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**Meta-Analysis**

**Efficacy of beta-blockers in the treatment of sepsis**

## Efficacy of beta-blockers in the treatment of sepsis

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### Abstract

This meta-analysis is to systematically evaluate the efficacy and safety of beta-blockers in the treatment of sepsis. A total of 17 articles that met the inclusion criteria were included, and 10,385 cases were obtained. The meta-analysis results showed that patients with sepsis with beta-blocker usage had a significantly lower 28-day mortality. The heart rate decreased over time in patients with sepsis using beta-blocker. Moreover, central venous blood oxygen saturation increased after 24, 48, 72 hours of treatment; lactic acid and cardiac troponin I decreased after 48, 72 hours of treatment; and tumor necrosis factor- $\alpha$ , interleukin-1 $\beta$  levels decreased significantly after 12, 24, 48, 72 hours of treatment ( $p < 0.05$ ). In conclusion, beta-blockers reduce 28-day mortality and heart rate.

### Introduction

Sepsis is a systemic inflammatory response syndrome caused by infection of the body. It is a common complication of severe trauma, hypoxia, reperfusion injury and major surgery. Sepsis accompanied by organ dysfunction can develop into severe sepsis, and hypotension caused by sepsis that has not improved with fluid therapy develops into septic shock. Patient with sepsis has a poor prognosis and a high mortality rate, and is the first cause of death for patients in the intensive care unit (Wang et al., 2012). Published studies have shown that about two-thirds and more of patients with severe sepsis experience varying degrees of heart damage (Muriova et al., 2010), and the pathogenesis may be related to microcirculation disorders (Lorigados et al., 2010), ischemia-reperfusion injury, superoxidative stress (Jaffee et al., 2018), changes in catecholamine levels, etc.

Beta-blocker selectively binds to beta-adrenergic receptors, so as to antagonize the activation of beta receptor by neurotransmitter and catecholamine (Ogrodowczyk et al., 2016). A number of clinical trials assessed in the previous meta-analysis showed beneficial results for beta-blocker usage in the patients with sepsis (Lee et al.,

2019). The purpose of this study is to systematically evaluate the efficacy and safety of beta-blockers in the treatment of sepsis with a view to provide more reliable evidence for its clinical practice and further research.

### Materials and Methods

#### Retrieval strategy

Computer search of MedLine, ISI Web of science, EMBase, Google scholar, Spinger Link, China National Knowledge Infrastructure, Wanfang Database, China Science and Technology Journal Database and Chinese Biomedical Literature Database were done. The time since the database was established until September 10, 2017.

The search is mainly based on the combination of subjective terms and random terms. No search restrictions were imposed, and all research related to the subject were collected as much as possible. The English search terms were "sepsis", "septic shock", "severe sepsis", "beta-blocker", " $\beta$ -blocker", "esmolol", "propranolol", "bisoprolol", "atenolol", "metoprolol". The Chinese search terms were “脓毒症”, “严重脓毒症”, “脓毒



性休克”，“β受体阻滞剂”，“β受体阻断剂”，“艾司洛尔”，“普萘洛尔”，“比索洛尔”，“阿替洛尔”，“美托洛尔”。

At the same time, we manually searched the references of included research and related reviews to prevent omissions, and contacted experts and corresponding authors in the field to obtain relevant information not found in the above search.

#### **Inclusion criteria**

According to the "International Guidelines for Management of Severe Sepsis and Septic Shock: 2012" (Phillips et al., 2012) and the "Chinese Guidelines for Management of Severe Sepsis and Septic Shock: 2014" (Zhi et al., 2015) published by the Society of Critical Care Medicine, Chinese Medical Association, the followings were included: a) study subjects were patients diagnosed with sepsis or severe sepsis or septic shock; b) intervention was the use of β-blockers; c) study subjects were adult patients (18 years of age or older); d) types of studies were randomized controlled studies (RCT) and non-randomized prospective and retrospective studies; and e) published collectable full text or original articles.

#### **Exclusion criteria**

Exclusion criteria were as follows: a) patients not diagnosed with sepsis or severe sepsis or septic shock; b) intervention measures without the use of beta-blockers; c) children (ages less than 18 years old); d) animal experiments; e) individual case reports; f) unable to extract available data from published articles; and g) repeatedly published articles, reviews, and articles with the same clinical data.

#### **Data extraction and quality evaluation**

Two researchers independently searched and read the literature, and evaluated the quality of the obtained literature. The literature obtained as final were cross-check. If there was any disagreement, find the original evidence and ask the third-party researchers to discuss again to reach an agreement. Relevant data were extracted from the included literature through multiple advanced search engines. If the information was incomplete or in doubt, contacted the author by email or phone to obtain accurate and complete information.

Regarding quality evaluation: For RCT, using the Jadad score system to evaluate the methodological quality of the included literature. 1-3 points were classified as low quality, and 4-7 points were classified as high quality (Jadad et al., 1997); for non-randomized prospective and retrospective studies, the Newcastle-Ottawa Scale (NOS) scale recommended by the Cochrane Collaboration for the quality evaluation of non-random research methodologies was used to evaluate the quality of the

included studies. 0-5 points were classified as low quality, 6-9 points were classified as high quality (Stang, 2010).

#### **Statistical analysis**

Statistical analysis was performed using STATA 11.0 software. The measurement data were expressed as standardized mean difference (SMD) and its 95% CI as the effect size, and the count data uses odd ratios (OR) and its 95% CI as the effect size. The heterogeneity between the results of the included studies was statistically analyzed using the  $\chi^2$  test, with a significance level of  $\alpha=0.1$ . When there was statistical homogeneity between the studies (when  $p>0.1$ ,  $I^2<50\%$ ), a fixed effect model was used for analysis. If there was statistical heterogeneity between the studies (when  $p\leq 0.1$ ,  $I^2>50\%$ ), a random effect model was used for analysis. A p-value  $<0.05$  was considered to be statistically significant.

## **Results**

#### **Literature search results**

At first, 852 related studies were retrieved. The duplicate publications were removed. Abstracts and case reports were excluded from the irrelevant studies. A total of 379 studies were initially included. After further reading, after layer-by-layer screening, 17 studies were finally included. The literature screening process and results were shown in Figure 1.

#### **Basic characteristics and quality evaluation of included studies**

The 17 included articles included RCT and non-randomized prospective and retrospective studies. Of these, there were 7 RCTs (Gong et al., 2013; Morelli et al., 2013; Ma, 2014; Yang et al., 2014; Gao et al., 2015; Liang et al., 2015; Xinqiang et al., 2015), 6 prospective studies (Gore and Wolfe, 2006; Balik et al., 2012; Chen et al., 2013; Tao et al., 2015; Morelli et al., 2016; Shang et al., 2016), and 4 retrospective studies (Schmittinger et al., 2008; Gutierrez et al., 2009; Macchia et al., 2012; Wei et al., 2013). There were no statistically significant differences in age, gender, and vital signs between the experimental group and the control group in the included studies. The baselines between the groups were consistent and had good comparability. The basic characteristics of the included studies were shown in Table I.

The results of the methodological study on quality evaluation of the included studies were shown in Table II and Table III. The 7 RCT studies used the Jadad scoring system for quality evaluation, of which 5 studies were  $\geq 4$  points and 2 studies were 3 points, indicated that the quality of the included articles were

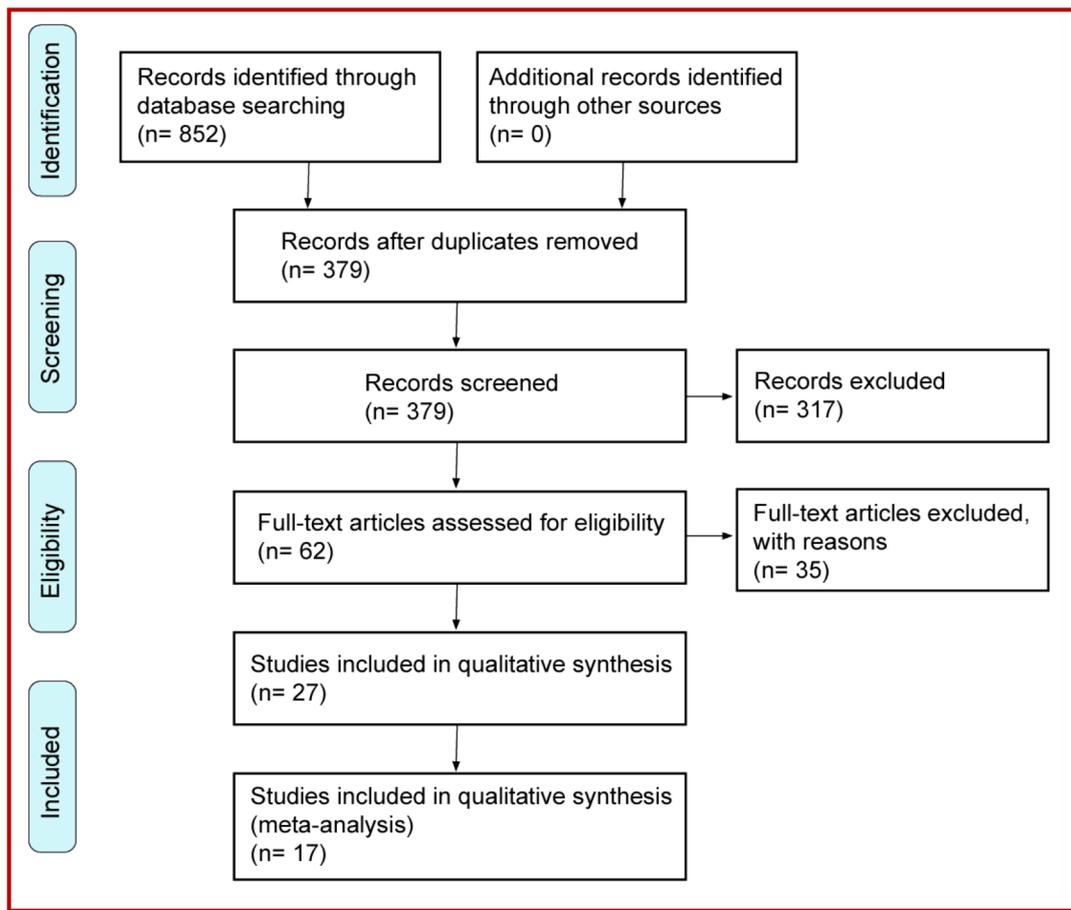


Figure 1: Flow diagram of included studies

good. The confidence level of the results was high.

