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Association between stress hyperglycemia ratio index and all-cause mortality in critically ill patients with atrial fibrillation: a retrospective study using the MIMIC-IV database

Siyuan Cheng[1], Hui Shen[3], Yucheng Han[1], Shaojie Han[1] and Yun Lu[2*]

Abstract

Background The stress hyperglycemia ratio (SHR) was developed to mitigate the influence of long-term chronic glycemic factors on stress hyperglycemia levels, which are associated with adverse clinical events, particularly cardiovascular events. However, studies examining the SHR index and its prognostic significance in patients with atrial fibrillation (AF) are lacking. This study aims to evaluate the relationship between the SHR index and all-cause mortality in critically ill patients with AF upon Intensive Care Unit admission.

Methods The patients' data were extracted from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database. All patients were categorized into four groups based on the SHR index. The outcomes include both primary and secondary endpoints, with the primary endpoints being 30-day and 365-day all-cause mortality, and the secondary endpoints being 90-day and 180-day all-cause mortality. The SHR index was analyzed using quartiles, and the Kaplan-Meier curve was employed to compare the outcomes across groups. Cox proportional-hazards regression and restricted cubic splines (RCS) were used to assess the relationship between the SHR index and the outcomes.

Results Out of a total of 1,685 participants, the average age was 63.12 years (range: 40.17 to 101.49), with 1,004 (59.58%) being male. Higher levels of the SHR index were associated with an increased risk of all-cause mortality at 30 days, 90 days, 180 days, and 365 days, as indicated by the Kaplan-Meier curves (log-rank $P < 0.01$). Additionally, Cox proportional-hazards regression analysis revealed that the risk of mortality at these time points was significantly higher in the highest quartile of the SHR index. Restricted cubic splines (RCS) analysis demonstrated U-shaped relationships between the SHR index and all-cause mortality, with inflection points at 0.73 for 30-day mortality and 0.76 for 365-day mortality. Compared to patients with SHR levels below these inflection points, those with higher levels had a 69.9% increased risk for 30-day all-cause mortality (hazard ratio [HR] 1.699; 95% confidence interval [CI] 1.336 to 2.159) and a 61.6% increased risk for 365-day all-cause mortality (HR 1.616; 95% CI 1.345 to 1.942).

*Correspondence:
Yun Lu
dr_guojunscu@163.com

Full list of author information is available at the end of the article

Conclusion In critically ill patients with AF, higher levels of the SHR index are significantly associated with an increased risk of all-cause mortality at 30 days, 90 days, 180 days, and 365 days. The SHR index may serve as a valid indicator for assessing the severity and guiding the treatment of AF patients in the ICU.

Keywords Atrial fibrillation, Stress hyperglycemia ratio, Prognosis, All-cause mortality

Introduction

In recent decades, cardiovascular disease has emerged as one of the leading causes of death worldwide. In 2021, approximately 20.5 million people died from cardiovascular diseases, representing about one-third of all global deaths [1]. Atrial fibrillation is among the most common persistent arrhythmias related to cardiovascular disease [2]. Currently, around 330 million people are affected by AF, with its incidence rising significantly with age, especially among those over 80 years old [3]. AF is associated with an increased all-cause mortality rate of 1.5 to 3.5 times, which poses a substantial medical and economic burden globally. Critically ill patients admitted to intensive care units (ICUs) often present with complex conditions. Research indicates that approximately 14% of ICU patients develop atrial fibrillation [4]. Despite this, there is a relative lack of studies on prognostic indicators for severe atrial fibrillation. Identifying and managing risk factors is essential for reducing mortality rates among these patients.

Studies have demonstrated that hyperglycemia in critically ill patients is associated with increased mortality and morbidity from myocardial infarction, heart failure, and cerebrovascular disease [5–8]. However, admission blood glucose levels alone do not accurately reflect chronic glucose levels. Hemoglobin A1c (HbA1c) is a laboratory indicator that represents average blood glucose levels over the past 8–12 weeks. Thus, it can provide a more comprehensive view of glucose control. Based on this, we have developed a new indicator: the Stress Hyperglycemia Ratio (SHR), which combines admission blood glucose and HbA1c levels [9]. Stress-induced hyperglycemia often arises when acute stress leads to elevated levels of glucagon, cortisol, catecholamines, and growth hormone. These physiological and pathological processes enhance gluconeogenesis, glycogenolysis, and inhibit peripheral glucose uptake. Higher SHR has been identified as an independent predictor of adverse cardiovascular outcomes, such as heart failure and myocardial infarction [10–11]. However, research on the impact of SHR on outcomes in patients with AF, particularly severe AF, remains limited.

Therefore, the aim of this study was to evaluate the impact of the baseline SHR at ICU admission on all-cause mortality in critically ill patients with AF. The results could potentially provide new insights into early identification and prognosis improvement strategies for these patients.

Method

Source of data

This study is a retrospective analysis utilizing data from the publicly available Medical Information Mart for Intensive Care IV (MIMIC-IV, version 2.2) database. MIMIC-IV, an enhancement over its predecessor MIMIC-III, includes data updates and table reconstructions. It encompasses clinical information from over 190,000 patients and 450,000 hospitalizations recorded between 2008 and 2019 at the Beth Israel Deaconess Medical Center (BIDMC) in Boston, MA, United States. The database provides detailed records on patient demographics, laboratory tests, medications, vital signs, surgical procedures, disease diagnoses, medication management, and follow-up survival status. To access the data, we completed the National Institutes of Health (NIH) training course on protecting human study participants and passed the Collaborative Institutional Training Initiative (CITI) exams. A waiver of informed consent was granted as the database does not contain protected health information and all patient data is anonymized.

Study design and population

Our analysis included 50,920 patients who were admitted to the ICU for the first time and were aged 18 years or older. We excluded patients based on the following criteria: (1) those who were not admitted to the ICU for the first time; (2) those lacking HbA1c or fasting blood glucose data within 24 h of admission; (3) those discharged or who died within 24 h of ICU admission; and (4) those without prognostic information. Ultimately, 1,685 patients met the inclusion criteria and were categorized into four groups based on quartiles of the SHR (Fig. 1).

Data extraction

Data extraction was performed using Navicat Premium (Version 16.1.15) with SQL. The study examined various variables categorized as follows: (1) Demographics: Age, gender, body mass index (BMI), marital status. (2) Past Medical History: Conditions such as myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, mild liver disease, severe liver disease, dementia, paraplegia, renal disease, acute kidney injury (7 days), malignant cancer, metastatic solid tumor, diabetes (with or without chronic comorbidities), and sepsis. (3) Vital Signs: Heart rate (HR), systolic blood pressure (SBP), diastolic blood

