ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 18, Issue 1, 2025

Online - 2455-3891
Print - 0974-2441

Review Article

REEVALUATING MEAN ARTERIAL PRESSURE TARGETS IN SEPSIS AND SEPTIC SHOCK: INSIGHTS FROM A SYSTEMATIC REVIEW AND META-ANALYSIS

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Received: 05 November 2024, Revised and Accepted: 18 December 2024

ABSTRACT

The conflicting evidence on the clinical impact of higher versus lower mean arterial pressure (MAP) targets in sepsis and septic shock underscores the urgent need to redefine optimal MAP thresholds to improve outcomes in these critical illnesses. This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines. A data search was conducted on July 1, 2024, for randomized controlled trials and observational studies published from January 2004 to December 2023, assessing patient outcomes based on MAP goal parameters. The primary outcomes were all-cause mortality and overall adverse events. Patients with elevated MAP targets exhibited significantly higher odds of all-cause mortality (odds ratio [OR]: 1.10, 95% confidence interval [CI]: 1.00–1.22), atrial fibrillation (OR: 2.52, 95% CI: 1.25–5.07), and supraventricular arrhythmia (OR: 1.81, 95% CI: 1.07–3.04) compared to those with lower MAP targets (all p≤0.05). In contrast, higher MAP patients with chronic hypertension and sepsis had significantly lower odds of requiring renal replacement therapy (RRT) (OR: 0.77, 95% CI: 0.62–0.97; p=0.03). No significant differences were observed in overall adverse events, acute myocardial infarction, intensive care unit length of stay, major bleeding, mesenteric ischemia, RRT, 28-day survival, or ventricular tachycardia between the groups. This study highlights that targeting higher MAP in sepsis patients may elevate the risk of cardiac complications, such as atrial fibrillation and supraventricular arrhythmia, without having substantial benefits in reducing mortality or adverse events.

Keywords: Sepsis, Septic shock, Mean arterial pressure, Higher mean arterial pressure, Lower mean arterial pressure, Infection

 DOI: http://dx.doi.org/10.22159/ajpcr.2025v18i1.53234. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

Sepsis, triggered by infectious processes and a dysregulated host immune response, significantly increases the risk of organ dysfunction and mortality. In the United States, more than 300 cases of sepsis occur per 100,000 individuals annually, with sepsis-related hospital management accounting for 5.2% of total in-hospital expenses (over $20 million) [1]. Sepsis outcomes are influenced by factors such as epidemiology, antibiotic use, resistance patterns, and microbiological profiles [2,3]. A recent meta-analysis by Fleischmann-Struzek *et al.* reported a 26.7% prevalence of sepsis-related deaths in hospital-treated patients [4], with genitourinary, abdominal, and pulmonary infections as the leading causes of death. Mortality rates were highest among patients with genitourinary sepsis (53.2%), followed by abdominal (28.0%) and pulmonary sepsis (22.4%) [5].

Current management guidelines recommend maintaining a mean arterial pressure (MAP) >65 mmHg to improve outcomes and minimize adverse events [6]. Sustained MAP levels <60–65 mmHg in sepsis worsen prognosis, increasing the risk of preventable organ failure and death [6]. Studies have shown that improving MAP to 65–75 mmHg can mitigate acute kidney injury by enhancing microcirculation [7]. However, prolonged blood pressure elevation may lead to reinjury and clinical complications, requiring high-dose vasoactive drugs. Proper hemodynamic management is essential for reducing organ failure and improving vital signs in septic patients.

Clinical studies report mixed findings regarding the optimal MAP target in sepsis. A meta-analysis by Yoshimoto *et al.* found no significant differences in mortality or adverse events between higher and lower MAP targets, though higher MAP was associated with reduced renal replacement therapy (RRT) but increased supraventricular arrhythmias [8]. Conversely, a meta-analysis by Rikhraj *et al.* showed no significant differences in RRT, neurologic outcomes, or mortality based on MAP targets [9]. Similarly, a meta-analysis by Sarkar *et al.* reported no differences in intensive care unit (ICU) stay duration, mechanical ventilation time, or mortality between patients with standard (60–70 mmHg) and elevated (>70 mmHg) MAP targets [10]. Given these discrepancies, this study critically reexamines and compares the clinical outcomes of different MAP targets in patients with sepsis and septic shock.

Clinical studies report mixed findings regarding the optimal MAP target in sepsis. A meta-analysis by Yoshimoto *et al.* found no significant differences in mortality or adverse events between higher and lower MAP targets. However, it reported reduced RRT in patients with higher MAP targets and increased supraventricular arrhythmias, without adequately discussing the clinical relevance of these adverse events [8]. Similarly, Rikhraj *et al.* showed no significant differences in RRT, neurologic outcomes, or mortality between MAP targets but did not explore subgroup-specific responses, such as those with chronic hypertension [9]. Sarkar *et al.* also found no differences in ICU stay, mechanical ventilation duration, or mortality between standard (60–70 mmHg) and elevated (>70 mmHg) MAP targets but lacked sufficient analysis of demographic factors like age, gender, and pre-existing comorbidities, which could influence MAP-related outcomes [10].

None of these meta-analyses provided a robust assessment of heterogeneity or publication bias, leaving potential variability between studies unexplored. Definitions of MAP thresholds were inconsistent, contributing to difficulties in comparing results. In addition, while

statistical significance was often reported, the clinical significance of findings, including the magnitude and practical impact of outcomes, was insufficiently addressed. Short-term outcomes, such as ICU stay and immediate mortality, were emphasized, while long-term follow-up and sustainability of results were missing. To address these gaps, future analyses should focus on standardized reporting (e.g., Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] guidelines), perform sensitivity and subgroup analyses (e.g., chronic hypertension), and incorporate a more granular exploration of adverse events and patient-centered outcomes.

METHODS

This study adhered to the updated PRISMA 2020 guidelines [11].

Study selection and data collection

Two independent authors conducted a comprehensive review of the scientific literature by searching major medical databases, including the Excerpta Medica Database (EMBASE), Scopus, Web of Science, Cochrane Library, Journal Storage (JSTOR), and PubMed. Only full-text articles or abstracts published in English were considered. The following search terms were employed: (1) Higher MAP, (2) Lower MAP, (3) MAP, (4) Sepsis, (5) Septic Shock, (6) Clinical Outcomes, and (7) Mortality. In addition, Medical Subject Headings terms were utilized to identify relevant studies. Manual exploration of review articles and their reference lists supplemented the search process. The data were initially extracted into a Microsoft Excel workbook and categorized into higher MAP (75–80 mmHg) and lower MAP (60–65 mmHg) target groups. A full-text review was performed by two independent authors to exclude duplicate studies. The data search was conducted on July 1, 2024, with data collection concluding on July 3, 2024. Double data entry was independently verified by a third author to eliminate data entry errors.

Inclusion and exclusion criteria

Studies published from January 2004 to December 2023, evaluating patient outcomes based on MAP targets in sepsis or septic shock, were included. Eligible studies consisted of randomized controlled trials (RCTs) (single/multicenter), *post hoc* analyses, and prospective and retrospective cohort studies. Studies such as review papers, editorials, letters, systematic reviews, meta-analysis, and pre-clinical assessments were excluded.

Primary and secondary outcomes

Primary outcomes included all-cause mortality and overall adverse events, while secondary outcomes encompassed acute myocardial infarction/injury, atrial fibrillation, ICU length of stay, major bleeding, mesenteric/bowel ischemia, RRT, RRT utilization in patients with chronic hypertension, supraventricular cardiac arrhythmia, survival at day 28, and ventricular tachycardia.

Statistical analysis

Cochrane Review Manager (Web version) was used to perform statistical analysis for primary and secondary endpoints [12]. Dichotomous data were analyzed using the Mantel–Haenszel random-effects method, and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated [13,14]. Continuous data were analyzed with the inverse variance random-effects approach, and mean differences with 95% CIs were assessed for both groups [15]. Heterogeneity was examined using Tau-squared, Chi-squared, and I-squared (I^2) tests [16-19]. I^2 values of 0–30%, 31–50%, and 51–100% indicated minimal, moderate, and high heterogeneity, respectively. Statistical significance was defined as $p \leq 0.05$ [20]. Sensitivity analyses, including subgroup analyses and exclusion of specific studies, were performed when significant heterogeneity (I^2>50%) was detected.

Risk of bias (ROB) Assessment

The ROB in observational studies was assessed using Cochrane's ROBINS I tool [21]. Biases regarding judgment, confounding, intervention classification, selection of results, outcome measures, missing data, and intervention deviation were evaluated [21]. For RCTs, ROB-2 tool was used to assess biases in randomization, result reporting, outcome measurement, missing data, and intended procedure deviation [22]. Biases were classified as critical, moderate, low, serious, and no information. ROB distribution was displayed through weighted bar (summary) plots and traffic light plots indicating domain-level assessments.

RESULTS

A total of 354 studies were identified from databases such as PubMed, Embase, Scopus, Web of Science, Cochrane Library, and JSTOR (Fig. 1).

After excluding 97 ineligible records (non-English language), 175 records were screened. Of the 78 reports sought for retrieval, 56 were not accessible. 22 studies were assessed for eligibility, and 7 were excluded due to duplicate data (n=3), dubious results (n=3), and inconsistent findings (n=1). Ultimately, 15 studies were included in the analysis [23-37]. The mean age of participants was 58 years, with more than 50% of males. Comorbidities included ascites, diabetes, hypertension, spontaneous bacterial empyema, systemic infections, ischemic heart disease, chronic kidney disease, liver cirrhosis, community-acquired pneumonia, and atherosclerotic disease. Most studies analyzed considered 75–80 mmHg as the higher MAP target and 60–65 mmHg as the lower MAP target. Tables 1 and 2 summarize the demographics and characteristics of patients, as well as the findings from each study.

Primary outcomes

All-cause mortality

Higher MAP patients (n=3495) had statistically significantly higher odds of all-cause mortality compared to lower MAP patients (n=3283) (OR: 1.10, 95% CI: 1.00–1.22; p=0.05) (Fig. 2). Low heterogeneity was observed (I^2=0%; p=0.76), indicating consistency across studies.

