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Unfractionated heparin or low-molecular-weight heparin for venous thromboembolism prophylaxis after hepatic resection

A meta-analysis

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Abstract

Background: Two systematic reviews summarized the efficacy and safety of pharmacological prophylaxis for venous thromboembolism (VTE) after hepatic resection, but both lacked a discussion of the differences in the pharmacological prophylaxis of VTE in different ethnicities. Therefore, we aimed to evaluate the efficacy and safety of low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) for VTE prophylaxis in Asian and Caucasian patients who have undergone hepatic resection.

Methods: We searched PubMed, Web of Science, Embase, China National Knowledge Infrastructure, Wanfang Data, and VIP databases for studies reporting the primary outcomes of VTE incidence, bleeding events, and all-cause mortality from January 2000 to July 2022.

Results: Ten studies involving 4318 participants who had undergone hepatic resection were included: 6 in Asians and 4 in Caucasians. A significant difference in VTE incidence was observed between the experimental and control groups (odds ratio [OR] = 0.39, 95% confidence interval [CI]: 0.20, 0.74, $P = .004$). No significant difference in bleeding events and all-cause mortality was observed (OR = 1.29, 95% CI: 0.80, 2.09, $P = .30$; OR = 0.71, 95% CI: 0.36, 1.42, $P = .33$, respectively). Subgroup analyses stratified by ethnicity showed a significant difference in the incidence of VTE in Asians (OR = 0.16, 95% CI: 0.06, 0.39, $P < .0001$), but not in Caucasians (OR = 0.69, 95% CI: 0.39, 1.23, $P = .21$). No significant differences in bleeding events were found between Asians (OR = 1.60, 95% CI: 0.48, 5.37, $P = .45$) and Caucasians (OR = 1.11, 95% CI: 0.58, 2.12, $P = .75$). The sensitivity analysis showed that Ejaz's study was the main source of heterogeneity, and when Ejaz's study was excluded, a significant difference in VTE incidence was found in Caucasians (OR = 0.58, 95% CI: 0.36, 0.93, $P = .02$).

Conclusion: This study's findings indicate that the application of UFH or LMWH for VTE prophylaxis after hepatic resection is efficacious and safe in Asians and Caucasians. It is necessary for Asians to receive drug prophylaxis for VTE after hepatic resection. This study can provide a reference for the development of guidelines in the future, especially regarding the pharmacological prevention of VTE in different ethnicities.

Abbreviations: CI = confidence interval, LMWH = low-molecular-weight heparin, NOS = Newcastle-Ottawa quality assessment scale, OR = odds ratio, UFH = unfractionated heparin, VTE = venous thromboembolism.

Keywords: all-cause mortality, bleeding, heparin, hepatic resection, VTE

1. Introduction

VTE which is characterized by deep venous thrombosis (DVT) or pulmonary thromboembolism, is a significant cause of morbidity and mortality in patients who have undergone open abdominal surgery.[1] The incidence of VTE is associated with increased age, obesity, malignancy, and extensive and prolonged resection. Patients undergoing hepatic resection often have most of the aforementioned risk factors and, therefore, have a higher incidence of VTE.[2,3] Currently, there is a lack of authoritative guidelines for VTE prophylaxis following hepatic resection. Previous studies have indicated that extended anticoagulation therapy after hepatic resection is both effective and safe.[4,5] However, some studies have

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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proposed different perspective.[3,6,7] Furthermore, a meta-analysis including 5 studies in which most patients were from the US and Europe, indicated that the application of perioperative chemical thromboprophylaxis reduces the incidence of VTE after hepatic resection without a significantly increased risk of bleeding, but a recent systematic review including 16 studies showed that the efficacy of VTE prophylaxis after hepatic resection has not been proven in Asian patients.[8] UFH and LMWH are recommended as VTE prophylaxis after major surgery.[9–11] Many studies have reported the efficacy and safety of UFH or LMWH for VTE prophylaxis after hepatic resection.[3,6,7,12–14] However, these results are controversial, particularly regarding the use of pharmacological prophylaxis for VTE after hepatic resection in Asian populations.[8,15] Additionally, 2 systematic reviews summarized the efficacy and safety of pharmacological prophylaxis for VTE after hepatic resection,[16,17] but both lacked a discussion of the difference in the pharmacological prophylaxis of VTE in different ethnicities. Therefore, we aimed to conduct a meta-analysis to quantitatively compare patients undergoing hepatic resection prophylaxis for VTE with UFH or LMWH among Asian and Caucasian patients.

