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Correlation between glycaemic variability and prognosis in diabetic patients with CKD

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Abstract

Introduction: Glycaemic variability (GV), rather than glucose level, has been shown to be an important factor associated with in-hospital mortality. The coefficient of variation of glucose (GLUCV) is one of the methods used to evaluate GV. However, the clinical significance of GLUCV in diabetes mellitus (DM) patients diagnosed with chronic kidney disease (CKD) as a risk factor for long-term adverse changes is unknown.

Material and methods: In this retrospective study, we extracted data of adult DM patients diagnosed with CKD from the Medical Information Mart for Intensive Care (MIMIC-IV). We sought to investigate the relationship between GV and in-hospital mortality as well as 30-day mortality. A non-parametric test was used to compare baseline characteristics between groups. Kaplan-Meier analysis and Cox regression model were used to analyse the risk factors associated with in-hospital and 30-day mortality.

Results: A total of 1572 DM patients with CKD were included in our data analysis. The quartile of the GLUCV values was used to assign subjects to 4 groups: GLUCV1 (GLUCV < 24), GLUCV2 (24 ≤ GLUCV < 31), GLUCV3 (31 ≤ GLUCV < 39) and GLUCV 4 (GLUCV ≥ 39). COX regression analysis revealed that the GLUCV was an independent risk factor for in-hospital and 30-day mortality [GLUCV2 group (HR = 0.639, 95% CI: 0.454–0.899, p = 0.010), GLUCV3 group (HR = 0.668, 95% CI: 0.476–0.936, p = 0.019), and GLUCV3 group (HR = 0.726, 95% CI: 0.528–0.999, p = 0.049)]. The Kaplan-Meier survival curve was steeper in the GLUCV1 and GLUCV4 groups, and the survival rate decreased in a time-dependent manner.

Conclusions: Herein, we validated GV as a mortality risk factor for DM patients with CKD. Therefore, monitoring and adjusting GV in hospitalized patients might have a significant treatment benefit.

Key words: *diabetes; chronic kidney disease; coefficient of variation of glucose; prognosis*

Introduction

Diabetes mellitus (DM) and chronic kidney disease (CKD) are 2 chronic diseases whose prevalence is on the rise [1]. Nearly half of diabetic patients eventually develop CKD [2], so managing glucose levels in DM patients with CKD is important. The dosage of hypoglycaemic drugs in diabetic patients should be adjusted according to renal function [3]. One of the significant barriers to glycaemic control in DM patients with CKD is hypoglycaemia; thus, close monitoring of glucose levels is essential [4]. Evaluation of long-term glycaemic control is an important aspect of management for DM patients. Several studies have confirmed associations between mortality in patients with diabetes and risk factors such as estimated glomerular filtration rate (eGFR), glycosylated haemoglobin A_{1c} (HbA_{1c}), and low-density lipoprotein cholesterol (LDL-C) [5–6]. However, few studies are being conducted to demonstrate the predictive value of glycaemic variability (GV). In recent years, numerous studies have revealed the possible adverse effects of fluctuations in the blood glucose of diabetics [7–9]. Data from the Verona Diabetes Study and the Taichung Diabetes Study suggest that GV is an independent predictor of mortality in patients with diabetes [10–12]. As a result, further research is needed to better understand the impact of abnormal blood glucose levels on the prognosis of DM patients. HbA_{1c} is traditionally regarded as the gold standard for evaluating blood glucose control [13], but clinically, GV is a more effective measure of glycaemic control than HbA_{1c}. GV refers to fluctuations in blood glucose levels, usually determined by measuring glucose levels or other related parameters over a given time interval (i.e. within a day, within a few days, or longer) [14]. New evidence shows that GV is associated with an increased risk of microvas-

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cular and macrovascular complications, hypoglycaemia, and mortality [15–17]. Using the MIMIC-IV database of critically ill patients, we investigated the relationship between glycaemic variability and in-hospital mortality as well as 30-day mortality in DM patients with CKD.

