3,5,6	0/12	NA

2 = PLT (platelet count), 3 = PT (prothrombin time), 4 = TT (thrombin time), 5 = APTT (activated partial thromboplastin time), 6 = FIB (fibrinogen), 7 = WBHSV (whole blood high shear viscosity), 8 = WBLSV (whole blood low shear viscosity), C = control group, d = day, E = experimental group, NA = date not vailable, Outcomes: 1 = D-D level (D-dimer level), sal = salvianolate, w = week.

Table 2

Meta-analysis results of salvianolate in preventing postoperative thrombus formation.

Outcomes	Study No.	Patients No. (E/C)	Statistical heterogeneity I^2 (%)	Statistical heterogeneity *P* value	Results OR/WMD (95% CI)	Results *P* value
DVT	7	381/378	4	.4	0.27 (0.16, 0.46)	**<.00001**
D-D	7	434/445	97	<.00001	-89.17 (-117.24, -61.10)	**<.00001**
PLT	9	494/505	80	<.00001	-12.15 (-19.26,-5.04)	**.0008**
PT	7	351/348	93	<.00001	0.87 (0.15,1.58)	**.02**
TT	2	143/117	89	.003	0.52 (-1.48,2.52)	.61
APTT	4	160/160	61	.05	1.57 (-0.14,3.28)	.07
FIB	8	464/475	84	<.00001	-0.32 (-0.49,-0.14)	**.0005**
WBHSV	2	98/98	51	.15	-0.59 (-0.70,-0.47)	**<.00001**
WBLSV	2	98/98	70	.07	-1.6 (-2.86,-0.34)	**.01**
ADR	4	223/260	0	.79	0.65 (0.18,2.35)	**.51**

ADR = adverse reaction, APTT = activated partial thromboplastin time, C = control group, D-D = D-dimer level, DVT = Deep-vein thrombosis, E = experimental group, FIB = fibrinogen, PLT = platelet count, PT = prothrombin time, TT = thrombin time, WBHSV = whole blood high shear viscosity, WBLSV = whole blood low shear viscosity.

3.3. Outcomes

Meta-analysis of all outcomes was conducted, and the results were showed in Table 2.

3.3.1. DVT incidence. Seven studies reported the DVT incidence,[18–24] and the results showed that the DVT incidence of the experimental group was significantly lower than that of the control group (4.98% and 16.4%, OR: 0.32, 95% CI: [0.16,0.57].$P < .00001$). There was no significant heterogeneity ($I^2 = 4\%$, $P = .4$), and the data were merged using a fixed-effect model. According to the dosage regimen, the subgroup analysis showed that the DVT incidence in salvianolate combined LMWH group was lower than that in LMWH group (2.75% and 14.24%, OR: 0.21, 95% CI: [0.08, 0.53].$P = .0009$), as shown in Figure 2.

3.3.2. D-D level. Seven studies reported D-D level,[19–21,23–26] and the results showed that the experimental group was significantly lower than the control group (MD: -89.17, 95% CI:[-117.24,-61.10].$P < .00001$). The study showed significant heterogeneity ($I^2 = 97\%$, $P < .00001$), and the random effects model was adopted. From the results of subgroup analysis according to the surgery type, the dosage regimen and administration time, there were still significantly heterogeneous (Fig. 3 A, B and C). However, after sensitivity analysis by elimination of all literatures one by one, the positive results of

