Journal of Translational Critical Care Medicine **2026** vol. 8(2) | e00004
DOI: 10.14218/JTCCM.2026.00004

Original Article

Nonlinear Dose–response Relationship between Norepinephrine and Microcirculatory Perfusion: Identifying the Tipping Point in Septic Shock

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Received: January 31, 2026 | **Revised:** February 27, 2026 | **Accepted:** March 12, 2026 | **Published online:** June 29, 2026

Abstract

Background and objectives: While norepinephrine (NE) is the cornerstone of septic shock resuscitation, "macrocirculation–microcirculation decoupling" at high doses remains a critical clinical challenge. This study aimed to explore the quantitative tipping point where the NE dose shifts from a life-saving vasopressor to a microcirculatory toxin in septic intensive care unit patients.

Methods: In this prospective observational study (January–September 2025), we used handheld vital microscopy to monitor sublingual microcirculation (microvascular flow index [MFI], total vessel density, perfused vessel density, proportion of perfused vessels [PPV], and heterogeneity index [HI]) in adult septic patients within 24 hours of admission and on Day 3. Beyond standard linear analysis, generalized additive models were employed to identify the dose–response thresholds associated with microcirculatory deterioration, adjusted for Acute Physiology and Chronic Health Evaluation II, interleukin-6, and systemic hemodynamics.

Results: Of 144 screened patients, 66 were analyzed. The NE dose showed strong linear correlations with lactate ($r = 0.583$, $P < 0.001$) and HI ($r = 0.444$, $P < 0.001$), and negative correlations with MFI ($r = -0.492$, $P < 0.001$). Crucially, generalized additive models analysis revealed a significant nonlinear "cliff effect": when the NE dose exceeds the 0.71–0.80 μg/kg/min threshold (PPV: 0.71 μg/kg/min, HI: 0.72 μg/kg/min, MFI: 0.80 μg/kg/min), microcirculatory perfusion parameters deteriorate abruptly (all $P < 0.05$). Multivariable Cox regression identified an NE dose of 0.80 μg/kg/min as an independent predictor of increased mortality (hazard ratio = 1.32, 95% confidence interval: 1.28–3.10, $P = 0.039$).

Conclusions: In patients with septic shock, higher NE doses were associated with impaired microcirculatory perfusion and worse outcomes. These findings support individualized vasopressor titration and suggest that microcirculatory monitoring may help identify patients at risk of vasopressor-associated microvascular dysfunction.

Introduction

Sepsis is a growing global burden, with accumulating evidence indicating increased long-term morbidity and mortality in both developed and developing countries.[1,2] Sepsis is characterized by a dysregulated host response to infection, leading to life-threatening organ dysfunction. This dysregulated host response induced by systemic inflammation induces vasodilation, leading to a relative insufficiency of effective circulating blood volume. This results in microcirculatory disruption and inadequate organ perfusion.[3,4] Thus, microcirculatory dysfunction may play a pivotal role in the development of multiple organ failures in critically ill patients.[5] Therefore, the primary goal of hemodynamic resuscitation in such patients is to restore microcirculatory perfusion and tissue oxygenation, prevent organ hypoxia, and maintain organ function.

Keywords: Sepsis; Norepinephrine; Microcirculation; Dose-response relationship; Mortality; Intensive care units.

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How to cite this article: Dai Y, Zhu Y, Hu C, Chen H, Peng Z, Li Y. Nonlinear Dose–response Relationship between Norepinephrine and Microcirculatory Perfusion: Identifying the Tipping Point in Septic Shock. *J Transl Crit Care Med* 2026;8(2):e00004. doi: 10.14218/JTCCM.2026.00004.

Norepinephrine (NE), an endogenous catecholamine produced by postganglionic sympathetic nerves and the adrenal gland, is considered the first-line vasopressor for septic shock.[6–8] NE effectively increases vascular tone and contractility to enhance tissue perfusion,[9] and protects cardiac function in the early stage by improving myocardial contractility and diastolic arterial pressure to restore coronary perfusion.[10] Studies have shown that NE administration helps ameliorate microcirculatory dysfunction.[11,12] However, this effect is dose-dependent.[11] With increasing doses, NE may exacerbate microcirculatory impairment, reduce tissue perfusion, and induce organ dysfunction.[13,14] High-dose NE may even exert multiple adverse prognostic effects on macro- and microcirculation through immune, metabolic, and coagulation pathways.[15,16] This suggests that only an appropriate NE dose is associated with improved tissue perfusion and organ function.

Although macrocirculation serves as the cornerstone of microcirculatory resuscitation, focusing solely on macrocirculatory resuscitation targets while ignoring microcirculatory responses may lead to therapeutic deviations.[17] Effective resuscitation relies on the coherence between macrocirculation and microcirculation,[18–20] that is, restoring "macrocirculation–microcirculation coupling." The proportion of perfused vessels (PPV) of microcirculatory perfusion can serve as an early independent predictor of outcomes in patients with sepsis.[21] Monitoring microcirculation to verify macrocirculation–microcirculation coupling provides crucial evidence for guiding NE use during hemodynamic resuscitation.[22] Based on the principle of sidestream dark field (SDF) imaging,[23] handheld non-invasive sublingual microscopes can be used to analyze microcirculatory changes in septic patients by assessing red blood cell velocity and perfused capillary density.[24–28]

Therefore, this study aimed to investigate the relationship between different NE doses and microcirculation as well as prognosis in septic intensive care unit (ICU) patients. Furthermore, we explored the dose–response relationship between NE and microcirculation, providing a rational reference for the treatment of septic patients and future research.

Materials and methods

Study design

This was a prospective observational study conducted in a 58-bed closed ICU in a tertiary hospital. The study protocol was approved by the Ethics Committee of Zhongnan Hospital of Wuhan University (No. 2025096K). Patients diagnosed with sepsis in the ICU between January 1, 2025, and September 1, 2025, were enrolled. All procedures adhered to the Declaration of Helsinki (as revised in 2024). All enrolled patients or their legally authorized representatives provided written informed consent to participate in the study.

Study population

Inclusion criteria

Patients meeting the Sepsis 3.0 diagnostic criteria (confirmed or highly suspected infection with Δ sequential organ failure assessment (SOFA) ≥ 2); who received initial resuscitation within 24 hours of ICU admission; were aged ≥ 18 years; and patients who underwent tracheal intubation and mechanical ventilation.

