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Original article

The concomitant use of ultra short beta-blockers with vasopressors and inotropes in critically ill patients with septic shock: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background: Septic shock is associated with systemic inflammatory response, hemodynamic instability, impaired sympathetic control, and the development of multiorgan dysfunction that requires vasopressor or inotropic support. The regulation of immune function in sepsis is complex and varies over time. However, activating Beta-2 receptors and blocking Beta-1 receptors reduces the proinflammatory response by influencing cytokine production. Evidence that supports the concomitant use of ultra short beta-blockers with inotropes and vasopressors in patients with septic shock is still limited. This study aimed to evaluate the use of ultra short beta-blockers and its impact on the ICU related outcomes such as mortality, length of stay, heart rate control, shock resolution, and vasopressors/inotropes requirements.

Methods: A systematic review and meta-analysis of randomized controlled trials including critically ill patients with septic shock who received inotropes and vasopressors. Patients who received either epinephrine or norepinephrine without beta-blockers "control group" were compared to patients who received ultra short beta-blockers concomitantly with either epinephrine or norepinephrine "Intervention group". MEDLINE and Embase databases were utilized to systematically search for studies investigating the use of ultra short beta-blockers in critically ill patients on either epinephrine or norepinephrine from inception to October 10, 2023. The primary outcome was the 28-day mortality. While, length of stay, heart rate control, and inotropes/ vasopressors requirements were considered secondary outcomes.

Results: Among 47 potentially relevant studies, nine were included in the analysis. The 28-day mortality risk was lower in patients with septic shock who used ultra short beta-blockers concomitantly with either epinephrine or norepinephrine compared with the control group (RR (95%CI): 0.69 (0.53, 0.89), $I2$=26%; P=0.24). In addition, heart rate was statistically significantly lower with a standardized mean difference (SMD) of -22.39 (95% CI: -24.71, –20.06) among the beta-blockers group than the control group. The SMD for hospital length of stay and

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the inotropes requirement were not statistically different between the two groups (SMD (95%CI): -0.57 (-2.77, 1.64), and SMD (95%CI): 0.08 (-0.02, 0.19), respectively).
Conclusion: The use of ultra short beta-blockers concomitantly with either epinephrine or norepinephrine in critically ill patients with septic shock was associated with better heart rate control and survival benefits without increment in the inotropes and vasopressors requirement.

1. Introduction

Sepsis is considered one of the frequent conditions that affect more than 19 millions of people each year (Rudd et al., 2018). It has been associated with high mortality rates and prolonged length of stay in the intensive care units (Sakr et al., 2018). According to Buchman, etal. 2020, the annual spending on hospitalizations and skilled nursing care for sepsis patients exceeded $62 bilions. The pathophysiology of sepsis involves a huge inflammatory and anti-inflammatory process with some hormonal and cellular involvement which can affect the cardiovascular system (Chaudhry et al., 2013). Impaired organ function, specifically the cardiovascular system, can have a profound impact on the body's hemodynamic stability. When sepsis involves the heart, it can impact the heart ventricles negatively resulting in a high mortality rate and slow recovery (Delano & Ward, 2016).

Managing sepsis and septic shock in the intensive care units (ICUs) necessitates a multifaceted approach. This approach involves promptly identifying the source of infection, administering appropriate antibiotics, providing fluid resuscitation, and offering vasopressors/inotropic support to maintain blood pressure (Evans et al., 2021). Starting vasopressors, such as norepinephrine, is a critical component of supportive care to sustain blood pressure and improve hemodynamics (Evans et al., 2021). Catecholamines are known to play a pivotal role in the cardiovascular complications associated with sepsis (Drosatos et al., 2015). During sepsis, the sympathetic nervous system becomes highly activated, leading to the excessive release of stress hormones and proinflammatory cytokines, which can strain the heart (Delano & Ward, 2016). Additionally, the surge in catecholamine release can have detrimental effects on the heart and blood vessels, potentially affecting recovery and prolonging ICU length of stay (Gubbi et al., 2020). Notably, excessive catecholamine release can also suppress the immune system's ability to combat infections (Bucsek et al., 2018).

Recent data explored the potential role of beta-blockers in the management of sepsis-induced cardiovascular complications (Biradar & Moran, 2011), (Mankowski et al., 2019). The use of beta-blockers in the ICU setting for sepsis management is a subject of ongoing investigation and debate. While traditionally clinicians used to refrain from using beta blockers due to concerns about potential negative effects on cardiac output, recent studies have suggested potential benefits in certain scenarios (Drosatos et al., 2015; Evans et al., 2021). These benefits include attenuating the cardiovascular effects of excessive sympathetic activation, which can contribute to organ dysfunction, and potentially improving patient outcomes.

To address the issue of excessive catecholamines during sepsis, several studies have evaluated the potential role of beta blockers in managing sepsis related cardiac complications (Bucsek et al., 2018; Coppola et al., 2015; Ge et al., 2023; Gubbi et al., 2020). The results of those studies found debatable data where clinical used to refrain from using beta blockers in this settings. According to Morelli, et al. the use of beta blockers achieved better circulatory outcomes and reduction in norepinephrine use (Morelli et al., 2013). M Balik, et al. found beta blockers to be cardioprotective in septic patients (Balik et al., 2012). Further data found better improvements in heart rate, faster normalization of acid-base disorders, and lower mortality rates in patients with sepsis (Chacko & Gopal, 2015).

