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Hemodynamic Characteristics and Clinical Outcomes of Norepinephrine Alone versus Norepinephrine Plus Dopamine in Septic Shock: A PICCO-Based Retrospective Cohort Study

Yujing He
First Affiliated Hospital of Xiamen University
Yaojie Fu
First Affiliated Hospital of Xiamen University
Xiaoyang Cai
Fujian Medical University
Guiyang Lu
First Affiliated Hospital of Xiamen University
Qiang Xie
xieqiang@xmu.edu.cn

Fujian Medical University

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Title page

Hemodynamic Characteristics and Clinical Outcomes of Norepinephrine Alone versus Norepinephrine Plus Dopamine in Septic Shock: A PICCO-Based Retrospective Cohort Study

Author information:

Yujing He MD[1], Yaojie Fu[3] MD,Xiaoyang Cai MD[1,2],Guiyang Lu MD[1],Qiang Xie PhD[2,4]. （Author List）

[1] Department of Critical Care Medicine, The First Affiliated Hospital of Xiamen University, School of Medicine, Xiamen University, Xiamen, China.

[2] Xiamen First Clinical Medical College of Fujian Medical University, Fuzhou, Fujian, China.

[3] Emergency Department, The First Affiliated Hospital of Xiamen University, Fujian Province, China.

[4] Department of Cardiology, Xiamen Key Laboratory of Cardiac Electrophysiology, Xiamen Institute of Cardiovascular Diseases, The First Affiliated Hospital of Xiamen University, School of Medicine, Xiamen University, Xiamen, China.

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Correspondence

Qiang Xie, PhD

1.Xiamen First Clinical Medical College of Fujian Medical University, Fuzhou, Fujian, China.

2.Department of Cardiology, Xiamen Key Laboratory of Cardiac Electrophysiology, Xiamen Institute of Cardiovascular Diseases, The First Affiliated Hospital of Xiamen University, School of Medicine, Xiamen University, Xiamen, Fujian Province ,China; No.10,Shanggu Road,361001, China.

E-mail: xieqiang@xmu.edu.cn

Guiyang Lu.MD

1.Department of Critical Care Medicine, The First Affiliated Hospital of Xiamen University, School of Medicine, Xiamen University, Xiamen, China.

E-mail: lgy840119@126.com

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Title Hemodynamic Characteristics and Clinical Outcomes of Norepinephrine Alone versus Norepinephrine Plus Dopamine in Septic Shock: A PICCO-Based Retrospective Cohort Study

Abstract

Background Sepsis and septic shock, as critical complications caused by severe infections in current clinical practice, continue to exhibit persistently high morbidity and mortality rates. This study aims to utilize Picco monitoring data to investigate the differences in vasopressor effects and clinical outcomes between norepinephrine monotherapy and norepinephrine combined with dopamine therapy in sepsis and septic shock.

Method A total of 83 patients with septic shock were retrospectively included. All of them received adequate fluid resuscitation and were primarily treated with norepinephrine (NE) alone or NE combined with dopamine (DA) to maintain a mean arterial pressure (MAP) of 65 mmHg. Hemodynamic parameters, including mean arterial pressure (MAP), cardiac output, and systemic vascular resistance, were closely monitored using Pulse - Indicated Continuous Cardiac Output (PICCO) technology throughout the study period.

