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Sugar is not always sweet: exploring the relationship between hyperglycemia and COVID-19 in a predominantly African American population

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ABSTRACT

Introduction The purpose of this study is to examine the effect of admission glucose in patients hospitalized with COVID-19 with and without diabetes mellitus in a largely African American cohort.

Design and methods This study included 708 adults (89% non-Hispanic Black) admitted with COVID-19 to an urban hospital between 1 March and 15 May 2020. Patients with diabetes were compared with those without and were stratified based on admission glucose of 140 and 180 mg/dL. Adjusted ORs were calculated for outcomes of mortality, intubation, intensive care unit (ICU) admission, acute kidney injury (AKI), and length of stay based on admission glucose levels.

Results Patients with diabetes with admission glucose >140 mg/dL (vs <140 g/dL) had 2.4-fold increased odds of intubation (95% CI 1.2 to 4.6) and 2.1-fold increased odds of ICU admission (95% CI 1.0 to 4.3). Patients with diabetes with admission glucose >180 mg/dL (vs <180 g/dL) had a 1.9-fold increased mortality (95% CI 1.2 to 3.1). Patients without diabetes with admission glucose >140 mg/dL had a 2.3-fold increased mortality (95% CI 1.3 to 4.3), 2.7-fold increased odds of ICU admission (95% CI 1.3 to 5.4), 1.9-fold increased odds of intubation (95% CI 1.0 to 3.7) and 2.2-fold odds of AKI (95% CI 1.1 to 3.8). Patients without diabetes with glucose >180 mg/dL had 4.4-fold increased odds of mortality (95% CI 1.9 to 10.4), 2.7-fold increased odds of intubation (95% CI 1.2 to 5.8) and 3-fold increased odds of ICU admission (95% CI 1.3 to 6.6).

Conclusion Our results show hyperglycemia portends worse outcomes in patients with COVID-19 with and without diabetes. While our study was limited by its retrospective design, our findings suggest that patients presenting with hyperglycemia require closer observation and more aggressive therapies.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Several studies to date have identified hyperglycemia, independent of diabetes, as a risk factor for worse clinical outcomes in patients hospitalized for a variety of acute illnesses, including COVID-19. However, none of the studies to date have focused on this relationship in the Black, African American population, one that has been disproportionately affected by COVID-19 pandemic.

WHAT THIS STUDY ADDS

⇒ In this paper, we show that in patients hospitalized with COVID-19, admission hyperglycemia, defined as glucose >140 or >180 mg/dL, portends worse outcomes in terms of mortality, intubation, intensive care unit admission, and acute kidney injury regardless of prior diagnosis of diabetes.

⇒ Our study is unique in that it examines this relationship in a majority of African American population.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings suggest the importance of screening for hyperglycemia in all patients admitted for COVID-19 regardless of prior diagnosis of diabetes as it may be a marker for more severe illness and indicate the need for closer observation and more aggressive therapies.

⇒ An important focus for research is whether glucose-lowering therapies improve major clinical outcomes in patients with COVID-19.

INTRODUCTION

SARS-CoV-2 was first reported in Wuhan, China in December 2019, and on 11 March 2020 coronavirus (COVID-19) was declared a pandemic by the WHO. The clinical spectrum of disease has widely ranged from asymptomatic, mild upper respiratory infection, severe viral pneumonia, respiratory failure to death.[1] Comorbidities such as diabetes mellitus (DM), hypertension, respiratory disease, cardiovascular disease (CVD) and obesity are proposed risk factors for severe COVID-19 infection and worse clinical outcomes.[2]

Patients with DM are known to confer greater susceptibility and severity to infection. The impact of DM on other acute infectious diseases has been described in previous

studies. One study which examined the outcomes of patients with diabetes infected with influenza A (H1N1) found that patients with diabetes were more likely to be hospitalized or require intensive care unit (ICU)-level care compared with patients without.[3] Similarly, a history of DM and ambient hyperglycemia have been shown to be independent predictors for morbidity and mortality in severe acute respiratory syndrome (SARS).[4]

Early investigations conducted during the pandemic revealed a similar relationship between COVID-19 and DM. Studies found that those with diabetes were more likely to experience worse outcomes and require more intensive therapies including ICU admission, invasive mechanical ventilation, greater length of hospital stay and death.[5–9] Results from a meta-analysis conducted by Kumar *et al* which analyzed data from 33 studies found diabetes to be associated with twofold increase in mortality and severity of COVID-19 when compared with patients without diabetes.[10]

Historically, hyperglycemia, independent of diabetes, has been identified as a risk factor for worse clinical outcomes in patients hospitalized for a variety of acute illnesses.[11] Recently, this relationship has been found among patients with COVID-19, although there is a paucity of literature on this.[12] Of the studies conducted to date, none have focused on this relationship in the Black, African American population, one that has been disproportionately impacted by COVID-19.[13 14]

