Effect of mean heart rate on 30-day mortality in older patients with sepsis: Data from the MIMIC-IV database

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ABSTRACT

Background: Sepsis is a critical condition with a significant risk of mortality. Advanced age is one factor in increasing mortality in intensive care.

Objectives: The aim of this study is to investigate the association between mean heart rate (MHR) and 30-day mortality among older patients with sepsis in the intensive care unit (ICU).

Methods: All older patients (age 65 or older) with sepsis for first time in ICU admission in Medical Information Mart for Intensive Care-IV (MIMIC-IV) were included in this retrospective study. The effect of MHR within 24 h of ICU admission on 30-day mortality was assessed according to multivariable Cox regression models, restricted cubic splines and two-piecewise Cox regression models.

Results: The total number of participants was 6598 (mean heart rate, 83.8 ± 14.3 bpm). A total of 1295 (19.6%) patients died within 30 days after ICU admission. MHR within 24 h of admission was associated with 30-day mortality (J-shaped association) in older patients with sepsis in the ICU, with an inflection point at about 74 bpm and a minimal risk observed at 73 to 82 bpm of MHR.

Conclusions: In this retrospective cohort study, there was a J-shaped association between MHR and 30-day mortality in older patients with sepsis admitted to the ICU and a minimal risk observed at 73 to 82 bpm of MHR. If further confirmed, this association may provide a theoretical basis for formulating the target strategy of heart rate therapy for these patients.

Keywords: Heart rate; 30-day mortality; Sepsis; Older patients; Intensive care unit. **[Am J Med Sci 2025;369(2):176–182.]**

BACKGROUND

Sepsis is a common condition with high morbidity and mortality which affecting millions of people worldwide every year.[1] Immune function decreases put older adults at increased risk both of developing an infection and for developing an infection with a more severe and protracted course.[2] Although advances in diagnosis and management of sepsis have led to significant improvements in outcomes across all ages, overall mortality in older adults remains high.

Heart rate is an important vital sign and its measurement can be used to identify patients at increased risk of disease progression and to guide the choice of therapy.[3,4] The relationship between heart rate variability and outcomes in patients with sepsis has been explored in previous studies.[5–7] However, most studies have been in the neonatal population.[8–10] There is a lack of evidence on the relationship between heart rate and outcomes in older patients with sepsis. Therefore, our aim was to investigate the correlation between MHR within 24 h of admission and 30-day mortality in older patients with sepsis.

MATERIALS AND METHODS

Data source

This was a retrospective cohort study of older patients with sepsis admitted to ICU. Data were extracted from the MIMIC-IV database (version: 2.2) (https://doi.org/10.13026/6mm1-ek67) between 2008 and 2019.[11] Na Li completed the Collaborative Institutional Training Examination and completed the data extraction (Record ID: 42,252,205). The Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center review boards approved the use of the MIMIC-IV database. All patient information is de-identified, so we do not require informed consent or ethical approval from patients.

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Table 1. Baseline characteristics of patients stratified by 30-day mortality.

