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Original Article

Glucose dysregulation and its association with COVID-19 mortality and hospital length of stay

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ABSTRACT

Background and aims: We investigate the impact of blood glucose on mortality and hospital length of stay (HLOS) among COVID-19 patients.
Methods: Retrospective study of 456 patients with confirmed COVID-19 and glycemic dysregulation in the New York City area.
Results: We found that impaired glucose adjusted for other organs systems involved (OR:1.87; 95% CI:1.36−2.57, $p < 0.001$), increased glucose nadir (OR:34.28; 95% CI:3.97−296.05, $p < 0.01$) and abnormal blood glucose levels at discharge (OR:5.07; 95% CI:2.31−11.14, $p < 0.001$) were each significantly associated with increased odds for mortality. New or higher from baseline insulin requirement during hospitalization (OR:0.34; 95% CI:0.15−0.78; $p < 0.05$) was significantly associated with decreased odds for mortality. Increased glucose peak ($B = 0.001$, SE=<0.001, $p < 0.001$), new or higher from baseline insulin requirement during hospitalization ($B = 0.11$, $SE = 0.03$, $p < 0.001$), and increased days to dysglycemia ($B = 0.15$, $SE = 0.04$, $p < 0.001$) were each significantly associated with increased HLOS. Increased glucose nadir ($B = -0.67$, $SE = 0.07$, $p < 0.001$), insulin intravenous drip ($B = -0.10$, $SE = 0.05$, $p < 0.05$), and increased proportion days endocrine system involved ($B = -0.25$, $SE = 0.06$, $p < 0.001$) were each significantly associated with decreased HLOS.
Conclusion: Glucose dysregulation adversely affects mortality and HLOS in COVID-19. These data can help clinicians to guide patient treatment and management in COVID-19 patients.

1. Introduction

COVID-19 disease caused by the novel acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1] has rapidly spread across the world [2] with individuals having variable presentations ranging from asymptomatic infection to critical illness [3,4]. Respiratory system involvement is the most common cause of hospitalization in COVID-19 disease, and this can progress to acute respiratory distress syndrome (ARDS) requiring mechanical ventilation in patients with severe disease [3]. COVID-19 affects multiple organ systems [3,5] including the endocrine system causing glucose dysregulation in approximately 50% of those who are hospitalized with COVID-19 [6].

Dysglycemia or glucose dysregulation involves both hyperglycemia and hypoglycemia [7]. Glucose dysregulation in COVID-19 disease has been described in studies primarily from China and Europe [6–10] and in two reports from the United States (US) [11,12]. These studies found worsening hyperglycemia in diabetic patients or new hyperglycemia in non-diabetic patients and hypoglycemia with insulin use. In a review of these multiple non-US studies of COVID-19 patients with or without diabetes, hyperglycemia positively correlated with worse prognosis and higher mortality [13]. Non-US studies on insulin use in COVID-19 patients and its association with mortality are mixed. Some report greater mortality with insulin use [9] while others report beneficial results with improved glucose control and a positive impact on mortality and severe disease [8,14]. Furthermore, a Chinese study showed

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that after insulin treatment the proportion of hypoglycemia was higher in non-survivors as compared to survivors [9].

COVID-19 and its impact on glucose dysregulation is not well studied in the US population. There is a working paper looking at peak glucose level during hospital stay and its association with mortality which found that those with hyperglycemia have longer hospital stay, higher risk of developing acute respiratory distress syndrome (ARDS), and increased mortality as compared to those without hyperglycemia [11]. Another study focusing on hypoglycemia during the first 2−3 days of hospital stay found that those admitted directly to the ICU with hypoglycemia had increased overall in-hospital mortality [12].

There do not appear to be any studies of glucose level at admission and its association with mortality or hospital length of stay (HLOS). In addition, no studies look at persistent glucose abnormalities at discharge or death, proportion of days the endocrine system was involved, or days to dysglycemia in COVID-19. We describe glucose dysregulation variables of glucose levels on admission, peak, nadir, as well as new or increased insulin use, proportion of days the endocrine system was involved, days to dysglycemia, and persistent dysglycemia at discharge or death in patients with COVID-19. We also conduct multivariate analyses for the association of glucose dysregulation variables with mortality and HLOS.