2. Method

2.1. Ethics statements

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[18] The protocol for this meta-analysis was registered with PROSPERO (registration number: CRD42022349271, http://www.crd.york.ac.uk/PROSPERO/). This study was based on the published literature. Ethical approval and patient consent were not obtained.

2.2. Search strategy

Two researchers independently completed the literature search for this meta-analysis, and discrepancies were resolved through full discussion. Eligible studies were searched in PubMed, Embase, Web of Science, China National Knowledge Infrastructure, Wanfang Data, and VIP databases. The retrieval time limit was January 2000 to July 2022. The language used was limited to English and Chinese. The following search terms were used: (heparin OR UFH OR UFH OR low molecular weight heparin OR LMWH OR LMWH OR enoxaparin OR lovenox OR nadroparin) AND (venous thrombus OR venous thrombus embolism OR VTE OR deep vein thrombosis OR deep venous thrombosis (DVT) OR pulmonary embolism OR PE OR pulmonary thromboembolism OR PTE OR portal vein thrombosis OR PVT OR mesenteric venous thrombosis OR hemorrhage OR hemorrhagic complication OR thromboembolic complication OR bleeding) AND (hepatectomy OR hepatectomies OR liver resection OR hepatic resection OR hepatic craniectomy OR hemi-hepatectomy OR hepatolobectomy OR surgery for colorectal liver metastases OR hepatic metastases of colorectal).

2.3. Inclusion and exclusion criteria

The inclusion criteria were as follows:

(1) patients who had undergone hepatic resection;
(2) patients in an experimental group who were treated with UFH of LWMH for VTE prophylaxis after hepatic resection and, patients in a control group who were not treated with pharmacological prophylaxis (the control group could receive nothing or conventional therapy such as mechanical thromboprophylaxis);
(3) the outcomes of the study included at least 1 of the following: VTE, bleeding events, and all-cause mortality; and
(4) studies were cohort studies, case-control studies, randomized controlled clinical trials (RCTs), or quasi-experimental studies.

Exclusion criteria were as follows:

(1) case reports, reviews, editorials, animal studies, or republished literature;
(2) studies without a control group;
(3) studies in which data research could not be extracted or the full text was not available; and
(4) studies missing primary outcome.

2.4. Data extraction

Two researchers independently completed the data extraction process, and discrepancies were resolved through full discussion. The following data were extracted: the article title, first author, publication year, study design, patient ethnicity, intervention, patient characteristics, and outcomes.

2.5. Quality assessment

Two researchers independently performed the quality assessment of each study. The Cochrane risk-of-bias tool 2.0 was used to assess the risk of bias in RCTs and quasi-experimental studies.[19] The Newcastle-Ottawa Quality Assessment Scale (NOS) was used to assess the quality of the cohort and case-control studies in this meta-analysis.[20] The NOS has 3 domains: selection of study, comparability, and outcome evaluation, with 8 items and a total score of 9 points. Except for item 5, which counts as 2 points (1 point for controlling age confounding factors and 1 point for controlling other important confounding factors), all other items count as 1 point. Scores ≤ 3 are regarded as low-quality studies, scores between 4 and 6 are considered as medium-quality studies, and scores > 7 are regarded as high-quality studies.

2.6. Statistical analysis

Meta-analyses were conducted using RevMan5.3 software according to the Cochrane Manual for Systematic Evaluation of Interventions. The pooled effect size of the meta-analyses was assessed using the OR and 95% CI. I^2 statistics and the Cochran Q test were used to assess statistical heterogeneity. The Mantel–Haenszel method for the fixed-effects model was applied when no significant heterogeneity was detected ($I^2 < 50\%$ or P-value for heterogeneity > 0.1). The Der Simonian–Laird method for the random-effects model was used when significant heterogeneity was detected ($I^2 \geq 50\%$ or P-value for heterogeneity ≤ 0.1). However, if obvious variation in the included studies was found, a random effects model was used. Subgroup analyses of the Asian and Caucasian patients were performed. Sensitivity analyses were performed to evaluate the reliability of the results by excluding studies individually. The publication bias of the included studies was assessed using funnel plots. Statistical significance was set at $P < .05$.

3. Results

3.1. Literature search and study characteristics

The initial literature search yielded a total of 610 articles. After removing duplicates, 136 articles remained. After screening titles and abstracts, 450 articles were excluded. Then, 24 articles met our inclusion criteria and were eligible for full-text evaluation. Finally, a total of 10 studies were included in the

analysis.[3,5–7,12,21–25] Among these studies, 4 were in Chinese,[7,23–25] and 6 were in English.[3,5,6,12,21,22] The flow diagram is shown in Figure 1.

