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The relationship between hemoglobin glycation index and all-cause mortality in ill critically patients with heart failure: a retrospective study in MIMIC-IV database

Yulong Wang[1†], Shanshan Tang[1†], Haokun Liu[1†] and Yongle Li[1*]

Abstract

Background Heart failure (HF) is a major cause of mortality in critically ill patients and often requires intensive care. The hemoglobin glycation index (HGI), defined as the difference between predicted glycated hemoglobin (HbA1c) and measured HbA1c, may provide additional prognostic insights beyond traditional glycemic metrics.

Methods We conducted a retrospective analysis of 8,098 adult patients with HF from the MIMIC-IV database (2008–2022). All were first-time ICU admissions with available hematologic and metabolic data. Patients were stratified into three groups (T1 ≤ −1.26, −1.26 < T2 < 1.74, T3 ≥ 1.74) based on HGI. Baseline characteristics were recorded within 24 h of ICU admission, including demographic data, disease severity scores, comorbidities, and medication use. Logistic regression and Cox proportional hazards models assessed the associations between HGI and in-hospital, 30-day, and 1-year all-cause mortality, adjusting for age, sex, race, comorbidities, laboratory results, and relevant treatments. Restricted cubic spline (RCS) analysis was performed to examine potential non-linear relationships. We used sensitivity analyses to increase the confidence in our primary outcome.

Results Patients in the lowest HGI group (T1) had significantly higher in-hospital, 30-day, and 1-year mortality than those in the other two groups. Specifically, T1 showed an 18.6% in-hospital mortality rate, compared with 12.3% and 9.7% in T2 and T3, respectively ($p < 0.001$). Fully adjusted models revealed that each 1-unit increase in HGI was associated with an approximate 12% reduction in in-hospital mortality risk (OR = 0.88; 95%CI: 0.83–0.93), and an 3% decreased risk of 1-year all-cause mortality (HR 0.97; 95%CI0.94~1.00). RCS analysis indicated a J-shaped relationship between HGI and mortality, underscoring the heightened risk associated with very low HGI. We conducted sensitivity analyses by separately excluding missing data, diagnosed sepsis, and diagnosed hepatic impairment, consistent with the primary analysis.

Conclusions In critically ill HF patients, extremely low HGI levels correlate with poorer short- and long-term survival. These findings suggest that HGI could serve as an adjunct risk stratification tool, prompting closer monitoring and potential intervention in patients with markedly low HGI.

Keywords Hemoglobin Glycation Index, Heart Failure, MIMIC-IV, All-Cause Mortality, Retrospective Study

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Background

Heart failure (HF) is a prevalent and serious condition that significantly impacts critically ill patients, contributing to high morbidity and mortality rates, especially within intensive care units (ICUs) [1, 2]. Its pathophysiology is multifaceted, involving dysregulated inflammatory, metabolic, and neurohormonal pathways, all of which complicate disease management and exacerbate patient outcomes [3, 4]. The global incidence of HF continues to rise, positioning it as one of the leading causes of hospitalization and death, particularly in the elderly and those with multiple comorbidities [5].

A key aspect of HF management is the monitoring of blood glucose control, which is often impaired in these patients [1]. Hemoglobin glycation, a process where glucose binds to hemoglobin, forms glycated hemoglobin (HbA1c), which is a marker commonly used to evaluate long-term blood glucose levels [6]. Recently, the hemoglobin glycation index (HGI) has emerged as a more nuanced marker of glucose variability [7]. Unlike HbA1c, which provides a static measure of average blood glucose, HGI reflects fluctuations in glucose levels over time, offering potentially greater insight into glucose metabolism dynamics [7, 8]. Elevated HGI has been associated with worse outcomes in patients with diabetes and cardiovascular diseases [9, 10], suggesting that it could be an important prognostic tool.

In the context of HF, impaired glucose metabolism and insulin resistance are frequent complications [3]. Emerging evidence suggests that HGI may be a valuable predictor of prognosis in critically ill patients with heart failure, potentially correlating with all-cause mortality. High glycemic variability, reflected by an elevated HGI, has been linked to poor clinical outcomes, including increased mortality [9–11]. However, the exact relationship between HGI and all-cause mortality in heart failure patients remains an area of ongoing investigation.

This study aims to evaluate the association between HGI and all-cause mortality in critically ill patients with heart failure using data from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database, providing valuable insights that could inform clinical management strategies for this high-risk population.

Method

Study design and setting

Data were sourced from the U.S. public critical care database, the MIMIC-IV 3.1 [12], which is hosted by the Beth Israel Deaconess Medical Center. This dataset includes information from 2008 to 2022, representing the American cohort.

Access to the databases was granted upon successful completion of the Collaborative Institutional Training Initiative certification (Certification numbers: 64820886 for Wang). Given the retrospective nature of this study and the use of publicly available data, informed consent was waived. This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (Clinical trial number: not applicable).

The cohort was selected based on the following inclusion criteria: (1) diagnosis of heart failure (HF); (2) first ICU admission. The exclusion criteria were: (1) age < 18 years; (2) ICU stay of less than 24 h; (3) missing HbA1c within 3 months pre-admission or FPG within 24 h of admission. Exclusion was restricted to cases lacking key variables essential for HGI calculation, namely admission glucose or HbA1c, resulting in 2,805 additional exclusions after initial screening. After applying these criteria, a final sample of 8,098 critically ill HF patients was included in the analysis. The sample size yielded EPV ratios of 64.25, 83.43, and 164.62 for in-hospital, 30-day, and 1-year mortality respectively, substantially exceeding the recommended threshold of 5–10 EPV for all outcomes and ensuring robust statistical power.

Data collection

We extracted baseline patient data within 24 h of ICU admission from the MIMIC-IV database17. This included demographic information (e.g., age, gender), as well as clinical variables such as disease severity measures (Sequential Organ Failure Assessment [SOFA], Simplified Acute Physiology Score II [SAPS II]). Additionally, vital signs (heart rate, mean arterial blood pressure [MBP]) and laboratory test results (e.g., white blood cell count [WBC], hemoglobin, platelets, potassium, sodium, chloride, albumin, and creatinine) were recorded. The duration of mechanical ventilation, ICU stay, and overall hospitalization were also measured.

