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Systematic Review
Effects of Levosimendan on Hemodynamics and Prognosis in Patients with Sepsis: A Meta-Analysis and Systematic Review

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Abstract

Sepsis represents a critical issue that arises when the body's immune system excessively reacts to an infection, resulting in harm to organs and tissues. Comprehending host-microorganism interactions is essential for formulating novel therapies and evaluating disease advancement. Therefore, this meta-analysis was intended to examine the impact of levosimendan on mortality and haemodynamics in sepsis patients. This meta-analysis examined Embase, PubMed, Cochrane Library, Web of Science, China National Knowledge Network (NKI) and Wanfang Database Data, Chinese Biomedical Literature Database (CBM) and VIP Database for levosimendan, sepsis and septic shock. This research examined publicly accessible clinically randomised controlled trials of levosimendan in sepsis patients, measuring left ventricular ejection fraction, work index, cardiac index and lactate level-all data integration, publication bias detection and sensitivity analysis were carried out. In this meta-analysis, 15 studies were involved. According to the findings, there was no statistically significant variance ($p>0.05$) in the 28-day death rate between the levosimendan-treated sepsis patients and the control category. Levosimendan, however, can lower the left ventricular function index, raise the left ventricular ejection fraction, enhance the cardiac index and successfully lower lactate levels in sepsis patients. However, the drug has shown positive effects in improving hemodynamic parameters and therefore, more clinical trials are necessary to verify the value of levosimendan in managing hemodynamic problems associated with sepsis.

Key words: Levosimendan, sepsis, hemodynamics, prognosis, immunological responses, systemic immune response, Left Ventricular Ejection Fraction (LVEF), Left Ventricular Stroke Work Index (LVSWI)

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Sepsis, a systemic immune response triggered by infection, involves activating pro-inflammatory and anti-inflammatory processes and complex interactions among the clotting system, the immune system endothelial cells. These physiological changes eventually lead to impaired hemodynamics and can trigger the failure of multiple organs. In the pathological process of sepsis, the influence of inflammatory mediators like nitric oxide, cytokines, the complement system and lipopolysaccharides on cardiomyocytes can significantly inhibit cardiac function[1,2]. First described in 1958, septic cardiomyopathy has not yet been uniformly defined. The most common definition of the condition is reversible myocardial dysfunction due to sepsis, usually diagnosed with an Left Ventricular Ejection Fraction (LVFE) of fewer than 50% its core features include left ventricular dilation and the ability to relapse to a normal clinical state early[2]. It has also been found that toll-like receptors, activation of nuclear factor kB, mitochondrial dysfunction and endothelial dysfunction dysregulation of autonomic nerves are related to the occurrence of sepsis cardiomyopathy, but the exact pathogenesis is still not fully understood. Current studies suggest that septic cardiomyopathy should be considered an acute syndrome of cardiac dysfunction associated with sepsis and independent of myocardial ischemia[3,4]. However, in clinical practice, there are still no precise diagnostic standards or rigorously evidence-based definitions of septic cardiomyopathy[4]. Compared to other positive inotropic medications, levosimendan is a novel medicine with a distinct mode of action. It does not work by raising the concentration of calcium ions within the cells of the heart muscle, but by augmenting the sensitivity of myocardial contractile proteins to calcium ions, thereby strengthening heart function is therefore classified as a calcium sensitizer[4,5]. This unique mode of action means that levosimendan does not increase intracellular calcium inflow and does not result in a rise in intracellular calcium that causes cardiac diastolic dysfunction. In clinical use, levosimendan is primarily used to treat patients with acute heart failure who do not respond well to conventional orthotropic drug therapy, but it is also used to treat conditions such as cardiogenic shock, pulmonary hypertension cardiac surgery[5,6]. In patients with septic shock and cardiac insufficiency, dobutamine is advised to be added to norepinephrine treatment rather than levosimendan while ensuring appropriate volume and arterial pressure. Only weak evidence supports this recommendation[6]. Compared with dobutamine, the effectiveness of levosimendan in reducing mortality and cardiac function in sepsis individuals and septic shock remains controversial. This investigation assessed the clinical effects of levosimendan on 28-day mortality and hemodynamics by comprehensively analysing the comparative studies between levosimendan and dobutamine or a blank control group, aiming to provide a reference for clinical treatment from the perspective of evidence-based medicine.

MATERIALS AND METHODS

Study area: The present investigation was carried out in the Surgical Intensive Care Unit, Shaoxing People's Hospital, China, from September, 2023 to December, 2023.

Selection of literature

Inclusion criteria: (1) Participants were over 18 years old and diagnosed as per international or Chinese guiding principles for the treatment of septic shock or sepsis[7], (2) No contraindications for levosimendan use, (3) Intervention measures: Levosimendan was used to treat the experimental category; the control category received other positive inotropic drugs or blank control no infusion dose schedule or time limit was set, (4) Study type: must be a randomized controlled trial and (5) Reported data should include 28-day or 30-day mortality rates.

