The Relationship Between the Admission Blood Glucose Level and 90-Day Mortality in Non-Diabetic Patients with Coronavirus Disease-2019

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ABSTRACT

Introduction: The admission blood glucose (ABG) level is associated with increased mortality in non-diabetics patients with Coronavirus disease-2019 (COVID-19) in short-term follow-up studies. However, post-discharge mortality has also increased in COVID-19. Thus, this study aimed to examine the relationship between ABG and 90-day mortality including the post-discharge period.

Methods: Non-diabetic patients who are hospitalized due to COVID-19 in 2020 were evaluated. Patients were divided into groups according to the ABG level. Groups 1, 2, and 3 have ABG level of <100 mg/dL, 100-139 mg/dL, and 140-199 mg/dL, respectively. Intensive care unit admission, in-hospital mortality, and 30- and 90-day mortality rates were evaluated as outcomes. COX regression analyzes were used to assess mortality risk factors.

Results: A total of 1207 non-diabetic patients, of whom 49.2% were females, with a mean age of 65.2±13.4 years, were included in the study. The patients were followed up for a median of 153 (inter quartile range: 107.5-251, maximum: 369) days. The in-hospital and 30-day mortality of group 2 was higher than group 1 in the univariate analysis but without statistical significance in multivariate analysis. Group 3 had worse outcomes than group 1 in both univariate and multivariate analysis at all endpoints. Group 3 had 2.533 adjusted hazard ratios (95% confidence interval: 1.628-3.941, p<0.001) 90-day mortality compared with group 1.

Conclusion: Non-diabetic patients with COVID-19 with an admission glucose level of ≥140 mg/dl had 2.5-fold increased all-cause mortality at 90 days. Therefore, being more careful in treating and following non-diabetic patients with COVID-19, especially those with hyperglycemia at admission, was recommended.

Keywords: Glucose, SARS-CoV-2, COVID-19, hyperglycemia, hospitalization, intensive care units

Introduction

Hyperglycemia in hospitalized patients is an independent risk factor that is strongly associated with adverse outcomes. Hyperglycemia disrupts neutrophil functions and movements, causing adverse effects on immunity. Additionally, it causes microvascular complications with endothelial dysfunction by increasing inflammatory responses and oxidative stress (1,2).

Many associated factors with mortality have been identified in patients hospitalized due to Coronavirus disease-2019 (COVID-19). Mortality rates increased nearly 2-fold in patients with a history of diabetes (3-6). Additionally, newly detected hyperglycemia in-hospital admission, even without a known history of diabetes, has shown association with increased mortality (7,8), as well as increased intensive care unit (ICU) admissions and prolonged hospital stays. Several studies have shown that patients with hyperglycemia without a history of diabetes have an even higher risk of mortality than those with known diabetes (9).

Studies that examined the newly developed hyperglycemia at hospital admission due to COVID-19 mainly examined in-hospital and 30-day mortality rates. These studies did not evaluate the long-term mortality (7,10). However, the mortality also increased in the post-discharge period in patients with COVID-19, and this rate has been reported to be approximately 10% (11-13). This study aimed to evaluate the relationship between at least 90 days mortality and admission blood glucose (ABG) level, including the post-discharge period.

Methods

A total of 1207 hospitalized patients with COVID-19 between March 2020 and December 2020 in Çanakkale Onsekiz Mart University Hospital were retrospectively analyzed. COVID-19 diagnoses were made either by polymerase chain reaction positivity or radiological findings. Patients with compatible diabetes diagnoses from the previously given International Classification of Diseases (ICD) codes, hemoglobin A1c (HbA1c) of ≥6.5% in

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their system records, using diabetes medication before admission, under 18 years of age, pregnant, and ABG of >200 mg/dL were excluded from the study. Patients with newly diagnosed diabetes were also excluded when the HbA1c is ≥6.5% during hospitalization. Patients were divided into groups according to the ABG level. Groups 1, 2, and 3 have ABG level of <100 mg/dL (5.6 mmol/L), 100-139 mg/dL (5.6-7.7 mmol/L), and 140-199 mg/dL (7.8-11.1 mmol/L), respectively. The study was approved by the Ethics Committee of Çanakkale Onsekiz Mart University Faculty of Medicine (approval number: 2021-07, date: 20.10.2021).

