Benefits of esmolol in sepsis and septic shock in adults: a meta-analysis of randomized controlled trials

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Research

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Abstract

Background

Sepsis affects millions of people each year, and brings substantial health and economic burden to the global. Esmolol may have the potential in the treatment of sepsis and septic shock in adults. However, current evidence remains controversial.

Methods

We systematically searched PubMed, EMBASE and the Cochrane Central Register of Controlled Trials from their inception to September 19, 2020 for randomized controlled trials (RCTs) evaluating the efficacy of esmolol in sepsis and septic shock in adults. A random-effects meta-analysis was performed to combine effect estimates. Two investigators independently screened articles, extracted data, and assessed the quality of included studies.

Results

Seven RCTs were included with a total of 463 patients with sepsis and/or septic shock. Overall, compared with standard treatment, esmolol significantly decreased 28-day mortality (risk ratio [RR] 0.68, 95% confidence interval [CI] 0.52 to 0.88), and heart rate (standardized mean difference [SMD] -1.83, 95% CI -2.95 to -0.70) and troponin I (TnI) level (SMD − 0.59, 95% CI -1.02 to -0.16) at 24 hours after treatment; no significant effect was found on the length of intensive care unit stay, mean arterial pressure, central venous pressure, central venous oxygen saturation, Stroke Volume Index, tumor necrosis factor-a, interleukin 6, White Blood Cells and PO2/FiO2.

Conclusions

Esmolol treatment may be safe and effective in decreasing 28-day mortality, controlling heart rate, and preventing myocardial damage, but no evidence of effect on lung injury in sepsis and septic shock after fluid resuscitation early. There were no significant adverse effects on tissue perfusion and oxygen utilization.

Introduction

Sepsis is defined as host's imbalance response to infection, leading to a variety of deleterious effects, including septic shock, multiple organ failure, and ultimately death (1). Sever sepsis, septic shock and their complications affect millions of people each year, and the mortality of in-hospital remains high at 25–30%, which brings substantial health and economic burden to the global (2–7).

Severe sepsis is a complex syndrome, characterized by one or more organs dysfunction, particularly heart dysfunction which is featured as hemodynamic disorder (8). Blanco et al[6] reported that the mortality of septic patients with myocardial dysfunction is significantly higher (70%) compared with septic patients without myocardial insufficiency (20%) (6). Some studies also confirmed that the mortality is two to three times higher when septic cardiomyopathy is present (5, 9). However, severe sepsis or septic shock demands vasopressor to maintain adequate tissue perfusion, which can incline patients to tachycardia and cardiac arrhythmias and increase the risk of adverse cardiovascular events (10, 11). Considering the function of β-adrenergic in cardiovascular dysfunction in sepsis, and the elevated risk for tachycardia and atrial fibrillation, beta-blockade is a reasonable therapeutic modality for improving outcomes in patients with sepsis and septic shock (12).

However, esmolol has not been widely applicated in clinical practice because several published studies on the effectiveness of esmolol in sepsis or septic shock remained conflicting (13–18). Hence, we conducted the meta-analysis to investigate the effect of esmolol on sepsis and septic shock treatment.

Methods

Literature search

We systematically searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) from their inception to September 19, 2020 for randomized controlled trials (RCTs), by using the following key words in all fields: “esmolol”, and “septic shock” or “sepsis”. We also scanned the reference lists from relevant studies and key review articles to locate relevant studies.

Study selection

Studies meeting the following inclusion criteria were included: (1) participants: patients with sepsis or septic shock aged ≥18 years with a heart rate of 95 beats/min or higher after early goal-directed therapy (EGDT); (2) intervention: continuous infusion of esmolol titrated to maintain target heart rate range between 75 and 100/min during the first 96 h; (3) comparison: basic treatment of sepsis; (4) outcomes: the primary outcome was 28-day mortality. The secondary outcomes were heart rate (HR), length of intensive care unit (ICU) stay, mean arterial pressure (MAP), central venous pressure (CVP), central venous oxygen saturation (ScvO2), lactic acid (Lac), Stroke Volume Index (SVI), Cardiac index (CI), troponin I (TnI), tumor necrosis factor-a (TNF-a), interleukin 6 (IL-6), White Blood Cells and PO2/FiO2. (5) design: RCTs. If data were duplicated or shared in more than one study, the first published study was included in the meta-analysis. The language was not restricted. Discrepancies regarding study inclusion between authors were resolved through discussion. Two of the authors (CC and JZ) independently evaluated the eligibility of all studies obtained from the databases according to the above selection criteria.

Data extraction and risk of bias assessment

Extracted data were entered into a standardized Excel file. Disagreements between authors were resolved by discussion. The following data were extracted: first author, year of publication, country, study design, participants (sample size, sex and age), intervention and control, and outcomes (primary and secondary outcomes). The Cochrane Collaboration’s tool for assessing risk of bias was used for each RCT, which includes the following criteria: adequacy of sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting and other biases (19). Disagreements were resolved by further checking the original articles. We also used the GRADE system to rate the quality of evidence from our meta-analysis by using GRADE pro.

Statistical analysis

We calculated a relative risk (RR) with 95% confidence interval (95% CI) for 28-day mortality and HR. As for the length of ICU stay, MAP, CVP, ScvO2, Lac, SVI, CI, TnI, TNF-a, IL-6, **WBC and** PO2/FiO2, standard mean differences (SMDs) between the experimental and control groups were combined. Heterogeneity in results across studies was examined by using Cochran’s Q and I^2 statistics (20). A random-effects model (21) was used to pool studies.

A sensitivity analysis was conducted to assess the influence of individual studies on the pooled result when P was < 0.10 or I^2 was > 50%, by excluding each study one by one and recalculating the combined results on the remaining studies. We used an asymmetry of the funnel plot proposed by Egger et al (20) to test the publication bias. All analyses of data were performed with Review Manager 5.3 (Cochrane Informatics and Knowledge Management Department, available from http://tech. cochrane. org/ United Kingdom).

Results

Figure 1 shows a flow diagram for selection process. A total of 549 records were

initially identified from databases search. 212 records were excluded for duplicates, and 308 publications were excluded after screening the titles and abstracts. The remaining 29 full-text articles were assessed for eligibility, of 22 studies were further excluded. The remaining 7 RCTs (13-18, 22) were included in the final meta-analysis.

Characteristics of included studies

The characteristics of studies included in our meta-analysis are summarized in Table 1. The seven studies were published between 2013 and 2019, and sample sizes range from 41 to 154. Orbegozo-Cortes et al (22) and Morelli et al (18) reported the same clinical trial, but with different follow-up times. Six included RCTs (13, 15-18, 22) involve septic shock, wang et al (14) reported the effect of esmolol and milrinone on severe sepsis patients who randomly divided into control, milrinone, and milrinone-esmolol groups. Wang et al 2017(16) used isotonic saline in control group, while the remained studies (13, 15, 17, 18) used blank control. Overall, 232 patients included in esmolol group while 231 patients in control group. All studies focused on adults at the mean age of 34-67.2 years and 38.0-69 years respectively in intervention and control arms. Three studies (13, 15, 16) commenced at 0.05mg/kg/h esmolol continuous intravenous titrate, while four trials (14, 15, 17, 18) commenced at 25mg/h esmolol continuous intravenous infusion, and adjust the dosage according to heart rate until reach the predefined threshold rate.

Quality assessment

Risk-of-bias assessment of the included studies is presented in Figure 2. The included trials had some methodological strengths and limitations. All included trials were adjudicated to be low risk of bias in random sequence generation, blinding of outcome assessment, incomplete outcome data and other bias. The risk of bias regard to allocation concealment was low risk except Yang et al 2014(15) with high risk where their patients allocated by a random number table predisposing them to an elevated risk of bias. Six RCTs were high risk of bias in blinding of participants and personnel because all of them had no mechanisms in place for blinding except Liu et al 2019(17). Wang et al 2017(16) was high risk of bias in selective reporting because reporting bias was not addressed, while the other trials were low risk.

We were unable to assess the publication bias using a funnel plot due to the small number of studies (<10) included in this analysis. Therefore, publication bias cannot be excluded.

Heterogeneity and sensitivity analysis

No heterogeneity was observed in MAP, CVP, Lac (12 hours (h)), CI (72 h), WBC, and PO2/FiO2 (24, 48h), low heterogeneity in 28-day mortality, TnI (24, 48 h), SVI (24 h) and PO2/FiO2 (72, 96h). We found high heterogeneity in the length of ICU stay, HR, ScvO2, Lac (24, 48, 72, 96 h), TnI (72 h), CI (12, 24, 48 h), SVI (48, 72 h), IL-6 and TNF-α. A sensitivity analysis was performed to evaluate the stability of the results, by excluding each study one by one and recalculating the combined RR or SMD on the remaining studies. This analysis confirmed the stability of the results: the overall effects did not show statistically significant reversal, and recalculated pooled RR and SMD were consistent and without apparent fluctuation (data not shown).

Primary outcomes

28-day mortality Five trials (13, 14, 16-18) with 422 cases were included for meta-analysis, shown in Figure 3. Overall, there was significantly effective on esmolol decreased 28-day mortality compared with the control (RR = 0.68, 95% CI: 0.52-0.88, $P = 0.004$, $I^2 = 45\%$).

Secondary outcomes

Heart rate Five trials (13-17) evaluated the effect between esmolol and control group. Our pooled analyses included 309 adults and found esmolol can significantly decrease heart rate at 24, 48, and 72 hours (SMD = -1.83, 95% CI -2.95, -0.70, $P = 0.001$, $I^2 = 94\%$; SMD = -1.68, 95% CI -2.8, -0.56, $P = 0.003$, $I^2 = 94\%$; SMD = -1.91, 95% CI -3.23, -0.60, $P = 0.004$, $I^2 = 94\%$, respectively), shown in Figure 4.

