

Review Article

Low-molecular-weight heparin treatment for acute lung injury/acute respiratory distress syndrome: a meta-analysis of randomized controlled trials

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Abstract: Low-molecular-weight heparin (LMWH) has achieved additional benefits among acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) patients. We aimed to evaluate the benefits of LMWH as an adjunctive therapy in ALI/ARDS patients by conducting meta-analysis. We made a comprehensive literature search using Pubmed, Embase, Cochrane Library, Wanfang, VIP, and CKNI until October 2016. Randomized controlled trials evaluating LMWH as an adjunctive therapy for ALI/ARDS patients were included. A total of 9 trials involving 465 patients were identified. Adjunctive treatment with LMWH significantly reduced the 28-day mortality (risk ratio [RR] 0.63; 95% confidence interval [CI] 0.41-0.96), 7-day mortality rate (RR 0.52; 95% CI 0.31-0.87), and activated partial thrombin time (weighted mean differences [WMD] -1.10 seconds; 95% CI -1.97 to -0.23) as well as increased the partial pressure of oxygen to fraction of inspired oxygen ratio ($\text{PaO}_2/\text{FiO}_2$) (WMD 74.48; 95% CI 52.18-96.78). However, the tested LMWH dose had no apparent effect on prothrombin time and platelet count. Subgroup analyses showed that the effect on $\text{PaO}_2/\text{FiO}_2$ improvement was more pronounced in the high LMWH dose (≥ 5000 U/day) subgroup. This meta-analysis suggests that adjunctive treatment with LMWH appears to have additional benefits in terms of reducing 7-day and 28-day mortality and increasing oxygen index among ALI/ARDS patients.

Keywords: Low-molecular-weight heparin, acute lung injury, acute respiratory distress syndrome, meta-analysis

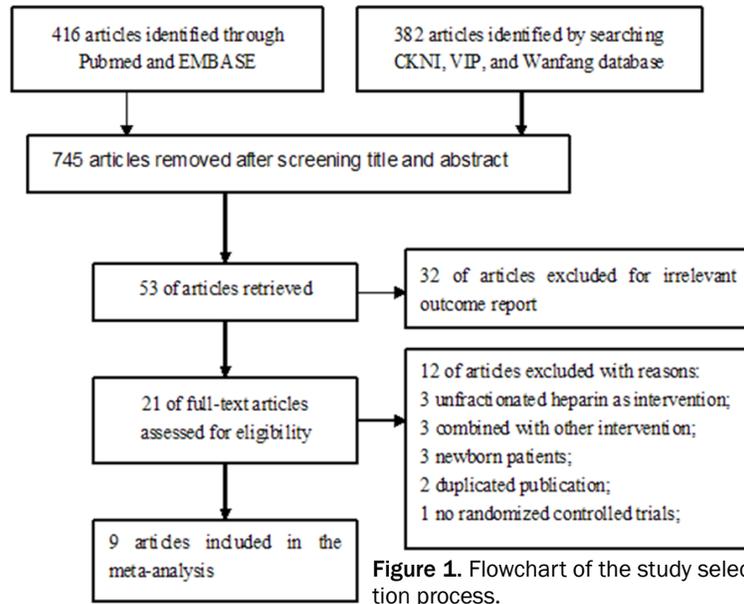
Introduction

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are lethal conditions of critical illness with a mortality rate of approximately 25%-40% [1, 2]. ALI/ARDS pathophysiology includes oxidative stress, lung deformation, activated inflammation, and intravascular coagulation [3]. Any proven pharmacological therapy does not currently exist in ALI/ARDS [4, 5]. Therefore, the development of novel therapies for ALI/ARDS is urgent.

Regardless of the initial triggering factors, fibrin deposition in the lumen of the lung alveoli from activation of coagulation and inhibition of fibrinolysis is crucial in ALI/ARDS pathophysiology [6]. Anticoagulants may be a promising therapeutic approach in ALI/ARDS [7]. Preclinical studies have shown a reduction in lung injury and/or improvement in oxygenation from anti-coagulant administration [8, 9]. Heparin can be

divided into unfractionated and low-molecular-weight heparin (LMWH). The unfractionated heparin has been introduced to the management of ALI/ARDS patients [10-12]. To the best of our knowledge, no randomized controlled trials (RCTs) of LMWH have been performed on the clinical setting of ALI/ARDS in the English literature. In China, only a few studies [13-21] investigated the benefits of LMWH as adjunctive therapy in ALI/ARDS patients. However, interpretation of these findings is limited due to small sample sizes. Furthermore, an optimal LMWH dose in ALI/ARDS management has not been well-characterized.

