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Original Article

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

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A B S T R A C T

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.

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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, prediagnosis 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 >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 anti-hyperglycemic 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, >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.\(^14\)\(^\text{15}\) 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.\(^16\)

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 >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 secretagogues, 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.
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 (HR 3.12, P <.014, CI 1.26-7.76) in 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).

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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.4,16 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 1: Baseline Characteristics for the Total Cohort (N = 133) and Patients With and Without Diabetes

| Characteristic                                | 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, %                               |                |               |            |         |
| Pre-ICU A1C, mmol/mol                        | 31.4 ± 7.9     | 31.2 ± 7.8    | 31.7 ± 7.8 | .112    |
| Body mass index, kg/m²                       |                |               |            |         |
| Body mass index category, kg/m²              |                |               |            |         |
| <18.5                                        | 1 (0.8%)       | 1 (1.5%)      | 0 (0%)     | .028    |
| 18.5-24.9                                    | 21 (15.8%)     | 15 (22.7%)    | 6 (10.5%)  | .040    |
| 25.0-29.9                                    | 43 (32.3%)     | 18 (27.3%)    | 25 (43.9%) | .028    |
| ≥30.0                                        | 58 (43.6%)     | 32 (48.5%)    | 26 (45.6%) | .541    |
| Preadmission DM-related comorbidities        |                |               |            |         |
| Hypertension                                 | 55 (41.4%)     | 32 (45.6%)    | 32 (54.6%) | .025    |
| Coronary artery disease                      | 19 (14.3%)     | 6 (8.5%)      | 13 (21.6%) | .040    |
| Congestive heart failure                     | 10 (7.5%)      | 2 (2.8%)      | 8 (13.9%)  | .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.
## 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       |
|-----------------------------------------------------|----------------|-------------|---------|
| **Demographics on ICU admission**                   |                |             |         |
| Age, y                                              | 55.6 ± 14.5a   | 58.1 ± 15.3 | .047    |
| Race/ethnicity                                      |                |             |         |
| Hispanic                                            | 6 (10.7%)      | 4 (26.7%)   | .047    |
| Non-Hispanic Black                                  | 5 (8.9%)       | 3 (20.0%)   | .047    |
| Non-Hispanic White                                  | 22 (39.3%)     | 4 (26.7%)   | .047    |
| Other/unknown                                       | 23 (41.1%)     | 4 (26.7%)   | .047    |
| **Comorbidities**                                   |                |             |         |
| Body mass index                                     |                |             | .510    |
| Hypertension                                        | 21 (37.5%)     | 2 (13.3%)   | .029    |
| Coronary artery disease                             | 4 (7.1%)       | 2 (13.3%)   | .167    |
| Congestive heart failure                            | 6 (10.7%)      | 4 (26.7%)   | .145    |
| Smoking status                                      |                |             | .285    |
| Nonsmoker                                           | 3 (5.4%)       | 6 (40.0%)   | .011    |
| Former smoker                                       | 10 (17.9%)     | 2 (13.3%)   | .272    |
| Current smoker                                      | 6 (10.7%)      | 4 (26.7%)   | .272    |
| Chronic kidney disease                              | 3 (5.4%)       | 1 (6.7%)    | .272    |
| Pre-ICU A1C, %                                      | 5.7 ± 0.5a     | 5.7 ± 0.5a  | .001    |
| Pre-ICU A1C, mmol/mol                               | 39 ± 5a        | 39 ± 5a     | .001    |
| Antihyperglycemic agent on admission                |                |             | .980    |
| Insulin                                             | 25 (44.6%)     | 9 (60.0%)   | .011    |
| **Laboratory data**                                 |                |             | .980    |
| Creatinine, mg/dL                                   | 0.91 (0.54)    | 1.17 (0.61) | .143    |
| Lactate, mmol/L                                     | 1.4 (1.0)      | 2.2 (1.6)   | .023    |
| Procalcitonin, ng/mL                                | 0.33 (0.70)a   | 1.26 (38.12)a| .028    |
| C-reactive protein, mg/L                            | 193.3 (201.7)a | 306.3 (277.8)ab | .036    |
| D-dimer, ng/mL                                      | 1285 (1700)a   | 4910 (4880)a| .011    |
| Interleukin-6, pg/mL                                | 141 (152)      | 388 (2836)  | .277    |
| Ferritin, ng/mL                                     | 916 (2507)     | 11 900 (2147) | .601    |
| **ICU medical interventions**                       |                |             |         |
| Glucocorticoids on days 1 or 2                      | 15 (26.8%)     | 9 (60.0%)   | .034    |
| Respiratory support on ICU admission                 |                |             | .123    |
| IMV                                                 | 31 (55.4%)     | 14 (93.3%)  | .754    |
| BiPAP or CPAP                                       | 3 (5.4%)       | 1 (6.7%)    | .645    |
| HFNC or NRB                                         | 12 (21.4%)     | 3 (20.0%)   | .047    |
| Other                                               | 10 (17.9%)     | 3 (20.0%)   | .435    |

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.

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.
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. Stress hyperglycemia has also been tied to elevated levels of proinflammatory cytokines and free fatty acids that increase insulin resistance. 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.

Hyperglycemia in association with elevated lactate has previously been reported to be especially deleterious in critical illness. 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. In our cohort, we found higher lactate levels in patients without a history of DM yet with EHG. Elevated lactate may occur in hyperglycemia treated with insulin infusions had a lower risk of 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

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Author Contributions

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

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