2. Subjects, materials and methods

2.1. Subjects

This retrospective study included 456 consecutive COVID-19 patients with laboratory confirmation (positive real-time reverse transcription polymerase chain reaction nasopharyngeal sample result for SARS-CoV-2) and abnormal blood glucose level from March 1, 2020 through May 15, 2020. We defined abnormal blood glucose level according to clinical practice guidelines of the Endocrine Society [15] as hypoglycemia with blood glucose level <60 mg/dL or hyperglycemia with blood glucose level >140 mg/dL at any time during hospitalization. Data are from patients that completed their hospital course with either discharged alive or death.

2.2. Definitions and variables

Demographics were age (years), sex (male, female), race/ethnicity (Caucasian, African American, Hispanic, Other), and insurance (private, uninsured or emergency Medicaid, regular Medicaid, Medicare). We collected information on home management of home steroid use, home oral glycemic use (i.e., metformin, sulfonylureas, meglitinides, thiazolidinediones), home insulin use (including pre-meal and/or long-acting insulin) all measured as no/yes. Comorbidities were obesity (no or yes if body mass index was $\geq$30 kg/m^2) and Charlson Comorbidity Index (CCI) (range 0−37) [16]. The CCI is used to predict a 10 year survival rate utilizing the following comorbid conditions: age, history of myocardial infarction, peripheral vascular disease, heart failure, dementia, cerebrovascular disease, connective tissue disease, chronic obstructive pulmonary disease (COPD), peptic ulcer disease, diabetes mellitus, chronic liver disease, renal disease, leukemia, lymphoma, solid tumor, and AIDS status [17].

Disease severity was measured by the Quick Sequential Organ Failure Assessment (qSOFA) (range 0−3) [18], ICU admission (no/yes), intubation on admission (no/yes), oxygen requirement during hospitalization (none, low FiO2 $\leq$55%, high FiO2 >55%, mechanical ventilation). ICU admission was defined as either admission to an ICU, FiO2 requirement >55%, or requirement of intravenous vasopressor support. Treatment management was vasopressor use (i.e., norepinephrine, vasopressin, epinephrine, dobutamine, midodrine), antibiotic, nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB), antiviral (remdesivir), antimalarial (hydroxychloroquine and chloroquine), steroid, convalescent plasma from COVID-19 donor, interleukin inhibitor (IL-6 inhibitor − tocilizumab), and therapeutic anticoagulation (e.g., heparin, enoxaparin, rivaroxaban, apixaban, warfarin), all measured as no/yes.

Eight organ systems were recorded: endocrine, cardiovascular, respiratory, renal, liver, hematologic, neurologic, and musculoskeletal. We defined each organ system involvement as follows. Endocrine was any blood glucose level >140 mg/dL or <60 mg/dL. Cardiovascular was troponin elevation >0.04 ng/mL, new onset of heart failure, AV block, ventricular tachycardia, inotrope use, or vasopressor use. Respiratory was nadir oxygen saturation <95% or any new requirement of oxygen therapy. Renal was any increase in creatinine level >0.3 mg/dL according to the AKIN criteria [19]. Liver was abnormal serum alanine aminotransferase 1.5 times upper limit (>60 IU/L) or abnormal total serum bilirubin >1.1 mg/dL. Hematologic was either white blood cell count <4 $\times$ 10^9/L or >11 $\times$ 109/L, absolute neutrophil count <1.8 $\times$ 109/L or >7 $\times$ 109/L, hemoglobin count <9.2 g/dL, or platelet count <110 $\times$ 109/L. Neurologic was a decrease in Glasgow Coma Scale score, change in mental status from baseline, new onset of seizures, or new onset of transient ischemic attack or cerebrovascular accident. Musculoskeletal was creatine kinase level >1000 units/L. The variable of number of organ systems involved was the sum of the 8 organ systems above which could range from 1 to 8, as inclusion for this study required presence of glucose dysregulation of dysglycemia.

