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Predicting 28-day all-cause mortality in patients admitted to intensive care units with pre-existing chronic heart failure using the stress hyperglycemia ratio: a machine learning-driven retrospective cohort analysis

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Abstract

Chronic heart failure (CHF) poses a significant threat to human health. The stress hyperglycemia ratio (SHR) is a novel metric for accurately assessing stress hyperglycemia, which has been correlated with adverse outcomes in various major diseases. However, it remains unclear whether SHR is associated with 28-day mortality in patients with pre-existing CHF who were admitted to intensive care units (ICUs). This study retrospectively recruited patients who were admitted to ICUs with both acute critical illness and pre-existing CHF from the Medical Information Mart for Intensive Care (MIMIC) database. Characteristics were compared between the survival and non-survival groups. The relationship between SHR and 28-day all-cause mortality was analyzed using restricted cubic splines, receiver operating characteristic (ROC) curves, Kaplan–Meier survival analysis, and Cox proportional hazards regression analysis. The importance of the potential risk factors was assessed using the Boruta algorithm. Prediction models were constructed using machine learning algorithms. A total of 913 patients were enrolled. The risk of 28-day mortality increased with higher SHR levels ($P < 0.001$). SHR was independently associated with 28-day all-cause mortality, with an unadjusted hazard ratio (HR) of 1.45 ($P < 0.001$) and an adjusted HR of 1.43 ($P < 0.001$). Subgroup analysis found that none of the potential risk factors, such as demographics, comorbidities, and drugs, affected the relationship (P for interaction > 0.05). The area under the ROC (AUC) curve for SHR was larger than those for admission blood glucose and HbA1c; the cut-off for SHR was 0.57. Patients with SHR higher than the cut-off had a significantly lower 28-day survival probability ($P < 0.001$). SHR was identified as one of the key factors for 28-day mortality by the Boruta algorithm. The predictive performance was verified through four machine learning algorithms, with the neural network algorithm being the best (AUC 0.801). For patients with both acute critical illness and pre-existing CHF, SHR was an independent predictor of 28-day all-cause mortality. Its prognostic performance surpasses those of HbA1c and blood glucose, and prognostic models based on SHR provide clinicians with an effective tool to make therapeutic decisions.

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Keywords Stress hyperglycemia ratio, Chronic heart failure, Mortality, Risk factor, Machine learning

Introduction

Heart failure (HF) is a clinical syndrome characterized by cardinal symptoms such as shortness of breath and fatigue, with or without signs like peripheral edema, pulmonary crackles, and elevated jugular venous pressure, it can be artificially divided into chronic HF (CHF) and acute HF based on whether the patient's symptoms and signs have acutely worsened to the point where they require urgent medical treatment [1]. CHF makes a significant threat to human health and places immense pressure on healthcare resources [2]. The global prevalence of HF ranges from 1 to 3% of the total population, depending on definitions, patient age, nations, and diagnostic capabilities. There are approximately 56.2 million HF patients worldwide [3, 4] In the last few decades, a plateau in incidence rates has been reached, and the number of new diagnoses is substantially decreasing in developed countries. Meanwhile, in developing countries, an increasing number of people are at risk of developing HF due to an increased prevalence associated with the aging population and changes in lifestyle [2]. The prognosis for CHF patients is typically poor with a high mortality, even in the most developed country, North America, 5-year mortality ranges from 45 to 75% [4]. Furthermore, the progressive decline in cardiac function not only severely impacts patients' quality of life, limits their daily activities, but also increases the risk of serious complications such as arrhythmias and renal failure [5, 6]. Additionally, CHF is associated with high treatment costs, which imposes a heavy economic burden on both families and society [2, 4]. These factors highlight the urgency and importance of CHF research, with significant value in exploring effective treatments and prognostic indicators.

Transient hyperglycemia due to stress is advantageous to enhance the ability of struggling with the acute severe illness, [7] that is, an essential survival response [8] However, long-term or continuous hyperglycemia adversely affects the cardiovascular system by impairing vascular endothelial function, promoting the formation and progression of atherosclerosis, and exacerbating coronary artery narrowing and blockage. In patients with CHF, stress hyperglycemia reduces cardiac blood supply, disrupt the normal metabolism of myocardial cells, and increases the workload of the heart, further deteriorates cardiac function, leads to a decrease in myocardial contractility and finally worsens HF [9, 10]. Moreover, stress hyperglycemia increases the body's inflammatory and oxidative stress responses, further damaging cardiac tissue [11–13]. Blood glucose levels have been incorporated into the Intermountain Risk Score, which has significant predictive value for both short-term and long-term mortality in patients with cardiovascular diseases, such as cardiogenic shock [14], and ST-segment elevation myocardial infarction [15]. These findings further corroborate the harm of hyperglycemia to the heart. For patients with CHF, they might face prolonged stress due to poor heart function and recurrent acute events, which induce a hyperglycemic state and oxidative stress [16–19] that may contribute to poor clinical outcomes [20]. Stress hyperglycemia at admission has been independently associated with poor prognosis in various diseases including stroke, [21, 22] sepsis, [23, 24] and acute coronary syndrome [25].

However, admission blood glucose (ABG) cannot differentiate whether hyperglycemia is induced by stress or is a result of a chronic high blood sugar status. Therefore, the stress hyperglycemia ratio (SHR), a relative hyperglycemia, was introduced as a new metric to assess stress hyperglycemia more accurately, and additionally, to eliminate the impact of chronic blood sugar levels on acute hyperglycemia [26] Multiple studies have demonstrated higher SHR levels were associated with the increased risk of adverse outcomes in patients with cardiovascular diseases such as acute coronary syndrome [27–29], acute decompensated HF [30] and sepsis [31].

Patients with pre-existing CHF are prone to be admitted to the intensive care units (ICUs) due to various acute critical illnesses, which pose a significant threat to the patients' lives [3, 32]. However, it is still unclear whether SHR is associated with the poor prognosis in patients admitted to ICUs with both acute critical illness and pre-existing CHF. Therefore, we conducted this study to explore the value of SHR in the prediction of mortality in this kind of patient.

Methods

Study design and participant

This is a retrospective study based on the clinical data of patients with CHF from MIMIC-IV version 2.2, which includes information on over 65,000 ICU admissions and more than 200,000 emergency department admissions at Beth Israel Deaconess Medical Center (BIDMC) in Boston, Massachusetts, between 2008 and 2019 [33]. The Institutional Review Board of BIDMC waived the requirement for informed consent and approved the sharing of research resources. The authors obtained access to the database (Certificate No.: 56073040). The participants were included according to the prespecified criteria: (1) age>18 years, (2) patients diagnosed with Pre-existing CHF on International Classification of Diseases 10th Revision, (3) Admitted to the ICU regardless of the reason. The exclusion criteria were as follows:

(1) patients who had not been tested blood glucose and glycated hemoglobin A1c (HbA1c) in the first laboratory test, (2) patients with a follow-up time of less than 28 days, (3) patients with incomplete data may severely affect the analysis of results. The primary outcome was the value of SHR in prediction of the 28-day in-hospital mortality.