Currently, high-quality trials supporting the use of LMWH in ALI/ARDS are limited. Previous meta-analysis has not particularly focused on the beneficial effects of LMWH in ALI/ARDS patients. Therefore, we sought to evaluate the additional benefits of adjunctive treatment with LMWH on the mortality and other clinical out-



comes in ALI/ARDS patients by conducting meta-analysis of RCTs.

Materials and methods

Literature search

We conducted this study in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of RCTs [22]. Articles published from inception to October 2016 were searched in Pubmed, Embase, Cochrane Library, Wanfang, VIP, and China National Knowledge Infrastructure. The following medical subject headings and keywords in combination were applied: “low molecular weight heparin” OR “heparin” AND “acute lung injury” OR “acute respiratory distress” OR “adult respiratory distress” AND randomized control trials OR RCTs. References of the retrieved articles were manually searched for any additional studies. In addition, we also searched for unpublished and ongoing trials in <http://www.clinicaltrials.gov>. Only articles published in English and Chinese were considered.

Study selection

Inclusion criteria were the following: 1) Trials included ALI or ARDS patients at ages 18 years or older; 2) LMWH therapy in addition to usual treatment was compared with usual treatment alone; and 3) Primary outcomes were all-cause mortality at day 7 or day 28, and oxygenation

index defined by the ratio of partial pressure of oxygen to fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$), whereas secondary outcomes were activated partial thrombin time (aPTT), prothrombin time, and platelet counts after treatment for 7 days. Exclusion criteria were the following: 1) Study design was not an RCTs; 2) Different regimens except for LMWH intervention were used between two groups; and 3) Trials evaluated unfractionated heparin as intervention.

Data extraction and quality assessment

Two authors independently extracted the information based on first author surname, publication year, study design, sample size, population characteristics, regimen of LMWH intervention and usual treatment, and main outcome measures. The risk of bias was evaluated by recommendation by the Cochrane Handbook for Systematic Reviews of Intervention, which measures random sequence generation, allocation concealment, blinding of participants or personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Any disagreement in data extraction and quality assessment was resolved by consensus.

Statistical analyses

All statistical analyses were performed by STATA 12.0 (Stata Corporation, College Station, TX, USA). Pooled estimates were expressed as risk ratio (RR) with 95% confidence interval (CI) for dichotomous outcomes and weighted mean difference (WMD) with 95% CI for continuous outcomes. Significant heterogeneity was considered as I^2 statistic >50% or p -value < 0.10 of the Cochrane Q test [23]. We selected a random effect model when significant heterogeneity was present. Otherwise, a fixed-effect model was applied. Publication bias assessment was scheduled if the retrieved trials were more than the recommended arbitrary minimum number of 10 articles [24]. Subgroup analyses were performed based on the type of

