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Evaluation of Glycemic Control and Predictors of Severe Illness and Death in Patients with Diabetes Hospitalized With COVID-19

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Abstract

Objectives: **To identify risk factors for severe disease and death among patients with diabetes and coronavirus disease 2019 (COVID-19) infection.**

Methods: **This retrospective cohort study conducted at three hospitals included 733 consecutive patients with DM admitted with confirmed COVID-19 (March 1 - December 31, 2020). Multivariable logistic regression was performed to identify predictors of severe disease and death.**

Results: **The mean age was 67.4 ± 14.3 years, 46.9% were males and 61.5% were African American. Among all patients, 116 (15.8%) died in the hospital. A total of 317 (43.2%) patients developed severe disease, 183 (25%) were admitted to an ICU and 118 (16.1%) required invasive mechanical ventilation. Increasing BMI (OR, 1.13; 95% CI, 1.02−1.25), history of chronic lung disease (OR, 1.49; 95% CI, 1.05−2.10) and increasing time since the last HbA1c test (OR, 1.25; 95% CI, 1.05−1.49) were the preadmission factors associated with increased odds of severe disease. Preadmission use of metformin (OR, 0.67; 95% CI, 0.47−0.95) or GLP-1 agonists (OR, 0.49; 95% CI, 0.27−0.87) was associated with decreased odds of severe disease. Increasing age (OR, 1.21; 95% CI, 1.09−1.34), co-existing chronic kidney disease greater than stage 3 (OR, 3.38; 95% CI, 1.67−6.84), ICU admission (OR, 2.93; 95% CI, 1.28−6.69) and use of invasive mechanical ventilation (OR, 8.67, 95% CI, 3.88−19.39) were independently associated with greater odds of in-hospital death.**

Conclusion: **Several clinical characteristics were identified to be predictive of severe disease and in-hospital death among patients with underlying diabetes hospitalized with COVID-19.**

Keywords: COVID-19, SARS-CoV-2, Diabetes, Mortality, Glucose

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of coronavirus disease 2019 (COVID-19), the disease that emerged in late 2019 in China. Its primary clinical feature is an acute pneumonic process with hypoxemic respiratory failure. As of June 2022, more than 542 million cases and 6.3 million deaths worldwide have occurred.[1]

Early into the COVID-19 pandemic, diabetes was identified as a major comorbidity associated with severe illness and mortality in hospitalized patients. According to the available published literature, the worldwide prevalence of diabetes among patients hospitalized with COVID-19 ranged from 4.7% up to 44%.[2] Furthermore, preexisting diabetes has been associated with a 20% increase in the odds of in-hospital mortality, based on the data from a retrospective cohort study[3] of 64,781 patients treated in 592 US hospitals.

A growing body of literature has identified that poor glycemic control was associated with worse COVID-19 outcomes. Studies[4,5] have shown that poorly controlled diabetes prior to the admission for COVID-19 was associated with worse outcomes. Additionally, reports[6,7] have revealed that poor

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inpatient glycemic control during COVID-19-related hospital stay was associated with poor outcomes as well. As yet, few studies have taken into account combined effects of both preadmission and glycemic control during hospitalization. As the pandemic continues, and with the emergence of multiple variants associated with enhanced transmissibility and increased virulence,[8] it remains important to understand how underlying diabetes affects COVID-19-related outcomes.

Therefore, this study aims to examine the diabetes-specific risk factors for severe disease and death. Furthermore, the goal was to evaluate both preadmission and inpatient glycemic control and its effect on hospital outcomes.

2. Methods

2.1. Study design and participants

This retrospective, observational, cohort, multisite study was conducted at three hospitals within one health care system. These hospitals, with a total of 875 beds, provide acute, primary and specialty care services to residents in various communities. This study was approved by the health care system Institutional Review Board.

All adult non-obstetric patients with diabetes consecutively admitted with a confirmed COVID-19 infection between March 1 and December 31, 2020 were included. A COVID-19 infection was defined by a positive qualitative polymerase-chain-reaction assay or antigen test. Diagnosis of diabetes was defined by using ICD-10 code in the electronic medical record (EMR), hemoglobin A1c (HbA1c) greater than 6.5% (47.5 mmol/mol) within 12 months prior to or during the hospitalization, and/or ongoing use of any anti-diabetic agents prior to the admission.