Data extraction

Data was extracted using Navicat software. Characteristics were collected at the time of the patients' admission including age, gender, vital signs [heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure (MAP), respiratory rate, body temperature, pulse oxygen saturation (SpO_2)], medical comorbidities (such as diabetes, liver disease, renal disease, and congestive HF), laboratory tests (such as white blood cell count, platelet count, serum electrolytes, pH, ABG, and HbA1c), commonly used drugs as well as the 28-day clinical outcome, survival or all-cause of death. In addition, the Oxford acute illness severity (OASIS) score was extracted to assess disease severity. SHR was calculated as ABG (mg/dL) / (28.7×HbA1c [%]–46.7) [26].

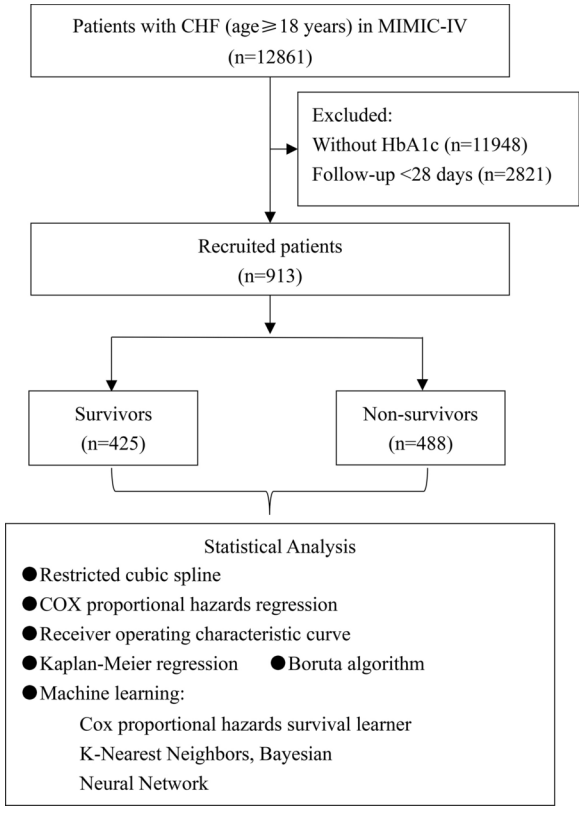

Fig. 1 Inclusion flow in this study. *CHF* Chronic heart failure, *HbA1C* Glycosylated hemoglobin

Statistical analysis

For continuous outcomes, normally distributed data are expressed as mean±standard deviation and compared using t-test, non-normally distributed data are expressed as medians (interquartile range) and compared by Wilcoxon signed-rank non-parametric tests. The normal distribution was tested for by Kolmogorov–Smirnov test. Missing continuous data were imputed using linear interpolation. Categorical data were expressed as frequency and percentage n (%) and compared between groups using the chi-square test. Restricted cubic splines (RCS) analysis was used to examine the relationship between SHR and mortality. The receiver operating characteristic (ROC) curve and the corresponding area under the ROC curve (AUC) were used to compare the predictive power of SHR, blood glucose, and HbA1c for 28-day mortality. Kaplan–Meier (KM) regression analysis was conducted to compare prognosis between groups with high and low SHR levels. Subgroup analysis was performed to further investigate whether the potential confounders affected the relationship between SHR and mortality. Cox proportional hazards regression was used to determine prognostic risk factors for CHF. Hazard ratios (HR) and 95% confidence intervals (95% CI) were reported as effect sizes. The Boruta algorithm in machine learning was used to rank the features according to its importance of predictive ability of 28-day mortality. Acceptable variables were subsequently integrated into the machine learning algorithm. The Cox proportional hazards survival learner (coxph), K-Nearest Neighbors (KNN), Bayesian, and Neural Network algorithms were employed to assess the 28-day death risk in CHF patients, respectively. The dataset of the included patients was randomly grouped into development and validation sets at a 7:3 ratio. The ROC curves and AUCs were utilized to assess model performance. Decision curve analysis (DCA) was implemented to evaluate clinical effectiveness, while calibration curves were employed to measure the accuracy of absolute risk predictions. A p-value<0.05 was considered statistically significant. Statistical analyses were conducted using R software (version 4.0.5) and SPSS (version 26.0, IBM Corporation, USA).

Results

Participant inclusion and baseline characteristics

There were 12,861 cases with CHF and older than 18 years being recorded in MIMIC-IV. 11,948 patients were excluded because the HbA1c was not reported, and 2821 cases were excluded because of short follow-up time (<28 days). Finally, 913 patients were recruited with 425 in survivor group and 488 in non-survivor group (Fig. 1). Among them, 539 (59%) participants were male; Within the 28-day follow-up, 488 (53.5%) patients died, while 425 (46.5%) patients survived. There were

significant differences between the survivor group and the non-survivor group in the age, vital signs (blood pressure, respiratory rate and body temperature), laboratory examinations (such as ABG, HbA1c and the other indicators). More patients met with congestive HF (25% versus 19.1%, P = 0.031) and less frequency of furosemide (42.2% versus 59.1%, P = 0.000) was used in non-survivors than those in the survivors. There were more patients in the survival group who had infection diseases (sepsis and pneumonia) and therefore received antibiotics. There was no significant difference in gender and the other comorbidities between the two groups. More characteristics were reported in Table 1.

SHR levels and its relation to 28-day in-hospital mortality analyzed by RCS

The SHR levels were significantly higher in the non-survivor group [1.2 (0.9, 1.6) vs. 1.1 (0.9, 1.4), P = 0.002]. RCS analysis revealed a significant relationship between SHR and 28-day mortality (P for overall < 0.001, Fig. 2A). The risk of 28-day mortality in CHF patients increased with higher SHR levels. After adjusting for potential risk factors (all the indicators with significant differences in Table 1, such as age, comorbid sepsis, pneumonia and congestive heart failure, vital signs, OASIS score, laboratory test indicators and drugs), the association between SHR and 28-day mortality remained significant (Fig. 2B).

COX proportional hazards regression and the subgroup analysis

COX proportional hazards regression analysis with and without adjustment (the characteristics with significant differences between the survivors and non-survivors) was performed to explore the relationship between SHR and 28-day in-hospital mortality. The results showed that the unadjusted HR was equal to 1.45 with 95% CI 1.32–1.59 (P < 0.001), and the adjusted HR was equal to 1.43 with 95% CI 1.29–1.58 (P < 0.001), which indicated that SHR were independently associated with 28-day all-cause mortality. Subgroup analysis was performed for the potential impact factors such as demographics (gender, age), comorbidities (diabetes, liver disease, renal disease, congestive HF, pneumonia, cerebral infarction, and sepsis), OASIS score, and drugs (furosemide, atorvastatin, aspirin and vancomycin). The results indicated that none of the aforementioned factors affected the prognostic prediction of SHR for patients with CHF (Fig. 3 and Supplementary Table S1). Higher SHR was associated with increased risk of 28-day mortality in CHF in each subgroup (both unadjusted HR and adjusted HR were above 1, P < 0.05, P for interaction > 0.05), meaning the baseline demographics, comorbidities, OASIS score and the commonly used drugs did not sway the relationship between SHR and 28-day mortality.

