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Patients with prediabetes are at greater risk of developing diabetes 5 months postacute SARS-CoV-2 infection: a retrospective cohort study

Alexander Y. Xu [1], Stephen H. Wang [1,2], Tim Q. Duong [1]

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AYX and SHW contributed equally.

AYX and SHW are joint first authors.

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[1]Radiology, Albert Einstein College of Medicine, Bronx, New York, USA
[2]Department of Surgery, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts, USA

Correspondence to
Dr Tim Q. Duong;
tim.duong@einsteinmed.edu

ABSTRACT

Introduction Patients with prediabetes who contract SARS-CoV-2 infection (COVID-19) could be at higher risk of developing frank diabetes compared those who do not. This study aims to investigate the incidence of new-onset diabetes in patients with prediabetes after COVID-19 and if it differs from those not infected.

Research design and methods Using electronic medical record data, 42 877 patients with COVID-19, 3102 were identified as having a history of prediabetes in the Montefiore Health System, Bronx, New York. During the same time period, 34 786 individuals without COVID-19 with history of prediabetes were identified and 9306 were propensity matched as controls. SARS-CoV-2 infection status was determined by a real-time PCR test between March 11, 2020 and August 17, 2022. The primary outcomes were new-onset in-hospital diabetes mellitus (I-DM) and new-onset persistent diabetes mellitus (P-DM) at 5 months after SARS-CoV-2 infection.

Results Compared with hospitalized patients without COVID-19 with history of prediabetes, hospitalized patients with COVID-19 with history of prediabetes had a higher incidence of I-DM (21.9% vs 6.02%, p<0.001) and of P-DM 5 months postinfection (14.75% vs 7.51%, p<0.001). Non-hospitalized patients with and without COVID-19 with history of prediabetes had similar incidence of P-DM (4.15% and 4.1%, p>0.05). Critical illness (HR 4.6 (95% CI 3.5 to 6.1), p<0.005), in-hospital steroid treatment (HR 2.88 (95% CI 2.2 to 3.8), p<0.005), SARS-CoV-2 infection status (HR 1.8 (95% CI 1.4 to 2.3), p<0.005), and hemoglobin A1c (HbA1c) (HR 1.7 (95% CI 1.6 to 1.8), p<0.005) were significant predictors of I-DM. I-DM (HR 23.2 (95% CI 16.1 to 33.4), p<0.005), critical illness (HR 2.4 (95% CI 1.6 to 3.8), p<0.005), and HbA1c (HR 1.3 (95% CI 1.1 to 1.4), p<0.005) were significant predictors of P-DM at follow-up.

Conclusions SARS-CoV-2 infection confers a higher risk for developing persistent diabetes 5 months post-COVID-19 in patients with prediabetes who were hospitalized for COVID-19 compared with COVID-19-negative counterparts with prediabetes. In-hospital diabetes, critical illness, and elevated HbA1c are risk factors for developing persistent diabetes. Patients with prediabetes with severe COVID-19 disease may need more diligent monitoring for developing P-DM postacute SARS-CoV-2 infection.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Prediabetes is a known risk factor for severe COVID-19 and poor outcomes, and COVID-19 has been associated with newly diagnosed diabetes among previously healthy individuals.

⇒ It remains unknown if COVID-19 is associated with progression to frank diabetes among patients with prediabetes, and if the progression is persistent.

WHAT THIS STUDY ADDS

⇒ Critical illness, hemoglobin A1c (HbA1c), steroid therapy, and COVID-19 are associated with in-hospital diabetes mellitus in patients with prediabetes, and in-hospital diabetes mellitus, critical illness, and HbA1c are associated with development of persistent diabetes.

⇒ Nearly 15% of patients with prediabetes with COVID-19 had persistent diabetes at an average of 5-month follow-up.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Patients with prediabetes who experience severe COVID-19 should be closely monitored for resolution of stress hyperglycemia after COVID-19 and possible progression to persistent frank diabetes.