Comorbidities were identified using ICD-9 codes, including conditions such as hypertension, myocardial infarction(MI), stroke, atrial fibrillation (AF), chronic obstructive pulmonary disease (COPD), diabetes, renal failure, and cancer (Table S1 in the Supplemental Material). The medication history, including insulin, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), calcium channel blockers (CCB), beta-blockers, statins, antiplatelets, and diuretics, was also documented. We employed a two-tiered approach to handling missing data: (1) Cases missing essential variables for HGI calculation (admission glucose or HbA1c) were excluded from the analysis as shown in our exclusion criteria; (2) For adjustment covariates with missing rates < 20%, we applied *MissForest* imputation to preserve sample size and statistical power. The specific missing rates for all imputed variables are detailed in Table S2 in the Supplemental Material. For

variables with missing data, missing values were imputed using multivariate interpolation based on chained equations, utilizing the R (MICE) package [13]. The missing rates of the study variables are shown in Table S2 in the Supplemental Material.

HGI calculation

Linear regression models of fasting blood glucose (FPG) and HbA1c levels were established based on data from all study patients. With HbA1c as the dependent variable and FPG as the independent variable, the linear regression equation was established [9]: predicted HbA1c = 0.007 * FPG + 5.37. The difference between the observed and predicted values of HbA1c is then calculated as HGI. Subsequently, X-tile software (version 3.6.1, Yale University, New Haven, CT, USA) was employed to determine optimal cut-off values for HGI based on survival outcomes, dividing the cohort into three groups (Figure S1): T1 (≤ -1.26), T2 ($-1.27 \leq$ HGI ≤ 1.73), and T3 (≥ 1.74). X-tile is a bioinformatics tool that identifies statistically optimal cut-points by evaluating all possible divisions of a continuous variable and selecting those that maximize the chi-square value for survival differences [14].

Outcomes

The primary outcomes were hospitalization mortality and 1-year mortality rates. The secondary outcome was the 30-day mortality rate.

Statistical analysis

Patients were divided into three groups based on their HGI values. Baseline characteristics were presented as means (± standard deviation) for normally distributed variables, and medians with interquartile ranges (25th and 75th percentiles) for non-normally distributed data. Categorical variables were expressed as percentages. Fisher's exact test was used to compare categorical data, while the Mann–Whitney U test and unpaired t-test were applied for skewed and normally distributed continuous variables, respectively.

To investigate the relationship between HGI and in-hospital and long-term all-cause mortality, both univariable and multivariable logistical regression model and Cox proportional hazards regression models were used for analysis. Variables that showed significant baseline differences or clinical relevance in both cohorts were incorporated into the final multivariable models. Model 1 was unadjusted; Model 2 was adjusted for age, gender, and race; Model 3 included adjustments for age, gender, race, body mass index (BMI), MI, AF, hypertension, diabetes, and stroke. Model 4 included all variables from Model 3, along with additional factors such as laboratory results and treatments, including hemoglobin, creatinine, ACEI/ARB use, beta-blocker use, insulin use. A restricted cubic spline (RCS) analysis was conducted to assess the association between HGI and all-cause mortality, adjusting for the same variables as in the multivariable models. Odd ratios(OR) and Hazard ratios (HR) with 95% confidence intervals (CI) were used to present the results. To further evaluate the potential of HGI to improve the identification of incident mortality with traditional predictive performance, we calculated the Area Under Curve (AUC).

Subgroup analyses were performed to evaluate the impact of HGI on all-cause mortality in various subgroups, stratified by age, gender, race, BMI, MI, stroke, diabetes. We used sensitivity analyses to increase the confidence in our primary outcome. All statistical analyses were performed using R software (version 4.2.1) and the Free Statistics Analysis Platform (version 2.0). A two-tailed P value < 0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 16,647 critically ill patients with HF were retrieved from the MIMIC IV database, and 13,842 patients were entered into the statistical analysis after exclusion of patients younger than 18 years of age and ICU stay time < 24 h. Then we exclusion of those with missing HbA1c and glucose. Finally, we included 8,098 critically ill patients with HF (Fig. 1). The participants were stratified into three distinct groups (Tertiles 1–3) based on their HGI levels: T1: ≤ -1.26, N = 818, T2: $-1.26 - 1.73$, N = 6445, T3: ≥ 1.74, N = 835. The mean age of the study cohort was 71.1 years, of which 3364 (41.5%) were female and of which 5410 (66.8%) were white.

A comparison of the three groups reveals that T2 has a higher mean age and a higher proportion of white individuals than the other groups. Patients in the T3 groups exhibited a significantly higher incidence of diabetes mellitus, MI, AF, renal failure, and stroke compared to the other three groups ($P < 0.05$). With regard to the severity of disease scores, significant differences were observed across all scores in the T1 groups. Specific baseline data can be found in Table 1.

Primary and secondary outcomes

Mortality rates were significantly higher in the T1 group at all time points compared to the other groups. Specifically, in-hospital mortality rates were 18.6%, 12.3% and 9.7% for the T1, T2, and T3 groups, respectively ($P < 0.001$). The 30-day mortality rates were 21.8%, 16.2% and 13.3%, respectively ($P < 0.001$), and the 1-year

