Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Endocrine Practice 27 (2021) 95–100

Contents lists available at ScienceDirect

Endocrine Practice

journal homepage: www.endocrinepractice.org

Original Article

Hyperglycemia is Associated With Increased Mortality in Critically Ill Patients With COVID-19

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ARTICLE INFO

Article history:
Received 16 November 2020
Received in revised form
24 December 2020
Accepted 30 December 2020
Available online 9 January 2021

Key words:
COVID-19
diabetes
hyperglycemia
mortality

ABSTRACT

Objective: To explore the relationship between hyperglycemia in the presence and absence of diabetes mellitus (DM) and adverse outcomes in critically ill patients with coronavirus disease 2019 (COVID-19).
Methods: The study included 133 patients with COVID-19 admitted to an intensive care unit (ICU) at an urban academic quaternary-care center between March 10 and April 8, 2020. Patients were categorized based on the presence or absence of DM and early-onset hyperglycemia (EHG), defined as a blood glucose >180 mg/dL during the first 2 days after ICU admission. The primary outcome was 14-day all-cause in-hospital mortality; also examined were 60-day all-cause in-hospital mortality and the levels of C-reactive protein, interleukin 6, procalcitonin, and lactate.
Results: Compared to non-DM patients without EHG, non-DM patients with EHG exhibited higher adjusted hazard ratios (HRs) for mortality at 14 days (HR 7.51, CI 1.70-33.24) and 60 days (HR 6.97, CI 1.86-26.13). Non-DM patients with EHG also featured higher levels of median C-reactive protein (306.3 mg/L, $P = .036$), procalcitonin (1.26 ng/mL, $P = .028$), and lactate (2.2 mmol/L, $P = .023$).
Conclusion: Among critically ill COVID-19 patients, those without DM with EHG were at greatest risk of 14-day and 60-day in-hospital mortality. Our study was limited by its retrospective design and relatively small cohort. However, our results suggest the combination of elevated glucose and lactate may identify a specific cohort of individuals at high risk for mortality from COVID-19. Glucose testing and control are important in individuals with COVID-19, even those without preexisting diabetes.

Introduction

Metabolic conditions are associated with differential morbidity and mortality from coronavirus disease 2019 (COVID-19). Recent work has highlighted the intersection between dysglycemia, diabetes mellitus (DM), and outcomes in COVID-19. Multiple studies have revealed a connection between DM and worse outcomes from

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; DM, diabetes mellitus; EHG, early hyperglycemia; EHR, electronic health record; ESRD, end-stage renal disease; HbA1C, hemoglobin A1c; ICU, intensive care unit; IL-6, interleukin 6; RRT, renal replacement therapy; T2DM, type 2 diabetes mellitus; TDI, total daily insulin.

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https://doi.org/10.1016/j.eprac.2020.12.015
1530-891X/

COVID-19, including increased mortality and organ failure.[1–4] Zhu and colleagues provided data suggesting that maintaining euglycemia (70-180 mg/dL) in patients with type 2 DM reduced the occurrence of death, acute respiratory distress syndrome, septic shock, acute kidney injury, and renal replacement therapy (RRT) in a cohort of hospitalized patients in China.[1] A number of other studies have also associated hyperglycemia with worse outcomes in hospitalized patients with COVID-19.[5–7] However, these studies have analyzed these questions in hospitalized populations predominantly outside of the intensive care unit (ICU), and the impact of hyperglycemia on mortality in critically ill patients with and without preexisting DM in the setting of COVID-19 remains unclear.[8]

In the era before COVID-19, studies of acutely ill, hospitalized individuals with stroke, myocardial infarction, trauma, and burns reported hyperglycemia increased mortality risk and complications to a greater extent in individuals without DM than in those with DM.[9–12] Similarly, individuals without DM with hyperglycemia admitted to neurosurgical, cardiac, or cardiothoracic ICUs had greater mortality.[13] We conducted this observational study to determine if hyperglycemia in the presence or absence of preexisting DM was associated with mortality risk in critically ill patients with COVID-19.

Methods

This retrospective, single-center study was conducted at an urban academic quaternary-care center. All patients were either admitted directly to the ICU or transferred to the ICU upon escalation of care for COVID-19 between March 10 and April 8, 2020. Electronic health record (EHR) automated query reports were used to identify all inpatients who tested positive for COVID-19 via detection of severe acute respiratory syndrome coronavirus 2 through nasopharyngeal polymerase chain reaction tests.

