


# J-Shaped Association Between Respiratory Rate and In-Hospital Mortality in Acute Myocardial Infarction Patients Complicated by Congestive Heart Failure in Intensive Care Unit

Dose-Response:  
An International Journal  
October-December 2024:1-11  
© The Author(s) 2024  
Article reuse guidelines:  
[sagepub.com/journals-permissions](https://sagepub.com/journals-permissions)  
DOI: 10.1177/15593258241303040  
[journals.sagepub.com/home/dos](https://journals.sagepub.com/home/dos)  


Kai Zhang<sup>1</sup> , Yu Shi<sup>1</sup>, Yu Han<sup>2,3</sup>, Tian Yi Cai<sup>4</sup>, Fang Ming Gu<sup>4</sup>, Zhao Xuan Gu<sup>4</sup>, Tianqi Zhang<sup>4</sup>, and Mao Xun Huang<sup>1</sup>

## Abstract

**Background:** While respiratory rate has proven to be a sensitive prognostic indicator in ICU settings, its relevance in the context of Acute Myocardial Infarction (AMI) patients complicated by Congestive Heart Failure (CHF) remains underexplored. Therefore, this study aims to investigate the relationship between respiratory rate and in-hospital mortality in this specific patient cohort. **Methods:** This retrospective cohort study utilized the Medical Information Mart for Intensive Care-IV database to analyze all AMI patients with concomitant CHF. The primary outcome, in-hospital mortality, was assessed through multivariate analysis. Logistic regression models, restricted cubic spline regression models, and subgroup analyses were employed to explore the association between respiratory rate and in-hospital mortality. **Results:** The study encompassed 5056 participants diagnosed with both CHF and AMI. After adjusting for confounding variables, each incremental unit rise in respiratory rate was associated with an 8% increase in the risk of patient mortality (OR = 1.08, 95% CI: 1.05~1.11,  $P < 0.001$ ). When comparing individuals with respiratory rates in the first tertile ( $\leq 17$  breaths per minute) and the third tertile ( $> 17-20$  breaths per minute) to those in the second tertile (17-20 breaths per minute), the adjusted ORs for in-hospital mortality were 1.09 (95% CI: 0.82~1.46,  $P = 0.546$ ) and 1.62 (95% CI: 1.27~2.06,  $P < 0.001$ ), respectively. A dose-response relationship depicted a J-shaped curve between respiratory rate and the risk of in-hospital mortality, with an inflection point at approximately 19 breaths per minute. Stratified analyses confirmed the robustness of this correlation. **Conclusions:** This study reveals a J-shaped association between respiratory rate and in-hospital mortality in ICU patients suffering from both AMI and CHF.

## Keywords

respiratory rate, in-hospital mortality, congestive heart failure, myocardial infarction, subgroup analysis, restricted cubic spline

<sup>1</sup> The Second Hospital of Jilin University, Changchun, China

<sup>2</sup> Department of Ophthalmology, First Hospital of Jilin University, Changchun, China

<sup>3</sup> Department of Cancer Center, The First Hospital of Jilin University, Changchun, China

<sup>4</sup> Jilin University Second Clinical School of Medicine, Changchun, China

Received 21 June 2024; accepted 4 November 2024

## Corresponding Authors:

Kai Zhang, Cardiovascular Surgery Department of the Second Hospital of Jilin University, No. 218, Zi Qiang Street, Changchun, Jilin province 130041, China.  
Email: [904958072@qq.com](mailto:904958072@qq.com)

Mao Xun Huang, the Second Hospital of Jilin University, No. 218, Zi Qiang Street, Changchun, Jilin province 130041, China.  
Email: [surgeonxun@126.com](mailto:surgeonxun@126.com)



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and

Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

## Introduction

Myocardial infarction (MI) is the most severe manifestation of coronary artery disease, affecting over 7 million people globally each year.<sup>1-3</sup> MI includes acute myocardial infarction (AMI), which is further classified into ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI).<sup>4,5</sup> AMI is associated with high mortality and poor prognosis, with heart failure being a leading cause of death.<sup>6</sup> Multimorbidity, defined as the presence of two or more chronic health conditions, is common among MI patients, significantly increasing the risk of mortality both during hospitalization and long-term, posing challenges to healthcare systems.<sup>7,8</sup> Despite advancements in treatment, patients with congestive heart failure (CHF) continue to face a poor prognosis, with a 5-year mortality rate of 40%–50%.<sup>9-12</sup> MI and heart failure often co-occur, exacerbating adverse outcomes, reducing quality of life, and lowering survival rates.<sup>13,14</sup> Therefore, investigating MI in patients with heart failure is critical for improving outcomes and identifying potential risk factors.

Researchers are increasingly focusing on simpler, more accessible vital signs. Respiratory rate, measured as breaths per minute, is regulated by neurons in the medulla oblongata and is one of the four key vital signs used to evaluate a patient's clinical condition.<sup>15-17</sup> Studies have linked respiratory rate to long-term mortality in specific populations. For instance, one study showed that mean nocturnal respiratory rate, assessed via polysomnography, was independently associated with all-cause mortality in older adults over 6- and 9-year follow-up periods.<sup>18</sup> Another study on MI inpatients found an independent association between respiratory rate and all-cause mortality over a 5-year follow-up.<sup>19</sup> Additionally, research on acute coronary syndrome identified nighttime respiratory rate as a predictor of mortality.<sup>20</sup> However, the relationship between respiratory rate and mortality in MI patients with concurrent heart failure remains underexplored.

This study aims to investigate the relationship between low and high respiratory rates and in-hospital mortality in a large cohort of American adults admitted to intensive care for AMI and CHF.