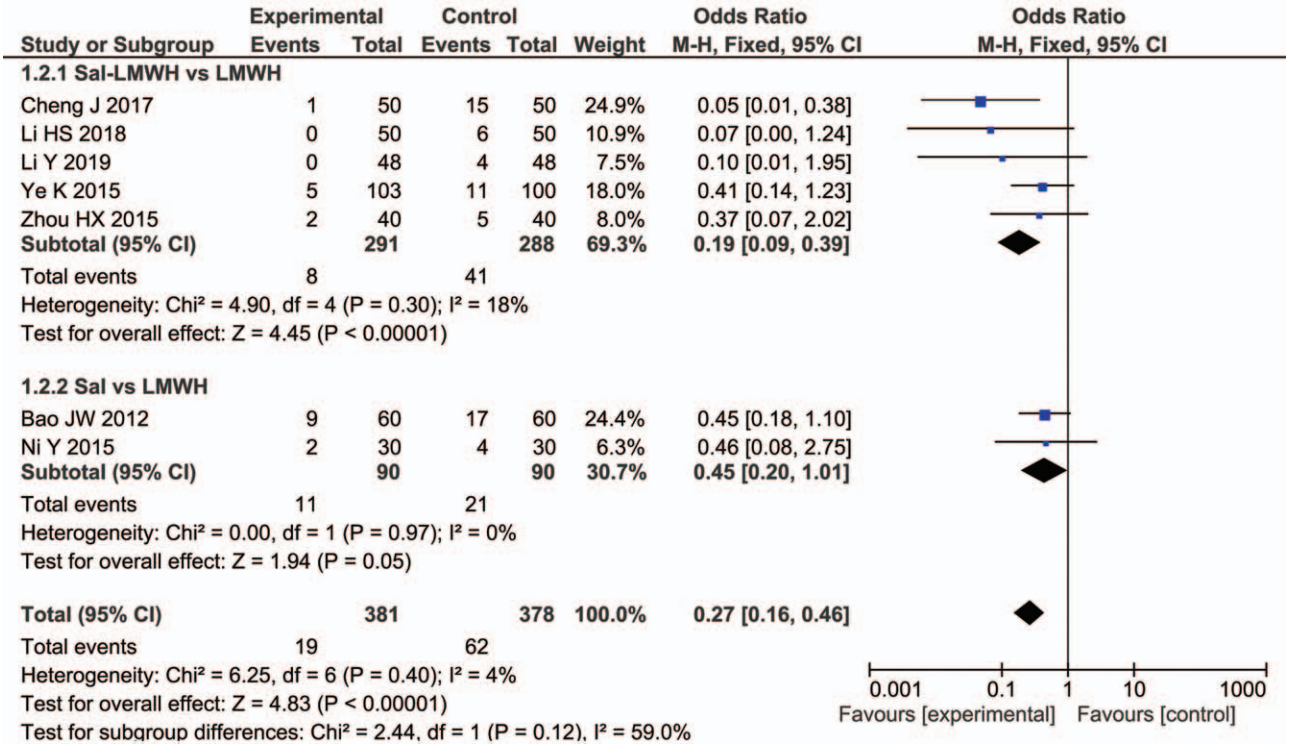

Figure 2. Forest plot of DVT incidence according to dosage regimen with a fix effect model.