ROC curves of SHR, ABG, and HbA1c

The ROC curves were plotted for SHR, ABG, and HbA1c (Fig. 4) to predict 28-day all-cause mortality in patients with CHF. SHR had an AUC of 0.924 (95% CI: 0.904–0.943, P < 0.001), outperforming both ABG [AUC: 0.910 (95% CI: 0.889–0.932), P < 0.001] and HbA1c [AUC: 0.917 (95% CI: 0.899–0.935), P < 0.001], which indicated that SHR offered a significant advantage in prediction over ABG and HbA1c. Additionally, we determined a cut-off value of 0.57 for SHR, with a sensitivity of 0.80 and specificity of 0.98. KM curves were plotted for patients divided by the cut-off of SHR.

KM analysis to compare the 28-day survival in subgroups with low versus high SHR

The participants were allocated into low-SHR and high-SHR subgroups for K-M analysis (Fig. 5). Compared to the low-SHR group, patients with higher SHR levels had significantly lower 28-day survival probability (P = 0.011).

Importance of factors in the impact on 28-day mortality ranked by Boruta algorithm

In the report from Boruta algorithm, the variables including SHR in the green area are identified as important factors, which have important roles in the model. SHR was one of the key factors in predicting 28-day hospital mortality in patients with CHF. The variables in the yellow area are suspected factors, which may be related to the adverse outcome to a certain extent, and the variables in the red area are unimportant factors (Fig. 6).

Establishment and validation of the machine learning prediction model

According to the pre-specified protocol, patients were assigned to development (n = 640) and validation (n = 273) groups, no significant differences were detected in the characteristics, suggesting that the two groups of patients originate from the same population and possess good comparability (Supplementary Table S2). The ROC curves of machine learning prediction model were shown in Fig. 7A. The AUC of Coxph, KNN, Bayes and Neutral Network were 0.793, 0.774, 0.786, 0.801, respectively, which indicated that the best performance was in the Neutral Network algorithm prediction model. The DCA curves demonstrated the KNN algorithm model presented a large net benefit and beard strong clinical effectiveness (Fig. 7B). Moreover, the calibration curve of KNN was highly in good agreement with the reference line, indicating excellent prediction performance (Fig. 7C). The characteristics of patients in the development set and validation set are reported in Supplementary Table S2. This table indicates that no significant differences were detected in as many as 62 characteristics, suggesting that the two groups of patients

Table 1 Baseline characteristics of patients with chronic heart failure

	Overall (n = 913)	Survivors (n = 425)	Non-survivors (n = 488)	z(χ2)/*p*
Demographics				
Age, years	66.7 (65.7, 67.7)	63.0 (53.5, 72.0)	72.0 (61.0, 82.0)	− 8.3/0.000
Male, n (%)	539 (59.0)	256 (60.2)	283 (58.0)	0.5/0.492
Comorbidities, n (%)				
Diabetes	364 (39.9)	164 (38.6)	200 (41.0)	0.5/0.461
Renal diseases	324 (35.5)	151 (35.5)	173 (35.5)	0.0/0.980
Liver diseases	291 (31.9)	140 (32.9)	151 (30.9)	0.4/0.518
COPD	34 (3.7)	11 (2.6)	23 (4.7)	2.9/0.091
Sepsis	306 (33.5)	163 (38.4)	143 (29.3)	8.4/0.004
Pneumonia	254 (27.8)	142 (33.4)	112 (23)	12.4/0.000
Asthma	71 (7.8)	39 (9.2)	32 (6.6)	2.1/0.140
SAP or UAP	67 (7.3)	32 (7.5)	35 (7.2)	0.0/0.836
AMI	12 (1.3)	5 (1.2)	7 (1.4)	0.1/0.733
ARDS	10 (1.1)	6 (1.4)	4 (0.8)	0.7/0.391
Cerebral infarction	126 (13.8)	65 (15.3)	61 (12.5)	1.5/0.222
Intracerebral hemorrhage	13 (1.4)	8 (1.9)	5 (1.0)	1.2/0.275
Congestive heart failure	203 (22.2)	81 (19.1)	122 (25.0)	4.6/0.031
Acute heart failure	84 (9.2)	38 (8.9)	46 (9.4)	0.1/0.800
Vital signs, median (IQR)				
Systolic pressure, mmHg	109.6 (108.6, 110.6)	109.6 (102.0, 119.8)	105.9 (97.7, 114.7)	− 4.7/0.000
Diastolic pressure, mmHg	59.2 (58.6, 59.9)	59.2 (53.7, 65.5)	57.4 (51.6, 63.9)	− 3.3/0.001
MAP, mmHg	73.3 (72.6, 73.9)	73.2 (68.0, 80.0)	71.3 (65.0, 76.8)	− 4.3/0.000
Respiratory rate, breathes per minute	21.4 (21.1, 21.7)	20.3 (17.4, 23.9)	21.6 (18.3, 24.8)	− 3.4/0.001
Body temperature, ℃	36.9 (36.8, 36.9)	36.9 (36.7, 37.3)	36.8 (36.5, 37.1)	− 4.7/0.000
Heart rate, beats per minute	91.8 (90.7, 93.0)	91.4 (79.4, 103.7)	91.2 (78.5, 103.8)	− 0.3/0.801
SpO_2, %	96.4 (96.2, 96.6)	97.2 (96.0, 98.6)	96.5 (94.7, 98.1)	− 4.7/0.000
Score, median (IQR)				
OASIS	39.5 (38.8, 40.1)	37.0 (29.0, 44.0)	41.0 (35.0, 48.0)	− 6.4/0.000
Laboratory examination, median (IQR)				
ABG, mg/dl	168.1 (161.9, 174.3)	137.0 (113.8, 170.0)	144.2 (115.0, 212.8)	− 3.3/0.001
HbA1c, %	6.3 (6.2, 6.4)	6.0 (5.0, 7.0)	6.0 (5.3, 7.0)	− 5.8/0.000
Hemoglobin, g/dl	9.9 (9.7, 9.9)	9.2 (8.1, 10.6)	9.7 (8.5, 11.4)	− 4.0/0.000
PLT, 10^9/L	199.4 (190.9, 208.0)	183.0 (112.3, 262.0)	173.3 (103.6, 246.0)	− 1.5/0.132
WBC, 10^9/L	15.0 (14.1, 16.0)	12.6 (8.1, 17.9)	14.1 (9.0, 19.4)	− 2.7/0.008
BUN, mg/dl	39.9 (38.0, 41.7)	30.0 (19.0, 46.0)	35.3 (22.0, 54.9)	− 3.4/0.001
Calcium, mmol/L	8.2 (8.1, 8.3)	8.2 (7.7, 8.7)	8.2 (7.6, 8.7)	− 1.2/0.226
Chloride, mmol/L	103.0 (102.6, 103.5)	103.0 (99.0, 107.0)	103.0 (98.0, 107.5)	− 0.1/0.915
Creatinine, mg/dl	2.1 (2.0, 2.2)	1.4 (0.9, 2.3)	1.8 (1.1, 2.7)	− 3.8/0.000
Sodium, mmol/L	37.9 (137.5, 138.3)	138.0 (134.5, 141.0)	138.0 (134.0, 141.5)	− 0.2/0.814
Potassium, mmol/L	4.4 (4.3, 4.4)	4.2 (3.9, 4.7)	4.4 (3.9, 4.9)	− 2.9/0.004
INR	1.9 (1.8, 1.9)	1.5 (1.2, 1.8)	1.6 (1.3, 2.2)	− 3.5/0.001
PT, s	20.2 (19.4, 21.0)	15.7 (13.5, 20.2)	17.2 (13.9, 23.2)	− 3.4/0.001
PTT, s	45.4 (44.0, 46.9)	35.9 (29.6, 45.4)	42.2 (30.8, 56.4)	− 4.1/0.000
ALT, U/L	172.3 (138.8, 205.8)	52.0 (21.5, 172.0)	51.0 (22.0, 172.0)	− 0.3/0.796
ALP, U/L	135.4 (128.6, 142.1)	130.0 (74.5, 135.0)	122.5 (82.0, 141.5)	− 1.0/0.360
AST, U/L	384.8 (287.6, 482.0)	75.0 (31.5, 385.0)	97.5 (36.3, 385.0)	− 1.7/0.096
pH	7.3 (7.3, 7.3)	7.0 (7.0, 7.0)	7.0 (7.0, 7.0)	− 1.5/0.000
SHR	1.3 (1.3, 1.3)	1.1 (0.9, 1.4)	1.2 (0.9, 1.6)	− 3.1/0.002
Drugs, n (%)				
Antiplatelet drugs				
Clopidogrel	108 (11.8)	44 (10.4)	64 (13.1)	1.7/0.197
Aspirin	419 (45.9)	194 (45.6)	225 (46.1)	0.0/0.889
Lipid regulating drugs				