## Method

### Data Source

This quantitative cohort study was conducted in Turkey between November 2023 and February 2024, using data from the publicly accessible Medical Information Mart for Intensive Care IV (MIMIC-IV) database, a collaboration between Beth Israel Deaconess Medical Center and the Laboratory for Computational Physiology at MIT.<sup>21-23</sup> The data, spanning 2008-2019, were downloaded from <https://mimic.physionet.org/>. MIMIC-IV contains comprehensive clinical information, including patient demographics, laboratory results, clinical

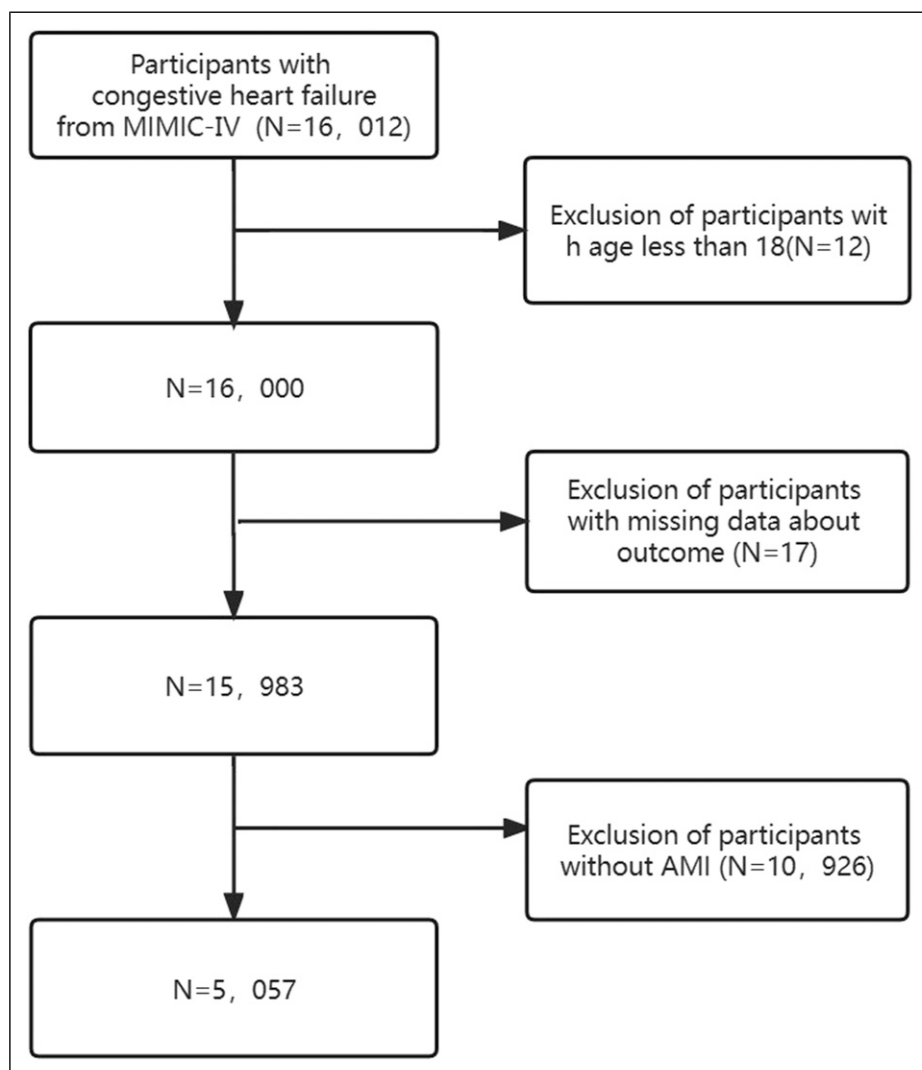
diagnoses, and medical records.<sup>24</sup> To access MIMIC-IV version 2.0, we completed the “Protecting Human Research Participants” exam after a National Institutes of Health (NIH) training course, with certification issued to the first author, Kai Zhang (Certification Number: 11639604). The database use was approved by the Institutional Review Boards of Beth Israel Deaconess Medical Center (2001-P-001699/14) and MIT (No. 0403000206), and patient consent was waived due to the retrospective and de-identified nature of the data.<sup>25-28</sup> This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. A total of 16,012 patients were initially enrolled, but exclusions were made for those under 18 ( $n = 12$ ), lacking outcome data post-ICU admission ( $n = 17$ ), or without a diagnosis of AMI ( $n = 10,926$ ). [Figure 1](#) details the screening process.

### Study Population and Data Extraction

Data extraction was performed using PgAdmin PostgreSQL (v10.18, Bedford, USA) and Navicat Premium (v15.0.12). Diagnosis information was retrieved from the ‘diagnoses\_icd’ and ‘d\_icd\_diagnoses’ tables. Acute myocardial infarction (AMI) and congestive heart failure (CHF) were identified based on the International Classification of Diseases (ICD). CHF was defined according to the ACC/AHA guidelines as clinical heart failure (stages C or D),<sup>29</sup> while AMI was defined based on the Third Universal definition of Myocardial Infarction.<sup>30</sup> ICD-9-CM codes (before 2015) and ICD-10-CM codes (after 2015) were used to identify CHF and MI from primary inpatient diagnoses. Specific codes are provided in the supplementary table ([Table S1](#)). Patients without ICU records were excluded, as vital signs were available only for ICU admissions. To avoid data duplication, only the first ICU admission was included.

### Expose and Outcome

The main exposure variable of this study was the respiratory rate. Respiratory rate, as the core variable, is mainly detected automatically by machines and recorded electronically to ensure the objectivity of data collection.<sup>31</sup> Respiratory rate measurement at baseline was taken following a 15 min passive supine position rest. Participants were asked to remain silent and still during the measurements. The database only records patients' data after admission, so we used the first respiratory rate level on the hospitalized days as the baseline respiratory rate. The recorded initial respiratory rate was treated as a continuous variable, and patients were categorized into three groups based on their respiratory rate tertiles on the first day of ICU admission: Q1 ( $\leq 17$  breaths per minute), Q2 (17-20 breaths per minute), and Q3 ( $> 20$  breaths per minute). Our primary outcome of interest was in-hospital mortality, identified as a binary indicator variable in the discharge records.



**Figure 1.** Flowchart of patient selection.

ICU mortality was exclusively determined during the first ICU admission.

### Covariates

Informed by prior literature and clinical insights, we identified the following covariates: (1) Demographic variables encompassing sex, age, and race; (2) Comorbidities, specifically chronic obstructive pulmonary disease (COPD), diabetes, hepatic failure (Hep F), Melanosis coli (MC), and diabetes; (3) Medical procedures, including ventilation and intubation; (4) Medication usage, consisting of norepinephrine, dopamine, epinephrine, phenylephrine, and vasopressin; (5) Basic vital signs such as temperature, heart rate, and systolic blood pressure (SBP); (6) Blood biochemical indicators, encompassing anion gap (AG), blood urea nitrogen (BUN), chloride, creatinine, hemoglobin (Hb), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration

(MCHC), mean corpuscular volume (MCV), platelet count, potassium, sodium, red blood cell distribution width (RDW), red blood cell (RBC) count, and white blood cell (WBC) count; and (7) Acute Physiology Score III (APSOIII) and Sequential Organ Failure Assessment Score (SOFA). Due to the fact that Severity scores can reflect the state of a disease and are closely related to respiratory rate and mortality, this article includes two common Severity scores in the MIMIC database, including Acute Physiology Score III (APSOIII) and Sequential Organ Failure Assessment Score (SOFA), as variables for consideration.

