Clinical Critical Care

E-ISSN 2774-0048

VOLUME 33 NUMBER 1

JANUARY-DECEMBER 2025

Clinical Critical Care
eISSN 2774-0048

Clinical Critical Care
Volume 33, Article ID e250007, 18 pages
https://doi.org/10.54205/ccc.v33.269549

META-ANALYSIS

Benefit of inodilators in septic shock patients: A systematic review and network meta-analysis

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OPEN ACCESS
Citation:
Suntornlekha N, Tajarernmuang P, Srisurapanont M, Chittawatanarat K. Benefit of inodilators in septic shock patients: A systematic review and network meta-analysis. Clin Crit Care 2025; 33: e250007.

Received: June 3, 2024
Revised: February 19, 2025
Accepted: February 20, 2025

Data Availability Statement:
The data and code were available upon reasonable request (Kaweesak Chittawatanarat, email address: kaweesak.chittaw@cmu.ac.th)

Funding:
No funding

Competing interests:
The authors declare that they have no conflicts of interest.

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ABSTRACT:

Background: The efficacy of inodilator agents, including dobutamine, levosimendan, and milrinone, in patients with septic cardiomyopathy on mortality outcomes is still a controversial issue. This systematic review and network meta-analysis aimed to assess the impact of inodilator agents on mortality outcomes and hemodynamic data when utilizing these inodilators compared to placebo.

Method: We conducted a network meta-analysis and searched PubMed, Embase, Cochrane Library, Scopus, and ClinicalTrials.gov for randomized controlled trials and prospective cohort studies examining the use of levosimendan, dobutamine, or milrinone in patients with septic shock. The primary outcomes were short-term mortality. The secondary outcome were ICU length of stay, and hemodynamic parameters.

Results: Fourteen studies involving 1164 participants were included in the analysis. In terms of short-term mortality, levosimendan ranked the highest with a relative risk (RR) of 0.93 (95% CI 0.77-1.13) compared to placebo. The second and third rankings were milrinone (RR of 0.91; 95% CI 0.65-1.27) and dobutamine (RR of 1.12; 95% CI 0.84-1.51), respectively. Regarding ICU length of stay, Levosimendan ranked the first with a mean difference (MD) of -0.83 (95% CI -2.58 to 0.93), while dobutamine, ranking second, demonstrated a MD of 0.30 (95% CI -2.45 to 3.05) compared to placebo. In terms of heart rate, levosimendan was the first ranking with a MD of 0.25 (95% CI -4.57 to 5.07) compared to placebo, followed by milrinone with a MD of 0.00 (95% CI -10.14 to 10.14), and dobutamine with a MD of 1.43 (95% CI -4.59 to 7.45). All results had very low certainty of evidence.

Conclusions: There were no statistically significant differences in short-term mortality, length of ICU stays, and tachyarrhythmia among septic shock patients treated with inodilator agents. The application of these agents in clinical practice should be tailored to individual patient characteristics. Further randomized controlled trials with larger sample sizes are necessary to establish more definitive evidence.

Keywords: Inodilator; Septic shock; Milrinone; Dobutamine; Levosimendan

INTRODUCTION

According to the pathophysiology of septic shock, cardiac output should be increased, while systemic vascular resistance should be decreased. However, it's important to note that some patients may develop sepsis-induced cardiomyopathy, which leads to the depression of cardiac contractility and consequently results in low cardiac output.

Sepsis-induced cardiomyopathy results in multiple inconclusive mechanisms related to endotoxin exposure, oxidative stress, coronary microvascular changes, mitochondrial dysfunction, and direct myocardial suppression resulting from abnormalities in calcium handling and myofilament sensitivity [1,2]. One study explains the theory of dysregulation in the septic inflammatory response caused by the combination of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) pathways [3]. This, in conjunction with the theory of Toll-like receptors expressing on cardiac myocytes, leads to the initiation of the inflammatory pathway and is associated with the inhibition of cardiac contractility [4,5].

The definition of sepsis-induced cardiomyopathy is a reversible myocardial dysfunction based on three clinical clues: systolic dysfunction, coronary perfusion failure, and elevated cardiac biomarkers. Another hypothesis suggests an explanation through sepsis-related cytokines such as tumor necrotic factor and interleukin-1B [6]. Thus, in some patients may develop mixed hemodynamically characters between septic and cardiogenic shock [7].

While it is known that septic cardiomyopathy is related to a decrease in cardiac output, the impact of inotropic drugs in this scenario remains unknown. The latest Surviving Sepsis Campaign recommendations encourage the use of inotropic drugs, specifically dobutamine in conjunction with norepinephrine or epinephrine alone, in septic shock patients who keep exhibiting persistent hypoperfusion despite maintaining appropriate fluid status [8]. Dobutamine, known for its inodilator effect, can improve cardiac output and oxygen transportation. Due to its vasodilatory effect, it can cause splanchnic vasodilatation and improve tissue oxygenation, leading to a reduction in hyperlactatemia and improvement in acidosis in the septic shock setting [9]. On the other hand, an excessive inotropic effect may lead to tachycardia without an increase in stroke volume due to the shortening of diastolic filling time [10].

Theoretically, the role of inodilator agents (e.g., dobutamine, levosimendan, and milrinone) may involve the improvement of acidosis and peripheral tissue perfusion in septic shock patients compared to inotropic agents alone. However, the evidence supporting the superiority of dobutamine over epinephrine is currently limited, and epinephrine is commonly used in lower-resource settings [11].

However, one observational study of 420 septic shock patients, comparing the use of different inotropic and inodilator agents, including epinephrine, dobutamine, levosimendan, and milrinone, showed an independent association with increased 90-day mortality [12]. The evidence of dobutamine combined with norepinephrine and norepinephrine alone is also warranted.

KEY MESSAGES:

Regarding very low certainty of evidence, there were no statistically significant changes in short-term mortality, length of ICU stays, or tachyarrhythmia between septic shock patients treated with inodilators. The use of these agents in clinical practice should be adjusted to each patient's unique characteristics.

Levosimendan, known as a calcium sensitizer agent, has previously emerged in the setting of decompensated cardiogenic shock and in cardiovascular operative settings. One systematic review and meta-analysis demonstrates that levosimendan can significantly improve NYHA class, BNP biomarkers, and left ventricular ejection fraction, but there is no difference in total mortality [13]. Thus, the use of levosimendan in sepsis has recently emerged. A meta-analysis of 3 randomized controlled trials comparing levosimendan and placebo demonstrate a non-significant difference in mortality outcomes [14]. Another meta-analysis comparing levosimandan and dobutamine also shows a non-superior outcome in mortality rate [15]. Thus, the Surviving Sepsis Campaign gives a weak recommendation against using levosimendan due to limited evidence.

Milrinone, also known as an inodilator agent, inhibits phosphodiesterase-3 (PDE-3), increasing intracellular calcium concentration in both myocardium and vascular smooth muscle cells. This action causes increasing in cardiac contractility and a peripheral vasodilatory effect, particularly in the setting of decompensated cardiogenic shock, especially during pulmonary hypertension crisis [16]. There is evidence supporting that PDE-3 inhibitors have a positive inotropic and lusitropic effect, leading to adequate diastolic perfusion time even in conditions of catecholaminergic surge and tachycardia [17]. There are two early clinical studies of milrinone and amrinone used in pediatric septic shock, demonstrating that they might improve cardiac function [18,19]. Especially in the setting of severe meningococcal septicemia, which involves severe vasoconstriction, the benefits of milrinone usage have been demonstrated [20]. One randomized controlled trial demonstrated the benefit of milrinone in improving cardiac index compared with a placebo in patients with septic cardiomyopathy.

Recently, data on appropriated inodilator agents in septic cardiomyopathy are still warranted. Thus, here comes this systematic review and network-meta analysis.

MATERIALS AND METHODS

This systematic review and network meta-analysis had been pre-registered in PROSPERO (CRD42023488607). The protocol has been followed through the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, version 2020 (PRISMA 2020) flow diagram [21]. Other concise details were provided in Supplementary Information Methods (SMethods)

Eligibility criteria

The eligible criteria for trial inclusion are as follows: (i) any age of participants who developed septic shock or septic cardiomyopathy; (ii) administration of any inodilator agents (e.g., dobutamine, levosimendan, or milrinone) in the intervention group; (iii) administration of another inodilator agent or placebo in the controls; and (iv) the outcome of short-term death defined as 28-days mortality (if those studies did not mention it, mortality in intensive care unit will be used instead), day duration in intensive care unit (ICU), and heart rates after administering those medications. Published prospective randomized controlled trials and prospective observational studies were all included. We also excluded animal and single-arm studies

Information sources

MEDLINE, Scopus, Embase, and the Cochrane Library databases were searched for the possibility of eligible studies from their inception up to December 13, 2023, and again on January 31, 2024. We also review the references of relevant articles from ClinicalTrial.gov. There were no limitations in publication year and languages. All language articles were accepted in this network meta-analysis but preference was given to English.