All the included studies were cohort studies. A total of 4318 patients underwent liver resection, of which 2551 and 1767 patients were in the experimental and control groups, respectively. The main characteristics of the 10 studies are summarized in Table 1. The NOS was used to evaluate the quality of the eligible cohort studies, and the scoring details are shown in Table 2.

3.2. VTE events

All studies reported the incidence of VTE events in 4318 pati ents,[3,5–7,12,21–25] including 2551 in the experimental group and 1767 in the control group. There was no significant heterogeneity between the studies (I^2 = 44%, P = .08); however, the variation in the included studies was significant, and the random-effects model was used for this analysis. The results showed a significant difference in the overall rate of VTE between the experimental and control groups (OR = 0.39, 95% CI: 0.20, 0.74, P = .004) (Fig. 2).

3.3. Bleeding events

Seven studies reported the incidence of bleeding events in 3074 patients,[6,7,12,21,23–25] including 1709 in the experimental group and 1365 in the control group. There was no heterogeneity between the studies (I^2 = 0%, P = .68); however, the variation in the included studies was significant, and the random-effects model was used for this analysis. The results showed that there was no significant difference in the overall rate of bleeding events between the experimental and control groups (OR = 1.29, 95% CI: 0.80, 2.09, P = .30) (Fig. 3).

3.4. All-cause mortality

Five studies reported all-cause mortality,[3,6,7,12,22] 1 of which only reported the total number of deaths in both groups,[6] and 4 studies included a total of 1484 patients in this meta-analysis,[3,7,12,22] including 874 in the experimental group and 610 in the control group. There was no heterogeneity between the studies (I^2 = 0%, P = .48) but the variation in the included studies was significant, and the random-effects model was used for this analysis. The results showed that there was no significant difference in all-cause mortality between the experimental and control groups (OR = 0.71, 95% CI: 0.36, 1.42, P = .33) (Fig. 4).

3.5. Subgroup analyses and sensitivity analysis

Using a random-effects model, subgroup analyses stratified by ethnicity showed a significant difference in the overall rate of VTE between the experimental and control groups in the Asian subgroup that included 6 studies[5,7,12,23–25] (OR = 0.16, 95% CI: 0.06,

