

# The Impact of Heart Rate Circadian Rhythm on In-hospital Mortality in Stroke and Critically Ill Patients: Insights from the eICU Collaborative Research Database

**Zhengning Yang**

Shaanxi University of Chinese Medicine

**Zhe Li**

Affiliated Hospital of Shaanxi University of Chinese Medicine

**Xu He**

Shaanxi University of Chinese Medicine

**Zhen Yao**

Shaanxi University of Chinese Medicine

**XiaoXia Xie**

Shaanxi University of Chinese Medicine

**Sha Zhang**

Shaanxi University of Chinese Medicine

**Yan Shen**

Shaanxi Provincial Hospital of Chinese Medicine

**Shaowei Li**

Shaanxi Provincial Hospital of Chinese Medicine

**Shuzhen Qiao**

Shaanxi Provincial Hospital of Chinese Medicine

**Zhenliang Hui**

Shaanxi Provincial Hospital of Chinese Medicine

**Chao Gao**

Xijing Hospital

**Jun Chen** (✉ [chj2002819@163.com](mailto:chj2002819@163.com))

Shaanxi Provincial Hospital of Chinese Medicine

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## Research Article

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# Abstract

## Background:

The dysregulation of the heart rate circadian rhythm has been documented to be an independent risk factor in multiple diseases. However, data showing the impact of dysregulated heart rate circadian rhythm in stroke and critically ill patients are scarce.

## Methods:

Stroke and critically ill patients in the ICU between 2014 and 2015 from the recorded eICU Collaborative Research Database were included in the current analyses. The impact of circadian rhythm of heart rate on in-hospital mortality was analyzed. Three variables, Mesor (rhythm-adjusted mean of heart rate), Amplitude (distance from the highest point of circadian rhythm of heart rate to Mesor), and Peak time (time when the circadian rhythm of heart rate reaches the highest point) were used to evaluate the heart rate circadian rhythm. The incremental value of circadian rhythm variables in addition to Acute Physiology and Chronic Health Evaluation (APACHE) IV score to predict in-hospital mortality was also explored.

## Results:

A total of 6,201 eligible patients were included. The in-hospital mortality was 16.2% (1,002/6,201). The circadian rhythm variables of heart rate, Mesor, Amplitude, and Peak time, were identified to be independent risk factors of in-hospital mortality. After adjustments, Mesor per 10 beats per min (bpm) increase was associated with a 1.17-fold (95%CI: 1.11, 1.24,  $P<0.001$ ) and Amplitude per 5 bpm was associated with a 1.14-fold (95%CI: 1.06, 1.24,  $P<0.001$ ) increase in the risk of in-hospital mortality, respectively. The risk of in-hospital mortality was lower in patients who had Peak time reached between 18:00-24:00 or 00:00-06:00; whereas the risk was highest in patients who had Peak time reached between 12:00-18:00 (OR: 1.33, 95%CI: 1.05, 1.68,  $P=0.017$ ). Compared with APACHE IV score only (c-index=0.757), combining APACHE IV score and circadian rhythm variables of heart rate (c-index=0.766) was associated with increased discriminative ability ( $P=0.003$ ).

## Conclusion:

Circadian rhythm of heart rate is an independent risk factor of the in-hospital mortality in stroke and critically ill patients. Including circadian rhythm variables regarding heart rate might increase the discriminative ability of the risk score to predict the short-term prognosis of patients.

## Introduction

Circadian rhythm is a representation of the solar day in the human body that allows the body to adapt to predictable changes in environmental time, and its coordination is essential for maintaining optimal physiological function and physical and mental health [1, 2]. Dysregulated circadian rhythm is associated

with a variety of diseases, such as cardiovascular disease, depression, anxiety, and metabolic obesity [2, 3].

Generally, circadian rhythms cause the heart rate to rise during the day and decrease at night [4]. The dysregulation of the heart rate circadian rhythm is an independent predictor of cardiovascular and nervous system diseases [5]. It has been shown that the level of ischemic or hemorrhagic lesions in the cerebral hemisphere and the brainstem may result in impaired heart rate of circadian rhythm variability [6]; however, among the stroke and critically ill patients, the impact of the impaired circadian rhythm of heart rate in terms of all-cause mortality, is still poorly understood.

The eICU Collaborative Research Database is one of the largest public databases in the world. It collects a large amount of high-quality clinical information of patients admitted to intensive care units (ICU) in 208 hospitals in the United States [7]. In the current analyses, based on data from the eICU Collaborative Research Database, we investigate the impact of circadian rhythm regarding heart rate on in-hospital mortality in stroke and critically ill patients.

## Methods

The current study collected data from the eICU Collaborative Research Database v2.0. The eICU Collaborative Research Database is a large public database created by the Philips Healthcare in collaboration with the Laboratory for Computational Physiology (LCP) at the Massachusetts Institute of Technology (MIT), covering routine data from 200,859 patients admitted to intensive care unit in 208 hospitals in the United States in 2014 and 2015, collecting a large amount of high-quality clinical information, including vital signs, nursing plan documents, disease severity, diagnostic information, treatment information [7, 8]. Data collection was in accordance with the ethical standards of the institutional review board of the Massachusetts Institute of Technology (no. 0403000206) and with the 1964 Declaration of Helsinki and its later amendments. The author obtained the access of the database (certification number: 40608375) and was responsible for the data extraction.