### Statistical Analyses

First, continuous variables were summarized as mean  $\pm$  standard deviation (SD) or median. Normality and homogeneity of variance determined the choice between t-tests and Mann-Whitney U tests for analysis. Categorical variables

were expressed as case numbers (percentage) and analyzed using the chi-square test (or Fisher's exact method).

Second, to mitigate confounding effects, multivariate regression analysis was employed to elucidate the relationship between respiratory rate and outcome variables. Model 1 included no adjustments. Model 2 adjusted for age, gender, and race, while Model 3 further adjusted for comorbidities (COPD, diabetes, MC, HepF). Model 4 extended adjustments to medical procedures (Vent, Intubated), medication usage (Norepinephrine, Dopamine, Epinephrine, Phenylephrine, Vasopressin), basic vital signs (Temperature, Heart Rate, SBP), blood biochemical indicators (AG, BUN, Chloride, Creatinine, Hb, MCH, MCHC, MCV, Platelet, Potassium, Sodium, RBC, RDW, WBC). Model 5 incorporated additional adjustments based on Model 4, including APSS and SOFA. Variance inflation factor (VIF) assessed multicollinearity (threshold: 5), with highly collinear variables eliminated to prevent overfitting.

Furthermore, we evaluated the non-linear relationship between respiratory rate and in-hospital mortality using smooth curve fitting (penalized spline method) and restricted cubic spline regression. The inflection point was identified via two-piecewise logistic regression and a recursive algorithm, with statistical significance set at  $P < 0.05$ .

Finally, to enhance the analysis's reliability, we conducted subgroup analyses to test for sensitivity, utilizing interaction tests to detect effect differences across subgroups.

All statistical analyses were performed using R software (version 4.1.1) and Free Statistics software (version 1.7). We used multiple imputation with chained equations to impute values for missing data. Free statistics software is a statistical software based on R language for data analysis, which has been widely used in multiple previous studies.<sup>32-34</sup> Two-sided probability values  $\leq 0.05$  were considered statistically significant. This cross-sectional study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

## Results

### Baseline Characteristics of Selected Participants

Table 1 displays the baseline characteristics of the study population, with a focus on clinical aspects. The participants were divided into three groups (Q1, Q2, and Q3) based on their baseline respiratory rate levels (Q1:  $\leq 17$  breaths per minute, Q2: 17-20 breaths per minute, Q3:  $> 20$  breaths per minute). The study included a total of 5056 subjects, comprising 3088 males and 1968 females, with a median age of  $73.5 \pm 12.4$  years.

Furthermore, compared to individuals with lower respiratory rates, those with higher respiratory rates exhibited several notable characteristics, including older age, increased levels of No epinephrine, Dopamine, Phenylephrine, Vasopressin, and Vented cases, as well as a decreased Intubated

rate. Additionally, there was a higher prevalence of colon melanosis, smaller diameters, elevated body temperature, increased heart rate, reduced SBP, higher AG, lower blood chlorine, higher Hb, decreased MCH, lower MCHC, elevated platelet count, higher RBC count, increased RDW, and elevated WBC count. These individuals also had a higher mortality rate and APS score.

### Association Between Respiratory Rate and In-Hospital Mortality in Acute Myocardial Infarction Patients with Congestive Heart Failure

Table 2 presents the results of a multivariable logistic regression analysis investigating the relationship between respiratory rate and in-hospital mortality among patients concurrently diagnosed with heart failure and AMI. The study examines odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) across different respiratory rate levels, shedding light on the risk of in-hospital mortality within this patient cohort.

In the fully adjusted model, where heart rate is treated as a continuous variable, each unit increase in respiratory rate was associated with an 8% rise in the risk of in-hospital mortality (OR = 1.08; 95% CI = 1.05~1.11;  $P < 0.001$ ). When respiratory rate was categorized into three groups, a significant positive association between respiratory rate and in-hospital mortality persisted after adjusting for potential confounders. In comparison to individuals with respiratory rate Q2 (17-20 breaths per minute), the adjusted OR values for respiratory rate and in-hospital mortality in Q1 ( $\leq 17$  breaths per minute) and Q3 ( $> 20$  breaths per minute) were 1.09 (95% CI: 0.82~1.46,  $P = 0.546$ ) and 1.62 (95% CI: 1.27~2.06,  $P < 0.001$ ), respectively (see Table 3). This trend was statistically significant ( $P$  for trend = 0.001).

### Dose-Response Relationships

In this investigation, we employed restricted cubic spline models (Figure 2) to explore nonlinear associations. Our results unveiled a J-shaped relationship between respiratory rate and in-hospital mortality in patients diagnosed with congestive heart failure, while accounting for potential confounding variables. Below a threshold of 19 breaths per minute, we observed a negative correlation between HR and the risk of in-hospital mortality (OR = 0.902 [95% CI 0.787~1.035],  $P = 0.1413$ ). Conversely, beyond this threshold, exceeding 19 breaths per minute, there was a significant increase in the risk of in-hospital mortality (OR = 1.104 [95% CI 1.059~1.151],  $P < 0.001$ ) (see Table 3).

### Subgroup Analysis

Subgroup analyses were conducted to assess potential effect modifications on the relationship between respiratory rate and