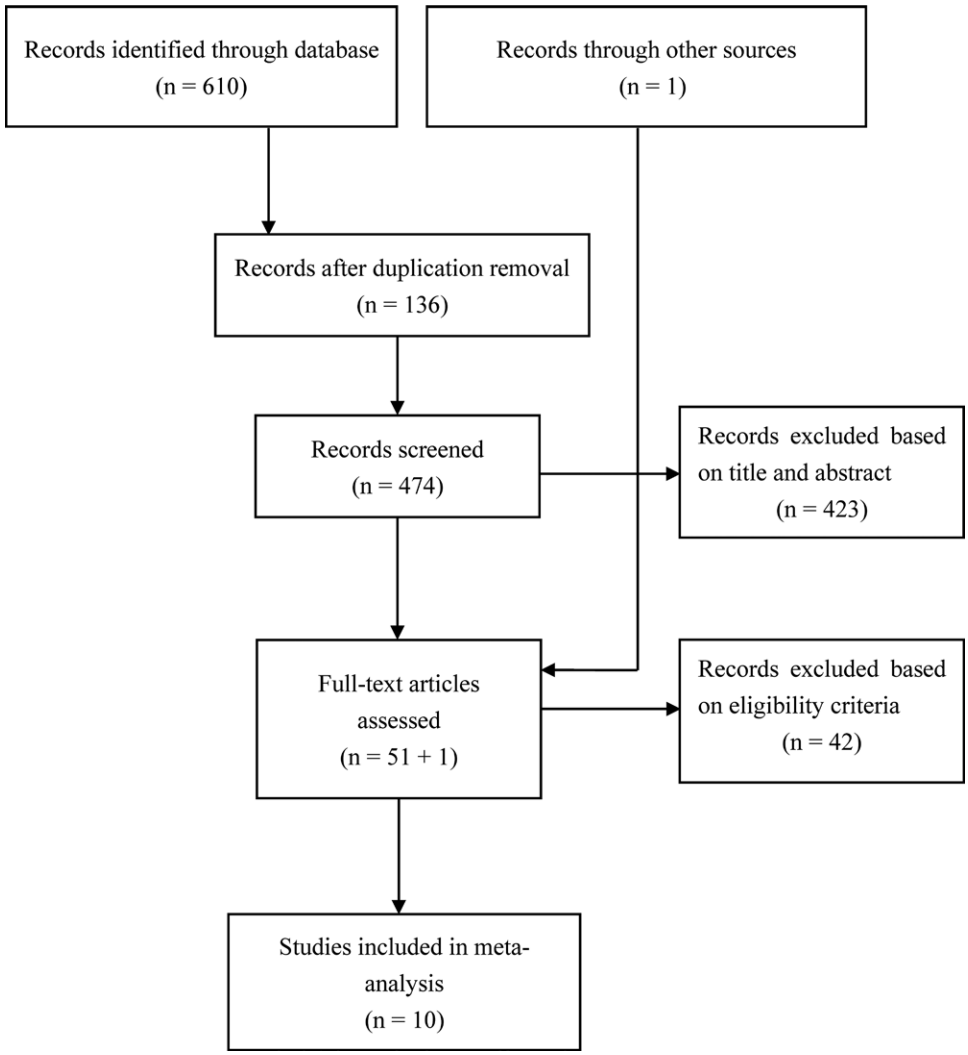

Figure 1. The flow diagram of the literature search.

Table 1

Characteristics of included studies.

Study	Ethnicity	Study design	Age, year		Sample size	Intervention		Duration of intervention	Outcomes
			Experimental	Control		Experimental	Control		
Meng 2006[21]	Asian	Retrospective study	49.4[a]	56.8[a]	30	LMWH	CT	7 days (1–7 d after surgery)	①②
Vivarelli 2010[18]	Caucasian	Retrospective study	65.0 ± 9.8[b]	63.0 ± 9.5[b]	229	Nadroparin calcium or Enoxaparin sodium	CT	≥7 days (From day after surgery until normal activity)	①②
Reddy 2011[19]	Caucasian	Retrospective study	58 (20) [c]	58 (21) [c]	419	UFH or Enoxaparin	CT	Not mentioned	①③
Ejaz 2014[3]	Caucasian	Retrospective study	58 (50–68) [c]	57 (47–64) [c]	592	LMWH or Levonox	CT	Not mentioned	①③
Nathan 2014[6]	Caucasian	Prospective study	60 (50–70) [c]		2147	UFH or LMWH	CT	Median 5 or 6 days	①②③
Yamashita 2014[12]	Asian	Retrospective study	69 ± 10[b]	65 ± 12[b]	281	Enoxaparin	CT	≤14 days (Within 24–36 h after surgery or 12 h after removal of epidural catheter)	①②③
Shan 2017[20]	Asian	Retrospective study	58.71 ± 8.60[b]	56.79 ± 10.9[b]	105	LMWH	CT	6 days (2–7 d after surgery)	①②
Wang 2018[5]	Asian	Prospective study	58.52 ± 8.71[b]	57.69 ± 8.38[b]	233	LMWH	CT	6 days (2–7 d after surgery)	①
Ma 2021[7]	Asian	Prospective study	52.7 ± 12.9[b]	50.9 ± 13.0[b]	192	Enoxaparin sodium	CT	Median 19 days	①②③
Xu 2021[22]	Asian	Prospective study	50.67 ± 5.31[b]	52.44 ± 6.10[b]	90	UFH or Enoxaparin	CT	Average 10.37 ± 2.71 days	①②

Table 2

Quality assessment of included studies.

Study	Selection				Comparability	Outcome			Score
	1	2	3	4	5	6	7	8	
Meng 2006[21]	*	*	*	*				*	5
Vivarelli 2010[18]	*	*	*	*	**	*	*	*	9
Reddy 2011[19]	*	*	*	*	**	*	*	*	9
Ejaz 2014[3]	*	*	*		*	*	*	*	7
Nathan 2014[6]	*	*	*		*	*		*	6
Yamashita 2014[12]	*	*	*	*	**	*		*	8
Shan 2017[20]	*	*	*	*	**	*		*	8
Wang 2018[5]	*	*	*	*	**	*		*	8
Ma 2021[7]	*	*	*	*	**		*	*	8
Xu 2021[22]	*	*	*	*	*	*		*	7

0.39, $P < .0001$), but no significant difference was observed in the Caucasian subgroup that included 4 studies[3,6,21,22] (OR = 0.69, 95% CI: 0.39, 1.23, $P = .21$) (Fig. 5). No significant difference in the incidence of bleeding events with UFH or LMWH for VTE prophylaxis after hepatic resection was found in the Asian subgroup that included 5 studies[7,12,23–25] (OR = 1.60, 95% CI: 0.48, 5.37, $P = .45$) or the Caucasian subgroup that included 2 studies[6,21] (OR = 1.11, 95% CI: 0.58, 2.12, $P = .75$) (Fig. 6).

