ORIGINAL ARTICLE

Does inpatient hyperglycemia predict a worse outcome in COVID-19 intensive care unit patients?

Aisha R. Saand[1] | Monica Flores[1] | Tariq Kewan[1] | Sura Alqaisi[1] | Mahmoud Alwakeel[1] | Lori Griffiths[2] | Xiaofeng Wang[3] | Xiaozhen Han[3] | Robert Burton[4] | Mohammed J. Al-Jaghbeer[5] | Francois Abi Fadel[5,6]

[1]Department of Internal Medicine, Cleveland Clinic Fairview Hospital, Cleveland, Ohio

[2]Cleveland Clinic, Quality Data Registries, Cleveland, Ohio

[3]Cleveland Clinic, Quantitative Health Sciences, Cleveland, Ohio

[4]Cleveland Clinic, Business Intelligence, Cleveland, Ohio

[5]Cleveland Clinic, Respiratory Institute, Cleveland, Ohio

[6]Cleveland Clinic, Lerner College of Medicine of Case Western Reserve University, Cleveland, Ohio

Correspondence
Monica Flores, Department of Internal Medicine, Cleveland Clinic Fairview Hospital, 18101 Lorain Ave, Cleveland, Ohio 44111, USA.
Email: floresm@ccf.org

Abstract

Background: We undertook this study to evaluate the association between hyperglycemia and outcomes in patients with coronavirus disease 2019 (COVID-19) admitted to the intensive care unit (ICU).

Methods: We conducted a multicenter retrospective study involving all adults with COVID-19 admitted to the ICU between March and May 2020. Patients were divided into normoglycemic (average blood glucose <140 mg/dL) and hyperglycemic (average blood glucose ≥140 mg/dL) groups. Outcomes such as mortality, need and duration of mechanical ventilation, and length of hospital and ICU stays were measured.

Results: Among 495 patients, 58.4% were male with a median age of 68 years (interquartile range [IQR]: 58.00-77.00), and baseline average blood glucose was 186.6 (SD ± 130.8). Preexisting diabetes was present in 35.8% of the studied cohort. Combined ICU and hospital mortality rates were 23.8%; mortality and mechanical ventilation rates were significantly higher in the hyperglycemic group with 31.4% vs 16.6% ($P = .001$) and 50.0% vs 37.2% ($P = .004$), respectively. Age above 60 years (hazard ratio [HR] 3.21; 95% CI 1.78, 5.78) and hyperglycemia (HR 1.79; 95% CI 1.14, 2.82) were the only significant predictors of in-hospital mortality. Increased risk for hyperglycemia was found in patients with steroid use (odds ratio [OR] 1.521; 95% CI 1.054, 2.194), triglycerides ≥150 mg/dL (OR 1.62; 95% CI 1.109, 2.379), and African American race (OR 0.79; 95% CI 0.65, 0.95).

Conclusions: Hyperglycemia in patients with COVID-19 is significantly associated with a prolonged ICU length of stay, higher need of mechanical ventilation, and increased risk of mortality in the critical care setting. Tighter blood glucose control (≤140 mg/dL) might improve outcomes in COVID-19 critically ill patients; evidence from ongoing clinical trials is needed.

KEYWORDS
COVID-19, critical care unit, glucose control, hyperglycemia, mortality

---

Aisha R. Saand and Monica Flores equally contributed to this article.

Highlights

- Hyperglycemia has been reported in almost half of the patients infected with coronavirus disease 2019.
- In critically ill patients, hyperglycemia is associated with increased morbidity and mortality, irrespective of preexisting diabetes.
- In our study, patients with blood glucose ≥140 mg/dL and admitted to the intensive care unit were found to have the worst outcomes in terms of mortality, mechanical ventilation need, and intensive care unit length of stay.
- Further studies are needed to clarify if outcomes significantly improve with tighter glucose targets.

