Synergistic Predictive Value of Dynamic Glycemic Trajectories and Variability Metrics for 28-Day Mortality in Critically Ill Heart Failure

Ping-yu Cai[1*], Wei-ze Lin[2*], Shu-han Chen[1*], Shi-hong Lin[3], Bao-ya Yang[4], Jun-han Chen[5#], Hui-li Lin[1#]

[1]Department of Cardiology, the Second Affiliated Hospital of Fujian Medical University, Quanzhou, Fujian Province, China

[2]Department of Cardiology, Fuzhou University Affiliated Provincial Hospital, Fuzhou, Fujian, China.

[3]Department of Emergency, the Second Affiliated Hospital of Fujian Medical University, Quanzhou, Fujian, China

[4]Department of Neurosurgery, the Second Affiliated Hospital of Fujian Medical University, Quanzhou, Fujian, China

[5]Cardiac Function Room, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, Fuzhou, Fujian, China

* These authors contributed equally to this work

Correspondence:

Hui-li Lin

Department of Cardiology, the Second Affiliated Hospital of Fujian Medical University, Quanzhou, Fujian Province, China

E-mail: 1627974150@qq.com

Jun-han Chen

Cardiac Function Room, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, Fuzhou, Fujian, China

E-mail: joyc9508@163.com

Abstract

Background: Glucose dynamics is one of the unique mechanisms in patients with critically ill heart failure (HF). The aim of this study is to evaluate the impact of dynamic blood glucose trajectories on 28-day mortality in critically ill HF patients.

Methods: Latent Category Growth Model (LCGM) was used to classify patients' blood glucose trajectories during the first 4 days of intensive care unit (ICU) admission. Kaplan-Meier survival analysis and Cox regression assessed the association between admission blood glucose levels, glucose trajectories, and 28-day mortality in critically ill HF patients. Subgroup analyses evaluated the robustness of the findings.

Results: A total of 6062 patients with critically ill HF were included in this retrospective cohort study, with 28-day mortality occurring in 1306 (21.54%) patients. The Kaplan Meier survival curve shows that the survival probabilities of different blood glucose trajectories from high to low are: class 1>class 3>class 2>class 4, and there are significant inter class differences. COX regression confirms that the predictive ability of blood glucose trajectory classification for mortality in patients with critically ill HF is superior to the blood glucose coefficient of variation. Subgroup analysis further evaluated the consistency of the association between blood glucose latent trajectory classification and 28-day mortality in different patient characteristics.

Conclusions: Dynamic blood glucose trajectories and variability indicators provide complementary information for predicting 28-day mortality in critically ill HF patients.

Keywords Critically ill heart failure, Blood glucose, Trajectory, 28-day mortality

Introduction

Heart failure (HF) is a deadly disease with a mortality rate comparable to cancer. Taking the Framingham study as an example, the five-year mortality rate of diagnosed patients is as high as 62% - 75% in males and 38% -42% in females, while the five-year survival rate of cancer patients in the United States during the same period is about 50% [1]. Despite the approval of numerous novel pharmacological therapies for HF in recent years, patient outcomes remain poor with persistently high incidence and mortality rates [2]. The situation is particularly dire for ICU patients, underscoring the urgent need for effective prognostic markers in clinical practice. Glucose dysregulation is common in critically ill patients, but results of previous trials on glycemic control have been controversial [3]. Previous studies have shown an association between blood glucose variability (GV) and critical illness prognosis, such as GV being an important predictor of short-term, medium-term, and long-term all-cause mortality in ICU patients with atrial fibrillation [4]. However, traditional indicators such as average blood glucose and GV may overlook the dynamic patterns of blood glucose changes, such as rising/falling trends and fluctuation frequency. Time dependent data, such as dynamic blood glucose trajectories, may provide more comprehensive pathophysiological information and become better predictive indicators.

Blood glucose fluctuations may cause more severe damage to the cardiovascular system than sustained glucose elevation, and their triggering effect on oxidative stress is more direct than chronic sustained glucose elevation [5]. In ICU, the blood glucose fluctuations of critically ill patients are particularly significant, which is mainly related to stress hormone secretion, overactivation of the

sympathetic nervous system, insulin resistance, and treatment interventions [6,7]. Previous studies have found a correlation between changes in blood glucose levels and the risk of 30-day mortality in patients with acute ischemic stroke [8]. Patients with continuously elevated blood glucose levels within 24 hours of admission have a significantly increased risk of 30-day mortality. The study found that the dynamic change of blood glucose within 24 hours of admission to the ICU was significantly related to the 30-day mortality rate of acute myocardial infarction (AMI) patients with diabetes mellitus (DM) [9]. The low average blood glucose level when admitted to the ICU or the rapid reduction of blood glucose to normal level through appropriate measures within 24 hours after admission to the ICU may be beneficial to reduce the 30-day mortality risk of AMI patients with DM [9].

However, the correlation between changes in blood glucose levels and the prognosis of patients with critically ill HF is still unclear. Here, this study aims to explore the correlation between the short-term longitudinal trajectory of blood glucose and 28-day mortality in this population, and compare the predictive efficacy of dynamic blood glucose trajectory and traditional GV indicators for 28-day mortality.

Methods

Data source and study design

This study utilized the Medical Information Mart for Intensive Care IV (MIMIC-IV) database (version 3.1). This publicly available database contains de-identified clinical data from over 190,000 adult patients admitted to the ICUs at Beth Israel Deaconess Medical Center between 2008 and 2019. As the institutional review boards of the Massachusetts Institute of Technology and Beth Israel

Deaconess Medical Center approved the establishment of the MIMIC-IV database for public research use and granted a waiver of informed consent requirement due to the de-identified nature of the data, obtaining additional informed consent for this study was not required.

