Submitted: 22 September, 2022 Accepted: 30 December, 2022 Published: 08 July, 2023 DOI:10.22514/sv.2023.064

Open Access
Signa Vitae

ORIGINAL RESEARCH

The effect of blood glucose variability on the survival of patients in the intensive care unit: a prospective observational study

Ozgur Diyar Yavuz[1], Asu Ozgultekin[2,*], Ferhunde Dilek Subasi[2], Osman Ekinci[2]

[1]Department of Anesthesiology and Intensive Care, Van Baskale State Hospital, 65600 Van, Turkey
[2]Department of Anesthesiology and Intensive Care, Haydarpaşa Numune Training and Research Hospital; University of Health Sciences, 34674 Istanbul, Turkey

***Correspondence**
asuozgultekin@yahoo.com
(Asu Ozgultekin)

Abstract

Although hypoglycemia and hyperglycemia are common in patients in the intensive care unit (ICU) and may negatively impact treatment outcomes, glycemic variability has recently gained attention as a promising risk factor in these patients. This study investigated the impact of hypoglycemia, hyperglycemia and glycemic variability on the outcomes of ICU patients. Daily blood glucose levels measured for the study participants were classified as within the reference range of 110–180 mg/dL or outside the reference range at <110 mg/dL or >180 mg/dL. Glycemic variability was classified as a fluctuation in daily blood glucose levels by >70 mg/dL. These measurements were standardized by dividing the number of daily blood glucose levels and glycemic variability outside the reference range by the number of daily levels within the reference range, which yielded the glycemic ratio (GR) and delta (Δ)-glucose ratio (ΔGR), respectively, and were compared between survivors and non-survivors. A total of 358 patients were prospectively assessed in this study. Our results showed that GR was 0.74 in survivors and 1.04 in non-survivors (p: 0.002), whereas ΔGR was 0.73 in survivors and 1.0 in non-survivors ($p < 0.001$). Additionally, the mortality rates were 54.4% and 30.6% for patients with an overall mean Δglucose >70 mg/dL and <70 mg/dL ($p < 0.001$), respectively. Altogether, an increase in overall mean Δglucose, ΔGR and GR resulted in an increased mortality risk in hypoglycemic and hyperglycemic ICU patients.

Keywords

Blood glucose control; Glycemic variability; Hyperglycemia; Intensive care unit; Mortality

1. Introduction

Hyperglycemia in the intensive care unit (ICU) may occur due to decompensated diabetes, newly diagnosed diabetes or stress hyperglycemia [1]. Burns, surgery, trauma, infection, myocardial ischemia and hypoxia are leading causes of stress, in which hyperglycemia may develop as a response to these conditions. Hyperglycemia can also be caused by several other factors, including steroid use, vasopressors, enteral and parenteral nutrition, infusion fluids high in glucose, and immobilization [2].

In healthy individuals, plasma glucose levels are maintained within a narrow range by insulin and counter-regulatory hormones such as glucagon, epinephrine, cortisol and growth hormones that balance the glucose metabolism between the liver and peripheral tissues [1, 3]. Although stress-induced hyperglycemia in ICU patients is considered an adaptive response to protect the body's normal functioning by providing glucose to tissues with poor perfusion at the microvascular level, recent studies have shown that hyperglycemia in critically ill patients might be a significant risk factor for mortality and morbidity [3, 4]. In addition, the accumulation of an excess glucose level in various tissues, such as renal tubular cells, endothelial cells, hepatocytes and brain neurons, can lead to the dysfunction of these tissues. Cytokines released during hyperglycemia and stress decrease endothelial nitric oxide levels, leading to impaired vascular reactions and perfusion, macrophage and neutrophil dysfunction, impairment in cytokine release and phagocytosis, and an increase in the production of free radicals and inflammation. Presently, there has been an increase in hypoglycemia in ICU patients due to strict glycemic control [5].

Hypoglycemia is defined as a plasma glucose level of <70 mg/dL, and severe hypoglycemia as a plasma glucose level of <40 mg/dL. Hypoglycemia is characterized by a decrease in plasma glucose level, subsequent activation of the sympathetic system, and impaired brain functions. Since glucose is the only energy source for the brain, untreated hypoglycemia can lead to acute impairment of brain functions, loss of consciousness, and death [6].

Although the negative effects of hyperglycemia in critically ill patients develop over several hours or days, acute hypoglycemia is an independent predictor of mortality, making it critical to implement effective preventive measures and timely diagnosis and treatment [7].