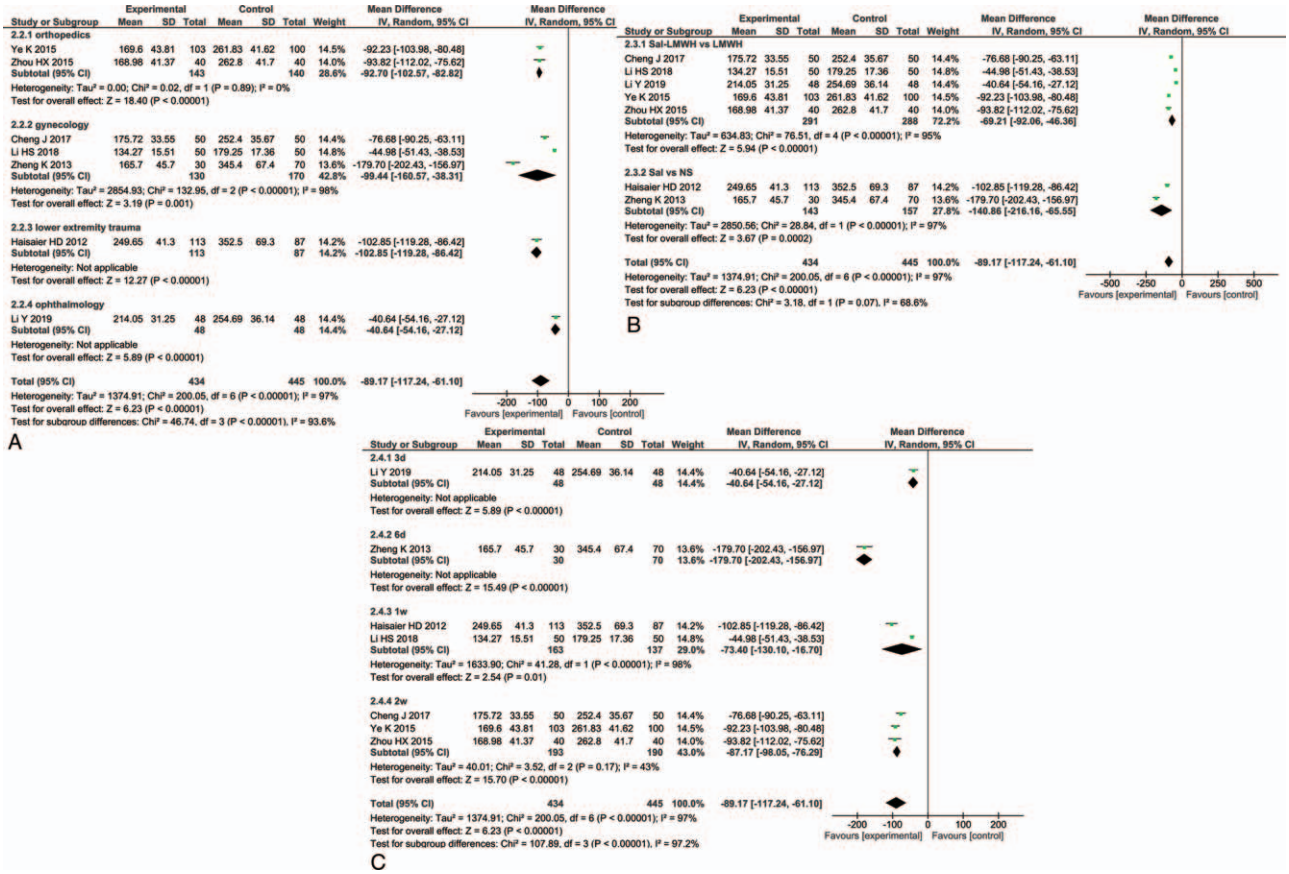

Figure 3. Forest plot of D-D level with a random effect model.

effect size were not affected, as shown in Supplemental Table 1, http://links.lww.com/MD2/A75, indicating that the analytical results were stable.

3.3.3. PLT. Nine studies reported PLT,[19–21,23–28] and the results showed that PLT in the experimental group was significantly lower than control group (MD: -12.15, 95% CI: [-19.26,-5.04]. $P = .0008$). There was significant heterogeneity ($I^2 = 80\%$, $P < .00001$), and the random effects model was adopted. Subgroup analysis according to administration time, showed no significant heterogeneity in each subgroup (Fig. 4).

3.3.4. PT. Seven studies reported PT.[19–24,28] Results showed that PT in the experimental group was significantly lower than the control group (MD: 0.87,95% CI:[0.15,1.58];$P < .05$). There was significant heterogeneity ($I^2 = 93\%$, $P < .00001$), and the random effects model was adopted. Subgroup analysis was performed according to the surgery type, and the results showed that there was no significant heterogeneity in each subgroup (Fig. 5).

3.3.5. TT. Two studies reported TT,[22,25] and the results showed no significant difference between the experimental group and the control group (MD: 0.52, 95% CI:[-1.48,2.52];$P = .61$).

3.3.6. APTT. Four studies reported APTT,[19,20,22,28] and the results showed no significant difference between the experimental group and the control group (MD: 1.57, 95% CI: [-0.14, 3.28]; $P = .07$).

3.3.7. FIB. Eight studies reported FIB,[19–21,23–26,28] and the results showed that FIB in the experimental group was significantly lower than that in the control group (MD: -0.32,95% CI:[-0.49,-0.14]; $P < .0005$). There was significant heterogeneity ($I^2 = 84\%$, $P < .00001$), and the random effects model was adopted. From the results of subgroup analysis according to the surgery type, the dosage regimen and administration time, there were still significant heterogeneity (Fig. 6 A, B and C). However, after sensitivity analysis by elimination of all literatures one by one, the positive results of effect size were not affected (Supplemental Table 2, http://links.lww.com/MD2/A76), indicating that the analytical results were stable.

3.3.8. WBHSV. Two studies reported WBHSV,[19,21] and the results showed that WBHSV in the experimental group was significantly lower than that in the control group (MD: -0.59, 95% CI: [-0.70,-0.47]; $P < .00001$). There was no significant heterogeneity ($I^2 = 51\%$, $P = .15$).