Variables	Total(*n* = 6598)	Survivors(*n* = 5303)	Non-survivors (*n* = 1295)	P-value
Gender, n(%)				< 0.001
Male	3867 (58.6)	3168 (59.7)	699 (54)	
Female	2731 (41.4)	2135 (40.3)	596 (46)	
Age, years	75.2 ± 6.7	74.9 ± 6.5	76.7 ± 7.0	< 0.001
BMI, kg/m^2	28.6 ± 6.1	28.8 ± 6.0	27.5 ± 6.4	< 0.001
race, n (%)				< 0.001
White	4724 (71.6)	3904 (73.6)	820 (63.3)	
Black	366 (5.5)	275 (5.2)	91 (7)	
Asian	158 (2.4)	128 (2.4)	30 (2.3)	
Hispanic or Latino	133 (2.0)	111 (2.1)	22 (1.7)	
Other	1217 (18.4)	885 (16.7)	332 (25.6)	
Minimum HR, bpm	68.7 ± 13.8	68.0 ± 13.1	71.3 ± 16.1	< 0.001
Maximum HR, bpm	102.9 ± 20.4	101.3 ± 19.4	109.1 ± 23.1	< 0.001
MHR, bpm	83.8 ± 14.3	82.9 ± 13.5	87.6 ± 17.0	< 0.001
MBP, mmHg	74.8 ± 8.7	74.8 ± 8.4	74.8 ± 9.8	0.769
Mean respiratory rate, times/min	19.1 ± 3.7	18.7 ± 3.4	20.8 ± 4.2	< 0.001
Mean spo2,%	97.3 ± 2.0	97.4 ± 1.8	96.7 ± 2.8	< 0.001
Mean blood glucose, mg/dl	131.9 (118.4, 155.3)	130.5 (118.5, 150.0)	143.3 (118.0, 182.1)	< 0.001
Mean body temperature, °C	36.8 ± 0.5	36.8 ± 0.5	36.8 ± 0.7	0.005
Lactate, mmol/L	3.1 ± 2.4	3.0 ± 2.1	3.7 ± 3.1	< 0.001
Anion gap, mEq/L	16.0 ± 5.0	15.3 ± 4.5	18.8 ± 5.8	< 0.001
White blood cell, 10^9/L	16.1 ± 13.0	15.7 ± 10.6	17.8 ± 19.9	< 0.001
SAPSII	44.0 ± 13.3	42.2 ± 12.3	51.6 ± 14.4	< 0.001
SOFA score	3.7 ± 2.0	3.6 ± 1.9	4.1 ± 2.3	< 0.001
Charlson comorbidity index	6.8 ± 2.4	6.5 ± 2.2	7.9 ± 2.6	< 0.001
Metastatic solid tumor, n (%)				< 0.001
No	6284 (95.2)	5132 (96.8)	1152 (89)	
Yes	314 (4.8)	171 (3.2)	143 (11)	
Congestive heart failure, n (%)				< 0.001
No	4198 (63.6)	3503 (66.1)	695 (53.7)	
Yes	2400 (36.4)	1800 (33.9)	600 (46.3)	
Dementia, n (%)				< 0.001
No	6288 (95.3)	5103 (96.2)	1185 (91.5)	
Yes	310 (4.7)	200 (3.8)	110 (8.5)	
Severe liver disease, n (%)				< 0.001
No	6415 (97.2)	5212 (98.3)	1203 (92.9)	
Yes	183 (2.8)	91 (1.7)	92 (7.1)	
Malignant cancer, n (%)				< 0.001
No	5787 (87.7)	4742 (89.4)	1045 (80.7)	
Yes	811 (12.3)	561 (10.6)	250 (19.3)	
Chronic pulmonary disease, n (%)				0.001
No	4636 (70.3)	3773 (71.1)	863 (66.6)	
Yes	1962 (29.7)	1530 (28.9)	432 (33.4)	
Diabetes, n (%)				0.691
No	5950 (90.2)	4786 (90.3)	1164 (89.9)	
Yes	648 (9.8)	517 (9.7)	131 (10.1)	
Renal disease, n (%)				< 0.001
No	4921 (74.6)	4049 (76.4)	872 (67.3)	
Yes	1677 (25.4)	1254 (23.6)	423 (32.7)	
Hospital LOS, days	12.7 ± 11.7	13.2 ± 12.5	10.4 ± 7.2	< 0.001
ICU LOS, days	6.2 ± 7.4	5.9 ± 7.8	7.4 ± 5.4	< 0.001

For each variable, mean ± standard deviation, median (interquartile range), or number (percent) was reported (as appropriate).
Abbreviations: BMI, body mass index; HR, heart rate; MHR, mean heart rate; bpm, beats per minute; MBP, mean blood pressure; SpO2, pulse oximetry derived oxygen saturation; SAPSII, the simplified acute physiology score II; SOFA, the sequential organ failure assessment; LOS, length of stay; ICU, intensive care unit.

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Study population

The inclusion criteria were as follows: patients ≥65 years old who met Sepsis-3 diagnostic criteria. Sepsis is defined by the presence of a documented or suspected infection in a patient with a change of ≥2 points in the Sequential Organ Failure Assessment (SOFA) total score. Exclusion criteria were (1) patients admitted to hospital or ICU several times; (2) patients with hospital or ICU stay <24 h; (3) patients who aged <65 years and aged ≥90years; (4) lack of MHR data; (5) lack of BMI data (Missing >30%) and BMI <15, >50 kg/m^2.

