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META ANALYSIS

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# The efficacy of low molecular weight heparin in severe acute pancreatitis: A systematic review and meta-analysis of randomized controlled trials

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**Objective:** The effects of low molecular weight heparin (LMWH) on severe acute pancreatitis (SAP) have been controversial. We aimed to evaluate the efficacy of LMWH on prognosis of SAP by systematic review and meta-analysis.

**Methods:** We searched relevant studies published up to March 2019 in five databases (MEDLINE/PubMed, EMBASE, the Cochrane Central Register of Controlled Trials in Cochrane Library, China National Knowledge Infrastructure, and the Chinese Journal of Science and Technology of VIP database).

**Results:** Sixteen randomized controlled trials with 1625 patients were included in the final analysis. Most studies were from China. In analysis of laboratory parameters and clinical scores, SAP patients receiving LMWH treatment had lower white blood cell counts, C-reactive protein level, Acute Physiology and Chronic Health Evaluation II score, and computed tomography severity index. In clinical outcomes, SAP patients who received LMWH treatment had shorter hospital stay (pooled mean difference [95% confidence interval; CI] −8.79 [−11.18, −6.40], $P < .01$), lower mortality (pooled risk ratio [RR] [95% CI] 0.33 [0.24-0.44], $P < .01$), lower incidences of multiple organ failure (pooled RR [95% CI] 0.34 [0.23-0.52], $P < .01$), pancreatic pseudocyst (pooled RR [95% CI] 0.49 [0.27-0.90], $P = .02$), and operation rate (pooled RR [95% CI] 0.39 [0.31-0.50], $P < .01$).

**Conclusions:** LMWH could improve the prognosis of SAP, and has a potential role in reducing hospital stay, mortality, incidences of multiple organ failure, pancreatic pseudocyst, and operation rate.

KEYWORDS
low molecular weight heparin, meta-analysis, prognosis, severe acute pancreatitis

## 1 | INTRODUCTION

Acute pancreatitis (AP) is an inflammatory disease of the pancreas with various clinical manifestations, and its incidence has been growing in recent years due to an increase in hypertriglyceridemia.[1,2] Severe acute pancreatitis (SAP) is usually complicated with systemic inflammation reaction syndrome and persistent organ failure, which has higher mortality than mild acute pancreatitis and moderately severe acute pancreatitis.[3] Coagulation system could be activated by systemic inflammatory cascade reaction, thus induces microcirculation disturbance and aggravating pancreatic tissue injury.[4] Moreover, systemic microcirculation disturbance can induce the development of

multiple organ failure (MOF), increasing the mortality of necrotizing pancreatitis up to 43%.[5] Therefore, coagulation system activation plays an important role in the pathogenesis of SAP, and coagulation dysfunction is a deteriorating factor in the prognosis of SAP.

Low molecular weight heparin (LMWH), an antithrombin agent, can inhibit inflammatory cascade by reducing the release of cytokines and inflammatory mediators including tumor necrosis factor-α, interleukin-1β, and interleukin-6,[6] thereby improving microcirculation and alleviating histological injury of pancreas.[7] It has been demonstrated that LMWH could decrease the incidence of pancreatic encephalopathy and improve the survival of SAP.[8] Moreover, LMWH combined with intensive insulin therapy could markedly shorten the intestinal recovery time and length of hospital stay, and reduce the incidence of MOF.[9] However, Tozlu et al reported that LMWH could not significantly reduce the operation rate and mortality in SAP.[10] Therefore, it is still debated whether LMWH is beneficial to the prognosis of SAP. Meanwhile, most of the clinical studies were single-center, small-sample studies, and high-quality investigations are lacking.

With the aim of evaluating the efficacy of LMWH on SAP, we qualitatively and quantitatively reviewed all of the relevant literatures published in English and Chinese regarding the LMWH treatment on SAP. Laboratory parameters, clinical scores, and outcomes were involved in the analysis.

## 2 | MATERIALS AND METHODS

### 2.1 | Literature search

A literature search was conducted on the major international and Chinese literature databases including PubMed, MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials in the Cochrane Library, China National Knowledge Infrastructure (CNKI), and the Chinese Journal of Science and Technology of VIP database (VIP) covering all articles published up to March 2019 without language restrictions. We used a mixture of free text and index terms to maximize retrieval of potentially relevant studies. The following terms were used for the MEDLINE/PubMed search: ("heparin" [MeSH Terms] OR "heparin, low-molecular-weight" [MeSH Terms] OR "low-molecular-weight heparin" [All Fields]) AND ("pancreatitis" [MeSH Terms] OR "acute pancreatitis" [All Fields] OR "necrotizing pancreatitis" [All Fields] OR "acute severe pancreatitis" [All Fields]). The search terms used in EMBASE were ("heparin"/exp OR "low molecular weight heparin") AND ("acute pancreatitis"/exp OR "acute pancreatitis"). The search terms used in Cochrane Library were: "low-molecular-weight heparin" AND "acute pancreatitis." The terms and concepts searched in CNKI and VIP included: ("heparin" OR "low-molecular-weight heparin") AND ("acute pancreatitis" OR "acute severe pancreatitis"). Manual retrieval of references from potentially relevant literatures was also performed to screen any additional studies which might have been missed.

### 2.2 | Study selection

The inclusion criteria of the studies were: (a) randomized controlled trial (RCT); (b) studies that investigated the efficacy of LMWH on SAP, and SAP was defined as AP complicated with organ failure and/or local complications according to the established guidelines;[11-14] (c) adult participants aged 18 years or older; (d) control group received conventional treatment, which included fluid resuscitation, administration of trypsin inhibitor, proton pump inhibitors, antibiotics, and symptomatic treatment, etc, while the experimental group received LMWH treatment with conventional treatment; (e) studies that clearly described dosage and course of LMWH treatment; (f) the results of study included any of the following aspects: the level of laboratory parameters including white blood cell (WBC) count, C-reactive protein (CRP) or procalcitonin (PCT), prothrombin time (PT), activated partial thromboplastin time (APTT) or fibrinogen (FIB), clinical scores including Acute Physiology and Chronic Health Evaluation (APACHE) II score or computed tomography severity index (CTSI), and clinical outcomes including length of hospital stay, mortality, incidences of MOF, pancreatic pseudocyst, infected necrosis, or operation rate. The primary outcomes were mortality and incidence of MOF. The secondary outcomes included length of hospital stay, incidences of pancreatic pseudocyst, infected necrosis, and operation rate.