This study focused on a study population in MIMIC-IV consisting of 6,656 individuals who were diagnosed with HF and non-consecutively admitted to the ICU. For patients with multiple ICU admissions, only data from their first eligible ICU admission were included. Patients were excluded based on the following criteria: ① Age less than 18 years or greater than 100 years; ②ICU length of stay (LOS) less than 4 days; ③Insufficient daily blood glucose data within 4 days after ICU admission; ④Lack of prognostic indicators for death. The patient selection flowchart is presented in Figure 1.

Data collection

Data extraction was performed using PostgreSQL (version 16.3) and Navicat Premium (version 17). The following patient data were extracted: demographic characteristics, vital signs, severity of illness scores, laboratory parameters, interventions and treatments, comorbidities and mortality outcomes. For vital signs, laboratory parameters, and severity of illness scores, the first recorded measurement within 24 hours of ICU admission was extracted. Variables exhibiting missing values for more than 20% of the study population were excluded from the analysis. For variables with missing rates below 20%, multiple imputation was employed to handle the missing data. We performed multiple imputation using the Multiple Imputation by Chained Equations (MICE) approach. The number of imputed datasets was specified as 10, and model

convergence was confirmed by examining diagnostic iteration history plots.

Definitions

Stress hyperglycemia was defined as a transient elevation of blood glucose in non diabetic patients. Operationally, it was identified as having at least one blood glucose measurement exceeding 180 mg/dL (10 mmol/L) within the first 24 hours following ICU admission.

Blood glucose measurement

Blood glucose data were collected as point-of-care testing measurements. Each patient underwent blood glucose monitoring at least once per day. This approach was adopted to avoid the natural exclusion of patients with well-controlled glucose who did not require frequent monitoring. The daily mean glucose value, calculated from all measurements on the same day, was used for trajectory analysis. We note that POCT devices were hospital-grade systems operating under strict institutional quality control protocols.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation or median (interquartile range), and comparisons were made using the Student's T-test (for normally distributed data) or Mann-Whitney U-test (for non-normally distributed data). Categorical variables were expressed as numbers (percentages) and analyzed using the chi-square test or Fisher’s exact test.

Latent Class Growth Modeling (LCGM) was applied to model blood glucose trajectories. The maximum number of iterations was set to 500, with a convergence criterion requiring the absolute change in the log-likelihood value during the final iterations to be less than 1×10^{-6}. We fitted LCGM models ranging from 1 to 6 latent

classes to determine the optimal number of classes. Model selection was based on the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), sample-size adjusted BIC (SABIC), and entropy. To confirm model adequacy, we ensured that the average posterior probability for all assigned classes exceeded 70%. Furthermore, model stability was maintained by requiring each identified class to comprise more than 3% of the overall cohort.

Kaplan-Meier survival curves were generated to assess the impact of four trajectory classes and glycemic variability coefficient quartiles on all-cause mortality at 28 days, with between-group differences evaluated using the log-rank test. Use Least Absolute Shrinkage and Selection Operator (LASSO) regression to screen potential candidates. Using univariate and multivariate Cox proportional hazards regression models to compare the predictive power of four trajectory classes and glycemic variability coefficient quartiles for mortality. The proportional hazards assumption was validated using Schoenfeld residual tests (P=0.16). The linearity assumption for continuous variables was tested using restricted cubic splines, and multicollinearity was assessed by calculating variance inflation factors (Table S1). All variance inflation factors were below 5. Subgroup analyses were performed to confirm the robustness of the findings. Finally, after handling missing data using mean imputation, we repeated the Cox regression analysis to evaluate the impact of the imputation strategy. Statistical analyses were performed using R statistical software (version 4.2.1; R Foundation, Vienna, Austria). A two-sided P-value of less than 0.05 was considered statistically significant.

Results

Baseline characteristics of the study population

A total of 6062 patients with critically ill HF were included (Figure1). The mean age was 73.48 years, and males accounted for 57.67%. 1306 patients (21.54%) died within 28 days. Their characteristics are shown in Table 1.

Identification of subpopulations

As shown in Table 2, this study fitted a LCGM ranging from 1 to 6 categories, and selected the optimal trajectory classification number based on multiple statistical indicators and clinical interpretability. The four types of models perform the best in key information criteria (BIC=250962.90; SABIC=250924.77; both are the lowest values), and the high entropy value of 0.89 indicates good classification certainty. In contrast, although the AIC of the five models is slightly lower, the significant increase in BIC and SABIC suggests a risk of overfitting, and the entropy value also drops to 0.85. In addition, considering clinical interpretability, we ultimately chose four types of models. Class 1 (Low glucose stratum): 129.11± 33.07 mg/dL,slowly decreasing, accounting for the largest proportion of patients (75.5%); Class 2 (Moderate glucose stratum): 179.88 ± 42.64 mg/dL,slowly increasing, accounting for 16% of patients; Class 3 (High glucose stratum): 297.17 ± 64.09 mg/dL,rapidly decreasing, accounting for 4.4% of patients.; Class 4 (High glucose stratum): 246.27 ± 70.26 mg/dL, gradually increasing, accounting for the smallest proportion of patients (4.1%) (Figure 2). Table S2 displays the baseline features of four potential categories.

In addition, we divided the population into four groups based on the quartiles of GV. The baseline characteristics are shown in Table S3. Comparing the age, ICU LOS, drugs, SIRS, LODS, vasoactive drug, ventilator, OASIS score and APS-III score, insulin, and

comorbidities among the four groups, significant differences were observed between the clusters for most variables. There was also a significant difference between mortalities at day 28 in the four trajectories.