Length of ICU stay Three trials (13, 17, 18) examined the length of ICU stay between esmolol and control, shown in Figure 5. The pooled analysis including 302 adults showed that there was no significant association with esmolol supplementation on septic shock treatment (SMD = -0.23, 95% CI: -0.96, 0.50, $P = 0.54$, $I^2 = 89\%$).

Mean arterial pressure Four trials (13-16) evaluated MAP between esmolol and control group, and 209 adults were included for meta-analysis. There was no significant difference at 12, 24, 48, and 72 hours (SMD = -0.21, 95% CI -0.52 to 0.10, P = 0.19; SMD = -0.26, 95% CI -0.53 to 0.02, P = 0.07; SMD = -0.02, 95% CI -0.29 to 0.25, P = 0.89; SMD = 0.07, 95% CI -0.25 to 0.39, P = 0.68, respectively), there were no heterogeneity detected, shown in Figure 6.

Lactic acid Six RCTs (13-18) including 463 patients showed that there was no significantly different between esmolol and control groups, and the pooled SMDs at 12, 24, 48, and 72 hours were 0.04 (95% CI: -0.27, 0.35; P = 0.79, I^2 = 0%), 0.15 (95% CI: -0.48, 0.78; P = 0.64, I^2 = 90%), -0.5 (95% CI: -1.01, 0.01; P = 0.06, I^2 = 83%), -0.60(95% CI: -1.24, 0.03; P = 0.06, I^2 = 88%) and -0.40 (95% CI: -0.93, 0.12; P = 0.13, I^2 = 80%) respectively, shown in Figure 7.

Stroke Volume Index Four studies (13-16) including 209 cases showed that there was no significantly different between esmolol and control groups, and the pooled SMDs at 24, 48 and 72 hours were 0.16 (95% CI: -0.12, 0.44; P = 0.27, I^2 = 7%), 0.44 (95% CI: -0.27, 1.15; P = 0.23, I^2 = 84%) and 0.43 (95% CI: -0.54, 1.41; P = 0.39, I^2= 88%) respectively, shown in Figure 8.

Cardiac index Four trials (13-16) with 209 adults reported that esmolol can significantly decrease the CI at 72 hours (SMD = -0.4, 95% CI: -0.73, -0.07, P = 0.02, I^2 = 0%) compared with control groups, but there were no difference at 12, 24 and 48 hours (SMD = -0.46, 95% CI: -1.52, 0.60, P = 0.39, I^2 = 90%; SMD = -0.11, 95% CI: -0.74, 0.53, P = 0.74, I^2 = 81%; SMD = -0.16, 95% CI: -0.76, 0.45, P = 0.61, I^2 = 79%, respectively), shown in Figure 9.

Central venous pressure Three studies (13-15) with149 adults included for meta-analysis, showing no significant difference at 24, 48 and 72 hours between esmolol and control groups (SMD = 0.19, 95% CI: -0.13, 0.52, P = 0.24, I^2 = 0%; SMD = -0.22, 95% CI: -0.55, 0.1, P = 0.17, I^2 = 0; SMD = 0.03, 95% CI: -0.29, 0.36, P = 0.84, I^2= 0%, respectively), shown in Figure 10.

Central venous oxygen saturation Two trials (13, 15) including 89 cases indicated that there was no significant difference at 24, 48 and 72 hours between esmolol and control groups (SMD = 0.86, 95% CI: -1.08, 2.79, P = 0.39, I^2 = 94%; SMD = 1.43, 95% CI: -0.7, 3.56, P = 0.19, I^2 = 95%; SMD = 1.87, 95% CI: -1.53, 5.26, P = 0.28, I^2 = 97%, respectively), shown in figure 11.

Troponin I Two trials (14, 15) with 101 adults were included for meta-analysis, showing that esmolol can significantly decrease the level of TnI at 24, 48 and 72 hours (SMD = -0.59, 95% CI: -1.02, -0.16, P = 0.008, I^2 = 13%; SMD = -0.97, 95% CI: -1.48, -0.45, P = 0.0002, I^2 = 33%; SMD = -1.63, 95% CI: -2.54, -0.73, P = 0.0004, I^2= 72%, respectively), shown in figure 12.

White Blood Cells Three studies (16-18) including 314 adults for meta-analysis, showing no significant difference between esmolol and control group (SMD = 0.86, 95% CI: -1.08, 2.79, P = 0.39, I^2 = 94%), shown in Figure 13.

Interleukin 6 Two trials (14, 16) with 120 cases were included for meta-analysis. The pooled analysis showed no significant difference between esmolol and control group (SMD = -0.24, 95% CI: -1.03, 0.55, P = 0.54, I^2 = 79%), shown in Figure 14.

Tumor necrosis factor-a Two studies (14, 16) including 120 patients showed that there was no significant difference between esmolol and control group (SMD = -0.42, 95% CI: -1.12, 0.27, P = 0.23, I^2= 72%), shown in Figure 15.

PO2/FiO2 Two studies (14, 18) including 214 patients showed that there was no significant difference between esmolol and control group at 24, 48, 72 and 96 hours (SMD = 0.06, 95% CI: -0.21, 0.33, P = 0.66, I^2= 0%; SMD = 0.06, 95% CI: -0.21, 0.32, P = 0.68, I^2= 0%; SMD = 0.24, 95% CI: -0.15, 0.64, P = 0.22, I^2= 46%; SMD = 0.24, 95% CI: -0.17, 0.66, P = 0.25, I^2= 51%), shown in Figure 16.

Quality of evidence

We used the GRADE system to determine the quality of evidence in our meta-analysis. 28-day mortality and PaO2/FiO2 had “very low” quality with a serious risk of bias, inconsistency and indirectness. The length of ICU stay and ScvO2 had “very low” quality with risk of bias, inconsistency and imprecision. HR, MAP, CVP and TnI had “very low” quality with risk of bias,

indirectness and imprecision. Lac, CI, SVI, TNF-a and IL-6 had “very low” quality with risk of bias, inconsistency, indirectness and imprecision. WBC had “low” quality with risk of bias and imprecision.

Discussion

We found that esmolol could reduce 28-day mortality, control heart rate and decrease the level of cardiac troponin I and CI at 72 hours, but there was no significant difference in the length of ICU stay, ScvO2, CVP, MAP, Lac, SVI, WBC, IL-6, TNF-a and PO2/FiO2 compared with the control group in severe sepsis and septic shock after adequately fluid resuscitation in early stage of standard treatment.

Two published meta-analyses (23, 24) showed that esmolol treatment can improve survival rate, and reduce TnI, but no influence in MAP and CVP in patients with sepsis and septic shock. A recent meta-analysis by Li et al (25) reported that esmolol was safe and effective in improving 28-day mortality and has no adverse effect on tissue perfusion. These results were consistent with our meta-analysis. However, there are several points to explain the difference among our meta-analysis, Shi et al (23), Liu et al (24) and Li et al (25). Firstly, Liu et al only included five RCTs and had the fewest participants in all published meta-analyses, Shi et al and Li et al both included the same six RCTs. While our meta-analysis updates the search time and adds an RCT (17) published at 2019, we have the largest participants in current. Secondly, Li et al (25) used fixed-effects model to pool the results of 28-day mortality. Considering studies included in this review varied markedly in terms of population, doses of esmolol, the baseline of HR, we therefore used random-effects model which not only weight each study by its inverse variance, but also considers both within- and between study variations to calculate pooled RRs and 95% CIs, which yields a more global and conservative estimate (26). Thirdly, all three meta-analyses analyzed outcomes by pooling various time points together. While our meta-analysis analyzed data at 12, 24, 48, 72 and 96 hours separately when possible, which made our findings more robust. Fourthly, Liu et al (24) only reported the results of survival rate, MAP, CVP, HR, ScvO2 and TnI. Shi et al (23) only reported the survival rate, TnI, CK-MB, MAP and CVP. Li et al (25) reported the results of 28-day mortality, HR, MAP, CVP, ScvO2, Lac and TnI. While Our meta-analysis additionally examined the effects of esmolol on the length of ICU stay, SVI, CI, IL-6, TNF-a, WBC and PaO2/FiO2 at different time points when possible, which made us more comprehensively understand the effectiveness of esmolol.

Sepsis related cardiovascular failure is mainly associated with sustained systemic adrenergic activation, particularly via the β1-adrenergic pathway (27), which augment cardiac contractility (28) and heart rate (29), increasing energy demands. When energy demand outstrips supply, the cardiac myocytes are at risk of cell death, elevating troponin levels indicative such injury (30, 31), leading to detrimental cardiac effects including fibroblast hyperplasia, myocyte necrosis and apoptosis, and increased risk of arrhythmia (32). Theoretically, adjusting the adrenergic system may be a new approach in the treatment of sepsis (33, 34). Aboab et al (35) reported that pigs with endotoxic shock were treated by continuously infusion esmolol, a selective beta-1 adrenergic blocker, was well tolerated and may offset sepsis-induced cardiac dysfunction. Suzuki et al (36) did an RCT found that infusing esmolol into septic rats can reduce heart rates, blood pressures, improved oxygen utilization of myocardium and preserved myocardial function, and didn’t increase the levels of lactate compared with controls. Ibrahim-zada et al (37) showed that esmolol can significantly improve survival in murine model of septic insult. A meta-analysis of 67 RCTs including 3766 patients showed that esmolol has the potential to protect against myocardial ischemia in patients undergoing noncardiac surgery (38).

