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Preadmission predictors of severe COVID-19 in patients with diabetes mellitus

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ABSTRACT

Objective: To explore predictors of severe COVID-19 disease in patients with diabetes hospitalized for COVID-19.
Methods: This is a retrospective observational study of adults with diabetes admitted for COVID-19. Bivariate tests and multivariable Cox regression were used to identify risk factors for severe COVID-19, defined as a composite endpoint of intensive care unit admission/intubation or in-hospital death.
Results: In 1134 patients with diabetes admitted for COVID-19, more severe disease was associated with older age (HR 1.02, $p < 0.001$), male sex (HR 1.28, $p = 0.017$), Asian race (HR 1.34, $p = 0.029$ [reference: white]), and greater obesity (moderate obesity HR 1.59, $p = 0.015$; severe obesity HR 2.07, $p = 0.002$ [reference: normal body mass index]). Outpatient diabetes medications were not associated with outcomes.
Conclusions: Age, male sex, Asian race, and obesity were associated with increased risk of severe COVID-19 disease in adults with type 2 diabetes hospitalized for COVID-19.
Summary: In patients with type 2 diabetes hospitalized for COVID-19 disease, we observed that age, male sex, Asian race, and obesity predicted severe COVID-19 outcomes of intensive care unit admission, intubation, or in-hospital death. The risk conferred by obesity increased with worsening obesity. Outpatient diabetes medications were not observed to be significant predictors of study outcomes.

1. Introduction

Diabetes has been identified as an independent risk factor for COVID-19 severity in multiple studies; however, data regarding predictors of poor clinical outcome among patients with diabetes are mixed.[1–3] Initial findings from Wuhan suggested age and pre-admission insulin therapy were associated with increased risk of mortality or poor prognosis.[1] The multicenter CORONADO study of admitted patients with diabetes and COVID-19 found that only body mass index (BMI) was associated with the composite outcome of tracheal intubation for mechanical ventilation and/or death within 7 days of admission. Age, treated obstructive sleep apnea, and microvascular and macrovascular complications of diabetes were found to be predictors of 7-day mortality, while outpatient insulin usage was not.[2] A recent analysis of pre-admission diabetes-specific risk factors in a predominantly Black population showed that obesity and outpatient insulin treatment predicted mortality.[3]

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2. Methods

2.1. Study design

To further clarify risk factors associated with COVID-19 severity in patients with diabetes, we conducted a retrospective cohort study in a large, racially diverse population of adults (≥18 years) with diabetes who were admitted to NewYork-Presbyterian (NYP) Weill Cornell Medical Center, NYP Queens Hospital, or NYP Lower Manhattan Hospital in New York City between March 1 and May 13, 2020. The primary outcome was a composite of equally weighted events for intensive care unit admission, invasive mechanical ventilation, or in-hospital mortality, which has been investigated as a clinically relevant statistical endpoint in prior studies.[4,5] Clinical courses were followed for all patients admitted during the study period until the occurrence of an event, discharge or until date last observed.

Data on demographics, medical history, and outpatient diabetes medications were queried and abstracted from electronic health records and manually verified. All inpatients with COVID-19 confirmed by reverse transcriptase-polymerase chain reaction were eligible for inclusion. Diabetes status was defined by documentation of type 1 or type 2 diabetes or by hemoglobin A1c (HbA1c) ≥ 6.5% within 90 days prior to or 10 days following the date of admission. BMI categories were defined according to the World Health Organization, including race-specific thresholds for Asian populations: (BMI [kg/m^2], overweight: 23.0–27.4; mild obesity: 27.5–32.4; moderate obesity: 32.5–37.4; severe obesity: ≥37.5).[6]

2.2. Statistical analysis

Bivariate tests (i.e., Wilcoxon rank-sum, chi-square and Fisher's exact) were used to explore associations between clinical and demographic variables and COVID-19 outcomes. Multivariable Cox regression adjusting for covariates selected by bivariate testing or clinical relevancy (i.e., age, sex, race, body mass index, coronary artery disease, congestive heart failure, cerebrovascular accident, hypertension, pulmonary disease, chronic kidney disease, smoking, and individualized outpatient diabetes medications) was used to assess independent risk factors for the composite outcome and mortality, separately. All analyses were based on non-missing data. The study was approved by the Institutional Review Board.

3. Results

A total of 1134 patients with diabetes were included in the analyses. Median age was 69 years (interquartile range [IQR] 60, 79) and 59% were male. Nearly all patients (96%) had documented type 2 diabetes. The race distribution was 26% white, 23% Asian, 16% Black and 35%

Table 1
Factors associated with composite outcome in bivariate and multivariable analyses.