Kaplan-Meier analysis stratified by latent trajectory classes and glycemic variability coefficient quartiles

The Kaplan Meier survival curve shows that the survival probability of different blood glucose trajectories, from high to low, is: class 1>class 3>class 2>class 4, and there is a significant inter class difference ($p<0.0001$) (Figure 3A). In addition, as the GV level increases, the survival probability gradually decreases (Figure 3B). The risk table below the curve presents the number of remaining patients in each group at 0, 10, 20, and 28 days. Although both blood glucose trajectory classification and GV quartiles can significantly stratify survival risk ($P<0.0001$), the degree of separation between blood glucose trajectory curves is greater. This usually means that there are greater differences between groups.

Comparison of Glycemic Trajectory Classification and Glycemic Variability Coefficient in Predicting 28-Days Mortality

Firstly, we conducted LASSO regression screening on 39 candidate factors (including blood glucose trajectory classification and quartiles of blood glucose coefficient of variation grouping) (Figure 4). The LASSO variable selection process retained 21 variables for the subsequent Cox model. These were: age, ICU LOS, glycemic trajectory classes, temperature, respiratory rate, SBP, SPO2, LODS, SIRS, APS-III, OASIS, WBC, BUN, PTT, PT, malignant cancer, severe liver disease, cerebrovascular disease, hypertension, diabetes, and vasoactive drug use (Table S4).

In order to further compare the predictive performance of blood glucose trajectory classification and quartiles grouping of blood glucose coefficient of variation on mortality, we constructed three COX regression models for comparison (Table S5). Model 1 adjusted the quartiles of blood glucose coefficient of variation grouping and the important variables screened by LASSO mentioned above (except for blood glucose trajectory classification). Model 2 adjusted all important variables screened by LASSO, including blood glucose trajectory classification. Model 3 adjusted for blood glucose trajectory classification, quartiles grouping of blood glucose coefficient of variation, and other important variables screened by LASSO. Firstly, we calculated the information entropy of three regression models. The results showed that Model 2 had the smallest AIC and BIC values, suggesting that Model 2 may be the optimal model. At the same time, we also conducted a likelihood ratio test. The results showed that compared to Model 1, Model 2 had a larger log Likelihood (p<0.001). Although Model 3 has the highest log Likelihood, there is no significant difference between it and Model 2 (P=0.18). In addition, the corresponding IDI and NRI values also indicate that Model 2 has better discriminative power than Model 1 (both P<0.05), and there is no significant difference compared to Model 3.

Table 3 shows the univariate Cox regression model and multivariate Cox regression model (i.e. Model 2) based on the classification of blood glucose latent trajectories for 28-day mortality, with Class 1 (lowest mortality rate) as the baseline reference. The results are consistent with K-M analysis. Additionally, following the use of mean imputation to handle missing data, we repeated the Cox

regression analysis, and the results were consistent with the primary analysis (Table S6).

Subgroup analysis

Subgroup analysis aims to evaluate the consistency of the association between blood glucose latent trajectory classification and 28-day mortality in different patient characteristics (Table 4). Although the increased risk of death related to Class 2 and Class 3 (especially Class 4) is common in the subgroups of gender, cerebrovascular disease, kidney disease and hypotension compared with Class 1 (interaction *P* value>0.05), significant effect modification was observed in the subgroups of diabetes status (interaction *P* value<0.001) and insulin use (interaction *P* value=0.048). It is worth noting that there was no significant difference in mortality risk between class 3 and class 1 in the group without insulin use (*P*=0.229); In the insulin group, the risk of death for class 3 was significantly higher than that for class 1 (*P*=0.005).

In addition, we also supplemented the predictive effect of blood glucose coefficient of variation on mortality in patients classified by different blood glucose trajectories (Table S7). Interestingly, in class 3, the higher the coefficient of variation of blood glucose, the lower the risk of death (*P*<0.001). In addition, in class 1, the group with high blood glucose coefficient of variation (Q4) had an increased risk of mortality (*P*=0.002). This compensates for the high mortality risk patients in class 1 (baseline reference group) that are easily overlooked in the prediction.

Discussion

In recent years, the clinical value of dynamic glucose changes, or glucose trajectories, has been increasingly recognized [8,10]. Compared to static measurements like baseline blood glucose,

continuously monitored trends provide a more accurate reflection of real-time metabolic status and have demonstrated superior predictive value [11]. This study is the first to explore the prognostic utility of dynamic glucose trajectories in critically ill HF patients. By analyzing 6,062 such patients from the MIMIC-IV database, we identified four distinct glucose trajectory classes and found significant associations with 28-day mortality. Our findings indicate that dynamic glucose trajectories and variability metrics offer complementary, and in some respects superior, prognostic information compared to traditional static or variability-only metrics.

An intriguing and central finding of our analysis was the differential mortality risk across trajectory classes. Specifically, we observed that the survival probability ranked as Class 1 > Class 3 > Class 2 > Class 4. The superior survival of Class 3 (high but rapidly decreasing glucose) compared to Class 2 (moderate but slowly increasing glucose) is particularly noteworthy. We interpret this to mean that the direction and speed of glucose change carry prognostic information beyond a single glucose value. The rapid decline in Class 3 likely represents a "responsive" phenotype, signaling that aggressive early intervention (e.g., insulin therapy, treatment of the underlying stressor) is effectively controlling a severe initial metabolic insult [9]. This is supported by our data showing near-universal insulin use (96.65%) and higher monitoring frequency in this class. In contrast, the gradual upward trend in Class 2 suggests a "worsening" or "persistently dysregulated" phenotype, indicating ongoing metabolic stress and potentially inadequate treatment response, despite a lower starting glucose level. This interpretation is further nuanced by our finding that, within Class 3, higher glucose variability was paradoxically

associated with lower mortality. This may imply that for patients presenting with markedly elevated glucose levels, the process of active correction—which inherently induces variability—is a marker of therapeutic engagement and physiological reserve, rather than a detrimental sign.