**Table 1.** Characteristics of the Study Population (N = 5056).

Variables	Total (n = 5056)	Q1 (n = 1391)	Q2 (n = 1733)	Q3 (n = 1932)	P value <sup>a</sup>
Age, mean ± SD	73.5 ± 12.4	71.9 ± 12.3	73.7 ± 12.2	74.4 ± 12.5	<0.001
Gender, n (%)					0.121
Male	3088 (61.1)	870 (62.5)	1072 (61.9)	1146 (59.3)	
Female	1968 (38.9)	521 (37.5)	661 (38.1)	786 (40.7)	
Race, n (%)					0.302
White	3590 (71.0)	989 (71.1)	1246 (71.9)	1355 (70.1)	
Black	506 (10.0)	145 (10.4)	152 (8.8)	209 (10.8)	
Other	960 (19.0)	257 (18.5)	335 (19.3)	368 (19)	
Medication situation					
Norepinephrine, n (%)					<0.001
No	3581 (70.8)	1038 (74.6)	1270 (73.3)	1273 (65.9)	
Yes	1475 (29.2)	353 (25.4)	463 (26.7)	659 (34.1)	
Dopamine, n (%)					0.001
No	4839 (95.7)	1347 (96.8)	1668 (96.2)	1824 (94.4)	
Yes	217 (4.3)	44 (3.2)	65 (3.8)	108 (5.6)	
Epinephrine, n (%)					0.032
No	4732 (93.6)	1311 (94.2)	1635 (94.3)	1786 (92.4)	
Yes	324 (6.4)	80 (5.8)	98 (5.7)	146 (7.6)	
Phenylephrine, n (%)					<0.001
No	4632 (91.6)	1304 (93.7)	1590 (91.7)	1738 (90)	
Yes	424 (8.4)	87 (6.3)	143 (8.3)	194 (10)	
Vasopressin, n (%)					<0.001
No	4601 (91.0)	1307 (94)	1599 (92.3)	1695 (87.7)	
Yes	455 (9.0)	84 (6)	134 (7.7)	237 (12.3)	
Medical procedures					
Vent, n (%)					<0.001
No	688 (13.6)	220 (15.8)	248 (14.3)	220 (11.4)	
Yes	4368 (86.4)	1171 (84.2)	1485 (85.7)	1712 (88.6)	
Intubated, n (%)					<0.001
No	3437 (68.0)	863 (62)	1199 (69.2)	1375 (71.2)	
Yes	1619 (32.0)	528 (38)	534 (30.8)	557 (28.8)	
Complicating disease					
COPD, n (%)					0.078
No	3256 (64.4)	930 (66.9)	1103 (63.6)	1223 (63.3)	
Yes	1800 (35.6)	461 (33.1)	630 (36.4)	709 (36.7)	
Hep F, n (%)					0.239
No	4965 (98.2)	1365 (98.1)	1709 (98.6)	1891 (97.9)	
Yes	91 (1.8)	26 (1.9)	24 (1.4)	41 (2.1)	
MC, n (%)					<0.001
No	4617 (91.3)	1296 (93.2)	1591 (91.8)	1730 (89.5)	
Yes	439 (8.7)	95 (6.8)	142 (8.2)	202 (10.5)	
Diabetes, n (%)					0.033
No	2520 (49.8)	656 (47.2)	864 (49.9)	1000 (51.8)	
Yes	2536 (50.2)	735 (52.8)	869 (50.1)	932 (48.2)	
Vital signs					
Temperature, mean ± SD	36.8 ± 0.5	36.7 ± 0.5	36.7 ± 0.5	36.8 ± 0.6	<0.001
Heart rate, mean ± SD	82.8 ± 14.8	77.9 ± 13.2	80.8 ± 13.6	88.2 ± 15.3	<0.001
SBP, mean ± SD	114.5 ± 15.9	115.3 ± 16.0	115.0 ± 15.8	113.6 ± 15.8	0.006
Blood biochemical indicators					
AG, mean ± SD	15.8 ± 4.6	14.8 ± 4.3	15.5 ± 4.3	16.7 ± 4.8	<0.001
BUN, mean ± SD	37.0 ± 25.9	36.4 ± 26.4	37.3 ± 26.8	37.3 ± 24.7	0.522
Calcium, mean ± SD	8.4 ± 0.8	8.4 ± 0.7	8.4 ± 0.8	8.5 ± 0.9	0.174

(continued)

**Table I.** (continued)

Variables	Total (n = 5056)	Q1 (n = 1391)	Q2 (n = 1733)	Q3 (n = 1932)	P value <sup>a</sup>
Chloride, mean ± SD	102.3 ± 6.7	103.0 ± 6.6	102.4 ± 6.8	101.8 ± 6.6	<0.001
Creatinine, mean ± SD	2.0 ± 1.8	2.1 ± 2.0	2.0 ± 1.7	1.9 ± 1.7	0.082
Hb, mean ± SD	10.3 ± 2.2	10.1 ± 2.1	10.3 ± 2.2	10.4 ± 2.2	<0.001
MCH, mean ± SD	29.7 ± 2.6	29.9 ± 2.6	29.8 ± 2.6	29.5 ± 2.7	<0.001
MCHC, mean ± SD	32.4 ± 1.7	32.7 ± 1.6	32.5 ± 1.6	32.2 ± 1.7	<0.001
MCV, mean ± SD	91.6 ± 7.1	91.5 ± 6.9	91.7 ± 7.1	91.6 ± 7.3	0.776
Platelet, mean ± SD	209.6 ± 99.4	195.5 ± 91.9	207.9 ± 97.1	221.3 ± 105.1	<0.001
Potassium, mean ± SD	4.4 ± 0.8	4.4 ± 0.7	4.4 ± 0.8	4.4 ± 0.8	0.863
Sodium, mean ± SD	137.9 ± 5.1	137.8 ± 4.8	138.0 ± 5.0	138.0 ± 5.3	0.288
RBC, mean ± SD	3.5 ± 0.8	3.4 ± 0.7	3.5 ± 0.8	3.5 ± 0.8	<0.001
RDW, mean ± SD	15.6 ± 2.4	15.5 ± 2.4	15.6 ± 2.3	15.7 ± 2.4	0.013
WBC, mean ± SD	12.4 ± 9.2	11.3 ± 5.6	12.0 ± 10.4	13.6 ± 9.9	<0.001
Hstatus, n (%)					<0.001
survival	4343 (85.9)	1266 (91)	1548 (89.3)	1529 (79.1)	
death	713 (14.1)	125 (9)	185 (10.7)	403 (20.9)	
SOFA, mean ± SD	3.6 ± 3.0	3.6 ± 2.8	3.5 ± 3.0	3.8 ± 3.3	0.005
APSI, mean ± SD	52.5 ± 22.5	49.0 ± 20.1	49.8 ± 21.2	57.6 ± 24.2	<0.001

Abbreviations: %, weighted proportion.; Hstatus: hospital status; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease.

Hep F, hepatic failure; AMI, acute myocardial infarction; APSIII, Acute Physiology III.

SOFA, Sequential Organ Failure Assessment; SBP, systolic blood pressure; AG, anion gap.

BUN, blood urea nitrogen; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular

hemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell.

RDW, red blood cell distribution width; WBC, white blood cell count.

Q1(≤17 breaths per minute)Q2(17-20 breaths per minute)Q3(>20 breaths per minute).