Patients' mortality status was inquired via the Turkish Central Death Registry in March 2021. ICU admission, in-hospital mortality, and 30- and 90-day mortality rates were evaluated as outcomes.

Acute renal failure was diagnosed by Kidney Disease: Improving Global Outcomes criteria (14). The Chronic Kidney Disease Epidemiology Collaboration equation was used to calculate the estimated glomerular filtration rate (eGFR) (15).

Statistical Analysis

Continuous variables with normal distribution were presented as mean ± standard deviation, whereas non-normally distributed variables as the median and interquartile range [(IQR): the difference between the 25th and 75th percentiles]. Numbers and percentages were used to express categorical variables. Normal distribution was evaluated with the Kolmogorov-Smirnov test. Analysis of variance was used to compare the three groups for data with normal distribution and the Kruskal-Wallis test used for those with non-normal distribution. Homogeneity of variances was evaluated with Levene's test. Pairwise post-hoc comparisons were made with the Tukey test if the variances were homogeneous and with the Tamhane T2 test if not if a significant difference was found between the three groups. In the variables, in which the groups were evaluated with the Kruskal-Wallis test, post-hoc analyses in pairs were evaluated using the Mann-Whitney U test by Bonferroni correction. Pearson's chi-square was used to test the distribution among categorical variables. Wherein, paired post-hocs were evaluated with the Z-test, with Bonferroni correction.

COX regression analyses were used to assess the risk factors for COVID-19-associated mortality. A single variable was used to calculate the unadjusted hazard ratios (HR). Gender, age, alanine transaminase (ALT), eGFR, co-morbidities as chronic lung disease, coronary artery disease, cerebrovascular disease, hypertension, and hyperlipidemia were used in the adjusted HR (aHR) analysis. In COX regression analyses, group 1 was used as the reference group to evaluate the outcomes of groups 2 and 3.

The Statistical Package for the Social Sciences version 19 for Windows was used for statistical analysis (IBM, Armonk, NY, USA). A statistically significant p-value of 0.05 was used.

Results

A total of 1207 patients with a mean age of 65.2±13.4 years, of whom 49.2% (594) were females, were included in the study. In all study groups, the in-hospital mortality rate was 11.1% (134). The 30- and 90-day mortality rates were 12.7% (153) and 16.7% (201), respectively.

Groups 1, 2, and 3 consisted of 285 (23.6%), 706 (58.5%), and 216 (17.9%) patients, respectively.

From groups 1 to 3, ICU Admission, in-hospital mortality, 30-day mortality, and 90-day mortality rates increased as blood sugar increased. In the post-hoc analysis, these differences were determined to be caused mainly by group 3. From groups 1 to 3, a decreased eGFR and a prolonged hospitalization were observed. Group 3 had higher ALT levels, hyperlipidemia history, and acute renal failure rates than other groups. Group 1 was younger and had a lower coronary artery disease rate. The general characteristics and comparisons of the groups are given in Table 1.

In-hospital mortality and 30-day mortality rates, which were significant for mortality in the univariate analysis for group 2 (ABG: 100-139 mg/dL), lost statistical significance in the multivariate analysis adjusted for multiple variables (gender, age, ALT, eGFR, and co-morbidities). In group 3, univariate analysis of 90-day mortality HR was 3.45 [95% confidence interval (CI): 2.231-5.335, p<0.001] and in the multivariate analysis of 90-day mortality aHR was 2,533 (95% CI: 1.628-3.941, p<0.001). In group 3 (ABG: 140-199 mg/dL), statistically, significant mortality increases were observed with all univariate and multivariate analysis outcomes. Univariate and multivariate HR and forest plot graphs of groups 2 and 3 according to reference group 1 are given in Figure 1 and 2, respectively.

