Hyperglycemia at Hospital Admission Is Associated With Severity of the Prognosis in Patients Hospitalized for COVID-19: The Pisa COVID-19 Study

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OBJECTIVE

To explore whether at-admission hyperglycemia is associated with worse outcomes in patients hospitalized for coronavirus disease 2019 (COVID-19).

RESEARCH DESIGN AND METHODS

Hospitalized COVID-19 patients (*N* = 271) were subdivided based on at-admission glycemic status: *1*) glucose levels <7.78 mmol/L (NG) (*N* = 149 [55.0%]; median glucose 5.99 mmol/L [range 5.38–6.72]), *2*) known diabetes mellitus (DM) (*N* = 56 [20.7%]; 9.18 mmol/L [7.67–12.71]), and *3*) no diabetes and glucose levels ≥7.78 mmol/L (HG) (*N* = 66 [24.3%]; 8.57 mmol/L [8.18–10.47]).

RESULTS

Neutrophils were higher and lymphocytes and PaO_2/FiO_2 lower in HG than in DM and NG patients. DM and HG patients had higher D-dimer and worse inflammatory profile. Mortality was greater in HG (39.4% vs. 16.8%; unadjusted hazard ratio [HR] 2.20, 95% CI 1.27–3.81, *P* = 0.005) than in NG (16.8%) and marginally so in DM (28.6%; 1.73, 0.92–3.25, *P* = 0.086) patients. Upon multiple adjustments, only HG remained an independent predictor (HR 1.80, 95% CI 1.03–3.15, *P* = 0.04). After stratification by quintile of glucose levels, mortality was higher in quintile 4 (Q4) (3.57, 1.46–8.76, *P* = 0.005) and marginally in Q5 (29.6%) (2.32, 0.91–5.96, *P* = 0.079) vs. Q1.

CONCLUSIONS

Hyperglycemia is an independent factor associated with severe prognosis in people hospitalized for COVID-19.

Diabetes is common among persons hospitalized for coronavirus disease 2019 (COVID-19), and it is associated with increased risk of mortality (1). Stress-induced hyperglycemia occurring at hospital admission for acute medical or surgical illness in individuals with no history of diabetes (2) is a worse predictor than diabetes for poor clinical outcomes and mortality (3). In subjects with severe acute respiratory syndrome, at-admission hyperglycemia was an independent predictor for mortality (4). Therefore, we have evaluated the impact of at-admission plasma glucose levels in hospitalized COVID-19 patients.

RESEARCH DESIGN AND METHODS

We retrospectively analyzed 271 adults with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection consecutively admitted to the University

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Hospital, Pisa, Italy, from 20 March to 30 April 2020. Clinical and laboratory data first recorded within 36 h after admission were anonymously obtained from electronic medical records. Based on at-admission glycemic status, we identified three groups: *1*) normoglycemia (NG) (<7.78 mmol/L), *2*) hyperglycemia and no history of diabetes (HG) (glycemia ≥7.78 mmol/L), and *3*) known diabetes mellitus (DM).

The primary end point of the study was in-hospital mortality, and need for mechanical ventilation, admission to intensive care unit (ICU), and adult respiratory distress syndrome were secondary end points. Continuous variables are presented as median (interquartile range or whole range) and categorical variables as number and percentage. Baseline characteristics were compared with the Kruskal-Wallis test for continuous variables and χ^2 test for categorical variables. Kaplan-Meier curves were generated to represent all-cause mortality survival by normoglycemia, hyperglycemia, and diabetes at baseline; log-rank test was used to compare survival distributions. Association of hyperglycemia and diabetes with all-cause mortality compared with normoglycemia was assessed by unadjusted and adjusted Cox proportional hazards models. Model 1 included age and sex, in addition to glucose categories. In model 2, adjunctive covariates significantly associated with mortality were added, i.e., hypertension, cerebrovascular disease, chronic obstructive pulmonary disease, chronic kidney disease, and cognitive impairment (dummy variables). Model 3 was further adjusted for biomarkers significantly associated with mortality in univariate regressions (continuous variables). Results are expressed as hazard ratio (HR) and 95% CI. A two-sided *P* value ≤0.05 was considered statistically significant.