To substantiate these findings, several meta-analyses have been published investigating the role of beta blockers use in septic patients (Li et al., 2020; P. Liu et al., 2018). Liu, Ping, et al. (2018) conducted a study encompassing five randomized controlled trials. Their findings suggested that the administration of beta blockers in patients with septic shock and sepsis resulted in a notable reduction in heart rate and an improvement in survival rates. However, there was no observed benefit on mean arterial pressure (MAP), central venous pressure (CVP), or central venous oxygen saturation (ScvO2) (Li et al., 2020). Sun, Wanli, et al. (2020) analyzed six studies and corroborated these findings. Their analysis indicated that the use of beta blockers in patients with septic shock and sepsis appeared to be safe, with the added advantage of reducing 28-day mortality rates (P. Liu et al., 2018). New research studies may have been published subsequent to the previous meta-analyses that could potentially enrich our understanding of the debated issue. It is therefore imperative that these updated findings be taken into account for a more thorough and comprehensive analysis (Cocchi et al., 2022; J. Wang et al., 2023). Including these studies might potentially alter the overall conclusions or effect sizes, leading to more precise estimates and a better understanding of the research question. In this updated meta-analysis, our aim is to systematically review and quantitatively analyze the current body of literature pertaining to the use of ultra short beta-blockers and its impact on the ICU related outcomes in septic shock patients.

2. Methods

The study strictly adhered to the reporting guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). Furthermore, the study was registered in the Prospective International Register of Systematic Reviews (PROSPERO) under the reference number CRD42023417235.

2.1. Search Strategy and Study Selection

From inception to October 10, 2023, MEDLINE and Embase databases were utilized to search systematically for randomized controlled trials (RCTs) investigating beta-blocker use in critically ill patients with septic shock requiring vasopressors or inotropes. Search terms related to septic shock, intensive care unit, and the use of inotropes/vasopressors, were combined with search terms related to beta-blockers. A detailed search strategy can be found in the Appendix Table A1. Additionally, we searched ClinicalTrials.gov to identify any ongoing or unpublished trials. Furthermore, we hand-searched the citation lists of the included studies and similar reviews for potentially eligible studies.

In this study, the eligibility criteria included enrolling in studies that included critically ill patients with septic shock who required vasopressors/inotropic support, specifically either epinephrine or norepinephrine and received ultra-short beta-blocker agents during their stay in the ICU. The dose and duration of the beta-blocker were not restricted. A search was conducted to identify relevant articles, the search results were imported into Abstrackr, a tool for abstract screening (Wallace et al., 2012). Two investigators (AH and OA) independently assessed the titles and abstarcts of the studies identified through the search strategy for eligibility.

Duplicate studies and those not meeting the predetermined inclusion and exclusion criteria were excluded from further consideration. Following the initial screening of abstracts, the full texts of the remaining studies were obtained and assessed for eligibility according to the predefined criteria. This process was carried out independently by two study authors, namely AH and OA. In case of any disagreements

between the two authors, a third investigator (KS) was consulted to reach a consensus. This approach added an additional layer of objectivity and reliability to the study's selection process.

2.2. Study Outcomes

The 28-day mortality was the prespecified primary outcome for this systematic review and meta-analysis. Secondary outcomes included ICU length of stay (LOS) measured in days, heart rate measured in beats per minute (bpm), and the dose requirement of vasopressors/inotropes. Meta-analyses were conducted if two or more studies reported sufficient data for the same outcome.

2.3. Data Extraction and Quality Assessment

The relevant data from the included studies were independently extracted by two authors (MF and RQ). Any disagreements were resolved by discussion with the senior author (KS). The extracted data was recorded using a standardized data collection form. We extracted information about the study design, number of patients, inclusion criteria, beta-blocker agent and dose, and relevant outcomes.

To assess the quality of the included studies we used the Cochrane collaboration tool to assess the risk of bias in randomized clinical trials (RoB2). The included studies were evaluated in five domains: randomization process, deviation from the intended intervention, missing outcome data, measurement of the outcome, and selection of the reported results. The data was extracted using a data extraction form and two reviewer authors made their judgment independently (RA, AA). The risk of bias was rated as high risk of bias, some concerns, and low risk of bias.

2.4. Data Synthesis

Quantitative synthesis of included studies was performed using R, version 4.3.1. We pooled the data using relative risk or risk ratios (RRs) when the number of events was available for the dichotomous mortality outcome. We planned to pool the data using the adjusted hazard ratios (HRs) and odds ratios (ORs) and their 95% confidence intervals of associations; however, we could not perform such analyses due to limited reporting of adjusted effect measures. For the continuous outcomes, ICU LOS, heart rate, and vasopressors dose requirement, we used the mean difference (MD) as the outcomes were reported on the same scale in all included studies. We expressed the uncertainty with 95% confidence intervals (CIs) for all effect estimates.

For studies that reported only the median and interquartile range, the data were converted to mean and standard deviation (SD) using the method described by Luo et al., 2018 and Wan et al. 2014 (Luo et al., 2018; Wan et al., 2014). If SD was not reported, we followed the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2011), either by calculating the SD from other available data (e.g., p-values or CIs) or by calculating the average SD when limited information were available to impute the missing SDs.