In addition to hyperglycemia and hypoglycemia in ICU patients, blood glucose variability has also been shown to create oxidative stress, causing more damage than hyperglycemia [8].

In this present study, we investigated the association of blood glucose levels outside the reference range and daily blood glucose variability with ICU mortality, and also examined the potential use of the cut-off values obtained for the data as a predictor of mortality.

2. Methods

Over the course of a year, patients admitted to the ICU of Haydarpasa Numune training and research hospital for medical and surgical reasons participated in this prospective, observational cohort study. Sample size analysis was performed using a 95% confidence interval and 90% power, which suggested that at least 358 patients should be enrolled.

2.1 Exclusion criteria

—Patients who were positive for Coronavirus Disease 2019 (COVID-19) at the time of admission to the intensive care unit were excluded as the reliability of glycemic measurements could have been affected by the intensive use of corticosteroid and high-dose vitamin C treatments. To make an evaluation independent of disease severity, patients with a Sequential Organ Failure Assessment (SOFA) score of >8 were excluded.

—Age <18 years

—ICU length of stay <24 hours

—Less than four readings of blood glucose monitoring per day

The measurements were taken using a STANDARD™ GlucoNavii GDH glucose meter (Gurgaon, Haryana 122052, India), and daily arterial blood gas and biochemistry measurements were compared. A dietitian in the ICU monitored patients' nutrition status in accordance with The European Society for Clinical Nutrition and Metabolism (ESPEN) nutrition protocol. Patients with diabetes mellitus (DM) were included in the study and evaluated by subgroup analysis.

2.2 Data and ratios assessment

2.2.1 Glucose level

Blood glucose levels were measured for each patient throughout their hospital stay and categorized into the following ranges:

—Within the reference range (WR): 110–180 mg/dL

—Outside the reference range (OR): <110 mg/dL or >180 mg/dL

The mean blood glucose level of each patient was obtained by calculating the number of blood glucose levels measured within and outside the reference range throughout the ICU stay and divided by the length of stay (LOS) (in days).

2.2.2 Glycemic Ratio (GR)

GR was calculated using the number of daily blood glucose levels outside the reference range (nOR) divided by the number of daily blood glucose levels within the reference range (nWR) measured for each patient during the entire ICU stay.

2.2.3 Delta (Δ)-glucose

This represents the difference between the daily maximum and minimum blood glucose levels for each patient. According to the glycemic follow-up protocol used in our ICU, we considered a glucose value between 110–180 mg/dL and this 70 mg/dL daily variation as normal. Accordingly, glycemic variability was defined as fluctuation in daily glucose levels of >70 mg/dL, which was calculated for each patient in terms of:

—Number of days when Δglucose was ≤ 70 mg/dL and

—Number of days when Δglucose was >70 mg/dL.

2.2.4 Delta (Δ)-glucose mean

This represents the arithmetic mean of daily Δglucose values calculated during hospitalization. Here, 70 mg/dL was considered the upper limit value for Δglucose. Daily Δglucose values for each patient were classified below and above the determined cut-off value.

2.2.5 Δglucose ratio (ΔGR)

This is the ratio of the number of days with a delta (Δ)-glucose of >70 mg/dL to the number of days with Δglucose of ≤ 70 mg/dL according to the daily measurements of each patient.

2.3 Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS, version 22, Chicago, IL, USA) software. The Kolmogorov-Smirnov test was used to examine whether variables were normally distributed. The data are expressed in percentage, median, interquartile range (IQR) and confidence interval (CI). Normally distributed data were analyzed using the *t*-test and Analysis of Variance (ANOVA) test, and non-normally distributed data were analyzed using the Mann-Whitney U test, Kruskal-Wallis test and survival tables. Receiver operating characteristic (ROC) analysis was performed. Significance level for comparing differences between data was set at $p < 0.05$.

3. Results

Of the 456 patients enrolled in the study, 358 met the criteria. The study flow chart is shown in Fig. 1. The mean age of this study cohort was 69.18 $\pm$ 17.99 years. Of them, 51.1% (n = 183) were males, and 32.1% (n = 115) were diabetic. The patients were admitted to the ICU for medical (respiratory, sepsis-related, neurological, amongst others) (n = 283; 79%) and surgical (trauma, postoperative conditions, amongst others) (n = 75; 21%) reasons. Respiratory ailments were the leading cause of ICU admission, accounting for 44.7% (n = 160) of all diagnoses. The mortality rate of the patients included in the study was 38.3% (Table 1). The mean SOFA score of this study was 4.3 $\pm$ 2.4, and the mean length of stay in the ICU was 10.4 $\pm$ 10.1 days.