Exclusion criteria

Pregnant patients or those with peripheral vascular disease; patients unable to undergo microcirculation assessment or obtain high-quality SDF images; patients who died within 24 hours of admission; and patients aged > 80 years.

Study methods and data collection

Microcirculation monitoring

After professional training in microcirculation assessment, the researchers used an SDF imaging device (Microsee V100 Sublingual Microcirculation Imaging System) to visualize the sublingual microcirculation. Following gentle wiping of oral secretions with gauze, the sublingual microcirculation probe was placed lightly under the tongue. For each patient, stable and clear microvascular images were acquired from 5 sites adjacent to the lingual frenulum for at least 20 seconds by adjusting light intensity and focal length. Image quality was evaluated according to the method described by Massey *et al*.,[29] and poor-quality images were excluded. Qualified images were analyzed using computer-aided software (AVA 3.0; MicroVision Medical; Amsterdam, the Netherlands) to assess microcirculatory parameters,[24] including the microvascular flow index (MFI), total vessel density (TVD), perfused vessel density (PVD), PPV, and heterogeneity index (HI). Descriptions and calculation methods for all parameters are presented in Supplementary Table 1. In addition, two researchers analyzed all parameters using software to identify small vessels (diameter < 20 μm) through manual verification,[30] as they are the primary sites of oxygen exchange.

Data collection

All the microcirculation parameters were collected when the enrolled septic patients had received adequate fluid resuscitation (30 mL/kg), with mean arterial pressure (MAP) ≥ 65 mmHg and no change in vasopressin usage within 2 hours. Two researchers simultaneously performed the assessments within 24 hours of ICU admission and on the third day. During microcirculation assessments, the following data were collected: demographic variables, hemodynamic parameters, laboratory values, vasopressor dose, sedative and analgesic medications, capillary refill time (CRT), and scoring systems, including SOFA score and acute physiology and chronic health evaluation (APACHE) II score as well as mottling score. After discharge, renal replacement therapy, length of ICU stay, and in-hospital mortality were also recorded.

Study outcomes

The primary outcome was 28-day mortality following enrollment. Secondary outcomes included 90-day mortality; mottling scores, lactate levels, and microcirculatory parameters, including MFI, PVD, TVD, PPV, HI, measured on Day 1 and Day 3, as well as their absolute changes between the two time points; NE dose on Day 1 and Day 3 along with the corresponding changes; and length of ICU stay.

Statistical analysis

Based on preliminary experiments and clinical practice, the correlation between NE dose and 28-day mortality was selected as the primary analytical variable.[31–33] The sample size was estimated using PASS 15.0 software for the log-rank test. With an effect size $f^2 = 0.15$, $\alpha = 0.05$, and power $(1-\beta) = 0.80$, the minimum sample size was calculated as 60. Considering a 10% attrition rate, 66 patients were planned for enrollment.

The Shapiro–Wilk test was used to assess the normality of the variables. Normally distributed variables were expressed as mean ± standard deviation, non-normally distributed variables as median (IQR), and categorical variables as counts (percentages, %). Intergroup comparisons were performed using an independent samples

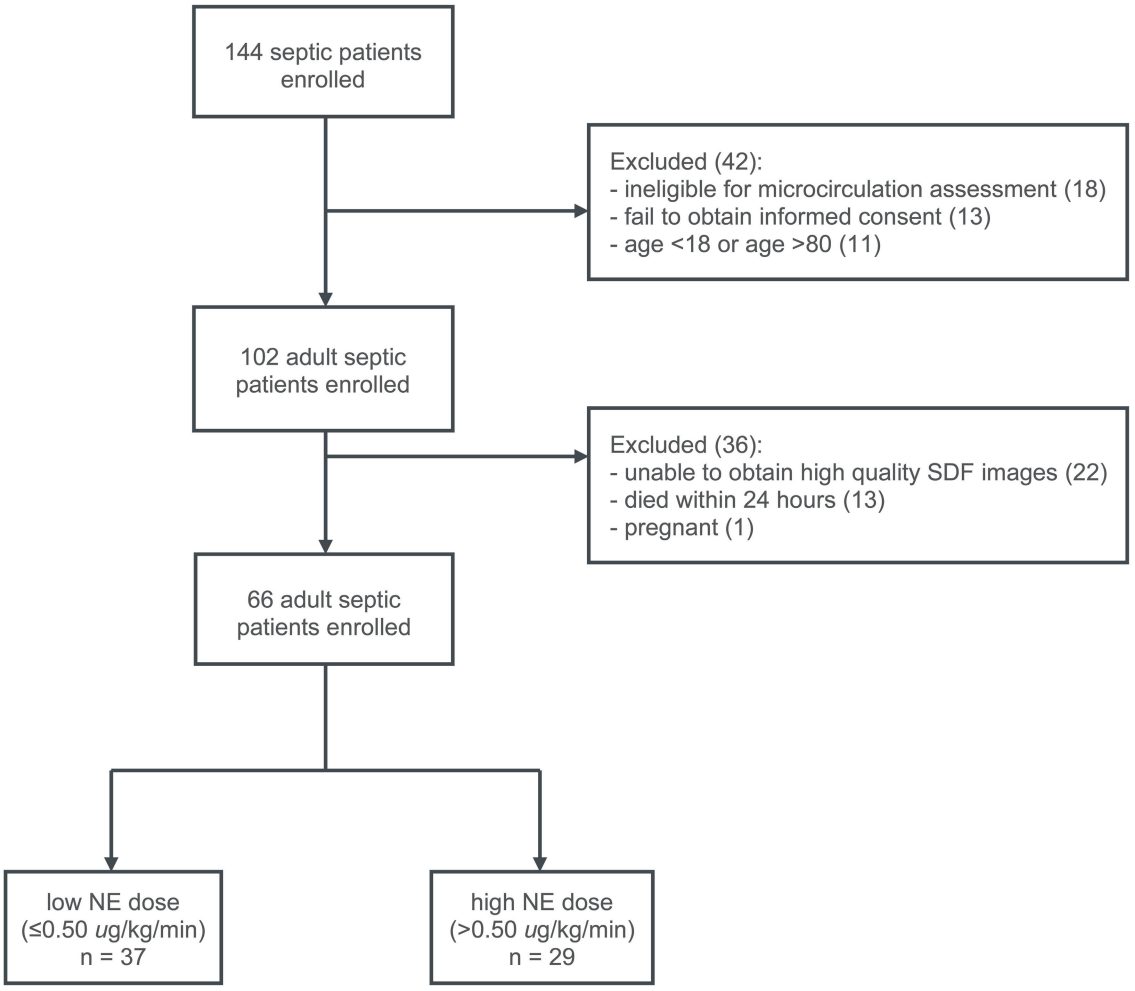

Fig. 1. Flow chart of inclusion and exclusion. NE, norepinephrine; SDF, sidestream dark field.

