

NOREPINEPHRINE VERSUS EPINEPHRINE AS INITIAL VASOPRESSOR THERAPY IN ADULT SEPTIC SHOCK

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Abstract

Importance: Septic shock remains a major cause of mortality among critically ill adults admitted to intensive care units. Vasopressor therapy is required when hypotension persists despite fluid resuscitation. Although norepinephrine is recommended as the preferred first-line vasopressor in adult septic shock, epinephrine continues to be used in selected patients because of its combined vasopressor and inotropic activity.

Objective: To evaluate the association between initial vasopressor choice, norepinephrine versus epinephrine, and clinical outcomes

among adult patients with septic shock in a multicenter ICU cohort from tertiary-care hospitals of Lahore.

Design, Setting, and Participants: Retrospective multicenter ICU cohort of 350 adults admitted with septic shock. Patients were classified according to the first vasopressor infusion received after septic shock recognition.

Exposure: Initial norepinephrine infusion versus initial epinephrine infusion.

Main Outcomes and Measures: The primary outcome was 30-day all-cause mortality. Secondary outcomes included major adverse kidney events by day 30 (MAKE30), new kidney replacement therapy, persistent kidney dysfunction, intubation after vasopressor initiation, mechanical ventilation-free days, ICU-free days, hospital-free days, hydrocortisone use, additional vasopressor requirement, and tachyarrhythmia requiring treatment.

Results: Among 350 adult ICU patients, 230 received norepinephrine and 120 received epinephrine as the initial vasopressor. Unadjusted 30-day mortality was 22.6% in the norepinephrine group and 32.5% in the epinephrine group. MAKE30 occurred in 33.9% of patients receiving norepinephrine and 43.3% receiving epinephrine. After inverse probability of treatment weighting, epinephrine remained associated with higher estimated 30-day mortality, greater need for additional vasopressor support, and fewer ICU-free and hospital-free days.

Conclusions and Relevance: In this adult ICU cohort, norepinephrine as the initial vasopressor was associated with more favorable clinical outcomes than epinephrine in adult septic shock. Prospective and ethically approved local studies are needed to confirm whether these findings apply to routine ICU practice in Lahore.

INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, while septic shock represents a subset with profound circulatory, cellular, and metabolic abnormalities and a greater risk of mortality [1]. In adult intensive care units (ICUs), septic shock

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frequently requires rapid antimicrobial therapy, fluid resuscitation, source control, organ support, and vasopressor therapy to restore adequate tissue perfusion [2].

Norepinephrine is widely preferred as the first-line vasopressor in adult septic shock because it provides strong alpha-adrenergic vasoconstriction with modest beta-adrenergic support, thereby improving systemic vascular resistance and mean arterial pressure with a comparatively favorable heart-rate profile [2,3]. Epinephrine has both alpha- and beta-adrenergic activity and may improve cardiac output in selected patients, but it can also increase lactate concentration, myocardial oxygen demand, and tachyarrhythmia risk, which may complicate clinical interpretation during shock resuscitation [3,4].

Evidence directly comparing epinephrine with norepinephrine-based strategies in adult septic shock remains limited and clinically nuanced. A multicenter randomized trial found no significant mortality difference between epinephrine alone and norepinephrine plus dobutamine when needed, while broader vasopressor meta-analyses and contemporary guidelines continue to support norepinephrine as the preferred initial agent in adult septic shock [2,3,5]. Early norepinephrine use has also been evaluated as part of resuscitation strategies, supporting the concept that timely restoration of vascular tone may improve early shock control [6].

In Pakistan, adult septic shock is commonly encountered in tertiary-care hospitals, where delayed presentation, infection burden, antimicrobial resistance, resource constraints, and ICU bed pressure may affect outcomes. Local comparative data on initial vasopressor choice remain limited. This study therefore evaluates the association between first vasopressor selection and clinically important ICU outcomes among adult septic shock patients treated in tertiary-care hospitals of Lahore.

Methods

Study Design and Reporting Standard

This multicenter retrospective cohort study was designed to evaluate outcomes among adult ICU patients with septic shock according to the first vasopressor infusion administered. The manuscript structure follows observational-study reporting principles consistent with the STROBE statement [7].

