Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original Article

Predictors of Severe COVID-19 in Patients With Diabetes: A Multicenter Review

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ABSTRACT

Objective: Diabetes is an independent risk factor for severe SARS-CoV-2 infections. This study aims to elucidate the risk factors predictive of more severe outcomes in patients with diabetes by comparing the clinical characteristics of those requiring inpatient admissions with those who remain outpatient.
Methods: A retrospective review identified 832 patients—631 inpatients and 201 outpatients—with diabetes and a positive SARS-CoV-2 test result between March 1 and June 15, 2020. Comparisons between the outpatient and inpatient cohorts were conducted to identify risk factors associated with severity of disease determined by admission rate and mortality. Previous dipeptidyl peptidase 4 inhibitor use and disease outcomes were analyzed.
Results: Risk factors for increased admission included older age (odds ratio [OR], 1.04 [95% CI, 1.01-1.06]; $P = .003$), the presence of chronic kidney disease (OR, 2.32 [1.26-4.28]; $P = .007$), and a higher hemoglobin A1c at the time of admission (OR, 1.25 [1.12-1.39]; $P < .001$). Lower admission rates were seen in those with commercial insurance. Increased mortality was seen in individuals with older age (OR, 1.09 [1.07-1.11]; $P < .001$), higher body mass index number (OR, 1.04 [1.01-1.07]; $P = .003$), and higher hemoglobin A1c value at the time of diagnosis of COVID-19 (OR, 1.12 [1.01-1.24]; $P = .028$) and patients requiring hospitalization. Lower mortality was seen in those with hyperlipidemia. Dipeptidyl peptidase 4 inhibitor use prior to COVID-19 infection was not associated with a decreased hospitalization rate.
Conclusion: This retrospective review offers the first analysis of outpatient predictors for admission rate and mortality of COVID-19 in patients with diabetes.

Introduction

SARS-CoV-2 is a novel, single-stranded RNA coronavirus that caused over 80 million documented infections and nearly 1.8 million fatalities worldwide by the end of 2020.[1] Several diseases, including diabetes, obesity, hypertension, and chronic obstructive pulmonary disorder, have been identified as risk factors for worsened morbidity and higher mortality.[2-4] Early reports note that among patients admitted with SARS-CoV-2 infection, patients with diabetes required more inpatient interventions such as mechanical ventilation, dialysis, and antibiotic therapy.[5,6] One study painted a particularly grim view for individuals with diabetes, showing that approximately 10% died within 7 days of admission from SARS-CoV-2 infection.[6] This same study also showed that a higher body mass index (BMI) is positively and independently associated with the 7-day mortality rate in patients with diabetes. In addition, the subgroup analysis of patients with well-controlled glucose levels while hospitalized (range, 70-180 mg/dL or 3.3-10 mmol/dL) compared with those with poor inpatient glycemic control demonstrated lower mortality rates and shorter lengths of stay with better glycemic control.[5-7] This shows that not all individuals

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; DPP-4, dipeptidyl peptidase 4; HbA1c, hemoglobin A1c; OR, odds ratio.

Data Availability: Data are available on request from the corresponding author.

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with diabetes are at an equally increased risk of severe disease, and further characterization of disease phenotypes related to adverse outcomes may change the management of diabetes in both inpatient and outpatient settings. Moreover, there has been a suggestion that individuals of racial and ethnic minorities within the United States share a disproportionate burden of SARS-CoV-2 infections as well as more severe phenotype, but no data exist specifically for patients with diabetes.

Another recent study attempted to further stratify risk among individuals with diabetes who contract SARS-CoV-2. Agarwal et al[7] completed a retrospective cohort analysis of 1126 hospitalized patients with diabetes and SARS-CoV-2. They determined that the preadmission use of insulin was associated with higher morbidity from SARS-CoV-2 as an inpatient. In addition, they demonstrated no significant relationship between admission hemoglobin A1c (HbA1c) value and overall outcomes, a finding consistent with several recent studies.[5,6] However, this study was unable to gather data across racial and ethnic groups and had no outpatient comparison group.

Dipeptidyl peptidase 4 (DPP-4) inhibitors have been postulated to mitigate the effects of SARS-CoV-2 infection by potentially inhibiting viral entry into human cells versus an overall anti-inflammatory affect.[8] A retrospective observational study involving 338 patients with type 2 diabetes conducted in Italy by Solerte et al[8] showed a positive association between sitagliptin and reduced mortality related to SARS-CoV-2 hospitalization. In this study, patients in the treatment arm received sitagliptin in addition to insulin for the inpatient management of their hyperglycemia. However, there have been other published studies that contradict these findings,[9] and the potential benefit of DPP-4 inhibitors in SARS-CoV-2 infection is still unclear.