Results The study results revealed that, compared to the NE group, patients in the NE + DA group had higher APACHE II scores (mean in the NE group: 21.34 vs mean in the NE + DA group: 26.87, $P < 0.001$). No significant differences were found between the two groups in terms of the vasopressor effects on sepsis complications, including acute respiratory distress syndrome (ARDS) (81.1% in the NE group vs 76.7% in the NE + DA group) and acute kidney injury (AKI) (66% in the NE group vs 83.3% in the NE + DA group). However, there was no difference in mechanical ventilation for these two major complications between the groups (mechanical ventilation: 79.2% in the NE group vs 76.7% in the NE + DA group), but there was a difference in continuous renal replacement therapy (CRRT) (CRRT: 39.6% in the NE group vs 73.3% in the NE + DA group, $P = 0.006$). Logistic regression analysis identified higher Acute Physiology and Chronic Health Evaluation II scores (OR = 1.26, $p = 0.0001$) and the use of DA + NE vasopressors (OR = 4.52, $p = 0.039$) as significant risk factors for mortality in patients with septic shock. Furthermore, the 7 - day mortality rate was 33.3% (10/83) in the DA + NE group when used as vasopressors, compared to 5.7% (3/83) in the NE treatment group ($P = 0.003$). The 28 - day mortality rate was 53.3% (16/83) in the DA + NE group versus 13.2% (7/83) in the NE treatment group ($P < 0.001$).In exploring potential reasons, we utilized PICCO to monitor hemodynamic data, including heart rate (HR), lactate (Lac), and mean arterial pressure (MAP). The study found that NE + DA increased lactate levels in patients with septic shock at different time points, which may have directly

contributed to patient mortality.

Conclusion In summary, this study indicates that compared with the use of norepinephrine alone, the use of norepinephrine in conjunction with dopamine (DA) for the treatment of septic shock does not effectively improve the patient's condition. NE monotherapy may represent a preferable vasopressor strategy; however, the observed association requires confirmation in prospective studies. Consequently, it is necessary to reassess these treatment modalities and investigate more efficacious strategies for managing septic shock.

Keywords Septic shock; Norepinephrine; Dopamine; Vasopressor; PICCO; Hemodynamic monitoring

Introduction

Septic shock continues to be a significant challenge in critical care medicine, with its severe circulatory, cellular, and metabolic abnormalities[1–3]. Septic shock mortality rates are still too high, even with improvements in intensive care management [4,5]. Vasopressors are usually administered as part of the basic hemodynamic management for these patients in order to guarantee appropriate perfusion pressure. Dopamine (DA) and norepinephrine (NE), two of these substances that are frequently used, have varying effects on regional and systemic hemodynamics [6, 7]. The debates over the best vasopressor combination and selection for treating septic shock have been highlighted by recent research [8, 9]. In order to maintain blood pressure and increase systemic vascular resistance, norepinephrine mainly acts on α-adrenergic receptors [10]. On the other hand, dopamine may improve renal perfusion by influencing both dopaminergic and β-adrenergic receptors. But there are risks as well, like excessive vasodilation and tachyarrhythmias [11,12]. The relative efficacy and safety profiles of norepinephrine (NE) alone versus NE combined with dopamine (DA) in septic shock remain unclear despite its extensive clinical use [13]. There is disagreement in the literature regarding whether combination therapy, as opposed to NE monotherapy, improves outcomes like organ dysfunction and mortality [14]. Furthermore, little is known about how specifically these agents affect sepsis-related complications like acute respiratory distress syndrome (ARDS) and acute kidney injury (AKI) [15, 16].

Understanding the optimal vasopressor strategy for septic shock is crucial for improving patient outcomes and reducing resource utilization in intensive care[17]. Clarifying the different effects of norepinephrine and dopamine on hemodynamics, organ function, and survival may guide clinical decisions [18]. Furthermore, identifying predictors of adverse outcomes associated with these treatments may facilitate the development of personalized medical strategies for critically ill patients [19]. Previous research has emphasized the complexities of vasopressor therapy in septic shock. For

instance, the study by De Backer et al. [20] demonstrated superior outcomes with norepinephrine compared to other vasopressors in achieving target hemodynamic endpoints and reducing mortality. Conversely, investigations by Asfar et al. and Russell et al. have suggested potential benefits of dopamine in improving renal function and reducing the need for renal replacement therapy, although its effects on survival are equivocal [21, 22]. However, whether these vasopressor strategies induce different systemic hemodynamic profiles remains insufficiently investigated. PICCO monitoring provides continuous assessment of cardiac function, vascular resistance, and fluid status, offering a potential approach to explore these differences.

Study Design and Methodology

This was a retrospective observational cohort study that enrolled 83 patients diagnosed with septic shock. All of them underwent rigorous fluid resuscitation before receiving either norepinephrine (NE) alone or NE combined with dopamine (DA). Hemodynamic parameters, including mean arterial pressure (MAP), cardiac output, and systemic vascular resistance, were closely monitored using Pulse Indicated Continuous Cardiac Output (PICCO) technology throughout the study period. All the data have been subjected to statistical analysis.