Searches, trial selection, and data collection

The medical subject heading (MeSHs) terms used to search the database were as follows: "sepsis" "septic" "shock" "cardiomyopathy " "inodilator*" "levosimendan" "dobutamine" "milrinone" with "human" filter. The details of the search strategy have been outlined in the supplementary content.

Two independent authors, NS and PT, screened the titles and abstracts of potentially eligible articles after removing duplicated articles from the database. Subsequently, the full text of possible studies were retrieved and evaluated for eligibility. Any disagreements between the two authors were resolved through discussions with the other two authors (MS and KC).

Finally, NS and PT independently extracted the data from eligible articles and arranged them into a Microsoft Excel data sheet. Another author (MS and KC) also rechecked those data before analysis.

Data items and risk of bias assessment

The data retrieved from the full text were as follows: first author, year of publication, country of the study process, sample size, and baseline characteristics of patients, including percentage of male, age, Sequential Organ Failure Assessment (SOFA) score, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and hemodynamic goals after receiving inodilator agents or placebo defined by mean arterial pressure (MAP), cardiac index (CI), and heart rates (HR).

The primary outcome was the short-term mortality rate. Short-term mortality was reported by 28-day mortality as the initial consideration and ICU mortality as the secondary consideration if the first outcomes were not available.

Secondary outcomes were days duration in ICU and heart rates after medication administration. For heart rate, the small value of outcome was preferred.

Data were extracted on an intention-to-treat analysis. Baseline characteristics, heart rates, and days in ICU were continuous data reported as mean values with standard deviations (SDs). While short-term death was a binary value also reported as a mean with SDs.

If the mean value were unavailable, we converted median with interquartile range (IQR) into mean with SDs using Wan's calculator Excel program. For data presented in bar graphs, we extracted mean values by using WebPlotDigitizer.

Two authors, NT and PT, had independently evaluated the methodological quality of included studies. The Cochrane Risk of Bias Tool version 2 (RoB2) [22] methodology was used as a protocol to assess for 5 domains of bias including process of randomization, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of reported result. Any disputes were discussed afterward.

Effect measures, network plots, transitivity assumption

We compared mean changes between groups using mean differences (MDs) for continuous data measured with the same rating scales, including days in ICU and heart rate values. Risk ratios (RR) were used as effect measurements to compare short-term deaths between groups.

Different inodilator agents and placebo were treated as independent treatments. We represented the comparisons of three outcomes by creating network diagrams. The transitivity among four comparators was illustrated in percentages of male participants, mean age, mean SOFA scores, and mean APACHE II scores.

Synthesis methods

We used the netmeta R-based package (version 2.8.2) in the R environment (version 4.3.1) [23,24] to provide statistical analyses. The random-effects model with a heterogeneity assessment was conducted by using the DerSimonian-Laird method. Forest plots and league tables were used to illustrate the comparisons between all treatment arms and placebo.

The probability of treatment ranks was represented via SUCRA diagrams (Surface Under the Cumulative Ranking Curve) [25]. We calculated the P-score to estimate the point and standard error of the NMA defined by a score ranging from 0 (worst/least favorable) to 1 (best/most favorable) [26].

Heterogeneity, inconsistency, sensitivity analysis, and reporting bias

Heterogeneity had been considered if the I^2 statistic over 50% [27]. A P-value less than 0.10 in the design-by-treatment interaction test [28] was used to identify global inconsistency. Whereas the Separate Indirect from Direct Evidence (SIDE) analysis with p-value less than 0.10 was used to identify local inconsistency [29,30].

To evaluate the robustness of results, sensitivity analysis was performed by high-risk bias trial exclusion. Funnel plots and Egger tests were used to represent the bias.

Certainty assessment

Certainty of effect was evaluated by using the Confidence in NMA approach (CiNeMA) software [31,32]. This semiautomated software assessed the six domains of each comparison, including within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence (or inconsistency). Rating scales ranged from low risk of concerns, some concerns, or major concerns. The risk and concerns from six domains were finally used to provide a single confidence level of high, moderate, low, or very low. Downgrading by one or two levels of overall confidence between each comparison was considered as the presence of some or major concerns in any domain, respectively.

Statistical analysis

The NMAs will be carried out using the 'netmeta' package in the R program (all in the latest versions).

Each inodilator agent and placebo will be considered as an independent treatment. A treatment will be drawn by a node for a network plot, and a comparison between the treatments was shown by an edge.

We will assess the intransitivity using mean age (SD), % of male participants, Body Mass Index (BMI), and study duration.

Significant heterogeneity defined as $I^2 > 50\%$

Significant inconsistency is defined by either a p-value < 0.10 in the design-by-treatment interaction model (global inconsistency) or by more than 15% of comparisons having a p-value < 0.10 for Separate Indirect from Direct Evidence (SIDE) splitting analysis (local inconsistency or direct and indirect effect inconsistency). For the network with inconsistency, we plotted a random-effect, net heat diagram to explore the inconsistency location (Krahn et al., 2013). Small-study effects will be visualized using the funnel plots and quantified using the Egger's test (if the included trials >/= 10).

We will calculate the treatment estimates of each outcome using a random-effects model, frequentist method NMA. Treatment estimates will be described using forest plots and league tables. Treatments will be ranked using the P-scores.

The confidence of NMA estimates will be assessed using the CINeMA (Confidence in Network Meta-Analysis) system.

To analyze of subgroups or subsets of data, sensitivity analyses will be used by excluding the trials with a high risk of bias.

RESULTS

Selection, characteristics, and transitivity of trials

A total of 3706 studies from MEDLINE, Scopus, Embase, and the Cochrane Library were searched, and 937 deduplicated studies were removed. After titles and abstracts screening, 34 studies were included for full-text review. The reasons for the 22 excluded reports were provided in supplementary information (STable 1). At last, 12 studies were explored from the database search. We also found more 3 relevant articles from handed and citational search from ClinicalTrial.gov. One was excluded due to study design mismatch [18,33]. The PRISMA flow diagram was represented in Figure 1.

A total of 14 studies involving RCTs and prospective cohorts were included in this NMA [34–47] with 1164 participants published between 2005 and 2023. These trials were conducted in 6 different countries, with China contributing the most (5 trials, 35.7%). The published languages were presented in English or Chinese.

Compared with placebo, the treatment arms were any of the inodilator agents, including dobutamine, levosimendan, or milrinone. Levosimendan was the most studied, contributing to 13 of 14 studies, while dobutamine was the second most popular agent, involving 9 studies. However, only one study evaluated the effects of milrinone.

Details of trial characteristics were illustrated in Table 1. The mean age of participants was demonstrated in medians [interquartile ranges, IQRs]: mean age, 61 [52.0 – 68.3] years; percentage of men, 59.9% [53.9% – 68.8%]; APACHE-II score, 23.5 [19.7 – 25.2]. SFigure 1 in the supplementary data represents a proportional distribution of characteristics between all treatment groups, indicating the transitivity of included trials. The global and local inconsistency of all outcomes couldn't be evaluated because of the non-closed looped comparison between treatment groups.

Risk of bias

As illustrated in SFigure 2A-B, most domains of all trials rated as low risk of bias.

According to one of 14 studies, it was a non-randomized trial, thus it led to be a high risk of overall bias. There were two studies found to be some concerns of bias in the deviations from the intended intervention and reported selection domain.

One of 14 studies (referred to as 7.1%) was found to have a high risk of bias in the domain of randomization process and some concerns of bias in the reported result selection domain [41]. Another 1 of 14 studies (referred to as 7.1%) was reported as some concerns due to the domain of deviations from intended interventions.

Analysis of data on short-term death

In this NMA, short-term death was primarily defined as 28-day mortality, with ICU mortality considered secondarily if initial data were not available for those participants. Thus, there were no missing data in this trial. Short-term mortality outcomes were included for 4 treatments from 14 pairwise comparisons in 14 trials.

