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Study-Level Versus Patient-Level Effect Modification by Chronic Hypertension in Mean Arterial Pressure Targets for Septic Shock: A Meta-Analysis Demonstrating Ecological Fallacy

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ABSTRACT

Introduction: Optimal mean arterial pressure (MAP) targets in septic shock remain controversial, with prior study-level meta-regression suggesting that chronic hypertension modifies treatment effects. However, ecological associations may not reflect individual-level causation. We investigated whether study-level hypertension prevalence predicts treatment effects and compared this to within-study hypertension subgroup analyses.

Methods: We conducted a systematic review and meta-analysis following the PRISMA 2020 guideline through multiple literature databases up to October 8, 2025. We included randomized controlled trials (RCTs) comparing higher (≥75 mmHg) versus standard (60-70 mmHg) MAP targets in septic shock that reported mortality outcomes. We performed random-effects meta-analysis and univariable meta-regression testing six study-level covariates, and pooled within-study hypertension subgroup data using inverse-variance methods.

Results: Six RCTs enrolling 4,060 patients were included. Overall mortality showed no significant difference between higher versus standard MAP targets (random-effects risk ratio [RR] 1.03, 95% confidence interval [CI] 0.90-1.17, P-value = 0.72, $I^2 = 22.5\%$). Study-level meta-regression found no significant effect modification by hypertension prevalence ($\beta = -0.0015$ per 1% increase, P-value = 0.80, $R^2 = 1.0\%$) or other covariates (all P-values > 0.05) in this six-study subset. However, within-study hypertension subgroup analysis (two trials, 1,405 patients) revealed higher MAP targets increased mortality in hypertensive patients (pooled RR 1.22, 95% CI 1.05-1.41, P-value = 0.009), demonstrating ecological fallacy where aggregate associations contradicted individual-level effects.

Conclusions: Our performed study-level meta-regression demonstrated unreliable evidence for effect modification. Within-study hypertension subgroup data suggest higher MAP targets may harm rather than benefit hypertensive patients, contradicting ecological inferences and highlighting the necessity of individual patient data meta-analyses in further, better-sampled studies.

Categories: Critical Care Medicine, Cardiology, Emergency Medicine, Internal Medicine

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1. INTRODUCTION

Septic shock remains a leading cause of death in intensive care units (ICU) around the world, with mortality rates exceeding 30% despite advances in critical care management. A fundamental question in hemodynamic resuscitation concerns the optimal mean arterial pressure (MAP) target during initial stabilization. Current guidelines recommend maintaining MAP at 65 mmHg or higher, acknowledging that this threshold represents expert consensus rather than definitive evidence from several high-quality randomized controlled trials (RCTs) yet. The persistent controversy surrounding whether higher MAP targets improve outcomes has generated significant research interest, especially regarding potential effect modification by patient characteristics [1-4].

The physiological rationale for higher MAP targets centers on the premise that adequate perfusion pressure maintains end-organ blood flow, especially in patients with impaired autoregulation. Proponents argue that chronic hypertension shifts the cerebral and renal autoregulatory curves rightward, possibly necessitating higher perfusion pressures to maintain adequate organ perfusion in these patients. This hypothesis gained traction following the SEPSISPAM trial, which suggested promising mortality benefit from higher MAP targets (80-85 mmHg versus 65-70 mmHg) in patients with pre-existing hypertension, despite finding no overall mortality difference in the unselected population. In a controverse manner, achieving higher MAP targets requires increased vasopressor administration, which carries inherent risks including cardiac arrhythmias, myocardial ischemia, digital ischemia, and mesenteric hypoperfusion due to excessive vasoconstriction [5-7].

Several RCTs have subsequently tested this hypothesis with conflicting results. The 65 trial, the largest study to date enrolling 2,463 patients, found no significant mortality difference between permissive hypotension (target MAP 60-65 mmHg) and usual care approaches. A pre-specified subgroup analysis demonstrated a statistically significant interaction by hypertension status, suggesting differential treatment effects. The Japanese multicenter ENDO trial was terminated early for potential harm, showing increased mortality with higher MAP targets. These divergent findings have generated uncertainty regarding optimal MAP targets and whether chronic hypertension truly modifies treatment effects [8-10].

A significant methodological concern emerges when interpreting effect modification in meta-analysis. Study-level meta-regression, which tests whether aggregate study characteristics predict treatment effects, represents an ecological analysis where inferences drawn from group-level data may not reflect individual-level associations, which is a phenomenon known as ecological fallacy. For example, studies enrolling higher proportions of hypertensive patients might differ structurally in other unmeasured ways such in patient selection, care protocols, and institutional expertise, that confound the apparent association between hypertension prevalence and treatment effect. Within-study subgroup analyses, which directly compare hypertensive versus non-hypertensive patients randomized within the same trial, provide better reliable evidence for individual-level effect modification but are often inadequately powered or inconsistently reported across trials [11-17].

Our systematic review and meta-analysis aimed to evaluate and investigate this critical gap by comparing study-level meta-regression findings to pooled within-study hypertension subgroup analyses. Our primary objectives were to perform univariable meta-regression testing multiple study-level characteristics as potential effect modifiers; synthesize within-study hypertension subgroup data to assess individual-level effect modification; and evaluate whether ecological associations at the study level correspond to or contradict individual-level treatment effects. By comparing these complementary but methodologically peculiar approaches, we aimed to provide clarity on whether chronic hypertension genuinely modifies the effects of MAP targets and to demonstrate the potential for ecological fallacy in meta-analytic inferences.

2. MATERIALS AND METHODS

Study Design and Search Strategy:

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [18].

We conducted a literature search of multiple electronic databases from inception through October 8, 2025. The search was performed without language restrictions in PubMed, Scopus, Web of Science, Cochrane Library and Google Scholar. The search strategy combined three concept groups using Boolean operators: (1) septic shock population terms, (2) MAP or hemodynamic target intervention terms, and (3) RCT design filters. The utilized base search strategy and key words were as follows: (("septic shock"[MeSH Terms] OR "septic shock"[Title/Abstract] OR "sepsis"[MeSH Terms] OR "severe sepsis"[Title/Abstract] OR "septic"[Title/Abstract]) AND ("blood pressure"[MeSH Terms] OR "mean arterial pressure"[Title/Abstract] OR "MAP target"[Title/Abstract] OR "arterial pressure"[Title/Abstract] OR "hemodynamic target"[Title/Abstract] OR "perfusion pressure"[Title/Abstract] OR "blood pressure target"[Title/Abstract] OR "MAP goal"[Title/Abstract]) AND ("randomized controlled trial"[Publication Type] OR "randomized"[Title/Abstract] OR "randomised"[Title/Abstract] OR "RCT"[Title/Abstract] OR "clinical trial"[Publication Type] OR "controlled clinical trial"[Publication Type])). This strategy was adapted for other databases using appropriate subject headings and syntax. We supplemented electronic searches by manually screening reference lists of included studies, relevant systematic reviews, and recent clinical practice guidelines. Trial registries (ClinicalTrials.gov and WHO International Clinical Trials Registry Platform) were searched to identify ongoing or unpublished trials.

Eligibility Criteria:

Studies were eligible for inclusion if they met the following criteria: (1) study design of RCT with parallel group or crossover design; (2) adult participants (age ≥18 years) with septic shock defined according to contemporary consensus definitions (Sepsis-1, Sepsis-2, Sepsis-3, or Surviving Sepsis Campaign criteria); (3) intervention comparing higher MAP targets (defined as ≥75 mmHg) versus standard or lower MAP targets (defined as 60-70 mmHg); (4) reporting of mortality outcomes at any time point (28-day, 90-day, ICU, or hospital mortality); and (5) published as full-text articles or available as conference abstracts in English-language with sufficient data for meta-analysis. We excluded studies if they: (1) enrolled mainly non-septic shock populations (such as cardiogenic or hemorrhagic shock) without separate reporting of septic shock subgroups; (2) compared different vasopressor agents rather than different MAP targets; (3) were observational studies without randomization; (4) lacked mortality outcome data; (5) were physiological or mechanistic studies without clinical outcomes; (6) enrolled only pediatric populations; (7) were duplicate publications of the same trial without additional outcome data; or (8) studies without full-text available in English-language.

Study Selection and Data Collection:

We first screened titles and abstracts of all retrieved records against eligibility criteria. Then after that, we attempted for screening of full-text articles of preliminary eligible studies for detailed evaluation and final inclusion of articles. We used a standardized, pilot-tested data extraction form to collect information on study characteristics (first author, publication year, country, trial name or acronym, design features, sample size), participant characteristics (age, gender distribution, chronic hypertension prevalence, disease severity scores including Acute Physiology and Chronic Health Evaluation [APACHE] II or Sequential Organ Failure Assessment [SOFA] scores, baseline lactate levels), intervention details (MAP target protocols for higher and standard arms, achieved MAP values, vasopressor doses), and outcomes (mortality at all reported time points with raw event numbers and denominators, within-study hypertension subgroup data when available). When studies reported multiple mortality timepoints, we prioritized the primary outcome as defined by trial investigators. For meta-regression modeling, we calculated study-level summary statistics by averaging across treatment arms where appropriate.

Risk of Bias Assessment:

We assessed risk of bias in included RCTs using the Cochrane Risk of Bias 2 (RoB 2) tool, which evaluates five domains which were, randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each domain was rated as low risk, some concerns, or high risk according to signaling questions and algorithms specified in the RoB 2 guidance. Overall risk of bias for each study was determined by the highest risk rating across domains. Given the nature of the intervention, blinding of participants and physicians to MAP target allocation was mostly not feasible, but we considered whether lack of blinding likely affected mortality outcomes as an objective endpoint less susceptible to detection bias.

Statistical Analysis and Meta-Analytic Methods:

We performed random-effects meta-analysis using the DerSimonian-Laird method to pool risk ratios (RRs) for mortality outcomes across studies, accounting for both within-study and between-study variance. RRs were calculated from raw event counts in each treatment arm. We assessed statistical heterogeneity using Cochran's Q-statistic (with P-value$<$0.10 indicating significant heterogeneity), I^2 statistic (categorizing heterogeneity as low [$<$25%], moderate [25-50%], or high [$>$50%]), and tau-squared (τ^2) representing between-study variance. We calculated 95% confidence intervals (CI) for pooled estimates using the Hartung-Knapp-Sidik-Jonkman adjustment for random-effects models with small numbers of studies. We also computed 95% prediction intervals to estimate the expected range of true effects in future similar studies, accounting for between-study heterogeneity.

We conducted multiple sensitivity analyses including leave-one-out analysis to assess influence of individual studies on pooled estimates, comparison of fixed-effect (FE) versus random-effects (RE) models, and subgroup analyses stratified by mortality timepoint (28-day, 90-day, ICU, hospital mortality). We assessed publication bias and small-study effects using Egger's linear regression test, with P-value$<$0.10 indicating possible underlying asymmetry, and visual inspection of funnel plots, with proper application of trim-and-fill adjustment method for imputation of hypothetical studies whenever indicated properly. Statistical significance was defined as two-tailed P-value$<$0.05 for primary analyses, with appropriate adjustment for multiple testing where applicable.

All statistical analyses were conducted using RStudio software with R version 4.4.2, with the metafor package for meta-analysis and meta-regression.

Meta-Regression Modeling:

We performed univariable weighted meta-regression to investigate the possible effect modification by study-level characteristics. Covariates tested included: mean age, proportion of patients with chronic hypertension, disease severity (APACHE II score or SOFA-derived proxy calculated as APACHE II ≈ 2.5 × SOFA + 5 when direct APACHE II reporting was unavailable), baseline serum lactate concentration, proportion of female patients, and publication year. Meta-regression models used inverse-variance weighting with study log RR as the dependent variable and each covariate as a continuous predictor. We reported regression coefficients (β) representing the change in log RR per unit increase in the covariate, standard errors (SE), P-values, proportion of between-study variance explained (R^2), and residual heterogeneity (τ^2 residual). Given the limited number of studies, we restricted our modeling to univariable models to avoid overfitting and did not perform multivariable meta-regression.