We studied the following glucose-specific variables: blood glucose level on admission (mg/dL), blood glucose peak during hospitalization (mg/dL), blood glucose nadir during hospitalization (mg/dL), any new or increase from baseline insulin requirement during hospitalization, requirement of intravenous insulin drip during hospitalization, proportion hospital days with abnormal blood glucose level (total number of days glucose involvement/total number of days hospitalized), days to dysglycemia, and abnormal blood glucose level persistent involvement at discharge. Thyroid-stimulating hormone (μIU/ml) was recorded for the small portion of patients where information was available. The primary outcome was mortality (no/yes). The secondary outcome was number of days for HLOS.

2.3. Statistical analysis

Descriptive analyses consisted of mean and standard deviation for the continuous variables and frequency and percentage for the categorical variables. The separate outcome variables of mortality and HLOS were each analyzed with two models. Model 1 consisted of univariate analyses that analyzed demographic, comorbidities, disease severity, and treatment management variables. Model 2 consisted of a multivariate analysis that included all the variables significant in the univariate analyses from Model 1 and added the glucose-specific variables. Mortality was analyzed with logistic regression. HLOS was analyzed with linear regression. The skewed variables were logarithmic transformed. All p-values were two-tailed. Analyses were performed with IBM SPSS Statistics version 26 (IBM SPSS Statistics for Windows. Armonk, NY: IBM Corporation; 2019).

3. Results

Table 1 shows the sample characteristics. For demographics, the

Table 1
Sample characteristics of 456 COVID-19 patients.

Variables	M (SD) or Frequency (Percent)
Demographics	
Age (years) [mean]	63.0 (14.49)
Sex (female)	170 (37.3)
Race/ethnicity	
Caucasian	119 (26.1)
African American	123 (27.0)
Hispanic	177 (38.8)
Other	37 (8.1)
Insurance	
Private	104 (22.8)
Uninsured/Emergency Medicaid	75 (16.4)
Regular Medicaid	165 (36.2)
Medicare	112 (24.6)
Home Management	
Home steroid (yes)	14 (3.1)
Home oral glycemic (yes)	125 (27.4)
Home insulin (yes)	67 (14.7)
Comorbidities	
Obese (yes)	176 (38.6)
CCI [mean]	3.4 (2.40)
Disease severity	
qSOFA [mean]	1.6 (0.66)
ICU (yes)	302 (66.2)
Intubation admission (yes)	43 (9.4)
Oxygen requirement hospitalization	
None	49 (10.7)
Low FiO2 (≤55%)	106 (23.2)
High FiO2 (>55%)	127 (27.9)
Ventilation	174 (38.2)
Treatment management	
Vasopressor (yes)	119 (26.1)
Antibiotic (yes)	432 (94.7)
NSAID (yes)	119 (26.1)
ACEi/ARBS (yes)	61 (13.4)
Antiviral(yes)	12 (2.6)
Antimalarial (yes)	386 (84.6)
Steroid (yes)	196 (43.0)
Convalescent plasma (yes)	48 (10.5)
Interleukin inhibitor (yes)	73 (16.0)
Anticoagulant (yes)	119 (26.1)
Organ involvement	
Number organs involved [mean]	4.9 (1.64)
Glucose specific	
Glucose admission [mean]	203.8 (133.39)
Glucose peak [mean]	312.5 (150.74)
Glucose nadir [mean]	110.8 (64.83)
New or higher (from baseline) insulin requirement during hospitalization (yes)	242 (53.1)
Insulin IV drip during hospitalization (yes)	54 (11.8)
Proportion days endocrine system involved [mean]	0.6 (0.32)
Days to dysglycemia [mean]	2.8 (3.75)
Abnormal blood glucose level persistent involvement at discharge (yes)	259 (56.8)
Thyroid-stimulating hormone [mean]	2.4 (4.92)
Outcomes	
Mortality (yes)	206 (45.2)
Length of stay (days) [mean]	12.7 (13.45)

Note: M = mean, SD = standard deviation, CCI=Charlson Comorbidity Index, qSOFA = quick Sepsis Related Organ Failure Assessment, ICU = intensive care unit, FiO2 = fraction of inspired oxygen, NSAID = nonsteroidal anti-inflammatory drug, ACEi = Angiotensin-converting-enzyme inhibitors, ARB = angiotensin II receptor blockers. Thyroid-stimulating hormone missing data and data only available for 133 patients.

mean age was 63 years, 37.3% were female, 65.8% were from either African American or Hispanic race/ethnicity, and more than half had Medicaid or were uninsured. More than a quarter were on antiglycemic therapy and slightly less than 40% were obese and. The mean CCI was 3.4 (out of 37 points) and disease severity mean qSOFA score was 1.6 (out of 3 points). The most common treatments administered were antibiotics (94.7%), antimalarial (84.6%), and steroids (43.0%). Mean number of organ systems involved was 4.9. Mean glucose on admission was 203.8 mg/dL. Mortality was 45.2% and the mean HLOS was 12.7 days.