Study population

This observational retrospective study was approved by the Ethics Committee of the First Affiliated Hospital of Xiamen University (Approval No. [2026] Scientific Research Ethics Review No. (076)). As the study involved the collection of existing clinical data with anonymization of patient information, the requirement for informed consent was waived by the ethics committee. A total of 83 hospitalized patients with positive blood culture sepsis between December 2017 and October 2020 were included. The inclusion criteria for this study encompass individuals meeting the following conditions:1) Diagnosis of sepsis in accordance with the International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [1]. 2) Positive blood culture results. Patients will be excluded if they meet any of the following criteria: 1) Presence of pre-existing conditions, such as organ dysfunction or HIV positivity, which independently contribute to complications. 2) Incomplete clinical data are essential for the analysis."

Diagnosis of complications, biomarkers and laboratory tests

Blood samples were promptly collected and analyzed using the Sysmex SE-9000 analyzer for Complete Blood Count and the Beckmann AU5831 analyzer for biochemical examination from Japan. Demographic characteristics, laboratory results upon admission, and treatment outcomes were retrieved

from the electronic medical records system. For ARDS, we adopt the 2012 Berlin definition, wherein ARDS is diagnosed when PaO2/FiO2 ≤ 300. Septic shock is diagnosed if, after fluid resuscitation, vasopressors are still necessary to maintain the mean arterial pressure (MAP) at 65 mmHg or higher, and the serum lactate level > 2 mmol/L. For AKI, diagnosis follows the criteria outlined in the KDIGO guidelines, signifying a ≥26.5 μmol/L increase in serum creatinine (SCr) within 48 hours or a ≥1.5-fold increase in SCr compared to the baseline value within 7 days, or a urine output <0.5 ml/(kg·h) for 6 hours.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation and compared using the t-test. Categorical variables were represented as frequency and percentage, and the chi-squared test was employed for comparisons. For all enrolled patients, univariate and multivariate logistic regression analyses were conducted to identify independent risk factors, presenting results as odds ratios (OR) with corresponding 95% confidence intervals (CI). All statistical analyses were performed using SPSS software version 26.0 (SPSS Inc, Chicago, IL, USA). A P-value <0.05 was considered statistically significant.

Results

Choosing the right vasopressor drugs is essential for treating sepsis or septic shock. By increasing systemic vascular resistance through vasoconstriction, NE, a strong α-adrenergic agonist, helps maintain stable hemodynamics and ensures appropriate tissue perfusion, particularly during hypotensive states brought on by sepsis [22]. In sepsis, lactate levels are an essential measure of tissue perfusion and metabolic condition and are strongly correlated with the prognosis and severity of the illness. Due to its beneficial effects on circulation and reduction of tissue hypoxia, NE monotherapy considerably lowers lactate levels at several time periods [20]. These studies, however, did not carry out comparable analyses based on the particular hemodynamic data.

As demonstrated in **Table 1**, our study results revealed that patients who received NE + DA had considerably higher Acute Physiology and Chronic Health Evaluation II (APACHE II) ratings than those who received NE alone (mean 26.87 vs. 21.34, P < 0.001). The incidence of sepsis-related sequelae, including acute respiratory distress syndrome (ARDS) (NE 81.1% vs. NE + DA 76.7%) and acute kidney damage (AKI) (NE 66% vs. NE + DA 83.3%), did not differ significantly in spite of these variations. While the groups' rates of mechanical ventilation were comparable (NE 79.2% vs. NE +

DA 76.7%), the NE + DA cohort's usage of continuous renal replacement therapy (CRRT) was significantly greater (73.3% vs. 39.6%, P = 0.006).