The exclusion criteria were: (a) patients who did not meet the diagnostic criteria of SAP; (b) patients who were allergic to LMWH, being pregnant or lactating, complicated by coagulation disorders, or undergoing hemodialysis; (c) studies without primary data; (d) studies did not provide sufficient data for review; and (e) animal studies, reviews, meta-analyses, case reports/case series, letters, comments and those without a control group. For duplicated studies, only that with the largest sample size and most recent data was included in the analysis.

### 2.3 | Study quality assessment

The quality of the studies was independently evaluated by two reviewers (Tang L and Guo Y) with the Cochrane Collaboration's tool for assessing the risk of bias.[15] The following items were taken into account: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and any other risk of bias.

### 2.4 | Data extraction

All of the included studies were screened by titles and abstracts first, and then examined in detail. Data from relevant articles were independently extracted by two reviewers (Qiu Q and Li GJ). Disagreement was resolved by discussion or in consultation with a third author (Tang L). The first author, year of publication, country, the amount of patients enrolled in the study, male to female ratio, therapeutic regime, dosage and course of LMWH therapy, laboratory parameters, APACHE II score or CTSI after treatment, and clinical outcomes of

both LMWH treatment and conventional treatment groups were extracted from each study.

### 2.5 | Statistical analysis

Statistical analysis and graphs were performed using the Review Manager (RevMan) software package version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Continuous variables were described as mean ± standard deviation, while dichotomous variables were described as numbers and percentages or frequencies. We assessed heterogeneity for these RCTs using $\chi^2$ test and $I^2$ statistics. Low heterogeneity was qualified as $P \geq .10$ and $I^2 < 50\%$, while high heterogeneity was regarded as $P < .10$ and $I^2 \geq 50\%$, by using the fixed-effect model. If statistical heterogeneity was not acceptable, a subgroup analysis according to the course of LMWH treatment was performed to test the source of heterogeneity. We calculated the mean difference (MD) and 95% confidence interval (CI) for continuous data, while the risk ratio (RR) and 95% CI were calculated for dichotomous data. The possibility of publication bias was evaluated using funnel plot when not less than 10 RCTs were enrolled. $P < 0.05$ was considered statistically significant.

## 3 | RESULTS

### 3.1 | Characteristics of the included studies

A flow diagram of the review process was shown in Figure 1. A total of 1086 studies were initially identified on the efficacy of LMWH on SAP. Two hundred and seventeen duplicated articles and an additional 853 articles were excluded because they did not meet the selection criteria. Finally, 16 RCTs were included in the systematic review.[9,10,16-29] Three RCTs were from in English,[9,10,29] while the remaining articles were in Chinese. Five studies[17,19,20,26,28] defined SAP as AP with any of the following conditions: organ failure, local complications such as abscess, pseudocyst or necrosis, Ranson score ≥ 3, APACHE II score ≥ 8, and CT grade D or E according to the *Practical guidelines for the management of acute pancreatitis in China (draft)* in 2004.[11] Seven studies[16,21-25,27] defined SAP as AP with persistent organ failure according to the *Practical guidelines for management of acute pancreatitis in China (Shanghai, 2013).*[12] Three studies[9,18,29] defined SAP as AP with organ failure and/or local complications according to the Atlanta classification of acute pancreatitis in 1992.[13] One study[10] defined SAP as AP with persistent organ failure according to the Atlanta classification of acute pancreatitis revised in 2012.[14] Laboratory parameters and clinical scores were assessed by the end of LMWH treatment on the 7th or 14th day after admission, and clinical outcomes were assessed before the patients were discharged from the hospital or their death.

### 3.2 | Characteristics of included studies and quality assessment

The characteristics of the included RCTs were shown in Table 1. A total of 1625 patients were enrolled in this systematic review and meta-analysis, including 820 patients received LMWH treatment and 805 patients received conventional treatment, respectively. Fifteen RCTs were conducted in China, while one RCT[10] was performed in Turkey. LMWH was administered by subcutaneous injection in all included RCTs. The dosage of LMWH varied slightly among these RCTs, which was close to or equal to 5000 U every 12 h. LMWH treatment lasted for 14 days in 11 RCTs[9,17-22,24,26-28] and 7 days in five RCTs.[10,16,23,25,29] The ratio of male to female was 1.35:1 (900 males and 665 females). However, the data on gender was not mentioned in one RCT[28] (Table 1). We summarized the laboratory

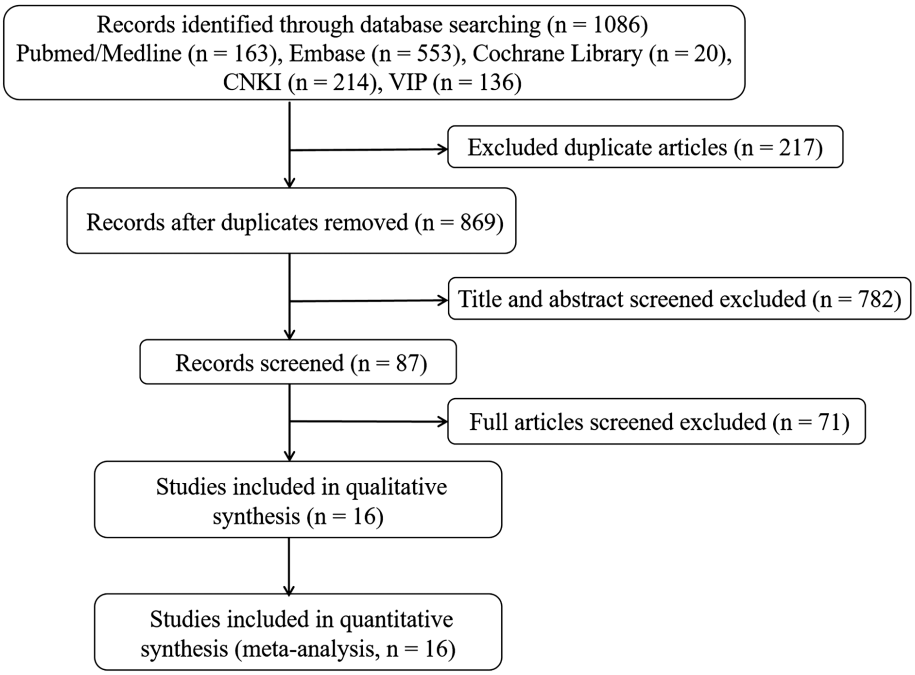


**FIGURE 1** Study flow diagram. CNKI, China National Knowledge Infrastructure; VIP, Chinese Journal of Science and Technology of VIP database