Table 2 shows logistic regression analyses for mortality. In the univariate analyses shown in Model 1, increased age, insurance of regular Medicaid and Medicare, increased CCI, increased qSOFA, ICU care, intubation at admission, oxygen requirement during hospitalization of high FiO2 and ventilation, vasopressor, antibiotic, antiviral, and increased number organs involved were each significantly associated with increased odds for mortality. Hispanic race/ethnicity was significantly associated with decreased odds for mortality. In the multivariate analysis shown in Model 2, increased age, insurance of regular Medicaid, oxygen requirement during hospitalization of ventilation, increased number organs involved, increased glucose nadir, and abnormal blood glucose level persistent involvement at discharge were each significantly associated with increased odds for mortality. Intubation at admission and new or higher (from baseline) insulin requirement during hospitalization were each significantly associated with decreased odds for mortality.

Table 3 shows linear regression analyses for HLOS. In the univariate analyses shown in Model 1, ICU care, oxygen requirement during hospitalization of low FiO2, high FiO2, and ventilation, vasopressor, antibiotic, NSAID, antiviral, steroid, convalescent plasma, Interleukin inhibitor, anticoagulant, and increased number organs involved were each significantly associated with increased HLOS. Increased age, female sex, and increased CCI were each significantly associated with decreased HLOS. In the multivariate analysis shown in Model 2, oxygen requirement during hospitalization of low FiO2, antibiotic, NSAID, steroid, convalescent plasma, anticoagulant, increased glucose peak, new or higher (from baseline) insulin requirement during hospitalization, and increased days to dysglycemia were each significantly associated with increased HLOS. Increased age, increased glucose nadir, insulin IV drip during hospitalization, and increased proportion days endocrine system involved were each significantly associated with decreased HLOS.

4. Discussion

Our study showed that glucose dysregulation adjusted for all other organ system involvement was associated with increased mortality. Among the glucose specific variables, glucose peak was not associated with mortality but was associated with increased HLOS, while glucose nadir was associated with increased odds for mortality and decreased HLOS. New insulin use or higher insulin requirements from baseline was associated with decreased odds for mortality and increased HLOS. Use of insulin drip was not associated with mortality and was associated with decreased HLOS. Increased proportion of days that patients experienced dysregulated glycemic control was not associated with mortality but was associated with decreased HLOS. Experiencing glycemic dysregulation later on during hospitalization was associated with increased HLOS but not associated with mortality. Glucose dysregulation at discharge or death was associated with increased odds for mortality but not with HLOS. We also found that increased age was associated with higher mortality and decreased HLOS. Sex and race/ethnicity was not associated with mortality or HLOS. Regular Medicaid patients but not uninsured had increased odds for mortality. Intubation on admission had lower odds for mortality, while ventilation during hospitalization had higher odds for mortality. Those with low oxygen requirements (Fio2 < 55%) during hospitalization had increased HLOS. Treatments (antibiotic, NSAID, steroid use, convalescent plasma, and anticoagulant) were associated with longer HLOS.

Table 2
Logistic regression analyses for mortality.