1 | INTRODUCTION

Since the World Health Organization (WHO) declared the coronavirus disease 2019 (COVID-19) outbreak a pandemic, approximately 821 909 deaths have been confirmed globally.[1] COVID-19 can result in severe disease with admissions to the intensive care unit (ICU), especially among older adults with severe underlying health conditions.[2] Multiple studies have attempted to analyze the different factors associated with mortality.[3] Age, gender, obesity, and other medical comorbidities (eg, chronic cardiac and pulmonary conditions, hypertension, diabetes, and chronic kidney disease) were the most common factors that might predict mortality in patients with COVID-19.[4] Hyperglycemia was one of the modifiable factors that has been shown to be associated with an increased risk of mortality.[5] Studies showed that laboratory values such as d-dimer, prolonged prothrombin time/activated partial thromboplastin time, lymphopenia, and neutrophilia might help in predicting disease severity and outcomes.[3,6]

Few studies examined the effect of hyperglycemia in COVID-19 critically ill patients. Results suggested that preexisting diabetes is associated with an increased risk of mortality, but also uncontrolled hyperglycemia is strongly associated with a prolonged in-hospital and ICU length of stay (LOS), and an increased risk of mortality.[5,7]

Management of hyperglycemia in critically ill patients is challenging. According to the American Diabetes Association (ADA), blood glucose levels should be maintained between 140 and 180 mg/dL in patients admitted to the ICU.[8] However, some studies suggested that tighter glucose control (<140 mg/dL) might provide some benefit in the outcome of patients with COVID-19.[9] It has been challenging to advocate strong evidence-based recommendations for the best treatment protocol for hyperglycemia in COVID-19 infection, considering the expanding nature of the disease and the lack of available data.

Therefore, the purpose of this study is to explore the effect of hyperglycemia on the outcomes of critically ill COVID-19 adult patients in an attempt to identify the blood glucose target that could improve outcomes in this population in the future.

2 | PARTICIPANTS AND METHODS

We conducted a multicenter retrospective cohort study across the Cleveland Clinic Enterprise, a 10-hospital health care system in northeast Ohio, serving an over 2.7 million population. The study was reviewed and approved by the Cleveland Clinic Institutional Review Board.

The study included all critically ill patients admitted to all ICUs between 15 March and 30 May 2020. The diagnosis of COVID-19 infection was established by reverse transcriptase polymerase chain reaction detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA nasopharyngeal swab. All our patients were classified to have severe disease according to the national protocol published by the Chinese National Health Commission.[10] Mean blood glucose was defined as the average blood glucose levels from the date of admission until the date of ICU discharge or death. Based on the American Association of Clinical Endocrinologists and American Diabetes Association Consensus Statement on Inpatient Glycemic Control, hyperglycemia in hospitalized patients was defined as any blood glucose value >140 mg/dL (>7.8 mmol/L). Therefore, patients were grouped as normoglycemic with a mean blood glucose <140 mg/dL or hyperglycemic with a mean blood glucose level of ≥140 mg/dL.[8,9] Overweight and obesity were defined as body mass index (BMI) ≥ 25 and 30 kg/m^2 respectively.

The primary end point included mortality difference between hyperglycemic and normoglycemic patients with

COVID-19 admitted to the ICU. The need for mechanical ventilation, duration of mechanical ventilation, LOS in the ICU and hospital, and risk factors associated with hyperglycemia were the secondary end points of interest. Patients were followed and data collected till hospital discharge, or ICU or hospital mortality.

2.1 | Data collection

Data were obtained from the Quality Data Registries with the support of electronic research associates. Collected data included baseline characteristics, demographics, clinical information, and laboratory values. Outcome variables including mortality, hospital and ICU LOS, the need of mechanical ventilation, and the duration of mechanical ventilation were obtained as well. A medical record number was used to identify patients. No personal information was collected.