**TABLE 1** Characteristics of studies included in the systemic review and meta-analysis

| First author (publication year) | Country | AP | APACHE II score before treatment, mean ± SD (LT vs CT) | Participants, n (LT/CT) | M/F, n (LT vs CT) | Mean age, years (total group or LT vs CT) | Dosage and frequency of LMWH | Course of LMWH treatment (d) | Laboratory parameters | Clinical scores | Clinical outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Li[18] (2003) | China | SAP | 11.6 ± 3.6 vs 11.5 ± 3.4 | 77/65 | 49/28 vs 33/32 | Not mentioned | 5000 U every 12 h | 14 | — | — | ①③④⑤⑥ |
| Lu[29] (2009) | China | SAP | 11.6 ± 3.6 vs 11.5 ± 3.4 | 135/130 | 84/51 vs 72/58 | 56.0 vs 54.0* | 100 μg/kg per day | 7 | ④⑤⑥ | ①② | ①②③⑥ |
| Yuan[26] (2009) | China | SAP | 13.8 ± 4.8 vs 13.9 ± 5.0 | 15/19 | 10/5 vs 13/6 | 48 ± 9 vs 46 ± 8 | 3000 U every 12 h | 14 | — | ① | ①②④ |
| Zhang[28] (2012) | China | SAP | Not mentioned | 30/30 | Not mentioned | 45.4 ± 12.4 | 40 mg every 12 h | 14 | ④⑥ | — | ②③④ |
| Huang[17] (2013) | China | SAP | Not mentioned | 40/40 | 26/14 vs 25/15 | 48.7 ± 9.2 vs 46.8 ± 9.2 | 4000 U every 12 h | 14 | ④ | — | ①②⑥ |
| Du[9] (2014) | China | SAP | 9.1 ± 3.3 vs 9.2 ± 3.4 | 34/33 | 17/17 vs 16/17 | 50.7 ± 9.6 vs 49.5 ± 9.4 | 5000 U every 12 h | 14 | ①④ | — | ①②③⑥ |
| Yan[25] (2015) | China | SAP | 11.6 ± 3.6 vs 11.5 ± 3.4 | 140/140 | 89/51 vs 77/63 | 48 ± 3 vs 46 ± 2 | 5000 U every 24 h | 7 | ④⑤⑥ | ①② | ①②③⑥ |
| Li[19] (2016) | China | SAP | Not mentioned | 19/21 | 12/7 vs 15/6 | 41.5 ± 13.5 vs 38.5 ± 12.5 | 100 mg/kg every 12 h | 14 | ③④⑥ | — | ③④ |
| Liu[20] (2016) | China | SAP | 11.5 ± 3.2 vs 11.2 ± 3.6 | 35/35 | 21/14 vs 24/11 | 43.5 ± 12.7 vs 44.2 ± 15.1 | 5000 U every 12 h | 14 | — | — | ①③④⑤⑥ |
| Ma[21] (2016) | China | SAP | Not mentioned | 47/46 | 24/23 vs 23/23 | 48.1 ± 6.1 vs 46.3 ± 6.1 | 5000 U every 12 h | 14 | ①② | ① | ②⑥ |
| Zhang[27] (2017) | China | HLSAP | Not mentioned | 42/42 | 23/19 vs 24/18 | 37.9 ± 2.8 vs 37.2 ± 2.3 | 5000 U every 12 h | 14 | — | — | ① |
| Hu[16] (2018) | China | SAP | 16.0 ± 4.3 vs 16.1 ± 4.4 | 34/32 | 19/15 vs 18/14 | 44.9 ± 6.9 vs 45.0 ± 7.1 | 0.01 mL/kg every 12 h | 7 | ①② | ① | - |
| Ou[22] (2018) | China | SAP | 14.2 ± 1.4 vs 14.4 ± 1.7 | 54/54 | 34/20 vs 32/22 | 43.3 ± 9.7 vs 42.1 ± 10.5 | 5000 U every 12 h | 14 | — | ①② | ①④ |
| Wu[23] (2018) | China | SAP | 12.4 ± 3.6 vs 13.2 ± 3.2 | 28/28 | 16/12 vs 17/11 | 47.8 ± 9.4 vs 48.3 ± 9.7 | 4000 U every 24 h | 7 | ④⑤⑥ | — | ② |
| Xu[24] (2018) | China | SAP | Not mentioned | 40/40 | 21/19 vs 20/20 | 48.1 ± 6.0 vs 46.3 ± 6.2 | 0.01 mL/kg every 12 h | 14 | ①② | ① | ②⑥ |
| Tozlu[10] (2019) | Turkey | SAP | Not mentioned | 50/50 | 22/28 vs 24/26 | 51 ± 16 vs 52 ± 20 | 1 mg/kg twice per day | 7 | — | — | ①②③④ |

*Median value. Abbreviations: AP, acute pancreatitis; APACHE, Acute Physiology and Chronic Health Evaluation; APTT, activated partial thromboplastin time; CRP, C-reactive protein; CT, conventional treatment; CTSI, computed tomography severity index; FIB, fibrinogen; HLSAP, hyperlipidemic severe acute pancreatitis; LMWH, low molecular weight heparin; LT, LMWH treatment; M/F, male/female; MAP, mild acute pancreatitis; MOF, multiple organ failure; PCT, procalcitonin; PT, prothrombin time; SAP, severe acute pancreatitis; SD, standard deviation; WBC, white blood cell.
Laboratory parameters: ① WBC; ② CRP; ③ PCT; ④ PT; ⑤ APTT; ⑥ FIB. Clinical scores: ① APACHE II; ② CTSI. Clinical outcome: ① Mean length of hospital stay; ② Mortality; ③ MOF occurrence rate; ④ Incidence of pancreatic pseudocyst; ⑤ Incidence of infected necrosis; ⑥ Operation rate.

parameters, clinical scores, and outcomes that were reported in the included RCTs in Table S1.