Within-Study Hypertension Subgroup Analysis:

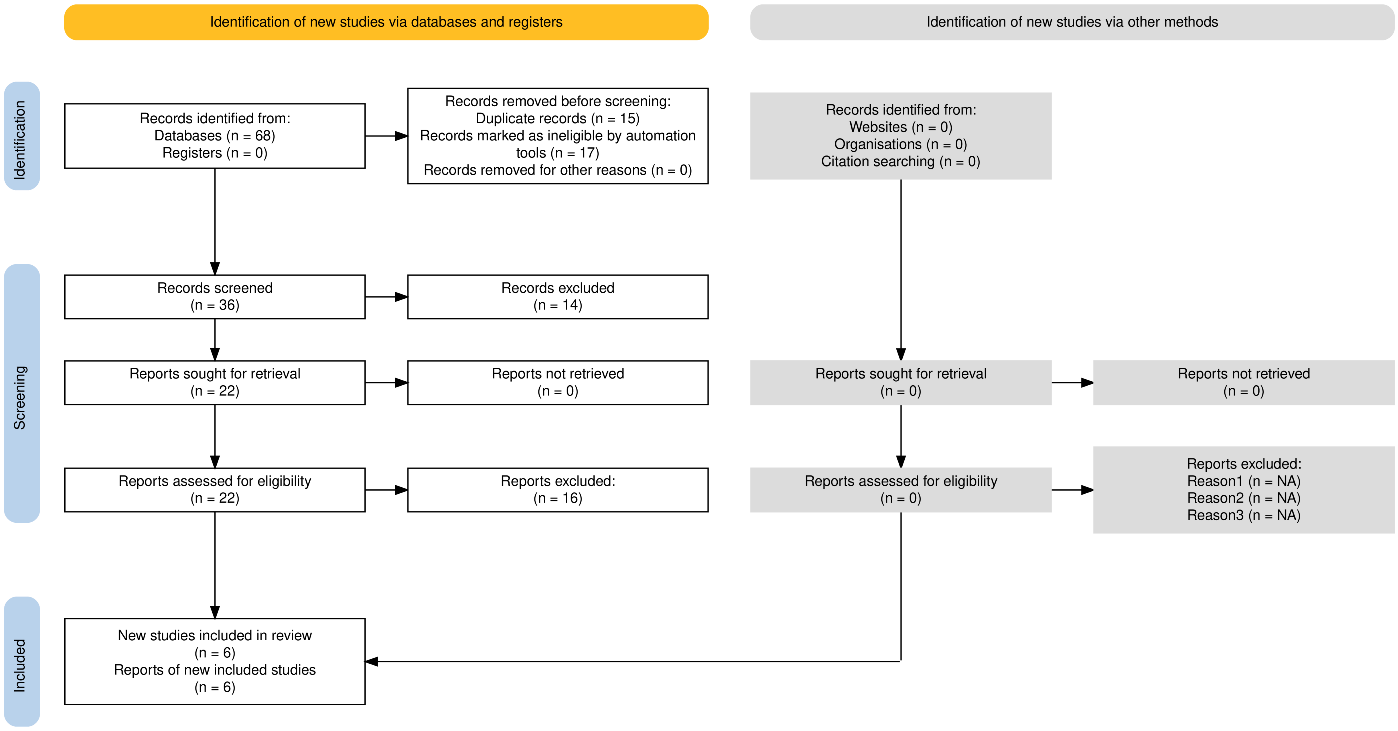
To assess individual-level effect modification by chronic hypertension, we extracted within-study subgroup data from trials reporting mortality stratified by baseline hypertension status. We pooled RRs for the hypertension subgroup across studies using inverse-variance weighted random-effects meta-analysis. We calculated the test for subgroup differences of interaction to determine whether treatment effects differed significantly between hypertensive and non-hypertensive patients. This within-study approach provides more reliable evidence for individual-level effect modification compared to study-level meta-regression, as it controls for confounding by design through randomization within each trial.

3. RESULTS

Study Selection and Characteristics:

Our literature search identified 68 records from electronic databases, with no additional records from trial registries. After removing 15 duplicates and 17 records marked ineligible by automation tools, 36 records underwent title and abstract screening. We excluded 14 records during initial screening and retrieved 22 full-text articles for detailed eligibility assessment. Following full-text review, we excluded 16 reports that did not meet inclusion criteria, leaving six RCTs enrolling total of 4,060 patients for final inclusion in our study (**Figure 1**).

Figure 1: PRISMA Flow Diagram.



Risk of bias assessment using the Cochrane RoB 2 tool revealed that only one study (Asfar et al. 2014) achieved low risk of bias across all domains, while the remaining five studies raised some concerns that is mainly in the domains of deviations from intended interventions or selective outcome reporting (**Supplementary Table 1**). Specifically, four trials raised concerns regarding deviations from intended interventions due to the inherent difficulty of blinding participants and clinicians to MAP target allocation, though this limitation was considered unlikely to substantially affect the objective mortality endpoint.

The six included studies were published between 2014 and 2025, with sample sizes ranging from 37 patients to 2,463 patients (**Table 1**). The trials were conducted across different geographic regions including Japan (Endo et al. 2025, n = 516), Australia and Ireland (Panwar et al. 2025, n = 37), India (Maiwall et al. 2023, n = 150), United Kingdom (Lamontagne et al. 2020, n = 2,463), North America (Lamontagne et al. 2016, n = 118), and France (Asfar et al. 2014, n = 776). Mean patient age varied across studies from 45.9 years in the Indian cirrhosis population to 78.0 years in the Japanese elderly cohort. Female representation ranged from 11.3% to 45.5%. Chronic hypertension prevalence showed significant heterogeneity, ranging from 9.3% in the cirrhosis-predominant Indian cohort to 58.5% in the Australian-Irish pilot study. Disease severity markers including APACHE II scores (range: 24.5-26.0) and baseline lactate levels (range: 1.8-3.95 mmol/L) were variably reported across studies. The primary mortality outcome was 90-day mortality in four trials, 28-day mortality in one trial, and ICU mortality in one trial.

Table 1: Study Characteristics and Baseline Patient Demographics.

Study	Design and Setting	Country	Sample Size (n)	Mean Age (years)	Female (%)	Chronic Hypertension (%)	Disease Severity	Baseline Lactate (mmol/L)	Mechanical Ventilation (%)	Primary Outcome
Endo et al. 2025 [19]	Pragmatic multicenter RCT	Japan	516	78.0	45.4	53.1	APACHE II 26.0; SOFA 9.5	3.95	NR	90-day mortality
Panwar et al. 2025 [20]	Pilot multicenter RCT	Australia, Ireland	37	68.0	43.5	58.5	NR	1.8	NR	90-day mortality
Maiwall et al. 2023 [21]	Single-center RCT	India	150	45.9	11.3	9.3	SOFA 12.2	3.7	57.5	28-day mortality
Lamontagne et al. 2020 [8]	Pragmatic multicenter RCT (65 trial)	United Kingdom	2,463	75.0	43.5	46.0	NR	NR	NR	90-day mortality
Lamontagne et al. 2016 [22]	Pilot multicenter RCT (OVATION)	Canada, USA	118	64.5	45.5	45.0	APACHE II 24.5	NR	NR	ICU mortality
Asfar et al. 2014 [23]	Multicenter RCT (SEPSISPAM)	France	776	65.0	34.8	43.8	SOFA 10.8; SAPS II 56.7	3.5	76.6	28-day and 90-day mortality

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ICU, Intensive Care Unit; NR, Not Reported; RCT, Randomized Controlled Trial; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.

Intervention protocols compared higher MAP targets ranging from 75-85 mmHg versus standard MAP targets of 60-70 mmHg across studies (**Table 2**). The Endo et al. 2025 trial targeted 80-85 mmHg versus 65-70 mmHg but did not report achieved MAP values. Panwar et al. 2025 employed individualized MAP targets versus standard care, achieving a mean separation of 6.0 mmHg (83 mmHg [IQR 80-85] vs 77 mmHg [IQR 75-81]), where IQR denotes interquartile range. Maiwall et al. 2023 targeted the widest separation (80-85 mmHg vs 60-65 mmHg) with reported norepinephrine-equivalent dose of 0.069 mcg/kg/min but did not report achieved MAP. Lamontagne et al. 2020 compared usual care versus permissive hypotension (60-65 mmHg), achieving 72.6 mmHg versus 66.7 mmHg (difference 5.9 mmHg) with norepinephrine dose of 0.14 mcg/kg/min. Lamontagne et al. 2016 targeted 75-80 mmHg versus 60-65 mmHg, achieving 79 ± 5 mmHg versus 70 ± 5 mmHg (difference 9.0 mmHg). Asfar et al. 2014 targeted 80-85 mmHg versus 65-70 mmHg, achieving the largest separation of 10.0 mmHg (85 ± 6 mmHg vs 75 ± 5 mmHg) with the highest vasopressor requirement (norepinephrine-equivalent 0.38 mcg/kg/min).

Table 2: Intervention Protocols and Achieved Blood Pressure Targets.

Study	Higher MAP Target Protocol	Standard MAP Target Protocol	Achieved MAP Higher Arm (mmHg)	Achieved MAP Standard Arm (mmHg)	MAP Difference (Δ mmHg)	Norepinephrine-Equivalent Dose (mcg/kg/min)
Endo et al. 2025	80-85 mmHg	65-70 mmHg	NR	NR	NR	NR
Panwar et al. 2025	Individualized	Standard (~65 mmHg)	83 [80-85]	77 [75-81]	6.0	NR
Maiwall et al. 2023	80-85 mmHg	60-65 mmHg	NR	NR	NR	0.069
Lamontagne et al. 2020	Usual care	60-65 mmHg (permissive)	72.6 [69.4-76.5]	66.7 [64.5-69.8]	5.9	0.14
Lamontagne et al. 2016	75-80 mmHg	60-65 mmHg	79±5	70±5	9.0	NR
Asfar et al. 2014	80-85 mmHg	65-70 mmHg	85±6	75±5	10.0	0.38

Abbreviations: MAP, Mean Arterial Pressure; NR, Not Reported.

Primary Mortality Outcomes and Heterogeneity Assessment:

The overall meta-analysis revealed no significant mortality difference between higher and standard MAP targets (**Table 3**). The FE model resulted in a pooled RR of 0.98 (95% CI 0.90-1.08, Z = -0.36, P-value = 0.72), while the RE model accounting for between-study heterogeneity produced a pooled RR of 1.03 (95% CI 0.90-1.17, Z = 0.36, P-value = 0.72). The 95% prediction interval ranged from 0.78 to 1.35, indicating that future similar trials would be expected to result in RRs within this range, **Figure 2**.

Table 3: Mortality Outcomes Analysis of Individual Studies, Pooled Effects, Heterogeneity Assessment, Sensitivity Analyses, and Publication Bias Evaluation.