Material and methods

Database

Data were extracted from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database, which was established with approval from Massachusetts Institute of Technology (MIT) and the Institutional Review Board. Our study relied entirely on publicly available anonymized data and thus did not require individual patient consent. To gain access to the MIMIC-IV database, Zhong and Gao both passed the National Institutes of Health's Protected Human Study Participant exam. This single-centre database included more than 50,000 intensive care unit (ICU) patients. Demographic characteristics, International Classification of Diseases, Ninth Revision (ICD-9) coding diagnosis, physiological indicators, laboratory indices, and medications used by the patients admitted to the Beth Israel Deaconess Medical Centre, Boston between 2008 and 2019 were also included [18].

Data extraction

The structured query language (SQL) PostgreSQL (version 9.6) was used to extract data such as demographic information, laboratory indicators, complications, treatment status, and prognoses from the MIMIC-IV database. Demographic characteristics include age, body mass index [BMI, weight (kg)/height (m)^2], sex, and race. At least 3 central laboratory measurements of venous glucose samples taken from the patients during the ICU stay were studied retrospectively. The coefficient of variation (CV) [standard deviation (SD)/average value (Ave)] of each patient was used as a measure of GV [19]. The quartile of the GLUCV values was used to divide subjects into 4 groups: GLUCV1 (GLUCV < 24), GLUCV2 (24 ≤ GLUCV < 31), GLUCV3 (31 ≤ GLUCV < 39), and GLUCV 4 (GLUCV ≥ 39). Other laboratory data include haemoglobin (Hb), HbA_{1c}, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), LDL-C, triglyceride (TG), creatinine, blood urea nitrogen, urine protein, potassium, and sodium levels. Insulin was considered the primary hypoglycaemic therapy, while continuous renal replacement therapy (CRRT) was one of the used renal replacement therapies. In addition, complications include coronary heart disease (CHD), hypertension, hyperlipidaemia, and sepsis. The first 24-hour data were used for all the above variables except blood glucose. The primary outcome variable of our study was death during hospitalization and death during a 30-day period.

Population select criteria and outcome

According to the International Diabetes Association, all patients were initially diagnosed using ICD-9 code (code =250) or that of the American Diabetes Association (ADA) [20]. In this study, DM patients were extracted according to the ICD-9 code (code = 250). According to the International Society of Nephrology, all patients were initially diagnosed using the chronic kidney disease classification ICD-9 (code = 585) or the kidney disease improving global outcomes (KDIGO) [21]. Herein, patients with chronic kidney disease were selected according to chronic kidney disease classification ICD-9 code (code = 585) and graded according to glomerular filtration rate (GFR). Our study excluded the following: (1) patients younger than 18 years; (2) patients who were admitted to the ICU for less than 48 hours; and (3) patients who had less than 3 venous blood glucose measurements during their ICU stay. Only the first ICU admission was chosen for patients hospitalized more than once.

Statistical analysis

All continuous data were tested using the normal distribution test and expressed as mean ± standard deviation (X ± S). Measurement data of non-normal distribution were represented by the median, 25th percentile, and 75th percentile [M (P25, P75)]. Discrete data were expressed using n (%). The rank-sum and chi-square tests were used to test continuous and discrete variables, respectively. In addition, the relationship between risk factors and in-hospital mortality as well as 30-day mortality was determined by multivariate COX risk ratios for the satisfied independent variables after the univariate COX proportional risk assumption (the elimination test level was 0.10). Meanwhile, COX risk proportion determination subgroup analysis was conducted to further investigate the relationship between GLUCV and mortality risk during hospitalization and within a 30-day period. A p-value < 0.05 was considered statistically significant. To assess the relationship between GLUCV1, GLUCV2, GLUCV3, GLUCV4, and 30-day all-cause mortality, survival analysis was performed by constructing the Kaplan-Meier survival curve.