Participants were excluded from this analysis if they had had a positive test more than 14 days prior to admission, as our idea was to focus on the acute illness. For better glycemic control assessment, we excluded patients with fewer than three glucose measurements during the hospitalization. Patients who were transferred between hospitals within the health system were treated as one hospital encounter. For patients who were discharged and subsequently readmitted, their data from both admission time frames were used, provided that inclusion and exclusion criteria had still been met.

2.2. Data collection

Data were extracted from EMR and included demographic information, diabetes history, comorbid conditions, laboratory results, level of oxygen supplementation, in-hospital diabetes, and COVID-19 treatments. The most recent HbA1c level prior to the discharge date was obtained from EMR. Time since HbA1c was defined as the difference between the HbA1c test date and the hospital discharge date. The outpatient diabetes treatment regimen was collected from the admission medication reconciliation.

All blood glucose levels, by laboratory serum measurement or by point-of-care testing, were collected for the entire duration of hospital stay. For each patient, the mean glucose level and standard deviation were calculated. Target glucose was defined as glucose level within the range of 70−180 mg/dL. The percentage of glucose readings in the target range was derived from the following formula: ([number of glucose readings within the target range per patient]/[total number of glucose readings per patient]). Glycemic variability (GV) was expressed as the percentage coefficient of variation for glucose (CV), derived from the following formula: ([SD of glucose]/[mean glucose]) x 100. Severe hypoglycemia was defined as at least one value less than 54 mg/dL (measured by laboratory measurement only). Severe hyperglycemia was defined as at least one value greater than 400 mg/dL.

Outcome measures included severe disease and in-hospital death. Diagnosis of severe disease was based on the WHO COVID-19 clinical progression scale[9] and included scores 6 to 10 (need for high flow nasal cannula, noninvasive positive pressure ventilation, mechanical ventilation and death). A score of 10 represented death and was used as another outcome variable.

2.3. Statistical analysis

Standard descriptive analyses were provided using mean values and standard deviations for continuous variables or frequency counts and percentages for categorical variables. If there was strong evidence of non-normality for any of the continuous variables, based on the Kolmogorov−Smirnov test and Q−Q plots, then the median and interquartile range (IQR) were reported.

We imputed missing values using multivariate imputation by chained equations (MICE) with predictive mean matching (MICE, R package, version 3.13.0).[10] A total of 10 datasets were imputed. All regression analyses were performed in each imputed dataset and model parameters were pooled. To identify predictors of severe disease, we performed multivariable logistic regression with

preadmission characteristics as covariates. Candidate variables for the in-hospital mortality model included both preadmission and data from the hospitalization. Given few events relative to the number of variables of interest, to protect against overfitting, variable selection was warranted. Elastic net regression was used to identify the important features affecting the mortality of the cohort (glmnet, R package, version 4.1-2).[11] We used 10-fold repeated cross-validation to train and tune our model on 80% of the sample. The model was then applied to the rest of the sample. Terms with non-zero coefficients in at least 50% of imputed datasets were included in the final model.[12] To investigate the potential influence of glycemic control metrics on mortality, we fitted another logistic regression model with the addition of CV and percentage in the target range as covariates.

Two-sided P values < 0.05 were considered statistically significant. All statistical analyses were performed using the R statistical software, version 4.1.0 (R Foundation for Statistical Computing).[13]

3. Results

3.1. Study participants

There were 774 COVID-19-related hospital admissions to the three hospitals during the study period that met the inclusion criteria. After excluding patients with repeated admissions (26 admissions), fewer than three glucose measurements during the hospitalization (8 patients), and more than 14 days between the initial COVID-19 test and admit date (7 patients), the final study cohort consisted of 733 patients.

The majority of patients had type 2 diabetes (726 [99%]). The mean age ±SD was 67.4 ± 14.3, 344 (46.9%) were males and 451 (61.5%) patients were African American. Hypertension was the most common comorbidity (662 [90.3%]). Metformin was the most widely prescribed antidiabetic medication (377 [51.4%]), followed by insulin (313 [42.7%]). Table 1 shows preadmission clinical characteristics by peak disease severity.