Using a random-effects model, sensitivity analysis showed a significant difference in the VTE incidence between the experimental and control groups in Caucasians when Ejaz's study[3] was excluded (OR = 0.58, 95% CI: 0.36, 0.93, $P = .02$).

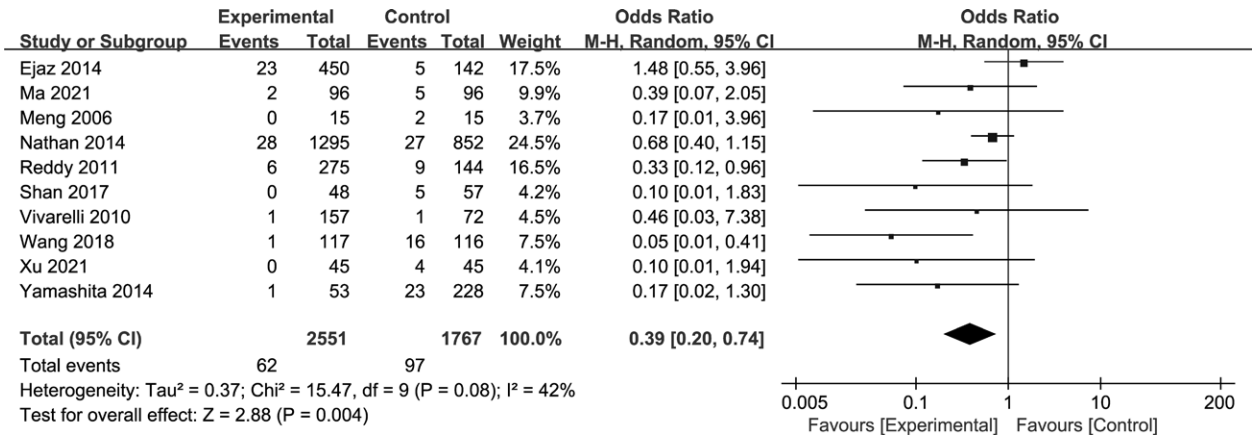

Figure 2. Forest plot comparing the efficacy of the experimental group vs. the control group on VTE events. VTE = venous thromboembolism.

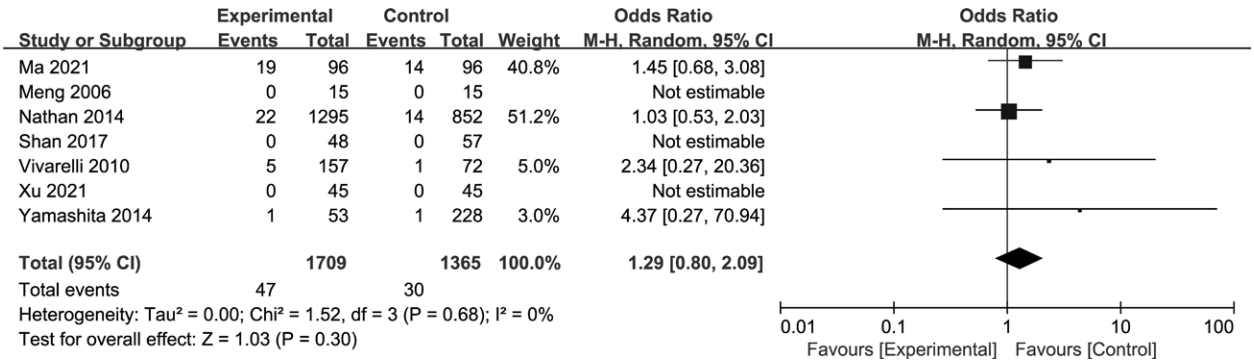

Figure 3. Forest plot comparing the safety of the experimental group vs. the control group on bleeding events.