## Data collection

All patients with a stroke diagnosis in the database was eligible for inclusion in this study. Patients were excluded for the following reasons: (1) Patients who were discharged or died within a full calendar day after hospitalization; (2) Absence of in-hospital vital status records; (3) Absence of consecutively recorded heart rate data; (4) After single cosinor transformation the circadian rhythm of heart rate was not existence. The following variables were extracted from the eICU database: demographics parameters (age, gender, ethnicity and body mass index (BMI)), heart rate (consecutively recorded every 5 minutes), in-hospital stay time, in-ICU stay time, comorbidities parameters (hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), coronary artery disease, heart failure, atrial fibrillation, cirrhosis, upper gastrointestinal bleed, chronic renal insufficiency, bone fractures),

medications parameters (Atropine, Amiodarone, Diltiazem, Metoprolol, Carvedilol, Digoxin), APACHE IV score, and in-hospital mortality.

## Outcomes

The primary outcome was in-hospital mortality. APACHE IV score has been validated for decision-making and quality improvement initiatives in the ICU. It provides a useful estimate of patients' mortality based on data within 24 hours of admission to the ICU [7, 9]. We therefore also explored the incremental value of circadian rhythm variables to APACHE IV score to predict the in-hospital mortality.

## Statistical analysis

The R software package *circacompare* was used to make the Single cosinor transformation for the heart rate data to analyze the characteristics of circadian rhythm. The mathematical model of the Single cosinor transformation is as follows:

$$y = k + \alpha * \cos(\tau(t - \varphi))$$

In this equation,  $y$  represents the heart rate,  $k$  represents the Mesor,  $\alpha$  represents Amplitude,  $\tau$  is the period,  $t$  refers to the time in hours,  $\varphi$  represents the Peak time [10]. The variables of Mesor, Amplitude, and Peak time were used to quantify the circadian rhythm of heart rate [11]. Mesor is a rhythm-adjusted mean of heart rate. When Mesor increases, the heart rate of the patient increases throughout the day. Amplitude is the distance from the highest point of circadian rhythm of heart rate to Mesor. When Amplitude increases, the fluctuation range of one-day heart rate increases. Peak time is the time when the circadian rhythm of heart rate reaches the highest point.

To investigate the impact of circadian rhythm on mortality, two steps of analyses were conducted. Step 1 compared the Group mean-cosinor differences of the three variables between in-hospital survivors and non-survivors (results shown in Figure 2), whereas Step 2 compared each variable in relation to outcomes with their respective lowest risk considered as the reference (results shown in Table 2 and Figure 3).

Continuous variables were shown as mean and standard deviation or median and interquartile range (IQR). Categorical variables were displayed as numbers and percentages. To compare the baseline characteristics of the survivors and non-survivors, the Wilcoxon rank sum test and Independent-sample T test was used for continuous variables when appropriate; the chi-square test was used for categorical variables. The logistic regression was used for the analyses in Step 2. In addition to a univariate model, one multivariate adjusted model was established by adjusting for Mesor, Amplitude, Peak time, APACHE IV score, age, BMI, Intervention, hypertension, diabetes mellitus, COPD, coronary artery disease, heart failure, atrial fibrillation, cirrhosis and chronic renal insufficiency. In order to evaluate the consistency of the results, the multivariate model was adjusted after multiple imputation for the missing data (results

shown in Supplementary Table 1 and Supplementary Table 2), and the covariate balancing propensity score be adjusted (results shown in Supplementary Table 3, Supplementary Table 4 and Supplementary Table 5). as subgroup analyses, the association between Mesor, Amplitude and Peak time and the in-hospital mortality was assessed according to the presence of coronary artery disease, heart failure and atrial fibrillation. Heart rate interfering medications have been used since the second calendar day was shown in Supplementary Table 6. In order to further explore whether medications have an effect on the circadian rhythm of heart rate to predict in-hospital mortality, the correlation between Mesor, Amplitude, Peak time and in-hospital mortality was evaluated according to the use of medications that affect heart rate, frequency of medications, medications action and time of medications. DeLong test was used to explore the incremental value of circadian rhythm variables to APACHE IV score to predict the in-hospital mortality.

R software (version 4.0.2, [www.rproject.org](http://www.rproject.org)) was used for statistical analysis, and  $P < 0.05$  was considered statistically significant.

## Results

### Demographic and clinical characteristics

Of the total of 200,859 patients enrolled in the eICU database, 6,201 patients were included in the current analyses (Figure 1). Baseline characteristics of stroke and critically ill patients are shown in Table 1. In-hospital death occurred in 1,002 (16.2%) patients. Compared with the survivors during hospitalization, the non-survivors were associated with older age, more often having comorbidities such as diabetes mellitus, COPD, heart failure, atrial fibrillation and Cirrhosis, fewer used medications interfering with heart rate since the second calendar day, and they also have higher APACHE  $\Sigma$  score.

