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Research article

Cardiac index and heart rate as prognostic indicators for mortality in septic shock: A retrospective cohort study from the MIMIC-IV database

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ABSTRACT

Background: Septic shock is a life-threatening condition that can lead to organ dysfunction and death. In the ICU, monitoring of cardiac index (CI) and heart rate (HR) is commonly used to guide management and predict outcomes in septic shock patients. However, there is a lack of research on the association between CI and HR and the risk of mortality in this patient population. Therefore, the aim of this study was to investigate the relationship between different levels of CI and HR and mortality in septic shock patients.

Methods: Data analysis was obtained from the MIMIC-IV version 2.0 database. Sepsis and septic shock were primarily defined by sepsis-3, the third international consensus on sepsis and septic shock. CI was computed using cardiac output (CO) and body surface area (BSA). To evaluate the incidence of CI with respect to each endpoint (7-, 14-, 21-, and 28-day mortality), a restricted cubic spline curve function (RCS) was used. The optimal cutoff value for predicted mortality was determined using the Youden index. Analyses of KM curves, cox regression, and logistic regression were conducted separately to determine the relationship between various CI and HR and 28-day mortality.

Results: This study included 1498 patients with septic shock. A U-shaped relationship between CI levels and risk of mortality in septic shock was found by RCS analysis ($p < 0.001$). CI levels within the intermediate range of 1.85–2.8 L/min/m^2 were associated with a mortality hazard ratio (HR) < 1. In contrast, low CI (HR = 1.87 95% CI: 1.01–3.49) and high CI (HR = 1.93 95% CI: 1.26–2.97) had a significantly increased risk of mortality. The AUC for heart rate prediction of mortality by Youden index analysis was 0.70 95%CI:0.64–0.76 with a cut-off value of 93.63 bpm. According to the characteristics of HR and CI, patients were divided into six subgroups HR↓+CI intermediate group (n = 772), HR↓+CI↓ group (n = 126), HR↓+CI↑ group (n = 294), HR↑+CI intermediate group (n = 132), HR↑+CI↓ group (n = 24), and HR↑+CI↑ group (n = 150). The KM curves, COX regression, and logistic regression analysis showed that the survival rates the of HR↓+CI intermediate group, HR↓+CI↓ group, and HR↓+CI↑ were higher than the other groups. The risk factors of HR↑+CI intermediate group, HR↑+CI↓, and HR↑+CI↑ with ICU 28-day

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mortality were HR = 2.91 (95% CI: 1.39–5.97), HR = 3.67 (95% CI: 1.39–11.63), and HR = 5.77 (95% CI: 2.98–11.28), respectively.

Conclusion: Our retrospective study shows that monitoring cardiac index and heart rate in patients with septic shock may help predict the organismal response and hemodynamic consequences, as well as the prognosis. Thus, healthcare providers should carefully monitor changes in these parameters in septic shock patients transferred to the ICU for treatment.

List of abbreviation

AaDO2	Alveolar-arterial oxygen partial pressure difference
APSIII	Acute Physiology Score III
AUC	Area Under the Cure
CI	Cardiac index
CO	Cardiac output
COPD	Chronic obstructive pulmonary disease
CVP	Central venous pressure
DBP	Diastolic blood pressure
ICU	Intensive care unit
HR	Heart rate
LODS	Logistic Organ Dysfunction System
MBP	Mean arterial blood pressure
MIMIC-IV	Medical Information Mart for Intensive Care IV
OR	Odd ratio
ROC	Receiver operating characteristic (curve)
RCS	Restricted cubic spline
SAPS II	Simplified Acute Physiology Score II
SBP	Systolic blood pressure
SOFA	Sequential Organ Failure Assessment (Score)

1. Introduction

Septic shock is a life-threatening condition characterized by dysregulated host response to infection, resulting in severe circulatory, cellular, and metabolic disturbances [1,2]. This rapidly evolving disease presents significant challenges in treatment and is associated with high mortality rates. Despite current intensive care unit (ICU) interventions such as aggressive fluid resuscitation, vasoactive drug administration, and mechanical ventilation, mortality rates remain unacceptably high, reaching up to 50% [3–6]. Therefore, early recognition of septic shock and prompt, effective treatment is essential [7–9].

During the initial phases of septic shock, the body increases cardiac output (CO) by increasing heart rate (HR), myocardial contractility, and other mechanisms to maintain hemodynamic stability [10]. Nonetheless, as the disease progresses and the cardiovascular system loses its adaptability to infection, cardiac output may progressively decrease, leading to inadequate organ perfusion and multiorgan failure, which increases the risk of death [5,11,12]. The cardiac index (CI) is the ratio of the volume of blood circulated by the heart to the body surface area (BSA) [13]. It is recommended that the cardiac index is one of the most important hemodynamic variables for assessing cardiac function and guiding the treatment of critically ill patients in the ICU [2]. Low CI may be associated with mortality in critically burned patients, and heart failure, according to prior research [14,15]. Tachycardia can be a symptom of sepsis caused by multiple potential determinants, such as fever, hypovolemia, sympathetic tone, and exogenous catecholamines [16]. According to reports [17,18], an elevated HR is an independent risk factor for mortality during severe sepsis and septic shock. Tachycardia can compromise the diastolic filling of the left ventricle (reduced cardiac output), alter coronary blood flow, and increase myocardial oxygen demand [19]. In addition, there has been no study that has demonstrated a correlation between CI and HR with the pathogenesis and prognosis of septic shock. The identification of CI and HR will therefore aid in the comprehension of the pathogenesis of septic shock as well as its function in diagnosis, treatment, and prognosis prediction.

In this retrospective study, we investigated the relationship between CI and HR and patient prognosis in a cohort of patients with septic shock. We discovered, through statistical methods and data analysis, that CI and HR were substantially correlated with survival in patients with septic shock, indicating that CI and HR may be useful predictors of prognosis in patients with septic shock. Our research provides clinicians with novel concepts and strategies for assessing the prognosis of patients with septic shock and developing more individualized treatment plans to enhance patient survival and treatment outcomes.

2. Research methodology

2.1. Data sources

We conducted a retrospective cohort study using electronic health records from the MIMIC-IV database, a large open-access database [20,21]. Between 2008 and 2019, the database included 76,944 intensive care patients admitted to Beth Israel Deaconess Medical Center in Boston, Massachusetts. One author, Ngan Chansokhon, has passed the Collaborative Institutional Training Initiative examination (certificate number: 10769308) and has been granted database access for data extraction.

2.2. Inclusion criteria

This retrospective cohort study was conducted based on MIMIC-IV (version 2.0) data. Inclusion criteria were as follows: Sepsis and septic shock were defined according to the third international consensus definition of sepsis and septic shock (sepsis-3) [6,9,22]. Sepsis is defined as life-threatening organ dysfunction resulting from a dysregulated host response caused by infection, clinically determined by a sequential organ dysfunction assessment (SOFA) score $\geq$2, which includes patients with confirmed or suspected infection. Septic shock was defined as MAP $<$65 mmHg or vasopressors within 24 h of ICU admission and serum lactate $>$2 mmol/L within 24 h of ICU admission. we used the time of first ICU admission only for patients with multiple ICU admissions. We excluded the following: (1) patients $<$18 years of age; (2) patients discharged 24 h after ICU admission; (3) patients who did not receive vasoactive drugs within 24 h after ICU admission; (4) congestive heart failure; (5) patients for whom CI and HR data were not collected; (6) patients whose time point of sepsis was not within the time frame of the first day of ICU admission.

2.3. Data collection and extraction

The data extraction process for this retrospective cohort study involved using the PostgreSQL tool (version 16.0) to collect patient medical data such as demographics, signs and symptoms, laboratory test results, and treatment. The data collection started within 24 h of admission to the ICU. The study focused on the use of vasoactive drugs such as vasopressin, epinephrine, phenylephrine, norepinephrine, dobutamine, and dopamine. The primary outcome measure was mortality at 28 days after admission to the ICU, while secondary outcomes included ICU mortality, in-hospital mortality, length of ICU stay, and length of hospital stay.

We collected data on cardiac output and calculated cardiac index within 24 h of admission to the ICU, representing the early phase of septic shock.

2.4. Definition of cardiac index

On the first day of ICU admission, we collect data on the cardiac output by passing it through the codes of item_id (228178, 228369, 220088, 224842, 229897, 227543). The cardiac index, which takes into account the patient's body size, can be calculated using the following formula:

$$CI = CO/BSA$$

where CI is the cardiac index expressed in L/min/m^2, CO is the cardiac output in L/min, and BSA is the body surface area in square meters (m^2). The Du Bois equation can be used to calculate BSA, which depends on the patient's weight and height, as follows [23]:

$$BSA = (0.007184) * \left(M^{0.425}\right) * (H)^{0.725}$$

Where M is the patient's body weight in kilograms and H is the patient's height in centimeters.