Patients were followed up for a median of 153 (IQR: 107.5-251, minimum: 1, maximum: 369) days. The Kaplan-Meier one minus survival graph of mortality between the groups during the follow-up periods is given in Figure 3 (log-rank p<0.001). The all-cause mortality rate was the highest in group 3 during the follow-up period.

Discussion

We found that ICU admission, in-hospital, 30-day, and 90-day all-cause mortality was higher in non-diabetic patients with ABG of 140-199 mg/dL, even after correction for other factors in our study, which had a maximum follow-up period of close to 1 year. Our study is among the first reports that investigated the effects of ABG on long-term mortality in non-diabetic patients with COVID-19 (16).

Our findings are consistent with those of other studies with a short-term follow-up that found increased mortality due to hyperglycemia in non-diabetic patients with COVID-19 (7,10,17). Unlike these studies, our study showed the effect of ABG level on long-term mortality. Mortality rates for the post-discharge period in patients with COVID-19 have been reported as approximately 10% (11-13). Therefore, long-term follow-up studies of patients are also important.

Diabetes mellitus, one of the most common co-morbidities in patients with COVID-19, has been reported from 7% to 30% in studies. People with diabetes with COVID-19 have higher hospital admission rates, severe pneumonia, and higher mortality than non-diabetics (18). Hyperglycemia that occurs during acute illness, called stress hyperglycemia, is also associated with adverse outcomes (19).

Various studies before the COVID-19 era have shown that high ABG is associated with increased mortality and morbidity in patients

Table 1. General characteristics and comparisons of the admission blood glucose groups

	Group 1 ABG <100 mg/dL	Group 2 ABG 100-139 mg/dL	Group 3 ABG 140-199 mg/dL	Total	p
Number of patients	285	706	216	1207	-
Age (years)	61.0±14.7*,**	66.1±13.1	67.8±11.9	65.2±13.5	<0.001
Female (%)	142 (49.8)	343 (48.6)	109 (50.5)	594 (49.2)	0.865
Glucose (mg/dL)	91.1±6.3	116.5±10.4	160.4±16.3	118.4±24.8	<0.001
ALT [median (IQR)] (IU/L)	17 (11-30)	17 (12-27)	20.5 (14-36)**,***	18 (12-29.5)	0.01
eGFR [median (IQR)]	88.6 (72.3-101.8)*	84.9 (62.7-98)***	78.4 (49.7-95.2)**	85.6 (61-98.5)	<0.0001
Number of hospitalization days [median (IQR)]	5 (4-10)*,**	6 (5-10)	7 (4-13)	6 (4-10)	0.01
Follow-up days count [median (IQR)]	204 (130-260)*	150 (109-256)***	125.5 (32.5-228)**	153 (107.5-251)	0.01
In-hospital mortality (n, %)	16 (5.6)	73 (10.3)	45 (20.8)**	134 (11.1)	<0.0001
30-day mortality (n, %)	20 (7)	80 (11.3)	53 (24.5)**	153 (12.7)	<0.001
90-day mortality (n, %)	29 (10.2)	105 (14.9)	67 (31)**	201 (16.7)	<0.0001
ICU admission (n, %)	28 (9.8)	96 (13.6)	55 (25.5)**	179 (14.8)	<0.0001
COPD-asthma (n, %)	43 (15.1)	111 (15.7)	36 (16.7)	190 (15.7)	0.891
Hypertension (n, %)	104 (36.5)	298 (42.2)	99 (45.8)	501 (41.5)	0.09
Coronary artery disease (n, %)	37 (13)*,**	144 (20.4)	59 (27.3)	240 (19.9)	<0.0001
Hyperlipidemia (n, %)	28 (9.8)	83 (11.8)	41 (19)**,***	152 (12.6)	0.005
Acute renal failure (n, %)	41 (14.4)	11 (16)	49 (22.7)**	203 (16.8)	0.03
Chronic renal failure (n, %)	8 (2.8)	23 (3.3)	1 (5.6)	43 (3.6)	0.2
Cerebrovascular disease (n, %)	15 (5.3)	50 (7.1)	16 (7.4)	8 (6.7)	0.52
ACE/ARB usage (n, %)	74 (26)	229 (32.4)	71 (32.9)	374 (31)	0.11