Table 2 shows laboratory values, COVID-19 and DM management by disease severity. A total of 183 (25%) patients were admitted to an ICU and 118 (16.1%) required invasive mechanical ventilation. A total of 317 (43.2%) patients developed severe disease, of which 201 (27.4%) survived and 116 (15.8%) died. Median (IQR) in-hospital length of stay for the cohort was 8 (5–13) days. Among inpatients with an ICU admission, median (IQR) in-hospital length of stay was 12 (6–21) days.

The total number of glucose values for the study population was 41,614. Of those, 8217 (19.7%) were performed through standard laboratory blood draws and 33,397 (80.3%) were obtained with point-of-care devices. The median (IQR) number of glucose testing per patient per day was 5.1 (4.6–5.9).

3.2. Preadmission risk factors for severe disease

Table 3 shows the unadjusted and adjusted odds of severe disease. In the adjusted analysis, increasing BMI (OR, 1.13; 95% CI, 1.02–1.25), history of COPD (OR, 1.49; 95% CI, 1.05–2.10) and increasing time since the last available HbA1c result (OR, 1.25; 95% CI, 1.05–1.49) were independently associated with increased odds of severe disease. On the other hand, preadmission use of metformin (OR, 0.67; 95% CI, 0.47–0.95) and GLP-1 agonists (OR, 0.49; 95% CI, 0.27–0.87) was associated with lower odds of severe disease.

3.3. Risk factors for in-hospital death

Table 4 shows unadjusted and adjusted odds of in-hospital mortality. In the adjusted analysis, variables independently associated with higher in-hospital mortality were increasing age (OR, 1.21; 95% CI, 1.09–1.34), history of CKD greater than stage 3 (OR, 3.38; 95% CI, 1.67–6.84), ICU admission (OR, 2.93; 95% CI, 1.28–6.69) and the use of invasive mechanical ventilation (OR, 8.67, 95% CI, 3.88–19.39).

In the univariate analysis, a CV greater than 36% was associated with higher odds of in-hospital death (OR, 1.56; 95% CI, 1.04–2.34) and having more than 50% of the BG values in the target range was associated with decreased odds of in-hospital death (OR, 0.62; 95% CI, 0.40–0.93). However, after controlling for other covariates, these terms were not independently predictive of in-hospital mortality (model 2).

4. Discussion

This study examined the characteristics and clinical outcomes of a cohort of patients with diabetes admitted with COVID-19. A total of 43.2% of patients developed severe disease and 15.8% died during the hospital stay. Our objective was to identify factors associated with severe disease and death.

Major comorbidities that were associated with increased odds of severe disease were obesity and chronic lung disease. Bello-Chavolla et al.[14] have previously observed that obese patients had higher rates of hospitalization and mortality with COVID-19.

Table 1. Preadmission clinical characteristics of patients with diabetes hospitalized with COVID-19, overall and by peak disease severity.

Characteristic	All patients (n = 733)	Missing data, n (%)	Mild disease[a] (n = 416)	Severe disease, excluding death[b] (n = 201)	Death (n = 116)
Demographic data					
Mean age, years	67.4 ± 14.3	–	66.8 ± 14.2	65.6 ± 14.7	72.3 ± 13.0
Male sex, n (%)	344 (46.9)	–	188 (45.2)	101 (50.2)	55 (47.4)
African American, n (%)	451 (61.5)	–	260 (62.5)	125 (62.2)	66 (56.9)
Ever smoker, n (%)	146 (19.9)	–	76 (18.3)	42 (20.9)	28 (24.1)
Mean BMI, kg/m^2	32.3 ± 8.3	28 (3.8)	31.8 ± 8.1	33.0 ± 8.2	32.6 ± 9.1
Comorbidities, n (%)					
Hypertension	662 (90.3)	–	376 (90.4)	177 (88.1)	109 (94.0)
Hyperlipidemia	578 (78.9)	–	334 (80.3)	149 (74.1)	95 (81.9)
CAD[c]	226 (30.8)	–	122 (29.3)	56 (27.9)	48 (41.4)
CKD stage 3 or higher	136 (18.6)	–	64 (15.4)	29 (14.4)	43 (37.1)
CVA or TIA	125 (17.1)	–	78 (18.8)	26 (12.9)	21 (18.1)
Chronic lung disease[d]	214 (29.2)	–	106 (25.5)	65 (32.3)	43 (37.1)
Diabetes history and outpatient treatment, n (%)					
Type 2 diabetes	726 (99.0)	–	413 (99.3)	199 (99.0)	114 (98.3)
Median HbA1c, %	7.4 (6.6–9.0)	60 (8.2)	7.4 (6.6–9.0)	7.5 (6.6–9.2)	7.3 (6.5–8.7)
Median HbA1c, mmol/mol	57.4 (48.6–74.9)	60 (8.2)	57.4 (48.6–74.9)	58.5 (48.6–77.1)	56.3 (47.5–71.6)
Median time since HbA1c, days	80 (9–330)	60 (8.2)	75 (6–299)	75 (10–306)	130 (25–469)
Insulin	313 (42.7)	–	166 (39.9)	84 (41.8)	63 (54.3)
Metformin	377 (51.4)	–	235 (56.5)	96 (47.8)	46 (39.7)
Sulfonylurea	142 (19.4)	–	84 (20.2)	36 (17.9)	22 (19.0)
Thiazolidinedione	21 (2.9)	–	12 (2.9)	8 (4.0)	1 (0.9)
DPP-4 inhibitor	70 (9.5)	–	41 (9.9)	18 (9.0)	11 (9.5)
GLP-1 agonist	65 (8.9)	–	44 (10.6)	17 (8.5)	4 (3.4)
SGLT2 inhibitor	41 (5.6)	–	25 (6.0)	15 (7.5)	1 (0.9)
Use of systemic steroids[e]	60 (8.2)	–	33 (7.9)	14 (7.0)	13 (11.2)