Exclusion criteria: (1) Repeatability study, (2) Limited to animal experiments or *in vitro* studies, (3) It was not indicated that the subjects were sepsis or septic shock individuals, (4) Study intervention did not include positive inotropic drugs other than levosimendan or the combination of intermediate and adult drugs and (5) Excluding conference papers and master's and doctoral dissertations.

Literature retrieval strategy: The two researchers independently conducted a comprehensive search on VIP, Embase, CNKI, Wanfang Data, Web of Science, China Biomedical Literature Database, PubMed and Cochrane Library, covering the period up to December 1, 2023. No language restrictions were set for the study. In addition, references to the included studies and related meta-analyses were tracked to further supplement the relevant literature resources. The collected literature data were imported into Note Express literature management software (v2.5.1.1154) duplicated and non-randomized controlled studies were excluded according to the title and abstract of the literature. For literature that is difficult to judge, carefully reviewing the

entire content determines if it meets the requirements for inclusion. Any disagreement during the selection process will be resolved via consultation with a third researcher.

Specify the database search according to the search strategy that combines the given subject term with the free term. The search strategy should include the following keywords: Shock, sepsis, septic shock, levosimendan, randomized controlled trial or study so on. English search terms include sepsis, bloodstream infection, pyemia, simendan, levosimendan, randomized controlled trial, etc.

Literature quality evaluation: The two researchers independently conducted an exhaustive review of the selected literature, employing the Cochrane risk bias assessment tool. The assessment concentrated on the following fundamental aspects: the implementation of random allocation methods, the proper concealment of the allocation scheme, the use of blind evaluation and the selective reporting of findings the presence of other potential sources of bias.

Data extraction: Extract key data from selected literature: (1) Basic information about the literature: The main author of the article the date of publication, (2) Key information about the subjects (including age, gender, diagnosis results sample size of the experimental and control categories), (3) The intervention method (involving the name of the drug used in the experimental and control categories, the dose the length of the continuous infusion) and (4) Outcome measures of the study: Primary outcome measures (mortality at 28 or 30 days), secondary outcome measures (including left ventricular ejection fraction, left ventricular function index, heart index and lactic acid level).

Statistical analysis: StataMP 14 software was employed to investigate the data and draw the forest map. Relative risk (RR) and 95% confidence interval (CI) are employed as representations for binary classification data. For weighted mean difference (WMD), continuous variables and 95% CI were employed to express them. The Q test was used to evaluate the heterogeneity of each study. If the Q test results show that the I2 value is less than 50% and the p value is superior than 0.1, it is considered that there is homogeneity among the investigations and then the fixed-effect model is used for analysis. In contrast, heterogeneity among the studies is indicated by an I2 value larger than 50% and a p-value less than 0.1, indicating that the random effects model should be employed for analysis. Using StataMP 14 software, Egger's linear regression quantitative test was run to evaluate publication bias and determine its presence. If the p-value of the detection result is <0.05, it indicates the existence of publication bias the shear compensation method and single study examination should be used for sensitivity analysis. If the p>0.05, there is no significant publication bias the results are reliable.

Ethical Consideration: This study protocol was approved by the Ethics Committee Shaoxing People's Hospital (Reg no: 2023/SEP/87/145). The research complies with the ethical guidelines and requirements of the Protocol of Helsinki statements.

RESULTS

Search result analysis: After a detailed search strategy, 345 relevant literature was selected. Among these papers, 172 were duplicates, 69 were reviews and systematic reviews, 12 involved animal experiments 7 were conference papers and dissertations. Further, 73 works of literature with inconsistent research content or substandard experimental design were excluded. In addition, three new papers meeting the inclusion criteria were added through other means. Therefore, 15 literatures were finally selected for meta-analysis. A total of 1337 subjects were included in this investigation, of whom 672 were allocated to the experimental category (levosimendan) and 665 were assigned to the control category (other positive inotropic agents or placebo) (Fig. 1). Finally, this study combined 15 randomized controlled studies with 28 or 30 days mortality as the primary outcome measure.

Meta-analysis results

28 days mortality analysis: Mortality rates at 28 days were compared between levosimendan and control groups in 15 studies 30-days mortality data were reported in 2 studies. The analysis's findings demonstrated that, when compared to the control group, sepsis patients receiving levosimendan did not demonstrate a statistically significant benefit in death after 28 days (p>0.05) (Fig. 2, 3).

LVEF analysis: An in-depth analysis of 10 studies found a statistically important variance in LVEF (Left Ventricular Ejection Fraction) among the levosimendan and control categories in the treatment of sepsis. The current result indicated that the intervention effect of levosimendan was significant and statistically noteworthy (p<0.05) (Fig. 4).