2.5. Statistical analysis

In this study, baseline characteristics and other clinical variables were compared between the categories of septic shock patients who survived and those who perished. Continuous variables were presented as mean $\pm$ standard deviation (SD) or median and interquartile range (IQR) according to their different distributions. We used T-tests, chi-square (χ2) tests, or Wilcoxon rank sum tests to compare the characteristics of the two groups of patients, as appropriate.

The restricted cubic spline model (RCS) [24]was employed to assess the potential nonlinear relationship between CI levels and mortality risk in septic shock patients. Using RCS curve analysis, we determined threshold characteristics of CI for predicting 7-day, 14-day, 21-day, and 28-day mortality following ICU admission. The area under the receiver operating characteristic (ROC) curve was used to evaluate the predictive performance of heart rate (HR) levels for 28-day mortality upon ICU admission, with the optimal threshold determined using the Youden index [25,26].

Patients were stratified into subgroups based on CI and HR thresholds, and survival curves at day 28 were estimated using the Kaplan-Meier method. Univariate and multivariate Cox regression or logistic regression analyses (with inclusion criteria of $P < 0.05$ for univariate Cox regression in multivariate analysis) were conducted to assess the association between CI and HR subgroups and mortality risk. All statistics were processed, analyzed, and plotted using R software version 4.2.3, and $P < 0.05$ was considered statistically significant.

3. Results

3.1. Patient characteristics

In the MIMIC-IV dataset, 15,352 patients met the criteria for sepsis 3.0, and 1498 patients with septic shock were ultimately included in this study (see Fig. 1 for a flowchart). The median age of the patients was 68.4 years (IQR: 60.5–77.4), with 66.4% being male and predominantly Caucasian. The mean CO level on the first day of ICU admission was 5.16 ± 1.50 L/min and the mean CI level was 2.57 ± 0.68 L/min/m^2 and the median mean HR was 83.2 bpm (IQR: 77.6–91.0). This corresponded to a similar trend of increase in the CI and CO values in all groups. The median length of stay in the ICU was 2.33 days (IQR: 1.33–2.08), and the ICU mortality rate was 98 (6.54%), with a total 28-day mortality rate of 117 (7.81%). Other clinical information, such as vital signs, comorbidities, medications, and laboratory tests in the ICU, are also presented in Table 1. Characteristics and outcomes differed significantly between survivors and non-survivors.

3.2. Association between cardiac index levels and mortality

RCS curve analysis revealed that the association between CI levels and risk of mortality (7-day mortality, 14-day mortality, 21-day mortality, and 28-day mortality) is U-shaped (nonlinear $P < 0.001$, Fig. 2A–H). Both low and high levels of cardiac index were associated with an increased risk of mortality. According to RCS's univariate Cox regression analysis, a cardiac index between 1.85 and 2.80 L/min/m^2 was not associated with mortality. With increasing CI up to 1.85 L/min/m^2, the risk of mortality decreased to a minimum and then increased with CI > 2.8 L/min/m^2 (HR > 1). In spite of additional adjustments for confounding variables, the shape of the regression curve remained unchanged. According to Table 2, patients were classified into low CI (CI < 1.85 L/min/m^2, n = 150), intermediate CI (intermediate CI:1.85–2.8 L/min/m^2, n = 904), and high CI (CI > 2.8 L/min/m^2, n = 444). Patients with lower CI levels (CI < 1.85 L/min/m^2) were more likely to be elderly, female, have a high CVP, utilize more epinephrine, and develop COPD complications. Patients with pancreatitis, respiratory failure, severe liver disease, 28-day ICU mortality, ICU mortality, hospital mortality, ICU stay time, and hospital stay time were all lower in the CI intermediate group (CI: 1.85–2.8 L/min/m^2). Interestingly, differences in diastolic blood pressure (DBP), systolic blood pressure (SBP), and mean blood pressure (MBP) among CI groups were not

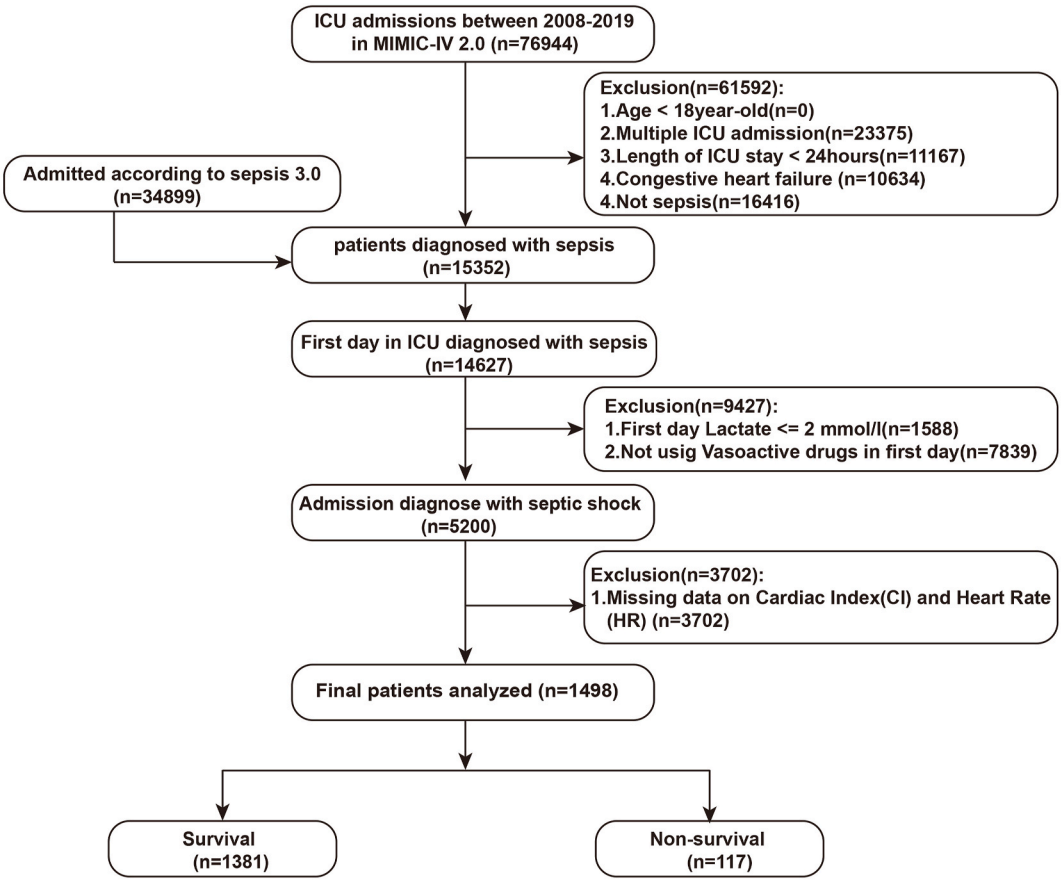


Fig. 1. Flow chart of the Study population. MIMIC Medical Information Mart for Intensive Care.

Table 1
Baseline characteristics of included septic shock.