Overall adverse events

No significant difference in overall adverse events was found between higher MAP (n=1928) and lower MAP (n=1861) patients (OR: 1.27, 95% CI: 0.90–1.78; p=0.17) (Fig. 3). Moderate heterogeneity was observed (I^2=46%; p=0.12).

Secondary outcomes

Acute myocardial infarction/injury

No statistically significant difference was found in acute myocardial infarction/injury between the two MAP groups (OR: 1.47, 95% CI: 0.35–6.22; p=0.60) (Fig. 4), with high heterogeneity (I^2=60%; p=0.60).

Atrial fibrillation

Patients with higher MAP had significantly higher odds of atrial fibrillation (OR: 2.52, 95% CI: 1.25–5.07; p=0.010) (Fig. 5), with minimal heterogeneity (I^2=0%; p=0.78).

Length of ICU stay

No significant difference was found in ICU length of stay between the two MAP groups (OR: 0.10, 95% CI: –0.19–0.38; p=0.50) (Fig. 6), with moderate heterogeneity (I^2=41%; p=0.18).

Major bleeding

There was no significant difference in major bleeding events between the two MAP groups (OR: 0.72, 95% CI: 0.45–1.14; p=0.16) (Fig. 7), with minimal heterogeneity (I^2=0%; p=0.95).

Mesenteric/bowel ischemia

No statistically significant difference was found in mesenteric/bowel ischemia between the two groups (OR: 0.81, 95% CI: 0.37–1.79; p=0.61) (Fig. 8), with moderate heterogeneity (I^2=0%; p=0.72).

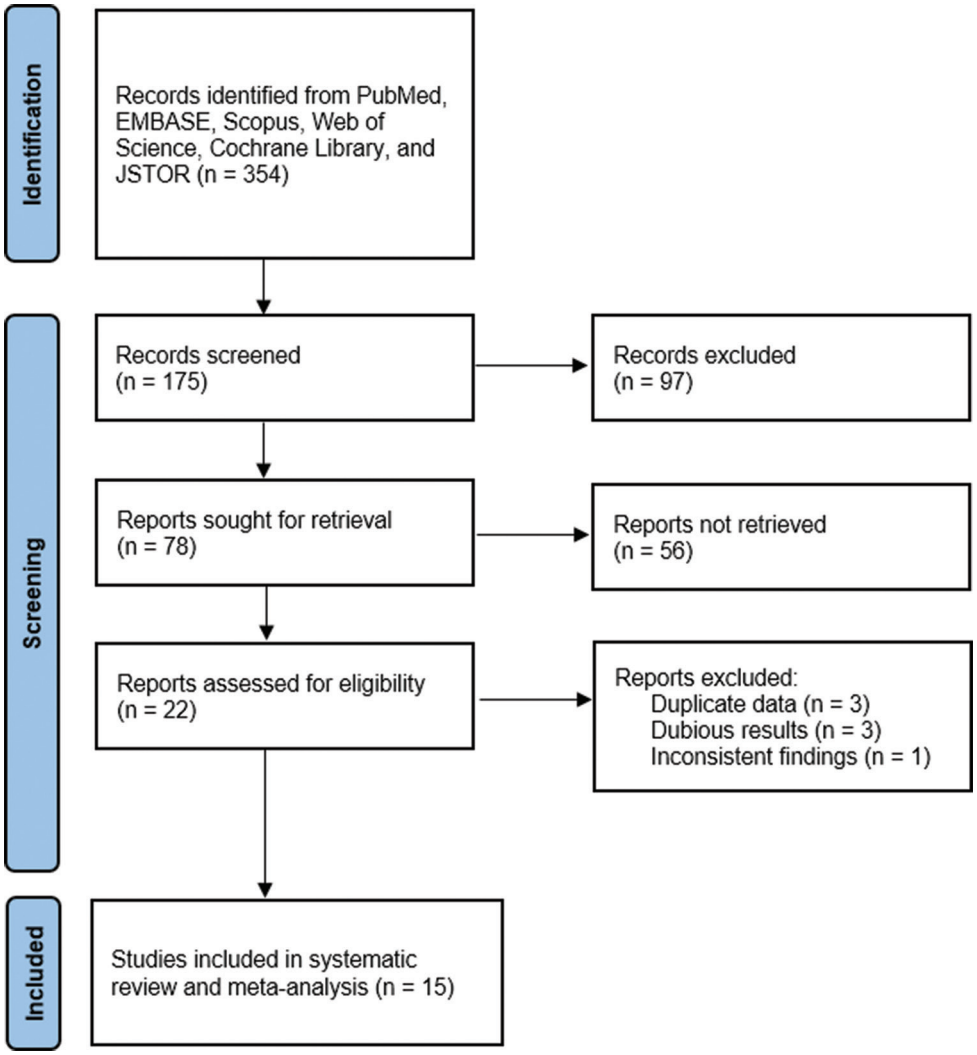

Fig. 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram

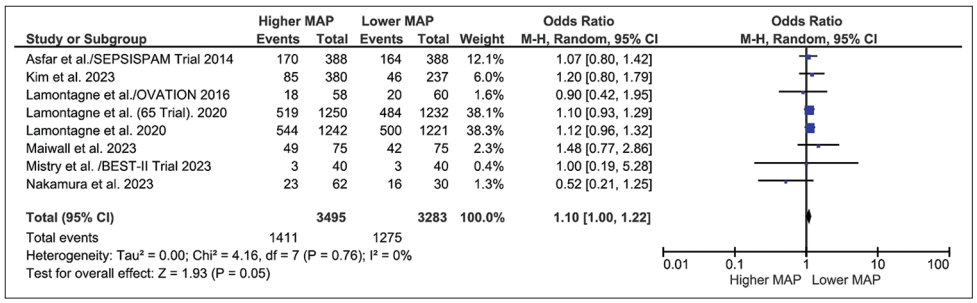

Fig. 2: All-cause mortality

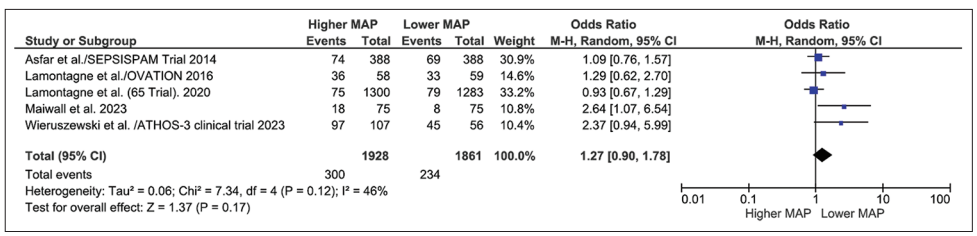

Fig. 3: Overall adverse events

Table 1: Baseline/demographic information

Characteristic	Studies selected									
	Maiwall *et al.*, 2023		Lamontagne *et al.*/OVATION 2016		Asfar *et al.*/SEPSISPAM Trial 2014		Lamontagne *et al.* (65 Trial). 2020		Wieruszewski *et al.*/ATHOS–3 clinical study 2023	
	Lower MAP	Higher MAP	Lower MAP	Higher MAP	Lower MAP	Higher MAP	Lower MAP	Higher MAP	Lower MAP	Higher MAP
Patients, n (%)	75	75	60	58	388	388	1283	1300	56	107
Age, years (median, IQR)	46.7±9.1	45.0±12.9	66±13	63±13	65±15	65±13	75.2 (70.4-80.5)	74.8 (70.1-80.8)	63.0 (53–73)	63.0 (51–75)
Sex (male), n (%)	65 (87%)	68 (91%)	-	-	250 (64.4)	267 (68.8)	696/1216 (57.2)	692/1239 (55.8)	-	-
Sex (females), n (%)	-	-	29 (48%)	25 (43%)	-	-	520/1216 (42.8)	547/1239 (44.1)	21 (37.5)	50 (46.7)
Weight (kg)	-	-	87±25	84±27	-	-	-	-	-	-
Sequential Organ Failure Assessment (SOFA) score	12.0±3.0	12.3±3.4	-	-	10.8±3.1	10.7±3.1	-	-	12 (10–14)	12 (10–13)
Elective surgical history, n (%)	-	-	-	-	5 (1.3)	2 (0.5)	53/1219 (4.3)	60/1239 (4.8)	-	-
Emergency surgical history, n (%)	-	-	-	-	55 (14.2)	47 (12.1)	-	-	-	-
Simplified Acute Physiology Score II	-	-	-	-	57.2±16.2	56.1±15.5	23.9 (8.8) (1213)	23.5 (8.8) (1239)	-	-
Body mass index	-	-	33±13	30±9	-	-	-	-	28.8 (23.9–35.4)	28.1 (24.2–32.9)
APACHE II score	-	-	24±8	25±6	-	-	20.9 (6.5) (1218)	20.6 (6.1) (1239)	27.0 (20–33)	27.0 (23–33)
Etiology (alcohol)	48 (64%)	49 (65%)	-	-	-	-	-	-	-	-
Ascites; n (%), grade 1–2	61 (81%)	57 (76%)	-	-	-	-	-	-	-	-
Ascites; n (%), grade 3	14 (19%)	18 (24%)	-	-	-	-	-	-	-	-
Admission source (emergency)	65 (87%)	67 (89%)	-	-	-	-	432/1219 (35.4)	420/1239 (33.9)	-	-
Admission source (wards)	10 (13%)	8 (11%)	-	-	-	-	461/1219 (37.8)	473/1239 (38.2)	-	-
Sepsis (Admission diagnosis)	-	-	46 (77%)	37 (64%)	-	-	364/1216 (29.9)	369/1239 (29.8)	-	-
Respiratory (Admission diagnosis)	-	-	14 (23%)	7 (12%)	-	-	-	-	-	-
Urinary (Admission diagnosis)	-	-	5 (8%)	3 (5%)	-	-	-	-	-	-
Abdominal (Admission diagnosis)	-	-	6 (10%)	5 (9%)	-	-	-	-	-	-
Other (Admission diagnosis)	-	-	21 (35%)	22 (38%)	-	-	-	-	-	-
Medical (versus surgical admission category)	-	-	50 (83%)	43 (74%)	-	-	-	-	-	-
MELD	32.5±5.5	31.5±7.3	-	-	-	-	-	-	-	-
Child-Pugh	12.8±1.5	12.6±1.8	-	-	-	-	-	-	-	-
AARC	9.8±1.5	10.0±1.4	-	-	-	-	-	-	-	-
Diabetes; n (%)	18 (24%)	14 (19%)	-	-	90 (23.2	75 (19.3)	-	-	-	-
Hypertension; n (%)	7 (9%)	7 (9%)	34 (57%)	19 (33%)	-	-	-	-	37 (66.1)	61 (56.5)