Our study examines the effect of admission blood glucose (BG) on outcomes in patients with COVID-19 hospitalized at SUNY Downstate Medical Center. The 376-bed hospital was designated a COVID-only hospital by Governor Andrew Cuomo from March through June 2020, located in East Flatbush, Brooklyn, a neighborhood in which 88% of its residents are African American and 15% are reported to have DM.[15]

METHODS

Study design

In this retrospective cohort study, we analyzed all adults admitted with COVID-19 to a designated COVID-19 hospital in Brooklyn, New York, from 1 March to 15 May 2020. COVID-19 was diagnosed via nasopharyngeal swab and subsequent reverse transcription PCR using the automated Cepheid machine. Data were collected from the HealthBridge Electronic Medical Record system. All patient identifiers were deidentified prior to data analysis. The SUNY Downstate Health Sciences Center Institutional Review Board and Privacy Board reviewed this study and determined that it is within exception category 4 according to federal regulations.

Subjects

The study cohort had 982 patients tested for COVID-19; 708 patients tested positive and were used for analysis. Patients were excluded if they were less than 18 years of age or if there were incomplete data (n=9) (see figure 1).

Primary predictors

The final study cohort was further categorized into subjects with and without diabetes, and further stratified by admission BG >140 or >180 mg/dL. Diabetes was defined as a diagnosis made by patient history, prior documentation in the electronic medical records and/or a current or recent (within 6 months) HbA1c ≥6.5% (48 mmol/mol). The admission BG of 140 and 180 mg/dL was chosen based on the targets for inpatient glucose control as published in the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation) trial and the resulting American Diabetes Association guidelines.[16 17]

Covariates

Covariates were age, sex, history of hypertension, CVD, chronic kidney disease (CKD), body mass index (BMI; kg/m^2), leukocytosis (white cell >9.5×10^9/L), serum creatinine >1.3 mg/dL, serum osmolality, and presence of diabetic ketoacidosis (DKA) on admission. Sex, serum creatinine, leukocytosis, presence of DKA, history of hypertension, CVD and CKD were adjusted for using a dichotomous approach. History of CVD includes having a history of coronary artery disease (atherosclerotic heart disease, history of myocardial infarction/non-ST-elevation

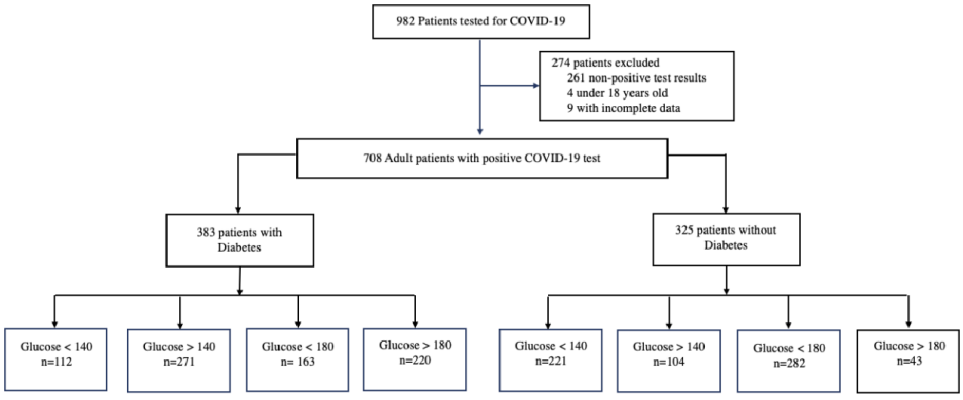

Figure 1. Study population criteria. Cohort was divided into patients with and without diabetes, and further stratified based on admission glucose cut-off points of 140 and 180 mg/dL.

myocardial infarction), congestive heart failure, arrhythmias, or valvular diseases. Medical history as listed was self-reported by the patient and added to the electronic record by the healthcare provider or was documented from a prior admission. BMI was calculated from each patient's height and weight as recorded on admission and entered by a healthcare provider. Overweight is defined as BMI 25–29.99 kg/m^2 while obesity is defined as BMI ≥30 kg/m^2. Leukocytosis and serum creatinine were based on admission values. Presence of DKA was defined as glucose ≥250 mg/dL, pH <7.31 or serum bicarbonate ≤18 and the presence of urine or serum ketones (beta-hydroxybutyrate). Serum osmolality was calculated using the equation (2×serum sodium)+(glucose/18).

Outcome measures

The primary outcome was inpatient mortality, while the secondary outcomes were intubation, ICU admission, acute kidney injury (AKI), and inpatient length of stay (LOS). AKI was diagnosed using the Kidney Disease Improving Global Outcomes (KDIGO) criteria.[18] The follow-up period was from admission to discharge or death. If data were collected while the patient was still in the hospital, outcome at that point in time was recorded.

Statistical analysis

Patient demographics, clinical characteristics, and outcomes were initially compared using Fisher's exact tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. Next, multivariate logistic regression analyses were performed using characteristics that were clinically relevant or were statistically significant at the p<0.05 level and the categorical outcomes of interest. A multiple linear regression was performed for the continuous outcome of LOS. The relationship between admission glucose and outcomes was explored using partial correlation analysis. All statistical analyses were performed using SAS Studio V.3.8 software.