t-test, Wilcoxon rank-sum test, chi-square test, or Fisher's exact test based on data distribution characteristics. Pearson and Spearman correlation analyses were used to evaluate associations between variables using the Benjamini–Hochberg method for false discovery rate (FDR) correction. Univariate and multiple linear regression analyses were used to assess the independent association between NE doses and microcirculatory parameters. Nonlinear relationships were analyzed using a GAM model and validated by piecewise regression, allowing preliminary exploration of the dose–response relationship between NE and microcirculatory parameters. Kaplan–Meier curves were plotted to illustrate survival, with a log-rank test for intergroup differences. The Cox proportional hazards regression model was used to assess the relationship between NE doses and mortality risk. Statistical analyses and figure preparation were performed using SPSS software (version 22.0), GraphPad Prism software (version 8.0), and R software (version 4.3.2). A two-tailed $P < 0.05$ was considered statistically significant.

Results

Cohort characteristics

A total of 144 adult ICU septic patients were consecutively enrolled after ICU admission. As 78 patients were excluded (Fig. 1) from further analysis, 66 adult septic patients receiving NE treatment in the ICU were enrolled. Microcirculatory parameters, NE dose, and relevant laboratory values were collected on Day 1 and Day 3 of ICU admission. Baseline characteristics were compared between the two groups stratified by NE dose of 0.50 μg/kg/min (an NE dose exceeding 0.50 μg/kg/min is commonly considered a high dose) (Table 1).[33] Both groups completed the preset fluid resuscitation protocol, with no statistically significant difference in baseline MAP ($P = 0.670$) and stable vasopressor usage. Compared to the low NE dose group (≤0.50 μg/kg/min, $n = 37$), patients in the high dose group (>0.50 μg/kg/min, $n = 29$) had higher Acute Physiology and Chronic Health Evaluation II (APACHE II) scores (29.24 ± 6.46 vs. 25.14 ± 5.94, $P = 0.010$), serum lactate (Lac) levels (3.20 [2.20, 7.70] vs. 1.40 [1.10, 1.90]) mmol/L, $P < 0.001$), and heart rates (113.72 ± 15.08 vs. 88.11 ± 18.57 bpm, $P < 0.001$) compared to the low-dose group. Notably, compared to the low-dose group, microcirculatory parameters were more deteriorated in the high-dose group: mottling scores (0 [0 to 2] vs. 0 [0 to 0], $P = 0.001$), HI (0.25 [0.11, 0.50] vs. 0.23 [0.11, 0.35], $P = 0.033$), MFI (2.83 [2.73, 2.98] vs. 2.92 [2.86, 2.98], $P = 0.031$), PPV (100.00 [97.10 to 100.00] vs. 100.00 [100.00 to 100.00], $P = 0.005$), and PVD (14.73 ± 3.77 vs. 17.22 ± 4.71 mm/mm^2, $P =$

Table 1. Baseline characteristics stratified by NE dose of 0.50 μg/kg/min

Characteristics	Overall *n* = 66	Low NE dose (≤ 0.50 μg/kg/min) *n* = 37	High NE dose (>0.50 μg/kg/min) *n* = 29	*P* value
Age (years)	61.65 (13.70)	61.16 (13.54)	62.28 (14.11)	0.750
Male, *n* (%)	50.0 (75.8)	25.0 (67.6)	25.0 (86.2)	0.140
Body mass index (kg/m^2)	23.43 (3.27)	24.17 (3.07)	22.48 (3.34)	0.039
Heart rate (bpm)	99.36 (21.29)	88.11 (18.57)	113.72 (15.08)	<0.001
Mean arterial pressure (mmHg)	81.50 (13.10)	82.14 (11.14)	80.69 (15.41)	0.670
CVP (cmH_2O)	13.13 (3.99)	13.04 (4.11)	13.24 (3.90)	0.840
Hemoglobin (g/L)	124.32 (12.58)	126.67 (9.98)	122.04 (13.71)	0.450
Leukocyte (×10^9/L)	11.80 (5.80, 17.22)	11.67 (7.99, 16.60)	12.20 (2.98, 22.11)	0.930
Lymphocyte (×10^9/L)	0.48 (0.23, 0.93)	0.47 (0.23, 0.79)	0.49 (0.23, 0.96)	0.870
Platelets (×10^9/L)	108.50 (57.00, 170.00)	83.00 (57.00, 150.00)	119.00 (57.00, 191.00)	0.460
Procalcitonin (ng/mL)	30.28 (3.14, 140.14)	22.59 (1.57, 68.48)	34.03 (11.51, 140.14)	0.390
IL-6 (pg/mL)	533.00 (64.30, 3,081.00)	245.16 (39.30, 654.00)	1,928.00 (382.00, 7,500.00)	<0.001
Serum creatinine (mmol/L)	169.85 (113.20, 245.00)	146.10 (85.00, 230.10)	215.00 (142.00, 287.00)	0.029
Urea nitrogen (mmol/L)	14.40 (11.06, 21.48)	13.50 (11.10, 19.00)	15.20 (11.06, 23.50)	0.210
pH level	7.35 (0.10)	7.38 (0.09)	7.32 (0.10)	0.009
Lactate (mmol/L)	1.90 (1.30, 4.10)	1.40 (1.10, 1.90)	3.20 (2.20, 7.70)	<0.001
CRT (s)	3.00 (2.00, 7.50)	2.00 (2.00, 4.00)	4.00 (2.00, 7.50)	0.100
Mottling score (points)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 2.00)	0.001
Peripheral perfusion index	0.64 (0.18, 2.20)	1.20 (0.35, 2.60)	0.22 (0.10, 1.30)	0.017
Microvascular flow index (points)	2.92 (2.81, 2.98)	2.92 (2.86, 2.98)	2.83 (2.73, 2.98)	0.031
Total vessel density (mm/mm^2)	16.01 (13.42, 18.44)	16.61 (13.83, 19.83)	15.02 (13.30, 16.48)	0.048
Perfused vessel density (mm/mm^2)	16.12 (4.46)	17.22 (4.71)	14.73 (3.77)	0.020
Proportion of perfused vessel (%)	100.00 (99.80, 100.00)	100.00 (100.00, 100.00)	100.00 (97.10, 100.00)	0.005
Heterogeneity index	0.23 (0.11, 0.36)	0.23 (0.11, 0.35)	0.25 (0.11, 0.50)	0.033
Fluid intake (mL)	2,562.25 (1,309.80, 3,139.00)	1,930.00 (1,060.90, 2,990.00)	2,771.50 (2,290.00, 4,463.00)	0.016
Combined vasopressor therapy[a], *n* (%)	32.0 (48.5)	16.0 (43.2)	16.0 (55.2)	0.480
Epinephrine, *n* (%)	1.0 (1.5)	0.0 (0.0)	1.0 (3.4)	0.900
Dobutamine, *n* (%)	1.0 (1.5)	1.0 (2.7)	0.0 (0.0)	>0.990
Terlipressin, *n* (%)	12.0 (18.2)	3.0 (8.1)	9.0 (31.0)	0.038
Methylene blue, *n* (%)	26.0 (39.4)	12.0 (32.4)	14.0 (48.3)	0.290
CRRT, *n* (%)	49.0 (74.2)	26.0 (70.3)	23.0 (79.3)	0.580
ECMO, *n* (%)	14.0 (21.2)	10.0 (27.0)	4.0 (13.8)	0.320
SOFA (points)	9.36 (3.11)	9.35 (3.36)	9.38 (2.82)	0.970
APACHE II (points)	26.94 (6.46)	25.14 (5.94)	29.24 (6.46)	0.010
ICU stay (days)	10.00 (5.00, 19.00)	10.00 (8.00, 19.00)	9.00 (3.00, 16.00)	0.110
28-day mortality, *n* (%)	30.0 (45.5)	11.0 (29.7)	19.0 (65.5)	0.008
90-day mortality, *n* (%)	34.0 (51.5)	15.0 (40.5)	19.0 (65.5)	0.077