It is important to contextualize these findings within our study cohort, which included a significant proportion of patients with pre-existing diabetes. This reflects the real-world clinical setting of HF, where diabetes is a prevalent comorbidity. Our expanded discussion acknowledges that the pathophysiology linking glucose to outcomes may differ between acute stress-induced dysregulation and chronic glucose elevation. The stratified analyses reinforce that the prognostic signal of glucose dynamics is particularly strong in non-diabetic patients, while in diabetic patients, the relationship is modulated by chronic disease and its management. This does not diminish the value of our findings but rather highlights that glucose trajectory is a versatile marker whose interpretation benefits from clinical context.

Our results align with and extend the existing literature on glycemic control in critical illness. Glucose variability (GV) has been established as an independent risk factor for adverse outcomes in ICU populations, including those with cardiovascular disease [4,18,22,23]. GV is thought to cause endothelial damage, exacerbate oxidative stress, and promote inflammation more potently than sustained glucose elevation [5,20]. Consistent with this, we found that higher GV quartiles were associated with progressively lower survival. However, our model comparison demonstrated that the predictive ability of glucose trajectory classification was superior to that of GV alone. This suggests that while GV captures the

magnitude of fluctuations, trajectory analysis additionally encapsulates the temporal pattern and direction of change, providing a more holistic view of metabolic dysregulation. This comprehensive picture may be especially valuable in HF, where neurohormonal activation and inflammatory cytokine release create a volatile metabolic milieu [6,7,14].

In subgroup analysis, the association between potential trajectory classification of blood glucose and 28-day mortality was generally consistent across different patient characteristics. Compared to Class 1, the increased risk of death in Class 2 and Class 3 (especially Class 4) is generally present in subgroups of gender, cerebrovascular disease, kidney disease, and hypotension. However, in the diabetes state and insulin use subgroup, we observed significant effect modification. It is worth noting that there is no significant difference in the risk of death between Class 3 and Class 1 patients who did not use insulin; Among patients who use insulin, the risk of death for Class 3 is significantly higher than for Class 1. This difference may be related to hypoglycemic events associated with insulin use and the increased risk of death resulting from it [26]. It should be noted that in the subgroup analysis stratified by insulin treatment status, certain trajectory categories exhibited relatively wide confidence intervals, which may be attributed to the limited sample size within these subgroups resulting in reduced estimation precision. Therefore, these findings should be interpreted with caution. Future studies should further stratify populations based on specific glucose-lowering regimens to investigate the impact of different antidiabetic treatments on the predictive performance of glucose trajectory models, particularly regarding insulin use. In addition, we further explored the predictive effect of GV on mortality

in patients classified by different blood glucose trajectories. It is worth noting that a negative correlation was observed between GV and mortality risk in Class 3 patients, with higher GV corresponding to lower mortality risk. This seemingly contradictory phenomenon may stem from the fact that the significant blood glucose fluctuations in this group of patients are mainly due to active hypoglycemic treatment, rather than metabolic disorders caused by the disease itself. However, further data analyses are warranted to ensure the robustness of this conclusion.

This study has several limitations that must be acknowledged. First, its retrospective and single-center design may limit the generalizability of the findings. Second, the requirement for at least four days of glucose data to model trajectories inevitably excluded patients who died early, introducing potential survivor bias. While comparable studies have used shorter observation windows [10], future work should determine the optimal balance between data density for modeling and minimizing this bias. Third, the frequency of glucose measurements was not standardized and was influenced by clinical condition and treatment intensity. Although this reflects real-world practice and our analysis showed adequate data density across all classes, it introduces heterogeneity. Fourth, the MIMIC-IV database does not provide detailed metadata on the specific models and precision of point-of-care glucose meters used. While all devices operated under institutional quality control, and our focus on longitudinal patterns is robust to random measurement error, we cannot fully quantify its potential impact. Finally, we employed LCGM for trajectory identification. While it provided clinically interpretable classes, future research could compare its

performance with more flexible methods like Growth Mixture Models.

Conclusion

In summary, this study suggests that dynamic blood glucose trajectories and variability indicators provide complementary information for predicting 28-day mortality in critically ill HF patients.

Abbreviations

AIC:Akaike information criterion; AMI:Acute myocardial infarction; APS III:Acute physiology score III ; BIC:Bayesian information criteria; BUN: Blood urea nitrogen; CVD，cardiovascular disease，DM:Diabetes mellitus; GV:glucose variability; HF:Heart failure; LASSO:Least Absolute Shrinkage and Selection Operator; LCGM: Latent category growth model; ICU: Intensive care unit; INR: International normalized ratio; LOS: Length of stay; MIMIC-IV: Medical Information Mart for Intensive Care IV; OASIS: Oxford acute severity of illness score; PT: Prothrombin time; PTT: Partial thromboplastin time; RBC: Red blood cell; SABIC:Sample-adjusted information criteria; SIRS: Systemic inflammatory response syndrome ; WBC: White blood cell.

Authors' contributions: Ping-yu Cai, Wei-ze Lin and Shu-han Chen designed the study. Bao-ya Yang and Shi-hong Lin extracted, collected and analyzed data. Jun-han Chen, Ping-yu Cai, Wei-ze Lin and Hui-li Lin reviewed the results, interpreted data, and wrote the manuscript. All authors read and approved the final manuscript.