2.2 | Statistical analysis

Descriptive statistics were used to characterize the cohort. Demographic variables were described using mean ± SD for continuous variables if they were normally distributed or as median (interquartile range, IQR) if they were not, and counts with percentages for categorical variables. The two-sample t test or Wilcoxon rank sum test was used to compare continuous variables between groups. In contrast, the chi-square test with continuity correction was applied to compare categorical variables. For the analysis of mortality, a multivariate Cox regression analysis to assess the effects of age, sex, and hyperglycemia was done. The optimal mean blood glucose cutoff points were evaluated by receiver operator characteristic (ROC) curve. Optimum cutoff values for laboratory tests were determined depending on sensitivity and specificity. Finally, univariate and multivariate logistic regression analysis was used to evaluate risk factors for developing hyperglycemia. All analyses were performed at a significance level of .05. IBM SPSS software version 20.0 (Armonk, NY: IBM Corp) (Statistical Package for the Social Sciences), R version 3.5.0 (The R Foundation for Statistical Computing, Vienna, Austria), and SAS 9.4 software (SAS Institute, Cary, North Carolina) were used for the above analyses.

3 | RESULTS

3.1 | Baseline characteristics

We identified 495 patients with severe COVID-19 infection. Demographics, clinical features, and laboratory values are summarized in Table 1. Among the evaluated patients, 289 (58.4%) patients were males with a median age of 68 years (IQR: 58.00-77.00). The mean value of blood glucose at the time of admission was 186.6 mg/dL (SD ± 130.8). White Caucasian race was the most prevalent in our cohort (54.9%). Preexistent diabetes, whether type 1 or type 2, was present in 177 (35.8%) of the studied cohort, being naturally more prevalent in the hyperglycemic group compared with the normoglycemic group (63.6% vs 9.1%, $P < .001$). Overweight was highly prevalent in our population, and the median BMI was 29.74 kg/m^2 (IQR: 25.61-34.92). Subcutaneous and intravenous insulin were used in 129 (26.0%) and 70 (14.1%) patients, respectively.

Most patients had normal leukocyte count at admission with a median of 7.97/mm^3 (IQR: 5.65-11.55). The COVID-19 patients with hyperglycemia had a higher median leukocyte count as compared with patients without hyperglycemia (8.5 [IQR: 5.52-12.38] vs 7.5 [IQR: 5.68-10.49]). Although not statistically significant, inflammatory markers such as ferritin, C-reactive protein, and interleukin-6 were higher in patients with hyperglycemia compared with patients in the normoglycemia group.

The median baseline glycosylated hemoglobin (HbA1c) levels (61.0 vs 42.0 mmol/mol, 7.7% vs 6.0%; $P = .002$), triglycerides levels (148 vs 122 mg/dL, $P = .033$), and APACHE III (Acute Physiology and Chronic Health Evaluation III) score (61 vs 53, $P = .006$) were higher in the ICU hyperglycemic group compared with the normoglycemic group. Also, as expected, patients requiring glucocorticoid treatment were more likely to have hyperglycemia: 114 (47.3%) patients in the hyperglycemia cohort were treated with glucocorticoid compared with 91 (36.0%) patients in the normoglycemia cohort. No statistical differences were found between the hyperglycemic and the normoglycemic groups for all other baseline characteristics.

3.2 | Outcomes

Regarding the outcomes described in Table 2, the combined ICU and in-hospital mortality rate was 23.8%. A total of 118 deaths, out of the 495 ICU patients with COVID-19 occurred across our health care system. The optimum cutoff value for mean blood glucose to predict mortality in critically ill COVID-19 patients was 140 mg/dL with a sensitivity of 70.3% and specificity of 55.5% (Figure S1 and Table S1). Compared with the normoglycemic group, the mortality rate was statistically higher in the group with hyperglycemia (31.4% vs 16.6%, $P < .001$). Also, mechanical ventilation was more prevalent in patients with hyperglycemia (50.0% vs 37.2%,