Patient age, sex, race, height, weight, preadmission diagnoses (diabetes, hypertension, chronic kidney disease [CKD], end-stage renal disease [ESRD] on RRT, coronary artery disease, congestive heart failure), and smoking status were recorded from patients' EHRs by standardized manual chart abstraction by trained reviewers. A diagnosis of DM was defined as having preexisting type 1 diabetes mellitus or type 2 diabetes mellitus (T2DM) by the presence of a corresponding International Classification of Diseases-9 or -10 diagnosis code, or the presence of a hemoglobin A1C (HbA1C) of $\geq$6.5% at any time prior to ICU admission. Prediabetes was defined as having a diagnosis of prediabetes in the medical record or an HbA1C of 5.7% to 6.4%. The type of antihyperglycemic medication used prior to admission was also recorded. Maximum glucose values, C-reactive protein (CRP), creatinine, D-dimer, ferritin, interleukin 6 (IL-6), lactate, and procalcitonin levels were recorded for the first 48 hours after ICU admission. Interventions, including the type of respiratory support and use of glucocorticoids during the ICU stay, were also recorded.

Body mass index (BMI) was calculated as weight (kg) / (height [m])^2. BMI was classified as follows: underweight, <18.5 kg/m^2; normal weight, 18.5 to 24.9 kg/m^2; overweight, 25 to 29.9 kg/m^2; and obese, $\geq$30 kg/m^2. Early hyperglycemia (EHG) was defined as a glucose level >180 mg/dL (10 mM) during the first 2 calendar days after ICU admission, in accordance with the American Association of Clinical Endocrinologists guidelines and conventional glucose control from the NICE-SUGAR study of ICU patients.[14,15] The decision to select this glucose cutoff value was also supported by a recent study in which hyperglycemia >180 mg/dL was associated with greater mortality in all hospitalized patients with COVID-19.[1]

The total daily insulin (TDI) dose (IU) received, calculated as the sum of all subcutaneous and intravenous insulin over a 24-hour period, was recorded for the first 14 calendar days of the ICU stay. If there was no documented insulin administered during a given ICU day, the TDI was recorded as zero. The TDI dose for each patient was then corrected for body weight by dividing TDI (IU) by weight (kg) to give the corrected TDI. Data were collected until hospital discharge, death, or completion of the 14-day interval, even if a patient was transferred out of the ICU during the 14-day follow-up period.

The primary outcome examined in this study was 14-day all-cause in-hospital mortality in patients with and without diabetes who did or did not experience EHG. We also analyzed all-cause in-hospital mortality at 60 days. The relationship between EHG in the presence or absence of diabetes, TDI, hyperlactatemia, and evidence of inflammatory response (CRP, D-dimer, ferritin, IL-6, and procalcitonin) were also examined.

The population of the study was divided into 4 subgroups based on the presence or absence of DM and EHG, and descriptive statistics were used to examine the population's baseline characteristics. ANOVA and *t*-tests were used to compare means of continuous variables between groups with normal data distributions, and Mann-Whitney tests and Kruskal-Wallis tests were used for data with non-normal distributions. Chi-square tests and Fisher exact tests were used to compare categorical variables as appropriate. Post hoc pairwise testing was performed with Tukey's honestly significant difference test for continuous data with normal distributions, the Dunn-Bonferroni method for continuous data with non-normal distributions, and adjusted standardized residuals for categorical data. Kaplan-Meier curves were generated, and log-rank tests were used to compare survival between the 4 subgroups. Cox proportional-hazards regression was performed to calculate mortality hazard ratios (HRs) with 95% CIs, adjusted for age, sex, hypertension, pre-ICU HbA1C, cardiovascular disease (presence of either congestive heart failure or coronary artery disease), CKD, ESRD on RRT, and glucocorticoid therapy within 48 hours after ICU admission. Statistical significance was defined as a 2-tailed P value <.05. Statistical analyses were conducted using SPSS software (version 25.0, IBM Corp.).