Variables	Model 1	Model 2
	Univariate	Multivariate
	OR (95% CI)	OR (95% CI)
Demographics		
Age (years)	1.04 (1.02, 1.06)***	1.07 (1.03, 1.11)***
Sex (female)	0.93 (0.64, 1.37)	–
Race/ethnicity		
Caucasian	1.00	1.00
African American	0.65 (0.39, 1.08)	0.66 (0.25, 1.71)
Hispanic	0.60 (0.38, 0.96)*	1.30 (0.49, 3.43)
Other	1.51 (0.71, 3.22)	1.60 (0.41, 6.19)
Insurance		
Private	1.00	1.00
Uninsured/Emergency Medicaid	1.37 (0.74, 2.55)	0.92 (0.30, 2.89)
Regular Medicaid	2.03 (1.22, 3.39)**	3.24 (1.20, 8.75)*
Medicare	2.38 (1.37, 4.13)**	2.42 (0.74, 7.91)
Home Management		
Home steroid (yes)	1.22 (0.42, 3.54)	–
Home oral glycemic (yes)	0.68 (0.45, 1.04)	–
Home insulin (yes)	0.79 (0.47, 1.34)	–
Comorbidities		
Obese (yes)	0.88 (0.60, 1.28)	–
CCI	1.18 (1.09, 1.28)***	1.09 (0.87, 1.37)
Disease severity		
qSOFA	1.50 (1.13, 2.00)**	1.05 (0.61, 1.81)
ICU (yes)	19.21 (10.39, 35.51)***	1.11 (0.13, 9.59)
Intubation admission (yes)	7.35 (3.20, 16.91)***	0.22 (0.06, 0.84)*
Oxygen requirement hospitalization		
None	1.00	1.00
Low FiO2 (≤55%)	1.66 (0.33, 8.31)	0.72 (0.11, 4.71)
High FiO2 (>55%)	16.29 (3.79, 70.06)***	6.84 (0.47, 99.88)
Ventilation	117.50 (27.01, 511.13)***	67.37 (3.96, 1,146.60)**
Treatment management		
Vasopressor (yes)	14.63 (8.23, 26.00)***	2.30 (0.85, 6.18)
Antibiotic (yes)	2.59 (1.01, 6.64)*	0.90 (0.11, 7.56)
NSAID (yes)	1.06 (0.70, 1.61)	–
ACEi/ARBS (yes)	0.65 (0.37, 1.13)	–
Antiviral (yes)	6.33 (1.37, 29.21)*	1.49 (0.12, 18.09)
Antimalarial (yes)	1.04 (0.63, 1.74)	–
Steroid (yes)	1.31 (0.90, 1.90)	–
Convalescent plasma (yes)	1.03 (0.57, 1.88)	–
Interleukin inhibitor (yes)	1.07 (0.65, 1.77)	–
Anticoagulant (yes)	0.84 (0.55, 1.28)	–
Organ involvement		
Number organs involved	3.03 (2.48, 3.71)***	1.87 (1.36, 2.57)***
Glucose specific		
Glucose admission [mean]	–	0.89 (0.08, 10.31)
Glucose peak [mean]	–	1.00 (0.995, 1.003)
Glucose nadir [mean]	–	34.28 (3.97, 296.05)**
New or higher (from baseline) insulin requirement during hospitalization (yes)	–	0.34 (0.15, 0.78)*
Insulin IV drip during hospitalization (yes)	–	3.10 (0.90, 10.70)
Proportion days endocrine system involved [mean]	–	1.42 (0.26, 7.93)
Days to dysglycemia [mean]	–	0.90 (0.26, 3.03)
Abnormal blood glucose level persistent involvement at discharge (yes)	–	5.07 (2.31, 11.14)***

Note: OR = odds ratio, CI = confidence interval, CCI=Charlson Comorbidity Index, qSOFA = quick Sepsis Related Organ Failure Assessment, ICU = intensive care unit, FiO2 = fraction of inspired oxygen, NSAID = nonsteroidal anti-inflammatory drug, ACEi = Angiotensin-converting-enzyme inhibitors, ARB = angiotensin II receptor blockers. *p < 0.05, **p < 0.01, ***p < 0.001, Model 2 Nagelkerke R Square = 0.77.

We found that glucose dysregulation adjusted for all other organ involvement had increased odds for mortality. Hyperglycemia is correlated with increased severity and mortality in COVID-19 [12,20]. Elevated blood glucose stimulates the expression of body ACE2 receptors allowing the entry of SARS-CoV-2 into the cells, leading to an inflammatory and hyper-immune response [20]. Increased SARS-CoV-2 viral replication has been observed within pancreatic cells in patients with higher glucose concentrations affecting insulin production [1]. A single US study with COVID-19 patients showed that hypoglycemia at any point during hospital stay in both those with and without diabetes has increased risk for mortality [12]. With regard to hypoglycemia, some suggest that hypoglycemia leads to the upregulation of the pro-inflammatory factor of lipopolysaccharide during active COVID-19 infection [21]. Lipopolysaccharide amplifies glucose transporter overexpression on monocytes to ensure monocytes are provided with enough glucose to combat infection but at the same time may trigger a cytokine storm worsening COVID-19 disease outcome [21].

