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ORIGINAL RESEARCH

The Association Between Glycemic Variability and In-Hospital Mortality in Patients with Chronic Obstructive Pulmonary Disease: A MIMIC-IV Database-Based Retrospective Cohort Study

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Purpose: The association between glycemic variability (GV) and the clinical outcomes of patients with chronic obstructive pulmonary disease (COPD) remains uncertain. This study aimed to assess the connection between GV and hospital mortality among hospitalized COPD patients.

Patients and Methods: Data from the MIMIC-IV database were used in this study. GV was analyzed as a continuous variable and in quartiles. Cox proportional hazards modeling with stepwise adjustment was used to assess the link between GV and in-hospital mortality, and HRs and 95% CIs were calculated. A restricted cubic spline model was applied to explore non-linear associations. Survival curves and Log rank tests were performed to assess survival differences. Subgroup analyses and interaction tests were conducted to determine the relationship across diverse populations.

Results: Our analysis encompassed 11873 patients, among whom 838 individuals died during their hospitalization. A significant association between GV and in-hospital mortality in COPD patients was found across all Cox proportional hazards models: the unadjusted model (HR [95% CI]: 1.849 [1.409, 2.427], $P < 0.001$), the partially adjusted model (HR [95% CI]: 1.880 [1.432, 2.468], $P < 0.001$), and the fully adjusted model (HR [95% CI]: 1.551 [1.110, 2.167], $P = 0.01$). The restricted cubic spline (RCS) models revealed a significant non-linear relationship (P-nonlinear < 0.001). Survival curves demonstrated significant differences in in-hospital survival rates across varying GV levels (log-rank $P < 0.0001$).

Conclusion: GV exhibited a strong association with in-hospital mortality among COPD patients, and significant differences were observed in in-hospital survival rates across varying GV levels.

Keywords: chronic obstructive pulmonary disease, in-hospital mortality, glycemic variability, MIMIC-IV database

Introduction

As a chronic disease, chronic obstructive pulmonary disease (COPD) carries high morbidity and mortality. The Global Burden of Disease study revealed that COPD ranked as the fifth leading cause of death in China in 2016 and the third leading cause of death globally, accounting for approximately 6% of all global deaths. By 2017, it had risen to the third leading cause of death worldwide.[1,2] According to the latest mortality projections from World Health Organization (WHO), the prevalence of COPD is expected to surge over the next four decades, driven by increased smoking rates in developing countries and demographic aging in high-income countries. It is projected that by 2060, more than 5.4 million people will die annually from COPD and its related complications. This condition is anticipated to result in substantial economic challenges for both families and society.[3–5]

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In the face of this severe trend in morbidity and mortality, thoroughly investigating the risk factors for mortality in COPD patients and identifying predictive indicators of the risk of mortality in COPD are crucial for the early identification of patients with poor prognoses and the development of personalized interventions during diagnosis and treatment. These findings hold substantial clinical implications for enhancing COPD patient outcomes and reducing in-hospital mortality.

Glycemic variability (GV) is an objective indicator reflecting blood glucose fluctuations. Current studies have shown that blood glucose fluctuations can activate oxidative stress pathways, impair endothelial cell function, exacerbate chronic inflammation, and cause vascular damage. GV may be even more harmful than persistent hyperglycemia.[6–8] Previous research has established an independent association between blood glucose fluctuations and the severity of diseases such as coronary artery disease[9] and acute kidney injury.[10] Oxidative stress and chronic inflammation are also key pathological mechanisms driving the progression and worsening of COPD.[11–14] A clinical study of 242 patients reveals a positive correlation between GV and the length of hospital stay in COPD patients, and it may have a negative impact on prognosis.[15] Therefore, GV is highly likely to serve as an important risk indicator for COPD exacerbation and mortality, with significant prognostic implications.

However, current studies have not clearly demonstrated an independent association between blood glucose fluctuations and COPD mortality. Therefore, this retrospective study, utilizing the MIMIC-IV database intended to investigate the relationship between GV and in-hospital mortality among COPD patients, aiming to establish GV as a novel prognostic indicator for forecasting the risk of mortality.

Materials and Methods

Data Source and Study Population

Data from the MIMIC-IV database (version 3.0; https://mimic.mit.edu) were leveraged in this retrospective cohort study. This publicly available dataset comprises de-identified health records of more than 50,000 intensive care unit (ICU) patients treated at Beth Israel Deaconess Medical Center (BIDMC), affiliated with Harvard Medical School, between 2008 and 2019. The current study adhered to the Declaration of Helsinki. Since all patient data used for analysis were fully anonymized, informed consent requirements were waived. The database was approved by the institutional review boards of both MIT and BIDMC. Our study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).[16] The study design, selection of research subjects, definition of exposure and outcome indicators, data collection procedures, and statistical analysis methods were all strictly implemented in accordance with the 22 core items of the STROBE checklist, so as to ensure the completeness and transparency of the study report. The detailed completion status of the STROBE checklist has been uploaded as STROBE checklist.