INTRODUCTION

Several commentaries, case reports, and a few cohort studies have drawn attention to the potential of new-onset type 2 diabetes (T2D) in COVID-19 survivors who had no history of diabetes or prediabetes.[1 2] SARS-CoV-2 viral particles could directly infect insulin-producing β-cells in the pancreas and subsequently impair insulin secretion.[3] Alternatively, systemic hypoxia, acute respiratory distress, pneumonia, shock, sepsis, inflammatory responses, cytokine storm, and metabolic distress due to SARS-CoV-2 infection could also cause insulin resistance and metabolic decompensation.[4–7]

It would not be surprising that individuals with prediabetes are more susceptible

of developing new-onset T2D after SARS-CoV-2 infection compared with the general population because they have underlying medical conditions and comorbidities, such as chronic inflammation, obesity, metabolic disorders, and hypertension, among others.[8] In addition, stress of hospitalization and COVID-19 treatments (eg, steroids) may confer additional risks of triggering new-onset T2D. It is unknown whether patients with COVID-19 with history of prediabetes are more susceptible to developing new-onset T2D compared with patients without COVID-19 with history of prediabetes. It is also unclear whether new-onset diabetes diagnosed during acute COVID-19 persists after resolution of the acute infection.

The goals of this study were to evaluate: (i) the incidence of new-onset diabetes among patients with COVID-19 with pre-existing prediabetes and whether the incidence of new-onset diabetes post-COVID-19 was higher than patients without COVID-19 with a history of prediabetes in the same catchment area and over the same duration, and (ii) whether new-onset diabetes was transient or persistent after acute COVID-19 disease has resolved. Predictive models were used to identify risk factors of new-onset diabetes among patients with prediabetes.

METHODS

Data sources

Health data came from the Montefiore Health System with 15 hospitals located in New York Metropolitan area. Electronic medical records (EMR) were extracted as described previously[9–12] using the Observational Medical Outcomes Partnership Common Data Model.

From March 11, 2020 to August 17, 2022, there were 42 877 patients with COVID-19, identified by PCR test. Using pre-COVID-19 pandemic data, we included only patients with prediabetes with a hemoglobin A1c (HbA1c) of 5.7%–6.5% prior to admission, two fasting glucose readings of 100–125 mg/dL, or a random glucose of 140–199 mg/dL prior to admission. We excluded patients with diabetes International Classification of Diseases 10th Revision (ICD-10) diagnosis codes, on diabetes medications regardless of diabetes diagnosis, with HbA1c ≥6.5% prior to admission, two fasting glucose readings >126 mg/dL, or two random glucose readings of ≥200 mg/dL prior to admission (these criteria were used to define diabetes mellitus (DM)). A control cohort was selected from patients without COVID-19 with history of prediabetes using propensity matching to generate a ratio of 1:3 exposed-unexposed. Controls were identified for each patient with COVID-19 matched by age, sex, and comorbidities using a caliper width of 0.25 SD. Standardized mean differences for age, sex, and comorbidities between COVID-19-positive and matched cohorts were <0.2 indicating adequate balance.

Clinical variables

Demographic data included age, sex, race, and ethnicity. Pre-existing comorbidities included body mass index (BMI), congestive heart failure (CHF), chronic kidney disease (CKD), hypertension (HTN), chronic obstructive pulmonary disease (COPD), and asthma that were designated by ICD-10 codes at admission or prior. Steroid treatment, hospitalization status, intensive care unit admission, and mortality were also extracted. Admission vital signs and laboratory data collected from hospitalized patients included HbA1c, blood glucose (BG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), troponin T (TnT), N-terminal pro-B-type natriuretic peptide (NT-proBNP), white blood cell count (WBC), blood urea nitrogen (BUN), creatinine (Cr), D-dimer (DDIM), ferritin (FER), lactate dehydrogenase (LDH), alanine aminotransferase (ALT), lymphocyte count (Lymph), prothrombin time (PT), platelet count (PLT), systolic blood pressure (SBP), temperature (TEMP), and C reactive protein (CRP).

Overall, patients in this study returned to the health system ~5 months after diagnosis on average. Data were collected at admission, and follow-up data were collected from any health system encounter, including hospitalizations and outpatient visits, at least 30 days after COVID-19 diagnosis.