Abbreviations: BMI = body mass index; CAD = coronary artery disease; CKD = chronic kidney disease; CVA = cerebrovascular accident; TIA = transient ischemic attack; HbA1c = hemoglobin A1c; DPP-4 = dipeptidyl peptidase 4; GLP-1 = glucagon-like peptide 1; SGLT-2 = sodium-glucose cotransporter-2.

Numerical data are expressed as mean ± SD or median (IQR). Categorical data are expressed as n (%).

[a] Included patients not on oxygen therapy or patients requiring low flow nasal cannula.

[b] Included patients requiring high flow nasal cannula, noninvasive positive pressure ventilation or invasive mechanical ventilation.

[c] Included patients with stable angina or history of acute coronary syndrome.

[d] Included patients with asthma, chronic obstructive pulmonary disease or pulmonary hypertension.

[e] Outpatient use of systemic steroids within 2 weeks prior to the admission.

Furthermore, by using casually ordered mediation analysis, they showed that obesity mediates 49.5% of the effects of diabetes on COVID-19 lethality. Obesity has been shown to decrease the immune response, decrease lung compliance and impair ventilation, thus leading to worse outcomes with respiratory infections.[15] Similarly, an underlying chronic obstructive pulmonary disease has been shown to increase the risk of severe pneumonia and poor outcomes with COVID-19.[16]

Our data did not show any significant association between hemoglobin A1c values and disease severity. This is consistent with multiple previous reports,[4,17] including the CORONADO study,[18] a nationwide multicenter observational study done in France. Interestingly, we found that increasing time since the last HbA1c test was associated with greater odds of severe disease. This remained significant even after adjustment for the HbA1c value, age, sex, comorbidities and diabetes medications. We did not find previous studies reporting similar results. It is possible to hypothesize that these patients had less access to health care or less regularity of general health checks.

In the multivariable analysis, use of metformin or GLP-1 agonists was associated with decreased odds of severe disease. Similar results were reported previously. A recent meta-analysis[19] of 17 studies with a total of 20,719 patients with diabetes found that metformin was associated with a 36% decrease in mortality and a 19% decrease in the disease severity. A recent study[20] showed that metformin attenuated SARS-CoV-2-induced ARDS, by inhibiting NLRP3 inflammasome activation and interleukin 1β production in cultured and alveolar macrophages. Another meta-analysis[21] of 9 studies showed that preadmission use of GLP-1 agonists was associated with lower mortality in COVID-19,

Table 2. In-hospital clinical characteristics of patients with diabetes hospitalized with COVID-19, overall and by peak disease severity.