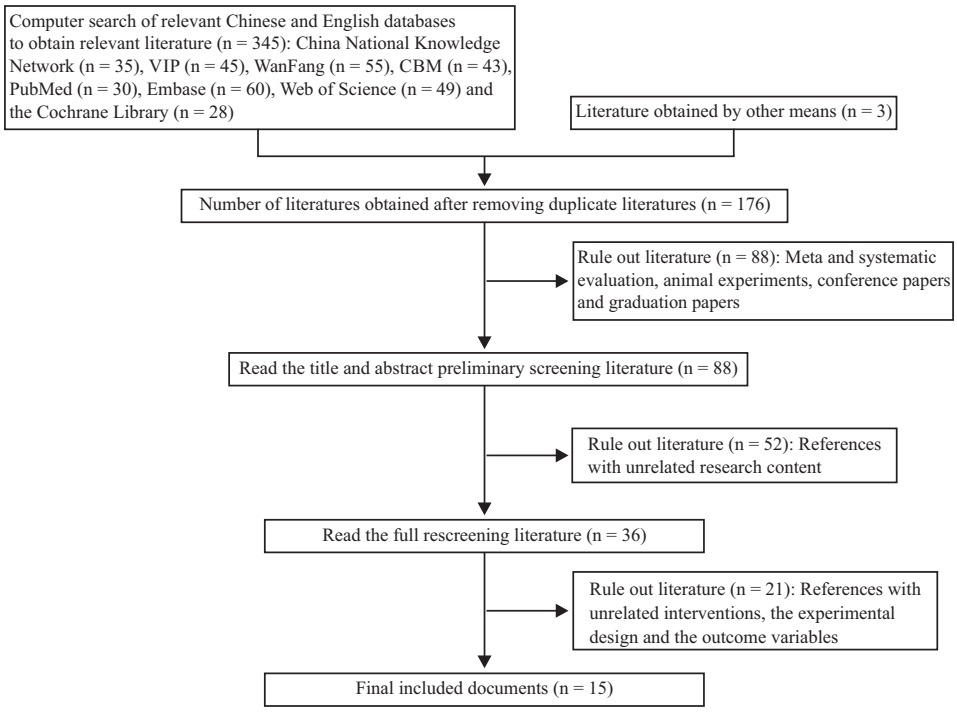

Fig. 1: Flow chart of document retrieval

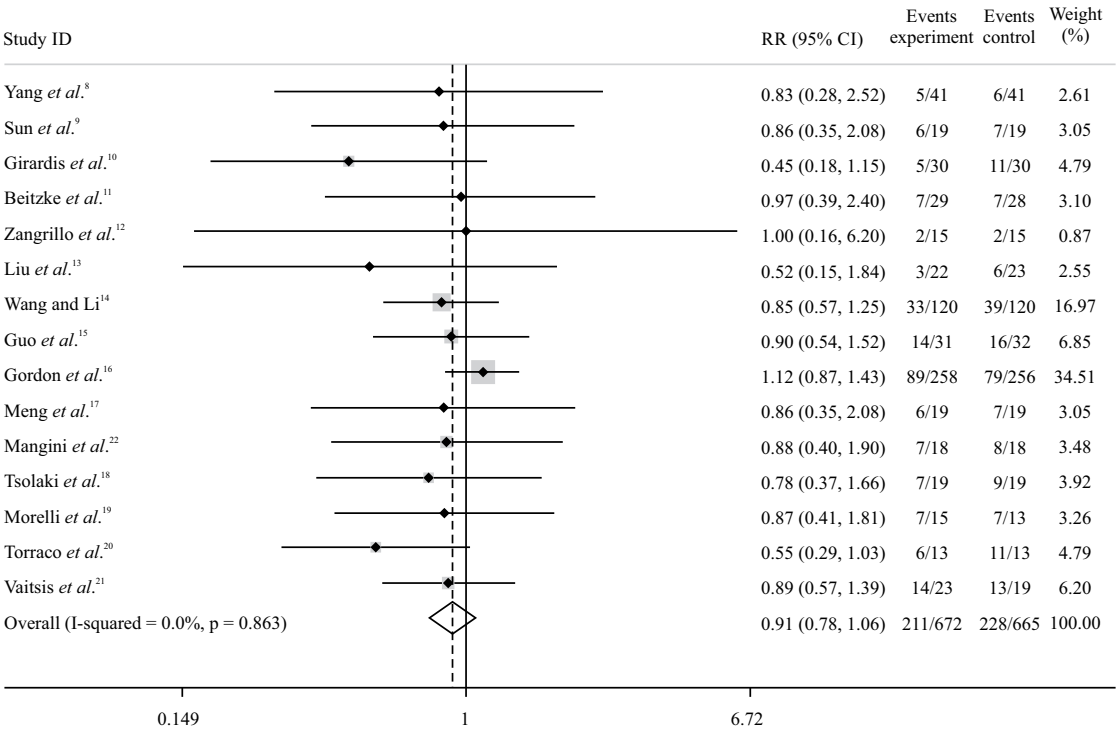

Fig. 2: Meta-analysis of 28 days mortality

Left Ventricular Work Index (LVSWI) analysis: According to four studies, levosimendan showed a statistically significant difference in the Left Ventricular Stroke Work Index (LVSWI) of sepsis patients compared with the control category and intervention effect was statistically momentous ($p<0.05$) (Fig. 5).