Primary outcome

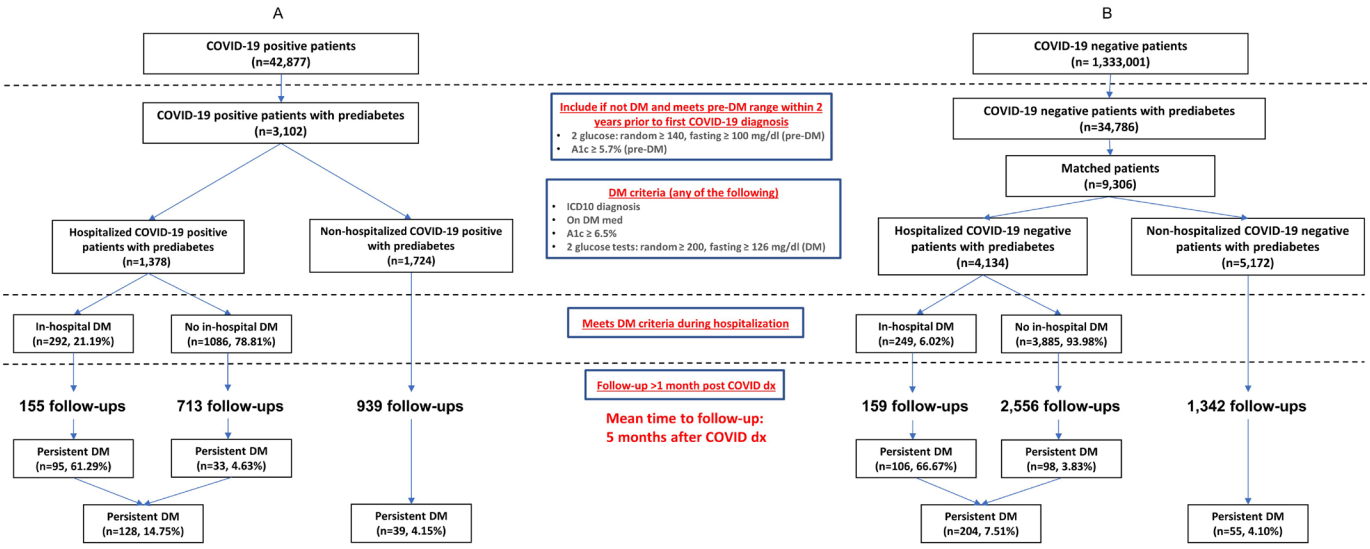
The primary outcomes were the incidence of new-onset in-hospital DM (I-DM) and new-onset persistent DM (P-DM) at follow-up. New-onset I-DM was defined using one of the following criteria: (1) HbA1c >6.5%, (2) any two fasting glucose measurements during hospitalization over 126 mg/dL, or (3) any two random glucose measurements during hospitalization >200 mg/dL. P-DM, or frank diabetes, at follow-up visit was defined by (1) initiation of an antihyperglycemic medication or (2) using one HbA1c or two glucose measurements over threshold obtained from 30 days post-COVID-19 positivity up to the follow-up visit. We also compared outcomes over time during the COVID-19 pandemic.

Predictive model

Multivariable Cox proportional hazard models (Python lifelines package) were run, with predictors of I-DM and P-DM expressed as adjusted HR and 95% CIs. For predicting I-DM, the covariates were age, sex, invasive mechanical ventilation (IMV), BMI, HbA1c, in-hospital steroid use, and SARS-CoV-2 infection status from both hospitalized patients with COVID-19 and without COVID-19. For predicting P-DM, the inputs were the same variables plus I-DM status. Univariate analysis was used to rank the top predictors of outcome by p value for incorporation into the final model.[11 13]

Statistical analysis

Statistical analysis was performed using Python SKlearn, Statsmodels, and SciPy packages. Group comparison



(C)	Hospitalized		Non-hospitalized	
	COVID+	COVID-	COVID+	COVID-
I-DM	21.19%***	6.02%	-	-
P-DM	14.75%***	7.51%	4.15%	4.10%

Figure 1 Patient selection flow chart for (A) patients with COVID-19 (COVID-19+) and (B) without COVID-19 (COVID-19–), and (C) summary of in-hospital diabetes mellitus (I-DM) and new-onset persistent diabetes mellitus (P-DM) of patients with COVID+ and COVID–. ***P<0.001 between COVID+ and COVID–.

for categorical variables used χ^2 or Fisher's exact tests, and for continuous variables used the Mann-Whitney U test. P<0.05 was considered statistically significant unless noted otherwise. Patients missing data for variables were excluded from those analyses.

Data and resource availability

De-identified datasets and analytic code used during the current study are available from the corresponding author on reasonable request.