Studies were pooled with either the random-effects or fixed-effect models. The random-effect model is deemed more appropriate than the fixed-effects model because of the differences in the included studies; however, we used the fixed-effect model when there were five studies or less reporting a study outcome. The use of fixed effect models has been recommended when there is a low number of included studies in the meta-analysis (i.e., 2 to 5) (Dettori et al., 2022). Statistical heterogeneity was assessed using the I2 statistic. I-square values $\geq$50% were indicative of high heterogeneity. The significance threshold was set at $P < .05$.

2.5. Summary of findings and assessment of the certainty of the evidence

We created a summary of the findings table using the primary outcomes and the main secondary outcomes. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of the body of evidence as it related to the studies that contributed data to the meta-analyses. We used methods and recommendations described in Chapter 12 of the Cochrane Handbook for Systematic Reviews of Interventions (Schünemann et al., 2017), using GRADEpro GDT software (GRADEpro GDT). We justified all decisions to downgrade the certainty of the evidence using footnotes and made comments to aid the reader's understanding of the review where necessary. Two review authors (HA, KA) independently judged the certainty of the evidence, with disagreements resolved by discussion.

3. Results

3.1. Search Results and Characteristics of the Included Studies

We initially retrieved forty-seven potentially relevant studies. No additional potential studies were identified through hand searching. Searching ClinicalTrials.Gov identified three potential ongoing clinical trials that are still in the recruitment phase. After screening the titles and abstracts for eligibility, we found that 37 studies were eligible for full-text review. Out of these, eight randomized controlled trials (RCTs) were included in the analysis. Two studies were double-blinded, and the remaining RCTs were non-blinded. Figure 1 illustrates the study selection process using a PRISMA flow diagram. The total number of patients included in all the analyzed studies was 603.

Esmolol was the beta-blocker used as an intravenous continuous infusion in all the incldued the studies, with the following doses: 0.05-0.2 mg/kg/min or 25 mg/hr continuous infusion. The maximum allowed dose was 300 mcg/kg/min for a duration of seven days or until the ICU discharge. The target heart rate in the intervention arm was either less than 100 bpm per minute within 24 hours or a decrease in heart rate by 20% compared to standard care.

Across all the studies, they include patients with septic shock requiring norepinephrine to maintain a mean arterial pressure (MAP) of 65 mm Hg or higher despite appropriate volume resuscitation.

Table 1 describes the characteristics of included studies, and Table 2 shows the outcomes reported in each study.

3.2. Quality Assessment Results

Based on the results of the quality assessment tool using RoB2, it was found that three of the studies included in the analysis had a low risk of bias. On the other hand, five of the studies were found to have some level of concern regarding the risk of bias, with four of them being assessed as having a high risk of bias (Cocchi et al., 2022; S. Wang et al., 2017; Xinqiang et al., 2015; Yang et al., 2014).

Most of the included studies had concerns about the randomization process and selection of the reported results domains due to limited data reported on allocation concealment and outcome time points. Also, the deviation from the intended intervention and the measurement of the outcome domains is due to the unblinded study design. Assessment of the quality of the included studies is presented in Figure 2.

3.3. Study Outcomes

3.3.1. 28-Day Mortality

As shown in Figure 3, six of the included studies reported the 28-days mortality, with a total of 522 patients. The overall risk ratio (RR) between the two groups favored the concomitant use of beta-blockers with inotropes and vasopressors (RR= 0.69; 95% CI= 0.53, 0.89; $\mathbf{I^2}$:26%), as shown in Figure 2. As per the summary of findings table (Table 1), there is low certainty of the evidence when pooling the data from the six studies in the outcome of 28-days mortality. The evidence was downgraded due to the risk of bias in the included studies, and due to the inconsistency of evidence as the control arm varied across studies.

3.3.2. Heart Rate Control

Five studies reported heart rate control while using the beta blocker: The pooled mean difference for heart rate between the groups was CI= -0.02, 0.19; I2= 0%), as shown in Figure 6.

Table: Grading of findings

Patient or population: Critically ill patients with septic shock on inotropes
Setting: Intensive care unit
Intervention: Beta-Blockers
Comparison: Control

Outcomes	Anticipated absolute effects* (95% CI) Risk with Control	Anticipated absolute effects* (95% CI) Risk with Beta-Blockers	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
28- Days Mortality (Mortality)	64 per 100	**44 per 100** (34 to 57)	**RR 0.69** (0.53 to 0.89)	522 (6 RCTs)	⨁⨁◯◯ Low[a]	Beta-Blockers likely result in a reduction in 28- Days Mortality.
ICU Stay	The mean ICU Stay was **13.91** days	MD **0.89 days lower** (2.76 lower to 1.64 higher)	-	342 (4 RCTs)	⨁◯◯◯ Very low[a,b]	There is uncertainty in the evidence of whether beta-blocker use can impact ICU length of stay.
Hear Rate Control	The mean hear Rate Control was **130.80** Beat per Minute	MD **22.39 Beat per Minute lower** (24.71 lower to 20.06 lower)	-	289 (4 RCTs)	⨁◯◯◯ Very low[a,b]	There is uncertainty in the evidence of whether beta-blocker use can impact heart rate.
Vasopressors Dose requirement	The mean vasopressors Dose requirement was **0.35** Mg	MD **0.08 Mg higher** (0.02 lower to 0.19 higher)	-	140 (2 RCTs)	⨁◯◯◯ Very low[a,b,c]	There is uncertainty in the evidence of whether beta-blocker use can vasopressors dose requirements.