Variables are displayed in mean (standard deviation), median (*Q1, Q3*) or *n* (%). [a]Combined use of NE and other vasoactive drugs, including epinephrine, dobutamine, terlipressin, and methylene blue. APACHE II, Acute Physiology and Chronic Health Evaluation II; CRRT, continuous renal replacement therapy; CRT, capillary refill time; CVP, central venous pressure; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IL-6, interleukin-6; NE, norepinephrine; Q1, first quartile; Q3, third quartile; SOFA, sequential organ failure assessment.

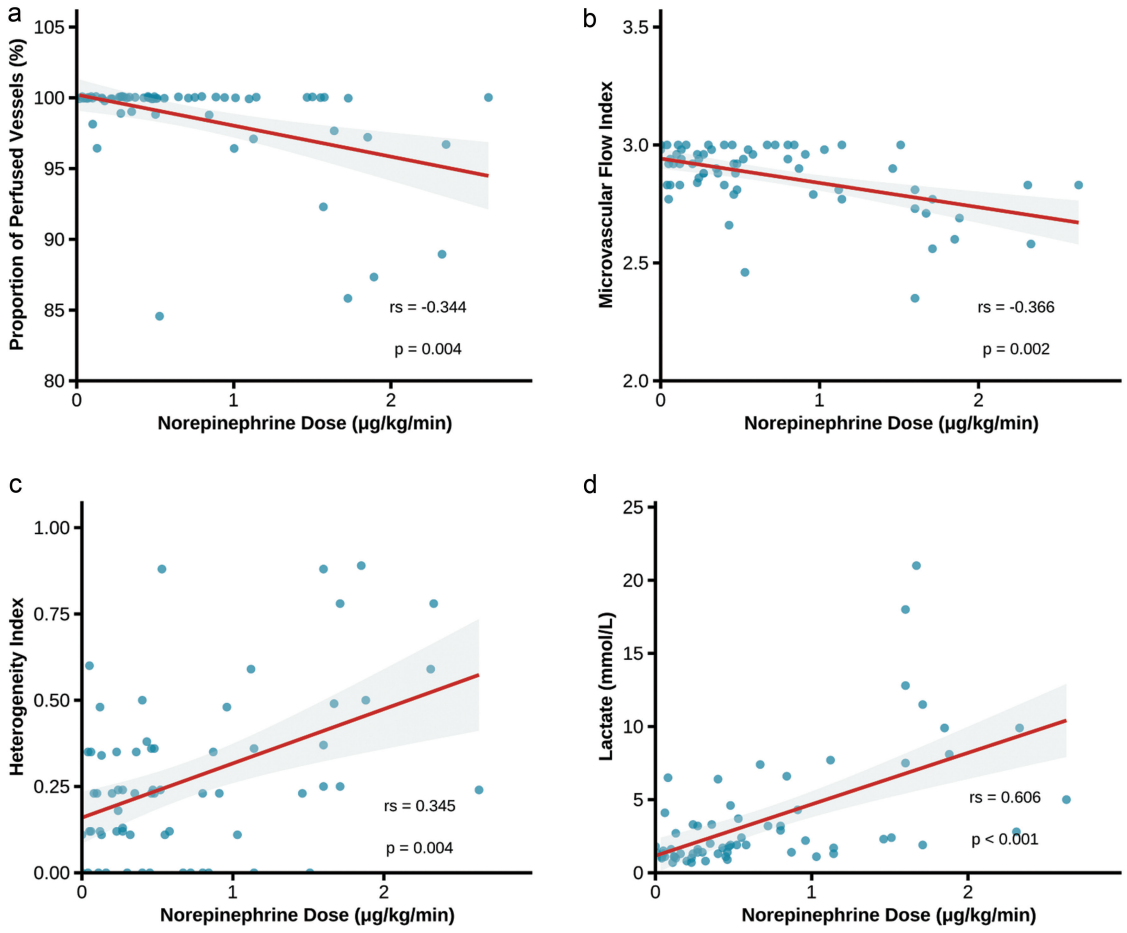

Fig. 2. Scatter plots of the association between NE dose and microcirculatory-related parameters. (a) Association between NE and PPV. (b) Association between NE and MFI. (c) Association between NE and HI. (d) Association between NE and Lac. Spearman rank correlation coefficients were used. HI, heterogeneity index; Lac, lactate; MFI, microvascular flow index; NE, norepinephrine; PPV, proportion of perfused vessels.

