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Original Article

Correlation of Hemoglobin A1C and Outcomes in Patients Hospitalized With COVID-19

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A B S T R A C T
Objective: Diabetes is a known risk factor for severe coronavirus disease 2019 (COVID-19). We conducted this study to determine if there is a correlation between hemoglobin A1C (HbA1C) level and poor outcomes in hospitalized patients with diabetes and COVID-19.

Methods: This is a retrospective, single-center, observational study of patients with diabetes (defined by an HbA1C level of >6.5% or known medical history of diabetes) who had a confirmed case of COVID-19 and required hospitalization. All patients were admitted to our institution between March 3, 2020, and May 5, 2020. HbA1C results for each patient were divided into quartiles: 5.1% to 6.7% (32-50 mmol/mol), 6.8% to 7.5% (51-58 mmol/mol), 7.6% to 8.9% (60-74 mmol/mol), and >9% (>75 mmol/mol). The primary outcome was in-hospital mortality. Secondary outcomes included admission to an intensive care unit, invasive mechanical ventilation, acute kidney injury, acute thrombosis, and length of hospital stay.

Results: A total of 506 patients were included. The number of deaths within quartiles 1 through 4 were 30 (25%), 37 (27%), 34 (27%), and 24 (19%), respectively. There was no statistical difference in the primary or secondary outcomes among the quartiles, except that acute kidney injury was less frequent in quartile 4.

Conclusion: There was no significant association between HbA1C level and adverse clinical outcomes in patients with diabetes who are hospitalized with COVID-19. HbA1C levels should not be used for risk stratification in these patients.

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Introduction

A novel coronavirus affecting humans was identified in 2019 and was later classified as SARS-CoV-2. Infection with this virus causes a respiratory disease known as COVID-19.1 There is a spectrum of disease severity in patients with COVID-19, including asymptomatic carriers, mild upper-respiratory symptoms, and severe systemic symptoms including acute respiratory failure, thrombophilia, and death.2 Several risk factors for severe disease have been determined, including increasing age, compromised immune function, and pre-existing conditions such as cardiovascular disease, obesity, and diabetes.3-5 Patients with diabetes comprise approximately one-third of confirmed cases of COVID-19.4 Several studies have demonstrated that patients with diabetes are at increased risk of severe disease and poor outcomes.5-8 In addition, elevated levels of glycemia during hospital admission has been demonstrated to correlate with poor outcomes.9,10 The correlation between hemoglobin A1C (HbA1C) levels and outcomes are less clear.11 Several studies have reported an association between higher HbA1C levels and worse outcomes in COVID-19, although all had small samples sizes, and 2
of these studies defined elevated HbA1C as >6.5% (>48 mmol/mol) without stratifying these patients further.12–13 Other studies have found no association between HbA1C levels and outcomes in patients with COVID-19, although several are limited by incomplete data.16–19 Our study was designed to specifically investigate the correlation between overall glycemia prior to hospitalization, based on HbA1C levels measured on admission, and outcomes in patients hospitalized with COVID-19.

Materials and Methods

This is a retrospective, single-center, observational study of patients with diabetes mellitus who had a confirmed case of SARS-CoV-2 infection on polymerase chain reaction testing of a nasopharyngeal sample and required hospital admission. Our institutional review board approved this study, and the requirement for informed consent was waived. All patients were admitted to the general medical floor or intensive care unit (ICU) at our institution between March 3, 2020, and May 5, 2020, inclusive of those dates. Patients were excluded if the hospital course was not completed prior to completion of data collection. Data were retrieved from EPIC electronic health record software and analyzed with Research Electronic Data Capture. Patients included in the study were considered to have confirmed infection if their initial test result was positive on admission or if they had at least 1 positive test result during admission, if testing was repeated for high clinical suspicion despite an initial negative result. All patients with confirmed COVID-19 infection had HbA1C tested on admission as part of our institution’s COVID-19 admission order set. The presence of diabetes was defined by a HbA1C level of >6.5% (48 mmol/mol) or a history of diabetes and current administration of at least 1 anti-hyperglycemic medication.

Variables

Collected variables included demographic information, comorbidities, laboratory data, and clinical data. Charts were reviewed to determine the diabetes subtype and the presence of medical comorbidities. Cardiovascular disease (CVD) was defined as the presence of coronary artery disease, congestive heart failure, or arrhythmia. Pulmonary disease included asthma and chronic obstructive pulmonary disease. Chronic kidney disease (CKD) was assessed based on a diagnosis of CKD from medical history. Patients were considered immunocompromised if they had a long-term glucocorticoid use, an active hematologic malignancy, a history of solid organ transplant, human immunodeficiency virus, or an acquired immunodeficiency syndrome. Medications utilized for the treatment of COVID-19 were recorded, including hydroxychloroquine, tocilizumab, remdesivir, and glucocorticoids.