A cohort of 40151 COPD patients was identified from the MIMIC-IV database as per International Classification of Diseases codes (ICD-9: 4911, 4912, 49120, 496; ICD-10: J44). For patients with multiple admissions, only their first admission records were utilized (n = 17867). The study further excluded the following patients: individuals aged under 18 years (n = 0), individuals with ICU length of stay <24 hours (n = 25), and individuals with missing blood glucose data or fewer than three blood glucose measurements (n = 5969). After applying these criteria, the final analysis cohort consisted of 11873 patients. The flowchart of patient inclusion and exclusion is shown in Figure 1.

Data Collection

The structured query language (SQL) was employed to systematically extract baseline demographic and clinical characteristics from the database. Baseline characteristics extracted from the MIMIC-IV database comprised four main categories: (1) demographics (gender, age, race, height, weight, marital status, body mass index [BMI]); (2) vital signs (systolic blood pressure, diastolic blood pressure); (3) severity at admission (assessed by the Systemic Inflammatory Response Syndrome [SIRS] score, Acute Physiology Score III [APS III], and the Sequential Organ Failure Assessment [SOFA] score on the first day of admission); (4) laboratory indicators (white blood cell count [WBC], platelet count [PLT], alanine aminotransferase [ALT], aspartate aminotransferase [AST], blood urea nitrogen [BUN], serum creatinine [SCr], glycated hemoglobin [HbA1c]); (5) steroid use and the number of measurements of blood glucose during

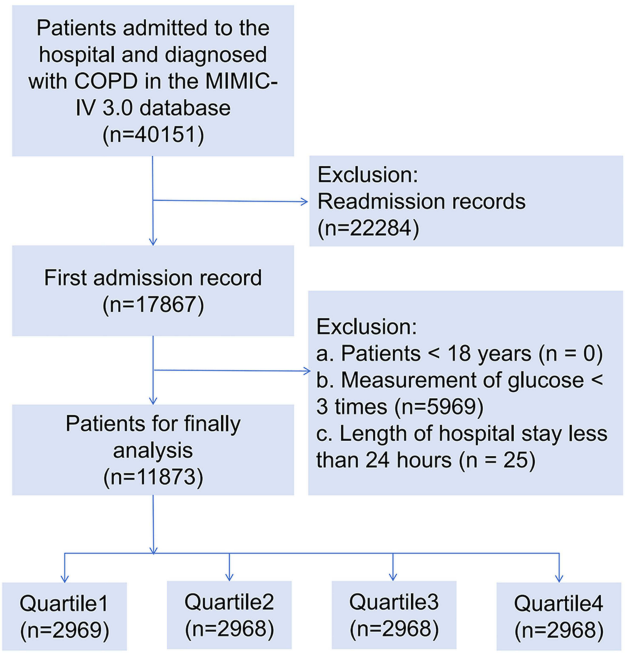

Figure 1 Flowchart of patient inclusion and exclusion from the MIMIC-IV database.
Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; MIMIC-IV, Medical Information Mart for Intensive Care-IV; ICU, Intensive Care Unit.

hospitalization. Additionally, information on relevant comorbidities and surgical history was collected, including congestive heart failure, pulmonary hypertension, hypertension, respiratory failure, chronic kidney disease, diabetes mellitus (DM), and pulmonary resection. For laboratory parameters measured multiple times, the initial measurements obtained within 72 hours of admission were used.

Exposure and Outcome

Overall GV was assessed by calculating the coefficient of variation (CV) of blood glucose, which was leveraged to describe blood GV as the ratio of the standard deviation (SD) of blood glucose measurements to their mean value. GV was appraised leveraging all available glucose measurements throughout the patient's hospital stay. The frequency of blood glucose measurements was determined according to clinical needs, and the number and timing of measurements were not standardized across patients. Furthermore, GV was calculated using blood glucose data collected prior to the occurrence of the outcome (death). Only patients with a minimum of three blood glucose measurements obtained during their ICU admission were enrolled. Given the absence of standardized clinical thresholds for CV in critically ill patients, CV was divided into four categories based on percentiles: Q1: <25% (<0.126), Q2: 25–50% (0.126–0.193), Q3: 50–75% (0.193–0.281), and Q4: 75–100% (>0.281). In-hospital mortality was designated as the primary outcome of this study.

Handling of Missing Values

To minimize bias caused by sample exclusion, variables with ≤20% missing values were handled using multiple imputation based on random forests, while variables with >20% missing values were handled through segmentation, with missing values incorporated as dummy variables in the models.