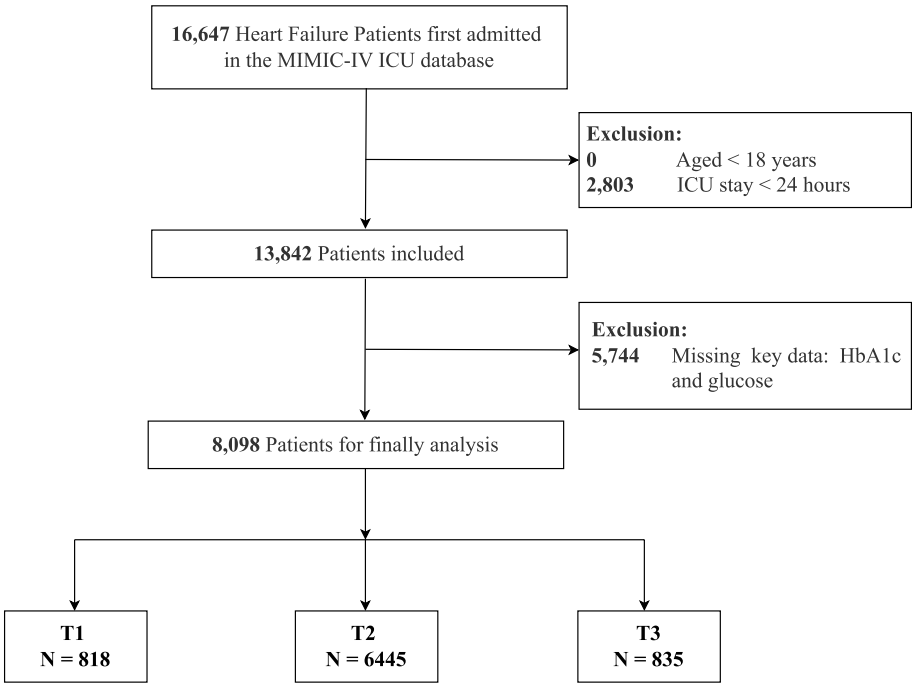

Fig. 1 The flowchart of patients' selection. Abbreviations: ICU, intensive care unit; MIMIC-IV, Medical Information Mart for Intensive Care IV. Note: T1, ≤ − 1.26;, T2: − 1.26 – 1.73; T3: ≥ 1.74

mortality rates were 39.2%,32.1% and 29.3% for the three groups ($P < 0.001$).

As shown in Fig. 2, Kaplan–Meier survival curves revealed significant differences in survival rates between the three HGI groups for both 30-day and 1-year mortality. Patients in the lowest HGI group (T1) had significantly lower survival rates at both 30 days and 1 year compared to those in the higher HGI groups (log-rank $P < 0.05$). However, no significant differences in survival rates were observed among the remaining groups (T1, and T2) at any of the time points.

To further analyze the association between HGI and the outcomes, the logistic regression and Cox proportional hazards model were performed using the T1 as the reference group. In the fully adjusted model, for each unit increase in HGI, the risk of in-hospital all-cause mortality decreased by 12% (OR = 0.88; 95%CI: 0.83–0.93; $P < 0.001$). When divided by groups of HGI and taking T1 as the reference, the risk was lower in T3 (OR = 0.44; 95%CI: 0.32–0.60; $P < 0.001$) (Table 2).

Similarly, in the fully adjusted model, each unit increase in HGI was associated with an 3% decreased risk of 1-year all-cause mortality ($P = 0.028$), with a significantly lower risk observed in T3 ($P = 0.001$). A similar pattern was found for 30-day all-cause mortality, where increased HGI levels were associated with higher mortality rates (Table 3).

The RCS curve analysis demonstrated a nonlinear relationship between HGI and all-cause mortality at both 30-day and 1-year follow-up. Specifically, HGI exhibited a J-shaped association with mortality at both time points (Fig. 3).

Figure S2 shows the discrimination analysis used to evaluate whether HGI could improve the risk stratification of incident mortality events. As we expected, we found that the joint HGI and OASIS model significantly outperformed OASIS alone, demonstrating an incremental prognostic value with a P-value < 0.05.

Subgroup analyses

In addition, we performed risk subgroup analyses of patient outcome events according to age, gender, race, BMI, MI, stroke, and diabetes. Results are presented in Fig. 4 and Figure S3-S4 in the Supplemental Material. For 1-year mortality, no significant interactions were observed between HGI tertiles and any subgroup (all P for interaction > 0.05). Overall, higher HGI levels (T3 vs. T1) were associated with a reduced risk of mortality (HR 0.75, 95% CI 0.63–0.90). This inverse association was consistent across subgroups, with notable effects in participants with BMI < 25 kg/m2 (HR 0.65, 95% CI 0.46–0.90) and those with a history of stroke (HR 0.68, 95% CI 0.47–0.98). Similarly, in participants aged ≥ 65 years (HR 0.78, 95% CI 0.64–0.96), males (HR