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Ethics approval and consent to participate: This study was conducted in accordance with the principles of the Helsinki Declaration. The MIMIC-IV database ensures patient privacy by de-identifying all personal information and assigning random codes for patient identification. Given the retrospective design and the use of anonymized data, the Ethics Committee of the Second Affiliated Hospital of Fujian Medical University granted a waiver for informed consent.

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Data Availability: The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare no competing interests.

Consent for publication: Not applicable.

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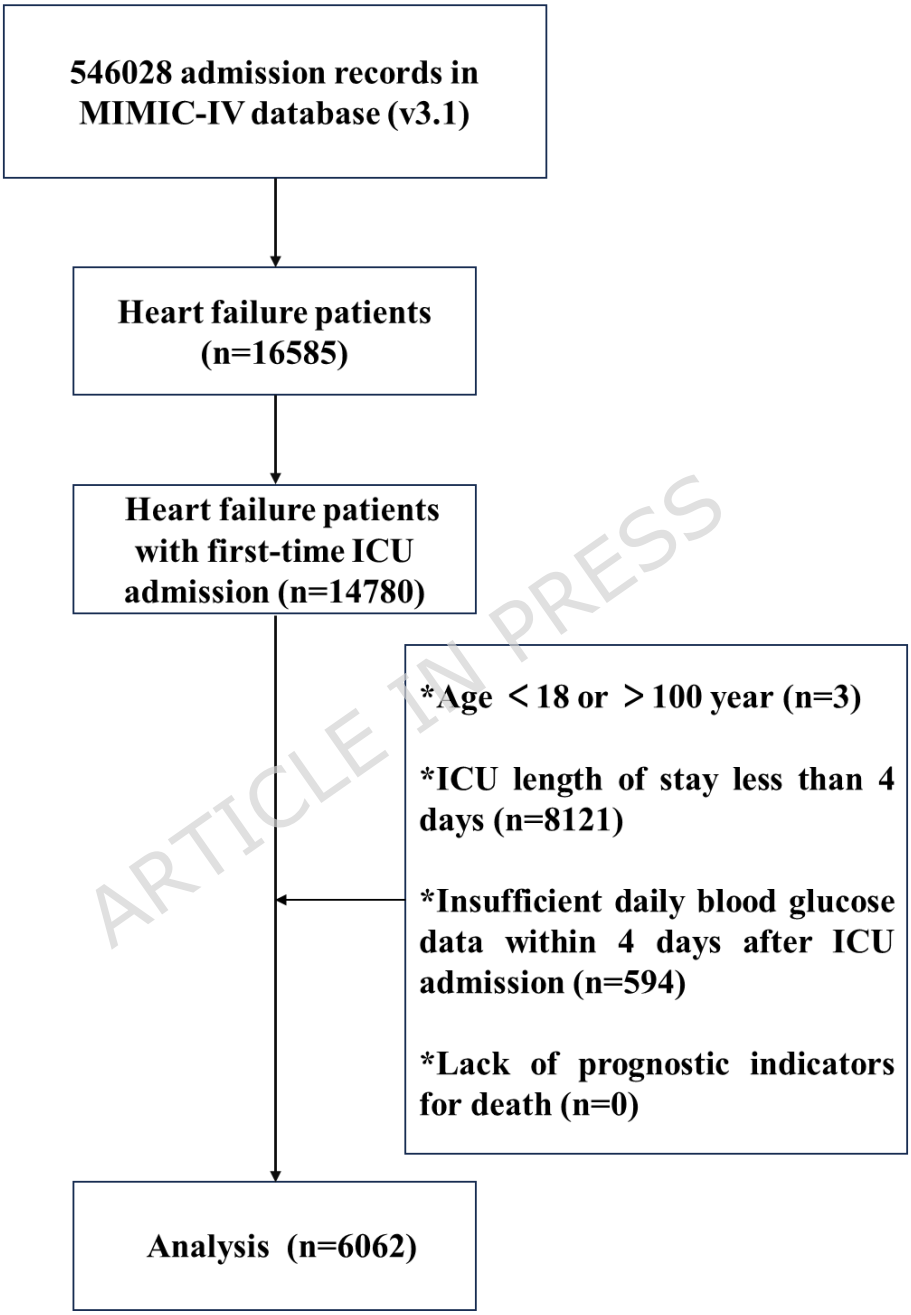

Figure 1. Flowchart of this study. ICU, intensive care unit; MIMIC IV, Medical Information Mart for Intensive Care IV.

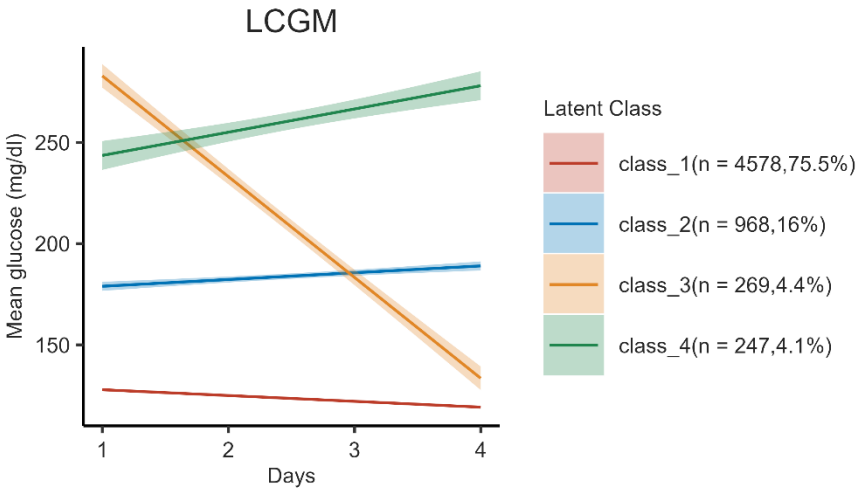

Figure 2. Blood glucose-based trajectories of critically ill heart failure patients. The light-colored shaded area around the line represents the 95% confidence interval.