0.020). Finally, the 28-day mortality rate in the high-dose group was significantly higher than that in the low-dose group (65.5% vs. 29.7%, $P = 0.008$).

Correlation between NE dose and microcirculatory parameters

In the total cohort ($n = 66$), the NE dose was significantly correlated with multiple microcirculatory parameters: negative correlations with MFI and PPV (MFI: $r = -0.492$, $P < 0.001$; PPV: $r = -0.420$, $P < 0.001$) ; positive correlations were observed with the HI, Lac, and mottling scores (HI: $r = 0.444$, $P < 0.001$; Lac: $r = 0.583$, $P < 0.001$; mottling score: $r = 0.364$, $P = 0.003$) (Fig. 2 and Supplementary Table 2). These associations remained statistically significant after FDR correction ($P < 0.05$). No significant correlations were found between the NE dose and CRT, PI, TVD, or PVD ($P > 0.05$).

Multivariate regression analysis of NE dose and microcirculatory parameters

Univariate linear regression analysis showed that NE dose was significantly positively correlated with the HI, Lac, and mottling score (HI: 0.157 (0.078, 0.237), $P < 0.001$; Lac: 3.518 (2.294, 4.742), $P < 0.001$; mottling score: 0.445 (0.161, 0.730), $P = 0.003$), and significantly negatively correlated with MFI and PPV (MFI: −0.103 (−0.149, −0.058), $P < 0.001$; PPV: −2.136 (−3.289, −0.983), $P < 0.001$). Based on baseline grouping and clinical significance, APACHE II scores, heart rates, and interleukin (IL)-6 levels were adjusted for multivariate regression analysis. Except for the mottling score, which no longer reached statistical significance after adjustment ($P = 0.115$), all other associations remained statistically significant ($P < 0.05$) (Table 2). GAM analysis was employed to analyze the nonlinear relationship between NE dose and microcirculatory parameters while also identifying inflection points in the dose–response curve. After adjusting for covariates, including APACHE II scores, heart rates, and IL-6 levels, the GAM analysis revealed significant nonlinear relationships between NE dose and microcirculatory parameters (all $P < 0.05$). Significant inflection points of the NE dose (Fig. 3) were identified within these nonlinear relationships, and piecewise regression was employed to validate the respective inflection points (MFI: 0.80 μg/kg/min, $P < 0.001$, $R^2 = 0.532$; PPV: 0.71 μg/kg/min, $P = 0.031$, $R^2 = 0.301$; HI: 0.72 μg/kg/min, $P = 0.014$, $R^2 = 0.460$; Lac: 1.65 μg/kg/min, $P < 0.001$, $R^2 = 0.455$; mottling score: 0.25 μg/kg/min, $P = 0.029$, $R^2 = 0.123$).

Relationship between dynamic changes in NE dose and microcirculatory function

Longitudinal analysis was performed using data from Day 1 and

Table 2. Univariate and multivariate analysis of NE and microcirculatory parameters

Parameters	Univariate analysis		Multivariate analysis (model-1[a])	
	Regression coefficient (95% CI)	*P* value	Regression coefficient (95% CI)	*P* value
Mottling Score	0.445 (0.161, 0.730)	0.003	0.342 (−0.086, 0.770)	0.115
MFI	−0.103 (−0.149, −0.058)	<0.001	−0.099 (−0.163, −0.034)	0.003
PPV	−2.136 (−3.289, −0.983)	<0.001	−1.698 (−3.391, −0.004)	0.049
HI	0.157 (0.078, 0.237)	<0.001	0.146 (0.031, 0.260)	0.013
Lac	3.518 (2.294, 4.742)	<0.001	2.502 (0.700, 4.305)	0.007

[a]model-1: APACHE II scores, heart rates, and IL-6 levels were adjusted. APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; HI, heterogeneity index; IL-6, interleukin-6; Lac, lactate; MFI, microvascular flow index; NE, norepinephrine; PPV, proportion of perfused vessels.

Day 3 to evaluate the dynamic relationship between changes in NE dose (ΔNE dose = NE dose $_{D3}$ – NE dose $_{D1}$) and changes in microcirculatory parameters (Δmicrocirculatory parameters = microcirculatory parameters $_{D3}$- microcirculatory parameters $_{D1}$). The correlation analysis showed that changes in NE dose were significantly positively correlated with changes in Lac and mottling score (ΔLac: $r = 0.653$, $P < 0.001$; Δmottling score: $r = 0.483$, $P < 0.001$), and significantly negatively correlated with changes in MFI ($r = -0.565$, $P < 0.001$). These correlations remained significant after FDR correction (P values for all parameters < 0.001) (Fig. 4). After adjusting for APACHE II scores, heart rates, and IL-6 levels, multivariate regression analysis further revealed sig-