RESULTS

Patient characteristics

Tables 1–3 show the baseline characteristics, relevant laboratory variables, and in-hospital outcomes of the study population. Seven hundred and eight patients were analyzed; the mean age of the cohort was 68, with 438 (62%) patients ≥65 years of age. The mean BMI among the study population was 29.5 kg/m^2. In this cohort, 363 (51%) were male and 628 (89%) were non-Hispanic Black. Baseline comorbidities included diabetes in 383 (54%), hypertension in 581 (82%), CVD in 559 (79%), CKD in 125 (18%), and obesity in 267 patients (38%).

As seen in table 1, there were no significant differences in baseline demographics in the group with diabetes compared with those without. Individuals with diabetes had a higher prevalence of comorbidities: hypertension (92% vs 70%, p≤0.001), CVD (88% vs 68%, p<0.001), CKD (25% vs 9%, p<0.001), and being overweight (32% vs 23%, p=0.01). The mean estimated glomerular filtration rate (GFR) for individuals with diabetes was significantly lower for those with diabetes compared with those without (46±33 mL/min vs 62±48 mL/min, p<0.001) and the number of individuals with estimated GFR <15 was greater in patients with diabetes (19% vs 14%, p<0.001). Within the diabetes cohort, 271 (71%) had BG >140 (mean 330 mg/dL, range 141–1330) and 220 (57%) had BG >180 (mean 377 mg/dL, range 181–1330) on admission. Of those without diabetes, 104 (32%) had BG >140 (mean 209 mg/dL, range 140–828) and 43 (13%) had BG >180 (mean 285 mg/dL, range 181–828) on admission.

Tables 2 and 3 show the patient characteristics and in-hospital outcomes according to admission BG >140 mg/dL vs <140 mg/dL and >180 mg/dL vs <180 mg/dL, respectively, in patients with and without diabetes. Among patients with diabetes, there was a larger prevalence of individuals with elevated white cell count and ferritin level in those with admission glucose >140 and >180 mg/dL (tables 2 and 3).

Patient outcomes

Table 2 reveals that among individuals both with and without diabetes, those with admission BG >140 mg/dL (vs BG <140 mg/dL) had significantly increased mortality, intubation, and ICU admission rates. Additionally, among patients without diabetes, those with admission BG >140 mg/dL had markedly increased frequency of AKI during their hospital course (43% vs 22%, p<0.001). Similarly, table 3 shows that patients without diabetes and admission BG >180 mg/dL had increased mortality, intubation, ICU admission, and AKI, while those with diabetes and admission BG >180 had increased mortality, ICU admission, and a trend towards significance for intubation (p=0.0534)

Table 4 shows the adjusted ORs for the main outcomes according to BG levels in the diabetes and non-diabetes cohorts. Given that DKA and hyperosmolar hyperglycemic syndrome are conditions which often contribute to morbidity and mortality, we adjusted ORs to account for the presence of DKA (31 patients, 4.4%) and serum osmolality.

Patients with diabetes and an admission glucose >140 mg/dL (vs <140 g/dL) had 2.4-fold increased odds of intubation (95% CI 1.2 to 4.6, p<0.011) and 2.1-fold increased odds of ICU admission (95% CI 1.0 to 4.3, p<0.04). Patients with diabetes with admission glucose >180 mg/dL (vs <180 g/dL) had a 1.9-fold increased mortality (95% CI 1.2 to 3.1, p<0.009).

Patients without diabetes with admission glucose >140 mg/dL had a 2.3-fold increased mortality (95% CI 1.3 to 4.3, p<0.007), 2.7-fold increased odds of ICU admission (95% CI 1.3 to 5.4, p<0.006), 1.9-fold increased odds of intubation (95% CI 1.0 to 3.7, p<0.05) and 2.2-fold odds of AKI (95% CI 1.1 to 3.8, p<0.03). Patients without diabetes with glucose >180 mg/dL had 4.4-fold increased odds of mortality (95% CI 1.9 to 10.4, p<0.001), 2.7-fold increased odds of intubation (95% CI 1.2 to 5.8, p<0.01)

Table 1 Baseline characteristics and in-hospital outcomes of the study population at baseline according to diabetes status