The quality assessment indicated that all of the included RCTs had no selection bias (random sequence generation), attrition bias, reporting bias and other bias. However, 10 (62.5%) RCTs had unclear risk in allocation concealment. Fourteen (87.5%) RCTs had unclear risk and one (6.3%) RCT had high risk in performance bias. Fifteen (93.8%) RCTs had unclear risk in detection bias. Quality assessment showed that the overall quality of included studies was acceptable. The bias of each study was shown in Figure 2.

### 3.3 | Effect of LMWH on inflammatory parameters in SAP

In the 16 RCTs for meta-analysis, four studies reported the WBC levels and three studies reported the CRP levels after LMWH treatment and conventional treatment. Heterogeneity in total group analysis of WBC was acceptable (heterogeneity: $P = .86$, $I^2 = 0\%$), and the level of WBC in LMWH treatment group was lower than that of conventional treatment group (pooled MDs [95% CI] = −1.81 [−2.01, −1.60], $P < .01$). However, significant heterogeneity was observed in total group analysis of CRP (heterogeneity: $P < .10$, $I^2 = 98\%$), and the level of CRP in LMWH treatment group was lower than that of conventional treatment group (pooled MDs [95% CI] = −14.99 [−26.52, −3.46], $P < .01$) (Figure 3). The course of treatment may influence the efficacy of LMWH; therefore, we conducted subgroup analysis according to the course of LMWH treatment. However, heterogeneity could still be observed in the subgroup analysis of CRP (Figure S1).

Besides WBC and CRP levels, only one study reported the PCT level after LMWH treatment and conventional treatment,[19] showing that the PCT level was significantly lower in LMWH treatment group than that of conventional treatment group (Table S1).

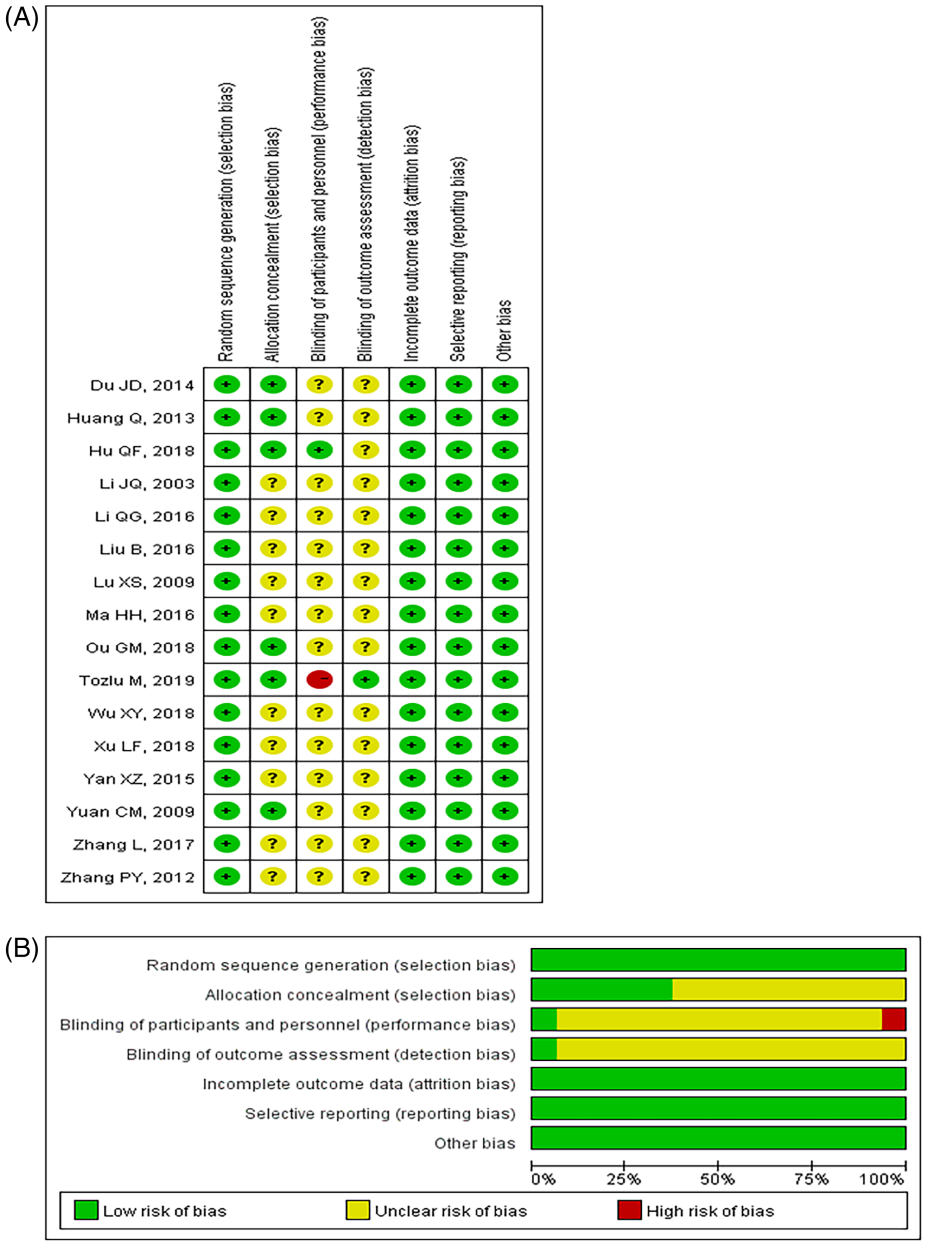


**FIGURE 2** Methodological quality of included studies according to the Cochrane Collaboration's tool for assessing risk of bias. A, Risk of bias summary. B, Risk of bias graph [Color figure can be viewed at wileyonlinelibrary.com]

### 3.4 | Effect of LMWH on coagulation parameters in SAP

The PT, APTT, and FIB levels were reported in seven, three, and five studies, respectively. Significant heterogeneity was observed in total group analyses (Figure 4). Although subgroup analyses of PT and FIB based on the course of LMWH treatment were conducted in these studies, heterogeneity could still be observed (Figures S2 and S3). Because the courses of LMWH treatment were 7 days in all the three included RCTs[23,25,29] that reported APTT, subgroup analysis of APTT was not conducted according to the course of LMWH treatment.