TABLE 1 Baseline characteristics of study population

Characteristics	All patients (N = 495)	Patients with hyperglycemia (n = 242)	Patients with normoglycemia (n = 253)	P value
Sex, n (%)				
Male	289 (58.4)	142 (58.7)	147 (58.1)	.897
Female	206 (41.6)	100 (41.3)	106 (41.9)	
Race, n (%)				
Caucasian	272 (54.9)	136 (56.2)	136 (53.8)	.024
African American	192 (38.8)	99 (40.9)	93 (36.8)	
Others	31 (6.3)	7 (2.8)	24 (9.5)	
Age, median (IQR), years	68.00 (58.00-77.00)	69.00 (59.00-77.25)	66.00 (56.00-77.00)	.231
Age category, n (%)				
<60 years old	145 (29.3)	64 (26.4)	81 (32.0)	.174
>60 years old	350 (70.7)	178 (73.6)	172 (68.0)	
BMI, median (IQR), kg/m^2	29.74 (25.61-34.92)	29.50 (25.22-34.79)	30.01 (25.78-35.26)	.653
BMI, n (%)				
BMI < 30 kg/m^2	254 (51.3)	127 (52.5)	127 (50.2)	.612
BMI > 30 kg/m^2	241 (48.7)	115 (47.5)	126 (49.8)	
Diabetes mellitus, n (%)	177 (35.8%)	154 (63.6%)	23 (9.1%)	<.001
Steroid use, n (%)	205 (41.4%)	114 (47.3%)	91 (36.0%)	.011
Types of insulin, n (%)				
SQ insulin	129 (26.0)	82 (33.9)	47 (18.6)	<.001
IV insulin	70 (14.1)	24 (9.9)	46 (18.2)	
Multiple routes	133 (26.9)	112 (46.3)	21 (8.3)	
APACHE III score, median (IQR)	46.00 (25.00-46.00)	61.0 (46.00-79.00)	53.0 (39.00-70.55)	.006
Laboratories values				
HbA1c, median (IQR), mmol/mol	64.00 (43.00-72.00)	61.0 (49.00-85.00)	42.00 (35.00-49.00)	.002
%	8.0 (6.1-8.7)	7.7 (6.6-9.9)	6.0 (5.4-6.6)	
C- reactive protein, median (IQR), mg/dL	12.30 (6.20-19.15)	13.00 (6.68-19.93)	11.60 (5.53-18.28)	.222
Ferritin, median (IQR), ng/mL	836.05 (444.35-1069.50)	896.80 (452.10-1751.00)	747.00 (435.60-1522.00)	.100
Fibrinogen, median (IQR), mg/dL	546.00 (427.75-683.75)	526.00 (427.00-690.00)	560.00 (427.00-690.00)	.396
d-dimer median (IQR), ng/mL	1465 (840.00-3062.50)	1410.00 (795.00-2900.00)	1530.00 (855.00-3325.00)	.498
Triglycerides, median (IQR), mg/dL	136.0 (103.00-202.25)	148.00 (108.25-23.25)	122.50 (92.75-184.25)	.033
White blood cell count, median (IQR), per mm^3	7.97(5.65-11.55)	8.5 (5.52-12.38)	7.35 (5.68-10.49)	.269
Interleukin-6, median (IQR), pg/mL	56.20 (22.40-139.50)	56.30 (26.55-121.70)	52.90 (17.75-167.35)	.944

Note: Continuous variables are described as mean ± SD for parametric variables and median (IQR) for nonparametric variables unless otherwise indicated. The *P* values <.05 were considered as statistically significant.

Abbreviations: APACHE III, Acute Physiology and Chronic Health Evaluation III; BMI, body mass index; HbA1c, glycosylated hemoglobin; IQR, interquartile range.