We found that glucose peak was not associated with mortality but was associated with increased HLOS. Previous research with COVID-19 patients report hyperglycemia as a predictor of mortality [22]. [-23] Our findings differ from this pattern. We suggest that our use of peak glucose level as a continuous variable representing the highest value during admission regardless of developing

Table 3
Linear regression analyses for length of stay.

Variables	Model 1	Model 2
	Univariate	Multivariate
	B (SE)	B (SE)
Demographics		
Age (years)	−0.004 (0.001)**	−0.003 (0.001)*
Sex (female)	−0.08 (0.04)*	−0.05 (0.03)
Race/ethnicity		–
Caucasian	Reference	
African American	−0.08 (0.05)	
Hispanic	0.06 (0.05)	
Other	−0.08 (0.07)	
Insurance		–
Private	Reference	
Uninsured/Emergency Medicaid	0.09 (0.06)	
Regular Medicaid	−0.06 (0.05)	
Medicare	−0.07 (0.05)	
Home Management		
Home steroid (yes)	0.04 (0.10)	–
Home oral glycemic (yes)	−0.05 (0.04)	–
Home insulin (yes)	−0.04 (0.05)	–
Comorbidities		
Obese (yes)	−0.01 (0.04)	–
CCI	−0.02 (0.01)**	−0.002 (0.01)
Disease severity		
qSOFA	−0.02 (0.03)	–
ICU (yes)	0.25 (0.04)***	0.03 (0.06)
Intubation admission (yes)	−0.09 (0.06)	–
Oxygen requirement hospitalization		
None	Reference	Reference
Low FiO2 (≤55%)	0.14 (0.06)*	0.09 (0.05)*
High FiO2 (>55%)	0.25 (0.06)***	0.04 (0.07)
Ventilation	0.36 (0.06)***	0.10 (0.08)
Treatment management		
Vasopressor (yes)	0.16 (0.04)***	−0.02 (0.04)
Antibiotic (yes)	0.31 (0.08)***	0.13 (0.06)*
NSAID (yes)	0.08 (0.04)*	0.07 (0.03)**
ACEi/ARBS (yes)	−0.01 (0.05)	–
Antiviral (yes)	0.22 (0.11)*	0.11 (0.08)
Antimalarial (yes)	0.08 (0.05)	–
Steroid (yes)	0.34 (0.03)***	0.09 (0.03)**
Convalescent plasma (yes)	0.53 (0.05)***	0.16 (0.05)**
Interleukin inhibitor (yes)	0.41 (0.05)***	0.07 (0.04)
Anticoagulant (yes)	0.31 (0.04)***	0.08 (0.03)*
Organ involvement		
Number organs involved	0.06 (0.01)***	0.02 (0.01)
Glucose specific		
Glucose admission [mean]	–	0.01 (0.08)
Glucose peak [mean]	–	0.001 (<0.001)***
Glucose nadir [mean]	–	−0.67 (0.07)***
New or higher (from baseline) insulin requirement during hospitalization (yes)	–	0.11 (0.03)***
Insulin IV drip during hospitalization (yes)	–	−0.10 (0.05)*
Proportion days endocrine system involved [mean]	–	−0.25 (0.06)***
Days to dysglycemia [mean]	–	0.15 (0.04)***
Abnormal blood glucose level persistent involvement at discharge (yes)	–	−0.05 (0.03)
Constant	–	1.96 (0.21)***

Note: B = unstandardized beta, SE = standard error, CCI=Charlson Comorbidity Index, qSOFA = quick Sepsis Related Organ Failure Assessment, ICU = intensive care unit, FiO2 = fraction of inspired oxygen, NSAID = nonsteroidal anti-inflammatory drug, ACEi = Angiotensin-converting-enzyme inhibitors, ARB = angiotensin II receptor blockers. *p < 0.05, **p < 0.01, ***p < 0.001, Model 2 adjusted R Square = 0.58.