Results

Baseline characteristics for the overall cohort (N = 133) and those with and without preexisting DM are shown in Table 1. The mean age of the entire cohort was 59 ± 14 years, and a majority (69%) were male. The mean BMI was 31.4 ± 7.9 kg/m^2. Obesity affected 43.6% of patients, while 32.3% were overweight. Two subjects (1.5%) had previously diagnosed type 1 diabetes mellitus, 44 (33.1%) had a diagnosis of T2DM, and an additional 16 (12.0%) had an HbA1C $\geq$6.5% prior to ICU admission and were included in the DM group in further analyses. The most common comorbidity was hypertension, which was observed in 55 patients (41.4%).

Individuals with DM were older than those without DM (63 ± 12 vs 56 ± 15 years, P = .007) and had a higher prevalence of hypertension (51.6% vs 32.4%, P = .025), coronary artery disease (21.6% vs 8.5%, P = .040), and congestive heart failure (12.9% vs 2.8%, P = .028). Neither BMI nor the burden of CKD was different between patients with and without DM. The mean pre-ICU HbA1C for patients with DM was 7.5% ± 2.0% (58 ± 22 mmol/mol). The most common antihyperglycemic medication for diabetes prior to hospital admission was metformin (n = 21, 34% of those with DM), followed by insulin (n = 13, 21%), dipeptidyl peptidase 4 inhibitors (n = 8, 13%), insulin secretagoges, including sulfonylureas and meglitinides (n = 7, 11%), and sodium-glucose cotransporter 2 inhibitors (n = 3, 5%).

Table 2 shows the characteristics of those who developed EHG, compared with those who did not, in the DM and non-DM groups.

Table 1
Baseline Characteristics for the Total Cohort (N = 133) and Patients With and Without Diabetes

	Total (N = 133)	No DM (n = 71)	DM (n = 62)	*P* value
Age, y	59 ± 14	56 ± 15	63 ± 12	.007
Female	41 (30.8%)	17 (23.9%)	24 (38.7%)	.066
Race/ethnicity				.348
Hispanic	20 (15.0%)	10 (14.1%)	10 (16.1%)	
Non-Hispanic Black	21 (15.8%)	8 (11.3%)	13 (21.0%)	
Non-Hispanic White	42 (31.6%)	26 (36.6%)	16 (25.8%)	
Other/unknown	50 (37.6%)	27 (38.0%)	23 (37.1%)	
Pre-ICU A1C, %		5.7 ± 0.5	7.5 ± 2.0	<.001
Pre-ICU A1C, mmol/mol		39 ± 5	58 ± 22	<.001
Body mass index, kg/m^2	31.4 ± 7.9	31.2 ± 7.8	31.7 ± 7.8	.694
Body mass index category, kg/m^2				.112
<18.5	1 (0.8%)	1 (1.5%)	0 (0%)	
18.5-24.9	21 (15.8%)	15 (22.7%)	6 (10.5%)	
25.0-29.9	43 (32.3%)	18 (27.3%)	25 (43.9%)	
≥30.0	58 (43.6%)	32 (48.5%)	26 (45.6%)	
Preadmission DM-related comorbidities				
Hypertension	55 (41.4%)	23 (32.4%)	32 (51.6%)	.025
Coronary artery disease	19 (14.3%)	6 (8.5%)	13 (21.6%)	.040
Congestive heart failure	10 (7.5%)	2 (2.8%)	8 (12.9%)	.028
Chronic kidney disease	9 (6.8%)	3 (4.2%)	6 (9.7%)	.212
ESRD on RRT	2 (1.5%)	0 (0%)	2 (3.2%)	.127
Smoking status				.541
Nonsmoker	76 (57.1%)	40 (56.3%)	36 (58.1%)	
Former smoker	26 (19.5%)	12 (16.9%)	14 (22.6%)	
Current smoker	8 (6.0%)	6 (8.5%)	2 (3.2%)	

Abbreviations: A1C = hemoglobin A1C; BMI = body mass index; DM = diabetes mellitus; ESRD = end-stage renal disease; ICU = intensive care unit; RRT = renal replacement therapy.
Data are expressed as either mean ± SD or counts (percentage). Available data were as follows: BMI (123 patients, 92.5%), pre-ICU A1C (98 patients, 73.7%). *P* values reflect statistical comparison between DM and No DM groups.