(*Contd...*)

Table 1: (*Continued*)

Characteristic	Studies selected									
	Maiwall *et al.*, 2023		Lamontagne *et al.*/OVATION 2016		Asfar *et al.*/SEPSISPAM Trial 2014		Lamontagne *et al.* (65 Trial). 2020		Wieruszewski *et al.*/ATHOS–3 clinical study 2023	
	Lower MAP	Higher MAP	Lower MAP	Higher MAP	Lower MAP	Higher MAP	Lower MAP	Higher MAP	Lower MAP	Higher MAP
MAP (mmHg)	57.2±8.8	57.8±6.8	-	-	73±14	74±15	69.9 (10.1)	71.1 (11.5)	65.7 (63.3–68.7)	65.7 (63.3–68.7)
Heart rate (beats/min)	94.2±19.5	90.3±20.5	-	-	103±24	104±27	-	-	-	-
Respiratory rate (breaths/min)	19.0±3.5	19.6±3.5	-	-	-	-	-	-	-	-
Arterial lactate (mmol/L)	3.5±2.2	3.9±2.7	-	-	3.7±3.7	3.3±3.2	-	-	2.4 (1.5–3.3)	3.1 (2.1–5.6)
Central venous pressure (cm of H2O)	14.5±4.2	14.4±4.3	-	-	-	-	-	-	-	-
PaO2:FiO2	311.4±185.6	307.1±218.6	-	-	-	-	-	-	-	-
Inferior vena cava diameter (in mm)	16.8±4.5	16.1±3.8	-	-	-	-	-	-	-	-
Norepinephrine dose (mg/kg/min)	0.065±0.056	0.073±0.065	-	-	-	-	761/1265 (60.2)	766/1280 (59.8)	-	-
Terlipressin; n (%)	22 (29%)	27 (36%)	-	-	-	-	-	-	-	-
Vasopressin; n (%)	49 (65%)	41 (54.7%)	-	-	-	-	-	-	34 (60.7)	79 (73.8)
Intravenous steroids, n (%)	56 (75%)	51 (68%)	-	-	-	-	-	-	10 (17.9)	28 (26.2)
Hemoglobin (g/dl)	8.0±1.3	7.7±1.5	-	-	-	-	-	-	-	-
Total leucocyte count (×103 cells/mm3)	16.4±10.9	18.4±11.8	-	-	-	-	-	-	-	-
Platelet count (×103 cells/mm3)	50.6±26.2	59.0±58.0	-	-	-	-	-	-	-	-
Serum total bilirubin (mg/dl)	13.6±8.2	13.9±9.8	-	-	-	-	-	-	-	-
International normalized ratio	3.7±1.9	4.2±2.9	-	-	-	-	-	-	-	-
Serum sodium (mEq/L)	130.9±10.0	132.1±11.2	-	-	-	-	-	-	-	-
Serum potassium (mEq/L)	3.9±0.7	3.9±0.9	-	-	-	-	-	-	-	-
Serum bicarbonate (mEq/L)	20.5±5.2	19.2±4.3	-	-	-	-	-	-	-	-
Anion gap	6.6±6.1	7.3±6.7	-	-	-	-	-	-	-	-
Serum calcium (mg/dL)	1.1±0.1	1.1±0.2	-	-	-	-	-	-	-	-
Serum magnesium (mg/dL)	1.9±0.4	2.2±1.2	-	-	-	-	-	-	-	-
Serum phosphate (mg/dL)	3.4±0.9	3.2±1.6	-	-	-	-	-	-	-	-
Serum creatinine (mg/dL)	0.9±0.4	0.9±0.5	-	-	-	-	-	-	-	-
Serum urea (mg/dL)	74.0±56.2	83.7±58.8	-	-	-	-	-	-	-	-
Serum chloride (mEq/L)	104.0±9.1	105.4±12.1	-	-	-	-	-	-	-	-
Pneumonia, n (%)	57 (77%)	48 (64%)	-	-	-	-	-	-	-	-

(*Contd...*)

Table 1: (*Continued*)

Characteristic	Studies selected									
	Maiwall *et al.*, 2023		Lamontagne *et al.*/OVATION 2016		Asfar *et al.*/SEPSISPAM Trial 2014		Lamontagne *et al.* (65 Trial). 2020		Wieruszewski *et al.*/ATHOS–3 clinical study 2023	
	Lower MAP	Higher MAP	Lower MAP	Higher MAP	Lower MAP	Higher MAP	Lower MAP	Higher MAP	Lower MAP	Higher MAP
Spontaneous bacterial peritonitis, n (%)	5 (7%)	9 (12%)	-	-	-	-	-	-	-	-
Urinary tract infection, n (%)	4 (5%)	0 (1.3%)	-	-	-	-	-	-	-	-
Spontaneous bacterial empyema, n (%)	0 (0)	1 (1%)	-	-	-	-	-	-	-	-
Spontaneous bacteremia, n (%)	1 (1%)	1 (1%)	-	-	-	-	-	-	-	-
Cellulitis, n (%)	1 (1%)	1 (1%)	-	-	-	-	-	-	-	-
Culture positive infections; n (%)	46 (61%)	45 (60%)	-	-	-	-	-	-	-	-
Urine NGAL (ng/ml or ml)	1,523.2±1,869.9	1,725.8±1,735.6	-	-	-	-	-	-	-	-
Serum cystatin C (mg/L)	2.0±0.8	2.0±0.9	-	-	-	-	-	-	-	-
Cumulative fluid (in ml)	1,095.5±1,272.3	1,364.3±1,330.0	-	-	-	-	-	-	-	-
Crystalloids+colloids (albumin)	-	-	-	-	-	-	-	-	-	-
Pancreatitis, n (%)	-	-	3 (5%)	0	-	-	-	-	-	-
Drug overdose, n (%)	-	-	1 (2%)	0	-	-	-	-	-	-
Pulmonary embolism, n (%)	-	-	2 (3%)	1 (2%)	-	-	-	-	-	-
Burn, n (%)	-	-	1 (2%)	2 (3%)	-	-	-	-	-	-
Admission diagnoses, without any association with hypotension, n (%)	-	-	2 (3%)	10 (17%)	-	-	-	-	-	-
Functional comorbidity index, n (%)	-	-	1.6±1.5	1.4±1.4	-	-	-	-	-	-
Days in hospital before randomization/enrolment, n (%)	-	-	1 (1, 3)	1 (1, 3)	-	-	-	-	-	-
Vasopressor hours, n (%)	-	-	11 (5, 17)	9 (3, 16)	-	-	-	-	-	-
Intensive care unit admission to randomization hours, n (%)	-	-	13 (8,21)	13 (8, 19)	-	-	-	-	-	-
Ischemic heart disease, n (%)	-	-	-	-	39 (10.1)	39 (10.1)	-	-	-	-
Chronic heart failure, n (%)	-	-	-	-	53 (13.7)	59 (15.2)	143/1283 (11.1)	143/1298 (11.0)	-	-
Chronic obstructive pulmonary disease, n (%)	-	-	-	-	47 (12.1)	58 (14.9)	-	-	-	-

(*Contd...*)

Table 1: (*Continued*)

Characteristic	Studies selected									
	Maiwall *et al.*, 2023		Lamontagne *et al.*/OVATION 2016		Asfar *et al.*/SEPSISPAM Trial 2014		Lamontagne *et al.* (65 Trial). 2020		Wieruszewski *et al.*/ATHOS–3 clinical study 2023	
	Lower MAP	Higher MAP	Lower MAP	Higher MAP	Lower MAP	Higher MAP	Lower MAP	Higher MAP	Lower MAP	Higher MAP
Chronic renal replacement therapy at ICU admission, n (%)	-	-	-	-	-	-	16/1204 (1.3)	18/1224 (1.5)	17 (30.4)	31 (29.0)
Complete assistance required for entire daily activities, n (%)	-	-	-	-	-	-	8/1211 (0.7)	5/1230 (0.4)	-	-
Acute/chronic kidney disease, n (%)	-	-	-	-	30 (7.7)	20 (5.2)	-	-	-	-
Chronic kidney disease warranting long-term dialysis, n (%)	-	-	-	-	12 (3.1)	5 (1.3)	-	-	-	-
Liver cirrhosis, n (%)	-	-	-	-	28 (7.2)	29 (7.5)	-	-	-	-
Cancer or autoimmune disease, n (%)	-	-	-	-	135 (34.8)	142 (36.6)	-	-	-	-
Chronic arterial hypertension, n (%)	-	-	-	-	173 (44.6)	167 (43.0)	590/1283 (46.0)	597/1299 (46.0)	-	-
Infection source (lung), n (%)	-	-	-	-	200 (51.5	202 (52.1)	-	-	-	-
Infection source (abdomen), n (%)	-	-	-	-	67 (17.3)	65 (16.8)	-	-	-	-
Infection source (urinary tract), n (%)	-	-	-	-	44 (11.3)	44 (11.3)	-	-	-	-
Infection source (Other), n (%)	-	-	-	-	73 (18.8)	72 (18.6)	-	-	-	-
Community-acquired infection	-	-	-	-	253 (65.2)	262 (67.5)	-	-	-	-
Arterial pH	-	-	-	-	7.30±0.13	7.30±0.12	-	-	-	-
Fluid therapy before inclusion — mL	-	-	-	-	2946±1360	2973±1331	-	-	-	-
Atherosclerotic disease, n (%)	-	-	-	-	-	-	187/1283 (14.6)	189/1299 (14.5)	-	-