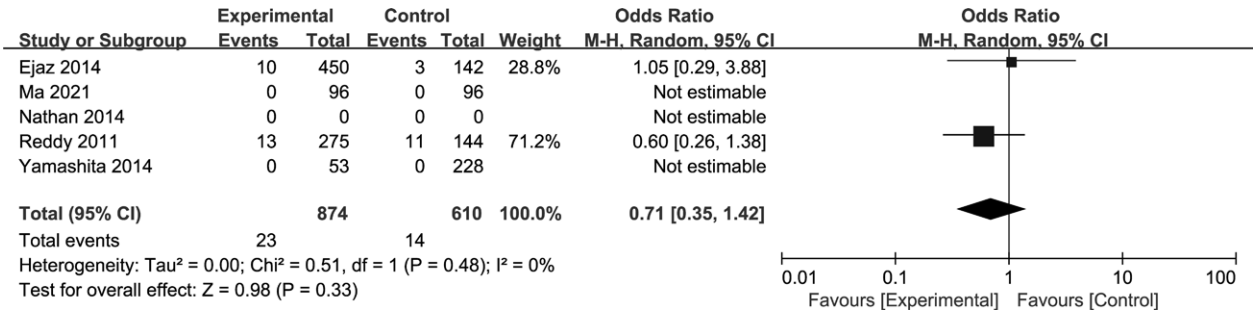

Figure 4. Forest plot comparing the safety of the experimental group vs. the control group on all-cause mortality.

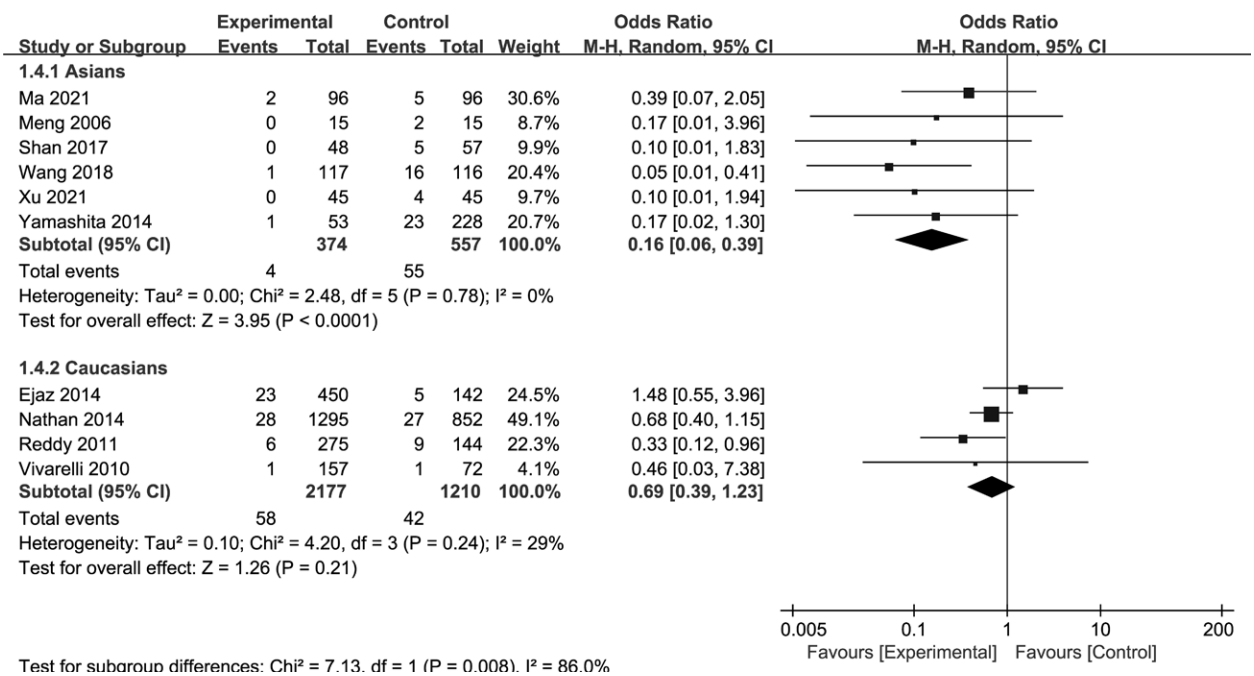

Figure 5. Forest plot of subgroup analysis comparing the efficacy of the experimental group vs. the control group on VTE events in Asians and Caucasians. VTE = venous thromboembolism.

3.6. Publication bias

The asymmetric funnel plot for the outcome of VTE suggested publication bias in this meta-analysis (Fig. 7). No significant publication bias was found for bleeding or all-cause mortality events.