Table 1 (continued)

	Overall (n = 913)	Survivors (n = 425)	Non-survivors (n = 488)	z(χ2)/*p*
Atorvastatin	216 (23.7)	101 (23.8)	115 (23.6)	0.0/0.944
Simvastatin	115 (12.6)	48 (11.3)	67 (13.7)	1.2/0.269
Diuretics				
Spironolactone	89 (9.7)	38 (8.9)	51 (10.5)	0.6/0.443
Furosemide	457 (50.1)	251 (59.1)	206 (42.2)	25.8/0.000
Antibacterial drugs				
Amoxicillin-clavulanic acid	12 (1.3)	6 (1.4)	6 (1.2)	0.1/0.809
Ampicillin sodium	27 (3.0)	19 (4.5)	8 (1.6)	6.3/0.012
Piperacillin tazobactam	196 (21.5)	113 (26.6)	83 (17.0)	12.4/0.000
Cefazolin	85 (9.3)	53 (12.5)	32 (6.6)	9.4/0.002
Ceftazidime	46 (5.0)	33 (7.8)	13 (2.7)	12.4/0.000
Ceftriaxone	99 (10.8)	51 (12.0)	48 (9.8)	1.1/0.294
Meropenem	126 (13.8)	87 (20.5)	39 (8.0)	29.7/0.000
Imipenem	5 (0.5)	3 (0.7)	2 (0.4)	0.4/0.545
Azithromycin	73 (8.0)	40 (9.4)	33 (6.8)	2.2/0.141
Erythromycin	29 (3.2)	19 (4.5)	10 (2.0)	4.3/0.037
Ciprofloxacin	191 (20.9)	114 (26.8)	77 (15.8)	16.8/0.000
Levofloxacin	87 (9.5)	49 (11.5)	38 (7.8)	3.7/0.055
Metronidazole	137 (15.0)	77 (18.1)	60 (12.3)	6.0/0.014
Vancomycin	436 (47.8)	237 (55.8)	199 (40.8)	20.4/0.000
Vasodilator drugs				
Nitroglycerin	129 (14.1)	78 (18.4)	51 (10.5)	11.7/0.001
Anti-arrhythmic drugs				
Amiodarone	107 (11.7)	60 (14.1)	47 (9.6)	4.4/0.036

COPD Chronic obstructive pulmonary disease, *SAP* Stable angina pectoris, *UAP* Unstable angina pectoris, *AMI* Acute myocardial infarction, *ARDS* Acute respiratory distress syndrome, *ABG* Admission blood glucose, *HbA1c* Glycosylated hemoglobin, *OASIS* Oxford acute illness severity score, *MAP* Mean arterial pressure, *SpO2* Pulse oxygen saturation, *PLT* Platelet count, *WBC* White blood cell count, *BUN* Blood urea nitrogen, *INR* International normalized ratio, *PT* Prothrombin time, *PTT* Partial thromboplastin time, *ALT* Alanine aminotransferase, *ALP* Alkaline phosphatase, *AST* Aspartate aminotransferase, *SHR* Stress hyperglycemia ratio

originate from the same population and possess good comparability.

Power of the study

The sample size was estimated using a method specifically designed for developing clinical prediction models, as put forward by biostatistics professors [34]. To achieve the expected power of test (a significance level of 0.05,two-tailed, and a desired power of 0.80) in the four machine learning algorithms used in this study, at least 439 participants were required for the sample (including 220 positive events) based on preliminary analysis (mortality of 0.53) and the top 15 important factors in the green zone (Fig. 6) ranked by Boruta algorithm, the calculations were performed by the R package (pmsampsize) [34]. In the current research, 913 patients were included in the sample, which included 488 positive events. This sample size exceeded the calculated sample size, providing sufficient power to detect the effects.

Discussion

This retrospective study exclusively investigated the relationship between the SHR and the mortality in patients with CHF. The study ultimately found that the SHR was an independent prognostic risk factor, regardless of the baseline demographics, comorbidities and drugs, which was validated by a variety of statistical methods and from multiple dimensions in this study.

The estimates of mortality rates in CHF varied greatly due to the differences in the study design, study population, definition for CHF, and cut-off values for left ventricular ejection fraction [4, 35]. Patients who suffered from pre-existing CHF only have an overall median survival of 2.1 years even if admitted to the hospital solely for HF (mostly non-ICU) [36] The patients included in this study also met with at least one acute critical illness at the time of ICU admission, such as sepsis, pneumonia, cardiovascular events, and liver and kidney diseases, which jointly contribute to poor prognosis, these are also the reasons why we chose the 28-day all-cause mortality rate. The mortality is consistent with the results of previous related studies. [37, 38]. The relatively high rates of hospital readmission and mortality have brought an enormous economic burden to society and families [4, 35]. Therefore, establishing early prediction models for prognosis and identifying patients at high risk of death can assist clinicians in formulating more proactive and reasonable treatment plans, serving to reduce risk of death.