RESULTS

Baseline characteristics, comorbidities, symptoms, and vitals at admission in the three groups are shown in Supplementary Table 1. Fifty-five percent of subjects (N = 149) had NG (median 5.99 mmol/L [range 5.38–6.72]), 56 (21%) had DM (9.18 mmol/L [7.67–12.71]), and 66 (24%) had HG (8.57 mmol/L [8.18–10.47). HbA_{1c} was higher in the DM group. There was no difference in lipids or blood pressure across groups, but use of statins (36.5%) and antihypertensive agents (76.8%) was greater in DM ($P < 0.05$) than in HG (10% and 33.3%, respectively) and NG (12% and 31.5%) patients. Estimated glomerular filtration rate was lower in DM than NG and HG patients (65.1 mL/min/1.73 m^2 [34.6–81.7]; $P < 0.01$). Neutrophil count was higher (5.8×10^9/L [3.7–8.7]; $P < 0.05$) and lymphocyte lower (0.7×10^9/L [0.5–1.2]; $P < 0.05$) in HG than in DM and NG patients; D-dimer was higher in HG and DM patients. Overall, the HG and DM groups had worse inflammatory profiles. PaO_2-to-FiO_2 ratio was the worst in HG patients (227 [140–290]; $P < 0.05$), with that for DM patients (262 [201–290]) in between that for HG and NG patients (295 [221–367]).

Over a mean ± SD observation period of 16.8 ± 12.6 days, 67 individuals died (24.7%). As compared with mortality rate in the NG group (25 deaths [16.8%]), mortality rate was higher in the HG group (26 deaths [39.4%]; unadjusted Cox regression HR 2.196, 95% CI 1.27–3.81, P = 0.005) but only marginally so in the DM group (16 of 56 [28.6%]; 1.73, 0.92–3.25, P = 0.086), with a comprehensive Kaplan-Meier log-rank of 8.590 (P = 0.014) (Fig. 1*A*). In model 1, HG (1.80, 1.03–3.15, P = 0.04) but not DM (1.07, 0.56–2.04) remained an independent predictor, with an independent role for age (1.07, 1.04–1.09, P = 0.002) and male sex (2.07, 1.16–3.68, P = 0.013) (Supplementary Table 2). Consistently, HRs for mortality remained significant in the HG group (2.11, 1.03–4.35, P = 0.042) after adjustment for clinical confounders (model 2) as well as for biomarkers (model 3; 2.39, 1.10–5.18, P = 0.028) (Supplementary Table 2). Upon stratification by quintiles (Q1–Q5) of glucose levels, mortality was higher in Q4 (n = 54; 24 deaths [44.4%]; HR 3.57, 95% CI 1.46–8.76, P = 0.005) and marginally higher in Q5 (n = 54; 16 deaths [29.6%]; 2.32, 0.91–5.96, P = 0.079) (Fig. 1*B*) compared with Q1 (n = 54; 6 deaths [11.1%]). HR of Q4 was preserved after correction for age and sex (P = 0.009), clinical covariates (P = 0.003), and biomarkers (P = 0.005). Mortality was also significantly higher in Q3 (Supplementary Table 3). Mortality increased throughout quintiles of glucose (log-rank 15.408, P = 0.004) even after exclusion of the DM group. Compared with that in Q1, mortality was higher in Q4 (n = 42; 18 deaths [42.9%]; 3.90, 1.32–11.56, P = 0.014) and Q3 (n = 43; 12 deaths [30.2%]; 3.11, 1.01–9.54, P = 0.047) and remained so after adjustment for age and sex (marginally), clinical confounders (P = 0.007 and P = 0.006 for Q4 and Q3, respectively), and biomarkers (Supplementary Table 3).

There was no difference in ICU admission or mechanical ventilation between DM and NG groups (Supplementary Table 4). Adult respiratory distress syndrome was more common in HG and DM; 45% of HG patients required ICU admission and 33.3% required mechanical ventilation (both P = 0.002). There was no difference in in-hospital secondary infections and duration of hospitalization.

CONCLUSIONS

Of 271 hospitalized patients, 21% had DM and slightly more (24%) had at-admission glycemia ≥7.78 mmol/L. None of them had a prior DM diagnosis, and they were not on any glucose-lowering treatment. Whether they had undiagnosed diabetes or new-onset diabetes is difficult to ascertain. However, they had lower HbA_{1c} than the patients with diabetes, supporting the recent development of hyperglycemia. Our data support the view that at-admission hyperglycemia is a poor prognostic parameter requiring careful evaluation and proper treatment. These subjects had the worst clinical/laboratory profile and worst outcome, with a mortality rate that was twice that of the NG group and 30% higher than in the DM group. In the whole population, univariate analysis showed age, hypertension, cerebrovascular disease, cognitive impairment, chronic obstructive pulmonary disease, chronic kidney disease, and sepsis to be associated with increased risk of mortality. However, after multiple adjustments, HG but not DM remained an independent predictor of mortality. This conclusion is supported by the association between mortality and quintiles of plasma glucose, which remained valid upon exclusion of DM from the analysis. Mortality increased across quintiles of plasma glucose, though Q5 did not reach statistical significance. This may be due to a threshold effect above which no further worsening in prognosis may occur. Alternatively, people presenting with marked hyperglycemia may have been treated more aggressively, thus reducing the impact of at-admission hyperglycemia.