<sup>a</sup>P values of multiple comparisons were corrected by the False Discovery Rate method.

in-hospital mortality in several subgroups. No significant interactions were detected in any of the subgroups when stratified by age, sex, race, dopamine, epinephrine, vasopressin, COPD, MC, and diabetes (see [Supplemental Figure](#)). It should be noted that, considering multiple testing, a *P*-value less than 0.05 for the interaction of norepinephrine and phenylephrine may not attain statistical significance.

## Discussion

This study represents the pioneering exploration of the association between respiratory rate and in-hospital mortality risk in patients diagnosed with Acute Myocardial Infarction (AMI) and Congestive Heart Failure (CHF). Specifically, our investigation focuses on discerning a J-shaped relationship between respiratory rate and in-hospital mortality among AMI and CHF patients admitted to the Intensive Care Unit (ICU), pinpointing an optimal respiratory rate of approximately 19 breaths per minute. This research contributes a novel, straightforward, and efficacious basic vital sign indicator for the early identification of mortality risk in AMI and CHF patients within the ICU.

A substantial body of evidence indicates that aberrant respiratory responses serve as prognostic indicators in cardiac diseases.<sup>35,36</sup> Quantification of these responses can be achieved through various stimuli. Patients displaying the most

abnormal ventilatory responses during exercise stress testing experience an unfavorable prognosis, even among those with preserved exercise capacity.<sup>36</sup> Aberrant responses can also be elicited without physical exertion, triggered by chemoreflex stimulation that escalates ventilation in response to rising carbon dioxide levels or declining oxygen levels. Nevertheless, despite compelling evidence from reflex measurements, these tests are unlikely to integrate into routine clinical practice for post-Myocardial Infarction (MI) patients due to the requisites of specialized expertise, equipment, and patient cooperation. Consistent with us, a prospective cohort study suggests that respiratory rate provides strong prognostic information that is independent and can complement existing risk assessments. A simple and inexpensive assessment of respiratory rate should be considered as a supplementary indicator for risk assessment after acute myocardial infarction.<sup>19</sup> Another study focusing on acute coronary syndrome suggests that nighttime respiratory rate is a predictive indicator of mortality in patients with acute coronary syndrome.<sup>20</sup> However, we are the first study to investigate the association between respiratory rate and mortality in a population with acute myocardial infarction and heart failure. Our investigation extends prior research by exploring the association between respiratory rate levels, both high and low, and in-hospital mortality in hospitalized patients with AMI and CHF in the United States.

**Table 2.** Multivariable Logistic Regression to Assess the Association of Respiratory Rate With In-Hospital Mortality Rate.

	Model 1		Model 2		Model 3		Model 4		Model 5	
	OR (95%CI)	P Value	OR (95%CI)	P Value	OR (95%CI)	P Value	OR (95%CI)	P Value	OR (95%CI)	P Value
Continuous variable	1.15 (1.13~1.18)	<0.001	1.15 (1.12~1.17)	<0.001	1.15 (1.12~1.17)	<0.001	1.11 (1.08~1.14)	<0.001	1.08 (1.05~1.11)	<0.001
Categorical variable										
Q1 ( $\leq 17$ )	0.83 (0.65~1.05)	0.117	0.87 (0.68~1.1)	0.237	0.87 (0.68~1.11)	0.256	1 (0.76~1.32)	0.991	1.09 (0.82~1.46)	0.546
Q2 (17-20)	1(Ref)		1(Ref)		1(Ref)		1(Ref)		1(Ref)	
Q3 ( $>20$ )	2.21 (1.83~2.66)	<0.001	2.18 (1.81~2.64)	<0.001	2.15 (1.78~2.61)	<0.001	1.76 (1.4~2.22)	<0.001	1.62 (1.27~2.06)	<0.001
P for trend		<0.001		<0.001		<0.001		<0.001		0.001

Abbreviations: the unit of Respiratory Rate is breaths per minute, %, weighted proportion. CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; HepF, hepatic failure; AMI, acute myocardial infarction; APSIII, Acute Physiology III; SOFA, Sequential Organ Failure Assessment; SBP, systolic blood pressure; AG, anion gap; BUN, blood urea nitrogen; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular

hemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell; RDW, red blood cell distribution width; WBC, white blood cell count. CI: confidence interval; OR: odds ratios, Ref: reference.

Model 1: No adjustment.

Model 2: Adjusted for demographic variables (sex, age, race).

Model 3: Adjusted for demographic variables, comorbidities (COPD, diabetes, MC, HepF).

Model 4: Adjusted for demographic variables, comorbidities, Medical Procedures (Vent, Intubated), Medication situation (Norepinephrine Dopamine Epinephrine Phenylephrine Vasopressin), Basic vital signs (Temperature Heart Rate SBP), Blood biochemical indicators (AG BUN Chloride Creatinine, Hb MCH MCHC MCV Platelet Potassium Sodium RBC RDW WBC).

Model 5: Adjusted for demographic variables, comorbidities, Medical Procedures, Medication situation, Basic vital signs, Blood biochemical indicators, APSIII, SOFA.

**Table 3.** Threshold Effect Analysis of Relationship of Respiratory Rate With In-Hospital Mortality Rate.

	Adjusted OR (95%CI)	P value
Two model		
Respiratory Rate $\leq 19$ breaths per minute	0.902 (0.787~1.035)	0.1413
Respiratory Rate $\geq 19$ breaths per minute	1.104 (1.059~1.151)	<0.001
Likelihood ratio test	-	0.016

Adjusted for demographic variables (sex, age, race), Concomitant disease (COPD, diabetes, MC, Hep F), Medical Procedures (Vent, Intubated), Medication situation (Norepinephrine Dopamine Epinephrine Phenylephrine Vasopressin), Basic vital signs (Temperature Heart Rate SBP), Blood biochemical indicators (AG BUN Chloride Creatinine Hb MCH MCHC MCV Platelet Potassium Sodium calcium RBC RDW WBC), APSIII, SOFA.

Abbreviations: %, weighted proportion. CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease.

Hep F, hepatic failure; AMI, acute myocardial infarction; APSIII, Acute Physiology III.

SOFA, Sequential Organ Failure Assessment; SBP, systolic blood pressure; AG, anion gap.