Characteristic	Studies selected							
	Lamontagne *et al.* 2017	Hall *et al.*, 2004		Legrand *et al.*, 2013	Wong *et al.*, 2015	Nakamura *et al.*, 2023		Zhao *et al.*, 2022
	All patients	Vasopressin	Norepinephrine	All patients	All patients	Lower MAP	Higher MAP	All patients
Patients, n (%)	63.9±14.2 (27–88)	50	49	137	- -	30	62	12041
Age, years (median, IQR)	-	-	-	- -	67.9 (54.4-77.0)	77.7±11.5	75.9±11.6	68.00 (58.00, 77.00)
Sex (male), n (%)	36 (64%)	30 (60)	28 (57)	60 (45)	61 (56.5)	20 (66.7)	43 (69.4)	5136 (42.7)
Sex (females), n (%)	20 (36%)	-	-	- -	- -	-	-	- -

(*Contd...*)

Table 1: (*Continued*)

Characteristic	Studies selected									
	Maiwall *et al.*, 2023		Lamontagne *et al.*/OVATION 2016		Asfar *et al.*/SEPSISPAM Trial 2014		Lamontagne *et al.* (65 Trial). 2020		Wieruszewski *et al.*/ATHOS–3 clinical study 2023	
	Lower MAP	Higher MAP	Lower MAP	Higher MAP	Lower MAP	Higher MAP	Lower MAP	Higher MAP	Lower MAP	Higher MAP
Weight (kg)	81.5±25.6 (35–145)	-	-	-	-	78 (64-91)		52.0±8.9	56.0±13.8	- -
Sequential Organ Failure Assessment (SOFA) score	-	-	-	-	-	-	-	8 (5, 11)	8 (6, 10)	6.00 (4.00, 9.00)
Elective surgical history, n (%)	-	41 (82)	41 (82)	-	-	-	-	-	-	- -
Emergency surgical history, n (%)	-	-	-	-	-	-	-	-	-	- -
Simplified Acute Physiology Score II	-	-	-	-	-	-	-	-	-	- -
Body mass index	28.5±8.6 (11.2–44.2)	-	-	-	-	-	-	-	-	- -
APACHE II score	25.0±7.9 (11–43)	67.5±27.9	76.1±28.0	-	-	64.5 (49.3 – 82.8)		20 (13.5, 25.5)	19 (14, 23)	-
Etiology (alcohol)	-	-	-	-	-	-	-	-	-	- -
Ascites; n (%), grade 1–2	-	-	-	-	-	-	-	-	-	- -
Ascites; n (%), grade 3	-	-	-	-	-	-	-	-	-	- -
Admission source (emergency)	-	-	-	-	-	-	-	-	-	- -
Admission source (wards)	-	-	-	-	-	-	-	-	-	- -
Sepsis (Admission diagnosis)	42 (75%)	-	-	-	-	-	-	-	-	- -
Respiratory (Admission diagnosis)	13 (23%)	-	-	-	-	3 (2.8)		-	-	-
Urinary (Admission diagnosis)	5 (9%)	-	-	-	-	-	-	-	-	- -
Abdominal (Admission diagnosis)	-	-	-	-	-	-	-	-	-	490 (4.1)
Other (Admission diagnosis)	-	-	-	-	-	-	-	-	-	- -
Medical (versus surgical admission category)	-	-	-	-	-	-	-	-	-	- -
MELD	-	-	-	-	-	-	-	-	-	- -
Child-Pugh	-	-	-	-	-	-	-	-	-	- -
AARC	-	-	-	-	-	-	-	-	-	- -
Diabetes; n (%)	-	-	-	20 (15)			-	-	-	2123 (17.6)
Hypertension; n (%)	-	-	-	59 (43)			-	-	-	2212 (18.4)
MAP (mmHg)	-	-	-	-	-	-	-	-	-	70.00 (60.00, 84.00)
Heart rate (beats/min)	-	-	-	-	-	-	-	-	-	- -
Respiratory rate (breaths/min)	-	-	-	-	-	-	-	-	-	- -
Arterial lactate (mmol/L)	-	-	-	-	-	-	-	4.7 (2.9, 8.1)	2.6 (1.6, 4.6)	2.30 (1.50, 3.90)
Central venous pressure (cm of H2O)	-	-	-	-	-	-	-	-	-	- -

(*Contd...*)

Table 1: (*Continued*)

Characteristic	Studies selected										
	Maiwall *et al.*, 2023		Lamontagne *et al.*/OVATION 2016		Asfar *et al.*/SEPSISPAM Trial 2014		Lamontagne *et al.* (65 Trial). 2020		Wieruszewski *et al.*/ATHOS–3 clinical study 2023		
	Lower MAP	Higher MAP	Lower MAP	Higher MAP	Lower MAP	Higher MAP	Lower MAP	Higher MAP	Lower MAP	Higher MAP	
PaO2:FiO2	-	-	-	-	-	-	-	-	-	-	-
Inferior vena cava diameter (in mm)	-	-	-	-	-	-	-	-	-	-	-
Norepinephrine dose (mg/kg/min)	-	-	-	131 (96)		-	-		-	-	-
Terlipressin; n (%)	-	-	-	-	-	-	-	-	-	-	-
Vasopressin; n (%)	-	-	-	-	-	-	-	6.7 (2.4, 19.8)	-	-	-
Intravenous steroids, n (%)	-	-	-	9 (7)			31 (29)	-	-		-
Hemoglobin (g/dl)	-	-	-	-	-	-	-	-	-	9.50 (8.20, 10.90)	
Total leucocyte count (×103 cells/mm3)	-	-	-	-	-	-	-	-	-	-	-
Platelet count (×103 cells/mm3)	-	-	-	-	-	-	-	-	-	153.00 (109.00, 213.00)	
Serum total bilirubin (mg/dl)	-	-	-	-	-	-	-	-	-	-	-
International normalized ratio	-	-	-	-	-	-	-	-	-	-	-
Serum sodium (mEq/L)	-	-	-	-	-	-	-	-	-	138.00 (135.00, 141.00)	
Serum potassium (mEq/L)	-	-	-	-	-	-	-	-	-	4.50 (4.10, 5.00)	
Serum bicarbonate (mEq/L)	-	-	-	-	-	-	-	-	-	-	-
Anion gap	-	-	-	-	-	-	-	-	-	-	-
Serum calcium (mg/dL)	-	-	-	-	-	-	-	-	-	-	-
Serum magnesium (mg/dL)	-	-	-	-	-	-	-	-	-	-	-
Serum phosphate (mg/dL)	-	-	-	-	-	-	-	-	-	-	-
Serum creatinine (mg/dL)	-	-	-	-	-		-	-	-	1.10 (0.80, 2.00)	
Serum urea (mg/dL)	-	-	-	-	-	-	-	-	-	-	
Serum chloride (mEq/L)	-	-	-	-	-	-	-	-	-	-	-
Pneumonia, n (%)	-	-	-	-	-	-	-	-	-	-	-
Spontaneous bacterial peritonitis, n (%)	-	-	-	-	-	-	-	-	-	-	-
Urinary tract infection, n (%)	-	-	-	-	-	-	-	-	-	-	-
Spontaneous bacterial empyema, n (%)	-	-	-	-	-	-	-	-	-	-	-
Spontaneous bacteremia, n (%)	-	-	-	-	-	-	-	-	-	-	-
Cellulitis, n (%)	-	-	-	-	-	-	-	-	-	-	-
Culture positive infections; n (%)	-	-	-	-	-	-	-	-	-	-	-

(*Contd...*)

Table 1: (*Continued*)

Characteristic	Studies selected									
	Maiwall *et al.*, 2023		Lamontagne *et al.*/OVATION 2016		Asfar *et al.*/SEPSISPAM Trial 2014		Lamontagne *et al.* (65 Trial). 2020		Wieruszewski *et al.*/ATHOS–3 clinical study 2023	
	Lower MAP	Higher MAP	Lower MAP	Higher MAP	Lower MAP	Higher MAP	Lower MAP	Higher MAP	Lower MAP	Higher MAP
Urine NGAL (ng/ml or ml)	-	-	-	-	-	-	-	-	-	611.00 (150.00, 1757.00)
Serum cystatin C (mg/L)	-	-	-	-	-	-	-	-	-	-
Cumulative fluid (in ml)	-	-	-	-	-	-	-	-	-	-
Crystalloids+colloids (albumin)	-	-	-	108 (79)			-	-	-	-
Pancreatitis, n (%)	-	-	-	-	-	-	-	-	-	-
Drug overdose, n (%)	1 (2%)	-	-	-	-	-	-	-	-	-
Pulmonary embolism, n (%)	-	-	-	-	-	-	-	-	-	-
Burn, n (%)	-	-	-	-	-	-	-	-	-	-
Admission diagnoses, without any association with hypotension, n (%)	-	-	-	-	-	-	-	-	-	-
Functional comorbidity index, n (%)	1.4±1.1 (0–4)	-	-	-	-	-	-	-	-	-
Days in hospital before randomization/enrolment, n (%)	0.9 (0.7–3.6) (0.1–56.7)	-	-	-	-	-	-	-	-	-
Vasopressor hours, n (%)	-	-	-	-	-	-	-	-	-	-
Intensive care unit admission to randomization hours, n (%)	-	-	-	-	-	-	-	-	-	-
Ischemic heart disease, n (%)	-	-	-	-	-	-	-	-	-	-
Chronic heart failure, n (%)	-	17 (34)	17 (34)	19 (14)		-	-	-	-	-
Chronic obstructive pulmonary disease, n (%)	3 (5%)	-	-	12 (9)			31 (29)	-	-	
Chronic renal replacement therapy at ICU admission, n (%)	-	-	-	-	-		-	-	-	-
Complete assistance required for entire daily activities, n (%)	-	-	-	-	-	-	-	-	-	-
Acute/chronic kidney disease, n (%)	-	-	-	-	-	-	-	-	-	-
Chronic kidney disease warranting long-term dialysis, n (%)	-	-	-	-	-	-	-	-	-	-
Liver cirrhosis, n (%)	-	-	-	10 (7)			14 (13.0)	-	-	

(*Contd...*)

Table 1: (*Continued*)

