Heliyon 9 (2023) e20898

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Early heart rate fluctuation and outcomes in critically ill patients with sepsis: A retrospective cohort study of the MIMIC-IV database

Junhui He [a,1], Jie Yang [b,1], Jin Liu [a,*]

[a] Department of Anesthesiology, West China Hospital, Sichuan University, Chengdu, China
[b] Department of Critical Care Medicine, West China Hospital, Sichuan University, Chengdu, China

ARTICLE INFO

Keywords:
Critical care
Heart rate fluctuation
Sepsis
Mortality
Large-sample data

ABSTRACT

Background: Heart rate (HR) abnormalities are common in critically ill patients, but the significance of HR fluctuation in sepsis remains unclear. We aimed to assess the association of HR fluctuation with intensive care unit (ICU) mortality, hospital mortality, and 28-day mortality in patients with sepsis and identify the cutoff value of HR fluctuation associated with the lowest risk of death.

Methods: We conducted a retrospective cohort study using the medical information mart for the intensive care IV database. HR fluctuation, defined as the difference between maximum and minimum HR within the first 24 h of ICU admission, was analyzed for its association with outcomes using restricted cubic spline and multivariable Cox regression models.

Results: Among 24,419 eligible patients with sepsis, HR fluctuation showed a J-shaped association with ICU mortality, hospital mortality, and 28-day mortality. The high HR fluctuation group ($\geq$ 35 bpm) had a significantly increased risk of ICU mortality ([hazard ratio, 95% confidence interval] 1.12,1.02–1.22, P = 0.013), hospital mortality (1.10,1.02–1.19, P = 0.013), and 28-day mortality (1.11,1.03–1.20, P = 0.007) compared to the control group (HR fluctuation 25–34 bpm). The low HR fluctuation group (< 25 bpm) showed no significant difference in the risk of mortality compared to the control group.

Conclusions: Our large-sample study suggests that early high HR fluctuation is indicative of poor prognosis in critically ill patients with sepsis. Early HR fluctuation may serve as a readily available "high-risk alert system" influencing therapeutic decision-making.

1. Introduction

Sepsis, characterized by life-threatening organ dysfunction caused by the host's immune response to infection [1,2], represents a significant global health challenge. A preliminary extrapolation estimated that 31.5 million sepsis cases and 19.4 million severe sepsis cases occur annually worldwide, with a potential death toll of 5.3 million [3]. In the United States, sepsis affects over 1.7 million patients annually, contributing to more than 50% of hospital mortality and accounting for approximately 5.2% ($20 billion) of total hospital costs [4,5]. Thus, early recognition, severity classification, and risk stratification are vital for improving patient outcomes.

Heart rate (HR) is a fundamental vital sign regulated by the autonomic nervous system, reflecting the body's metabolic demands [6,

* Corresponding author. Department of Anesthesiology, West China Hospital, Sichuan University, Chengdu, Sichuan, China.
E-mail address: scujinliu@gmail.com (J. Liu).
[1] The authors have contributed equally to this work.

https://doi.org/10.1016/j.heliyon.2023.e20898
Received 6 March 2023; Received in revised form 7 October 2023; Accepted 10 October 2023
Available online 11 October 2023

7]. In the intensive care unit (ICU), patients with sepsis may experience dysregulated heart rate circadian rhythm due to several factors: (1) sepsis-related circulatory dysfunction; (2) sepsis treatments, including vasopressors, sedatives, mechanical ventilation, and other organ support therapies; (3) ICU environment, exposing patients to varying levels of light and sound.

HR variability is commonly used to assess circadian rhythm dysregulation in heart rate. Growing evidence suggests that reduced or abnormal HR variability might increase the risk of mortality among patients with sepsis [8–10]. Recently, the concept of HR fluctuation has emerged as a simpler and more direct indicator, defined as the difference between maximum and minimum HR within 24 h. To date, limited studies have explored the association between different HR fluctuation levels and disease prognosis. Some studies have shown that HR fluctuation is associated with short- and long-term mortality risk in patients with chronic heart failure, myocardial infarction, and critically ill patients in the ICU [11–13]. Nevertheless, it remains unclear what the magnitude of HR fluctuation means to patients with sepsis. Therefore, our study aimed to investigate the association of different HR fluctuation levels with ICU mortality, hospital mortality, and 28-day mortality. Additionally, we aimed to identify the cutoff value of HR fluctuation associated with the lowest risk of death in critically ill patients with sepsis.

2. Materials and methods

2.1. Study design and participants

This retrospective cohort study utilized the medical information mart for intensive care IV (MIMIC-IV, version 1.0). The MIMIC-IV database comprises 76,540 ICU stays from a tertiary hospital (2008–2019), encompassing various clinical variables such as demographics, comorbidities, physical measurements, laboratory results, imaging, diagnoses, medication/interventions, and survival data [14]. Inclusion criteria involved patients aged 18 years or older diagnosed with sepsis according to the sepsis 3.0 definition [15, 16]. Only patients with available HR records and key variables measured within the first 24 h of ICU admission were considered. In cases of multiple ICU stay records, only the initial record was selected. Patients with ICU stays shorter than 24 h were excluded. We obtained authorization to access the MIMIC IV database (Date of Agreement: April 12, 2021). The individual information of the patients included in this database was anonymous, and ethical review and informed consent were waived.