In the group with DM, those who had EHG had higher HbA1C values than those who did not (7.8% ± 2.2% [62 ± 24 mmol/mol] vs 6.5% ± 1.0% [48 ± 10 mmol/mol], $P < .001$), but no difference in HbA1C was observed between those without DM who developed EHG and those who did not. The distribution of patients on invasive mechanical ventilation or other modalities of respiratory support was not statistically different between the 4 subgroups. More people with EHG received systemic glucocorticoids in the non-DM group than those in the DM group. Only 2 patients (13.3%) in the subgroup without DM with EHG had a diagnosis of hypertension, while the other subgroups demonstrated prevalence closer to 40% ($P < .001$).

Kaplan-Meier survival analysis revealed the subgroup without DM with EHG had the highest mortality of the 4 subgroups at 14 days ($P = .030$) and 60 days ($P = .045$) (Fig.). Cox proportional-hazards regression analysis demonstrated an increased crude HR for 14-day mortality (HR 3.12, $P = .014$, CI 1.26-7.76) in those without DM with EHG compared with the group without DM with no EHG (Table 3). This effect persisted after adjusting for age, sex, hypertension, pre-ICU HbA1C, cardiovascular disease, CKD, ESRD on RRT, and glucocorticoid therapy within 48 hours after ICU admission (HR 7.51, $P = .009$, CI 1.70-33.24). A similar pattern was observed for 60-day mortality for the same subgroup (crude HR 3.04, $P = .009$, CI 1.33-6.98; adjusted HR 6.97, $P = .004$, CI 1.86-26.13). Glucocorticoid therapy within the first 48 hours after ICU admission did not impact mortality at 14 days ($P = .088$) or 60 days ($P = .273$).

To understand why EHG might be associated with mortality in the group without DM but not in the group with DM, we analyzed inflammatory markers from the first 48 hours after ICU admission in the 4 subgroups. Notably, the subgroup without DM with EHG demonstrated higher levels of median CRP (306.3 mg/L, $P = .036$), procalcitonin (1.26 ng/mL, $P = .028$), D-dimer (4910 ng/mL, $P = .011$), and lactate (2.2 mmol/L, $P = .023$) than the other subgroups (Table 2). IL-6 ($P = .277$) and ferritin ($P = .601$) levels were not higher in the non-DM subgroup with EHG than in the other subgroups. We then analyzed the TDI doses across the 4 subgroups. The highest prevalence of insulin use in the ICU was in those with DM and EHG compared with the other subgroups. The subgroup without DM and no EHG had the lowest corrected TDI (mean ± standard deviation, 0.03 ± 0.09 IU/kg), while the subgroup with DM and EHG exhibited the highest (0.39 ± 0.32 IU/kg); the subgroups without DM with EHG (0.13 ± 0.23 IU/kg) and with DM and no EHG (0.07 ± 0.10 IU/kg) had intermediate values ($P < .001$).

Discussion

Our study found critically ill patients with COVID-19 without DM with EHG exhibited markedly increased mortality as well as higher levels of lactate, procalcitonin, and CRP. This combination of elevated biomarkers of systemic inflammation and lactate suggests a systemic inflammatory response leading to stress hyperglycemia in the group without preexisting DM. Several studies in hospitalized individuals with COVID-19 have reported that hyperglycemia is associated with more severe infection and adverse outcomes, such as respiratory failure requiring mechanical ventilation, multiorgan failure, and death.[8,16] Our findings are consistent with another retrospective study from northeast Italy that showed new-onset diabetes or admission hyperglycemia were predictors of more severe COVID-19. This association was stronger among patients without preexisting diabetes than those with a history of diabetes.[17] Moreover, the inflammatory response observed in our cohort is corroborated by a retrospective study from Wuhan, China, which found elevation of similar inflammatory biomarkers portended a greater risk of mortality.[18]

Hyperglycemia is a marker of stress and inflammation that potentially contributes to adverse metabolic responses to infection. Deleterious clinical outcomes associated with hyperglycemia have previously been described in patients with and without diabetes in the setting of acute myocardial infarction, stroke, burns, and

Table 2
Characteristics for the Overall Cohort (N = 133), Stratified by DM, and Early-Onset Hyperglycemia