ICU: Intensive care unit, ACE: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker, COPD: chronic obstructive pulmonary disease, ALT: alanine aminotransferase, ABG: admission blood glucose, post-hoc tests: *p<0.05 group 1 vs group 2, **p<0.05 group 1 vs group 3, ***p<0.05 group 2 vs group 3

hospitalized for trauma, surgery, infectious diseases (sepsis and pneumonia), cardiovascular diseases, and cerebrovascular diseases (20-23). Even without a history of diabetes, the risk of mortality is higher in cases with the hyperglycemic course during hospitalization. Some studies also revealed that newly developed hyperglycemia without a history of diabetes during hospitalization was related to higher mortality than known patients with diabetes (9). Angiotensin-Converting Enzyme II (ACE-2) is one of the receptors that allow the entry of the severe acute respiratory syndrome-coronavirus-2 (SARS-COV-2) into the cell. Acute hyperglycemia increases ACE-2 expression, whereas chronic hyperglycemia decreases ACE-2 expression (24). It may explain why newly developed hyperglycemia has a worse prognosis than those with known diabetes. Additionally, patients with hyperglycemia with known diabetes are likely to be promptly treated, and the fact that hyperglycemia is a marker of critical diseases that may increase mortality may also explain this condition (25).

The relationship between long-term mortality with ABG was also investigated in cardiovascular diseases before the COVID-19 era (21,26,27). Similar to our findings, ABG was associated with increased long-term mortality.

The causes of hyperglycemia during hospitalization can be listed as treatments that contain dextrose, glucocorticoid, increased anti-insulin hormones, and increased inflammatory response (28,29). Our study was conducted according to the first ABG level groups, thus the effect of secondary hyperglycemia due to glucocorticoid treatment on the analysis was prevented (17).

Hyperglycemia induces an exaggerated inflammatory response that results in harmful microvascular complications (30). Additionally, hyperglycemia can affect multiple biochemical pathways that can facilitate many steps of SARS-CoV-2 infection. Hyperglycemia may trigger ACE-2 receptor expression, which may increase the susceptibility to COVID-19 infection and the risk of severe disease and multi-organ failure (31). The association of hyperglycemia with increased mortality is multifactorial (1).

Some differences were determined in the definition of hyperglycemia in studies that examine the effect of hyperglycemia on mortality in non-diabetics. Some studies used a definition of hyperglycemia above 140 mg/dL, thus patients with a level above 200 mg/dL were not excluded in some studies. Our study excluded the ABG of >200 mg/dL to eliminate the overlap with the diagnosis of diabetes.