It was noted that PT and APTT levels in the LMWH treatment group was not significantly different from those in the conventional treatment group (pooled MD [95% CI] 0.73 [−0.26, 1.72], $P$ = .15; and pooled MD [95% CI] −0.92 [−3.36, 1.51], $P$ = .46, respectively). However, the FIB level in LMWH treatment group was significantly higher than that of the conventional treatment group (pooled MD [95% CI] 0.39 [0.04-0.74], $P$ = .03) (Figure 4).

### 3.5 | Effect of LMWH on clinical scores in SAP

The commonly used clinical scores, APACHE II score and CTSI, were reported in seven and three studies, respectively. Significant heterogeneity was observed in these studies (both $P$ < .10, $I^2$ = 96% for APACHE II score and 86% for CTSI; Figure 5). Moreover, heterogeneity existed in subgroup analyses of APACHE II score and CTSI according to the course of LMWH treatment (Figures S4 and S5). And we found that APACHE II score and CTSI were significantly lower in LMWH treatment group than in the conventional treatment group (pooled MD [95% CI] −2.51 [−3.67, −1.35] and − 1.92 [−2.65, −1.19], respectively, $P$ < .01) (Figure 5).

### 3.6 | Effect of LMWH on clinical outcomes in SAP

A total of 10 RCTs compared the length of hospital stay between LMWH treatment group (622 patients) and conventional treatment group (608 patients). Significant heterogeneity was observed in total group analysis ($P$ < .10, $I^2$ = 89%; Figure 6). The pooled mean hospital stay in LMWH treatment group was shorter than that of the conventional treatment group (pooled MD [95% CI] −8.79 [−11.18, −6.40], $P$ < .01) (Figure 6). Similarly, the course of LMWH treatment was an important factor influencing its efficacy. Thereby, subgroup analysis was conducted. Unfortunately, heterogeneity was still observed (Figure S6). The mean length of hospital stay in both 7-day and 14-day LMWH treatment subgroups was both shorter than those of the conventional treatment subgroups (Figure S6).

Ten RCTs including 1115 SAP patients investigated the mortality, and eight RCTs including 1024 patients investigated MOF. Seven RCTs including 554 patients reported the incidence of pancreatic pseudocyst, and two RCTs including 212 patients reported infected necrosis. Eight RCTs including 1077 patients investigated operation rate. No significant heterogeneity was observed in the pooled analysis of mortality ($P$ = .79, $I^2$ = 0%), incidences of MOF ($P$ = .88, $I^2$ = 0%), pancreatic pseudocyst ($P$ = .85, $I^2$ = 0%), infected necrosis ($P$ = .70, $I^2$ = 0%), and operation rate ($P$ = .99, $I^2$ = 0%) (Figure 7). Thus, subgroup analysis was not conducted. Compared with conventional treatment group, the pooled RR (95% CI) of mortality, incidences of MOF, pancreatic pseudocyst, infected necrosis, and operation rate in LMWH treatment group were 0.33 (0.24-0.44) ($P$ < .01), 0.34 (0.23-0.52) ($P$ < .01), 0.49 (0.27-0.90) ($P$ = .02), 0.34 (0.09-1.26) ($P$ = .11), and 0.39 (0.31-0.50) ($P$ < .01), respectively (Figure 7). Therefore, the clinical outcomes in LMWH treatment group were better than those of the conventional treatment group.

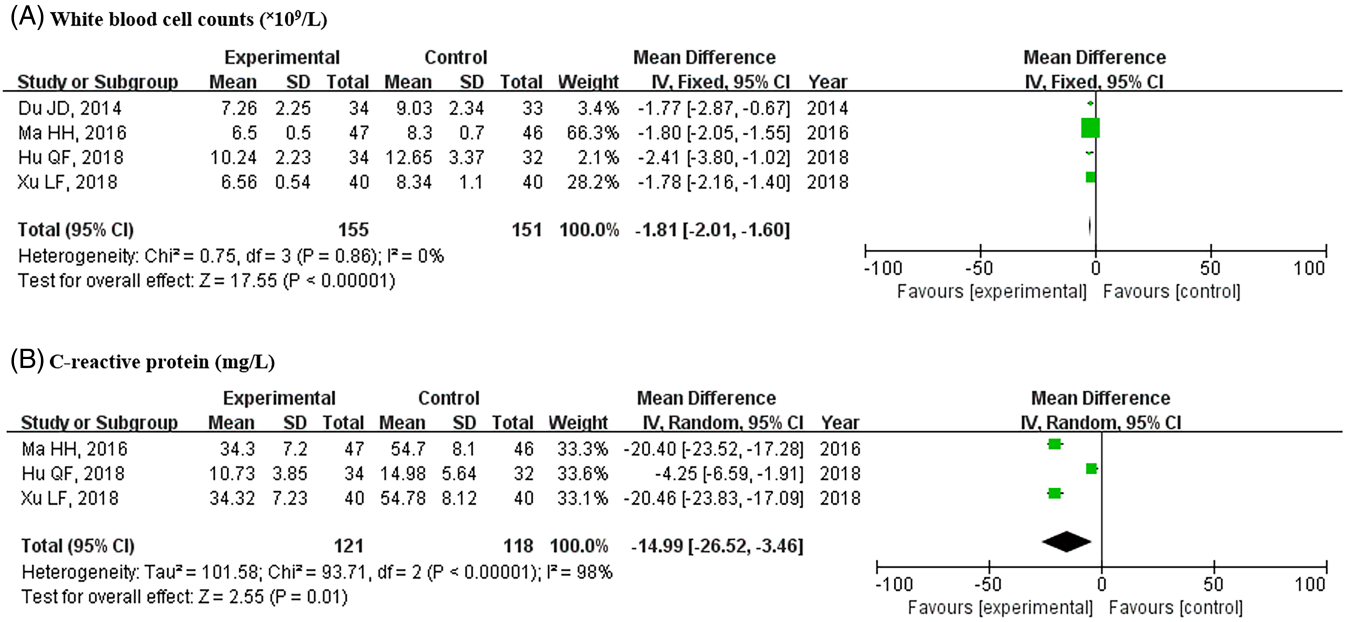


**FIGURE 3** Forest plot of meta-analyses of A, white blood cell count and B, C-reactive protein in low molecular weight heparin treatment group and conventional treatment group [Color figure can be viewed at wileyonlinelibrary.com]