2.2. Data extraction

The MIMIC-IV (v1.0) database, developed and managed by the MIT Computational Physiology Laboratory, is accessible on PhysioNet—an online platform for sharing biomedical signal recordings and open-source software for analysis [14]. Data extraction for this study was conducted by author Yang, who completed the Collaborative Institutional Training Initiative (CITI) course and obtained certification (number: 42,061,840) for the "Conflicts of Interest" and "Data or Specimens Only Research" exams. PostgreSQL software (v13.0) and Navicate Premium software (v 15.0) were used for data extraction by running Structured Query Language (SQL). The codes used for calculating demographic characteristics, laboratory indicators, comorbidities, and severity scores were obtained from the GitHub repository (https://github.com/MIT-LCP/mimic-code).

The following clinical variables were extracted for analysis: *baseline variables* measured within 24 h of ICU admission, including demographics (age, sex, weight, race), vital signs (heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure [MAP], temperature, saturation of pulse oxygen [SpO2]), disease severity (Sequential Organ Failure score [SOFA], Charlson comorbidity index [CCI]), care unit type, comorbidities (hypertension, myocardial infarction, heart failure, chronic pulmonary disease, cerebrovascular disease, liver disease, renal disease, diabetes, cancer), source of infection, laboratory findings (white blood cell count, hemoglobin, platelets, serum creatinine, blood urea nitrogen, serum glucose, prothrombin time, serum potassium, serum sodium, serum chlorine), and clinical treatments (vasopressor[including norepinephrine, epinephrine, dopamine, and dobutamine], mechanical ventilation, renal replacement therapy [RRT]). *Outcome variables* included ICU mortality, hospital mortality, 28-day mortality, ICU length of stay (ICU LOS), and hospital length of stay (hospital LOS).

2.3. Exposure, follow-up, and outcomes

HR fluctuation was determined by subtracting the minimum HR from the maximum HR within the initial 24 h of ICU admission [17]. The HR fluctuation was categorized into three groups, with a reference range (control group) defined as 25–34 bpm. The low HR fluctuation group was defined as < 25 bpm, while the high HR fluctuation group was defined as ≥ 35 bpm [18].

The primary outcome was ICU mortality, and secondary outcomes included hospital mortality, 28-day mortality, ICU length of stay, and hospital length of stay.

The follow-up period started at ICU admission, with different endpoints based on the outcome measures. The ICU mortality endpoint was patient death or ICU discharge, whichever came first. The hospital mortality endpoint was patient death or hospital discharge, whichever came first. For 28-day mortality, the endpoint was patient death or admission within 28 days after ICU admission (day 0), whichever came first.

2.4. Statistical analysis

Normally distributed continuous variables were reported as mean $\pm$ standard deviation (SD), while abnormally distributed continuous variables were presented as medians and interquartile ranges (IQRs). Group comparisons for continuous variables were

conducted using an F test or Kruskal-Wallis test based on variable distribution. Classification variables were expressed as numbers and percentages, and group differences were assessed using chi-square or Fisher's exact test, as appropriate.

We assessed the nonlinear association of HR fluctuation as a continuous exposure with a given outcome. First, potential confounders were selected based on biological plausibility, risk factors identified in the literature or ≥10% change in relative risk in our study (Supplementary Table S1), and multivariable analysis was utilized to control for confounding variables. Second, restricted cubic splines were applied to investigate the association between HR fluctuation and the outcome. The spline models included full covariate adjustment, and the number of knots was determined using 3–5 knots and selecting the optimal model based on the minimized Akaike information criterion [19]. Furthermore, to determine the cutoff value of HR fluctuation, a two-line piecewise linear model with a single "change point" was estimated by testing all possible values and selecting the value with the highest likelihood.

We further examined the association of HR fluctuation as a categorical variable with a given outcome. The risks of mortality were compared by log-rank test in the low and high HR fluctuation against the control group in Kaplan-Meier survival analysis and multivariable Cox models were used to determine hazard ratios (HRs) and 95% confidential intervals (95%CIs). Furthermore, outcomes of ICU LOS and hospital LOS were categorized by the median, followed by conducting multivariable logistic regression models to obtain odds ratios (ORs) and 95%CIs.

Predefined subgroup analyses were conducted to assess the effect of HR fluctuation on mortality based on the direction of HR fluctuation ("Decrease" [highest heart rate precedes lowest heart rate] vs "Increase" [highest heart rate follows lowest heart rate]); congestive heart failure (Yes vs No); myocardial infarct (Yes vs No), hypertension (Yes vs No). Two sensitivity analyses were performed to test the robustness of the study: excluding patients with outlier heart rate values (< 40 bpm or > 180 bpm) and utilizing propensity score matching (PSM) to control for confounding factors. Before conducting PSM, patients were categorized into two groups based on HR fluctuation: HR fluctuation < 35 bpm and HR fluctuation ≥ 35 bpm. Propensity scores were estimated using a multivariable logistic regression model. One-to-one nearest neighbor matching with a caliper width of 0.25 was performed. Hazard ratios (95%CIs) were obtained from conditional Cox models in the matched cohort.

In addition, logistic regressions were performed to analyze the impact of baseline risk factors on the cutoff value of HR fluctuation. Clinically relevant variables or those showing an univariable association ($p < 0.10$) were included in the multivariable logistic regression model. The results were presented as ORs with corresponding 95%CIs.

Statistical significance was defined as a two-sided p value < 0.05. All analyses were conducted using R software (v 4.0.4) and STATA (v 16.0).