hyperglycemia led to results of no correlation with mortality. Our finding of glucose peak associated with increased HLOS is similar to findings of patients with hyperglycemia associated with increased HLOS [11,23]. This is likely because the often-seen high glucose peak levels requires treatment and monitoring that prolongs hospital stay. Glucose nadir was associated with increased odds for mortality and decreased HLOS. There is only one US study focusing on hypoglycemia and its association with mortality in COVID-19 patients that found that development of hypoglycemia during the first 2−3 days of hospital stay was associated with increased odds for mortality [12]. Our finding of glucose nadir associated with increased odds for mortality is similar to this study. As hypoglycemia triggers a series of events leading to upregulation of pro-inflammatory factors that can lead to a cytokine storm [21], we suggest that this is the reason for the association with mortality. We did not find any association between glucose level on admission and either mortality or HLOS. Glucose patterns during hospitalization are indicative of COVID-19 prognosis during hospitalization [24]. We suggest that particularly with prolonged hospitalization, glucose dysregulation during hospital stay rather than at admission is what determines patient outcomes.

New insulin use or higher insulin requirements from baseline were associated with decreased odds for mortality and increased HLOS. Intensive glucose control reduces mortality [25]. Also, a non-

US study showed a decrease in mortality among hospitalized COVID-19 patients treated with insulin infusions [22]. Our findings are similar to this pattern. Better controlled glucose is likely to limit viral replication [1] and thus decrease mortality. The observed increase in HLOS is likely a consequence of increased need for in-hospital treatment completion or a consequence of a decrease in mortality. We found that the use of insulin intravenous drip during hospitalization was not associated with mortality but was associated with decreased HLOS. Intravenous Insulin therapy is still being debated about whether it is effective and safe for COVID-19 patients. Some report a benefit with intensive insulin therapy [22] while others report harm with intravenous insulin therapy [9]. Our findings support a benefit for insulin therapy. In our hospital, the insulin intravenous drip is administered mainly to those in the ICU with uncontrolled glucose levels. Others report that COVID-19 ICU patient length of stay was significantly prolonged in patients with uncontrolled blood glucose [26]. We suggest that the insulin drip allowed us to better control the average blood sugars of these patients and thus reduce their HLOS.

We found that increased proportion of days that patients experienced dysregulated glycemic control was associated with decreased HLOS, whereas increased days to dysglycemia was associated with increased HLOS. Patients that had persistent glucose dysregulation at discharge or death had increased odds for mortality but no association with HLOS. The finding of greater proportion of days of dysglycemia and its association with decreased HLOS is likely because patients were clinically improving and discharged before their hyperglycemia fully resolved and thus their glucose remained elevated upon discharge. Others also report that shortage of resources during the early pandemic led to insufficient dysglycemia treatment before either discharge or death [27]. Our finding of increased HLOS in patients that experienced a delayed onset in glycemic dysregulation can be explained by variable COVID-19 disease progression from mild to perhaps moderate disease as seen in a large study involving the progressive course of admitted COVID-19 patients where glucose dysregulation was used as a marker of disease severity [28]. Another possible explanation is that it takes time to control glucose levels which extend hospital stay [23]. Patients that continued to have glucose dysregulation at discharge or death had increased odds for mortality. This is likely because those patients who died were more likely to have dysglycemia upon death.

We found that increased age was associated with increased mortality and shorter HLOS. Increased age has been looked at by large scale studies in COVID-19 and was associated with mortality [29,30]. This increased mortality with older age is reflected in the observed shorter HLOS; similarly observed by others [31]. Regarding sex, in our cohort there was no difference in mortality and HLOS. This association is consistent with others that show a similar risk of death among the sexes who suffer from COVID-19 severe disease [32]. As glucose dysregulation is a marker of increased severity of COVID-19 disease [33], our study is similar to this pattern.