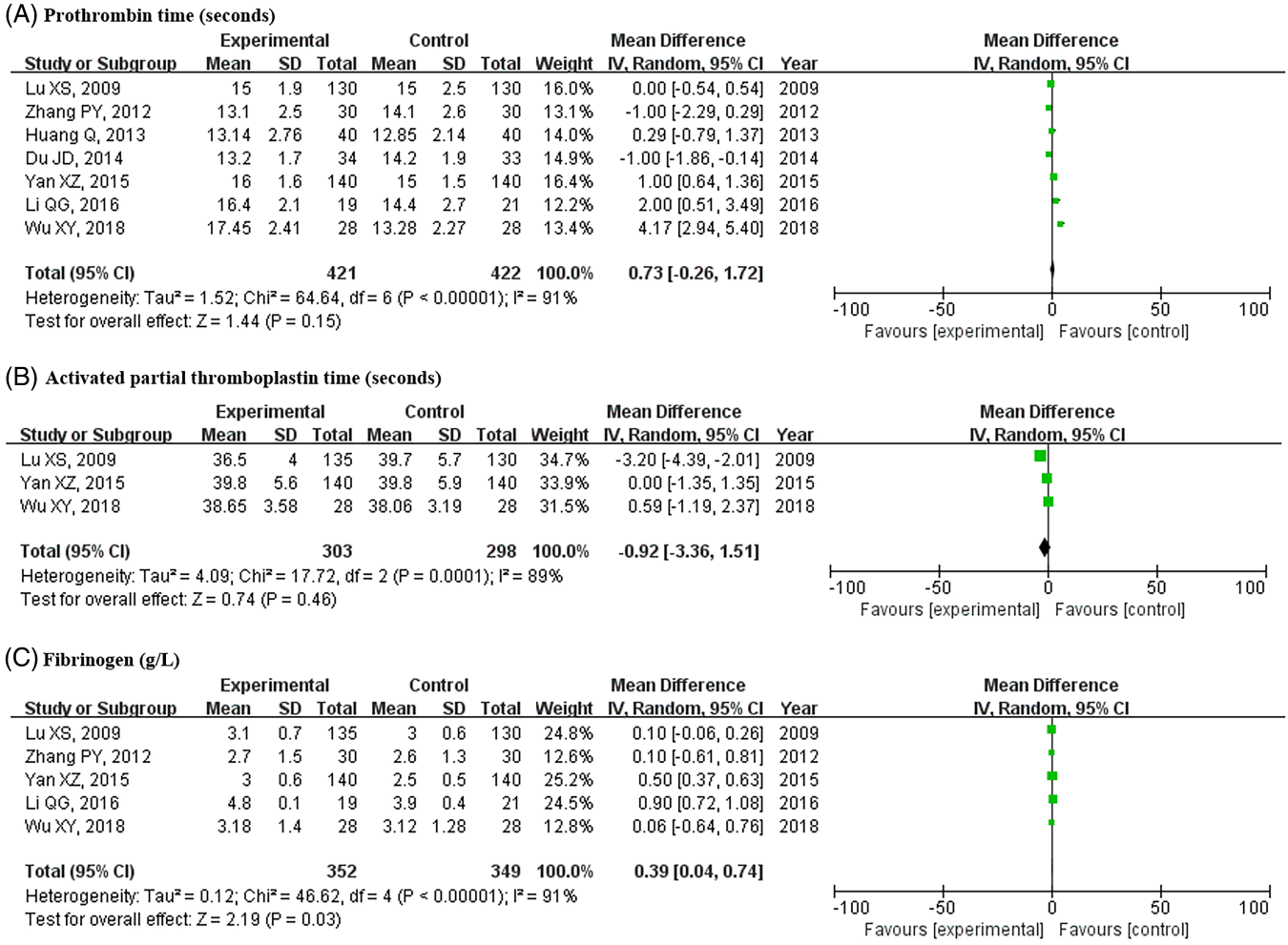


**FIGURE 4** Forest plot of meta-analyses of A, prothrombin time, B, activated partial thromboplastin time and C, fibrinogen in low molecular weight heparin treatment group and conventional treatment group [Color figure can be viewed at wileyonlinelibrary.com]

### 3.7 | Sensitivity analysis

One RCT[27] focused on hyperlipidemic severe acute pancreatitis, which was different from the other 15 RCTs including SAP related to the causes such as biliary and alcoholic causes. Therefore, we conducted sensitivity analysis to ascertain whether etiology of SAP influenced the final results. This RCT compared the mean length of hospital stay, but not other laboratory parameters or clinical outcomes, between LMWH treatment group and conventional treatment group. Excluded data from the RCT[27] did not alter the results of heterogeneity and pooled MD (heterogeneity: $P < .01$, $I^2 = 90\%$; pooled MD [95% CI] −9.04 [−11.71, −6.36], $P < .01$) (Figure S7). The mean length of hospital stay was still shorter in LMWH treatment group than that of conventional treatment group after excluding this study.

### 3.8 | Publication bias

Ten RCTs were enrolled in the meta-analysis when comparing length of hospital stay and mortality. The funnel plots did not show any significant asymmetry, suggesting that publication bias was less likely (Figure S8).

## 4 | DISCUSSION

LMWH is often used in SAP patients to prevent thrombosis. However, the efficacy of LMWH on SAP patients remains controversial. Here, we performed a systematic review and meta-analysis including 16 articles to investigate the efficacy of LMWH on SAP patients compared with conventional therapy, and demonstrated that LMWH treatment could improve the prognosis of SAP by reducing mean length of hospital stay, mortality, incidences of MOF, pancreatic pseudocysts, and operation rate, as well as decreasing the levels of inflammatory parameters and severity scores.