Result

Patient characteristics

The 1572 diabetic patients with CKD consisted of 993 males (63.2%) and 579 females (36.8%), with an average age of 61.0 ± 12.1 years. During hospitalization, 1271 patients survived and 301 died, with a fatality rate of 19.2%. There were 362 cases of GLUCV1 (GLUCV < 24) based on the level of blood glucose variation coefficient during hospitalization, including 238 male cases and 124 female cases, with an average age of 70.0 ± 11.1 years. In contrast, there were 403 GLUCV2 (24 ≤ GLUCV < 31) cases, including 264 male cases and 139 female cases, with an average age of 69.8 ± 12.3 years. A total of 400 cases were assigned to GLUCV3 (31 ≤ GLUCV < 39), including 239 male cases and 161 female cases, with an average age of 68.2 ± 11.4 years. There were 407 cases of GLUCV4 (GLUCV ≥ 39), including 252 male and 155 female cases, with an average age of 66.3 ± 12.7 years. Statistically significant differences were found in age, BMI, blood pressure, creatinine, urea nitrogen, blood sodium, haemoglobin, mean blood glucose, HbA_{1c}, insulin treatment, CRRT treatment, sepsis, and CKD stage among the 4 groups (p < 0.05). There were a total of 1513 patients receiving insulin hypoglycaemic treatment, accounting for 96.2%. According to KDIGO guidelines, there were 29 patients with stage CKD1, accounting for 1.8%; 105 patients with CKD2, accounting for 6.7%; 490 patients (31.2%) with CKD3; 563 patients (35.8%) with stage 4 CKD; and 385 patients with CKD5 stage, accounting for 24.5%. Only 15.2% of the subjects received kidney replacement therapy. The main complications were CHD, hypertension, sepsis, and hyperlipidaemia. (Fig. 1, Tab. 1).

Evaluation of risk factors for in-hospital mortality and 30-day mortality

All baseline data of patients were included in the COX regression equation, and after screening and elimina-

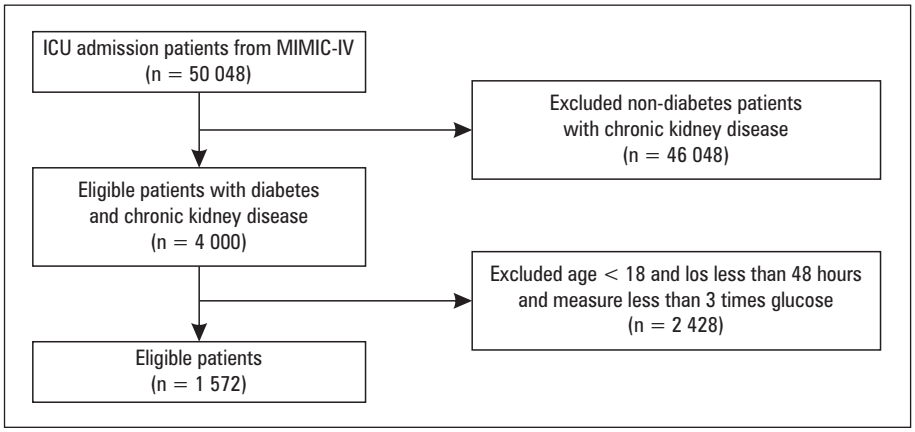

Figure 1. *Flowchart. ICU — intensive care unit; MIMIC-IV — Medical Information Mart for Intensive Care*

Table 1. ***Baseline characteristics of patients grouped by quartile of coefficient of variation of glucose (GLUCV) levels***

