

Associations of variability in blood glucose and systolic blood pressure with mortality in patients with coronary artery disease: A retrospective cohort study from the MIMIC-IV database

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ABSTRACT

Aims: Variability of metabolic parameters, such as glycemic variability (GV) and systolic blood pressure variability (SBPV), are associated with adverse cardiovascular outcomes. However, whether these parameters have additive effects on mortality in patients with coronary artery disease (CAD) hospitalized in the intensive care unit (ICU) remains unclear.

Methods: We retrospectively enrolled patients with CAD from the Medical Information Mart for Intensive Care-IV database. The highest tertile of variability was defined as high variability. A variability scoring system was established, which assigned 0 points to tertile 1, 1 point to tertile 2, and 2 points to tertile 3 for GV and SBPV. **Results:** Among 4237 patients with CAD, 400 patients died in hospital, and 967 patients died during 1-year follow-up. High GV and high SBPV were associated with an increased risk of mortality. The effects of GV and SBPV on in-hospital mortality were partially mediated by ventricular arrhythmias (18.0 % and 6.6 %, respectively). The risk of mortality gradually increased with the number of high-variability parameters and increasing variability scores.

Conclusions: GV and SBPV have additive effects on the risk of mortality in patients with CAD hospitalized in the ICU. Ventricular arrhythmias partially mediate the effects of GV and SBPV on in-hospital mortality.

1. Introduction

Coronary artery disease (CAD) remains a significant global health concern, which is the leading cause of morbidity and mortality and causes a heavy public health and economic burden worldwide [1]. Therefore, identifying the potential risk factors for CAD is of great significance for risk estimation and prognosis evaluation.

Recently, variability in metabolic parameters, such as glycemic variability (GV) and systolic blood pressure variability (SBPV), have received increasing attention [2–5]. GV and SBPV are considered cardiovascular risk factors independent of blood glucose and systolic blood pressure (SBP) [6–8]. Elevated GV levels were associated with a prolonged heart rate-corrected QT interval in patients with type 2 diabetes,

which increased the risk of severe ventricular arrhythmias, including ventricular tachycardia and ventricular fibrillation [9]. It has been reported that higher short-term GV is independently associated with an increase in the risk of ventricular tachycardia and ventricular fibrillation in patients hospitalized in the ICU [10]. In addition, elevated SBPV can reflect enhanced sympathetic nervous system activity and thus may induce the development of fatal ventricular arrhythmias [11,12].

Although the underlying mechanisms may be different, both GV and SBPV are closely associated with adverse cardiovascular outcomes [2–5]. Furthermore, several studies have shown that visit-to-visit (i.e., long-term) GV and SBPV have additive effects on increasing the risk of adverse cardiovascular events, including myocardial infarction, stroke, atrial fibrillation, and new-onset heart failure in the general population

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[6–8]. However, whether short-term GV and SBPV during hospital stay have additive effects on mortality in patients with CAD hospitalized in the ICU has not been demonstrated. Moreover, the potential mechanisms underlying the interactions between variability in different metabolic parameters and adverse cardiovascular outcomes are still poorly understood. In the present study, we investigated whether GV and SBPV had additive effects on the risk of mortality in CAD patients admitted to the ICU and whether ventricular arrhythmias mediated the effects of GV and SBPV on mortality.

2. Methods

2.1. Data source

This study is a retrospective analysis of a large online international database called the Medical Information Mart for Intensive Care-IV (MIMIC-IV) database (version 2.2) [13], which contains >50,000 deidentified records between 2008 and 2019 from the Beth Israel Deaconess Medical Center (Boston, Massachusetts) [14]. The institutional review board of the Massachusetts Institute of Technology (Cambridge, Massachusetts) and Beth Israel Deaconess Medical Center (Boston, Massachusetts) approved the establishment of the database. One author (HM He) received permission to access the MIMIC-IV database (certification number: 55642259). This study complied with the principles of the Helsinki Declaration. The data from the MIMIC-IV database were deidentified; therefore, individual informed consent was not needed.

2.2. Study population

In the present study, we retrospectively included patients who were diagnosed with CAD (in the top 3 ranks) according to International Classification of Diseases (ICD)-9 codes (410.xx–414.xx) and ICD-10 codes (I20.x–I22.x and I25.x). Patients with a length of intensive care unit (ICU) stay less than 24 h were excluded from our analysis ($n = 1058$). In addition, patients younger than 18 years ($n = 0$), patients with less than 3 blood glucose measurements ($n = 2895$), and patients with less than 10 SBP measurements ($n = 30$) were also excluded from the analysis. If a patient had multiple hospitalization records, only the first record was analyzed. Therefore, in total, we obtained 4237 patients with CAD from the database. The patient inclusion and exclusion flow diagram is shown in [Supplementary Fig. 1](#).