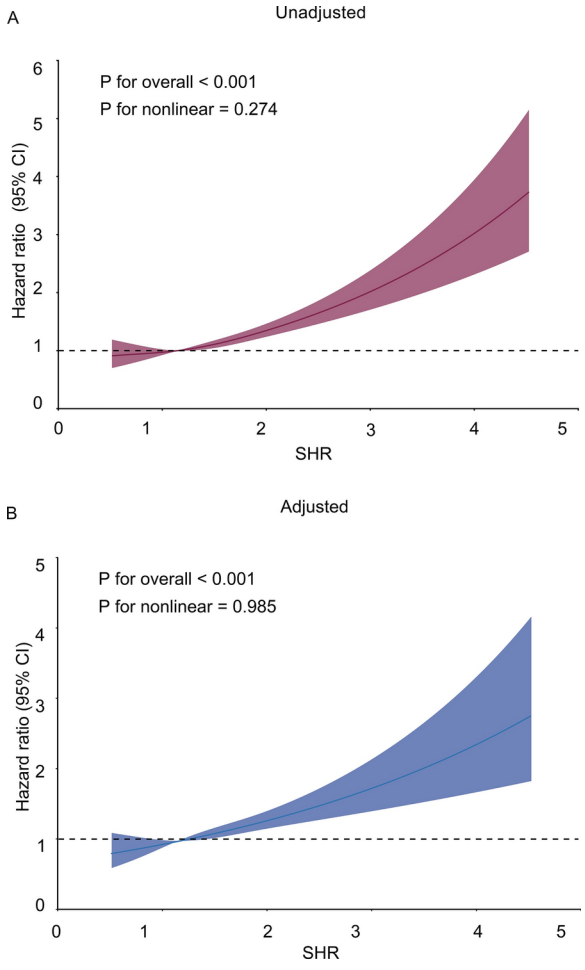

Fig. 2 The association between SHR and 28-day mortality by restricted cubic spline method **A** The unadjusted evaluation; B The adjusted evaluation. *CI* Confidence interval, *SHR* Stress hyperglycemia ratio

The Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) pooled the data from 30 cohort studies (involving 39 372 patients) and identified 13 independent predictors of mortality with various predictive strength in patients with CHF [39]. One observational study has externally validated the MAGGIC risk score could be considered as a powerful and simple method to stratify the risk of mortality [40]. Another retrospective cohort analysis constructed a nomogram prediction model of in-hospital mortality with similar 13 risk factors [41]. With an increasing understanding of the relationship between inflammation and CHF [42] some scholars have established a clinical outcome risk stratification model based on multiple plasma biomarkers [43]. However, these models involve too many parameters and are complex to operate. Therefore it needs simple and easy-to-use parameters to assess the risk of mortality, such as heart rate [44], echocardiography [45] and the combination of several commonly used laboratory indicators in clinical practice [46]. In critically ill patients, SHR has been concerned because it eliminates the influence of baseline glucose on stress hyperglycemia regardless of whether the patient has diabetes or not [26, 47]. Considering that stress hyperglycemia can occur in all populations, this study includes patients with and without diabetes to reflect the universality of SHR.

In this study, RCS analysis clearly demonstrated that the risk of 28-day mortality gradually rose with the increase of SHR. This relationship remains stable after adjusting for confounding factors. Meanwhile it was validated by proportional hazards regression and the subgroup analysis based on the potential impact factors, which demonstrated the broad applicability and stability of the relationship between SHR and the mortality. This finding might have important clinical implications, as physicians can calculate SHR early in the patient's admission to quickly assess their prognostic risk and develop more personalized and targeted treatment protocols. This result aligns with previous research in other critical illnesses including acute myocardial infarction [21], stroke [26], sepsis [27]. These results further emphasize the importance of SHR in prognostic assessment for CHF patients.

Another finding was the cut-off of SHR, it is 0.57 according to the ROC analysis, which was lower than those for long-term prognosis in patients with CHF [48] and poor prognosis acute coronary syndrome [29]. The results of KM analysis based on the cut-off also strongly support this view point. The 28-day survival rate in patients with SHR level larger than 0.57 was significantly lower than in those with SHR lower than 0.57, which indicated that SHR could be used as an effective stratification tool to differentiate prognostic risk. Additionally, the AUC of SHR was superior to both admission glucose and HbA1c, which suggested that SHR could more accurately reflect the severity and prognosis of the patient's condition, potentially provide more comprehensive and precise information compared to traditional blood glucose markers. The strength of SHR might be attributed to the fact that SHR takes into account both acute glucose elevation and chronic glucose levels, therefore SHR better reflects the patient's glucose metabolism during stress and its impact on prognosis [26].

It is well-known that the poor prognosis might not be driven by only one factor. As shown in Table 1, there are significant differences between survivors and non-survivors in multiple characteristics involving age, comorbidities, vital signs, laboratory test indicators, and clinical medication use, although it is not possible to make definitive judgments relying solely on basic statistical methods. Therefore, the Boruta algorithm was adopted to determine the importance of various factors in the influence on the poor prognosis, which showed that SHR played an important role in the model and was identified

Variables		Unadjusted HR (95%CI)	P	P for interaction		Adjusted HR (95%CI)	P	P for interaction
All patients	913 (100.00)	1.45 (1.32 ~ 1.59)	<.001		913 (100.00)	1.43 (1.29 ~ 1.58)	<.001	
OASIS				0.199				0.252
<25	69 (7.56)	1.32 (1.01 ~ 1.73)	0.042		69 (7.56)	7807.41 (5936.54 ~ 10267.87)	<.001	
≥25	844 (92.44)	1.54 (1.39 ~ 1.71)	<.001		844 (92.44)	1.50 (1.34 ~ 1.68)	<.001	
Gender				0.997				0.414
Female	374 (40.96)	1.44 (1.23 ~ 1.68)	<.001		374 (40.96)	1.33 (1.12 ~ 1.58)	0.001	
Male	539 (59.04)	1.46 (1.29 ~ 1.64)	<.001		539 (59.04)	1.49 (1.31 ~ 1.70)	<.001	
Age				0.576				0.434
<65	390 (42.72)	1.50 (1.27 ~ 1.78)	<.001		390 (42.72)	1.41 (1.16 ~ 1.71)	<.001	
≥65	523 (57.28)	1.42 (1.27 ~ 1.58)	<.001		523 (57.28)	1.43 (1.26 ~ 1.62)	<.001	
Diabetes				0.946				0.988
No	549 (60.13)	1.46 (1.29 ~ 1.65)	<.001		549 (60.13)	1.45 (1.26 ~ 1.67)	<.001	
Yes	364 (39.87)	1.44 (1.24 ~ 1.66)	<.001		364 (39.87)	1.37 (1.15 ~ 1.64)	<.001	
Renal disease				0.710				0.840
No	589 (64.51)	1.44 (1.30 ~ 1.60)	<.001		589 (64.51)	1.43 (1.27 ~ 1.61)	<.001	
Yes	324 (35.49)	1.52 (1.17 ~ 1.97)	0.002		324 (35.49)	1.80 (1.35 ~ 2.40)	<.001	
Liver disease				0.889				0.314
No	622 (68.13)	1.44 (1.29 ~ 1.62)	<.001		622 (68.13)	1.38 (1.22 ~ 1.57)	<.001	
Yes	291 (31.87)	1.47 (1.25 ~ 1.72)	<.001		291 (31.87)	1.48 (1.26 ~ 1.75)	<.001	
Congestive heart failure				0.985				0.339
No	710 (77.77)	1.45 (1.31 ~ 1.60)	<.001		710 (77.77)	1.42 (1.28 ~ 1.59)	<.001	
Yes	203 (22.23)	1.47 (1.06 ~ 2.04)	0.021		203 (22.23)	1.94 (1.27 ~ 2.94)	0.002	
Pneumonia				0.063				0.259
No	659 (72.18)	1.40 (1.27 ~ 1.55)	<.001		659 (72.18)	1.40 (1.26 ~ 1.57)	<.001	
Yes	254 (27.82)	1.92 (1.42 ~ 2.60)	<.001		254 (27.82)	1.66 (1.13 ~ 2.43)	0.010	
Cerebral infarction				0.223				0.285
No	787 (86.20)	1.49 (1.35 ~ 1.64)	<.001		787 (86.20)	1.46 (1.30 ~ 1.63)	<.001	
Yes	126 (13.80)	1.26 (0.94 ~ 1.70)	0.121		126 (13.80)	1.15 (0.86 ~ 1.53)	0.349	
Sepsis				0.307				0.263
No	607 (66.48)	1.47 (1.33 ~ 1.63)	<.001		607 (66.48)	1.47 (1.31 ~ 1.65)	<.001	
Yes	306 (33.52)	1.32 (1.05 ~ 1.65)	0.017		306 (33.52)	1.29 (0.95 ~ 1.74)	0.097	
Furosemide				0.748				0.440
No	456 (49.95)	1.39 (1.26 ~ 1.54)	<.001		456 (49.95)	1.42 (1.26 ~ 1.61)	<.001	
Yes	457 (50.05)	1.48 (1.16 ~ 1.89)	0.002		457 (50.05)	1.49 (1.12 ~ 1.98)	0.006	
Atorvastatin				0.186				0.159
No	697 (76.34)	1.42 (1.28 ~ 1.57)	<.001		697 (76.34)	1.40 (1.25 ~ 1.57)	<.001	
Yes	216 (23.66)	1.77 (1.34 ~ 2.35)	<.001		216 (23.66)	1.53 (1.07 ~ 2.19)	0.018	
Aspirin				0.069				0.356
No	494 (54.11)	1.39 (1.24 ~ 1.55)	<.001		494 (54.11)	1.38 (1.21 ~ 1.57)	<.001	
Yes	419 (45.89)	1.76 (1.43 ~ 2.17)	<.001		419 (45.89)	1.57 (1.24 ~ 1.99)	<.001	
Vancomycin				0.421				0.448
No	477 (52.25)	1.39 (1.24 ~ 1.55)	<.001		477 (52.25)	1.39 (1.23 ~ 1.58)	<.001	
Yes	436 (47.75)	1.53 (1.30 ~ 1.81)	<.001		436 (47.75)	1.58 (1.29 ~ 1.95)	<.001	