Data extraction

Structured Query Language (SQL) and Navicate Premium software (version 16.1.7) were used to extract the data. The variables extracted include: (1) baseline characteristics:age,gender,ethnicity,BMI; (2) vital signs and laboratory parameters within 24 h of ICU admission; (3) severity scoring system:Sequential Organ Failure Assessment (SOFA) score,Simplified Acute Physiology Score II (SAPS II) score and Charlson comorbidity index; (4) comorbidities: chronic heart failure (CHF) ,chronic pulmonary disease,dementia,severe liver disease,malignant cancer,renal disease and diabetes.

Variable definition and primary outcome

The MHR was defined as the calculated mean of heart rate measurements within 24 h of admission to the ICU. The primary outcome was mortality within 30 days.

Statistical analysis

All analyses were performed with the statistical software package, R (http://www.r-project.org, The R Foundation), and Free Statistics software, version 1.7. Participants were divided into three groups based on the 25th and 50th percentile of the MHR. A median was used to replace missing data. Continuous variables are presented as mean ± standard deviation (SD) or median with interquartile ranges (IQR) and compared using appropriate statistical tests such as Student's *t*-test and Wilcoxon rank-sum test. Categorical variables are reported as frequencies and percentages, and their differences were analyzed using the Chi-squared test or Fisher's exact test.

Four models were applied in the COX regression analysis to assess the association between MHR and 30-day mortality. The hazard ratio (HR) is calculated every 10 times/minute increase when MHR is a

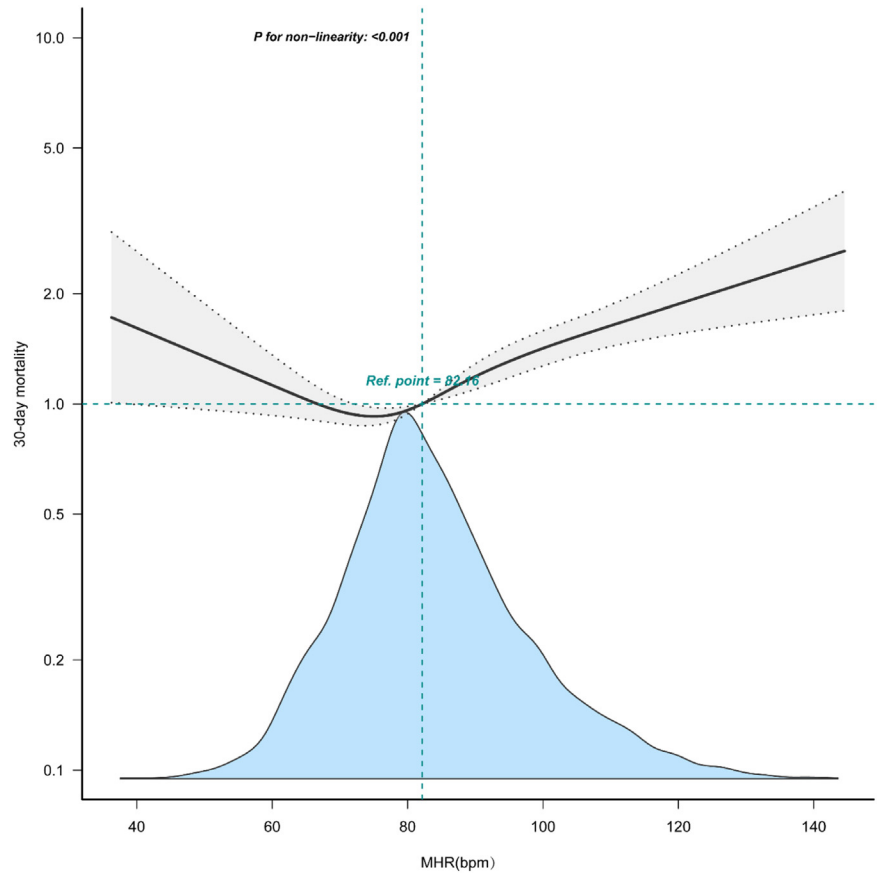

FIG. 1. Dose-response relationship between MHR and 30-day mortality.
Abbreviations: MHR, mean heart rate.