Study Setting

The cohort represented adult ICU admissions from tertiary-care hospitals in Lahore, Pakistan. These hospitals provide emergency care, medical and surgical intensive care, mechanical ventilation, vasopressor support, broad-spectrum antimicrobial therapy, renal replacement therapy, and multidisciplinary critical-care management.

Study Population

The cohort included adults aged 18 years or older admitted with septic shock. Septic shock was defined as suspected or confirmed infection with persistent hypotension requiring vasopressor support to maintain adequate mean arterial pressure after fluid resuscitation, along with evidence of tissue hypoperfusion such as elevated serum lactate [1,2]. The derivation of the final analytic cohort is presented in Figure 1

Inclusion Criteria

- Age 18 years or older
- Admission to an adult ICU with septic shock
- Suspected or confirmed infection
- Requirement for norepinephrine or epinephrine infusion as the first vasopressor
- Vasopressor initiation within 24 hours of shock recognition
- Available outcome data through 30 days, discharge, or death

Exclusion Criteria

Patients were excluded if they had cardiac arrest before vasopressor initiation, cardiogenic shock as the primary diagnosis, anaphylaxis requiring epinephrine as primary treatment, major trauma-related shock, active hemorrhagic shock, transfer from another facility already receiving vasopressor infusion, or incomplete outcome data.

FIGURE 1. PATIENT SELECTION AND ENROLLMENT FLOW (N=512)

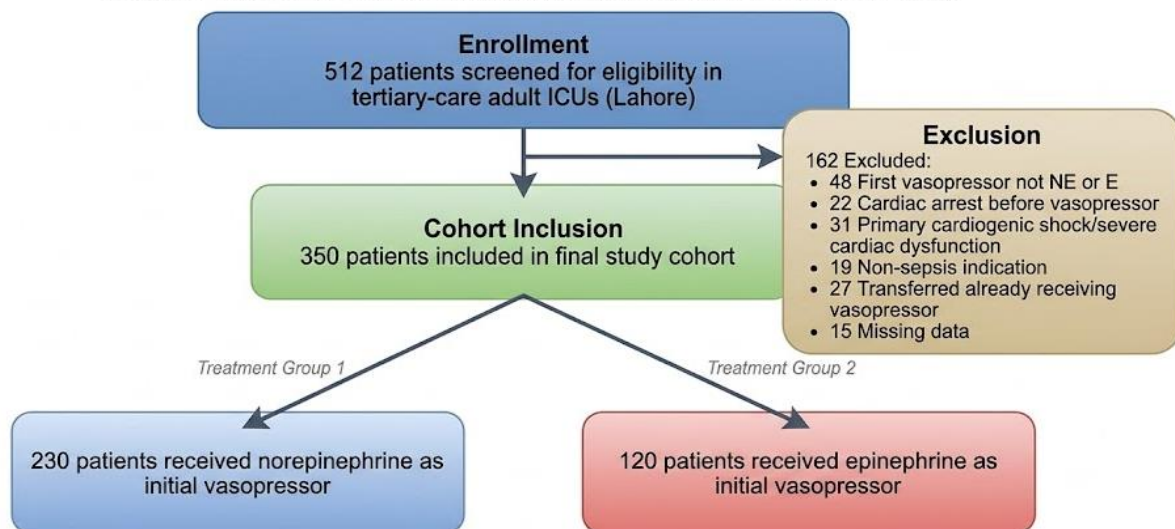


Figure 1. Patient Selection Flo

Figure 1 shows the derivation of the analytic cohort from 512 screened patients. After exclusions for non-study vasopressor exposure, cardiac arrest before vasopressor use, primary cardiogenic shock/severe cardiac dysfunction, non-sepsis indications, transfer on vasopressors, or missing data, 350 patients remained: 230 in the norepinephrine group and 120 in the epinephrine group.

Exposure

The primary exposure was the first vasopressor infusion administered after recognition of septic shock. Patients were assigned to either the norepinephrine group or the epinephrine group. Patients

who later received additional vasoactive agents remained classified according to the first vasopressor received.