LMWH and ALI/ARDS

Table 1. Characteristics of clinical trials included in meta-analysis

Study/Year	Primary disease	Disease definition	Sample Size, % Male, and Age (LMWH/Control)	Intervention		Main outcomes
				LMWH Group	Control (UT) Group	
Xiao JS et al 2007 [13]	ARDS/ALI	①	LMWH: 22 (55.6%); 43±10 years; Control: 22 (56.3%); 40±11 years	LMWH 4100 U/12 h (SC) + UT	Antibiotics, protecting gastric mucosa, supplement blood capacity, maintaining balance of water and electrolyte, nutritional support	PaO ₂ /FiO ₂ , 7-day mortality, PLC, aPTT, PT
Zhu JB et al 2010 [14]	ARDS/ALI	②	LMWH: 16; Control: 12 (59.5%); 43±10 years	LMWH 5000 U/day (SC) + UT	Anti-infection, nutritional support, maintaining balance of water and electrolyte, and mechanical ventilation	7-day mortality, PLC, aPTT
Zha JA et al 2012 [15]	ARDS/ALI	②	LMWH1: 15 (53.3%); 56.3±9.6 years; LMWH2: 18 (61.1%); 62.1±9.7 years; Control: 9 (66.7%); 60.2±10.8 years	LMWH1: LMWH 5000 U/12 h (SC) + UT; LMWH2: LMWH 5000 U/12 h (Inhalation) + UT	Anti-infection, expectorants, nutritional support, maintaining balance of water and electrolyte, and mechanical ventilation	PaO ₂ /FiO ₂ , 7-day mortality, PLC, aPTT
Liu CY et al 2013 [16]	ARDS	①	LMWH: 42 (NP); 40.4±12.2 years; Control: 38 (NP); 42.2±11.0 years	LMWH 5000 U/12 h (SC) + UT	Mechanical ventilation, antibiotics, supplement blood capacity, maintaining balance of water and electrolyte, nutritional support	PaO ₂ /FiO ₂ , 28-day mortality, aPTT, PT
Gao SW 2014 [17]	ARDS/ALI	②	LMWH: 30 (56.7%); 60.5±9.1 years; Control: 30 (53.3%); 60.2±10.8 years	LMWH 5000 U/day (Inhalation) + UT	Broad spectrum antibiotics, supplement blood capacity, nutritional support, maintaining balance of water and electrolyte, and mechanical ventilation	PaO ₂ /FiO ₂ , 7-day mortality, aPTT, PT
Xie NL et al 2014 [18]	ARDS/ALI	①	LMWH: 22 (54.5%); 60.5±9.1 years; Control: 20 (55%); 61.8±9.6 years	LMWH 5000 U/day (Inhalation) + UT	Broad spectrum antibiotics, nutritional support, supplement blood capacity, maintaining balance of water and electrolyte, and mechanical ventilation	7-day mortality
Qi F et al 2014 [19]	ARDS/ALI	②	LMWH: 33; Control: 32 (72.3%); 66.8±15.2 years	LMWH 4100 U/12 h (SC) + UT	Broad spectrum antibiotics, supplement blood capacity, nutritional support, maintaining balance of water and electrolyte, and mechanical ventilation	PaO ₂ /FiO ₂ , 28-day mortality
Liang et al 2016 [20]	ARDS/ALI	①	LMWH: 21(66.7%); 66.01±3.65 years; Control: 21(71.4%); 67.83±3.92 years	LMWH 6000 U/24 h (SC) + UT	Anti-infection, nutritional support, and maintaining balance of water and electrolyte	PaO ₂ /FiO ₂ , 28-day mortality, aPTT, PT
Yan et al 2016 [21]	ARDS	①	LMWH: 32 (NP); NP; Control: 30 (NP); NP	LMWH 4100 U/24 h (SC) + UT	Broad spectrum antibiotics, supplement blood capacity, nutritional support, maintaining balance of water and electrolyte, and mechanical ventilation	PaO ₂ /FiO ₂ , 28-day mortality, aPTT, PT

Abbreviations: LMWH, low-molecular weight heparin; NP, not provided; UT, usual treatment; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; SC, subcutaneous; FiO₂, fraction of inspired oxygen; PaO₂, partial pressure of oxygen in arterial blood; aPTT, activated partial thrombin time; PLC, platelet counts; PT, prothrombin time. ① American-European consensus diagnostic criteria: acute hypoxia with PaO₂/FiO₂ ratio <200 (ARDS) <300 (ALI), bilateral lung infiltrates, no clinical evidence of left atrial hypertension or pulmonary artery occlusion pressure ≤18 mmHg; ② Branch of Chinese Medical Association diagnostic criteria: acute onset, hypoxia with PaO₂/FiO₂ ratio <200 (ARDS) <300 (ALI), bilateral lung infiltrates on chest radiograph, pulmonary artery occlusion pressure ≤18 mmHg or no evidence of raise left atrial pressure.