Patient or population: Critically ill patients with septic shock on inotropes
Setting: Intensive care unit
Intervention: Beta-Blockers
Comparison: Control

Outcomes	Anticipated absolute effects* (95% CI) Risk with Control	Anticipated absolute effects* (95% CI) Risk with Beta-Blockers	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

significantly lower in beta-blockers group, (MD= -22.39; 95% CI= -24.71, –20.06; I2=86%), as shown in Figure 5.

3.3.3. ICU Length of Stay (LOS)

ICU LOS was reported in four RCTs, as shown in Figure 4. There was no difference in the ICU LOS between the beta-blocker group and the control arm (MD= -0.89; 95% CI= -2.76, 0.98; I^2=82%). There is very low certainty of evidence in the outcome of ICU LOS due to the high risk of bias in the included studies. In addition, the evidence was down-graded due to the inconsistency, as the control arms differed across studies. Finally, the evidence was downgraded due to the high and un-explained heterogeneity in the results.

3.3.4. Vasopressors Dose Requirement

Only two studies reported vasopressors dose requirement between the two groups, which was not statistically significant (MD= 0.08, 95%;

4. Discussion

In this meta-analysis, we investigated the concomitant use of ultra-short beta blockers and inotropes or vasopressors in critically ill patients with septic shock. We included eight randomized controlled trials comprising 300 patients in the beta-blocker group and 303 in the control group. All the included studies in this meta-analysis were comparing Esmolol in addition to the standard of care to the standard of care alone.

Our findings showed a favorable effect of the ultra-short beta-blockers on the 28- days of all-cause mortality and heart rate compared to the control groups. However, our results did not show any significant differences in the length of ICU stay between the beta-blocker groups and the control groups. Similarly, there was no notable distinction in the vasopressor requirements between the beta-blocker and control groups. In agreement with our findings, previous meta-analyses investigated beta-blockers, either esmolol or landiolol benefit in a patient with septic