Table 1 Baseline characteristics of participants

Variables	Total ($n=8098$)	T1 ($n=818$)	T2 ($n=6445$)	T3 ($n=835$)	*P* value
Demographics					
Age, (year)	71.1(13.1)	68.3 (13.5)	72.0 (13.1)	66.7 (12.2)	< 0.001
Gender female, *n* (%)	3364(41.5)	330 (40.3)	2698 (41.9)	336 (40.2)	0.051
Race, *n* (%)					< 0.001
White	5410 (66.8)	538 (65.8)	4395 (68.2)	477 (57.1)	
Other	2688 (33.2)	280 (34.2)	2050 (31.8)	358 (42.9)	
Vital signs					
BMI, (kg/m^2)	29.7 (7.9)	28.5 (7.6)	29.6 (7.8)	31.8 (8.2)	< 0.001
respiratory rate, (min^{-1})	19.5 (6.7)	20.3 (6.2)	19.4 (6.4)	19.5 (8.9)	< 0.001
Heart rate, (min^{-1})	19.5(6.7)	90.4 (21.7)	86.7 (19.5)	88.2 (19.6)	< 0.001
MBP, (mmHg)	82.2(18.2)	82.4 (19.4)	82.0 (17.8)	83.7 (17.7)	0.032
Scores					
SOFA (score)	5.0 (3.0, 8.0)	7.0 (4.0, 10.0)	5.0 (3.0, 8.0)	5.0 (3.0, 8.0)	< 0.001
SAPSII (score)	47.0 (36.0, 64.0)	55.0 (41.0, 76.0)	46.0 (35.0, 62.0)	48.0 (37.0, 64.0)	< 0.001
OASIS (score)	33.1 (9.0)	35.2 (9.6)	32.9 (8.9)	32.4 (8.8)	< 0.001
Co-morbidities, *n* (%)					
Hypertension	7229 (89.3)	716 (87.5)	5734 (89)	779 (93.3)	< 0.001
Myocardial infarction	2960 (36.6)	306 (37.4)	2269 (35.2)	385 (46.1)	< 0.001
Stroke	1489 (18.4)	114 (13.9)	1209 (18.8)	166 (19.9)	0.002
Atrial fibrillation	4717 (58.2)	465 (56.8)	3868 (60)	384 (46)	< 0.001
COPD	2723 (33.6)	267 (32.6)	2200 (34.1)	256 (30.7)	0.111
Renal failure	3288 (40.6)	370 (45.2)	2514 (39)	404 (48.4)	< 0.001
Sepsis	4377 (54.1)	517 (63.2)	3433 (53.3)	427 (51.1)	< 0.001
Diabetes	3915 (48.3)	279 (34.1)	2827 (43.9)	809 (96.9)	< 0.001
Laboratory tests					
Glucose, (mg/ml)	130.0 (107.0, 172.8)	99.0 (86.0, 117.0)	115.0 (104.0, 130.0)	137.0 (123.0, 160.0)	< 0.001
HbA1c,(%)	6.5 (1.6)	5.2 (0.8)	6.2 (0.9)	10.0 (1.7)	< 0.001
Hemoglobin, (g/dl)	10.2 (2.3)	9.9 (2.5)	10.3(2.3)	10.4 (2.3)	< 0.001
WBC, (K/μL)	10.9 (7.9, 15.0)	11.6 (8.0, 16.6)	10.8 (7.9, 14.8)	11.0 (8.1, 15.3)	< 0.001
Platelet, (K/μL)	187.0 (138.0, 252.0)	181.0 (126.0, 252.8)	185.0 (138.0, 250.0)	203.0 (153.5, 263.0)	< 0.001
Potassium, (mmol/L)	4.3 (0.8)	4.4 (0.8)	4.3 (0.7)	4.3 (0.7)	< 0.001
Sodium, (mmol/L)	138.2 (5.2)	137.3 (5.7)	138.3 (5.1)	138.0 (5.3)	< 0.001
Chloride, (mmol/L)	102.7 (6.9)	101.5 (7.2)	102.9 (6.8)	102.0 (6.8)	< 0.001
Creatinine, (mg/dl)	1.2 (0.9, 1.9)	1.4 (1.0, 2.5)	1.2 (0.9, 1.8)	1.3 (1.0, 2.1)	< 0.001
BUN, (mg/dl)	25.0 (17.0, 41.0)	27.0 (18.0, 45.0)	24.0 (17.0, 40.0)	27.0 (18.0, 44.0)	< 0.001
ALT, (U/L)	24.0 (15.0, 51.0)	25.0 (15.0, 64.0)	24.0 (15.0, 50.0)	25.0 (15.0, 48.0)	0.136
Albumin, (g/dl)	3.4 (0.7)	3.3 (0.7)	3.5 (0.7)	3.4 (0.6)	< 0.001
PT (s)	14.9 (13.0, 17.8)	14.7 (12.7, 18.4)	14.9 (13.0, 17.8)	14.3 (12.6, 17.1)	< 0.001
Treatments, *n* (%)					
ACEI/ARB	1865 (23.0)	156 (19.1)	1495 (23.2)	214 (25.6)	0.005
Beta-blockers	6030 (74.5)	570 (69.7)	4828 (74.9)	632 (75.7)	0.004
Statin	5351 (66.1)	503 (61.5)	4218 (65.4)	630 (75.4)	< 0.001
Anti-platelet	5590 (69.0)	551 (67.4)	4430 (68.7)	609 (72.9)	0.026
Diuretics	6413 (79.2)	617 (75.4)	5119 (79.4)	677 (81.1)	0.011
Digoxin	696 (8.6)	55 (6.7)	578 (9)	63 (7.5)	0.051
CCB	2430 (30.0)	252 (30.8)	1891 (29.3)	287 (34.4)	0.010
OACs	2195 (27.1)	193 (23.6)	1799 (27.9)	203 (24.3)	0.005
Insulin	5887 (72.7)	545 (66.6)	4545 (70.5)	797 (95.4)	< 0.001
Mortality, *n* (%)					
In-hospital	1028 (12.7)	152 (18.6)	795 (12.3)	81 (9.7)	< 0.001
30-days	1335 (16.5)	178 (21.8)	1046 (16.2)	111 (13.3)	< 0.001
1-year	2634 (32.5)	321 (39.2)	2068 (32.1)	245 (29.3)	< 0.001

Abbreviations: *BMI* Body mass index, *MBP* Mean blood pressure, *SOFA* Sequential organ failure assessment, *COPD* Chronic obstructive pulmonary disease, *WBC* White blood cell, *BUN* Blood urea nitrogen, *ALT* Alanine aminotransferase, *PT* Prothrombin time, *ACEI/ARB* Angiotensin converting enzyme inhibitors/angiotension receptor antagonists, *CCB* Calcium channel blocker, *OACs* oral anticoagulation medications