Table 1

	All (n=83)	NE (n=53)	NE+DA (n=30)	P value
Age, years	60.00 [50.50, 67.00]	59.00 [50.00, 64.00]	62.00 [54.00, 73.75]	0.103
Gender, female	31 (37.3)	20 (37.7)	11 (36.7)	1.000
BMI	23.03 [21.36, 24.36]	23.18 [21.36, 24.80]	22.90 [21.62, 24.22]	0.842
Pre-existing conditions				
Hypertension	20 (24.1)	13 (24.5)	7 (23.3)	1.000
Diabetes	15 (18.1)	9 (17.0)	6 (20.0)	0.963
Tumor	30 (36.1)	20 (37.7)	10 (33.3)	0.870
Autoimmune disease	7 (8.4)	3 (5.7)	4 (13.3)	0.425
The main infected site				
Pulmonary	29 (34.9)	16 (30.2)	13 (43.3)	0.334
Bloodstream	36 (43.4)	21 (39.6)	15 (50.0)	0.493
Abdominal	17 (20.5)	8 (15.1)	9 (30.0)	0.182
Urinary	9 (10.8)	6 (11.3)	3 (10.0)	1.000
Hepatobiliary	10 (12.0)	8 (15.1)	2 (6.7)	0.434
Other	7 (8.4)	5 (9.4)	2 (6.7)	0.980
ICU complication				
ARDS	66 (79.5)	43 (81.1)	23 (76.7)	0.841
AKI	60 (72.3)	35 (66.0)	25 (83.3)	0.151
Apache II	23.34 (6.64)	21.34 (5.15)	26.87 (7.54)	<0.001
Therapy				
Mechanical ventilation	68 (81.9)	42 (79.2)	26 (86.7)	0.584
CRRT	43 (51.8)	21 (39.6)	22 (73.3)	0.006
Outcomes				
Length of stay in ICU, days	10.00 [6.00, 18.50]	9.00 [6.00, 14.00]	10.00 [7.00, 20.75]	0.328
Length of stay in hospital, days	23.00 [12.50, 37.50]	24.00 [14.00, 38.00]	22.00 [11.00, 35.50]	0.772
7-day mortality	13 (15.7)	3 (5.7)	10 (33.3)	0.003
28-day mortality	23 (27.7)	7 (13.2)	16 (53.3)	<0.001
ICU mortality	19 (22.9)	6 (11.3)	13 (43.3)	0.002

The death rates for patients treated with DA + NE as vasopressors were significantly higher at 7 days (DA + NE 33.3% vs. NE 5.7%, P = 0.003) and 28 days (DA + NE 53.3% vs. NE 13.2%, P < 0.001). Additionally, as shown **in Table 2,** we discovered that the use of DA + NE vasopressors (OR = 4.52, p = 0.039) and higher APACHE II scores (OR = 1.26, p = 0.0001) were independent predictors of mortality among patients with septic shock, according to logistic regression analysis.