LMWH and ALI/ARDS

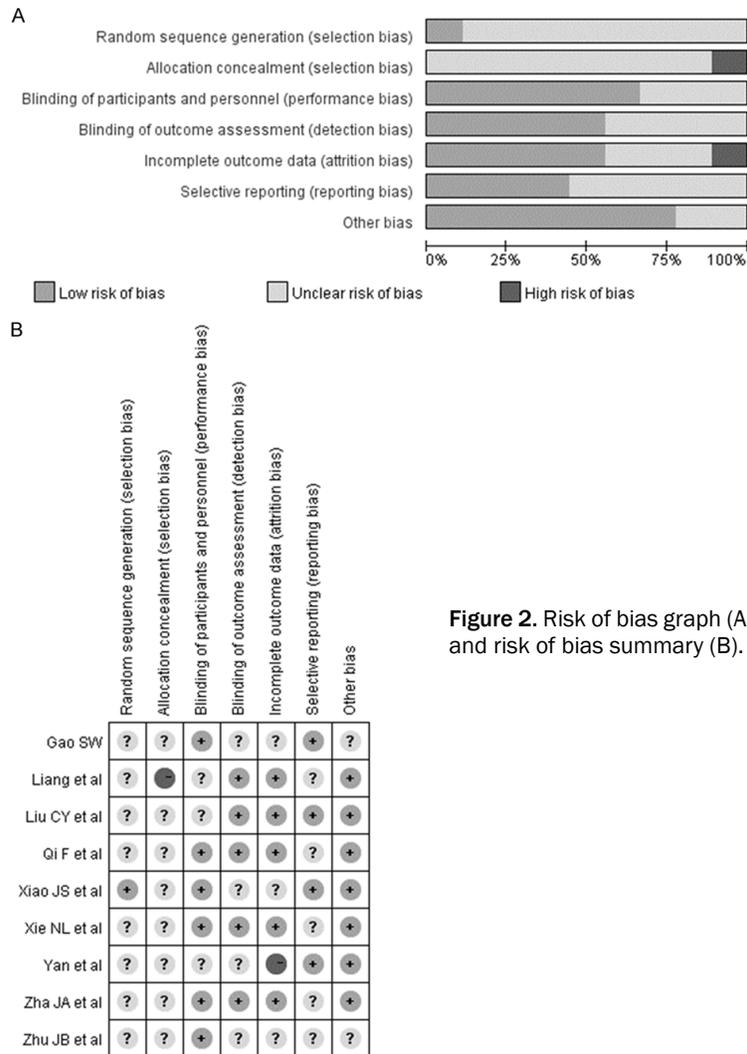


Figure 2. Risk of bias graph (A) and risk of bias summary (B).

plus usual treatment and 214 received the usual treatment alone. All the included RCTs were conducted in China and published between 2007 and 2016. The sample size of patients ranged from 28 to 80. The mean of patients ranged from 40 to 66.8 years. Five trials [11, 14, 16, 18, 19] defined ALI/ARDS according to American-European consensus diagnostic criteria [25] and four trials [12, 13, 15, 17] defined ALI/ARDS based on the Chinese Medical Association diagnostic criteria [26]. The course of LMWH intervention was 7 days and the dose of LMWH ranged from 4100-1000 U/day. **Table 1** summarizes the baseline characteristics of the included RCTs, which have unclear risk of bias (**Figure 2**). Although all included trials announced the randomization, only one trial [13] mentioned detailed methods. Allocation concealment, sample size calculation, or dropout/withdrawal was not mentioned in any trial.

Mortality rate

Five trials [11-13, 15, 16] reported 7-day mortality rate and four trials [14, 17-19] reported the 28-day mortality rate as an outcome. As shown in **Figure 3**, heterogeneity was not significant across the trials, so we selected a fixed-effect model. Pooled analysis indicated that LMWH significantly reduced the 7-day mortality rate (RR 0.52; 95% CI 0.31-0.87; $I^2 = 0\%$, $P = 0.575$) and 28-day mortality rate (RR 0.63; 95% CI 0.41-0.96; $I^2 = 0\%$, $P = 0.534$) in a fixed-effect model.

Oxygenation index

A total of seven trials [11, 13-15, 17-19] reported oxygenation index data defined by $\text{PaO}_2/\text{FiO}_2$ ratio after 7-day LMWH treatment. As shown in **Figure 4**, LMWH treatment significantly increased $\text{PaO}_2/\text{FiO}_2$ (WMD 74.48; 95%

disease (ALI/ARDS vs. ARDS), sample size (≥ 50 vs. <50), diagnosis of ALI/ARDS (American-European criteria vs. Chinese criteria), and dose of LMWH used (≤ 5000 U/d vs. >5000 U/d).

Results

Search results and study characteristics

We initially retrieved 798 potentially relevant citations. After scanning the titles and abstracts, a total of 53 citations were taken for detailed evaluation. After applying our pre-defined inclusion criteria, we further excluded 44 articles. Finally, a total of 9 trials [11-19] were included in the meta-analysis (**Figure 1**). The nine trials had a combined total of 465 patients. Of 465 patients, 251 received LMWH