2.3. Data extraction and definitions

According to the codes provided by the Massachusetts Institute of Technology Laboratory for Computational Physiology (<https://github.com/MIT-LCP/mimic-code>), patient demographic, comorbidity, laboratory examination, and treatment data were extracted from the MIMIC-IV database. In the present study, only patients with more than 3 blood glucose measurements and more than 10 SBP measurements were included in the analysis to reduce the bias resulting from fewer measurements [3,5,10]. In addition, we extracted all blood glucose and SBP values used in the calculation of GV and SBPV to compute the mean blood glucose and mean SBP. Navicat Premium software (version 15.0.29) with a structured query language was used to extract the data.

Since there is currently no gold standard method for evaluating variability in blood glucose and SBP, a widely used method, which was based on the coefficient of variation of blood glucose measurements and SBP measurements within 72 h after ICU admission [5,15], was used to assess GV and SBPV in our study. In addition, a sensitivity analysis that included all blood glucose measurements and SBP measurements during the ICU stays to calculate GV and SBPV was performed. In the vast majority of our patients, the SBP was automatically documented at least once per hour by monitoring devices. The outliers of SBP (>300 or <40 mmHg) were removed and not included in the analysis ($<1\%$ of the

data) [5]. Since the assessment method of GV was not specified by guidelines, the method we used was based on published studies [3,10]. The frequency and timing of blood glucose measurements were not standardized and were determined by the physician due to the real-world nature of the study. The coefficient of variation (percentage) was calculated based on the ratio of standard deviation to the mean (standard deviation/mean $\times 100$).

We defined ventricular arrhythmias as ventricular tachycardia and ventricular fibrillation in our study [10]. Data on ventricular arrhythmias were extracted from the “chartevents” table in the MIMIC-IV database, where the heart rhythm (including the time to occurrence of ectopic ventricular rhythms) information was recorded in detail. To fulfill the temporal ordering assumption (exposure preceded mediators and mediators preceded outcomes) and avoid reverse mediation, ventricular arrhythmias at baseline (within 24 h after ICU admission) were excluded from the analysis [10]. Antihypertensives include angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, alpha-blockers, beta-blockers, calcium channel blockers, and diuretics. Antidiabetic drugs include insulin and other antidiabetic agents (such as metformin, sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, alpha-glucosidase inhibitors, glucagon-like peptide-1 [GLP-1] receptor agonists, and sodium-glucose cotransporter-2 [SGLT-2] inhibitors). Hypoglycemia was defined as blood glucose <70 mg/dL.

2.4. Study endpoint

The primary endpoint of the present study was in-hospital mortality, and the secondary endpoint was 1-year mortality. In-hospital death information was derived from the “hospital expire flag” column of the “admissions” table in the MIMIC-IV database. The date of death was extracted from the “dod” column of the “patients” table in the MIMIC-IV database, which was obtained from hospital records and state records. The 1-year follow-up data were available for all patients.

2.5. Statistical analysis

For continuous variables, data were summarized as means $\pm$ standard deviations or medians (interquartile ranges), depending on the distribution normality of the variable. For categorical variables, data were summarized as frequencies (percentages). Patients were stratified into two groups according to their survival status. Student's *t*-test, the Mann-Whitney *U* test, and the chi-squared test were used to evaluate between-group differences, as appropriate.

Based on the distributions of GV and SBPV, lower, middle, and upper tertile groups were created (GV: <14.9 , 14.9 – 26.3 , >26.3 ; SBPV: <11.1 , 11.1 – 13.8 , >13.8); the highest tertile was defined as high, and the lower two tertiles were defined as low. Kaplan-Meier survival analysis was performed to estimate survival curves. Variables with a *p* value < 0.05 in the univariate analysis and variables that were considered clinically significant were entered into the multivariate analysis. Logistic regression analysis and Cox proportional hazard regression analysis were used to investigate the associations of GV and SBPV with in-hospital and 1-year mortality. In addition, mediation analysis was used to determine whether the effects of GV and SBPV on in-hospital mortality were mediated by ventricular arrhythmias.