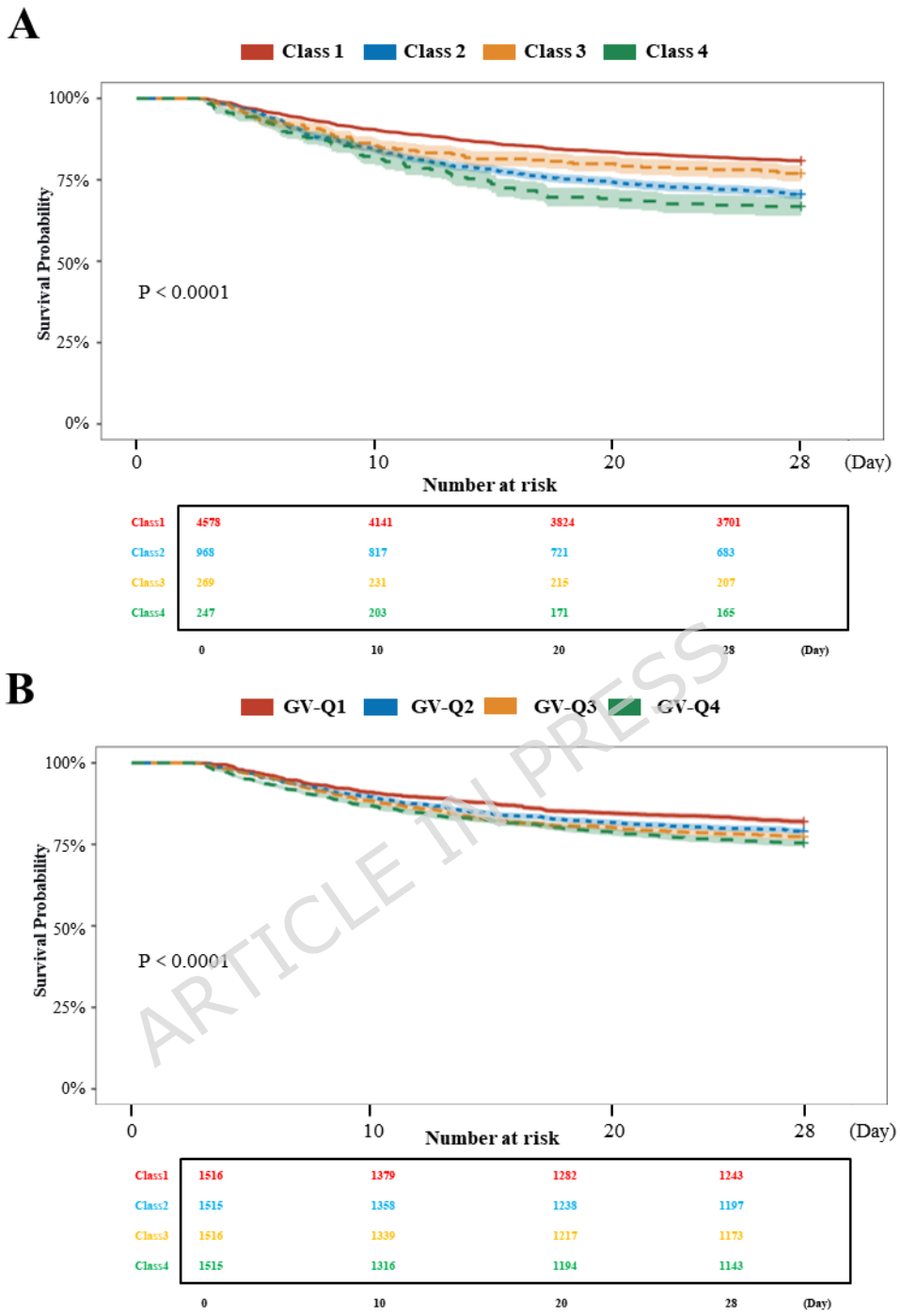

Figure 3. Kaplan–Meier curves for 28-day survival, stratified by four trajectory classes (A) and glycemic variability coefficient quartiles (B).

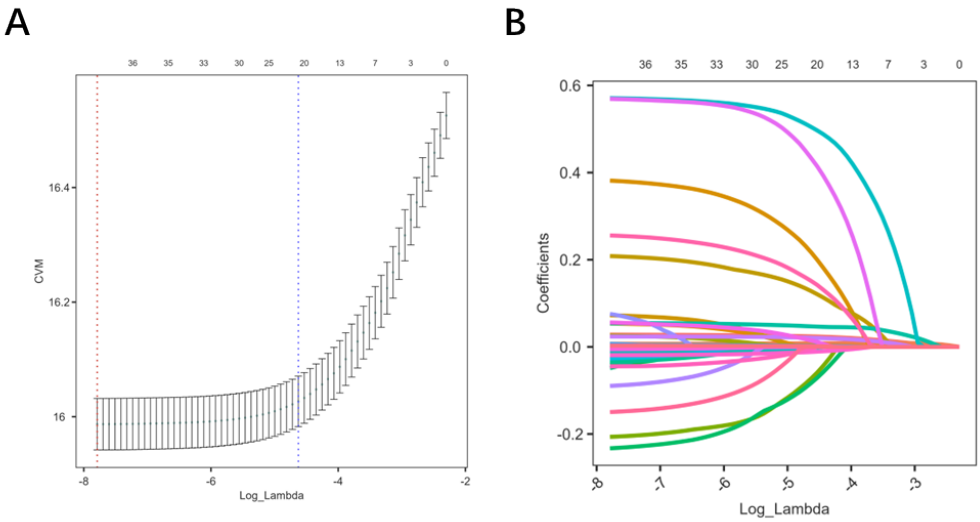

Figure 4. Feature selection. (A) A minimum criteria and a 1-SE criteria were used to draw the dotted vertical lines representing the optimal values. A lambda value of 0.0093 was chosen (1-SE criteria). (B) Tuning parameter (λ) selection using LASSO penalized cox regression with tenfold cross-validation.