Characteristic	Total, n (%) n=708	Diabetes n=383	No diabetes n=325	P value
Age, mean±SD (years)	68±14	69±12	66±17	0.11
<45	47 (7%)	11 (3%)	36 (11%)	**<0.001**
45–64	223 (32%)	118 (31%)	105 (32%)	
≥65	438 (62%)	254 (66%)	184 (57%)	
Male sex	363 (51%)	192 (50%)	171 (53%)	0.55
Body Mass Index (BMI), mean (kg/m^2)	29.50	29.21	29.85	0.64
Race				
Black	628 (89%)	339 (89%)	289 (89%)	
White	39 (6%)	22 (6%)	17 (5%)	
Asian	5 (1%)	3 (1%)	2 (1%)	
Hispanic	5 (1%)	1 (0%)	4 (1%)	
Unknown	31 (4%)	18 (5%)	13 (4%)	
Comorbidities				
Hypertension	581 (82%)	354 (92%)	227 (70%)	**<0.001**
Cardiovascular disease (CVD)	559 (79%)	338 (88%)	221 (68%)	**<0.001**
Chronic kidney disease (CKD)	125 (18%)	95 (25%)	30 (9%)	**<0.001**
Overweight	196 (28%)	121 (32%)	75 (23%)	**0.01**
Obese	267 (38%)	141 (37%)	126 (39%)	0.64
Laboratory values on admission*				
Blood Glucose ≤140 mg/dL	333 (47%)	112 (29%)	221 (68%)	
Blood Glucose 141–180 mg/dL	112 (16%)	51 (13%)	61 (19%)	
Blood Glucose >180 mg/dL	263 (37%)	220 (57%)	43 (13%)	**<0.001**
White cell >9.5×10^9/L†	258 (36%)	147 (38%)	111 (34%)	0.27
CRP >8 mg/L†	588/619 (95%)	326/344 (95%)	262/276 (95%)	>0.99
Ferritin >233 mcg/L†	498/575 (87%)	274/320 (86%)	224/255 (88%)	0.44
Creatinine >1.3 mg/dL†	392 (55%)	238 (62%)	154 (47%)	**<0.001**
GFR, mean±SD	53±41 mL/min	46±33 mL/min	62±48 mL/min	**<0.001**
<15 mL/min	109 (17%)	69 (19%)	40 (14%)	**<0.001**
15–29 mL/min	99 (15%)	59 (16%)	40 (14%)	
30–59 mL/min	211 (32%)	128 (35%)	83 (28%)	
>60 mL/min	236 (36%)	105 (29%)	131 (45%)	
Outcomes				
Mortality	283 (40%)	160 (42%)	123 (38%)	0.32
Intubation	163 (23%)	92 (24%)	71 (22%)	0.53
ICU admission	146 (21%)	83 (22%)	63 (19%)	0.46
Acute kidney injury (AKI)	260 (37%)	166 (43%)	94 (29%)	**<0.001**
Length of stay, mean±SD (days)	8.2±8.7	8.7±9.0	7.5±8.4	**0.03**

Bold values indicate statistical significance.
*89 patients had missing CRP values (n=89) and 133 patients had missing ferritin values (n=133).
†values indicare the upper limit of normal.
CRP, C-reactive protein; GFR, glomerular filtration rate; ICU, intensive care unit.

and 3-fold increased odds of ICU admission (95% CI 1.3 to 6.6, p<0.008).

A partial correlation analysis was performed to explore the relationship between admission glucose levels and outcomes. Through this we found there to be a positive correlation between glucose and mortality in the diabetes (r=0.140, p=0.007) and non-diabetes groups (r=0.254, p<0.001). These correlations were

Table 2 Baseline characteristics and in-hospital outcomes of the study population at baseline according to admission glucose >140 mg/dL vs <140 mg/dL