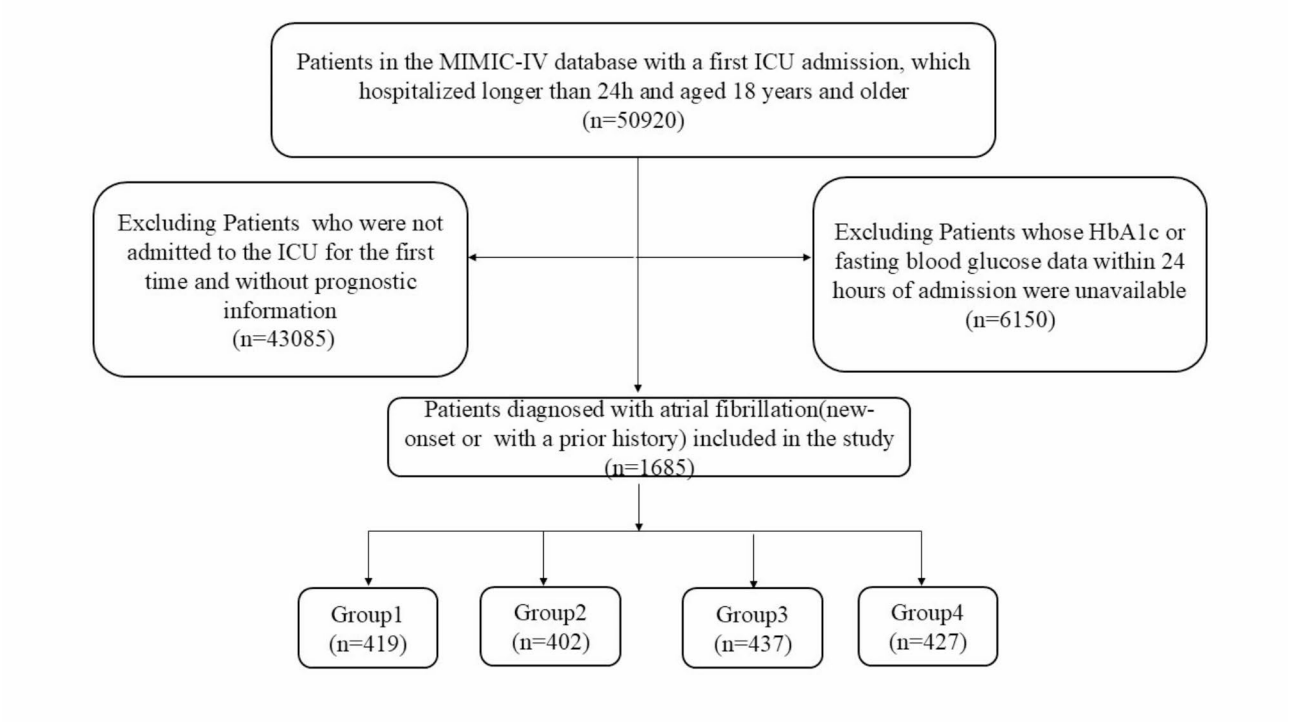

Fig. 1 Flow of included patients through the trial

pressure (DBP), mean blood pressure (MBP), respiratory rate (RR), temperature (T), and pulse blood oxygen saturation (SpO2). (4) Laboratory Indicators: Glucose (mean glucose, maximum glucose, admission glucose), hemoglobin A1c (HbA1c), hematocrit, hemoglobin, platelets, white blood cells (WBC), basophils, eosinophils, lymphocytes, monocytes, neutrophils, blood urea nitrogen (BUN), creatinine, eGFR(estimated glomerular filtration rate chloride), sodium, potassium, fibrinogen, prothrombin time (PT), partial prothrombin time (PTT), international normalized ratio (INR), alanine aminotransferase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and lactate. (5) Length of Stay (LOS) and Outcomes: LOS in hospital, LOS in ICU, hospital death, ICU death, 30-day mortality, 90-day mortality, 180-day mortality, and 365-day mortality. (6) Disease Severity Scores: Charlson Comorbidity Index (CCI), Acute Physiology Score III (APS III), Simplified Acute Physiology Score II (SAPS II), Oxford Acute Severity of Illness Score (OASIS), and Sequential Organ Failure Assessment (SOFA). Initial measurements of all blood biochemical variables were taken upon hospital admission and before any therapeutic interventions. Variables with more than 20% missing values were excluded from the analysis. For variables with missing values less than 20%, data imputation was performed using a random forest approach.

Outcomes

The primary outcomes of the present study were 30-day and 365-day all-cause mortality, while the secondary outcomes included 90-day and 180-day all-cause mortality.

Calculation of SHR and eGFR

SHR was calculated as [(admission glucose (mg/dl))/(28.7×HbA1c (%)-46.7)], admission glucose and HbA1c were obtained directly from MIMIC IV. This study utilizes the MDRD (Modification of Diet in Renal Disease) equation to estimate the eGFR. The specific formula is as follows: $eGFR = 186 \times (Scr^{-1.154}) \times (age^{-0.203}) \times (0.742$ if female), where Scr refers to serum creatinine, measured in mg/dL, and age is expressed in years. This formula has been widely used for evaluating renal function in patients with chronic kidney disease.

Statistical analysis

First, a normality test was conducted on continuous variables. For non-normally distributed data, the Wilcoxon rank-sum test was applied, and results were expressed as medians with interquartile ranges (IQR). Categorical variables were analyzed using Chi-square or Fisher's exact tests and presented as absolute numbers with percentages.

Kaplan-Meier (KM) curves were utilized to determine the incidence of major and secondary outcomes, stratified by the SHR index. Univariate Cox analyses assessed the relationship between the SHR index and 30-day,

90-day, 180-day, and 365-day mortality. Multivariate Cox proportional hazards regression models included clinically relevant variables or those with a univariate relationship to the outcomes. The final model variables were carefully selected based on the number of events available. Model 1 included only the SHR index, while Model 2 adjusted for age, SOFA score, heart rate, mean blood pressure, white blood cell count, gender, marital status, history of myocardial infarction, congestive heart failure, diabetes without complications, diabetes with complications, and renal disease. In both models, the lowest quartile of the SHR index served as the reference group.

The SHR index was also analyzed as a continuous variable using restricted cubic splines (RCS) to clarify the dose-response association with the risk of major and secondary outcomes. If the association was nonlinear, a recursive algorithm was employed to determine the inflection point between the SHR index and mortality at 30, 90, 180, and 365 days. To further explore the relationship between the SHR index and mortality at these time points, a two-stage Cox proportional hazards model was applied on either side of the inflection point.

Additionally, stratified analysis was performed based on gender (male, female), age (<60 years or ≥60 years), diabetes status, history of myocardial infarction, and congestive heart failure.

All statistical analyses were conducted using SPSS software (version 22.0, IBM Corporation, United States) and R software (version 4.3.2, R Foundation for Statistical Computing, Austria), with a significance level set at $P<0.05$.

Results

Baseline characteristics of study individuals

This study analyzed data from 50,920 patients in the MIMIC-IV database, with 1,685 AF patients meeting the inclusion criteria. The mean age of the participants was 63.12 years (range: 40.17 to 101.49 years), and 59.58% were male. Based on the quartiles of the SHR index at admission, the study participants were divided into four groups: Q1 (<0.83), Q2 (0.83≤SHR<0.96), Q3 (0.96≤SHR<1.19), and Q4 (SHR>1.19). Table 1 presents the baseline characteristics of these groups. Participants in the highest SHR index group (Q4) were older and had a higher prevalence of myocardial infarction, congestive heart failure, diabetes, paraplegia and mild liver disease. They also had elevated levels of RR, glucose, HbA1c, hematocrit, hemoglobin, monocytes, neutrophils, BUN, creatinine, fibrinogen, ALT, AST, and lactate, along with lower levels of chloride, eosinophils, eGFR and lymphocytes compared to the other groups.

In terms of disease severity scores at ICU admission, the Q4 group consistently had higher scores across all categories and the longest ICU stay. Mortality rates were significantly higher in the Q4 group across all time points compared to the other groups: 30-day mortality (13.82% vs. 10.07% vs. 6.97% vs. 8.59%, $P=0.007$), 90-day mortality (19.91% vs. 13.96% vs. 10.20% vs. 14.56%, $P=0.001$), 180-day mortality (22.72% vs. 17.62% vs. 13.43% vs. 17.42%, $P=0.006$), and 365-day mortality (26.70% vs. 21.05% vs. 15.17% vs. 19.57%, $P<0.001$). No significant differences in mortality rates were observed between Q2, Q3, and Q4 groups.

Study outcomes

The Kaplan-Meier curves (Fig. 2) revealed differences in survival rates among the four SHR quartile groups for 30-day and 365-day mortality. Differences in 90-day and 180-day mortality are shown in Supplementary Fig. 1. Patients in the highest SHR index group (Q4) exhibited significantly lower survival rates at 30 days, 90 days, 180 days, and 365 days compared to those in lower SHR index groups (log-rank $P<0.05$). However, no significant differences in survival rates were observed among the remaining three groups (Q1, Q2, and Q3) at any of the time points (30-day, 90-day, 180-day, and 365-day).

Relationship between SHR and clinical outcomes of patients with AF

To investigate the independent effects of the SHR index on mortality, two Cox regression models were utilized (Tables 2 and 3). After adjusting for age, heart rate, MBP, BMI, gender, marital status, diabetes mellitus, hypertension, cerebral infarction, myocardial infarct (Model 2), the hazard ratios (HR) and 95% confidence intervals (CIs) for the SHR index categories (<0.83, 0.83–0.96, 0.96–1.19, ≥1.19) were as follows: for 30-day all-cause mortality, the HRs were 1.00 (reference), 0.80 (0.49 ~ 1.32), 1.08 (0.70 ~ 1.69), and 1.64 (1.07 ~ 2.49) respectively. After adjusting for age, heart rate, MBP, WBC, INR, eGFR, BMI, gender, marital status, diabetes mellitus, hypertension, cerebral infarction, myocardial infarct (Model 3), the hazard ratios (HR) and 95% confidence intervals (CIs) for the SHR index categories (<0.83, 0.83–0.96, 0.96–1.19, ≥1.19) were as follows: for 30-day all-cause mortality, the HRs were 1.00 (reference), 0.79 (0.48 ~ 1.30), 1.08 (0.69 ~ 1.69), and 1.38 (1.03 ~ 3.47) respectively. For 365-day all-cause mortality, the HRs in model 2 were 1.00 (reference), 0.78 (0.56 ~ 1.09), 1.03 (0.77 ~ 1.40), and 1.44 (1.08 ~ 1.92) respectively. The HRs in model 3 were 1.00 (reference), 0.78 (0.56 ~ 1.09), 1.06 (0.78 ~ 1.43), and 1.26 (0.95 ~ 1.69) respectively. These findings indicate that patients with an SHR index of ≥1.19 have a higher risk of both 30-day and 365-day all-cause mortality compared to those with an SHR index of <1.19. Similar trends were observed for 90-day and 180-day all-cause mortality, as detailed in Supplementary Tables 1–2.

