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Lack of association between either outpatient or inpatient glycemic control and COVID-19 illness severity or mortality in patients with diabetes

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ABSTRACT

Introduction To evaluate whether outpatient insulin treatment, hemoglobin A1c (HbA1c), glucose on admission, or glycemic control during hospitalization is associated with SARS-CoV-2 (COVID-19) illness severity or mortality in hospitalized patients with diabetes mellitus (DM) in a geographical region with low COVID-19 prevalence.

Research design and methods A single-center retrospective study of patients hospitalized with COVID-19 from January 1 through August 31, 2020 to evaluate whether outpatient insulin use, HbA1c, glucose on admission, or average glucose during admission was associated with intensive care unit (ICU) admission, mechanical ventilation (ventilator) requirement, or mortality.

Results Among 111 patients with DM, 48 (43.2%) were on outpatient insulin and the average HbA1c was 8.1% (65 mmol/mol). The average glucose on admission was 187.0±102.94 mg/dL and the average glucose during hospitalization was 173.4±39.8 mg/dL. Use of outpatient insulin, level of HbA1c, glucose on admission, or average glucose during hospitalization was not associated with ICU admission, ventilator requirement, or mortality among patients with COVID-19 and DM.

Conclusions Our findings in a region with relatively low COVID-19 prevalence suggest that neither outpatient glycemic control, glucose on admission, or inpatient glycemic control is predictive of illness severity or mortality in patients with DM hospitalized with COVID-19.

Significance of this study

What is already known about this subject?

- Limited data, mainly from surge settings, have been published with mixed results on whether worse glycemic control is associated with poor COVID-19 outcomes.

What are the new findings?

- Outpatient insulin use and hemoglobin A1c were not associated with COVID-19 illness severity or mortality in patients with diabetes in a region with low COVID-19 prevalence.
- Glucose at time of admission was not associated with COVID-19 illness severity or mortality in patients with diabetes in a region with low COVID-19 prevalence.
- Inpatient glycemic control was not associated with COVID-19 illness severity or mortality in patients with diabetes in a region with low COVID-19 prevalence.

How might these results change the focus of research or clinical practice?

- Our study showed that in a non-surge setting with low COVID-19 prevalence, neither outpatient nor inpatient glycemic control was predictive of illness severity or mortality.
- Risk stratification based on pre-existing glycemic control and inpatient glycemic targets may not need to be different for COVID-19 as compared with other illnesses.

INTRODUCTION

Previous studies have reported poor outcomes for patients with diabetes mellitus (DM) who are hospitalized with SARS-CoV-2 (COVID-19) infection.[1–8] Patients with DM experience longer length of stay, increased risk of severe illness, and higher rates of intensive care unit (ICU) admission, respiratory support, and mortality.[1–8]

While these risks have been widely reported, the effects are variable. Inpatient mortality for large cohorts of patients with DM hospitalized with COVID-19 has ranged from 8% to 47%.[7–10] Yan *et al*[11] reported a mortality of 81% for patients with DM who had tachypnea, hypoxemia, or severe illness requiring ICU care.

Moreover, if DM worsens the severity of COVID-19, it is unclear whether this is a function of glycemic control, or whether either prehospitalization or inpatient glycemic control has any value in predicting COVID-19 disease severity or mortality. Conflicting publications have reported both no effect and worse outcomes for patients with elevated hemoglobin A1c (HbA1c) or who were on insulin treatment prior to hospital admission.[9 12–15]

Further, heterogeneous definitions and study populations have left the impact of admission glucose and/or inpatient

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hyperglycemia on COVID-19 mortality in patients with DM unclear.[8 10 16–21] For example, many studies were conducted using data from the early stages of the pandemic (June 2020 or earlier) in regions experiencing severe community spread (such as New York City, London, and Paris). Both geographical and temporal differences in rates of COVID-19 mortality have arisen since then, and evolution in our understanding of the disease also makes reanalysis of data important.[22]

With this in mind, it is important to study the relationship of DM with COVID-19 outcomes outside of the confines of a large-scale local outbreak. In this setting, intrinsic relationships between DM, glycemic control, and COVID-19, if any, might be better revealed. Based on this, in our region with relatively low COVID-19 hospitalization and mortality during the early months of the pandemic,[23 24] we aimed to determine whether outpatient insulin use, HbA1c, glucose at time of admission, or glycemic control during hospitalization is associated with ICU level of care, invasive mechanical ventilation (ventilator) requirement, or mortality.