4. Discussion

Our study's findings showed that the application of UFH and LMWH for VTE prophylaxis after hepatic resection was efficacious and safe, which is in line with findings of previous meta-analyses. Interestingly, a significant difference in the incidence of VTE was only observed in Asians in the subgroup analysis.[5,7,12,23–25] In 4 cohort studies of Caucasians,[3,6,21,22] no significant difference was found in the incidence of VTE. There was no significant difference in the incidence of bleeding events between UFH and LMWH for VTE prophylaxis after hepatic resection in Asian or Caucasian patients. Limited by the number of included studies, subgroup analyses of all-cause mortality

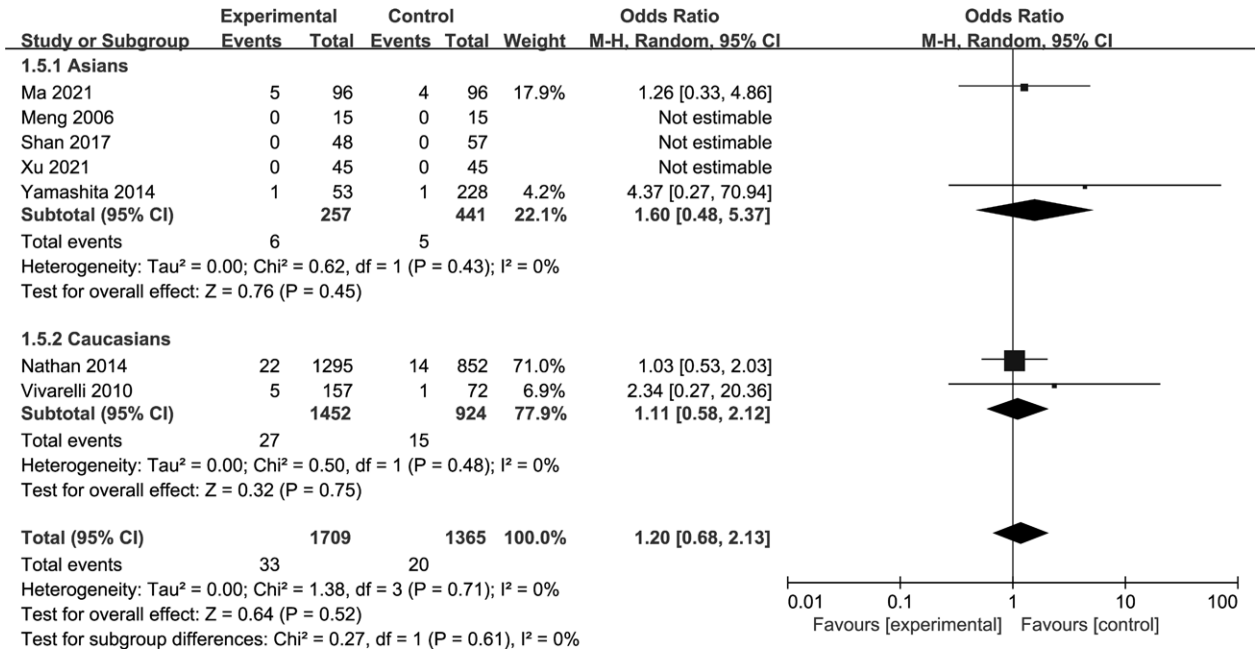

Figure 6. Forest plot of subgroup analysis comparing the safety of the experimental group vs. the control group on bleeding events in Asians and Caucasians.