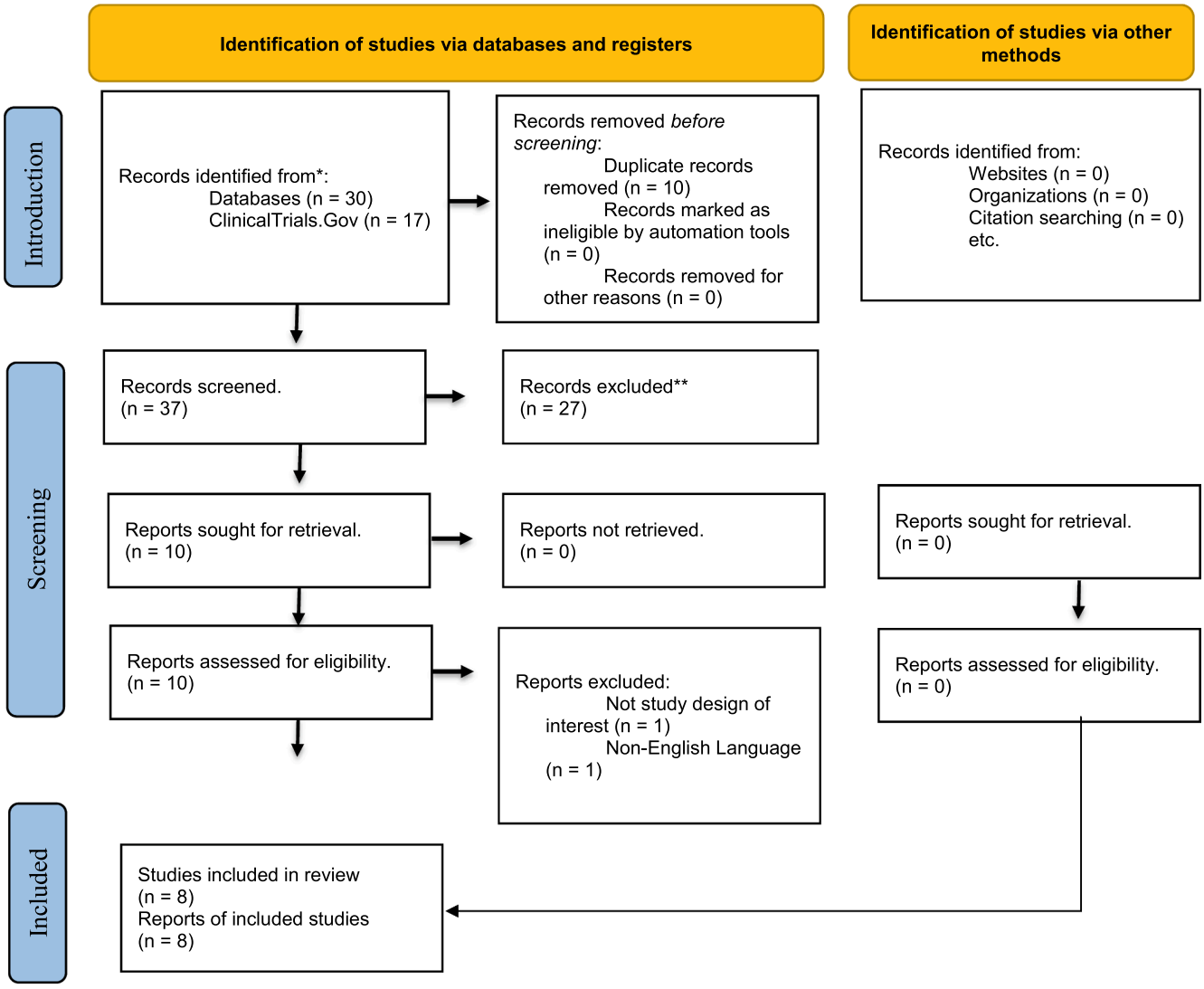

Fig. 1. PRISMA flow diagram. *From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

shock or sepsis found a significant reduction in the 28 days mortality and heart rate in the beta-blocker group compared to the control group (Li et al., 2020; Zhang et al., 2022), with no significant effect on the length of ICU stay (Hasegawa et al., 2021).

Our primary outcome findings showed a 28-day all-cause mortality benefit of the ultra-short beta-blocker in critically ill patients with septic shock; we included six studies in the analysis; the 28 days mortality benefit of all of the studies was in favor of beta-blocker use, but only two studies were significant (Morelli et al., 2013; Xinqiang et al., 2015). The difference can be related to the variability in the included subjects, the different sample sizes, and the different methods of esmolol administration, either with or without loading doses, and the time to reach the predefined HR targets. Indeed, this finding is consistent with a previous meta-analysis that included 11 randomized clinical trials and comprised 2103 critically ill patients, showing a lower mortality risk for more than 14 days in the beta-blockers group compared to the control group. However, there was no significant difference in the mortality risk in less than 14 days' term (Heliste et al., 2022). Another multicenter propensity score study included 1556 patients on beta-blocker therapy before ICU admission matched to 1556 patients with non-previous use of beta-blockers and found a lower 30-day mortality risk in patients who were on beta-blockers (Christensen et al., 2011). In our meta-analysis, the certainty of the evidence was "low" and there is insufficient evidence to estimate the true effect of beta-blockers on mortality in critically ill patients with septic shock or sepsis.

Previous studies have associated tachycardia during septic shock with a higher risk of mortality (Leibovici et al., 2007). Our second finding revealed a notable decrease in heart rate within the beta-blocker group when compared to the control group. A previous meta-analysis, encompassing six trials and involving 349 patients, demonstrated that esmolol had a significant effect in reducing heart rate at various time points post-administration, spanning from 12 to 72 hours. The standardized mean difference between the esmolol group and the control group ranged from -1.31 to -1.91. In another meta analysis that included four trials and 326 patients the heart rate were also significantly lower between the study groups at 24 hours with a mean difference of (-11.96) between esmolol group and control group. In our meta-analysis, we included five studies that showed a mean heart rate between 84-93 beats/min for patients in the beta-blockers group and 95-118 beats/min in the control group. Some of the included studies had predetermined heart rate targets below 100 beats/ min or below 95 beats/ min; however, the 28-day mortality benefit for these targets was controversial (H. Liu et al., 2019; Morelli et al., 2013; J. Wang et al., 2023; S. Wang et al., 2017). In a previous study, an increased heart rate above 95 beats/min for more than 12 hours was associated with cardiac complications in critically ill patients in an ICU setting (Sander et al.,