Table 2 presents patient outcomes according to blood glucose level, GR and Δglucose classification. Non-survivors were found to have significantly higher blood glucose levels outside the reference range and Δglucose >70 mg/dL, as well as a significantly higher GR and ΔGR ($p < 0.001$ and $p < 0.002$).

The mortality rate was significantly higher in patients with a mean Δglucose of >70 mg/dL (54.4%) than in those with a mean Δglucose of ≤70 mg/dL (30.6%) ($p < 0.001$) (Table 3).

The normal reference range of blood glucose levels in our clinic is 110–180 mg/dL, based on which the patients were divided into three groups, whereby 253 (70.5%) had mean glucose levels within the reference range, 48 (13.5%) below the reference range, and 57 (16%) above the reference range. Although the group with values above the reference range had a slightly higher mortality rate, the difference between this group and those below the reference range was not statistically significant ($p = 0.164$).

The subgroup analysis of 115 diabetic patients included in the study showed statistically significant differences between diabetic and non-diabetic patients in regard to blood glucose levels, Δglucose, GR and ΔGR ($p < 0.001$) (Table 4). Increased GR and ΔGR were found to correlate significantly with increased mortality in non-diabetic patients, but this was not the case in diabetic patients.

A comparison of patients' ICU outcomes based on the status of DM showed no statistically significant difference between the patients. The mortality rate in the DM (+) group and DM (-) group was 40.9% and 37% ($p > 0.05$), respectively.

Table 5 illustrates the subgroup analysis of all patients included in this study and shows statistically significant differences between medically and surgically treated patients in regard to GR and ΔGR ($p = 0.001$ and $p < 0.001$).

Survival analysis based on mean Δglucose showed significantly lower 14- and 28-day survival for patients with a mean value of >70 mg/dL ($p = 0.001$ and $p = 0.001$) (Table 6).

We also analyzed the correlation of mean blood glucose level, GR, Delta (Δ)-glucose mean and ΔGR with the length of mechanical ventilation and ICU LOS and found that these durations were weakly correlated with Δglucose ratio only and had no significant correlation with the other parameters.

ROC analysis was performed for blood glucose measurements and ratios predicted ICU outcomes (discharge/death). Although the results showed that the areas under the curve were significant, these cut-off values were found to be poor predictors of mortality (Fig. 2). According to the mean Δglucose survival analysis, the mean survival time was 24.4 days in patients with a mean Δglucose of ≤70 mg/dL and 14.0 days in patients with a mean Δglucose of >70 mg/dL ($p = 0.001$) (Fig. 3).

4. Discussion

The harmful effects of severe hyperglycemia can be very broad, ranging from electrolyte disorders such as hypokalemia, hypomagnesemia, hypophosphatemia, osmotic diuresis, dehydration and coma to diabetic ketoacidosis caused by accelerated lipolysis and ketogenesis due to insulin deficiency in patients with type 1 DM.

TABLE 1. Demographic characteristics, reasons for hospitalization, presence of diabetes mellitus and ICU outcomes.

Variable	n	%
Sex		
Female	175	48.9
Male	183	51.1
Age		
18–45	42	11.7
46–64	63	17.6
65–84	188	52.5
85+	65	18.2
Reasons for hospitalization		
Respiratory	160	44.7
Cardiovascular	7	2.0
Sepsis	37	10.3
Neurological	44	12.3
Gastrointestinal	6	1.7
Trauma	11	3.1
Others	29	8.1
Orthopedic Postoperative	45	12.6
General Surgery Postoperative	10	2.8
Neurosurgery Postoperative	5	1.4
Urology Postoperative	4	1.1
DM		
Non-diabetic	243	67.9
Diabetic	115	32.1
ICU Outcomes		
Alive	221	61.7
Dead	137	38.3
Total	358	100.0

DM: diabetes mellitus; ICU: intensive care unit.

Hyperglycemia can also impair phagocytosis functions and affect cellular immunity, increasing susceptibility to infections. Increased morbidity is caused by factors such as disrupting the patient's immune mechanism and increased inflammatory cytokines, which can lead to oxidative stress and endothelial dysfunctions. Hyperglycemia may also increase the release of free fatty acids, affect endothelial nitric oxide production, disrupt endothelium-dependent vasodilation, increase the risk of ischemia by increasing myocardial oxygen demand, reduce myocardial contractility and cause cardiac rhythm disorders [9].

These findings have encouraged ICU professionals to practice strict glycemic control, which has unfortunately led to an increase in hypoglycemia in some practices [7].