Table 1. Characteristics of included patients.

Variable	Overall	Survivor	Death	*p*-value
	N = 6,062	N = 4,756	N = 1,306	
Age, median (IQR)	73.48 (18.29)	72.36 (18.59)	77.47 (16.14)	<0.001
Male, n (p%)	3,496.00 (57.67%)	2,742.00 (57.65%)	754.00 (57.73%)	0.959
ICU LOS, median (IQR)	5.50 (4.88)	5.22 (4.38)	6.80 (5.38)	0.009
Temperature, median (IQR)	36.67 (0.67)	36.67 (0.67)	36.61 (0.67)	0.002
Heart rate, median (IQR)	87.00 (26.00)	86.00 (26.00)	89.00 (29.00)	0.001
Respiration rate, median (IQR)	19.00 (8.00)	19.00 (7.00)	20.00 (8.00)	<0.001
Systolic blood pressure, median (IQR)	117.00 (35.00)	118.00 (35.00)	114.00 (34.00)	<0.001
Diastolic blood pressure, median (IQR)	66.00 (24.00)	67.00 (24.50)	65.00 (24.00)	0.023
Mean blood pressure, median (IQR)	79.00 (24.00)	80.00 (25.00)	78.00 (24.00)	0.012
Spo2, median (IQR)	97.00 (6.00)	98.00 (6.00)	97.00 (6.00)	<0.001
Blood urea nitrogen, median (IQR)	27.00 (26.00)	25.00 (24.00)	35.00 (33.00)	<0.001
Creatinine, median (IQR)	1.30 (1.10)	1.20 (1.00)	1.40 (1.40)	<0.001

Sodium, median (IQR)	138.00 (6.00)	138.00 (6.00)	138.00 (6.00)	0.321
Potassium, median (IQR)	4.20 (0.90)	4.20 (0.90)	4.30 (1.10)	0.003
Calcium, median (IQR)	8.40 (1.00)	8.40 (0.95)	8.40 (1.00)	0.907
White blood cell, median (IQR)	11.30 (7.80)	11.10 (7.70)	12.10 (8.30)	<0.001
Red blood cell, median (IQR)	3.51 (1.14)	3.53 (1.17)	3.43 (1.10)	<0.001
Platelet, median (IQR)	192.00 (119.00)	192.00 (116.00)	192.00 (135.00)	0.191
Hemoglobin, median (IQR)	10.40 (3.40)	10.40 (3.40)	10.10 (3.00)	<0.001
International normalized ratio, median (IQR)	1.40 (0.50)	1.30 (0.40)	1.40 (0.70)	<0.001
Prothrombin time, median (IQR)	14.90 (5.40)	14.80 (4.90)	15.50 (7.50)	<0.001
Partial thromboplastin time, median (IQR)	33.30 (15.10)	33.00 (14.60)	34.30 (17.40)	<0.001
Blood glucose coefficient of variation, median (IQR)	0.21 (0.16)	0.20 (0.15)	0.22 (0.17)	<0.001
SIRS, median (IQR)	3.00 (1.00)	3.00 (1.00)	3.00 (1.00)	<0.001
LODS, median (IQR)	6.00 (4.00)	6.00 (4.00)	7.00 (4.00)	<0.001
APS III, median (IQR)	49.00 (26.00)	47.00 (23.00)	58.00 (27.00)	<0.001
OASIS, median (IQR)	35.00 (11.00)	34.00 (11.50)	37.00 (11.00)	<0.001

Renal disease, n (p%)	2,360.00 (38.93%)	1,780.00 (37.43%)	580.00 (44.41%)	<0.001
Malignant cancer, n (p%)	607.00 (10.01%)	386.00 (8.12%)	221.00 (16.92%)	<0.001
Severe liver disease, n (p%)	238.00 (3.93%)	153.00 (3.22%)	85.00 (6.51%)	<0.001
Myocardial infarct, n (p%)	2,063.00 (34.03%)	1,608.00 (33.81%)	455.00 (34.84%)	0.487
Cerebrovascular disease, n (p%)	1,010.00 (16.66%)	748.00 (15.73%)	262.00 (20.06%)	<0.001
Chronic pulmonary disease, n (p%)	2,293.00 (37.83%)	1,787.00 (37.57%)	506.00 (38.74%)	0.44
Diabetes, n (p%)	2,547.00 (42.02%)	2,015.00 (42.37%)	532.00 (40.74%)	0.29
Hypertension, n (p%)	1,469.00 (24.23%)	1,208.00 (25.40%)	261.00 (19.98%)	<0.001
Vasoactive drug, n (p%)	3,369.00 (55.58%)	2,536.00 (53.32%)	833.00 (63.78%)	<0.001
Insulin, n (p%)	4,215.00 (69.53%)	3,307.00 (69.53%)	908.00 (69.53%)	0.996
Ventilator, n (p%)	5,691.00 (93.88%)	4,470.00 (93.99%)	1,221.00 (93.49%)	0.509

ICU LOS: Length of Stay in the Intensive Care Unit, Spo2: Saturation of Peripheral Oxygen, SIRS: Systemic Inflammatory Response Syndrome, LODS: Logistic Organ Dysfunction System, APS III: Acute Physiology Score III, OASIS: Oxford Acute Severity of Illness Score.