Variables	ALL N = 1498	Survival N = 1381	Non-survival N = 117	P value
ICU mortality,n (%)	98 (6.54%)	4 (0.29%)	94 (80.3%)	<0.001
Hospital mortality,n (%)	113 (7.54%)	8 (0.58%)	105 (89.7%)	<0.001
ICU stay time, days	2.33 [1.33; 5.08]	2.29 [1.32; 4.90]	3.91 [2.06; 8.97]	<0.001
Hospital stay time, days	7.28 [5.23; 12.2]	7.32 [5.28; 12.2]	5.58 [2.20; 11.3]	<0.001
Age, (years)	68.4 [60.5; 77.4]	68.6 [60.8; 77.3]	66.7 [52.8; 78.0]	0.181
Gender, n (%)				0.004
Female	503 (33.6%)	449 (32.5%)	54 (46.2%)	
Male	995 (66.4%)	932 (67.5%)	63 (53.8%)	
Ethnicity:				0.003
white	1094 (73.0%)	1024 (74.1%)	70 (59.8%)	
black	63 (4.21%)	57 (4.13%)	6 (5.13%)	
other	341 (22.8%)	300 (21.7%)	41 (35.0%)	
BMI	30.9 (6.62)	31.0 (6.57)	29.7 (7.12)	0.059
BSA	2.01 (0.24)	2.01 (0.24)	1.94 (0.26)	0.003
Severity score				
SOFA	6.00 [4.00; 9.00]	6.00 [4.00; 9.00]	13.0 [10.0; 15.0]	<0.001
SAPSII	39.0 [31.0; 49.0]	38.0 [31.0; 48.0]	56.0 [43.0; 66.0]	<0.001
APSIII	41.0 [30.0; 68.0]	40.0 [29.0; 60.0]	92.0 [68.0; 113]	<0.001
LODS	5.00 [3.00; 8.00]	5.00 [3.00; 7.00]	11.0 [8.00; 13.0]	<0.001
Vital signs				
SBP mean, (mmHg)	111 (8.54)	111 (8.19)	109 (11.7)	0.042
DBP mean, (mmHg)	57.1 (6.99)	56.9 (6.76)	59.1 (9.03)	0.013
MBP mean, (mmHg)	74.0 (6.36)	74.0 (6.08)	74.0 (9.07)	0.950
Respiratory rate mean, (min^{-1})	17.5 [15.9; 19.6]	17.3 [15.8; 19.2]	21.9 [18.5; 25.1]	<0.001
Heart rate mean, (min^{-1})	83.2 [77.6; 91.0]	82.7 [77.4; 89.9]	96.5 [82.0; 109]	<0.001
Laboratory Test				
SPO2 mean, (%)	97.7 (1.77)	97.9 (1.43)	96.0 (3.56)	<0.001
Glucose mean, (mg/dl)	137 (28.4)	136 (26.2)	147 (45.6)	0.010
Lactate max, (mmol/L)	4.04 (2.40)	3.82 (2.04)	6.64 (4.19)	<0.001
PH max	7.44 (0.06)	7.45 (0.05)	7.39 (0.08)	<0.001
PaO2 max, (mmHg)	395 (105)	405 (94.7)	277 (141)	<0.001
PaCO2 max, (mmHg)	50.5 (8.85)	50.3 (8.34)	51.9 (13.4)	0.207
AaDO2 max, (mmHg)	382 (141)	378 (139)	434 (148)	<0.001
PaO2/FiO2 max, (mmHg)	368 (152)	372 (150)	320 (168)	0.001
Total CO2 max, (mmol/L)	27.1 (3.25)	27.3 (2.94)	24.4 (5.12)	<0.001
Hemoglobin max	12.4 (1.57)	12.4 (1.57)	12.3 (1.66)	0.506
Chloride max, (mmol/L)	108 (3.75)	108 (3.70)	109 (4.26)	0.035
Calcium max, (mmol/L)	1.28 (0.13)	1.28 (0.13)	1.21 (0.16)	<0.001
Potassium max, (mmol/L)	5.28 (0.81)	5.30 (0.79)	5.03 (0.99)	0.006
Sodium max, (mmol/L)	138 (2.82)	138 (2.71)	139 (3.90)	0.175
Platelets max, ($\times 10^9$/L)	190 (74.6)	187 (70.9)	222 (104)	0.001
WBC max, ($\times 10^9$/L)	16.6 (6.60)	16.6 (6.43)	17.2 (8.40)	0.397
Aniongap max	14.3 (4.66)	13.7 (4.01)	21.1 (6.15)	<0.001
BUN max, (mg/dL)	21.6 (12.2)	20.5 (10.8)	35.0 (18.0)	<0.001
Creatinine max, (μmol/L)	1.26 (0.89)	1.18 (0.79)	2.19 (1.39)	<0.001
Fibrinogen max	223 (90.8)	218 (83.2)	279 (143)	<0.001
INR max	1.58 (0.49)	1.54 (0.41)	2.10 (0.90)	<0.001
PT max,(s)	17.3 (4.85)	16.9 (4.08)	22.3 (8.83)	<0.001
PTT max,(s)	46.8 (26.6)	45.8 (25.8)	59.0 (31.7)	<0.001
CVP mean, (mmHg)	12.6 (4.77)	12.4 (4.66)	14.6 (5.57)	<0.001
CO mean, (L/min)	5.16 (1.50)	5.13 (1.46)	5.49 (1.93)	0.049
CI mean, ($L/min/m^2$)	2.57 (0.68)	2.55 (0.65)	2.85 (0.95)	0.001
PAPS mean, (mmHg)	33.7 (6.35)	33.6 (6.45)	34.9 (4.74)	0.004
PAPD mean, (mmHg)	18.0 (4.01)	17.9 (4.07)	19.1 (3.05)	<0.001
PAPM mean, (mmHg)	24.2 (4.80)	24.1 (4.89)	25.3 (3.50)	0.001
eGFR max, (ml/min)	81.8 (38.9)	83.6 (30.4)	60.5 (89.6)	0.006
CRRT,n (%)	55 (3.67%)	38 (2.75%)	17 (14.5%)	<0.001
Drugs				
Dobutamine,n (%)	28 (1.87%)	19 (1.38%)	9 (7.69%)	<0.001
Dopamine,n (%)	28 (1.87%)	18 (1.30%)	10 (8.55%)	<0.001
Epinephrine,n (%)	340 (22.7%)	309 (22.4%)	31 (26.5%)	0.365
Norepinephrine,n (%)	397 (26.5%)	307 (22.2%)	90 (76.9%)	<0.001
Phenylephrine,n (%)	1247 (83.2%)	1181 (85.5%)	66 (56.4%)	<0.001
Vasopressin,n (%)	216 (14.4%)	154 (11.2%)	62 (53.0%)	<0.001
Comorbidity				
Pancreatitis,n (%)	19 (1.27%)	16 (1.16%)	3 (2.56%)	0.181
COPD,n (%)	42 (2.80%)	36 (2.61%)	6 (5.13%)	0.135

(*continued on next page*)

Table 1 (*continued*)

Variables	ALL N = 1498	Survival N = 1381	Non-survival N = 117	P value
Diabetes,n (%)	413 (27.6%)	395 (28.6%)	18 (15.4%)	0.003
Hypertention,n (%)	896 (59.8%)	846 (61.3%)	50 (42.7%)	<0.001
Malignant cancer,n (%)	103 (6.88%)	91 (6.59%)	12 (10.3%)	0.189
Obesity,n (%)	236 (15.8%)	221 (16.0%)	15 (12.8%)	0.438
Renal disease,n (%)	199 (13.3%)	181 (13.1%)	18 (15.4%)	0.579
Respiratory failure,n (%)	275 (18.4%)	205 (14.8%)	70 (59.8%)	<0.001
Severe liver disease,n (%)	52 (3.47%)	38 (2.75%)	14 (12.0%)	<0.001

*Data are expressed as median (IQR) or number (percentage). Comparisons between groups were made using analysis of variance (or the Kruskal-Wallis test) and Chi-square (or Fisher's exact) tests. Statistical significance ($P < 0.05$).
SOFA, Sequential Organ Failure Assessment; SAPS II, Simplified Acute Physiology Score II; APSIII, Acute Physiology Score III; LODS, Logistic Organ Dysfunction System; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean arterial blood pressure; CVP, central venous pressure; CO, cardiac output; CI, cardiac index; PAPS, pulmonary artery systolic pressure; PAPD, pulmonary artery diastolic pressure; PAPM, pulmonary mean artery pressure; WBC, white blood cell; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; AaDO2, alveolar-arterial oxygen gradient; CRRT, continuous renal replacement therapy; COPD, chronic obstructive pulmonary disease.

statistically significant. Additionally, we observed distinct patterns in vasopressor usage across CI groups. Patients with low CI predominantly received vasopressors such as dobutamine, epinephrine, and vasopressin, while those with intermediate CI were more frequently administered phenylephrine. Moreover, our study revealed a correlation between lactate levels and CI. In the low CI group, the mean lactate level (Lactate max) was higher (4.88 mmol/L) compared to the intermediate (3.71 mmol/L) and high (4.43 mmol/L) CI groups.