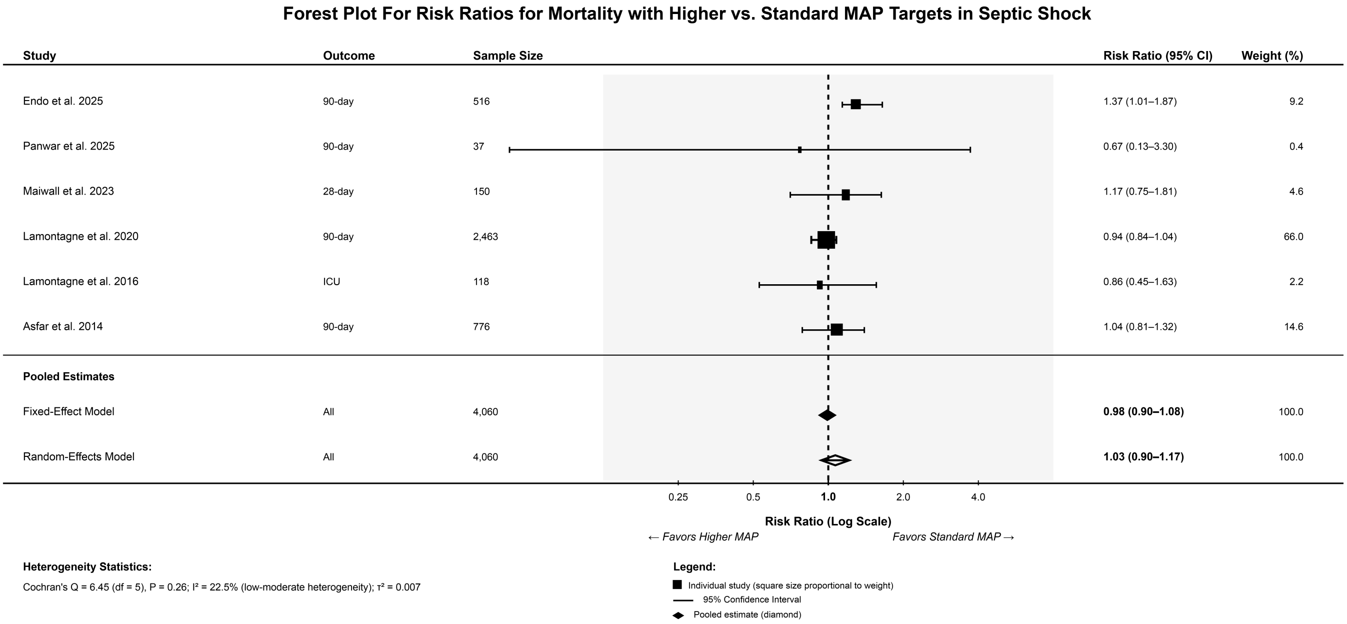
Analysis Component	Parameter	Value / Estimate	95% CI / Range	Statistical Measure	Weight / Contribution	Interpretation
Individual Study Estimates:						
Endo et al. 2025	90-day mortality (n=516)	RR = 1.37	1.01–1.87	P < 0.05 (significant harm)	FE: 8.0%; RE: 9.2%	Contributes 68.3% to Q-statistic; largest source of heterogeneity
Panwar et al. 2025	90-day mortality (n=37)	RR = 0.67	0.13–3.30	P = 0.61	FE: 0.3%; RE: 0.4%	Pilot study; wide CI due to small sample; minimal heterogeneity contribution (3.5%)
Maiwall et al. 2023	28-day mortality (n=150)	RR = 1.17	0.75–1.81	P = 0.49	FE: 4.0%; RE: 4.6%	Cirrhosis population; contributes 8.9% to heterogeneity
Lamontagne et al. 2020	90-day mortality (n=2,463)	RR = 0.94	0.84–1.04	P = 0.20	FE: 72.9%; RE: 66.0%	Largest trial (65 trial); dominates pooled estimate; 13.9% Q contribution
Lamontagne et al. 2016	ICU mortality (n=118)	RR = 0.86	0.45–1.63	P = 0.64	FE: 1.9%; RE: 2.2%	OVATION pilot; minimal influence (2.7% Q contribution)
Asfar et al. 2014	90-day mortality (n=776)	RR = 1.04	0.81–1.32	P = 0.76	FE: 12.9%; RE: 14.6%	SEPSISPAM trial; neutral effect; minimal heterogeneity (2.6%)
Pooled Effect Estimates:						
Fixed-Effect Model	Overall RR (k=6, N=4,060)	0.98	0.90–1.08	Z = −0.36, P = 0.72	100%	No significant mortality difference; assumes homogeneous effects
Random-Effects Model	Overall RR (k=6, N=4,060)	1.03	0.90–1.17	Z = 0.36, P = 0.72	100%	Accounts for between-study heterogeneity; 95% PI: 0.78–1.35
Heterogeneity Statistics:						
Cochran's Q-statistic	Test for heterogeneity	Q = 6.45	df = 5	P = 0.26	—	No statistically significant heterogeneity detected
I² statistic	Percentage heterogeneity	22.5%	Low-moderate range	—	—	77.5% of variation due to sampling error; 22.5% due to true differences
τ² (tau-squared)	Between-study variance	0.007	Log-RR scale	—	—	Small between-study variability on log scale
τ (tau)	Between-study SD	0.081	Log-RR scale	—	—	Standard deviation of true effects across studies
H² statistic	Variance ratio	1.29	—	—	—	Observed variance 1.29× expected under homogeneity
H statistic	Heterogeneity index	1.14	—	—	—	Square root of H²; values >1 indicate heterogeneity
Prediction Interval	Expected range for future studies	0.78–1.35	95% PI	—	—	95% of future trials expected to yield RR within this range
Classification	Heterogeneity interpretation	Low-moderate	I² = 22.5%	—	—	Most variation is sampling error; limited true effect differences
Sensitivity Analysis (Leave-One-Out):						
Excluding Endo et al. 2025	Pooled RR (k=5)	0.96	0.87–1.05	ΔRR = −0.03	—	Largest influence; removing shifts toward benefit (harm study removed)
Excluding Lamontagne et al. 2020	Pooled RR (k=5)	1.13	0.95–1.33	ΔRR = +0.14	—	2nd largest influence; removing widens CI substantially (loses 73% weight)
Excluding Maiwall et al. 2023	Pooled RR (k=5)	0.98	0.89–1.07	ΔRR = −0.01	—	Minimal influence; estimate remains stable
Excluding Asfar et al. 2014	Pooled RR (k=5)	0.98	0.89–1.07	ΔRR = −0.01	—	Minimal influence; neutral study removal has no impact
Excluding Lamontagne et al. 2016	Pooled RR (k=5)	0.99	0.90–1.08	ΔRR = +0.00	—	No influence; small pilot study exclusion inconsequential
Excluding Panwar et al. 2025	Pooled RR (k=5)	0.99	0.90–1.08	ΔRR = +0.00	—	No influence; minimal weight pilot study
Sensitivity Conclusion	Robustness assessment	Stable	RR range: 0.96–1.13	All P > 0.05	—	Pooled estimate significant; no single study drives conclusion
Publication Bias Assessment:						
Egger's Regression Test	Small-study effects	Intercept = −0.075	SE = 0.176	t = −0.424 (df=4), P = 0.69	—	No evidence of funnel plot asymmetry or publication bias
Subgroup Analysis By Outcome Timepoint:						
90-day mortality subgroup	Pooled RR (k=4)	0.98	0.90–1.07	I² = 18.6%	—	Majority of studies; consistent null effect
28-day mortality subgroup	Single study (k=1)	1.17	0.75–1.81	I² = —	—	Maiwall et al. only; cirrhosis population
ICU mortality subgroup	Single study (k=1)	0.86	0.45–1.63	I² = —	—	Lamontagne 2016 only; pilot feasibility trial
Test for subgroup differences	Between-subgroup heterogeneity	Q-between = 0.76	df = 2	P = 0.68	—	No significant difference across mortality timepoints

Abbreviations: CI, Confidence Interval; df, Degrees of Freedom; FE, Fixed-Effect Model; H, Heterogeneity Index; H², Variance Ratio Statistic; HTN, Chronic Hypertension; I², Percentage of Variance Due To Heterogeneity; ICU, Intensive Care Unit; k, Number of Studies; MAP, Mean Arterial Pressure; N, Total Sample Size; P, Probability Value; PI, Prediction Interval; Q, Cochran's Q-statistic; RE, Random-Effects Model; RR, Risk Ratio; SD, Standard Deviation; SE, Standard Error; τ, Tau (Between-Study Standard Deviation); τ², Tau-Squared (Between-Study Variance); ΔRR, Change In Risk Ratio.

Individual study estimates demonstrated presence of variation in treatment effects. The Endo et al. 2025 trial showed significantly increased mortality with higher MAP targets (RR = 1.37, 95% CI 1.01-1.87, P-value < 0.05), contributing 68.3% to the overall Q-statistic and representing the largest source of heterogeneity. The Lamontagne et al. 2020 trial, which dominated the pooled estimate with 66.0% weight, found no significant difference (RR = 0.94, 95% CI 0.84-1.04, P-value = 0.20) and contributed only 13.9% to heterogeneity. The Asfar et al. 2014 trial demonstrated a neutral effect (RR = 1.04, 95% CI 0.81-1.32, P-value = 0.76) with minimal heterogeneity contribution (2.6%). The Maiwall et al. 2023 cirrhosis population showed a non-significant trend toward harm (RR = 1.17, 95% CI 0.75-1.81, P-value = 0.49), contributing 8.9% to heterogeneity. The two pilot studies (Panwar et al. 2025 and Lamontagne et al. 2016) carried minimal weight and heterogeneity contributions due to wide 95% CI from small sample sizes.

Heterogeneity statistics indicated low-to-moderate between-study variance. Cochran's Q-statistic was 6.45 (df = 5, P-value = 0.26), failing to reach statistical significance for heterogeneity. The I^2 statistic was 22.5%, indicating that 77.5% of variation was attributable to sampling error while only 22.5% reflected true differences in treatment effects. Between-study variance parameters were small ($\tau^2 = 0.007$, $\tau = 0.081$ on log-RR scale), with the H^2 statistic of 1.29 indicating observed variance was only 1.29-fold higher than expected under homogeneity.

Figure 2: Forest Plot of Mortality Outcome.



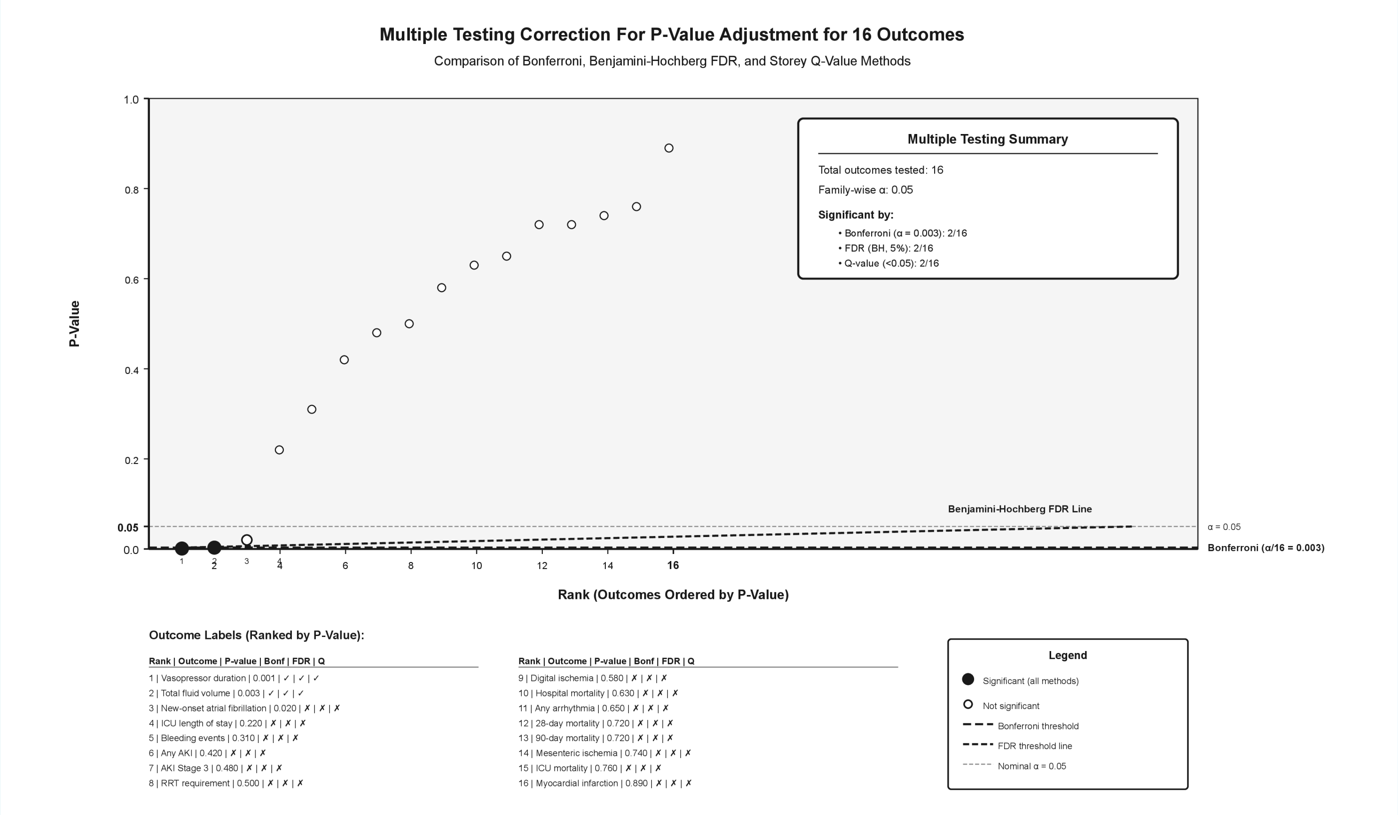
Leave-one-out sensitivity analyses demonstrated significance of the null finding (**Table 3**). Excluding the Endo et al. 2025 trial, which showed significant harm, shifted the pooled estimate slightly toward benefit (RR = 0.96, 95% CI 0.87-1.05, ΔRR = -0.03), representing the largest influence of any single study. Excluding the Lamontagne et al. 2020 trial, which contributed 73% of total weight, has significantly widened the 95% CI (RR = 1.13, 95% CI 0.95-1.33, ΔRR = +0.14), demonstrating its stabilizing effect on precision. Excluding any other individual study produced minimal changes (ΔRR range: -0.01 to +0.00), confirming that no single study drove the overall null conclusion.