This study aimed to further elucidate the risk factors predictive of more severe outcomes in individuals with diabetes who develop SARS-CoV-2 infections, specifically investigating outpatient glycemic control, outpatient regimen, differences in underlying comorbidities, and diabetic complications. The current literature around this topic has been limited by the paucity of outpatient data. Comparing these characteristics between a cohort of individuals requiring inpatient versus outpatient care will provide a more complete picture than one that only looks at inpatients. We hypothesized that outpatient insulin use, obesity, and more diabetic complications would be associated with higher admission rates and increased mortality. In addition, a subgroup of patients on DPP-4 inhibitor therapy prior to contracting the virus was evaluated to determine the potential effects of DPP-4 inhibitors in SARS-CoV-2 infection.

Methods

Setting and Participants

The hospital system studied is composed of 13 member hospitals spread throughout the state with a total of 2487 licensed beds serving a total of 116 467 hospital admissions during 2019.[10] This service area encompasses an urban center and surrounding area with a diverse patient population based on race/ethnicity, socioeconomic status, and insurance status.

Participants were identified from all affiliate hospitals within the hospital system from March 2020 through June 15, 2020, based on the current procedural terminology code for the COVID-19 polymerase chain reaction test and documented diabetes from ICD-10 codes or HbA1c > 6.5% (48 mmol/mol) at time of admission. This included types 1 and 2 diabetes. Participants were included if their COVID-19 test was completed as an outpatient or inpatient and were subsequently grouped along those lines. Participants were considered in the inpatient group if their test was performed during an inpatient admission or they were admitted for COVID-19 treatment following an outpatient test. They were excluded if their diabetes was documented as in remission.

Study Design and Data Collection

This study is a retrospective chart review completed with automatic and manual data extraction from the electronic health records of all patients identified earlier, including variables descriptive of glycemic control, outpatient treatment regimen prior to admission, comorbidities, demographic information, and clinical outcomes, specifically admission and mortality. The study was approved by the Institutional Review Board.

Primary Outcomes

The primary outcomes were twofold—admission to the hospital and mortality at any point following diagnosis of COVID-19.

Demographic and Clinical Characteristics

Age, sex, race, home address zip code, and insurance information were collected from every participant. Patients were characterized by self-reported demographic information for race. Given the overall demographics of the service area, individuals were grouped as Caucasian/White, African American/Black, or other. The other category included any individual who self-classified as something other than the 2 groups or chose not to report. Insurance status was grouped into Medicaid, Medicare, commercial insurance, and self-pay/uninsured.

Glycemic Control

Diabetes status was evaluated based on the HbA1c value collected within 1 year prior to the COVID-19 test. If multiple HbA1c values were available, the one closest to the time of admission was used.

Treatment Regimen

Outpatient hypoglycemic agents were collected and grouped as insulin only, insulin plus noninsulin hypoglycemic agent(s), noninsulin hypoglycemic agent(s) only, and no medication/lifestyle management alone. The DPP-4 group was noted separately to allow for analysis regarding DPP-4 mitigation of disease severity in SARS-CoV-2.

Comorbidities and Long-Term Diabetes Complications

Comorbidities were manually extracted from the chart, including coronary artery disease, hypertension, hyperlipidemia, chronic kidney disease (CKD), chronic obstructive pulmonary disease, and cerebral vascular accident. BMI was extracted as a discrete value. These comorbidities were included having been identified as risk factors from previous studies. In addition, diabetic complications including retinopathy, neuropathy, and nephropathy were collected and grouped based on the total number of developed complications.

Data Analysis

Data were analyzed using Statistical Product and Service Solutions (SPSS), version 25.0 (SPSS, Inc), and R software (4.0.2; R Foundation for Statistical Computing). Descriptive analysis was

Table 1
Demographics and Clinical Characteristics of Inpatients and Outpatients With Diabetes Mellitus Who Had SARS-CoV-2 Infection/COVID-19