LMWH and ALI/ARDS

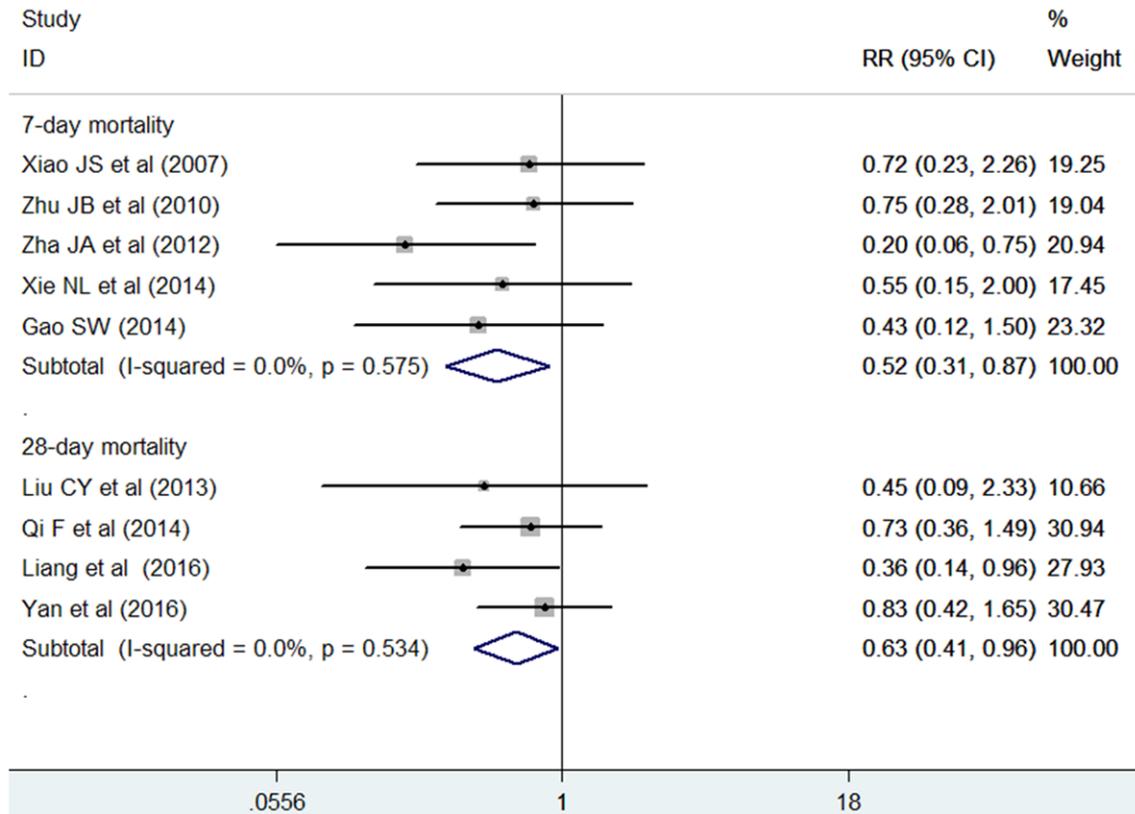


Figure 3. Forest plots showing RR and 95% CI of 7-day and 28-day mortality comparing with or without low-molecular weight heparin treatment.

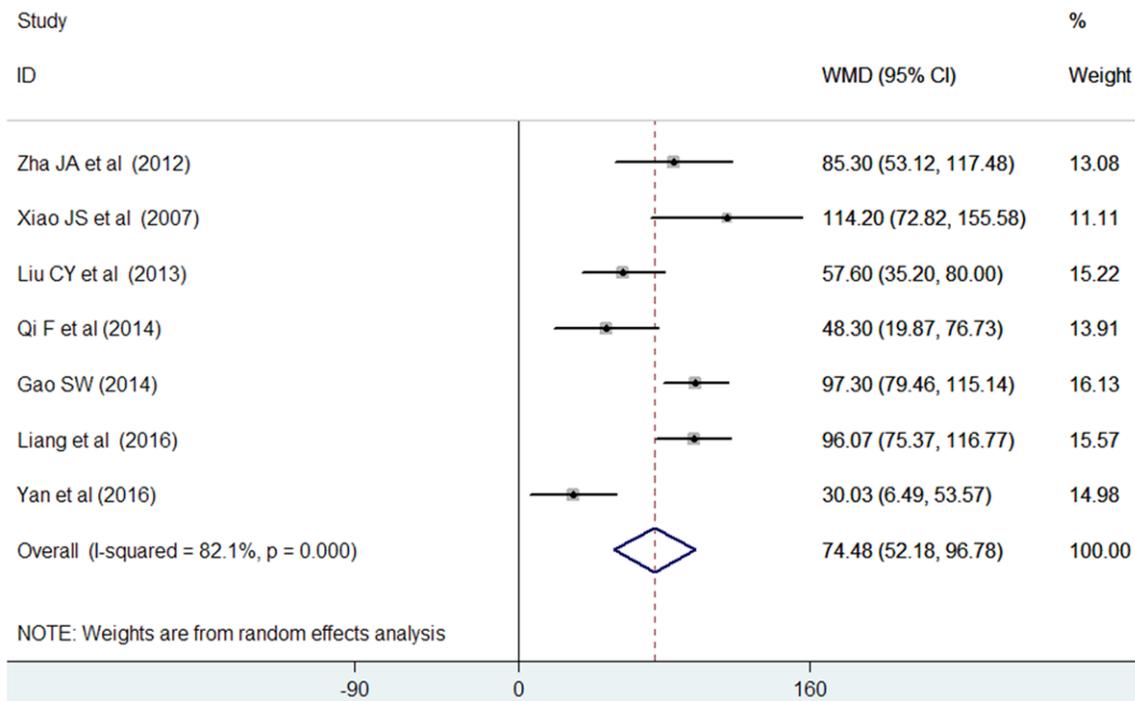


Figure 4. Forest plots showing WMD and 95% CI of oxygenation index comparing with or without low-molecular weight heparin treatment.