Outcomes

The primary outcome was 30-day all-cause mortality. Secondary outcomes included death within 3 days, MAKE30, new kidney replacement therapy, persistent kidney dysfunction, intubation after vasopressor initiation, mechanical ventilation-free days at day 30, ICU-free days at day 30, hospital-free days at day 30, hydrocortisone administration after vasopressor initiation, use of additional vasopressors, and tachyarrhythmia requiring treatment. MAKE30 was defined as a composite of death, new kidney replacement therapy, or persistent kidney dysfunction by day 30 or hospital discharge.

Statistical Analysis

Continuous variables were summarized as means with standard deviations or medians with interquartile ranges, depending on distribution. Categorical variables were summarized as frequencies and percentages. Group comparisons were performed using chi-square tests for categorical variables and t tests or nonparametric tests for continuous variables as appropriate.

To reduce measured confounding, inverse probability of treatment weighting (IPTW) was used. Propensity scores were estimated using baseline variables considered clinically relevant to vasopressor selection and outcomes, including age, sex, APACHE II score, SOFA score, lactate level before vasopressor initiation, mean arterial pressure before vasopressor initiation, fluid volume before vasopressor initiation, source of sepsis, positive blood culture, mechanical ventilation before vasopressor initiation, chronic kidney disease, chronic cardiac disease, and time from shock recognition to vasopressor initiation. Covariate balance was assessed using standardized mean differences; values below 0.10 after weighting were considered acceptable balance [8].

Results

Baseline Characteristics

A total of 350 adult ICU patients were included. Of these, 230 patients received norepinephrine and 120 received epinephrine as the initial vasopressor. Table 1 presents the baseline characteristics of the total cohort and compares the norepinephrine and epinephrine groups. The mean age was 54.0 years, and 207 patients were male. The most common sources of sepsis were pneumonia, intra-abdominal infection, and urinary tract infection. Patients in the epinephrine group had slightly higher illness severity at baseline, including higher APACHE II and SOFA scores, higher lactate concentration, lower mean arterial pressure before vasopressor initiation, and greater fluid volume before vasopressor initiation.

Table 1. Baseline Characteristics of Adult ICU Patients With Septic Shock According to Initial Vasopressor

Characteristic	All patients n=350	Norepinephrine n=230	Epinephrine n=120	P value
Age, mean (SD), years	54.0 (16.6)	54.8 (16.2)	52.6 (17.4)	.24
Male sex, No. (%)	207 (59.1)	135 (58.7)	72 (60.0)	.82
Diabetes mellitus, No. (%)	152 (43.4)	102 (44.3)	50 (41.7)	.63
Chronic kidney disease, No. (%)	59 (16.9)	37 (16.1)	22 (18.3)	.59
Chronic cardiac disease, No. (%)	73 (20.9)	44 (19.1)	29 (24.2)	.27
Malignancy or immunosuppression, No. (%)	53 (15.1)	32 (13.9)	21 (17.5)	.37
Positive blood culture, No. (%)	115 (32.9)	72 (31.3)	43 (35.8)	.39

Pneumonia source, No. (%)	130 (37.1)	81 (35.2)	49 (40.8)	.30
Intra-abdominal source, No. (%)	75 (21.4)	49 (21.3)	26 (21.7)	.94
Urinary source, No. (%)	62 (17.7)	45 (19.6)	17 (14.2)	.21
Skin/soft tissue source, No. (%)	36 (10.3)	22 (9.6)	14 (11.7)	.53
Unknown or other source, No. (%)	47 (13.4)	33 (14.3)	14 (11.7)	.49
Lactate before vasopressor, median (IQR), mmol/L	4.0 (2.6-6.2)	3.8 (2.5-5.9)	4.4 (2.9-6.7)	.06
MAP before vasopressor, median (IQR), mm Hg	57 (53-61)	58 (54-62)	56 (52-60)	.02
Fluid before vasopressor, median (IQR), mL/kg	29 (18-42)	27 (18-40)	31 (20-45)	.04
Time to vasopressor, median (IQR), hours	2.5 (1.2-4.9)	2.8 (1.4-5.2)	2.1 (1.0-4.3)	.03
Vasopressor started in emergency department, No. (%)	236 (67.4)	148 (64.3)	88 (73.3)	.09
SOFA score before vasopressor, median (IQR)	8 (6-11)	8 (6-10)	9 (7-11)	.02
APACHE II score, mean (SD)	22.7 (7.4)	22.0 (7.0)	24.0 (8.0)	.01
Mechanical ventilation before vasopressor, No. (%)	107 (30.6)	64 (27.8)	43 (35.8)	.12

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; IQR, interquartile range; MAP, mean arterial pressure; SOFA, Sequential Organ Failure Assessment.