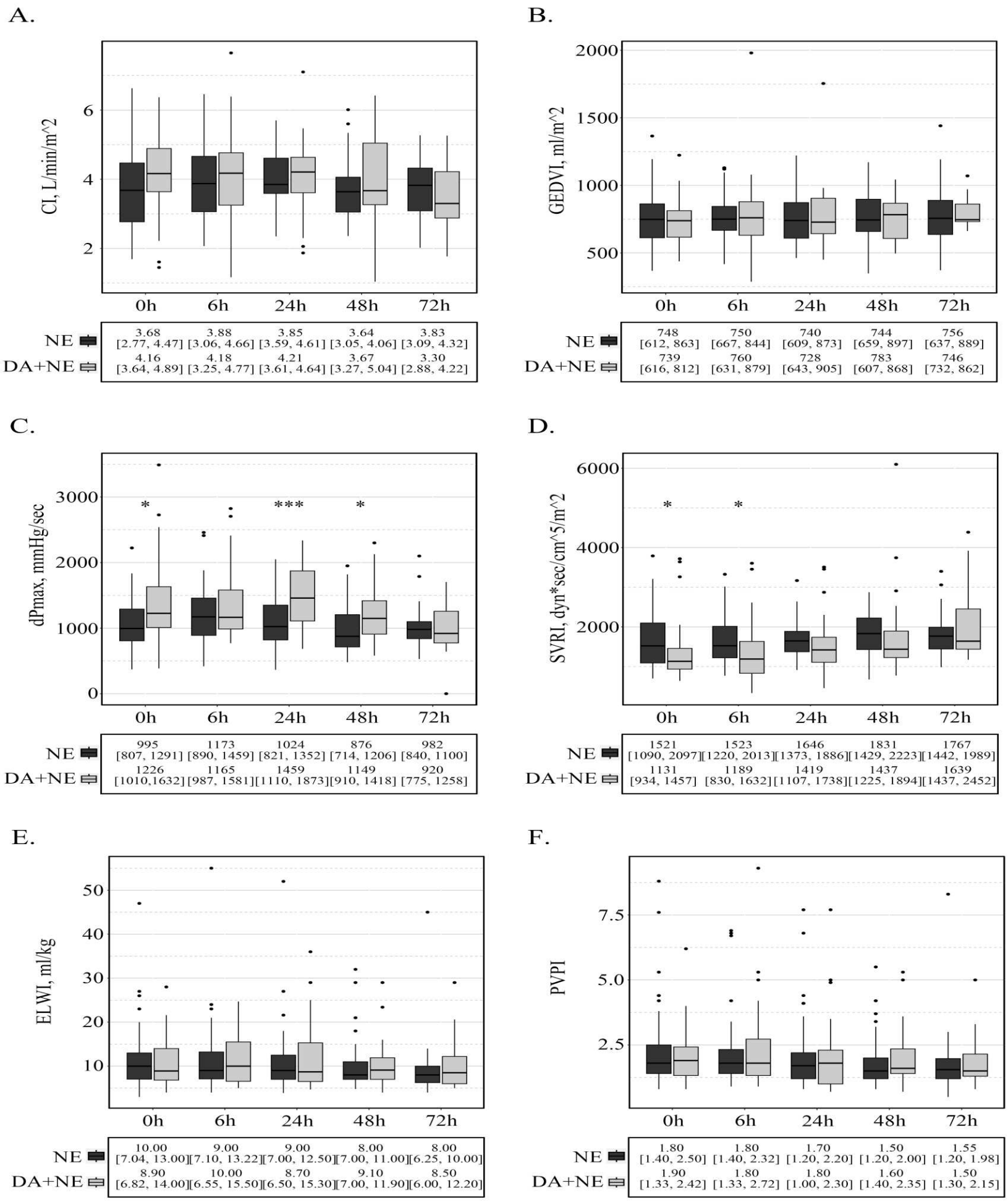
Table 2

	All (n=83)	NE (n=53)	NE+DA (n=30)	P value

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ICU mortality	19 (22.9)	6 (11.3)	13 (43.3)	0.002

To further investigate norepinephrine (NE) is superior to its combination with dopamine (DA) in vasopressor use for improving prognosis and survival in patients with sepsis or septic shock, we also supervised PICCO data and analyzed from the following aspects. According to our PICCO data analysis results (**as shown in Figure 1)**, during the early treatment phase (0 h and 6 h), compared with the NE + DA group, the NE group could significantly increase the systemic vascular resistance index (SVRI), which may reflect the superiority of NE in vasoconstriction. Hemodynamic stability, which is especially important for proper tissue perfusion during sepsis, is maintained by a high SVRI. Additionally, our study revealed that individuals in the NE treatment group were able to considerably lower their dPmax at 24 hours. These findings suggest different cardiac contractility responses between vasopressor strategies.

Figure 1



The pulmonary vascular permeability index (PVPI) and extravascular lung water index (ELWI) did not differ statistically significantly between the NE and NE + DA groups; nevertheless, this also suggests the selection of these parameters in the two treatment approaches might not have significant effects on patient outcomes. These findings emphasize the importance of selecting vasopressors in the treatment of sepsis or septic shock. NE monotherapy may be superior to NE + DA combination therapy in maintaining hemodynamic stability and reducing cardiac load. We analyzed the results of basic vital signs data (**Figure 2)**. In the NE group, heart rate (HR) steadily increased at 0 hours, 6 hours, 24 hours, and 48 hours. The largest increase in mean arterial pressure (MAP) was observed at 6 hours. Notably,

the NE group consistently showed significant decreases in lactate levels at multiple time points compared to the NE + DA group. A significant difference ($P < 0.001$) was found between using norepinephrine alone and combining norepinephrine with dopamine, based on survival analysis using the log-rank test. The survival rate of sepsis patients treated with norepinephrine alone was higher (**Figure 3**).