Emerging data have shown that anticoagulation therapy may cause massive upper gastrointestinal bleeding in AP.[30] LMWH has not been recommended as a conventional therapy in treating SAP patients by the currently established guidelines,[14] although LMWH combined with insulin are recommended for hyperlipidemic acute pancreatitis

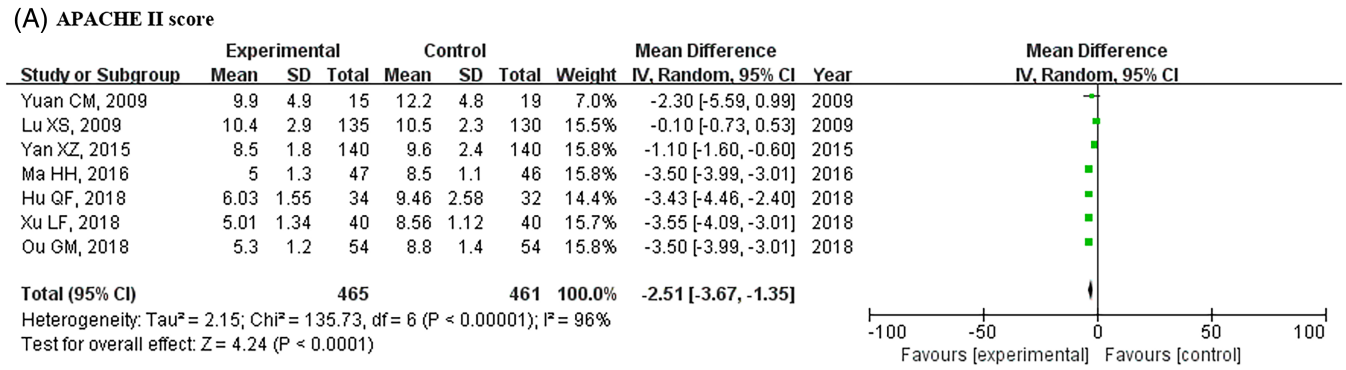


**FIGURE 5** Forest plot of meta-analyses of A, acute physiology and chronic health evaluation (APACHE) II score and B, computed tomography severity index in low molecular weight heparin treatment group and conventional treatment group. CTSI, computed tomography severity index [Color figure can be viewed at wileyonlinelibrary.com]

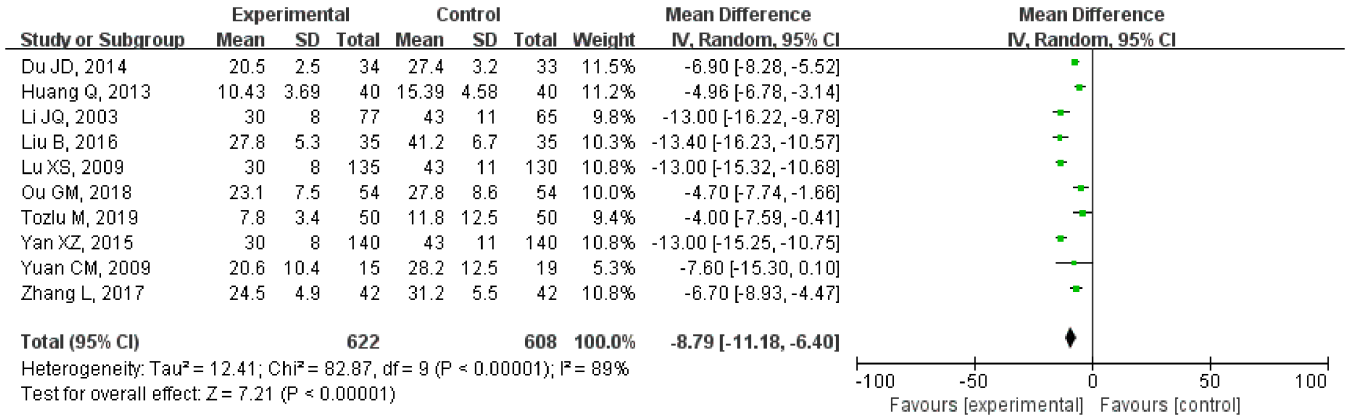


**FIGURE 6** Forest plot of meta-analysis of mean length of hospital stay in low molecular weight heparin treatment group and conventional treatment group [Color figure can be viewed at wileyonlinelibrary.com]

patients to decrease serum lipid level. The findings of our systematic review supported the point of view that LMWH treatment was of benefit for prognosis of SAP and was safe to be used, since none of the enrolled studies reported that LMWH increased risk of bleeding or caused serious bleeding. Meanwhile, our meta-analysis showed that LMWH did not significantly prolong PT and APTT. The FIB level in LMWH treatment group was higher than that of the conventional treatment group, suggesting that LMWH could decrease the consumption of FIB and promote recovery of coagulation dysfunction. In clinical practice, the course of LMWH treatment has not been determined yet. In the meta-analysis, since the mean length of hospital stay were shorter in both 7-day and 14-day LMWH treatment subgroups than those of the conventional treatment subgroups, 7-day LMWH treatment is recommended because of an reduced risk of bleeding, while the course of treatment could be prolonged to 14 days when the SAP patients have high risk of embolization.