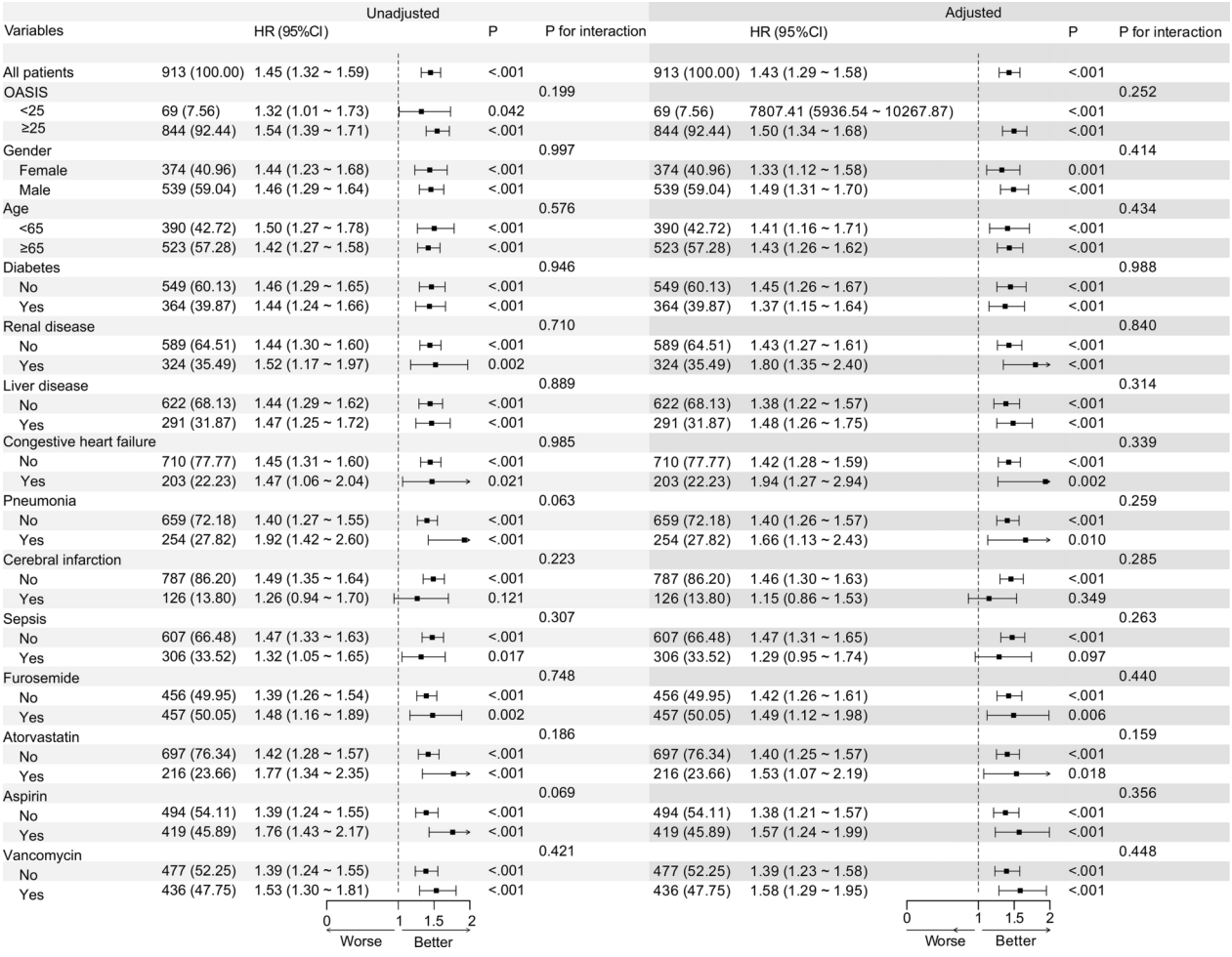

Fig. 3 COX proportional hazards regression and the subgroup analysis. *OASIS* Oxford acute illness severity score, *HR* Hazard ratio

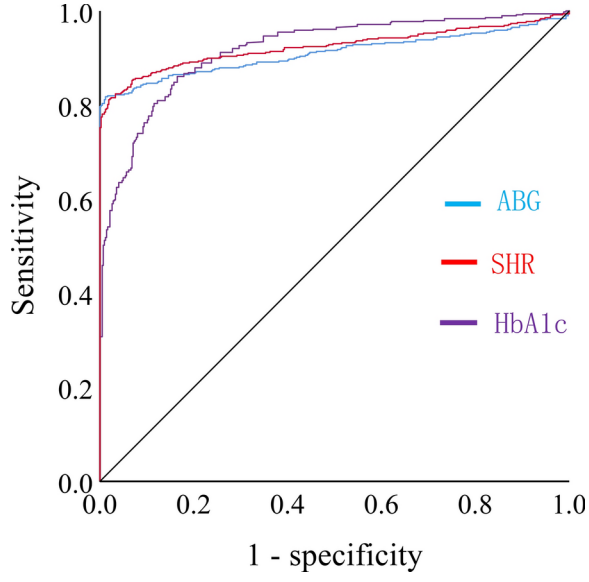

Fig. 4 Prediction performance for 28-day all-cause mortality by ROC curves. *SHR* Stress hyperglycemia ratio, *ABG* Admission blood glucose, *HbA1C* Glycosylated hemoglobin