Characteristic	No DM (n = 71)		DM (n = 62)		*P*
	No EHG (n = 56)	EHG (n = 15)	No EHG (n = 15)	EHG (n = 47)	
Demographics on ICU admission					
Age, y	55.6 ± 14.5[a]	58.1 ± 15.3	61.2 ± 15.1	63.1 ± 11.6[a]	.047
Female	14 (25.0)	3 (20.0%)	5 (33.3%)	19 (40.4%)	.285
Race/ethnicity					.298
Hispanic	6 (10.7%)	4 (26.7%)	1 (6.7%)	9 (19.1%)	
Non-Hispanic Black	5 (8.9%)	3 (20.0%)	2 (13.3%)	11 (23.4%)	
Non-Hispanic White	22 (39.3%)	4 (26.7%)	6 (40.0%)	10 (21.3%)	
Other/unknown	23 (41.1%)	4 (26.7%)	6 (40.0%)	17 (36.2%)	
Comorbidities					
Body mass index					.510
<18.5	1 (2.0%)	0 (0%)	0 (0%)	0 (0%)	
18.5-24.9	10 (19.6%)	5 (33.3%)	1 (8.3%)	5 (11.1%)	
25.0-29.9	14 (27.5%)	4 (26.7%)	5 (41.7%)	20 (44.4%)	
≥30.0	26 (51.0%)	6 (40.0%)	6 (50.0%)	20 (44.4%)	
Hypertension	21 (37.5%)	2 (13.3%)[a]	6 (40.0%)	26 (55.3%)[a]	.029
Coronary artery disease	4 (7.1%)	2 (13.3%)	4 (26.7%)	9 (19.1%)	.163
Congestive heart failure	2 (3.6%)	0 (0%)	2 (13.3%)	6 (12.8%)	.167
Smoking status					.345
Nonsmoker	31 (55.4%)	9 (60.0%)	6 (40.0%)	30 (63.8%)	
Former smoker	10 (17.9%)	2 (13.3%)	6 (40.0%)	8 (17.0%)	
Current smoker	6 (10.7%)	0 (0%)	0 (0%)	2 (4.3%)	
Chronic kidney disease	3 (5.4%)	0 (0%)	1 (6.7%)	5 (10.6%)	.497
ESRD on RRT	0 (0%)	0 (0%)	1 (6.7%)	1 (2.1%)	.272
Pre-ICU A1C, %	5.7 ± 0.5[a]	5.7 ± 0.5[b]	6.5 ± 1.0[c]	7.8 ± 2.2[abc]	<.001
Pre-ICU A1C, mmol/mol	39 ± 5[a]	39 ± 5[b]	48 ± 10[c]	62 ± 24[abc]	<.001
Antihyperglycemic agent on admission					
Insulin	25 (44.6%)[a]	9 (60.0%)[b]	9 (60.0%)[c]	44 (93.6%)[abc]	<.001
Laboratory data[d]					
Creatinine, mg/dL	0.91 (0.54)	1.17 (0.61)	0.96 (0.52)	1.00 (0.69)	.143
Lactate, mmol/L	1.4 (1.0)[a]	2.2 (1.6)[a]	1.8 (1.0)	1.6 (1.1)	.023
Procalcitonin, ng/mL	0.33 (0.70)[a]	1.26 (38.12)[a]	0.42 (2.48)	0.38 (1.27)	.028
C-reactive protein, mg/L	193.3 (201.7)[a]	306.3 (277.8)[ab]	152.5 (189.2)	166.2 (141.7)[b]	.036
D-dimer, ng/mL	1285 (1700)[a]	4910 (4880)[a]	1140 (2590)	2400 (2455)	.011
Interleukin-6, pg/mL	141 (152)	388 (2836)	164 (198)	177 (492)	.277
Ferritin, ng/mL	916 (2507)	11 900 (2147)	11 227 (1801)	11 295 (1871)	.601
ICU medical interventions					
Glucocorticoids on days 1 or 2	15 (26.8%)[a]	9 (60.0%)[a]	2 (13.3%)	16 (34.0%)	.034
Respiratory support on ICU admission					.123
IMV	31 (55.4%)	14 (93.3%)	8 (53.3%)	35 (74.5%)	
BiPAP or CPAP	3 (5.4%)	1 (6.7%)	1 (6.7%)	3 (6.4%)	
HFNC or NRB	12 (21.4%)	0 (0%)	3 (20.0%)	7 (14.9%)	
Other	10 (17.9%)	0 (0%)	3 (20.0%)	2 (4.3%)	

Abbreviations: A1C = hemoglobin A1C; BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; DM = diabetes mellitus; EHG = early-onset hyperglycemia; ESRD = end-stage renal disease; HFNC = high-flow nasal cannula; HSD = honestly significant difference; ICU = intensive care unit; IMV = invasive mechanical ventilation; NRB = non-rebreather mask; RRT = renal replacement therapy.
Data are expressed as either mean ± SD or counts (percentage).
Superscripts (a,b,c) indicate significant pairwise differences between subgroups. Significance was determined by Tukey's HSD posthoc tests for continuous and normally distributed data, Dunn-Bonferroni post hoc method for continuous and nonnormally distributed data, and adjusted standardized residuals for categorical data.
[d] Laboratory data are maximum values between ICU calendar days 1 and 2 and expressed as median (interquartile range).