Characteristic	Diabetes n=383	Diabetes (<140) n=112	Diabetes (>140) n=271	P value	No diabetes n=325	No diabetes (<140) n=221	No diabetes (>140) n=104	P value
Age, mean±SD (years)	69±12	68±11	69±12	0.36	66±17	64±17	70±15	**0.005**
<45	11 (3%)	3 (3%)	8 (3%)	0.68	36 (11%)	31 (14%)	5 (5%)	**0.005**
45–64	118 (31%)	38 (34%)	80 (30%)		105 (32%)	77 (35%)	28 (27%)	
≥65	254 (66%)	71 (63%)	183 (68%)		184 (57%)	113 (51%)	71 (68%)	
Male sex	192 (50%)	48 (43%)	144 (53%)	0.07	171 (53%)	118 (53%)	53 (31%)	0.72
Race				0.43				0.42
Black	339 (89%)	101 (90%)	238 (88%)		289 (89%)	196 (87%)	93 (89%)	
White	22 (6%)	6 (5%)	16 (6%)		17 (5%)	13 (6%)	4 (4%)	
Asian	3 (1%)	1 (1%)	2 (1%)		2 (1%)	1 (0%)	1 (1%)	
Hispanic	1 (0%)	1 (1%)	0 (0%)		4 (1%)	4 (2%)	0 (0%)	
Unknown	18 (5%)	3 (3%)	15 (6%)		13 (4%)	7 (3%)	6 (6%)	
Comorbidities								
Hypertension	354 (92%)	106 (95%)	248 (92%)	0.40	227 (70%)	154 (70%)	73 (70%)	>0.99
CVD	338 (88%)	100 (89%)	238 (88%)	0.73	221 (68%)	154 (70%)	67 (64%)	0.37
CKD	95 (25%)	30 (27%)	65 (24%)	0.60	30 (9%)	19 (9%)	11 (11%)	0.55
Overweight	121 (32%)	30 (27%)	91 (34%)	0.23	75 (23%)	50 (23%)	25 (24%)	0.78
Obese	141 (37%)	50 (45%)	91 (34%)	0.05	126 (39%)	86 (39%)	40 (38%)	>0.99
Laboratory values on admission								
White cell >9.5×10^9/L†	147 (38%)	28 (25%)	119 (44%)	**<0.001**	111 (34%)	69 (31%)	42 (40%)	0.13
CRP >8 mg/L†	326 (95%)	90 (94%)	236 (95%)	0.60	262 (95%)	175 (94%)	87 (97%)	0.56
Ferritin >233 mcg/L†	274 (86%)	66 (76%)	208 (89%)	**0.004**	224 (88%)	143 (87%)	81 (90%)	0.55
Creatinine >1.3 mg/dL†	238 (62%)	71 (63%)	167 (62%)	0.82	154 (47%)	94 (43%)	60 (58%)	**0.01**
GFR, mean±SD (mL/min)	46±33	44±37	47±32	0.17	62±48	65±51	55±38	0.16
<15	69 (19%)	33 (31%)	36 (14%)	**0.003**	40 (14%)	29 (14%)	11 (12%)	0.08
15–29	59 (16%)	13 (12%)	46 (18%)		40 (14%)	21 (10%)	19 (21%)	
30–59	128 (35%)	30 (28%)	98 (39%)		83 (28%)	56 (28%)	27 (30%)	
>60	105 (29%)	31 (29%)	74 (29%)		131 (45%)	97 (48%)	34 (37%)	
Outcomes								
Mortality	160 (42%)	37 (33%)	123 (45%)	**0.03**	123 (38%)	68 (31%)	55 (53%)	**<0.001**
Intubation	92 (24%)	15 (13%)	77 (28%)	**0.002**	71 (22%)	37 (17%)	34 (33%)	**0.002**
ICU admission	83 (22%)	13 (12%)	70 (26%)	**0.002**	63 (19%)	30 (14%)	33 (32%)	**<0.001**
AKI	166 (43%)	43 (38%)	123 (45%)	0.22	94 (29%)	49 (22%)	45 (43%)	**<0.001**
Length of stay, mean±SD (days)	8.7±9.0	8.0±8.3	9.1±9.3	0.34	7.5±8.4	7.2±8.0	8.1±9.2	0.08

Bold values indicate statistical significance values.
*89 patients had missing CRP values (n=89) and 133 patients had missing ferritin values (n=133).
†Values indicate the upper limit of normal.
AKI, acute kidney injury; Bold values, Bold values indicate statistical significance; CKD, chronic kidney disease; CRP, C-reactive protein; CVD, cardiovascular disease; GFR, glomerular filtration rate; ICU, intensive care unit.

Table 3 Baseline characteristics and in-hospital outcomes of the study population at baseline according to admission glucose >180 mg/dL vs <180 mg/dL

Characteristic	Diabetes n=383	Diabetes (<180) n=163	Diabetes (>180) n=220	P value	No diabetes n=325	No diabetes (<180) n=282	No diabetes (>180) n=43	P value
Age, mean±SD (years)	69±12	69±12	68±12	0.43	66±17	66±17	69±15	0.27
<45	11 (3%)	4 (2%)	7 (3%)	0.90	36 (11%)	34 (12%)	2 (5%)	0.37
45–64	118 (31%)	49 (30%)	69 (31%)		105 (32%)	91 (32%)	14 (33%)	
≥65	254 (66%)	110 (67%)	144 (65%)		184 (57%)	157 (56%)	27 (63%)	
Male sex	192 (50%)	73 (45%)	119 (54%)	0.08	171 (53%)	151 (54%)	20 (47%)	0.42
Race				0.62				0.65
Black	339 (89%)	143 (88%)	196 (89%)		289 (89%)	250 (89%)	39 (91%)	
White	22 (6%)	8 (5%)	14 (6%)		17 (5%)	16 (6%)	1 (2%)	
Asian	3 (1%)	2 (1%)	1 (0%)		2 (1%)	2 (1%)	0 (0%)	
Hispanic	1 (0%)	1 (1%)	0 (0%)		4 (1%)	4 (1%)	0 (0%)	
Unknown	18 (5%)	9 (6%)	9 (4%)		13 (4%)	10 (4%)	3 (7%)	
Comorbidities								
Hypertension	354 (92%)	151 (93%)	203 (92%)	NS	227 (70%)	197 (70%)	30 (70%)	NS
CVD	338 (88%)	141 (87%)	197 (89%)	0.42	221 (68%)	190 (67%)	31 (72%)	0.60
CKD	95 (25%)	43 (27%)	52 (24%)	0.55	30 (9%)	27 (10%)	3 (7%)	0.78
Overweight	121 (32%)	51 (31%)	70 (32%)	NS	75 (23%)	67 (24%)	8 (19%)	0.56
Obese	141 (37%)	68 (42%)	73 (33%)	0.11	126 (39%)	102 (36%)	24 (56%)	**0.02**
Laboratory values on admission*								
White cell >9.5×10^9/L†	147 (38%)	46 (28%)	101 (46%)	**<0.001**	111 (34%)	91 (32%)	20 (47%)	0.08
CRP >8 mg/L†	326 (95%)	131 (94%)	195 (96%)	0.46	262 (95%)	225 (94%)	37 (100%)	0.23
Ferritin >233 mcg/L†	274 (86%)	100 (79%)	174 (90%)	**0.005**	224 (88%)	194 (88%)	30 (86%)	0.89
Creatinine >1.3 mg/dL†	238 (62%)	106 (65%)	132 (60%)	0.34	154 (47%)	129 (46%)	25 (58%)	0.14
GFR, mean±SD (mL/min)	46±33	43±35	48±32	0.05	62±48	63±49	60±43	0.81
<15	69 (19%)	41 (26%)	28 (14%)	**0.03**	40 (14%)	37 (14%)	3 (8%)	0.26
15–29	59 (16%)	25 (16%)	34 (17%)		40 (14%)	31 (12%)	9 (24%)	
30–59	128 (35%)	49 (31%)	79 (39%)		83 (28%)	73 (29%)	10 (26%)	
>60	105 (29%)	42 (27%)	63 (31%)		131 (45%)	115 (45%)	16 (42%)	
Outcomes								
Mortality	160 (42%)	55 (34%)	105 (48%)	**0.006**	123 (38%)	94 (33%)	29 (67%)	**<0.001**
Intubation	92 (24%)	31 (19%)	61 (28%)	0.05	71 (22%)	52 (18%)	19 (44%)	**<0.001**
ICU admission	83 (22%)	27 (17%)	56 (26%)	**0.04**	63 (19%)	46 (16%)	17 (40%)	**0.001**
AKI	166 (43%)	67 (41%)	99 (45%)	0.47	94 (29%)	73 (26%)	21 (49%)	**0.003**
Length of stay, mean±SD (days)	8.7±9.0	8.3±9.4	9.0±8.7	0.40	7.5±8.4	7.3±7.6	8.8±12.4	0.27