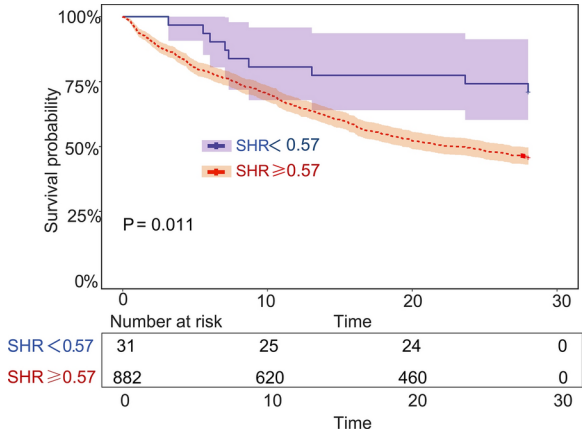

Fig. 5 Kaplan–Meier survival curve for mortality according to SHR cut-off SHR: stress hyperglycemia ratio

as a critical feature within the green zone. Important characteristics also include age and indicators of disease severity, such as pH, OASIS, SpO_2, and MAP. Meropenem is the only drug categorized as a significant influencing factor, possibly since the patients in this study were

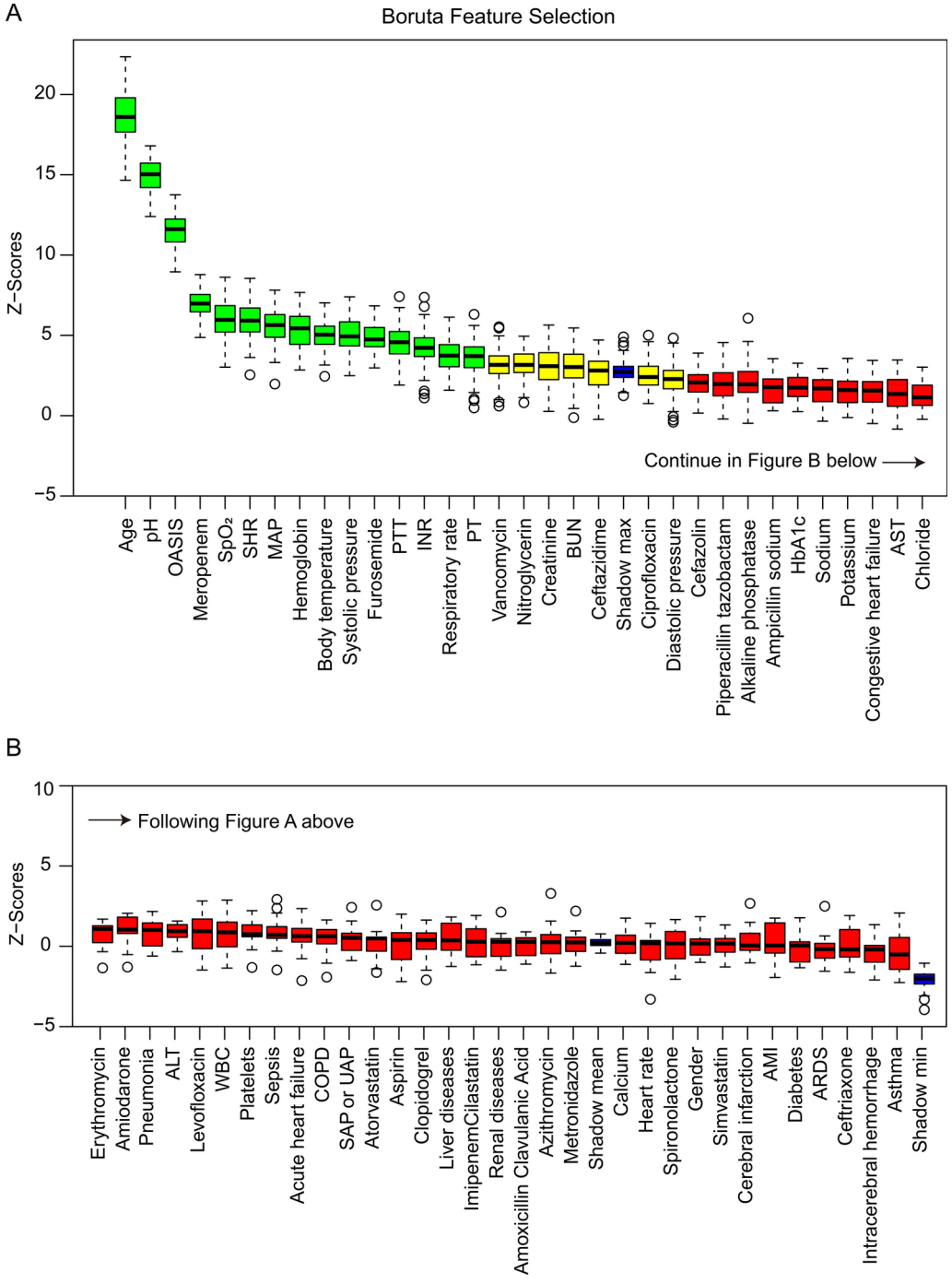

Fig. 6 Importance of potential risk factors of 28-day mortality ranked by Boruta algorithm. The horizontal axis is the name of each variable, and the vertical axis is the Z value of each variable. The box plot shows the Z value of each variable during model calculation. The green boxes represent important variables, the red boxes represent unimportant variables, and the yellow boxes represent potentially important variables. *ABG* Admission blood glucose, *HbA1c* Glycosylated hemoglobin, *OASIS* Oxford acute illness severity score, *MAP* Mean arterial pressure, *SpO_2* Pulse oxygen saturation, *SHR* Stress hyperglycemia ratio, *MAP* Mean arterial pressure, *PTT* Partial thromboplastin time, *INR* International normalized ratio, *PT* Prothrombin time, *BUN* Blood urea nitrogen, *HbA1C* Glycosylated hemoglobin, *AST* Aspartate aminotransferase, *ALT* Alanine aminotransferase, *COPD* Chronic obstructive pulmonary disease, *WBC* White blood cell count, *SAP* Stable angina pectoris, *UAP* Unstable angina pectoris, *AMI*: acute myocardial infarction, *ARDS* Acute respiratory distress disease