**Table 1**

Baseline characteristics of stroke and critically ill patients

Variables	In-hospital survivors (N=5,199)	In-hospital non-survivors (N=1,002)	P value
Age, years (mean (SD))	65.1 (14.5)	67.7 (13.6)	<0.001
Sex, Male (n/N (%))	2704 (52.0)	511 (50.8)	0.577
Ethnicity (n /N (%))			0.075
Caucasian	3830 (73.7)	728 (72.6)	
African American	690 (13.3)	113 (11.3)	
Hispanic	256 (4.9)	61 (6.1)	
Asian	109 (2.1)	32 (3.2)	
Native American	20 (0.4)	2 (0.2)	
Other/Unknown	294 (5.6)	66 (6.6)	
BMI (mean (SD))	28.7 (7.3)	28.4 (7.2)	0.209
Comorbidities (n/N (%))			
Hypertension	1737 (33.4)	329 (32.8)	0.751
Diabetes mellitus	712 (13.7)	174 (17.4)	0.003
COPD	234 (4.5)	62 (6.2)	0.027
Coronary artery disease	247 (4.8)	60 (6.0)	0.116
Heart failure	283 (5.4)	86 (8.6)	<0.001
Atrial fibrillation	695 (13.4)	160 (16.0)	0.033
Cirrhosis	25 (0.5)	20 (2.0)	<0.001
Upper gastrointestinal bleed	62 (1.2)	12 (1.2)	1
Chronic renal insufficiency	86 (1.7)	18 (1.8)	0.852
Bone fractures	58 (1.1)	11 (1.1)	1
Intervention (n/N (%))	1078 (20.7)	160 (15.9)	<0.001
APACHE II score (median [IQR])	51.0 [37.0, 67.0]	77.5 [59.0, 97.0]	<0.001
In-hospital time, hours (median [IQR])	185.7 [113.0, 329.2]	133.4 [75.3, 241.6]	<0.001
In-ICU time, hours (median [IQR])	79.6 [52.0, 156.7]	95.7 [60.1, 177.9]	<0.001
Data are mean (standard deviation) or median [interquartile range] or number (percentages)			

## Circadian rhythm analyzed by Group mean-cosinor differences

During hospitalization, between the survivors and non-survivors the Mesor were respectively 80.29 and 87.30 bpm (absolute difference: 7.01 bpm, 95%CI: 6.94,7.08,  $P<0.001$ , Figure 2); the Amplitude were respectively 1.55 and 1.06 bpm (absolute difference: -0.49 bpm, 95%CI: -0.59,-0.39,  $P<0.001$ , Figure 2); and the Peak time were respectively at 22.73 hours and 20.69 hours (absolute difference: -2.04 hours, 95%CI: -2.37,-1.68,  $P<0.001$ , Figure 2).

## Mesor, Amplitude and Peak time in relation to the outcomes

After adjusted to confounding factors, Mesor per 10 bpm increase was associated with a 1.17-fold increase (95%CI: 1.11, 1.24,  $P<0.001$ , Table 2, Figure 3a), and Amplitude per 5 bpm was associated with a 1.14-fold (95%CI: 1.06, 1.24,  $P<0.001$ , Table 2, Figure 3b) increase in the risk of in-hospital mortality, respectively. The increase in the risk of mortality for Mesor became evident after reaching ~70bpm, whereas for Amplitude was reaching 5 bpm (Figure 3). The risk of in-hospital mortality was lower in patients who had Peak time reached between 18:00-24:00 or 00:00-06:00; whereas the risk was highest in patients who had Peak time reached between 12:00-18:00 (OR: 1.33, 95%CI: 1.05, 1.68,  $P=0.017$ , Table 2, Figure 3c). The missing data in the variable was displayed in Supplementary Table 1. After after multiple imputation for the missing values in variables, the results were consistent with the previous results (Supplementary Table 2). After adjustment for covariates, the Mesor, Amplitude and Peak time were significantly associated with in-hospital mortality in stroke and critically ill patients (Table 2, Figure 3), and this association persisted when adjusted for the covariat balancing propensity score (Supplementary Table 3, Supplementary Table 4 and Supplementary Table 5).

**Table 2**

Risk factors of in-hospital mortality in stroke and critically ill patients

Variables	In-hospital Mortality			
	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Mesor (per 10 bpm increase)	1.33 (1.27, 1.39)	<0.001	1.17 (1.11, 1.24)	<0.001
Amplitude (per 5 bpm increase)	1.32 (1.23, 1.40)	<0.001	1.14 (1.06, 1.24)	<0.001
Peak time				
18:00-24:00	Reference		Reference	
00:00-06:00	0.99 (0.83, 1.19)	0.921	1.00 (0.81, 1.25)	0.985
06:00-12:00	1.46 (1.21, 1.77)	<0.001	1.20 (0.95, 1.52)	0.119
12:00-18:00	1.56 (1.29, 1.88)	<0.001	1.33 (1.05, 1.68)	0.017
APACHE IV score	1.04 (1.03, 1.04)	<0.001	1.03 (1.03, 1.04)	<0.001
Sex	0.96 (0.84, 1.10)	0.553		
Age	1.01 (1.01, 1.02)	<0.001	1.00 (1.00, 1.01)	0.144
Ethnicity				
Caucasian	0.79 (0.35, 2.14)	0.609		
African American	0.68 (0.29, 1.87)	0.412		
Hispanic	0.99 (0.41, 2.77)	0.988		
Asian	1.22 (0.49, 3.52)	0.685		
Native American	0.42 (0.06, 2.04)	0.314		
Other/Unknown	0.93 (0.39, 2.59)	0.878		
BMI	0.99 (0.98, 1.00)	0.213	1.00 (0.99, 1.01)	0.720
Intervention	0.73 (0.60, 0.87)	<0.001	0.54 (0.43, 0.67)	<0.001
Hypertension	0.97 (0.84, 1.12)	0.723	0.97 (0.80, 1.16)	0.714
Diabetes mellitus	1.32 (1.10, 1.58)	0.002	0.96 (0.75, 1.22)	0.724
COPD	1.40 (1.04, 1.86)	0.022	0.93 (0.62, 1.35)	0.697
Coronary artery disease	1.28 (0.95, 1.70)	0.099	1.07 (0.73, 1.55)	0.714
Heart failure	1.63 (1.26, 2.09)	<0.001	1.13 (0.80, 1.57)	0.489
Atrial fibrillation	1.23 (1.02, 1.48)	0.029	0.88 (0.69, 1.12)	0.314
Cirrhosis	4.22 (2.31, 7.60)	<0.001	2.50 (1.17, 5.22)	0.016