Although the role of coagulation dysfunction in SAP pathogenesis has not been well understood, it is known that coagulation dysfunction is one of the common complications in SAP. Emerging evidence showed that coagulation dysfunction and inflammation could promote progression of SAP.[31] Proinflammatory cytokines, particularly interleukin-6, together with impaired endothelial cells could activate

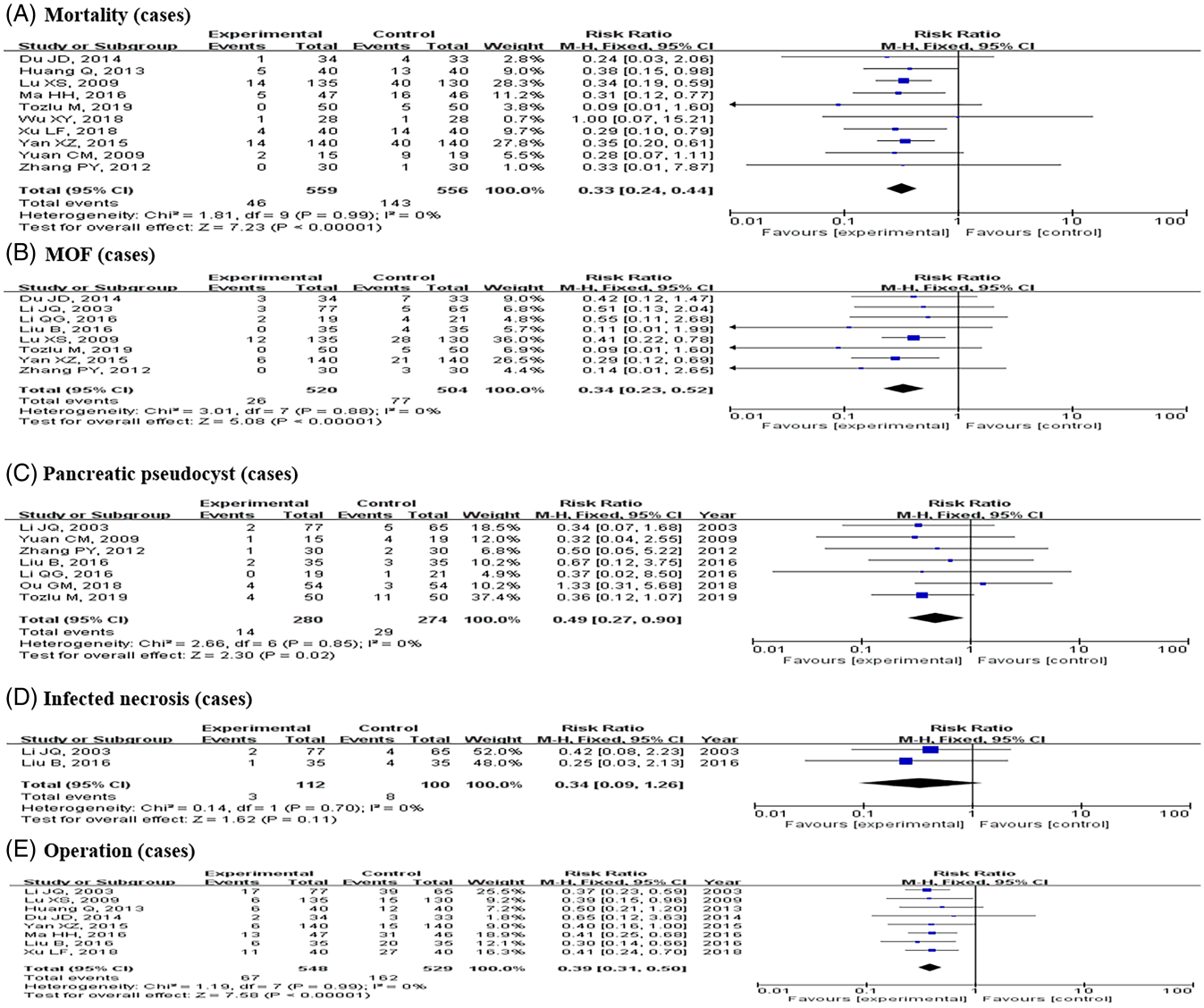


**FIGURE 7** Forest plot of meta-analyses of clinical outcomes, including A, mortality, B, multiple organ failure (MOF), C, pancreatic pseudocyst, D, infected necrosis and E, operation, in low molecular weight heparin treatment group and conventional treatment group [Color figure can be viewed at wileyonlinelibrary.com]

the coagulation process in local or systemic inflammatory state, inducing a hypercoagulable state.[32] Coagulation activation causes the formation of microvascular thrombosis in many organs, such as lungs, kidneys, and mesenteric vessels, which further aggravates microcirculation disturbance. Meanwhile, microcirculation disturbance could influence capillary permeability and leukocyte endothelial interaction, leading to reduction of blood flow in the organs, even inducing MOF.

LMWH, an effective anticoagulation agent, can inhibit blood coagulation cascade through indirect interaction with antithrombin III[33] so as to reduce blood viscosity and improve microcirculation.[34] Besides its anticoagulation effect, LMWH could also inhibit inflammation during the progression of disease.[35,36] It has also been demonstrated that LMWH can downregulate proinflammatory cytokine production, induce a profound change in human neutrophils to generate neutrophil extracellular traps to control inflammation,[36] and reduce the occurrence of pancreatic encephalopathy through inhibition of inflammatory activation in animal experiment.[37] Our meta-analysis showed the levels of WBC and CRP were lower in LMWH treatment group than in the conventional treatment group, supporting that LMWH had anti-inflammatory effect. Therefore, LMWH may be beneficial to reduce the mean length of hospital stay and complications of SAP.

This systematic review provided useful information on the application of LMWH and showed that LMWH had clinical implications for the management of SAP. Only RCTs were included in this meta-analysis, while case–control studies and nonrandomized clinical controlled studies were excluded. Heterogeneity was significant in the comparison of laboratory parameters, clinical scores, and length of hospital stay in total group analyses. Since the course of treatment mainly affects the efficacy of LMWH and prognosis of SAP, subgroup analyses were performed. The results showed that heterogeneity was still observed in subgroup analyses. In addition, the differences in

equipment for blood testing and evaluators might be the source of heterogeneity as well. However, the included studies did not provide information on them. Thus, we did not perform subgroup analysis based on the differences in equipment and evaluators.

In conclusion, the results of the present systematic review and meta-analysis showed that LMWH could improve the prognosis of SAP by reducing the length of hospital stay, mortality, incidences of MOF, pancreatic pseudocyst, and operation rate. Therefore, LMWH treatment was of benefit for the clinical outcomes of SAP patients. Further prospective multicenter studies should be performed to further confirm its efficacy and safety on SAP patients.

## CONFLICTS OF INTEREST

The authors declare no conflict of interests.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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