Table 1 Baseline characteristics of patients grouped according to SHR index quartiles

Variables	Total ($n=1685$)	Q1 (SHR<0.83, $n=419$)	Q2 (0.83 ≤ SHR<0.96, $n=402$)	Q3 (0.96 ≤ SHR<1.19, $n=437$)	Q4 (SHR ≥ 1.19, $n=427$)	*P*
Demographics						
Age, years	63.12(40.17,101.49)	62.72 (41.80,98.41)	54.92 (35.01,83.49)	63.68 (42.00,100.82)	73.00 (46.45,128.62)	< 0.001
Gender, n (%) Male Female	1004 (59.58) 681 (40.42)	256 (61.10) 163 (38.90)	247 (61.44) 155 (38.56)	249 (56.98) 188 (43.02)	252 (59.02) 175 (40.98)	0.520
BMI Mean, kg/m^2	28.00 (24.50, 31.90)	27.20 (23.55,31.50)	28.25 (25.33,32.20)	27.80 (24.30,32.20)	28.10 (24.60,31.70)	0.076
Marital Status, n (%) Married Single Widowed Divorced	970 (57.57) 263 (15.61) 335 (19.88) 117 (6.94)	236 (56.32) 69 (16.47) 85 (20.29) 29 (6.92)	231 (57.46) 61 (15.17) 84 (20.90) 26 (6.47)	252 (57.67) 62 (14.19) 95 (21.74) 28 (6.41)	251 (58.78) 71 (16.63) 71 (16.63) 34 (7.96)	0.784
Past medical history						
Myocardial Infarct, n (%) No Yes	1190 (70.62) 495 (29.38)	293 (69.93) 126 (30.07)	304 (75.62) 98 (24.38)	315 (72.08) 122 (27.92)	278 (65.11) 149 (34.89)	0.009
Congestive Heart Failure, n (%) No Yes	929 (55.13) 756 (44.87)	249 (59.43) 170 (40.57)	238 (59.20) 164 (40.80)	242 (55.38) 195 (44.62)	200 (46.84) 227 (53.16)	< 0.001
Peripheral Vascular Disease, n (%) No Yes	1395 (82.79) 290 (17.21)	345 (82.34) 74 (17.66)	325 (80.85) 77 (19.15)	364 (83.30) 73 (16.70)	361 (84.54) 66 (15.46)	0.547
Cerebral infarction, n (%) No Yes	1383 (70.62) 302 (17.92)	355 (84.73) 64 (15.27)	328 (81.59) 74 (18.41)	346 (79.18) 91 (20.82)	354 (82.90) 73 (17.10)	0.190
Chronic Pulmonary Disease, n (%) No Yes	1156 (68.61) 529 (31.39)	282 (67.30) 137 (32.70)	282 (70.15) 120 (29.85)	293 (67.05) 144 (32.95)	299 (70.02) 128 (29.98)	0.645
Rheumatic Disease, n (%) No Yes	1625 (96.44) 60 (3.56)	410 (97.85) 9 (2.15)	386 (96.02) 16 (3.98)	419 (95.88) 18 (4.12)	410 (96.02) 17 (3.98)	0.354
Peptic Ulcer Disease, n (%) No Yes	1659 (98.46) 26 (1.54)	415 (99.05) 4 (0.95)	399 (99.25) 3 (0.75)	430 (98.40) 7 (1.60)	415 (97.19) 12 (2.81)	0.067
Mild Liver Disease, n (%) No Yes	1579 (93.71) 106 (6.29)	395 (94.27) 24 (5.73)	378 (94.03) 24 (5.97)	421 (96.34) 16 (3.66)	385 (90.16) 42 (9.84)	0.002
Severe Liver Disease, n (%) No Yes	1668 (98.99) 17 (1.01)	416 (99.28) 3 (0.72)	400 (99.50) 2 (0.50)	433 (99.08) 4 (0.92)	419 (98.13) 8 (1.87)	0.269
Dementia, n (%) No Yes	1665 (98.81) 20 (1.19)	412 (98.33) 7 (1.67)	399 (99.25) 3 (0.75)	433 (99.08) 4 (0.92)	421 (98.59) 6 (1.41)	0.589
Paraplegia, n (%) No Yes	1512 (89.73) 173 (10.27)	390 (93.08) 29 (6.92)	361 (89.80) 41 (10.20)	383 (87.64) 54 (12.36)	378 (88.52) 49 (11.48)	0.049
Renal Disease, n (%) No Yes	1307 (77.57) 378 (22.43)	325 (77.57) 94 (22.43)	317 (78.86) 85 (21.14)	349 (79.86) 88 (20.14)	316 (74.00) 111 (26.00)	0.185
AKI 2 day, n (%) No Yes	460 (27.30) 1225 (72.70)	123 (29.36) 296 (70.64)	112 (27.86) 290 (72.14)	112 (25.63) 325 (74.37)	113 (26.46) 314 (73.54)	0.632
Malignant Cancer, n (%) No Yes	1603 (95.13) 82 (4.87)	391 (93.32) 28 (6.68)	388 (96.52) 14 (3.48)	419 (95.88) 18 (4.12)	405 (94.85) 22 (5.15)	0.154

Table 1 (continued)