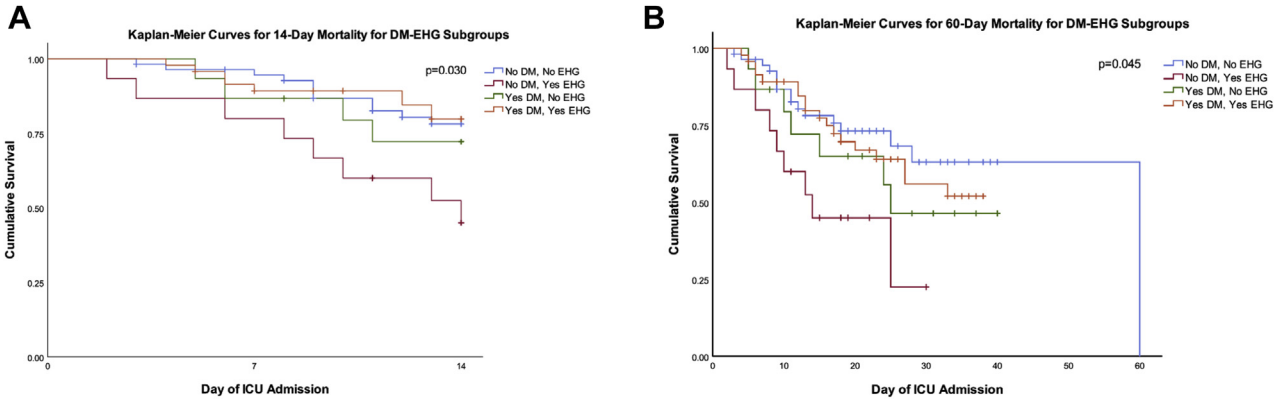

Fig. Kaplan-Meier plots showing 14-day (A) and 60-day (B) survival for individuals without diabetes without early hyperglycemia (No DM, No EHG), without diabetes with early hyperglycemia (No DM, Yes EHG), with diabetes without early hyperglycemia (Yes DM, No EHG), and with diabetes with early hyperglycemia (Yes DM, Yes EHG). *DM* = diabetes mellitus; *EHG* = early-onset hyperglycemia.

Table 3
Crude and Adjusted HRs for 14-Day and 60-Day Mortality by DM-EHG Subgroup

Crude mortality	14-day mortality			60-day mortality		
	HR	*P*	CI	HR	*P*	CI
No DM, No EHG	ref	…	…	ref	…	…
No DM, Yes EHG	3.12	.014	1.26-7.76	3.04	.009	1.33-6.98
Yes DM, No EHG	1.36	.603	0.43-4.26	1.58	.315	0.65-3.89
Yes DM, Yes EHG	0.92	.850	0.38-2.22	1.25	.530	0.63-2.48
Adjusted mortality[a]	14-day mortality			60-day mortality		
	HR	*P*	CI	HR	*P*	CI
No DM, No EHG	ref	…	…	ref	…	…
No DM, Yes EHG	7.51	.008	1.70-33.24	6.97	.004	1.86-26.13
Yes DM, No EHG	1.94	.403	0.41-9.24	3.31	.062	0.94-11.64
Yes DM, Yes EHG	1.16	.852	0.25-5.42	2.62	.127	0.76-9.00

Abbreviations: A1C = hemoglobin A1C; CI = confidence interval; DM = diabetes mellitus; EHG = early-onset hyperglycemia; HR = hazard ratio; ICU = intensive care unit.