Statistical Analysis

Continuous variables were presented using mean ± SD or median with interquartile range (IQR). Comparisons of continuous variables were conducted via *t*-tests or analysis of variance (ANOVA), or, where appropriate, Mann–Whitney *U*-tests or Kruskal–Wallis tests. Categorical variables were summarized as numbers or percentages (%), and between-group comparisons were executed via Pearson's chi-square test or Fisher's exact test.

GV was included as both a continuous variable and as an IQR quartile variable in Cox proportional hazards models to probe into the association between GV and in-hospital mortality among COPD patients. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were calculated, progressively adjusting for potential confounders. Model 1 was unadjusted. Model 2 was adjusted for confounders regarding demographics (age, sex, and race). Model 3 was further adjusted based on Model 2 by adding BMI, ALT, AST, SCr, PLT, WBC, hypertension, congestive heart failure, respiratory failure, chronic kidney disease, and steroid use. To prevent multicollinearity in the multivariable model, the variance inflation factor (VIF) was calculated for each variable in Model 3, and variables with a VIF > 5 were excluded. To capture possible non-linear associations between GV and mortality risk, a restricted cubic spline (RCS) analysis was implemented. To examine differences in survival rates among patients with varying GV levels, survival curves were plotted, and a Log rank test was conducted. Finally, to investigate the relationship between GV and mortality in populations with different characteristics, subgroup analyses were performed based on age, sex, BMI, HbA1c levels, serum creatinine, platelet levels, the use of steroids or not, and the presence of comorbidities such as DM, hypertension, respiratory failure, or chronic kidney disease. Interaction tests were also conducted. To mitigate potential bias from including younger patients in prognostic analysis, we performed a sensitivity analysis in the subgroup of patients aged ≥40 years. R v4.4.1 was employed for all analyses, with statistical significance defined at $P < 0.05$.

Results

Study Population

11873 patients were included in this study, among whom 838 died during hospitalization. The median follow-up time for patients was 7 days. Most participants were males, individuals aged over 60 years, and White participants. In the survivor group, compared to the non-survivor group, patients had significantly longer hospital stays and a significantly higher likelihood of comorbid respiratory failure and chronic kidney disease. As presented in Table 1, laboratory analyses revealed elevated levels of SCr, and WBC, whereas PLT values were notably reduced.

Table 1 Baseline Demographic and Clinical Characteristics of Survivors and Non-Survivors

Characteristic	Overall (n= 11,873)	Survivors (n=11035)	Non-Survivors (n=838)	p-value
Follow-up time (day)	7 [4~11]	7 [4~11]	8 [4~15]	<0.001
Gender, n (%)				0.021
Female	5699 (48%)	5329 (48%)	370 (44%)	
Male	6174 (52%)	5706 (52%)	468 (56%)	
Age (years), n (%)				<0.001
< 40 years	88 (0.7%)	85 (0.8%)	3 (0.4%)	
40–60 years	2384 (20%)	2278 (21%)	106 (13%)	
> 60 years	9401 (79%)	8672 (79%)	729 (87%)	
Race, n (%)				<0.001
White	8922 (75%)	8417 (76%)	505 (60%)	
Asian	177 (1.5%)	158 (1.4%)	19 (2.3%)	
Black	905 (7.6%)	863 (7.8%)	42 (5.0%)	
Hispanic	244 (2.1%)	231 (2.1%)	13 (1.6%)	
Other	1625 (14%)	1366 (12%)	259 (31%)	

(*Continued*)

Table 1 (Continued).

Characteristic	Overall (n= 11,873)	Survivors (n=11035)	Non-Survivors (n=838)	p-value
Marital status, n (%)				<0.001
Divorced	1239 (10%)	1181 (11%)	58 (6.9%)	
Married	4716 (40%)	4397 (40%)	319 (38%)	
Single	2877 (24%)	2731 (25%)	146 (17%)	
Widowed	2105 (18%)	1977 (18%)	128 (15%)	
Other	936 (7.9%)	749 (6.8%)	187 (22%)	
BP (SDP/DBP, mmHg), n (%)				<0.001
<140/90	4913 (41%)	4771 (43%)	142 (17%)	
≥140/90	1615 (14%)	1568 (14%)	47 (5.6%)	
≥160/100	439 (3.7%)	421 (3.8%)	18 (2.1%)	
≥180/110	136 (1.1%)	133 (1.2%)	3 (0.4%)	
BMI (kg/m2), n (%)				<0.001
< 18.5	316 (2.7%)	299 (2.7%)	17 (2.0%)	
18.5–23.9	1482 (12%)	1414 (13%)	68 (8.1%)	
24.0–29.9	2403 (20%)	2313 (21%)	90 (11%)	
≥30	2772 (23%)	2687 (24%)	85 (10%)	
Comorbidity diseases, n (%)				
Congestive heart failure	4727 (40%)	4315 (39%)	412 (49%)	<0.001
Pulmonary hypertension	1299 (11%)	1148 (10%)	151 (18%)	<0.001
Hypertension	4925 (41%)	4639 (42%)	286 (34%)	<0.001
Respiratory failure	3421 (29%)	2798 (25%)	623 (74%)	<0.001
Chronic kidney disease	3161 (27%)	2888 (26%)	273 (33%)	<0.001
Diabetes mellitus	4046 (34%)	3758 (34%)	288 (34%)	0.9
Laboratory tests, n (%)				
ALT (IU/L)				<0.001
<40	4613 (39%)	4223 (38%)	390 (47%)	
40-120	1098 (9.2%)	967 (8.8%)	131 (16%)	
120-400	413 (3.5%)	342 (3.1%)	71 (8.5%)	
>400	179 (1.5%)	142 (1.3%)	37 (4.4%)	