Variables	Total ($n=1685$)	Q1 (SHR<0.83, $n=419$)	Q2 (0.83 ≤ SHR<0.96, $n=402$)	Q3 (0.96 ≤ SHR<1.19, $n=437$)	Q4 (SHR ≥ 1.19, $n=427$)	*P*
Metastatic Solid Tumor, n (%)	1661 (98.58)	410 (97.85)	394 (98.01)	432 (98.86)	425 (99.53)	0.318
No	24 (1.42)	9 (2.15)	8 (1.99)	5 (1.14)	2 (0.47)	
Yes						
Diabetes Mellitus, n (%)	1097 (65.10)	268 (63.96)	302 (75.12))	309 (70.71)	218 (51.05)	< 0.001
No	588 (34.90)	151 (36.04)	100 (24.88)	128 (29.29)	209 (48.95)	
Yes						
Hypertension, n (%)	345 (20.47)	76 (18.14)	89 (22.14)	94 (21.51)	86 (20.14)	0.493
No	1340 (79.53)	343 (81.86)	313 (77.86)	343 (78.49)	341 (79.86)	
Yes						
Sepsis-3, n (%)	746 (44.27)	180 (42.96)	194 (48.26)	203 (46.45)	169 (39.58)	0.057
No	939 (55.73)	239 (57.04)	208 (51.74)	234 (53.55)	258 (60.42)	
Yes						
Laboratory indicators						
Glucose Max, mg/dl	132.00 (111.00, 168.00)	118.76 (100.00,142.00)	123.00 (108.00,141.75)	134.00 (117.00,160.00)	172.00 (132.00,236.00)	< 0.001
Glucose Mean, mg/dl	130.50 (119.59, 149.00)	123.55 (112.55,135.84)	126.08 (116.00,137.24)	130.50 (120.69,145.55)	151.03 (131.17,182.97)	< 0.001
First Glucose, mg/dl	122.00 (102.00, 157.00)	93.00 (85.00,102.50)	108.50 (102.00,117.00)	129.00 (119.00,145.00)	183.00 (157.00,238.50)	< 0.001
HbA1c	5.90 (5.60, 6.50)	6.10 (5.80,6.70)	5.90 (5.60,6.20)	5.90 (5.60,6.40)	6.00 (5.60,6.70)	< 0.001
Hematocrit Min, vol%	28.90 (24.80, 34.80)	28.00 (24.30,33.75)	29.10 (25.33,34.77)	29.40 (24.50,35.40)	30.00 (25.70,35.55)	0.002
Hemoglobin Min, g/dl	9.80 (8.40, 11.70)	9.40 (8.30,11.20)	9.90 (8.60,11.70)	9.80 (8.20,11.80)	10.20 (8.70,12.05)	< 0.001
Platelets Min, 10^9/L	155.00 (117.00, 215.00)	148.00 (114.00,207.50)	151.00 (118.00,210.75)	161.00 (117.00,216.00)	169.00 (119.00,223.50)	0.112
WBC Max, 10^9/L	13.20 (9.80, 17.20)	13.00 (9.30,17.00)	12.90 (9.40,17.28)	13.10 (10.20,16.90)	13.80 (10.70,17.60)	0.058
Basophils Max, 10^9/L	3.60 (2.51, 4.49)	3.71 (2.52,4.82)	3.63 (2.64,4.34)	3.50 (2.50,4.45)	3.58 (2.34,4.54)	0.246
Eosinophils Max, 10^9/L	13.25 (7.76, 17.08)	15.98 (10.93,20.08)	14.42 (10.21,17.33)	12.40 (7.59,15.60)	11.00 (4.33,14.75)	< 0.001
Lymphocytes Max, 10^9/L	158.27 (124.20, 194.29)	173.74 (137.89,207.38)	159.75 (136.39,193.16)	151.87 (126.87,187.99)	147.24 (102.00,185.94)	< 0.001
Monocytes Max, 10^9/L	44.23 (32.40, 55.92)	41.26 (29.81,52.76)	42.96 (31.52,52.45)	44.57 (32.92,54.11)	48.30 (36.00,63.20)	< 0.001
Neutrophils Max, 10^9/L	918.56 (709.63, 1150.06)	848.64 (665.15,1075.59)	881.11 (677.05,1120.75)	947.94 (738.27,1150.06)	998.01 (806.98,1251.36)	< 0.001
BUN Max, mg/dl	21.00 (16.00, 30.00)	21.00 (14.50,28.00)	19.00 (15.00,26.00)	21.00 (15.00,28.00)	24.00 (17.00,36.00)	< 0.001
Creatinine Max, mg/dl	1.10 (0.80, 1.40)	1.00 (0.80,1.40)	1.00 (0.80,1.30)	1.00 (0.80,1.30)	1.20 (0.90,1.70)	< 0.001
eGFR Mean, mL/min/1.73m^2	64.79 (45.92, 86.24)	67.30 (48.49,86.74)	68.49 (52.06,86.30)	67.43 (46.99,87.42)	56.70 (37.88,78.27)	< 0.001
Chloride Min, mEq/L	104.00 (101.00, 107.00)	105.00 (101.50,107.00)	104.00 (102.00,107.00)	104.00 (101.00,107.00)	103.00 (99.00,106.00)	< 0.001
Calcium Min, mg/dl	8.30 (8.07, 8.60)	8.31 (8.04,8.60)	8.34 (8.10,8.60)	8.30 (8.02,8.70)	8.30 (8.00,8.60)	0.250
Sodium Max, mmol/l	140.00 (137.00, 142.00)	140.00 (138.00,142.00)	140.00 (137.00,141.00)	140.00 (138.00,142.00)	140.00 (137.00,142.00)	0.407
Potassium Max, mmol/l	4.50 (4.20, 4.80)	4.50 (4.20,4.90)	4.50 (4.20,4.80)	4.40 (4.10,4.70)	4.50 (4.20,4.95)	0.001
Fibrinogen Min, mg/dl	283.00 (212.00, 333.17)	268.57 (200.00,328.87)	275.00 (208.00,321.15)	286.84 (215.00,331.67)	299.29 (228.13,349.91)	< 0.001
ALT Max, U/L	40.96 (27.00, 67.72)	41.30 (27.11,66.52)	36.59 (24.75,56.72)	40.96 (27.83,67.92)	46.76 (29.30,80.22)	**< 0.001**
ALP Max, U/L	83.42 (68.22, 103.70)	85.59 (69.00,106.95)	80.06 (67.70,98.75)	83.11 (69.00,101.00)	86.14 (67.91,108.45)	0.081
AST Max, U/L	63.12 (40.17, 101.49)	62.72 (41.80,98.41)	54.92 (35.01,83.49)	63.68 (42.00,100.82)	73.00 (46.45,128.62)	**< 0.001**
Lactate Max, mmol/l	2.30 (1.87, 3.10)	2.40 (1.90,3.10)	2.20 (1.83,2.90)	2.20 (1.82,3.00)	2.40 (1.91,3.40)	**0.001**
INR Max	1.40 (1.20, 1.60)	1.50 (1.30,1.60)	1.40 (1.30,1.70)	1.40 (1.20,1.60)	1.40 (1.20,1.70)	0.101
PT Max, s	15.70 (13.80, 17.85)	16.06 (14.30,17.70)	15.80 (14.00,17.90)	15.50 (13.40,17.70)	15.60 (13.60,18.00)	0.070
PTT Max, s	35.70 (30.30, 52.90)	36.30 (30.70,51.25)	36.00 (31.00,49.45)	35.00 (29.20,52.10)	36.10 (30.15,61.60)	0.070
Vital signs						
HR Mean, beats/min	82.00 (75.00, 90.00)	81.00 (75.00,89.00)	81.00 (74.00,88.00)	82.00 (75.00,90.00)	83.00 (75.00,92.00)	0.097

Table 1 (continued)

Variables	Total ($n=1685$)	Q1 (SHR<0.83, $n=419$)	Q2 (0.83 ≤ SHR<0.96, $n=402$)	Q3 (0.96 ≤ SHR<1.19, $n=437$)	Q4 (SHR ≥ 1.19, $n=427$)	*P*
RR Mean, times/min	18.00 (16.39, 19.94)	17.89 (16.25,19.56)	17.62 (16.14,19.62)	17.92 (16.52,19.68)	18.34 (16.69,20.85)	**<0.001**
SBP Mean, mmHg	115.59 (107.58, 126.58)	114.97 (107.10,124.58)	115.14 (107.28,124.82)	116.00 (108.96,127.39)	116.04 (107.59,128.20)	0.323
DBP Mean, mmHg	59.28 (53.39, 65.70)	58.39 (53.16,64.74)	58.75 (53.45,64.93)	60.04 (53.44,67.05)	59.50 (53.29,66.37)	0.178
MBP Mean, mmHg	75.79 (70.52, 82.34)	75.52 (70.08,80.73)	75.05 (70.39,82.02)	76.82 (71.29,83.09)	75.96 (70.40,83.14)	**0.038**
Temperature Mean, ℃	36.70 (36.51, 36.91)	36.68 (36.52,36.85)	36.69 (36.53,36.88)	36.70 (36.50,36.93)	36.71 (36.51,36.97)	0.373
SPO_2 Mean, %	97.61 (96.39, 98.62)	97.79 (96.52,98.68)	97.57 (96.62,98.71)	97.58 (96.37,98.64)	97.53 (96.11,98.45)	0.152
Disease Severity Score						
Charlson Comorbidity Index	6.00 (5.00, 8.00)	6.00 (5.00,8.00)	6.00 (5.00,8.00)	6.00 (5.00,8.00)	7.00 (5.00,8.00)	**<0.001**
APSIII score	41.00 (31.00, 57.00)	39.00 (29.00,54.00)	39.00 (30.00,51.00)	41.00 (32.00,57.00)	44.00 (35.00,67.50)	**<0.001**
SAPSII score	36.00 (30.00, 45.00)	35.00 (29.00,45.00)	36.00 (30.00,43.00)	37.00 (30.00,44.00)	37.00 (31.00,46.00)	0.036
OASIS score	32.00 (26.00, 38.00)	31.00 (26.00,37.00)	31.00 (26.00,37.00)	32.00 (27.00,39.00)	34.00 (27.00,40.00)	0.003
SOFA score	3.00 (2.49, 4.00)	3.18 (2.54,4.00)	3.00 (2.46,4.00)	3.00 (2.42,4.00)	3.04 (2.53,4.00)	0.178
Length Of Stay (LOS)						
LOS in hospital	9.25 (6.44, 13.85)	9.11 (6.47,13.95)	9.05 (6.66,13.03)	9.10 (6.08,13.76)	9.92 (6.81,15.02)	0.234
LOS in ICU	2.33 (1.30, 4.31)	2.18 (1.24,4.03)	2.25 (1.28,4.08)	2.53 (1.33,4.31)	2.80 (1.47,5.28)	**0.003**
Outcomes						
Hospital Death, n (%) No Yes	1550 (91.99) 135 (8.01)	387 (92.36) 32 (7.64)	380 (94.53) 22 (5.47)	398 (91.08) 39 (8.92)	385 (90.16) 42 (9.84)	0.111
ICU Death, n (%) No Yes	1609 (95.49) 76 (4.51)	402 (95.94) 17 (4.06)	392 (97.51) 10 (2.49)	414 (94.74) 23 (5.26)	401 (93.91) 26 (6.09)	0.070
30-day mortality, n (%) No Yes	1518 (90.09) 167 (9.91)	383 (91.41) 36 (8.59)	374 (93.03) 28 (6.97)	393 (89.93) 44 (10.07)	368 (86.18) 59 (13.82)	0.007
90-day mortality, n (%) No Yes	1437 (85.28) 248 (14.72)	358 (85.44) 61 (14.56)	361 (89.80) 41 (10.20)	376 (86.04) 61 (13.96)	342 (80.09) 85 (19.91)	0.001
180-day mortality, n (%) No Yes	1384 (82.14) 301 (17.86)	346 (82.58) 73 (17.42)	348 (86.57) 54 (13.43)	360 (82.38) 77 (17.62)	330 (77.28) 97 (22.72)	0.006
365-day mortality, n (%) No Yes	1336 (79.29) 349 (20.71)	337 (80.43) 82 (19.57)	341 (84.83) 61 (15.17)	345 (78.95) 92 (21.05)	313 (73.30) 114 (26.70)	<0.001

AKI, acute kidney injury; BMI, body mass index; HbA1c, hemoglobin A1c; WBC, white blood cell; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate transaminase; INR, international normalized ratio; PT, prothrombin time; PTT, partial prothrombin time; HR, heart rate; RR, respiratory rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; SPO2, pulse blood oxygen saturation; APSIII, acute physiology score; SAPSII, simplified acute physiology score; OASIS, oxford acute severity of illness score; SOFA, sequential organ failure assessment; ICU, intensive care unit.