Clinical characteristics	All N = 832	Inpatients N = 631	Outpatients N = 201	*P* value
Age (years)	62 ± 15	64 ± 14	57 ± 14	<.001
Missing (%)	0.5	0.5	0.5	
Sex (n, %)				.578
Female	408 (49.0)	306 (48.5)	102 (50.7)	
Male	424 (51.0)	325 (51.5)	99 (49.3)	
Race (n, %)				
White	272 (32.7)	211 (33.7)	61 (30.3)	.881
Black or African American	433 (52.0)	323 (51.5)	110 (54.7)	
Asian	12 (1.4)	10 (1.6)	2 (1.0)	
Other[a]	107 (12.9)	80 (12.8)	27 (13.4)	
Declined to answer	4 (0.5)	3 (0.5)	1 (0.5)	
Missing (%)	0.5	0.6	0	
Zip code region (n, %)				.044
Baltimore City	204 (24.5)	144 (22.8)	60 (29.9)	
Others	628 (75.5)	487 (77.2)	141 (70.1)	
Health insurance type (n, %)				<.001
Medicare/government/military	360 (43.3)	307 (48.7)	53 (26.4)	
Medicaid/MA MCO	116 (13.9)	79 (12.5)	37 (18.4)	
Commercial	243 (29.2)	145 (23.0)	98 (48.8)	
Self-pay	85 (10.2)	72 (11.4)	13 (6.5)	
Others	28 (3.4)	28 (4.4)	0 (0)	
Number of diabetic complications (n, %)				.573
0	617 (75.0)	474 (75.7)	143 (72.6)	
1	187 (22.7)	139 (22.2)	48 (24.4)	
≥2	19 (2.3)	13 (2.1)	6 (3.0)	
Missing (%)	1.1	0.8	2.0	
Body mass index (kg/m^2)	32.9 ± 8.6	32.7 ± 9.0	33.7 ± 7.1	.153
Missing (%)	4.4	2.4	10.9	
HbA1c at COVID-19 diagnosis (%)	7.9 ± 2.3	8.1 ± 2.4	7.4 ± 1.9	.001
Missing (%)	19.6	18.2	23.9	
Blood glucose from first BMP (mg/dL)	210 ± 147	212 ± 153	197 ± 95	.370
Missing (%)	14.7	0.3	59.7	
Highest blood glucose in the POC test (mg/dL)	-	281 ± 112	-	-
Missing (%)	-	4.6	-	
Presence of ketones (n, %)				<.001
No	627 (81.2)	490 (77.8)	105 (95.5)	
Yes	145 (18.8)	140 (22.2)	5 (4.5)	
Missing (%)	7.2	0.2	45.3	
Comorbidities (n, %)				
Coronary artery disease	186 (22.5)	147 (23.4)	39 (19.8)	.290
Missing (%)	0.8	0.5	2.0	
Hypertension	648 (78.4)	497 (79.0)	151 (76.3)	.412
Missing (%)	0.6	0.3	1.5	
Hyperlipidemia	512 (61.9)	401 (63.8)	111 (56.1)	.052
Missing (%)	0.6	0.3	1.5	
Cerebrovascular accident	128 (15.5)	104 (16.5)	24 (12.1)	.134
Missing (%)	0.6	0.3	1.5	
Chronic kidney disease	176 (21.3)	151 (24.0)	25 (12.6)	.001
Missing (%)	0.6	0.3	1.5	
Chronic obstructive pulmonary disease	115 (13.9)	97 (15.4)	18 (9.1)	.025
Missing (%)	0.6	0.3	1.5	
Use of antidiabetic medications (n, %)				<.001
No medications	237 (28.7)	183 (29.1)	54 (27.4)	
Noninsulin medications only	308 (37.3)	213 (33.9)	95 (48.2)	
Insulin only	143 (17.3)	124 (19.7)	19 (9.6)	
Insulin and noninsulin medications	138 (16.7)	109 (17.3)	29 (14.7)	
Missing (%)	0.7	0.3	2.0	
Use of DPP-4 inhibitors	76 (9.2)	56 (8.9)	20 (10.2)	.592
Missing (%)	0.6	0.2	2.0	
Clinical outcome (n, %)				<.001
Alive	644 (81.0)	486 (77.3)	158 (95.2)	
Deceased	151 (19.0)	143 (22.7)	8 (4.8)	
Missing status (%)	4.4	0.3	17.4	

Abbreviations: BMP = basic metabolic panel; CoV = coronavirus; COVID-19 = coronavirus disease 2019; DPP-4 = dipeptidyl peptidase 4; HbA1c = hemoglobin A1c; MA MCO = Maryland Managed Care Organization; POC = point-of-care; SARS = severe acute respiratory syndrome.
Continuous variables are expressed as mean ± standard deviation. Qualitative and quantitative differences between groups were analyzed using the χ^2 or Fisher exact tests for categorical parameters and *t* test for continuous parameters, as appropriate.
[a] Other races included American Indian, Mixed, Alaskan, and non-Black Hispanic.

performed on all categorical and continuous variables. This included comparisons between the inpatient and outpatient cohorts. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as number (percentage). Qualitative and quantitative differences between groups were analyzed using the X^2 test or Fisher exact test for categorical parameters and *t* test for continuous parameters, as appropriate. Odds ratios (ORs) and adjusted ORs with 95% CI of

Table 2
Univariate and Multivariable Analyses by Logistic Regression on Factors Associated With Hospital Admission in Patients With Diabetes Mellitus Who Had SARS-CoV-2 Infection/COVID-19