To consolidate our findings, we explored the association between the number of high-variability parameters and mortality. The highest tertile (T3) and lower 2 tertiles (T1–T2) of variability were used to define high variability and low variability, respectively. The robustness of the results across subgroups was assessed by subgroup analyses. Furthermore, we established a variability scoring system ranging from 0 to 4 points. This scoring system assigned 0 points to tertile 1, 1 point to tertile 2, and 2 points to tertile 3 for GV and SBPV [6]. The combined scores were subsequently calculated as the variability score. For statistical analysis, R statistical software (R Foundation for Statistical Computing, Vienna, Austria, version 4.3.1) and SPSS statistical software (version 25.0, SPSS,

Inc., Chicago, Illinois, United States) were used. Significance was set at $p < 0.05$ (*), $p < 0.01$ (†), and $p < 0.001$ (‡).

3. Results

3.1. Baseline characteristics

The mean age of our study cohort was 71.2 ± 12.3 years, and 1438 (33.9 %) patients were females. Non-survivors were older, and more likely to have acute myocardial infarction, chronic heart failure, peripheral vascular disease, cerebrovascular disease, and chronic kidney disease than the survivors. Compared with the survivors, non-survivors were less likely to be treated with antiplatelets, antihypertensives, and antidiabetic drugs. Higher GV and SBPV and higher levels of baseline serum creatinine, white blood cells, platelets, and glucose were observed in the non-survivors (Table 1).

3.2. The correlation between GV and SBPV

The Pearson correlation coefficient between GV and SBPV was 0.113 ($p < 0.001$), indicating that although there was a certain degree of correlation between them, there may exist independent mechanisms for their effects on prognosis (Supplementary Fig. 2).

Table 1
Baseline characteristics of study population.

Variables	Survivors (n = 3270)	Non-survivors (n = 967)	p-value
Demographics			
Age, years	69.6 ± 12.0	76.5 ± 11.7	<0.001
Age ≥ 75 years, n (%)	1118 (34.2)	579 (59.9)	<0.001
Female, n (%)	1041 (31.8)	397 (41.1)	<0.001
Body mass index, kg/m ²	29.4 ± 6.2	28.2 ± 7.2	<0.001
Vital signs			
Systolic blood pressure, mmHg	120.2 ± 22.3	120.8 ± 24.8	0.445
Diastolic blood pressure, mmHg	65.1 ± 16.2	66.9 ± 19.8	0.008
Heart rate, bpm	83.5 ± 16.3	88.2 ± 19.9	<0.001
Comorbidities			
Acute myocardial infarction, n (%)	1837 (56.2)	779 (80.6)	<0.001
Hypertension, n (%)	2574 (78.7)	779 (80.6)	0.215
Diabetes, n (%)	1395 (42.7)	428 (44.3)	0.398
History of myocardial infarction, n (%)	538 (16.5)	151 (15.6)	0.569
Chronic heart failure, n (%)	1347 (41.2)	640 (66.2)	<0.001
Peripheral vascular disease, n (%)	506 (15.5)	215 (22.2)	<0.001
Cerebrovascular disease, n (%)	414 (12.7)	179 (18.5)	<0.001
Chronic kidney disease, n (%)	1130 (34.6)	662 (68.5)	<0.001
Treatment			
Antiplatelets, n (%)	3066 (93.8)	831 (86.1)	0.038
Statins, n (%)	2957 (90.5)	766 (79.4)	0.187
Antihypertensives, n (%)	3101 (94.9)	872 (90.4)	<0.001
Antidiabetic drugs, n (%)	2444 (74.8)	640 (66.3)	<0.001
Laboratory measurements			
Serum creatinine, mg/dL	1.0 (0.8–1.3)	1.4 (1.0–2.2)	<0.001
White blood cells, 10 ⁹ /L	10.9 (8.0–14.6)	12.2 (8.7–16.5)	<0.001
Hemoglobin, g/dL	11.1 ± 2.5	10.7 ± 2.3	<0.001
Platelets, 10 ⁹ /L	205.1 ± 89.3	222.6 ± 107.3	<0.001
Glucose, mg/dL	130.0 (108.0–169.0)	150.0 (117.0–212.0)	<0.001
HbA1c, %	6.6 ± 1.6	6.6 ± 1.5	0.561
GV, %	22.5 ± 14.8	26.9 ± 16.9	<0.001
SBPV, %	12.6 ± 3.1	13.7 ± 4.3	<0.001
Mean blood glucose, mg/dL	143.1 ± 44.0	159.9 ± 61.6	<0.001
Mean systolic blood pressure, mmHg	115.5 ± 12.3	113.3 ± 15.0	<0.001
Length of ICU stay, days	3.0 (2.0–4.0)	4.0 (2.0–7.0)	<0.001

Abbreviations: GV, glycemic variability; HbA1c, hemoglobin A1c; ICU, intensive care unit; SBPV, systolic blood pressure variability.