### Meta-analysis results

#### Main outcome indicators (28-day mortality)

Comparison of 28-day mortality in 7 included studies showed that there was heterogeneity among groups ( $I^2 = 80.4\%$ ) and were analyzed using a random effects model. Meta-analysis results showed that there was a statistically significant difference in mortality between the experimental group and the control group [ $OR$  (95%  $CI$ ) = 0.525 (0.263, 0.787),  $p < 0.001$ ], indicated that beta-blockers can reduce the sepsis mortality (Figure 2).

#### Secondary outcome indicators

##### Hemodynamic indicators (heart rate)

Twelve articles reported the heart rate of the two groups, of which the 2, 3, and 4 hours groups were homogeneous between studies and combined using a fixed effect model; The 6, 12, 24, 48, and 72 hours groups were heterogeneous, and they were combined using a random effects model. Meta-analysis results showed that the  $SMD$  (95%  $CI$ ) of heart rate after each time point were [-1.633 (-2.283, -0.984)], [-1.653 (-2.346, -0.960)], [-2.537 (-3.044, -2.030)], [-1.346 (-2.335, -0.356)], [-

1.484 (-2.027, -0.940)], [-2.051 (-2.570, -1.531)], [-1.946 (-2.652, -1.239)], [-2.701 (-3.552, -1.851)] (all  $p < 0.05$ ), the difference was statistically significant, suggested that the use of beta-blockers is meaningful for slowing the heart rate of patients with sepsis (Figure 3).

##### Mean arterial pressure

Seven articles reported the mean arterial pressure of the two groups. The study groups at each time point were homogeneous, and they were combined using a fixed effect model. Meta-analysis results showed that after 24 hours of treatment, the mean arterial pressure in the experimental group was lower than that in the control group, and the difference was statistically significant ( $SMD = -0.217$ , 95%  $CI = -0.361 \sim -0.072$ ,  $p = 0.003$ ). There was no significant difference in mean arterial pressure results between the two groups of treatments at other time points (Figure 4).

##### Central venous pressure

Eight articles reported central venous pressure in the two groups, of which the 4 and 12 hours groups were homogeneous and combined using a fixed effect model; the 24, 48, and 72 hours groups were heterogeneous, and were combined using random effects model. Meta-

Table I

## Basic characteristics of included studies

Included studies	n		Gender (Male/Female)		Age (mean $\pm$ SD)		Intervention measures	APACHE II		Study type
	T	C	T	C	T	C		T	C	
Morelli et al., 2013	77	77	54 / 7	53 / 24	66 (IQR : 52-75)	69 (IQR : 58-78)	Esmolol	N/A	N/A	RCT
Yang et al., 2014	21	20	N/A	N/A	51.0 $\pm$ 22.6	51.0 $\pm$ 22.6	Esmolol	20.1 $\pm$ 9.2	21.3 $\pm$ 8.3	RCT
Liang et al., 2015	30	30	14 / 16	13 / 17	54.3 $\pm$ 4.3	54.2 $\pm$ 4.5	Metoprolol	N/A	N/A	RCT
Gao et al., 2015	33	29	13 / 20	N/A	51.7 $\pm$ 10.0	N/A	Esmolol	17.1 $\pm$ 4.9	18.3 $\pm$ 5.2	RCT
Gong et al., 2013	42	47	20 / 22	26 / 21	42.5 $\pm$ 11.5	41.8 $\pm$ 12.4	Esmolol	11.7 $\pm$ 3.4	13.4 $\pm$ 2.7	RCT
Liu et al., 2015	24	24	14 / 10	13 / 11	61.4 $\pm$ 6.9	61.2 $\pm$ 6.4	Esmolol	20.8 $\pm$ 3.1	21.2 $\pm$ 2.7	RCT
Ma, 2014	45	45	25 / 20	23 / 22	40.9 $\pm$ 10.3	41.7 $\pm$ 10.5	Esmolol	15.4 $\pm$ 3.6	14.8 $\pm$ 4.1	RCT
Shang et al., 2016	75	76	4 / 21	53 / 23	N/A	N/A	Esmolol	24.2 $\pm$ 7.7	25.5 $\pm$ 7.8	Prospective study
Balik et al., 2012	10		4/6		54.4 $\pm$ 19		Esmolol	21.5 $\pm$ 6.2		Prospective study with self-contrast method
Gore and Wolfe, 2006	6		N/A		41 $\pm$ 7		Esmolol	17 $\pm$ 2		Prospective study with self-contrast method
Morelli et al., 2016	45		33 / 12		61 $\pm$ 18		Esmolol	N/A		Prospective study with self-contrast method
Yu et al., 2015	15		9 / 6		65 $\pm$ 16		Esmolol	21 $\pm$ 9		Prospective study with self-contrast method
Chen et al., 2013	16		14 / 2		58 $\pm$ 6		Esmolol	N/A		Prospective study with self-contrast method
Schmittinger et al., 2008	40		21 / 9		71 $\pm$ 13		Metoprolol	N/A		Retrospective study with self-contrast method
Wei et al., 2013	10		8 / 2		56 $\pm$ 8		Esmolol	N/A		Retrospective study with self-contrast method
Gutierrez et al., 2009	29	54	15 / 14	26 / 28	58.9 $\pm$ 16.7	53.6 $\pm$ 17.9	$\beta$ -blockers	79.9 $\pm$ 23.5		Retrospective study
Macchia et al., 2012	1061	8404	522 / 539	4186 / 4218	72.0 $\pm$ 10.6	72.0 $\pm$ 13.0	$\beta$ -blockers	N/A		Retrospective study

T: treatment group; C: control group; N/A: Not applicable; IQR: interquartile range

Table II						
Using the Jadad scoring system to evaluate the quality of included RCT studies						
Studies	Random method	Allocation concealment	Blinding	Withdrew/lost	Scores	Quality grade
Morelli et al., 2013	Appropriate	Appropriate	Appropriate	Described	7	High
Yang et al., 2014	Appropriate	Unclear	Unclear	Not described	4	High
Liang et al., 2015	Appropriate	Unclear	Unclear	Not described	4	High
Gao et al., 2015	Appropriate	Unclear	Unclear	Described	5	High
Gong et al., 2013	Unclear	Unclear	Unclear	Not described	3	Low
Liu et al., 2015	Appropriate	Appropriate	Appropriate	Not described	6	High
Ma, 2014	Unclear	Unclear	Unclear	Not described	3	Low

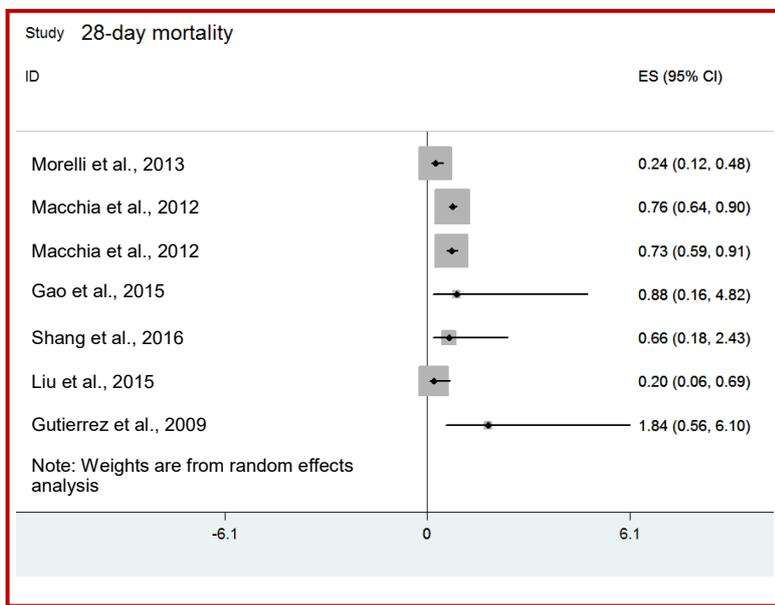


Figure 2: Meta-analysis of beta-blocker on the 28-day mortality

analysis results showed that there was no significant difference in central venous pressure results between the experimental group and the control group at each time point ( $p > 0.05$ ) (Figure 5).

**Cardiac index**

Six articles reported the cardiac index of the two groups, of which the 3 and 6 hours groups were homogeneous between studies and were combined using a fixed effect model; the 12, 24, 48, and 72 hours groups were heterogeneous, and they were combined using a random effects model. Meta-analysis results showed that there was no significant difference in cardiac index between the experimental group and the control group at each time point ( $p > 0.05$ ) (Figure 6).