3.3.9. BLSV. Two studies reported WBLSV,[19,21] and the results showed that WBLSV in the experimental group was significantly lower than the control group (MD: -1.60, 95% CI: [-2.86,-0.34]; $P = .01$). The study showed significant heterogeneity ($I^2 = 70\%$, $P = .07$).

3.3.10. Incidence of adverse reactions. Four studies reported the incidence of adverse reactions.[19,23,24,26] As shown in Figure 7, there was no significant heterogeneity ($I^2 = 0$, $P = .79$).

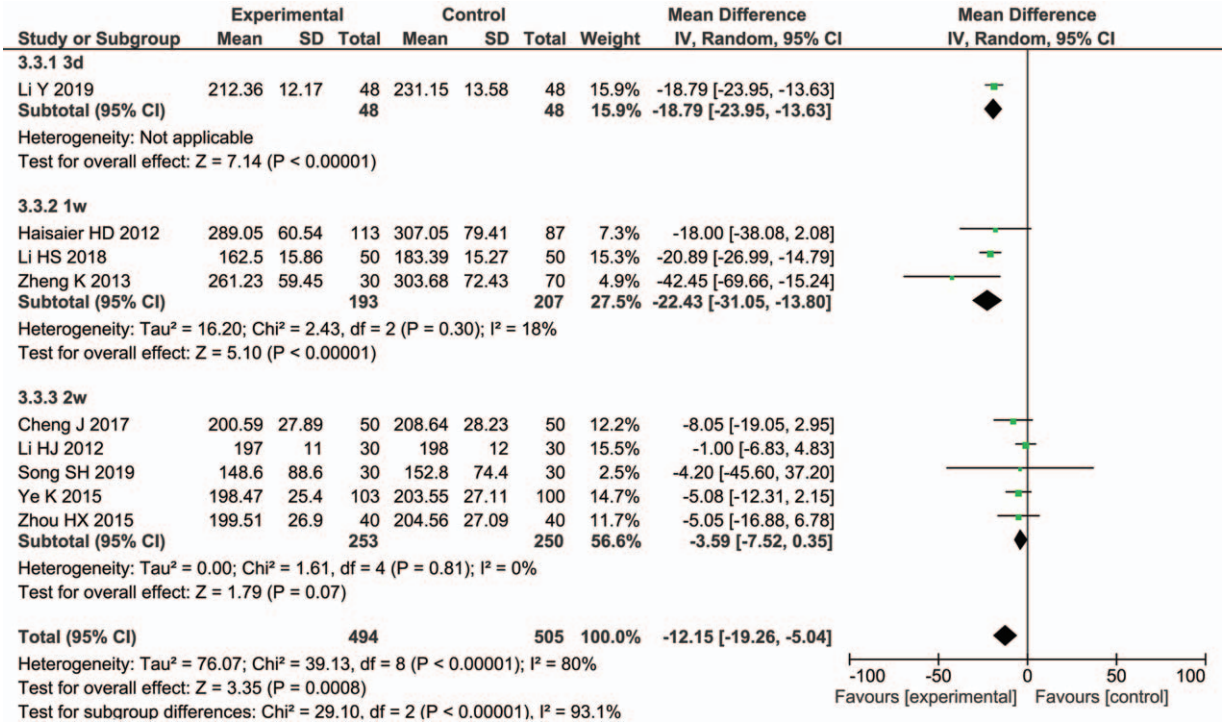

Figure 4. Forest plot of PLT level according to administration time with a random effect model.