Upper gastrointestinal bleed	1.00 (0.51, 1.80)	0.989		
Chronic renal insufficiency	1.09 (0.63, 1.77)	0.748	0.75 (0.39, 1.38)	0.379
Bone fractures	0.98 (0.49, 1.81)	0.961		
OR Odd ratio, CI Confidential interval, bpm beats per min, BMI Body mass index, APACHE Acute Physiology and Chronic Health Evaluation.				

## Disease's effect on the circadian rhythm of heart rate to predict outcomes

Mesor, Amplitude and Peak time were stratified according to the patients with and without coronal artery disease, heart failure and atrial fibrillation (Supplementary Table 7, Supplementary Table 8 and Supplementary Table 9). There was no significant interaction between the effects of Mesor, Amplitude and Peak time on in-hospital mortality and the existence of coronary artery disease (Supplementary Figure 1), but the association between Peak time and in-hospital mortality was affected by heart failure (Supplementary Figure 2), and the association between Mesor and in-hospital mortality was affected by atrial fibrillation (Supplementary Figure 3).

## Medication's effect on the circadian rhythm of heart rate to predict outcomes

The medications that affect the heart rate was shown in Supplementary Table 6. Mesor, Amplitude and Peak time were stratified according to the use of medications that affect heart rate, frequency of medications, medications action and time of medications. (Supplementary Table 10, Supplementary Table 11, Supplementary Table 12 and Supplementary Table 13). There was no significant interaction between the effects of Mesor, Amplitude and Peak time on in-hospital mortality and the medications use frequency and the medications action (Supplementary Figure 4, Supplementary Figure 5), but the association between Amplitude and in-hospital mortality was affected by the use of medications that affect heart rate and time of medications (Supplementary Figure 6, Supplementary Figure 7).

## Discriminative ability of the APACHE IV score and heart rate circadian rhythm in predicting in-hospital mortality

To investigate the incremental value of circadian rhythm variables in addition to APACHE IV score to predict the in-hospital mortality, the discriminative ability of three prognostic models were shown in Figure 4. Model 1 was calculated with circadian rhythm variables of heart rate (Mesor, Amplitude and Peak time). Model 2 was based on APACHE IV score only. Model 3 combined APACHE IV score with the circadian rhythm variables of heart rate. Compared with Model 2 (c-index=0.757), the Model 3 (c-

index=0.766) was associated with increased discriminative ability ( $P=0.003$ ), at the expense of adding three circadian rhythm variables. The missing APACHE IV score was shown in Supplementary Table 1. The incremental value of circadian rhythm variables to the APACHE IV score in predicting in-hospital mortality remained after multiple imputation for missing data of the APACHE IV score (Supplementary Figure 8).

## Discussion

The main findings of the current analysis can be summarized as follows: (1) The circadian rhythm variables of heart rate, Mesor, Amplitude, and Peak time, were the independent risk factors of in-hospital mortality in stroke and critically ill patients. (2) Mesor per 10 bpm increase and Amplitude per 5 bpm increase were associated with a 1.17-fold and a 1.14-fold increase in the risk of in-hospital mortality, respectively. The risk of in-hospital mortality was highest in patients whom had Peak time reached between 12:00-18:00. (3) The effects of Mesor, Amplitude, and Peak time on in-hospital mortality were not associated with the presence of coronary artery disease, but Peak time was associated with the presence of heart failure and Mesor was associated with the presence of atrial fibrillation. (4) The effects of Mesor, Amplitude, and Peak time on in-hospital mortality were not associated with the medications use frequency and the medications action, but Amplitude was associated with the use of medications that affect heart rate and time of medications. (5) Compared with APACHE IV score only, combining APACHE IV score and circadian rhythm variables of heart rate was associated with increased discriminative ability.

Stroke is the second leading cause of death and the third leading cause of disability worldwide in the past five years [12]. Stroke patients can benefit from extensive care [13]. Previous studies using the eICU database, a multi-center intensive care unit database, found that high mechanical power of ventilation was independently associated with higher in-hospital mortality among ICU patients who received invasive ventilation for at least 48 hours [7, 14]. There is 5.5% (11,063/200,859) of the stroke patients in the database. In other studies, the mortality of stroke patients is 20%-30% [15, 16]. In the eICU database, the mortality of stroke patients is 14.1% (1,565/11,063). The study of the eICU database has found that there is a general low mortality among the patients enrolled [8], which needs to be further explored.