Variables n (%) or X ± S or M (P25, P75)	Quartile of GLUCV1	Quartile of GLUCV2	Quartile of GLUCV3	Quartile of GLUCV4	p value
Quartile range	< 24	24–31	31–39	≥ 39	
n	362	403	400	407	
Race, n (%)					**0.239**
White, n (%)	235 (14.9%)	260 (16.5%)	251 (16.0%)	233 (14.8%)	
Yellow, n (%)	8 (0.5%)	8 (0.5%)	10 (0.6%)	15 (1.0%)	
Black, n (%)	41 (2.6%)	55 (3.5%)	56 (3.6%)	70 (4.5%)	
Others, n (%)	78 (5.0%)	80 (5.1%)	83 (5.3%)	89 (5.7%)	
Gender, n (%)					**0.234**
Female, n (%)	124 (7.9%)	139 (8.8%)	161 (10.2%)	155 (9.9%)	
Male, n (%)	238 (15.1%)	264 (16.8%)	239 (15.2%)	252 (16.0%)	
Age [years]	72.0 ± 11.1	69.8 ± 12.3	68.2 ± 11.4	66.3 ± 12.8	< 0.001
BMI [kg/m^2]	31.2 (26.9–35.5)	30.3 (26.1–34.7)	30.8 (26.0–34.7)	29.5 (24.9–32.8)	< 0.001
Blood pressure					
Systolic blood pressure [mm Hg]	119.7 (109.0–133.0)	119.7 (101.0–126.0)	119.7 (102.0–125.8)	119.7 (115.0–129.0)	0.001
Diastolic blood pressure [mm Hg]	55.6 (51.0–62.3)	55.6 (49.0–59.0)	55.6 (48.0–58.0)	55.6 (53.0–59.0)	0.002
Laboratory indices					
Creatinine [mg/dL]	1.7 (1.3–2.8)	1.9 (1.4–3.3)	2.1 (1.5–3.6)	2.3 (1.5–3.7)	< 0.001
Blood urea nitrogen [mg/dL]	33.0 (24.0–52.3)	38.0 (26.0–55.0)	43.0 (29.0–65.0)	45.0 (30.0–69.0)	< 0.001
Total cholesterol [mg/dL]	136.7 ± 22.6	135.1 ± 17.7	134.9 ± 21.0	135.8 ± 21.0	0.289
Triglyceride [mg/dL]	184.4 (184.4–184.4)	184.4 (184.4–184.4)	184.4 (184.4–184.4)	184.4 (184.4–184.4)	0.540
HDL-C [mg/dL]	38.6 ± 6.5	38.6 ± 6.4	37.8 ± 6.1	38.3 ± 7.0	0.413
LDL-C [mg/dL]	71.6 ± 16.0	69.4 ± 12.5	70.0 ± 16.4	69.5 ± 15.4	0.178
Potassium [mEq/L]	4.4 (3.9–4.9)	4.4 (4.0–4.8)	4.5 (4.0–5.0)	4.5 (4.0–5.1)	0.052
Sodium [mEq/L]	139.0 (135.8–141.0)	138.0 (135.0–141.0)	138.0 (135.0–141.0)	137.0(134.0–141.0)	0.024
Haemoglobin [g/dL]	10.6 ± 2.2	10.3 ± 2.1	10.3 ± 2.0	10.1 ± 2.1	0.014
Urine protein [mg/dL]	113.5 (30.0–113.5)	113.5 (30.0–113.5)	113.5 (32.5–113.5)	113.5 (30.0–113.5)	0.949
Mean of glucose [mg/dL]	19.2 (16.1–22.0)	27.4 (25.9–29.1)	34.7 (32.8–36.7)	46.7 (42.1–54.1)	< 0.001

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Table 1. *Baseline characteristics of patients grouped by quartile of coefficient of variation of glucose (GLUCV) levels*

Variables n (%) or X ± S or M (P25, P75)	Quartile of GLUCV1	Quartile of GLUCV2	Quartile of GLUCV3	Quartile of GLUCV4	p value
Haemoglobin A_{1c} (%)	7.5 (7.4–7.5)	7.5 (7.4–7.5)	7.5 (7.5–7.5)	7.5 (7.5–7.5)	< 0.001
Hypoglycaemic medication [n (%)]					
Insulin	322 (20.5%)	395 (25.1%)	395 (25.1%)	401 (25.5%)	< 0.001
Renal replacement therapy [n (%)]					
CRRT	38 (2.4%)	53 (3.4%)	86 (5.5%)	66 (4.2%)	< 0.001
Complications [n (%)]					
CHD	16 (1.0%)	9 (0.6%)	12 (0.8%)	9 (0.6%)	0.235
Hyperlipidaemia	201 (12.8%)	233 (14.8%)	219 (13.9%)	202 (12.8%)	0.120
Hypertension	22 (1.4%)	35 (2.2%)	38 (2.4%)	25 (1.6%)	0.162
Sepsis	86 (5.5%)	97 (6.2%)	107 (6.8%)	133 (8.5%)	0.016
CKD1					**< 0.001**
CKD2	10 (0.6%)	6 (0.3%)	2 (0.1%)	11 (0.7%)	
CKD3	39 (2.5%)	27 (1.7%)	16 (1.0%)	23 (1.5%)	
CKD4	138 (8.8%)	131 (8.3%)	116 (7.4%)	105 (6.7%)	
CKD5	108 (6.9%)	147 (9.4%)	160 (10.2%)	148 (9.4%)	
Outcomes [n (%)]					
In-hospital mortality	69 (22.9%)	64 (21.3%)	69 (22.9%)	99 (32.9%)	0.013
30-day mortality	81 (23.3%)	77 (22.1%)	79 (22.7%)	111 (31.9%)	0.021
365-day mortality	88 (30.0%)	83 (21.7%)	87 (22.7%)	125 (32.6%)	0.004