Bold values indicate statistical significance at p<0.05.
*89 patients had missing CRP values (n=89) and 133 patients had missing ferritin values (n=133).
†Values indicate the upper limit of normal.
AKI, acute kidney injury; CKD, chronic kidney disease; CRP, C-reactive protein; CVD, cardiovascular disease; GFR, glomerular filtration rate; ICU, intensive care unit.

Table 4 Adjusted ORs for the association between admission glucose levels and outcomes in patients with and without diabetes

	Mortality*			Intubation*			ICU admission*			Acute kidney injury*		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
With diabetes												
Glucose >140 vs <140	1.5	0.9 to 2.5	<0.15	2.4	1.2 to 4.6	<0.01	2.1	1.0 to 4.3	<0.04	1.24	0.7 to 2.1	<0.43
Glucose >180 vs <180	1.9	1.2 to 3.1	<0.009	1.5	0.8 to 2.6	<0.18	1.3	0.8 to 2.4	<0.33	1.04	0.7 to 1.7	<0.08
Glucose 141–180 vs ≤140	0.7	0.3 to 1.6	<0.45	3.3	1.3 to 8.9	<0.02	3.9	1.2 to 9.9	<0.02	1.66	0.8 to 3.7	<0.21
Without diabetes												
Glucose >140 vs <140	2.3	1.3 to 4.3	<0.007	1.9	1.0 to 3.7	<0.05	2.7	1.3 to 5.4	<0.006	2.2	1.1 to 3.8	<0.03
Glucose >180 vs <180	4.4	1.9 to 10.4	<0.001	2.7	1.2 to 5.8	<0.01	3.0	1.3 to 6.6	<0.008	2.0	0.9 to 4.4	<0.09
Glucose 141–180 vs ≤140	1.4	0.7 to 2.9	<0.38	1.2	0.5 to 2.7	<0.70	1.8	0.8 to 4.3	<0.19	1.7	0.8 to 3.8	<0.17

*Adjusted for age, sex,† creatinine,† hypertension,† cardiovascular disease,† chronic kidney disease,† BMI, osmolality, leukocytosis† and diabetic ketoacidosis†
†Dichotomous (ie, male/female, normal/abnormal, present/absent, as appropriate).
BMI, body mass index; ICU, intensive care unit.

similar and statistically significant when examined for each of the other outcomes reported in the diabetes and non-diabetes groups (intubation r=0.24 and r=0.16, respectively, p<0.001 and p<0.002; ICU admission r=0.19 and r=0.23, respectively, both p<0.001; AKI r=0.11 and r=0.25, respectively, p<0.04 and p<0.001). These correlations remained statistically significant after adjusting for all relevant covariates listed above, with the exception of mortality in the diabetes group (r=0.09, p<0.10).

Patients with and without diabetes, with an admission BG 141–180 mg/dL, had no significant difference in mortality when compared with those with admission glucose ≤140 mg/dL. After controlling for all covariates, there were no differences in outcomes between individuals with and without diabetes, with the exception of length of hospital stay. The length of hospital stay was greater in those with diabetes when compared with those without (8.7±9 days vs 7.5±8.4 days, p=0.03). These results were not statistically significant after controlling for categories of admission glucose.