Compared to placebo groups, there were no significant differences in all treatment arms comparisons. Levosimendan had a non-significant trend of lower short-term mortality compared to placebo [RR = 0.83, 95% CI = 0.60 to 1.15]. These considerations were outweighed by one study, Torraco A, et al. 2014, demonstrating a P-value of 0.001. However, this results in NMA having high heterogeneity ($I^2 = 54\%$, p = 0.09). There was only one study comparing milrinone and placebo, which showed no statistically

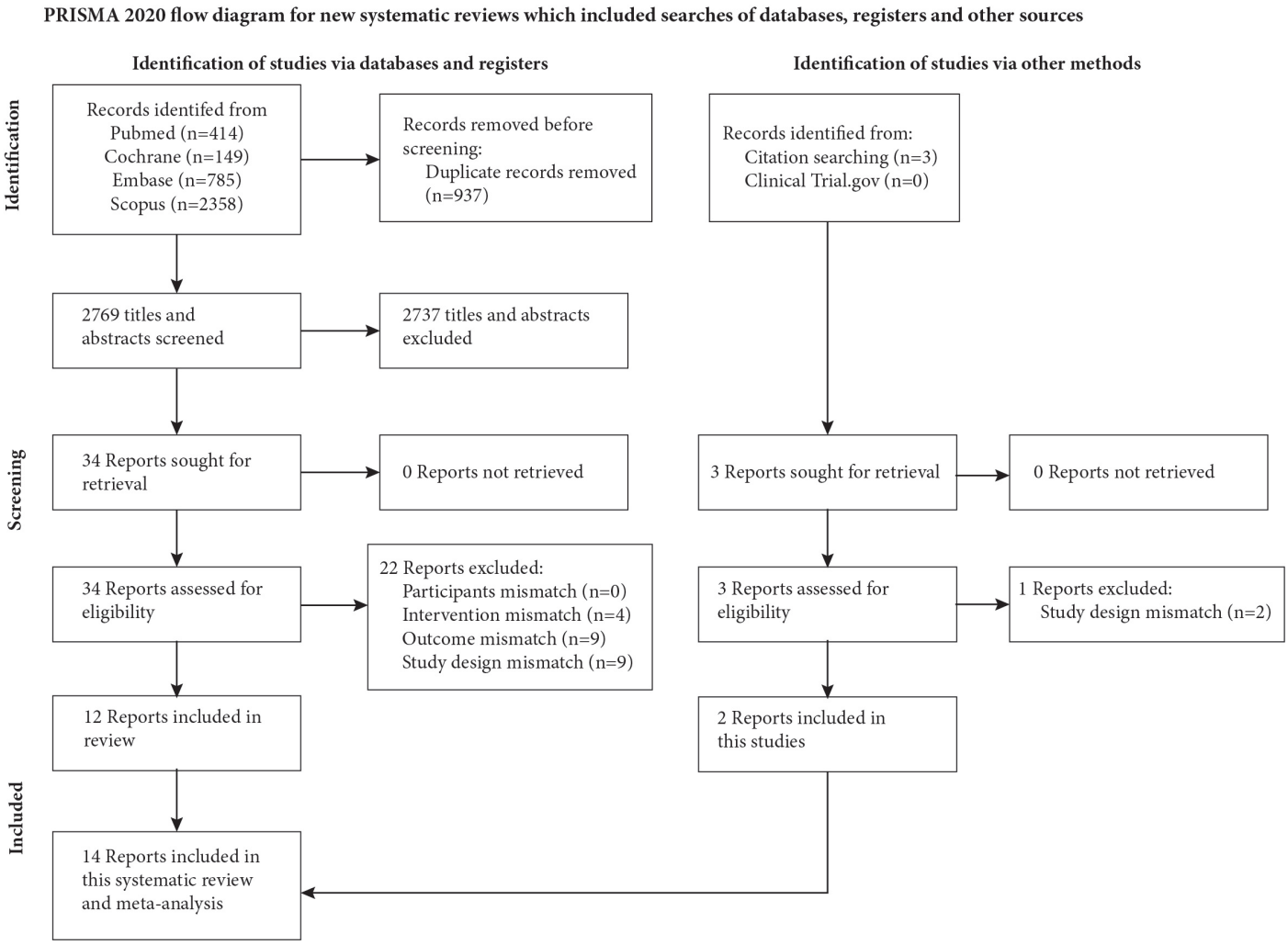

Figure 1. PRISMA flow.

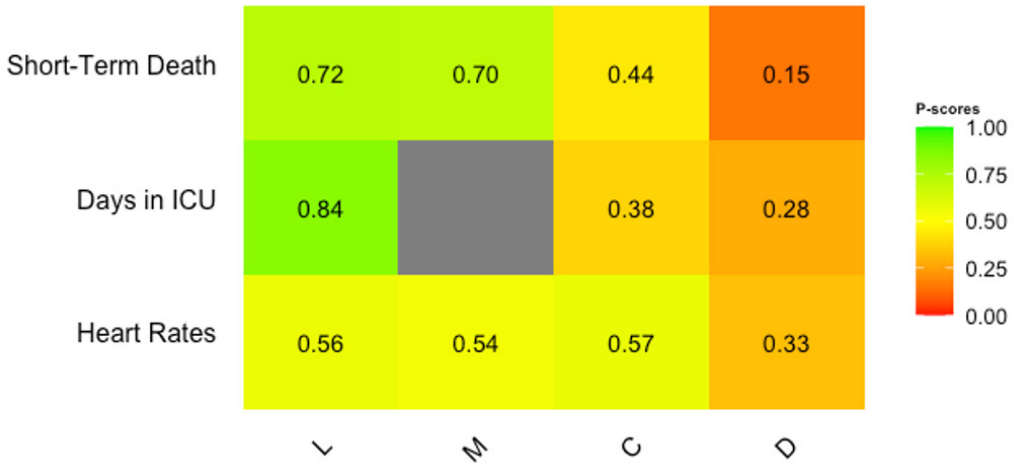

Figure 2. Rank diagram.

Abbreviations: C: Control; D: Dobutamine; L: Levosimendan; M: Milrinone

Table 1. Trial characteristics: design, population, intervention and outcomes.

Study	Study design	Measure, intervention, and participants		
Morelli 2005	RCT Italy	Intervention (n) Dose (mcg/kg/min), durations Mean age (SD) Percentage of men Mean APACHE II (SD) Mean CI (SD) Mean MAP	Levosimendan (15) 0.2, 24 hours 61.5 (7.0) 73.3% 24.4 (1.6) 4.5 (0.2) 75.0 (3.3)	Dobutamine (13) 5, 24 hours 62.4 (7.3) 76.9% 23.7 (2.1) 4.2 (0.2) 73.9 (1.7)
Wang 2015	RCT China	Intervention (n) Dose (mcg/kg/min), durations Mean age (SD) Percentage of men Mean APACHE II (SD) Mean CI (SD) Mean MAP	Milrinone (30) Load 30 mcg/kg then 0.375-0.5,n/a 38.2 (9.0) 63.3% 20.8 (5.6) 3.2 (0.5) 69.0 (21.0)	Control (30) n/a 37.5 (9.0) 66.7% 20.6 (5.8) 2.2 (0.6) 70.0 (21.0)
Hajjej 2017	RCT Italy	Intervention (n) Dose (mcg/kg/min), durations Mean age (SD) Percentage of men Mean APACHE II (SD) Mean CI (SD) Mean MAP	Levosimendan (10) n/a 49.6 (22.3) 80% n/a 4.4 (1.3) 77.0 (22.3)	Dobutamine (10) n/a 51.3 (38.7) 90% n/a 4.2 (1.0) 79.0 (19.7)
Gordon 2016	RCT UK	Intervention (n) Dose (mcg/kg/min), durations Mean age (SD) Percentage of men Mean APACHE II (SD) Mean CI (SD) Mean MAP	Levosimendan (258) 0.05 – 0.2, 24hours 66.6 (12.6) 56.2 25.6 (7.4) 2.8 (1.1) 74.0 (8.9)	Placebo (257) n/a 68.0 (14.1) 56.0 25.3 (6.7) 3.1 (1.3) 73.0 (8.9)
Meng 2016	RCT China	Intervention (n) Dose (mcg/kg/min), durations Mean age (SD) Percentage of men Mean APACHE II (SD) Mean CI (SD) Mean MAP	Levosimendan (19) 0.2, 24 hours 55.4 (17.5) 68.4% 18.4 (4.5) 3.5 (0.3) 68.1 (1.8)	Dobutamine (19) 5, 24 hours 50.2 (13.6) 57.9% 19.5 (4.3) 3.1 (0.4) 67.9 (1.9)
Wang 2017	RCT China	Intervention (n) Dose (mcg/kg/min), durations Mean age (SD) Percentage of men Mean APACHE II (SD) Mean CI (SD) Mean MAP	Levosimendan (120) 0.1 -0.2, 24 hours 70.3 (5.2) 57.5% n/a n/a n/a	Placebo (120) n/a 69.6 (4.5) 54.2% n/a n/a n/a
Torraco 2014	RCT Italy	Intervention (n) Dose (mcg/kg/min), durations Mean age (SD) Percentage of men Mean APACHE II (SD) Mean CI (SD) Mean MAP	Levosimendan (13) 0.2, 24 hours 69.3 (18.2) 85% n/a n/a 69.3 (1.6)	Placebo (13) n/a 68.0 (18.2) 62% n/a n/a 69.3 (1.6)
Tsolaki 2023	Prospective observational study Greece	Intervention (n) Dose (mcg/kg/min), durations Mean age (SD) Percentage of men Mean APACHE II (SD) Mean CI (SD) Mean MAP	Levosimendan (14) n/a, 24 hours 56.3 (40.3) 64.3% 24.8 (18.9) n/a 64.6 (6.5)	Placebo (9) n/a 70.6 (27.9) 55.6% 18.3 (21.8) n/a 63.0 (12.2)