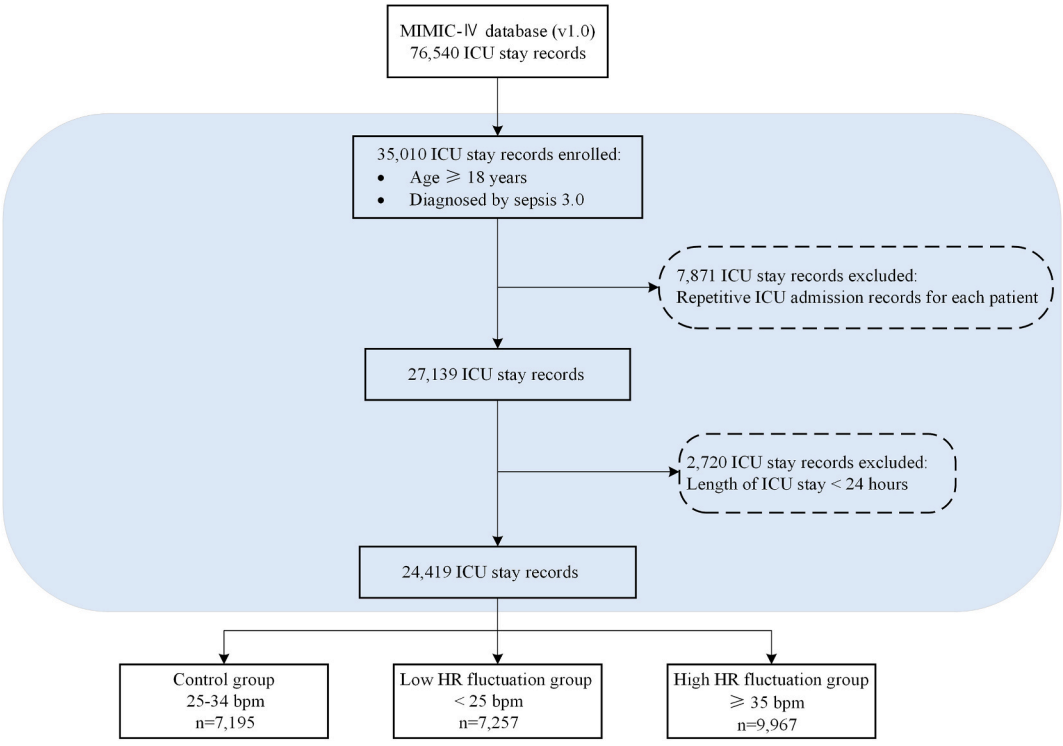

Fig. 1. Flowchart of the study. MMIC-IV, Medical Information Mart for Intensive Care IV; ICU, intensive care unit; HR, heart rate; bpm, beats per minute.

Table 1
Baseline characteristics among different heart rate (HR) fluctuation groups.