Tachycardia is commonly in severe septic cardiomyopathy in order to compensate for the low cardiac output (24). An observation study (11) found that prolonged elevated heart rate was associated with increasing the incidence of major cardiac events in critically ill. Beta-blockers have effects on reducing heart rate, anti-inflammatory, improving myocardial oxygen supply and demand balance, and have effects on hemodynamics, metabolic and immune regulation in sepsis. Beta-blockers may be a new method for the treatment of sepsis, especially for patients with high catecholamine level and tachycardiac (39). Esmolol is commonly used in the intensive care unit because of its rapid effect and ease of titration (40). We found that esmolol can significantly decrease HR and CI at 72 hours compared with the control group, but there were no differences in SVI, MAP and CVP at various point times between esmolol and control groups, indicating that esmolol didn’t affect the cardiac systolic function. Considering the decreased CI was mainly associated with the decreased HR. Core and Wolfe (41) found that esmolol

reduces the heart rate with comparable decrease in cardiac output in moderately severe septic patients, which may improve myocardial blood flow with the potential benefit toward decreasing the incidence of cardiac demise, and didn't affect oxygen utilization or hepatic, peripheral blood flow. The level of Lac and ScvO2 usually reflect the tissue infusion and oxygen metabolism early, we found no significant difference between esmolol group and control group, the result was consistent with Li et al (25) and Liu et al (24), suggesting that the dose control of esmolol did not have an adverse effect on tissue perfusion and circulatory function. Thus, there was no evidence to prove that esmolol infusion adversely affect organ perfusion and oxygen, energy utilization.

The monocytes were activated in sepsis causing abundant release of proinflammatory factors such as TNF-a, IL-6, and high mobility group box-1(HMGB-1) (42), which could cause significant myocardial depression and depress myocardial contractile function, even developing to septic cardiomyopathy (43). Suzuki et al (36) showed that esmolol could significantly reduce TNF-a concentrations in sepsis rats and improve oxygen utilization of the myocardium and preserve myocardial function. Wang et al (14) showed that esmolol combined with milrinone could reduce the level of TNF-a, IL-6 and HMGB-1, improve patients' cardiac function and reduce mortality. While Wang et al (16) found esmolol could not reduce the level of proinflammatory factors. Our meta-analysis also found there were no significant difference in WBC, IL-6 and TNF-a levels between the two groups, indicating that the improvement of cardiac function may irrelevant to the changes of inflammatory mediators in serum. But the including participants were few, and the quality of evidence was "very low". Thus, we need more larger precisely RCTs to confirm this issue.

Mehta et al (44) showed that the level of TnI concentration in serum correlates with myocardial dysfunction in septic shock, and high serum TnI predicts increased severity of sepsis and higher mortality. We found esmolol could significantly reduce the level of TnI concentration in serum, further to confirm that esmolol has the function of cardiac protective.

The present study showed that esmolol can significantly decrease 28-day mortality compared with the control group. The result was consistent with published meta-analyses (23–25). An observation study with 9465 patients suggests that patients who receive chronic β-blocker prescription may have a survival advantage if they subsequently develop sepsis (45). Liu et al (13) showed that esmolol can significantly shorten the length of ICU stay and reduce 28-day mortality. Interestingly, Fuchs et al (46) displayed an increased length of ICU stay despite showing substantial 90-day mortality benefits in septic patients. While our study found there was no difference between esmolol and control groups in the length of ICU stay. Considering the heterogeneity was high, we leave-one-out sensitivity analysis revealed the result was robust. But the quality of evidence was "very low", we have no enough evidence to confirm that esmolol has no effect on the length of ICU stay.

Berk et al (47) did an animal experiment showed that propranolol can reduce lung injury in dogs with sepsis. Morelli et al (18) found esmolol can significantly improve PaO2/FiO2 in septic shock patients compared with control group. While Wang et al (14) found that there was no difference between esmolol and control groups. Our meta-analysis also found no difference between the experiment and control groups. Considering the including participants were few and the quality of evidence was "very low", we still have no enough evidence to conclude that esmolol has no effective on lung injury.

This study has several strengths. Firstly, our meta-analysis had the largest number of

participants and studies in current. Secondly, we analyzed data at various time points separately when possible, which made our findings more robust, while previous meta-analyses analyzed outcomes by pooling various time points together. Thirdly, we additionally examined the effects of esmolol on the length of ICU stay, SVI, CI, IL-6, TNF-a, WBC and PaO2/FiO2 at different time points when possible, which made us more comprehensively understand the effectiveness of esmolol.

This study also has several limitations. Firstly, we were unable to assess the publication bias due to the small number of studies included in this analysis. Therefore, publication bias cannot be fully excluded. Secondly, different sepsis patients have distinct individual differences in myocardial inhibition and the methods of esmolol treatment for sepsis were different, which may affect the pooling results. Thirdly, the method and optimal dose of esmolol treatment remains unidentifiable. Finally, the qualities of evidence were "low" or "very low", we need more larger precisely RCTs to confirm this issue.

Conclusions

Esmolol treatment may be safe and effective in decreasing 28-day mortality, controlling heart rate, and preventing myocardial damage, but no evidence of effect on lung injury in sepsis or septic shock after fluid resuscitation early. There were no significant adverse effects on tissue perfusion and oxygen utilization, and irrelative with the change of systemic inflammation in serum. However, the current participants were few and the quality of evidences were “very low”. Thus, we need more larger precisely RCTs to confirm this issue.

Abbreviations

RCTs: randomized controlled trials; RR: risk ratio; CI: confidence interval; SMD: standardized mean difference; CENTRAL: Cochrane Central Register of Controlled Trials; EGDT: early goal-directed therapy; HR: heart rate; intensive care unit: ICU; WBC: White Blood Cell; ScvO2: central venous oxygen saturation; MAP: mean arterial pressure; CVP: central venous pressure; Lac: lactic acid; TnI: troponin I; SVI: Stroke Volume Index; CI: Cardiac index; TNF-a.: tumor necrosis factor-a; IL-6: interleukin6; HMGB-1: high mobility group box-1.

Declarations

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Availability of data and materials

The datasets used and analyzed during the current study were available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Authors’ contributions

Chun Chen and Zemei Zhou initiated and coordinated the study. Jing Zhang and Chun Chen were responsible for the data collection and data analysis. Studies were reviewed by Zemei Zhou. Chun Chen wrote the first draft of the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Characteristics of included studies in meta-analysis.

Authors	Country	study design	Age (years)	Comparisons	No. of patients	Target HR	APACHE II score	Outcomes
			(mean±SD)		(male)	(beats/min)	(I/C)	
Morelli et al	Italian	RCT	66±17.03	esmolol[a]	77 (54)	80-94	NA	28-day mortality, Lac, WBC
2013			69±14.82	control[b]	77 (53)		NA	length of ICU stay, PO2/FiO2
Yang et al	China	RCT	51.0±22.6	esmolol[c]	21(NA)	<100	20.1±9.2	HR, ScvO2, MAP, CVP, Lac,
2014			55.0±25.4	control[b]	20(NA)		21.3±8.3	TnI, CI, SVI
Orbegozo Cortes	Italian	RCT	66±17.03	esmolol[a]	77 (54)	80-94	NA	28-day mortality
et al 2014			69±14.82	control[b]	77 (53)		NA	length of ICU stay
Wang et al	China	RCT	34±28.89	esmolol[d]	30(19)	75-94	21.2 ± 5.7	28-day mortality, HR, MAP, CVP
2015			38±27.41	control[e]	30(19)		20.8 ± 5.6	Lac, TnI, CI, SVI, TNF-α, IL-6,
Liu et al	China	RCT	61.4±6.9	esmolol[f]	24(NA)	<100	20.75±3.05	28-day mortality, length of ICU stay
2015			61.2±6.4	control[b]	24(NA)		21.21±2.67	HR, ScvO2, MAP, CVP, Lac, CI, SVI
Wang et al	China	RCT	67.2±12.5	esmolol[g]	30(18)	<95	18.4±6.3	28-day mortality, HR, MAP, Lac
2017			62.5±14.5	control[h]	30(21)		15.7±6.3	CI, SVI, TNF-α, IL-6, WBC
Liu et al	China	RCT	58±15	esmolol[j]	50(29)	80-100	18.8±6.5	28-day mortality, length of ICU stay
2019			57±18	control	50(28)		19.1±7.5	HR, Lac, WBC

Footnotes:

a: Continuous esmolol infusion commenced at 25mg/h and progressively increased the rate at 20-minute intervals in increments of 50mg/h, or more slowly at the discretion of the investigators, to reach the target heart rate between 80/min and 94/min within

12 hours.

b: basic treatment

c: Micro pump with dosage of esmolol 0.05mg/kg/min to control HR below 100/min within 2 hours.

d: Continuous intravenous infusion of esmolol, milrinone that commenced with a loading dosage of 30μg/kg and was maintained at 0.375–0.5μg/kg/min.

e: Continuous intravenous infusion of milrinone that commenced with a loading dosage of 30μg/kg and was maintained at 0.375–0.5μg/kg/min.

f: Micro pump with dosage of esmolol 0.05mg/kg/min to control HR below 100/min within 24 hours.

g: Continuous intravenous esmolol infusion for 24h, initial dose was 0.05mg/kg/h, to control HR below 95/min within 4 hours.

h: Isotonic saline was given to control group through intravenous line at 3mL/h for 24h.

j: Continuous esmolol micro pump commenced at 25mg/h to maintain HR 80-100/min within 12 hours.

HR: heart rate; WBC: White Blood Cell; ScvO2: central venous oxygen saturation; MAP: mean arterial pressure; CVP: central venous pressure; TnI: troponin I. SVI: Stroke Volume Index; CI: Cardiac index; TNF-a.: tumor necrosis factor-a; IL-6: interleukin6.