3.3. Risk of mortality according to GV tertiles and SBPV tertiles

Supplementary Fig. 3A and 3B show the Kaplan-Meier survival curves of GV and SBPV for 1-year mortality. As shown in Supplementary Table 1, the risk of mortality increased progressively with incrementally increased levels of GV (all p values for trend < 0.05). The upper tertile of SBPV had a greater risk of mortality than the lower tertile did, whereas the risk of mortality was similar in the middle tertile compared with the lower tertile. Compared with the lowest tertile of GV, the highest tertile had a 1.5-fold risk of in-hospital mortality (odds ratio [OR] = 1.498, 95 % confidence interval [CI] 1.092–2.055) and a 1.4-fold risk of 1-year mortality (hazard ratio [HR] = 1.400, 95 % CI 1.169–1.677) after adjusting for potential confounders. For the highest tertile of SBPV compared with the lowest tertile, a 2.3-fold risk of in-hospital mortality (OR = 2.274, 95 % CI 1.707–3.029) and a 1.4-fold risk of 1-year mortality (HR = 1.418, 95 % CI 1.215–1.656) were observed (Supplementary Table 1).

3.4. The mediating effect of ventricular arrhythmias on the associations of GV and SBPV with in-hospital mortality

There were 600 (14.2 %) patients who developed ventricular arrhythmias. A higher GV was an independent risk factor for ventricular arrhythmias (highest tertile vs. lowest tertile: OR = 1.464, 95 % CI 1.142–1.877). Similarly, a higher SBPV was also independently associated with an increased risk of ventricular arrhythmias (highest tertile vs. lowest tertile: OR = 1.413, 95 % CI 1.136–1.758) (Supplementary Table 2). The effects of GV and SBPV on in-hospital mortality were partially mediated by ventricular arrhythmias (proportion mediated: 18.0 % and 6.6 %, respectively) (Table 2).

3.5. Risk of mortality according to the combination of GV and SBPV

Supplementary Fig. 3C shows the Kaplan-Meier survival curves of the combination of GV and SBPV for 1-year mortality. Compared with patients in the low GV and low SBPV group (GV < 26.3 and SBPV < 13.8), patients in the high GV and high SBPV group (GV > 26.3 and SBPV > 13.8) had the greatest risk of both in-hospital (OR = 2.746, 95 % CI 1.934–3.899) and 1-year mortality (HR = 1.773, 95 % CI 1.460–2.154) after adjustment (Table 3). These associations were independent of baseline blood glucose, mean blood glucose, baseline SBP, and mean SBP.

In addition, the method that only included blood glucose measurements and SBP measurements within 72 h after the ICU admission to calculate GV and SBPV may also introduce bias. Therefore, we conducted a sensitivity analysis that included all blood glucose measurements and SBP measurements during the ICU stays to calculate GV and SBPV. We found that our main results remained unchanged, indicating the robustness of our results (Supplementary Table 3).

A total of 298 (7.0 %) patients developed hypoglycemia during their ICU stays. In the sensitivity analysis, we further adjusted for hypoglycemia and discovered that our main results remained unchanged (Supplementary Table 3).

3.6. Associations of the number of high-variability parameters and variability scores with mortality

As the number of high-variability parameters increased, there was a sequential increase in in-hospital mortality (from 0 to 2 parameters: 6.2 vs. 9.7 vs. 20.6 %) and 1-year mortality (from 0 to 2 parameters: 17.9 vs. 24.3 vs. 35.7 %). As shown in Supplementary Table 4, there was a graded trend toward an increased risk of mortality with an increasing number of high-variability parameters (all p values for trend < 0.05). Compared with the group that did not contain any high-variability parameters, the risk of in-hospital mortality increased by 188 % (OR = 2.881, 95 % CI 2.036–4.077), and the risk of 1-year mortality increased by 80 % (HR =

Table 2

The mediating effect of ventricular arrhythmias on the association of high GV and high SBPV with in-hospital mortality.

	Direct effect		Indirect effect		Proportion mediated (%)
	Coefficients (95 % CIs)	p value	Coefficients (95 % CIs)	p value	
High GV ^a	0.019 (0.002–0.040)	0.028	0.004 (0.001–0.010)	0.030	18.0
High SBPV ^b	0.052 (0.035–0.070)	<0.001	0.004 (0.001–0.010)	0.004	6.6

Abbreviations: GV, glycemic variability; SBPV, systolic blood pressure variability.