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Table 2. Hazard ratio and 95 % CI of mean heart rate for 30-day mortality.

Variable	Number of deaths (%)	Model 1		Model 2		Model 3		Model4	
		HR (95 % CI)	P-value	HR (95 % CI)	P-value	HR (95 % CI)	P-value	HR (95 % CI)	P-value
MHR per10, bpm	1295 (19.6)	1.22 (1.18~1.27)	<0.001	1.23 (1.19~1.28)	<0.001	1.21 (1.16~1.25)	<0.001	1.12 (1.08~1.16)	<0.001
MHR tertials, bpm									
< 73	289 (18.3)	1.26 (1.06~1.49)	0.008	1.23 (1.04~1.46)	0.016	1.17 (0.99~1.38)	0.073	1.08 (0.91~1.28)	0.389
≥ 73,<82	251 (14.9)	1(Ref)		1(Ref)		1(Ref)		1(Ref)	
≥82	755 (22.6)	1.6 (1.38~1.84)	<0.001	1.63 (1.41~1.88)	<0.001	1.5 (1.3~1.73)	<0.001	1.32 (1.14~1.53)	<0.001
P for trend			<0.001		<0.001		<0.001		0.001

Abbreviations: MHR, mean heart rate; bpm, beats per minute, HR, hazard ratio; CI, Confidence interval.
Model 1: no adjusted.
Model 2: adjusted for gender, age, and race.
Model 3: adjusted for model 2 plus BMI, mean blood glucose, mean body temperature, white blood cell, SpO2, and MBP.
Model 4: adjusted for model 3 plus SOFA score, SAPS II, and Charlson's comorbidity index.

continuous variable. Covariates were adjusted for with a change of >10 % in impact estimates or based on their associations with the outcomes of interests. Model I was not adjusted. Model II was adjusted for age, gender. Model III was adjusted for Model II plus BMI, mean glucose, mean temperature, White blood cell (WBC), pulse oximetry derived oxygen saturation (SpO2) and mean blood pressure (MBP). Model IV was adjusted for Model III plus Charlson comorbidity index, SAPSII and SOFA.

In addition, we used restricted cubic spline (RCS) models to investigate the possible non-linear association between MHR and 30-day mortality. We investigate the dose-response curve between MHR and 30-day mortality after adjusting variables in Model IV. We utilized a two-piece-wise logistic regression model with smoothing to analyze the association threshold between MHR and 30-day mortality after adjusting the variables in Model IV. The likelihood-ratio test and the bootstrap resampling method were used in determining inflection points. A subgroup analysis was conducted based on gender, race, chronic pulmonary disease, diabetes CHF, and renal disease. Kaplan−Meier method was used to estimate the absolute risk of each event for each group. $P < 0.05$ indicates a statistically significant difference.

RESULTS

Baseline characteristics of study participants

The patient selection flowchart is shown in Supplementary S1 and 6598 patients were included in this study. 1295 (19.6 %) patients died within 30 days of being admitted to the ICU. The mean heart rate was 83.8 bpm (SD 14.3) and higher heart rate parameters in deceased patients compared to survivors. The mean age was 75.2 years (SD 6.7) and the male was 58.6 %. The mean blood glucose was 131.9 mg/dl. Lactate, anion gap and mean respiratory rate were markedly elevated, compared with Survivors. SOFA score, SAPS II and Charlson comorbidity index were higher among non-survivors. Compared to survivors, it was more likely to be combined with many other diseases (Table 1).

Effects of MHR on 30-day mortality in older patients with sepsis

A univariate Cox analysis regression model was used to examine variables for predicting 30-day mortality (Supplementary S2). There were significant differences among the variables, such as age, gender, BMI, MHR, chronic pulmonary disease, renal disease, HR, mean respiratory rate, temperature, SpO2, anion gap, Lactate, SOFA score, and SAPSII score are all statistically significant ($p < 0.05$).