Figures

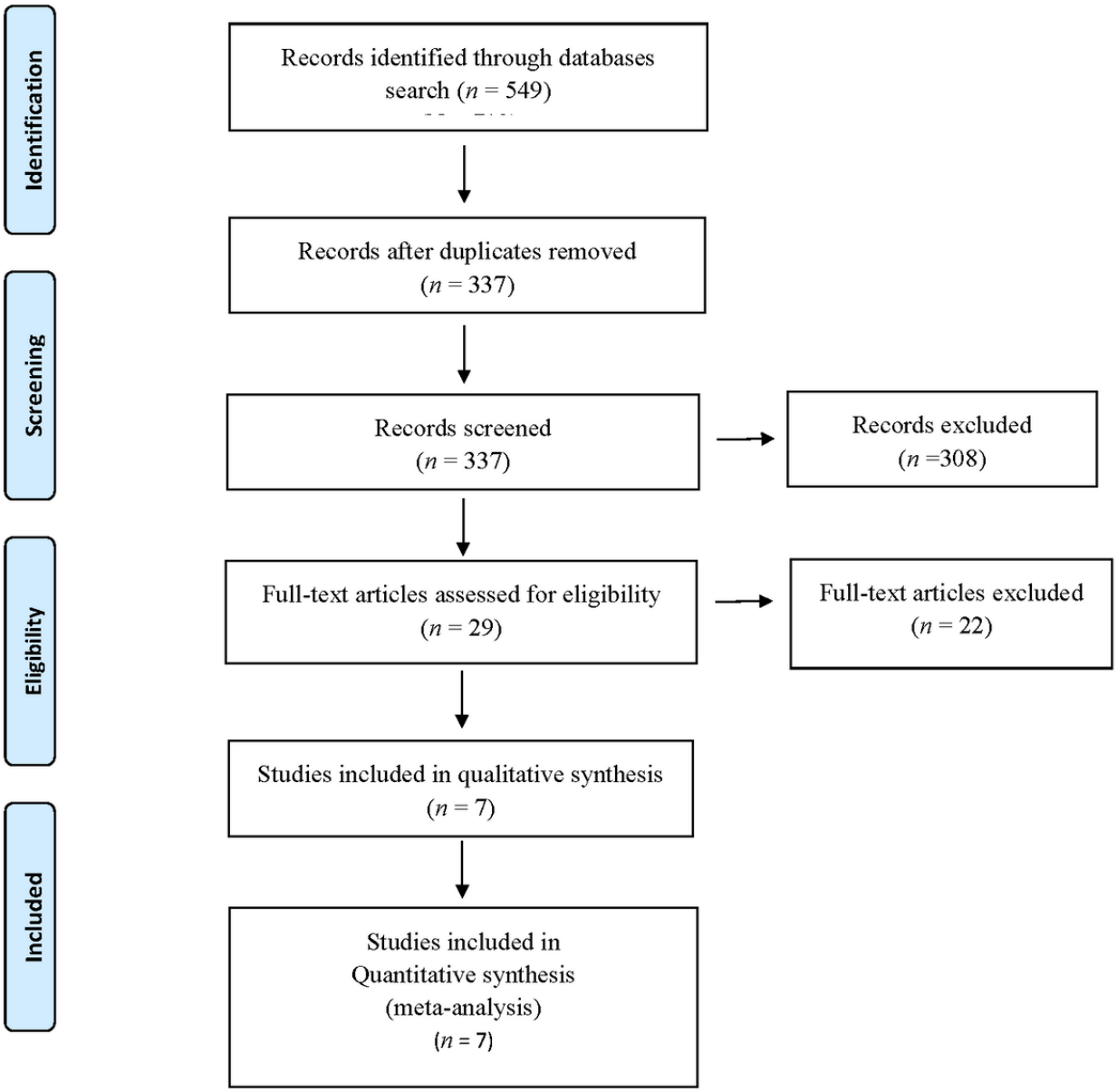

Figure 1

Study of flow diagram. All studies were randomized controlled trials.

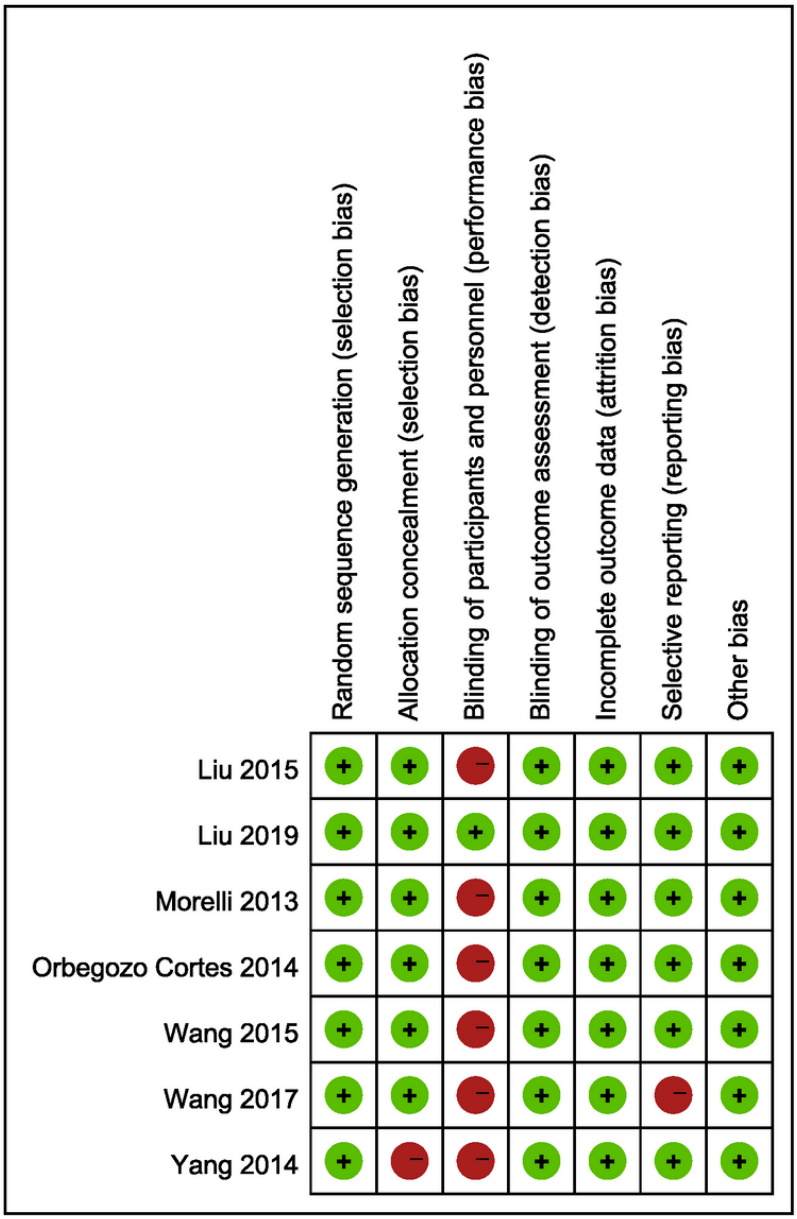

Figure 2

Risk of bias summary of the included studies.

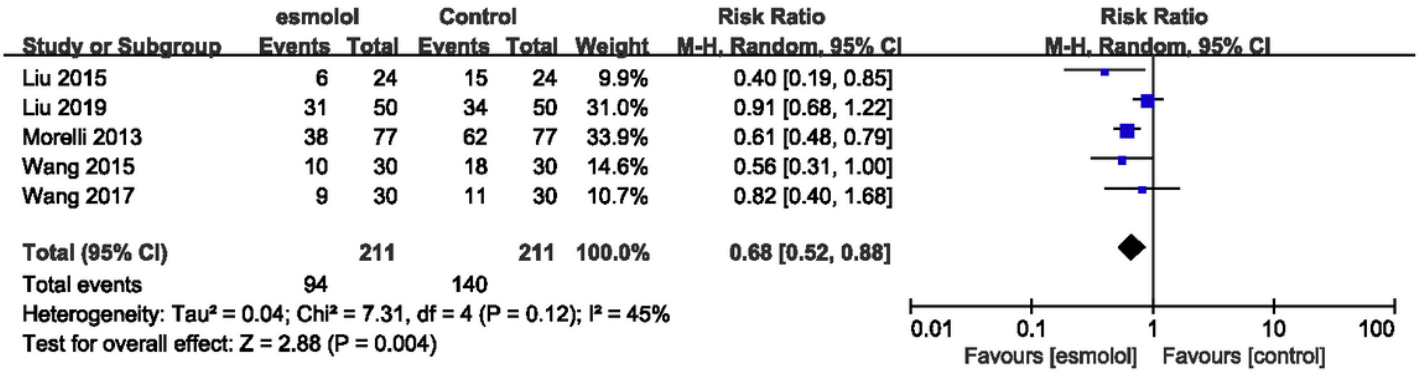

Figure 3

Forest plot of 28-day mortality.