RESULTS

Incidence of I-DM and P-DM among patients with and without COVID-19

Figure 1A shows the patient selection flow chart for COVID-positive cohort. Among the 42 877 patients with COVID-19, 3102 were identified as having a history of prediabetes. Among patients with prediabetes, 1378 (44.42%) were hospitalized and 1724 (45.58%) were not hospitalized for COVID-19. Of those who were hospitalized, 21.19% (n=292/1378) were diagnosed with I-DM. Of those with I-DM, 155 returned and 61.29% (n=95/155) were found to have P-DM. Of those without I-DM, 713 returned and an additional 4.53% (n=33/713) developed P-DM. Combining patients with and without I-DM, the average of P-DM at follow-up was 14.75% (n=128/868).

There were 1724 non-hospitalized patients with COVID-19 with history of prediabetes, of which 939 returned; 4.15% (n=39) had P-DM at follow-up, which was significantly lower than the hospitalized cohort (4.15% vs 14.75%, p<0.0001).

Figure 1B shows the patient selection flow chart for the COVID-19 cohort. Among the 34 786 patients without COVID-19 with history of prediabetes, 9306 were identified as propensity-matched controls. Of the controls, 4134 (44.42%) were hospitalized and 5172 (55.58%) were not hospitalized. Of those hospitalized. 249 (6.02%) had I-DM. Of those hospitalized and had I-DM, 159 returned and 66.67% (n=106/159) had P-DM. Of those hospitalized and without I-DM, 2556 returned and an additional 3.83% (n=98/2556) were diagnosed with P-DM. Combining patients with and without I-DM, the rate of P-DM at follow-up was 7.51% (n=204/2715). There were 5172 non-hospitalized patients without COVID-19 with history of prediabetes with 1342 follow-up visits where 4.10% (n=55/1342) had P-DM at follow-up, which was significantly lower than the hospitalized cohort (4.10% vs 7.51%, p<0.0001).

When comparing patients with and without COVID-19, hospitalized patients with COVID-19 had a significant higher incidence of I-DM (21.19% vs 6.02%, p<0.001) and P-DM (14.75% vs 7.51%, p<0.001) compared with patients without COVID-19, but non-hospitalized patients with COVID-19 had a similar incidence of P-DM (4.15% vs 4.10%, p>0.05) compared with patients without COVID-19 (figure 1C).

There were no significant differences in demographics, race, ethnicity, and major comorbidities (p>0.05) between patients who did or did not return for follow-up

Table 1 Baseline characteristics of (A) all patients with COVID-19 with history of prediabetes and matched cohort of patients without COVID-19, (B) hospitalized patients, and (C) hospitalized patients with follow-up