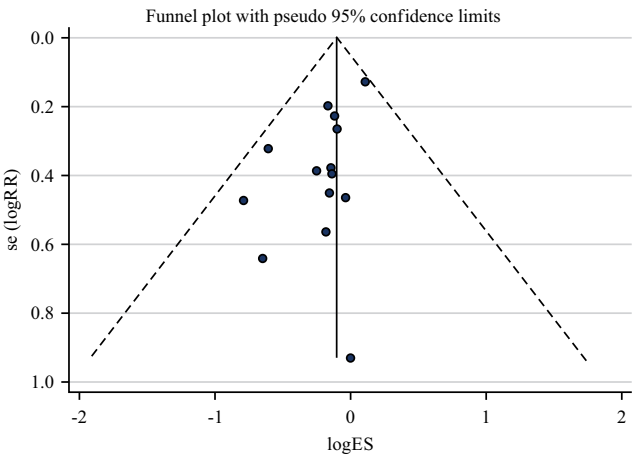

Fig. 3: Funnel plot of 28 days mortality

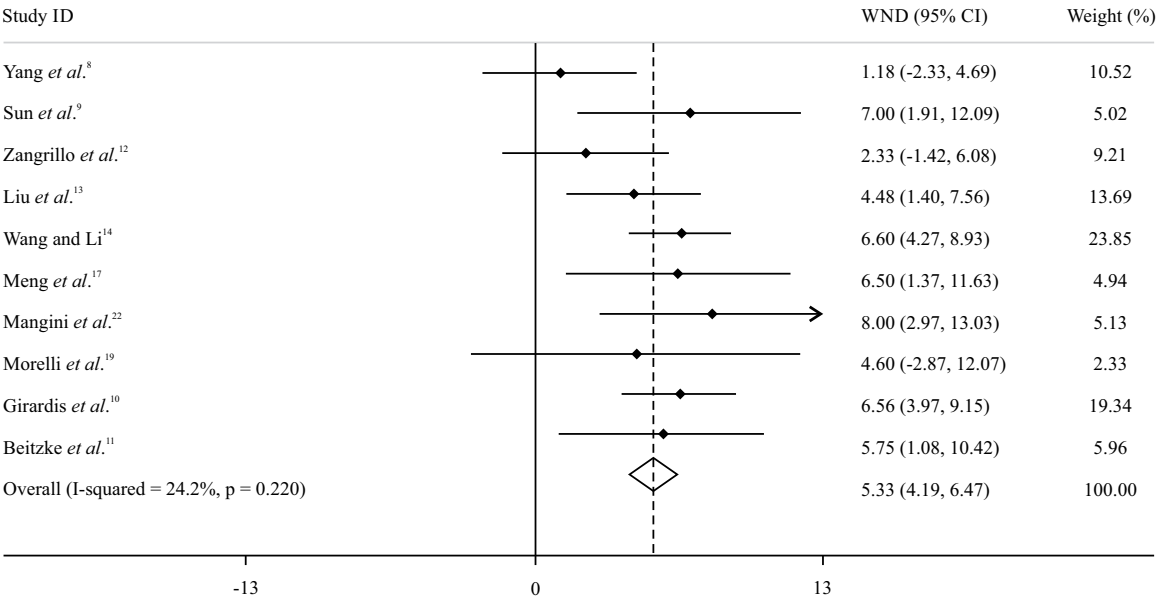

Fig. 4: Meta-analysis of LVEF

Cardiac index (CI) analysis: Seven studies have reported the cardiac index (CI) of levosimendan versus a control group in patients with sepsis. These studies consistently showed that sepsis sufferers administered levosimendan exhibited statistically important differences in cardiac indices compared to controls ($p<0.05$) (Fig. 6).

Lactic acid (Lac) analysis: Comparative studies on lactic acid (Lac) levels between levosimendan and the control group were detailed in seven academic papers. The meta-analysis's findings revealed a statistically significant variation in lactate levels among patients with sepsis receiving levosimendan treatment and the control category ($p<0.05$) (Fig. 7).