**Stroke volume index**

Five articles reported the stroke volume index of the two groups, of which the 3 hours group was

homogeneous between studies and combined using a fixed effect model; the 12, 24, 48, and 72 hours groups were heterogeneous, and they were combined using a random effects model. Meta-analysis results showed that there was no significant difference in the stroke volume index between the experimental group and the control group at each time point ( $p > 0.05$ ) (Figure 7).

**Systemic vascular resistance index**

Six articles reported the systemic vascular resistance index of the two groups. The studies were homogeneous at each time point and were combined using a fixed effect model. Meta-analysis showed that there was no significant difference in systemic vascular resistance index between the experimental group and the control group at each time point ( $p > 0.05$ ) (Figure 8).

**Noradrenaline dosage**

Two articles reported norepinephrine dosage in the two

Table III

## Quality evaluation of included non-randomized prospective and retrospective studies using the NOS scale

Included studies	Selection			Comparability			Outcome			Scores	Quality grade
	Representativeness of exposure group	Selection of non-exposed groups	Exposure confirmation	No outcome at the start of the study	Primary factor	Other factors	Outcome measurement	Sufficient follow-up time	Proper follow-up		
Shang et al., 2016	*	*	*		*	*	*	*	*	7	High
Balik et al., 2012		*	*		*	*	*	*	*	6	High
Gore and Wolfe, 2006		*	*		*	*	*	*	*	6	High
Morelli et al., 2016		*	*		*	*	*	*	*	6	High
Yu et al., 2015		*	*		*	*	*	*	*	6	High
Chen et al., 2013		*	*		*	*	*	*	*	6	High
Schmittinger et al., 2008	*	*	*		*	*	*	*	*	8	High
Wei et al., 2013		*	*		*	*	*	*	*	7	High
Gutierrez et al., 2009		*	*		*	*	*	*	*	7	High
Macchia et al., 2012	*	*	*		*	*	*	*	*	8	High

groups. The studies were homogeneous at each time point and were combined using a fixed effect model. Meta-analysis results showed that there was no significant difference in norepinephrine between the experimental group and the control group at each time point ( $p>0.05$ ) (Figure 9).

#### Left ventricular ejection fraction

Six articles reported the left ventricular ejection fraction of the two groups, of which the 4, 48, and 72 hours groups were homogeneous between studies and were combined using a fixed effect model; The 12 and 24 hours groups were heterogeneous, and they were combined using a random effects model. Meta-analysis results showed that the left ventricular ejection fraction of the experimental group was higher than that of the control group after 12 hours of treatment, and the difference was statistically significant (SMD= 0.398, 95% CI= 0.067, 0.730,  $p=0.019$ ); there was no significant difference in left ventricular ejection fraction between the two groups of treatments at other time points (Figure 10).

#### Tissue perfusion indicators

##### Central venous blood oxygen saturation

Four articles reported central venous oxygen saturation (ScvO<sub>2</sub>) in two groups, of which the 12 hours group had homogeneity between studies and was combined using a fixed effect model; the 24, 48, and 72 hours groups were heterogeneous, and were combined using a random effects model. Meta-analysis results showed that there was no significant difference in ScvO<sub>2</sub> between the experimental group and the control group after 12 hours of treatment; the SMD (95% CI) of ScvO<sub>2</sub> after 24, 48, and 72 hours of treatment were [0.634 (0.194, 1.073)], [0.973 (0.313, 1.632)], [1.054 (0.441, 1.667)] (all  $p<0.05$ ), the difference was statistically significant, suggested that beta-blockers can increase central venous blood oxygen saturation (Figure 11).

##### Blood lactic acid

Six articles reported blood lactic acid levels in the two groups, of which the 2 hours group had homogeneity between studies and were combined using a fixed effect model; the 12, 24, 48, and 72 hours groups were heterogeneous, and they were combined using a random effects model. Meta-analysis results showed that there was no statistically significant difference in lactic acid levels between the experimental group and the control group after 2, 12, and 24 hours of the treatment; SMD (95% CI) of blood lactic acid level after 48 and 72 hours of the treatment were [-1.697 (-3.006,-0.388)], [-2.102 (-3.279, -0.926)] (all  $p<0.05$ ), and the

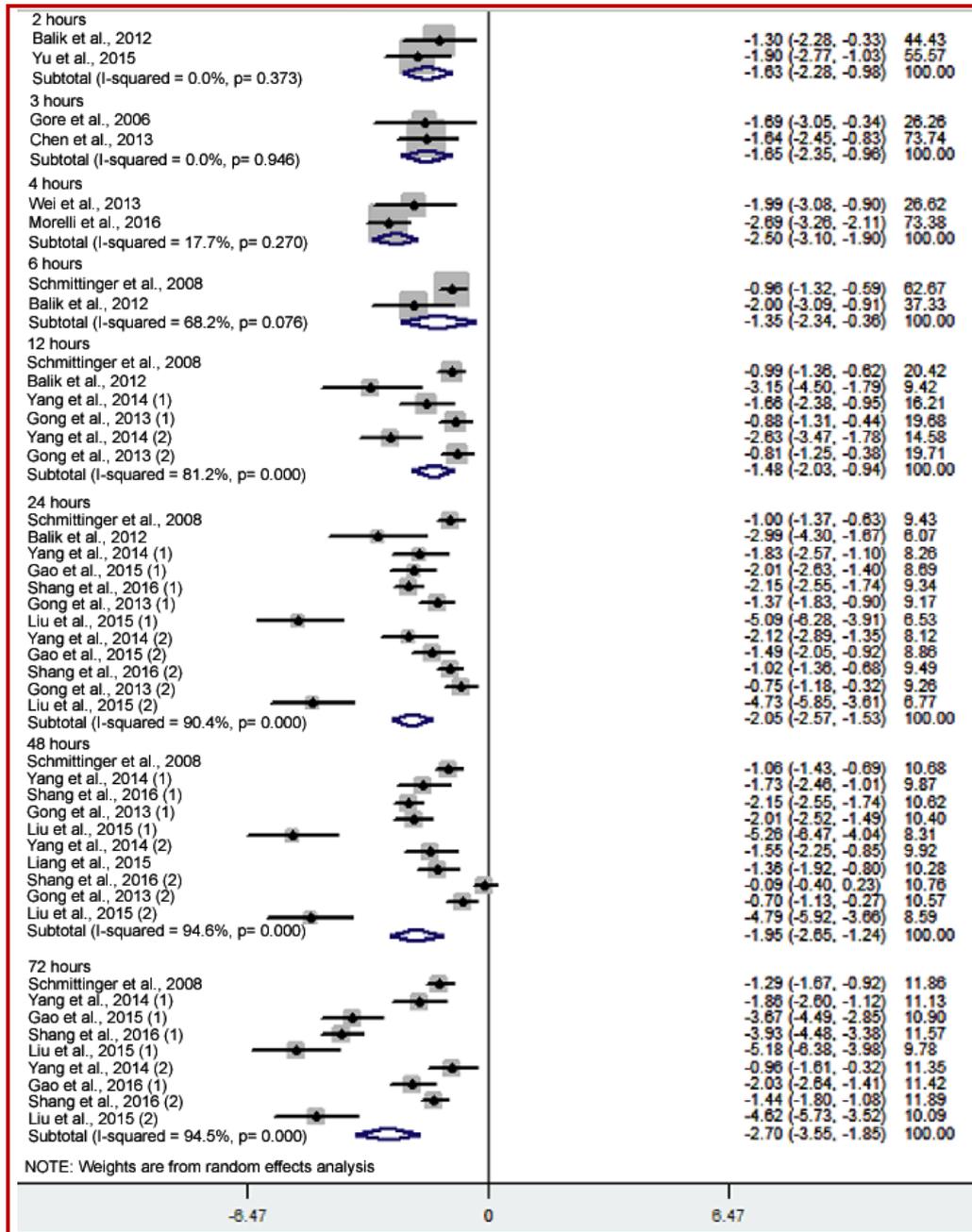


Figure 3: Meta-analysis of beta-blocker on the heart rate (digit within the parenthesis means the number of studies for comparison)

difference was statistically significant (Figure 12).

**Other physiological indicators**

**Cardiac troponin I**

Two articles reported cardiac troponin I (cTnI) in two groups, of which the 12 hours group had homogeneity between studies and was combined using a fixed effect model; the 24, 48, and 72 hours groups were heterogeneous, and were combined using a random effects model. Meta-analysis results showed that the

SMD (95% CI) of cTnI after 48 and 72 hours of the treatment were [-1.217 (-2.282, -0.151)], [-1.725 (-2.579, -0.872)] (all p<0.05) and the difference was statistically significant; there was no significant difference in cTnI between the two groups of treatments at other time points (Figure 13).