^a Adjusted for age, gender, body mass index, acute myocardial infarction, hypertension, diabetes, chronic heart failure, cerebrovascular disease, chronic kidney disease, antiplatelets, statins, antihypertensives, antidiabetic drugs, baseline blood glucose, and mean blood glucose.

^b Adjusted for age, gender, body mass index, acute myocardial infarction, hypertension, diabetes, chronic heart failure, cerebrovascular disease, chronic kidney disease, antiplatelets, statins, antihypertensives, antidiabetic drugs, baseline systolic blood pressure, and mean systolic blood pressure.

Table 3

The association of the combination of GV and SBPV with mortality.

		Group			
		Low GV and low SBPV (GV < 26.3 and SBPV < 13.8)	High GV and low SBPV (GV > 26.3 and SBPV < 13.8)	Low GV and high SBPV (GV < 26.3 and SBPV > 13.8)	High GV and high SBPV (GV > 26.3 and SBPV > 13.8)
In-hospital mortality					
Unadjusted	1.000	1.451 (1.077–1.954)*	1.809 (1.364–2.400) [†]	3.940 (2.978–5.215) [‡]	
Model 1	1.000	1.436 (1.060–1.944)*	1.706 (1.283–2.268) [†]	3.935 (2.951–5.246) [‡]	
Model 2	1.000	1.093 (0.770–1.549)	1.800 (1.310–2.474) [†]	2.746 (1.934–3.899) [‡]	
1-year mortality					
Unadjusted	1.000	1.424 (1.202–1.686) [†]	1.398 (1.179–1.658) [†]	2.323 (1.946–2.774) [‡]	
Model 1	1.000	1.424 (1.199–1.691) [†]	1.266 (1.067–1.502) [†]	2.288 (1.911–2.738) [‡]	
Model 3	1.000	1.146 (0.953–1.377)	1.308 (1.100–1.555) [†]	1.773 (1.460–2.154) [‡]	

Abbreviations: GV, glycemic variability; SBPV, systolic blood pressure variability.

Model 1 adjusted odds ratio for age, gender, and body mass index.

Model 2 adjusted odds ratio for age, gender, body mass index, acute myocardial infarction, hypertension, diabetes, chronic heart failure, cerebrovascular disease, chronic kidney disease, antiplatelets, statins, antihypertensives, antidiabetic drugs, baseline blood glucose, mean blood glucose, baseline systolic blood pressure, and mean systolic blood pressure.

Model 3 adjusted hazard ratio for age, gender, body mass index, acute myocardial infarction, hypertension, diabetes, chronic heart failure, peripheral vascular disease, cerebrovascular disease, chronic kidney disease, antiplatelets, statins, antihypertensives, antidiabetic drugs, baseline blood glucose, mean blood glucose, baseline systolic blood pressure, and mean systolic blood pressure.

* $p < 0.05$.

[†] $p < 0.01$.

[‡] $p < 0.001$.

1.800, 95 % CI 1.484–2.183) in the group containing two high-variability parameters. Subgroup interaction tests revealed that these associations were more pronounced in the subgroup of patients without hypertension (Fig. 1). However, due to the large overlap in confidence intervals, it was not permitted to conclude that the association between the number of high-variability parameters and in-hospital mortality was more pronounced in the subgroup of patients without diabetes, even if the interaction p value was statistically significant (interaction p value = 0.007) (Fig. 1).

For the variability scoring system, higher variability scores were associated with greater risk of in-hospital mortality (from 0 to 4 points:

5.7 vs. 7.0 vs. 6.4 vs. 11.8 vs. 20.6 %) and 1-year mortality (from 0 to 4 points: 15.1 vs. 19.0 vs. 21.6 vs. 25.4 vs. 35.7 %). With increasing variability scores, the ORs of in-hospital mortality gradually increased (1.195 [0.738–1.935] for 1 point, 0.902 [0.565–1.440] for 2 points, 1.858 [1.169–2.954] for 3 points, and 2.941 [1.799–4.808] for 4 points), and the HRs of 1-year mortality gradually increased (1.235 [0.947–1.609] for 1 point, 1.188 [0.924–1.527] for 2 points, 1.492 [1.150–1.935] for 3 points, and 2.034 [1.544–2.679] for 4 points) (Fig. 2).