Publication bias assessment

Mortality publication bias: In 15 trials assessing levosimendan's impact on sepsis patient's 28 days mortality, funnel plot analysis found that the scatter distribution was symmetrical. Egger's test was further employed to quantitatively evaluate publication bias the outcomes exhibited that there was significant publication bias ($p = 0.015$). To further investigate this bias, the shear supplement method was used for correction, but no virtual

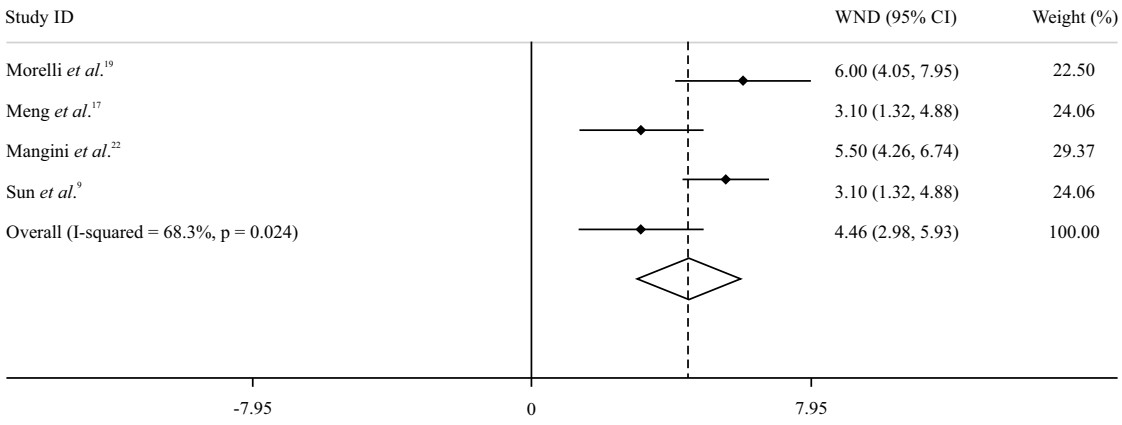

Fig. 5: Meta-analysis of LVSWI

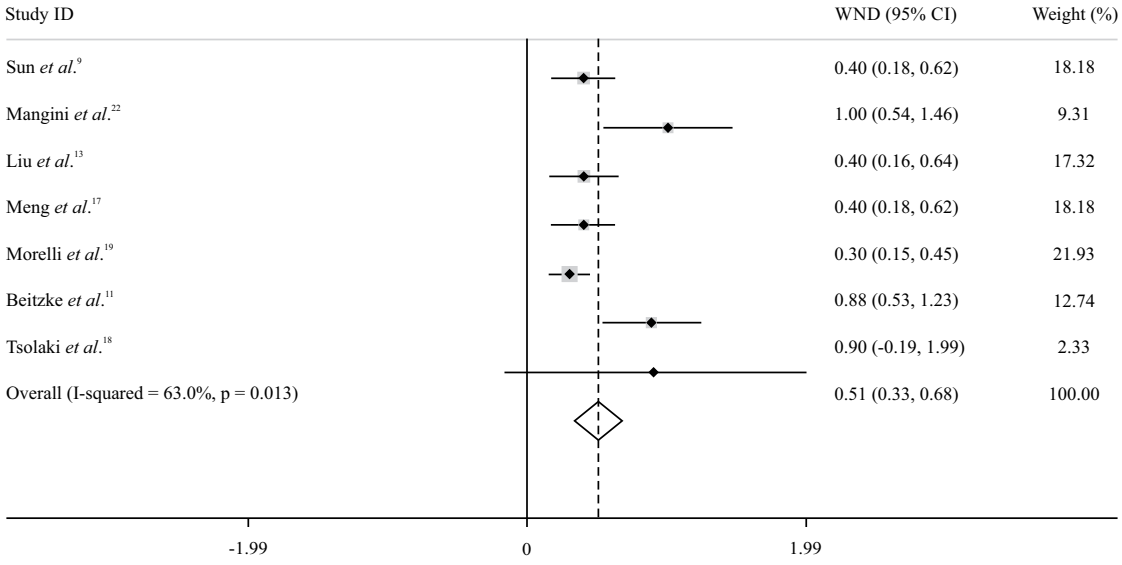