3.3. Relationship between cardiac index and mortality

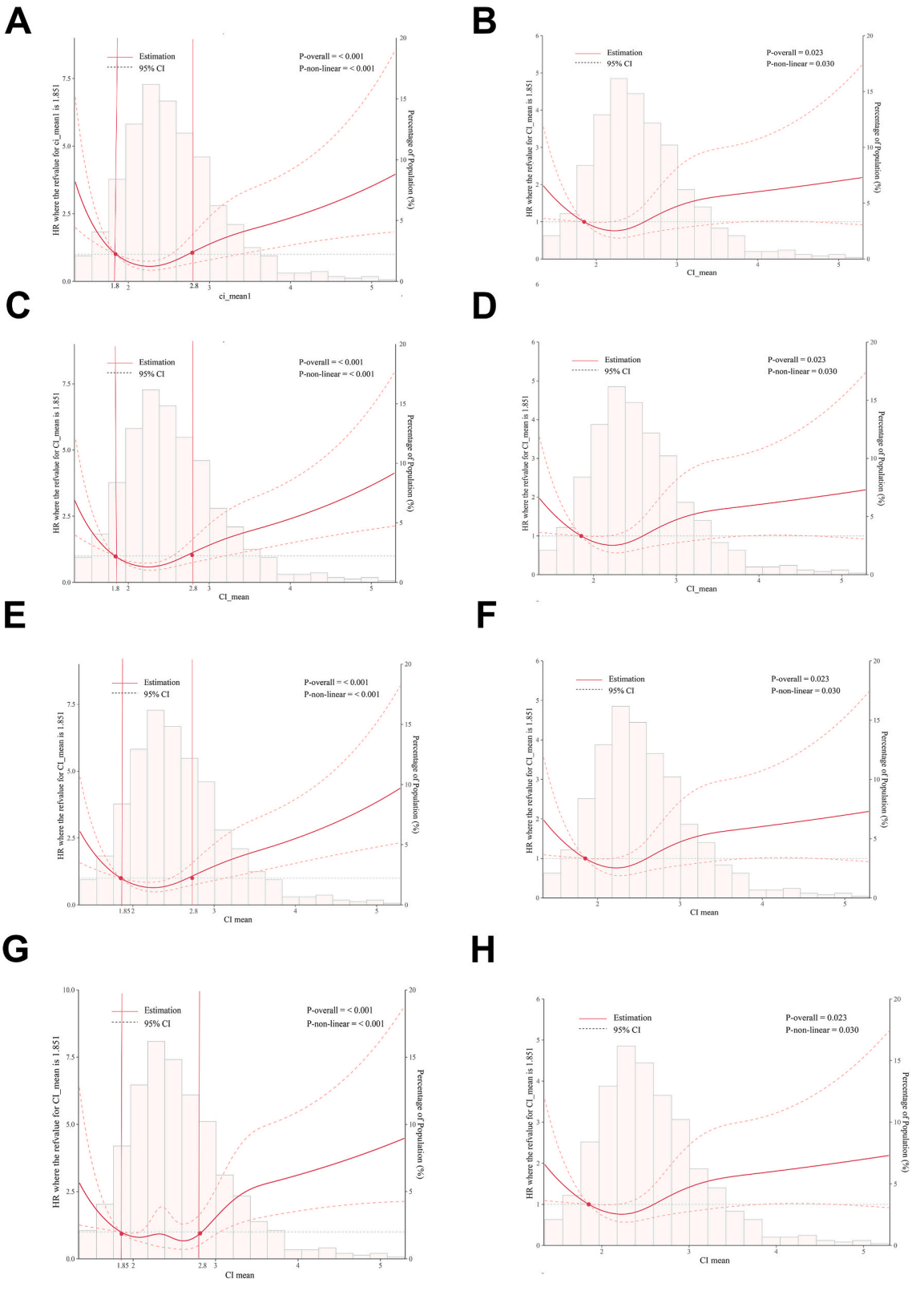
Kaplan-Meier survival curves for all patients stratified by CI revealed that patients with a cardiac index between 1.85 and 2.8 L/min/m^2 had the lowest risk of 28-day mortality after ICU admission (log-rank $P < 0.001$, Fig. 3). In addition, CI < 1.85 L/min/m^2 and CI > 2.8 L/min/m^2 were associated with an increased risk of mortality compared to the group with a cardiac index between 1.85 and 2.8 L/min/m^2, with little difference between these two groups. Next, we conducted Cox and logistic regression analyses to identify independent risk factors and calculated HR and OR for the primary endpoint as well as the cardiac index for each secondary endpoint. Table S1 and Table 3 summarize the results of univariate and multivariate Cox and logistic regression analyses. Using a cardiac index of 1.85–2.8 L/min/m^2 as a reference (Model 3, Table 3), multivariable Cox regression analyses revealed that a low cardiac index (HR = 1.87, 95% CI: 1.01–3.49) and a high cardiac index (HR = 1.93, 95% CI: 1.26–2.97) were associated with 28-day ICU mortality in patients with septic shock (both $P < 0.05$). Meanwhile, using the cardiac index of 1.85–2.80 L/min/m^2 as a reference, multivariate logistic regression analysis revealed that the fully adjusted OR for ICU mortality was 2.23 (95% CI: 1.03–4.22) in the low cardiac index group and 1.96 (95% CI: 1.16–3.33) in the high cardiac index group. Consequently, the risk of mortality by categorical cardiac index level suggests a U-shaped relationship.

3.4. Using heart rate to predict 28-day ICU mortality due to septic shock

Based on the ROC curve and Youden index of ICU 28-day mortality, patients with a mean HR less than 93.63 bpm were classified as belonging to the low HR group (n = 1192), and those with a mean HR greater than or equal to 93.63 bpm were classified as belonging to the High HR rate group (n = 306) (AUC = 0.70 95%CI:0.63–0.76, Fig. 4A). The Kaplan-Meier curves indicated that the group with the higher heart rate had a significantly higher mortality rate than the group with the lower HR (log-rank $P < 0.001$, Fig. 4B). The patient outcomes varied substantially based on stratified HR levels (Table S2).

3.5. Cardiac index and heart rate values in relation to mortality in septic shock

The patients were divided into six subgroups based on the threshold characteristics of CI and HR: Q1 [HR↓+CI intermediate group (n = 772)], Q2 [HR↓+CI↓ group (n = 126)], Q3 [HR↓+CI↑ group (n = 294)], Q4 [HR↑+CI intermediate group (n = 132)], Q5 [HR↑+CI↓ group (n = 24)], and Q6 [HR↑+CI↑ group (n = 150)]. The Kaplan-Meier curves revealed differences between the groups (Q1, Q2, Q3, Q4, Q5, and Q6), with substantially higher mortality in Q5 and Q6 compared to the other groups (log-rank $P < 0.001$, Fig. 5). Next, we performed Cox and logistic regression analyses to identify independent risk factors and calculated HR and OR for the primary endpoint, as well as cardiac index and heart rate for each secondary endpoint. The results of univariate and multivariate Cox regression and logistic regression analysis are summarised in Table S3 and Table 4. Using Q1 as a reference, univariate Cox regression analyses revealed that risk factors associated with 28-day mortality in the Q4, Q5, and Q6 groups at unadjusted (HR) of 4.60 (95% CI: 2.54–8.30), 8.68 (95% CI: 3.57–21.09), and 9.32 (95% CI: 5.70–15.23), respectively (all $P < 0.05$), whereas Q2 and Q3 were not associated with the risk of 28-day (both $P > 0.05$); Adjusted for the three distinct models, the correlations remained statistically significant; HRs for Q4, Q5, and Q6 were 2.89 (95% CI: 1.53–5.48), 4.20 (95% CI: 1.61–10.94), and 4.95 (95% CI: 2.75–8.91), respectively, and were associated with 28-day ICU mortality in patients with septic shock (all $P < 0.05$). The same result, Multivariate



(caption on next page)

Fig. 2. Association between cardiac index levels and 7-, 14-,21-, and 28-day mortality in patients with septic shock.
(A) The crude model for predicting 7-day mortality. (B) The predictive model adjusted for Age, Gender, BMI, SBP-mean, glucose-mean, AaDO2-max, PaO2/fiO2 ratio-max, platelets-max, creatinine-max, pt-max, and eGFR-max for 7-day mortality. (C) The crude model for predicting 14-day mortality. (D) The predictive model adjusted for Age, Gender, BMI, SBP-mean, glucose-mean, AaDO2-max, PaO2/fiO2 ratio-max, platelets-max, creatinine-max, pt-max, and eGFR-max for 14-day mortality. (E) The crude model for predicting 21-day mortality. (F) The predictive model adjusted for Age, Gender, BMI, SBP-mean, glucose-mean, AaDO2-max, PaO2/fiO2 ratio-max, platelets-max, creatinine-max, pt-max, and eGFR-max for 21-day mortality. (G) The crude model for predicting 28-day mortality. (H) The predictive model adjusted for Age, Gender, BMI, SBP-mean, glucose-mean, AaDO2-max, PaO2/fiO2 ratio-max, platelets-max, creatinine-max, pt-max, and eGFR-max for 28-day mortality.

logistic regression analysis, adjusted for model 3, yielded ORs of 2.87 (95% CI: 1.37–5.84), 3.72 (95% CI: 1.07–11.83), and 5.77 (95% CI: 2.98–11.28) for Q4, Q5, and Q6 for risk-related ICU mortality, respectively.