LMWH and ALI/ARDS

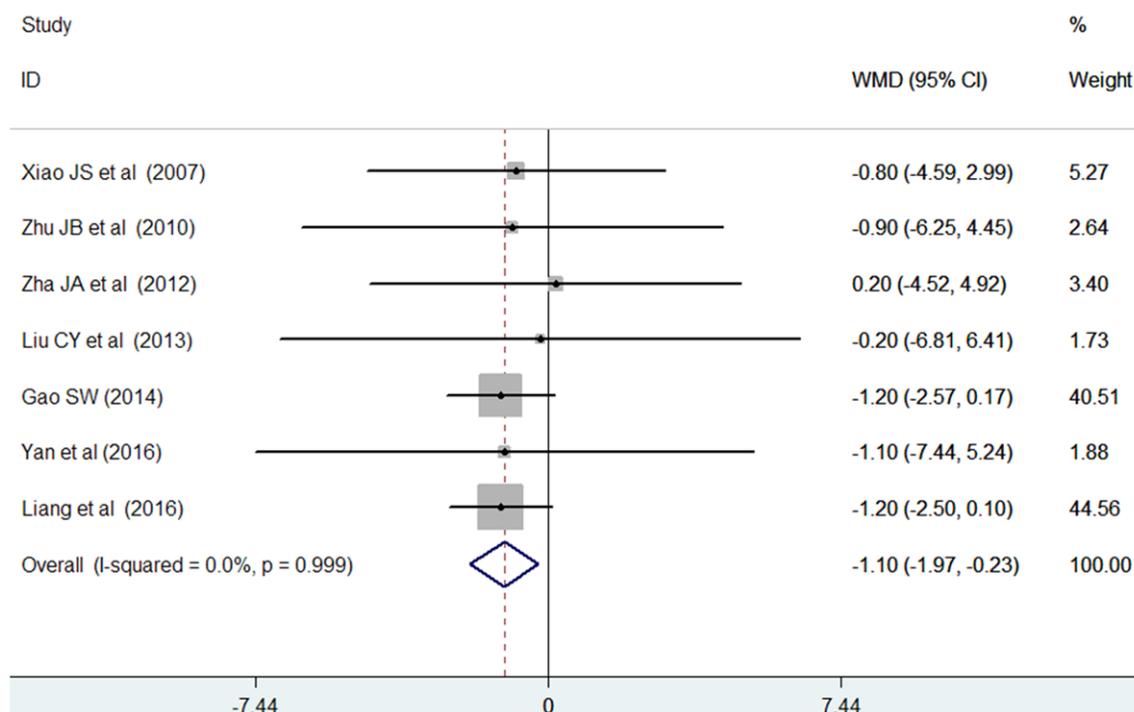


Figure 5. Forest plots showing WMD and 95% CI of activated partial thrombin time comparing with or without low-molecular weight heparin treatment.