Fig. 6: Meta-analysis of cardiac index

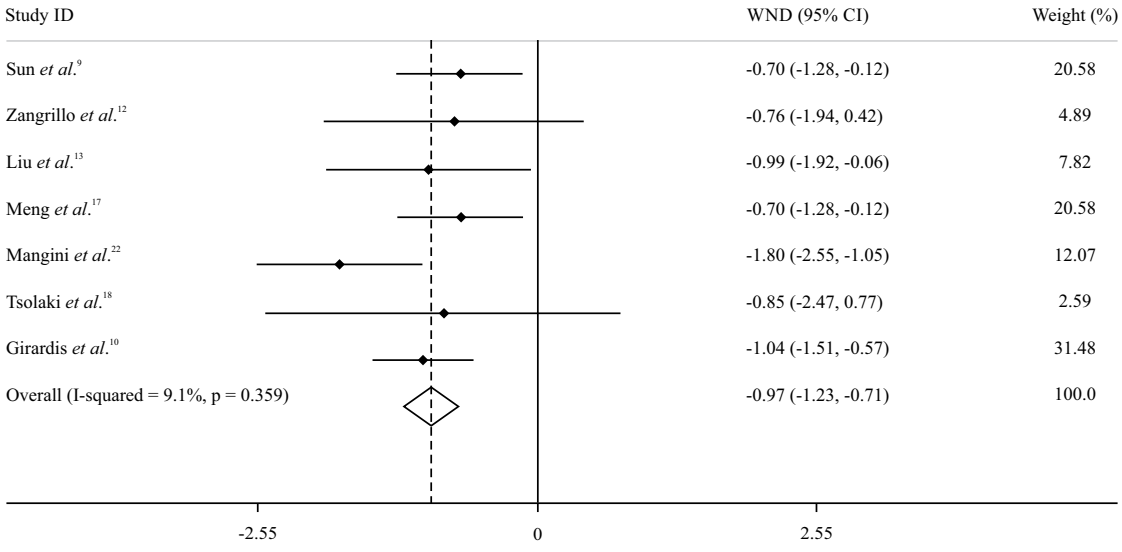

Fig. 7: Meta-analysis of lactic acid

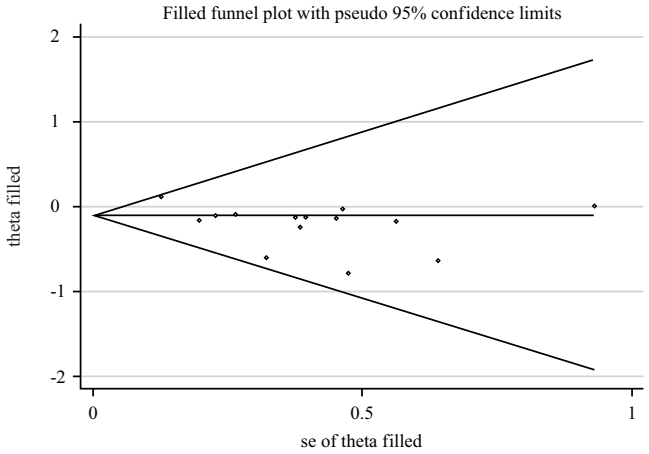

Fig. 8: Shear supplement method of 28 days mortality

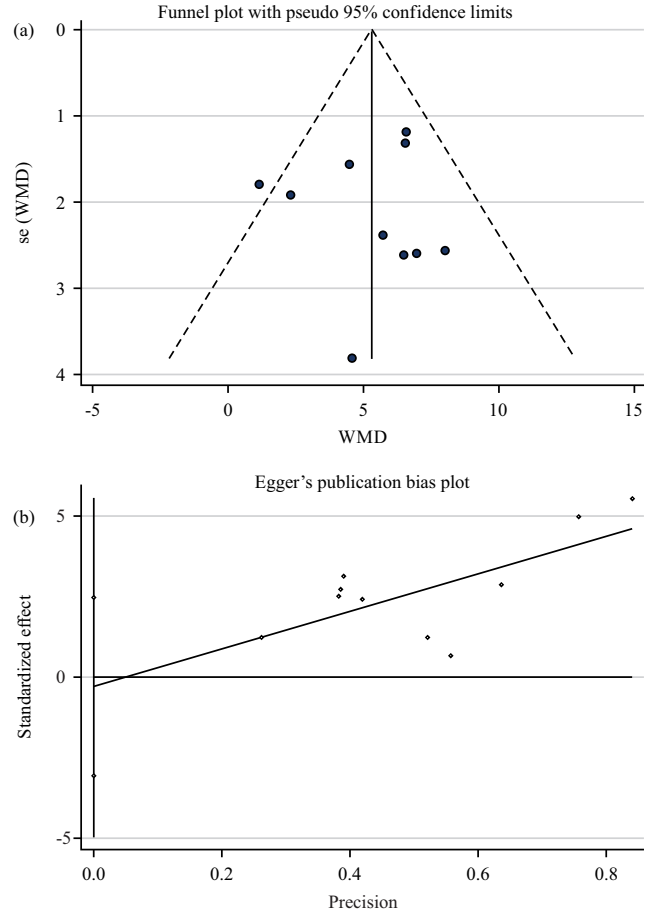

Fig. 9(a-b): Egger's test of LVEF

shear supplement literature or data was added. In addition, a single impact assessment for each study found little change in the combined effect size and inter-study heterogeneity after the exclusion of any study, indicating high stability and reliability of the overall results, so the results can be considered credible (Fig. 8).