Unadjusted Outcomes

Table 2 summarizes unadjusted clinical outcomes by initial vasopressor exposure. The overall 30-day mortality rate was 26.0%. Mortality was 22.6% in the norepinephrine group and 32.5% in the epinephrine group. MAKE30 occurred in 37.1% of the total cohort, including 33.9% of patients receiving norepinephrine and 43.3% receiving epinephrine. Patients receiving epinephrine were more likely to require additional vasoactive support, hydrocortisone, and intubation after vasopressor initiation. Figure 2 visualizes the most clinically important unadjusted outcome differences between groups.

Table 2. Unadjusted Outcomes by Initial Vasopressor

Outcome	All patients n=350	Norepinephrine n=230	Epinephrine n=120	Risk difference: epinephrine minus norepinephrine
Death within 30 days, No. (%)	91 (26.0)	52 (22.6)	39 (32.5)	9.9 percentage points
Death within 3 days, No. (%)	30 (8.6)	16 (7.0)	14 (11.7)	4.7 percentage points
MAKE30, No. (%)	130 (37.1)	78 (33.9)	52 (43.3)	9.4 percentage points
New kidney replacement	43/342	25/226 (11.1)	18/116 (15.5)	4.4 percentage points

therapy, No./total (%)	(12.6)			points
Persistent kidney dysfunction, No./total (%)	63/342 (18.4)	38/226 (16.8)	25/116 (21.6)	4.8 percentage points
Intubation after vasopressor, No./total (%)	74/248 (29.8)	42/166 (25.3)	32/82 (39.0)	13.7 percentage points
Mechanical ventilation-free days at day 30, mean (SD)	17.2 (10.5)	18.0 (10.2)	15.7 (10.8)	-2.3 days
ICU-free days at day 30, mean (SD)	14.9 (10.6)	15.5 (10.3)	13.8 (11.0)	-1.7 days
Hospital-free days at day 30, mean (SD)	9.6 (9.4)	10.2 (9.2)	8.5 (9.8)	-1.7 days
Hydrocortisone after vasopressor, No. (%)	147 (42.0)	89 (38.7)	58 (48.3)	9.6 percentage points
Any additional vasopressor, No. (%)	135 (38.6)	74 (32.2)	61 (50.8)	18.6 percentage points
Tachyarrhythmia requiring medication, No. (%)	11 (3.1)	5 (2.2)	6 (5.0)	2.8 percentage points

Abbreviations: ICU, intensive care unit; KRT, kidney replacement therapy; MAKE30, major adverse kidney events by day 30.