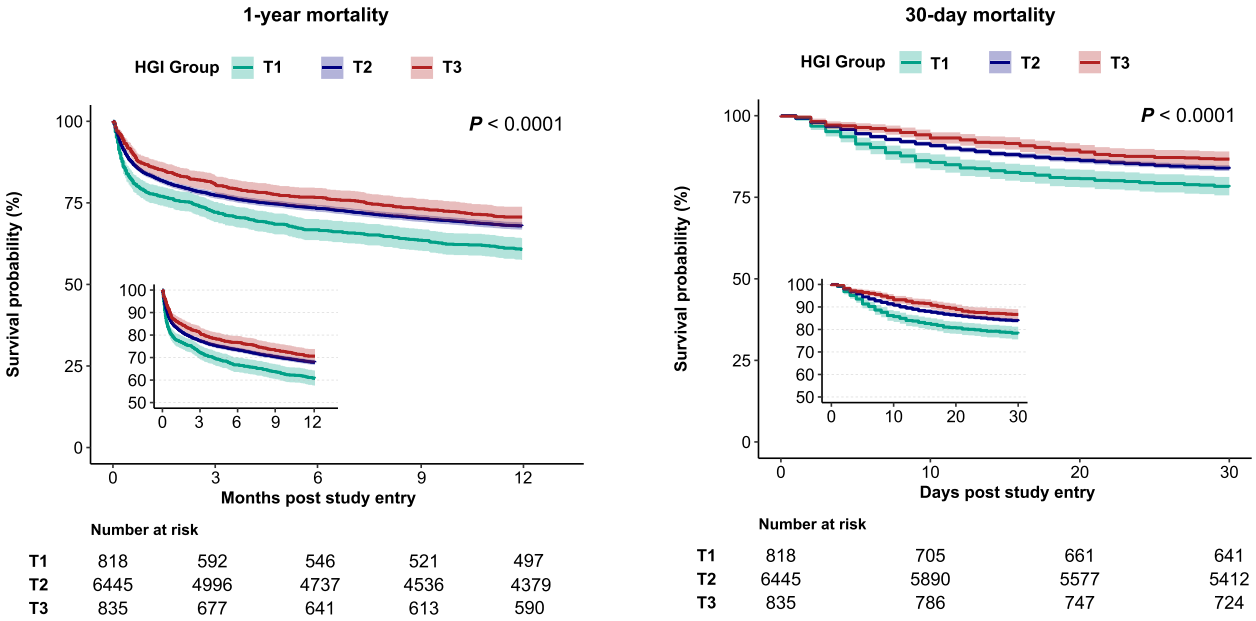

Fig. 2 Kaplan–Meier analyses for different endpoints among the three group. Note: left, 1-year mortality; right, 30-day mortality

Table 2 Associations between HGI and in-hospital mortality in the Logistic regression model

	Model 1		Model 2		Model 3		Model 4	
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
HGI	0.91 (0.87~0.96)	<0.001	0.91 (0.87~0.96)	0.001	0.85 (0.81~0.9)	<0.001	0.88 (0.83~0.93)	<0.001
HGI **tertiles**								
T1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
T2	0.62 (0.51~0.75)	<0.001	0.56 (0.46~0.68)	<0.001	0.54 (0.45~0.66)	<0.001	0.66 (0.54~0.82)	<0.001
T3	0.47 (0.35~0.63)	<0.001	0.47 (0.35~0.63)	<0.001	0.37 (0.27~0.51)	<0.001	0.44 (0.32~0.60)	<0.001

Abbreviations: *HGI* Hemoglobin glycation index, *OR* Odds ratio, *CI* Confidence interval, *HR* Hazard ratio, *Ref* Reference

Stands for HGI were continuous variable per 1 unit

Model 1 adjusted for: none;

Model 2 adjusted for: covariates included in demographics;

Model 3 adjusted for: model 2 + covariates included in vital signs and comorbidities;

Model 4 adjusted for: model 3 + covariates included in laboratory tests and treatments

0.74, 95% CI 0.59–0.94), and those without MI (HR 0.73, 95% CI 0.58–0.92), T3 showed a lower mortality risk compared to T1. For 30-day and in-hospital mortality, the associations with HGI were broadly similar to those for 1-year mortality, with no significant interactions across subgroups (all P for interaction > 0.05). Higher HGI levels (T3) were linked to reduced 30-day mortality (HR 0.60, 95% CI 0.47–0.76) and in-hospital mortality (OR 0.44, 95% CI 0.32–0.60), with consistent effects across strata.

Sensitivity analysis

We conducted sensitivity analyses by separately excluding missing data, diagnosed sepsis, and diagnosed hepatic impairment, yielding 1-year mortality HRs for T2 and T3 of 0.82 and 0.71, 0.67 and 0.73, 0.86 and 0.80, respectively, consistent with the primary analysis. This suggests that data imputation, sepsis, and hepatic impairment have limited impact, and the results remain robust (Fig. 5).

Discussion

This retrospective study, involving 8,098 critically ill HF patients from the MIMIC-IV database, represents one of the first comprehensive evaluations of the relationship between the HGI and mortality outcomes. In this large-scale cohort study, the HGI showed a J-shaped correlation with the first 1-year mortality risk after adjustment

Table 3 Associations between HGI and 30-days, 1-year mortality in the Cox regression model

	Model 1		Model 2		Model 3	Model 3	Model 4	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
30-day mortality								
HGI	0.93 (0.89 ~ 0.97)	< 0.001	0.94 (0.90 ~ 0.98)	0.004	0.89 (0.85 ~ 0.93)	< 0.001	0.92 (0.88 ~ 0.96)	< 0.001
HGI **tertiles**								
T1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
T2	0.71 (0.61 ~ 0.84)	< 0.001	0.63 (0.54 ~ 0.74)	< 0.001	0.62 (0.53 ~ 0.73)	< 0.001	0.75 (0.64 ~ 0.88)	< 0.001
T3	0.57 (0.45 ~ 0.73)	< 0.001	0.59 (0.47 ~ 0.75)	< 0.001	0.49 (0.39 ~ 0.63)	< 0.001	0.60 (0.47 ~ 0.76)	< 0.001
1-year mortality								
HGI	0.96 (0.94 ~ 0.99)	0.01	0.98 (0.95 ~ 1.01)	0.211	0.93 (0.9 ~ 0.96)	< 0.001	0.97 (0.94 ~ 1.00)	0.028
HGI **tertiles**								
T1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
T2	0.77 (0.68 ~ 0.87)	< 0.001	0.68 (0.61 ~ 0.77)	< 0.001	0.67 (0.59 ~ 0.75)	< 0.001	0.82 (0.73 ~ 0.92)	0.001
T3	0.68 (0.58 ~ 0.81)	< 0.001	0.72 (0.61 ~ 0.85)	< 0.001	0.59 (0.5 ~ 0.71)	< 0.001	0.75 (0.63 ~ 0.90)	0.001

Abbreviations: *HGI* Hemoglobin glycation index, *HR* Hazard ratio, *CI* Confidence interval, *Ref* Reference

Stands for HGI index were continuous variable per 1 unit

Model 1 adjusted for: none;

Model 2 adjusted for: covariates included in demographics;

Model 3 adjusted for: model 2 + covariates included in vital signs and comorbidities;

Model 4 adjusted for: model 3 + covariates included in laboratory tests and treatments