Table 1
Characteristics of the included studies

Author	Study Status	Year	Study site	Design	Intervention	Primary outcome	Secondary outcome
Liu Xinqiang et al	published	2015	Italy	Double-blinded (RCT)	Esmolol dose 0.05 mg · kg(-1) · min(-1) with the dosage adjusted to maintain HR lower than 100 bpm within 24 hours.	LOS in ICU and 28-day mortality	Hemodynamic parameters [HR, MAP, CVP, cardiac index (CI), stroke volume index (SVI), systemic vascular resistance index (SVRI)] and tissue oxygen metabolism parameters [central venous oxygen saturation (ScvO2), lactate level (Lac)] before and 24, 48, 72 hours after the treatment.
Andrea Morelli et al.	published	2013	Rome, Italy	Non-blinded RCT	Esmolol infusion titrated to maintain heart rate between 80/min and 94/min	Reduction in heart rate below the predefined threshold of 95/min and to maintain heart rate between 80/min and 94/min by esmolol treatment over a 96-hour period.	Hemodynamic and organ function measures; norepinephrine dosages at 24, 48, 72, and 96 hours; and adverse events and mortality occurring within 28 days after randomization.
H Liu et al	published	2019	China	Non-blinded RCT	Esmolol initial dose of 25 mg/hr for 7 days or to the day the patient left the ICU for 7 days	28 d mortality	Heart rate, norepinephrine dosages, lactate level, inflammatory markers in per day during the trial; acute physiology and chronic health evaluation (APACHE II) and sequential organ failure assessment (SOFA) on day 1, 3, 5, 7; length of hospital stay, length of mechanical ventilation, medication time of vasoactive agent.
Michael N Cocchi et al.	published	2022	Israel	Non-blinded RCT	Esmolol was titrated to a heart rate of 80 to 94 per minute, starting at 50 mcg/kg/min and subsequently increasing every 20 min in increments of 50 mcg/kg/min (or slower at the discretion of the clinical team) until target was achieved. The maximum allowed dose was 300 mcg/kg/min. Esmolol was continued for 24 h, unless held or discontinued by the clinical team at their discretion, or if any of the stopping parameters were reached.	Improvement in hemodynamics as measured by the difference in norepinephrine equivalent dose (NED) between groups at 6 hours after initiation of study drug.	Assessing differences in inflammatory biomarkers and oxygen consumption (VO2)
Junyi Wang et al	published	2023	China	Double blinded (RCT)	Low dose of Esmolol was used as the starting dose for titration, with a loading dose of 0.5 mg/kg followed by continue intravenous pumping at 0.05 mg/kg/min for maintenance. If the effect is not favorable after 4 min, give the loading dose again and increase the maintenance dose by 0.05 mg/kg/min. The maximum maintenance dose can be increased to 0.2 mg/kg/min.	Evaluated changes in myocardial contractility after Esmolol lowered heart rate mainly using GLS, and selected the values of GLS at 48 h after admission, when, the heart rate reached target heart rate after using Esmolol	Daily dosage of nor- epinephrine, ratio of reaching target heart rate, values of GEF and dP/dtmax, length of ICU and in-hospital, dura- tion of mechanical ventilation and follow-up records of 28d and 90d
Shengqiang Yang et al	published	2014	China	Non-blinded RCT	Esmolol was giving to patients in treatment group in order to control the heart rate (HR) below 100 bpm within 2 hours	.	
Shupeng Wang et al	published	2017	China	Non-blinded RCT	Continuous intravenous esmolol infusion for 24 hours, initial dose was 0.05 mg×kg-1×h-1, and was titrated to decrease the heart rate by 20% as compared with the value at the time of enrollment or below 95 bpm		
Raouf Ramzy Gadallah et al	Published	2020	Egypt	Non-blinded RCT	Esmolol intravenous infusion by starting dose of 0.05-0.2 mg/kg/min and the dose was titrated every 20 min	Heart rate	MAP, central venous oxygen saturation measured from the central venous line, central venous pressure, serum lactate, APACHE II score (on admis- sion), SOFA recorded daily for the first week beside ICU stays (in days), and 28-day mortality.

Abbreviations: - RCT: Randomized controlled trial, LOS: length of stay, HR: Heart rate

Table 2
Reported Outcomes per Study

Author	28-day mortality	ICU LOS	Heart rate in 24 hour	The change in the dose of norepinephrine.
Liu Xinqiang et al	Reported	Reported	Reported	NA
Andrea Morelli et al.	Reported	Reported	NA	NA
H Liu et al	Reported	NA	NA	NA
Michael N Cocchi et al.	NA	Reported	Reported	Reported
Junyi Wang et al	Reported	Reported	Reported	Reported
Shengqiang Yang et al	NA	Reported	NA	NA
Shupeng Wang et al	Reported	Reported	NA	NA
Raouf Ramzy Gadallah et al	Reported	Reported	Reported	NA

2005). Increased heart rate during septic shock will increase the cardiac oxygen demand, negatively impacting myocardial performance by shortening the diastolic time and reducing coronary perfusion. The association between a specific heart rate target and mortality is controversial (van Loon et al., 2019). These controversial findings may be attributed to the differences in the initiation time and dose or duration of treatment or the patient's disease status. The certainty of the evidence is "very low" to conclude the benefit of using beta blockers to reduce heart rate in critically ill patients with septic shock or sepsis.

Further, we found no significant difference in the pooled estimate of ICU LOS between the beta-blocker group and the control group. This finding is consistent with previous meta-analysis that included four trials and 342 patients, the ICU LOS was not significantly different between esmolol group and the control group. In our meta-analysis, four studies underwent analysis, revealing mean lengths of ICU stays at approximately eight days (Cocchi et al., 2022), 11 days (J. Wang et al., 2023), 14 days (Xinqiang et al., 2015), and 19 days (Morelli et al., 2013). Despite the mortality benefits observed in the analyzed studies, this advantage did not translate into a reduction in the duration of ICU stay. Specifically, the two studies with shorter ICU stays did not show significance in terms of 28-day mortality (J. Wang et al., 2023) or in-

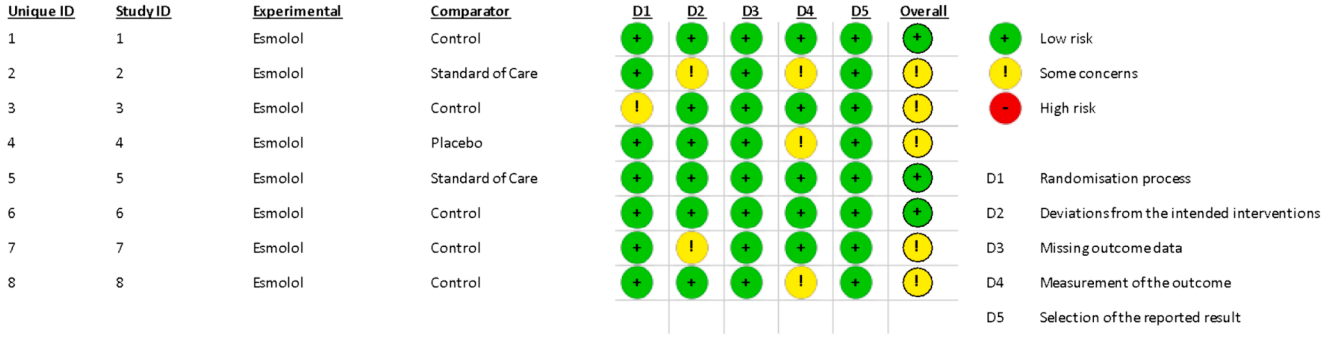

Fig. 2. The quality assessment results of included studies in the meta-analysis, based on the QUADAS-2 evaluation tool.