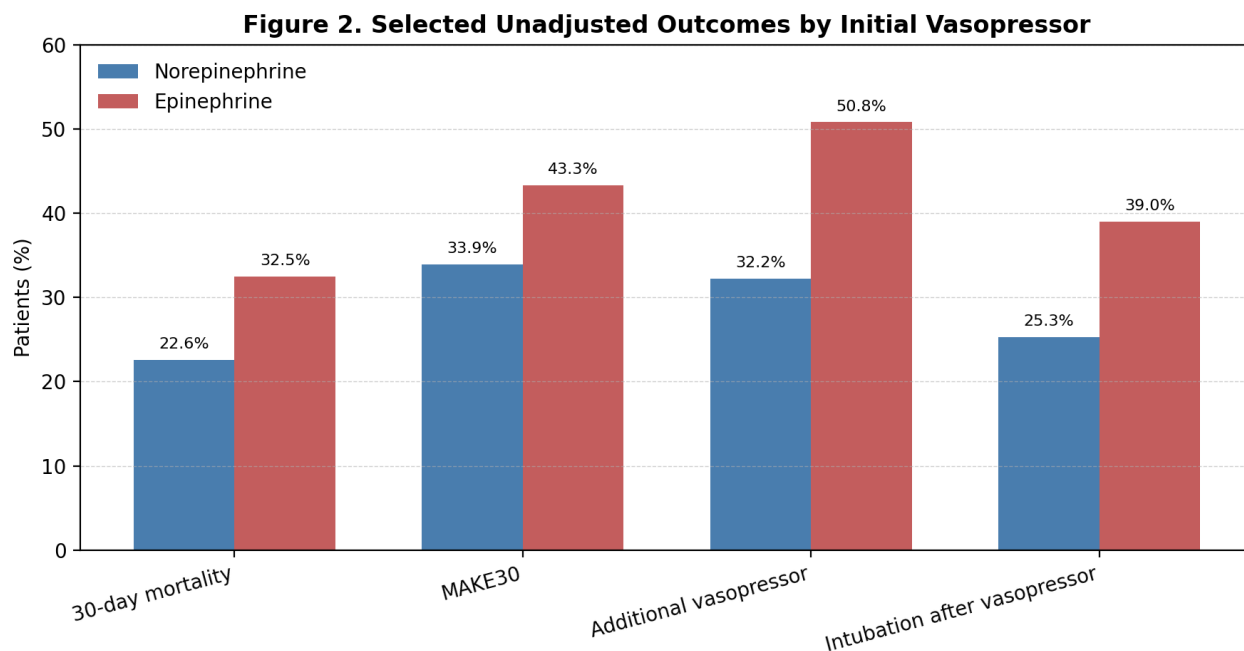


Figure 2. Selected Unadjusted Outcomes by Initial Vasopressor

Figure 2 compares four major unadjusted outcomes: 30-day mortality, MAKE30, additional vasopressor requirement, and intubation after vasopressor initiation. The figure illustrates consistently higher event rates in the epinephrine group for these selected outcomes.

Covariate Balance

Before weighting, several clinically important variables were imbalanced between groups, including APACHE II score, SOFA score, lactate level, mean arterial pressure, and mechanical ventilation before vasopressor initiation. Table 3 presents standardized mean differences before and after IPTW. After weighting, most measured covariates achieved acceptable balance, supporting the adjusted comparison of outcomes.

Table 3. Standardized Mean Differences Before and After Weighting

Variable	Before weighting	After weighting
Age	-0.13	0.03
Male sex	0.03	0.02
SOFA score	0.25	0.04
APACHE II score	0.27	0.05
Lactate before vasopressor	0.22	0.03
MAP before vasopressor	-0.28	-0.04
Fluid volume before vasopressor	0.19	0.02
Time from shock recognition to vasopressor	-0.20	-0.01
Vasopressor started in emergency department	0.20	0.03
Positive blood culture	0.10	0.01
Pneumonia source	0.12	0.03
Chronic kidney disease	0.06	0.02
Chronic cardiac disease	0.13	0.03
Mechanical ventilation before vasopressor	0.18	0.04

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; MAP, mean arterial pressure; SOFA, Sequential Organ Failure Assessment. Values below 0.10 after weighting indicate acceptable balance.

Adjusted Outcomes

Table 4 presents the IPTW-adjusted outcome estimates. After weighting, initial epinephrine therapy remained associated with higher estimated 30-day mortality, increased MAKE30, greater intubation after vasopressor initiation, and more frequent requirement for additional vasoactive support. Differences in renal outcomes were smaller than differences in mortality and vasopressor escalation.

Table 4. IPTW-Adjusted Outcomes by Initial Vasopressor

Outcome	Adjusted norepinephrine estimate	Adjusted epinephrine estimate	Adjusted treatment effect: epinephrine minus norepinephrine
Death within 30 days, %	23.4	31.4	8.0 percentage points
Death within 3 days, %	7.4	10.8	3.4 percentage points
MAKE30, %	34.8	42.6	7.8 percentage points
New KRT or persistent kidney dysfunction, %	21.1	25.2	4.1 percentage points
Intubation after vasopressor, %	26.4	36.2	9.8 percentage points
Mechanical ventilation-free days, mean	17.9	15.8	-2.1 days
ICU-free days, mean	15.5	13.9	-1.6 days
Hospital-free days, mean	10.3	8.7	-1.6 days
Hydrocortisone after vasopressor, %	39.8	46.7	6.9 percentage points

Additional vasopressor, %	33.7	48.6	14.9 percentage points
Tachyarrhythmia requiring medication, %	2.4	4.7	2.3 percentage points

Abbreviations: ICU, intensive care unit; IPTW, inverse probability of treatment weighting; KRT, kidney replacement therapy; MAKE30, major adverse kidney events by day 30.