The detection of nonlinear relationships

The RCS (restricted cubic splines) curve analysis revealed a nonlinear relationship between the SHR index and all-cause mortality across various time points: 30-day, 90-day, 180-day, and 365-day. Specifically, the SHR index demonstrated a U-shaped association with mortality at the 30-day and 365-day marks (see Fig. 3A and B), as well as with 90-day and 180-day mortality (refer to Supplementary Fig. 2A and Fig. 2B).

To further investigate this nonlinear relationship, both Cox proportional hazard models and two-piecewise Cox proportional hazard models were employed (P for log-likelihood ratio < 0.05 in both models) (see Tables 4 and 5 and Supplementary Tables 3–4). The analysis identified an inflection point of 0.73 for 30-day all-cause mortality and an inflection point of 0.76 for mortality at the other time points.

When the SHR index exceeded 0.73, each additional unit increase in the SHR level was associated with a 69.9% rise in the risk of 30-day all-cause mortality ($P<0.001$; 95% CI:1.336–2.159). For 365-day all-cause mortality, an SHR index above 0.76 correlated with a 61.6% increased risk per additional unit of SHR ($P<0.001$; 95% CI: 1.345–1.942). Similarly, for 90-day and 180-day all-cause mortality, each unit increase in SHR above 0.76 was associated with a 57.3% and 59.6% increase in risk,

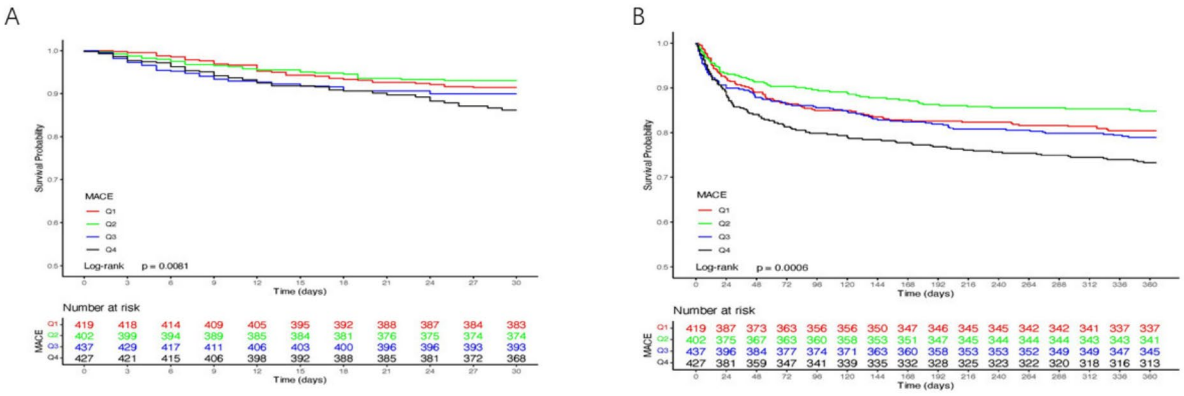

Fig. 2 Kaplan-Meier survival analysis curves for all-cause mortality. Kaplan-Meier curves of 30-day (**A**) and 365-day (**B**) all-cause mortality stratified by SHR index

Table 2 Cox proportional hazard models for 30-day all-cause mortality

Variables	Model1		Model2		Model3	
	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*
SHR quantile						
1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
2	0.81 (0.49 ~ 1.33)	0.406	0.80 (0.49 ~ 1.32)	0.386	0.79 (0.48 ~ 1.30)	0.359
3	1.20 (0.77 ~ 1.87)	0.412	1.08 (0.70 ~ 1.69)	0.723	1.08 (0.69 ~ 1.69)	0.727
4	1.65 (1.09 ~ 2.50)	**0.018**	1.64 (1.07 ~ 2.49)	**0.022**	1.38 (0.90 ~ 2.11)	0.141
HR for trend	2.52 (1.40 ~ 4.51)		2.51 (1.37 ~ 4.60)		1.89 (1.03 ~ 3.47)	
P for trend		**0.002**		**0.003**		**0.040**

HR: Hazard Ratio, CI: Confidence Interval

Model1: Crude

Model2: Adjust: Age, Heart Rate, MBP, BMI, Gender, Marital Status, Diabetes Mellitus, Hypertension, Cerebral Infarction, Myocardial Infarct

Model3: Adjust: Age, Heart Rate, MBP, WBC, INR, eGFR, BMI, Gender, Marital Status, Diabetes Mellitus, Hypertension, Cerebral Infarction, Myocardial Infarct

Table 3 Cox proportional hazard models for 365-day all-cause mortality

Variables	Model1		Model2		Model3	
	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*
SHR quantile						
1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
2	0.76 (0.55 ~ 1.06)	0.104	0.78 (0.56 ~ 1.09)	0.141	0.78 (0.56 ~ 1.09)	0.153
3	1.09 (0.81 ~ 1.47)	0.558	1.03 (0.77 ~ 1.40)	0.825	1.06 (0.78 ~ 1.43)	0.713
4	1.43 (1.08 ~ 1.90)	**0.013**	1.44 (1.08 ~ 1.92)	**0.014**	1.26 (0.95 ~ 1.69)	0.114
HR for trend	2.06 (1.37 ~ 3.10)		2.03 (1.33 ~ 3.09)		1.64 (1.08 ~ 2.49)	
P for trend		**< 0.001**		**< 0.001**		**0.021**

HR: Hazard Ratio, CI: Confidence Interval

Model1: Crude

Model2: Adjust: Age, Heart Rate, MBP, BMI, Gender, Marital Status, Diabetes Mellitus, Hypertension, Cerebral Infarction, Myocardial Infarct

Model3: Adjust: Age, Heart Rate, MBP, WBC, INR, eGFR, BMI, Gender, Marital Status, Diabetes Mellitus, Hypertension, Cerebral Infarction, Myocardial Infarct

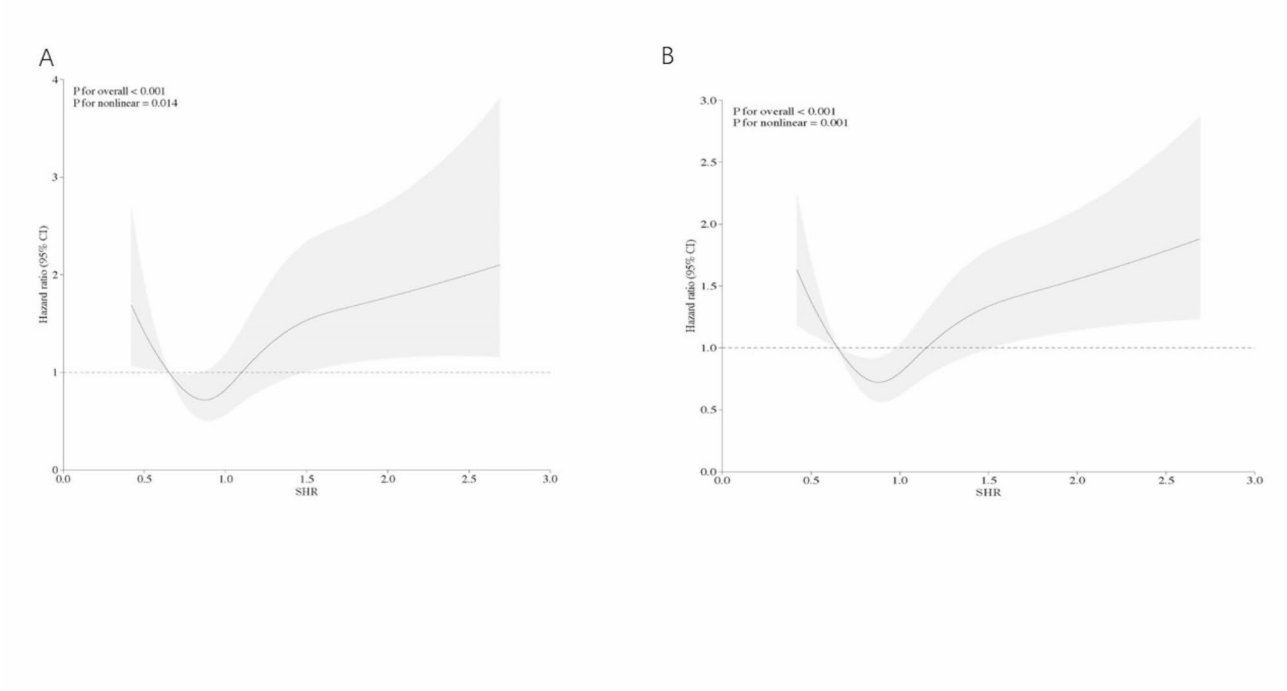

Fig. 3 RCS of SHR index with all-cause mortality. RCS of SHR index with 30-day (A) and 365-day (B) all-cause mortality