Age, male gender, multiple pre-existing co-morbidities, and renal/hepatic dysfunction are critical factors that predict COVID-19 mortality (32). Therefore, a factor should be corrected in terms of the main influencing factors to correctly evaluate the relationship with mortality. Univariate analysis of ABG of 100-140 mg/dL was significant for mortality, but without significance, after the multivariate analysis was adjusted for
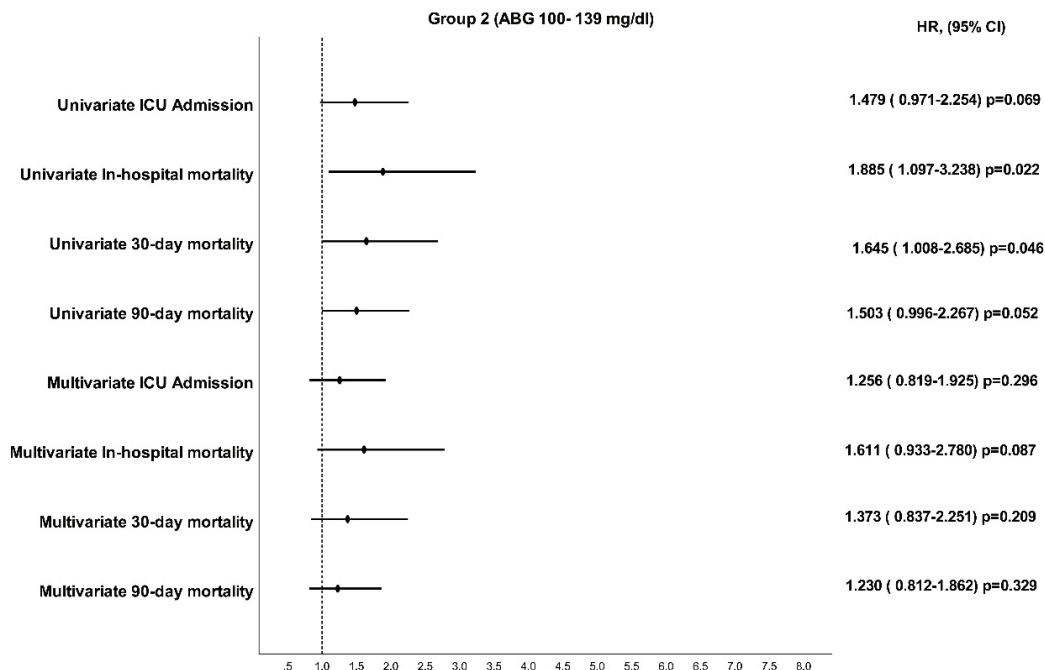
Figure 1. Univariate and multivariate hazard ratios and forest plot graph of group 2 according to the reference group 1

ABG: Admission blood glucose, HR: hazard ratios, CI: confidence interval, ICU: intensive care unit
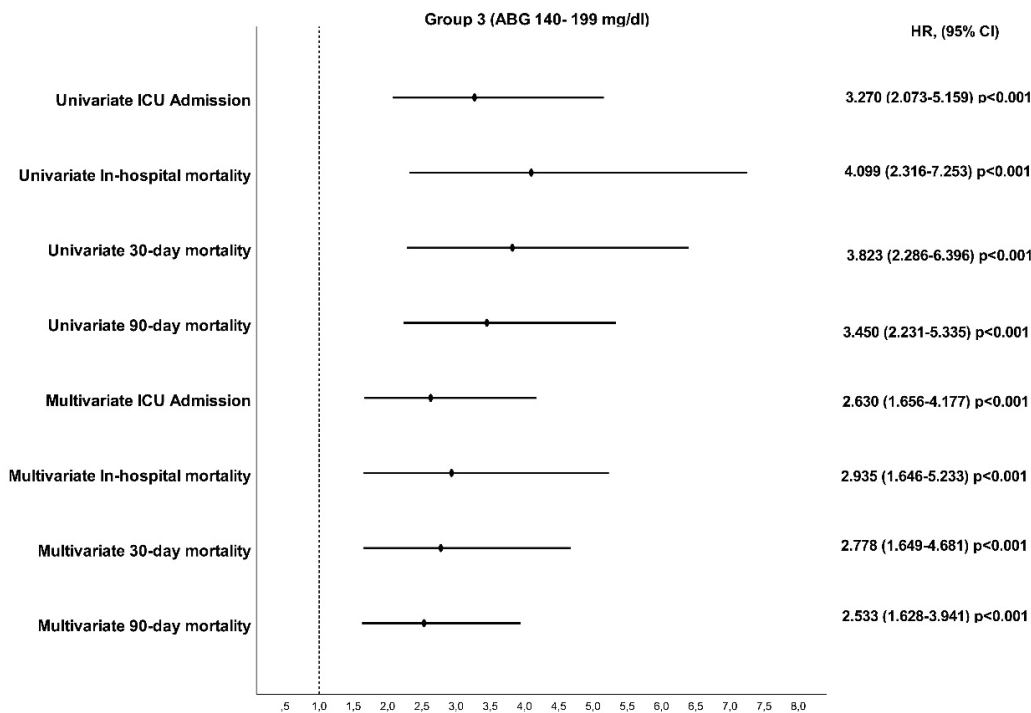

Figure 2. Univariate and multivariate hazard ratios and forest plot graph of group 3 according to the reference group 1

ABG: Admission blood glucose, HR: hazard ratios, CI: confidence interval, ICU: intensive care unit

covariates. The effect of mildly elevated blood sugar (100-140 mg/dL) on mortality can be ignored. The guidelines defined hyperglycemia as any glucose level above 140 mg/dL in hospitalized patients (33,34). Other studies revealed that blood sugar influences mortality when it is >140 mg/dL (10,21).