Table 1. (Continued) Trial characteristics: design, population, intervention and outcomes.

Study	Study design	Measure, intervention, and participants		
Memis 2012	RCT Turkey	Intervention (n) Dose (mcg/kg/min), durations Mean age (SD) Percentage of men Mean APACHE II (SD) Mean CI (SD) Mean MAP	Levosimendan (15) 0.1, 24 hours 54.9 (18.9) 53.3% 30.1 (7.5) n/a 85.2 (3.4)	Dobutamine (15) 10, 24 hours 56.2 (14.9) 53.3% 27.0 (8.4) n/a 72.8 (3.4)
Morelli 2010	RCT Italy	Intervention (n) Dose (mcg/kg/min), durations Mean age (SD) Percentage of men Mean APACHE II (SD) Mean CI (SD) Mean MAP	Levosimendan (20) 0.2, 24 hours 65.6 (15.1) 70% n/a 4.2 (1.2) 71.3 (3.1)	Dobutamine (20) 5, 24 hours 66.0 (19.1) 65% n/a 4.1 (1.3) 72.6 (3.9)
Yang 2018	RCT China	Intervention (n) Dose (mcg/kg/min), durations Mean age (SD) Percentage of men Mean APACHE II (SD) Mean CI (SD) Mean MAP	Levosimendan (15) 0.2, 24 hours 87.9 (8.7) 53.3% 23.3 (3.6) n/a 83 (10)	Dobutamine (15) 5, 24 hours 88.1 (6.5) 53.3% 23.9 (7.4) n/a 80 (11)
Sun 2023	RCT China	Intervention (n) Dose (mcg/kg/min), durations Mean age (SD) Percentage of men Mean APACHE II (SD) Mean CI (SD) Mean MAP	Levosimendan (15) 0.2, 24 hours 52.3 (15.9) 46.6% 18.9 (4.2) 2.1 (0.2) 67.1 (1.9)	Dobutamine (15) 5, 24 hours 42.7 (15.1) 46.6% 19.0 (4.2) 1.7 (0.3) 67.0 (1.9)
Alhashemi 2009	RCT Saudi Arabia	Intervention (n) Dose (mcg/kg/min), durations Mean age (SD) Percentage of men Mean APACHE II (SD) Mean CI (SD) Mean MAP	Levosimendan (21) 0.05-2, 24 hours n/a n/a 21.0 (7.0) 2.8 (0.4) n/a	Dobutamine (21) 5-20, 7 days n/a n/a 27.0 (7.0) 3.2 (0.4) n/a
Vaitsis 2009	RCT Greece	Intervention (n) Dose (mcg/kg/min), durations Mean age (SD) Percentage of men Mean APACHE II (SD) Mean CI (SD) Mean MAP	Levosimendan (23) 0.1 – 0.2, 24 hours n/a n/a n/a 1.7 (0.1) n/a	Dobutamine (19) n/a n/a n/a n/a 1.4 (0.1) n/a

significant difference in short-term mortality [RR = 0.91, 95% CI = 0.65 to 1.27]. The comparison between dobutamine and levosimendan demonstrated that levosimendan seemed to have a trend of higher short-term mortality. However, there was no statistically significant difference with low heterogeneity (I^2 = 0%, p = 0.99) (see SFigure 3A, SFigure 4A, Table 2). The league table also showed a non-statistical difference among the treatments (see Table 3A).

The SUCRA plot showed that milrinone was rated as the first rank and levosimendan, respectively (see SFigure 5A) while in the net rank diagram, levosimendan had 4 comparisons rated as first rank (P-score = 0.72; RR = 0.93; 95% CI = 0.77 to 1.13). Milrinone was the second rank in only 1 comparison (P-score = 0.70; RR = 0.91; 95% CI = 0.65 to 1.27) (see Figure 2). The funnel plot did not suggest significantly reporting publication bias (p-value of the Egger test = 0.05) (see SFigure 6). In the sensitivity analysis, after excluding one of levosimendan trials due to high risk of bias, the result still demonstrated the low heterogeneity of data (I^2 = 0%). However, The rank order of levosimendan was dropped into the second rank, and the first rank was replaced by milrinone (see SFigure 7).

Analysis of data on days in ICU

The data of days in ICU were not reported in 6 trials. Results were from 3 treatments with 8 pairwise comparisons of 8 studies.

The overall trend showed non-significant results that levosimendan groups had lower days in ICU compared to placebo groups, which outweigh 2 studies. Reporting a mean difference (MD), Gordon 2016 had MD of -0.13 [95% CI = -1.50 to 1.24] and Wang 2017 had MD of -1.67 [95% CI = -3.38 to 0.04]. Dobutamine had trend of lower days in ICU compared to levosimendan but there was no statistically significant difference with MD of 1.40 [95% CI = -1.40 to 4.21] outweigh from Memis 2012 [MD of 5.40; 95% CI = -0.82 to 11.62] and Morelli 2010 [MD of 13.00; 95% CI = -0.57 to 26.57]. Additional data also showed low heterogeneity of the net days in ICU comparisons (I^2 = 0%; p = 0.38 and I^2 = 37%; p = 0.18, respectively). Overall net pairwise comparisons demonstrated no statistically significant difference and low heterogeneity with I^2 = 27.2% (see SFigure 3B, SFigure 4B, Table 2). The league table also showed a non-statistical difference among the treatments (see Table 3B).

SUCRA demonstrated that levosimendan rated as the first rank order (see SFigure 5B). The similar results had been observed with the net rank diagram as levosimendan posed as the first rank with 3 direct comparisons (P-score = 0.84; MD = -0.83; 95% CI = -2.58 to 0.93) (see Figure 2). The funnel plot demonstrated a low risk of publication bias. However, the Egger test cannot be confirmed due to fewer than 10 studies (see SFigure 6). The sensitivity analysis after excluding one levosimendan's study due to high risk of bias showed low heterogeneity data after excluding the high-risk bias trial (I^2 = 39.1%) and the rank order of levosimendan was still not changed (see SFigure 7).

Analysis of data on heart rates (HR)

The data reporting heart rate outcomes were available in 10 of 14 studies with 4 treatments and 10 pairwise comparisons.

Reporting as MD, Levosimendan had no statistically significant difference in heart rate rising after administration of medication compared to placebo [MD of -0.51; 95% CI -7.13 to 6.12]. Milrinone also had no statistically significant difference in heart rate surging compared to placebo [MD of -0.00; 95% CI = -9.37 to 9.37]. Levosimendan had a trend of raising heart rate compared to dobutamine outweighed by Sun 2023 [MD of 1.03; 95% CI = -2.26 to 4.32]. Additional data revealed a net comparison as low heterogeneity (I^2 = 17.1%) (see SFigure 3C, SFigure 4C, Table 2). The league table also showed a non-statistical difference among the treatments (see Table 3C).