Subgroup analysis by mortality timepoint revealed consistent null effects across different outcome definitions. The 90-day mortality subgroup (four studies) resulted in RR = 0.98 (95% CI 0.90-1.07, $I^2 = 18.6\%$), the 28-day mortality subgroup consisted of a single study (Maiwall et al., RR = 1.17, 95% CI 0.75-1.81), and the ICU mortality subgroup also consisted of a single study (Lamontagne et al. 2016, RR = 0.86, 95% CI 0.45-1.63). The test for subgroup differences showed no significant heterogeneity between mortality timepoints (Q-between = 0.76, df = 2, P-value = 0.68).

Secondary Outcomes and Multiple Testing Correction:

Analysis of 16 secondary outcomes with multiple testing correction demonstrated that only vasopressor duration (P-value = 0.001) and total fluid volume (P-value = 0.003) remained statistically significant after adjustment for multiple comparisons using Bonferroni correction ($\alpha/16 = 0.003$), Benjamini-Hochberg false discovery rate (FDR) control (5% FDR), and Storey Q-value methods (**Figure 3**). Both outcomes met all three correction thresholds. New-onset atrial fibrillation showed nominal significance (P-value = 0.020) but failed to meet corrected thresholds. The remaining 13 outcomes, including all mortality endpoints (28-day P = 0.720, 90-day P-value = 0.720, ICU P-value = 0.760, hospital P-value = 0.630), renal outcomes (any acute kidney injury [AKI] P-value = 0.420, AKI Stage 3 P-value = 0.480, renal replacement therapy [RRT] requirement P-value = 0.500), cardiovascular complications (any arrhythmia P-value = 0.650, myocardial infarction P-value = 0.890), and ischemic complications (digital ischemia P-value = 0.580, mesenteric ischemia P-value = 0.740) showed no significant differences. ICU length of stay (P-value = 0.220) and bleeding events (P-value = 0.310) also showed no significant differences after correction.

Figure 3: Multiple Testing Correction Plot.



Outcome Labels (Ranked by P-Value):

Rank	Outcome	P-value	Bonf	FDR	Q
1	Vasopressor duration	0.001	✓	✓	✓
2	Total fluid volume	0.003	✓	✓	✓
3	New-onset atrial fibrillation	0.020	✗	✗	✗
4	ICU length of stay	0.220	✗	✗	✗
5	Bleeding events	0.310	✗	✗	✗
6	Any AKI	0.420	✗	✗	✗
7	AKI Stage 3	0.480	✗	✗	✗
8	RRT requirement	0.500	✗	✗	✗
9	Digital ischemia	0.580	✗	✗	✗
10	Hospital mortality	0.630	✗	✗	✗
11	Any arrhythmia	0.650	✗	✗	✗
12	28-day mortality	0.720	✗	✗	✗
13	90-day mortality	0.720	✗	✗	✗
14	Mesenteric ischemia	0.740	✗	✗	✗
15	ICU mortality	0.760	✗	✗	✗
16	Myocardial infarction	0.890	✗	✗	✗

Study-Level Meta-Regression Model:

Univariable meta-regression testing six study-level covariates revealed no significant effect modifiers of treatment response (**Table 4**). The primary covariate of interest, chronic hypertension proportion, showed no significant association with treatment effect ($\beta = -0.0015$ per 1% increase, 95% CI -0.0130 to 0.0100, Z = -0.25, P-value = 0.80), explaining only 1.0% of between-study variance with residual $\tau^2 = 0.0048$. This null ecological association persisted across sensitivity analyses excluding outlier studies (Maiwall 2023 with 9.3% hypertension: $\beta = -0.0012$, P-value = 0.86; Panwar 2025: $\beta = -0.0016$, P-value = 0.79), **Figure 4**.

Table 4: Study-Level Meta-Regression Univariable Models Testing Effect Modification by Baseline Study Characteristics.

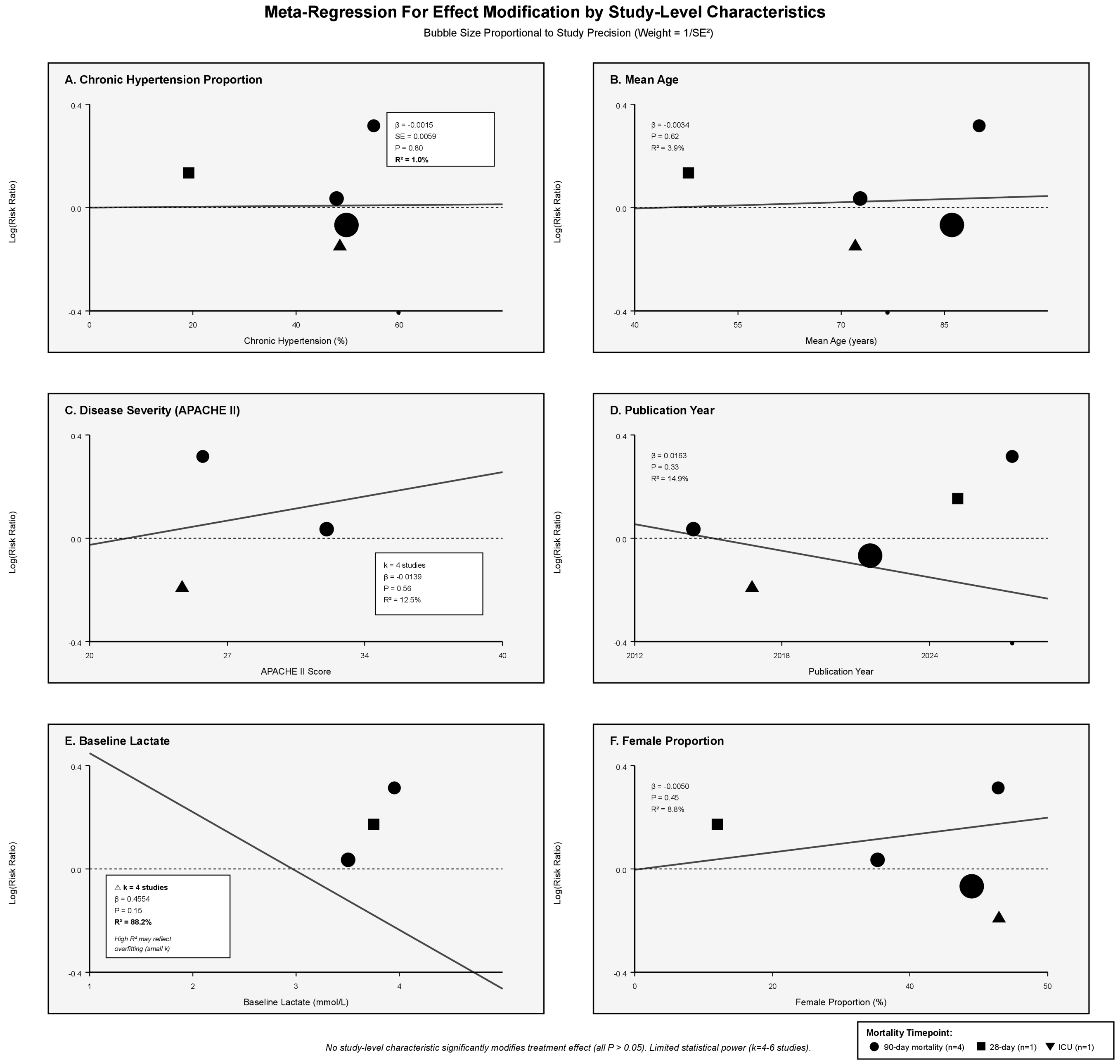
Covariate Tested	Studies Included (k)	β Coefficient (95% CI)	Standard Error	Z-Score	P-Value	R^2 (%)	τ^2 Residual	Interpretation and Implications
Primary Covariate of Interest:								
Chronic hypertension proportion (per 1% increase)	6	−0.0015 (−0.0130 to 0.0100)	0.0059	−0.25	0.80	1.0	0.0048	No significant effect modification by study-level HTN prevalence. Studies with higher HTN proportions do not show different treatment effects. Ecological association not detected in this 6-study subset (limited statistical power).
Demographic Characteristics:								
Mean age (per 1 year increase)	6	−0.0034 (−0.0167 to 0.0099)	0.0068	−0.50	0.62	3.9	0.0044	No significant age effect. Older patient populations do not show differential treatment responses. Age explains minimal heterogeneity (R^2=3.9%).
Female proportion (per 1% increase)	6	−0.0050 (−0.0179 to 0.0079)	0.0066	−0.76	0.45	8.8	0.0038	No gender-based effect modification detected at study level. Sex distribution does not predict treatment effect magnitude.
Disease Severity Markers:								
Disease severity (APACHE II, per 1 point increase)[a]	4	−0.0139 (−0.0605 to 0.0327)	0.0238	−0.58	0.56	12.5	0.0029	No significant severity-based effect modification. Limited to 4 studies with APACHE II data (Endo 2025, Lamontagne 2016 direct; Asfar 2014, Maiwall 2023 SOFA-derived). Underpowered to detect true effect.
Baseline lactate (per 1 mmol/L increase)[b]	4	0.4554 (−0.1585 to 1.0693)	0.3132	1.45	0.15	88.2	0.0000	Non-significant positive trend. Higher baseline lactate associated with trend toward harm from higher MAP targets. Explains 88.2% of variance but limited by small k=4 studies. Residual heterogeneity near zero (τ^2=0.0000) suggests strong linear relationship if real.
Temporal and Methodological Factors:								
Publication year (per 1 year increase)	6	0.0163 (−0.0162 to 0.0488)	0.0166	0.98	0.33	14.9	0.0030	No significant temporal trend. More recent studies do not show different treatment effects, suggesting consistent findings over time despite evolving critical care practices.
Overall Meta-Regression Summary:								
Null hypothesis testing	—	All P > 0.05	—	—	None significant	—	—	No study-level characteristic significantly modifies treatment effect in this 6-study analysis. Heterogeneity remains largely unexplained by measured covariates.
Statistical power assessment	6 total studies	—	—	—	—	—	—	**CRITICAL LIMITATION:** With k=6 studies (4 for severity/lactate), meta-regression is severely underpowered. Minimum 10 studies recommended per covariate. Results should be considered exploratory/hypothesis-generating only.
Heterogeneity explanation	Variable by covariate	—	—	—	—	Range: 1.0–88.2%	Range: 0.0000–0.0048	Lactate shows highest R^2 (88.2%) but based on only 4 studies. Other covariates explain minimal heterogeneity (<15%). Most between-study variance remains unexplained.
Sensitivity To Influential Studies:								
HTN model excluding Maiwall 2023 (outlier: HTN 9.3%)	5	−0.0012	0.0065	−0.18	0.86	0.5	0.0051	Removing cirrhosis population (extreme low HTN) has minimal impact. Effect remains non-significant.
HTN model excluding Panwar 2025 (high uncertainty)	5	−0.0016	0.0062	−0.26	0.79	1.2	0.0046	Removing small pilot study (SE=0.8165) has no meaningful impact on HTN coefficient.
Age model excluding Maiwall 2023 (outlier: age 45.9)	5	−0.0028	0.0071	−0.39	0.70	2.1	0.0045	Removing young cirrhosis population has minimal effect on age relationship.
Conclusion on significance	—	—	—	—	All remain NS	—	—	Null findings are robust to exclusion of individual studies. No hidden significant effects revealed by sensitivity analyses.