Table 4 Threshold effect analysis of SHR index on 30-day all-cause mortality in AF patients

30-day mortality	HR (95% CI), *P*-value
Fitting by the standard linear regression	1.593(1.238–2.049) < 0.001
Fitting model by two-piecewise linear regression	
Inflection point	0.73
SHR < 0.73	0.059(0.004–0.783) 0.032
SHR ≥ 0.73	1.699(1.336–2.159) < 0.001
P for Log-likelihood ratio	0.029

Table 5 Threshold effect analysis of SHR index on 365-day all-cause mortality in AF patients

365-day mortality	HR (95% CI), *P*-value
Fitting by the standard linear regression	1.502(1.239–1.82) < 0.001
Fitting model by two-piecewise linear regression	
Inflection point	0.76
SHR < 0.76	0.105(0.019–0.568) 0.009
SHR ≥ 0.76	1.616(1.345–1.942) < 0.001
P for Log-likelihood ratio	0.005

SHR, stress hyperglycemia ratio; The inflection of threshold effect analysis of SHR index on 365-day all-cause mortality was 0.76.

respectively ($P<0.001$; 95% CI: 1.260–1.964 for 90-day and $P<0.001$; 95% CI 1.306–1.949 for 180-day mortality).

SHR, stress hyperglycemia ratio; The inflection of threshold effect analysis of SHR index on 30-day all-cause mortality was 0.73.

Stratified analyses

To further explore whether the relationship between SHR levels and all-cause mortality at 30-day, 90-day, 180-day, and 365-day intervals persists across different conditions, subgroup analyses were conducted for gender, age, BMI, diabetes status, cerebral infarction, myocardial infarct, and congestive heart failure. The hazard ratios (HRs) for 30-day, 90-day, 180-day, and 365-day all-cause mortality were significant ($P<0.05$) in subgroups of individuals aged ≥ 60 years and females (Fig. 4). However, no statistical significance ($P>0.05$) was observed for these HRs in subgroups of individuals aged < 60 years and males, particularly for 90-day all-cause mortality (Supplementary Fig. 3).

The correlation between SHR levels and 180-day and 365-day all-cause mortality was statistically significant ($P<0.05$) regardless of whether patients had a history of cerebral infarction or myocardial infarction (Fig. 5, Supplementary Fig. 4). In contrast, the HRs for 30-day, 90-day, 180-day, and 365-day all-cause mortality were significant ($P<0.05$) only in patients without congestive heart failure (Figs. 4 and 5, Supplementary Figs. 3–4). Furthermore, the HRs for 30-day, 90-day, 180-day, and 365-day all-cause mortality were significant ($P<0.05$) in

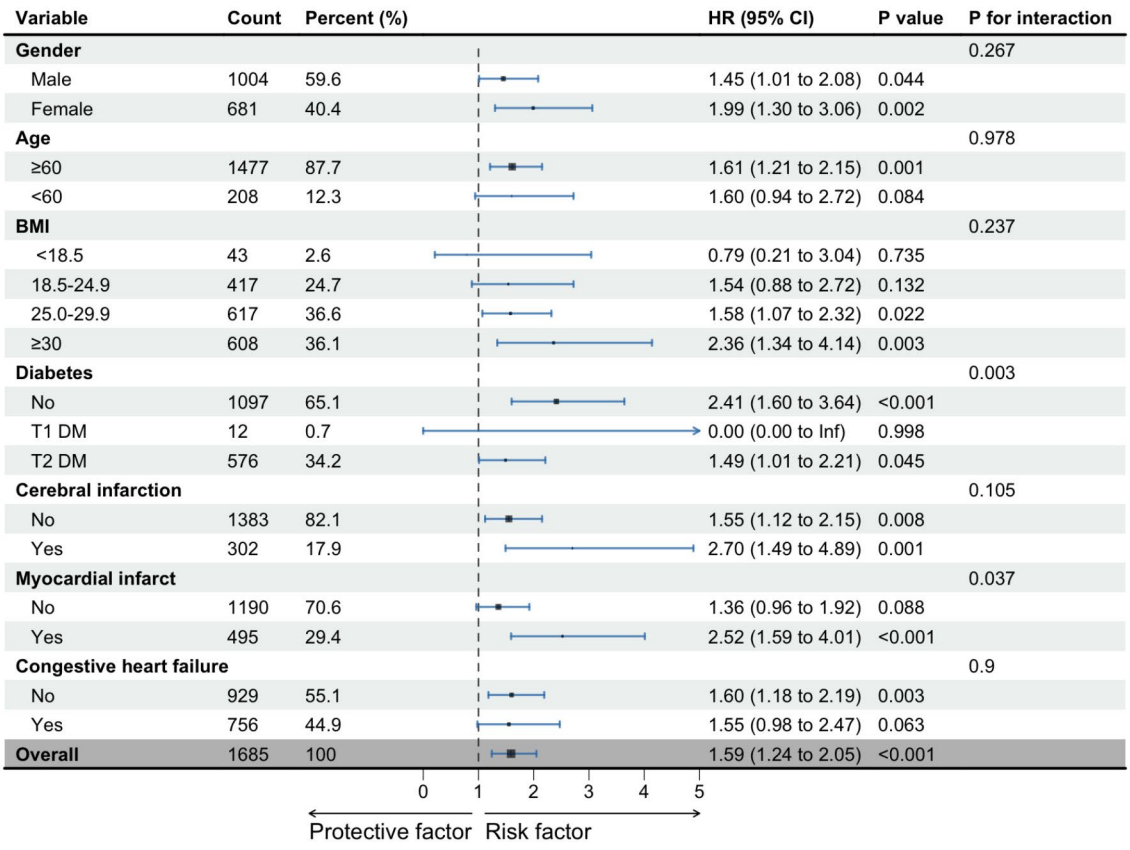

Fig. 4 Forest plots of stratified analyses of SHR index and 30-day all-cause mortality. BMI, body mass index; T1 DM, type1 diabetes mellitus; T2 DM, type2 diabetes mellitus

patients without diabetes. But, the significance of HRs for type2 Diabetes Mellitus (T2 DM) only could be observed in 30-day and 365-day all-cause mortality ($P<0.05$). Lastly, the HRs for 30-day, 90-day, 180-day, and 365-day all-cause mortality were significant ($P<0.05$) in patients with a BMI of 25 or more.

Interaction analysis revealed no significant differences ($P>0.05$) in all-cause mortality at 90 days, 180 days, and 365 days based on gender, age (below or above 60 years), BMI (<18.5, 18.5 ~ 24.9, 25.0 ~ 29.9, ≥30) or the presence of myocardial infarction or congestive heart failure (Fig. 5, Supplementary Figs. 3–4). However, a significant difference ($P<0.05$) in 30-day all-cause mortality was observed between patients with and without myocardial infarction (Fig. 4) and a significant difference ($P<0.05$) in 365-day all-cause mortality was also observed between patients with and without cerebral infarction (Fig. 5). When we further focus on the subgroup analysis of diabetes and its types, we find that different types of diabetes have significant differences ($P<0.05$) in 30-day and 90-day all-cause mortality. And at these two time points, it can be seen that type 2 diabetes has a greater impact on mortality, and the difference between it and type 1 diabetes is statistically significant (Fig. 4, Supplementary Fig. 3).