BMI — body mass index; HDL-C — high-density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol; CRRT — continuous renal replacement therapy; CHD — coronary heart disease; CKD — chronic kidney disease; M (P25, P75) — median, 25% percentile and 75% percentile; X ± S — mean ± standard deviation

tion by univariate COX regression analysis (the test level of the elimination variables was 0.10), the results showed that age (hazard ratio [HR] = 1.016, 95% confidence interval [CI]: 1.005–1.027, p < 0.001), sepsis (HR = 1.852, 95% CI: 1.471–2.333, p = 0.023), GLUCV2 group (HR = 0.639, 95% CI: 0.454–0.899, p = 0.010), and GLUCV3 group (HR = 0.668, 95% CI: 0.476–0.936, p = 0.019) were independent risk factors for death during hospitalization. In GLUCV grouping, taking the GLUCV1 group as the reference group, the GLUCV2 and GLUCV3 groups were both found to be protective factors for mortality during hospitalization (HR < 1). Moreover, COX regression analysis also showed that age (HR = 1.016, 95% CI: 1.005–1.027, p = 0.004), CRRT (HR =2.007, 95% CI: 1.562–2.578, p < 0.001), creatinine (HR = 0.926, 95% CI: 0.869–0.986, p = 0.017), sepsis (HR = 3.318, 95% CI: 1.862–2.886, p < 0.001), GFR (HR = 0.982, 95% CI: 0.973–0.991, p < 0.001), and GLUCV3 group (HR = 0.726, 95% CI: 0.528–0.999, p = 0.049) were independent risk factors for death within 30 days. In GLUCV grouping, the GLUCV1 group was taken as the reference group, and the GLUCV3 group was found to be a protective factor for mortality during hospitalization (Tab. 2, 3).

Table 2. *Cox regression model analysing the risk factors associated with in-hospital mortality*

	HR (95% CI)	p value
Age	1.025 (1.014–1.036)	< 0.001
Sepsis	1.852 (1.471–2.333)	0.023
GLUCV1 group	1	1
GLUCV2 group	0.639 (0.454–0.899)	0.010
GLUCV3 group	0.668 (0.476–0.936)	0.019
GLUCV4 group	0.869 (0.635–1.189)	0.379

GLUCV — coefficient of variation of glucose; HR — hazard ratio; CI — confidence interval

Subgroup analyses

To further determine the reliability of the relationship between the coefficient of variation in blood glucose and the risk of in-hospital death, we included age, sex, BMI, and complications in the subgroup analysis. We found that a high coefficient of glycaemic variability was associated with an increased risk of death in hospitalized patients without hyperlipidaemia (HR = 1.003, 95% CI: 1.000–1.004, p = 0.018) or BMI < 28 (HR = 1.003, 95% CI: 1.000–1.005, p = 0.026). Also, COX regres-

Table3. Cox ***regression model analysing the risk factors associated with 30-day mortality***

	HR (95% CI)	p value
Age	1.016 (1.005–1.027)	0.004
CRRT	2.007 (1.562–2.578)	< 0.001
Creatine	0.926 (0.869–0.986)	0.017
Sepsis	3.318 (1.862–2.886)	< 0.001
GFR	0.982 (0.973–0.991)	< 0.001
GLUCV1 group	1	1
GLUCV2 group	0.827 (0.604–1.131)	0.234
GLUCV3 group	0.726 (0.528–0.999)	0.049
GLUCV4 group	1.093 (0.814–1.469)	0.554