The SUCRA plot showed milrinone rated as the first rank order and levosimendan as the second rank order, respectively (see SFigure 5C). Levosimendan had 3 direct comparisons posed as first rank by the net rank diagram (P-score = 0.56; MD = 0.25; 95% CI = -4.57 to

Table 2. Direct comparison.

No. of study	Comparison drug (n)	Heterogeneity I^2	Outcome measurement	RR/MD (95% CI)	P-value
Short-term mortality					
4	L(405) vs C (399)	54%	RR	0.83 (0.60-1.15)	0.09
1	M(30) vs C(30)	-	RR	0.91 (0.65-1.27)	-
9	D(147) vs L(153)	0%	RR	1.20 (0.96-1.50)	0.99
Day durations in ICU					
3	L(392) vs C(386)	0%	MD	-0.73 (-1.80 to 0.34)	0.38
5	D(84) vs L(84)	37%	MD	1.40 (-1.40 to 4.21)	0.18
Heart rate					
3	L(285) vs C(279)	31%	MD	-0.51 (-7.13 to 6.12)	0.23
1	M(30) vs C(30)	-	MD	-0.00 (-9.37 to 9.37)	-
6	D(92) vs L(94)	10%	MD	1.03 (-2.26 to 4.32)	0.35

Abbreviations: C: Control; D: Dobutamine; L: Levosimendan; M: Milrinone

Table 3A. League table of short-term mortality.

L	**.**	**0.93 (0.77 to 1.13)**	**0.83 (0.67 to 1.04)**
1.03 (0.70 to 1.51)	M	0.91 (0.65 to 1.27)	.
0.93 (0.77 to 1.13)	0.91 (0.65 to 1.27)	C	.
0.83 (0.67 to 1.04)	0.81 (0.52 to 1.26)	0.89 (0.66 to 1.19)	D

Abbreviations: C: Control; D: Dobutamine; L: Levosimendan; M: Milrinone

Table 3B. League table of length of ICU stay.

L	**-0.83 (-2.58 to 0.93)**	**-1.13 (-3.24 to 0.99)**
-0.83 (-2.58 to 0.93)	C	.
-1.13 (-3.24 to 0.99)	-0.30 (-3.05 to 2.45)	D

Abbreviations: C: Control; D: Dobutamine; L: Levosimendan

Table 3C. League table of heart rate.

C	**-0.25 (-5.07 to 4.57)**	**0.00 (-10.14 to 10.14)**	**.**
-0.25 (-5.07 to 4.57)	L	.	-1.18 (-4.79 to 2.43)
-0.00 (-10.14 to 10.14)	0.25 (-10.97 to 11.47)	M	.
-1.43 (-7.45 to 4.59)	-1.18 (-4.79 to 2.43)	-1.43 (-13.22 to 10.36)	D

Abbreviations: C: Control; D: Dobutamine; L: Levosimendan; M: Milrinone

5.07). Milrinone had one comparison and was posed as second rank (P-score = 0.54; MD = 0.00; 95% CI = -10.14 to 10.14) (see Figure 2). The possibility of low risk of bias was observed by the funnel plot without Egger test evaluation according to the fewer number of studies (see SFigure 6). After excluding one of the levosimendan studies, the sensitivity analysis showed low heterogeneity of data (I^2 = 27.6%) without changing the levosimendan rank order (see SFigure 7).

Summary of treatment ranking

The overview of inodilators's possibility ranking was illustrated in Figure 2 based on P-score. Levosimendan ranked first in two outcomes of short-term death and days in ICU. Milrinone ranked second in short-term death outcome, but the third ranking was shown in heart rate outcome. At last, the controls were posed as the first rank in heart rate outcome.

Certainty of evidence

The certainty of evidence for all outcomes investigated in this study has been assessed as very low [STable 2, SFigure 3]. This evaluation is primarily influenced by major concerns related to imprecision and incoherence across the data. Specifically, the evidence is markedly compromised by a high risk of bias from imprecision indicated by wide 95% confidence intervals in all comparisons. Such variability suggests a substantial uncertainty about the effect sizes and limits the reliability of these findings. Additionally, the evidence is also weakened by incoherence, with a high risk of bias due to the absence of closed-loop comparisons leading to unestimating both global and local inconsistencies. Thus, these could signal that the true effect may be substantially different from the reported outcomes.

DISCUSSION

Main findings and interpretation of results

This is the first presentation of a network meta-analysis aimed to assess the comparative efficacy of three commonly used inodilator agents, including levosimendan, dobutamine, and milrinone, in patients with septic shock and septic cardiomyopathy. In the septic shock management, the most beneficial inodilator agents are still curious. Even in the septic shock management guideline [48], in which dobutamine is preferable. But the level of evidence is not strong enough due to a lack of supporting data.

Our analysis included endpoints such as short-term mortality, length of ICU stay, and heart rate as key outcomes to evaluate the clinical benefits of these agents.

Our analyses reveal no statistically significant differences among the three inodilator agents and placebo regarding short-term mortality, length of ICU stays, or heart rate outcomes. This indicates that, regarding these specific endpoints, the use of levosimendan, dobutamine, milrinone, or the absence of treatment may provide similar clinical efficacy and safety profiles in the context of survival rates and tachyarrythmia conditions.

Comparisons the present results with those of previous studies

The lack of significant differences in short-term mortality aligns with the previous studies and meta-analyses confirming the similar outcomes across these agents [12,15,37]. These consistency findings reinforce the fact that inodilator agents may exert distinct pharmacological and hemodynamic actions; their overall impact on hard clinical outcomes in terms of short-term mortality may not significantly differ.

Similarly, our findings found no significantly difference in the length of ICU stay among septic shock patients treated with levosimendan, dobutamine, or milrinone. This is an important analysis as ICU duration is one of the crucial parameters influencing the utilization of healthcare resources. The comparable length of ICU stay observed across these agents suggest that none of them may confer a substantial advantage in terms of facilitating earlier ICU discharge. Thus, it's probably the most cost-effective to use the cheapest and easily available ones.

Furthermore, our analysis did not reveal any significantly differences in heart rate raising among the three inodilator agents administration. While these agents may lead to varying mechanisms of action affecting inotropic and chronotropic effects, our findings suggest that these different agents may not translate into clinically significant variations in tachyarrhythmias.

Limitation of evidence and review process

It is essential to recognize some limitations in our research. First, the availability of high-quality data differed among research, incorporating the possibility of publication bias into our study. Second, the certainty levels of evidence in all outcomes resulted in extremely low certainty rates due to imprecision and incoherence. Furthermore, because this analysis focused just on short-term outcomes, longer-term data may provide additional insights into the efficacy and safety of these drugs. Finally, patient variables, particularly baseline ventricular systolic function and sepsis severity, may influence distinct treatment responses, which we cannot fully understand in our research.

Implications for practice and research

Accounting for the non-statistically significant results, our analysis did not identify a superior efficacy in terms of short-term mortality, weaning from ICU, and tachyarrhythmias outcomes. Moreover, the very low certainty of evidence may suggest clinician to imply in clinical practice with caution.

Rather than focusing on the comparative efficacy, clinicians should initially select a choice of inodilator agents with cost-effectiveness, safety profiles, baseline patient comorbidities, and clinical context.

At last, the uncertainty rating of evidence leads to further research, including well-designed randomization-controlled trials with standardized outcomes measurement and longer follow-up periods to enhance our understanding of the benefits and risks of those inodilator agents used.

CONCLUSION

While our network meta-analysis found no statistically significant difference in short-term mortality, length of ICU stay, and tachyarrythmia outcomes, the certainty of evidence was assessed as very low. Further research is still warranted to identify appropriate indications for inodilator agents's utilization in septic shock patients.