Discussion

To our knowledge, this is the first retrospective study to explore the relationship between SHR levels and all-cause mortality in patients with severe AF. Our findings reveal a U-shaped relationship between SHR index levels and mortality rates at 30, 90, 180, and 365 days. These results

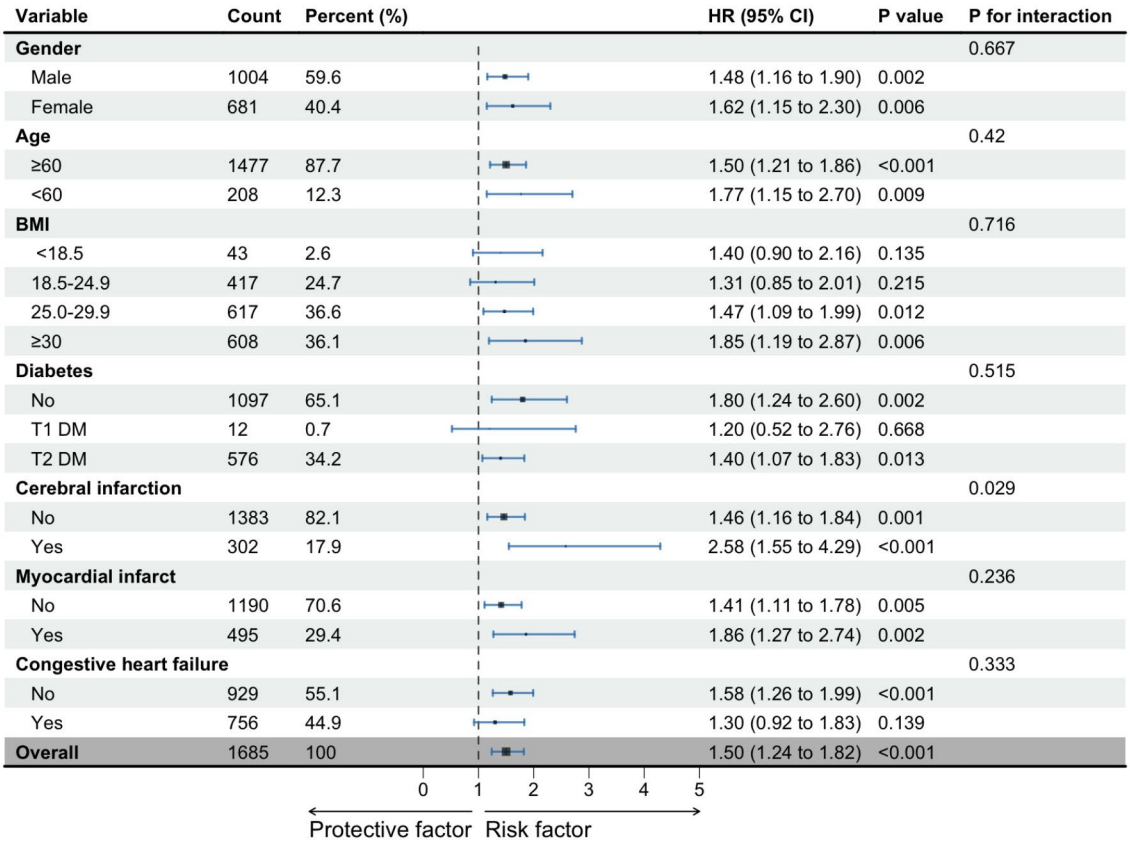

Fig. 5 Forest plots of stratified analyses of SHR index and 365-day all-cause mortality. BMI, body mass index; T1 DM, type1 diabetes mellitus; T2 DM, type2 diabetes mellitus

suggest that once a certain turning point is reached, there is a direct correlation between an increase in the SHR index level and an increase in the likelihood of mortality. The findings of this research are anticipated to provide guidance for treatment approaches aimed at mitigating mortality risk in individuals with severe AF.

Stress-induced hyperglycemia is frequently observed in critically ill patients, leading to insulin resistance (IR), inflammatory responses, and significant disturbances in glucose metabolism [12]. Admission blood glucose levels alone do not provide a comprehensive assessment of hyperglycemia, as they do not account for chronic glucose fluctuations. SHR is a straightforward and effective measure for evaluating stress-induced hyperglycemia [13]. Clinical studies have confirmed that SHR is independently associated with thrombus burden [14], severity of coronary artery disease [15], cerebral edema following acute cerebral infarction [16], and increased infection risk during hospitalization [17]. Beyond its correlation with various diseases, SHR is also used to predict clinical outcomes. For example, in patients with acute myocardial infarction, elevated SHR has been significantly linked to long-term all-cause mortality in both US and Chinese cohorts [18]. In acute decompensated heart failure patients, SHR exhibited a U-shaped correlation with mortality and rehospitalization rates [6]. Importantly, SHR has also been independently associated with the risk of major adverse cardiovascular events (MACE) [19]. In summary, SHR is not only associated with cardiovascular risk factors such as IR but also has the potential to serve as a valuable clinical prognostic indicator, particularly in cardiovascular disease.

The correlation and mechanism between SHR and atrial fibrillation

Atrial fibrillation is characterized by a rapid and irregular heartbeat, leading to symptoms such as palpitations, fatigue, dizziness, and more. If AF resolves spontaneously within 7 days, it is classified as paroxysmal atrial fibrillation; if it persists beyond 7 days, it is classified as persistent atrial fibrillation [20]. Insulin resistance (IR) can promote the excessive generation of reactive oxygen species (ROS) in mitochondria, which directly affect atrial ion channels, particularly through oxidative modifications of intracellular calcium-regulating proteins. This can lead to intracellular calcium overload and delayed afterdepolarization, contributing to atrial electrical remodeling [21]. IR also promotes the increase of various pro-inflammatory factors, such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP). The infiltration of these inflammatory factors into atrial muscle tissue can further enhance atrial fibrosis and cardiac diastolic dysfunction, exacerbating atrial structural remodeling [22–23]. Both atrial electrical remodeling and atrial structural remodeling are crucial mechanisms in the onset and maintenance of AF. Moreover, IR can increase the expression of angiotensinogen (AGT), angiotensin II (Ang II), and Ang II receptors, activate the renin-angiotensin-aldosterone system (RAAS), and induce atrial fibrillation [24–25]. Thus, IR is a significant risk factor for AF, potentially contributing to its development by increasing inflammation and oxidative stress.

Stress-induced hyperglycemia often occurs in response to stress or severe illness. This condition arises from the excessive activation of the sympathetic nervous system, which promotes the massive release of adrenaline and noradrenaline. These stress hormones act on the liver, enhancing glycogenolysis and gluconeogenesis, significantly increasing blood glucose levels [26]. Simultaneously, sympathetic activation inhibits insulin secretion and reduces insulin sensitivity, exacerbating insulin resistance and making blood glucose control more challenging [27]. The stress hyperglycemia ratio (SHR) as a method to assess stress-induced hyperglycemia can serve as an indicator for evaluating the stress response. Furthermore, a higher SHR indicates that the body's stress response has not been resolved and that autonomic nervous dysfunction persists (excessive activation of the sympathetic nervous system and inhibition of the parasympathetic nervous system). Cardiac electrical function varies due to the interplay between the sympathetic and parasympathetic branches of the autonomic nervous system. Excessive activation of the sympathetic nervous system and inhibition of the parasympathetic nervous system can lead to shortened atrial action potential duration and accelerated depolarization. These electrophysiological changes shorten the atrial effective refractory period, making atrial tissue more prone to local reentrant electrical activity, which forms the basis for atrial fibrillation [28]. Furthermore, imbalance in sympathetic nervous system activation is a characteristic of autonomic remodeling in long-term persistent atrial fibrillation [29]. In addition, metabolic disturbances promoted by sustained sympathetic excitation provide an environment conducive to the occurrence of atrial fibrillation. In experimental models of acute atrial fibrillation, activation of the sympathetic nervous system and changes in atrial metabolism have been reported, characterized by increased glycolysis without a concomitant increase in glucose oxidation [30]. Stimulation of β-adrenergic receptors in the liver and adipocytes is associated with increased glycogenolysis and lipolysis, leading to elevated serum glucose and free fatty acid levels [31]. Serum free fatty acids can induce a state of insulin resistance, characterized by reduced uptake of nutrients (free fatty acids and glucose) and subsequent limitations in oxidative metabolism. Systemic and cardiac metabolic changes can create a metabolic profile of inhibited glycolysis, and an enhanced state of glycolytic inhibition may continuously provoke episodes of atrial fibrillation [32]. In summary, autonomic nervous dysfunction under stress conditions is closely related to the occurrence and development of atrial fibrillation.