	Prediabetic		Hospitalized		Hospitalized at follow-up	
	COVID-19 (n=3102)	Non-COVID-19 (n=9306)	COVID-19 (n=1378)	Non-COVID-19 (n=4134)	COVID-19 (n=868)	Non-COVID-19 (n=2715)
Demographics, n (%)						
Age, mean years (±SD)	56.8 (18.8)	57.0 (18.1)	63.8 (18.9)	63.7 (17.9)	62.1 (18.8)***	64.9 (16.9)
Male	1142 (36.8%)	3436 (36.9%)	586 (42.5%)	1779 (43.0%)	362 (41.7%)	1144 (42.1%)
Hispanic	1292 (41.7%)***	3321 (35.7%)	581 (42.2%)**	1538 (37.2%)	370 (42.6%)*	1025 (37.8%)
White	265 (8.5%)	834 (9.0%)	155 (11.2%)	495 (12.0%)	95 (10.9%)	295 (10.9%)
Black	1132 (36.5%)	3324 (35.7%)	499 (36.2%)	1477 (35.7%)	318 (36.6%)	1001 (36.9%)
Asian	90 (2.9%)	272 (2.9%)	21 (1.5%)*	107 (2.6%)	14 (1.6%)	73 (2.7%)
Other	323 (10.4%)***	1555 (16.7%)	122 (8.9%)***	517 (12.5%)	71 (8.2%)**	321 (11.8%)
Comorbidities, n (%)						
BMI (kg/m^2)	29.19 (6.68)**	29.74 (6.04)	28.54 (6.68)*	29.12 (6.1)	27.41 (6.59)***	29.04 (6.6)
CHF	95 (3.1%)	231 (2.5%)	73 (5.3%)	201 (4.9%)	46 (5.3%)	179 (6.6%)
CKD	327 (10.5%)	957 (10.3%)	220 (16.0%)	655 (15.8%)	143 (16.5%)	505 (18.6%)
Hypertension	1418 (45.7%)	4155 (44.6%)	724 (52.5%)	2171 (52.5%)	459 (52.9%)	1517 (55.9%)
COPD/Asthma	634 (20.4%)	1946 (20.9%)	263 (19.1%)	794 (19.2%)	181 (20.9%)	589 (21.7%)
Lab values, mean (±SD)						
HbA1c (%)	5.7 (0.36)***	5.8 (0.26)	5.69 (0.43)**	5.76 (0.3)	5.68 (0.51)*	5.7 (0.36)
Glucose (mg/dL)	112.15 (26.27)***	101.27 (39.51)	115.89 (28.41)***	112.05 (32.28)	100.81 (21.48)	101.16 (20.76)
HDL (mg/dL)	48.85 (12.8)***	51.84 (12.54)	47.84 (13.86)***	50.31 (12.28)	46.45 (13.66)***	49.52 (12.36)
LDL (mg/dL)	102.53 (31.58)**	105.77 (31.75)	93.2 (31.06)***	102.28 (32.47)	95.84 (33.7)*	100.03 (31.91)
CRP (mg/dL)	6.08 (5.86)***	6.25 (11.78)	6.48 (6.01)***	7.34 (12.82)	4.31 (5.42)	3.18 (4.81)
FER (ng/mL)	714.62 (870.51)***	152.11 (219.37)	728.84 (885.21)***	208.53 (269.4)	330.69 (534.26)**	177.9 (265.52)
LDH (U/L)	322.21 (140.12)***	269.33 (139.39)	329.54 (143.94)**	277.19 (142.62)	322.07 (176.08)**	254.24 (85.03)
BNP (pg/mL)	411.8 (881.05)***	1178.87 (2877.01)	459.38 (921.3)***	1187.72 (2891.42)	374.12 (631.25)	454.76 (870.78)
Cr (mg/dL)	1.13 (0.65)***	0.99 (0.38)	1.2 (0.73)*	1.06 (0.44)	1.0 (0.52)	0.96 (0.32)
DDIM (µg/mL FEU)	1.61 (1.63)	50.1 (174.36)	1.67 (1.67)	50.1 (174.36)	1.91 (2.08)	10.0 (60.31)
ALT (U/L)	28.27 (19.43)***	26.45 (25.86)	29.3 (20.71)***	27.93 (30.46)	24.18 (18.59)	22.1 (12.74)
Lymph (k/µL)	1.34 (0.81)***	1.82 (0.84)	1.25 (0.75)***	1.69 (0.84)	1.81 (0.97)***	1.9 (0.82)
PLT (k/µL)	221.08 (71.97)***	243.15 (71.54)	214.09 (73.7)***	234.74 (72.53)	249.91 (73.81)*	244.57 (68.15)
PT (s)	14.19 (1.81)	14.27 (1.87)	14.37 (1.86)	14.29 (1.88)	14.54 (2.23)	14.49 (2.28)
WBC (k/µL)	7.05 (3.23)***	7.81 (3.4)	7.19 (3.25)***	8.39 (3.91)	7.18 (2.73)	7.16 (2.59)
TEMP (°F)	98.59 (0.79)***	98.16 (0.48)	98.59 (0.82)***	98.16 (0.5)	98.12 (0.48)	98.17 (0.54)
TnT (ng/mL)	0.048 (0.210)	0.042 (0.150)	0.057 (0.233)**	0.042 (0.151)	0.045 (0.148)	0.026 (0.046)

Continued

Table 1 Continued

	Prediabetic		Hospitalized		Hospitalized at follow-up	
	COVID-19 (n=3102)	Non-COVID-19 (n=9306)	COVID-19 (n=1378)	Non-COVID-19 (n=4134)	COVID-19 (n=868)	Non-COVID-19 (n=2715)
SBP (mm Hg)	130.54 (19.03)	130.42 (17.51)	129.83 (19.73)***	132.94 (19.43)	130.99 (19.75)	130.02 (18.22)
BUN (mg/dL)	18.63 (11.38)**	16.32 (7.25)	20.8 (13.06)***	17.66 (8.56)	16.76 (8.73)	15.52 (6.17)
Outcomes, n (%)						
IMV	161 (5.2%)***	85 (0.9%)	152 (11.0%)***	84 (2.0%)	54 (6.2%)***	45 (1.7%)
In-hospital death	158 (5.1%)***	62 (0.7%)	151 (11.0%)***	61 (1.5%)	–	–
In-hospital steroid usage	337 (10.9%)***	261 (2.8%)	289 (21.0%)***	234 (5.7%)	180 (20.7%)***	161 (5.9%)