Identifying the indicators of severity or mortality in stroke patients may be helpful in stratifying the risk of patients, extending patients' survival time and improving their prognosis in terms of treatment. Previous studies have found that hypertension is the strongest independent risk factor for stroke [12]. Thomas Jensen et al [17]. found that the independent risk factors of stroke include diabetes mellitus. Carmine Marini et al [18]. found that the independent risk factors of stroke include atrial fibrillation. Joseph P. Broderick et al [19]. found that the independent risk factors of stroke include heart failure. After adjusting these previous factors, we still found that variables of heart rate circadian rhythm such as Mesor, Amplitude and Peak time are independent risk factors for stroke. We also found that the effects of Mesor on in-hospital mortality is associated with the presence of atrial fibrillation, but Peak time is associated with the presence of heart failure. Circadian rhythm of heart rate was affected and regulated by adrenal, sympathetic/parasympathetic nervous system, hypothalamus and pituitary activity [20]. For

the brain-injured patients, a study found that there were significant changes in the circadian rhythms of heart rate, blood pressure, body temperature, cortisol, and blood melatonin compared to healthy subjects [21]. Desynchronization between circadian rhythm and metabolism can lead to atherosclerosis and thrombosis, which can lead to serious cardiovascular events, including myocardial infarction and cardiac arrest, increasing the risk of death [22]. Our findings might be explained by the fact that serious adverse cardiovascular events caused by changes of heart rate circadian rhythm appear to be related to the rhythmic disorders of neurohormones associated with the cardiovascular system such as melatonin, after stroke [23, 24].

In the current analyses, Mesor, Amplitude, and Peak time were used to evaluate the heart rate circadian rhythm. It has been shown that in healthy people who has normal circadian rhythm, the Peak time of heart rate mainly occurs between 12:00-18:00 [25]. Another study showed that the heart rate circadian rhythm of healthy young men showed a bimodal pattern, with Peak time occurring around 10:00 and 20:00 [26]. We showed that the risk of death in stroke and critically ill patients was relatively increased when the Peak time of heart rate occurred between 12:00-18:00, whereas those who had Peak time of heart rate occurred between 18:00-24:00 or 00:00-06:00 were associated with a lower risk. Animal studies have shown that heart rate of mice normally peak at night, but this tends could be reversed after a malignant stroke [27].

In previous studies, the sports causes an increase in the Amplitude of heart rate, which decrease in healthy people who exposed to sedentary conditions [28]. We found that the mortality rate of stroke and critically ill patients increased with the increase of Mesor and Amplitudes of heart rate circadian rhythm. After the adjusted model, Mesor per 10 bpm increase and Amplitude per 5 bpm increase were associated with a 1.17-fold and a 1.14-fold increase in the risk of in-hospital mortality, respectively. Animal studies have shown a rapid increase in mean heart rate in post-malignant stroke mice, with an increase of about 100 bpm from pre-malignant stroke [27]. Mean heart rate was significantly higher in patients with stroke than in those with normotensive, and heart rate variability was greater in patients with ischemic stroke than in patients with hemorrhagic stroke [29]. At present, no evidence has been found to explain the increase in mortality with increased Amplitude of heart rate in stroke and critically ill patients, which requires further investigation. Other studies have found that in patients with essential hypertension, flat circadian rhythms predict an increased risk of cardiovascular disease and a risk of death [30]. The reason for this difference in results may be the difference in the subjects we studied, and the changes of heart rate of circadian rhythm in the influence of the difference of patients with different diseases need to be further research.

We further explored whether medications have an effect on the circadian rhythm of heart rate to predict in-hospital mortality. By orally administering the drugs according to the circadian rhythm of the physiological process and the optimal time of administration, the effectiveness of the drugs can be improved while minimizing its adverse side effects [31]. When medications that affect the heart rate were used, the heart rate increases or slows down, and the effect of heart rate amplitude on in-hospital mortality in stroke and critically ill patients was related to the use and time of medication. But this effect

remains limited in circadian rhythm of heart rate predict in-hospital mortality. Perhaps the use of other medications that can significantly regulate the circadian rhythm of heart rate, such as melatonin [32], can achieve a better intervention effect on the outcome.

APACHE score is widely used to assess the severity and prognosis of critically ill patients [33]. There are four versions of APACHE score, and APACHE IV score is currently the latest version, which is based on variables within 24 hours of admission to the ICU and has good discrimination and calibration for predicting hospital mortality [34]. The APACHE IV score we use came from the eICU database [7]. APACHE IV scores include heart rate variables. We found that superimposing the characteristics of circadian rhythm of heart rate, such as Mesor, Amplitude and Peak time on the APACHE IV score could increase its predictive effect on mortality. In the future, the improvement of the APACHE IV score can be considered to plus the variable of heart rate circadian rhythm to enhance the prediction ability of mortality in stroke and critically ill patients.

## Limitations

Imbalances exist among the sub-categories assessed in the current study. Although statistical methods were performed to try to estimate the true effects between groups, the inability to eliminate the impact of unmeasurable confounders, such as different management patterns in each center.