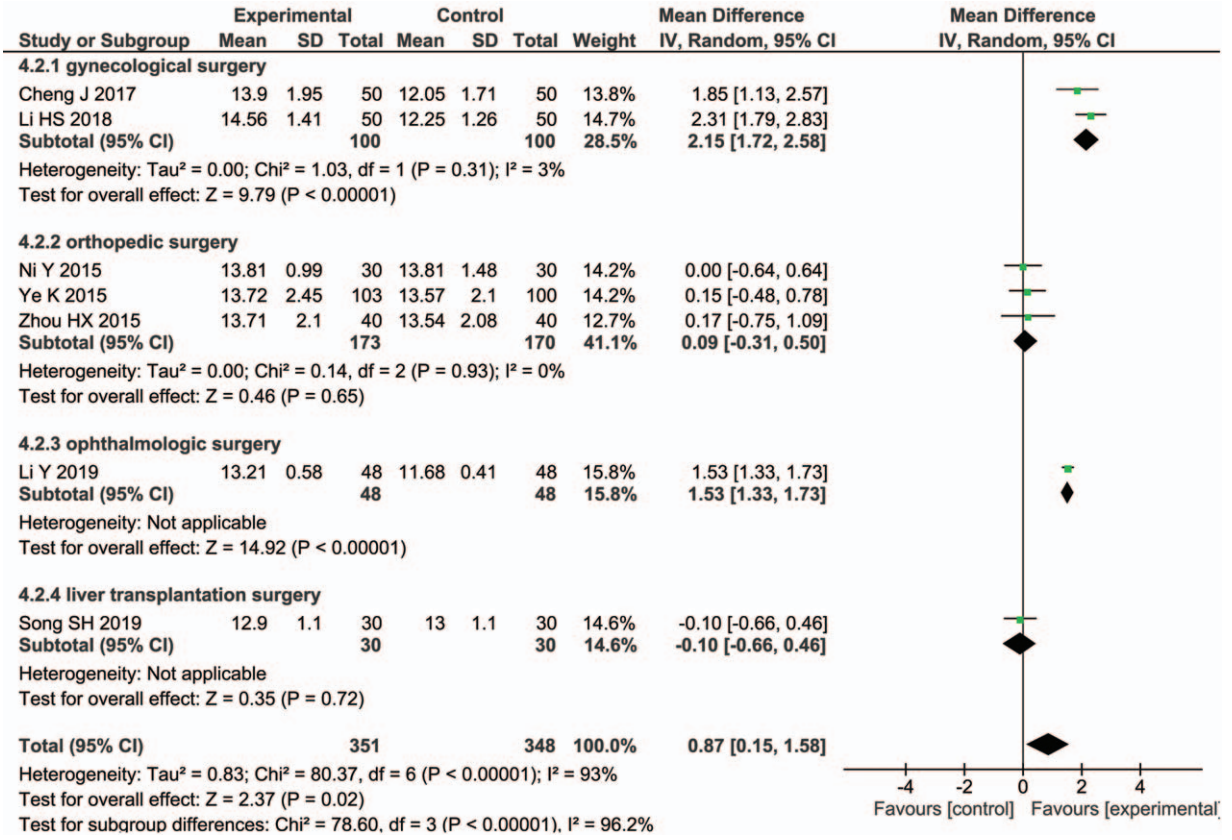

Figure 5. Forest plot of PT level according to surgery types with a random effect model.