DISCUSSION

Our study revealed that hyperglycemia portends worse outcomes in patients hospitalized for COVID-19, regardless of prior diagnosis of diabetes. Several other observational studies have examined the relationship between hyperglycemia and outcomes in patients hospitalized with COVID-19. However, our study is unique in that it examines this relationship in a largely African American cohort, a group disproportionately affected by the virus.

Our results are consistent with several other studies published examining the relationship between serum glucose levels and outcomes in patients with COVID-19. Studies conducted by Wang *et al* and Alahmad *et al* examined the effect of fasting blood glucose (FBG) on outcomes in patients with COVID-19, and found that those with FBG ≥126 had increased odds of 28-day mortality and ICU admission, respectively.[19 20] An Italian study of Coppelli *et al* analyzed their cohort by three groups: normoglycemia defined as admission glucose <140 mg/dL (<7.78 mmol/L), hyperglycemia without prior diagnosis of DM defined as glucose >140 mg/dL and prior diagnosis of DM regardless of admission glucose levels.[21] They found that the group with glucose >140 mg/dL on admission without prior diagnosis of DM had two times greater inpatient mortality than those of the normal glycemia group, and 30% increased mortality when compared with those with known DM.[21] These findings are consistent with our results which reveal that individuals without diabetes with admission BG >140 mg/dL have twofold increased odds of mortality when compared with those with admission BG <140 mg/dL. Similarly, another retrospective study conducted in northern Italy found that elevated FBG on admission was associated with increased risk of ICU admission or death in patients with COVID-19. This association was stronger among

patients *without* pre-existing diabetes when compared with those with diabetes.[22] A large retrospective cohort study (n=11 312) from Spain found admission hyperglycemia (BG >180 mg/dL) to be an independent risk factor for mortality, mechanical ventilation, and ICU admission regardless of pre-existing diabetes in patients with COVID-19 when compared with those with BG <140 mg/dL.[12] Like our study, the studies described above analyzed outcomes according to admission BG levels, thus excluding patients with hyperglycemia which have resulted from inpatient therapies (ie, steroids).[12]

The association between hyperglycemia (without a prior diagnosis of diabetes) and worse outcomes in hospitalized patients suffering from acute illness is a well-known phenomenon demonstrated prior to this pandemic. Specifically, a large retrospective study conducted in 1998 by Umpierrez *et al* found that patients admitted to the hospital with new hyperglycemia (FBG >126 mg/dL or random BG >200 mg/dL) without a prior diagnosis of diabetes had increased mortality, longer LOS, and higher ICU admission rates, when compared with patients with a history of diabetes and those with normoglycemia.[23] Another study conducted by Frisch *et al*[24] reported a significant association between perioperative hyperglycemia and mortality rate in patients who underwent non-cardiac surgery.[24] However, as with the association between COVID-19 and hyperglycemia, it is unclear whether hyperglycemia initiates worsening disease, or if it occurs as a result of severe illness itself.

While the pathogenesis of the novel COVID-19 (SARS-CoV-2) remains unclear, the other coronaviruses, SARS-CoV and Middle East respiratory syndrome (MERS-CoV), have been studied more closely to date. Hyperglycemia was found to be an independent predictor of mortality in SARS-CoV and MERS-CoV.[4] One study found that SARS directly damages the islet cells of the pancreas, including the beta cells, which results in impaired insulin secretion and transient insulin-dependent diabetes, which resolves with resolution of disease.[25] If the pathogenesis of SARS-CoV-2 is similar, this would support the hypothesis that hyperglycemia is a result of severe COVID-19 infection itself, rather than the cause. Additionally, inflammation, which occurs because of infection, causes an increase in counter-regulatory stress hormones which leads to insulin resistance and thus hyperglycemia.[21] This phenomenon is often referred to as stress hyperglycemia.

On the contrary, hypotheses have been proposed to explain why hyperglycemia may trigger worsening illness in patients with COVID-19. One hypothesis is that the severity of COVID-19 infection is directly correlated with the concentration of glycosylated SARS-CoV-2 viral particles and glycosylated ACE-2 receptor in the lung epithelium.[26] This receptor is thought to be the primary entry point for the SARS-COV-2 virus into the epithelium. Thus, persistent hyperglycemia causing a direct increase in the glycosylated viral particles and ACE-2 receptors in the lung epithelium would enhance viral propagation and could potentially increase disease severity.[26] Hyperglycemia alone is known to induce a state of metabolic inflammation, ultimately generating a cytokine storm, which is hypothesized to cause multiorgan failure in individuals with severe COVID-19 infection.[27] The retrospective cohort study conducted by Zhu *et al*[7] found that patients with diabetes hospitalized for COVID-19 who had well-controlled BG throughout their stay had decreased inflammatory markers including lower neutrophil count, and lower levels of interleukin-6, C-reactive protein (CRP), and lactate dehydrogenase (LDH) when compared with those with poorly controlled glucose.[7] Similarly, the study conducted by Mazori *et al* (n=133) which found that among critically ill patients admitted to the ICU with COVID-19, individuals without DM and early-onset hyperglycemia (EHG), defined as BG >180 mg/dL during the first 2 days after ICU admission, had increased 14 and 60-day mortality when compared with those without DM and no EHG.[28] These patients were found to have elevated levels of inflammatory markers including CRP, D-dimer, procalcitonin, and lactate.