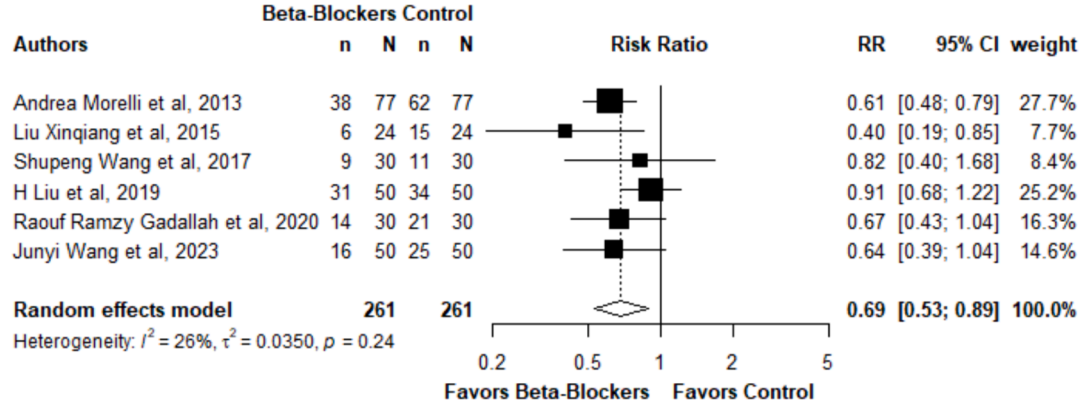

Fig. 3. Forest plot showing the 28-day mortality risk ratio using fixed-effects models in patients receiving beta-blockers concomitantly versus no beta-blockers.

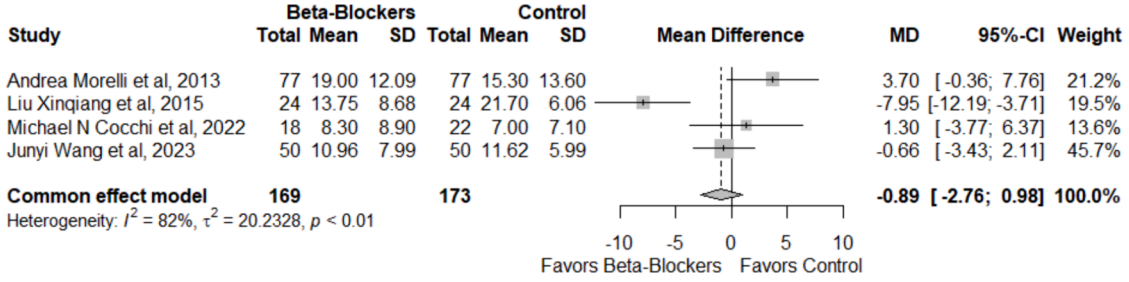

Fig. 4. Forest plot showing the mean differences of ICU LOS using fixed-effects models in patients receiving beta-blockers concomitantly versus no beta-blockers.

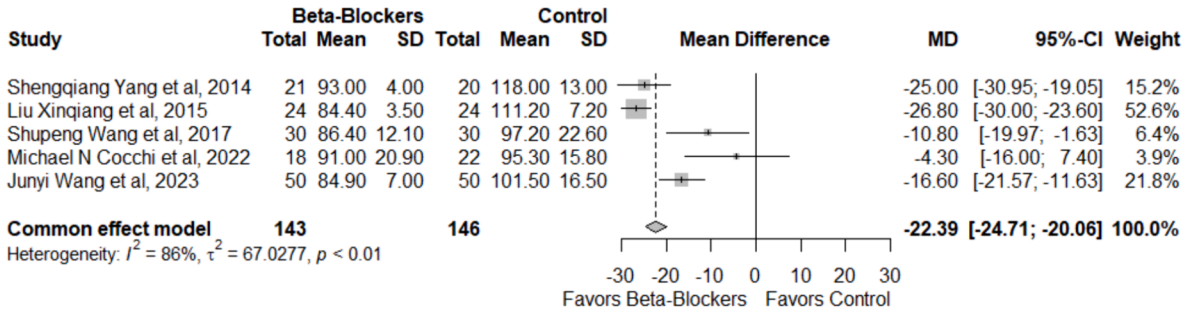

Fig. 5. Forest plot showing the mean differences of heart rate using fixed-effects models in patients receiving beta-blockers concomitantly versus control.