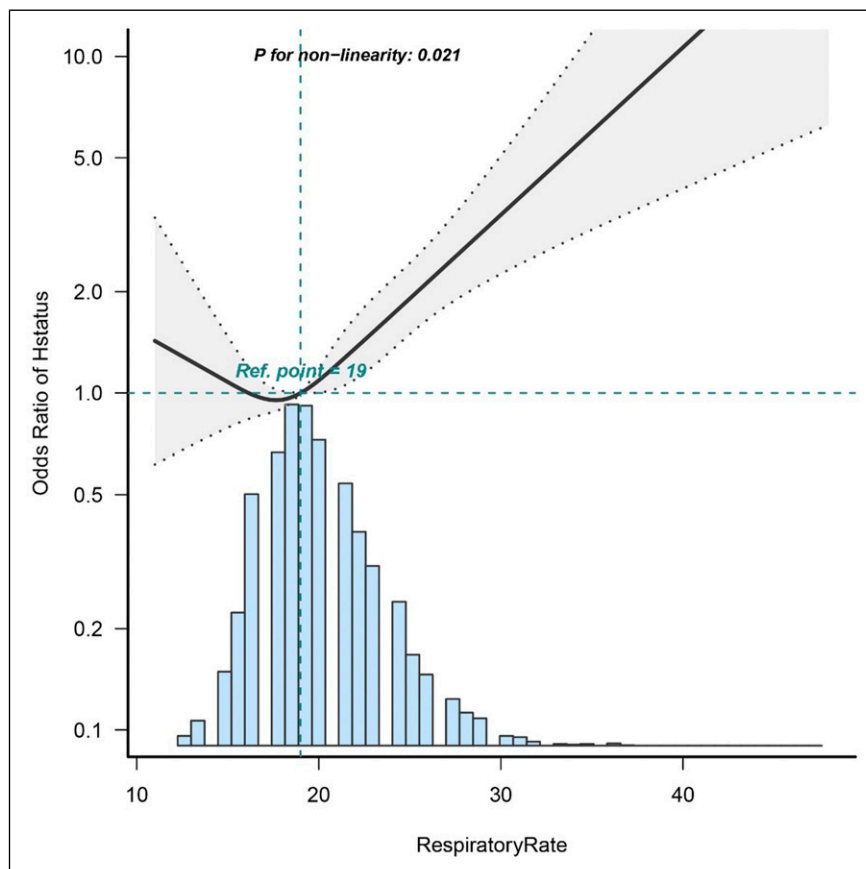
BUN, blood urea nitrogen; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular

hemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell; RDW, red blood cell distribution width; WBC, white blood cell count.

CI: confidence interval; OR: odds ratios, Ref: reference.

To investigate the non-linear relationship between respiratory rate and in-hospital mortality among individuals with heart failure, this study employed smooth curve fitting and generalized additive models. Subgroup analyses were conducted to assess primary findings' consistency. The association between respiratory rate and in-hospital mortality exhibits a J-shaped pattern, signifying an inflection point at 19 breaths per minute. When the respiratory rate is less than the threshold of 19 breaths, the curve shows a decrease in mortality as the respiratory rate increases. This may be due to further improvement in ventilation, increased oxygen concentration, improved systemic metabolism, improved physical condition, and decreased mortality in clinical practice. In addition, low RR may be related to mental state, sedation, and mechanical

ventilation, which requires further research in the future. These results suggest the potential benefit of maintaining a stable respiratory rate around 19 breaths per minute for congestive heart failure (CHF) and acute myocardial infarction (AMI) patients in the ICU. These findings underscore the importance of monitoring respiratory rate vigilantly in clinical practice, considering both low and high levels, and implementing timely interventions to enhance patient prognosis. Forced vital capacity (FVC) and FEV1, key indicators of pulmonary function, are established predictors of mortality, regardless of smoking habits, not only in cardiovascular disease but also in all-cause mortality.<sup>37,38</sup> Furthermore, disease-specific studies focusing on interstitial pneumonia<sup>39</sup> and cystic fibrosis,<sup>40</sup> which are lung conditions associated



**Figure 2.** Dose-Response Relationships between Respiratory Rate with In-hospital mortality rate odds ratio.

with declining pulmonary function, have demonstrated a negative correlation between pulmonary function and respiratory rate. Counting respiratory rate is a simple, cost-effective method that does not require specialized equipment and can be applied across medical and care settings. Conversely, conducting pulmonary function tests can be challenging and potentially harmful, particularly for ICU patients, as they necessitate maximal effort from patients.<sup>41,42</sup> Moreover, advanced wearable devices for automatic respiratory rate detection have recently emerged,<sup>43</sup> despite facing technical and cost-effectiveness challenges. As such devices become more prevalent, respiratory rate information will likely become more accessible in the near future.<sup>43</sup> Consequently, we can conclude that respiratory rate may serve as an alternative measure to pulmonary function in assessing mortality risk among ICU patients. Our study provides a new perspective on potential targets for maintain an appropriate respiratory rate at the management of ICU. Respiratory rate, as one of the most common vital indicators in ICU patients, maintaining an appropriate range is of great significance in improving prognosis. We believe that this strategy is feasible and promising and deserves the attention of clinicians.

The J-shaped relationship between respiratory rate and in-hospital mortality in myocardial infarction (MI) patients with

heart failure likely reflects multiple physiological and pathological mechanisms. For low respiratory rates, slow or deep breathing activates the parasympathetic nervous system, increasing vagal tone, which reduces heart rate and blood pressure, enhancing cardiac oxygen supply and decreasing the risk of arrhythmias and MI, thereby lowering mortality. Low respiratory rates also improve heart rate variability (HRV), a marker of cardiac adaptability, which is associated with reduced mortality. Furthermore, slower breathing enhances alveolar ventilation, improving oxygen exchange and arterial oxygen saturation—critical for cardiovascular function. Additionally, slow breathing reduces chronic inflammation and oxidative stress, key drivers of atherosclerosis and cardiovascular disease progression. In contrast, high respiratory rates, such as rapid shallow breathing, are linked to sympathetic overactivation, leading to elevated heart rate, blood pressure, and vasoconstriction, which increases cardiac workload and oxygen consumption. This heightened strain raises the risk of arrhythmias and acute myocardial ischemia, contributing to higher mortality. High respiratory rates also correlate with reduced HRV, indicating impaired autonomic regulation and increased susceptibility to stress-induced events like sudden cardiac death and heart failure. Moreover, rapid breathing can cause respiratory alkalosis, leading to coronary artery spasm, decreased oxygen supply, and



arrhythmias, further elevating mortality risk. Lastly, high respiratory rates may promote inflammation and oxidative stress, accelerating atherosclerosis and worsening cardiovascular outcomes.