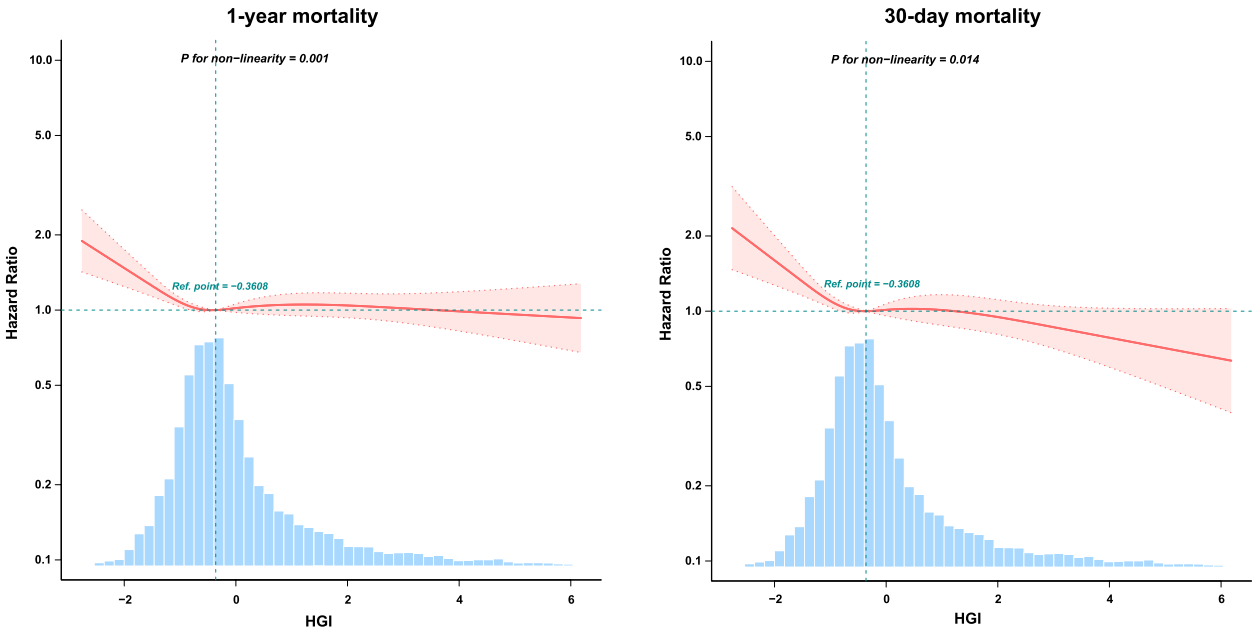

Fig. 3 Dose–response relationship between the HGI and all-cause mortality in patients with heart failure. Note: Adjusted for covariates included in demographics, vital signs, comorbidities, laboratory tests and treatments. Solid and dashed lines indicate the predicted value and 95% CI. left, 1-year mortality; right, 30-day mortality

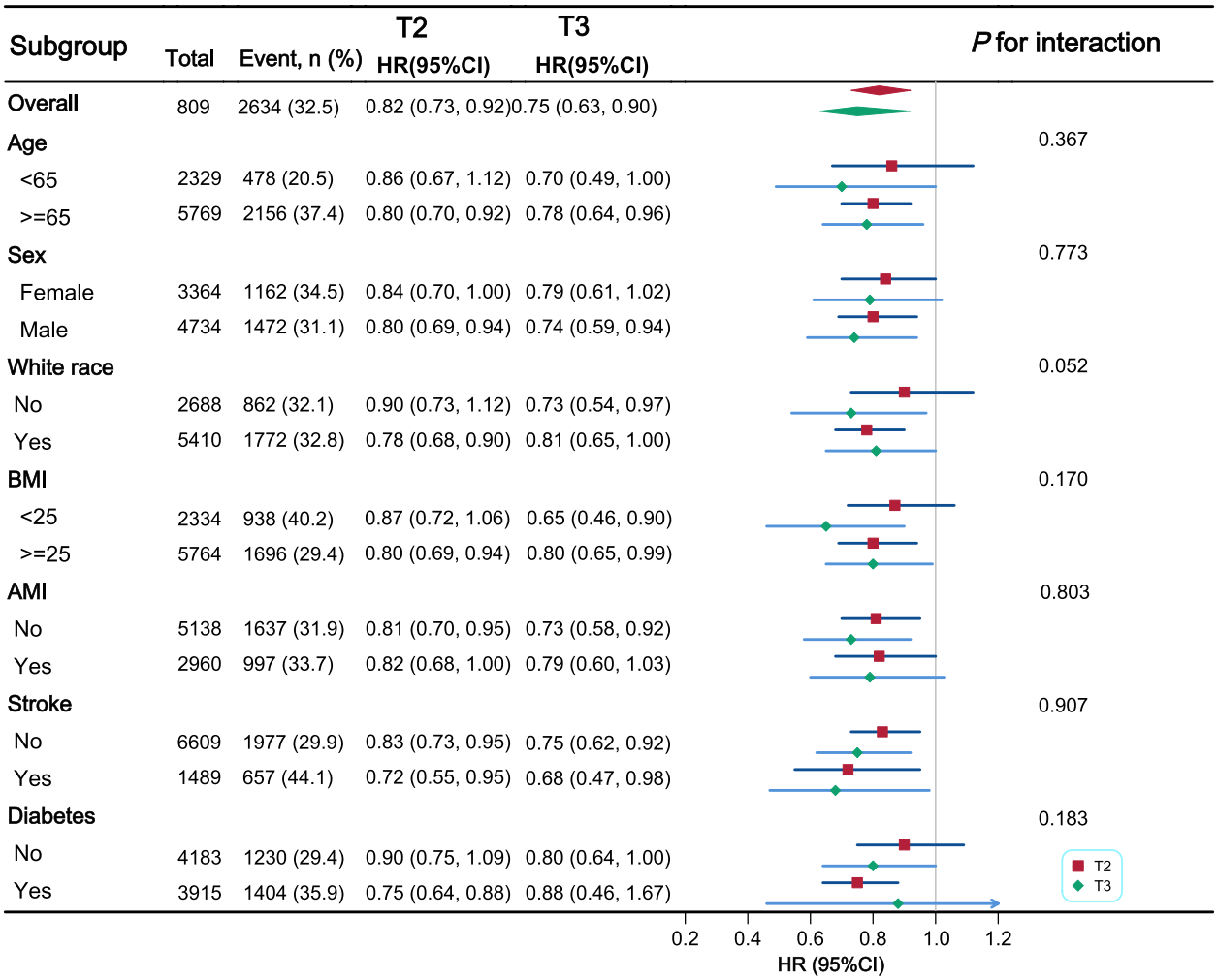

Fig. 4 Forest plot of subgroup analysis for 1-year mortality. Abbreviations: OR, odd ratio; CI, confidence interval; BMI, body mass index; MI, myocardial infarction. Note: T1 as reference group. Adjusted for covariates included in demographics, vital signs, comorbidities, laboratory tests and treatments