**Tumor necrosis factor-α**

Three articles reported tumor necrosis factor-α (TNF-α) in two groups, of which the 12 and 24 hours groups had

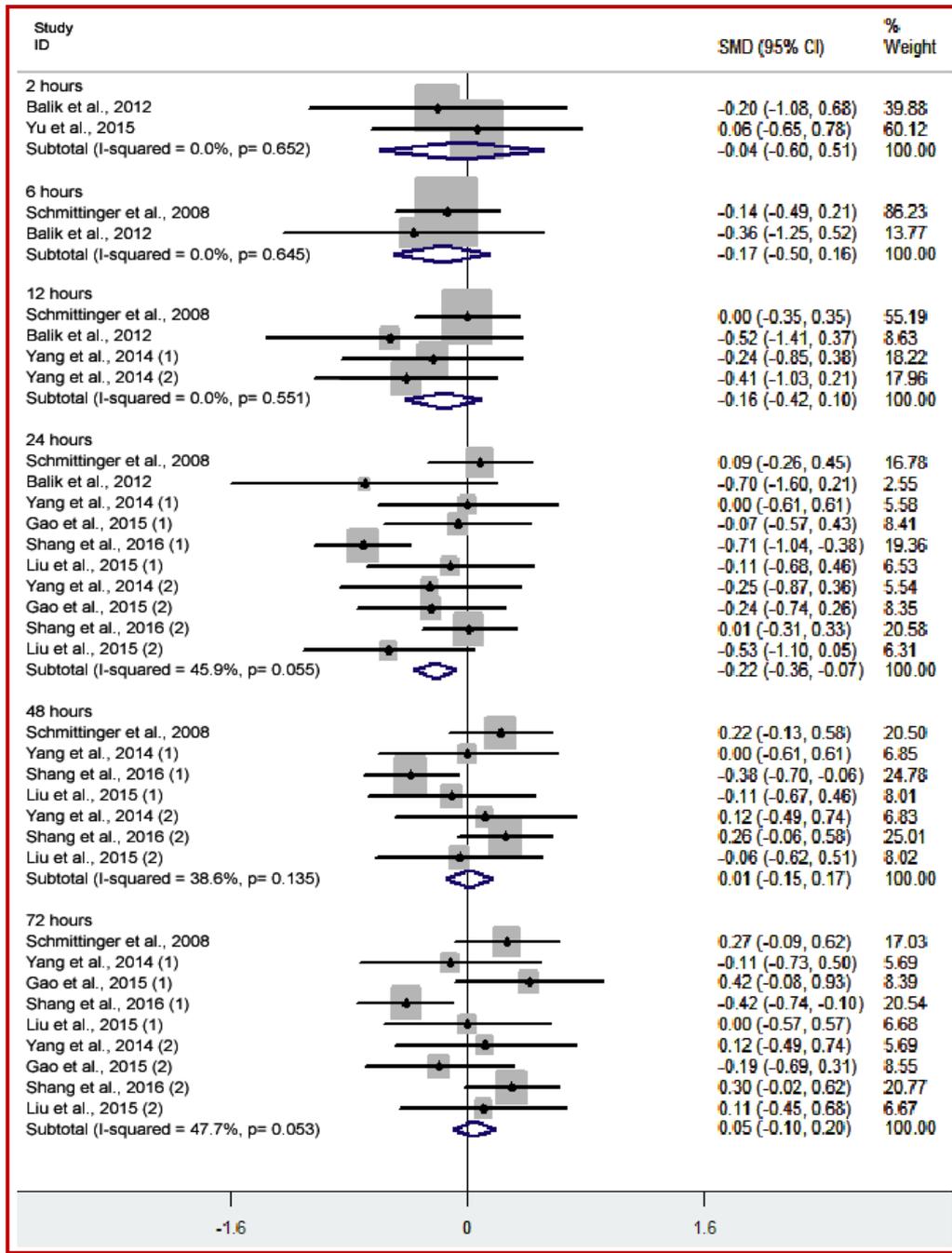


Figure 4: Meta-analysis of  $\beta$ -blocker on the mean arterial pressure (digit within the parenthesis means the number of studies for comparison)

homogeneity between studies and were combined using a fixed effect model; The 48 and 72 hours groups were heterogeneous, and they were combined using a random effects model. Meta-analysis results showed that compared with the control group, the levels of TNF- $\alpha$  decreased significantly at 12, 24, 48, and 72 hours of the treatment in the experimental group, and the difference between the experimental group and the control group was statistically significant ( $p < 0.05$ ) (Figure 14).

**Interleukin-1 $\beta$**

Three articles reported interleukin-1 $\beta$  (IL-1 $\beta$ ) in the two groups. The study groups at each time point were heterogeneous and were combined using a random effects model. Meta-analysis results showed that compared with the control group, the IL-1 $\beta$  level in the experimental group decreased significantly at 12, 24, 48, 72 hours of the treatment, and the difference between the experimental group and the control group was

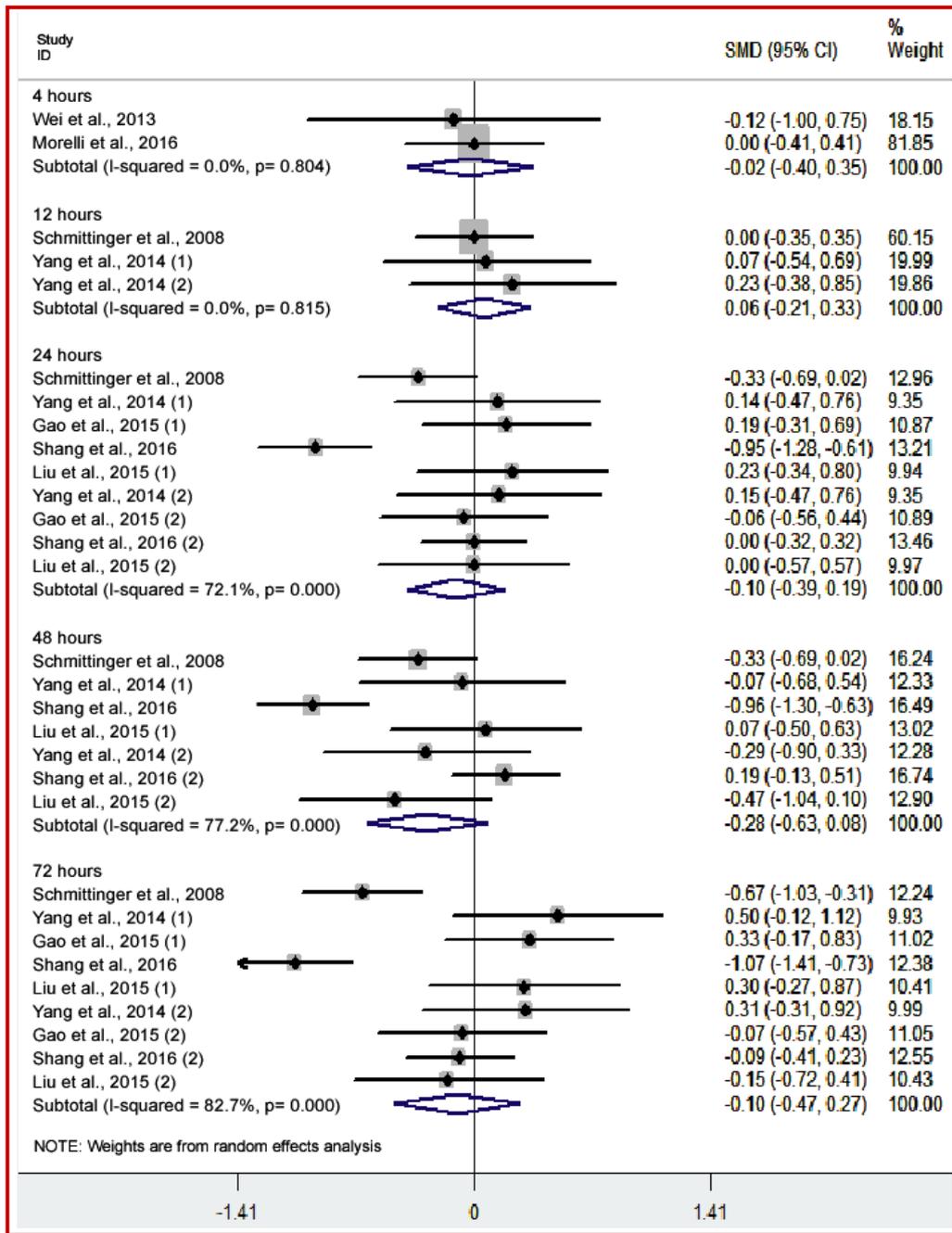


Figure 5: Meta-analysis of beta-blocker on the central venous pressure (digit within the parenthesis means the number of studies for comparison)

statistically significant ( $p < 0.05$ ) (Figure 15).

### Discussion

In recent years, with the continuous deepening of the understanding of sepsis, the research of beta-blockers in the field of intensive medicine has gradually increased. The analysis of the efficacy of beta-blockers in the treatment of sepsis in this study showed that beta-

blockers can effectively reduce the 28-day mortality rate, heart rate, blood lactic acid, cTnI, TNF- $\alpha$  and IL-1 $\beta$  levels in patients with sepsis, and can effectively increase left ventricular ejection fraction and ScvO<sub>2</sub> levels, and have little effect on central venous pressure, cardiac index, stroke volume index, systemic vascular resistance index and norepinephrine. Its role in reducing mean arterial pressure levels at 24 hours of the treatment remains to be confirmed.