P = .004), but no statistically significant difference was found regarding the duration of mechanical ventilation (6.8 vs 7.1, *P* = .564) between the two groups. Although the hyperglycemic cohort had a statistically significant higher ICU LOS compared with the normoglycemic cohort (5.5 vs 3.5, *P* < .001), no significant differences were appreciated in the overall median hospital LOS between both groups (15.9 vs 15.8, *P* = .754).
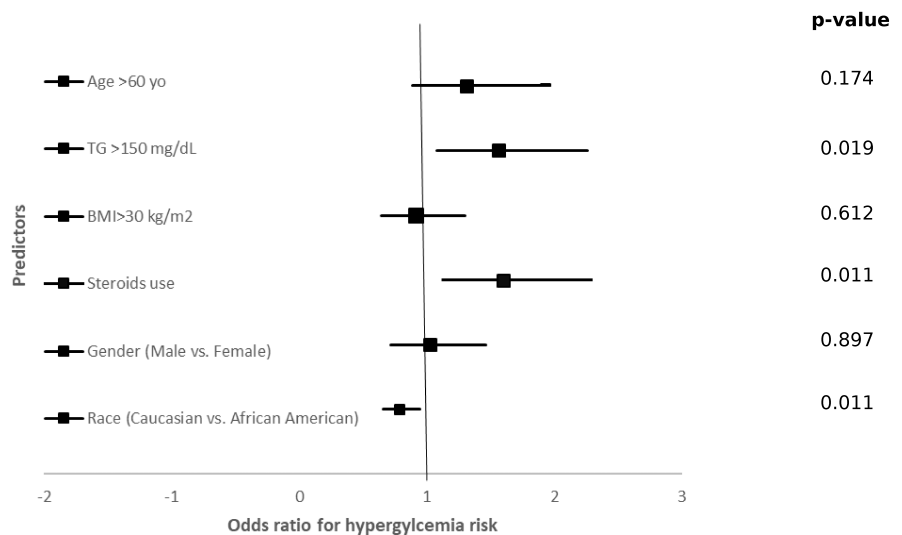
TABLE 2　Outcomes in patients with COVID-19 admitted to ICU

Variables	Patients with hyperglycemia (n = 242)	Patients with normoglycemia (n = 253)	P value
Intensive care unit length of stay, median (IQR), days	5.53 (5.50-16.41)	3.40 (6.36-16.39)	<.001
Hospital length of stay, median (IQR), days	15.85 (10.25-22.73)	15.83 (11.06-24.03)	.754
Mechanical ventilation, n (%)	121 (50.0)	94 (37.2)	.004
Duration of mechanical ventilation, median (IQR), days	6.81 (2.93-13.37)	7.08 (3.49-11.62)	.564
Disposition at discharge, n (%)			
Alive	166 (68.6)	211 (83.4)	<.001
Dead	76 (31.4)	42 (16.6)	

Note: P values <.05 were considered as statistically significant.

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; IQR, interquartile range.

FIGURE 1　Forest Plot showing univariate logistic regression analysis with odds ratios (95% confidence interval) of different predictors for hyperglycemia in patients admitted to ICU with COVID-19. ICU, Intensive Care Unit; TG, Triglycerides; BMI, Body mass Index

TABLE 3　Univariate and multivariate analyses for predictors of hyperglycemia in patients with COVID-19 admitted to ICU

Variables	Univariate analysis				Multivariate analysis			
	P value	OR	95% CI Lower	Upper	P value	OR	95% CI Lower	Upper
Age ≥ 60 years	.174	1.310	0.888	1.933				
Triglycerides ≥ 150 mg/dL	.019	1.559	1.076	2.259	.013	1.625	1.109	2.379
BMI ≥ 30 kg/m^2	.612	0.913	0.641	1.299				
Steroid use	.011	1.598	1.114	2.291	.025	1.521	1.054	2.194
Gender (male vs female)	.897	1.024	0.716	1.464				
Race (Caucasian vs African American)	.011	0.788	0.655	0.948	.015	0.791	0.655	0.956

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; ICU, intensive care unit; OR, odds ratio.

Univariate and multivariate linear regression analyses were performed to explore the factors predicting hyperglycemia among our patients (Figure 1). The results showed that glucocorticoid use (odds ratio [OR] 1.52; 95% CI 1.05, 2.19), triglycerides ≥ 150 mg/dL (OR 1.62; 95% CI 1.11, 2.38), and Caucasian vs African American

race (OR 0.79; 95% CI 0.65, 0.95) were statistically significant predictors for increased risk of hyperglycemia in critically ill patients with COVID-19 infection (Table 3). Also, history of diabetes mellitus was a significant predictor of hyperglycemia (OR 17.5; 95% CI 10.59, 28.91).