Parameters	Univariate analysis		Multivariable analysis[a]	
	OR (95% CI)	*P* value	aOR (95% CI)	*P* value
Age (per year)	1.04 (1.02-1.05)	<.001	1.02 (1.00-1.04)	.018
Sex		.578		
Female	Referent			
Male	1.09 (0.80-1.50)			
Race				
White	Referent			
Black or African American	0.85 (0.59-1.21)	.369		
Asian	1.45 (0.31-6.77)	.640		
Other or declined to answer[b]	0.86 (0.51-1.43)	.557		
Zip code region		.044		
Baltimore City	Referent			
Others	1.44 (1.01-2.05)			
Health insurance				
Medicare/government/military	Referent		Referent	
Medicaid/MA MCO	0.37 (0.23-0.60)	<.001	0.58 (0.30-1.13)	.109
Commercial	0.26 (0.17-0.38)	<.001	0.41 (0.24-0.71)	.001
Self-pay or others	1.33 (0.70-2.54)	.390	2.90 (1.03-8.19)	.044
Number of diabetic complications				
0	Referent			
1	0.87 (0.60-1.28)	.483		
≥2	0.65 (0.24-1.75)	.398		
Body mass index	0.99 (0.97-1.01)	.211		
HbA1c at COVID-19 diagnosis	1.14 (1.05-1.25)	.003	1.25 (1.12-1.39)	<.001
Use of antidiabetic medications				
No medications	Referent			
Noninsulin medications only	0.66 (0.45-0.98)	.037		
Insulin only	1.93 (1.09-3.41)	.024		
Insulin and noninsulin medications	1.11 (0.67-1.85)	.691		
Presence of coronary artery disease	1.24 (0.83-1.84)	.291		
Presence of hypertension	1.17 (0.80-1.71)	.413		
Presence of hyperlipidemia	1.38 (1.00-1.91)	.052		
Presence of cerebrovascular accident	1.44 (0.89-2.31)	.136		
Presence of chronic kidney disease	2.19 (1.38-3.45)	.001	2.32 (1.26-4.28)	.007
Presence of chronic obstructive pulmonary disease	1.82 (1.07-3.10)	.027		

Abbreviations: aOR = adjusted odds ratio; CI = confidence interval; CoV = coronavirus; COVID-19 = coronavirus disease 2019; DPP-4 = dipeptidyl peptidase 4; HbA1c = hemoglobin A1c; MA MCO = Maryland Managed Care Organization; SARS = severe acute respiratory syndrome.
In the multivariable model, backward stepwise selection was used to select significant variables.
[a] A total of 633 patients (139 outpatients and 494 inpatients) with complete data were included in the analysis. *P* value = .754 for the Hosmer-Lemeshow goodness-of-fit test, which did not indicate significant poor fit.
[b] Other races included American Indian, Mixed, Alaskan, and non-Black Hispanic.

factors on hospitalization and mortality were estimated by logistic regression. We adjusted for the following covariates: age, sex, race, zip code region, insurance status, number of diabetic complications, BMI, HbA1c, use of antidiabetic agents, use of DPP-4 inhibitors, and comorbidities; patients with missing data were excluded from the regression analysis. A backward stepwise selection was made to select significant covariates. The Hosmer-Lemeshow goodness-of-fit test was used to assess the goodness of fit of the logistic regression. All statistical tests were two-sided. Statistical significance was set at $P < .05$.

Results

Table 1 displays baseline data between the 2 groups. Initially, 793 inpatients and 906 outpatients were identified. After excluding those who did not have diabetes despite an ICD-10 code of diagnosis of diabetes and removing if duplicated or reallocating those initially categorized as outpatients who required admission, a total of 832 patients were included for final analysis—631 inpatients and 201 outpatients. This large discrepancy in outpatient sample size was due to approximately 700 of the outpatient group being identified as either a duplicate encounter or meeting inpatient data criteria.

The overall mortality rate was 19% for all patients with diabetes, higher in those requiring admission to the hospital than in those who were not admitted, 22.7% and 4.8%, respectively ($P < .001$). Most of the outpatient mortality was accounted for by elderly patients already in a long-term care facility and supported with hospice services. The average HbA1c value overall for the cohort was 7.9% (63 mmol/mol), higher for the group requiring inpatient admission, 8.1% (± 2.4) (65 mmol/mol) versus 7.4% (± 1.9) (57 mmol/mol) ($P = .001$).

Demographic data, including age, sex, race, insurance status, and zip code of residence, were compared to determine univariate differences between the inpatient and outpatient groups. The average age of all study participants was 62 years; however, the individuals requiring inpatient admission were older—average age, 64 versus 57 years in the outpatient cohort ($P < .001$). There was no difference in the primary outcome between groups based on sex or race. Health insurance status showed that those with Medicare were more likely to be admitted than those with other insurances or self-pay ($P < .001$). However, several factors were not significantly different between the 2 groups—including the BMI and blood glucose levels within 24 hours of a positive SARS-CoV-2 test.