3.6. Univariate characteristics of cardiac index and heart rate levels

According to Table S4, the HR↓+CI intermediate group had the lowest mortality (28-day ICU mortality, ICU mortality, and hospital mortality), while the HR↑+CI↓ and HR↑+CI↑ groups had the highest mortality. The characteristics and outcomes of the other categories varied significantly.

4. Discussion

To our knowledge, this is the first study to assess the short-term effects of cardiac index and heart rate on survival in critically ill patients in septic shock. This retrospective cohort study is based on the observation of the association between having different cardiac index and heart rate levels and mortality from shock in patients with sepsis. The cardiac index was calculated based on cardiac output CO and body area. We used a restricted three-sample curve based on the COX regression model in detail to assess the incidence of the cardiac index with each endpoint (7-, 14-, 21-, and 28-day mortality). The optimal heart rate thresholds for predicting mortality using the Youden index. KM curves, cox regression, and logistic regression analyses were performed to assess the association between having different CIs and heart rates with 28-day mortality. Our findings imply a U-shaped relationship between cardiac index and septic shock mortality risk. Mortality was lowest in patients with septic shock when the cardiac index was between 1.85 and 2.8 L/min/m^2, whereas cardiac index CI $<$ 1.85 L/min/m^2 and cardiac index $>$2.8 L/min/m^2 were associated with an increased risk of mortality. Furthermore, we discovered that tachycardia (mean HR $>$ 93.63 bpm) was associated with an increased risk of mortality in septic shock. In addition, different levels of cardiac index and heart rate had distinct effects on the mortality risk in various populations.

The cardiac index is a well-established parameter for assessing the cardiac circulatory status and predicting prognosis in patients with septic shock and a reduced cardiac index or an excessive cardiac index is linearly associated with increased mortality. Despite contradictory evidence from previous studies regarding the effect of cardiac output on patients with septic shock [10,27], cardiac output is extensively used to guide fluid therapy. One study demonstrated that the cardiac index calculated from LVOT beat volume decreased with increasing severity of tricuspid regurgitation [28]. A retrospective study also demonstrated a U-shaped interaction between cardiac index and the prognosis of patients with severe functional tricuspid regurgitation by Kaplan-Meier analysis, with the highest mortality in the low cardiac index (CI $<$ 1.6 L/min/m^2) and high cardiac index (CI $>$ 2.6 L/min/m^2) clusters and the lowest mortality in the intermediate cardiac index cluster (CI: 1.6–2.6 L/min/m^2) had the lowest mortality rates; the results of this study, although very similar to our findings but this study by multivariate COX regression analysis only high cardiac output status (CI $>$ 2.6 L/min/m^2) was associated with poor prognosis in patients with severe functional mitral regurgitation [29]. About 40 years ago, Abraham and his colleagues observed that survivors of septic shock had significantly higher cardiac indexes before the shock episode than nonsurvivors. This observation suggests that inducing patients to achieve higher, or even “supranormal," levels of cardiac output may be beneficial [30]. This early hypothesis has sparked an ongoing discussion regarding the potential benefits and risks of this strategy for patients with septic shock. Nonetheless, a second prospective regression study involving patients with hemorrhagic shock and increased cardiac output values to a supernormal endpoint (cardiac index $>$4.5 L/min/m^2) revealed that supernormal cardiac output values did not enhance prognosis [31]. Furthermore, in our present study, it has been shown that when cardiac index CI $<$ 1.85 L/min/m^2 and cardiac index $>$2.8 L/min/m^2 are associated with a higher risk of mortality. One possible explanation for these results is that, unlike many other studies in this field, the heterogeneity of the critically ill patients in this study influenced the findings. Thus, although some individuals may have benefited from the trial strategy, these positive results may have had detrimental effects on other patients who may have been adequately resuscitated due to receiving excessive fluids or vasoactive medications. There is no doubt that achieving and maintaining intermediate levels of cardiac output (cardiac index: 1.85–2.8 L/min/m^2) is associated with improved prognosis in patients with septic shock.

In patients with septic shock, blood pressure is often monitored instead of blood flow, indicating that clinicians generally consider blood pressure as a reliable indicator of blood flow. However, in reality, there is poor correlation between DBP, SBP, MAP, and CI in patients with septic shock. Our study findings confirm the lack of significant correlation between DBP, SBP, and MBP with CI in patients with septic shock. This is consistent with previous research, which found a correlation coefficient of only 0.07 between MAP and CI after fluid challenge in 51 patients with septic shock [32]. It is worth noting that there is also no clinical correlation between MAP and CI in 100 patients undergoing major abdominal surgery under general anesthesia [33]. Therefore, blood pressure monitoring cannot adequately replace cardiac index monitoring, especially in patients with septic shock.

Our study found that among patients with lactate levels equal to or greater than 2 mmol/L, those who did not survive had

Table 2
Baseline characteristics and outcomes of septic shock patients stratified by cardiac index on Day 1.

Variables	CI < 1.85 L/min/m^2 N = 150	CI:1.85–2.8 L/min/m^2 N = 904	CI > 2.8 L/min/m^2 N = 444	P value
Outcomes				
28-day ICU mortality,n (%)	14 (9.33%)	45 (4.98%)	58 (13.1%)	<0.001
ICU mortality,n (%)	14 (9.33%)	38 (4.20%)	46 (10.4%)	<0.001
Hospital mortality,n (%)	15 (10.0%)	42 (4.65%)	56 (12.6%)	<0.001
ICU stay time, days	4.07 [2.29; 7.56]	2.24 [1.30; 4.26]	2.34 [1.32; 5.97]	<0.001
Hospital stay time, days	9.11 [6.58; 14.1]	7.04 [5.25; 11.2]	7.14 [5.04; 13.9]	<0.001
Age, (years)	76.8 [68.0; 81.9]	70.7 [62.9; 78.7]	62.0 [54.0; 69.5]	<0.001
Gender, Male	57 (38.0%)	608 (67.3%)	330 (74.3%)	<0.001
Ethnicity:				0.951
white	110 (73.3%)	663 (73.3%)	321 (72.3%)	
black	7 (4.67%)	35 (3.87%)	21 (4.73%)	
other	33 (22.0%)	206 (22.8%)	102 (23.0%)	
BMI	31.5 (6.82)	31.1 (6.44)	30.2 (6.87)	0.024
BSA	1.97 (0.26)	2.01 (0.25)	2.00 (0.24)	0.099
Severity score				
SOFA	8.00 [5.00; 11.0]	6.00 [4.00; 9.00]	7.00 [5.00; 11.0]	<0.001
SAPSII	43.0 [37.0; 52.0]	39.0 [31.0; 48.0]	39.0 [30.0; 51.0]	<0.001
APSIII	46.5 [32.0; 79.8]	39.0 [29.0; 60.0]	45.0 [30.0; 75.5]	<0.001
LODS	6.00 [4.00; 10.0]	5.00 [3.00; 7.00]	5.00 [3.00; 8.00]	<0.001
Vital signs				
SBP mean, (mmHg)	110 (8.51)	111 (8.04)	111 (9.50)	0.807
DBP mean, (mmHg)	57.6 (8.26)	56.7 (6.47)	57.6 (7.50)	0.070
MBP mean, (mmHg)	74.9 (6.00)	73.8 (5.78)	74.1 (7.49)	0.135
Respiratory rate mean, (min^{-1})	16.8 [15.3; 18.8]	17.3 [15.9; 19.2]	18.4 [16.4; 20.9]	<0.001
Heart rate mean, (min^{-1})	82.3 [77.6; 88.8]	82.1 [77.0; 88.8]	86.8 [79.0; 98.6]	<0.001
Laboratory Test				
SPO2 mean, (%)	97.8 (2.17)	97.9 (1.45)	97.4 (2.13)	<0.001
Glucose mean, (mg/dl)	136 (24.2)	134 (23.0)	142 (37.4)	<0.001
Lactate max, (mmol/L)	4.88 (2.88)	3.71 (1.96)	4.43 (2.86)	<0.001
PH max	7.47 (0.06)	7.45 (0.05)	7.42 (0.06)	<0.001
PaO2 max, (mmHg)	422 (99.2)	412 (93.2)	351 (116)	<0.001
PaCO2 max, (mmHg)	50.2 (10.7)	50.1 (8.31)	51.3 (9.19)	0.073
AaDO2 max, (mmHg)	384 (132)	382 (138)	383 (149)	0.977
PaO2/FiO2 max, (mmHg)	403 (166)	367 (149)	358 (150)	0.007
Total CO2 max, (mmol/L)	27.0 (3.55)	27.4 (2.84)	26.6 (3.84)	<0.001
Hemoglobin max	12.0 (1.55)	12.4 (1.52)	12.5 (1.67)	0.003
Chloride_max, (mmol/L)	110 (3.87)	108 (3.63)	108 (3.90)	<0.001
Calcium_max, (mmol/L)	1.28 (0.13)	1.28 (0.12)	1.26 (0.14)	0.040
Potassium_max, (mmol/L)	5.40 (0.84)	5.32 (0.77)	5.16 (0.87)	<0.001
Sodium_max, (mmol/L)	138 (3.25)	138 (2.68)	138 (2.92)	0.184
Platelets_max, (× 109/L)	184 (60.3)	189 (69.3)	195 (88.1)	0.199
WBC max, (× 109/L)	16.2 (5.91)	16.5 (6.49)	16.9 (7.05)	0.528
BUN max, (mg/dL)	21.7 (11.7)	20.5 (10.8)	23.8 (14.5)	<0.001
Creatinine max, (μmol/L)	1.25 (0.77)	1.18 (0.83)	1.42 (1.03)	<0.001
Fibrinogen_max	202 (60.4)	215 (79.5)	246 (114)	<0.001
INR max	1.71 (0.55)	1.53 (0.43)	1.65 (0.58)	<0.001
PT max, (s)	18.7 (5.48)	16.8 (4.21)	17.9 (5.62)	<0.001
PTT max, (s)	58.0 (33.7)	45.6 (25.6)	45.5 (24.9)	<0.001
CVP mean, (mmHg)	14.5 (4.75)	12.6 (4.53)	12.0 (5.09)	<0.001
CO mean, (L/min)	3.22 (0.56)	4.72 (0.80)	6.72 (1.45)	<0.001
CI mean, (L/min/m2)	1.64 (0.18)	2.34 (0.25)	3.36 (0.64)	0.000
PAPS mean, (mmHg)	35.9 (6.70)	33.7 (6.43)	32.8 (5.86)	<0.001
PAPD mean, (mmHg)	20.4 (4.29)	18.0 (3.96)	17.1 (3.67)	<0.001
PAPM mean, (mmHg)	26.4 (5.01)	24.2 (4.83)	23.4 (4.42)	<0.001
eGFR max, (ml/min)	73.6 (29.7)	82.9 (29.7)	82.2 (54.7)	0.024
CRRT,n (%)	8 (5.33%)	17 (1.88%)	30 (6.76%)	<0.001
Drugs				
Dobutamine,n (%)	7 (4.67%)	11 (1.22%)	10 (2.25%)	0.017
Dopamine,n (%)	2 (1.33%)	18 (1.99%)	8 (1.80%)	0.960
Epinephrine,n (%)	59 (39.3%)	202 (22.3%)	79 (17.8%)	<0.001
Norepinephrine,n (%)	47 (31.3%)	187 (20.7%)	163 (36.7%)	<0.001
Phenylephrine,n (%)	119 (79.3%)	781 (86.4%)	347 (78.2%)	<0.001
Vasopressin,n (%)	29 (19.3%)	98 (10.8%)	89 (20.0%)	<0.001
Comorbidity				
Pancreatitis,n (%)	3 (2.00%)	7 (0.77%)	9 (2.03%)	0.079
COPD,n (%)	9 (6.00%)	21 (2.32%)	12 (2.70%)	0.060