Characteristic	Studies selected									
	Maiwall *et al.*, 2023		Lamontagne *et al.*/OVATION 2016		Asfar *et al.*/SEPSISPAM Trial 2014		Lamontagne *et al.* (65 Trial). 2020		Wieruszewski *et al.*/ATHOS–3 clinical study 2023	
	Lower MAP	Higher MAP	Lower MAP	Higher MAP	Lower MAP	Higher MAP	Lower MAP	Higher MAP	Lower MAP	Higher MAP
Cancer or autoimmune disease, n (%)	-	-	-	39 (28)			6 (5.6)	-	-	
Chronic arterial hypertension, n (%)	29 (52%)	-	-	-	-	-	-	-	-	- -
Infection source (lung), n (%)	-	-	-	28 (20)		-	-	-	-	996 (8.3)
Infection source (abdomen), n (%)	4 (7%)	-	-	78 (57)			25 (23.4)	-	-	490 (4.1)
Infection source (urinary tract), n (%)	-	-	-	9 (7)			24 (22.4)	-	-	1284 (10.7)
Infection source (Other), n (%)	-	-		-	-		-	-	-	- -
Community-acquired infection	-	-		-	-	-	-	-	-	- -
Arterial pH	-	-		-	-	-	-	-	-	- -
Fluid therapy before inclusion — mL	-	-		-	-	-	-	-	-	- -
Atherosclerotic disease, n (%)	-	-		-	-	-	-	-	-	- -

Characteristic	Studies selected							
	Kim *et al.*, 2023		Collet *et al.*, 2019		Wang *et al.*, 2022		Liang *et al.*, 2017	
	Lower MAP	Higher MAP	All patients		All patients		All patients	
Patients, n (%)	237	380	72		66		32	
Age, years (median, IQR)	-	-	72 (61, 83)		63.5 (52-70.3)	-	-	-
Sex (male), n (%)	-	-	30 (42)		45 (68.2)	-	-	-
Sex (females), n (%)	-	-	-	-	-	-	-	-
Weight (kg)		-	-	-	61.3±9.7	-	-	-
Sequential Organ Failure Assessment (SOFA) score	-	-	9 (7, 12)		11.7±2.1	-	-	-
Elective surgical history, n (%)	-	-	-	-	-	-	-	-
Emergency surgical history, n (%)	-	-	-	-	-	-	-	-
Simplified Acute Physiology Score II	-	-	-	-	-	-	-	-
Body mass index	-	-	24 (21, 27)		22.6±3.3	-	-	-
APACHE II score	-	-	-	-	21.5 (16-26.3)	-	-	-
Etiology (alcohol)	-	-	-	-	-	-	-	-
Ascites; n (%), grade 1–2	-	-	-	-	-	-	-	-
Ascites; n (%), grade 3	-	-	-	-	-	-	-	-

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Table 1: (*Continued*)

Characteristic	Studies selected									
	Maiwall *et al.*, 2023		Lamontagne *et al.*/OVATION 2016		Asfar *et al.*/SEPSISPAM Trial 2014		Lamontagne *et al.* (65 Trial). 2020		Wieruszewski *et al.*/ATHOS–3 clinical study 2023	
	Lower MAP	Higher MAP	Lower MAP	Higher MAP	Lower MAP	Higher MAP	Lower MAP	Higher MAP	Lower MAP	Higher MAP
Admission source (emergency)	-	-	-	-	-	-	-	-		
Admission source (wards)	-	-	-	-	-	-	-	-		
Sepsis (Admission diagnosis)	-	-	-	-	56 (84.8)	-	-	-		
Respiratory (Admission diagnosis)	-	-		-	-	-		-		
Urinary (Admission diagnosis)	-	-	-	-	-	-	-	-		
Abdominal (Admission diagnosis)		-	43 (60)		-	-	-	-		
Other (Admission diagnosis)	-	-	-	-	-	-	-	-		
Medical (versus surgical admission category)	-	-	-	-	-	-	-	-		
MELD	-	-	-	-	-	-	-	-		
Child-Pugh	-	-	-	-	-	-	-	-		
AARC	-	-	-	-	-	-	-	-		
Diabetes; n (%)	-	-	21 (26)		-	-	-	-		
Hypertension; n (%)	-	-	47 (65)		-	-	-	-		
MAP (mmHg)	-	-	-	-	-	-	-	-		
Heart rate (beats/min)	-	-	-	-	-	-	-	-		
Respiratory rate (breaths/min)	-	-	-	-	-	-	-	-		
Arterial lactate (mmol/L)	-	-	-	-	-	-		-		
Central venous pressure (cm of H2O)	-	-	-	-	-	-	-	-		
PaO2:FiO2	-	-	-	-	-	-	-	-		
Inferior vena cava diameter (in mm)	-	-	-	-	-	-	-	-		
Norepinephrine dose (mg/kg/min)	-	-	-	-	-	-	-	-		
Terlipressin; n (%)	-	-	-	-	-	-	-	-		
Vasopressin; n (%)	-	-	-	-	-	-	-	-		
Intravenous steroids, n (%)	-	-		-	-	-	-	-		
Hemoglobin (g/dl)	-	-	-	-	-	-	-	-		
Total leucocyte count (×103 cells/mm3)	-	-	-	-	-	-	-	-		
Platelet count (×103 cells/mm3)	-	-	-	-	-	-	-	-		
Serum total bilirubin (mg/dl)	-	-	-	-	-	-	-	-		

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Table 1: (*Continued*)

Characteristic	Studies selected									
	Maiwall *et al.*, 2023		Lamontagne *et al.*/OVATION 2016		Asfar *et al.*/SEPSISPAM Trial 2014		Lamontagne *et al.* (65 Trial). 2020		Wieruszewski *et al.*/ATHOS–3 clinical study 2023	
	Lower MAP	Higher MAP	Lower MAP	Higher MAP	Lower MAP	Higher MAP	Lower MAP	Higher MAP	Lower MAP	Higher MAP
International normalized ratio	-	-	-	-	-	-	-	-		
Serum sodium (mEq/L)	-	-	-	-	-	-	-	-		
Serum potassium (mEq/L)	-	-	-	-	-	-	-	-		
Serum bicarbonate (mEq/L)	-	-	-	-	-	-	-	-		
Anion gap	-	-	-	-	-	-	-	-		
Serum calcium (mg/dL)	-	-	-	-	-	-	-	-		
Serum magnesium (mg/dL)	-	-	-	-	-	-	-	-		
Serum phosphate (mg/dL)	-	-	-	-	-	-	-	-		
Serum creatinine (mg/dL)	-	-	-	-	-	-	-	-		
Serum urea (mg/dL)	-	-	-	-	-	-	-	-		
Serum chloride (mEq/L)	-	-	-	-	-	-	-	-		
Pneumonia, n (%)	-	-	-	-	33 (50)	-	-	-		
Spontaneous bacterial peritonitis, n (%)	-	-	-	-	-	-	-	-		
Urinary tract infection, n (%)	-	-	-	-	-	-	-	-		
Spontaneous bacterial empyema, n (%)	-	-	-	-	-	-	-	-		
Spontaneous bacteremia, n (%)	-	-	-	-	-	-	-	-		
Cellulitis, n (%)	-	-	-	-	-	-	-	-		
Culture positive infections; n (%)	-	-	-	-	-	-	-	-		
Urine NGAL (ng/ml or ml)	-	-	-	-	-	-	-	-		
Serum cystatin C (mg/L)	-	-	-	-	-	-	-	-		
Cumulative fluid (in ml)	-	-	-	-	-	-	-	-		
Crystalloids+colloids (albumin)	-	-	-	-	-	-	-	-		
Pancreatitis, n (%)	-	-	-	-	-	-	-	-		
Drug overdose, n (%)	-	-	-	-	-	-	-	-		
Pulmonary embolism, n (%)	-	-	-	-	-	-	-	-		
Burn, n (%)	-	-	-	-	-	-	-	-		
Admission diagnoses, without any association with hypotension, n (%)	-	-	-	-	-	-	-	-		
Functional comorbidity index, n (%)	-	-	-	-	-	-	-	-		
Days in hospital before randomization/enrolment, n (%)	-	-	-	-	-	-	-	-		

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Table 1: (*Continued*)

Characteristic	Studies selected									
	Maiwall *et al.*, 2023		Lamontagne *et al.*/OVATION 2016		Asfar *et al.*/SEPSISPAM Trial 2014		Lamontagne *et al.* (65 Trial). 2020		Wieruszewski *et al.*/ATHOS–3 clinical study 2023	
	Lower MAP	Higher MAP	Lower MAP	Higher MAP	Lower MAP	Higher MAP	Lower MAP	Higher MAP	Lower MAP	Higher MAP
Vasopressor hours, n (%)	-	-	-	-	-	-	-	-		
Intensive care unit admission to randomization hours, n (%)	-	-	-	-	-	-	-	-		
Ischemic heart disease, n (%)	-	-	15 (21)		-	-	-	-		
Chronic heart failure, n (%)	-	-	-	-	-	-	-	-		
Chronic obstructive pulmonary disease, n (%)	-	-	14 (19)		-	-	-	-		
Chronic renal replacement therapy at ICU admission, n (%)	-	-	-	-	-	-	-	-		
Complete assistance required for entire daily activities, n (%)	-	-	-	-	-	-	-	-		
Acute/chronic kidney disease, n (%)	-	-	-	-	13 (19.7)		-	-		
Chronic kidney disease warranting long-term dialysis, n (%)	-	-	-	-	-	-	-	-		
Liver cirrhosis, n (%)	-	-	-	-	14 (21.2)		-	-		
Cancer or autoimmune disease, n (%)	-	-	-	-	-	-	-	-		
Chronic arterial hypertension, n (%)	-	-	-	-	-	-	-	-		
Infection source (lung), n (%)	-	-	-	-	-	-	-	-		
Infection source (abdomen), n (%)	-	-	-	-	-	-	-	-		
Infection source (urinary tract), n (%)	-	-	-	-	-	-	-	-		
Infection source (Other), n (%)	-	-	-	-	-	-	-	-		
Community-acquired infection	-	-	-	-	-	-	-	-		
Arterial pH	-	-	-	-	-	-	-	-		
Fluid therapy before inclusion — mL	-	-	-	-	-	-	-	-		
Atherosclerotic disease, n (%)	-	-	-	-	-	-	-	-		