Variables	Control group: 25-34 bpm (n = 7,195)	Low HR fluctuation group: < 25 bpm (n = 7,257)	High HR fluctuation group: ≥ 35 bpm (n = 9,967)	Overall (n = 24,419)	p
Demographics					
Age, year, median (IQR)	68.0 [57.0, 79.0]	69.0 [58.0, 79.0]	68.0 [56.0, 79.0]	68.0 [57.0, 79.0]	<0.001
Male, no. (%)	4,200 (58.4)	4,234 (58.3)	5,711 (57.3)	14,145 (57.9)	0.257
Weight, kg, median (IQR)	79.4 [67.2, 95.3]	81.0 [68.1, 96.1]	78.5 [66.0, 93.2]	79.4 [67.0, 94.9]	<0.001
Ethnicity, no. (%)					<0.001
White	4,918 (68.4)	4,986 (68.7)	6,559 (65.8)	16,463 (67.4)	
Black	577 (8.0)	688 (9.5)	827 (8.3)	2,092 (8.6)	
Others	1,700 (23.6)	1,583 (21.8)	2,581 (25.9)	5,864 (24.0)	
Severity of disease					
SOFA, median (IQR)	3.0 [2.0, 4.0]	3.0 [2.0, 5.0]	3.0 [2.0, 4.0]	3.0 [2.0, 4.0]	<0.001
Charlson comorbidity index, median (IQR)	2.0 [1.0, 4.0]	3.0 [1.0, 5.0]	2.0 [1.0, 4.0]	3.0 [1.0, 4.0]	<0.001
Admission ICU unit					<0.001
CVICU/CCU, no. (%)	2,348 (32.6)	2,543 (35.0)	2,528 (25.4)	7,419 (30.4)	
MICU/SICU, no. (%)	3,748 (52.1)	3,896 (53.7)	5,663 (56.8)	13,307 (54.5)	
Others, no. (%)	1,099 (15.3)	818 (11.3)	1,776 (17.8)	3,693 (15.1)	
Comorbidities					
Congestive heart failure, no. (%)	2,019 (28.1)	2,517 (34.7)	2,953 (29.6)	7,489 (30.7)	<0.001
Myocardial infarct, no. (%)	1,286 (17.9)	1,400 (19.3)	1,714 (17.2)	4,400 (18.0)	0.002
Hypertension, no. (%)	3,157 (43.9)	2,959 (40.8)	4,143 (41.6)	10,259 (42.0)	<0.001
Chronic pulmonary disease, no. (%)	1,905 (26.5)	1,988 (27.4)	2,574 (25.8)	6,467 (26.5)	0.070
Diabetes, no. (%)	2,181 (30.3)	2,517 (34.7)	2,793 (28.0)	7,491 (30.7)	<0.001
Renal disease, no. (%)	1,490 (20.7)	1,996 (27.5)	2,005 (20.1)	5,491 (22.5)	<0.001
Liver disease, no. (%)	1,007 (14.0)	1,273 (17.5)	1,365 (13.7)	3,645 (14.9)	<0.001
Cerebrovascular disease, no. (%)	1,105 (15.4)	998 (13.8)	1,518 (15.2)	3,621 (14.8)	0.009
Cancer, no. (%)	1,089 (15.1)	1,072 (14.8)	1,686 (16.9)	3,847 (15.8)	<0.001
Source of infection					
Skin/soft tissue/bone/joint, no. (%)	394 (5.5)	428 (5.9)	574 (5.8)	1,396 (5.7)	0.536
Central nervous system, no. (%)	80 (1.1)	75 (1.0)	122 (1.2)	277 (1.1)	0.495
Pulmonary, no. (%)	1,335 (18.6)	1,273 (17.5)	2,218 (22.3)	4,826 (19.8)	<0.001
Gastrointestinal, no. (%)	383 (5.3)	432 (6.0)	580 (5.8)	1,395 (5.7)	0.222
Genitourinary, no. (%)	1,298 (18.0)	1,283 (17.7)	1,937 (19.4)	4,518 (18.5)	0.007
Vital signs					
Lowest heart rate, bpm, median (IQR)	71.0 [61.0, 82.0]	72.0 [64.0, 83.0]	69.0 [59.0, 80.0]	70.0 [61.0, 81.0]	<0.001
Highest heart rate, bpm, median (IQR)	100.0 [91.0, 112.0]	91.0 [82.0, 102.0]	118.0 [105.0, 132.0]	104.0 [91.0, 119.0]	<0.001
Mean heart rate, bpm, median (IQR)	84.4 [75.6, 95.8]	81.3 [72.2, 92.1]	89.7 [79.2, 101.4]	85.5 [75.8, 97.5]	<0.001
Direction of HR fluctuation[a]					<0.001
Decrease	3,644 (50.6)	3,753 (51.7)	5,575 (55.9)	12,972 (53.1)	
Increase	3,530 (49.1)	3,482 (48.0)	4,392 (44.1)	11,404 (46.7)	
Same	0 (0.0)	22 (0.3)	0 (0.0)	22 (0.1)	
Unknown	21 (0.3)	0 (0.0)	0 (0.0)	21 (0.1)	
Systolic pressure, mmHg, median (IQR)	113.6 [105.4, 123.9]	112.5 [104.4, 123.3]	113.0 [104.6, 123.9]	113.0 [104.8, 123.7]	<0.001
Diastolic pressure, mmHg, median (IQR)	60.2 [54.5, 66.7]	58.8 [52.9, 65.5]	61.4 [55.5, 68.4]	60.3 [54.4, 67.0]	<0.001
Mean arterial pressure, mmHg, median (IQR)	75.4 [70.0, 81.7]	74.0 [68.7, 80.7]	76.0 [70.5, 82.9]	75.2 [69.8, 81.9]	<0.001
Respiratory rate, bpm, median (IQR)	18.7 [16.6, 21.6]	18.7 [16.5, 21.5]	19.6 [17.1, 22.6]	19.0 [16.8, 22.0]	<0.001
Temperature, °C, median (IQR)	36.9 [36.6, 37.2]	36.8 [36.6, 37.1]	36.9 [36.6, 37.3]	36.9 [36.6, 37.2]	<0.001
SpO_2, %, median (IQR)	97.4 [96.0, 98.6]	97.2 [95.8, 98.5]	97.3 [95.8, 98.6]	97.3 [95.9, 98.6]	<0.001
Laboratory findings					
Hemoglobin, g/dL, median (IQR)	10.9 [9.3, 12.7]	10.7 [9.1, 12.4]	11.0 [9.4, 12.8]	10.9 [9.3, 12.7]	<0.001
Platelet count, $\times 10^9$/L, median (IQR)	200.0 [143.0, 267.0]	195.0 [135.0, 265.0]	202.0 [146.0, 279.0]	200.0 [142.0, 271.0]	<0.001

(*continued on next page*)

Table 1 (*continued*)