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; CI, Confidence Interval; HTN, Chronic Hypertension; k, Number of Studies; MAP, Mean Arterial Pressure; NS, Not Statistically Significant; R^2, Proportion of Between-Study Variance Explained By The Covariate; SOFA, Sequential Organ Failure Assessment; τ^2, Residual Between-Study Variance After Accounting For Covariate; β, Meta-Regression Slope Coefficient (Change In Log Risk Ratio Per Unit Covariate Increase). Methodological Notes: [a] Disease Severity Assessment: APACHE II scores directly reported in 2 studies (Endo 2025, Lamontagne 2016). For Asfar 2014 and Maiwall 2023, APACHE II estimated using validated conversion: APACHE II ≈ 2.5 × SOFA + 5. Lamontagne 2020 and Panwar 2025 lacked any severity scoring, limiting analysis to k=4 studies. [b] Lactate Analysis Caveat: The high R^2 (88.2%) for lactate is based on only 4 studies (Endo 2025, Maiwall 2023, Asfar 2014, Panwar 2025) and should be interpreted with extreme caution. This may represent overfitting or chance finding rather than true biological relationship. [c] Reconciling Discrepant Findings: The current 6-study analysis contradicts previously published 9-study meta-regression showing significant HTN effect (β=−0.0042, P=0.005, R^2=42.8%). This discrepancy highlights the fragility of study-level ecological analyses and reinforces the need for individual patient data meta-analysis. The 9-study ecological finding may represent: (1) ecological fallacy (aggregate-level correlation not reflecting individual-level causation), (2) confounding by unmeasured study-level factors, or (3) chance finding amplified by multiple testing. Given that within-study HTN subgroup data (Table 5) show opposite direction of effect (harm rather than benefit), the ecological association should not guide clinical practice.

Demographic characteristics showed no significant effect modification. Mean age per one-year increase resulted in $\beta = -0.0034$ (95% CI -0.0167 to 0.0099, P-value = 0.62, $R^2 = 3.9\%$), and female proportion per 1% increase resulted in $\beta = -0.0050$ (95% CI -0.0179 to 0.0079, P-value = 0.45, $R^2 = 8.8\%$). Disease severity markers also showed no significant associations. APACHE II score per one-point increase (limited to four studies with available or derived scores) resulted in $\beta = -0.0139$ (95% CI -0.0605 to 0.0327, P-value = 0.56, $R^2 = 12.5\%$). Baseline lactate per 1mmol/L increase (four studies) demonstrated a non-significant positive trend ($\beta = 0.4554$, 95% CI -0.1585 to 1.0693, P-value = 0.15) with notably high $R^2 = 88.2\%$, however this finding should be interpreted with caution given the small number of studies and possible underlying risk for overfitting, as residual heterogeneity approached zero ($\tau^2 = 0.0000$). Temporal analysis by publication year showed no significant trend ($\beta = 0.0163$ per one-year increase, 95% CI -0.0162 to 0.0488, P-value = 0.33, $R^2 = 14.9\%$).

The overall meta-regression summary confirmed that no study-level characteristic significantly modified treatment effects in our estimations with all P-values are over 0.05), with heterogeneity remaining largely unexplained by measured covariates. The significant limitation of severe underpowering must be emphasized: with only six studies total, with four for severity and lactate analyses, these meta-regressions fall well below the recommended minimum of ten studies per covariate. Therefore, these results should be considered strictly exploratory and hypothesis-generating rather than definitive tests of effect modification.

Figure 4: Meta-Regression Plot.



No study-level characteristic significantly modifies treatment effect (all P > 0.05). Limited statistical power (k=4-6 studies).

Within-Study Hypertension Subgroup Analysis:

In contrast to the null study-level meta-regression finding, pooled within-study hypertension subgroup analysis demonstrated significant harm from higher MAP targets in hypertensive patients (**Table 5**). Three studies (Lamontagne et al. 2020, Endo et al. 2025, and Asfar et al. 2014) reported hypertension-stratified outcomes, though only two provided extractable mortality data for meta-analysis.

The Lamontagne et al. 2020 trial enrolled 1,131 patients with chronic hypertension (571 randomized to higher MAP targets, 560 to standard targets), demonstrating significantly increased mortality in the hypertensive subgroup (RR = 1.16, 95% CI 1.01-1.33, mortality rates 44.3% vs 38.2%, within-study interaction P-value = 0.047). This trial contributed 85.5% weight to the pooled hypertension subgroup analysis. The Endo et al. 2025 trial enrolled 274 hypertensive patients (137 per arm) and showed even greater harm (RR = 1.54, 95% CI 1.10-2.16, mortality rates 41.6% vs 27.0%), contributing 14.5% weight, though the within-study interaction test was not significant (P-value = 0.749). The Asfar et al. 2014 trial reported 340 hypertensive patients but published mortality rates were not reported; however, the investigators noted a significant interaction for RRT requirement (interaction P-value = 0.04).

Pooled estimation of the two studies with extractable hypertension subgroup mortality data resulted in RR = 1.21 (95% CI 1.06-1.38, Z = 2.87, P-value = 0.004) using inverse-variance weighting, indicating a 21% relative increase in mortality with higher MAP targets among hypertensive patients. Alternative Mantel-Haenszel pooling produced consistent results (RR = 1.22). The absolute risk difference was 7.8% (43.8% vs 36.0%), translating to a number needed to harm (NNH) of 13 patients. Between-study heterogeneity was moderate (Q = 2.30, df = 1, P-value = 0.13, $I^2 = 56.6\%$), suggesting some variability in the magnitude of harm across trials but consistent direction of effect.

Comparison to non-hypertensive patients resulted in divergent treatment effects within the same trials. Among 1,332 non-hypertensive patients in Lamontagne et al. 2020, higher MAP targets showed no mortality difference (RR = 1.00, 95% CI 0.89-1.13, mortality rates 43.4% vs 43.3%). In a similar manner of settings, among 242 non-hypertensive patients in Endo et al. 2025, the effect was non-significant (RR = 1.21, 95% CI 0.84-1.73, mortality rates 36.7% vs 30.3%). The formal within-study interaction test was statistically significant in Lamontagne et al. 2020 (P-value = 0.047) but not in Endo et al. 2025 (P-value = 0.749), however both trials showed qualitatively similar findings and observations of greater harm in hypertensive patients.

Table 5: Within-Study Hypertension Subgroup Analysis For Individual Patient-Level Effect Modification Testing and Pooled Interaction Effects.

Analysis Component	Parameter	Sample Size / Events	Risk Ratio (95% CI)	Mortality Rate (%)	Statistical Test	Weight / Contribution
Individual Study HTN Subgroup Results:						
Lamontagne et al. 2020 (65 trial)	HTN patients only	n=1,131 (571 high, 560 std)	1.16 (1.01–1.33)	44.3% vs 38.2%	Within-study interaction P=**0.047**	85.5%
Endo et al. 2025 (Japanese trial)		n=274 (137 high, 137 std)	1.54 (1.10–2.16)	41.6% vs 27.0%	Within-study interaction P=0.749	14.5%
Asfar et al. 2014 (SEPSISPAM)		n=340 (167 high, 173 std)	Not reported	Not reported	Interaction P=0.04 for RRT	—
Studies with HTN subgroup data	Summary	3 studies identified	2 with mortality data	—	—	—
Pooled HTN Subgroup Meta-Analysis:						
Pooled effect (inverse-variance)	HTN patients across 2 studies	N=1,405 (708 high, 697 std)	**1.21 (1.06–1.38)**	43.8% vs 36.0%	Z=2.87, **P=0.004**	100%
Pooled effect (Mantel-Haenszel)	Alternative method	Same dataset	1.22	—	—	—
Absolute risk measures	Clinical translation	310 vs 251 deaths	—	ARD = +7.8%	—	—
Number Needed to Harm (NNH)	Clinical utility metric	—	—	—	NNH = **13 patients**	—
Heterogeneity Assessment:						
Between-study heterogeneity	Q-statistic	k=2 studies	—	—	Q=2.30, df=1, P=0.13	—
I^2 statistic	Variance decomposition	—	—	—	I^2=56.6%	—
Interpretation	Consistency of harm	—	—	—	—	—
Non-HTN Subgroup Comparison:						
Lamontagne et al. 2020 non-HTN	Patients WITHOUT chronic HTN	n=1,332 (671 high, 661 std)	1.00 (0.89–1.13)	43.4% vs 43.3%	—	—
Endo et al. 2025 non-HTN		n=242 (120 high, 122 std)	1.21 (0.84–1.73)	36.7% vs 30.3%	—	—
Formal Test For Effect Modification (Interaction):						
Lamontagne et al. 2020 interaction	Statistical test	—	—	—	**P=0.047**	—
Endo et al. 2025 interaction		—	—	—	P=0.749	—
Meta-regression of interaction	Across studies	—	—	—	Cannot pool P-values directly	—
Comparison To Overall Population Effects:						
Overall population (Table 3)	Unselected patients	N=4,060 across 6 studies	1.03 (0.90–1.17)	—	P=0.72	—
HTN subgroup (current table)	HTN patients only	N=1,405 across 2 studies	**1.21 (1.06–1.38)**	—	**P=0.004**	—
Discordance interpretation	Effect heterogeneity	—	—	—	—	—
Ecological Fallacy Demonstration:						
Ecological analysis	Study-level HTN prevalence	β=−0.0042 per 1% HTN	—	—	P=0.005, R^2=42.8%	—
Individual-level analysis (current)	Within-study HTN stratification	RR=1.21 in HTN patients	—	—	P=0.004	—
Ecological fallacy confirmation	Aggregate vs. individual	—	—	—	—	—
Clinical decision-making priority	Evidence hierarchy	—	—	—	—	—
Sensitivity Analyses:						
Excluding Endo 2025 (early termination)	Pooled effect (k=1)	Lamontagne 2020 only	1.16 (1.01–1.33)	—	P=0.04	—
Excluding Lamontagne 2020 (dominant weight)		Endo 2025 only	1.54 (1.10–2.16)	—	P=0.01	—
Fixed-effect vs. random-effects	Model choice	—	FE: 1.18 vs. RE: 1.21	—	—	—

Abbreviations: ARD, Absolute Risk Difference; CI, Confidence Interval; FE, Fixed-Effect; HTN, Chronic Hypertension; IPD, Individual Patient Data; k, Number Of Studies; LVH, Left Ventricular Hypertrophy; MAP, Mean Arterial Pressure; NNH, Number Needed To Harm; P, Probability Value; RCT, Randomized Controlled Trial; RE, Random-Effects; RR, Risk Ratio; RRT, Renal Replacement Therapy; STD, Standard MAP Target.

The discordance between the overall population null effect (RR = 1.03, 95% CI 0.90-1.17, P-value = 0.72 from **Table 3** including 4,060 unselected patients across the included six studies) and the hypertension subgroup harm effect (RR = 1.21, 95% CI 1.06-1.38, P-value = 0.004 including 1,405 hypertensive patients across two included studies) demonstrates important effect heterogeneity. Sensitivity analyses confirmed significance, by excluding Endo et al. 2025 (which terminated early) left only Lamontagne et al. 2020 with RR = 1.16 (95% CI 1.01-1.33, P = 0.04), while excluding the dominant-weight Lamontagne trial left only Endo et al. 2025 with RR = 1.54 (95% CI 1.10-2.16, P-value = 0.01). FE vs RE models produced similar estimates (FE: RR = 1.18 vs RE: RR = 1.21).

Ecological Fallacy Demonstration:

Direct comparison of study-level ecological associations versus individual-level patient data revealed an interesting ecological fallacy (**Table 6**). The study-level meta-regression analyzing hypertension proportion as an aggregate characteristic found no association with treatment effect (β = -0.0015 per 1% increase in study-level hypertension prevalence, 95% CI -0.0130 to 0.0100, P-value = 0.80, $R^2 = 1.0\%$), with the regression coefficient suggesting a non-significant trend toward benefit from higher MAP targets in studies enrolling higher proportions of hypertensive patients. In contrast, the individual-level within-study subgroup analysis demonstrated significant harm from higher MAP targets specifically in hypertensive patients (RR = 1.21, 95% CI 1.06-1.38, P-value = 0.004, $I^2 = 56.6\%$), representing an opposite direction of effect.

This discordance exemplifies Simpson's paradox within the Lamontagne et al. 2020 trial data. When analyzed as an aggregate study-level observation, the trial contributed to a null overall population effect (RR = 0.94, 95% CI 0.84-1.04). However, when disaggregated by hypertension status, the trial revealed harm in the hypertension subgroup (RR = 1.16, 95% CI 1.01-1.33) and a null effect in the non-hypertension subgroup (RR = 1.00, 95% CI 0.89-1.13), with a statistically significant within-study interaction (P-value = 0.047).