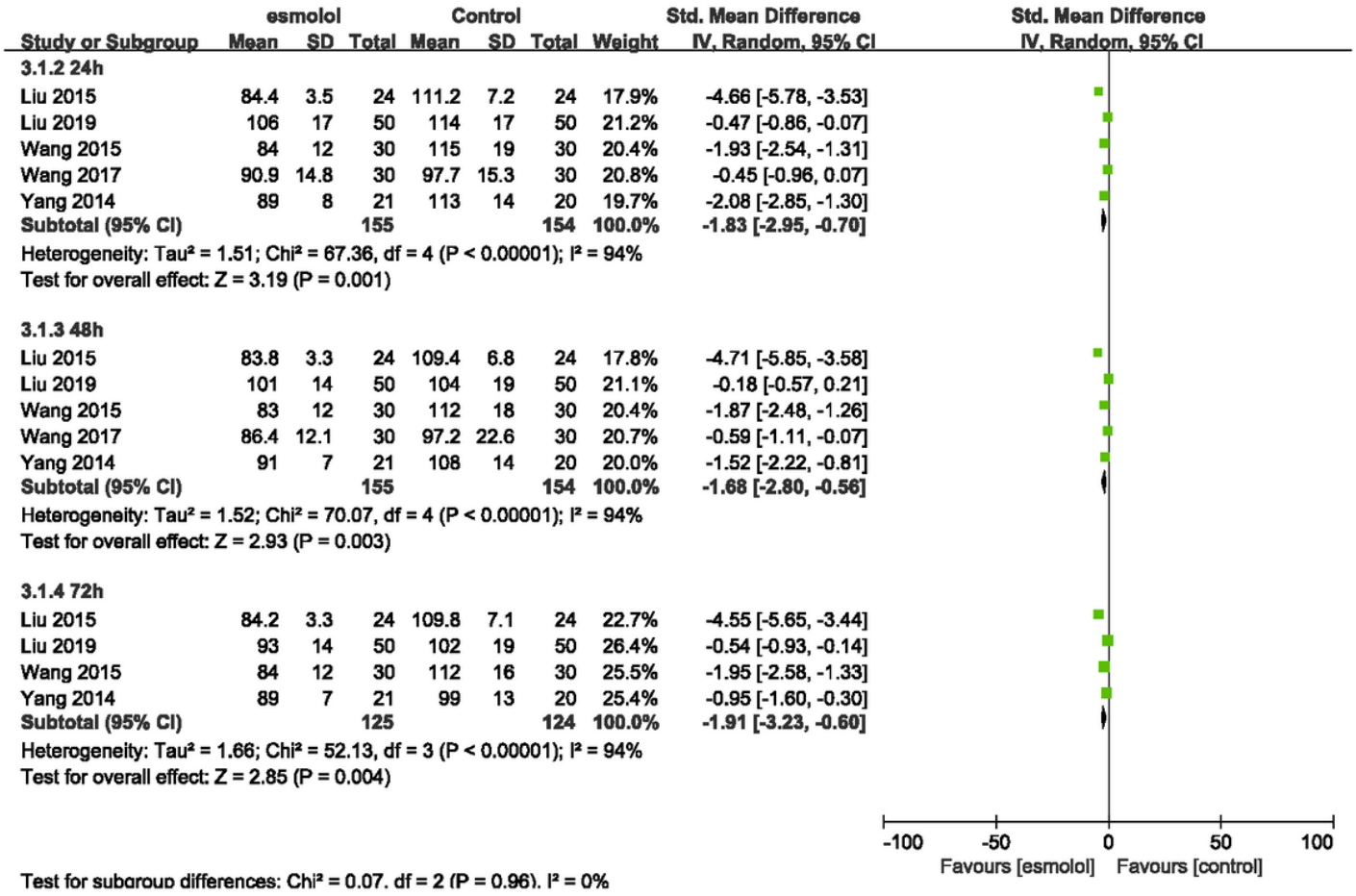

Figure 4

Forest plot of heart rate.

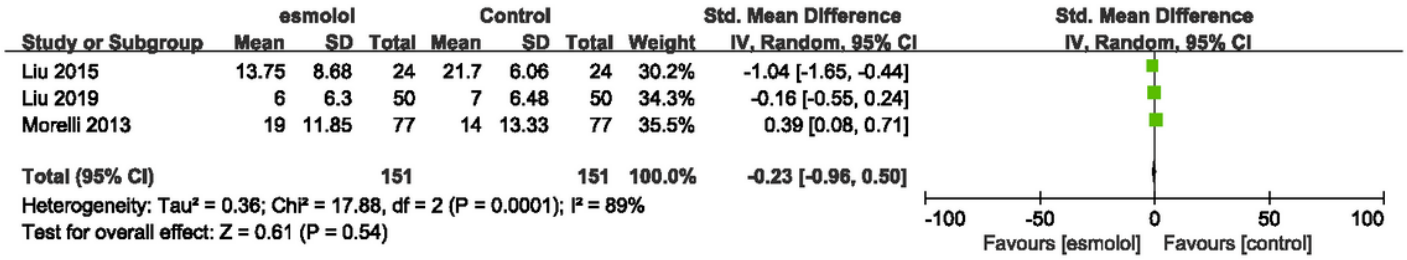

Figure 5

Forest plot of the length of ICU stay.

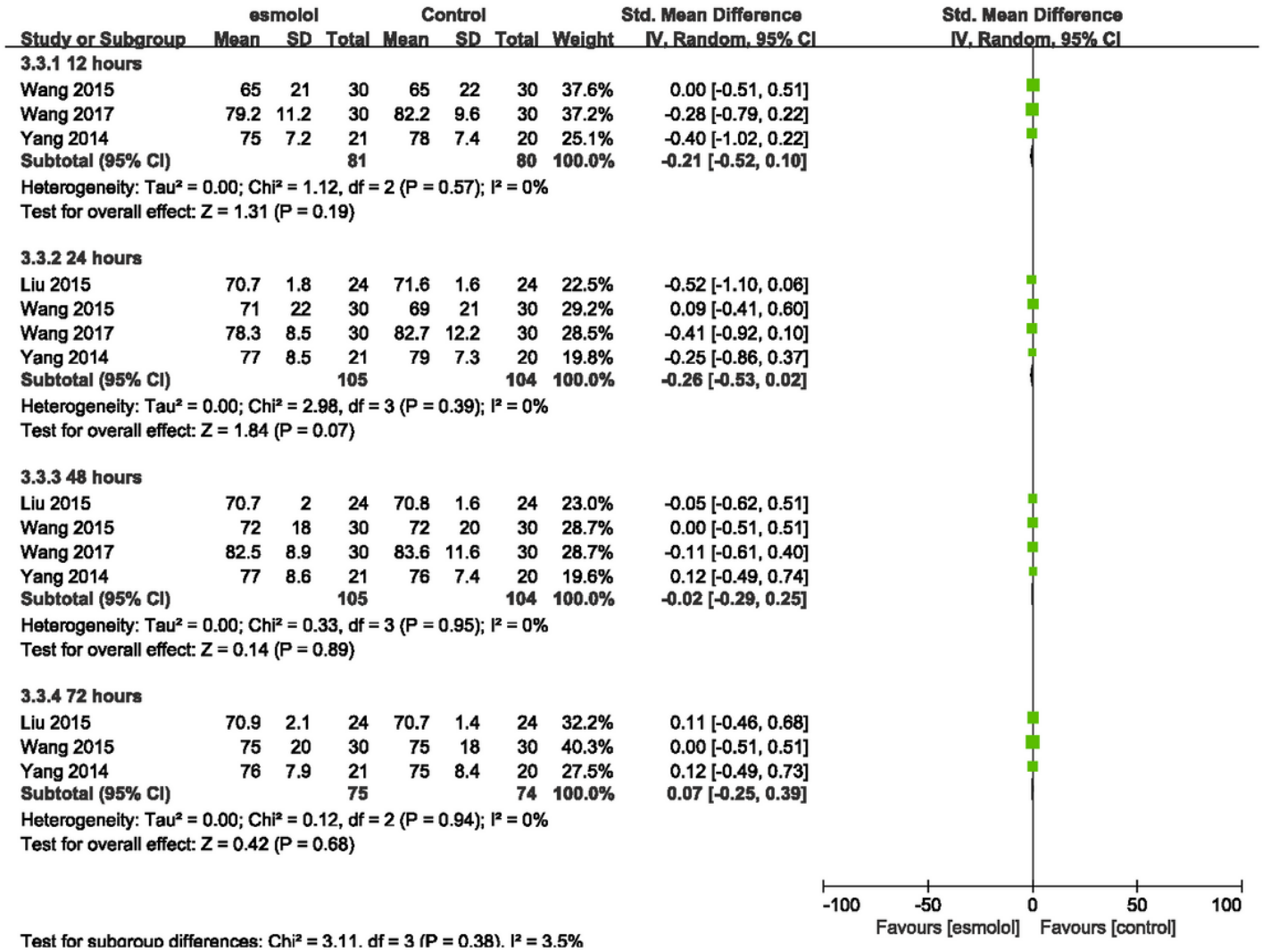

Figure 6

Forest plot of mean arterial pressure.