[a] Adjusted for age, sex, hypertension, pre-ICU hemoglobin A1C, glucocorticoid therapy within 48 hours after ICU admission, cardiovascular disease (presence of either congestive heart failure or coronary artery disease), chronic kidney disease, and end-stage renal disease on renal replacement therapy.

trauma.[11,12,19,20] Stress hyperglycemia has been linked to increased levels of counterregulatory hormones, such as glucagon, cortisol, and catecholamines, which promote hyperglycemia through insulin resistance, which leads to increased hepatic gluconeogenesis and decreased glucose disposal as well as relative insulin deficiency.[21] Stress hyperglycemia has also been tied to elevated levels of proinflammatory cytokines and free fatty acids that increase insulin resistance.[21] These responses induce myriad adverse sequelae, including the generation of reactive oxygen species, advanced glycation end-product generation, and immune dysregulation that can perpetuate and exacerbate critical illness.[21,22]

Hyperglycemia in association with elevated lactate has previously been reported to be especially deleterious in critical illness.[23] In a study of patients with systemic inflammatory response syndrome in an emergency department setting, hyperglycemia was found to predict mortality only if elevated lactate was also present.[24] In our cohort, we found higher lactate levels in patients without a history of DM yet with EHG. Elevated lactate may occur in the setting of sepsis due to increased lactate production by aerobic glycolysis rather than impaired clearance.[25] Lactate contributes to insulin resistance and impairs glucose uptake in skeletal muscle, as has previously been shown in preclinical studies.[26] In individuals with T2DM and insulin resistance without acute illness, elevated lactate levels have previously been reported early in the disease due to increased aerobic glycolysis.[27] It remains to be determined whether the chronic metabolic adaptation to insulin resistance in diabetes is somehow protective from the deleterious effects of stress hyperglycemia and hyperlactatemia in critical illness.

Recognition of the deleterious effects of hyperglycemia in critical illness in non-COVID-19 settings has led to a number of studies examining whether intensive insulin therapy reduces mortality in these patients. Although some randomized studies found tight glycemic control in critically ill patients was beneficial,[28,29] ambitious glycemic control can result in hypoglycemia associated with harm, as seen in the NICE-SUGAR and VISEP studies.[15,30] In hospitalized patients with COVID-19 in Italy, hyperglycemia those with hyperglycemia treated with insulin infusions had a lower risk of progression to severe disease and mortality.[31] Due to the retrospective nature of our study, we reported TDI dose received (corrected for body weight) in the clinical setting. Interestingly, the subgroup with DM and EHG received the highest doses of insulin, which may reflect greater insulin resistance in this group compared with the EHG without DM group. We did not have serum C-peptide levels in these patients to make any assessment of pancreatic β cell function.

Our study featured several strengths and limitations. Our manual EHR review allowed us to probe more deeply the relationship between DM, EHG, and our outcomes of interest and to detect a patient population at increased risk of mortality. Our adjusted analyses for 14-day and 60-day all-cause in-hospital mortality further permitted a better understanding of the short- and long-term effects of DM and hyperglycemia. As with all retrospective research, there may have been unexplored confounders that impacted our results. Additional limitations of this study include its single-center design and smaller sample size, both of which limit the generalizability of our findings and limit our statistical power to detect significant differences in some subgroups. Further investigation is necessary to determine whether our results can be replicated in other ICU cohorts of patients with COVID-19.

Overall, our data showed critically ill patients with COVID-19 without DM with EHG had significantly increased mortality and higher levels of inflammatory markers. Our study raises a number of questions regarding the relationship between mortality, glucose, and lactate levels in individuals with COVID-19 critical illness. It is unclear why individuals with preexisting diabetes did not develop such significant elevations in lactate levels in the setting of hyperglycemia as those without preexisting diabetes. Further questions include whether the combination of elevated glucose and lactate can be used as clinical biomarkers to identify a subgroup of patients at particularly high risk of subsequent mortality and if the addition of such interventions as intensive insulin therapy to anti-inflammatory therapies may ameliorate this risk and improve outcomes in individuals with COVID-19.

Disclosure

The authors have no multiplicity of interest to disclose. Dr Mathews receives funding from the NIH/NHLBI (1K23HL130648) and serves on the BREATHE Trial Steering Committee, funded by Roivant/Kinevant Sciences, for work unrelated to the current study. Dr Gallagher received research funding from Alkeon Capital Management and has served as an advisor/consultant for Novartis and Seattle Genetics for work unrelated to the current study.

Author Contributions

A.Y.M. and I.R.B. have contributed equally.

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