A J-shaped association of MHR with 30-day mortality was observed in multivariable-adjusted restricted cubic spline analyses (Fig. 1, $p < 0.001$). In the multivariable Cox models presented in Table 2, our finding showed that there was an increased risk of 30-day

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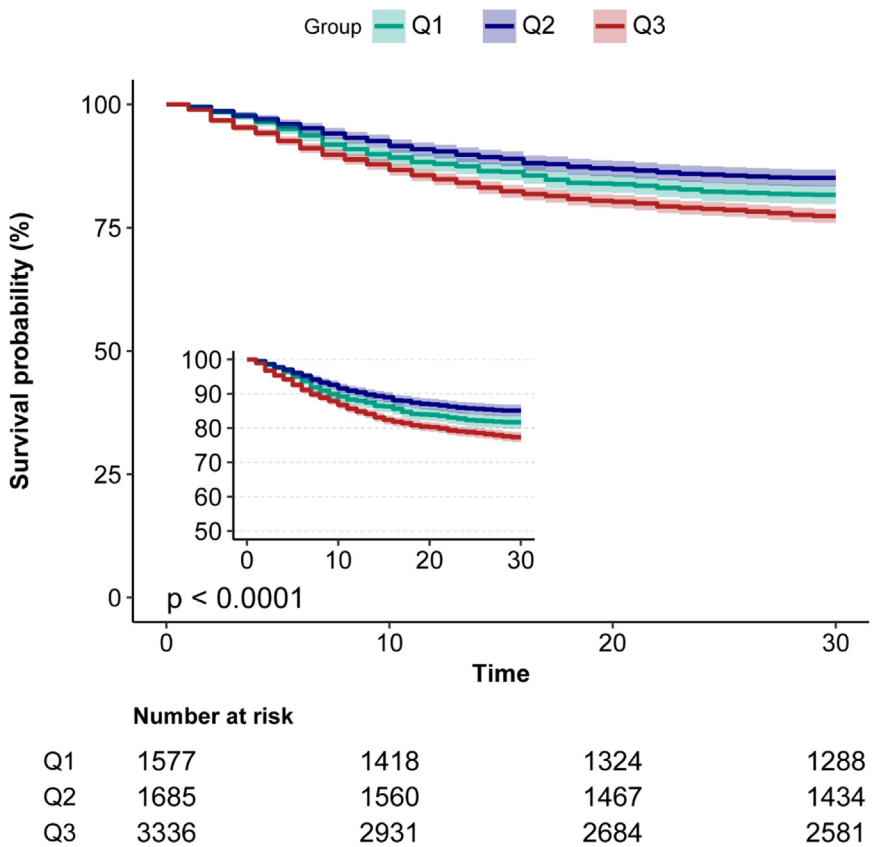

FIG. 2. Kaplan–Meier analysis for 30-day survival probability in older patients with sepsis.
Q1:MHR< 73 bpm; Q2:≥73,<82 bpm; Q3≥82 bpm
Abbreviations: MHR, mean heart rate; bpm, beats per minute.

mortality among patients in group 1 (<73 bpm; adjusted HR, 1.08; 95 % CI, 0.91–1.28) and group 3 (≥ 82 bpm; adjusted HR, 1.32; 95 % CI, 1.14–1.53) compared to those in group 2 (≥73, <82 bpm).When MHR was used as a continuous variable, there was a significant 12 % increase in 30 days mortality per 10 unit of MHR (adjusted HR = 1.12, 95 % CI: 1.08–1.16, $P < 0.001$). Kaplan–Meier curve showed there was lowest mortality by day 30 in patients with 73≤MHR <82 bpm ($p < 0.0001$,Fig. 2). We found that the turning point of MHR was 74 bpm by using a two-piece Cox regression model. At MHR≥74 bpm, with each 1-bpm increment in MHR, the risk of 30-day mortality increased 1.8% (HR 1.018, 95 % CI 1.013–1.023, P < 0.001) (Table 3).

Supplementary S3 shows the stratified analyses of the associations between MHR and 30-day mortality. The outcome was still robust after subgroup analysis by confounders, and we did not observe any significant interaction in the subgroups.

Table 3. Threshold analyses of MHR on 30-day mortality using two-piecewise regression models.

Threshold of MHR, bpm	Adjusted Model	
	HR (95 % CI)	P-value
< 74	0.9921 (0.973,1.0116)	0.4264
≥74	1.018 (1.013,1.023)	< 0.001
Likelihood Ratio test		0.009

Abbreviations: MHR, mean heart rate; bpm, beats per minute; HR, hazard ratio; CI, confidence interval.
Adjustment factors included gender, gender, age, race, BMI, mean blood glucose, mean body temperature, white blood cell, SpO2, MBP, SOFA score, SAPS II, and Charlson's comorbidity index.