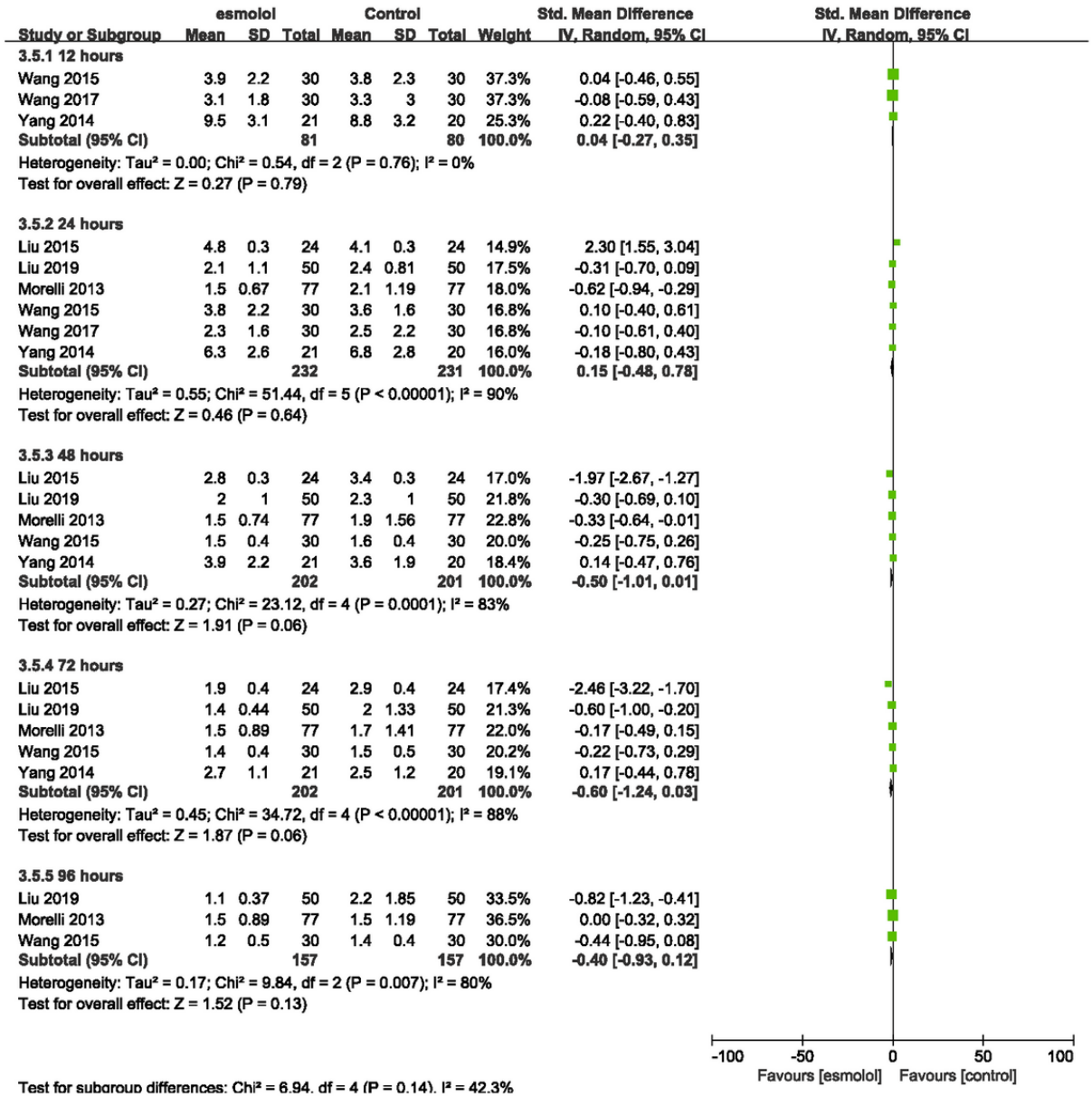

Figure 7

Forest plot of lactic acid.

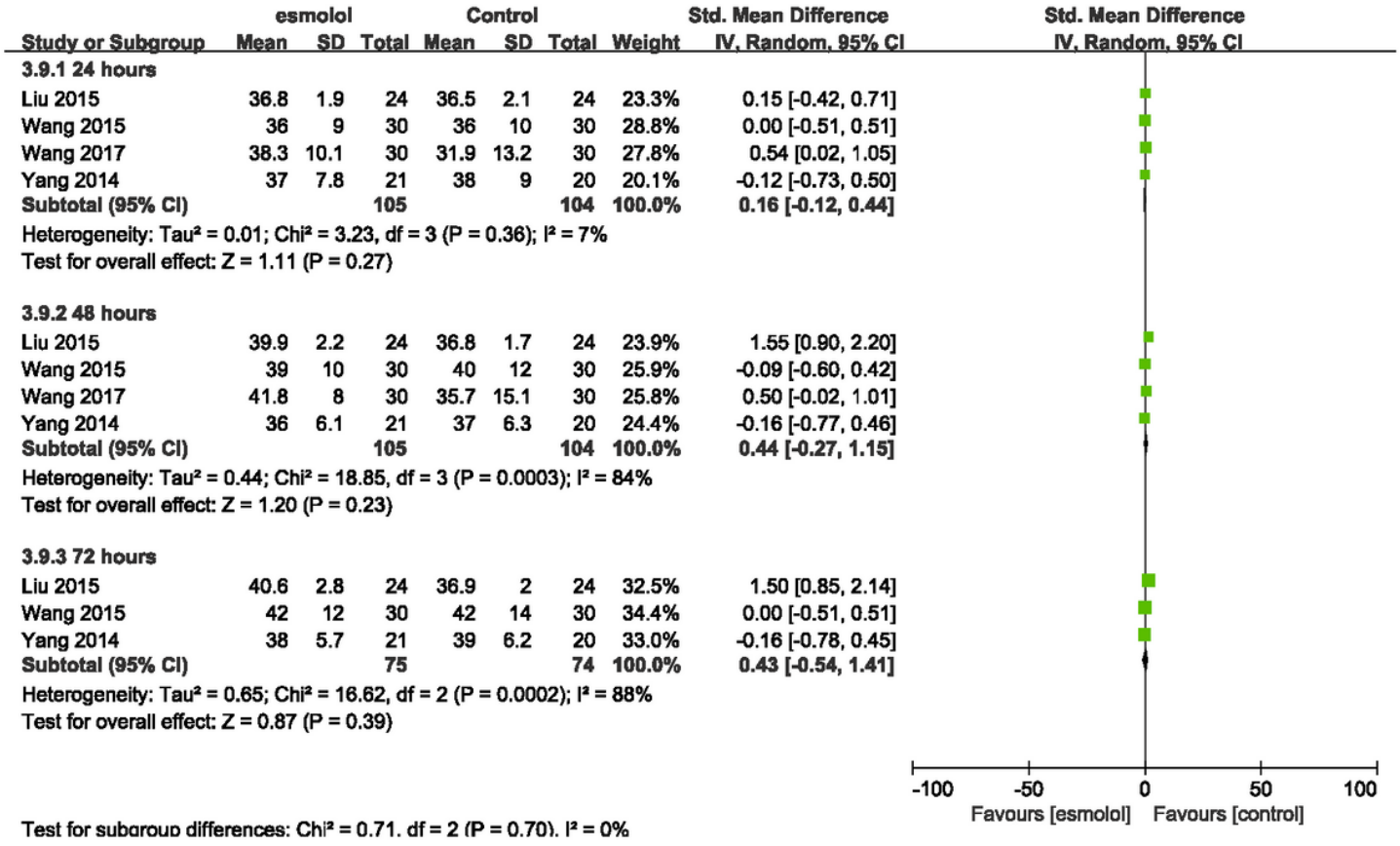

Figure 8

Forest plot of stroke volume index.

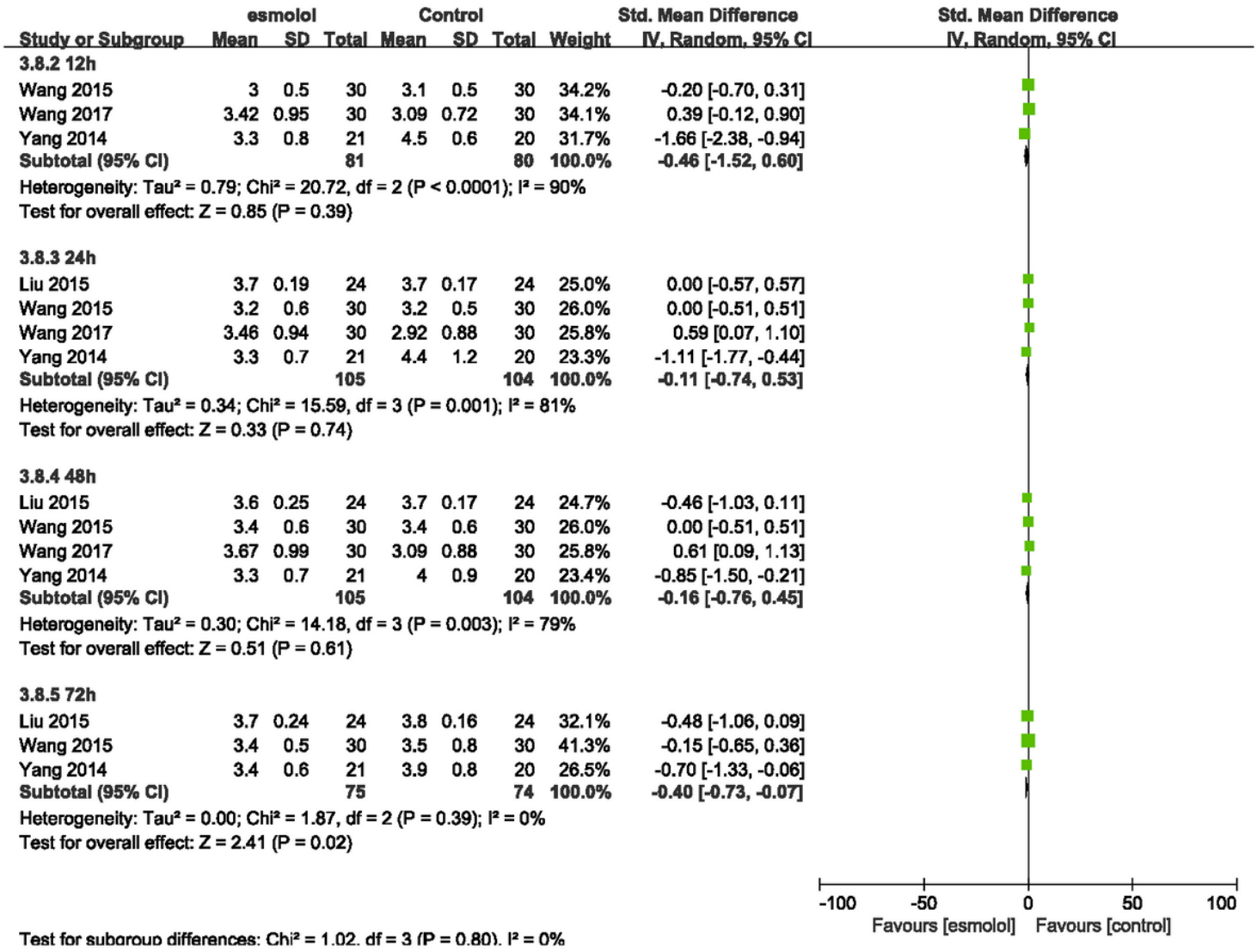

Figure 9

Forest plot of cardiac index.