*P<0.05, **p<0.01, ***p<0.001 between patients with and without COVID-19 within each group.
Laboratory data were obtained at hospitalization.
ALT, alanine aminotransferase; BMI, body mass index; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; Cr, creatinine; CRP, C-reactive protein; DDIM, D-dimer; FER, ferritin; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; Lymph, lymphocyte count; PLT, platelet count; PT, prothrombin time; SBP, systolic blood pressure; TEMP, temperature; TnT, troponin T; WBC, white blood cell.

visits (data not shown). The mean time to follow-up visit was 5 months (median 3.5 months).

Baseline characteristics of patient cohorts

Table 1 shows the baseline characteristics of the COVID-19-positive and matched COVID-19-negative cohorts (controls), hospitalized patients, and hospitalized patients with follow-up. Overall, the COVID-19 cohort had more Hispanic patients, patients of 'other' race, and lower BMI than controls (all p<0.01) (table 1A). There were significant differences in most lab values (HbA1c, initial glucose measurement, HDL, LDL, CRP, FER, LDH, BNP, Cr, ALT, Lymph, PLT, WBC, TEMP, and BUN, all p<0.01) between groups, and patients with COVID-19 had more IMV (5.2% vs 0.9%, p<0.001), in-hospital mortality (5.1% vs 0.7%, p<0.001), and in-hospital steroid use (10.9% vs 2.8%, p<0.001).

Among all hospitalized patients (table 1B), the COVID-19 cohort had more Hispanic patients, fewer patients of 'other' race, and a lower BMI (all p<0.05). Again, there were significant differences in most lab values, IMV (11.0% vs 2.0%, p<0.001), in-hospital mortality (11.0% vs 1.5%, p<0.001), and in-hospital steroid use (21.0% vs 5.7%, p<0.001) between COVID-19 and control groups.

Of all hospitalized patients with a follow-up visit (table 1C), patients with COVID-19 were older, more Hispanic, and less of 'other' race than controls (all p<0.05). Patients with COVID-19 had lower BMI, higher rates of IMV (6.2% vs 1.7%, p<0.001), and higher rates of in-hospital steroid use (20.7% vs 5.9%, p<0.001) than controls. HbA1c, HDL, LDL, and Lymph levels during hospitalization were lower, while FER, LDH, and PLT levels were higher, for patients with COVID-19 compared with controls (all p<0.05).

Features of patients with COVID-19 with and without I-DM

Table 2 shows characteristics of patients with COVID-19 with history of prediabetes with and without I-DM during hospitalization, hospitalized patients with and without P-DM at follow-up, and non-hospitalized patients with and without P-DM at follow-up.

During hospitalization, there were no significant differences in demographics and major comorbidities (except CKD) between with and without I-DM groups (p>0.05). Most lab values (HbA1c, glucose, HDL, CRP, FER, LDH, BNP, Cr, DD, ALT, Lymph, WBC, TnT, BUN) were significantly different between groups (p<0.05), but not LDL, PLT, or PT (p>0.05). IMV (34.9% vs 4.6%, p<0.001), steroid use (41.8% vs 19.7%, p<0.001), and mortality rate (29.1% vs 6.1%, p<0.001) were significantly higher in the I-DM group compared with those without I-DM.

At follow-up for the hospitalized cohorts, there were no significant differences in demographics and major comorbidities between with and without P-DM groups (p>0.05). Many lab values (HbA1c, glucose, HDL, CRP, FER, LDH, BNP, Cr, ALT, Lymph, WBC, TnT, BUN, PLT, and PT) were significantly different between groups

Table 2 Characteristics of patients with COVID-19 with history of prediabetes during (A) hospitalization, (B) hospitalized patients at follow-up, and (C) non-hospitalized patients at follow-up