ACKNOWLEDGEMENT

None

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SUPPLEMENTARY MATERIALS

Beneft of inodilator agents in septic shock patients: A systematic review and network meta-analysis of Randomized controlled trials

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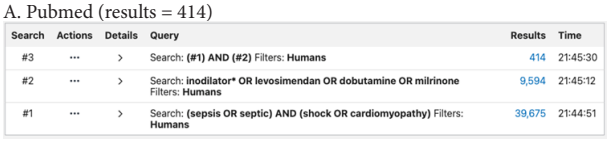
List of abbreviations:	List of treatment abbreviations
• MD = Mean difference • HR = Heart rate • ICU = Intensive care unit • NMA = Network meta-analysis • RR = Risk ratio • SIDE = Separate Indirect from Direct Evidence • SUCRA = Surface Under the Cumulative Ranking Curve	• L = Levosimedan • D = Dobutamine • M = Milrinone • C = Control/placebo

CONTENTS

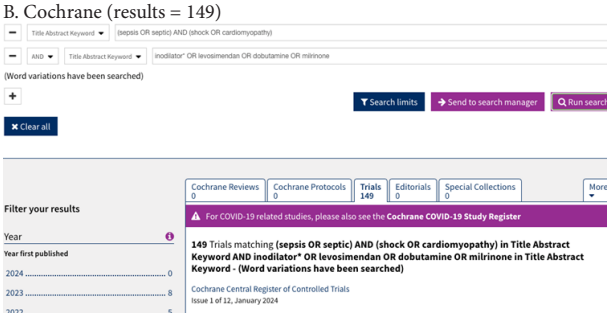
SMethod 1 : Search strategy and results

A. Pubmed (results = 414)

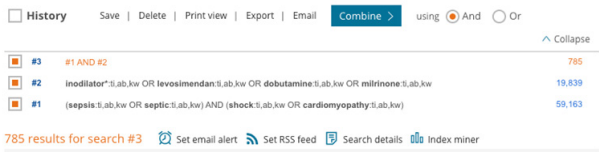


Search	Actions	Details	Query	Results	Time
#3	···	›	Search: **(#1) AND (#2)** Filters: **Humans**	414	21:45:30
#2	···	›	Search: **inodilator* OR levosimendan OR dobutamine OR milrinone** Filters: **Humans**	9,594	21:45:12
#1	···	›	Search: **(sepsis OR septic) AND (shock OR cardiomyopathy)** Filters: **Humans**	39,675	21:44:51

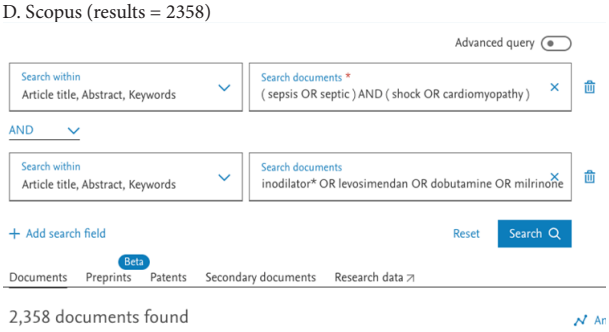
B. Cochrane (results = 149)



C. Embase (results = 785)



D. Scopus (results = 2358)



E. Clinicaltrials.gov (n = 0)
Condition or disease: (sepsis OR septic) AND (shock OR cardiomyopathy)
Interention/treatment: inodilator* OR levosimendan OR dobutamine OR milrinone
Apply Filter: with results

SUPPLEMENTARY TABLE (STable)

STable 1: Excluded Trials with Reasons

References No.	Trials from database searches (n = 22)	Reason for exclusion
(1)	Barton 1996	Study design mismatch
(2)	Bishara T 2010	Study design mismatch (Retrospective study)
(3)	Hernandez 2013	Study design mismatch (Crossectional study)
(4)	Possagnoli 2015	Study design mismatch (Retrospective study)
(5)	Nguyen 2016	Study design mismatch (Retrospective study)
(6)	Sato 2019	Study design mismatch (Retrospective study)
(7)	Zhu 2021	Study design mismatch (Retrospective study)
(8)	Chobngam 2021	Study design mismatch (protocol)
(9)	Wu 2022	Study design mismatch (Retrospective study)
(10)	Kortgen 2006	Intervention mismatch
(11)	Curig O 2012	Intervention mismatch
(12)	Kara 2019	Intervention mismatch
(13)	Wilkman 2013	Intervention mismatch
(14)	Lebuffe 2001	Outcome mismatch
(15)	Backer 2006	Outcome mismatch
(16)	Michaloupou 2007	Outcome mismatch
(17)	Kumar 2007	Outcome mismatch
(18)	Sandra 2009	Outcome mismatch
(19)	Samran 2010	Outcome mismatch
(20)	Meddeb B 2015	Outcome mismatch
(21)	Antclif 2019	Outcome mismatch
(22)	Guo S. 2021	Outcome mismatch

	Trials from other searches (n = 2)	Reason for exclusion
(23)	Schmittinger C. 2008	Study design (Retrospective study)

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23. Schmittinger CA, Dünser MW, Haller M, Ulmer H, Luckner G, Torgersen C, et al. Combined milrinone and enteral metoprolol therapy in patients with septic myocardial depression. Crit Care Lond Engl. 2008;12(4):R99.

STable 2: CINeMA Confidence rating of each treatment comparison.
Judgements for the six domains across all evaluated treatment effect are reported. The default summary judgment is "High" confidence; downgraded by one level each for a "Some concerns" and two levels each for a "Major concerns". The final confidence is rated as of "High", "Moderate", "Low", or "Very low".

A.Short-term mortality

data.std.cr_random_RR_Report

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reason(s) for downgrading
C:L	4	No concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	["Imprecision","Incoherence"]
C:M	1	No concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	["Imprecision","Incoherence"]
D:L	9	No concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	["Imprecision","Incoherence"]
C:D	0	No concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	["Imprecision","Incoherence"]
D:M	0	No concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	["Imprecision","Incoherence"]
L:M	0	No concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	["Imprecision","Incoherence"]

B.Day durations in ICU

data.dayicu.cr_random_MD_Report

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reason(s) for downgrading
C:L	3	No concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	["Imprecision","Incoherence"]
D:L	5	No concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	["Imprecision","Incoherence"]
C:D	0	No concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	["Imprecision","Incoherence"]

C.Heart rate

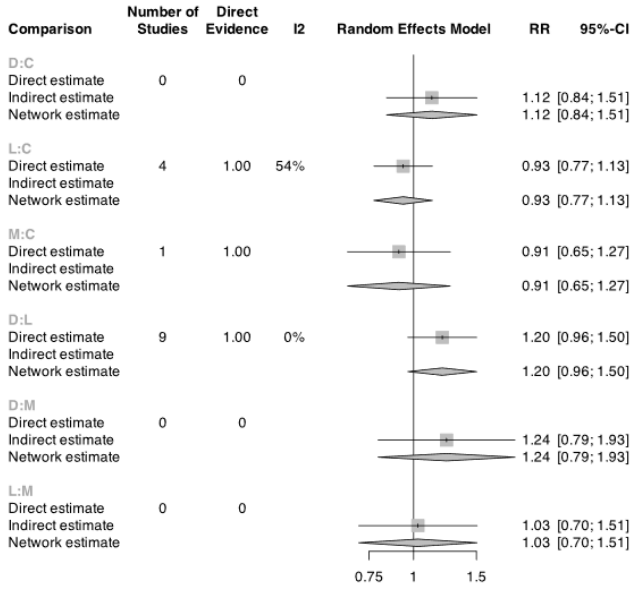
data.hr.cr_random_MD_Report

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reason(s) for downgrading
C:L	3	No concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	["Imprecision","Incoherence"]
C:M	1	No concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	["Imprecision","Incoherence"]
D:L	6	No concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	["Imprecision","Incoherence"]
C:D	0	No concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	["Imprecision","Incoherence"]
D:M	0	No concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	["Imprecision","Incoherence"]
L:M	0	No concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	["Imprecision","Incoherence"]

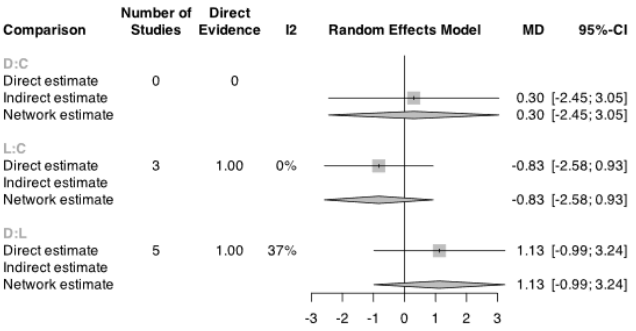
SUPPLEMENTARY FIGURES (SFigures)

SFigure 1: The analysis of Separate indirect from direct evidence (SIDE) (back-calculation method)