The employed methodology in this study offers notable advantages. Firstly, this study represents the inaugural effort to analyze the relationship between respiratory rate and mortality in patients with Acute Myocardial Infarction (AMI) and Congestive Heart Failure (CHF) utilizing the MIMIC-IV database. Secondly, given the retrospective nature of cohort studies, the presence of confounding factors necessitates consideration. To mitigate their influence inherent in observational studies, logistic regression analysis was employed with multiple models, and subgroup analyses were conducted with appropriate categorization. Thirdly, the non-linearity of the study was assessed through the use of a smooth curve fitting diagram, revealing consistent outcomes. Lastly, it is important to emphasize that no patients incurred harm or violation throughout the course of this investigation.

Several limitations should be acknowledged. First, as a retrospective study, it is subject to inherent limitations, including a lower level of evidence compared to prospective studies, underscoring the need for future validation through prospective case-control studies. Second, despite adjusting for as many variables as possible, unmeasured factors and residual confounding may still influence the results. Third, the inclusion of only American participants limits the generalizability of our findings to other populations. Lastly, potential sources of bias, particularly those related to differential errors in measuring disease or exposure, must be considered. Future research will utilize our own database.

## Conclusions

Our population-based cohort study provided the epidemiologic evidence that myocardial infarction patients complicated by congestive heart failure have a J-shaped association between respiratory rate and in-hospital mortality. Clinicians should not ignore that respiratory rate is a main factor associating risk for mortality in patients. Additional studies are warranted to confirm our findings in prospective cohorts and to elucidate the potential mechanisms underlying the relationship.<sup>44,45</sup>

## Acknowledgments

We appreciate Dr Jie Liu of the Department of Vascular and Endovascular Surgery, Chinese PLA General Hospital for statistics, study design consultations and editing the manuscript.

## Author Contributions

KZ contributed as First authors of this manuscript. YH, FMG, ZXG and RZ were responsible for the concept and design of the study. TQZ

and TYC explain the analysis. KZ and MXH are responsible for data recovery. MXH is the primary corresponding author. All authors critically revised the important intellectual content of the paper and approved the final draft.

## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study received funding from the Jilin Provincial Health Talent Special Fund (Project No. 2024WSZX-D18).

## Ethical Statement

### Ethical Approval

The establishment of this database was approved by the Massachusetts Institute of Technology (Cambridge, MA, USA) and Beth Israel Deaconess Medical Center (Boston, MA, USA), and informed consents were exempted due to all patients' data were anonymized before the data were obtained. The MIMIC-IV database is publicly accessible with Institutional Review Board (IRB) approval from both the Beth Israel Deaconess Medical Center (2001-P-001699/14) and the Massachusetts Institute of Technology (0403000206). We also complied with all relevant ethical regulations regarding the use of the data in our study. All reports adhered to the guidelines for Strengthening the Reporting of Observational Studies in Epidemiology and the Declaration of Helsinki.

## ORCID iD

Kai Zhang  <https://orcid.org/0000-0002-4069-6319>

## Supplemental Material

Supplemental material for this article is available online.

## References

1. Fan Y, Wu Y, Peng Y, et al. Sleeping late increases the risk of myocardial infarction in the middle-aged and older populations. *Front Cardiovasc Med.* 2021;8:709468.
2. Juul Belling H, Hofmeister W, Andersen DC. A systematic exposition of methods used for quantification of heart regeneration after apex resection in zebrafish. *Cells.* 2020;9(3):548.
3. Gao J, Zhang X, Xu M, Deng S, Chen X. The efficacy and safety of sacubitril/valsartan compared with ACEI/ARB in the treatment of heart failure following acute myocardial infarction: a systematic review and meta-analysis of randomized controlled trials. *Front Pharmacol.* 2023;14:1237210.
4. Tang XF, He C, Zhu P, et al. Hyperuricemia is associated with 2- and 5-year adverse outcomes in patients with ST-segment