Figure 2

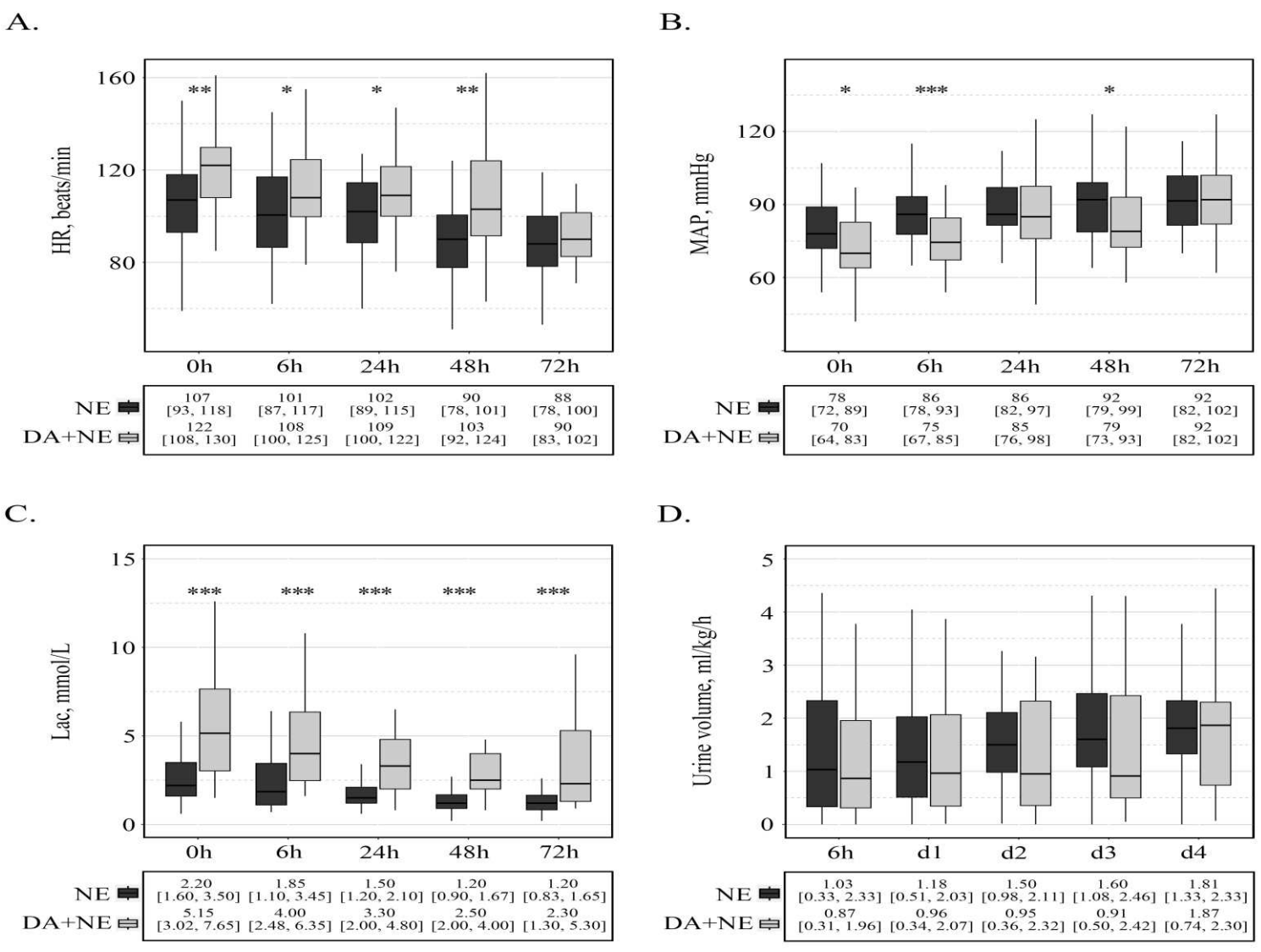
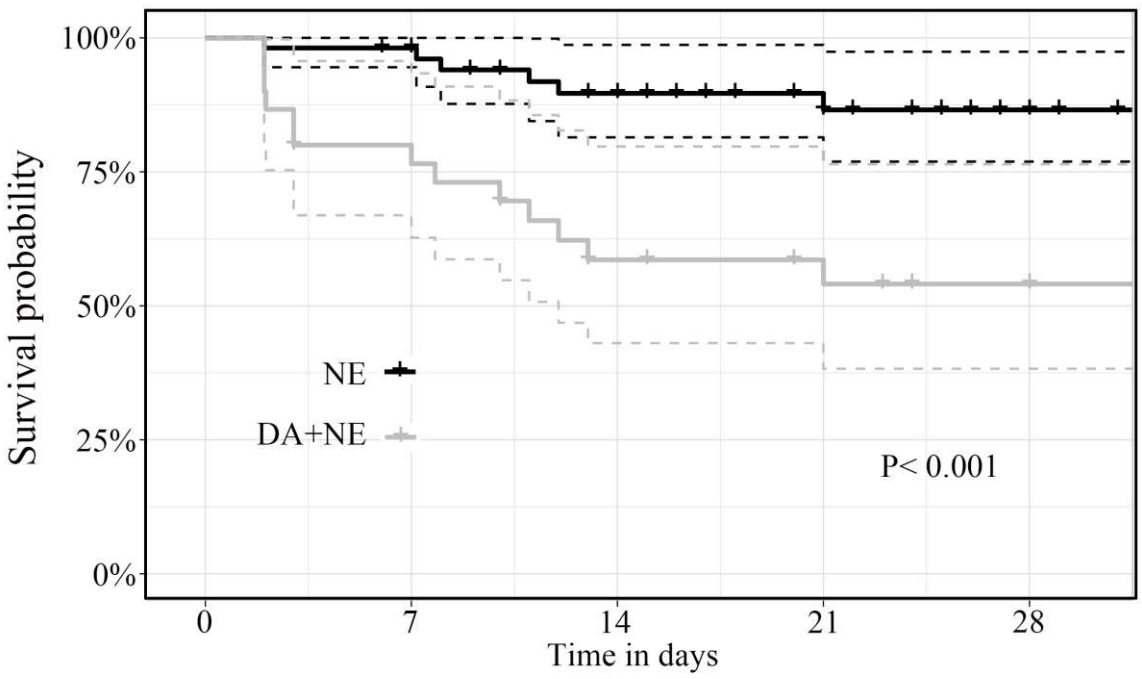