4. Discussion

In this analysis of 4237 patients with CAD from the MIMIC-IV database, we investigated whether GV and SBPV had additive effects on the risk of mortality. Furthermore, whether these associations were mediated by ventricular arrhythmias was also explored. We found that high variability in blood glucose and SBP was associated with an increased risk of in-hospital and 1-year mortality. The effects of GV and SBPV on in-hospital mortality were partially mediated by ventricular arrhythmias. Patients with two high-variability parameters had a greater risk of mortality than patients with one or no high-variability parameters, especially in the population without hypertension. Furthermore, there was an incrementally higher risk of mortality with increasing variability scores. These associations were independent of baseline blood glucose, mean blood glucose, baseline SBP, and mean SBP. These findings indicate that high variability in blood glucose and SBP has additive effects on the prognosis of CAD patients hospitalized in the ICU. GV and SBPV have the potential to serve as useful clinical tools for improving risk stratification.

As an important factor that can affect cardiovascular outcomes, increasing attention has been given to the variability in metabolic parameters. Oxidative stress is considered one of the predominant mechanisms by which high variability in blood glucose contributes to adverse cardiovascular outcomes [16]. Several studies have shown that intermittent increases in blood glucose levels (high GV) generate more oxidative stress markers and aggravate apoptosis than persistent hyperglycemia [17–19]. High GV has been demonstrated to be associated with increased vulnerability of coronary plaques, cardiac fibrosis, and adverse cardiac remodeling [20–22]. A recent study based on a total of 1841 consecutive patients with acute coronary syndrome and diabetes hospitalized in the ICU reported that higher GV determined by the standard deviation of glucose during hospitalization was significantly associated with major cardiovascular events (including new-onset myocardial infarction, acute heart failure, and cardiac death) [2]. Another recent study based on an acute heart failure population also revealed that patients with GV higher than 21 %, assessed by the coefficient of variation of glucose during hospitalization, had a 1.92-fold increased risk of 6-month mortality and a 1.56-fold increased risk of 1-year mortality than those with GV lower than 21 % [3].

Increased blood pressure variability facilitates the impairment of

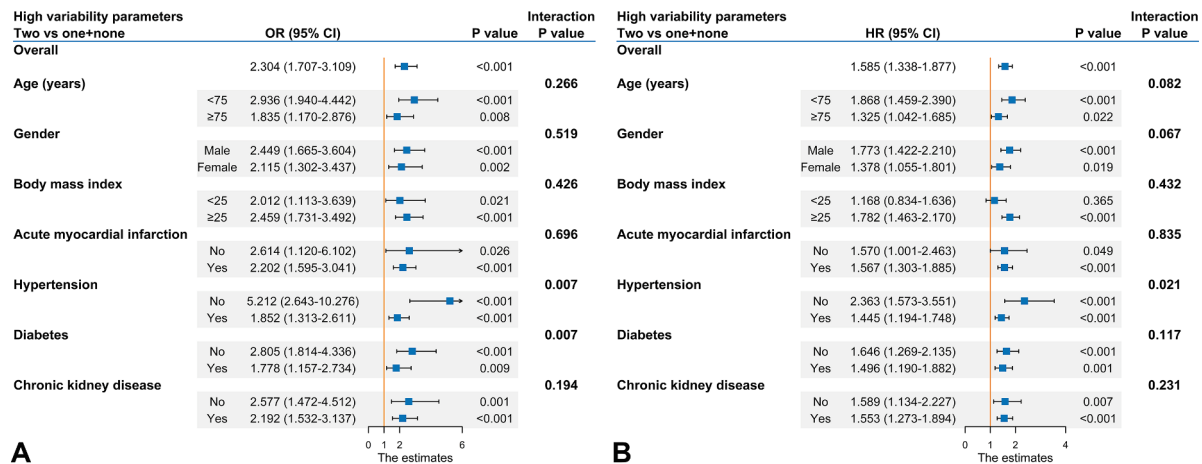


Fig. 1. Forest plots for the association between the number of high-variability parameters and mortality. (A) In-hospital mortality; (B) 1-year mortality. Adjusted for the covariates as in Table 3. Abbreviations: CI, confidence interval; HR, hazard ratio; OR, odds ratio.