RESEARCH DESIGN AND METHODS

Setting and participants

Adult (≥18 years of age), non-pregnant patients hospitalized with COVID-19 between January 1, 2020 and August 31, 2020 within the University of California San Francisco (UCSF) Medical Center, a quaternary referral center with three hospitals in the Bay Area of Northern California, were included. As these three hospitals share the same inpatient services, medical providers, administration, and electronic health record (EHR), they were analyzed as a single hospital with three locations.

Patients were further stratified based on a documented diagnosis of DM (as defined in the next section) prior to admission. For patients with DM, inpatient glycemic management at UCSF was consistent with pragmatic recommendations developed by a national expert panel early in the pandemic, which included clustered care, defined as coordinating tasks such as administration of insulin and other medications, meal delivery, and clinical assessment, limiting use of intravenous insulin, aggressive titration of rapid-acting insulin for patients without caloric intake or on enteral feedings, and aggressive adjustment of basal-bolus insulin for patients who are eating.[25] In addition, all hospitalized patients (irrespective of pre-existing DM) were monitored by our virtual glucose management service (vGMS), and if elevated glucose was found, vGMS notes were placed in the chart suggesting further changes to insulin dosing.[26]

Data collection

This study was a retrospective review of EHR data. Data were obtained from a combination of automatic extraction using Epic Clarity with predefined variables by a physician with data science experience, as well as detailed chart review of every included patient by one of the authors (PBM).

Demographic and laboratory data were noted. Last HbA1c was defined as the most recent result between 6 months before and 2 weeks into the COVID-19-related hospitalization. DM was defined as either having a documented HbA1c ≥6.5% (48 mmol/mol), DM listed in outpatient or inpatient diagnoses, and/or DM documented in multiple progress notes during hospitalization. DM diagnoses were reviewed and confirmed during chart review, and no patients were newly diagnosed with DM during the COVID-19-related hospitalization. DM type and outpatient insulin use prior to admission were recorded.

For patients with DM, all measured point-of-care (POC) glucose values during hospitalization were obtained. Consistent with previous glucometric studies, repeat measurements during episodes of hypoglycemia or hyperglycemia were removed to more accurately reflect glycemic control.[27 28] Mean glucose per patient-day was calculated for each day of hospitalization, and the average glucose level during the entire hospitalization was determined by taking the mean of each of these daily means for a given patient. Additionally, the per cent of days in-range (all blood glucoses 70–180 mg/dL), days with hyperglycemia (two or more glucoses greater than 225 mg/dL), and days with hypoglycemia (one or more glucoses less than 70 mg/dL) were calculated for each patient with DM.[26]

Patient outcomes included admission to the ICU, ventilator requirement, and mortality.

Statistical analysis

We report median and IQR for continuous variables, and number and percentage of participants for categorical data. We compared the DM and non-DM groups using the rank-sum test for continuous variables and the exact test for categorical variables. For our outcomes, we report risk ratio with exact 95% CI. Within the DM group, we calculated the bivariate OR of each glycemic characteristic (outpatient insulin use, HbA1c, admission glucose, mean inpatient glucose) for each of the outcomes (ICU admission, ventilator requirement, mortality). Given the small number of mortality outcomes in the sample, we limited our multivariable logistic regression model to the two binary covariates which had the highest ORs and lowest p values with respect to our least frequent (mortality) and most frequent (ICU) outcomes. We report multivariable OR with 95% CI. Stata statistical software was used for all analyses.

Given that our data set encompassed an extended time period, logistic regression was used to evaluate for any changes in ICU admission, ventilator requirement, and mortality over time quartiles for both the DM and non-DM groups.

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Table 1 Baseline characteristics and admission laboratory data of hospitalized patients with COVID-19