The endpoint was all-cause mortality only, which has the potential to dilute the effect of other clinical outcomes regarding circadian rhythm. However, the use of all-cause mortality reduces the risk of adjudication bias due to incomplete, skewed, or inadequate supporting evidence.

77.3% (155,285/200,859) of the ethnic groups in the eICU database are Caucasian, and because the proportion of Caucasian is relatively high, the results of the study lack an explanation for people of other races.

## Conclusion

We found that the changes of heart rate circadian rhythm can predict in-hospital mortality in stroke and critically ill patients. Adding circadian rhythm variables such as Mesor, Amplitude and Peak time can increase the predictive effect of APACHE IV score on in-hospital mortality. For medications able to affect heart rate, differences in whether to use or when they were prescribed had an impact on the circadian rhythm variables in the prediction of in-hospital mortality.

## Abbreviations

APACHE: Acute Physiology and Chronic Health Evaluation; BMI: Body mass index; ICU: Intensive care unit; IQR: Interquartile range; OR: Odds ratio; CI Confidential interval; SD: Standard deviation; bpm: beats per

min; ROC: receiver operating characteristic; LCP:Laboratory for Computational Physiology; MIT:Massachusetts Institute of Technology; COPD:chronic obstructive pulmonary disease

## **Declarations**

## **Funding**

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## **Availability of data and materials**

Data analyzed during the present study are currently stored in the eICU database (<https://eicu-crd.mit.edu>). After completing the required training course (the Collaborative Institutional Training Initiative) and requesting access to the eICU Collaborative Research Database, researchers can seek to use the database. The author ZN Y obtained the access of the database (certification number: 40608375).

## **Ethics approval**

Data collection was in accordance with the ethical standards of the institutional review board of the Massachusetts Institute of Technology (no. 0403000206) and with the 1964 Declaration of Helsinki and its later amendments.

## **Competing interests**

All authors declares that they have no conflict of interest.

## **Consent for publication**

All the authors mutually agree for its submission and publication in Critical Care.

## **Authors' contributions**

J C conceived this study. ZN Y extracted the data. J C, C G and Z L designed the statistical analyses. S Z, Y S, SW L, SZ Q and ZL H performed the statistical analyses. ZN Y, X H, Z Y and XX X wrote the first draft of the manuscript. J C and C G reviewed and modified the final manuscript. All authors read, critically reviewed, and approved the final manuscript.

# Consent to participate

All the authors agree to participate in this research and are responsible for their works.