Characteristic	Bivariate analysis					Multivariable analysis		
	Total N	Overall[a]	Composite outcome Yes, N = 476[a]	Composite outcome No, N = 658[a]	p-Value	HR	95% CI	p-Value
Age (years)	1134	69 (60, 79)	70 (62, 80)	67 (58, 76)	**<0.001**	1.02	1.01, 1.02	**<0.001**
Sex	1134				0.3			
Female		464 (41%)	186 (39%)	278 (42%)		–	–	–
Male		670 (59%)	290 (61%)	380 (58%)		1.28	1.04, 1.57	**0.017**
Race	1075				**0.008**			
White		281 (26%)	116 (25%)	165 (27%)		–	–	–
Asian		248 (23%)	128 (28%)	120 (19%)		1.34	1.03, 1.74	**0.029**
Black		175 (16%)	68 (15%)	107 (17%)		1.06	0.77, 1.44	0.7
Other		371 (35%)	143 (31%)	228 (37%)		1.11	0.85, 1.44	0.4
BMI (kg/m^2)	1134	28 (24, 32)	27 (24, 32)	28 (24, 32)	0.4			
BMI categories	1134				0.084			
Underweight		39 (3.4%)	24 (5.0%)	15 (2.3%)		1.65	1.05, 2.60	**0.031**
Normal		280 (25%)	113 (24%)	167 (25%)		–	–	–
Overweight		385 (34%)	163 (34%)	222 (34%)		1.14	0.88, 1.46	0.3
Obesity		430 (38%)	176 (37%)	254 (39%)		1.36	1.05, 1.76	**0.020**
Mild		252 (22.2%)	101 (21%)	151 (22.9%)		1.22	0.92, 1.62	0.2
Moderate		110 (9.7%)	46 (9.7%)	64 (9.7%)		1.59	1.09, 2.32	**0.015**
Severe		68 (6%)	29 (6.1%)	39 (5.9%)		2.07	1.29, 3.30	**0.002**
CAD	1134	291 (26%)	141 (30%)	150 (23%)	**0.011**	1.17	0.94, 1.46	0.15
CHF	1134	127 (11%)	61 (13%)	66 (10%)	0.2	1.07	0.79, 1.45	0.6
CVA	1134	123 (11%)	57 (12%)	66 (10%)	0.3	1.04	0.77, 1.40	0.8
HTN	1134	930 (82%)	393 (83%)	537 (82%)	0.7	0.87	0.68, 1.13	0.3
Pulmonary	1134	224 (20%)	88 (18%)	136 (21%)	0.4	1.01	0.79, 1.30	>0.9
CKD	1134	206 (18%)	94 (20%)	112 (17%)	0.3	0.95	0.73, 1.23	0.7
Smoking	1133	272 (24%)	118 (25%)	154 (23%)	0.6	1.02	0.81, 1.27	0.9
Hemoglobin A1c (%)	689	7.60 (6.70, 9.30)	7.70 (6.80, 9.20)	7.60 (6.70, 9.40)	0.7	[b]	[b]	[b]
Metformin	1134	511 (45%)	194 (41%)	317 (48%)	**0.016**	0.92	0.74, 1.13	0.4
Sulfonylureas	1134	212 (19%)	84 (18%)	128 (19%)	0.5	0.97	0.75, 1.26	0.8
DPP-4 inhibitors	1134	248 (22%)	109 (23%)	139 (21%)	0.5	0.92	0.73, 1.16	0.5
GLP-1 analogs	1134	50 (4.4%)	14 (2.9%)	36 (5.5%)	0.057	0.69	0.39, 1.21	0.2
Insulin	1134	326 (29%)	132 (28%)	194 (29%)	0.6	0.99	0.79, 1.23	0.9
SGLT2 inhibitors	1134	70 (6.2%)	31 (6.5%)	39 (5.9%)	0.8	1.02	0.69,1.05	>0.9

Statistical tests performed: Wilcoxon rank-sum test; chi-square test of independence; Fisher's exact test.
Pulmonary disease comprised chronic obstructive pulmonary disease, asthma, interstitial lung disease, obstructive sleep apnea, pulmonary hypertension, cystic fibrosis, and pneumothorax.
BMI = body mass index, CAD = coronary artery disease, CHF = congestive heart failure, CI = Confidence Interval, CKD = chronic kidney disease, CVA = cerebrovascular disease, DPP = dipeptidyl peptidase-4, GLP-1 = glucagon-like peptide-1, HTN. = hypertension, HR = hazard ratio, Ref = reference category.
[a] Statistics presented: median (interquartile range); n (%).

[b] Covariate not included in multivariable analysis due to missing data and lack of signal in bivariate analysis.

other (patient-selected category). The median HbA1c (n = 689) was 7.6% (IQR 6.7, 9.3). The composite outcome occurred in 476 (42%) patients, and in-hospital mortality occurred in 339 (30%).

Multivariable Cox regression analysis showed that, age, male sex, Asian race, underweight and obesity were independently associated with greater risk of the composite outcome (Table 1). Age, male sex, and underweight were also associated with higher mortality.

In a separate multivariable model containing extended BMI classes, accounting for age, sex, race, comorbidities and outpatient diabetes medications, we observed a J-shaped curve for the risk of the composite outcome, with both lowest and highest BMI categories conferring greater risk compared to normal BMI and increasing risk with greater severity of overweight/obesity: underweight (HR 1.65; 95% CI 1.05, 2.60), overweight (HR 1.14; 0.88, 1.46), mild obesity (HR 1.22; 0.92, 1.62), moderate obesity (HR 1.59; 1.09, 2.32) and severe obesity (HR 2.07; 1.29, 3.30). In addition to age, male sex, and underweight, another independent risk factor for mortality was severe obesity (HR 1.76; 1.02, 3.03).