Glycemic variability in ICU patients has started to attract researchers' attention, similar to hyperglycemia and hypoglycemia in this setting. In addition to adequate control of hyperglycemia and hypoglycemia, low glycemic variability

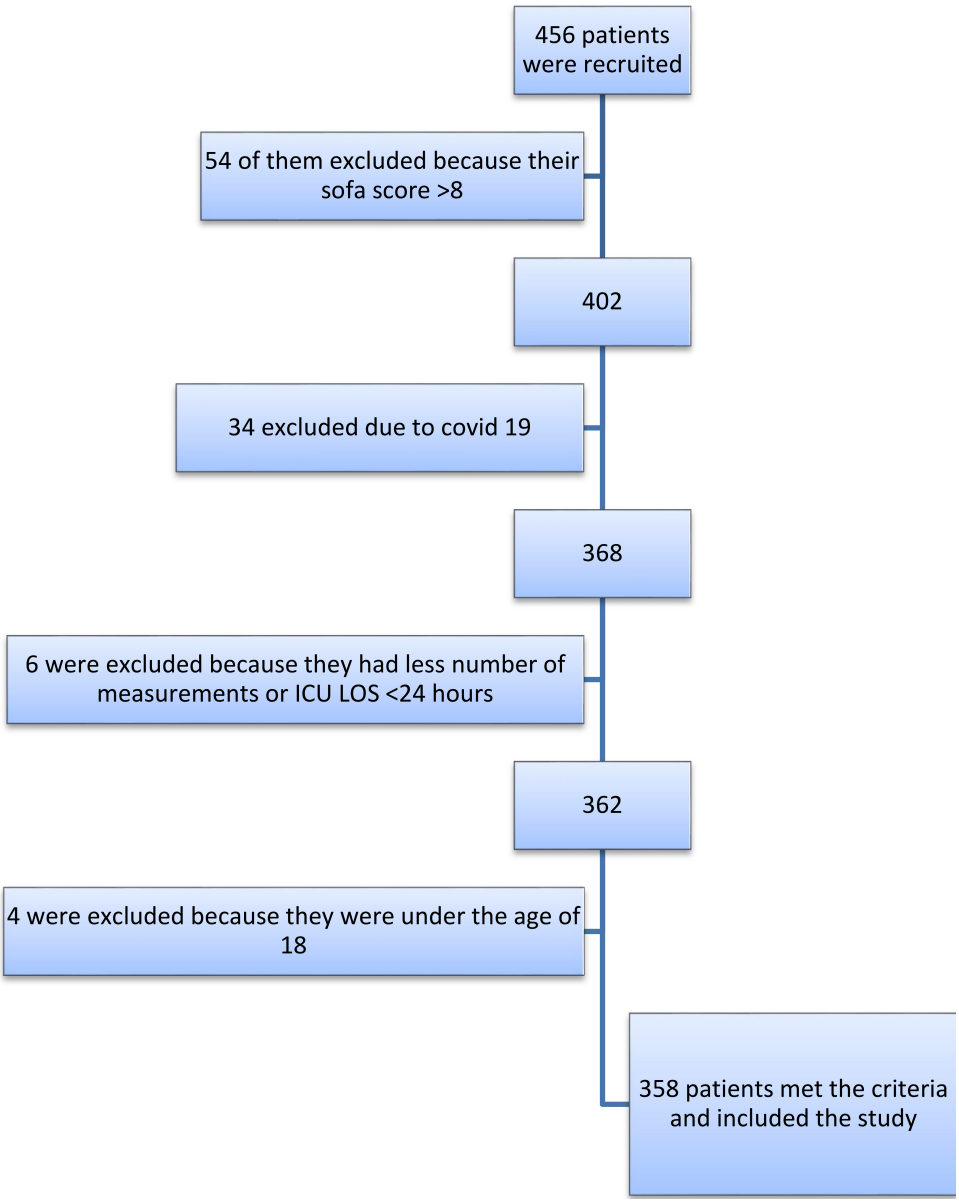

FIGURE 1. Study flow chart with the inclusion and exclusion criteria. ICU: intensive care unit; LOS: length of stay.

TABLE 2. Comparison of the number of measurements of blood glucose levels outside the reference range (OR <110 mg/dL or >180 mg/dL) and within the reference range (WR: 110–180 mg/dL) in survivors and non-survivors.