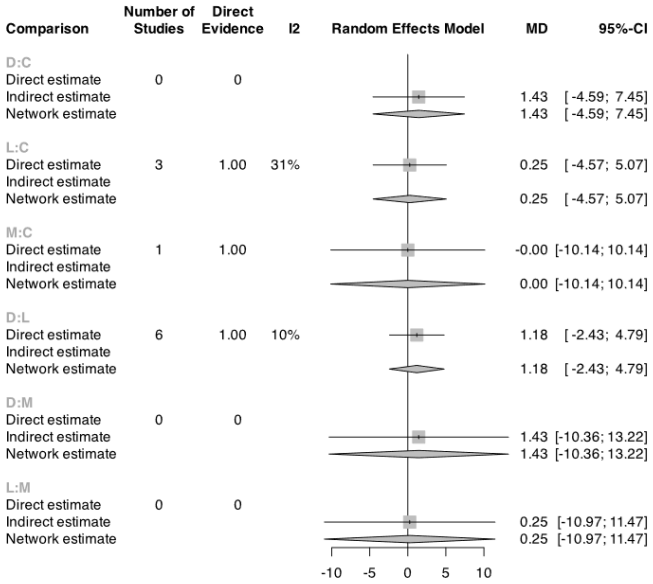
A. Short-term mortality



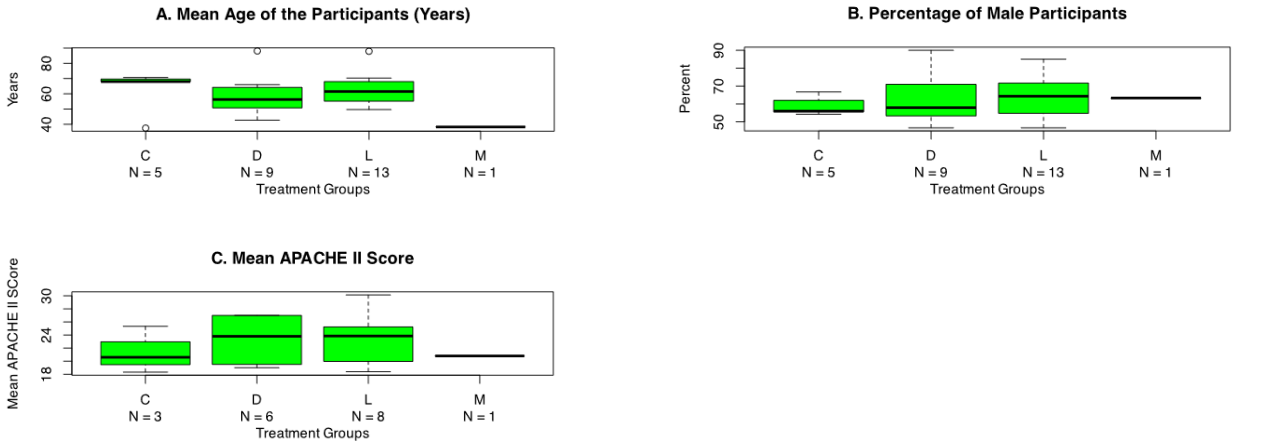
B. Day durations in ICU



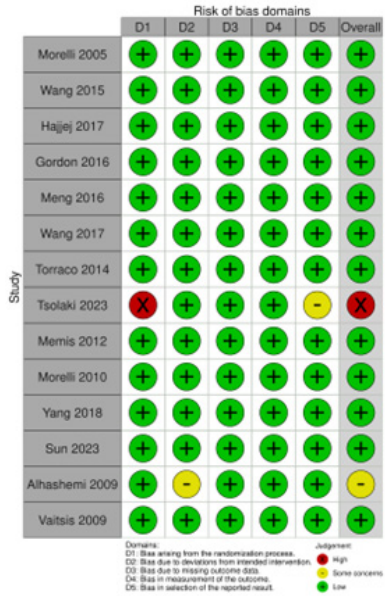
C. Heart rate



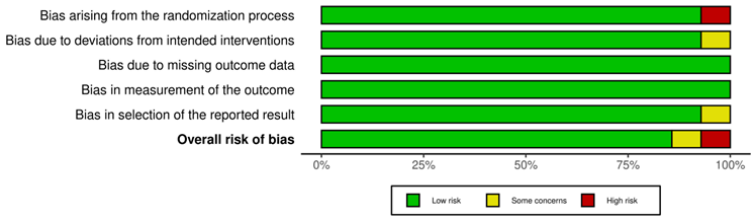
SFigure 2: Transitivity Assessment
Box-and-whisker diagrams of baseline characteristics for assessing the balance of potential effect modifiers.
Each diagram displays the distribution of data based on five summary numbers, including the minimum (lower end of the line), the first quartile (Q1) (lower end of the box), median (midline in the box), the third quartile (Q3) (upper end of the box), and the maximum (upper end of the line).



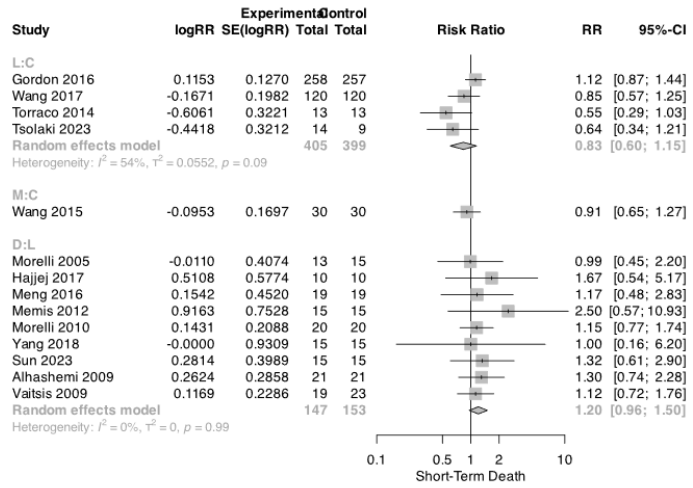
SFigure 3: Risk of Bias Assessment
A. Risk of bias in individual trials



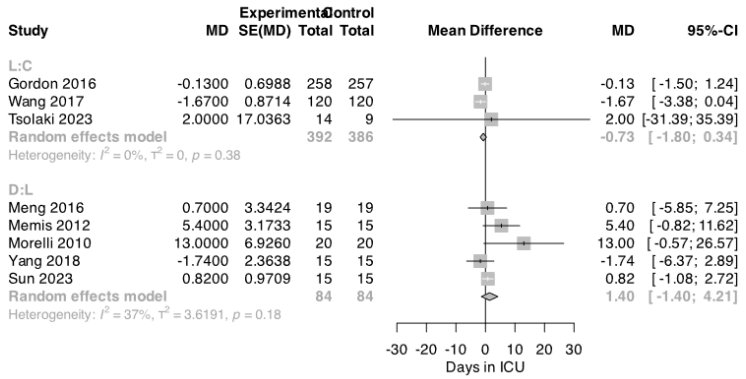
B. Risk of bias across trials



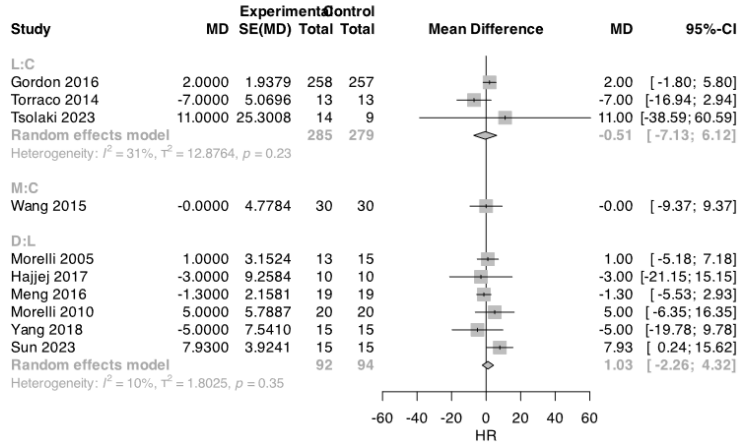
SFigure 4: Forest plots of pairwise comparisons
A. Short-term mortality



B. Day durations in ICU

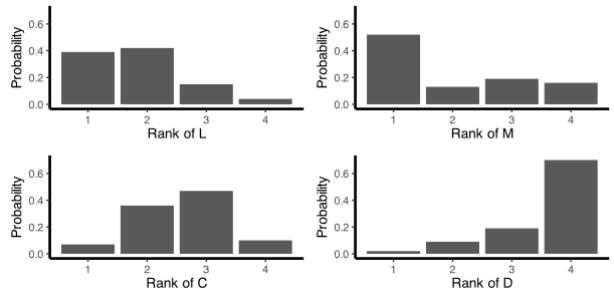


C. Heart rate

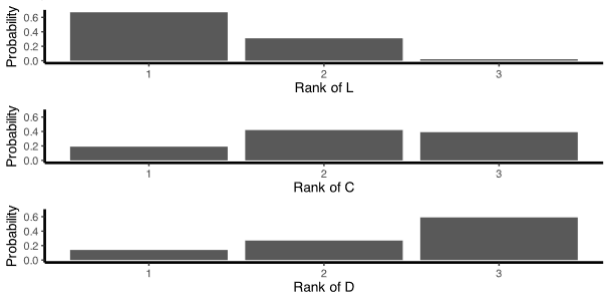


SFigure 5: Plots of the surface under the cumulative ranking curve (SUCRA)
The SUCRA plots of the rank probability of each treatment for short-term mortality, length of ICU stay and heart rate
A SUCRA value gives the probability of an agent to be ranked in each order, with a value of 1 meaning that an agent is certain to be in that order. A value of 0 means that such agent is least likely to be ranked in that order.