A multivariable Cox regression analysis was conducted to assess predictors of ICU mortality. Age older than 60 (HR 3.21; 95% CI 1.78, 5.78) and hyperglycemia with mean ICU glucose ≥140 mg/dL (HR 1.79; 95% CI 1.14, 2.82) were associated with increased ICU mortality (Figure 2). On the other hand, diagnosis of diabetes mellitus, whether type 1 or type 2, gender, race, BMI, or being on mechanical ventilation were not predictors for increased ICU mortality (Table 4).
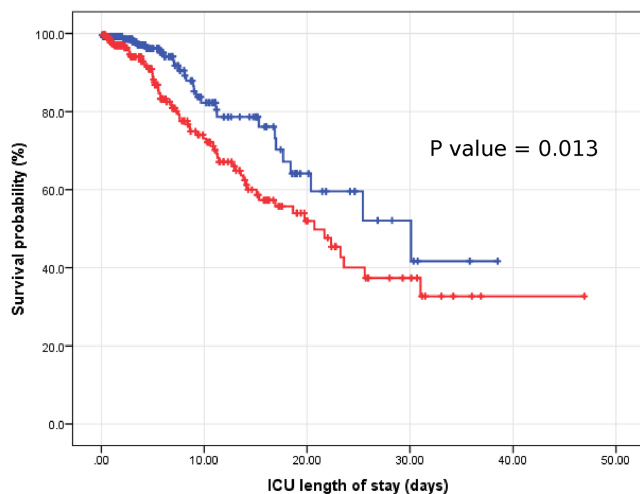

FIGURE 2 Kaplan-Meier curve for survival probability in the hyperglycemic group and the normoglycemic group. ICU, Intensive Care Unit

4 | DISCUSSION

Our retrospective study aimed to evaluate the association between hyperglycemia and outcomes in patients with severe COVID-19. In our cohort, 49% of all patients with severe COVID-19 admitted to the medical ICU were found to have hyperglycemia. Our results revealed that blood glucose ≥140 mg/dL and age above 60 years were associated with worst outcomes determined by an increase in mortality rate, severe APACHE III scores, prolonged ICU LOS, and higher need for mechanical ventilation.

Hyperglycemia is a common complication in critically ill patients and is associated with increased morbidity and mortality, irrespective of preexisting diabetes.[11] Hyperglycemia was reported in half of the patients with COVID-19 in a preliminary report from Wuhan, China.[12] In the study reported by Sardu et al, 25 out of 59 (42%) patients with COVID-19 were hyperglycemic during admission.[9] In our study, we noticed a higher percentage of hyperglycemic events among our patients. This can be explained by the fact that all patients included in our study were critically ill and managed in the ICU. Also, 41% of our cohort required steroids during admission.

Diabetes has been described as a risk factor for worse prognosis and mortality in patients with COVID-19.[13] Among 7162 patients with COVID-19 reported to the Centers for Disease Control and Prevention (CDC) from 12 February to 28 March 2020, diabetes was present in 32% of ICU patients,[14] similar to the percentage seen in our study population (35%). A retrospective study with 7337 patients with COVID-19, including 952 (12.9%) with preexisting diabetes, revealed significantly higher mortality (7.8% vs 2.7%, adjusted HR: 1.49) and increased medical intervention rates in patients with diabetes vs those without diabetes.[15] A meta-analysis of 16 003 patients also reported that diabetes was associated with a two-fold

TABLE 4 Multivariate Cox regression analysis for survival of patients with COVID-19 admitted to ICU

Variables	Coefficient	SE	P value	HR	95% CI Lower	Upper
Age (≥60 vs <60 years)	1.165	0.299	<.001	3.215	1.788	5.780
Gender (male vs female)	−0.317	0.189	.093	0.728	0.503	1.054
Weight (BMI ≥ 30 vs <30 kg/m^2)	−0.238	0.189	.206	0.788	0.544	1.140
Average blood glucose						
(≥140 vs <140 mg/dL)	0.586	0.232	.011	1.796	1.141	2.828
Race (Caucasian vs African American)	0.055	0.108	.662	1.057	0.854	1.307
Diabetes mellitus	−0.194	0.221	.383	0.823	0.535	1.275
Mechanical ventilation	0.092	0.194	.635	1.102	0.753	1.613

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; HR, hazard ratio; ICU, intensive care unit.

increase in mortality and severity of COVID-19 presentation when compared with patients without diabetes.[16] The CORONADO study, a multicenter French prospective observational study, revealed no association between HbA1c level and mortality.[17,18] A retrospective study from China comparing patients with COVID-19 with and without diabetes revealed diabetes was not significantly associated with higher in-hospital mortality (HR 1.58; 95% CI, 0.84-2.99).[19] Moreover, age ≥70 years and underlying hypertension were independent risk factors for in-hospital mortality in patients with diabetes. Despite the conflicting evidence supporting that diabetes can increase the risk of mortality, our study did not show a statistically significant association between preexisting diabetes and mortality.