Variables	Control group: 25-34 bpm (n = 7,195)	Low HR fluctuation group: < 25 bpm (n = 7,257)	High HR fluctuation group: ≥ 35 bpm (n = 9,967)	Overall (n = 24,419)	p
WBC count, × 10^9/L, median (IQR)	11.1 [7.8, 15.4]	11.1 [7.6, 15.2]	11.2 [8.0, 16.0]	11.1 [7.8, 15.6]	<0.001
Urea, mg/dL, median (IQR)	21.0 [15.0, 33.0]	23.0 [16.0, 39.0]	21.0 [14.0, 33.0]	21.0 [15.0, 35.0]	<0.001
Creatinine, mg/dL, median (IQR)	1.0 [0.8, 1.5]	1.1 [0.8, 1.9]	1.0 [0.8, 1.5]	1.1 [0.8, 1.6]	<0.001
Blood glucose, mg/dL, median (IQR)	130.5 [114.8, 155.6]	130.1 [113.3, 156.4]	133.4 [114.5, 163.0]	131.4 [114.1, 159.3]	<0.001
Prothrombin time, s, median (IQR)	14.0 [12.4, 15.9]	14.0 [12.6, 16.8]	14.0 [12.4, 16.2]	14.0 [12.5, 16.3]	<0.001
Calcium, mmol/L, median (IQR)	8.5 [8.1, 8.9]	8.5 [8.1, 8.9]	8.5 [8.1, 9.0]	8.5 [8.1, 8.9]	<0.001
Chloride, mmol/L, median (IQR)	107.0 [103.0, 111.0]	106.0 [102.0, 110.0]	107.0 [103.0, 110.0]	107.0 [102.0, 110.0]	<0.001
Sodium, mmol/L, median (IQR)	140.0 [137.0, 143.0]	140.0 [137.0, 142.0]	140.0 [138.0, 143.0]	140.0 [137.0, 143.0]	<0.001
Potassium, mmol/L, median (IQR)	4.5 [4.1, 4.9]	4.5 [4.1, 5.0]	4.5 [4.1, 5.0]	4.5 [4.1, 5.0]	0.048
Treatment					
Vasopressor[b], no. (%)	2,320 (32.2)	2,491 (34.3)	4,000 (40.1)	8,811 (36.1)	<0.001
Mechanical ventilation, no. (%)	3,993 (55.5)	3,681 (50.7)	6,208 (62.3)	13,882 (56.8)	<0.001
RRT, no. (%)	187 (2.6)	291 (4.0)	361 (3.6)	839 (3.4)	<0.001
Outcome					
ICU mortality, no. (%)	752 (10.5)	779 (10.7)	1,462 (14.7)	2,993 (12.3)	<0.001
Hospital mortality, no. (%)	1,068 (14.8)	1,129 (15.6)	1,935 (19.4)	4,132 (16.9)	<0.001
28-day mortality, no. (%)	1,006 (14.0)	1,072 (14.8)	1,836 (18.4)	3,914 (16.0)	<0.001
ICU LOS, days, median (IQR)	3.0 [2.0, 6.0]	3.0 [2.0, 6.0]	3.0 [2.0, 7.0]	3.0 [2.0, 6.0]	<0.001
Hospital LOS, days, median (IQR)	8.0 [5.0, 15.0]	9.0 [5.0, 15.0]	9.0 [6.0, 17.0]	9.0 [5.0, 16.0]	<0.001

IQR, interquartile range; SOFA, sequential organ failure assessment; ICU, intensive care unit; CVICU, Cardiac vascular intensive care unit; CCU, Coronary care unit; MICU, Medical intensive care unit; SICU, surgical intensive care unit; SpO2, Saturation of Pulse Oxygen; WBC, white blood cell; RRT, Renal Replacement Therapy; LOS, length of stay; bpm, beats per minute.

[a] Direction of HR fluctuation was categorized as "Same" (highest and lowest heart rates occur simultaneously), "Decrease" (highest heart rate precedes lowest heart rate), "Increase" (highest heart rate follows lowest heart rate), or "Unknown".

[b] Vasopressor including norepinephrine, epinephrine, dopamine, and dobutamine.

3. Results

The study participants were shown in Fig. 1. A total of 76,540 ICU stay records from the MIMIC-IV database (v 1.0) were assessed, and 24,419 ICU stay records were included in the analysis. Participants were categorized into the control group (n = 7,195), low HR fluctuation group (n = 7,257), and high HR fluctuation group (n = 9,967) based on different HR fluctuation levels. The baseline demographics, severity of disease, admission ICU unit, comorbidities, source of infection, signs and symptoms, laboratory findings, and related treatment information for each group were demonstrated in Table 1.

In the study, among the 24,419 patients, ICU mortality was 12.3% (2,993 patients), hospital mortality was 16.9% (4,132 patients), and 28-day mortality was 16.0% (3,914 patients). The median length of stay in the ICU was three days (IQR, two to six days), and the

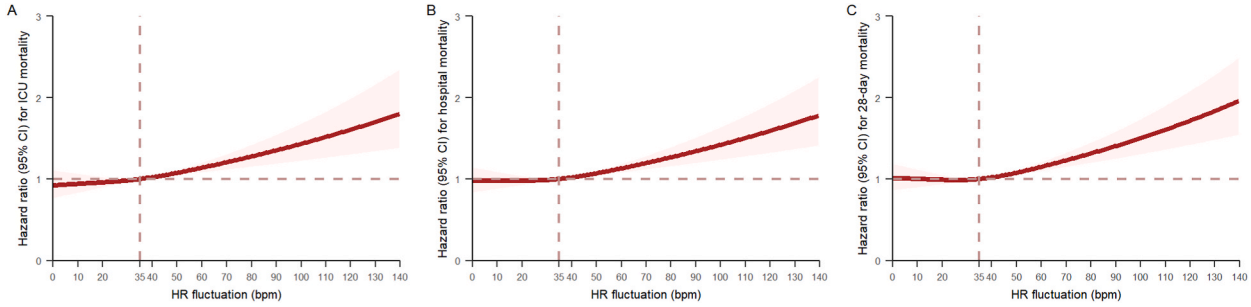

Fig. 2. Spline function plot of the association between HR fluctuation and outcomes in the total study participants: A) ICU mortality, B) hospital mortality, and C) 28-day mortality. Vertical dashed lines indicated the reference condition. All analyses were adjusted for age, sex, race, weight, Charlson comorbidity index, SOFA score, admission ICU unit, pulmonary infection, genitourinary infection, respiratory rate, mean arterial pressure, SpO2, temperature, WBC count, Platelet count, hemoglobin, creatinine, urea, blood glucose, prothrombin time, sodium, chloride, calcium, potassium, vasopressor, mechanical ventilation, and RRT. HR, heart rate; CI, confidence interval; ICU, intensive care unit; SOFA, sequential organ failure assessment; SpO2, Saturation of Pulse Oxygen; WBC, white blood cell; bpm, beats per minute; RRT, Renal Replacement Therapy.

median length of stay in the hospital was nine days (IQR, five to 16 days) for all participants (Table 1).