(*Continued*)

Table 1 (Continued).

Characteristic	Overall (n= 11,873)	Survivors (n=11035)	Non-Survivors (n=838)	p-value
AST (IU/L)				<0.001
<40	4175 (35%)	3882 (35%)	293 (35%)	
40-120	1455 (12%)	1260 (11%)	195 (23%)	
120-400	517 (4.4%)	423 (3.8%)	94 (11%)	
>400	224 (1.9%)	167 (1.5%)	57 (6.8%)	
HbA1c (%)				0.5
<=6	806 (6.8%)	742 (6.7%)	64 (7.6%)	
6-8	553 (4.7%)	521 (4.7%)	32 (3.8%)	
>8	246 (2.1%)	230 (2.1%)	16 (1.9%)	
PLT (K/uL)	210 [158~272]	211 [159~273]	194 [133~264]	<0.001
SCr (mg/dL)	1.00 [0.80~1.40]	1.00 [0.70~1.40]	1.30 [0.90~1.90]	<0.001
WBC (K/uL)	9.2 [6.8~12.6]	9.1 [6.8~12.4]	11.5 [7.9~16.4]	<0.001
Steroid use	1205 (10%)	982 (8.9%)	223 (27%)	<0.001
The glucose readings	7 [4~13]	7 [4~12]	13 [7~23]	<0.001
GV	0.19 [0.13~0.28]	0.19 [0.12~0.27]	0.26 [0.18~0.35]	<0.001
GV (IQR)				<0.001
Q1	2969 (25%)	2898 (26%)	71 (8.5%)	
Q2	2968 (25%)	2807 (25%)	161 (19%)	
Q3	2968 (25%)	2709 (25%)	259 (31%)	
Q4	2968 (25%)	2621 (24%)	347 (41%)	

Notes: Continuous variables were presented as median (IQR). Categorical variables were presented as frequencies (percentages). The inter-group comparison was conducted using Wilcoxon rank sum test, Pearson's Chi-squared test, and Fisher's exact test.

Modeling Results

The results of the Cox proportional hazards regression analysis revealed that GV was significantly associated with in-hospital mortality in COPD patients.

When GV was treated as a continuous variable, the Cox regression analysis demonstrated that GV was an independent risk factor for in-hospital mortality in COPD patients, with a statistically significant association observed in the unadjusted (Model 1) (HR = 1.849, 95% CI 1.409–2.427, $P < 0.001$), the partially adjusted (Model 2) (HR = 1.880, 95% CI 1.432–2.468, $P < 0.001$), and the fully adjusted (Model 3) (HR = 1.551, 95% CI 1.110–2.167, P =0.01).

When GV was treated as a categorical variable, compared to Q1, the risk of mortality in Q4 was significantly increased in all models, with statistical significance observed in the unadjusted (Model 1) (HR =2.34, 95% CI 1.805–3.034, $P < 0.001$), the partially adjusted (Model 2) (HR = 2.249, 95% CI 1.734–2.916, $P < 0.001$), and the fully adjusted (Model 3) (HR = 1.314, 95% CI 1.006-0.716, $P = 0.045$) (Table 2).

Table 2 Results of Cox Proportional Hazards Model Analysis

Variables	Model 1		Model 2		Model 3	
In-hospital mortality	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
GV (Continuity)	1.849(1.409, 2.427)	<0.001	1.88(1.432, 2.468)	<0.001	1.551(1.110, 2.167)	0.01
GV (Categorical)						
Q1 (<0.126)	Ref		Ref		Ref	
Q2 (0.126–0.193)	1.302(0.983, 1.725)	0.066	1.22(0.921, 1.617)	0.166	0.861(0.648, 1.144)	0.302
Q3 (0.193–0.281)	1.796(1.377, 2.343)	<0.001	1.681(1.288, 2.194)	<0.001	1.048(0.799, 1.376)	0.733
Q4 (>0.281)	2.34(1.805, 3.034)	<0.001	2.249(1.734, 2.916)	<0.001	1.314(1.006, 1.716)	0.045

Notes: Model 1 was unadjusted. Model 2 was adjusted for confounders regarding demographics (age, gender and race). Model 3 was further adjusted based on Model 2 by adding BMI, ALT, AST, SCr, PLT, WBC, hypertension, congestive heart failure, respiratory failure, chronic kidney disease and steroid use.