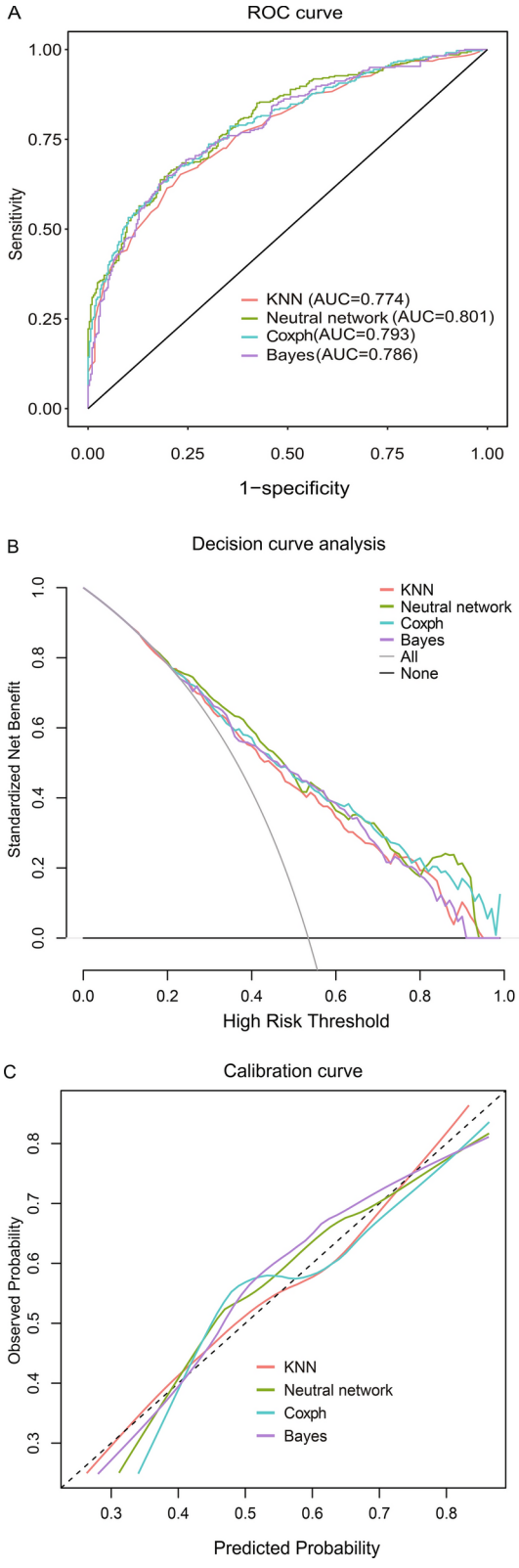

Fig. 7 Establishment and validation of the machine learning prediction model. A ROC curve of the machine learning model. B DCA of the machine learning model. C Calibration curve of the KNN algorithm model. *KNN* K-Nearest Neighbors, *Coxph* Cox proportional hazards survival

from the ICU and had a relatively high prevalence of co-existing infectious diseases. Despite their clinical importance, comorbidities (congestive HF, sepsis, diabetes and pneumonia) and other medications were not listed in the green area. As shown in Fig. 3 and Supplementary Table 1, further subgroup analysis of Cox proportional hazards regression based on important characteristics also indicates that these characteristics do not significantly affect the relationship between SHR and 28-day mortality. These findings further validate the relationship between SHR and mortality in patients with CHF, while also providing strong support for constructing a prognostic model based on SHR. However, we also observed that variables in the yellow zone, marked as tentative important features, may be somewhat related to adverse outcomes in CHF patients. This suggests that in future studies, we could further explore the potential interactions between these variables and SHR, as well as their combined influence on the prognosis of CHF patients, to gain a more comprehensive understanding of prognostic factors in CHF.

The prediction performance was acceptable when tested by four commonly used machine learning models (coxph, KNN, Bayes, Neutral Network) with the neural network algorithm being the best (AUC 0.801). The calibration curve indicated that the fitted curve was close to the reference curve, and the DCA curve showed that the model had significant net benefit. These results suggest that the model had high accuracy and clinical practicability. This prognostic model provided clinicians with a practical and intuitive tool to make more informed treatment decisions for patients with both acute critical illness and pre-existing CHF more effectively. Just as in coronary artery disease and atrial fibrillation, the predictive performance of machine learning algorithms was especially important for cardiologists and experts in the ICU who face challenges in trying to make optimal clinical decision-making [49].

This study has several strengths. Various statistical methods, including RCS analysis, Kaplan–Meier analysis, ROC curve analysis, the Boruta algorithm, subgroup analysis, Cox regression analysis, and machine learning, were employed to thoroughly investigate the relationship between the SHR and 28-day all-cause mortality in patients with CHF from multiple dimensions. This comprehensive use of multiple methods enhances the reliability and persuasiveness of the study results, allowing for a more complete revelation of the role of SHR in the prognostic evaluation of CHF patients. Compared to other similar studies, our research is methodologically more rigorous and comprehensive [39–43]. For example, in the variable selection process, we utilized difference analysis, univariate Cox regression, and the Boruta algorithm, which not only identified SHR as an important feature

but also revealed several potentially significant features, providing directions for future research. Furthermore, we predicted the 28-day all-cause mortality of CHF patients using various machine learning models. Moreover, SHR has several advantages, it is simple, easy to measure, fast, non-invasive, and highly accurate [26].

However, as a retrospective study, there are several limitations, such as the potential for selection bias, which may prevent the included patients from fully representing all patients of this category. The sample size is limited in the current database, and objectively, we cannot determine its size. Since the outcomes of interest have already occurred and exposure factors cannot be controlled, the results of the study can only suggest a correlation between SHR and mortality but cannot prove whether there is a causal relationship between SHR and the prognosis. There is a small amount of incomplete data, and the filled data may affect the results to a certain extent. Additionally, the data for this study came from a single database with racial limitations, meaning the findings may only be applicable to the studied population. Therefore, these findings should provoke further multicenter and prospective studies to validate the predictive value of SHR in prognosis.

Conclusion

For patients admitted to ICUs with both acute critical illness and pre-existing CHF, SHR was identified as an independent predictor of 28-day all-cause mortality. Its prognostic value surpasses those of HbA1c and blood glucose, and prognostic models based on SHR were successfully constructed with machine learning algorithm, which provide clinicians with an effective tool to make therapeutic decisions. More multicenter clinical studies are needed to provide stronger evidence.

Abbreviations

HF	Heart failure
CHF	Chronic heart failure
ABG	Admission blood glucose
SHR	Stress hyperglycemia ratio
BIDMC	Beth Israel Deaconess Medical Center
ICD	International Classification of Diseases
MAP	Mean arterial pressure
SpO_2	Pulse oxygen saturation
HbA1c	Glycated hemoglobin
OASIS	Oxford acute illness severity
RCS	Restricted cubic splines
ROC	Receiver operating characteristic
AUC	Area under the curve
KM	Kaplan–Meier
HR	Hazard ratios
CI	Confidence intervals
Coxph	Cox proportional hazards
KNN	K-Nearest Neighbors
DCA	Decision curve analysis
MAGGIC	Meta-Analysis Global Group in Chronic Heart Failure

Supplementary Information

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Supplementary material 1.

Author contributions

Q.L. and H.L. conceived and designed the study, explained the results and revised the manuscript. H.L. X.Y., and B.D. conducted the study, collected and analyzed the data, drafted the manuscript. All authors reviewed and revised the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval

The study was conducted in accordance with the guidelines of the Helsinki Declaration. As the MIMIC-IV database is publicly available, and all data are de-identified to remove patients' information. The approval was obtained from the Institutional Review Board in advance, and ethical review was not required.

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