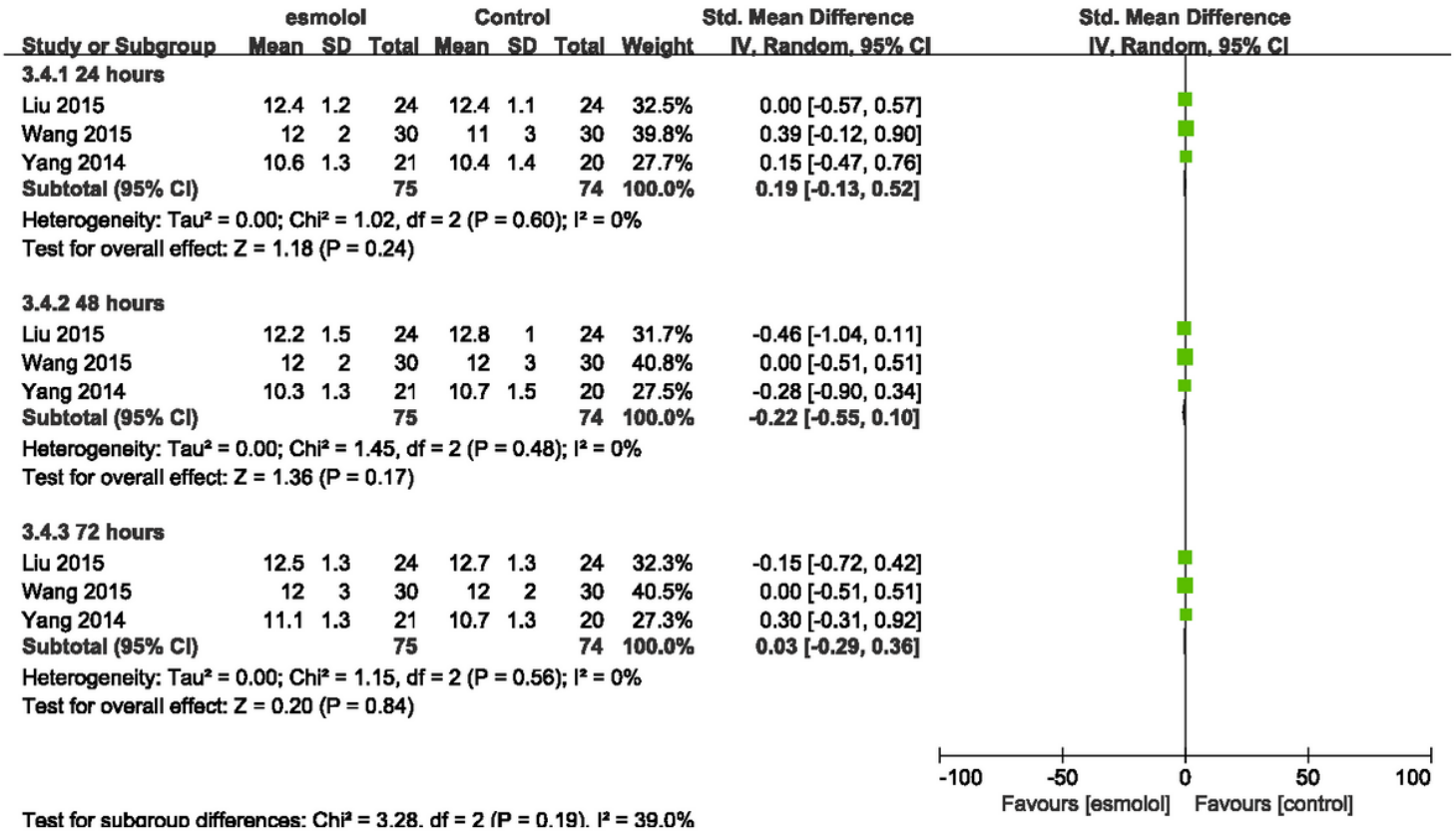

Figure 10

Forest plot of central venous pressure.

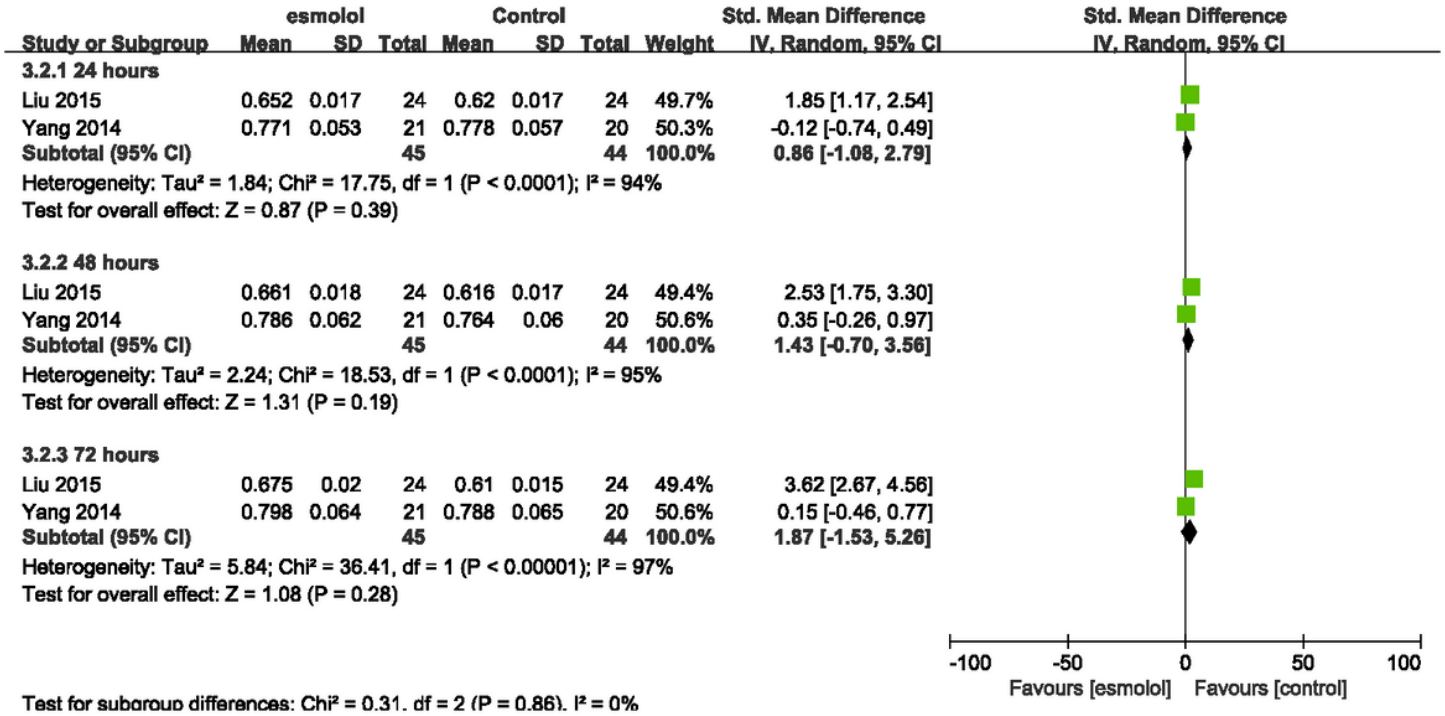

Figure 11

Forest plot of central venous oxygen saturation.