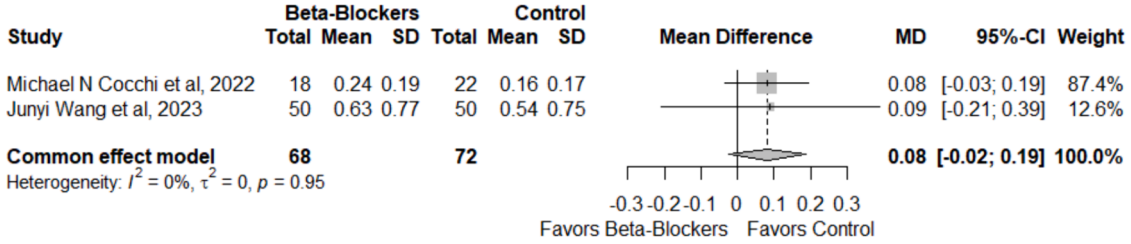

Fig. 6. Forest plot showing the mean differences of Vasopressors dose requirement using fixed-effects models in patients receiving beta-blockers concomitantly versus no beta-blockers.

hospital mortality (Cocchi et al., 2022). This finding may be due to the difference in the underlying clinical situation and disease severity among the included patients; in addition, both studies had a small sample size and investigated mortality as a secondary outcome. The certainty of the evidence was "very low" which limits our conclusion on the effect of beta-blockers on the ICU length of stay in critically ill patients with septic shock or sepsis.

Moreover, the pooled estimate of the vasopressor requirements dose was not significantly different between the beta-blocker and control groups. We included two studies in the analysis and both studies used norepinephrine as the vasopressor of choice (Cocchi et al., 2022; J. Wang et al., 2023). the first study showed that the mean difference in vasopressor dose requirements was significantly different between the esmolol group and control group at 12 h with higher vasopressor dose requirements in the esmolol group, but the difference was not significant at six hours and 24 hours with a decline in vasopressor dose requirement over the study time points (Cocchi et al., 2022). In another trial, there was no notable discrepancy in vasopressor needs between the Esmolol group and the control group, despite a rise in vasopressor dose requirement at 48 hours. This increase was followed by a subsequent decline in requirements at 72 hours in both groups (J. Wang et al., 2023). This result aligns with a prior meta-analysis, indicating no significant variance in vasopressor requirement at both 48 and 72 hours (Heliste et al., 2022). The higher doses of vasopressor required by the esmolol-treated group can be attributed to the hypotensive effect of esmolol, however, the decline in vasopressor requirements along both studies' time points may be related to the disease remission and the improvement in the patient's clinical status. Therefore, the timing for starting beta-blockers and dose titration with concomitant use of vasopressors should be carefully evaluated to avoid excessive hypotension and the need for vasopressor dose escalation (Levy et al., 2021). The actual effect of beta-blockers on vasopressor dose requirements in critically ill patients with septic shock or sepsis is inconsistent, as the certainty of the evidence was "very low" and limited to two RCTs.

The current surviving sepsis adult guideline has no particular recommendations regarding the use of beta blockers in critically ill patients with septic shock. The use of beta-blockers in septic shock patients is a unique approach to improve patient survival. The use of beta-blockers seems to counter the adrenergic effect of catecholamines released during sepsis. However, the mechanism by which beta-blockers alleviate the adrenergic consequences during septic shock is unclear. Specific clinical details, such as defined patients' eligibility criteria for beta-blocker treatment, the required therapeutic doses for this specific indication, and the optimal duration of treatment and time for treatment initiation, need further investigation.

The uniqueness of our study compared to prior meta-analyses: firstly, we emphasize on the impact of ultra short beta blockers in patients with septic shock on two specific catecholamines (Norepinephrine and Epinephrine), secondly, its status as an updated analysis of randomized control studies, providing insights beyond previous works by including most recent studies with larger sample size. Embase was included in our search to ensure that our search is inclusive of conference proceedings. All the randomized clinical trials that were included underwent a quality assessment using the Cochrane risk of bias tool for randomized trials (RoB2). This meta-analysis has some limitations; only a limited number of studies were included, and none were evaluated as a low risk of bias. All the included studies investigated the effect of Esmolol in septic shock patients, so the findings cannot be extrapolated to different types of beta-blockers or different kinds of shock; moreover, Norepinephrine is the only vasopressor investigated in the included studies. Other medications that might affect hemodynamic stability in critically ill patients with septic shock were not reported. Publication bias was not assessed because the included studies are less than ten studies. This topic is of interest to the medical community and there are several ongoing trials being done on this matter.

5. Conclusion

The use of beta-blockers concomitantly with either epinephrine or norepinephrine in critically ill patients with septic shock was associated with better heart rate control and survival benefits without increment in the inotropes and vasopressors requirement. A well-designed RCTs are required to build robust evidence about the actual effect of beta-blockers in critically ill patients with septic shock or sepsis.

CRediT authorship contribution statement

Khalid A. Al Sulaiman: Writing – review & editing. **Hadeel A.**

Alkofide: Methodology. **Mashael E. AlFaifi:** Writing – original draft. **Sarah S. Aljohani:** Writing – original draft. **Abdullah F. Al Harthi:** Project administration. **Rahaf A. Alqahtani:** Writing – review & editing. **Ashwaq M. Alanazi:** Writing – original draft. **Lama H. Nazer:** Writing – original draft. **Abdulrahman I. Al Shaya:** Writing – original draft. **Ohoud A. Aljuhani:** Writing – review & editing, Conceptualization, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Consent for publication

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jsps.2024.102094.

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