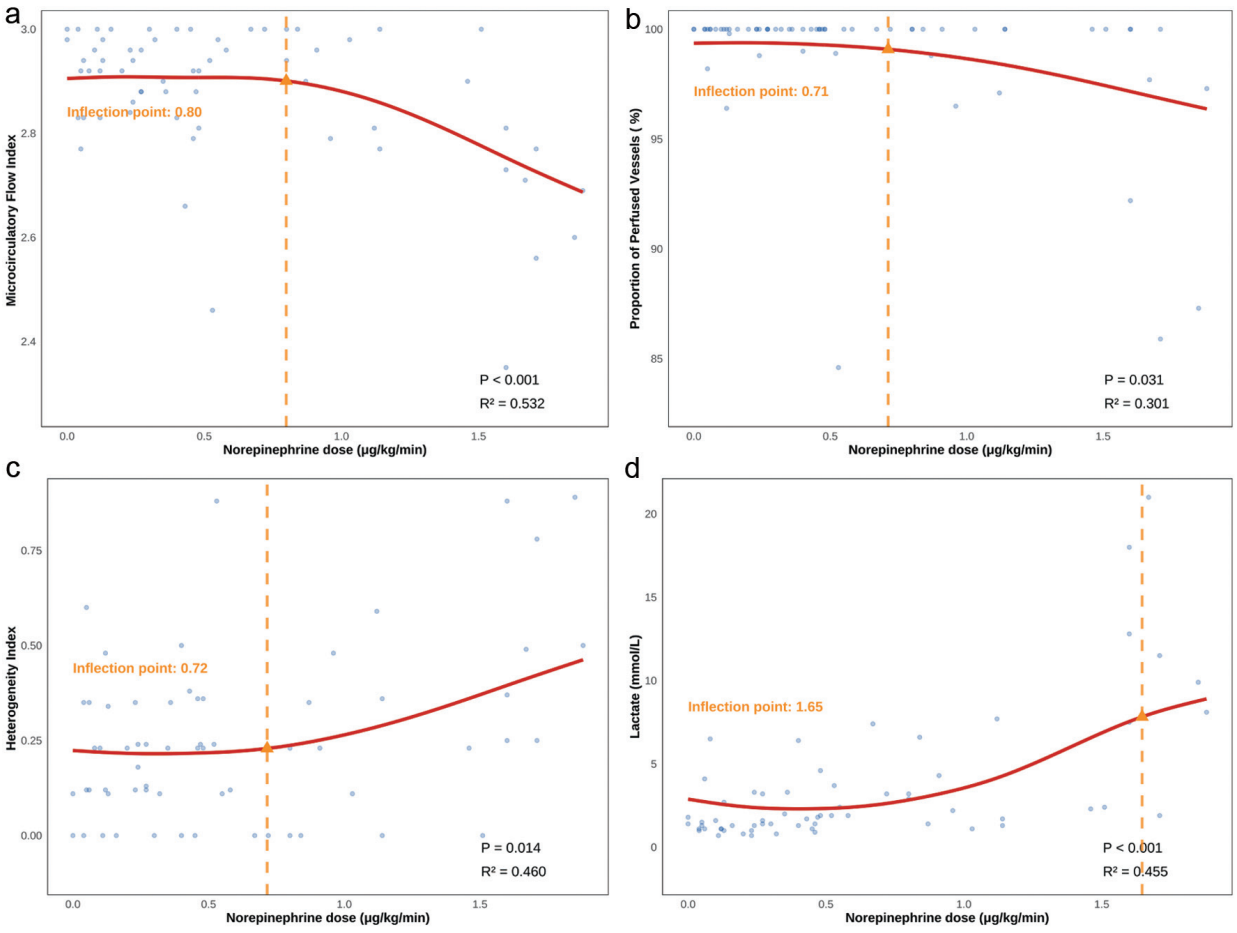

Fig. 3. GAM curves of the nonlinear association between NE dose and microcirculatory-related parameters. (a) Nonlinear association between NE and MFI. (b) Nonlinear association between NE and PPV. (c) Nonlinear association between NE and HI. (d) Nonlinear association between NE and Lac. Adjusted for APACHE II scores, heart rates, and IL-6 levels, GAM analysis was employed to fit the trend between NE dose and microcirculatory parameters, with the point of maximum curvature on the trend line identified as the NE dose inflection point. APACHE II, Acute Physiology and Chronic Health Evaluation II; GAM, generalized additive model; HI, heterogeneity index; IL-6, interleukin-6; Lac, lactate; MFI, microvascular flow index; NE, norepinephrine; PPV, proportion of perfused vessels.

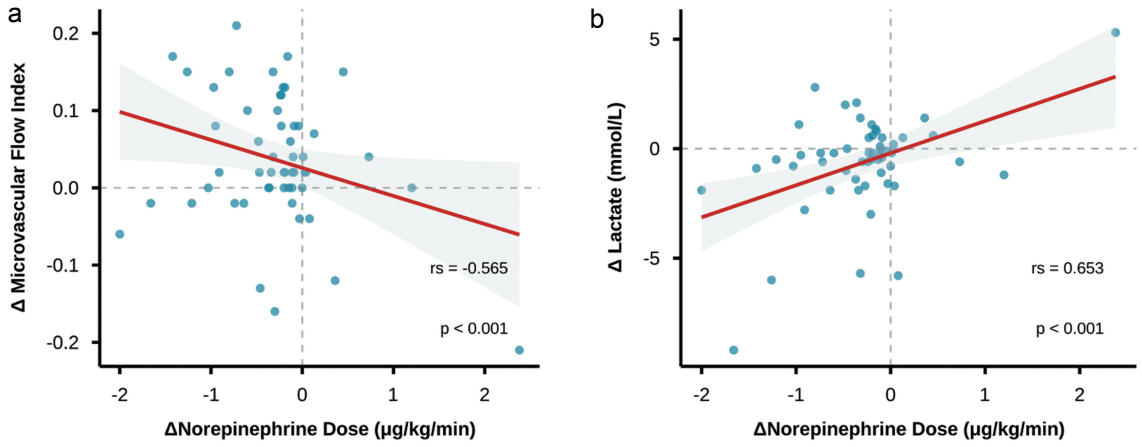

Fig. 4. Scatter plots of the association between NE dose changes and microcirculatory-related parameter alterations. (a) Association between NE changes and MFI changes. (b) Association between NE changes and Lac changes. Spearman rank correlation coefficients were used. Lac, lactate; MFI, microvascular flow index; NE, norepinephrine.

nificant correlations between changes in NE dose and changes in Lac, MFI, and mottling scores (ΔLac: $P < 0.001$; ΔMFI: $P < 0.001$; Δmottling score: $P = 0.003$). No statistically significant association was observed between NE dose changes and alterations in PPV, PI, HI, TVD, PVD, or CRT (all $P > 0.05$ for correlation and regression after adjustment) (Fig. 5).

Relationship between NE dose and prognosis

Survival analysis was conducted based on a universally recognized high NE dose (0.5 μg/kg/min) and NE cutoff dose (0.8 μg/kg/min), with cut-off values determined via GAM analysis (PPV: 0.71 μg/kg/min, HI: 0.72 μg/kg/min, MFI: 0.80 μg/kg/min). Given that MFI serves as the primary indicator for assessing microcirculatory perfusion, this value was selected as the prognostic cutoff point. Kaplan–Meier survival curves and log-rank tests indicated that overall survival rates in the high-dose group were significantly lower than those in the low-dose group in both subgroups (all the log-rank $P < 0.05$). (Fig. 6). Univariate Cox regression models showed that the risk of death was significantly higher in the high NE dose group compared to the low-dose group (cut-off value = 0.50 μg/kg/min: hazard ratio [HR] = 2.28, 95% confidence interval [CI]: 1.16–4.51, $P = 0.017$; cut-off value = 0.80 μg/kg/min: HR = 2.52, 95% CI: 1.78–4.99, $P = 0.008$). Remarkably, after adjusting for confounding factors, including APACHE II scores, heart rates, and IL-6 levels, the independent effect of NE dose (>0.8 μg/kg/min) remained statistically significant (fully adjusted HR = 1.32, 95% CI: 1.28–3.10, $P = 0.039$), whereas the effect of the high-dose group (>0.5 μg/kg/min) was no longer significant (fully adjusted HR = 1.05, 95% CI: 0.78–2.47, $P = 0.083$).