Variables	Patient outcome				
	Survivors		Non-survivors		
	Median	IQR (25th–75th)	Median	IQR (25th–75th)	*p*
n-OR/LOS	2.0	3	3.0	5.5	<0.001
n-WR/LOS	4.0	7	4.0	7	0.348
GR	0.50	1	0.57	1.08	0.002
n-Δglucose >70 mg/dL	1.0	3	3.0	5	<0.001
n-Δglucose ≤70 mg/dL	4.0	9	5.0	9	0.745
ΔGR	0.14	0.5	0.43	1.17	<0.001

IQR: interquartile Range; n-OR: number of measurements of blood glucose levels outside the reference range; LOS: length of stay; n-WR: number of measurements of blood glucose levels within the reference range; GR: glycemic ratio (n-OR/n-WR); ΔGR: Δglucose ratio (n-Δglucose >70 mg/dL divided by n-Δglucose ≤70 mg/dL).

TABLE 3. Comparison of patient outcomes by mean Δglucose.

Variables		Mean Δglucose		*p*
		≤70 mg/dL	>70 mg/dL	
Patient outcome				
Survivor	n	168	52	
	%	69.4	45.6	<0.001
Non-survivor	n	76	62	
	%	30.6	54.4	<0.001

TABLE 4. Comparison of Δglucose and blood glucose levels based on the status of diabetes mellitus.

Variables	Status of DM				
	Non-Diabetic		Diabetic		
	Median	IQR (25th–75th)	Median	IQR (25th–75th)	*p*
Glucose					
n-OR/LOS	2	3	3	4	<0.001
n-WR/LOS	4	9	4	5	0.157
GR	0.34	0.81	0.92	1.17	<0.001
Δglucose					
n-Δglucose >70 mg/dL	1	3	3	6	<0.001
n-Δglucose ≤70 mg/dL	4	10	3	4	0.001
ΔGR	0.14	0.5	0.75	1.91	<0.001

DM: diabetes mellitus; IQR: interquartile Range; OR: number of measurements of blood glucose levels outside the reference range; LOS: length of stay; n-WR: number of measurements of blood glucose levels within the reference range; GR: glycemic ratio (n-OR/n-WR); ΔGR: Δglucose ratio (n-Δglucose >70 mg/dL divided by n-Δglucose ≤70 mg/dL).

TABLE 5. Comparison of Δglucose ratio (ΔGR) and glycemic ratio (GR) in medical and surgical patients.

Variables	Reasons for admission to ICU				
	Group Medical		Group Surgical		
	Median	IQR (25th–75th)	Median	IQR (25th–75th)	*p*
Glycemic Ratio (GR)	0.50	0.80	0.23	1.00	0.001
Δglucose ratio (ΔGR)	0.25	1.00	0.00	0.50	<0.001

IQR: interquartile range; ICU: intensive care unit.

TABLE 6. The 14- and 28-day survival rates according to mean Δglucose.

Variables	Mean ΔGlucose		*p*
	≤70 mg/dL	>70 mg/dL	
14-days survival	0.62	0.49	0.001
28-days survival	0.61	0.46	0.001

has also been associated with better outcomes [10]. Oxidative stress resulting from rapid changes in blood glucose levels was found to be more harmful than consistent hyperglycemia [11]. Additionally, increased neuronal damage, mitochondrial damage and increased coagulation activity have also been associated with glycemic variability in critically ill patients [12].

One study investigating the effects of glycemic variability on ICU mortality found that glycemic variability was associated with an increase in mortality risk, while a mean blood glucose level was not associated with mortality [13]. Another study based on non-diabetic patients found that patients with a mean blood glucose level of 70–99 mg/dL had a mortality rate of 10.2% during their ICU stay if their glycemic variability (standard deviation/mean blood glucose) was <15% and a mortality rate of 58.3% if their glycemic variability was up to 50%. Patients with a mean blood glucose level between 110 and 119 mg/dL had an ICU mortality rate of 10.6% and 55.6% when their glycemic variability was <15% and up to 50%, respectively [14]. A study on ICU patients with severe acute pancreatitis showed that the overall mortality rate was 43.5% but could increase to 62.5% with an increase in glycemic variability index, which was calculated as the square of the