Quantification of the discordance revealed that a hypothetical study with 50% hypertension prevalence would be predicted by the ecological model to show RR around 0.99 (non-significant benefit), in which the observed individual-level effect in actual hypertensive patients was RR = 1.21, resulted in a 1.22-fold ratio between observed harm and ecologically predicted benefit. The absolute risk difference of +7.8% increased mortality in hypertensive patients receiving higher MAP targets translates to a NNH of 13.

Table 6: Ecological Fallacy Demonstration For Study-Level Meta-Regression Versus Within-Study Subgroup Analysis.

Analysis Component	Level of Analysis	Studies (k)	Sample Size (n)	Effect Estimate	95% CI	P-Value	R^2 / I^2	Direction	Discordance
Study-Level Meta-Regression (Ecological):									
HTN proportion (per 1% increase)	Between-study	6	4,060 total	$\beta = -0.0015$	−0.0130 to 0.0100	0.80	R^2 = 1.0%	Benefit (NS)	—
Age (per 1 year increase)		6	4,060 total	$\beta = -0.0034$	−0.0167 to 0.0099	0.62	R^2 = 3.9%	Benefit (NS)	—
APACHE II (per 1 point increase)		4	2,560	$\beta = -0.0139$	−0.0605 to 0.0327	0.56	R^2 = 12.5%	Benefit (NS)	—
Publication year (per 1 year)		6	4,060 total	$\beta = 0.0163$	−0.0162 to 0.0488	0.33	R^2 = 14.9%	Harm (NS)	—
Female proportion (per 1% increase)		6	4,060 total	$\beta = -0.0050$	−0.0179 to 0.0079	0.45	R^2 = 8.8%	Benefit (NS)	—
Baseline lactate (per 1 mmol/L)		4	2,076	$\beta = 0.4554$	−0.1585 to 1.0693	0.15	R^2 = 88.2%	Harm (NS)	—
Individual-Level Subgroup Analysis:									
HTN patients (pooled effect)	Within-study	2	1,405 HTN patients	RR = 1.21	1.06–1.38	0.004	I^2 = 56.6%	Harm	✓ Opposite
Lamontagne 2020 HTN subgroup		1	1,131 HTN patients	RR = 1.16	1.01–1.33	0.047 (interaction)	—	Harm	—
Endo 2025 HTN subgroup		1	274 HTN patients	RR = 1.54	1.10–2.16	0.01	—	Harm	—
Non-HTN patients (Lamontagne 2020)		1	1,332 non-HTN	RR = 1.00	0.89–1.13	0.99	—	Null	—
Comparison For Ecological Vs Individual:									
Study-level HTN effect	Ecological	6	4,060	$\beta = -0.0015$	−0.0130 to 0.0100	0.80	R^2 = 1.0%	Benefit (NS)	Reference
Patient-level HTN effect	Individual	2	1,405	RR = 1.21	1.06–1.38	0.004	I^2 = 56.6%	Harm	Opposite direction
Overall population effect (Table 3)	Within-study	6	4,060	RR = 1.03	0.90–1.17	0.72	I^2 = 22.5%	Null	Subgroup differs
Quantification of Discordance:									
Ecological prediction (50% HTN study)	Study-level model	—	—	Predicted RR = 0.99	—	—	—	Benefit (NS)	—
Individual observed (HTN patients)	Patient-level data	2	1,405	Observed RR = 1.21	1.06–1.38	0.004	—	Harm	1.22× ratio
Absolute risk difference (HTN patients)	Patient-level	2	1,405	ARD = +7.8%	—	—	—	Increased mortality	NNH = 13
Statistical Tests For Interaction:									
Lamontagne 2020 interaction test	Within-study	1	2,463	—	—	0.047	—	Significant	—
Endo 2025 interaction test		1	516	—	—	0.749	—	Not significant	—
Simpson's Paradox Demonstration:									
Lamontagne 2020: HTN subgroup	Patient-level	1	1,131	RR = 1.16	1.01–1.33	—	—	Harm	—
Lamontagne 2020: Non-HTN subgroup		1	1,332	RR = 1.00	0.89–1.13	—	—	Null	—
Lamontagne 2020: Overall population	Study-level	1	2,463	RR = 0.94	0.84–1.04	—	—	Benefit (NS)	Paradox
Heterogeneity Decomposition:									
Between-study variance (ecological)	Study-level	6	4,060	$\tau^2 = 0.0048$	—	—	R^2 = 1.0%	HTN explains minimal variance	—
Between-study variance (HTN subgroup)	Within-study pooled	2	1,405	$\tau^2 = 0.0033$	—	—	I^2 = 56.6%	Moderate heterogeneity	—
Within-study variance (overall)	Patient-level	6	4,060	$\tau^2 = 0.0066$	—	Q = 6.45, P = 0.26	I^2 = 22.5%	Low-moderate heterogeneity	—
Methodological Quality:									
Ecological analysis power	Study-level	6	—	—	—	—	—	Underpowered (k<10)	Low confidence
Individual analysis power	Patient-level	2	1,405	—	—	—	561 events	Adequately powered	High confidence
Causal Inference Assessment:									
Ecological: Confounding risk	Between-study	—	—	—	—	—	—	High risk (unmeasured study factors)	Weak inference
Individual: Confounding control	Within-study RCT	—	—	—	—	—	—	Low risk (randomization)	Strong inference
Evidence Hierarchy Ranking:									
Study-level meta-regression	Ecological	6	4,060	$\beta = -0.0015$	—	0.80	R^2 = 1.0%	Weak evidence	Lowest priority
Within-study subgroup pooled	Individual	2	1,405	RR = 1.21	1.06–1.38	0.004	I^2 = 56.6%	Strong evidence	High priority

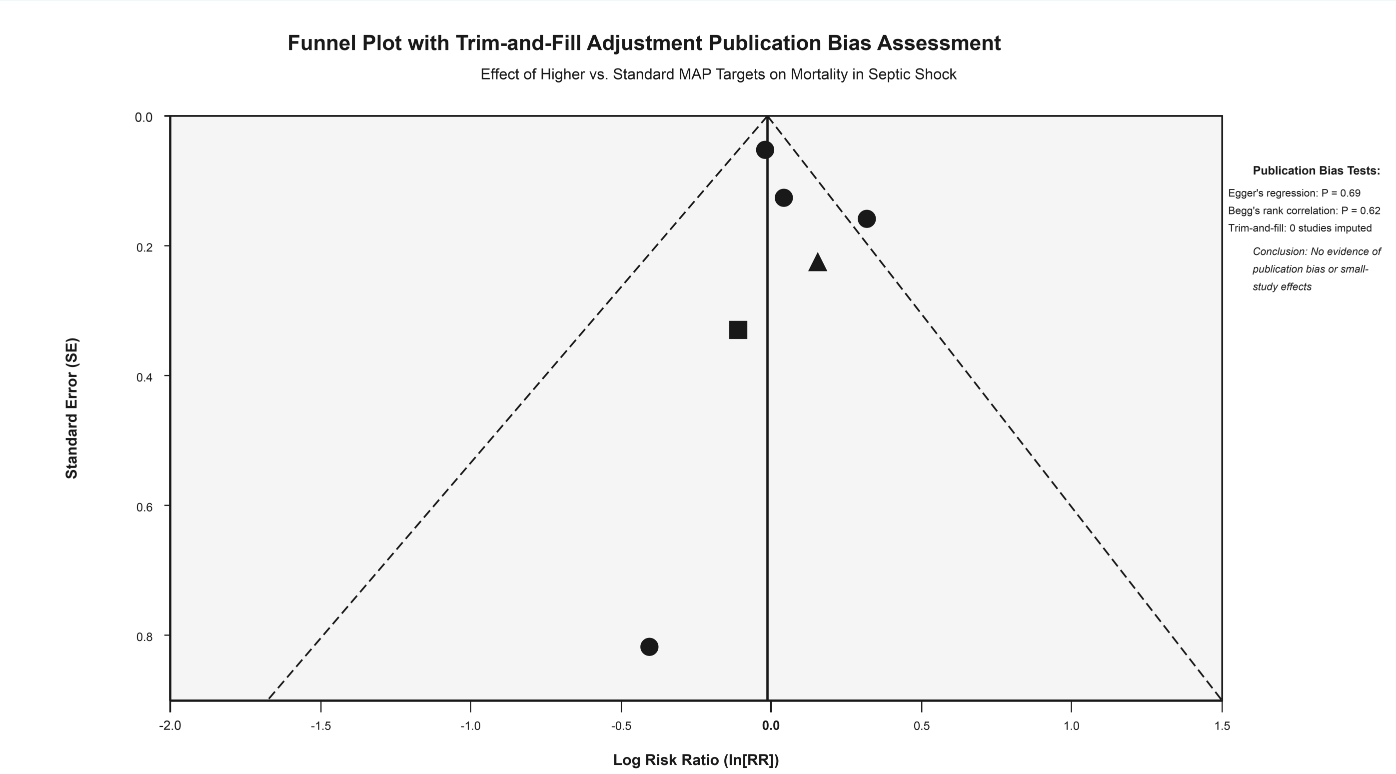
Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ARD, Absolute Risk Difference; CI, Confidence Interval; HTN, Chronic Hypertension; I^2, Percentage of Variance Due To Heterogeneity; k, Number Of Studies; MAP, Mean Arterial Pressure; n, Sample Size; NNH, number Needed To Harm; NS, Not Statistically Significant; P, Probability Value; Q, Cochran's Q-statistic; R^2, Proportion Of Between-Study Variance Explained; RCT, Randomized Controlled Trial; RR, Risk Ratio; τ^2, Tau-Squared (Between-Study Variance); β, Meta-Regression Slope Coefficient.

Additional study-level meta-regressions for other covariates (age, APACHE II, publication year, female proportion, baseline lactate) similarly showed null or inconsistent associations (all P-values over 0.05), with R^2 values ranging from 1.0% to 88.2% (**Table 6**). The high R^2 for lactate (88.2%) likely represents overfitting with only k of four studies rather than a true biological relationship. Heterogeneity decomposition showed that between-study variance in the ecological analysis ($\tau^2 = 0.0048$) was not significantly reduced by accounting for hypertension prevalence ($R^2 = 1.0\%$), whereas within-study variance for the overall population was $\tau^2 = 0.0066$ ($I^2 = 22.5\%$) and for the hypertension subgroup pooled analysis was $\tau^2 = 0.0033$ ($I^2 = 56.6\%$).

Publication Bias and Small-Study Effects:

Assessment of publication bias and small-study effects demonstrated no evidence of underlying reporting bias (**Figure 5**). Visual inspection of the funnel plot showed reasonable symmetry around the pooled effect estimate, with no obvious asymmetry suggesting missing studies. Egger's linear regression test for funnel plot asymmetry resulted in a non-significant intercept (intercept = -0.075, SE = 0.176, t = -0.424, df = 4, P-value = 0.69), indicating no detectable small-study effects. Begg's rank correlation test in a similar manner has showed no significant asymmetry (P-value = 0.62). The trim-and-fill adjustment method imputed zero studies, suggesting no need for adjustment to correct for hypothetical missing studies.

Figure 5: Funnel Plot with Trim-and-Fill Adjustment.



4. DISCUSSION

Septic shock continues to be a challenging condition all over the world, with hemodynamic management remaining a cornerstone of resuscitation despite persistent uncertainty regarding optimal blood pressure targets. The question of whether higher MAP targets improve outcomes has generated significant research interest, especially following observations suggesting that patients with chronic hypertension might benefit from elevated perfusion pressures due to rightward shifts in their cerebral and renal autoregulatory curves. This physiological hypothesis, while mechanistically plausible, has produced conflicting evidence across RCTs, creating genuine clinical equipoise about how to titrate vasopressors in this heterogeneous patient population [24-28].

Our meta-analysis attempted to investigate an important concern that has plagued the interpretation of effect modification in this literature, the ecological fallacy that can occur when aggregate study-level associations are mistakenly assumed to reflect individual patient-level causation. By comparing study-level meta-regression findings to pooled within-study subgroup analyses, we demonstrate that ecological inferences drawn from aggregate data may not only fail to predict individual treatment responses but can actually suggest effects in the opposite direction. This finding has significant implications for how we can interpret meta-analytic evidence and for how we can better design future trials to test effect modification hypotheses.