RCS

The link between GV and in-hospital mortality risk exhibited significant nonlinearity, as demonstrated by RCS analysis in unadjusted, partially adjusted, and fully adjusted models (all *P*-nonlinear < 0.0001). HR reached its peak when GV was approximately 0.5, as shown in Figure 2.

Survival Curve

The survival curve analysis showed significant differences in survival outcomes from Q1 to Q4. The survival rate was the highest in Q1 and the lowest in Q4, as illustrated in Figure 3.

Subgroup Analysis

Subgroup analyses were executed based on age, sex, BMI, HbA1c, SCr, platelet levels, and the presence or absence of comorbid conditions such as DM, hypertension, respiratory failure, and chronic kidney disease. Results suggested that the association between GV and the risk of mortality was significant in the following subgroups: patients aged >60 years, females, those with BMI in the overweight range, non-DM patients, non-chronic kidney disease patients, those with HbA1c ≤ 6%, serum creatinine < 1.2 mg/dL, and platelet count ≤ 440 × 10^9/L. Additionally, regardless of hypertension

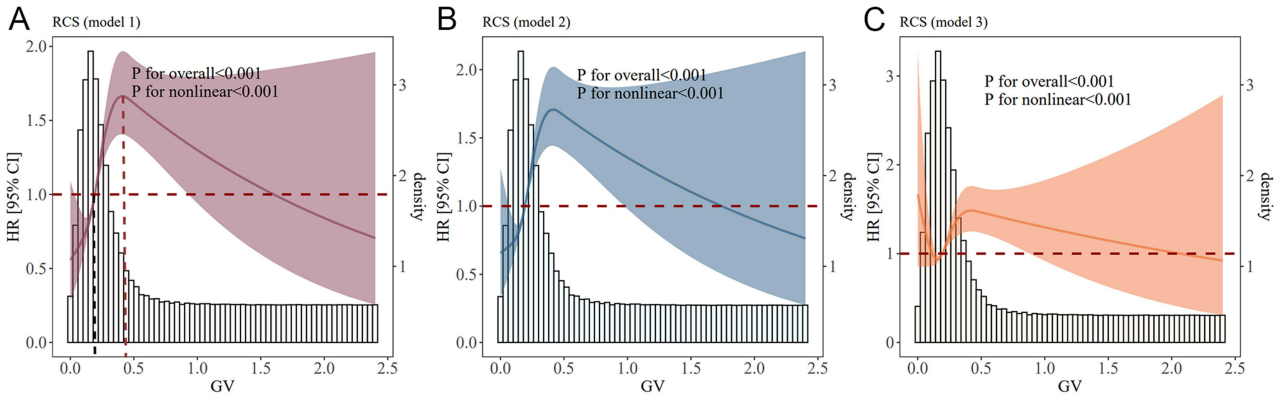

Figure 2 Significant nonlinear relationship between GV and in-hospital mortality. (**A**) model 1; When the GV value aligns with the position of the black vertical line, the hazard ratio (HR) equals 1, which denotes the baseline risk level. When the GV value corresponds to the position of the red vertical line, the risk of in-hospital mortality reaches the maximum level. (**B**) model 2; (**C**) model 3. Model 1 was unadjusted. Model 2 was adjusted for confounders regarding demographics (age, gender and race). Model 3 was further adjusted based on Model 2 by adding BMI, ALT, AST, SCr, PLT, WBC, hypertension, congestive heart failure, respiratory failure, chronic kidney disease and steroid use.