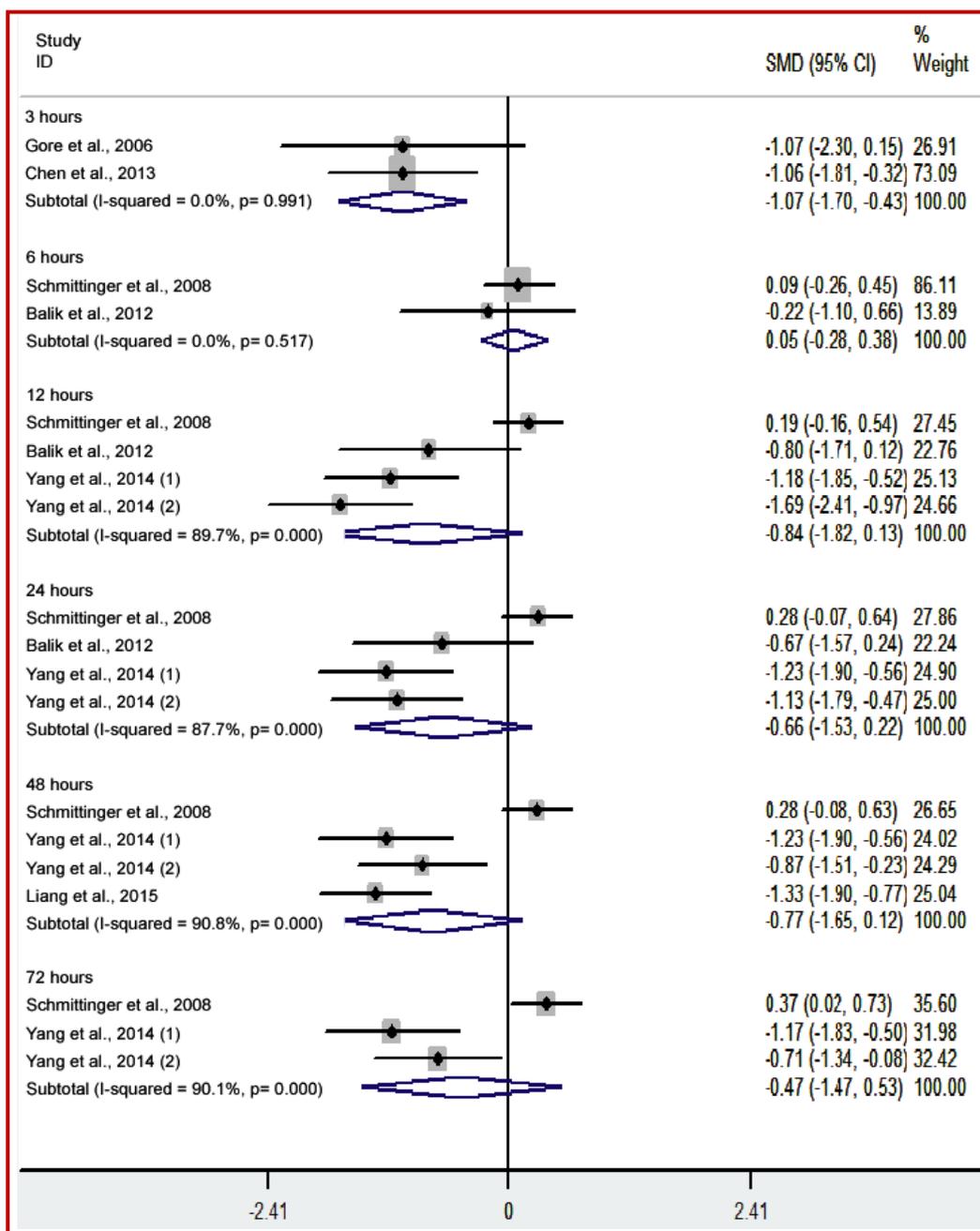


Figure 6: Meta-analysis of beta-blocker on the cardiac index (digit within the parenthesis means the number of studies for comparison)

Previous study has suggested that patients with severe sepsis who have taken beta-blockers for a long time before admission have a better clinical prognosis than those who have not taken beta-blockers (Macchia et al., 2012). Seven studies included in this study reported 28-day mortality, and analysis showed that beta-blockers can effectively reduce 28-day mortality in patients with sepsis. This study confirmed that beta-blockers can significantly improve the clinical prognosis of patients with sepsis.

Studies have shown that beta-blockers can improve immune function, cardiovascular function and coagulation function in patients with sepsis (Xu et al., 2015; Duff et al., 2016; Schlager et al., 2016). However, due to its direct effect on the heart, sometimes it can cause or exacerbate hypotension, which makes clinical physicians are very cautious about the application of this kind of drugs. The slowing of heart rate has positive effect in preventing myocardial damage and malignant arrhythmia caused by sepsis, and this study confirmed that beta-blockers did not show significant

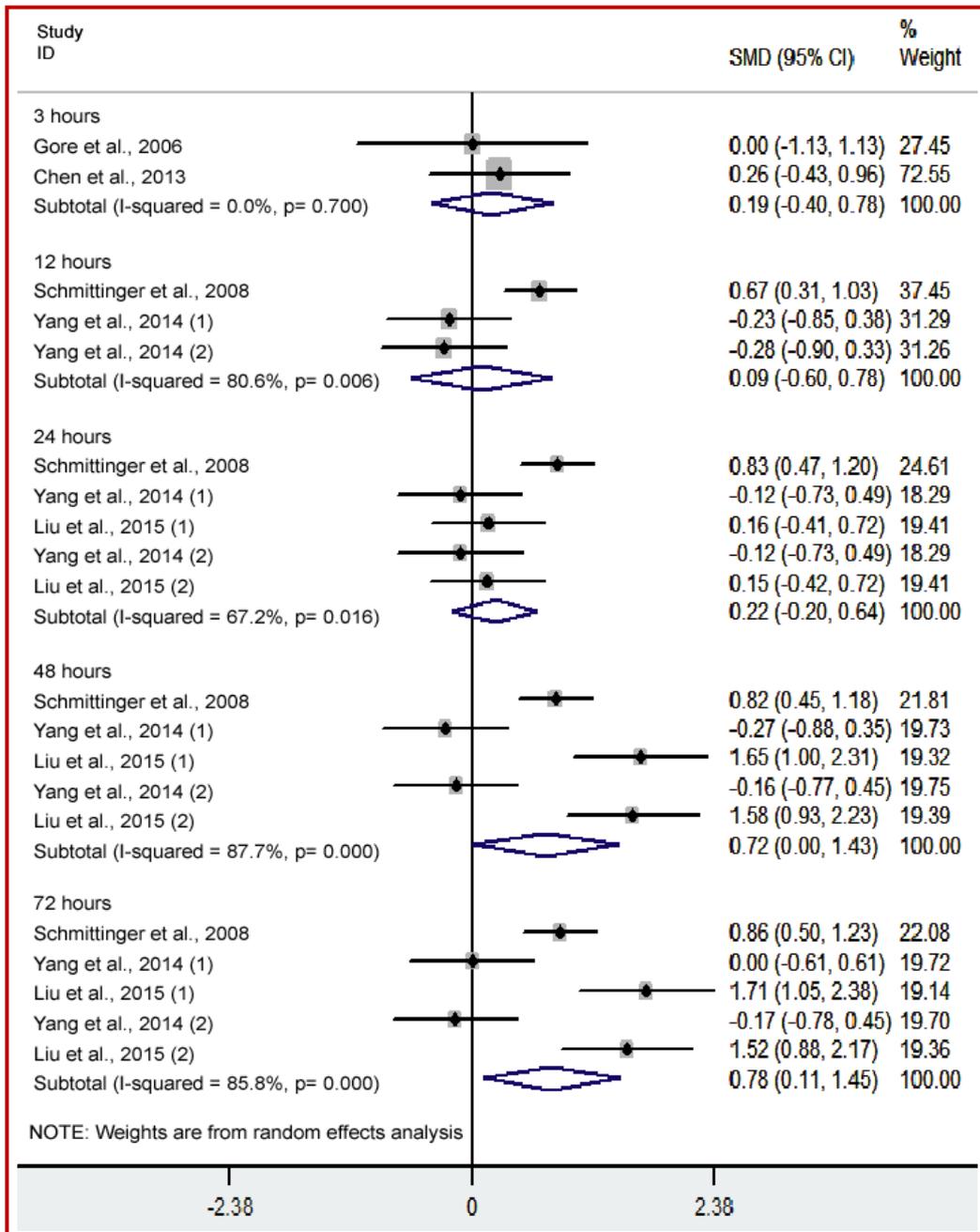


Figure 7: Meta-analysis of  $\beta$ -blocker on the stroke volume index (digit within the parenthesis means the number of studies for comparison)

changes in central venous pressure, cardiac index, stroke volume index, systemic vascular resistance index and norepinephrine while heart rate decreased, which suggested that beta-blockers can maintain hemodynamic stability while reducing heart rate, which may be closely related to improving the clinical prognosis of patients.