4. Discussion

To our knowledge, this study is the first to assess risk factors utilizing race-specific BMI cut-offs in a diverse U.S. cohort of patients with diabetes. Our study corroborated previous reports highlighting the increased risk of COVID-19 severity conferred by age, male sex, and obesity in patients with diabetes, but outpatient diabetes medications were not found to be independent predictors of increased COVID-19 severity. Metformin demonstrated a protective effect in unadjusted bivariate analysis that was not confirmed after adjustment for multiple covariates. The association of diabetes medications with COVID-19 severity has been inconsistent in the literature with some observing a reduced risk of mortality with outpatient metformin usage,[7–9] while others finding no effect.[4] One explanation for this difference in observations may be the dose of metformin,[7] which requires a level of granularity that is often absent in retrospective studies. Prospective studies are needed to better understand the effect of antihyperglycemic therapies and risk of severe COVID-19 disease.

Study limitations included incomplete data on glycemic outcomes and lack of information regarding diabetes duration, diabetes-related complications, and socioeconomic status. Additionally, certain covariates (e.g., ethnicity, Asian subgroups, dose or strength of diabetes medication) were not included in our multivariable model due to lack of granularity in the dataset, while other potential covariates (e.g., cirrhosis, hepatitis, human immunodeficiency virus, active cancer, transplant status, inflammatory bowel disease, rheumatologic disorder) were excluded due to the small proportion of individuals with these characteristics. Finally, given that our cohort predominantly had type 2 diabetes, our findings cannot be applied to populations with type 1 diabetes.

The strengths of our study included a racially diverse population with a significant Asian proportion, utilization of race-specific BMI thresholds for obesity classification, and delineation of a graded risk with increasing BMI above normal that was statistically significant for moderate and severe obesity. The increased risk of COVID-19 severity in Asian patients is not unexpected,[10–12] but the data are mixed.[13,14] The multicenter COVID-19 Cardiovascular Disease Registry reported increased risk of mortality with Asian race.[12] In contrast, individual centers in New York found no increased risk,[13,14] a difference that might be attributable to the diversity of our patient population drawn from Manhattan and Queens. Furthermore, our data found that the increased risk associated with Asian race persisted in a diabetes-specific cohort. The inconsistent results reported among these studies may be attributable to the heterogeneity of the Asian population and should be elucidated with further research in Asian subgroups. Race is universally recognized as a social determinant of health, whether due to intrinsic pathophysiologic variations or external socioeconomic differences.

In this retrospective cohort study of patients with type 2 diabetes hospitalized for COVID-19 disease, the risk of severe COVID-19 disease was associated with older age, higher BMI, male sex, and Asian race but not with outpatient diabetes medications. Further exploration of specific patient populations will help improve risk stratification and inform personalized care.

CRediT authorship contribution statement

Alpana P. Shukla, M.D.: Conceptualization, Methodology, Supervision, Writing-Original draft, Writing-Review & editing
Beverly G. Tchang, M.D.: Visualization, Writing-Original draft, Writing-Review & editing
Tiffany Lam, B.A.: Data curation, Writing-Review & editing
Ian Steller, M.S.: Data curation, Writing-Review & editing
Samir Touhamy II, M.S.: Data curation, Writing-Review & editing
Gulce Askin, M.P.H.: Formal analysis, Methodology, Writing-Review & editing
Felicia A. Mendelsohn Curanaj, M.D.: Methodology, Writing-Review & editing
Jane J. Seley, D.N.P.: Methodology, Writing-Review & editing
Daniel Lorber, M.D.: Resources, Writing-Review & editing
Monika M. Safford, M.D.: Resources, Writing-Review & editing
Louis J. Aronne, M.D.: Methodology, Funding acquisition, Writing-Review & editing
Laura C. Alonso, M.D.: Conceptualization, Methodology, Writing-Review & editing.

Declaration of competing interest

LJA reports receiving consulting fees from and serving on advisory boards for Jamieson Laboratories, Pfizer, Novo Nordisk, Eisai, Erx Pharmaceuticals, Real Appeal, Janssen Pharmaceuticals, and Gelesis; receiving research funding from Aspire Bariatrics, Allurion, Eisai, AstraZeneca, Gelesis, Janssen Pharmaceuticals and Novo Nordisk; having equity interests in Intellihealth Corp, Allurion, Erx Pharmaceuticals, Zafgen, Gelesis, Myos Corp., and Jamieson Laboratories; and serving on a board of directors for Intellihealth Corp., Myos Corp. and Jamieson Laboratories. MMS reports receiving salary support for investigator-initiated research unrelated to the topic from Amgen, Inc. BGT serves as a consultant for Novo Nordisk. All other authors have nothing to disclose.

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