Characteristic	All patients (n = 733)	Mild disease[a] (n = 416)	Severe disease, excluding death[b] (n = 201)	Death (n = 116)
COVID-19 disease severity, n (%)				
Highest supplemental oxygen required				
Nasal cannula	315 (43.0)	308 (74.0)	0 (0)	7 (6.0)
HFNC, NIPPV	192 (26.2)	0 (0)	158 (78.6)	34 (29.3)
IMV	118 (16.1)	0 (0)	43 (21.4)	75 (64.7)
Median duration of the highest oxygen support, days	4 (2–8)	3 (0–6)	5 (3–9)	5 (2–10)
ICU admission	183 (25)	13 (3.1)	84 (41.8)	86 (74.1)
New VTE during hospital stay	40 (5.5)	15 (3.6)	14 (7.0)	11 (9.5)
Medications used, n (%)				
Dexamethasone	362 (49.4)	179 (43.0)	134 (66.7)	49 (42.2)
Systemic glucocorticoids other than dexamethasone	136 (18.6)	42 (10.1)	53 (26.4)	41 (35.3)
Remdesivir	235 (32.1)	104 (25.0)	101 (50.2)	30 (25.9)
Tocilizumab	50 (6.8)	3 (0.7)	26 (12.9)	21 (18.1)
Laboratory values				
Median admission creatinine, mg/dL	1.3 (0.9–2.1)	1.2 (0.9–1.9)	1.2 (0.9–2.0)	1.7 (1.2–3.2)
Median admission leukocyte count, × 10^c cells/μL	7.0 (5.3–9.3)	6.7 (5.1–9.0)	7.2 (5.5–9.4)	7.6 (5.8–10.0)
Median admission BG, mg/dL	170 (121–237)	165 (120–229)	184 (132–239)	170 (113–259)
Median glucose CV, %	30.8 (23.0–40.0)	27.9 (21.2–37.9)	32.5 (25.8–41.6)	34.7 (25.9–43.8)
Median % of BG readings in target range	42.9 (24.6–73.4)	49.3 (24.9–85.7)	37.7 (23.7–59.6)	40.4 (24.9–64.4)
Severe hypoglycemia, n (%)	38 (5.2)	14 (3.4)	16 (8.0)	8 (6.9)
Severe hyperglycemia, n (%)	255 (34.8)	119 (28.6)	85 (42.3)	51 (44.0)
Diabetes management, n (%)				
DKA on admission	20 (2.7)	8 (1.9)	6 (3.0)	6 (5.2)
Insulin drip	58 (7.9)	10 (2.4)	20 (10.0)	28 (24.1)
Insulin aspart (sliding scale only)	247 (33.7)	165 (39.7)	49 (24.4)	33 (28.4)
Combination insulin[c]	423 (57.7)	203 (48.8)	147 (73.1)	73 (62.9)
New diabetes diagnosis	27 (3.7)	8 (1.9)	17 (8.5)	2 (1.7)

Abbreviations: HFNC = high flow nasal cannula; NIPPV = noninvasive positive pressure ventilation; IMV = invasive mechanical ventilation; ICU = intensive care unit; VTE = venous thromboembolism; BG = blood glucose; CV = coefficient of glucose variation; DKA = diabetic ketoacidosis.

Numerical data are expressed as mean ± SD or median (IQR). Categorical data are expressed as n (%). No data are missing.

[a] Included patients not on oxygen therapy or patients requiring low flow nasal cannula.

[b] Included patients requiring HFNC, NIPPV or IMV.

[c] Included any combination of the sliding scale insulin aspart, insulin glargine or scheduled (e.g., mealtime) insulin aspart.

even after adjustment for age, gender, comorbidities and use of other medications such as metformin and insulin. Previous research[22] demonstrated anti-inflammatory effects of GLP-1 agonists, especially during respiratory infections. A study[22] on a mouse model of influenza H9N2 virus-induced acute lung injury demonstrated that liraglutide alleviated the severity of lung injury. Liraglutide did not affect viral titers in infected lungs, but it decreased levels of cytokines such as IL-1β, IL-6 and TNF-α in bronchoalveolar lavage fluid. We did not see a significant association with the use of other medications, including insulin (OR, 1.20; 95% CI, 0.84–1.71).