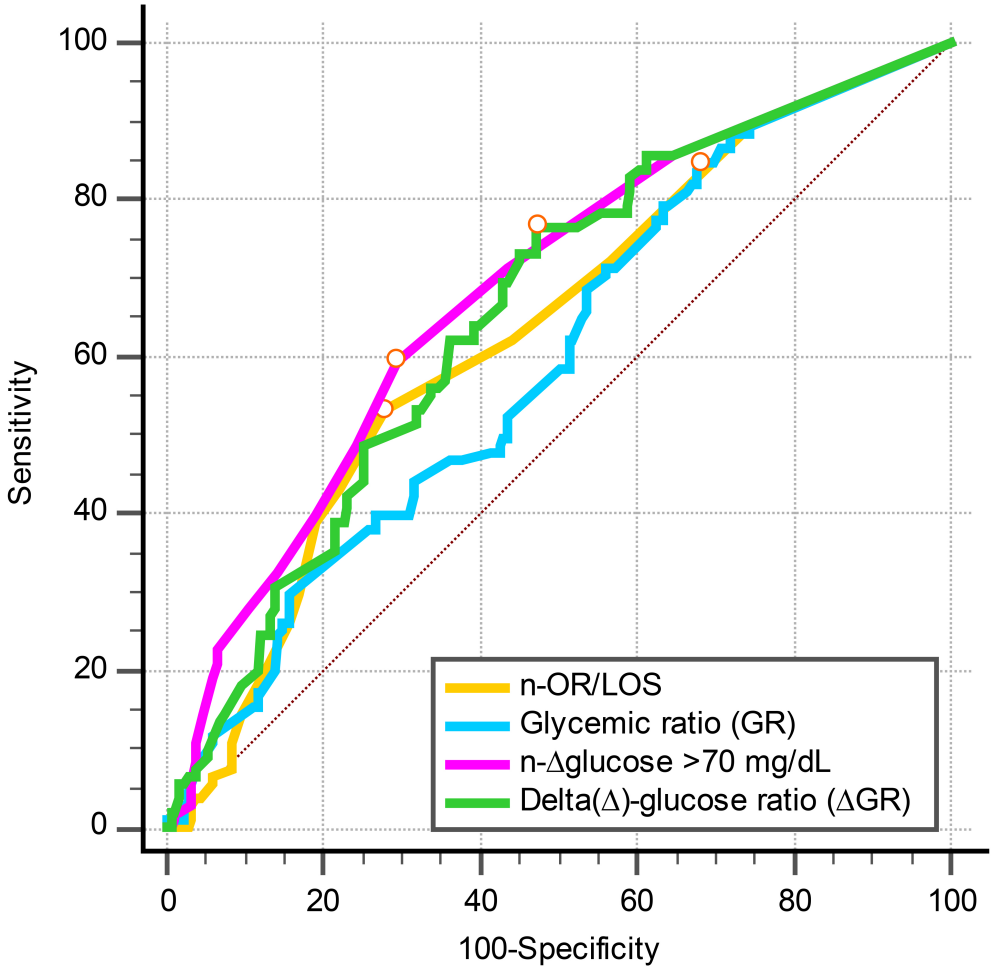

FIGURE 2. Areas under the ROC curve (AUC). n-OR/LOS AUC = 0.632, $p < 0.001$, Glycemic Ratio (GR) AUC = 0.597, $p = 0.005$, n-Δglucose >70mg/dL AUC = 0.682, $p < 0.001$, Delta (Δ)-glucose ratio (ΔGR) AUC = 0.658, $p < 0.001$. n-OR: Number of measurements of blood glucose levels outside the reference range; LOS: Length of stay.