(*continued on next page*)

Table 2 (*continued*)

Variables	CI < 1.85 L/min/m^2 N = 150	CI:1.85–2.8 L/min/m^2 N = 904	CI > 2.8 L/min/m^2 N = 444	P value
Diabetes,n (%)	45 (30.0%)	272 (30.1%)	96 (21.6%)	0.004
Hypertention,n (%)	88 (58.7%)	579 (64.0%)	229 (51.6%)	<0.001
Malignant cancer,n (%)	7 (4.67%)	51 (5.64%)	45 (10.1%)	0.005
Obesity,n (%)	23 (15.3%)	142 (15.7%)	71 (16.0%)	0.980
Renal disease,n (%)	29 (19.3%)	120 (13.3%)	50 (11.3%)	0.042
Respiratory failure,n (%)	37 (24.7%)	131 (14.5%)	107 (24.1%)	<0.001
Severe liver disease,n (%)	6 (4.00%)	8 (0.88%)	38 (8.56%)	<0.001

SOFA, Sequential Organ Failure Assessment; SAPS II, Simplified Acute Physiology Score II; APSIII, Acute Physiology Score III; LODS, Logistic Organ Dysfunction System; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean arterial blood pressure; CVP, central venous pressure; CO, cardiac output; CI, cardiac index; PAPS, pulmonary artery systolic pressure; PAPD, pulmonary artery diastolic pressure; PAPM, pulmonary mean artery pressure; WBC, white blood cell; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; AaDO2, alveolar-arterial oxygen gradient; CRRT, continuous renal replacement therapy; COPD, chronic obstructive pulmonary disease.

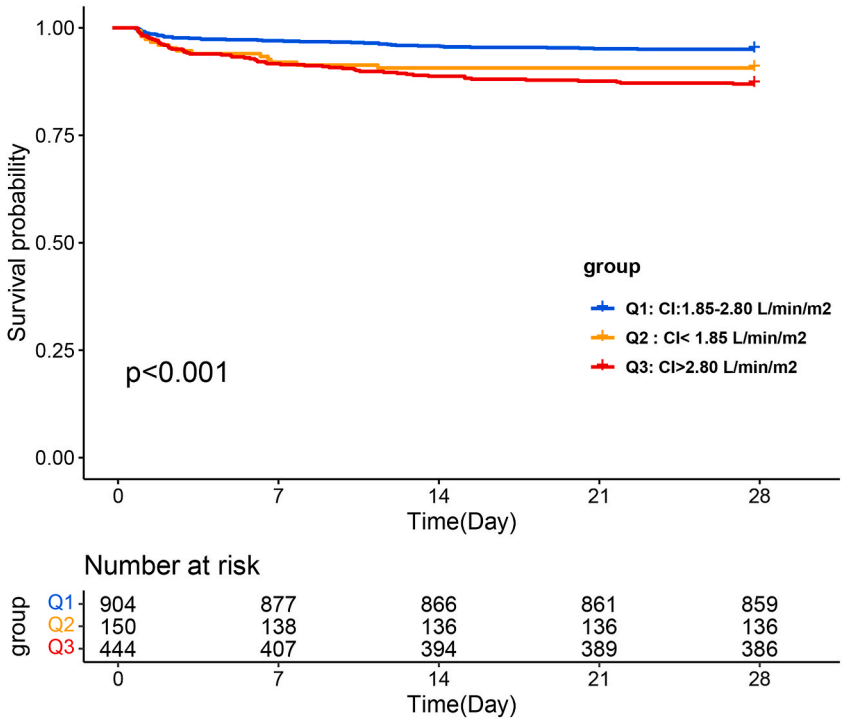


Fig. 3. Kaplan-Meier curve for survival analysis of three groups stratified by cardiac index levels.

significantly higher lactate levels (6.64 mmol/L) compared to survivors (3.82 mmol/L). Additionally, distinct patterns in vasopressor usage were observed across CI groups. Patients with low CI were more likely to receive vasopressors such as dobutamine, epinephrine, and vasopressin, while those with intermediate CI were predominantly administered phenylephrine. Furthermore, our study identified a correlation between lactate levels and cardiac index. Specifically, lactate levels were significantly higher in the low CI group compared to the intermediate and high CI groups. This association may suggest inadequate tissue perfusion and disruption of lactate metabolism [34,35]. Patients with low CI tend to have worse heart function and use more drugs that promote myocardial contraction and vasoconstriction, resulting in reduced CI, which leads to tissue hypoperfusion, microcirculation disturbance, and lactic acid accumulation.This finding suggests that the combined monitoring of cardiac index and lactate levels may help better understand the clinical status and prognosis of patients with septic shock.

In our retrospective observational study, tachycardia (mean HR > 93.63 bpm) was found to be associated with increased mortality in septic shock. Tachycardia is an essential clinical manifestation in sepsis and multiple organ dysfunction syndrome patients and an independent in-hospital risk factor in critically ill patients [16,18,36–38]. As a compensatory response to sepsis, tachycardia has been underappreciated in septic patients or in septic shock. To date, only a handful of substantial studies have researched the relationship between tachycardia and mortality in septic shock, and these studies have demonstrated that survival is higher in those with relatively low heart rates or a decrease in heart rate 24 h after admission to the intensive care unit, in response to improved hemodynamics, and

Table 3
Univariate and multivariate Cox/logistic regression analyses were conducted to examine the relationship between cardiac index and the prognosis of patients with septic shock.