These findings, which build on existing evidence (5–9), are not surprising, since associations between at-admission hyperglycemia and in-hospital mortality in

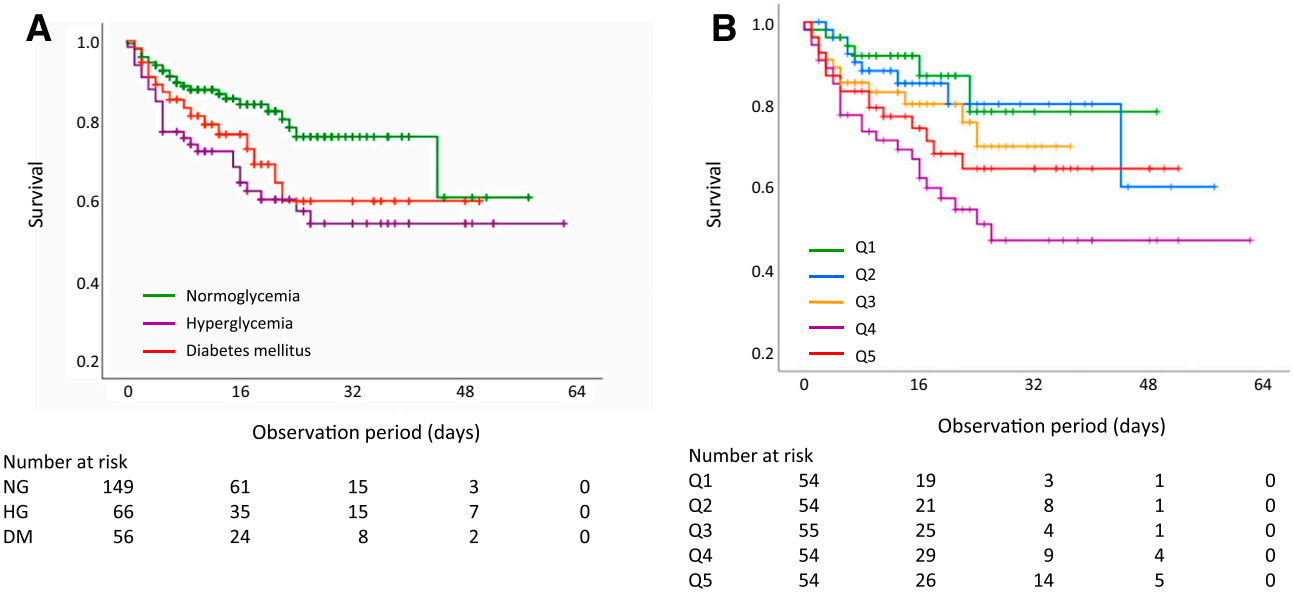

Figure 1—*A*: Kaplan-Meier analysis showing survival during hospitalization in COVID-19 patients. *B*: Kaplan-Meier analysis showing survival during hospitalization in COVID-19 patients stratified by quintiles of at-admission plasma glucose levels.

patients with critical illness, trauma, and acute cardiovascular events have been reported (4,10). At-admission hyperglycemia may be the consequence of counterregulatory hormone and cytokine storm exacerbating insulin resistance and adversely affect the immune response (2,11). However, a bidirectional relationship between COVID-19 and hyperglycemia may be postulated. Acute hyperglycemia increases urinary ACE2 activity and protein levels (12), thus favoring SARS-CoV-2 virulence. With sustained hyperglycemia, ACE2 expression is reduced and its anti-inflammatory effect restrained, contributing to the severity of the infection. The ACE2 receptor is expressed, among other tissues, in pancreatic β-cells, adipocytes, and to some extent skeletal muscle (13). SARS-CoV-2 can then damage organs and systems involved in glucose homeostasis, accounting for development of hyperglycemia or worsening of diabetes. This may account for at-admission hyperglycemia and/or new-onset diabetes and DKA in COVID-19 patients (5,14,15). Irrespective of the underlying mechanisms, our results support the need of proper recognition of the poor prognosis associated with at-admission hyperglycemia, although no final evidence is available on the effect of glycemic control on outcomes.

Our study has limitations including the relatively small size of the three groups and the incomplete set for some inflammatory parameters. Nonetheless, our results are in line with a rich literature on at-admission hyperglycemia and poor prognosis in many conditions. The cutoff of 7.78 mmol/L may be considered arbitrary, although it is commonly used (9). Of interest, a receiver operating characteristic analysis identified a cutoff glucose level of 7.7 mmol/L (Supplementary Fig. 1). Finally, the importance of at-admission hyperglycemia is supported by increase in mortality across plasma glucose quintiles where no predefined cutoff is selected.

In summary, in our study, at-admission hyperglycemia emerges as a main and independent factor associated with poor prognosis in people hospitalized for COVID-19.

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