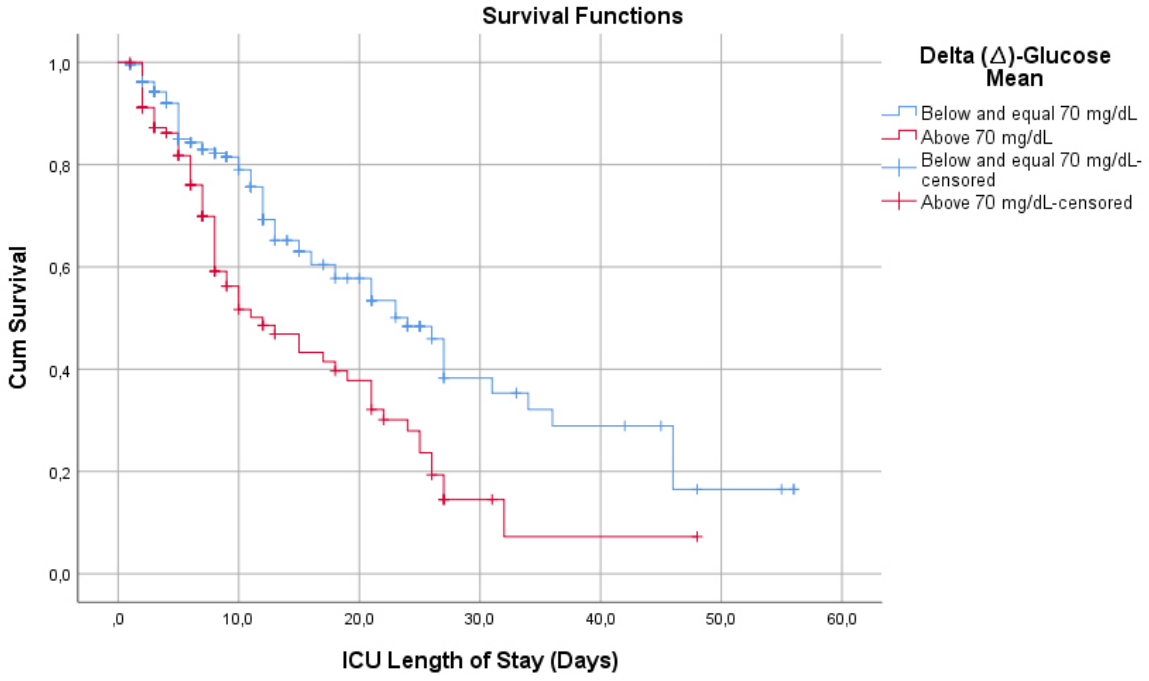

FIGURE 3. ΔGlucose-mean survival curves. ICU: intensive Care Unit.

difference between two consecutive blood glucose measurements divided by the indicated time interval [15]. A study on patients with massive cerebral infarction reported that the mean blood glucose level and glycemic variability were significantly correlated with mortality for the first 28 days. Moreover, patients with a glycemic variability index of $<$15%, 15%–30%, 30%–50%, and $>$50% were reported to have a mortality rate of 0%, 8.70%, 23.81%, and 38.46%, respectively [16].

In regard to statistical assessment, patients with values below and above the reference range were combined into a single group, named the group with values outside the reference range. We found that their GR, standardized as nOR/nWR measurement, was significantly higher in non-survivors (1.04) than in survivors (0.74) ($p < 0.002$).

The cut-off value for glycemic variability (Δglucose) used in our study was the 70 mg/dL difference between the normal range of blood glucose levels (110–180 mg/dL) and a maximum difference of $\leq$70 mg/dL between blood glucose values measured during the day was considered normal. The ΔGR was calculated based on the number of days with variability above the cut-off value divided by the number of days with variability below the cut-off. This value was found to be significantly higher in non-survivors than in survivors (0.73 *vs.* 1.0; $p < 0.001$). Additionally, we also found that an increase of 0.085 units in the number of measurements with values above the cut-off for Δglucose could increase mortality risk by a factor of 1.088 (8.8%).

Further analysis of the association between GR, ΔGR and mortality did not yield a significant cut-off value for prognosis.

One study describing the "diabetes paradox" reported that patients with uncontrolled diabetes might be less affected by glycemic variability in ICU settings [17], and similar results were found in our study based on subgroup analysis performed on diabetic patients.

The length of mechanical ventilation and LOS in the ICU can be affected by numerous factors. Therefore, it is evident that glucose values and glycemic variability alone might not accurately predict the length of mechanical ventilation and LOS in the ICU.

Although previous studies investigating the relationship between ICU mortality and blood glucose values used different comparison techniques, they reported that the effect of glycemic variability on mortality was a more useful technique than the effect of mean blood glucose. Moreover, ours and other studies support the hypothesis that increased blood glucose variability in ICU patients was indeed associated with increased mortality.

The blood glucose values used in our study include those measured as part of the daily routine in the ICU. This can be problematic because it may overlook significant fluctuations in blood glucose occurring outside measurement time points, thereby preventing early intervention. To eliminate this problem, "Computer-Based Decision Support Systems" have been implemented in current ICU practices. The increased use of these systems could reduce the preventable glycemic variability observed in ICUs and mortality in the future.

Irregular measurement frequency was one of the limitations of our study, as it was challenging to fully monitor the glucose value. Since this was an observational study, routine follow-ups were not interfered for instance, if the blood sugar remains stable, at least 4 measurements are usually taken; otherwise, a maximum of 24 measurements might be needed. Thus, the main determinant in the follow-up is the course of blood sugar.

5. Conclusions

This study showed that increased glycemic variability in ICU patients led to increased ICU mortality. In patients with a mean Δglucose $>$70mg/dL, mortality was found to be significantly increased for those with a higher glycemic ratio and Δglucose ratios were also found to be high in patients who died in the ICU. These data show that high glycemic variability could significantly increase mortality. Although many factors affect mortality in ICU, the importance of glucose monitoring is very clear, at least in this investigated cohort. Based on this, we recommend the close monitoring of blood glucose levels. Particularly, in patients with extreme values and frequent attacks, the importance of glucose monitoring might be more important; thus, we recommend that glucose monitoring should continue without decreasing the frequency of measurement. In addition, more effective and personalized protocols and decision support systems should also be implemented to reduce blood glucose variability.