Figure 3



Number at risk: n(%)

NE	53 (100)	51 (96)	39 (74)	29 (55)	18 (34)
DA+NE	30 (100)	23 (77)	15 (50)	13 (43)	10 (33)
	0	7	14	21	28

Analysis and Discussion

According to the Surviving Sepsis Guidelines, norepinephrine should be administered to patients in septic shock in order to maintain stable hemodynamics [23, 24].Furthermore, it is stated that in certain locations where norepinephrine is available, dopamine or adrenaline may be recommended as alternatives; however, caution should be exercised due to the potential risk of arrhythmia [25].The 2021 guidelines observed the function of endogenous positive inotropic drugs in patients with heart failure and chronic hypoperfusion while preserving a suitable blood volume and blood pressure. Patients may switch from norepinephrine to dopamine (as in the Early Goal Directed Therapy trial) or epinephrine, which has higher β-receptor agonistic activity [26].Additionally, some research has shown that norepinephrine and dobutamine together can lower the 28-day mortality rate for septic shock patients, particularly those with low cardiac output [27, 28]. Given that dopamine and norepinephrine are both first-line medications for the treatment of sepsis and septic shock, some researchers carried out an RCT study in 2010.The findings [20] indicated that while dopamine was more likely to induce arrhythmia in patients, there was no statistically significant difference in the 28-day mortality rates between the use of dopamine and norepinephrine.