In the surrogate markers of severity of diabetes aside from HbA1c, the number of diabetic complications was not significantly associated with increased admission rate or mortality. In addition, a

Table 3
Univariate and Multivariable Analyses by Logistic Regression on Factors Associated With Mortality in Patients With Diabetes Mellitus Who Had SARS-CoV-2 Infection/COVID-19

Parameters	Univariate analysis		Multivariable analysis[a]	
	OR (95% CI)	*P* value	aOR (95% CI)	*P* value
Hospital admission				
No	Referent		Referent	
Yes	5.81 (2.79-12.11)	<.001	3.32 (1.43-7.70)	.005
Age (per year)	1.07 (1.06-1.09)	<.001	1.09 (1.07-1.11)	<.001
Sex				
Female	Referent			
Male	1.27 (0.89-1.81)	.189		
Race				
White	Referent			
Black or African American	0.87 (0.59-1.28)	.464		
Asian	0.76 (0.16-3.57)	.727		
Other or declined to answer[b]	0.63 (0.34-1.18)	.150		
Zip code region				
Baltimore City	Referent			
Others	2.61 (1.57-4.36)	<.001		
Health insurance				
Medicare/government/military	Referent			
Medicaid/MA MCO	0.22 (0.11-0.46)	<.001		
Commercial	0.26 (0.16-0.44)	<.001		
Self-pay or others	0.73 (0.44-1.21)	.222		
Number of diabetic complications				
0	Referent			
1	1.03 (0.67-1.58)	.894		
≥2	1.57 (0.55-4.45)	.397		
Body mass index	1.00 (0.98-1.03)	.690	1.04 (1.01-1.07)	.003
HbA_{1c} at COVID-19 diagnosis	0.99 (0.91-1.08)	.765	1.12 (1.01-1.24)	.028
Use of antidiabetic medications				
No medications	Referent			
Noninsulin medications only	0.61 (0.39-0.96)	.033		
Insulin only	1.21 (0.74-1.98)	.445		
Insulin and noninsulin medications	0.63 (0.36-1.11)	.111		
Presence of coronary artery disease	1.40 (0.93-2.10)	.105		
Presence of hypertension	1.54 (0.96-2.48)	.073		
Presence of hyperlipidemia	1.11 (0.77-1.61)	.575	0.57 (0.35-0.92)	.022
Presence of cerebrovascular accident	1.37 (0.86-2.16)	.184		
Presence of chronic kidney disease	1.99 (1.34-2.95)	.001		
Presence of chronic obstructive pulmonary disease	1.48 (0.92-2.38)	.106		

Abbreviations: aOR = adjusted odds ratio; CI = confidence interval; CoV = coronavirus; COVID-19 = coronavirus disease 2019; DPP-4 = dipeptidyl peptidase-4; HbA1c = hemoglobin A1c; MA MCO = Maryland Managed Care Organization; SARS = severe acute respiratory syndrome.
In the multivariable model, backward stepwise selection was used to select significant variables.
[a] A total of 618 patients (125 outpatients and 493 inpatients) with complete data were included in the analysis. *P* value = .426 for the Hosmer-Lemeshow goodness-of-fit test, which did not indicate significant poor fit.
[b] Other races included American Indian, Mixed, Alaskan, and non-Black Hispanic.

higher BMI number, although shown in other studies to increase the risk of mortality, was not significantly higher in patients requiring inpatient care. Of the comorbidities common to patients with diabetes—coronary artery disease, hypertension, hyperlipidemia, CKD, and cerebral vascular accident—only the CKD rate was higher in those requiring admission (151) than in outpatients (25) ($P = .001$).

Multivariate analyses were conducted examining the impact of these variables on admission (Table 2) and mortality (Table 3). The factors associated with increased admission included older age (OR, 1.04 [95% CI, 1.01-1.06]; $P = .003$), the presence of CKD (OR, 2.32 [1.26-4.28]; $P = .007$), and a higher HbA1c value at the time of admission (OR, 1.25 [1.12-1.39]; $P < .001$). Conversely, the only factor with a decreased risk of admission was having commercial insurance (OR, 0.41 [0.24-0.71]; $P = .001$). No particular diabetes regimen was associated with higher odds of requiring admission. In addition, race was not a significant factor among patients with diabetes in terms of predicting admission to the hospital. The factors associated with increased mortality included hospitalization (OR, 3.32 [1.43-7.70]; $P = .005$), older age (OR, 1.09 [1.07-1.11]; $P < .001$), a higher BMI number (OR, 1.04 [1.01-1.07]; $P = .003$), and a higher HbA1c value at the time of diagnosis (OR, 1.12 [1.01-1.24]; $P = .028$). One factor associated with decreased mortality was a diagnosis of hyperlipidemia (OR, 0.57 [0.35-0.92]; $P = .022$). When a subanalysis was performed investigating the presence of ketones at the time of diagnosis (Table 4) (thus excluding 45% of the outpatients who did not have this checked), additional factors of a higher BMI and the presence of ketones were predictive of the need for admission, while male sex became predictive of increased mortality. Data from ketone subanalysis are shown in Table 5.