Our analysis highlighted that increasing age, coexisting CKD greater than stage 3, admission to the ICU and the use of invasive mechanical ventilation were independent predictors of in-hospital mortality in patients with diabetes. These results are in agreement with multiple previous studies and systematic reviews.[23,24]

We also examined inpatient glycemic control and its association with the outcomes. Patients who died in the hospital more frequently had less than 50% of BG in the target range and a CV greater than 36%. However, after accounting for other factors, these patients had similar odds of death as patients with over 50% of BG in target or a CV under 36%. A potential explanation for this might be that the impact of glycemic control on mortality was too small to be detected, when compared to age, CKD or use of mechanical ventilation. A similar lack of association of inpatient glycemic control, estimated via mean glucose per patient-day, on illness severity and mortality has been reported previously.[25] On the other hand, several previous studies[6,26,27] have demonstrated that hyperglycemia was associated with a higher risk of severe disease and death during COVID-19 admission. However, these studies had different estimations of hyperglycemia, such as by using the highest 2 h postprandial BG,[26] admission fasting BG[27] or the mean BG on days 2–3.[6]

Table 3. Univariable and multivariable association of preadmission factors with severe disease[a].

Characteristic	Unadjusted Odds Ratio (95% CI)	P value	Adjusted Odds Ratio (95% CI)	P value
Age (5-year increments)	1.03 (0.98–1.08)	0.26	1.06 (0.99–1.13)	0.10
Male sex vs. female	1.18 (0.88–1.58)	0.28	1.33 (0.96–1.84)	0.08
African American race vs. other[b]	0.91 (0.67–1.23)	0.54	0.91 (0.66–1.26)	0.58
Ever smoker	1.27 (0.88–1.82)	0.20	1.18 (0.80–1.75)	0.40
BMI (increments of 5 kg/m^2)	1.06 (0.97–1.16)	0.17	1.13 (1.02–1.25)	0.025
HTN	0.98 (0.60–1.62)	0.94	0.92 (0.52–1.62)	0.77
HLD	0.82 (0.58–1.17)	0.28	0.74 (0.49–1.13)	0.16
CAD[c]	1.18 (0.86–1.61)	0.31	0.94 (0.64–1.37)	0.73
CKD stage 3 or higher	1.62 (1.11–2.35)	0.012	1.38 (0.90–2.12)	0.14
CVA or TIA	0.75 (0.51–1.12)	0.16	0.67 (0.44–1.03)	0.07
Chronic lung disease[d]	1.51 (1.10–2.08)	0.012	1.49 (1.05–2.10)	0.024
Type 2 diabetes vs. type 1	1.57 (0.11–2.60)	0.46	0.62 (0.13–3.07)	0.56
HbA1c (%)	0.98 (0.92–1.05)	0.56	0.99 (0.92–1.07)	0.84
Log days since the last HbA1c	1.20 (1.02–1.41)	0.025	1.25 (1.05–1.49)	0.012
Use of insulin	1.30 (0.97–1.75)	0.08	1.20 (0.84–1.71)	0.32
Use of metformin	0.63 (0.47–0.84)	0.002	0.67 (0.47–0.95)	0.025
Use of sulfonylurea	0.89 (0.61–1.28)	0.52	0.90 (0.61–1.34)	0.61
Use of TZD	0.98 (0.40–2.35)	0.97	1.08 (0.42–2.76)	0.87
Use of DPP-4 inhibitor	0.92 (0.55–1.51)	0.75	0.94 (0.55–1.61)	0.82
Use of GLP-1 agonist	0.60 (0.34–1.02)	0.06	0.49 (0.27–0.87)	0.016
Use of SGLT-2 inhibitor	0.83 (0.43–1.57)	0.57	1.22 (0.60–2.46)	0.58
Outpatient use of steroids	1.08 (0.63–1.84)	0.77	0.87 (0.50–1.54)	0.64

Abbreviations: BMI = body mass index; HTN = hypertension; HLD = hyperlipidemia; CAD = coronary artery disease; CKD = chronic kidney disease; CVA = cerebrovascular accident; TIA = transient ischemic attack; HbA1c = hemoglobin A1c; TZD = thiazolidinedione; DPP-4 = dipeptidyl peptidase 4; GLP-1 = glucagon-like peptide 1; SGLT-2 = sodium-glucose cotransporter-2.

[a] Based on 733 patients and 317 events. Severe disease was defined as need for high flow nasal cannula, noninvasive positive pressure ventilation, invasive mechanical ventilation or death during the hospitalization. Univariable and multivariable logistic regression was performed with preadmission characteristics as covariates. Multiple imputation was used to estimate missing values for BMI, HbA1c and time since HbA1c.

[b] Other includes White, Asian, Hispanic/Latino or unknown.