Characteristics	Univariate Model		Multivariable Model					
			Model 1		Model 2		Model3	
	HR/OR (95%CI)	P value	HR/OR (95%CI)	P value	HR/OR (95%CI)	P value	HR/OR (95%CI)	P value
28-day ICU mortality (Cox regression)								
Q1 :	1.94 (1.06–3.53)	0.031*	2.11 (1.15–3.86)	0.015*	2.00 (1.08–3.73)	0.027*	1.87 (1.01–3.49)	0.048*
Q2 :	Reference		Reference		Reference		Reference	
Q3 :	2.73 (1.85–4.03)	<0.001*	2.33 (1.54–3.53)	<0.001*	1.99 (1.30–3.03)	0.001*	1.93 (1.26–2.97)	0.002*
ICU mortality (logestic regression)								
Q1 :	2.35 (1.20–4.35)	0.009*	2.51 (1.28–4.70)	0.005*	2.47 (1.20–4.84)	0.011*	2.23 (1.03–4.22)	0.034*
Q2 :	Reference							
Q3 :	2.63 (1.69–4.13)	<0.001*	2.28 (1.42–3.67)	<0.001*	1.98 (1.18–3.33)	0.009*	1.96 (1.16–3.33)	0.012*

Notes: The relationship between cardiac index and 28-day ICU mortality and ICU mortality was analyzed using Cox regression and logistic regression models, respectively. Model 1 was adjusted by: Age, and BMI. Model 2 was adjusted by: Age, BMI, SBP-mean, glucose-mean, AaDO2-max, PaO2/FiO2 ratio-max, potassium-max, platelets-max, creatinine-max, and ptt-max. Model 3 was adjusted by: Age, BMI, SBP-mean, glucose-mean, AaDO2-max, PaO2/FiO2 ratio-max, potassium-max, platelets-max, creatinine-max, ptt-max, CVP-mean, PAPS-mean, and hypertension, severe liver disease. * Statistical significance ($P < 0.05$).
Abbreviations: ICU, intensive care unit; CI, confidence interval; HR, hazard ratio; OR, odds ratio; BMI, body mass index; SBP, systolic blood pressure; AaDO2, alveolar-arterial oxygen gradient; CVP, central venous pressure; PAPS, pulmonary artery systolic pressure.

increased morbidity and mortality in those with no decrease in heart rate 0–24 h after ICU admission. Heart rate is a clinically accessible index that influences cardiac output and is an important indicator of fluid resuscitation effectiveness [39–41]. Currently, the value of heart rate for sepsis assessment and short-term prognosis has been rarely reported. In our retrospective observational study, tachycardia (mean HR > 93.63 bpm) was found to be associated with increased mortality in septic shock, and these findings are consistent with recent studies.

Previous retrospective studies investigating the effect of cardiac output on the prognosis of septic shock were limited by a single cardiac output measurement within 24 h of ICU admission and did not take into account the interaction between cardiac index and heart rate. Theoretically, single-test indices have the potential to substantially alter results to the point where they are unreliable. To address this deficiency, we combined the strengths of cardiac index and heart rate to conduct a subgroup analysis correlating septic shock with the risk for mortality in the short term following ICU admission (mortality in ICU and mortality at 28 days). After adjusting for confounding variables, the HR↑+CI intermediate group, the HR↑ +CI↓ group, and the HR↑ +CI↑ group were found to be associated with mortality in patients with septic shock in our study. Notably, our results also found that the HR↑+CI↓ group, and HR↑+CI↑ group were at the highest risk of increased mortality compared to the other groups, in contrast, HR↓ +CI↓ and HR↓ +CI↑ were not associated with the risk of short-term mortality in septic shock patients admitted to the ICU. Patients with a rapid heart rate, regardless of whether they had a high or low CI, had the highest morbidity and mortality, whereas those with a slower heart rate, regardless of whether they had a high or low CI, had relatively lower mortality. This suggests that the more pronounced the response of the organism, the worse the prognosis of the patient, and that high or low CI affects the prognosis, so we studied patients with septic shock that supervised fluid resuscitation by lowering the heart rate (HR < 93 bpm) and assessing the volume status may improve the prognosis of the patient by maintaining a intermediate range of cardiac index (the optimal range is 1.85–2.8 L/min/m^2).

One of the important clinical manifestations of sepsis and septic shock is rapid cardiac arrhythmia [42]. Rapid heart rate can affect the diastole of the heart and thus affect cardiac output. Rapid heart rate indicates a higher sympathetic excitability, which means a stronger response, higher oxygen consumption, and an increased risk of arrhythmia. The control of rapid heart rate plays a crucial role in stabilizing hemodynamics and improving cardiac diastolic function, especially in patients with septic shock. Increasing evidence suggests that in critically ill patients, controlling heart rate alone, such as with beta-blockers, amiodarone, propafenone, alpha-2 receptor agonists, etc., can improve hemodynamics without necessarily restoring the heart rate to sinus rhythm [43]. The decrease in heart rate is often accompanied by an increase in cardiac index and a decrease in central venous pressure, reflecting an improvement in myocardial work efficiency [44]. Beta-blockers can inhibit sympathetic nervous system excitation, reduce catecholamine release, thereby lowering heart rate, reducing myocardial contractility, and lowering myocardial oxygen consumption [45,46]. Previous studies have shown that even at low doses, esmolol can reduce the heart rate of patients with septic shock, increase cardiac output without increasing adverse events, and significantly improve survival rates [47,48]. However, there are also reports that when esmolol is used to treat septic shock with the goal of reducing heart rate by 20%, there is an increased risk of hypotension occurring alongside heart rate reduction, leading to a decrease in cardiac index [49]. The pathogenesis of rapid cardiac arrhythmias associated with sepsis and septic shock is complex, and there is still much controversy in its treatment. The selection and use of antiarrhythmic drugs require further research.

Our study has numerous benefits. The present study is based on a large sample from the MIMIM-IV database, which allows us to adjust for changing covariates and obtain more clinical data. Moreover, the information in the MIMIC-IV database was compiled between 2008 and 2019 and is comparatively recent [21,50]. In addition, we visualized the longitudinal association between cardiac index or heart rate and 28-day mortality during ICU admission and suggested that intensive care unit clinicians should pay more attention to cardiac index and heart rate in the early stages of septic shock disease, especially when patients present with low or high

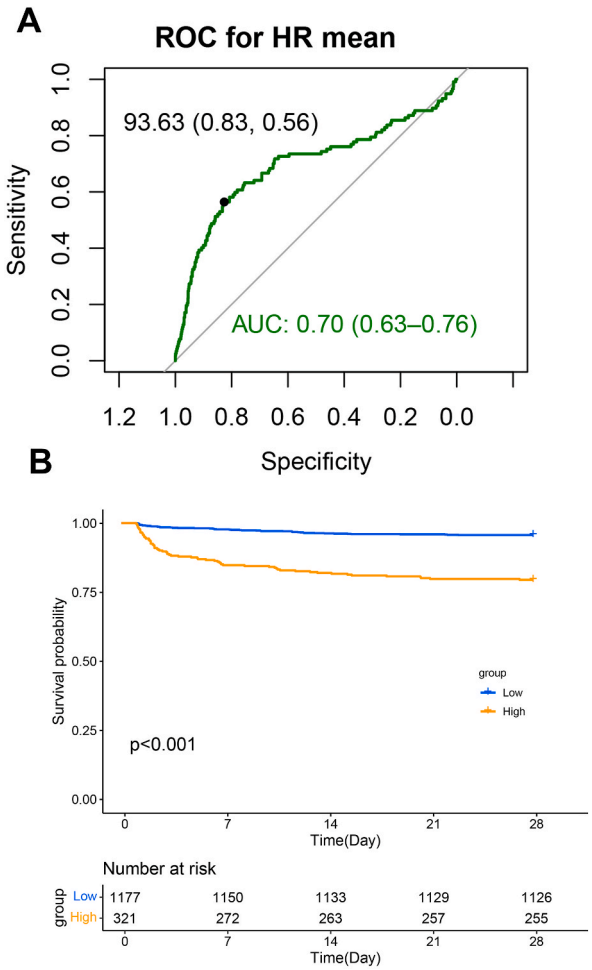


Fig. 4. Association between heart rate and 28-day mortality in patients with septic shock.
(A) Receiver Operating Characteristic (ROC) curve analysis of heart rate predicts 28-day mortality in patients with septic shock risk stratification. The AUC of heart rate was 0.70 (0.63–0.76), and the cut-off value was 93.63 bpm. (B) Kaplan-Meier curve for survival analysis of two groups stratified by heart rate levels.

cardiac index and rapid heart rate symptoms. The results showed a U-shaped relationship between cardiac index and short-term mortality in septic shock, with an optimal range of 1.85–2.80 L/min/m^2 for cardiac index and a heart rate of less than 93 bpm when possible, in order not to affect increased mortality. In order to predict the prognosis of septic shock, it is crucial to assess cardiac index in combination with heart rate. The interaction between accelerated heart rate (HR $>$ 93.63 bpm) and the cardiac index was more significant in causing increased mortality, especially tachycardia, and the low or high cardiac index was more significantly associated with 28-day mortality. Our results simply reflect the true effects of cardiac index and heart rate measurements in real-world clinical practice and confirm the benefits of cardiac index and heart rate measurements in septic shock, regardless of the initial levels of these two indices. Clinicians should not disregard the measurements but rather consider how to implement adjusted cardiac index and heart rate management appropriately. However, this study has several limitations. First, owing to the design of the retrospective cohort study, a causal relationship could not be established. Second, the software we simply used to screen for septic shock is not identical to septic shock. Last but not least, we only calculated cardiac index from CO, and CO was extracted by distinct item IDs, and we were unable to identify the device or detection technique used to determine the source of CO values. Given the limitations of this study, further evidence of CO or CI should be confirmed by additional prospective randomized trials.