Whether acute hyperglycemia and target glycemic management play a role in COVID-19 severity and outcome is still to be determined. In the study published by Bode et al[5] among 493 patients discharged alive, the median LOS was longer in patients with diabetes and/or uncontrolled hyperglycemia (≥180 mg/dL) compared with patients without diabetes or hyperglycemia (5.7 vs 4.3 days, $P < .001$). Another study reported that higher admission fasting blood glucose levels in COVID-19 was an independent predictor of ICU admission and poor outcomes, irrespective of steroid use.[20] Also, tight glycemic control has shown to have a protective effect with improved outcomes in patients with COVID-19 with hyperglycemia. Sardu et al reported that a more substantial drop in glucose levels, obtained by insulin infusion, is associated with better outcomes in patients with COVID-19.[9] Our study results came to the same conclusion that critically ill patients with COVID-19 with uncontrolled blood glucose ≥140 mg/dL had the worst overall outcome in terms of disease severity, mortality, need for mechanical ventilation, and LOS. On the other hand, the use of glucocorticoid therapy, history of diabetes, BMI, and mechanical ventilation were not predictors of mortality in our study. This can be explained by the severity of the disease in the included population compared with other studies that compared patients with mild, moderate, and severe disease.

Preliminary results from the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial showed that dexamethasone decreased mortality in patients with COVID-19 requiring mechanical ventilation or oxygen support.[21] However, further reports have highlighted the potentially harmful effects of systemic corticosteroids in these patients.[22] Steroid-induced hyperglycemia is a significant side effect in patients with and without diabetes that may result in worse outcomes and should be considered in the management of patients with COVID-19.[23] Our results revealed a statistically significant increased risk in the development of uncontrolled hyperglycemia with steroid use. Moreover, our results revealed that a high triglyceride level (≥150 mg/dL) was significantly associated with hyperglycemia.

Despite being a multicenter cohort, our study has multiple limitations. The primary limitation is the retrospective and observational nature of the study, which did not allow us to generalize our results, especially in those with less severe disease. Secondly, patients with severe disease received various treatment modalities that might have a significant effect on glycemic levels.

Our study successfully analyzed the association of hyperglycemia in critically ill patients with COVID-19 using mean glucose levels above 140 mg/dL with outcomes such as LOS (ICU and hospital), need and length of ventilation, and mortality. The fact that our study used mean average glucose levels during the entire ICU stay and not only portrayed admission glucose levels, allowed us to examine the effects of hyperglycemia in critically ill patients with COVID-19 in a more precise manner.

Based on our results, patients with blood glucose ≥140 mg/dL have an increased mortality rate and a longer ICU LOS. Over the past two decades, there have been considerable changes in the management of blood glucose control in the acute care setting from tight glycemic control (80-110 mg/dL) to a more moderate glycemic control (140-180 mg/dL).[24,25] There are currently no clear guidelines or recommendations regarding optimal glycemic targets in patients with COVID-19, especially in the critical care setting. Given the findings mentioned above, randomized clinical trials assessing specialized insulin protocols and the optimal target of tighter glucose control are needed. Further studies are also needed to assess the effect of triglyceride levels on blood glucose control and to evaluate if better control of triglyceride levels with the use of statins may optimize glucose control and improve mortality in patients with COVID-19.

ACKNOWLEDGEMENTS

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

ORCID

Monica Flores https://orcid.org/0000-0001-8925-0257

REFERENCES

1. Hopkins, J. Mortality analyses; 2020. https://coronavirus.jhu.edu/data/mortality. Accessed September 8, 2020.

2. Team CC-R. Severe outcomes among patients with coronavirus disease 2019 (COVID-19) - United States, February 12-March 16, 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69(12):343-346.