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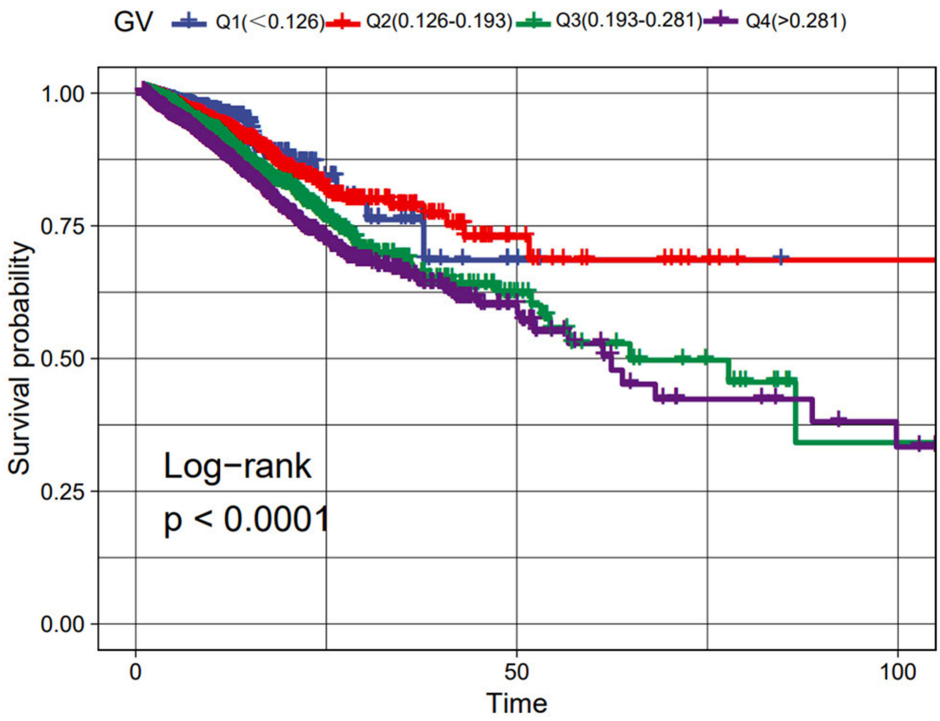

Figure 3 Survival curves in COPD patients with different levels of GV.

status, elevated GV was significantly associated with the risk of mortality. Moreover, interactions between GV and certain subgroups, including serum creatinine and sex, were observed (Figure 4).

Sensitivity Analysis

Given that the majority of COPD patients were aged 40 years or older, we conducted a sensitivity analysis in the subgroup of patients aged ≥40 years to mitigate potential bias in prognostic analysis introduced by including younger patients. The results showed that the in-hospital mortality of COPD patients over 40 years old was significantly correlated with GV in the unadjusted model, partially adjusted model, and fully adjusted model of Cox risk regression analysis. This result was consistent with the results of the total population. The specific data are shown in Appendix 1.

Discussion

Leveraging data from the MIMIC-IV database, this retrospective analysis incorporated 11873 COPD patients to investigate the association between GV and in-hospital mortality in COPD patients. The study found that GV was notably associated with in-hospital mortality in COPD patients, and the RCS analysis showed a significant nonlinear relationship between GV and in-hospital mortality in this population. COPD patients with different levels of GV showed significant differences in in-hospital survival rates. Therefore, evaluating GV can help assess the prognosis of hospitalized COPD patients.

DM is one of the common comorbidities in COPD and has a negative impact on the progression and prognosis of COPD patients.[17] According to statistics, the 5-year mortality risk for patients with both COPD and DM is approximately 20%.[18] On one hand, insulin resistance in DM promotes the release of pro-inflammatory factors in tissues, exacerbating pulmonary inflammation and thereby impairing lung function.[19] On the other hand, the chronic hyperglycemic state in DM patients increases the risk of pulmonary infections by impairing immune function and enhancing the virulence of infectious microorganisms.[17] Persistent hyperglycemia can also damage lung tissue structure through oxidative stress and chronic inflammatory pathways, accelerate pulmonary microvascular disease, and compromise the diffusion capacity of the lung.[20,21] Additionally, it may cause pulmonary autonomic neuropathy, leading to impaired mucociliary clearance and