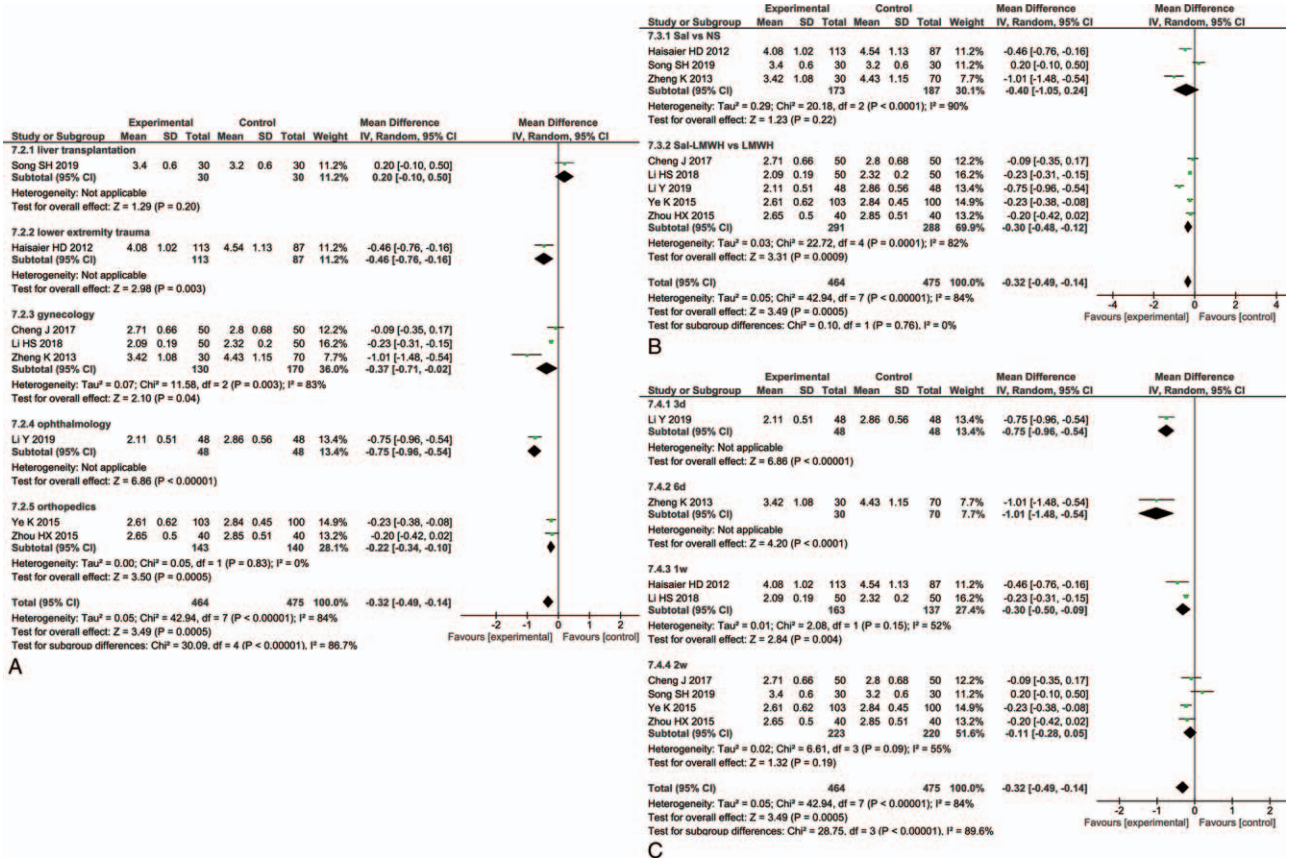

Figure 6. Forest plot of FIB level with a random effect model.

A fixed-effect model showed that there was no statistically significant difference between the experimental group and the control group (1.79% and 2.31%, OR: 0.64, 95% CI: [0.18, 2.33].$P=.79$).

3.4. Risk bias assessment of included studies

On the whole, the risk bias is moderate as shown in Figure 8 (green means low risk of bias, red means high risk of bias, and yellow means that the risk of bias cannot be determined). In the included studies, 5 studies specifically described the method of random sequence generation and allocation concealment,[19–21,23,28] which were considered as the risk of low bias. The blind method was not described, which was medium risk of bias. There was no loss of follow-up in all studies, and the incomplete of the outcome data was low deviation risk. Selective reporting and other bias were considered as low risk of bias.

4. Discussion

This study is the first meta-analysis of RCT studies on salvianolate in the VTE prevention in perioperative period. Our analysis indicated that salvianolate combined with LMWH had significant advantage (2.75% and 14.23%, $P=.0009$) in

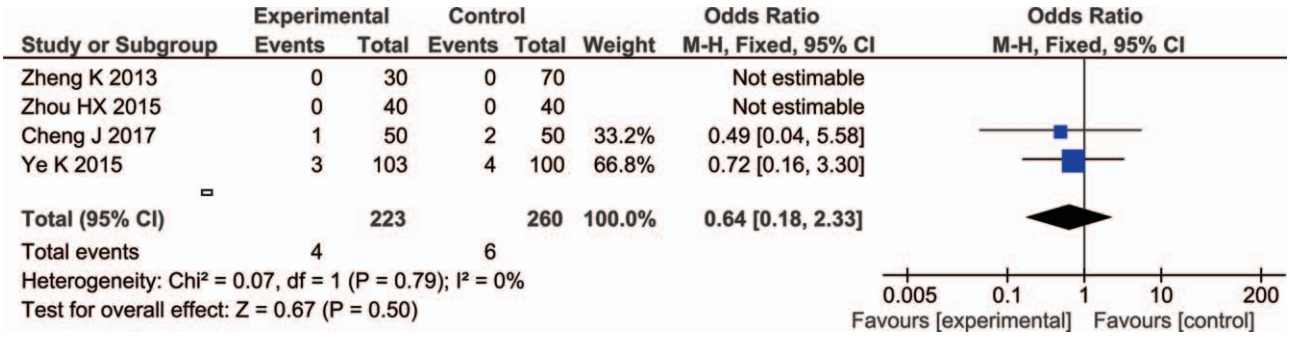

Figure 7. Forest plot of incidence of adverse reactions with a fix effect model.