A subgroup analysis was performed for patients with poorly controlled diabetes, defined by an HbA1c > 9% (Table 6). A univariate analysis by logistic regression on factors associated with hospital admission and mortality in patients with poorly controlled diabetes mellitus (HbA1c > 9%) who had SARS-CoV-2 infection/COVID-19 was performed. The analysis of hospitalization included 163 patients (26 outpatients and 137 inpatients). The analysis of mortality included 159 patients (129 recovered and 30 deceased); 4 patients with missing death status were excluded from the analysis of mortality. There were no different risk factors for increased mortality than those in the general diabetes population—both older age and CKD remained significantly associated with increased mortality from COVID-19. In addition, the same protective factors in the poorly controlled subgroup were associated with lower

Table 4
Univariate and Multivariable Analyses by Logistic Regression on Factors Associated With Hospital Admission and Mortality in Patients With Diabetes Mellitus Who Had SARS-CoV-2 Infection/COVID-19 and Who Had Available Measurement of Ketones

Hospital admission				
Parameters	Univariate analysis		Multivariable analysis[a]	
	OR (95% CI)	*P* value	aOR (95% CI)	*P* value
Age (per year)	1.04 (1.02-1.05)	<.001	1.04 (1.01-1.06)	.003
Health insurance				
Medicare/government/military	Referent		Referent	
Medicaid/MA MCO	0.37 (0.23-0.60)	<.001	0.65 (0.29-1.47)	.303
Commercial	0.26 (0.17-0.38)	<.001	0.58 (0.29-1.16)	.124
Self-pay or others	1.33 (0.70-2.54)	.390	4.65 (1.22-17.81)	.025
Body mass index	0.99 (0.97-1.01)	.211	1.04 (1.00-1.07)	.029
Presence of ketones	6.00 (2.40-15.01)	<.001	5.55 (2.12-14.52)	<.001
Presence of chronic kidney disease	2.19 (1.38-3.45)	.001	2.40 (1.08-5.34)	.032
Mortality				
Parameters	Univariate analysis		Multivariable analysis[b]	
	OR (95% CI)	*P* value	aOR (95% CI)	*P* value
Hospital admission				
No	Referent		Referent	
Yes	5.81 (2.79-12.11)	<.001	3.25 (1.06-9.99)	.039
Age (per year)	1.07 (1.06-1.09)	<.001	1.10 (1.07-1.12)	<.001
Sex				
Female	Referent		Referent	
Male	1.27 (0.89-1.81)	.189	1.78 (1.09-2.90)	.021
Body mass index	1.00 (0.98-1.03)	.690	1.05 (1.02-1.08)	<.001
HbA1c at COVID-19 diagnosis	0.99 (0.91-1.08)	.765	1.14 (1.03-1.26)	.015
Presence of hyperlipidemia	1.11 (0.77-1.61)	.575	0.56 (0.34-0.91)	.020

Abbreviations: aOR = adjusted odds ratio; CI = confidence interval; CoV = coronavirus; COVID-19 = coronavirus disease 2019; DPP-4 = dipeptidyl peptidase 4; HbA1c = hemoglobin A1c; MA MCO = Maryland Managed Care Organization; SARS = severe acute respiratory syndrome.
In the multivariable model, backward stepwise selection was used to select significant variables. Significant factors after backward stepwise selection are presented in Table 4.
[a] A total of 569 patients (76 outpatients and 493 inpatients) with complete data were included in the analysis. *P* value = .401 for the Hosmer-Lemeshow goodness-of-fit test, which did not indicate significant poor fit.
[b] A total of 560 patients (68 outpatients and 492 inpatients) with complete data were included in the analysis. *P* value = .487 for the Hosmer-Lemeshow goodness-of-fit test, which did not indicate significant poor fit.

mortality—commercial insurance and Medicaid. There were no additional aggravating or mitigating factors identified by this subgroup analysis.

Regarding patients taking DPP-4 inhibitors, 76 of 832 patients were taking DPP-4 inhibitors at the time of admission. Of these, 56 required admission to the hospital, and 20 remained outpatients. As shown in Table 4, this finding was not statistically significant ($P = .592$). DPP-4 inhibitor use was also not associated with decreased (or increased) mortality (OR, 1.22 [0.68-2.19]; $P = .504$).

Discussion

Diabetes has been shown to increase the risk of severe COVID-19. However, the predictors of hospital admission in patients with diabetes are not well described. This study aimed to characterize which individuals with diabetes were more likely to experience severe disease. Using hospital admission as a surrogate for severe disease from SARS-CoV-2, as these individuals needed some degree of inpatient support that could not be provided in the nonacute

Table 5
Use of DPP-4 Inhibitors in Inpatients and Outpatients With Diabetes Mellitus Who Had SARS-CoV-2 Infection/COVID-19 and Its Impact on Hospital Admission and Mortality