3. Gupta S, Hayek SS, Wang W, et al. Factors associated with death in critically ill patients with coronavirus disease 2019 in the US. *JAMA Intern Med.* 2020;180:1436.

4. Grasselli G, Greco M, Zanella A, et al. Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy. *JAMA Intern Med.* 2020;180: 1345-1355.

5. Bode B, Garrett V, Messler J, et al. Glycemic characteristics and clinical outcomes of COVID-19 patients hospitalized in the United States. *J Diabetes Sci Technol.* 2020;14(4):813-821.

6. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost.* 2020;18(4): 844-847.

7. Wang S, Ma P, Zhang S, et al. Fasting blood glucose at admission is an independent predictor for 28-day mortality in patients with COVID-19 without previous diagnosis of diabetes: a multi-Centre retrospective study. *Diabetologia.* 2020;63(10):2102-2111.

8. American Diabetes A. 15. Diabetes care in the hospital: standards of medical care in diabetes-2020. *Diabetes Care.* 2020;43 (suppl 1):S193-S202.

9. Sardu C, D'Onofrio N, Balestrieri ML, et al. Outcomes in patients with hyperglycemia affected by COVID-19: can we do more on glycemic control? *Diabetes Care.* 2020;43(7):1408-1415.

10. Pei-Fang W. Diagnosis and treatment protocol for novel coronavirus pneumonia (trial version 7). *Chin Med J (Engl).* 2020; 133(9):1087-1095.

11. Falciglia M. Causes and consequences of hyperglycemia in critical illness. *Curr Opin Clin Nutr Metab Care.* 2007;10(4):498-503.

12. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet.* 2020;395 (10223):507-513.

13. Apicella M, Campopiano MC, Mantuano M, Mazoni L, Coppelli A, del Prato S. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. *Lancet Diabetes Endocrinol.* 2020;8(9):782-792.

14. Team CC-R. Preliminary estimates of the prevalence of selected underlying health conditions among patients with coronavirus disease 2019 - United States, February 12-March 28, 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69(13):382-386.

15. Zhu L, She Z-G, Cheng X, et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. *Cell Metab.* 2020;31(6):1068-1077 e3.

16. Kumar A, Arora A, Sharma P, et al. Is diabetes mellitus associated with mortality and severity of COVID-19? A meta-analysis. *Diabetes Metab Syndr.* 2020;14(4):535-545.

17. Cariou B, Hadjadj S, Wargny M, et al. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. *Diabetologia.* 2020;63(8):1500-1515.

18. Scheen AJ, Marre M, Thivolet C. Prognostic factors in patients with diabetes hospitalized for COVID-19: findings from the CORONADO study and other recent reports. *Diabetes Metab.* 2020;46:265-271.

19. Shi Q, Zhang X, Jiang F, et al. Clinical characteristics and risk factors for mortality of COVID-19 patients with Diabetes in Wuhan, China: a two-center, retrospective study. *Diabetes Care.* 2020;43(7):1382-1391.

20. Liu SP, Zhang Q, Wang W, et al. Hyperglycemia is a strong predictor of poor prognosis in COVID-19. *Diabetes Res Clin Pract.* 2020;167:108338.

21. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19 - preliminary report. *N Engl J Med.* 2020. [Online ahead of print].

22. Theoharides TC, Conti P. Dexamethasone for COVID-19? Not so fast. *J Biol Regul Homeost Agents.* 2020;34(3):1241-1243.

23. Bonaventura A, Montecucco F. Steroid-induced hyperglycemia: an underdiagnosed problem or clinical inertia? A narrative review. *Diabetes Res Clin Pract.* 2018;139:203-220.

24. NICE-SUGAR Study Investigators for the Australian and New Zealand Intensive Care Society Clinical Trials Group and the Canadian Critical Care Trials Group, Finfer S, Chittock D, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med.* 2009;360(13):1283-1297.

25. Clain J, Ramar K, Surani SR. Glucose control in critical care. *World J Diabetes.* 2015;6(9):1082-1091.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.