DISCUSSION

Our study demonstrated that MHR within 24 h of ICU admission was independently associated with 30-day mortality. A typical J-shaped curve relationship between MHR and 30-day mortality was observed in our study population, with an inflection point of 74 bpm and the lowest risk observed at 73≤MHR<82 bpm.

Previous studies have found an association between heart rate and the prognosis of heart failure, cancer, myocardial infarction, brain hemorrhage and many other

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diseases.[12–15] Heart rate has been previously reported in predicting mortality in patients with sepsis. Morelli A et al. reported that the heart rate of 80–94 bpm is a sufficient therapeutic threshold and reducing HR may be a viable therapeutic target for a specific subset of septic patients.[16] In another sepsis cohort, A higher MHR was associated with an increased risk of death.[17] A meta-analysis study suggests that chronically elevated HR is associated with an increased incidence of major cardiac events in critically ill patients and that esmolol controls HR to reduce 28-day mortality in patients with sepsis.[18] Our finding is consistent with previous studies that have shown a correlation between tachycardia and poor outcomes in sepsis patients. However, few studies have examined the association that exists between heart rate and prognosis in the older sepsis patients.

Our study concerns short-term mortality in older sepsis patients. The mean age of the study population was 75.2 years. Higher heart rate parameters in deceased patients compared to survivors. Heart rate control in patients with sepsis has been shown in many studies to be associated with improved survival. The underlying pathophysiology of sepsis-induced tachycardia is calcium dysregulation and excessive adrenergic responses.[19] Tachycardia may reflect the severity of infection, the degree of inflammation, and the activation of the sympathetic nervous system, which can lead to cardiovascular dysfunction and organ damage.[20]

Our findings have important clinical implications. The measurement of heart rate is a simple and non-invasive procedure that can be easily performed in the ICU. The identification of patients at higher risk of mortality based on heart rate can help clinicians to initiate early interventions and optimize patient outcomes. For example, patients with a higher heart rate may require more aggressive fluid resuscitation, vasopressor support, or other interventions aimed at reducing inflammation and improving organ function.

Our study has several limitations. Firstly, the data is limited to patients who were admitted to intensive care units (ICUs), which may not accurately represent the entire population of older sepsis patients. Furthermore, the MIMIC database only includes patients from a single healthcare system in the United States, which may not be representative of other healthcare systems or patient populations in different countries. This limits the generalizability of any findings from the analysis. Another limitation is the potential for confounding variables, such as comorbidities or medications, that may impact both heart rate and mortality. These variables may not be fully accounted for in the analysis, leading to inaccurate conclusions. Finally, while the MIMIC database provides a wealth of clinical data, it may not capture all relevant information for analyzing the relationship between heart rate and mortality in elderly sepsis patients. For example, factors such as social determinants of health or patient preferences may play a role in outcomes but may not be captured in the database. Thus, further research using multiple databases and accounting for additional factors is necessary to fully understand this relationship.

CONCLUSIONS

In conclusion, our study demonstrates that the MHR within 24 h of ICU admission is a J-shaped association with 30-day mortality in older sepsis patients. A minimal risk observed at 73 to 82 bpm of MHR. Further studies are needed to confirm our findings and explore potential interventions to reduce heart rate and improve outcomes in septic patients.

AVAILABILITY OF DATA AND MATERIALS

All datasets used during the present study are publicly available in the MIMIC-IV v2.2 database (https://mimic.physionet.org/).

ETHICS STATEMENT

MIMIC-IV is an anonymized public database. The Massachusetts Institute of Technology (MIT) and Beth Israel Deaconess Medical Center (BIDMC) institutional review boards approved the project and waived informed consent.

AUTHORS' CONTRIBUTIONS

All authors contributed to the study conception and design. NL and YX.M designed the study. QZ and JN L drafted the manuscript. QZ and NL extracted the data from the MIMIC-IV database. QZ and YX.M performed the statistical analysis. NL guided the literature review. All authors read and approved the final manuscript.

DECLARATIONS OF COMPETING INTEREST

All authors declared no conflict of interest in this study.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.amjms.2024.08.006.

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