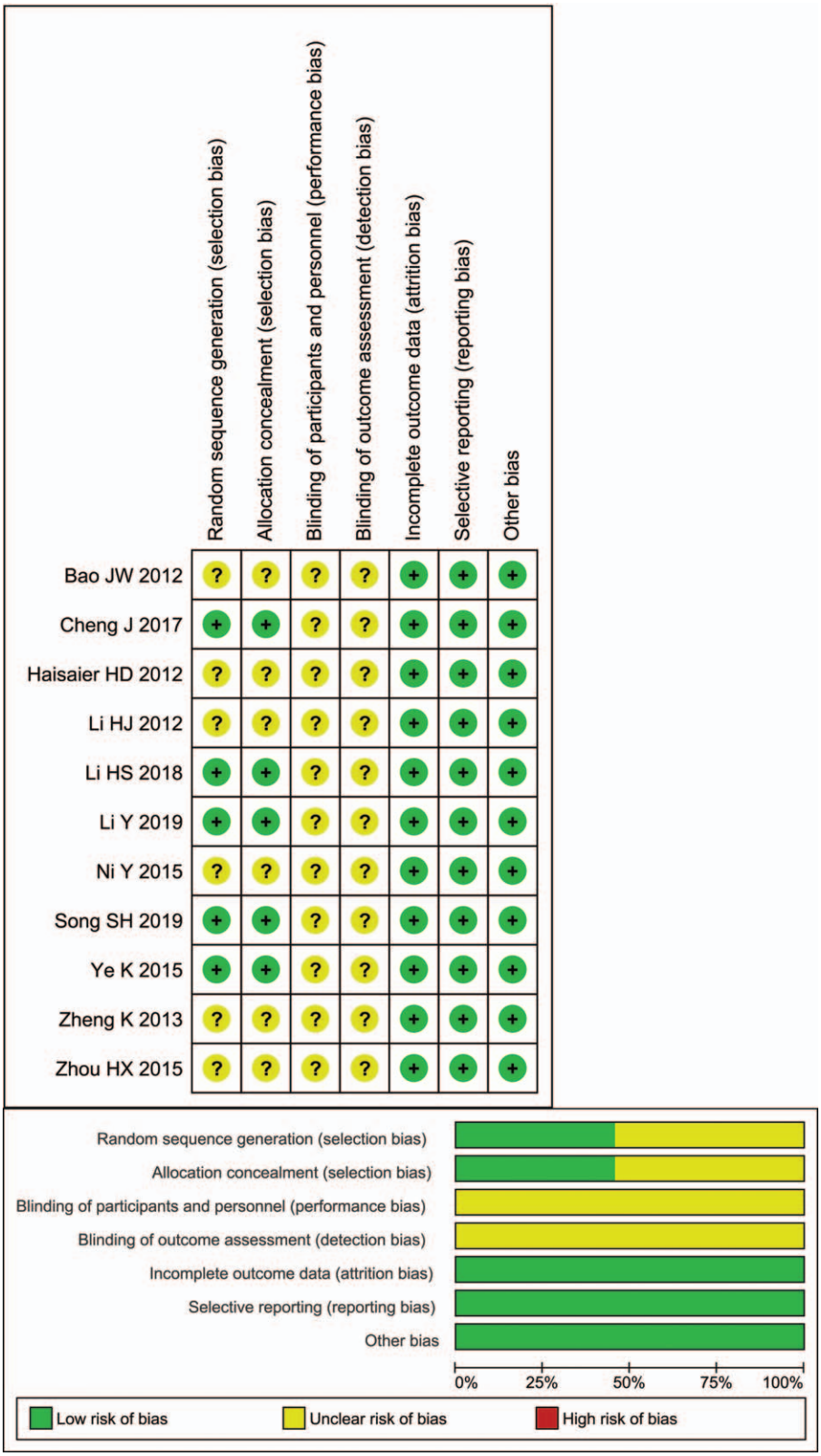

Figure 8. Risk bias graph and Risk bias summary.

preventing thrombus formation after surgery than LMWH alone. The incidence of adverse reactions of salvianolate combined with LMWH was comparable to LMWH (1.79% and 2.31%, $P = .51$). This analysis including 11 RCTs consisted of five surgery types, gynecology, orthopedics, ophthalmology, liver transplantation, and lower extremity trauma. Outcomes of DVT, D-D, PLT, FIB, PT, WBHSV and WBLSV showed significant difference, while TT and APTT had no significant difference

between the experimental group and control group. In terms of the incidence of adverse reactions, four studies were clearly reported and statistically analyzed, while others merely described no significant adverse reactions. These results suggested that salvianolate or combined with LMWH was as safe as control groups for thrombosis prevention.