AVAILABILITY OF DATA AND MATERIALS

All data are available on request.

AUTHOR CONTRIBUTIONS

ODY and AO—Conceptualization, Methodology, Formal analysis and investigation; AO—Writing—original draft preparation, writing—review and editing; AO and OE—Resources; OE—Supervision. All authors read and approved the final manuscript. All authors agreed with the content and that all gave explicit consent to submit and that they obtained consent from the responsible authorities at the institute/organization where the work has been carried out.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

After obtaining the patient consent, approval was obtained from the University of Health Sciences, Haydarpasa Numune Training and Research Hospital Ethic Committee of Scientific Studies (id: HNHEAH-KAEK 2021/112). The authors declare that they give their consent regarding the publication of this article.

ACKNOWLEDGMENT

We thank Burak Mete for his statistical contributions to our study.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Montori VM. Hyperglycemia in acutely ill patients. JAMA. 2002; 288: 2167.

[2] Sakharova OV, Inzucchi SE. Endocrine assessments during critical illness. Critical Care Clinics. 2007; 23: 467–90.

[3] Vanhorebeek I, Van den Berghe G. Diabetes of injury: novel insights. Endocrinology and Metabolism Clinics of North America. 2006; 3: 859–872.

[4] Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. The Journal of Clinical Endocrinology & Metabolism. 2002; 87: 978–982.

[5] Mehta RL. Glycemic control and critical illness: is the kidney involved? Journal of the American Society of Nephrology. 2007; 18: 2623–2627.

[6] Çelik S, Olgun N. Hypoglycemia and hyperglycemia in intensive care unit. Yoğun Bakım Hemşireliği Dergisi. 2016; 20: 57–64.

[7] Krinsley JS, Grover A. Severe hypoglycemia in critically ill patients: risk factors and outcomes. Critical Care Medicine. 2007; 35: 2262–2267.

[8] Chang C, Hsieh C, Huang J, Huang I. Acute and chronic fluctuations in blood glucose levels can increase oxidative stress in type 2 diabetes mellitus. Acta Diabetologica. 2012; 49: 171–177.

[9] Durmaz Akyol A. Diabetes and Intensive Care Patients. Yoğun Bakım Hemşireliği Dergisi. 2009; 13: 30–39.

[10] Upreti V, Singh M, Singh Y, Kannapur A, Nakra M, Kotwal N. Effect of glycemic variability on mortality in ICU settings: a prospective observational study. Indian Journal of Endocrinology and Metabolism. 2018; 22: 632.

[11] Chang C, Hsieh C, Huang J, Huang I. Acute and chronic fluctuations in blood glucose levels can increase oxidative stress in type 2 diabetes mellitus. Acta Diabetologica. 2012; 49: 171–177.

[12] Brownlee M. The pathobiology of diabetic complications. Diabetes. 2005; 54: 1615–1625.

[13] Donati A, Damiani E, Domizi R, Botticelli L, Castagnani R, Gabbanelli V, *et al*. Glycaemic variability, infections and mortality in a medical-surgical intensive care unit. Critical Care & Resuscitation. 2014; 16: 13–23.

[14] Krinsley JS. Glycemic variability and mortality in critically ill patients: the impact of diabetes. Journal of Diabetes Science and Technology. 2009; 3: 1292–1301.

[15] Zuo Y, Kang Y, Yin W, Wang B, Chen Y. The association of mean glucose level and glucose variability with intensive care unit mortality in patients with severe acute acute pancreatitis. Journal of Critical Care. 2012; 27: 146–152.

[16] Chen QY, Zhang DH, Zhang XF, Wang LM, Guan JH. The relationship between the levels and variability of blood glucose and the prognosis of massive cerebral infarction. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2013; 25: 749–753. (In Chinese)

[17] Krinsley JS, Fisher M. The diabetes paradox: diabetes is not independently associated with mortality in critically ill patients. Hospital Practice. 2012; 40 :31–35.

How to cite this article: Ozgur Diyar Yavuz, Asu Ozgultekin, Ferhunde Dilek Subasi, Osman Ekinci. The effect of blood glucose variability on the survival of patients in the intensive care unit: a prospective observational study. Signa Vitae. 2023; 19(4): 194-201. doi: 10.22514/sv.2023.064.