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## Figures

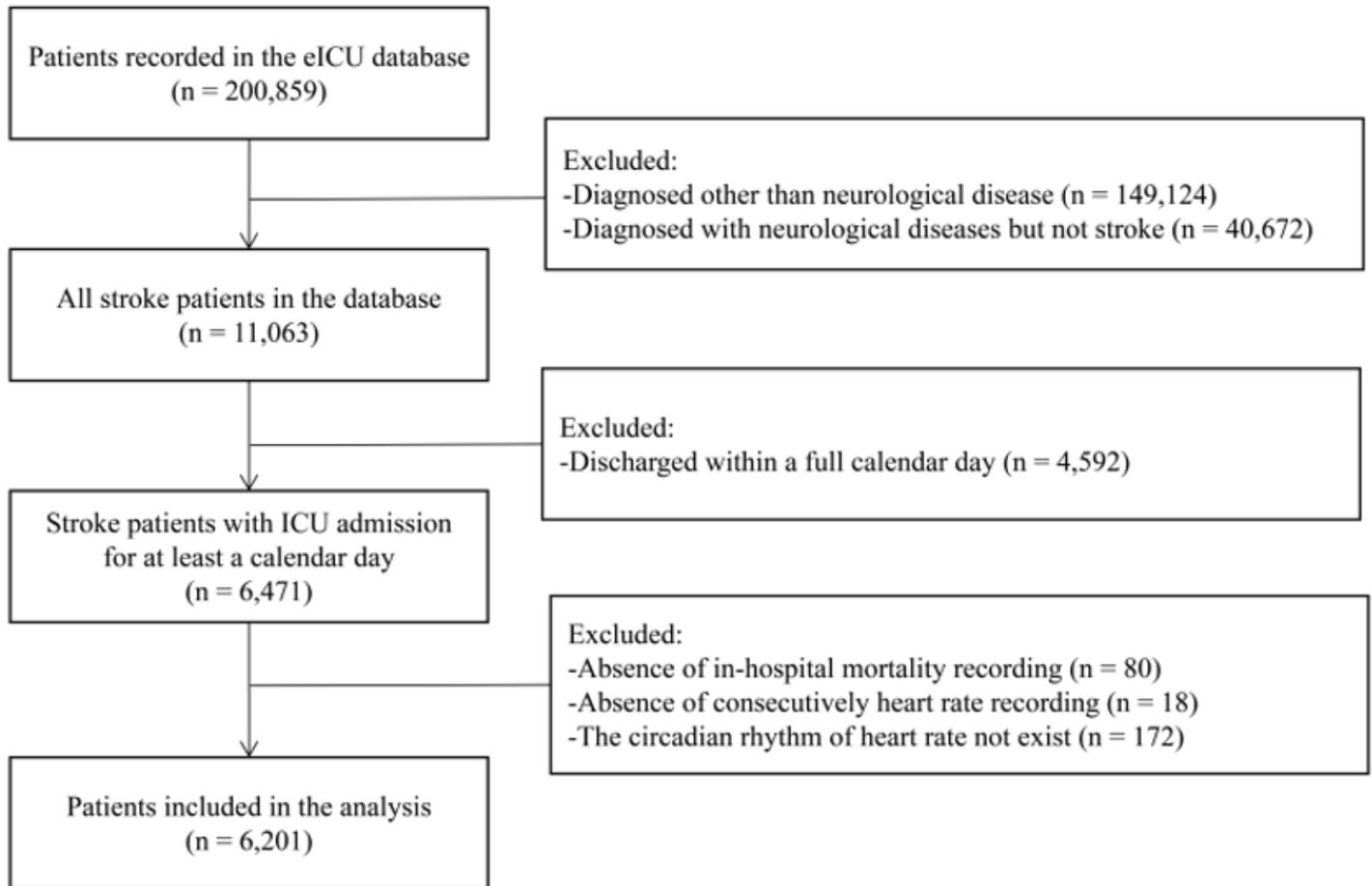


Figure 1

Flow chart of subject the study

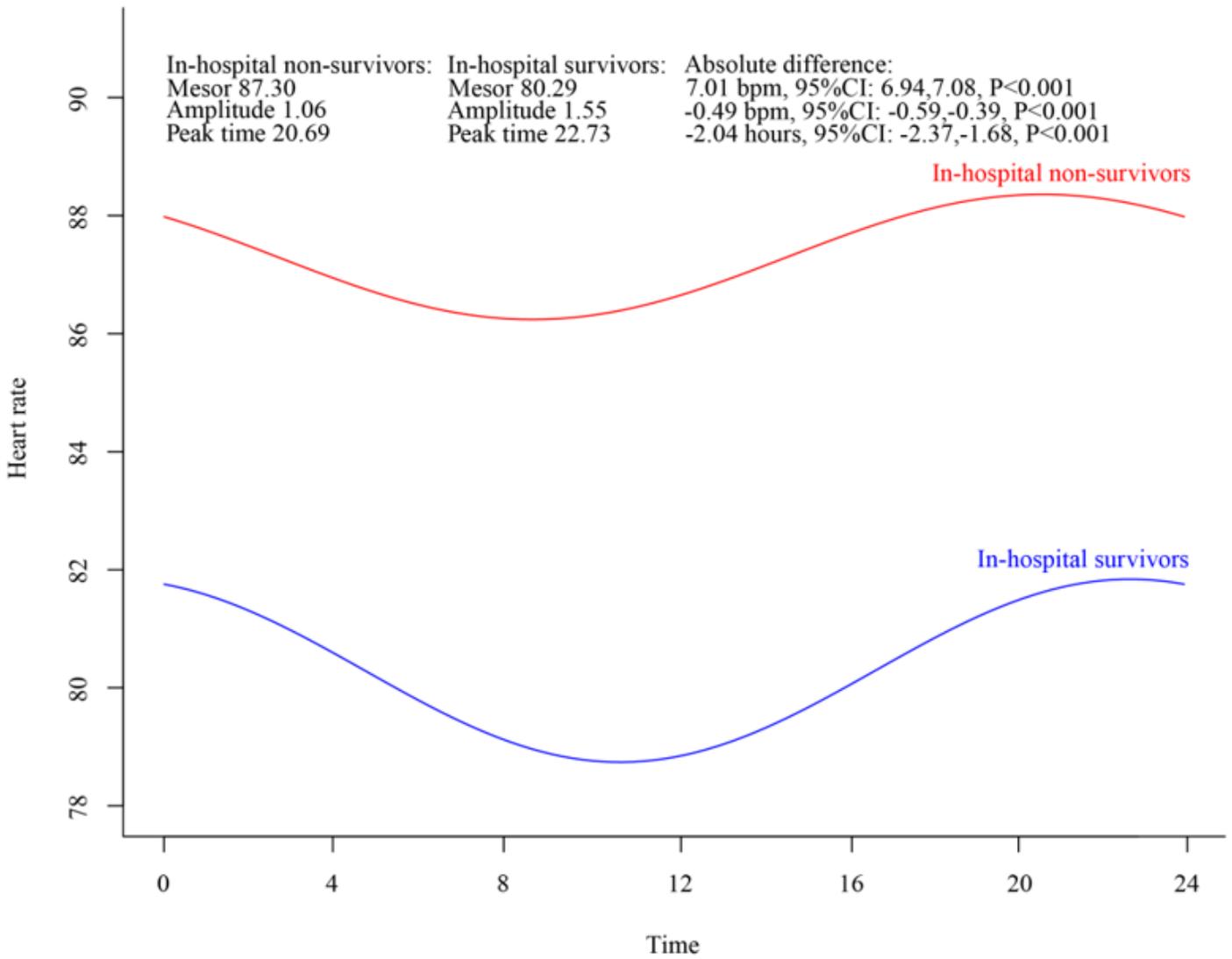


Figure 2

Cosine curves showing the characteristics of heart rate circadian rhythm

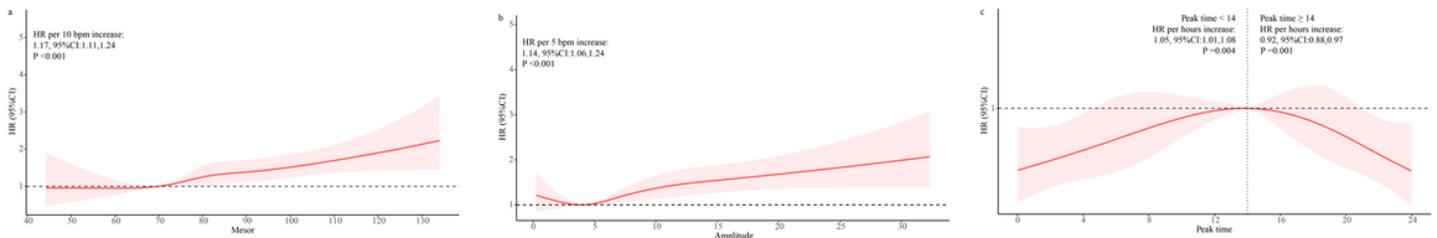


Figure 3

Restricted cubic splines showing the association of predicted Mesor, Amplitude and Peak time of heart rate with in-hospital mortality