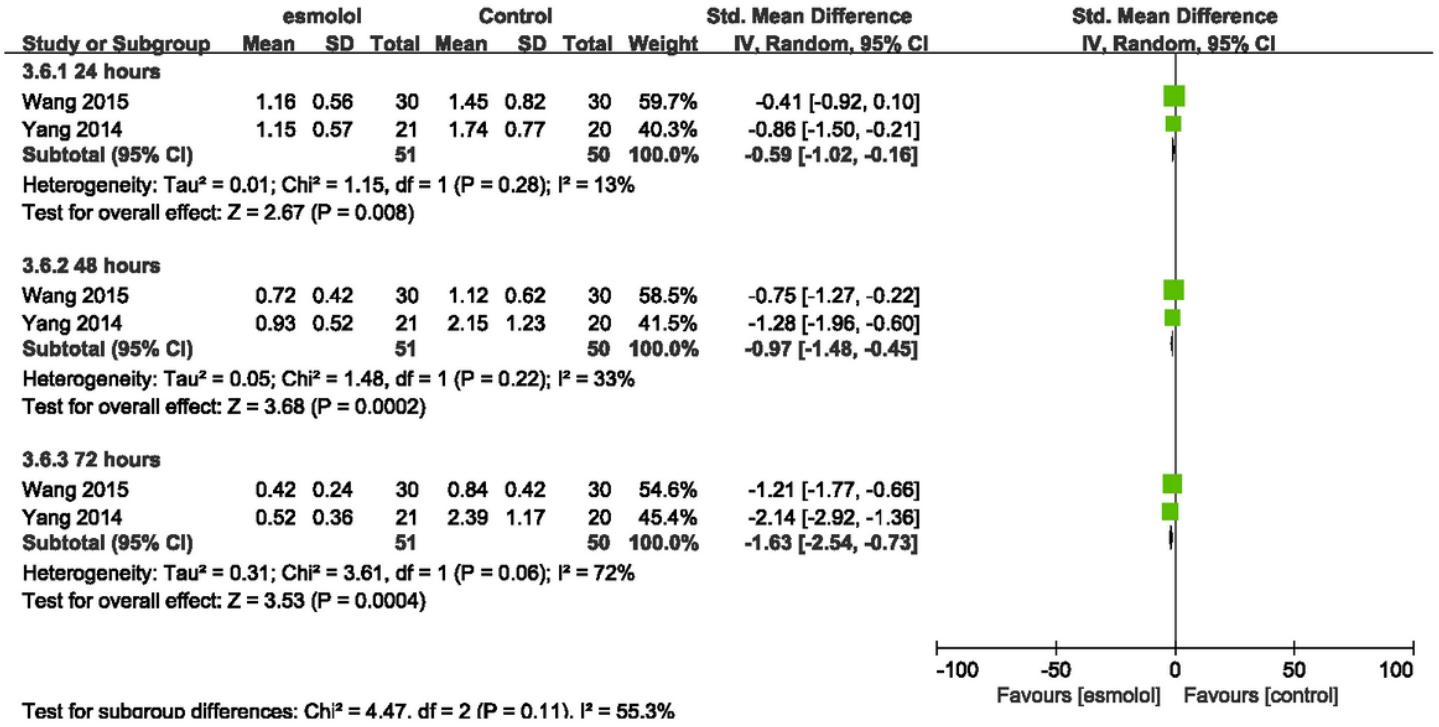

Figure 12

Forest plot of troponin I.

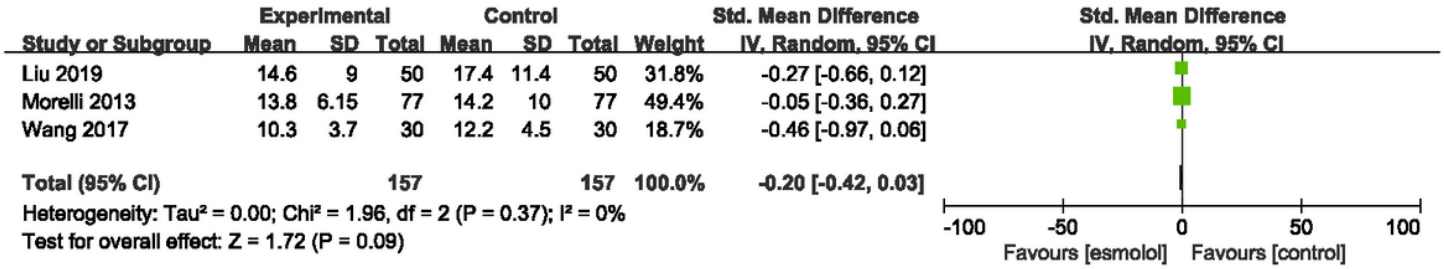

Figure 13

Forest plot of white blood cells.

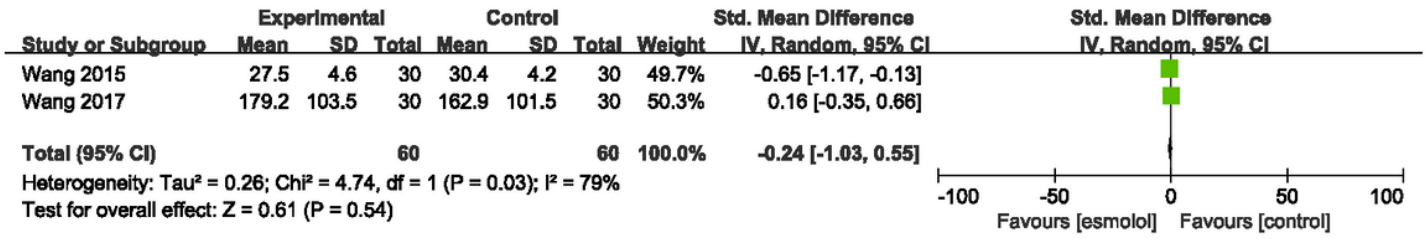

Figure 14

Forest plot of interleukin 6.

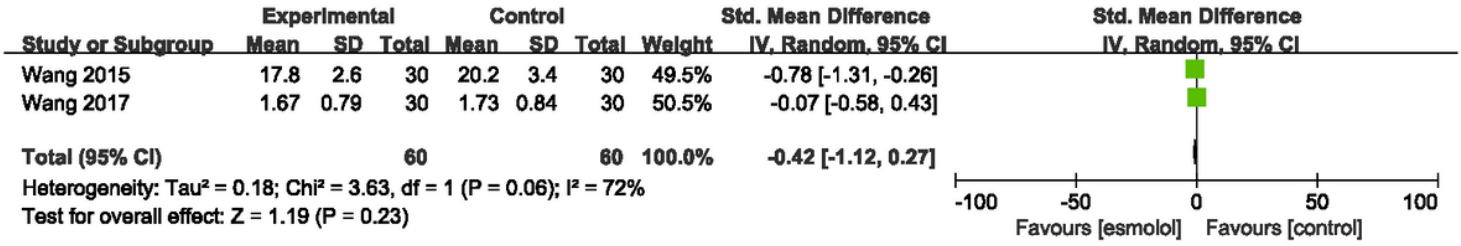

Figure 15

Forest plot of tumor necrosis factor-a.

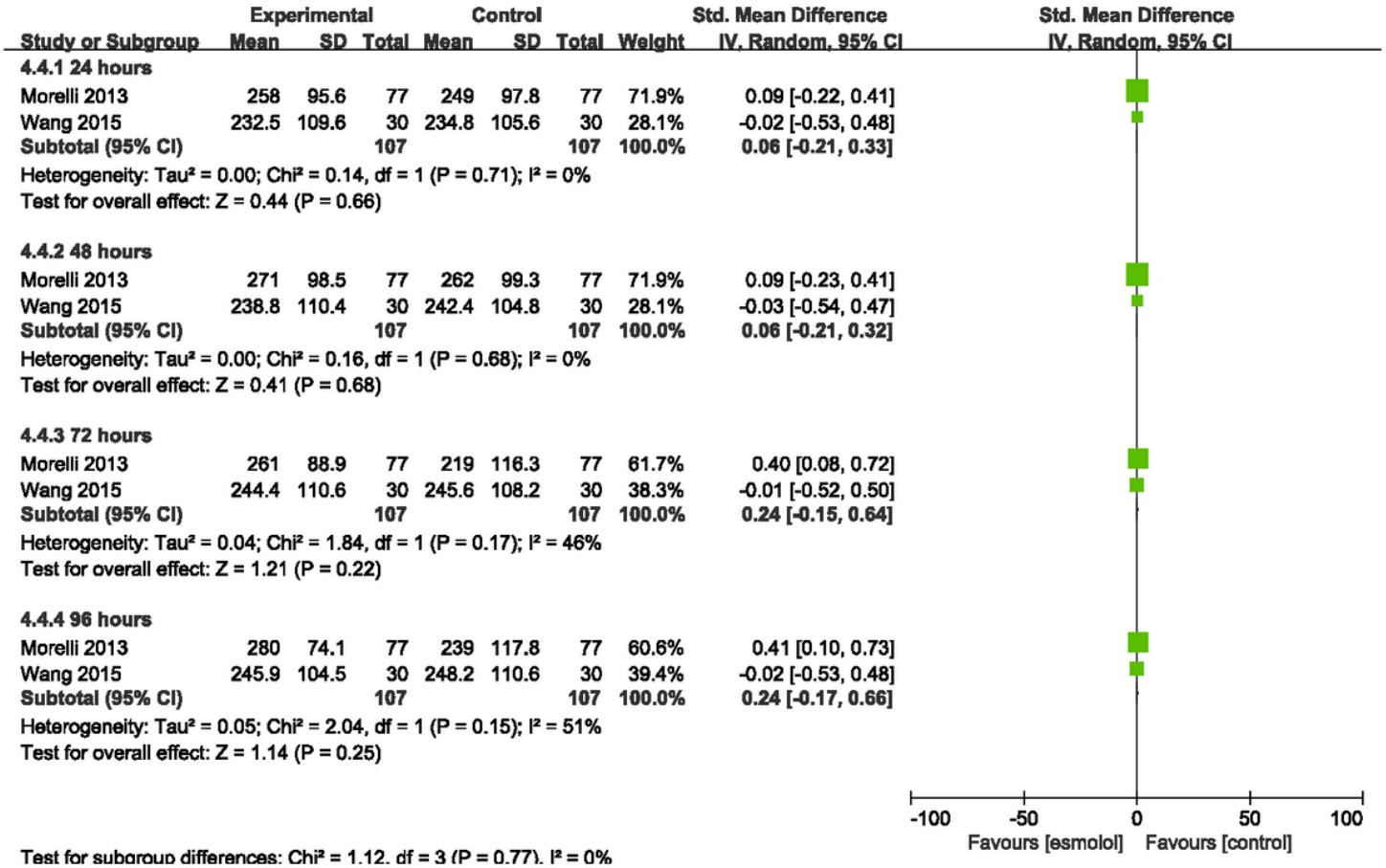

Figure 16

Forest plot of PO2/FiO2.