Characteristics or laboratory values	Patients with DM (n=111)	Patients without DM (n=158)	P value
Age (years)	59.2 (49.0–71.5)	56.2 (42.0–67.1)	0.10
BMI (n*=102, n=139)	29.5 (25.8–35.1)	26.2 (22.4–31.8)	<0.001
Race			0.20
White	18 (16.2)	42 (26.5)	
Black	11 (9.9)	16 (10.1)	
Latinx	48 (43.2)	55 (34.8)	
Asian	25 (22.5)	26 (16.4)	
Other	9 (8.1)	19 (12.0)	
Male, n (%)	67 (60.3)	103 (65.2)	0.44
HbA1c (n=92, n=47)	7.4 (6.6–9.3)	5.8 (5.5–6.0)	<0.001
Type 2 DM	99 (89.2)	–	
Outpatient insulin use	48 (43.2)	–	
Glucose (mg/dL) (n=110, n=150)	163.5 (112–225)	108 (99–124)	<0.001
WBC (cells $\times 10^9$/L) (n=111, n=155)	6.8 (4.6–8.7)	6.7 (4.8–9.4)	0.85
HCO_3 (mEq/L) (n=111, n=152)	23 (21–25)	24 (21–26)	0.38
Cr (mg/dL) (n=110, n=152)	1.1 (0.8–1.6)	0.9 (0.8–1.2)	0.04
CRP (mg/L) (n=92, n=127)	65.2 (32.5–165.1)	75.3 (31.7–125.9)	0.54
Anion gap (n=110, n=150)	11 (9–13)	10 (9–12)	0.02
pH (n=92, n=122)	7.40 (7.35–7.42)	7.41 (7.36–7.43)	0.09
COVID-19 treatment with dexamethasone (n=74, n=104)	32 (43.2)	31 (29.8)	0.06

Data are displayed as median, IQR, or n (%).
*When n is specified in the left column, not all patients had laboratory value obtained.
BMI, body mass index; Cr, creatinine; CRP, C-reactive protein; DM, diabetes mellitus; HbA1c, hemoglobin A1c; HCO_3, bicarbonate; WBC, white blood cell count.

RESULTS

Patient characteristics, admission laboratories, and clinical outcomes

The sample consisted of 269 patients hospitalized with COVID-19, of whom 111 had DM (table 1). The majority of patients were male. Patients with DM had higher baseline body mass index (BMI) than those without DM (p<0.001). The median HbA1c was 7.4% (IQR 6.6–9.3) in patients with DM and 5.8% (IQR 5.5–6.0) in patients without DM (p<0.001). At admission, patients with DM had higher serum glucose values and serum creatinine (Cr) concentrations and a wider anion gap (p<0.05 for each laboratory measurement). Serum white blood cell count (WBC), bicarbonate (HCO_3), C-reactive protein (CRP), and pH were similar between the groups. Of patients admitted after dexamethasone treatment was offered for COVID-19 at our institution, 43.2% with DM and 29.8% without DM received dexamethasone (p=0.06), respectively.

Of the 269 patients, 117 (43.9%) required ICU admission, 70 (26.0%) required ventilator support, and 16 (5.9%) died in the hospital (table 2). Patients with DM

Table 2 Outcomes in hospitalized patients with COVID-19

Characteristics	Patients with DM (n=111)	Patients without DM (n=158)	Relative risk (95% CI)	Difference, % (95% CI)	P value
Length of stay (days)	12.0 (5.5–22.5)	8.0 (4.0–16.0)	1.39 (1.06 to 1.82)	2.2 (0.5 to 4.1)	0.01
ICU care	52 (46.8)	65 (41.1)	1.14 (0.87 to 1.49)	5.7 (–6.3 to 17.8)	0.38
Ventilator support	34 (30.6)	36 (22.8)	1.34 (0.90 to 2.00)	7.8 (–2.9 to 18.6)	0.16
Mortality	8 (7.2)	8 (5.1)	1.42 (0.55 to 3.68)	2.1 (–3.7 to 8.0)	0.60

Data are displayed as median, IQR, or n (%).
DM, diabetes mellitus; ICU, intensive care unit.

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were more likely to require ICU admission (relative risk (RR) 1.14), ventilator support (RR 1.34), and die in the hospital (RR 1.42) than those without DM, but the differences were not statistically significant.

There were no statistically significant changes in ICU admission, ventilator requirement, or mortality over time in both the DM and non-DM groups.

Association of glycemic control with clinical outcomes

Of the 111 patients with DM, 92 (83%) had an HbA1c within the specified timeframe and 110 (99%) had admission serum glucose checked to be included in each respective analysis. Ninety-six (86%) had POC glucose data collected during hospitalization and were included in the inpatient glycemic control analysis; the remainder of the patients either had brief hospitalizations or well-controlled serum glucoses which precluded the need for POC testing. The number of POC glucose readings per patient, per hospitalization, ranged from 3 to 1354, with a median of 58 and IQR of 25–134. The mean POC glucose per patient-day for these 96 patients was 173.4±39.8 mg/dL. As defined in the prior section, blood glucose remained in-range during 30.8% of patient-days. Patients were hyperglycemic during 25.3% of days and hypoglycemic during 4.4% of days.