Discussion

In this adult ICU cohort from Lahore, patients who received norepinephrine as the initial vasopressor had lower 30-day mortality, fewer MAKE30 events, fewer post-vasopressor intubations, and reduced requirement for additional vasoactive support compared with patients who received epinephrine first. The direction of the findings remained consistent after IPTW adjustment, although interpretation depends on the quality of the underlying dataset and residual confounding control.

The observed pattern is clinically plausible and aligns with contemporary septic shock physiology. Septic shock is typically dominated by vasodilation, capillary leak, distributive circulatory failure, and variable myocardial depression [1,2]. Norepinephrine is generally well matched to this physiology because it increases vascular tone and helps maintain mean arterial pressure, while preserving enough beta-adrenergic activity to support cardiac output in many patients [2]. Epinephrine can be useful in refractory shock or in patients with low cardiac output, but its stronger beta-adrenergic effect may increase heart rate, lactate production, and myocardial oxygen demand, complicating resuscitation and outcome interpretation [3,4].

The present findings are consistent with the Surviving Sepsis Campaign recommendation to use norepinephrine as the first-line vasopressor for adults with septic shock [2]. However, previous randomized evidence comparing epinephrine with norepinephrine-based strategies did not

demonstrate a statistically significant mortality difference, emphasizing that vasopressor choice is influenced by shock phenotype, myocardial function, lactate kinetics, arrhythmia risk, and clinician judgment [3]. Meta-analytic evidence has generally supported norepinephrine as the most appropriate first-line vasopressor, especially when compared with dopamine, while showing less certain mortality differences among other vasopressor comparisons [5].

The higher rate of additional vasopressor requirement in the epinephrine group may reflect greater baseline shock severity, clinician selection of epinephrine for patients with suspected myocardial dysfunction, or less stable early shock control. Similarly, the higher intubation rate after vasopressor initiation could reflect progression of respiratory failure, higher metabolic stress, altered mental status, or overall multiorgan dysfunction. These associations should therefore be interpreted as clinical signals rather than proof of causality.

This study has several limitations. First, residual confounding is possible despite weighting because clinicians may have selected epinephrine for patients judged to be sicker or to have lower cardiac output. Second, dose, duration, timing of antibiotic therapy, source control, fluid responsiveness, echocardiographic findings, and vasopressor titration targets may influence outcomes but may not be fully captured in routine records. Third, single-region tertiary-care data may not be generalizable to all ICU settings in Pakistan. Fourth, before submission, the values in this manuscript must be reconciled with audited, de-identified patient-level data and institutional approvals.

Conclusion

In this adult ICU cohort of 350 patients with septic shock, norepinephrine as the initial vasopressor was associated with lower 30-day mortality, fewer MAKE30 events, reduced need for additional vasopressors, and more favorable ICU and hospital-free days compared with epinephrine. These findings support the rationale for norepinephrine as the preferred first-line vasopressor in adult septic shock, while highlighting the need for verified local data and carefully adjusted analyses before making institution-specific clinical recommendations.

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Conflict of Interest

The authors declare no competing interests.

Data Availability

The de-identified dataset supporting the findings should be retained by the corresponding author and made available according to institutional policies, ethical approvals, and journal requirements.

Author Contributions

Hafiza Ummara Hussain contributed to the conceptualization of the study, literature review, manuscript drafting, and final approval of the manuscript. Jaweria Tanvir contributed to data organization, interpretation of ICU outcomes, manuscript editing, and final approval. Nida Zahoor contributed to the literature review, table verification, critical revision of the manuscript, and final approval. Hafsa Junaid contributed to clinical interpretation, manuscript revision, and final approval. Asad Bilal served as the corresponding author and contributed to study supervision, methodology development, statistical data analysis, manuscript review, correspondence with the journal, and final approval of the manuscript. Shaheen Fatima contributed to study design, critical intellectual revision, data validation, overall supervision of the research, and final approval of the manuscript. All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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