Laboratory Values

Laboratory values include initial laboratory tests (HbA1C, serum creatinine, serum glucose, alanine transaminase, aspartate transaminase, β-hydroxybutyrate, white blood cell count, and absolute neutrophil count), all of which were collected within 24 hours of admission. Interleukin-6, D-dimer, procalcitonin, and inflammatory markers (C-reactive protein, erythrocyte sedimentation rate, ferritin, lactate dehydrogenase) were recorded, as available throughout hospitalization.

Primary and Secondary Outcomes

The primary outcome was in-hospital mortality. Secondary outcomes included admission to the ICU, invasive mechanical ventilation, acute kidney injury (AKI), acute thrombosis, and length of hospital stay. AKI was defined as per the Kidney Disease: Improving Global Outcomes guidelines as an increase in serum creatinine by 0.3 mg/dl within 48 hours, an increase in serum creatinine to ≥1.5 times baseline, or a urine volume <0.5 mL/kg/h for 6 hours.20

Data Analysis

HbA1C results for each patient were divided into quartiles: 5.1% to 6.7% (32–50 mmol/mol), 6.8% to 7.5% (51–58 mmol/mol), 7.6% to 8.9% (60–74 mmol/mol), and >9% (75 mmol/mol). Since quartile 4 encompassed a wide range of HbA1C values, HbA1C was also evaluated as a continuous variable. A subgroup analysis was performed in patients >65 years of age to assess the impact that age may have on primary and secondary outcomes.

Data were summarized by these subgroups and presented as median (25th percentile–75th percentile) and frequency (percentage), as appropriate. Continuous variables were assessed for normality using the Kolmogorov-Smirnov test and visual graphs, including histograms and Q-Q plots. Demographics and clinical characteristics were compared between groups via Kruskal-Wallis, χ², and Fisher exact tests based on the type and distribution of the data. Multiple logistic regression models were used to find factors associated with the outcomes. Akaia Information Criterion and Hosmer and Lemeshow goodness-of-fit tests were used to assess the model fit. SAS 9.4 software was utilized to perform all analyses and a P < .05 was considered to be statistically significant.

Results

In total, 506 patients met eligibility criteria and were included in this study. The mean age was 66 years, 58% were male, and 94% had type 2 diabetes. Demographics, comorbidities, treatment, and laboratory results are presented in Table 1. The most common comorbidity was hypertension, in 381 patients (75%), followed by CVD in 147 patients (29%).

Patients in quartile 4 (HbA1C levels >9% [75 mmol/mol]) were younger, less likely to have CVD or be immunocompromised, less likely to carry a new diagnosis of diabetes, and more likely to be treated with insulin and metformin prior to hospitalization, compared with those in other quartiles. As expected, serum glucose level on admission was highest in quartile 4. In addition, patients in quartile 4 were less likely to be treated with glucocorticoids. No other significant differences were present among the groups.

The overall mortality rate was 25% (n = 125). A total of 206 (41%) patients had AKI, 143 (28%) patients were admitted to the ICU, 124 (25%) patients required invasive mechanical ventilation, and 37 (7%) patients had acute thrombosis.

Table 2 illustrates primary and secondary outcomes within each quartile. The number of deaths within quartiles 1 through 4 were 30 (25%), 37 (27%), 34 (27%), and 24 (18%), respectively. No significant difference was seen among quartiles in the primary outcome or any of the secondary outcomes, with the exception of a lower frequency of AKI in quartile 4. In a multivariable model (Supplementary Table 1), adjusting for age, diabetes type, CVD, CKD, immunocompromised state or active malignancy, glucocorticoid use, and laboratory values (creatinine, aspartate transaminase, serum glucose, and D-dimer), AKI was less frequent in quartile 4 (adjusted odds ratio = 0.42, 95% confidence interval = 0.2–0.91, P = .02). For patients in quartile 4, only the presence of
Data are presented as frequency (%) unless otherwise stated.

Data are presented as median (interquartile range) or frequency (%).

Abbreviations: ICU = intensive care unit; IQR = interquartile range.

In order to confirm that our observed outcomes were not a function of the quartile ranges that were used in this study, we analyzed HbA1C as a continuous variable and assessed its relationship to outcomes (Table 4). Results were unchanged, with a lower frequency of AKI as the HbA1C level increased. Other outcomes were not significantly associated with HbA1C.

**Table 4**

Comparisons of Clinical Outcomes Between Hemoglobin A1C Groups

| Outcomes                  | Hemoglobin A1C quartiles | P value<sup>a</sup> |
|---------------------------|--------------------------|---------------------|
|                          | 5.1-6.7 (n = 121)        | 6.8-7.5 (n = 135)   | 7.6-8.9 (n = 126) | 9.0-17.1 (n = 124) | Overall (N = 506) |
| Mortality                 |                         |                     |                   |                     |                   |
| Acute kidney injury       | 30 (25.2)                | 37 (27.4)           | 34 (27.2)         | 24 (19.4)           | 125 (25.0)        | .41               |
| Acute thrombosis          | 10 (8.5)                 | 9 (6.7)             | 9 (7.1)           | 9 (7.1)             | 37 (7.4)          | .95               |
| Admission to the ICU      | 34 (28.6)                | 38 (28.2)           | 37 (29.4)         | 34 (27.4)           | 143 (28.4)        | .99               |
| Mechanical ventilation    | 31 (26.1)                | 30 (22.2)           | 34 (27)           | 29 (23.4)           | 124 (24.6)        | .79               |
| Length of stay, days, mean (IQR) | 7 (4-13)               | 9 (5-14)            | 8 (4-14)          | 7 (5-11)            | 8 (4-14)          | .55               |

Abbreviations: ICU = intensive care unit; IQR = interquartile range.