5. Conclusion

There is a U-shaped association between cardiac index and short-term mortality risk rate in patients with septic shock, with an optimal range of 1.85–2.8 L/min/m^2. A rapid heart rate combined with low and high CI may be associated with poor prognosis in septic shock. Of note, a mean heart rate below 93.63 bpm may be associated with improved prognostic outcomes in septic shock.

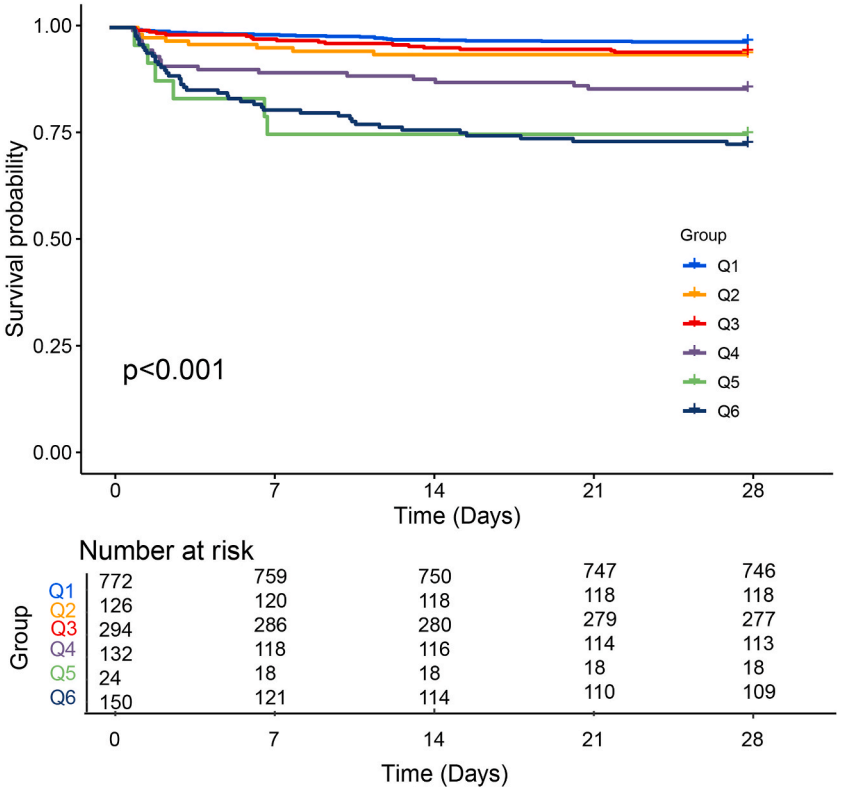


Fig. 5. Kaplan-Meier curve for survival analysis of subgroups stratified by cardiac index and heart rate levels.

Table 4
Univariate and multivariate Cox/logistic regression analyses were conducted to examine subgroup analyses of the relationship between different combinations of cardiac indices and heart rate with the prognosis of patients with septic shock.

Characteristics	Univariate Model		Multivariable Model					
			Model 1		Model 2		Model3	
	HR/OR (95%CI)	P value	HR/OR (95%CI)	P value	HR/OR (95%CI)	P value	HR/OR (95%CI)	P value
28-day								
ICU mortality (Cox regression)								
Q1	Reference		Reference		Reference		Reference	
Q2	2.93 (0.87–4.26)	0.104	1.93 (0.87–4.28)	0.107	1.87 (0.84–4.19)	0.128	1.81 (0.81–4.08)	0.149
Q3	1.73 (0.94–3.19)	0.078	1.71 (0.92–3.18)	0.088	1.44 (0.77–2.69)	0.257	1.35 (0.71–2.55)	0.363
Q4	4.60 (2.54–8.30)	<0.001*	4.60 (2.54–8.33)	<0.001*	2.79 (1.48–5.26)	0.001*	2.89 (1.53–5.48)	0.001*
Q5	8.68 (3.57–21.09)	<0.001*	8.68 (3.57–21.13)	<0.001*	4.08 (0.60–10.41)	0.003*	4.20 (1.61–10.94)	0.003*
Q6	9.32 (5.70–15.23)	<0.001*	9.23 (5.39–15.83)	<0.001*	4.91 (2.75–8.77)	<0.001*	4.95 (2.75–8.91)	<0.001*
ICU mortality (Cox regression)								
Q1	Reference		Reference		Reference		Reference	
Q2	1.95 (0.81–4.22)	0.11	1.94 (0.80–4.24)	0.113	1.99 (0.79–4.59)	0.121	1.90 (0.75–440)	0.15
Q3	1.76 (0.93–3.24)	0.076	1.75 (0.91–3.27)	0.085	1.32 (0.65–2.61)	0.433	1.27 (0.63–2.55)	0.506
Q4	4.77 (2.54–8.82)	<0.001*	4.81 (2.55–8.97)	<0.001*	2.82 (1.35–5.71)	0.004*	2.91 (1.39–5.97)	0.004*
Q5	10.10 (3.43–26.54)	<0.001*	9.75 (6.06–19.36)	<0.001*	3.89 (1.14–12.05)	0.022*	3.67 (1.39–11.63)	0.032*
Q6	10.77 (6.40–18.39)	<0.001*	10.75 (6.05–19.36)	<0.001*	5.76 (3.00–11.15)	<0.001*	5.77 (2.98–11.28)	<0.001*

Notes: The relationship between cardiac index and 28-day ICU mortality and ICU mortality was analyzed using Cox regression and logistic regression models, respectively.
Model 1 was adjusted by: Age and BMI; Model 2 was adjusted by: Age, BMI, SBP-mean, glucose-mean, AaDO2, PaO2/FiO2 ratio-max, chloride-max, potassium-max, platelets-max, creatinine-max, fibrinogen-max, pt-max, and ppt-max; Model 3 was adjusted by: Age, BMI, SBP-mean, glucose-mean, AadO2, PaO2/FiO2 ratio-max, chloride-max, potassium-max, platelets-max, creatinine-max, fibrinogen-max, pt-max, ppt-max, CVP-mean, PAPS-mean, eGFR-max, hypertension, and severe liver disease. * Statistical significance ($P < 0.05$).
Abbreviations: ICU, intensive care unit; CI, confidence interval; HR, hazard ratio; OR, odds ratio; BMI, body mass index; SBP, systolic blood pressure; AaDO2, alveolar-arterial oxygen gradient; CVP, central venous pressure; PAPS, pulmonary artery systolic pressure.

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Consent for publication

Not applicable.

Data availability statement

All raw data utilized in this study was sourced from the MIMIC IV (version 2.0) database, which is publicly accessible. The dataset used for this research can be obtained from the following URL: https://physionet.org/content/mimiciv/2.0/

Ethics approval and consent to participate

One of the authors, Chansokhon Ngan, who has completed the “Protecting Human Research Participants" examination (Record ID: 10769308), accessed the database and conducted data extraction. MIMIC-IV database used in the present study was approved by the Institutional Review Boards (IRB) of Institutional Review Boards of Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology and was given a waiver of informed consent.

CRediT authorship contribution statement

Chansokhon Ngan: Methodology, Investigation, Formal analysis, Data curation, Project administration, Software, Writing – original draft. **Xueying Zeng:** Formal analysis, Methodology, Writing – original draft. **Thongher Lia:** Writing – review & editing, Software, Formal analysis. **Wanhong Yin:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **Yan Kang:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Yan Kang reports financial support was provided by West China Hospital of Sichuan University.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e28956.

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