GLUCV — coefficient of variation of glucose; CRRT — continuous renal replacement therapy; GFR — glomerular filtration rate; HR — hazard ratio; CI — confidence interval

sion showed that age ≤ 65 years (HR = 1.004, 95% CI: 1.002–1.006, p = 0.002), male sex (HR = 1.003, 95% CI: 1.001–1.005, p = 0.008), no hyperlipidaemia (HR = 1.004, 95% CI: 1.004, p = 0.002) 1.002–1.007, p = 0.001), sepsis (HR = 1.004, 95% CI: 1.001–1.006, p = 0.002), and BMI < 28 (HR = 1.004, 95% CI: 1.001–1.006, p = 0.002) were significant factors. Moreover, a high coefficient of glycaemic variability was associated with an increased risk of 30-day mortality (Tab. 4, 5).

Kaplan-Meier analysis

The Kaplan-Meier survival curve of GLUCV patients in the 4 groups was statistically significant ($p < 0.05$). The curves of the GLUCV1 and GLUCV4 groups were steeper than those of the other 2 groups, and the survival rate decreased in a time-dependent manner, as shown in Figure 2.

Discussion

HbA_{1c} is commonly used clinically to assess the most recent blood glucose levels of patients [22]. The coefficient of glycaemic variability has been used as an alternative to assessing patients' average blood glucose levels in recent years [23]. This study investigated the link between glycaemic coefficient variation and long-term outcomes in 1572 DM patients with CKD. Herein, GLUCV was found to be an independent risk factor for mortality during hospitalization and within 30 days. Our findings suggest that GLUCV may be able to predict all-cause mortality in diabetic patients with CKD.

In 2006, emerging literature began to define associations between CV and mortality in various critically ill patient populations. Over a 4-year period, Egi et al. examined blood glucose data from 7049 Australian patients admitted to 5 different ICUs [24–26]. Non-sur-

Table 4. ***The relationship between risk factors and in-hospital mortality with coefficient of variation of blood glucose was analysed in subgroups***

	HR (95% CI)	p value
Age		
> 65	0.994 (0.981–1.008)	0.415
≤ 65	1.002 (1.000–1.004)	0.087
Gender		
Male	1.002 (1.000–1.004)	0.082
Female	0.999 (0.995–1.002)	0.543
Hyperlipidaemia		
No	1.003 (1.000–1.004)	0.018
Yes	0.987 (0.971–1.003)	0.118
Hypertension		
No	1.000 (0.998–1.001)	0.688
Yes	1.029 (0.994–1.066)	0.107
Sepsis		
No	0.999 (0.994–1.003)	0.538
Yes	1.002 (1.000–1.004)	0.100
BMI		
< 28	1.003 (1.000–1.005)	0.026
≥ 28	0.995 (0.980–1.010)	0.520

BMI — body mass index; HR — hazard ratio; CI — confidence interval

Table 5. ***The relationship between risk factors and 30-day mortality with the coefficient of variation of blood glucose was analysed in subgroups***

	HR (95% CI)	p value
Age		
> 65	0.996 (0.985–1.007)	0.449
≤ 65	1.004 (1.002–1.006)	0.002
Gender		
Male	1.003 (1.001–1.005)	0.008
Female	0.999 (0.996–1.003)	0.633
Hyperlipidemia		
No	1.004 (1.002–1.007)	0.001
Yes	0.992 (0.978–1.007)	0.293
Hypertension		
No	1.000 (0.999–1.001)	0.943
Yes	1.013 (0.981–1.047)	0.413
Sepsis		
No	0.998 (0.993–1.004)	0.587
Yes	1.004 (1.001–1.006)	0.002
BMI		
< 28	1.004 (1.001–1.006)	0.002
≥ 28	0.999 (0.994–1.004)	0.587