- elevation myocardial infarction undergoing percutaneous coronary intervention. *Front Endocrinol.* 2022;13:852247.
5. Wang Z, Ye D, Ye J, et al. ADAMTS-5 decreases in coronary arteries and plasma from patients with coronary artery disease. *Dis Markers.* 2019;2019:6129748.
  6. Sheng QH, Hsu CC, Li JP, Hong T, Huo Y. Combining fragmented QRS and TIMI score for predicting in-hospital short-term prognosis after acute myocardial infarction. *J Zhejiang Univ - Sci B.* 2018;19(5):349-353.
  7. Hayward CJ, Batty JA, Westhead DR, et al. Disease trajectories following myocardial infarction: insights from process mining of 145 million hospitalisation episodes. *EBioMedicine.* 2023;96:104792.
  8. Olbrich H, Kridin K, Zirpel H, et al. Cutaneous lupus erythematosus is associated with an increased risk of cardiac and vascular diseases: a large-scale, propensity-matched global retrospective cohort study. *EBioMedicine.* 2023;93:104639.
  9. Chen J, Normand SLT, Wang Y, Krumholz HM. National and regional trends in heart failure hospitalization and mortality rates for Medicare beneficiaries, 1998-2008. *JAMA.* 2011;306(15):1669-1678.
  10. Crnko S, Printezi MI, Zwetsloot PPM, et al. The circadian clock remains intact, but with dampened hormonal output in heart failure. *EBioMedicine.* 2023;91:104556.
  11. Petersen TB, de Bakker M, Asselbergs FW, et al. HF<sub>r</sub>EF subphenotypes based on 4210 repeatedly measured circulating proteins are driven by different biological mechanisms. *EBioMedicine.* 2023;93:104655.
  12. Kresoja KP, Unterhuber M, Wachter R, et al. Treatment response to spironolactone in patients with heart failure with preserved ejection fraction: a machine learning-based analysis of two randomized controlled trials. *EBioMedicine.* 2023;96:104795.
  13. Selzer A. Myocardial infarction and heart failure. *Calif Med.* 1948;68(5):350-352.
  14. Jenča D, Melenovský V, Stehlik J, et al. Heart failure after myocardial infarction: incidence and predictors. *ESC Heart Fail.* 2021;8(1):222-237.
  15. Smith JC, Ellenberger HH, Ballanyi K, Richter DW, Feldman JL. Pre-Bötzinger complex: a brainstem region that may generate respiratory rhythm in mammals. *Science.* 1991;254(5032):726-729.
  16. Bateman RM, Sharpe MD, Jagger JE, et al. 36th international symposium on intensive care and emergency medicine : Brussels, Belgium. 15-18 march 2016. *Crit Care.* 2016;20(Suppl 2):94.
  17. Monsieurs KG, Nolan JP, Bossaert LL, et al. European resuscitation council guidelines for resuscitation 2015: section 1. Executive summary. *Resuscitation.* 2015;95:1-80.
  18. Baumert M, Linz D, Stone K, et al. Mean nocturnal respiratory rate predicts cardiovascular and all-cause mortality in community-dwelling older men and women. *Eur Respir J.* 2019;54(1):1802175.
  19. Barthel P, Wensel R, Bauer A, et al. Respiratory rate predicts outcome after acute myocardial infarction: a prospective cohort study. *Eur Heart J.* 2013;34(22):1644-1650.
  20. Eick C, Grogga-Bada P, Reinhardt K, et al. Nocturnal respiratory rate as a predictor of mortality in patients with acute coronary syndrome. *Open Heart.* 2018;5(2):e000887.
  21. Li Y, Zhao L, Wang Y, et al. Development and validation of prediction models for neurocognitive disorders in adult patients admitted to the ICU with sleep disturbance. *CNS Neurosci Ther.* 2022;28(4):554-565.
  22. Wong AKI, Charpignon M, Kim H, et al. Analysis of discrepancies between pulse oximetry and arterial oxygen saturation measurements by race and ethnicity and association with organ dysfunction and mortality. *JAMA Netw Open.* 2021;4(11):e2131674.
  23. Xu Y, Han D, Xu F, et al. Using restricted cubic splines to study the duration of antibiotic use in the prognosis of ventilator-associated pneumonia. *Front Pharmacol.* 2022;13:898630.
  24. Pisani M, Orsi FA, Annichino-Bizzacchi JM, Barco S, De Paula EV. Venous thromboembolism in critically ill patients with pneumonia in the pre-COVID-19 era: data from a large public database. *Res Pract Thromb Haemost.* 2022;6(7):e12816.
  25. Ge X, Zhu L, Li M, et al. A novel blood inflammatory indicator for predicting deterioration risk of mild traumatic brain injury. *Front Aging Neurosci.* 2022;14:878484.
  26. Rojas JC, Carey KA, Edelson DP, Venable LR, Howell MD, Churpek MM. Predicting intensive care unit readmission with machine learning using electronic health record data. *Ann Am Thorac Soc.* 2018;15(7):846-853.
  27. O'Donnell TFX, Schermerhorn ML, Liang P, et al. Weekend effect in carotid endarterectomy. *Stroke.* 2018;49(12):2945-2952.
  28. Li J, Li R, Gao Y, et al. Nocturnal mean arterial pressure rising is associated with mortality in the intensive care unit: a retrospective cohort study. *J Am Heart Assoc.* 2019;8(19):e012388.
  29. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American college of cardiology/American heart association task force on clinical practice guidelines and the heart failure society of America. *Circulation.* 2017;136(6):e137-e161.
  30. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Nat Rev Cardiol.* 2012;9(11):620-633.
  31. Johnson AEW, Bulgarelli L, Shen L, et al. MIMIC-IV, a freely accessible electronic health record dataset. *Sci Data.* 2023;10(1):1.
  32. Wu B, Guo Y, Yang HH, Gao QG, Tian Y. Predicting bone metastasis risk based on skull base invasion in locally advanced nasopharyngeal carcinoma. *Front Oncol.* 2022;12:812358.
  33. Xu W, Huo J, Chen G, et al. Association between red blood cell distribution width to albumin ratio and prognosis of patients

- with sepsis: a retrospective cohort study. *Front Nutr.* 2022;9:1019502.
34. Cai S, Wang Q, Ma C, et al. Association between glucose-to-lymphocyte ratio and in-hospital mortality in intensive care patients with sepsis: a retrospective observational study based on Medical Information Mart for Intensive Care IV. *Front Med.* 2022;9:922280.
  35. Ponikowski P, Chua TP, Anker SD, et al. Peripheral chemoreceptor hypersensitivity: an ominous sign in patients with chronic heart failure. *Circulation.* 2001;104(5):544-549.
  36. Ponikowski P, Francis DP, Piepoli MF, et al. Enhanced ventilatory response to exercise in patients with chronic heart failure and preserved exercise tolerance: marker of abnormal cardio-respiratory reflex control and predictor of poor prognosis. *Circulation.* 2001;103(7):967-972.
  37. Gupta RP, Strachan DP. Ventilatory function as a predictor of mortality in lifelong non-smokers: evidence from large British cohort studies. *BMJ Open.* 2017;7(7):e015381.
  38. Sin DD, Wu L, Man SF. The relationship between reduced lung function and cardiovascular mortality: a population-based study and a systematic review of the literature. *Chest.* 2005;127(6):1952-1959.
  39. Javaheri S, Sicilian L. Lung function, breathing pattern, and gas exchange in interstitial lung disease. *Thorax.* 1992;47(2):93-97.
  40. Hart N, Polkey MI, Clément A, et al. Changes in pulmonary mechanics with increasing disease severity in children and young adults with cystic fibrosis. *Am J Respir Crit Care Med.* 2002;166(1):61-66.
  41. Allen SC, Baxter M. A comparison of four tests of cognition as predictors of inability to perform spirometry in old age. *Age Ageing.* 2009;38(5):537-541.
  42. Carvalhaes-Neto N, Lorino H, Gallinari C, et al. Cognitive function and assessment of lung function in the elderly. *Am J Respir Crit Care Med.* 1995;152(5 Pt 1):1611-1615.
  43. Hernandez-Silveira M, Ahmed K, Ang SS, et al. Assessment of the feasibility of an ultra-low power, wireless digital patch for the continuous ambulatory monitoring of vital signs. *BMJ Open.* 2015;5(5):e006606.
  44. Infanger DW, Cao X, Butler SD, et al. Silencing nox4 in the paraventricular nucleus improves myocardial infarction-induced cardiac dysfunction by attenuating sympathoexcitation and periinfarct apoptosis. *Circ Res.* 2010;106(11):1763-1774.
  45. Zhao Y, Xiang R, Peng X, et al. Transection of the cervical sympathetic trunk inhibits the progression of pulmonary arterial hypertension via ERK-1/2 Signalling. *Respir Res.* 2019;20(1):121.