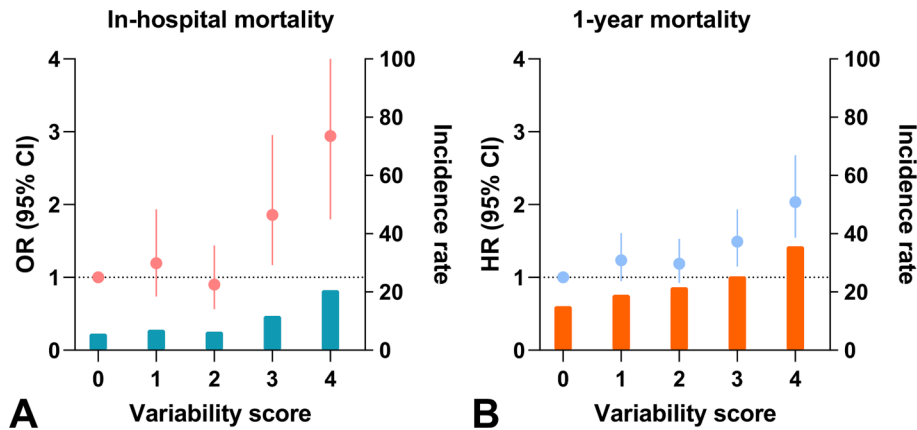


Fig. 2. Associations of the variability scores with (A) in-hospital mortality and (B) 1-year mortality. This scoring system assigned 0 points to tertile 1, 1 point to tertile 2, and 2 points to tertile 3 for GV and SBPV. The combined scores for GV and SBPV were then calculated as variability scores, which ranged from 0 to 4. Adjusted for the covariates as in Table 3. Abbreviations: CI, confidence interval; HR, hazard ratio; OR, odds ratio.

endothelial function by inhibiting the production of nitric oxide, thereby promoting atherogenesis [23]. In addition, increased blood pressure variability contributes to adverse cardiac remodeling and impaired diastolic and systolic cardiac functions, increasing the risk of poor cardiovascular outcomes [24,25]. Gosmanova et al [4] discovered that patients with increased visit-to-visit SBPV had higher risks of all-cause mortality, coronary heart disease, stroke, and end-stage renal disease in a large cohort of United States veterans, which was independent of baseline SBP. However, the SBPV in their study was calculated by using outpatient blood pressure measurements. According to a retrospective analysis of ICU patients from the MIMIC-III database, higher SBPV, which was based on the variability of SBP values within 72 h of ICU admission, was independently associated with in-hospital mortality even after adjustment for mean arterial pressure [5]. Our results also showed that the risks of in-hospital and 1-year mortality increased progressively with increasing levels of GV and SBPV.

More importantly, recent studies have begun to focus on the additive effects of different cardiovascular risk factors on patient prognosis. Kim et al [6] explored the association of visit-to-visit variability in metabolic parameters, including fasting blood glucose, cholesterol concentrations, blood pressure, and body weight, with mortality and cardiovascular events in a general population. The correlations between variability in different metabolic parameters were not strong. Compared with the lowest quartile of variability in each metabolic parameter, patients with higher variability in each metabolic parameter were associated with

increased risks for mortality, myocardial infarction, and stroke. Moreover, as the number of high-variability metabolic parameters increased, the risk of adverse cardiovascular outcomes graded elevated. Similar results were observed for the associations of the number of high-variability metabolic parameters with the risk of atrial fibrillation [7] and heart failure [8]. These findings indicated that these metabolic parameters have additive effects on prognosis in the general population. Moreover, a population-based study of type 1 diabetes in Scottish individuals has consistently shown that visit-to-visit hemoglobin A1c variability and SBPV have additive effects on mortality [26]. However, these associations have not yet been described in an ICU population. In the present study, we found that elevated GV and SBPV were strongly associated with an increased risk of mortality. Furthermore, a graded increase in the risk of both in-hospital and 1-year mortality was observed with an increasing number of high-variability metabolic parameters and rising variability scores. These associations were independent of baseline blood glucose, mean blood glucose, baseline SBP, and mean SBP.

The specific mechanism underlying the additive effects of GV and SBPV on the risk of mortality is currently poorly understood. Abnormal GV and SBPV lead to endothelial dysfunction and cardiovascular remodeling through the activation of oxidative stress, which subsequently increases the risk of adverse cardiovascular outcomes [27]. Additionally, both high GV and high SBPV are markers of augmented sympathetic nervous system activity [11,28] and are strongly associated

with fatal ventricular arrhythmias [10,12], resulting in an increased risk of mortality. In the present study, we found that both high GV and high SBPV were independent risk factors for ventricular arrhythmias and that ventricular arrhythmias partially mediated the effects of GV and SBPV on in-hospital mortality. Although the above-mentioned mechanisms may exist, the magnitude of the mediating role of ventricular arrhythmias in them is different in our study (proportion mediated: 18.0 % for GV and 6.6 % for SBPV). Furthermore, consistent with the findings of previous studies exploring the correlations between variability in different metabolic parameters in the general population [6], we also confirmed a significant but weak correlation between GV and SBPV in patients with CAD admitted to the ICU (Pearson correlation coefficient = 0.113, $p < 0.001$). This also suggested that the associations of GV and SBPV with mortality were mediated through some of the same mechanisms and interrelated mechanisms; however, many different mechanisms were also at play, which may in part account for why GV and SBPV have additive effects on prognosis. The interaction between GV and SBPV and the precise mechanisms underlying the additive effects of these two variables on patient prognosis require further elucidation.