In the early stages of severe infection and septic shock, the sympathetic nervous system is over-activated, catecholamines are released excessively, tissues, organs

and microcirculation are in an hypermetabolism state, and oxygen demand exceeds oxygen supply. Even if blood pressure and heart rate are in the normal range, ScvO<sub>2</sub> may decrease. Blood lactic acid level and ScvO<sub>2</sub> can reflect the patient's tissue perfusion and oxygen metabolism at an early stage (Trzeciak et al., 2007). When the body's oxygen supply decreases or the oxygen demand exceeds the oxygen supply, ScvO<sub>2</sub> decreases and blood lactic acid levels increase. Lactic acid is a product of anaerobic metabolism, and its

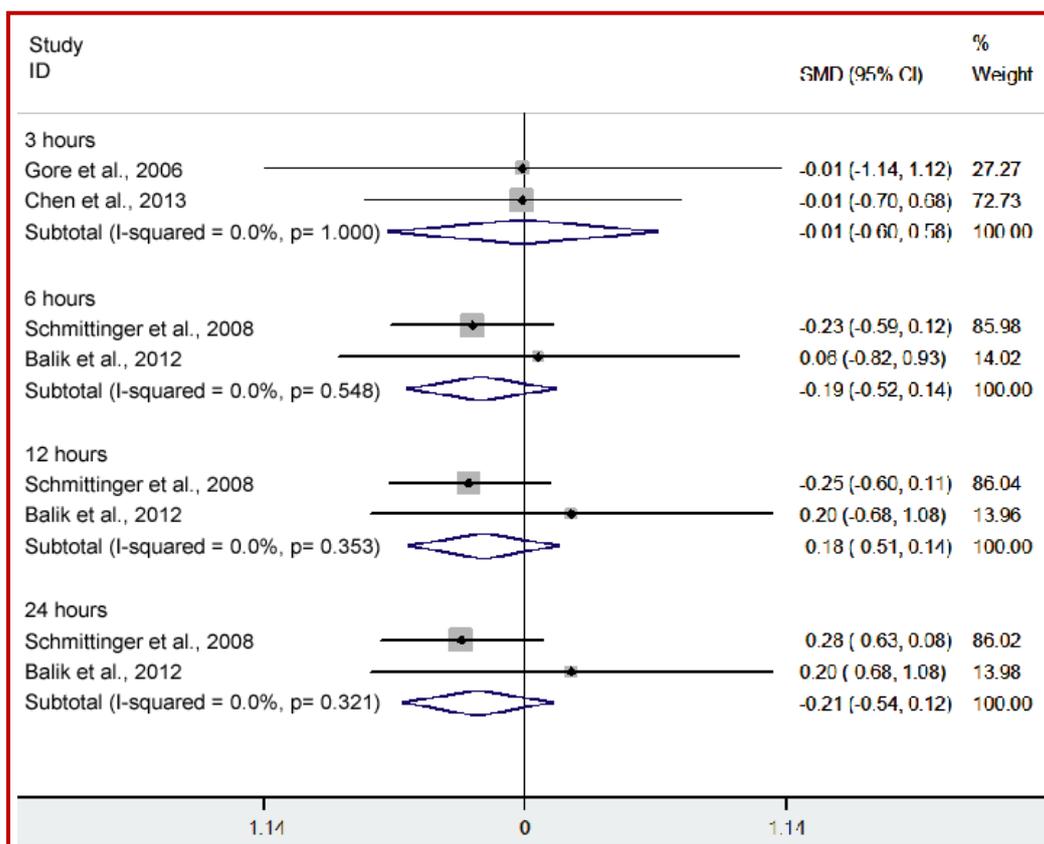


Figure 8: Meta-analysis of  $\beta$ -blocker on the systemic vascular resistance index (digit within the parenthesis means the number of studies for comparison)

concentration is a common indicator of tissue oxygen supply. The change of its value is related to the disease outcome and prognosis (Jansen et al., 2009). Only by improving the hypoperfusion of peripheral tissues and correcting the abnormal cellular oxygen metabolism can the clinical outcome and prognosis be improved (Carre and Singer, 2008). The results of this study found that  $ScvO_2$  in the experimental group was significantly higher than that in the control group after 24 hours of the treatment, and the level of lactic acid in the experimental group was significantly lower than that in the control group after 48 hours of the treatment. It is shown that beta-blockers can improve tissue oxygen metabolism, correct cellular oxygen metabolism abnormalities, and ultimately improve the outcome and prognosis of patients with sepsis on the basis of controlling heart rate, maintaining hemodynamics and improving cardiac function.

An increase in cTnI is indicative of a poor prognosis in patients with sepsis (Lazzeri et al., 2008). The results of this study found that cTnI in the experimental group was significantly lower than that in the control group after 48 hours of treatment, further confirmed that  $\beta$ -blockers can effectively reduce the degree of myocardial injury in patients with sepsis and have a protective effect on the myocardium. In the initial stage of sepsis,

it is mainly characterized by the release of a large number of pro-inflammatory mediators (Duncan et al., 2010). The excessive release of inflammatory mediators of TNF- $\alpha$  and IL-1 $\beta$  turn cytokines from protective effect to damaging effect, causes imbalance of pro-inflammatory/anti-inflammatory mediators and turn into multiple organ failure (Chandra et al., 2006). The results of this study confirmed that, after 12 hours of treatment, the application of beta-blockers can significantly reduce the expression of TNF- $\alpha$  and IL-1 $\beta$ , thereby preventing them from progressing to multiple organ failure.

## Conclusion

The usage of beta-blockers can effectively reduce 28-day mortality and heart rate, and it has significant effect on central venous blood oxygen saturation, lactic acid, cardiac troponin I, tumor necrosis factor- $\alpha$  and interleukin-1 $\beta$ . However, caution should be used in patients with sepsis, especially for severe sepsis and severe shock patient. The timing of application, choice of dosage form, dose selection, and impact on patient prognosis need to be confirmed by further large-scale clinical studies.

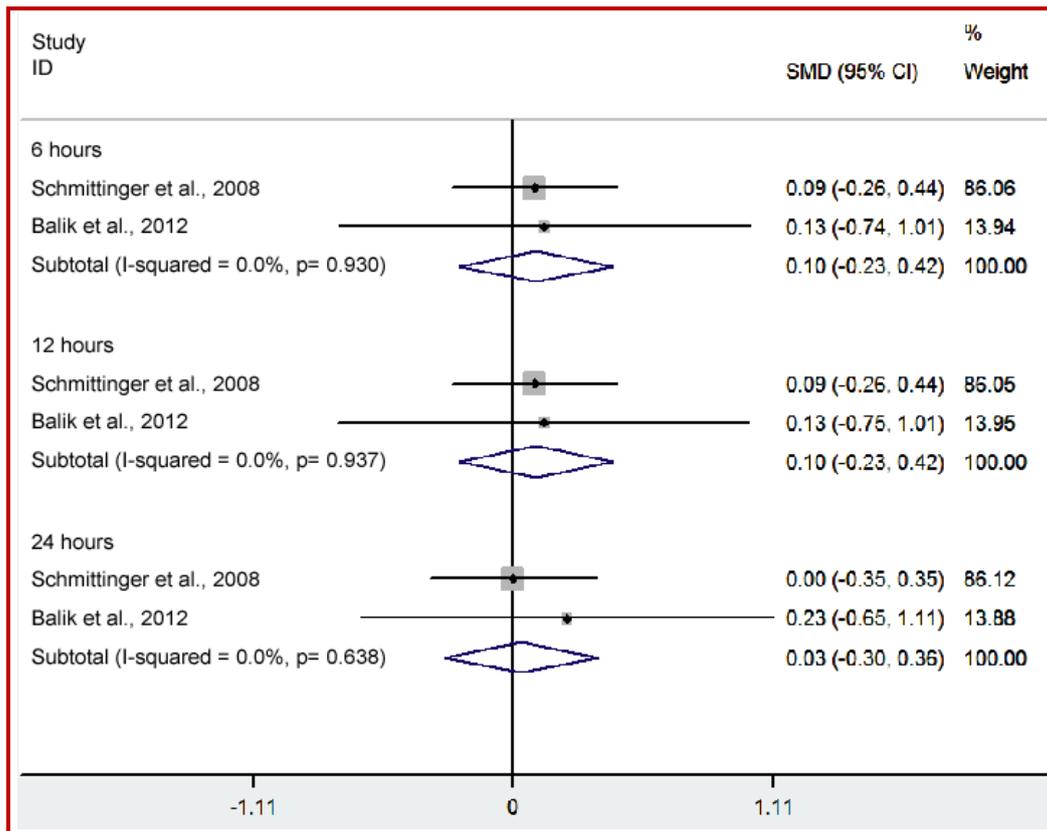


Figure 9: Meta-analysis of beta-blocker on the noradrenaline dosage (digit within the parenthesis means the number of studies for comparison)