[c] Included patients with stable angina or history of acute coronary syndrome.

[d] Included patients with asthma, chronic obstructive pulmonary disease or pulmonary hypertension.

Although not statistically significant (OR 1.36; 95% CI, 1.00–1.84; p = 0.05), a trend was observed with increasing time since the last HbA1c test and greater odds of death during hospital stay. As a similar signal was not observed with the markers of inpatient control, this demonstrates the importance of outpatient control and overall social determinants of health with regards to hospital outcomes.

Table 4. Univariable and multivariable logistic regression of factors associated with in-hospital death[a].

Characteristic	Unadjusted Odds Ratio (95% CI)	P value	Adjusted Odds Ratio (95% CI)	P value
Model 1				
Age (5-year increment)	1.17 (1.09–1.27)	<0.001	1.21 (1.09–1.34)	<0.001
CKD greater than stage 3	3.32 (2.14–5.12)	<0.001	3.38 (1.67–6.84)	0.001
Log days since the last HbA1c	1.37 (1.09–1.72)	0.007	1.36 (1.00–1.84)	0.05
Admission to ICU	15.37 (9.72–24.89)	<0.001	2.93 (1.28–6.69)	0.011
Need for IMV	24.42 (15.08–40.32)	<0.001	8.67 (3.88–19.39)	<0.001
Admission serum creatinine (mg/dL)	1.09 (1.02–1.16)	0.005	0.95 (0.85–1.07)	0.41
Use of steroids other than DXM	3.00 (1.93–4.65)	<0.001	1.48 (0.81–2.70)	0.20
Use of tocilizumab	4.48 (2.43–8.15)	<0.001	0.99 (0.44–2.24)	0.98
Use of insulin drip	6.23 (3.54–10.94)	<0.001	2.02 (0.93–4.40)	0.07
Model 2				
CV greater than 36%	1.56 (1.04–2.34)	0.032	0.73 (0.42–1.28)	0.28
Percentage in target greater than 50%	0.62 (0.40–0.93)	0.023	0.80 (0.46–1.37)	0.41

Abbreviations: CKD = chronic kidney disease; HbA1c = hemoglobin A1c; ICU = intensive care unit; IMV = invasive mechanical ventilation; DXM = dexamethasone, CV = coefficient of glucose variation.

[a] Based on 733 patients and 116 events (in-hospital death). Model 1 included terms with non-zero coefficients from elastic net regression. Model 2 included all terms from Model 1 with addition of CV and percentage in target range. Rather than treating as continuous variables, CV and percentage in target range were divided into two groups (≤36%,>36% and ≤50%,>50, respectively). Multiple imputation method was used to estimate missing values for time since HbA1c variable.

Several limitations of this study should be discussed. First, this was a retrospective observational study. The definition of clinical conditions and outpatient medications relied on the accuracy of hospital EMR and admission medication reconciliation. Second, due to the nature of observational studies, this study can only detect association, rather than causality. Third, glucose monitoring was not continuous. However, the average number of BG values per patient per day was 5.1, which allowed enough data for glycemic control assessment. Fourth, although we collected data on different insulin modalities, we did not collect exact insulin doses used for each patient. This raises the possibility that the amount of insulin use could have affected the outcomes. Further prospective studies, potentially with the use of continuous glucose monitoring, should be done for a better understanding of the association of glycemic control and hospital outcomes.

Notwithstanding these limitations, this study provides a comprehensive evaluation of preadmission characteristics, diabetes management and inpatient glycemic control. The study also sheds light on factors predictive of severe disease or death during admission with acute COVID-19 in a population with underlying diabetes.

5. Conclusions

In a population with underlying diabetes, co-existing obesity, chronic lung disease and longer time since the last HbA1c were the factors associated with increased odds of severe disease during the admission with COVID-19. Preadmission use of metformin or GLP-1 agonists was associated with decreased odds of severe disease. Older patients, patients with a co-existing chronic kidney disease, patients admitted to ICU and on mechanical ventilation all had higher odds of in-hospital death.

Author contributions

J.M.: data collection, data analysis, writing − original draft; N.P.: data collection, writing − original draft; M.T., S.J., J.L. and S.A.: data collection, writing − review & editing; A.T.: conceptualization, supervision, writing - review & editing. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that they have no competing or conflicts of interests.

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