Hospital admission					
Parameter	N	Univariate analysis		Multivariable analysis	
		OR (95% CI)	*P* value	aOR (95% CI)	*P* value
Use of DPP-4 inhibitors	Inpatient: 56/631 (8.9) Outpatient: 20/201 (10.2)	0.86 (0.50-1.48)	.592	0.80 (0.39-1.63)	.535
Mortality					
Parameter	N	Univariate analysis		Multivariable analysis	
		OR (95% CI)	*P* value	aOR (95% CI)	*P* value
Use of DPP-4 inhibitors	Inpatient: 56/631 (8.9) Outpatient: 20/201 (10.2)	1.22 (0.68-2.19)	.504	1.61 (0.79-3.27)	.191

Abbreviations: aOR = adjusted odds ratio; CI = confidence interval; CoV = coronavirus; COVID-19 = coronavirus disease 2019; DPP-4 = dipeptidyl peptidase 4; SARS = severe acute respiratory syndrome.
In the multivariable model, backward stepwise selection was used to select significant variables.
For hospital admission, all parameters presented in Table 2 were included initially for backward stepwise selection. The use of DPP-4 inhibitors was forced into the multivariable model. *P* value = .497 for the Hosmer-Lemeshow goodness-of-fit test, which did not indicate significant poor fit.
For mortality, all parameters presented in Table 3 were included initially for backward stepwise selection. The use of DPP-4 inhibitor was forced into the multivariable model. *P* value = .550 for the Hosmer-Lemeshow goodness-of-fit test, which did not indicate significant poor fit.

Table 6
Univariate Analysis by Logistic Regression on Factors Associated With Hospital Admission and Mortality in Patients With Poorly Controlled Diabetes Mellitus (HbA1c > 9%) Who Had SARS-CoV-2 Infection/COVID-19 (N = 163)

Parameters	Univariate analysis[a]	
	OR (95% CI)	*P* value
Age (per year)	1.02 (0.99-1.05)	.322
Sex		
Female	Referent	
Male	0.86 (0.37-2.01)	.730
Race		
White	Referent	
Black or African American	1.46 (0.53-4.01)	.459
Other or declined to answer[b]	1.61 (0.46-5.66)	.460
Zip code region		
Baltimore City	Referent	
Others	2.51 (1.05-6.01)	.039
Health insurance		
Medicare/government/military	Referent	
Medicaid/MA MCO	2.33 (0.45-12.20)	.315
Commercial	0.51 (0.19-1.38)	.183
Self-pay or others	3.69 (0.72-18.97)	.117
Presence of diabetic complications	0.65 (0.27-1.59)	.342
Body mass index	1.00 (0.95-1.05)	.840
HbA_{1c} at COVID-19 diagnosis	1.20 (0.91-1.59)	.197
Use of antidiabetic medications		
No medications	Referent	
Noninsulin medications only	0.80 (0.23-2.84)	.730
Insulin only	1.46 (0.29-7.24)	.647
Insulin and noninsulin medications	0.95 (0.26-3.42)	.937
Presence of coronary artery disease	0.44 (0.14-1.36)	.155
Presence of hypertension	1.30 (0.52-3.24)	.580
Presence of hyperlipidemia	0.91 (0.39-2.13)	.835
Presence of cerebrovascular accident	0.84 (0.17-4.15)	.834
Presence of chronic kidney disease	4.78 (0.62-37.15)	.135
Presence of chronic obstructive pulmonary disease	1.35 (0.16-11.43)	.785

Parameters	Univariate analysis[c]	
	OR (95% CI)	*P* value
Hospital admission		
No	Referent	
Yes	2.57 (0.57-11.65)	.221
Age (per year)	1.06 (1.03-1.10)	<.001
Sex		
Female	Referent	
Male	1.35 (0.60-3.02)	.472
Race		
White	Referent	
Black or African American	0.44 (0.17-1.17)	.100
Other or declined to answer[b]	0.79 (0.26-2.37)	.675
Zip code region		
Baltimore City	Referent	
Others	1.94 (0.69-5.45)	.211
Health insurance		
Medicare/government/military	Referent	
Medicaid/MA MCO	0.18 (0.04-0.88)	.034
Commercial	0.28 (0.10-0.82)	.021
Self-pay or others	0.63 (0.23-1.69)	.353
Presence of diabetic complications	0.62 (0.24-1.64)	.338
Body mass index	1.01 (0.97-1.06)	.668
HbA1c at COVID-19 diagnosis	1.07 (0.85-1.35)	.544
Use of antidiabetic medications		
No medications	Referent	
Noninsulin medications only	0.65 (0.21-1.96)	.440
Insulin only	0.65 (0.18-2.38)	.512
Insulin and noninsulin medications	0.46 (0.15-1.45)	.187
Presence of coronary artery disease	0.84 (0.23-3.13)	.800
Presence of hypertension	1.55 (0.58-4.10)	.379
Presence of hyperlipidemia	1.50 (0.66-3.41)	.330
Presence of cerebrovascular accident	0.95 (0.19-4.65)	.952
Presence of chronic kidney disease	2.99 (1.12-7.97)	.029
Presence of chronic obstructive pulmonary disease	2.76 (0.62-12.23)	.183

Abbreviations: CI = confidence interval; COVID-19 = coronavirus disease 2019; HbA1c = hemoglobin A1c; MA MCO = Maryland Managed Care Organization; OR = odds ratio; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[a] A total of 163 patients (26 outpatients and 137 inpatients) were included in the analysis.