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## Conflict of Interest

Authors declare no conflict of interest

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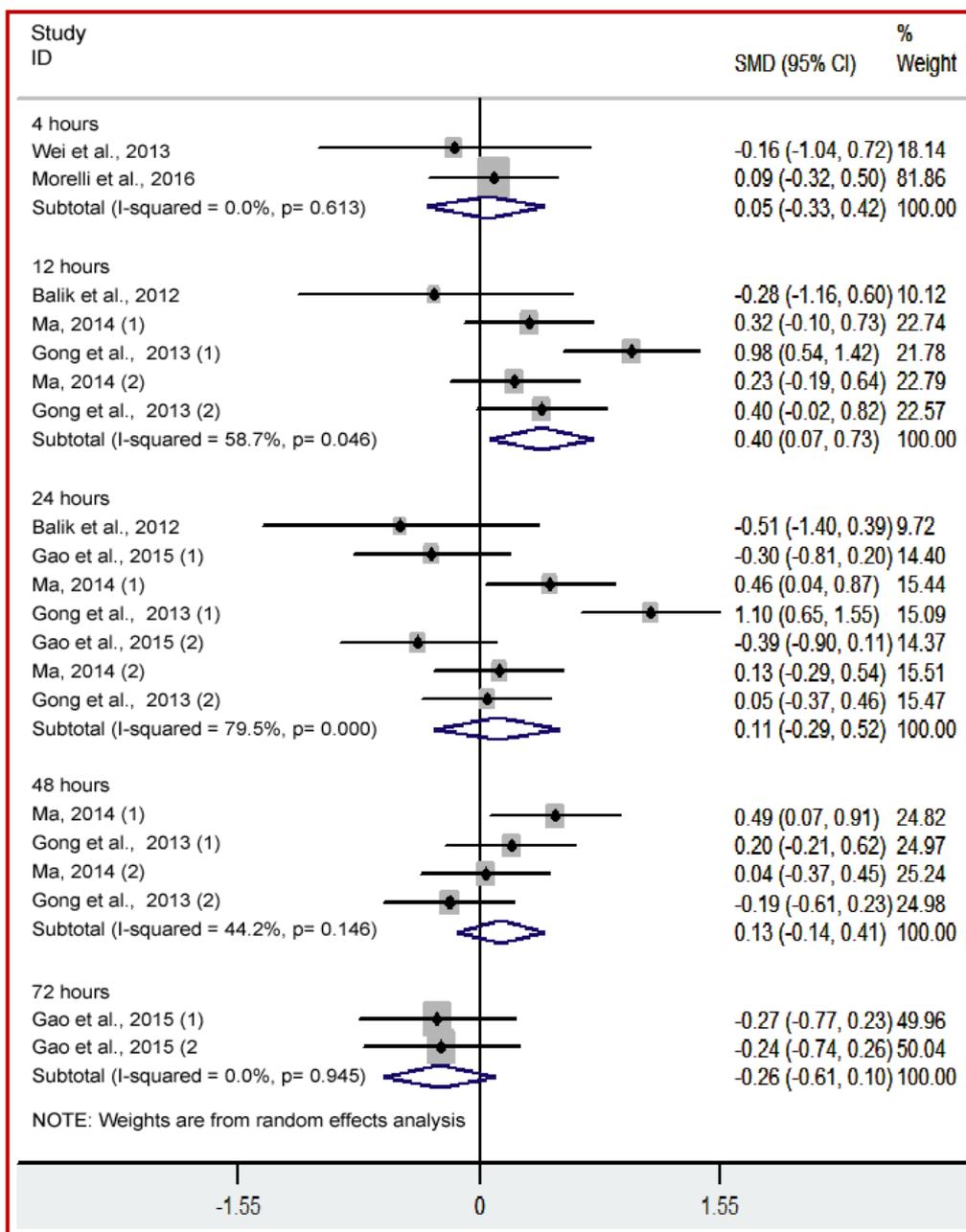


Figure 10: Meta-analysis of beta-blocker on the left ventricular ejection fraction (digit within the parenthesis means the number of studies for comparison)

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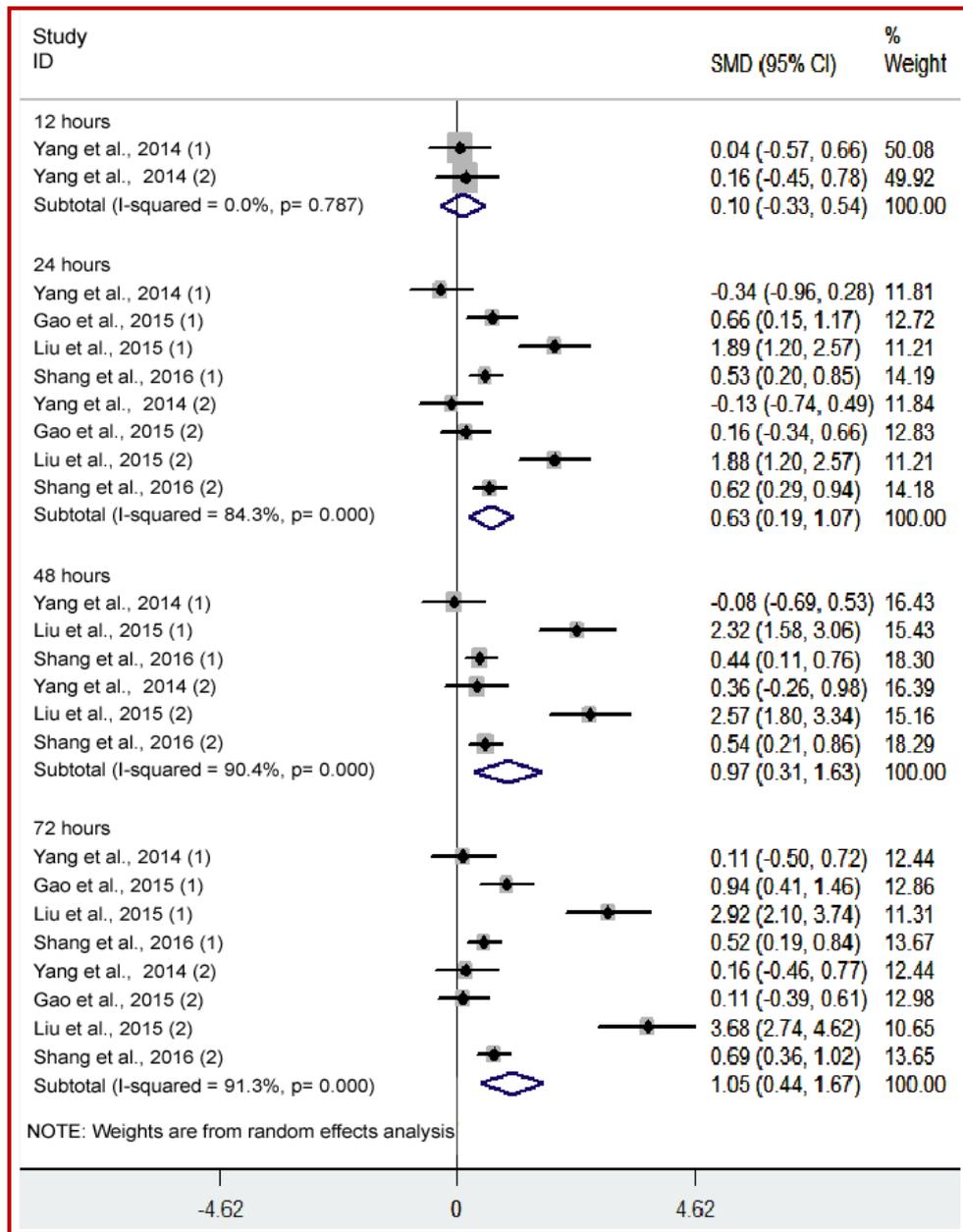


Figure 11: Meta-analysis of beta-blocker on the central venous blood oxygen saturation (digit within the parenthesis means the number of studies for comparison)

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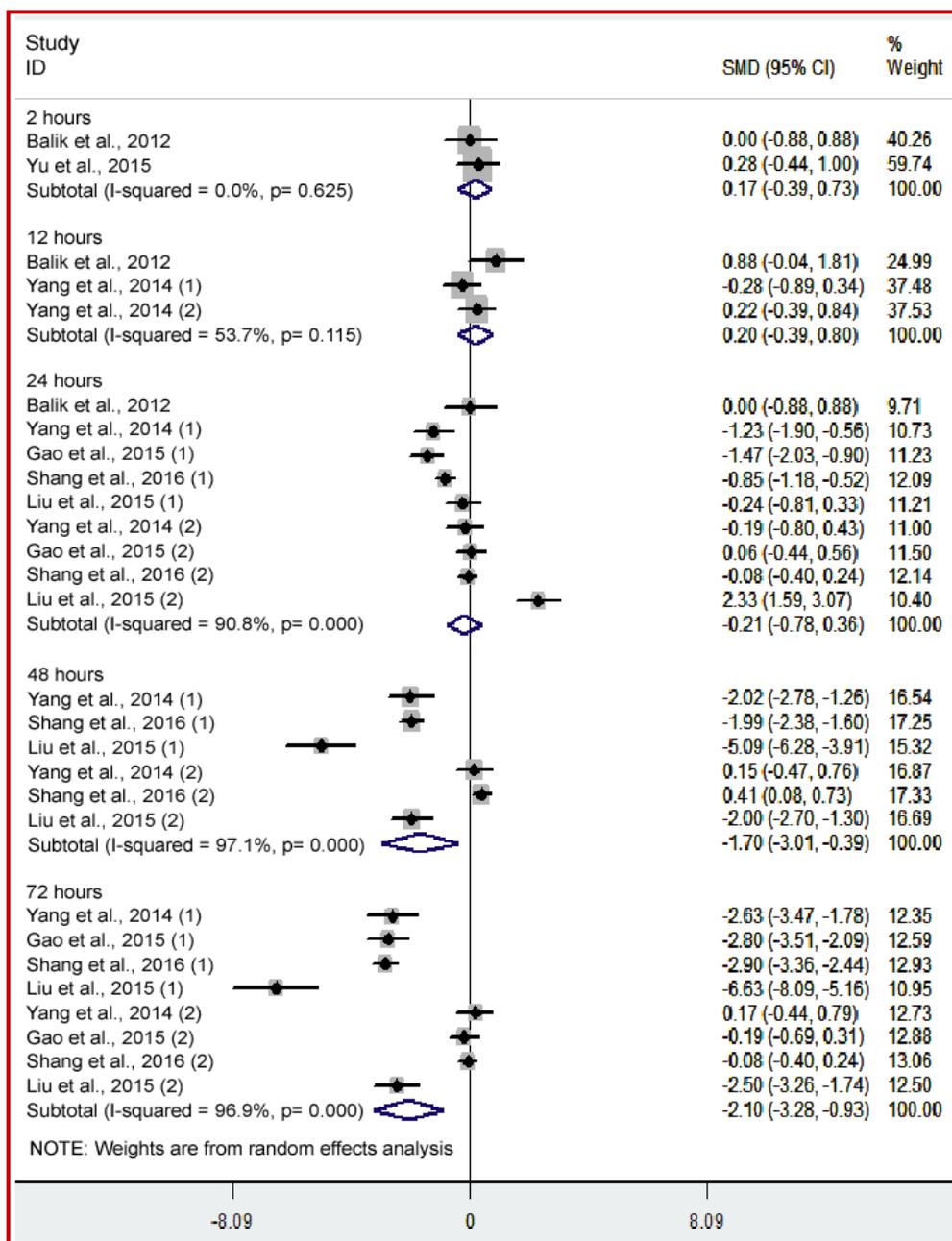