If hyperglycemia is in fact an independent risk factor for disease severity, the next question to be answered is whether improving glucose control would improve outcomes in patients with COVID-19. A few studies to date have examined the impact of adequate glucose control on clinical outcomes in these patients. The study conducted by Zhu *et al*[7] in China (n=7337) found that among patients with diabetes hospitalized for COVID-19, well-controlled glucose defined as serum glucose 70–180 mg/dL during patient admission was associated with significantly decreased mortality compared with those with poorly controlled glucose defined as the upper limit of glycemic variability exceeding 180 mg/dL.[7] Specifically, those in the well-controlled BG group had a decreased all-cause mortality when compared with those in the poorly controlled cohort. Additionally, the patients in the well-controlled BG group had a decreased frequency of acute respiratory distress syndrome (ARDS), acute heart injury, AKI, septic shock, and disseminated intravascular coagulation (DIC) when compared with the poorly controlled glucose group.[7] However, this study excluded patients without diabetes, thus the effect of hyperglycemia in this population is unknown. Similarly, a study in Italy found that patients with COVID-19 and hyperglycemia treated with insulin infusions had a decreased risk of severe disease and death.[29]

Another study performed by Bode *et al* on 1122 patients hospitalized for COVID-19 within 88 hospitals in the USA studied the clinical outcomes of patients with diabetes and/or uncontrolled hyperglycemia (defined as ≥2 BG values >180 mg/dL over a 24-hour period).[5] Their study found that patients with uncontrolled hyperglycemia without DM had a significantly increased mortality rate when compared with those with DM, 41.7% and 14.8%, respectively (p<0.001). These studies suggest that glucose control during admission might improve outcomes in patients with COVID-19.

It should be noted that while our findings are consistent with others published on the relationship between hyperglycemia and outcomes in COVID-19, our study did not reveal significantly worse outcomes in patients with diabetes compared with those without, except for AKI and LOS, which is different from previous studies (see table 1). Our study revealed similar mortality rates in patients with diabetes compared with those without (42% vs 38%, p=0.32) whereas the retrospective cohort study by Zhu *et al* found that patients with DM had a significantly greater mortality rate than those without (HR 1.49, p=0.005).[7] Since only 30% of our study cohort (n=205) had available HbA1c values within 6 months of admission, the diagnosis of diabetes was largely based on patient history and/or prior documentation. Thus, some patients were likely to be misclassified.

This study has several other limitations. Although our study sample size is larger than the studies conducted by Coppelli *et al*, Wang *et al*, Mazori *et al*, and Alahmad *et al*, our study cohort remains relatively small which could have predisposed to error. In terms of statistical analysis, evaluating the associations between patient characteristics and outcomes with a multivariate logistic regression model is suboptimal given that it only allows for the calculation of adjusted ORs. It is known that ORs can exaggerate an association between variables. Therefore, there is a chance that the ORs found may have overestimated the strength of the association.[30] Additionally, it should be noted that it is possible that some patients with DKA on admission were missed as not all patients had urine or plasma ketone level collected on admission, one of which is needed to diagnose DKA. However, the prevalence of DKA in our population (4.4%) was similar to what was found by Khan *et al*[31] (3.1%) in their study of a similar population.[31]

Despite these limitations, our study has several strengths. Our analysis included patients with and without diabetes and analyzed the effects of two different admission glucose cut-offs (>140 and >180 mg/dL). While other studies have included minority populations, our study is unique in that it is the first study to explore the effects of admission hyperglycemia on outcomes in COVID-19 in a primarily African American population (n=628, 89%). This is important as African American, Black populations are disproportionately affected by the COVID-19 pandemic. A study conducted by Acosta *et al* across the USA found that blacks had a 3.17 times increased risk of ICU admission and 2.58 times increased risk of death when compared with whites.[32] Another study conducted in California found that hospital admissions in African Americans were more than two times that of whites.[33] While both studies among others explored outcomes in African Americans, neither examined the effect of admission hyperglycemia in this population.

In conclusion, our study revealed that hyperglycemia portends worse outcomes in patients with COVID-19, with and without diabetes. These findings suggest that patients with hyperglycemia require closer observation and more aggressive therapies, emphasizing the importance of screening for hyperglycemia in all patients who test positive for COVID-19. However, whether hyperglycemia is a marker or a cause of more severe COVID-19 is unclear at this time. This raises the testable hypothesis that intensive glucose control may improve outcomes in patients with COVID-19. Future research must be conducted to determine the role of hyperglycemia in the pathogenesis of COVID-19.

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