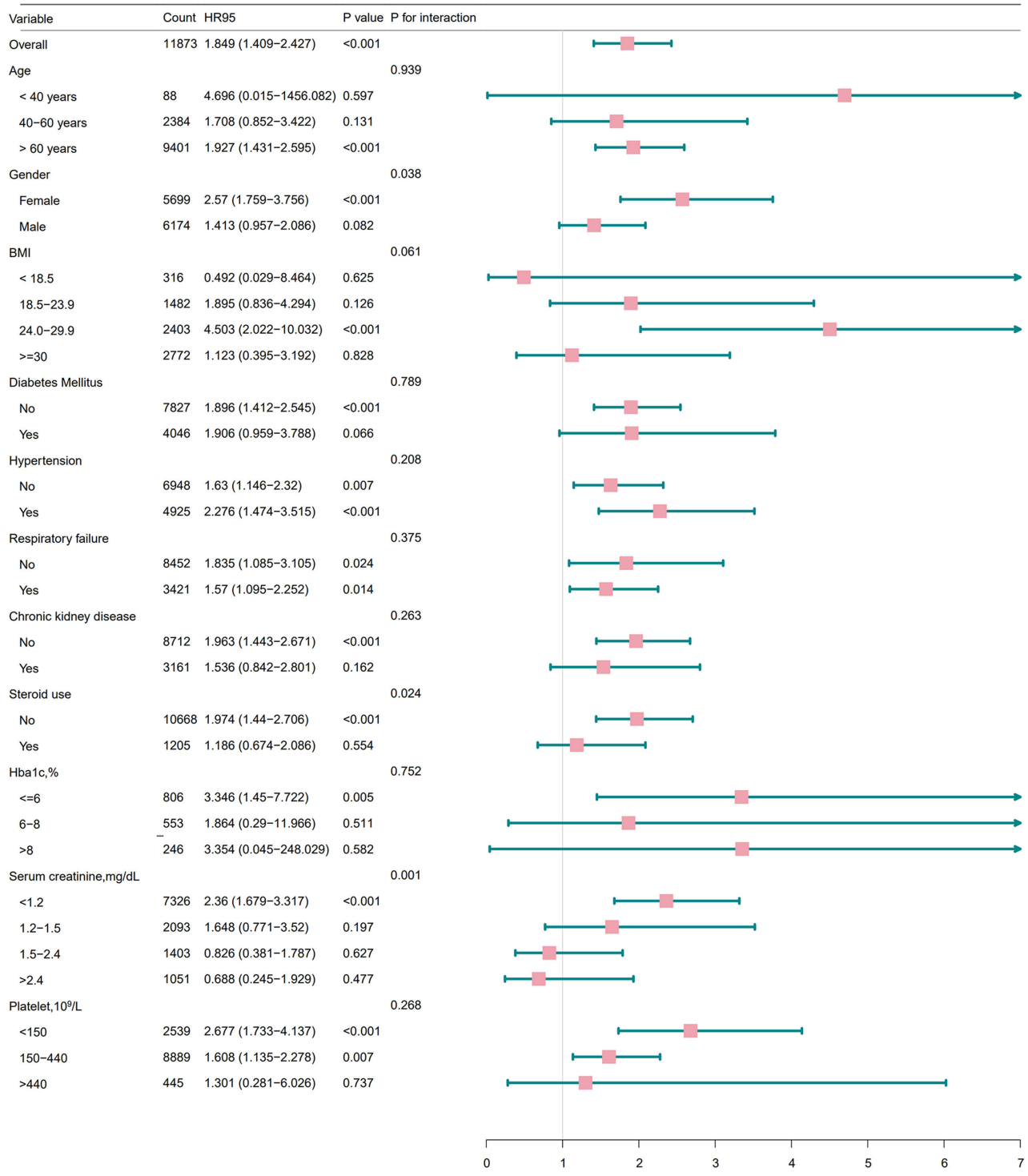

Figure 4 Forest plots for subgroup analyses of GV with in-hospital mortality: basic patient information, including age, sex, and BMI; other confounding factors, including whether they have diabetes, hypertension, respiratory failure, chronic kidney disease, steroid use; subgroup analysis of different glycated hemoglobin, SCr and platelet levels.

further increasing the risk of infections.[22] Therefore, for COPD patients with comorbid DM, active blood glucose management and high-quality glycemic control should be implemented to improve their prognosis.

In the blood glucose management of patients with comorbid DM, glycemic control targets are commonly based on HbA1C. However, HbA1C cannot fully reflect the short-term fluctuations and acute changes in blood glucose.[23,24]

Compared to chronic persistent hyperglycemia, some studies have revealed that acute glycemic fluctuations more strongly trigger oxidative stress[25] and are independently associated with the risk of various complications.[26] Therefore, short-term fluctuations in blood glucose also need to be considered. GV is an indicator of short-term fluctuations in blood glucose. It can provide some references for blood glucose management in COPD patients with diabetes.

Elevated GV may be associated with factors such as stress-induced hyperglycemia and acute hypoglycemia. Stress-induced hyperglycemia is observed in COPD patients regardless of whether they have underlying DM. COPD is primarily characterized by incompletely reversible airflow limitation, and acute exacerbations caused by infections are a significant reason for hospitalization in COPD patients. In severe cases, stimuli such as infection and persistent hypoxia caused by airflow limitation can trigger overactivation of the sympathetic nervous system and stress-induced insulin resistance. These responses lead to increased secretion of hyperglycemic hormones, promoting hepatic glycogen breakdown and ultimately resulting in stress-induced hyperglycemia.[27] Stress-induced hyperglycemia is a self-protective mechanism that ensures energy supply to vital organs. However, severe glycemic fluctuations can activate oxidative stress, leading to airway epithelial cell damage and apoptosis. These fluctuations also mediate the release of inflammatory mediators such as interleukin-6 and tumor necrosis factor-α, exacerbating chronic airway inflammation in COPD. Additionally, they can alter parasympathetic nerve signaling, inducing bronchial hyperresponsiveness.[28] These mechanisms collectively worsen COPD and contribute to poor prognosis.