Discussion

This prospective observational study systematically investigated the relationship between NE dose and microcirculatory perfusion in ICU septic patients through a combination of cross-sectional and longitudinal analysis, and further verified the independent association between NE dose and patient prognosis. The findings not only provide new evidence for understanding the dose-dependent effect of NE on microcirculation but also offer actionable insights for optimizing NE dosage strategies in sepsis management. Correlation and regression analysis consistently showed that NE dose was significantly correlated with microcirculation in ICU septic patients (HI, MFI, PPV, Lac, and mottling score), and this association remained stable after adjusting for multiple confounding factors, with the exception of the mottling score. The most significant finding of this study is the exploration of a nonlinear dose–response relationship between NE and microcirculation. When the NE dose exceeds the threshold range of 0.71–0.80 μg/kg/min, which is based on the GAM-derived inflection points of key microcirculatory parameters (PPV: 0.71 μg/kg/min, HI: 0.72 μg/kg/min, MFI: 0.80 μg/kg/min), microcirculation in septic patients deteriorates significantly. This threshold applies to mechanically ventilated adult patients with septic shock who have completed initial fluid resuscitation. Clinical application requires individualized adjustment based on the patient's underlying disease and vascular responsiveness. However, this dosage range appears inconsistent in terms of the mottling score and lactate levels. In the GAM fitting model, the R^2 value for NE and mottling score was 0.123, potentially due to factors such as subjective bias, temperature management, and sample size constraints. Moreover, when the NE dose exceeds 0.50 μg/kg/min, which is often considered a rather high NE dose, it is frequently combined with methylene blue or other vasopressors in clinical practice.[33] This may influence lactate metabolism and NE dosage requirements.[34] Longitudinal data further showed that an increase in NE dose was significantly negatively correlated with improvements in microcirculatory perfusion. Furthermore, this study identified an association between NE doses and patient prognosis. The multivariate Cox regression model confirmed that high-dose NE (cut-off value = 0.80 μg/kg/min) may be an independent risk factor for death. As a core catecholamine vasoactive agent, NE may exacerbate oxidative stress by accelerating systemic metabolism and inducing mitochondrial uncoupling.[35] Oxidative stress stimulates excessive reactive oxygen species (ROS) production, mediating endothelial cell toxicity. Damaged endothelial cells further exacerbate oxidative stress by releasing proinflammatory mediators (e.g., TNF-α and IL-6) and downregulating antioxidant enzymes (e.g., superoxide dismutase [SOD] and catalase), creating a vicious cycle that ultimately promotes microthrombus formation and induces organ dysfunction.[36,37] De Backer *et al*.[38] and Kindermans *et al*.[39] proposed the concept of "macrocirculation–microcirculation uncoupling" in septic shock, noting that normal macrocirculation

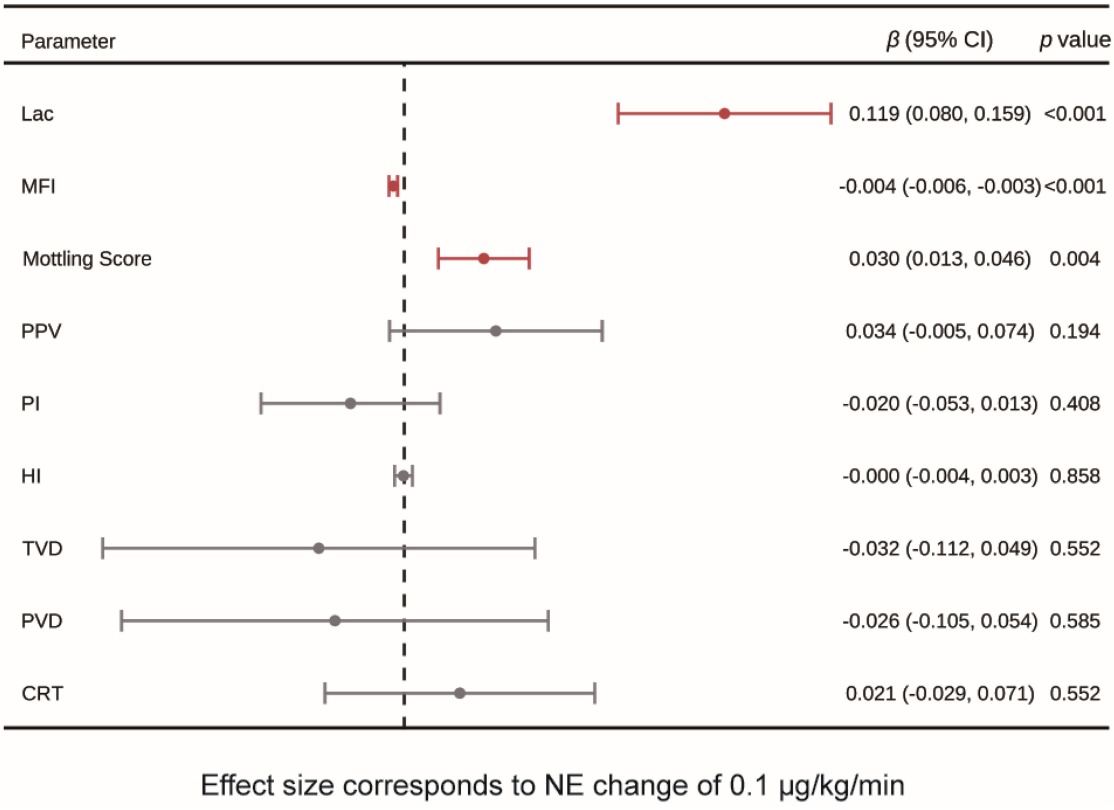

Fig. 5. Forest plot of the association between changes in NE dose and microcirculatory-related parameter alterations. (Adjusted for APACHE II scores, heart rates, and IL-6 levels). APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; CRT, capillary refill time; HI, heterogeneity index; IL-6, interleukin-6; Lac, lactate; MFI, microvascular flow index; NE, norepinephrine; PI, perfusion index; PPV, proportion of perfused vessels; PVD, perfused vessel density; TVD, total vessel density.