<sup>a</sup> P values are from the Kruskal-Wallis test for continuous variables and from the χ<sup>2</sup> test or Fisher exact test for categorical variables.
ABSTRACT

Purpose: The aim of this study was to examine the relationship between chronic hyperglycemia and COVID-19 outcomes, with a focus on the role of long-term insulin therapy and HbA1C levels.

Methods: This retrospective cohort study included 12,186 hospitalized patients with COVID-19. Demographic, clinical, laboratory, and outcomes data were collected. Long-term insulin therapy was categorized into quartiles. Univariate logistic regression models were used to assess the risk of developing acute kidney injury (AKI) and mortality.

Results: Most patients were hospitalized within 6 days of symptom onset, with 14.4% having HbA1C > 9% (75 mmol/mol). The risk of AKI was lower in patients in quartile 4 of HbA1C levels, with odds ratios of 0.91 (95% CI: 0.82-1.01) for mortality. No differences were observed in outcomes of patients treated with metformin, but when adjusting for age and the presence of comorbidities, including CKD, HbA1C levels > 9% (75 mmol/mol) were still associated with a lower risk of AKI.

Conclusions: Long-term insulin therapy and HbA1C levels were not significant risk factors for worse outcomes in hospitalized patients with COVID-19. However, higher HbA1C levels were associated with a lower risk of AKI. Further studies are needed to confirm these findings and to understand the mechanisms behind these associations.

Keywords: hyperglycemia, COVID-19, AKI, mortality, long-term insulin therapy, HbA1C.
no association between HbA1C levels and mortality, including in patients with HbA1C levels >9% (75 mmol/mol). This study was limited in that only 18% of patients had HbA1C measured within 1 week of hospitalization, although most patients (75%) had HbA1C measured within 1 year of admission. Finally, a smaller study of 166 hospitalized patients found no differences in mortality rates based on HbA1C levels. Our study, with HbA1C measured in all cases on admission, confirms and supports the findings of these studies.

While long-term management of glycemia may not have a direct impact on mortality in COVID-19, optimal management of glycemia during hospitalization has been linked to a reduction in mortality. Sarud et al showed that a substantial reduction in blood glucose, with utilization of insulin infusion, improved outcomes and prognosis in patients with COVID-19. In addition, Zhu et al found lower in-hospital death rates from COVID-19 (1.1% vs 11%) in patients with well-managed glycemia (defined as blood glucose between 70 and 180 mg/dL) compared with rates in patients with hyperglycemia (glucose level of >180 mg/dL) during hospitalization. Mazori et al reported lower survival rates for patients without diabetes who had early hyperglycemia (glucose level of >180 mg/dL) in the 1st 2 days of ICU admission than for patients with or without diabetes who did not have hyperglycemia. Main- taining optimal glycemic targets has been associated with a reduction in inflammatory cytokines and coagulation factors, theorizing the mechanism behind improvement in outcomes. Although admission glucose levels were recorded in our study, we did not evaluate overall inpatient glycemia and its effect on primary and secondary outcomes. This would be an important focus of future studies.

Our study holds clinical significance when determining treatment plans and assessing mortality risk in hospitalized patients. Our findings are indeed reassuring for patients with a history of diabetes, specifically those with suboptimal chronic glycemia. Nonetheless, optimal glycemic management during the course of illness remains an important aspect for the treatment of COVID-19 to limit the incidence of poor outcomes.

The main strengths of our study are a robust sample size and the availability of HbA1C levels for all subjects. The latter differentiates our study from the previous studies that found no correlation between HbA1C levels and outcomes in COVID-19. HbA1C levels were available for 846 of the 1317 patients (64%) in the CORONADO study, whereas only 18% of patients in the study by Agarwal et al had HbA1C levels measured within 1 week of hospitalization.

However, our study has several limitations. It is a single-center retrospective study, and our results would be strengthened by prospective multicenter studies. We did not compare outcomes with those of patients without diabetes, so we cannot draw conclusions regarding the impact of diabetes on outcomes. Lastly, HbA1C levels may be misleading or skewed in patients with chronic medical conditions, such as CKD or anemia, and may not be an accurate reflection of long-term glycemia in some patients.

Conclusion

This study analyzed the impact of HbA1C levels on admission and outcomes in 506 patients hospitalized with COVID-19. There was no increase in mortality, acute renal failure, acute thrombosis, admission to the ICU, need for invasive mechanical ventilation, or hospital length of stay in patients with higher HbA1C levels. HbA1C levels should not be used for risk stratification for patients with diabetes who are hospitalized with COVID-19.

Disclosure

The authors have no multiplicity of interest to disclose.

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