Table 2: Systematic review study characteristics

Authors	Study type	Sample size	Study aim	Primary and secondary endpoints	Inferences
Maiwall *et al*., 2023	A randomized, open-label, controlled study	N=150 Higher MAP (n=75) Lower MAP (n=75)	To compare the effectiveness of lower MAP and higher MAP approaches in reducing the prevalence of septic shock, cirrhosis, and mortality in critically ill patients	28-day mortality (primary endpoint) AKI (secondary endpoint) Shock reversal (secondary endpoint) Overall adverse events Intradialytic hypotension	Compared to patients with lower MAP, those with higher MAP had a reduced incidence of intradialytic hypotension, greater AKI reversal, and greater adverse events incidences (all P<0.001)
Lamontagne *et al.*/ OVATION 2016	A randomized, pilot, multicenter, controlled study	N=118 Higher MAP (n=58) Lower MAP (n=60)	To compare the outcomes of higher MAP and lower MAP vasopressor therapy targets in patients with septic shock	MAP differences across the study groups (primary endpoint) Hospital mortality (secondary endpoint) Cardiac arrhythmias (secondary endpoint)	Vasopressor therapy deviations were reduced in patients with higher MAP, versus those with lower MAP (8% vs. 12%; P=0.05) No statistically significant differences in the hospital mortality (33% vs. 30%) and cardiac arrhythmia (36% vs. 20%) prevalence were observed between the higher MAP and lower MAP study groups (all P>0.05)
Asfar *et al.*/ SEPSISPAM Trial 2014	A randomized, open-label, multicenter study	N=776 Higher MAP (n=388) Lower MAP (n=388)	To compare the primary and secondary outcomes based on the higher and lower MAP targets in patients with septic shock	28-day mortality (primary endpoint) Serious adverse events (secondary endpoint) Atrial fibrillation (secondary endpoint) Renal replacement therapy for chronic hypertension (secondary endpoint)	The renal replacement therapy requirement was reduced in patients with higher MAP targets, compared to those with low-target MAP The low-target MAP patients had a reduced incidence of new-onset atrial fibrillation, versus the high-target MAP patients The higher MAP and lower MAP target groups did not statistically differ in mortality rates (HR: 1.04) and serious adverse events (p>0.05)
Lamontagne *et al*. (65 Trial). 2020	A randomized, pragmatic, multicenter clinical study	N=2600 Higher MAP (n=1291) Lower MAP (n=1307)	To evaluate 90-day mortality between higher MAP and lower MAP patients with septic shock, receiving vasopressors in the intensive care unit	90-day all-cause mortality (primary endpoint) Mortality at discharge (secondary endpoint) Advanced renal/respiratory support duration (secondary endpoint) Health-related quality of life (secondary endpoint)	No statistically significant difference in 90-day all-cause mortality was observed between the higher MAP and lower MAP patients (ARD: −2.85%; 95% CI, −6.75–1.05; P=0.15)
Wieruszewski *et al.*/ATHOS–3 clinical study 2023	Anexploratory post hoc assessment of a randomized double-blind controlled study	N=321 Low norepinephrine-equivalent dose group (Placebo [n=48] Angiotensin II [n=56]) High norepinephrine-equivalent dose group (Placebo [n=110] Angiotensin II [n=107])	To compare higher clinical outcomes in MAP and lower MAP, angiotensin-II-treated patients with vasodilatory shock, based on their baseline vasopressor dose	28-day survival difference in patients with baseline norepinephrine-equivalent dose≤0.25 µg/kg/min (primary outcome) 28-day survival difference in patients with baseline norepinephrine-equivalent dose>0.25 µg/kg/min (secondary outcome)	Patients with baseline norepinephrine-equivalent dose≤0.25 µg/kg/min, who received angiotensin II, had two times greater overall survival than those in the placebo group (HR: 0.509; 95% CI: 0.274–0.945, P=0.03)

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Table 2: Systematic review study characteristics

Authors	Study type	Sample size	Study aim	Primary and secondary endpoints	Inferences
Lamontagne *et al.* 2017	A prospective, observational, multicenter analysis	N=56 Days with vasopressors (n=56) Days without vasopressors (n=41)	To compare MAP findings among patients treated with vasopressors, for septic shock	MAP values (primary outcome) MAP findings versus baseline attributes (secondary outcome)	The average MAP target was>10 mmHg than the recommended value (i.e., 65 mmHg) in patients with severe hypotension, who were treated with vasopressors
Hall *et al*. 2004	A single-center retrospective, cohort study	Patients treated with vasopressin for septic shock (N=50) Patients treated with norepinephrine for septic shock (N=49) Patients treated with dopamine for septic shock (N=51)	To evaluate septic shock patients for the early blood pressure outcomes of titrated catecholamines versus vasopressin	Post-vasopressor infusion 1-h MAP (primary outcome) Impact of vasopressin therapy on the following secondary outcomes: 28-day mortality Venous thromboembolism Peripheral vascular necrosis Atrial arrhythmias Acute respiratory distress syndrome Acute myocardial infarction Hospital length of stay	>70 mmHg 1-h MAP increase was achieved in patients, treated with fixed-dose vasopressin Post-vasopressin MAP differences were not observed between the study groups, despite adjusting for baseline MAP, renal dysfunction, and APACHE III score No statistically significant differences in the 28-day mortality were observed between the dopamine (60%), norepinephrine (65%), and vasopressin (52%)-receiving patients (all P>0.05)
Legrand *et al*. 2013	A retrospective analysis	N=137 Acute kidney injury-positive patients (n=69) Acute kidney injury-negative patients (n=68)	To compare the relationship between acute kidney injury and systemic hemodynamics, including MAP, in patients with severe sepsis	Post-admission 5-day persistent/new acute kidney injury (primary outcome) Length of the intensive care unit stay (secondary outcome) In-hospital mortality (secondary outcome)	No statistically significant relationship was observed between acute kidney injury and systemic hemodynamics in patients with septic shock
Wong *et al*. 2015	A retrospective study	N=107 KDIGO <2 group KDIGO ≥2 group	To compare pre-morbid MAP changes in patients with septic acute kidney injury	Median MAP deficit Median mean perfusion pressure deficit Central venous pressure	Patients with a higher MPP deficit had statistically significant MPP and MAP deficits in the severe acute kidney injury/ septic shock setting (p<0.05)
Nakamura *et al*., 2023	A prospective observational analysis	N=92 Higher MAP (n=62) Lower MAP (n=30)	To compare the outcomes of bolus loading between higher MAP and lower MAP patients (i.e., vasopressin responders vs. non-responders)	Post-loading catecholamine index change Hospital/intensive care unit stay duration In-hospital mortality Post-vasopressin administration steroid use	Post-loading catecholamine index change<0 was predicted by MAP change, with a specificity and sensitivity of 0.77 and 0.92, respectively
Zhao *et al*., 2022	A multicenter observational analysis	N=17,874 Patients without acute kidney injury (n=12,041) Patients with acute kidney injury (n=5,833)	To evaluate patients, with acute kidney injury and sepsis, for blood pressure targets	MAP level Diastolic blood pressure	Patients with sepsis, acute kidney injury, and hypertension require elevated diastolic blood pressure (54–62 mm Hg vs. 50–60 mmHg) and greater MAP (70–80 mmHg vs. 65–73 mmHg), compared to those without hypertension

(*Contd*...)

Table 2: Systematic review study characteristics

Authors	Study type	Sample size	Study aim	Primary and secondary endpoints	Inferences
Kim *et al*., 2023	A retrospective analysis	To evaluate the relationship between survival and hypotension in patients with sepsis, with normal lactate levels	N=2,032 Higher MAP (n=380) Lower MAP (n=237)	Urinary/abdominal infections Pulmonary infections In-hospital mortality Antibiotic administration rates	A higher prevalence of urinary/abdominal infections and lower occurrences of systemic inflammatory response and pulmonary infections were observed in patients with reduced MAP, versus those with higher MAP Patients with lower MAP had higher antibiotic administration rates at all time points, during sepsis resuscitation, compared to those with higher MAP (P<0.05) No statistically significant differences in in-hospital (13.9% vs. 12.7%) and intensive care unit (22.4% vs. 19.4%) mortality rates were observed between the study groups (P>0.05)
Collet *et al*., 2019	A prospective cohort analysis	N=72	To evaluate the association of microcirculation with systemic circulation in patients, treated in the intensive care unit, for sepsis	MAP range assessment (primary endpoint) Tissue oxygen saturation (secondary endpoint) Tissue oxygen desaturation (secondary endpoint) Tissue oxygen resaturation (secondary endpoint)	MAP range (72–78 mmHg) was observed during the analysis of 60 fluid challenges Patients with median MAP (74 mmHg), who required hemodynamic support, had an elevated mortality rate due to multiple organ failure Tissue oxygen resaturation had a statistically significant relationship with diastolic arterial pressure (p=0.04)
Wang *et al*., 2022	A prospective cohort analysis	N=66 Non-feeding intolerance group (n=19) Feeding intolerance group (n=47)	To evaluate the ability of MAP, norepinephrine equivalent dose, and norepinephrine dose to identify optimal enteral nutrition initiation time for vasopressor-treated septic shock patients	The occurrence of feeding intolerance, following enteral nutrition initiation Hospital-acquired infections The mean intensive care unit length of stay	The enteral nutrition initiation guidance was predicted by norepinephrine equivalent dose/MAP The norepinephrine dose was inferior to MAP in terms of providing enteral nutrition initiation guidance
Liang *et al*., 2017	An observational prospective cohort analysis	N=32	To evaluate the impact of norepinephrine dosage on the septic patients' arterial pressure	Variations in the systolic and diastolic blood pressures MAP variations	The dosage of norepinephrine minimized MAP in the treated patients MAP variation, systemic vascular resistance, and systolic/diastolic blood pressure variations had positive correlations with dynamic arterial elastance

AKI: Acute kidney injury, ARD: Absolute risk difference, HR: Hazard ratio, KDGIO: Kidney disease: Improving global outcomes, MAP: Mean arterial pressure, CI: Confidence interval, HR: Hazard ratio