for covariates including age, gender, race, BMI, MI, AF, hypertension, diabetes, stroke, hemoglobin, creatinine, ACEI/ARB use, beta-blocker use, insulin use. The 1-year mortality risk increased as HGI decreased, with a more pronounced effect observed at lower HGI levels.

The ECS and ACC guidelines emphasize that a critical aspect of HF management is monitoring blood glucose control [1, 15]. Traditionally, glucose metabolism has been assessed using FPG and HbA1c, which evaluate short-term and long-term glycemic control, respectively [16, 17]. However, HbA1c may not fully reflect individual variations, particularly when factors such as red blood cell lifespan, hemoglobin glycation ability, or genetic differences are present [18–20]. In such cases, the measured HbA1c may deviate from the theoretical value predicted by average blood glucose. Therefore, Hempe et al. first introduced the concept of the HGI by assessing the average blood glucose and HbA1c levels in 128 children and adolescents with type 1 diabetes [21]. The HGI quantifies this deviation by subtracting the HbA1c predicted from FPG-based linear regression from the observed HbA1c, thereby providing insight into individualized glycation patterns [9].

Multiple studies have confirmed that HGI is suitable for evaluating the incident risk and outcomes prognosis of various chronic diseases [9, 21–23], especially for DM-related complications, and could act as a predictive indicator of intensive hypoglycemic-strategy-related adverse reactions [24]. Previous research on the relationship between HGI and cardiovascular or all-cause mortality has largely focused on the notion that a higher HGI is associated with a worse prognosis [25–27]. A study involving 2,934 individuals from a Chinese population found that HGI is associated with the incidence of stroke,

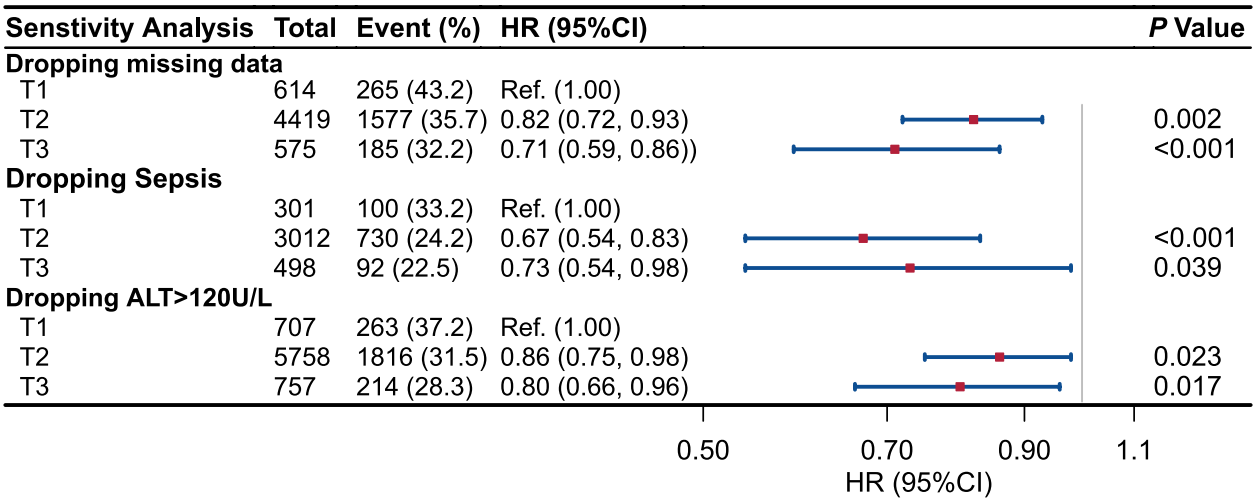

Fig. 5 Sensitivity analysis for 1-year mortality. Abbreviations: HR, hazard ratio; CI, confidence interval; Ref., reference. Note: Adjusted for covariates included in demographics, vital signs, comorbidities, laboratory tests and treatments

with a higher HGI linked to an increased risk of stroke [25]. Similarly, a randomized controlled trial focusing on diabetic patients demonstrated a strong association between high HGI and adverse cardiovascular events [26]. These studies linked high HGI to stroke and cardiovascular events in chronic populations, emphasizing glycation and glucose variability over long-term follow-up, unlike our acute ICU-based HF cohort where low HGI predominates due to metabolic stress and malnutrition. Mechanistically, a high HGI often indicates that HbA1c significantly exceeds what can be explained by blood glucose levels alone [9]. This suggests that the patient may have a higher susceptibility to glycation, potentially accompanied by more persistent or fluctuating blood glucose levels and an inflammatory state [27–29].

However, some researchers have also observed that low HGI may be associated with poor outcomes in certain populations [30–32]. For instance, in the REACTION cohort, low HGI was associated with increased chronic cardiovascular event risk in a general population [30], while an analysis of 5,260 high-risk coronary artery disease patients from MIMIC showed higher long-term mortality with low HGI [31]. Similarly, Cheng et al. [33] reported in 1,531 acute decompensated heart failure ADHF patients that the lowest HGI tertile had higher all-cause (28.2%) and cardiovascular mortality (17.1%) than the highest tertile. Our study aligns with these findings, demonstrating in 8,098 critically ill HF patients from MIMIC-IV that the lowest HGI tertile had elevated in-hospital mortality (18.6%) compared to the highest, with greater disease severity (SOFA: 5.2 vs. 4.8) and malnutrition (albumin: 3.3 g/dL vs. 3.4 g/dL) in T1 (Table 1). Unlike the REACTION and MIMIC studies focusing on general populations or chronic outcomes, we targeted acute HF in ICU patients; compared to Cheng et al.'s negative linear trend, our J-shaped relationship underscores unique risks at extremely low HGI in critical care. These differences highlight HGI's prognostic versatility across populations and HF severities.