Table 2. Statistics for selecting the optimal number of latent trajectory classes.

Model Name	G	log-likelihood	conv	npm	AIC	BIC	SABIC	entropy	class1 (%)	class2 (%)	class3 (%)	class4 (%)	class5 (%)	class6 (%)
Model1	1.00	-130329.49	1.00	3.00	260664.98	260685.11	260675.58	1.00	100.00					
model2	2.00	-126654.46	1.00	6.00	253320.92	253361.18	253342.11	0.92	84.84	15.16				
model3	3.00	-125962.02	1.00	9.00	251942.04	252002.43	251973.83	0.89	77.86	4.29	17.85			
model4	4.00	-125429.19	1.00	12.00	250882.38	250962.90	250924.77	0.89	75.52	15.97	4.44	4.07		
model5	5.00	-125162.45	1.00	15.00	250354.89	250455.54	250407.87	0.85	6.09	4.03	69.61	1.81	18.46	
model6	6.00	-125162.45	1.00	18.00	250360.89	250481.67	250424.47	0.60	66.13	0.00	1.81	21.97	4.03	6.05

AIC, Akaike information criterion; BIC, Bayesian information criteria; SABIC, sample-adjusted information criteria.

Table 3. Cox regression model for 28-day mortality based on glycemic trajectory classes.

Class	Univariable COX Regression		Multivariate COX Regression	
	HR (95% CI)	***p*-value**	**HR (95% CI)**	***p*-value**
Class 1	1.00 Reference		1.00 Reference	
Class 2	1.641 (1.535-1.754)	□0.001	1.551 (1.442-1.668)	□0.001
Class 3	1.251 (1.1-1.423)	0.001	1.187 (1.036-1.359)	0.013
Class 4	1.916 (1.711-2.145)	□0.001	1.858 (1.644-2.099)	□0.001

HR: Hazard ratio; 95% CI, 95% confidence interval;

Multivariate COX Regression: adjusted for age□ICU LOS□temperature□respiratory rate□SBP□SpO_2□LODS□SIRS□APS-III □ OASIS □ WBC □ BUN □ PTT □ PT □ malignant cancer □ severe liver disease □ cerebrovascular disease □ hypertension□diabetes□vasoactive drug

Table 4. Subgroup cox regressions of different clusters and 28-day mortality.

Variable	Group	HR (95% CI)	*P*_value	*P*_for_interaction
Gender				
Male	Class1	Reference		0.438
	Class2	1.59 (1.44-1.75)	<0.001	
	Class3	1.23 (1.03-1.47)	0.021	
	Class4	2.03 (1.75-2.36)	<0.001	
Feamle	Class1	Reference		
	Class2	1.46 (1.31-1.64)	<0.001	
	Class3	1.18 (0.95-1.46)	0.126	
	Class4	1.5 (1.2-1.88)	<0.001	
Cerebrovascular disease				
NO	Class1	Reference		0.323
	Class2	1.55 (1.43-1.68)	<0.001	
	Class3	1.16 (1.00-1.35)	0.051	
	Class4	1.95 (1.7-2.23)	<0.001	
YES	Class1	Reference		
	Class2	1.41 (1.2-1.66)	<0.001	
	Class3	1.21 (0.89-1.64)	0.225	
	Class4	1.47 (1.12-1.93)	0.005	
Diabetes				
NO	Class1	Reference		<0.001
	Class2	1.94 (1.75-2.15)	<0.001	
	Class3	1.18 (0.91-1.53)	0.217	
	Class4	2.92 (2.21-3.87)	<0.001	
YES	Class1	Reference		
	Class2	1.28 (1.15-1.41)	<0.001	
	Class3	1.12 (0.95-1.31)	0.185	
	Class4	1.64 (1.43-1.89)	<0.001	

Renal disease				
NO	Class1	Reference		0.212
	Class2	1.55 (1.4-1.71)	<0.001	
	Class3	1.23 (1.03-1.48)	0.023	
	Class4	1.61 (1.33-1.96)	<0.001	
YES	Class1	Reference		
	Class2	1.55 (1.39-1.72)	<0.001	
	Class3	1.13 (0.92-1.38)	0.256	
	Class4	2.11 (1.8-2.48)	<0.001	
Hypension				0.337
NO	Class1	Reference	<0.001	
	Class2	1.51 (1.4-1.64)	0.152	
	Class3	1.12 (0.96-1.31)	<0.001	
	Class4	1.88 (1.65-2.15)	<0.001	
YES	Class1	Reference		
	Class2	1.68 (1.41-2.01)	<0.001	
	Class3	1.6 (1.22-2.08)	0.001	
	Class4	1.73 (1.25-2.39)	0.001	
insulin				0.048
NO	Class1	Reference		
	Class2	1.63 (1.35-1.97)	<0.001	
	Class3	0.54 (0.2-1.46)	0.229	
	Class4	5.86 (2.17-15.82)	<0.001	
YES	Class1	Reference		
	Class2	1.58 (1.46-1.71)	<0.001	
	Class3	1.22 (1.06-1.41)	0.005	
	Class4	1.87 (1.65-2.12)	<0.001	

HR: Hazard ratio; 95% CI, 95% confidence interval.

Each subgroup analysis was adjusted (except for the subgroup variable) for age、ICU LOS、temperature、respiratory rate、sbp、spo2、lods、sirs、apsiii、oasis、wbc、bun、ptt、pt、Malignant cancer、severe

liver disease cerebrovascular disease hypertension diabetes vasoactive drug.