hemodynamic parameters (e.g. MAP and CVP) do not guarantee adequate microcirculatory perfusion. Our data directly corroborate this perspective: although there was no statistically significant difference in MAP or CVP between the high- and low-dose NE groups, microcirculatory function deteriorated markedly in the high-dose group. This highlights the limitation of overreliance on macrocirculatory parameters to guide NE therapy. Clinicians may mistakenly consider normal MAP a sign of effective resuscitation, while microcirculatory damage persists. This aligns with findings from Auchet *et al*.[40] and Reinikainen *et al*.,[41] collectively emphasizing a key concept: in the treatment of septic shock, NE should not be regarded as a harmless supportive measure but rath-

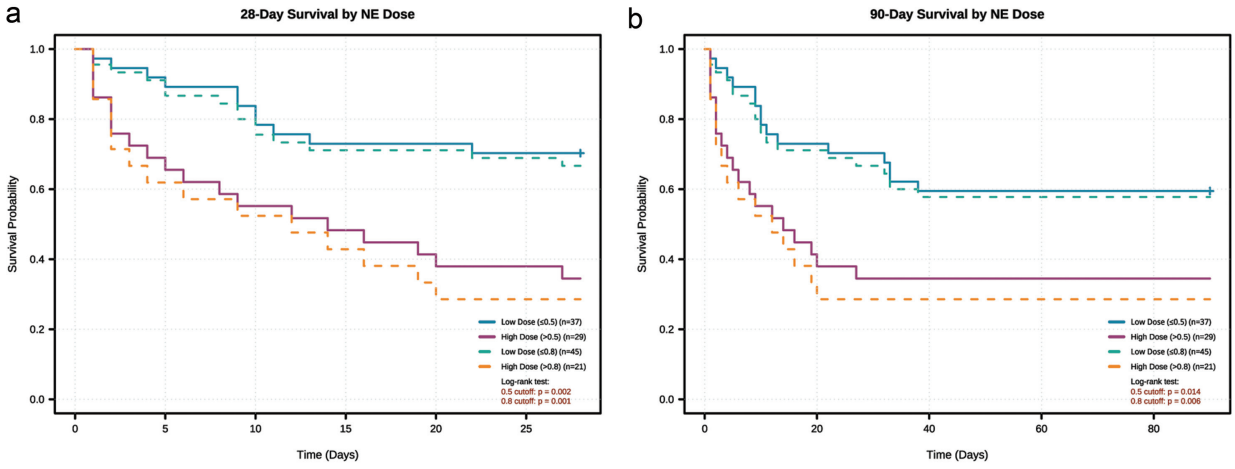

Fig. 6. Kaplan–Meier survival curves for 28-day survival (a) and 90-day survival (b). Survival probabilities were stratified by different NE doses. The log-rank test was used to compare the survival differences between the groups. NE, norepinephrine.

er a therapeutic drug that requires careful weighing and precise regulation. Further evidence from MARTIN C *et al*.[42] indicated a significant increase in mortality risk when NE doses exceed 0.5–1.0 μg/kg/min, a range similar to our findings. This study attempted to refine the optimal dose threshold by exploring the relationship between microcirculation and NE. Van Genderen *et al*.[43] previously proposed a resuscitation strategy guided by peripheral perfusion. Our findings conclude that dynamically adjusting NE dosage to optimize microcirculatory perfusion, combined with individualized dose titration based on lactate clearance rather than solely targeting MAP $\geq$ 65 mmHg,[44,45] represents a safer and more personalized management strategy for treating septic patients. In summary, microcirculatory dysfunction induced by high-dose NE use may be a key mediating link in the increased risk of death in septic patients. Clinical practice should rationally employ microcirculatory monitoring technologies to achieve refined hemodynamic management of sepsis patients. This approach can prevent excessive NE from further deteriorating microcirculation, ultimately improving patient outcomes.

Admittedly, this study has several limitations. First, as a single-center observational study, residual confounding and bias cannot be entirely excluded, despite multivariate adjustments and multiple analytical methods. Second, the sample size was relatively limited. While meeting statistical requirements, it constrained subgroup analyses and precluded the use of a more appropriate restricted cubic spline analysis to precisely depict dose–response curves when exploring dose–response relationships. Finally, while preliminary exploration of the relationship between NE and microcirculation was conducted, the underlying mechanisms linking NE to microcirculation and mortality require further validation through basic experimental studies. Future research should employ multicenter randomized controlled trials to compare the proposed "microcirculation-guided NE therapy" with traditional mean arterial pressure-guided therapy, verifying its impact on 28-day and 90-day mortality rates. Large-scale cohort studies should be conducted to further define precise NE thresholds across different populations. Finally, integrating basic experiments with clinical research will elucidate the molecular mechanisms by which NE regulates microcirculation, providing a theoretical foundation for developing targeted intervention strategies.

Conclusions

This study showed that higher NE doses were associated with worse microcirculatory dysfunction and poorer prognosis. This indicates that when the NE infusion dose exceeds 0.71–0.80 μg/kg/min (PPV: 0.71 μg/kg/min, HI: 0.72 μg/kg/min, MFI: 0.80 μg/kg/min), microcirculatory dysfunction should be noted. This provides important evidence for the precise regulation of NE doses in sepsis management, emphasizing the significance of integrating microcirculation monitoring to avoid further deterioration caused by excessive NE use and thereby improve patient prognosis.

Supporting information

Supplementary material for this article is available at https://doi.org/10.14218/JTCCM.2026.00004.

Acknowledgments

None.

Funding

This work was supported by the National Natural Science Foundation of China (Nos. 82272208 and 82572484 to ZP).

Conflict of interest

ZP is an associate editor-in-chief of *Journal of Translational Critical Care Medicine*. The authors declare no other conflicts of interest.

Author contributions

Conceptualization (ZP, YL), methodology (CH), data curation (YD, HC), formal analysis (YD, HC), validation (YZ, HC), visualization (YD), writing—original draft (YD, YZ), writing—review and editing (YD, YZ, CH, YL), supervision (CH, ZP, YL), project administration (ZP), and funding acquisition (ZP). All authors read and approved the final manuscript.

Ethical statement

The study protocol was approved by the Ethics Committee of Zhongnan Hospital of Wuhan University (No. 2025096K). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2024). All enrolled patients or their legally authorized representatives provided written informed consent to participate in the study.

Data sharing statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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