Several studies have suggested that the appropriate selection of antidiabetic drugs and antihypertensives may contribute to reducing GV and SBPV. For example, newer classes of antidiabetic medications, such as GLP-1 receptor agonists [29] and SGLT-2 inhibitors [30], may be ideal agents for reducing GV. Data from several randomized controlled trials and meta-analyses indicated that the effect of calcium channel blockers and thiazide diuretics on reducing SBPV was greater than that of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and beta-blockers [31,32]. Future studies are required to evaluate whether these medications have a positive impact on cardiovascular outcomes through reducing GV and SBPV.

5. Limitations

First, as in all retrospective observational cohort studies, causality could not be determined. In addition, the generalizability of the results may be compromised by the single-center, retrospective, observational design of the present study. Second, excluding patients with fewer than 3 blood glucose measurements and fewer than 10 SBP measurements may have led to selection bias. Moreover, as a real-world study, the frequency and timing of blood glucose measurements were not standardized, which may also cause bias. However, since the timing of blood glucose measurements for the calculation of GV was not specified by guidelines, the method based on published studies [3,10] that we used might be justified. Third, the method that only included blood glucose measurements and SBP measurements within 72 h of the ICU admission to calculate GV and SBPV may also introduce bias. However, the sensitivity analysis that included all blood glucose measurements and SBP measurements during the ICU stays to calculate GV and SBPV confirmed the robustness of our findings (Supplementary Table 3). Fourth, since many factors can affect the long-term outcome of patients, we did not explore the mediators of the effects of GV and SBPV on 1-year mortality. Fifth, the MIMIC-IV database contains only medication data during hospitalization. It lacks medication data before admission and after discharge. Therefore, our conclusions should be applied with caution to patients with diabetes or hypertension (previous use of antidiabetic drugs and antihypertensive drugs). Sixth, since GLP-1 receptor agonists and SGLT-2 inhibitors have cardiovascular protective effects, they may confound our conclusions compared with other oral antidiabetic drugs. However, our study population was derived from an ICU database, where most patients were prescribed with insulin (3084 patients, 72.8 %) rather than other antidiabetic drugs (289 patients, 6.8 %). Only 4 patients were prescribed GLP-1 receptor agonists and 1 patient was prescribed SGLT2 inhibitors in the present study. It is unlikely that the GLP-1 receptor agonists and SGLT-2 inhibitors confounded our results or conclusions. Finally, despite accounting for multiple important confounders, the risk of residual measured and unmeasured confounders may still exist.

Further prospective multicenter studies are warranted to confirm our findings. Despite the above limitations, this is the only study that evaluates the potential additive effects of short-term GV and SBPV on prognosis and explores the potential mediators of the effects of GV and SBPV on mortality in patients with CAD hospitalized in the ICU. This has potential implications for exploring the underlying mechanisms of variability in different metabolic parameters on cardiovascular prognosis in the future. Moreover, it may contribute to the optimal management of blood glucose and blood pressure in clinical practice.

6. Conclusions

High variability in blood glucose and SBP has additive effects on the prognosis of CAD patients admitted to the ICU. The effects of GV and SBPV on in-hospital mortality were partially mediated by ventricular arrhythmias. Consequently, the variability of metabolic parameters, including GV and SBPV, was supported as a valuable tool for risk stratification in patients with CAD hospitalized in the ICU.

CRedit authorship contribution statement

Hao-ming He: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Ying-ying Xie:** Writing – review & editing, Writing – original draft, Software, Methodology, Formal analysis. **Zhe Wang:** Writing – review & editing, Writing – original draft, Software, Formal analysis. **Jie Li:** Writing – review & editing, Writing – original draft, Software, Formal analysis. **Shu-wen Zheng:** Writing – review & editing, Writing – original draft, Software, Formal analysis. **Xue-xi Li:** Writing – review & editing, Writing – original draft, Formal analysis. **Si-qi Jiao:** Writing – review & editing, Writing – original draft, Visualization, Validation. **Fu-rong Yang:** Writing – review & editing, Writing – original draft, Visualization, Validation. **Yi-hong Sun:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data used in the present study were obtained from the MIMIC-IV database (version 2.2). The availability of these data is restricted, and a license is needed. However, the data are available from the author Haoming He (hmhe7411@126.com) upon reasonable request and need to be approved by the Medical Information Mart for Intensive Care Institute.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.diabres.2024.111595>.

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