Figure 12: Meta-analysis of beta-blocker on the blood lactic acid (digit within the parenthesis means the number of studies for comparison)

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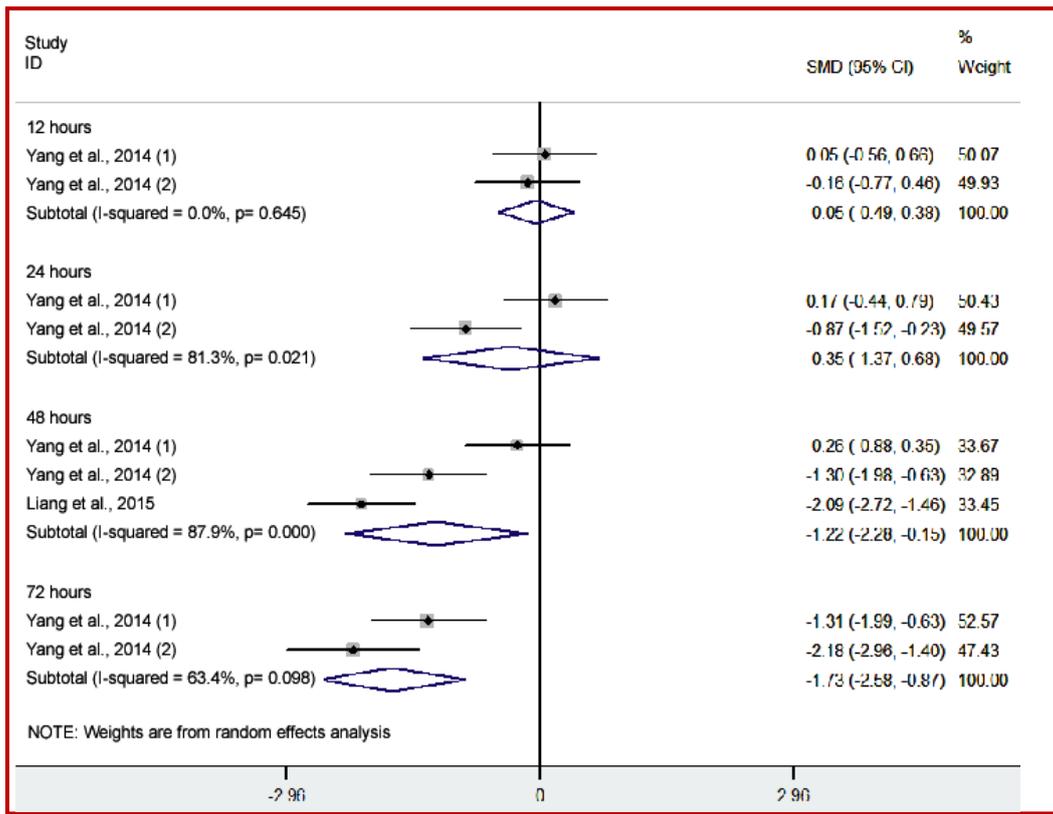


Figure 13: Meta-analysis of  $\beta$ -blocker on the cardiac troponin I (digit within the parenthesis means the number of studies for comparison)

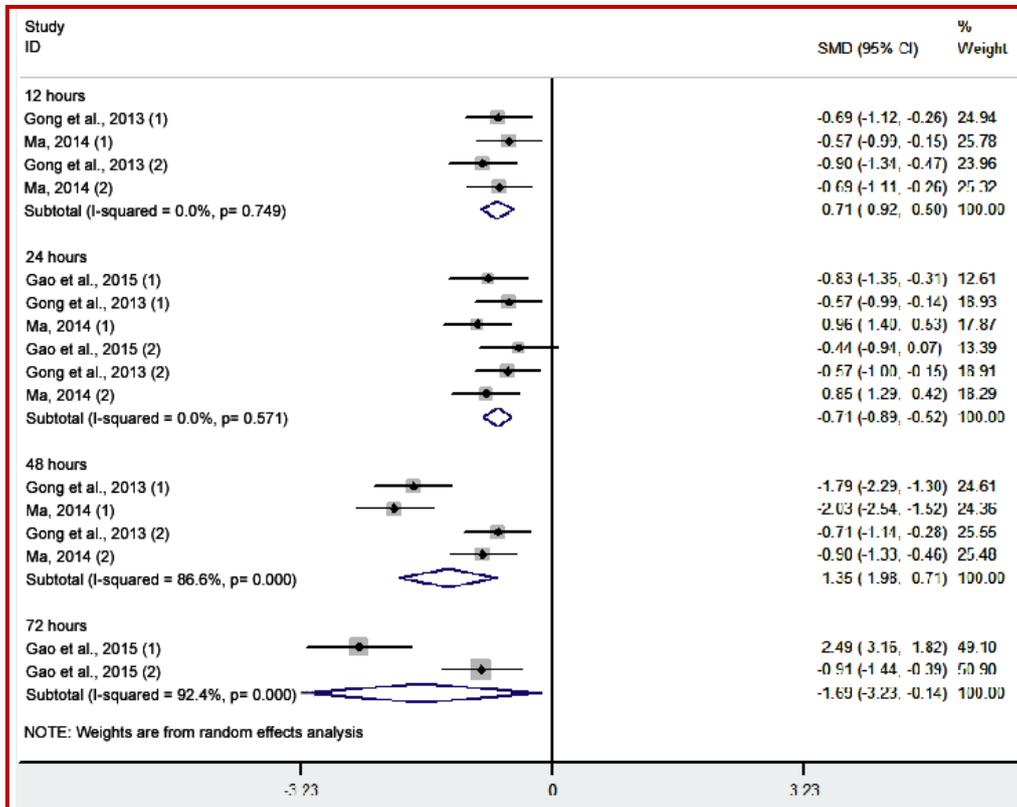


Figure 14: Meta-analysis of  $\beta$ -blocker on the tumor necrosis factor- $\alpha$  (digit within the parenthesis means the number of studies for comparison)

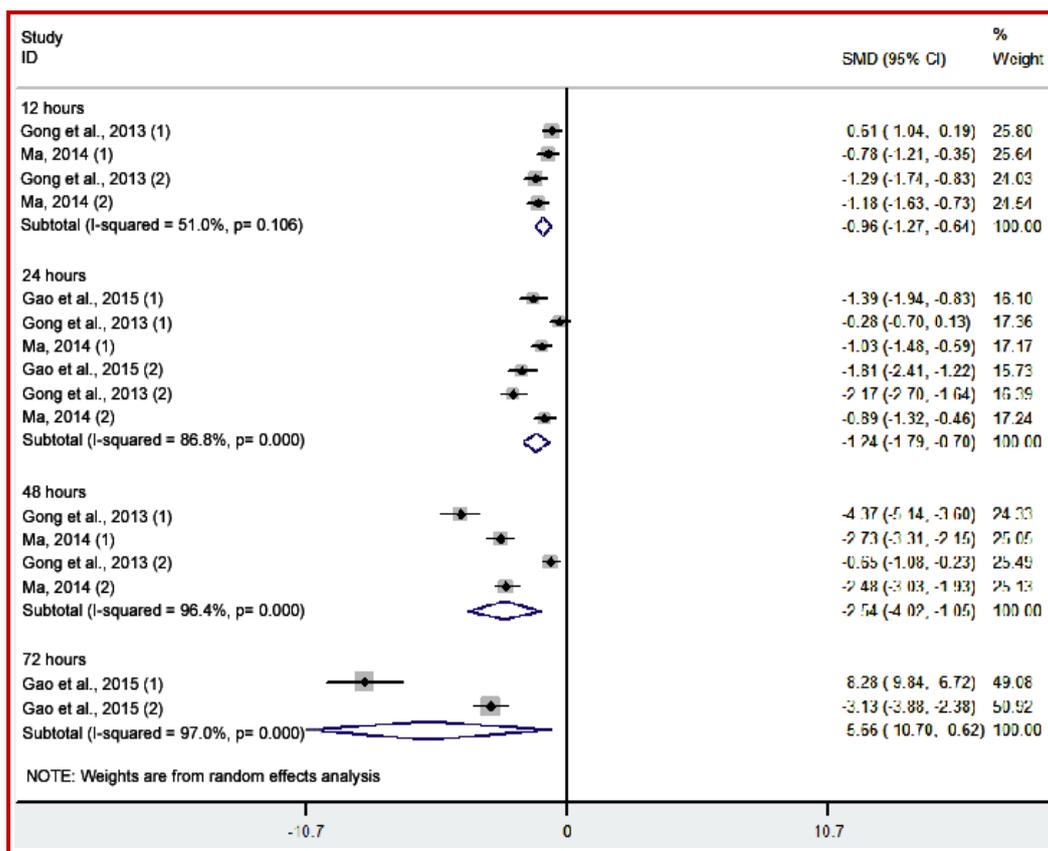


Figure 15: Meta-analysis of beta-blocker on the interleukin-1 $\beta$  (digit within the parenthesis means the number of studies for comparison)

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