a Mesor of heart rate and in-hospital mortality. b Amplitude of heart rate and in-hospital mortality. c Peak time of heart rate and in-hospital mortality.

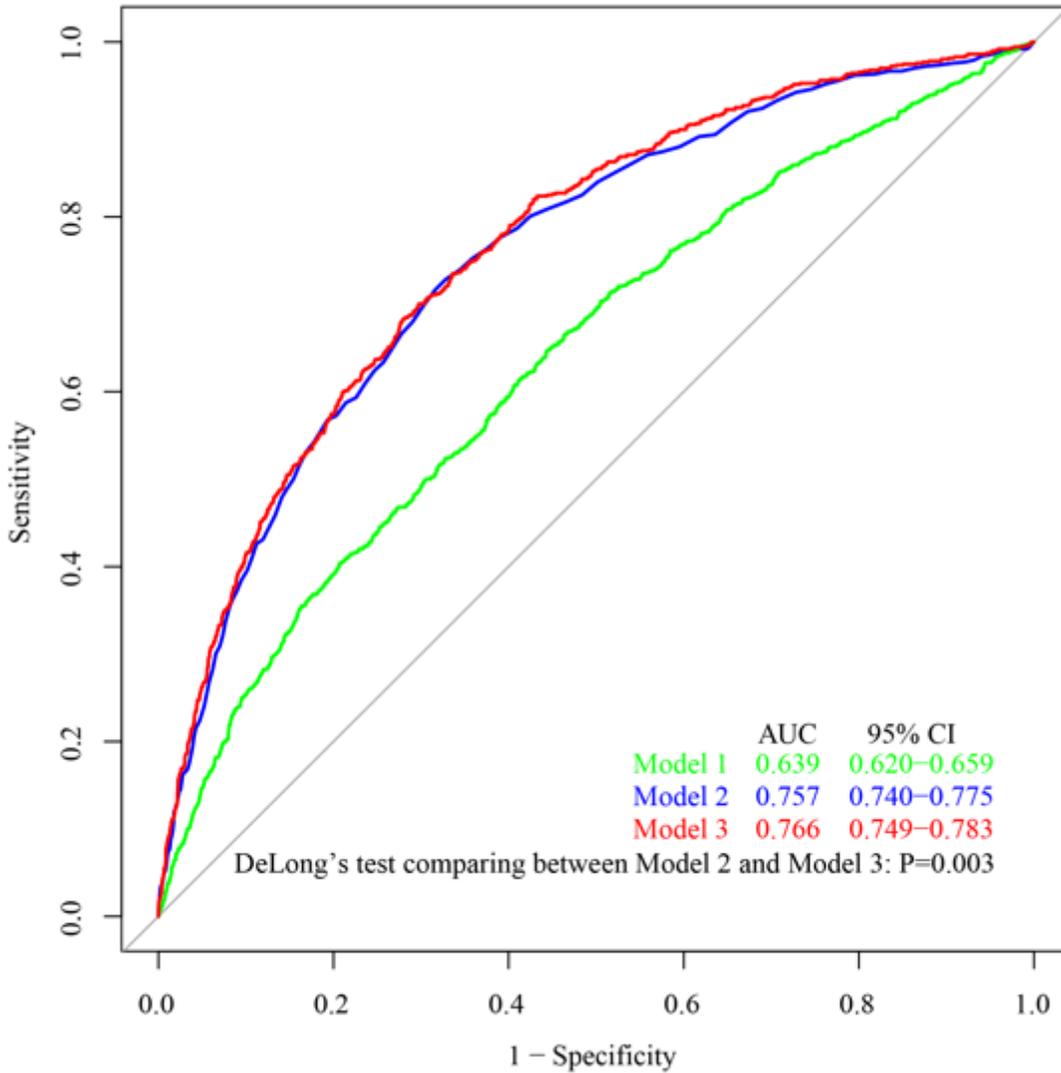


Figure 4

### Discriminative ability of the APACHE IV score and heart rate circadian rhythm in predicting in-hospital mortality

Model 1 use Mesor, Amplitude and Peak time of heart rate. Model 2 use APACHE IV score only. Model 3 use APACHE IV score, Mesor, Amplitude and Peak time of heart rate.

## Supplementary Files

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