In our analysis, some studies showed heterogeneity. After subgroup analysis according to the surgery type and administration time, the heterogeneity of PLT and PT was eliminated. For outcomes of D-D and FIB, heterogeneity could not be eliminated through subgroup analysis. We conducted a sensitivity analysis to remove one study at a time, heterogeneity still existed. However, it did not affect the overall results of the two outcomes, indicating that the data were relatively stable. The data from the study ""Zheng K, 2013"" seemed to be outlier.[26] In this study, thirty subjects were included in the experimental group and seventy subjects in the control group. The sample size varies greatly in the two groups, resulting in low test efficiency, and even false significance. Therefore, the "Mean Difference" was lower than that of other studies, which was reflected in the left outlier in the forest plot.

Salvianolate injection can promote blood circulation, and remove blood stasis. The main pharmacological effects of salvianolate are to reduce the elevation of ST segment of electrocardiogram, reduce the infarct area and reduce the LDH function of serum.[11,29] In addition, it can inhibit ADP-induced platelet aggregation in rats.[30] Salvianolate, the extraction of Danshen, contains mainly magnesium lithospermate B (≥85%), rosmarinic acid (≥10.1%) and lithospermic acid. Salvianolic acid B, one of the highest extract, has been confirmed in the experiments in vivo and in vitro with functions of anti-oxidation, regulating blood lipid, reducing C-reactive protein (CRP) level, inhibiting the large amount of platelet aggregation, and eliminating free radicals.[31] As freeze-dried powder, the properties of salvianolate are more stable. The drug have the following functions: fighting platelet adhesion, reducing CRP level, resisting myocardial ischemia, promoting hemodynamic recovery, reducing ischemia reperfusion injury, promoting blood lipid metabolism, resisting arteriosclerosis, reducing inflammation and improving endothelial cell function.[32] There were lots of animal studies which proved salvianolate affecting cytokine gene expression, cardiomyocytic apoptosis and improving heart function after acute myocardial infarction.[31–34]

Salvianolate, a common drug for stabilizing heart disease and angina pectoris, is considered to be off-label for preventing thromboembolism (VTE) or anticoagulation at present. However, many clinical studies have showed that salvianolate can effectively inhibit the DVT incidence, and prevent VTE of perioperative patients in the real world. The latest studies have proved that salvianolate can inhibit the incidence of DVT, D-D level, platelet aggregation and adhesion, reduce fibrinogen, and prolong PT, TT, as well as APTT.[19–21] Moreover, salvianolate may play an anti-thrombotic role indirectly through relieving postoperative clinical symptoms of pain and swelling, protecting vascular endothelium, and improving hemodynamics, such as WBHSV, plasma viscosity.[19,21,22,35] Salvianolate was off-label medication on VTE prevention, whereas our meta-analysis could provide certain evidence for VTE prevention in perioperative patients to improve rational drug use. In the future, the indication of VTE prevention may be included in the drug instruction or guidance of salvianolate after more high quality and appreciable quantity of RCTs to verify our conclusion.

This analysis also has several limitations: lack of large-scale RCTs, no follow-up information and no detailed description about carrying out blinding. Moreover, there is a grey literature,[26] which can be extracted detailed data. However, it still may cause a certain degree of bias in this analysis. Since the drug is only listed in China, 11 included RCTs are only conducted in China. More worldwide-center and high-quality RCTs are expected to verify the evidence of this analysis.

In conclusion, our analysis showed that salvianolate combined with LMWH had significant advantage than LMWH alone to prevent thrombus after surgery. The incidence of adverse reactions of salvianolate was comparable to LMWH. In view of limited RCTs, researchers should conduct more expanded multicenter trials and high-quality of RCTs, which is beneficial to clinical application of VTE prevention in perioperative period.

Author contributions

Conceptualization: Duo-lu Li, Chong-Zhen Qin.
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Visualization: Li-chong Wang.
Writing – original draft: Yu-na Chai.
Writing – review & editing: Dangchi Li, Duo-lu Li.

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