In critically ill patients, those with underlying DM experience more pronounced glycemic fluctuations. This is due to the impaired or failed β-cell function in patients with DM, which results in insufficient insulin levels, reduced blood glucose regulation capacity, and a greater likelihood of blood glucose fluctuations.[29] However, DM itself may exert a protective effect against the adverse reactions caused by glycemic fluctuations. Studies[9,30] have shown that GV is more strongly associated with mortality in non-DM patients compared to DM patients. This finding aligns with the subgroup analysis results of this study. The findings may be due to the poorer tolerance of non-DM patients to glycemic fluctuations, resulting in stronger physiological responses such as oxidative stress. In contrast, DM patients, in a prolonged hyperglycemic state, experience negative feedback stimulation of their glucose regulatory systems, which provides better buffering capacity against stress-induced glycemic fluctuations.[31] This phenomenon may explain why GV is positively associated with in-hospital mortality at lower levels, but negatively associated with mortality at higher levels.

In addition, acute hypoglycemia can also lead to high GV. A cohort study[32] indicated that acute hypoglycemia in ICU patients—caused by factors such as enteral nutrition, mechanical ventilation, sedative medications, and intensive glycemic control therapies—is significantly associated with poor clinical outcomes. These findings indicate that both acute increases and decreases in blood glucose, resulting in high GV, are indicative of mortality risk.

For critically ill hospitalized patients, insulin therapy is commonly used for blood glucose management. However, the optimal range for glycemic control remains controversial. Intensive insulin therapy (IIT), which requires strict blood glucose control within 4.4–6.1 mmol/L, has been associated with greater glycemic fluctuations and an increased incidence of hypoglycemic events. The risks associated with such strict control may far outweigh the potential benefits.[33] Currently, methods such as continuous glucose monitoring (CGM) provide an effective approach to the clinical monitoring of GV. Exploring the relationship between GV and mortality in hospitalized COPD patients can assist in the early clinical assessment of patient prognosis. It can also help optimize glycemic control strategies by adopting more stable and gentle methods to regulate blood glucose levels.

Limitations

Since this study is retrospective and observational, it is infeasible to establish a causal relationship between GV and in-hospital mortality in COPD patients. Future prospective randomized controlled trials are needed to further investigate the connection between the two. In addition, GV only reflects the absolute magnitude of blood glucose fluctuations. Therefore, the findings of this study do not fully capture the impact of blood glucose fluctuations at different mean glucose levels or trends in glucose variation on the prognosis of hospitalized COPD patients. Although HbA1C was included in the subgroup analysis to address this limitation, the results were not statistically significant. In the future, additional blood glucose-related indicators, such as the stress hyperglycemia ratio and time in target glucose range, could be incorporated into comprehensive analyses to further enhance the role of GV in risk stratification and prognostic prediction for COPD patients. Moreover, variables such as diet, income, lifestyle, and the use of insulin, and other

hypoglycemic agents during hospitalization may also influence the results. However, these factors were not included in the analysis of this study. Finally, this study is based on the MIMIC-IV database, which predominantly includes White populations. Therefore, the conclusions drawn from this study may have limited applicability to Asian populations.

Conclusion

In conclusion, this study finds that GV is significantly associated with the prognosis of hospitalized COPD patients. The findings may help clinicians identify COPD patients with poor prognoses at an early stage, provide additional evidence supporting the benefits of glycemic control in these patients, and confirm the necessity of stable glycemic management. These results also offer guidance for a comorbidity management model for treating lung disease and DM concurrently.

Data Sharing Statement

The data for this study were obtained from the MIMIC-IV database (version 3.0). The original MIMIC database mining data, data cleaning records, and statistical analysis datasets used in this study are retained by He Jiajia, the first author of this manuscript. Researchers interested in accessing the data must first ensure that they have completed the official data use application and authorization process for the MIMIC database. They should then send a formal application Email to He Jiajia (first author of this manuscript) at 20230931615@bucm.edu.cn, clearly stating the purpose of data use, the intended research direction, and the academic background information of the individual or team. The first author will respond to the application within 7 working days and provide the research-related data on the premise that the applicant is confirmed to have met the MIMIC database usage specifications and relevant research ethics requirements.

Ethics Approval and Informed Consent

Ethical approval from the IRB of the Medical Emergency Center in Minhang District of Shanghai was not required because the MIMIC-IV database is publicly available, written informed consent was attained prior to data capture, and all participant data were anonymized.

Author Contributions

All authors have made substantial contributions to the reported work, whether in the conception, study design, execution, data acquisition, analysis or interpretation, or all of these areas, have participated in drafting, revising or critically reviewing the article, have given final approval of the version to be published, have agreed on the journal to which the article is being submitted and been responsible for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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