Both of these medications have varying degrees of effect on α-adrenergic and β-adrenergic receptors [29, 30]. Although the α-adrenergic action narrows blood arteries, it may also decrease regional blood flow and cardiac output [31], particularly in the kidneys, internal organs, and skin.
Through inotropic and chronotropic effects, the β-adrenergic impact contributes to the maintenance of blood flow and the enhancement of internal organ

perfusion [32]. This adrenergic stimulation can also have unexpected consequences, including increased cellular metabolism and immunosuppressive effects. Dopamine also stimulates dopamine receptors, resulting in proportional increases in internal organ and kidney perfusion, and may promote the resolution of pulmonary edema. However, dopamine stimulation can have harmful immune effects by altering hypothalamic - pituitary function, leading to significant decreases in prolactin and growth hormone levels[33].

Therefore, dopamine and norepinephrine may exert different effects on the kidneys, internal organ regions, and the pituitary axis. However, the clinical implications of these differences remain uncertain. Consensus guidelines and expert recommendations indicate that either drug can serve as the preferred vasopressor for shock patients [23,24]. Nevertheless, observational studies have demonstrated that the use of dopamine may be linked to a higher mortality rate compared to norepinephrine [34].The Acute Patient Sepsis Occurrence and Perioperative Mortality (SOAP) study, which included 1,058 shock patients, revealed that dopamine was an independent risk factor for death in the intensive care unit (ICU) [35].According to recent studies and data analysis [20,36], treating sepsis and septic shock with norepinephrine (NE) alone seems to be associated with improved outcomes than using NE and dopamine (DA) together. The β-adrenergic effects of DA can cause arrhythmias and cardiac suppression, especially at higher doses, even though the combination of NE and DA may enhance renal blood flow and encourage diuresis [11, 37]. Because NE is an α-adrenergic agonist, its effects are more direct and stable, which reduces negative cardiovascular effects and promotes cardiovascular stability [38, 39].

Our study contributes to the ongoing discussion about the best vasopressor approach in septic shock. Clinicians should carefully consider the risks of adding dopamine, particularly in patients with higher APACHE II scores, even though norepinephrine is still the recommended medication due to its efficacy in maintaining hemodynamic stability. Future research ought to delve deeper into the underlying mechanisms. Our study has inherent limitations due to its retrospective design. Future studies might reduce bias and improve the validity of the results by using a more exacting randomized controlled trial methodology. To further explain the differences in treatment outcomes at the tissue and cellular levels, such studies could also incorporate additional pathophysiological or molecular biology data. We did not examine how responses varied across patient subgroups (e.g., age, disease severity, or comorbidities), even though the article's conclusion emphasizes the advantages of NE alone. Patients receiving combined norepinephrine and dopamine had greater illness severity, reflected by higher APACHE II scores, which may partially explain the observed differences in outcomes. Although

multivariable analysis was performed, residual confounding cannot be completely excluded. Future research can use a more individualized study approach to create more accurate treatment plans.

Conclusion

In conclusion, NE monotherapy may represent a preferable vasopressor strategy in septic shock; however, prospective studies are required to confirm these findings. NE's ability to increase systemic vascular resistance and improve tissue perfusion, which helps lower lactate levels, supports its role in maintaining hemodynamic stability. To enhance the care of septic patients, future studies should explore the mechanisms of these medications more thoroughly, especially within the context of personalized treatment approaches.

Declarations

Abbreviations

PICCO: Pulse Indicator Continuous Cardiac Output; NA: Norepinephrine; DA: Dopamine.

Ethics approval and consent to participate

This retrospective cohort study was approved by the Ethics Committee of the First Affiliated Hospital of Xiamen University(Approval No. [2026-076]). As the study involved the collection of existing clinical data with anonymization of patient information, the requirement for informed consent was waived by the ethics committee. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to patient privacy restrictions but may be made available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Yujing He, Yaojie Fu, Xiaoyang Cai, and Guiyang Lu were primarily responsible for the experimental design, data acquisition, and preliminary analysis. Xie served as the corresponding author, providing overall project supervision, conceptual guidance, and critical revisions to the manuscript. All authors have read and approved the final version of this work.

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