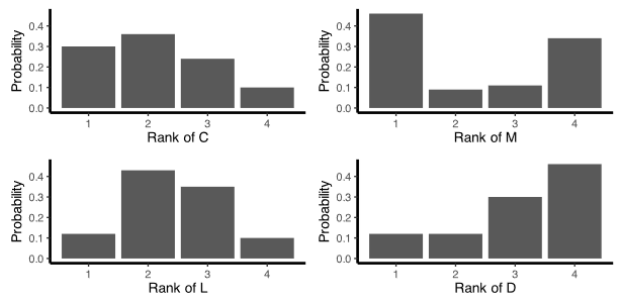
A. Short-term mortality



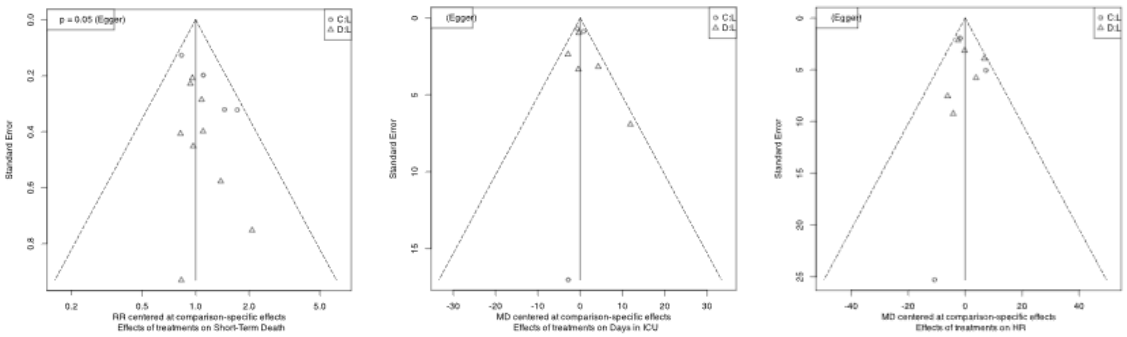
B. Day durations in ICU



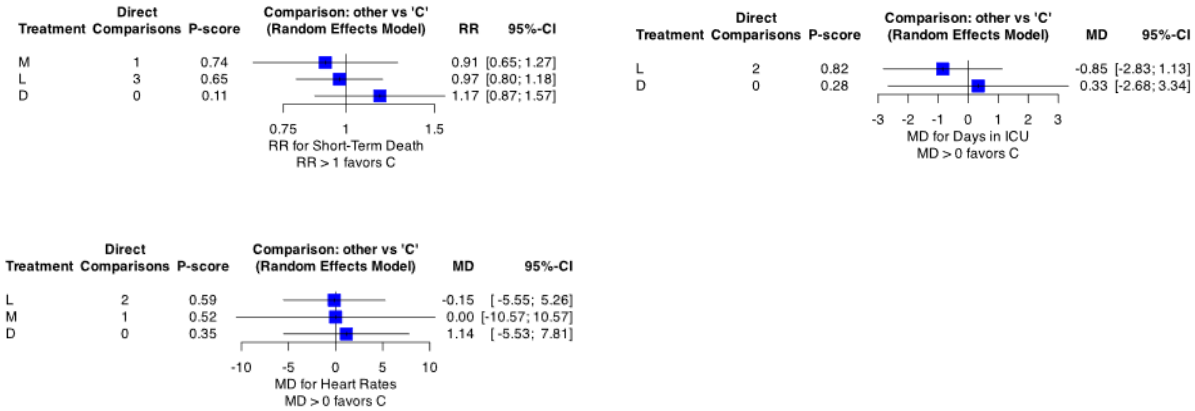
C. Heart rate



SFigure 6: Funnel Plots
Funnel plots and p values of the Egger test of the treatment-effect estimates of individual treatment comparisons against standard errors.

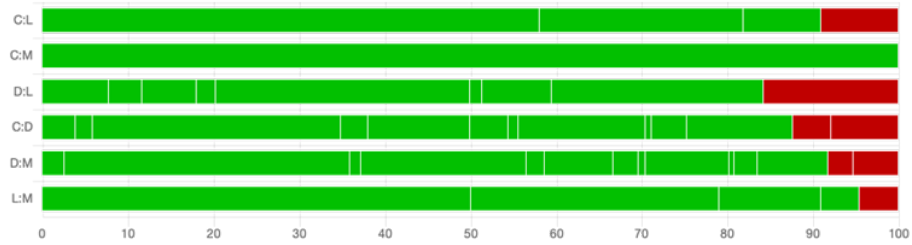


SFigure 7: Sensitivity analysis - forest plots of the treatment effects of second-generation antipsychotics for psychosis in PD after excluding the trials with a high risk of bias.

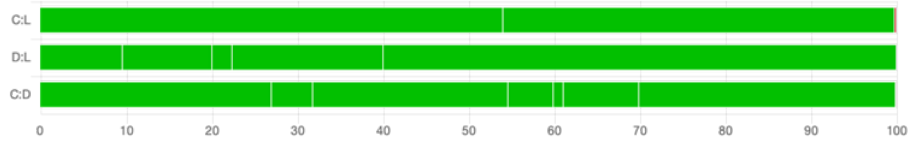


SFigure 8: Risk of Within-Study Bias Bar Chart
Each bar represents a relative treatment effect estimated from the network. White vertical lines separate the percentage contribution of different trials. Each bar shows the percentage contribution from trials judged to be at low (green), moderate (yellow), and high (red) risk of bias.

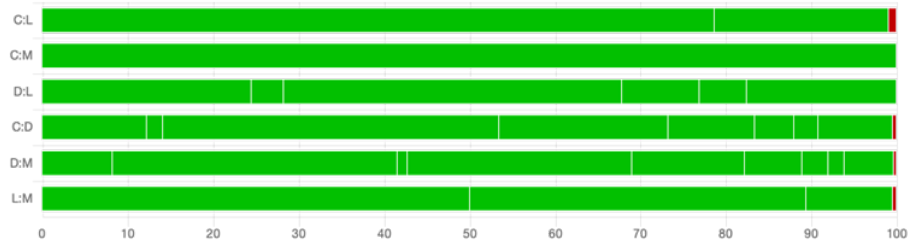
A. Short-term mortality



B. Day durations in ICU

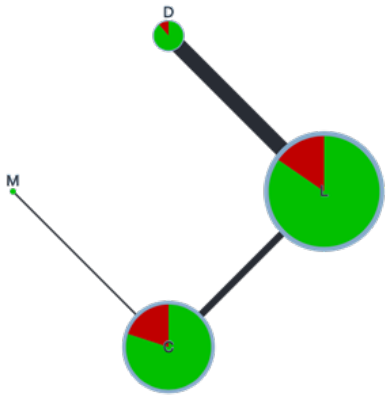


C. Heart rate

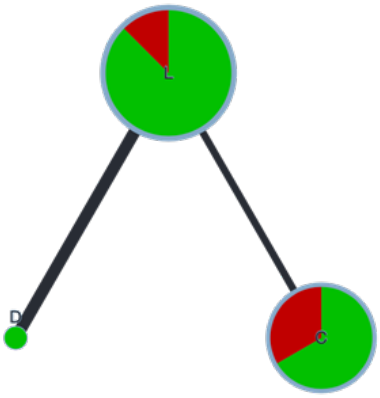


SFigure 9 : Net plot of studies

A. Short-term mortality



B. Day durations in ICU



C. Heart rate