Supplementary Fig. S1 showed a J-shaped association of HR fluctuation with ICU mortality, hospital mortality, and 28-day mortality. Using a flexible model with a restricted cubic spline and two-line piecewise linear components, the change point of HR fluctuation was determined to be 36.42 bpm (standard error, 0.17). Based on this, the cutoff value for HR fluctuation was defined as 35 bpm (Fig. 2).

In Supplementary Fig. S2, the survival curves demonstrated a significant association between the high HR fluctuation group and the highest risk of ICU mortality, hospital mortality, and 28-day mortality, followed by the low HR fluctuation group and control group (log-rank $P < 0.0001$). Multivariable Cox models showed that, compared to the control group, the high HR fluctuation group had an increased risk of ICU mortality ([adjusted hazard ratio, 95% confidence interval], 1.12, 1.02–1.22, $P = 0.013$), hospital mortality (1.10, 1.02–1.19, $P = 0.013$), and 28-day mortality (1.11, 1.03–1.20, $P = 0.007$). The low HR fluctuation group had no significant difference in mortality risk compared to the control group (Fig. 3). Subgroup analyses did not identify any subgroup effects (Supplementary Figs. S3–5). Both sensitivity analyses confirmed the robustness of the results (Supplementary Figs. S6–9).

Supplementary Fig. S10 seemed to illustrate a U-shaped association of HR fluctuation with ICU LOS, and hospital LOS. Multivariable logistic regression models indicated that both the high and low HR fluctuation groups, compared to the control group, had an increased risk of ICU LOS ([adjusted odds ratio [95% confidence interval]: 1.16 [1.09–1.25], $P < 0.001$; 1.11 [1.03–1.19], $P = 0.008$) and hospital LOS (1.12 [1.05–1.19], $P = 0.001$; 1.08 [1.01–1.16], $P = 0.030$) (Supplementary Fig. S11).

Among patients with sepsis, the multivariable analysis identified several factors independently associated with a higher risk of HR fluctuation $\geq$ 35 bpm. These factors included age $\geq$ 65 years ([adjusted odds ratio, 95% confidence interval], 1.10, 1.03–1.17, $P = 0.003$), male (1.06,1.00–1.13, $P = 0.040$), admission to the MICU/SICU (1.33, 1.24–1.43) or other ICU units (1.47, 1.34–1.62, $P < 0.001$), comorbidity with cancer (1.12, 1.05–1.20, $P = 0.001$), genitourinary infection (1.12,1.05–1.20, $P = 0.001$), and various physiological variables, such as the mean arterial pressure, respiratory rate, temperature, SpO2, hemoglobin, blood glucose, calcium, and sodium (all $P < 0.05$). Vassopressor (1.37,1.28–1.46, $P < 0.001$), mechanical ventilation (1.36, 1.28–1.44, $P < 0.001$), and RRT (1.27,1.09–1.48, $P = 0.002$) were also associated with a higher risk of HR fluctuation $\geq$ 35 bpm (Supplementary Table S2).

4. Discussion

Our study revealed a J-shaped association between early HR fluctuation (measured as the difference between maximum and minimum HR within the first 24 h of ICU admission) and ICU mortality, hospital mortality, and 28-day mortality in patients with sepsis. Notably, the risk of these outcomes increased significantly when HR fluctuation was greater than or equal to 35 bpm. Additionally, we also identified risk factors independently associated with HR fluctuation greater than or equal to 35 bpm, including social