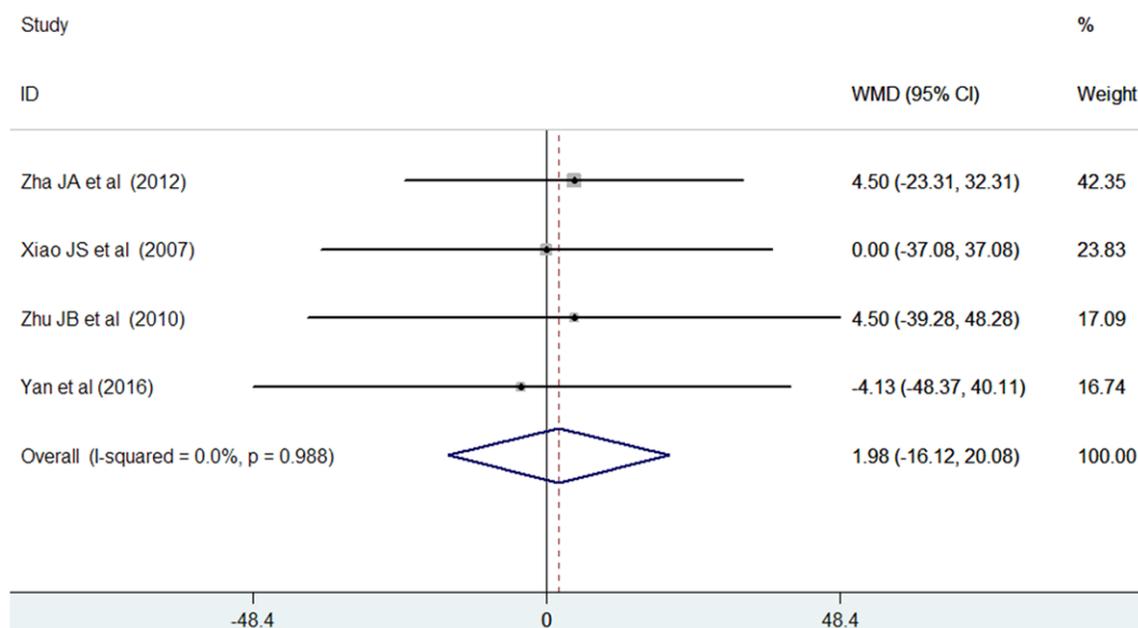


Figure 6. Forest plots showing WMD and 95% CI of platelet counts comparing with or without low-molecular weight heparin treatment.

CI 52.18-96.78) compared with that of the usual treatment in a random effect model. Significant heterogeneity was present across the included trials ($I^2 = 82.1\%$, $P < 0.001$).

Platelet counts, prothrombin time, and aPTT

A total of seven trials [11-15, 18, 19] reported aPTT data. Pooled analysis showed that LMWH

LMWH and ALI/ARDS

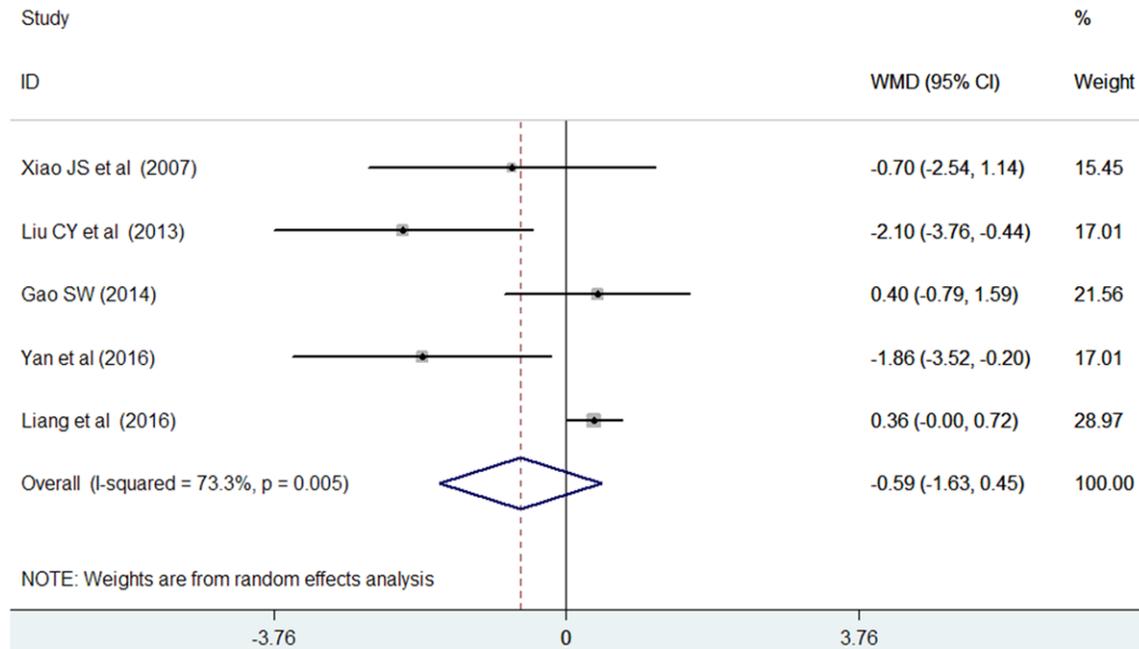


Figure 7. Forest plots showing WMD and 95% CI of prothrombin time comparing with or without low-molecular weight heparin treatment.