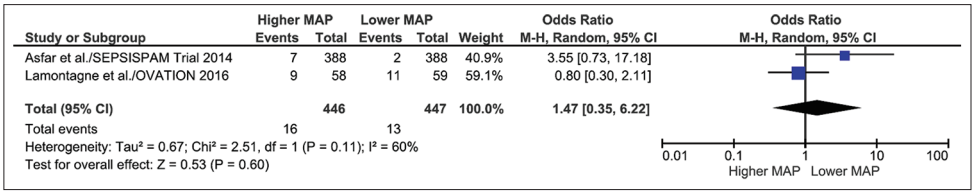

Fig. 4: Acute myocardial infarction/injury

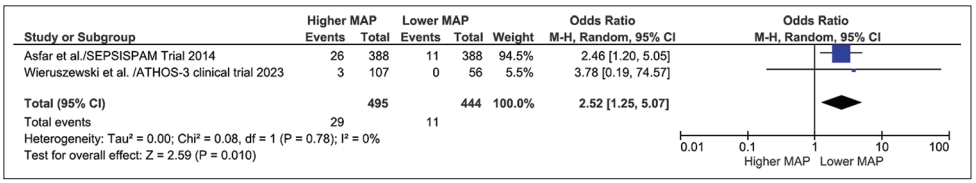

Fig. 5: Atrial fibrillation

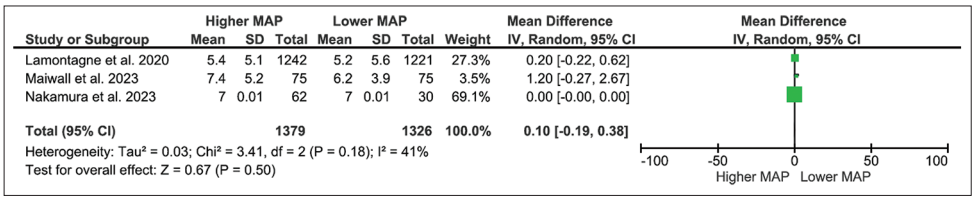

Fig. 6: Length of stay in the intensive care unit

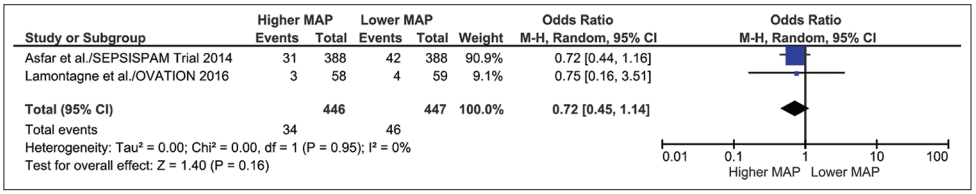

Fig. 7: Major bleeding

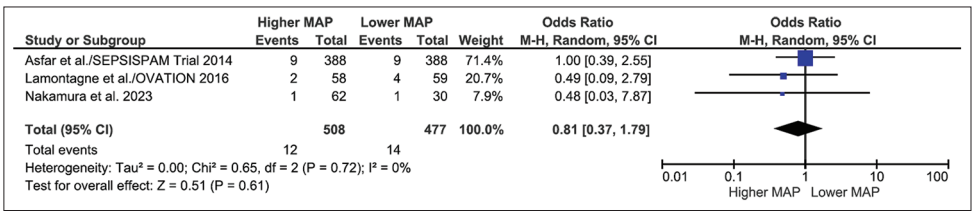

Fig. 8: Mesenteric/bowel ischemia

RRT

No significant difference in RRT utilization was observed between higher MAP (n=2944) and lower MAP (n=2902) patients (OR: 0.99, 95% CI: 0.88–1.11; p=0.80) (Fig. 9), with low heterogeneity (I^2=0%; p=0.89).

RRT in chronic hypertension

Patients with chronic hypertension in the higher MAP group (n=735) had significantly lower odds of requiring RRT compared to the lower MAP group (n=731) (OR: 0.77, 95% CI: 0.62–0.97; p=0.03) (Fig. 10), with low heterogeneity (I^2=0%; p=0.32).

Supraventricular cardiac arrhythmia

Higher MAP patients had higher odds of supraventricular cardiac arrhythmia (OR: 1.81, 95% CI: 1.07–3.04; p=0.03) (Fig. 11), with low heterogeneity (I^2=23%; p=0.27).

Survival at day 28

No statistically significant difference in 28-day survival was found between the two groups (OR: 0.76, 95% CI: 0.44–1.31; p=0.32) (Fig. 12), with high heterogeneity (I^2=59%; p=0.12).

Ventricular tachycardia

There was no significant difference in the incidence of ventricular tachycardia between the two groups (OR: 0.91, 95% CI: 0.55–1.52; p=0.73) (Fig. 13), with moderate heterogeneity (I^2=46%; p=0.15).

ROB analysis

The ROB analysis of the five RCTs revealed concerns related to the randomization process in studies by Maiwall *et al.*, Lamontagne *et al.* (2016), and Lamontagne *et al.* (2020) (Fig. 14).

In addition, the study by Lamontagne *et al.* (2020) showed concerns regarding missing outcome data. Overall, a low risk of confounding or

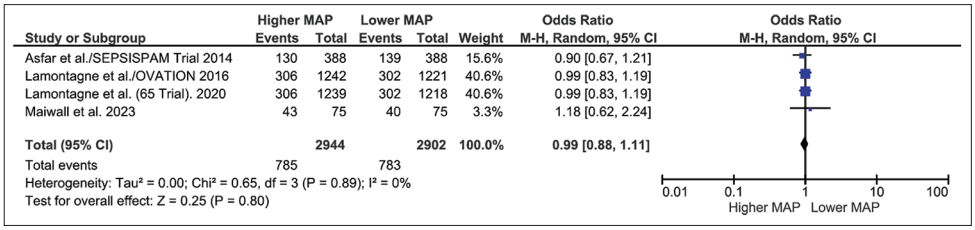

Fig. 9: Renal replacement therapy

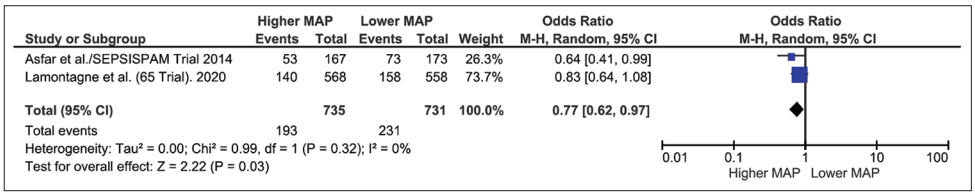

Fig. 10: Renal replacement therapy utilization for patients with chronic hypertension

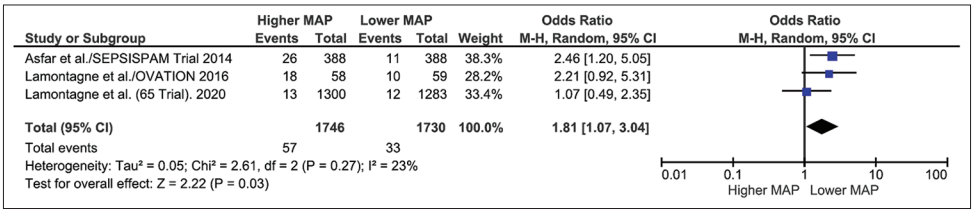

Fig. 11: Supraventricular cardiac arrhythmia

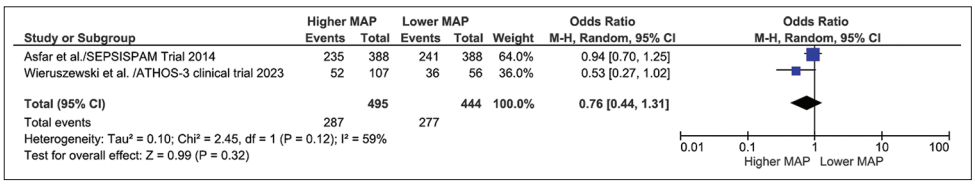

Fig. 12: Survival (at day 28)

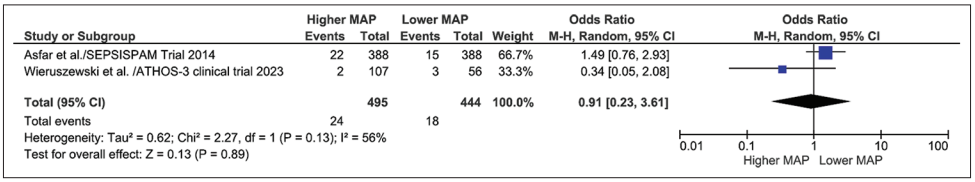

Fig. 13: Ventricular tachycardia

bias due to randomization, intended procedure deviation, outcome data loss, outcome assessment, and result selection was reported in four of the five RCTs. The summary plot revealed a low ROB with some bias-related concerns in 75–80% of studies, and 20–25% of studies showed moderate bias concerns (Fig. 15).

In the analysis of 10 observational studies, moderate bias was observed in intervention classification in two studies, intervention deviation in three studies, outcome measurement in three studies, and result selection in two studies (Fig. 16).

Seven of the 10 (70%) studies had overall low bias, whereas 3 (30%) studies had moderate bias (Fig. 17).

DISCUSSION

This meta-analysis examined the clinical relationship between higher and lower MAP targets and outcomes in septic shock and sepsis patients. Compared to patients with a lower MAP target, those with a higher MAP target had statistically significantly higher odds of all-cause mortality, atrial fibrillation, and supraventricular cardiac arrhythmia. Conversely, patients with chronic hypertension who received a higher MAP target experienced lower rates of RRT compared to those in the lower MAP group. However, no statistically significant differences were observed in overall adverse events, acute myocardial infarction/injury, and length of ICU stay, major bleeding, mesenteric/bowel ischemia, RRT, survival at day 28, or ventricular tachycardia.

This analysis also revealed concerns regarding missing outcome data and biases related to randomization in some of the included studies. Despite these concerns, the overall strength of the results was supported by the low ROB in most randomized and observational studies.