The analysis in this study not only confirms a significant association between HGI values and adverse outcomes in heart failure patients, but also highlights the need for increased attention to patients with extremely low HGI levels. From a mechanistic perspective, a very low HGI may indicate significant metabolic disturbances or reduced red blood cell lifespan, which could lead to HbA1c inaccurately reflecting blood glucose control [34, 35]. Additionally, stress hyperglycemia could also potentially contribute to numerically high FPG and then low HGI [32]. Stress hyperglycemia may exist after onset of stroke and deteriorate the outcome of HF. In critically ill HF patients, this may be further influenced by factors such as increased inflammation, malnutrition, and multi-organ dysfunction, which together increase the risk of mortality [36, 37]. In our study, we also found that the low HGI group was often associated with lower BMI, lower blood glucose levels, hemoglobin levels, and albumin levels, as well as higher creatinine levels (Table 1). Similarly, our stratified analysis also showed that patients with comorbid diabetes, advanced age, or abnormal BMI exhibited differential survival outcomes at different HGI levels. This supports the notion raised in previous literature that HGI can be used to identify high-risk subgroups and assist in determining individualized treatment strategies.

In addition, we observed a higher proportion of Whites in the T2 group (68.2%) compared to T1 (65.8%) and T3

(57.1%) (Table 1, $P < 0.001$), aligning with its intermediate HGI range ($-1.26 < HGI < 1.74$) and mortality outcomes in our J-shaped association. This racial distribution may reflect genetic influences on HGI and heart failure prognosis. Whites often exhibit lower HbA1c relative to glucose levels, potentially due to polymorphisms in genes like G6PD, which modulates red cell oxidative stress, altering hemoglobin structure, and SLC4A1, affecting glycation rates, all more prevalent in European ancestry [38].

Clinically, relying solely on HbA1c or short-term blood glucose levels may not fully assess the true metabolic status of critically ill patients [20]. Using HGI as a supplementary measure can help identify potential high-risk groups that may be overlooked in routine glucose monitoring. It is recommended that HGI be integrated into routine assessments, especially for patients with fluctuating glucose levels, to optimize individualized treatment strategies and improve prognosis. Additionally, incorporating HGI into predictive models may enhance the accuracy of risk stratification, aiding in the early identification of metabolic imbalances and guiding timely interventions to reduce complications. Regarding the findings of this study, clinicians should be particularly attentive to extreme cases: when HGI is markedly low, it is important to consider whether the patient has nutritional metabolic issues, anemia, or other hidden risks. Furthermore, risk stratification based on HGI could be combined with other clinical scores (OASIS, SOFA, SAPS III) to provide additional decision support for the comprehensive management of critically ill heart failure patients.

Of course, this study has several limitations. First, as a retrospective single-center database study, although multiple confounding factors were adjusted for, potential bias cannot be completely eliminated. Second, the HGI was calculated only using admission or early data, which does not reflect the dynamic changes of HGI throughout the hospitalization or during long-term follow-up. Third, the impact of acute stress on FPG, HbA1c, and red blood cell metabolism cannot be ignored, especially in critically ill patients, where various interfering factors such as infections, inflammation, blood transfusions, and hormonal fluctuations may play a role. Finally, the study primarily focuses on all-cause mortality as the outcome, and lacks in-depth analysis of cardiovascular-specific mortality or other endpoints, such as readmission rates and complications. Future studies could further explore these aspects in larger populations or with longer follow-up periods.

Conclusion

In this large-scale retrospective study of critically ill heart failure patients from the MIMIC-IV database, we demonstrated that the HGI is significantly associated with all-cause mortality. Specifically, a J-shaped relationship was observed between HGI and mortality. Patients with extremely low HGI levels exhibited the highest risk, highlighting the potential impact of metabolic disturbances, inflammation, or malnutrition on mortality in this population. HGI may serve as a valuable supplementary marker for risk stratification and prognosis in this population. Future studies are needed to validate these findings and explore the mechanisms linking HGI to mortality, as well as its potential role in guiding individualized treatment strategies.

Abbreviations

HF	Heart failure
ICUs	Intensive care units
HbA1c	Glycated hemoglobin
HGI	Hemoglobin glycation index
MIMIC-IV	Medical Information Mart for Intensive Care IV
SOFA	Sequential Organ Failure Assessment
SAPS II	Simplified Acute Physiology Score II
MBP	Mean arterial blood pressure
WBC	White blood cell count
AF	Atrial fibrillation
COPD	Chronic obstructive pulmonary disease
MI	Myocardial infarction
ACEI	Angiotensin-converting enzyme inhibitors
ARB	Angiotensin receptor blockers
CCB	Calcium channel blockers
RCS	Restricted cubic spline
FPG	Fasting blood glucose
OR	Odd ratios
HR	Hazard ratios
CI	Confidence intervals

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Authors' contributions

Y.W. contributed to the conception and design of the study , S.T. and H.L. are responsible for data analysis, results visualization, and manuscript writing, Y.L. provided professional advice for the revision of the manuscript, Y.L. were responsible for the review and revision of the manuscript and the funding of the study. All contributors had unrestricted access to the data and collectively assumed responsibility for the accuracy and integrity of the information.
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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the guidelines of the Helsinki Declaration. The MIMIC-IV database was supported by grants from the National Institute of Biomedical Imaging and Bioengineering (NIBIB) of the National Institutes of Health (NIH) under award numbers R01-EB001659 (2003–2013) and R01-EB017205 (2014–2022) and approved by the Institutional Review Boards of Beth Israel Deaconess Medical Center (Boston, MA) and the Massachusetts Institute of Technology (Cambridge, MA). As the data

are publicly available (in the MIMIC-IV), the ethical approval and requirement for informed consent were waived for this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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