The correlation and mechanism between SHR and all-cause mortality

Our study's results reveal a U-shaped relationship between the SHR and all-cause mortality over various time frames (30, 90, 180, and 365 days). After adjusting for potential confounders, mortality risk was notably higher when SHR exceeded 0.73 or 0.76. This finding aligns with previous research indicating a U-shaped correlation between SHR and poor outcomes, such as in studies of acute coronary syndrome where SHR was linked to the incidence of MACE [7, 13]. The mechanisms behind this U-shaped association are still not entirely clear, but several factors might contribute:

The mechanisms underlying the U-shaped association remain unclear, but they may involve the following aspects: (1) Stress-induced hyperglycemia can trigger oxidative stress. A rapid rise in blood sugar leads to excessive production of reactive oxygen species [33]. Research quantifying oxidative stress by measuring the 24-hour urinary excretion rate of free 8-iso prostaglandin F2α (8-iso PGF2α) found that individuals with hyperglycemia had higher excretion rates of 8-iso PGF2α [34]. (2) Elevated SHR might impair fibrinolysis, which is essential for breaking down thrombosis. In hyperglycemic patients, the plasma concentration of plasminogen activator inhibitor-1 (PAI-1) is abnormally high, indicating

hypofibrinolysis. Reducing blood glucose levels decreases PAI-1 concentration, suggesting a link between glucose levels and fibrinolysis [35, 36]. (3) Endothelial dysfunction in patients with high SHR is characterized by an imbalance between dilating factors (such as nitric oxide and prostacyclin) and contracting factors (such as endothelin and angiotensin II), leading to a predominance of contractile factors [37]. (4) Disturbances in the fibrinolytic system and endothelial dysfunction can activate and promote platelet adhesion, resulting in increased platelet aggregation [38]. (5) Uncontrolled elevated glucose levels can have detrimental effects, such as impairing wound healing, increasing infection risk, and prolonging hospital stays, ultimately contributing to non-cardiovascular mortality [39].

Poor prognosis of high SHR and differences among different subgroups

Our study also revealed that AF patients in the highest quartile of the SHR had a worse survival prognosis compared to those in the lower SHR quartiles. These high SHR patients also had a higher prevalence of comorbid conditions such as heart failure, myocardial infarction, liver disease, and more severe disease scores. In the multivariate regression model, it can be observed that in the primary outcomes of this study, after adjusting factors such as INR, eGFR, WBC, etc., it can still be observed that the mortality rate increases with the increase of SHR, and this trend is statistically significant. In summary, it can be seen that high SHR is closely related to the poor prognosis of patients with atrial fibrillation.

Subgroup analysis indicated that female and elderly AF patients (≥60 years old) with high SHR were at a higher risk of all-cause mortality. Although statistical interactions did not show significant differences between these groups and males or younger patients, attention should be focused on these high-risk groups. Additionally, AF patients with high SHR and a history of myocardial infarction were at significantly higher risk of all-cause mortality compared to those without myocardial infarction. This increased mortality risk may be linked to several pathophysiological mechanisms. Following myocardial infarction, an inflammatory response involving cytokines like TNF-α, IL-6, and CRP, coupled with increased stress hormones, can disrupt glucose metabolism and elevate glucagon levels. This situation can lead to transient hyperglycemia and acute insulin resistance, which increases oxidative stress. Elevated oxidative stress contributes to the production of vasoconstrictive mediators, exacerbating damage to the coronary endothelium [40–41]. Furthermore, due to insufficient insulin and reduced myocardial cell glycolysis substrates, the heart relies on free fatty acids as an alternative energy source. This shift can impair myocardial contractility, potentially leading to heart failure [42]. These interconnected pathophysiological processes contribute to the poor prognosis observed in AF patients with high SHR.

Interestingly, the subgroup analysis revealed that non-diabetic AF patients with high SHR had a higher all-cause mortality rate compared to their diabetic counterparts. And the interactive analysis confirmed statistically significant differences in 30-day and 90-day all-cause mortality between diabetic and non-diabetic patients. Current studies suggest that non-diabetic patients face a higher risk of adverse events than diabetic patients [43–44]. Several mechanisms might explain this observation: Firstly, diabetes is associated with a chronic inflammatory state that involves different pathophysiological mechanisms [45]. Throughout the course of diabetes, patients often adapt to chronic oxidative stress and sustained higher levels of hyperglycemia compared to non-diabetic individuals. Moreover, diabetic patients who have been treated with insulin, which has a better anti-inflammatory effect [46–47].

Further analysis of diabetic patients reveals that type 2 diabetes patients exhibit a higher mortality rate compared to those with type 1 diabetes, particularly in the 30-day and 90-day all-cause mortality outcomes. Currently, there is no definitive evidence distinguishing the impact of different types of diabetes on atrial fibrillation prognosis and the underlying mechanisms. Therefore, we hypothesize several potential reasons: Type 1 diabetes patients typically respond well to insulin therapy, allowing for stricter blood glucose control and reduced fluctuations, whereas type 2 diabetes patients often experience insulin resistance, making glycemic control more challenging and fluctuations more pronounced. Moreover, type 1 diabetes generally manifests at a younger age, with patients more likely to adopt proactive treatment strategies, including lifestyle modifications, pharmacotherapy, and, when necessary, rhythm control or atrial fibrillation ablation. In contrast, type 2 diabetes tends to develop later in life, with patients often showing less willingness to pursue treatment and having more complications, both of which negatively impact prognosis. Of course, these differences require further research for validation and exploration.

Significance and limitations of this study

Our study indicates that the SHR index, which combines glycosylated hemoglobin and the initial blood glucose level at admission, is an effective alternative indicator for clinically assessing critically ill patients with AF. The management of critically ill patients in the ICU is a crucial aspect of medical practice. As a readily available and uncomplicated measure, the SHR index may help physicians quickly identify high-risk patients, potentially

leading to reduced mortality rates and improved patient outcomes.

This study has several limitations. It is a retrospective analysis conducted at a single medical center using observational data from the MIMIC-IV database, which makes it difficult to establish a definitive cause-and-effect relationship. Although we adjusted for various variables and performed subgroup analyses, potential confounding factors may still affect our findings, for example, the "untargeted" INR in this study population may due to the use of non-warfarin anticoagulants or the influence of unknown drugs or foods. Additionally, our study had a modest sample size, and it is essential to get data from a cohort study with a higher sample size in order to substantiate our research findings. Moreover, the blood glucose levels used were the first recorded values upon ICU admission, and it is unclear if these measurements were taken from fasting patients. Our study also could not establish the biological validity of the correlation between the SHR index and all-cause mortality in critically ill patients with AF. We were also unable to determine the exact timing of AF onset and the primary cause of death, which may limit the clinical significance of our findings. Finally, the significant amount of missing data from echocardiograms, electrocardiograms, and inflammatory markers prevented this study from collecting information and parameters related to left ventricular hypertrophy, atrial enlargement, mitral valve stenosis, and variations in inflammatory markers. This data deficiency has had a substantial impact on the comprehensive assessment of factors influencing all-cause mortality in patients with atrial fibrillation.

Conclusion

The present study identified the SHR index as a potential predictor of all-cause mortality at 30 days, 90 days, 180 days, and 365 days in critically ill patients with AF. Additionally, a U-shaped association was observed between the SHR index level and the risk of all-cause mortality in these patients. SHR index could serve as a valuable indicator for assessing the severity and guiding the treatment of ICU patients with AF.

Abbreviations

AF	Atrial fibrillation
BMI	Body mass index
CI	Confidence interval
DM	Diabetes mellitus
eGFR	Estimated glomerular filtration rate
ICU	Intensive care unit
INR	International normalized ratio
HbA1c	Hemoglobin A1c
HR	Hazard ratio
MIMIC-IV	Medical information mart for intensive care IV
MBP	Mean blood pressure
RCS	Restricted cubic splines
SHR	Stress hyperglycemia ratio

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-024-02462-1 .

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Supplementary Material 7

Supplementary Material 8

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Author contributions

Siyuan Cheng and Yun Lu designed the study. Hui Shen and Yuchen Han extracted the data. Siyuan Cheng and Shaojie Han analyzed the data. Siyuan Cheng drafted the manuscript. Yun Lu revised the manuscript. The final version was approved by all authors.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

Ethics approval

The data was extracted from Medical Information Mart for Intensive Care IV (MIMIC-IV, Version 2.2). The identification information was concealed and privacy of patients in MIMIC-IV were protected. Thus, there were no additional consent procedures from institutional ethics committee.

Author details

[1]Department of Cardiology, The First Affiliated Hospital of Jinan University, Guangzhou 510630, China
[2]Department of Cardiac Surgery, Xuzhou Central Hospital, Xuzhou 221000, China
[3]Department of Emergency, The Fourth Affiliated Hospital of Soochow University (Suzhou Dushu Lake Hospital), Suzhou 215000, China

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