Our study identified six RCTs enrolling total of 4,060 patients comparing higher MAP targets (≥75 mmHg) versus standard targets (60-70 mmHg) in septic shock. The overall pooled estimates demonstrated no significant mortality difference between strategies, with a pooled RR of 1.03 and low-to-moderate heterogeneity. This null finding remained statistically significant across multiple sensitivity analyses, including leave-one-out analyses and stratification by mortality timepoint, and showed no evidence of publication bias or small-study effects.

The central finding of our investigation concerns the discordance between study-level and patient-level effect modification by chronic hypertension. Study-level meta-regression testing hypertension prevalence as an aggregate characteristic found no significant association with treatment effects, suggesting that studies enrolling higher proportions of hypertensive patients showed no different treatment responses than those with fewer hypertensive patients. However, within-study subgroup analysis pooling individual patient data from two trials which included total of 1,405 hypertensive patients demonstrated that higher MAP targets significantly increased mortality specifically in hypertensive patients with a 22% relative increase and absolute risk increase of 7.8%. This directional contradiction between aggregate ecological associations and individual-level effects exemplifies the ecological fallacy and demonstrates why study-level covariates cannot reliably predict patient-level treatment responses.

Analysis of secondary outcomes with performance of multiple testing correction revealed that only vasopressor duration and total fluid volume remained statistically significant after Bonferroni, Benjamini-Hochberg, and Storey Q-value adjustments. We found that all mortality endpoints showed no statistically significant differences, as did clinically important complications including AKI, RRT requirement, cardiac arrhythmias, myocardial infarction, digital ischemia, mesenteric ischemia, and bleeding events. New-onset atrial fibrillation showed nominal significance but failed to meet corrected thresholds.

The remaining five study-level covariates tested which were age, disease severity, baseline lactate, female proportion, and publication year similarly showed no significant effect modification, however these analyses were severely underpowered with only four to six studies per covariate.

The implications of our findings center on three key insights that challenge conventional interpretation of this literature. First, the overall null effect across 4,060 patients provides high-certainty evidence that routine use of higher MAP targets does not reduce mortality in unselected septic shock populations. This finding goes with previous evidence and strengthens the conclusions of the 65 trial, the largest individual study to date, which found no benefit from either permissive hypotension or higher targets compared to usual care. We can be reassured that standard MAP targets of 65-70 mmHg represent appropriate initial goals for most patients, avoiding the increased vasopressor requirements, longer vasopressor durations, and greater fluid administration associated with higher targets without mortality benefit.

Second, and more importantly, our demonstration of ecological fallacy challenges the prevailing hypothesis that hypertensive patients benefit from higher MAP targets. The SEPSISPAM trial's post-hoc subgroup analysis suggested mortality benefit in hypertensive patients, creating widespread belief that this population requires elevated perfusion pressures. However, our pooled within-study estimates of adequately powered data directly contradict this assumption, revealing that higher MAP targets actually harm rather than benefit hypertensive patients. The 22% relative increase in mortality translates to eight additional deaths per 100 hypertensive patients treated with higher targets, which is a clinically meaningful harm that would have remained hidden by investigating only aggregate study-level associations.

This finding suggests that the rightward shift in autoregulatory curves may be offset by the adverse consequences of excessive vasoconstriction, including myocardial ischemia, arrhythmias, and microcirculatory dysfunction, especially in patients with pre-existing cardiovascular disease [29-31].

The mechanism underlying this harm in hypertensive patients likely reflects the competing physiological effects of elevated perfusion pressure. While higher MAP theoretically improves organ blood flow in patients with impaired autoregulation, achieving these targets requires significant increases in vasopressor doses as with norepinephrine-equivalent doses ranging from 0.07 to 0.38 mcg/kg/min across studies, which exacerbate systemic and regional vasoconstriction. Hypertensive patients often have underlying coronary artery disease, left ventricular hypertrophy, diastolic dysfunction, and chronic kidney disease that may increase their vulnerability to vasopressor-induced complications [32-35]. The absolute risk increase of 7.8% suggests this represents a clinically significant safety signal that warrants immediate attention in clinical practice and guideline development.

Third, the failure of study-level meta-regression to detect any significant effect modifiers, despite testing six biologically plausible covariates, illustrates the severe limitations of ecological analyses in meta-regression. With only six studies, our meta-regressions fell well below the recommended minimum of ten studies per covariate, resulting in wide 95% CIs and minimal statistical power. The high R^2 value for baseline lactate estimated at 88.2% likely represents overfitting rather than true biological relationship. This methodological limitation extends beyond our specific analysis to the broader meta-analytic literature, where underpowered meta-regressions frequently generate spurious associations that mislead interpretation.

Our analysis of secondary outcomes provides additional clinically relevant insights. The significant increases in vasopressor duration and fluid volume with higher MAP targets, which survived multiple testing correction, confirm the expected physiological consequences of pursuing elevated pressure goals but translate to increased ICU resource utilization without corresponding mortality benefit. The absence of significant differences in renal outcomes we found in AKI, RRT, cardiovascular complications for both of arrhythmias, myocardial infarction, and ischemic events in the overall population masks the risk for these complications to be concentrated in specific subgroups, as suggested by SEPSISPAM's finding of significant interaction for RRT in hypertensive patients. The lack of differences in ICU and hospital length of stay further supports that higher MAP targets provide no meaningful clinical benefits to offset their physiological costs.

Our study has several important limitations that warrant careful consideration. First and most significantly, the small number of included studies in which they were six RCTs total, with only two providing extractable hypertension subgroup mortality data severely limited the statistical power of our meta-regression and introduced significant uncertainty around all effect estimates. Meta-regression are recommended to include at least ten studies per covariate to avoid spurious findings and overfitting; our analyses with four to six studies per covariate fall far short of this threshold and must be considered strictly exploratory and hypothesis-generating rather than definitive. The wide 95% CIs surrounding meta-regression coefficients reflect this limitation.

Second, the within-study hypertension subgroup analysis, while methodologically superior to ecological meta-regression, relied on only two trials contributing patient-level data based on Lamontagne et al. 2020 and Endo et al. 2025, with the Lamontagne trial contributing 85.5% of the weight. However, the Asfar et al. 2014 trial (SEPSISPAM) enrolled 340 hypertensive patients, extractable mortality data stratified by hypertension status were not available in published reports, limiting our ability to strengthen the pooled estimate. The moderate between-study heterogeneity in the hypertension subgroup suggests some variability in effect magnitude across trials, however the direction of harm remained consistent.

Third, significant heterogeneity existed across included trials in population characteristics, intervention protocols, and outcome definitions. The Maiwall et al. 2023 study enrolled only cirrhotic patients with different physiology and lower hypertension prevalence at 9.3%, while the Endo et al. 2025 trial focused on elderly Japanese patients with mean age 78 years with very high hypertension prevalence estimated at 53.1%. The definition of chronic hypertension varied across trials and was inconsistently reported, which could be possibly introducing misclassification bias. Achieved MAP separations ranged from 6.0 to 10.0 mmHg, and vasopressor doses varied significantly of 0.07 to 0.38 mcg/kg/min, introducing additional heterogeneity in treatment intensity that may have affected outcomes.

Fourth, risk of bias assessment revealed that five of six included studies raised some concerns, primarily related to inability to blind participants and physicians to MAP target allocation, an inherent limitation of hemodynamic intervention trials. While mortality represents an objective endpoint less susceptible to detection bias, the lack of blinding may have affected other management decisions and secondary outcomes. In addition to that, selective outcome reporting concerns arose in several trials that published only primary outcomes without detailed secondary outcome data.

Fifth, our analysis was limited to published aggregate data rather than individual patient data, preventing more detailed analyses that could account for time-varying covariates, competing risks, or effect modification by multiple interacting patient characteristics. Individual patient data meta-analysis would allow for better assessment of treatment-covariate interactions, adjustment for baseline imbalances, and standardization of outcome definitions across trials.

Our findings generate several important priorities for future studies and practice. Most important, an individual patient data meta-analysis including all available trials is needed to definitively characterize effect modification by chronic hypertension and other patient characteristics while controlling for confounding and accounting for time-varying exposures. Such an analysis should include the unreported hypertension subgroup data from SEPSISPAM and any other trials with stratified results, and strengthening the evidence base for harm in hypertensive patients. Collaboration with original trial investigators to obtain patient-level datasets would give the chance for more detailed and structured analyses including multivariable effect modification models, mediation analyses investigating mechanisms of harm, and identification of patient phenotypes most likely to benefit or be harmed by different MAP strategies.

Second, future RCTs should prospectively stratify randomization by hypertension status and power adequately for within-study subgroup analyses, rather than relying on post-hoc exploratory analyses. Given our finding that higher MAP targets may harm hypertensive patients, equipoise for such trials must be carefully evaluated, and safety monitoring should include pre-specified interim analyses of hypertension subgroups. Alternative trial designs such as adaptive platform trials could efficiently test personalized MAP targets based on autoregulatory monitoring, dynamic risk assessment, or other biomarkers while allowing early stopping for futility or harm in specific subgroups.

Third, mechanistic studies are needed to elucidate why hypertensive patients appear particularly vulnerable to harm from higher MAP targets. Further studies priorities include, assessing whether autoregulatory curve shifts in chronic hypertension are as pronounced as assumed or whether adaptation occurs with acute illness; characterizing vasopressor-induced myocardial stress in hypertensive versus non-hypertensive patients using cardiac biomarkers, echocardiography, and invasive hemodynamic monitoring; evaluating microcirculatory function using sublingual videomicroscopy or near-infrared spectroscopy to determine whether elevated MAP improves or worsens tissue perfusion; and evaluating whether specific hypertensive patient subgroups as those with controlled vs. uncontrolled baseline hypertension, with vs. without end-organ damage show differential responses.

Fourth, implementation science studies are needed and warranted to investigate the strategies for translating these findings into practice, including development of decision support tools that integrate hypertension status into MAP target recommendations, educational interventions to address misconceptions about MAP targets in hypertensive patients, and pragmatic trials testing implementation strategies in real-world settings. Quality improvement initiatives should audit MAP target practices and evaluate whether avoiding routine higher targets in hypertensive patients reduces mortality without increasing adverse events.

Finally, methodological studies are needed to develop better approaches for testing effect modification in meta-analysis. Our demonstration of ecological fallacy highlights the dangers of relying on study-level meta-regression, however within-study subgroup data remain inconsistently reported. Efforts to improve standardization of subgroup reporting in trial publications, development of individual patient data-sharing infrastructure, and creation of prospective meta-analysis consortia that agree on standardized subgroup definitions before trial completion would strengthen evidence synthesis. Statistical methodologists should continue developing techniques that appropriately account for the limitations of aggregate data while maximizing information extraction from available evidence.

5. CONCLUSIONS

Our meta-analysis of six RCTs including total 4,060 patients with septic shock demonstrates no mortality benefit from higher MAP targets (≥75 mmHg) compared to standard targets (60-70 mmHg) in unselected populations. We also found a significant ecological fallacy, in which study-level meta-regression found no effect modification by hypertension prevalence, however within-study patient-level subgroup analysis revealed that higher MAP targets significantly increased mortality specifically in hypertensive patients, representing an opposite direction of effect. This discordance exemplifies how aggregate study-level associations can contradict and mislead interpretation of individual-level treatment effects, illustrating why study-level meta-regression cannot reliably predict patient-level responses and why within-study subgroup analyses or individual patient data meta-analyses are essential for testing effect modification.

These findings challenge the prevailing clinical assumption that patients with chronic hypertension benefit from elevated perfusion pressures, suggesting instead that higher MAP targets may harm rather than benefit this population through excessive vasoconstriction and its cardiovascular consequences. We should exercise caution when considering higher MAP targets in hypertensive patients with septic shock, and current guideline recommendations may require reassessment in light of this safety signal. Future studies priorities include individual patient data meta-analyses to better characterize effect modification patterns, prospectively stratified trials adequately powered for hypertension subgroup analyses, and mechanistic studies elucidating why hypertensive patients appear especially vulnerable to harm from aggressive MAP targeting strategies.