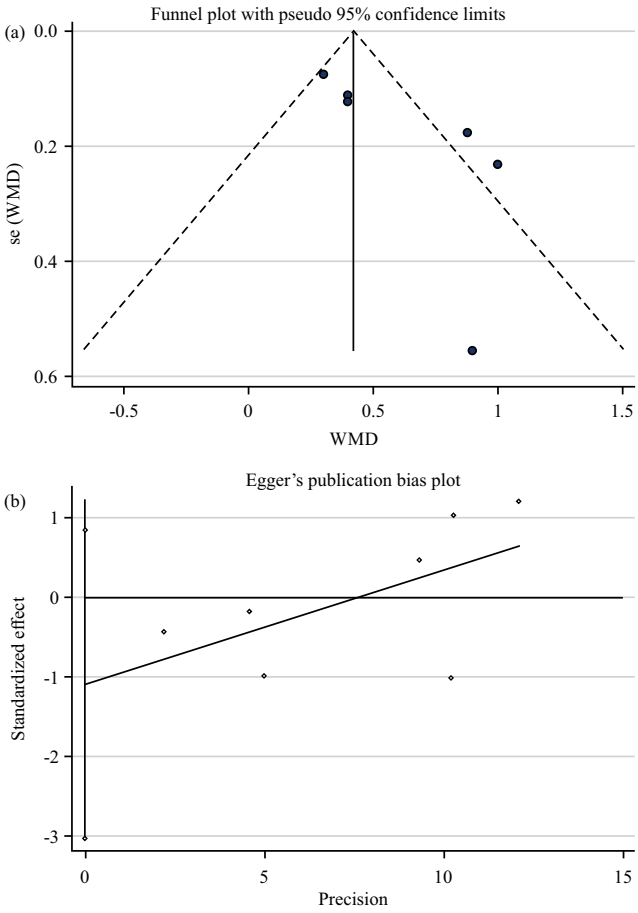

Fig. 10(a-b): Egger's test of cardiac index

LVEF publication bias: The 10 studies involved in the secondary outcome measure Left Ventricular Ejection Fraction (LVEF) were assessed for bias the funnel plot showed a symmetrical scatter distribution. For a more quantitative examination of publication bias, Egger's test was used. The outcome revealed a p-value of 0.814, which suggested that the study's findings were consistent (Fig. 9a-b).

CI publication bias: In assessing the bias of the results of seven studies involving the secondary outcome indicator CI, the scatter distribution of the funnel plot was observed to be roughly symmetric. The results of a quantitative investigation of publication bias using Egger's test revealed a p-value of 0.205, representing the stability of the conclusions obtained (Fig. 10a-b).

Lac publication bias: The data bias of 7 kinds of literature involved in the secondary outcome index Lac was evaluated the scatter distribution of the funnel plot was symmetric. The Egger's test was employed for publication bias quantitative analysis the p-value was 0.870, indicating that the conclusion was robust (Fig. 11a-b).

DISCUSSION

The therapy group's 28 days mortality results showed no discernible variation (treated with levosimendan) versus the control group (treated with conventional therapy or other positive inotropic drugs) especially in sepsis patients. The 28 days mortality rate did not differ significantly among the control category and the levosimendan therapy group. In addition, meta-analysis results published by other scholars[8-23] also showed that levosimendan did not pointedly diminish the mortality of sepsis patients, which agreed with the study's conclusions. Levosimendan, as opposed to conventional positive inotropic medication treatment, was linked to a considerably decreased death rate in individuals experiencing septic shock in a different meta-analysis. Researchers observed that levosimendan, as opposed to dobutamine, dramatically decreased mortality