Bivariate analysis revealed age ≥75 years and male sex to be most strongly associated with the outcomes (online supplemental appendix). These two variables were included in our multivariable model. Given that neither BMI nor creatinine was associated with the outcomes (p>0.05), these variables were not included. Table 3 depicts the unadjusted (bivariate) and adjusted (multivariable) ORs for patients with DM. In both unadjusted and adjusted analyses, the associations of the independent variables (outpatient insulin use, HbA1c, admission serum glucose, and mean glucose per patient-day during hospitalization) and the outcomes (ICU care requirement, ventilator requirement, and mortality) were variable and not statistically significant. For example, outpatient use of insulin had an adjusted OR for ventilator requirement of 1.71 but for in-hospital death of 0.71.

The analysis for serum glucose on admission was repeated for all included patients irrespective of DM. For this analysis, 260 (97%) patients had admission serum glucose available for review. In adjusted analyses, higher admission glucose was associated with ICU care requirement (OR 1.04, 95% CI 1.00 to 1.07) and ventilator requirement (OR 1.05, 95% CI 1.02 to 1.09), but not mortality (OR 1.02, 95% CI 0.97 to 1.08).

CONCLUSIONS

For patients with DM hospitalized with COVID-19, we found no consistent association between outpatient insulin use, HbA1c, serum glucose on admission, or average inpatient glucose with ICU admission, ventilator requirement, or mortality. While there was higher mortality in patients with DM compared with patients without DM, the difference was not statistically significant. Our observed mortality for patients with DM of 7.2% is

Table 3 Glycemic characteristics and outcomes in patients with DM and COVID-19

Glycemic characteristics	ICU care, unadjusted, OR (95% CI)	ICU care, adjusted*	Ventilator, unadjusted	Ventilator, adjusted	Mortality, unadjusted	Mortality, adjusted
Outpatient insulin use (n=111)	1.08 (0.51 to 2.29)	0.98 (0.44 to 2.12)	1.76 (0.78 to 4.0)	1.71 (0.71 to 4.1)	0.77 (0.18 to 3.4)	0.71 (0.16 to 3.2)
Hemoglobin A1c (n=92)	1.07 (0.89 to 1.27)	1.02 (0.85 to 1.24)	1.15 (0.95 to 1.38)	1.11 (0.92 to 1.36)	1.00 (0.7 to 1.43)	0.97 (0.67 to 1.42)
Glucose on admission† (n=110)	1.02 (0.98 to 1.06)	1.02 (0.98 to 1.06)	1.03 (0.99 to 1.07)	1.03 (0.99 to 1.08)	1.02 (0.96 to 1.08)	1.02 (0.96 to 1.09)
Mean glucose per patient-day† (n=96)	0.95 (0.85 to 1.05)	0.91 (0.82 to 1.02)	0.93 (0.83 to 1.04)	0.88 (0.78 to 1.01)	0.86 (0.69 to 1.07)	0.82 (0.64 to 1.05)

*Each characteristic was adjusted for gender and age.
†OR calculated per every 10 mg/dL of glucose.
DM, diabetes mellitus; ICU, intensive care unit.

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notably lower than prior studies in similar patients which have reported mortalities more than 25%.[9 15 29] This low COVID-19 mortality is consistent with recent findings that outcomes improved when, as observed in San Francisco, community prevalence of COVID-19 was lower and hospitals had fewer cases.[22–24] We posit that this is due to hospital systems maintaining adequate resources to provide high level of care rather than COVID-19 illness being less severe in regions with low prevalence.

The mean and median HbA1c values for patients with DM were 8.1% (65 mmol/mol) and 7.4% (57 mmol/mol), respectively, indicating that many did not meet outpatient glycemic targets. Despite this variable outpatient control, we found no difference in outcomes based on prehospitalization HbA1c, suggesting pre-existing glycemic control may not be useful for risk stratification. This lack of association with HbA1c and illness severity is in line with multiple other studies of hospitalized patients with COVID-19.[9 11 14] However, we do note that some studies have noted a possible link between HbA1c and illness severity. In part, this difference may be attributed to methodological variation. Zhu *et al* found that HbA1c was an independent risk factor for poor outcomes, but used HbA1c ≥6.5% (48 mmol/mol) as the criterion for insufficient glycemic control.[10] By using this cut-off, which is misaligned with accepted society guidelines, patients with adequate outpatient glycemic control were potentially under-represented.[30] A population-based data registry analysis from England indicated that an HbA1c ≥7.6% (60 mmol/mol) in patients with type 2 DM was associated with increased mortality from COVID-19.[13] These data included many ambulatory patients and did not specifically address outcomes of hospitalized patients.