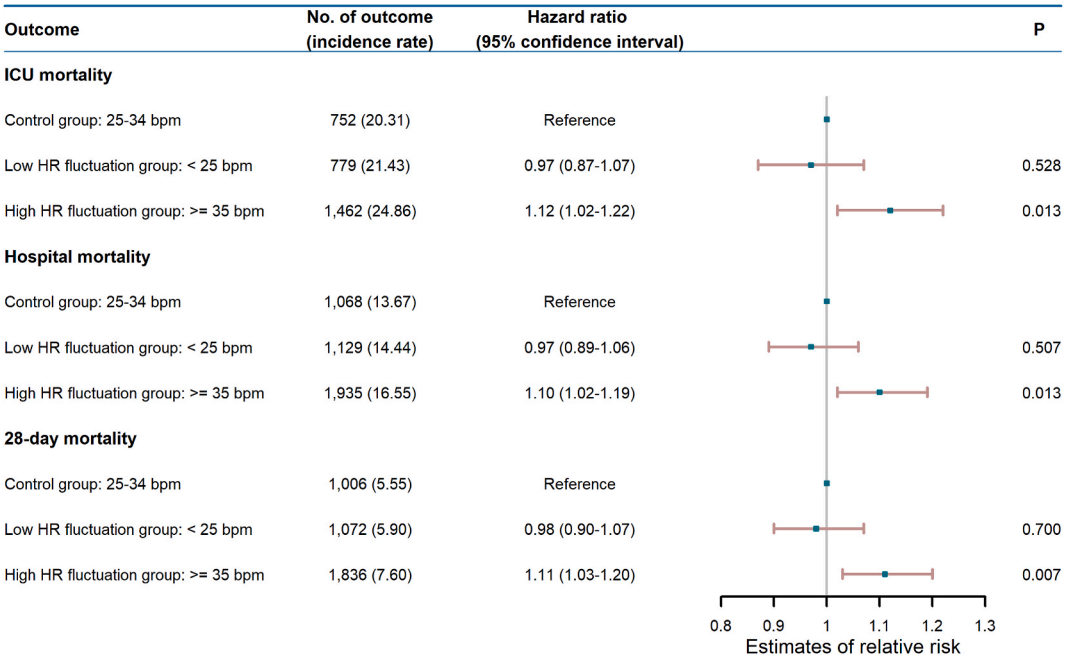

Fig. 3. The adjusted hazard ratios of different HR fluctuation groups and outcomes in the total study participants. Incidence rate: number of cases per 1000 person-years. All analyses were adjusted for age, sex, race, weight, Charlson comorbidity index, SOFA score, admission ICU unit, pulmonary infection, genitourinary infection, respiratory rate, mean arterial pressure, SpO2, temperature, WBC count, Platelet count, hemoglobin, creatinine, urea, blood glucose, prothrombin time, sodium, chloride, calcium, potassium, vasopressor, mechanical ventilation, and RRT. HR, heart rate; ICU, intensive care unit; SOFA, sequential organ failure assessment; SpO2, Saturation of Pulse Oxygen; WBC, white blood cell; bpm, beats per minute; RRT, Renal Replacement Therapy.

demographics, comorbidities, disease severity, and treatment variables.

Based on a large sample from the MIMIC-IV database, we initially evaluated the significance of early HR fluctuation in patients with sepsis, building upon existing evidence from observational studies highlighting HR fluctuation as a prognostic factor in various conditions [11–13,20]. To enhance internal validity, we employed multivariable regression and propensity score matching to control for confounders. Our findings, supported by both nonlinear and categorical analyses, provide robust evidence for the association between early HR fluctuation and mortality risk in patients with sepsis.

For critically ill patients in the ICU, a previous report indicated a U-shaped relationship between HR fluctuation and mortality risk. However, our study revealed a different pattern in patients with sepsis. We observed a J-shaped association between early HR fluctuation and ICU mortality, hospital mortality, and 28-day mortality. Notably, the risk of these outcomes significantly increased when HR fluctuation was greater than or equal to 35 bpm, in contrast to the control group (HR fluctuation 25–34 bpm). Interestingly, a prior study also found a J-shaped curve for the association between HR fluctuation and mortality in patients with myocardial infarction, supporting our findings to some extent [12]. These results suggest that the association between HR fluctuation and mortality risk may vary depending on the patient population and underlying disease.

Our findings underscore the importance of early assessment of HR fluctuation in predicting sepsis prognosis. Determining risk factors independently associated with high HR fluctuation can help identify high-risk patients. Thus, early HR fluctuation may serve as a readily available "high-risk alert system" and influence therapeutic decision-making. Clinicians should prioritize monitoring and timely intervention for individuals in the high HR fluctuation group.

Although the underlying mechanisms for the observed association remain unclear, it is believed that an elevated HR fluctuation could be a potential indicator of the severity of the infection and the body's response to it, enhanced by subsequent immune dysregulation, microcirculatory derangements, and end-organ dysfunction. High sympathetic stress is implicated in patients with sepsis, leading to myocardial depression and reduced ejection fraction in nearly half of the patients [21]. Additionally, patients with sepsis suffer changes in coronary circulation, circulating volume, and vessel tone, all of which can affect cardiac function and heart rate [22]. Elevated HR fluctuation may reflect the degree of these changes, and thus, the severity of the infection and associated adverse outcomes. Furthermore, elevated HR fluctuation may be an indicator of autonomic dysfunction, which is common in sepsis and associated with a poor prognosis [13].

4.1. Limitations

Several limitations exist in our study. First, although the MIMIC-IV database provides a large sample size, the data were collected from a single center, introducing potential selection bias and limiting the generalizability of our findings. Second, HR fluctuation is influenced not only by the patient's condition but also by underlying diseases, medications/interventions, and environmental factors. Therefore, the presence of residual or unmeasured confounding factors cannot be ruled out. We mitigated this by adjusting for numerous variables in the multivariable regression model and utilizing propensity score matching. Consistency between the main analysis and sensitivity analysis strengthens the robustness of the association between early HR fluctuation and mortality risk in patients with sepsis. Third, as a retrospective cohort study, causality cannot be established.

5. Conclusions

In summary, early high HR fluctuation was independently associated with increased risk of ICU mortality, hospital mortality, and 28-day mortality in patients with sepsis. Timely monitoring and intervention in response to changes in HR fluctuation are crucial for improving outcomes.

Data availability statement

The datasets generated and analyzed during the current study are available in the Medical Information Mart for Intensive Care IV (MIMIC-IV, v 1.0) database.

The publicly available repository can be found below: https://physionet.org/content/mimiciv/1.0.

Ethics statement

We obtained authorization to access the MIMIC IV database (Date of Agreement: April 12, 2021). The individual information of the patients included in this database was anonymous, and ethical review and informed consent were waived.

Consent for publication

Not applicable.

Funding statement

This work was funded by the National Natural Science Foundation of China (No. 82071557) and the 1.3.5 Project for Disciplines of Excellence of West China Hospital of Sichuan University (No. ZY2016101).

CRediT authorship contribution statement

Junhui He: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Jie Yang:** Writing – review & editing, Methodology, Formal analysis. **Jin Liu:** Writing – review & editing, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The present study data was based on the MIMIC-IV database. We would like to thank all staff and patients involved in the construction of the MIMIC-IV database.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e20898.