The findings support the current understanding that there is no clear benefit between high MAP and low MAP target strategies in

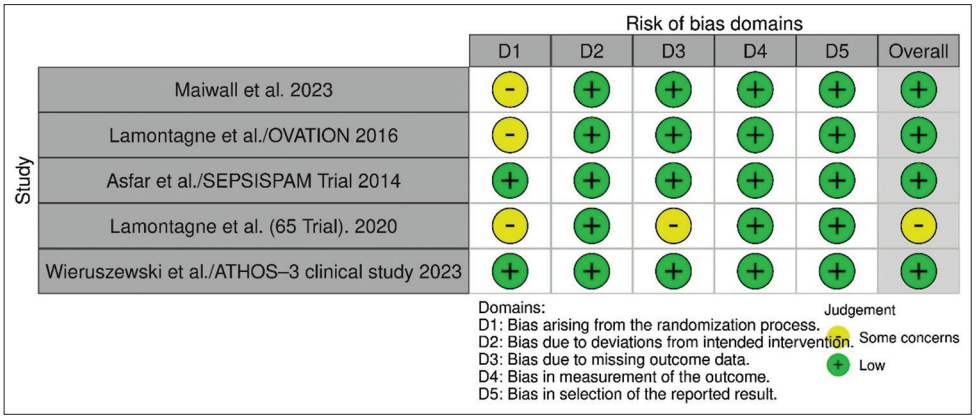

Fig. 14: Risk of bias analysis of five randomized controlled studies (traffic light plot)

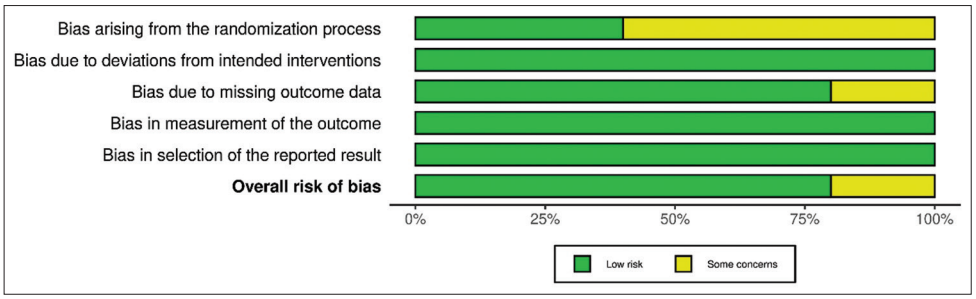

Fig. 15: Risk of bias analysis of five randomized controlled studies (summary plot)

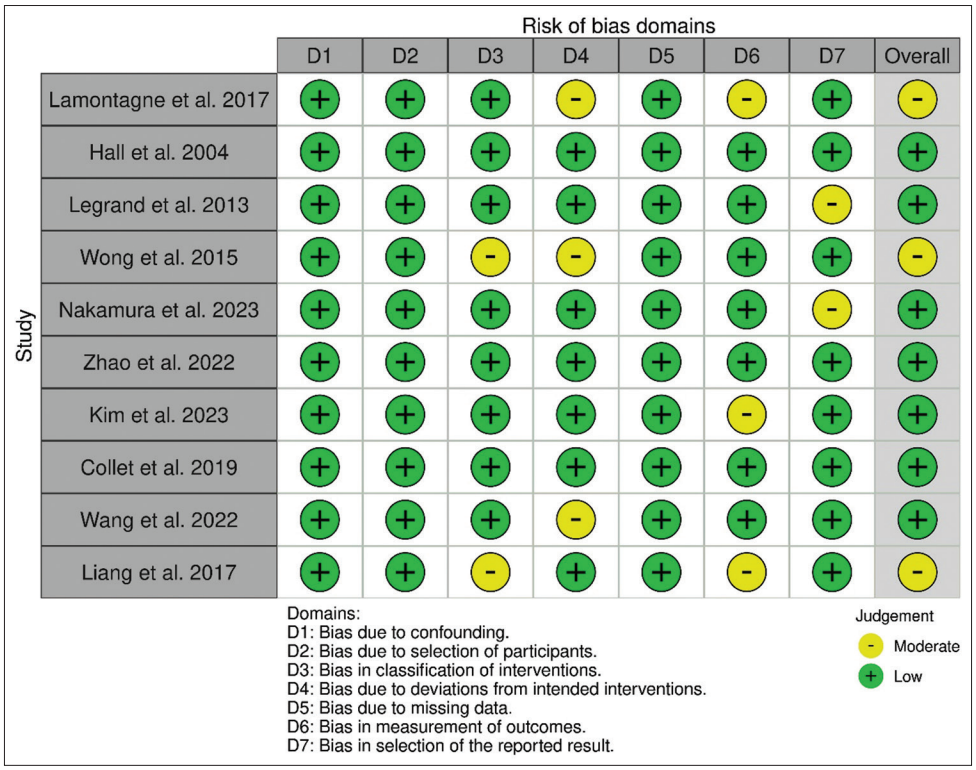

Fig. 16: Risk of bias analysis of 10 observational studies (traffic light plot)

improving clinical outcomes for sepsis and septic shock patients. The higher occurrence of atrial fibrillation, supraventricular arrhythmias, and all-cause mortality in the higher MAP group may be attributed to prolonged administration of elevated vasopressor doses [6]. On the other hand, the observed benefit in renal function for higher MAP patients is likely due to the use of norepinephrine [38]. Importantly, while low initial MAP can cause organ and tissue hypoperfusion, the administration of elevated vasopressor doses to raise MAP can lead to tissue reinjury and adverse cardiovascular events [39].

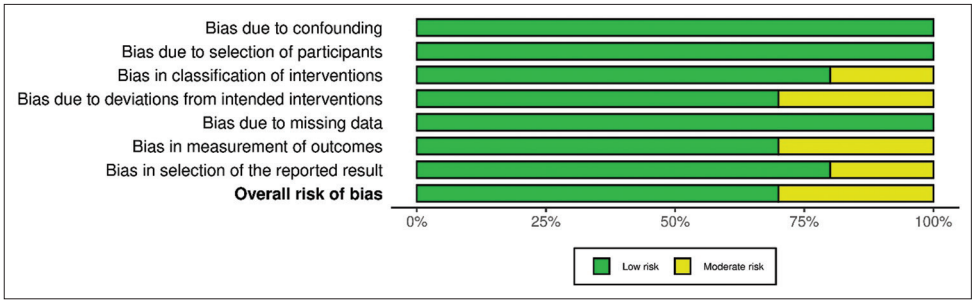

Fig. 17: Risk of bias analysis of 10 observational studies (summary plot)

Globally, MAP plays a crucial role in the management of sepsis, serving as a key determinant in maintaining organ perfusion pressure [40]. ICUs prioritize achieving specific systolic blood pressure (SBP) targets to optimize overall blood pressure and adjust vasopressor doses for stable hemodynamics. This combined focus on both MAP and SBP underscores the complexity of managing adequate organ perfusion in critical care settings [41].

In the current study, there was no statistically significant difference in the utilization of RRT between patients with higher MAP (n=2944) and lower MAP (n=2902) targets (OR: 0.99, 95% CI: 0.88–1.11; p=0.80). Low heterogeneity was observed (I^2=0%; p=0.89), indicating consistent results across studies. These findings are similar to those from a previous meta-analysis [42], which also reported no significant difference in mortality (risk ratio [RR]: 1.06, 95% CI: 0.98–1.15) or RRT utilization (RR: 0.96, 95% CI: 0.83–1.11) among sepsis and septic shock patients. This suggests that higher MAP targets do not offer substantial renal protection or survival benefits.

Notably, significant differences were observed in patients with chronic hypertension. In this cohort, patients with higher MAP (n=735) had statistically lower odds of requiring RRT compared to those in the lower MAP group (n=731) (OR: 0.77, 95% CI: 0.62–0.97; p=0.03). This suggests that for hypertensive patients with sepsis, maintaining a higher MAP may help preserve renal function and reduce the need for RRT. This finding contrasts with the systematic review by Dari *et al.* [7], which found no significant benefit of a high-normal MAP strategy on renal outcomes. Our results, however, indicate that chronic hypertension could be a key factor influencing the effectiveness of MAP management, which was not adequately explored in Dari *et al.* [7]. These findings suggest that a personalized assessment of the MAP target for each sepsis or septic shock patient, considering on-going medications, pre-existing conditions, and medical history, is essential for optimizing outcomes.

Limitations and future research

This study has notable limitations, including the lack of clinical outcome assessments based on patient age, gender, medication status, and comorbidities. In addition, the reliability of the outcomes may be questioned since this analysis included both observational and randomized studies. The moderate-to-high heterogenecity observed in some of the studies could also impact the validity of the overall results. To address these limitations, future studies should conduct more detailed demographic analyses, assessing the impact of MAP targets on different age groups, genders, and specific comorbidities such as diabetes and heart disease. RCTs with standardized methodologies are essential to reduce biases and provide more robust evidence regarding optimal MAP targets. Long-term follow-up in future research could help evaluate the sustainability of outcomes and identify any late-emerging adverse events related to different MAP strategies. Such research would help refine personalized treatment approaches in sepsis and septic shock management, ultimately improving patient care.

CONCLUSION

This meta-analysis reveals that higher MAP targets in sepsis are linked to increased risks of supraventricular arrhythmias, atrial fibrillation, and all-cause mortality, without offering a survival benefit. These findings underscore the need for a paradigm shift toward personalized MAP targets, particularly for patients with comorbidities like hypertension. Further RCTs should explore the complex interplay between MAP targets, vasopressor use, and organ function to refine management strategies. Individualized approaches tailored to patient profiles may improve survival and reduce complications in sepsis and septic shock.

CONFLICT OF INTEREST

Nil.

FUNDING

Nil.

ACKNOWLEDGMENTS

Nil.

CONTRIBUTION OF AUTHORS

Dr. Madhu A Yadav and Dr. GH Midhun Kumar involved in collection of articles, statistical analysis, manuscript writing, and final editing of manuscript. Dr. Rekha A Assadi involved in the collection of articles, manuscript writing, and statistical analysis. Dr. Neha K Kudumula and Dr. GH Midhun Kumar involved in final screening of articles editing and proofreading.

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