We did not find an association between race/ethnicity and mortality or HLOS. Studies on the association of race/ethnicity with COVID-19 disease have mixed results. Some studies report that Black, Hispanic, and Asian race/ethnicities have an overly high number of infections and deaths [30,34]. However, other studies that control for confounders like comorbidities report no associations for race/ethnicity and severe outcomes [35]. Our study is similar to this pattern. Increased mortality was also observed among patients that had regular Medicaid. Only one study looking at insurance status COVID-19 patients suggests that uninsured or underinsured individuals have higher rates of hospital admission [36]. There are no studies on insurance status and the association with mortality or HLOS in patients with glucose dysregulation and COVID-19**.** Patients with Medicaid are those of low socioeconomic status and often have a greater degree of comorbidities and present to healthcare setting late in the course of their illness [37] and thus this can lead to increased mortality. We did not show increased mortality in those who are uninsured/emergency Medicaid. This can occur because these patients tend to be younger and healthier undocumented workers [37].

We did not find any association for obesity, CCI, or qSOFA with mortality or HLOS. Obesity is described as a risk factor for severe COVID-19 disease in some studies [38]. However, others do not report this association [39]. CCI is designed to estimate 10-year mortality based on patient's comorbidities [40,41] but it is not tailored for estimating COVID-19 mortality that is short-term. One study from China found that the existing predictive tool of SOFA score is accurate at predicting mortality in COVID-19 patients [42]. However, another study from the US found qSOFA to be inaccurate for predicting mortality [43]. These researchers explained that qSOFA considers the predictive score value of all organ systems as equal while COVID-19 has a propensity to affect the respiratory system to a greater degree [43]. We propose that CCI and SOFA or related qSOFA scores are not useful prediction tools estimating mortality in COVID-19 for those with glucose dysregulation.

We found that patients who were intubated on admission had lower odds for mortality while those who mere mechanically ventilated during hospitalization had increased odds for mortality. Low FiO2 during hospitalization was associated with increased HLOS. In a large New York retrospective study, intubation on admission was also shown to be protective with a lower odd for mortality [44]. One likely explanation is that healthcare workers were intubating patients early particularly at the beginning of the pandemic thus suggesting that early intubation benefited mortality. However, patients who required intubation and mechanical ventilation during hospitalization were likely those with critical illness and therefore had increased mortality. Our finding is supported by others showing similar outcomes among mechanically ventilated patients during hospitalization [45]. Patients with low oxygen requirements (Fio2 < 55%) during hospitalization arguably have less severe disease but still require monitoring leading to longer hospital course. This is consistent with others who showed that monitoring for response to medical treatments leads to prolonged hospital stay in non-COVID-19 patients [46]. Certain COVID-19 treatments (antibiotic, NSAID, steroid use, convalescent plasma, and anticoagulant) were associated with a longer HLOS. These observations are best explained by patients having to complete the therapies which were mainly given intravenously which often prolong hospital stay. This pattern for HLOS is found by others as well [46]. However, one prospective study from United Kingdom showed no association of NSAIDs use on HLOS [47] and others found decreased HLOS in patients receiving corticosteroids [48] or convalescent plasma [49] given early in the course of the illness in patients with COVID-19 regardless of dysglycemia status. This can be explained that in the early phases of the pandemic both corticosteroids and convalescent plasma were given late in the course of the COVID-19 disease thus extending the hospital course. Currently, the recommendation is to give these therapies early in the treatment course and thus shortening HLOS [50]. In addition, our results might differ because we studied patients infected with COVID-19 and concomitant glycemic dysregulation.

Our study has several strengths and limitations. Our strengths are the inclusion of many racial/ethnic minorities from a large safety-net hospital and adjusting our analyses for relevant covariates. Our limitations are the retrospective study design and that our study was performed in the early phases of the pandemic when standard treatment guidelines were not available.

5. Conclusion

In conclusion, impaired glucose regulation in COVID-19 patients adjusted for all other organ system involvement was associated with increased odds for mortality during hospitalization. Glucose nadir and presence of glycemic dysregulation at discharge were associated with increased mortality, while patients that required new insulin therapy or increased dosing from baseline had decreased mortality. HLOS was increased in those that experienced high glucose peak, required new insulin therapy or increased dosing from baseline, and those that developed dysglycemia later in the hospitalization. However, those that received insulin drip had lower HLOS. These data can provide clinicians with information for treating COVID-19 patients with glucose dysregulation to help guide their patient management.

Declaration of competing interest

All authors have no conflicts of interest to report for the manuscript “Glucose Dysregulation and its Association with COVID-19 Mortality and Hospital Length of Stay”.

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