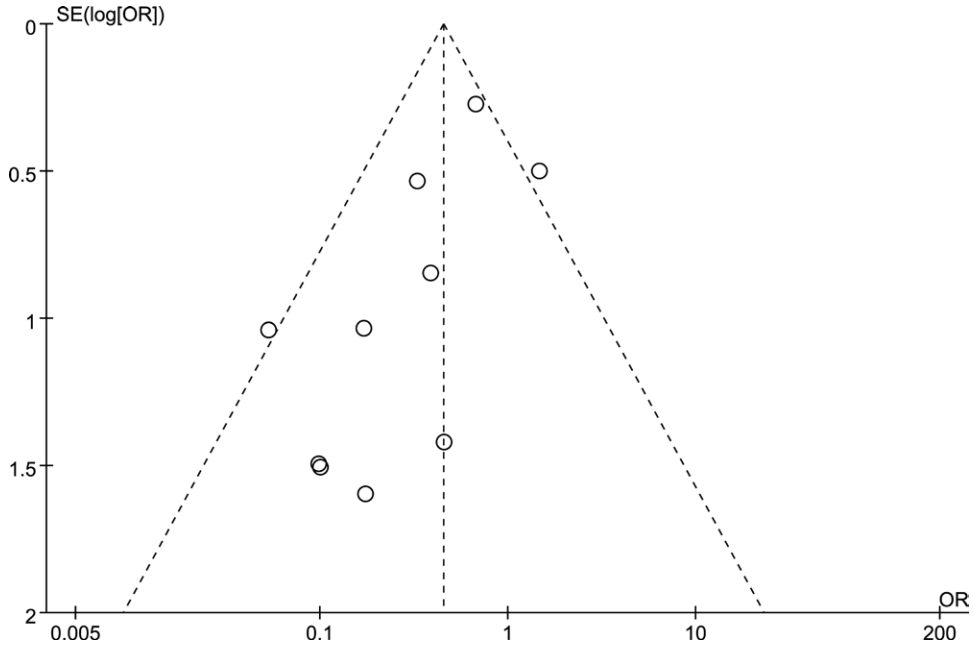

Figure 7. Funnel plot for the outcome of VTE events. VTE = venous thromboembolism.

with UFH or LMWH for VTE prophylaxis after hepatic resection in Asian or Caucasian patients were not performed. There could be a higher incidence of VTE after surgery in Caucasians than in Asians, and Asians with a low incidence of VTE after surgery often do not receive post-operative VTE prophylaxis.[26,27] Previous findings suggested that routine pharmacologic prevention of VTE may not be necessary in Asians as a result of the 3 times higher risk-benefit ratio of prophylaxis than in Caucasians.[14] Moreover, the safety and effectiveness of chemical thromboprophylaxis against VTE after liver resection are still controversial, especially in Asians, and it is important to build evidence to classify risks individually according to each race.[8] Asians have different risk factors, treatment patterns, and a higher risk of all-cause mortality than patients from other countries.[28] Recently, the incidence of VTE across Asia has been increasing, which may be attributable to the aging population, dietary changes, and increasing incidence of obesity and diabetes.[15] This fact reminds us that it is necessary to pay attention to the prevention of VTE after hepatectomy in the Asian population. However, our meta-analysis indicated that UFH and LMWH are effective and safe for VTE prophylaxis after hepatectomy in Asians. These findings may provide a reference for the development of guidelines for pharmacological prevention of VTE after hepatic resection in different ethnicities in the future.

To determine the reason for the inefficacy of UFH or LMWH for VTE prophylaxis after hepatic resection in Caucasians, we performed a sensitivity analysis on the subgroup of Caucasians.

When Ejaz's study was excluded, a significant difference was found in the incidence of VTE. After reviewing this article, we concluded that this difference may be attributed to the selection of participants, as the history of VTE (29/454 in the experimental group vs. 1/145 in the control group) was significantly different between the experimental and control groups. A previous study indicated that the VTE incidence was significantly associated with a history of VTE in patients,[29,30] and confounding factors influenced the results of this study. To our best knowledge, this study is the first meta-analysis to quantitatively assess the efficacy and safety of UFH and LMWH for VTE prophylaxis after hepatic resection. This study is also the first meta-analysis to study the efficacy and safety of UFH and LMWH in the prevention of VTE after liver resection in different ethnicities.

Nevertheless, this meta-analysis has several limitations. First, no RCTs were included, which increased the risk of bias in the meta-analysis. Second, the studies included patients with many risk factors for VTE, such as age, operative time, history of VTE, and malignancies. Due to insufficient study data, clinical conditions and various risk factors of the patients were not included, which may have influenced our results. Third, UFH and LMWH are similar but different anticoagulants in terms of the efficacy and safety in VTE.[31] The interventions of 3 studies included 2 drugs (used single or sequential but not simultaneously), and a direct comparison of the 2 similar and different anticoagulants (UFH vs. LMWH) for VTE prophylaxis after hepatic resection is lacking. Fourth, the funnel plot indicated a possible publication bias, which may have overestimated the efficacy of the 2 anticoagulants. Hence, more large-scale, high-quality studies are still necessary to confirm the efficacy and safety of UFH or LMWH for VTE prophylaxis after hepatic resection.

In general, our meta-analysis indicated that the application of UFH or LMWH for VTE prophylaxis after hepatic resection was also efficacious and safe in Asians, as in Caucasians. In the future, it may be necessary to use UFH or LMWH to prevent VTE in Asian patients after hepatectomy. Although this meta-analysis has some limitations that cannot be resolved, the results are reliable. Larger sample sizes and high-quality RCTs are needed to confirm these results. Given the lack of guidelines for pharmacological prevention of VTE after hepatic resection, we hope this meta-analysis can provide a reference for developing guidelines, especially regarding the use of pharmacological prevention of VTE in different ethnicities.

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