Table 2. Subgroup analyses on PaO₂/FiO₂ ratio

Subgroup	Number of trials	Pooled WMD	95% CI	Heterogeneity	
				I ² statistic	P-value
Sample size					
≥50	4	59.08	27.87-90.29	86.8%	<0.001
<50	5	96.12	88.07-112.16	0.0%	0.558
Dose of LMWH					
≥5000 U/d	4	84.64	66.54-103.74	65.2%	0.035
<5000 U/d	3	61.10	18.22-103.98	83.4%	0.002
Criteria of ALI/ARDS					
American-European	4	72.53	47.97-108.27	86.8%	<0.001
China	3	78.12	37.65-107.40	75.6%	0.017
Type of disease					
ALI/ARDS	5	87.66	68.49-106.83	63.8%	0.096
ARDS	2	44.06	17.05-71.08	62.3%	0.031

Abbreviations: LMWH, low-molecular-weight heparin; WMD, weight mean difference; CI, confidence interval; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; FiO₂, fraction of inspired oxygen; PaO₂, partial pressure of oxygen in arterial blood.

73.3%, P = 0.005) in five trials (**Figure 7**) [11, 14, 15, 18, 19].

Subgroup analyses and sensitivity analyses

Subgroup and sensitivity analyses were performed based on PaO₂/FiO₂ ratio. **Table 2** describes the detailed results of subgroup analyses. Sensitivity analyses revealed that the single trial did not significantly influence the overall pooled results from the sequential removal of one trial at each turn (data not shown).

treatment had significantly lower aPTT (WMD -1.10 seconds; 95% CI -1.97 to -0.23; I² = 0%, P = 0.999) than the usual treatment in a fixed-effect model (**Figure 5**). However, statistical significant differences in platelet counts (WMD 1.98; 95% CI -16.12 to 20.08; I² = 0%, P = 0.989) were not significant in four trials (**Figure 6**) [11-13, 19] and prothrombin time (WMD -0.59 seconds; 95% CI -1.63 to 0.45; I² =

Discussion

This meta-analysis indicates that adjunctive treatment with LMWH within the initial 7-day onset of disease appears to reduce 48% risk of 7-day mortality and 37% risk of 28-day mortality in ALI/ARDS patients. Furthermore, adjunctive treatment with LMWH significantly improves PaO₂/FiO₂ ratio and reduces aPTT level.

A primary therapeutic goal in ALI/ARDS is to increase the oxygenation by reducing the pulmonary inflammation. In the current meta-analysis, PaO₂/FiO₂ ratio was significantly higher in the LMWH treatment group than in the control group. Subgroup analyses indicated that the effect of LMWH on PaO₂/FiO₂ was more pronounced in the high-dose LMWH subgroup.

The extent of coagulopathy was independently associated with adverse clinical outcomes in the ALI/ARDS patients [27]. Nebulized heparin significantly reduced the activation of coagulation in the lungs of ALI patients [28]. However, administration of intravenous unfractionated heparin at therapeutic doses was not associated with lower mortality in critically ill ALI patients [12]. LMWH possessed a much more predictable anticoagulant response than unfractionated heparin because LMWH did not bind to plasma proteins.

A major concern is the risk of hemorrhage during LMWH application. In terms of anticoagulant and antithrombotic parameters, the tested LMWH dose in our analysis slightly lowered aPTT level but had no apparent effect on prothrombin time and platelet count. However, four cases with a slight increase in bleeding during venous catheter and endotracheal intubation were present in two trials [13, 16]. In addition, two cases with progressively declining platelet count were reported in one trial [16]. Despite the absence of organ hemorrhage and severe bleeding events in the included trials, monitoring the hemorrhagic complications during LMWH use is recommended.

Several limitations of the current meta-analysis were notable. First, the methodological quality of individual trials was relatively low. In particular, the sample size of individual trials was too small and lacked statistical power. Moreover, we did not find report allocation concealment, sample size calculations, or dropout/withdrawal. Second, the results of subgroup analyses should be interpreted with caution given the small number of included trials. Third, a wide variation exists in both dose and route of LMWH administration. However, meta-regression techniques with less than 10 trials during further assessment of LMWH dose-response were inaccurate. Unfortunately, conclusions regarding the optimal regimen of LMWH cannot be drawn from this meta-analysis. Finally, all included trials were

only from Chinese literature, limiting the generalizability of the findings.

Conclusion

Adjunctive LMWH use appears to reduce 7-day and 28-day mortality as well as improve the oxygenation index in ALI/ARDS patients. LMWH therapy within the initial 7-day-onset of disease shows promising effects in ALI/ARDS patients. Given the methodological flaws of the included trials, more well-designed trials with larger sample sizes are needed to confirm the current findings.

Disclosure of conflict of interest

None.

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