Study Limitations

Our study has several limitations. There may be undetected confounding factors because it is a retrospective study of data during an outbreak. Patients without diabetes-related ICD codes, medications history, and reports were selected; however, the fact that the HbA1c measurement
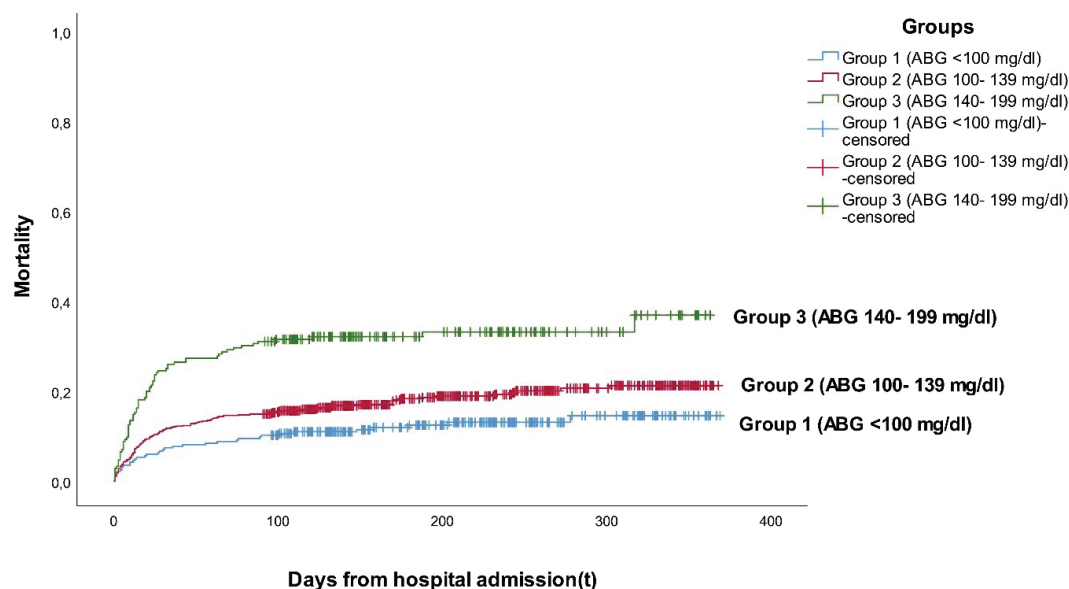
Figure 3. The Kaplan-Meier one minus survival graph of groups (log-rank p<0.001)

ABG: Admission blood glucose

was scarce among the patients is a limiting factor in excluding the history of diabetes. The ABG value taken in the fasting state or randomly could not be determined. However, our study examined the effect of ABG level on mortality rather than diagnosing new diabetes. All-cause mortality was evaluated in the analysis, thus data on exact causes of death were insufficient. The strengths of our study are the large, real-life cohort of hospitalized patients with COVID-19 and the long-term follow-up. Whether hyperglycemia treatment improves outcomes in those with high ABG levels requires a different study design. Following the guidelines, when the hospitalized patient's blood sugar levels reached >180 mg/dL, insulin was administered to lower the blood sugar level (34).

Conclusion

Non-diabetic COVID-19 patients with an admission glucose level of ≥140 mg/dL had a 2.5-fold increased all-cause mortality at 90 days. Being more careful in treating and following a non-diabetic patient with COVID-19, especially those with elevated serum glucose at admission, is recommended.

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