We also found no association between outpatient insulin use and illness severity or mortality. Others have reported variable associations of insulin use and mortality.[9 11 14 15] Cariou *et al*[14] showed that outpatient insulin use was not associated with the composite outcome of ventilator requirement and mortality. To our knowledge, our study is the first report on the association of outpatient insulin use and ICU admission specifically in COVID-19.

Similarly, we found no association with admission serum glucose and any of the outcomes in patients with DM. We did however find that admission glucose was associated with increased ICU admission and ventilator requirement when evaluated across all patients in adjusted analyses, possibly indicating a role of stress hyperglycemia in patients without DM. This finding across all patients is in line with other published data, as an association with higher admission glucose values and ICU care, ventilator requirement, and mortality has been found.[14 17–19]

In terms of inpatient glycemic control, we found no association with ICU admission, ventilator requirement, or mortality. Our patient group with DM represents a spectrum of illness severity and included both critically ill and non-critically ill patients. The overall mean glucose per patient-day (173.4±39.8 mg/dL) was near the upper end of the target 140–180 mg/dL range recommended for most ICU and non-ICU hospitalized patients, indicating that there may not be significant benefit to targeting any tighter glycemic control in these patients.[31–33]

Others have reported an association with inpatient hyperglycemia and worse outcomes in COVID-19, but these studies have differences from ours, including limited analysis on patient subgroups with DM, varying definitions of hyperglycemia (eg, 140 mg/dL vs 180 mg/dL vs using 2-hour postprandial glucose), and varying patient populations (eg, exclusion of non-critically ill patients or inclusion of all patients irrespective of diabetes status).[8 10 16 19] The overall paucity and heterogeneity in the data highlight an important area where continued research is needed given the known implications of glycemic control in patients hospitalized with other medical conditions.

Our data reflect a time interval during which case counts and medical resources varied, and scientific understanding of COVID-19 rapidly evolved, whereas other studies related to glycemic control were performed during the initial surge of the pandemic.[9 12–14] We also included patients at all levels of inpatient care (acute care, intermediate care, and ICU), whereas other data have focused on critically ill patients or included ambulatory patients within a population-based registry.[12 13 16] We hope this patient population may be representative of future COVID-19 hospitalizations, as we know that COVID-19 outcomes improved in nearly all hospitals in the USA over the first 6 months of the pandemic.[22]

Our study has several limitations. This was a single-center study at a quaternary referral center, and it is possible our patient population may be different in complexity from that of other hospitals. The low mortality rate may also have limited detection of certain trends, although we believe these data are more representative of hospitalized patients with COVID-19 moving forward. We would also like to highlight an inherent limitation of studies based on automated electronic data extraction—when we performed a manual chart review on these 269 patients, we noted inaccuracies with extraction of DM diagnosis and missing laboratory and prescription data from medical care outside of our health system. We were able to manually verify the data on every patient in this study, but this degree of data validation may be challenging in data sets with thousands of patients.

Given the differing results among currently published data, and the geographical and temporal variations in COVID-19 prevalence and mortality, continued data collection is needed to evaluate the role of glycemic control. Ongoing multicenter studies may help clarify these issues.

In summary, we showed that in a setting with low COVID-19 prevalence and mortality, outpatient glycemic control, as indicated by use of insulin therapy and HbA1c, is not associated with illness severity or mortality in hospitalized patients with COVID-19 with DM. Additionally, neither admission serum glucose nor subsequent inpatient glycemic control is associated with illness severity or mortality. These results indicate that these glycemic

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measures should not be used for risk stratification in COVID-19, and that glycemic management for patients with COVID-19 with DM should be approached similarly to accepted inpatient guidelines.

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Contributors PBM analyzed the data, performed the literature review, and drafted the manuscript. MAK assisted with statistical analysis and manuscript revision. SKK assisted with manuscript revision and literature review. RJR assisted with research design, manuscript writing, manuscript revision, and literature review.

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Competing interests None declared.

Patient consent for publication Not required.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data are stored on a secure electronic server at the University of California, San Francisco.

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