BMI — body mass index; HR — hazard ratio; CI — confidence interval

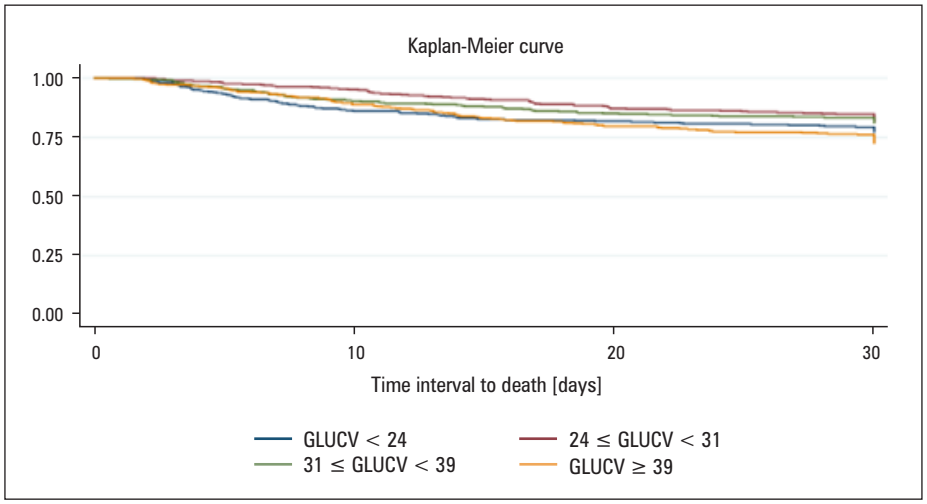

Figure 2. *Kaplan-Meier curve; GLUCV — coefficient of variation of glucose*

vivors had higher SD and CV, and multivariate analysis revealed that SD and CV were both significantly related to mortality [19]. In the present study, we found that GV was significantly associated with in-hospital and 30-day mortality.

COX regression subgroup analysis revealed that a high coefficient of glycaemic variation increased the risk of in-hospital death among hospitalized patients without hyperlipidaemia or BMI < 28, indicating the reliability of the relationship between the coefficient of glycaemic variation and the risk of in-hospital death. Meanwhile, a high coefficient of glycaemic variability was associated with an increased risk of 30-day mortality in male patients aged ≤ 65 years, without hyperlipidaemia, with sepsis, and with BMI < 28. Thus, to reduce the risk of death, we should pay close attention to the blood glucose fluctuations of ICU patients in the above subgroups. GLUCV could be used as a factor for the long-term prognosis of DM patients with CKD. Variations in blood glucose levels may indicate an increased risk of death due to poor health and complications. Previous studies have considered associations between baseline comorbidities and mortality; however, they could only account for a fraction of these associations [23]. In addition, glucose fluctuations have been shown to lead to the overproduction of superoxide, a key risk factor in the pathogenesis of diabetic complications. Increased complications of diabetes further increase mortality [27–28].

Our study has several advantages, including a retrospective cohort study design and follow-up of patients with out-of-hospital outcomes. Nevertheless, the study also had several limitations. Firstly, unlike RCTs, glucose measurements in this study were taken from clinical follow-up, so the frequency and interval between measurements varied from patient to patient. Although we adjusted the effect of glucose measurement frequency on variability, the difference in spacing between glucose measurements was not fully addressed. Secondly, we did not extract the relevant system scores of severe patients due to a lack of information, which may affect our results. Finally, not all participants underwent measurement of baseline HbA_{1c}, which has been identified as an independent risk factor for macrovascular events that may result in an increase in mortality [28].

In conclusion, glycaemic variability is a valid independent predictor of all-cause mortality in DM patients with CKD. In diabetic patients with chronic kidney disease, strict control of glycaemic variability may provide additional protection against mortality. Further randomized controlled trials investigating the beneficial effects of maintaining stable blood glucose levels are required to validate our findings and confirm direct causality.

Contributions

M.G. designed the study and helped write the manuscript, Z.Z. collected and analysed the data, Y.Y. performed data analyses, and F.L. designed, supervised, and wrote the manuscript. The final manuscript has been read and approved by all authors.

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Conflict of interest

The authors declare no conflict of interest.

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Ethical approval

The MIMIC IV database used in the present study was approved by the Institutional Review Board (IRB) of the MIT and did not contain protected health information.

Informed consent

The MIMIC IV is a publicly and freely available database, and patient consent is not needed prior to use.

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