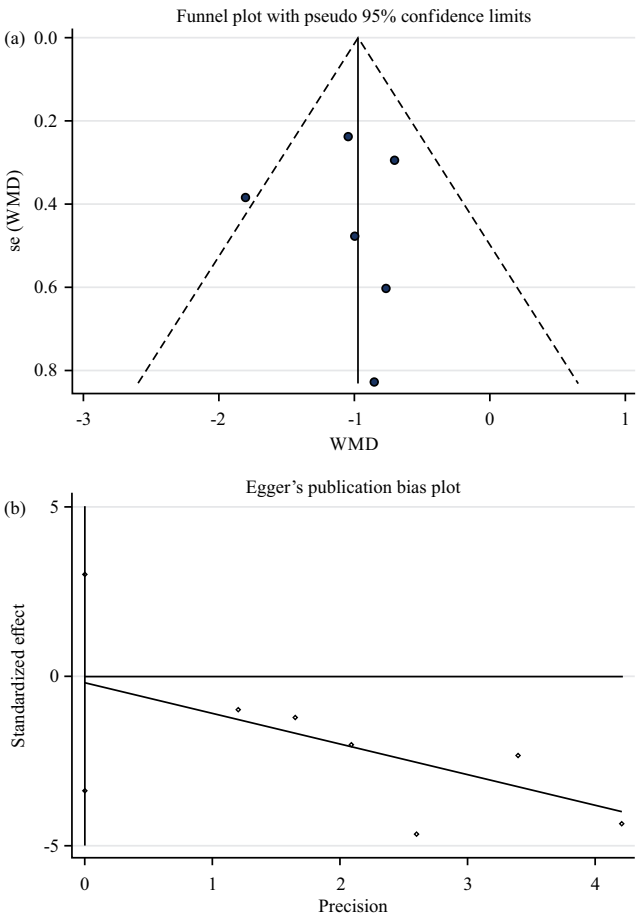

Fig. 11(a-b): Egger's test of lactic acid

in a trial of individuals with septic cardiomyopathy. This difference may be due to the heterogeneity of the literature and study subjects analyzed, as well as subtle differences in the statistical methods used. Therefore, to strengthen the support of evidence-based medicine, more prospective and multi-centre clinical studies were still needed to further explore. Further, study findings investigating levosimendan's impact on hemodynamic parameters revealed that, in comparison to the control category, levosimendan showed statistically momentous differences in Left Ventricular Ejection Fraction (LVEF), Left Ventricular Stroke Work Index (LVSWI), cardiac index (CI) and lactic acid (Lac) in sepsis patients. Specifically, levosimendan increased LVEF, decreased LVSWI, increased CI and decreased Lac levels in sepsis individuals.

In a randomized, double-blind clinical investigation of individuals with acute episodes of chronic heart failure, comparing levosimendan with dobutamine, the study found that the treatment group treated with levosimendan had better hemodynamic improvements than the dobutamine group[23,24]. In addition, in a prospective single-centre study of the properties of hemodynamics in end-stage stable heart failure patients, levosimendan was associated with improved hemodynamics in study subjects[25-28]. This literature consistently shows that levosimendan has a positive effect in improving hemodynamics in heart failure individuals. Also, a retrospective study evaluated the impact of levosimendan combined with neoactin on left heart function and hemodynamics in patients with septic shock[29,30]. The results exhibit that this combination therapy significantly improved left heart function and hemodynamics in septic shock individuals. Although there is relatively little research on levosimendan in the area of sepsis and septic shock, in the published literature, levosimendan still shows a positive advantage over its neutral inotropic drugs, which agrees with the findings of this investigation[31,32]. However, to obtain more in-depth and specific research results, more clinical data are still needed.

The limitation of this meta-analysis is that most of the studies included had a small sample size the number of patients in one study accounted for one-third of the total population, which may lead to deviations between the

final results and actual clinical situation and experimental data. Some studies utilized 28 days mortality as their major end measure, whereas others used 30 days mortality this difference in data measures may have influenced the results. In addition, dobutamine was one of the inconsistent medications utilized in the control group, conventional treatment group epinephrine, etc. Differences in drug type, dosage infusion speed may also lead to deviations in results. For secondary outcome measures, differences in the time of data collection and less number of investigations and experiments that could be included may lead to bias in the results. Therefore, the application effect of levosimendan in individuals with sepsis and septic shock still needs to be further verified and improved through more prospective multi-center clinical trials.

CONCLUSION

The levosimendan did not show an advantage in reducing mortality in sepsis individuals compared to dobutamine or conventional treatment strategies. However, the drug increased Left Ventricular Ejection Fraction(LVEF) and cardiac index (CI), while decreasing Left Ventricular Stroke Work Index (LVSWI) and lactate levels. Because of the small sample size and lack of high-quality research support based on this meta-analysis, the conclusions still need to be validated with more clinical data. Therefore, the application of levosimendan in clinical practice should be cautious. The insufficient number of studies currently makes subgroup assessment impossible to process. Ultimately, none of the studies considered had data stratified by sex, hence, the current study did not investigate the impact of sex-related characteristics. A subsequent study needs to examine the influence of variables such as sex and age on the therapeutic efficiency of levosimendan.

SIGNIFICANCE STATEMENT

This meta-analysis aimed to investigate levosimendan's effects on mortality and hemodynamics in patients with sepsis. Levosimendan did not show an advantage in reducing mortality in sepsis individuals compared to dobutamine or conventional treatment strategies, according to the study outcomes. However, the drug increased LVEF and CI, while decreasing LVSWI and lactate levels. Because still requires validation with more clinical data due to the small sample size and lack of high-quality research support based on this meta-analysis. In the future, the influence of variables such as sex and age on the therapeutic efficiency of levosimendan will be investigated.

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