References

[1] A. Rhodes, L.E. Evans, W. Alhazzani, et al., Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016, Intensive Care Med. 43 (3) (2017) 304–377, https://doi.org/10.1007/s00134-017-4683-6.
[2] R.S. Hotchkiss, L.L. Moldawer, S.M. Opal, et al., Sepsis and septic shock, Nat. Rev. Dis. Prim. 2 (1) (2016), 16045, https://doi.org/10.1038/nrdp.2016.45.
[3] C. Fleischmann, A. Scherag, N.K. Adhikari, et al., Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations, Am. J. Respir. Crit. Care Med. 193 (3) (2016) 259–272, https://doi.org/10.1164/rccm.201504-0781OC.
[4] C.M. Torio, R.M. Andrews, National Inpatient Hospital Costs: the Most Expensive Conditions by Payer, 2011, Healthcare Cost and Utilization Project (HCUP) Statistical Briefs, Rockville (MD), 2006.
[5] V. Liu, G.J. Escobar, J.D. Greene, et al., Hospital deaths in patients with sepsis from 2 independent cohorts, JAMA. 312 (1) (2014) 90–92, https://doi.org/10.1001/jama.2014.5804.
[6] G. Heusch, Heart rate in the pathophysiology of coronary blood flow and myocardial ischaemia: benefit from selective bradycardic agents, Br. J. Pharmacol. 153 (8) (2008) 1589–1601, https://doi.org/10.1038/sj.bjp.0707673.
[7] J.C. Reil, M. Böhm, The role of heart rate in the development of cardiovascular disease, Clin. Res. Cardiol. 96 (9) (2007) 585–592, https://doi.org/10.1007/s00392-007-0537-5.
[8] N. Liu, M.L. Chee, M.Z.Q. Foo, et al., Heart rate n-variability (HRnV) measures for prediction of mortality in sepsis patients presenting at the emergency department, PLoS One. 16 (8) (2021), e0249868, https://doi.org/10.1371/journal.pone.0249868.
[9] J.Z. Pong, S. Fook-Chong, Z.X. Koh, et al., Combining heart rate variability with disease severity score variables for mortality risk stratification in septic patients presenting at the emergency department, Int. J. Environ. Res. Publ. Health. 16 (10) (2019), https://doi.org/10.3390/ijerph16101725.
[10] de Castilho F.M., Ribeiro A.L.P., da Silva J.L.P., et al., Heart rate variability as predictor of mortality in sepsis: a prospective cohort study, PLoS One. 12 (6) (2017) e0180060,doi:10.1371/journal.pone.0180060.
[11] R.M. Cubbon, N. Ruff, D. Groves, et al., Ambulatory heart rate range predicts mode-specific mortality and hospitalisation in chronic heart failure, Heart. 102 (3) (2016) 223–229, https://doi.org/10.1136/heartjnl-2015-308428.
[12] Q. Guo, H. Li, H. Ouyang, et al., Heart rate fluctuation and mortality in critically ill myocardial infarction patients: a retrospective cohort study, Front Cardiovasc Med. 8 (2021), 577742, https://doi.org/10.3389/fcvm.2021.577742.
[13] Q. Guo, Z. Xiao, M. Lin, et al., Heart rate fluctuation predicts mortality in critically ill patients in the intensive care unit: a retrospective cohort study, Ann. Transl. Med. 9 (4) (2021) 334, https://doi.org/10.21037/atm-20-7897.
[14] A.L. Goldberger, L.A. Amaral, L. Glass, et al., PhysioBank, PhysioToolkit, and PhysioNet: components of a new research resource for complex physiologic signals, Circulation. 101 (23) (2000) E215–E220, https://doi.org/10.1161/01.cir.101.23.e215.
[15] M. Singer, C.S. Deutschman, C.W. Seymour, et al., The third international consensus definitions for sepsis and septic shock (Sepsis-3), JAMA. 315 (8) (2016) 801–810, https://doi.org/10.1001/jama.2016.0287.
[16] M. Shankar-Hari, G.S. Phillips, M.L. Levy, et al., Developing a new definition and assessing new clinical criteria for septic shock: for the third international consensus definitions for sepsis and septic shock (Sepsis-3), JAMA. 315 (8) (2016) 775–787, https://doi.org/10.1001/jama.2016.0289.
[17] Q. Guo, H. Li, H. Ouyang, et al., Heart rate fluctuation and mortality in critically ill myocardial infarction patients: a retrospective cohort study, Frontiers in Cardiovascular Medicine. 8 (2021), https://doi.org/10.3389/fcvm.2021.577742.
[18] Q. Guo, Z. Xiao, M. Lin, et al., Heart rate fluctuation predicts mortality in critically ill patients in the intensive care unit: a retrospective cohort study, Ann. Transl. Med. 9 (4) (2021), https://doi.org/10.21037/atm-20-7897, 334-334.
[19] F.E. Harrell Jr., Regression Modeling Strategies: with Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis, Springer, 2015.
[20] J. Oikawa, H. Fukaya, S. Ishii, et al., Variation in heart rate range by 24-h Holter monitoring predicts heart failure in patients with atrial fibrillation, ESC Heart Fail. 9 (5) (2022) 3092–3100, https://doi.org/10.1002/ehf2.14035.
[21] A. Rudiger, M. Singer, Mechanisms of sepsis-induced cardiac dysfunction, Crit. Care Med. 35 (6) (2007) 1599–1608, https://doi.org/10.1097/01.CCM.0000266683.64081.02.
[22] R. Sato, M. Nasu, A review of sepsis-induced cardiomyopathy, J Intensive Care. 3 (2015) 48, https://doi.org/10.1186/s40560-015-0112-5.