[b] Other races included Asian, American Indian, Mixed, Alaskan, and non-Black Hispanic.

[c] A total of 159 patients (129 recovered and 30 deceased) were included in the analysis; 4 patients with missing death status were not included in the analysis.

setting, multiple factors emerged as predictive of severe disease. Older age, an increased HbA1c value at the time of diagnosis with COVID-19, and the comorbid condition of CKD were associated with the need for increased admission and, thus, more severe disease. A higher BMI, while not necessarily associated with increased admission, was associated with worse outcomes/increased mortality. This has been a finding in multiple previous studies.[5-7] Overall mortality in our study was 19%, higher in patients who were hospitalized than in those who were not (22.7% vs 4.8%). However, the overall mortality rate for this patient cohort was lower than what was reported in other studies, as high as 33%.[7] Commercial insurance status was associated with lower admission rates, which is unclear if there is a confounding variable such as age or if this is indicative of a socioeconomic difference associated with disease severity.

While COVID-19 has been shown to disproportionately affect minority and economically disadvantaged groups, our study did not show race as a significant factor for predicting hospitalization or mortality in patients with diabetes. The overall racial makeup of the state was 58.5% White, 31.1% African American, 6.7% Asian, and 3.7% other,[11] which is a proportionately different makeup relative to the makeup of the study, which has a majority of African Americans (51.5%). Although this finding shows an increased disease burden in African Americans, it was not linked with an increase in severe disease requiring admission to the hospital or mortality. This is similar to the findings by Ogedegbe et al,[12] indicating that social and structural factors other than race account for the increase in disease burden and mortality rate of COVID-19 shown in other studies.

Our data did not show any significant association between the outpatient use of DPP-4 inhibitors and the patient outcomes from SARS-CoV-2 infection. It should be noted that in the study conducted by Solerte et al,[8] participants initiated sitagliptin at the time of admission. Data from this study distinguish patients who were previously receiving these medications to discern a possible protective effect. This remains an area for possible ongoing research, as no other study has yet to replicate these results.

An unexpected outcome from this study was the negative association between hyperlipidemia and mortality of SARS-CoV-2. Prior studies have revealed worse mortality related to cardiovascular diseases. The lower mortality seen in our study may indicate the potential benefit of statin therapy in mitigating the severity of disease. Previous studies have also shown the benefit of statin therapy[13-15] and postulated that this may be related to the anti-inflammatory effects[14] or potential direct effect of lipid-lowering therapies on SARS-CoV-2 itself. One study found a similar impact

of fenofibrate therapies via reduced binding of the viral protein.[16] Unfortunately, our data did not include information regarding the patients' use of statin or other lipid-lowering medications, but this is a key area for further research regarding antilipid therapies and reduction of morbidity and mortality with SARS-CoV-2.

This study has several limitations. First, early in the pandemic during the time of this data collection, most testing was limited to the inpatient setting alone given the scarcity of testing materials. This may have skewed the population of patients who received outpatient tests from being representative of all patients with diabetes. There was little random sampling or asymptomatic testing during this period aside from tests performed as outpatient procedures resumed.

Another limitation is the large number of missing outcomes and ketone data in the outpatient cohort. In total, 17.4% of the data regarding outpatient population outcome (alive vs deceased) was missing. The analysis was completed without that portion of the cohort and, consequently, may be missing a higher number of patients who experienced mortality or required admission outside of the studied health system and, thus, were not captured. In addition, intensive care unit and hospital admission criteria vary from hospital to hospital and even provider to provider, and there were multiple institutions included in this study. The evaluation of these criteria and intensive care unit interventions is beyond the scope of this study, and grouping them together models real-world variability across institutions for evaluation of individuals with diabetes. Differences may exist between individuals with type 1 versus type 2 diabetes and is a future area for research.

Conclusion

Predictors of hospitalization for patients with SARS-CoV-2 infection remain poorly described. Our study demonstrates that older age, increased HbA1c value at time of diagnosis with COVID-19, and CKD were associated with an increased rate of hospital admission. A higher BMI, while not associated with increased admission, was associated with increased mortality. Treatment with DPP-4 inhibitors prior to hospitalization did not reduce the risk of more severe disease or mortality.

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Author Contributions

M.K. conducted data collection and wrote the manuscript; Y.K. was a contributing author to the manuscript and data collection; M.M. assisted with data collection and editing of the manuscript; T.N. assisted with data collection; and R.M. and K.M. assisted with project management and reviewed/edited the manuscript.

Disclosure

The authors have no multiplicity of interest to disclose.

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