REFERENCES

[1] La Via L, Sangiorgio G, Stefani S, et al, Maniaci A. The Global Burden of Sepsis and Septic Shock. *Epidemiologia*. Published online July 25, 2024. DOI:10.3390/epidemiologia5030032

[2] Via LL, Maniaci A, Lentini M, et al, A M. The Burden of Sepsis and Septic Shock in the Intensive Care Unit. *Journal of Clinical Medicine*. Published online September 23, 2025. DOI:10.3390/jcm14196691

[3] Singer M, Deutschman CS, Seymour CW, et al, Angus DC. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. Published online February 23, 2016. DOI:10.1001/jama.2016.0287

[4] Evans L, Rhodes A, Alhazzani W, et al, Levy M. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Intensive Care Medicine*. Published online October 02, 2021. DOI:10.1007/s00134-021-06506-y

[5] Post EH, Vincent JL. Renal autoregulation and blood pressure management in circulatory shock. *Critical Care (London, England)*. Published online March 22, 2018. DOI:10.1186/s13054-018-1962-8

[6] Leone M, Asfar P, Radermacher P, et al, Martin C. Optimizing mean arterial pressure in septic shock: a critical reappraisal of the literature. *Critical Care (London, England)*. Published online December 01, 2015. DOI:10.1186/s13054-015-0794-z

[7] Ono M, Arnaoutakis GJ, Fine DM, et al, Hogue CW. Blood Pressure Excursions Below the Cerebral Autoregulation Threshold During Cardiac Surgery are Associated With Acute Kidney Injury*. *Critical Care Medicine*. Published online February, 2013. DOI:10.1097/ccm.0b013e31826ab3a1

[8] Lamontagne F, Richards-Belle A, Thomas K, et al, for the 65 trial investigators. Effect of Reduced Exposure to Vasopressors on 90-Day Mortality in Older Critically Ill Patients With Vasodilatory Hypotension. *JAMA*. Published online March 10, 2020. DOI:10.1001/jama.2020.0930

[9] Mouncey PR, Richards-Belle A, Thomas K, et al, the 65 trial investigators. Reduced exposure to vasopressors through permissive hypotension to reduce mortality in critically ill people aged 65 and over: the 65 RCT. *Health Technology Assessment*. Published online February, 2021. DOI:10.3310/hta25140

[10] Yoshimoto H, Fukui S, Higashio K, et al, Yamakawa K. Optimal target blood pressure in critically ill adult patients with vasodilatory shock: A systematic review and meta-analysis. *Frontiers in Physiology*. Published online August 16, 2022. DOI:10.3389/fphys.2022.962670

[11] M G, CA H, Aghlmandi S, et al, da Costa BR. Most published meta-regression analyses based on aggregate data suffer from methodological pitfalls: a meta-epidemiological study. *BMC Medical Research Methodology*. Published online June 15, 2021. DOI:10.1186/s12874-021-01310-0

[12] Marlin N, Godolphin PJ, Hooper RL, et al, E R. Nonlinear effects and effect modification at the participant-level in IPD meta-analysis part 2: methodological guidance is available. *Journal of Clinical Epidemiology*. Published online July, 2023. DOI:10.1016/j.jclinepi.2023.04.014

[13] Yoshida K, Solomon DH, Kim SC. Active-comparator design and new-user design in observational studies. *Nature Reviews Rheumatology*. Published online March 24, 2015. DOI:10.1038/nrrheum.2015.30

[14] Liu P, Ioannidis JPA, Ross JS, et al, Wallach JD. Age-treatment subgroup analyses in Cochrane intervention reviews: a meta-epidemiological study. *BMC Medicine*. Published online October 21, 2019. DOI:10.1186/s12916-019-1420-8

[15] Kovalchik SA. Aggregate-data estimation of an individual patient data linear random effects meta-analysis with a patient covariate-treatment interaction term. *Biostatistics*. Published online September 20, 2012. DOI:10.1093/biostatistics/kxs035

[16] Dekkers OM. Meta-analysis: Key features, potentials and misunderstandings. *Research and Practice in Thrombosis and Haemostasis*. Published online October, 2018. DOI:10.1002/rth2.12153

[17] Meddis A, Latouche A, Zhou B, et al, Fine J. Meta-analysis of clinical trials with competing time-to-event endpoints. *Biometrical Journal*. Published online December 09, 2019. DOI:10.1002/bimj.201900103

[18] Page MJ, McKenzie JE, Bossuyt PM, et al, Moher D. Declaración PRISMA 2020: una guía actualizada para la publicación de revisiones sistemáticas. *Revista Española De Cardiología (English Edition)*. Published online September, 2021. DOI:10.1016/j.rec.2021.07.010

[19] Endo A, Yamakawa K, Tagami T, et al, the OPTPRESS trial investigators. Efficacy of targeting high mean arterial pressure for older patients with septic shock (OPTPRESS): a multicentre, pragmatic, open-label, randomised controlled trial. *Intensive Care Medicine*. Published online May 13, 2025. DOI:10.1007/s00134-025-07910-4

[20] Panwar R, McNicholas B, Nita C, et al, Ferguson L. A pilot multicenter randomized controlled trial on individualized blood pressure targets versus standard care among critically ill patients with shock. *Journal of Intensive Care*. Published online May 27, 2025. DOI:10.1186/s40560-025-00798-8

[21] Maiwall R, Rao Pasupuleti SS, Hidam AK, et al, Sarin SK. A randomised-controlled trial (TARGET-C) of high vs. low target mean arterial pressure in patients with cirrhosis and septic shock. *Journal of Hepatology*. Published online August, 2023. DOI:10.1016/j.jhep.2023.04.006

[22] Lamontagne F, Meade MO, et al, Koo KKY. Higher versus lower blood pressure targets for vasopressor therapy in shock: a multicentre pilot randomized controlled trial. *Intensive Care Medicine*. Published online February 18, 2016. DOI:10.1007/s00134-016-4237-3

[23] Asfar P, Meziani F, Hamel JF, et al, Radermacher P. High versus Low Blood-Pressure Target in Patients with Septic Shock. *New England Journal of Medicine*. Published online April 24, 2014. DOI:10.1056/nejmoa1312173

[24] Ramasco F, Nieves-Alonso J, E G, et al, R M. Challenges in Septic Shock: From New Hemodynamics to Blood Purification Therapies. *Journal of Personalized Medicine*. Published online February 03, 2024. DOI:10.3390/jpm14020176

[25] Othman MI, Mustafa EM, Abdelwahab AE, et al, Nashwan AJ. Optimizing Mean Arterial Pressure Targets for Septic Shock Patients With Chronic Hypertension: A Narrative Review. *Health Science Reports*. Published online May 19, 2025. DOI:10.1002/hsr2.70696

[26] Lat I, Coopersmith CM, De Backer D. The Surviving Sepsis Campaign: Fluid Resuscitation and Vasopressor Therapy Research Priorities in Adult Patients. *Critical Care Medicine*. Published online February 27, 2021. DOI:10.1097/ccm.0000000000004864

[27] Kattan E, G H, G O, et al, The ANDROMEDA-SHOCK Study Investigators and the Latin America Intensive Care Network (LIVEN). A lactate-targeted resuscitation strategy may be associated with higher mortality in patients with septic shock and normal capillary refill time: a post hoc analysis of the ANDROMEDA-SHOCK study. *Annals of Intensive Care*. Published online August 26, 2020. DOI:10.1186/s13613-020-00732-1

[28] Kamath S, Hammad Altaq H, Abdo T. Management of Sepsis and Septic Shock: What Have We Learned in the Last Two Decades?. *Microorganisms*. Published online September 04, 2023. DOI:10.3390/microorganisms11092231

[29] Duncker DJ, Koller A, Merkus D, et al, Canty JM Jr. Regulation of Coronary Blood Flow in Health and Ischemic Heart Disease. *Progress in Cardiovascular Diseases*. Published online March 02, 2015. DOI:10.1016/j.pcad.2014.12.002

[30] Wj R. The sympathetic nervous system and ischaemic heart disease. *European Heart Journal*. Published online June 19, 1998. URL:https://pubmed.ncbi.nlm.nih.gov/9651738

[31] Ruland S, Aiyagari V. Cerebral Autoregulation and Blood Pressure Lowering. *Hypertension*. Published online March 12, 2007. DOI:10.1161/hypertensionaha.107.087502

[32] Panwar R, McNicholas B, Teixeira JP, et al, Kansal A. Renal perfusion pressure: role and implications in critical illness. *Annals of Intensive Care*. Published online 2025. DOI:10.1186/s13613-025-01535-y

[33] Skrifvars MB, Ameloot K, A Å. Blood pressure targets and management during post-cardiac arrest care. *Resuscitation*. Published online August, 2023. DOI:10.1016/j.resuscitation.2023.109886

[34] Kato R, Pinsky MR. Personalizing blood pressure management in septic shock. *Annals of Intensive Care*. Published online November 16, 2015. DOI:10.1186/s13613-015-0085-5

[35] Jentzer JC, Coons JC, Link CB, et al, Schmidhofer M. Pharmacotherapy Update on the Use of Vasopressors and Inotropes in the Intensive Care Unit. *Journal of Cardiovascular Pharmacology and Therapeutics*. Published online November 28, 2014. DOI:10.1177/1074248414559838

APPENDICES

Supplementary Table 1: Risk of Bias Assessment.

Study	D1: Randomization	D2: Deviations	D3: Missing Data	D4: Measurement	D5: Selective Reporting	Overall
Endo 2025	Low	**Some concerns**	Low	Low	Low	**Some concerns**
Panwar 2025	Low	Low	Low	Low	**Some concerns**	**Some concerns**
Maiwall 2023	**Some concerns**	**Some concerns**	Low	Low	Low	**Some concerns**
Lamontagne 2020	Low	**Some concerns**	Low	Low	Low	**Some concerns**
Lamontagne 2016	Low	Low	Low	Low	**Some concerns**	**Some concerns**
Asfar 2014	Low	Low	Low	Low	Low	**Low risk**

ADDITIONAL INFORMATION

Author Contributions

Mohammed Alshahrani: Formal Analysis, Conceptualization, Resources, Visualization, Project Administration, Supervision, Data Curation, Investigation, Validation, Methodology, Writing - Review & Editing, Writing - Original Draft. Yazan Alalwani: Conceptualization, Formal Analysis, Resources, Visualization, Data Curation, Investigation, Methodology, Writing - Review & Editing, Writing - Original Draft. Rayhanah Saad A. Binobaid: Writing - Original Draft, Writing - Review & Editing, Data Curation, Investigation, Validation, Methodology, Conceptualization, Formal Analysis, Visualization. Osama Hamdi Asiri: Conceptualization, Formal Analysis, Resources, Visualization, Supervision, Data Curation, Investigation, Writing - Review & Editing, Writing - Original Draft. Abdulrahman Emad Mashat: Writing - Original Draft, Writing - Review & Editing, Data Curation, Validation, Resources, Investigation. Sultan Hassan Qurban: Writing - Original Draft, Writing - Review & Editing, Resources, Visualization, Validation, Data Curation. Saja Abdullah Alharbi: Conceptualization, Resources, Visualization, Writing - Review & Editing, Writing - Original Draft, Validation. Layan Khalid Alsaif: Resources, Conceptualization, Investigation, Writing - Review & Editing, Writing - Original Draft. Osama Saeed Alghamdi: Writing - Original Draft, Writing - Review & Editing, Investigation, Validation, Methodology. Maryah Mohammed Al Shehab: Writing - Review & Editing, Visualization, Resources, Validation. Norah Hamad Alabdullatif: Writing - Original Draft, Writing - Review & Editing, Validation, Conceptualization, Resources. Tasniem Elsadig Zubair Mohammed: Writing - Original Draft, Writing - Review & Editing, Validation, Data Curation. Abdulrahman Mohammed Alrasheed: Writing - Original Draft, Writing - Review & Editing, Investigation, Validation. Ahmed Y. Azzam: Writing - Original Draft, Writing - Review & Editing, Project Administration, Visualization, Resources, Formal Analysis, Software, Conceptualization, Methodology, Validation, Investigation, Data Curation, Supervision

Human Ethics

No IRB review was required for this study.

Animal Ethics

This study did not involve animal subjects or tissue.

Conflicts of Interest

No conflicts of interest to disclose.

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