	During hospitalization		At follow-up		Non-hospitalized at follow-up	
	I-DM (n=292, 21.19%)	Non-I-DM (n=1086)	P-DM (n=128, 14.75%)	Non-P-DM (n=740)	P-DM (n=39, 4.15%)	Non-P-DM (n=900)
Demographics, n (%)						
Age, mean years (±SD)	66.0 (16.8)	63.1 (19.4)	61.7 (18.1)	62.2 (18.8)	56.4 (17.0)	52.8 (15.9)
Male	134 (45.9%)	452 (41.6%)	57 (44.5%)	305 (41.2%)	14 (35.9%)	275 (30.6%)
Hispanic	127 (43.5%)	455 (41.9%)	57 (44.5%)	313 (42.3%)	15 (38.5%)	385 (42.8%)
White	29 (9.9%)	126 (11.6%)	12 (9.4%)	83 (11.2%)	1 (2.6%)	71 (7.9%)
Black	101 (34.6%)	397 (36.6%)	48 (37.5%)	269 (36.4%)	16 (41.0%)	319 (35.4%)
Asian	6 (2.1%)	16 (1.5%)	3 (2.3%)	12 (1.6%)	3 (7.7%)	27 (3.0%)
Other	29 (9.9%)	92 (8.5%)	8 (6.2%)	63 (8.5%)	4 (10.3%)	98 (10.9%)
Comorbidities, n (%)						
BMI (kg/m^2)	29.8 (7.52)	28.3 (6.55)	29.07 (6.65)	27.04 (6.52)	25.81 (3.0)	30.28 (7.44)
CHF	17 (5.8%)	56 (5.2%)	6 (4.7%)	40 (5.4%)	1 (2.6%)	20 (2.2%)
CKD	58 (19.9%)*	162 (14.9%)	21 (16.4%)	126 (17.0%)	2 (5.1%)	78 (8.7%)
Hypertension	157 (53.8%)	567 (52.2%)	63 (49.2%)	421 (56.9%)	26 (66.7%)*	411 (45.7%)
COPD/Asthma	53 (18.2%)	210 (19.3%)	27 (21.1%)	164 (22.2%)	9 (23.1%)	208 (23.1%)
Retinopathy	–	–	1 (0.8%)	–	0 (0.0%)	–
Peripheral neuropathy	–	–	2 (1.6%)*	–	0 (0.0%)	–
Lab values, mean (±SD)						
HbA1c (%)	5.9 (0.58)***	5.68 (0.36)	6.15 (0.78)***	5.65 (0.36)	6.4 (1.05)***	5.68 (0.28)
Glucose (mg/dL)	142.09 (51.54)***	109.58 (20.37)	119.7 (44.06)***	96.99 (16.23)	149.48 (78.96)***	94.77 (14.98)
HDL (mg/dL)	46.31 (14.81)**	48.11 (13.71)	40.19 (12.94)***	47.24 (13.73)	37.79 (14.32)	48.38 (11.29)
LDL (mg/dL)	82.64 (26.76)	96.21 (32.08)	88.68 (34.99)	97.65 (33.13)	111.96 (44.82)***	112.05 (30.12)
CRP (mg/dL)	8.65 (6.38)***	5.41 (5.34)	7.85 (6.9)**	2.89 (3.73)	8.4 (7.68)**	2.19 (2.6)
FER (ng/mL)	1023.64 (1072.69)***	623.87 (812.28)	1017.36 (1398.92)***	176.81 (240.44)	1535.73 (1937.81)	125.13 (145.29)
LDH (U/L)	396.88 (199.97)***	307.51 (122.7)	409.31 (228.46)**	283.15 (129.0)	259.33 (80.74)	232.68 (77.67)
BNP (pg/mL)	613.89 (1090.68)*	348.18 (695.61)	406.79 (580.94)	314.71 (541.2)	129.5 (104.5)	96.64 (192.36)
Cr (mg/dL)	1.6 (1.24)***	1.12 (0.6)	1.25 (0.98)*	0.96 (0.41)	0.95 (0.3)	0.86 (0.24)
DDIM (µg/mL FEU)	2.25 (2.42)***	1.51 (1.47)	2.96 (2.72)	1.33 (1.21)	4.32 (3.78)	1.33 (2.5)
ALT (U/L)	34.9 (24.5)***	26.81 (18.24)	39.88 (46.09)***	21.36 (12.69)	27.58 (15.76)	22.63 (12.74)
Lymph (k/µL)	1.15 (0.71)*	1.29 (0.75)	1.55 (0.87)**	1.85 (0.96)	2.21 (0.83)*	2.12 (0.83)
PLT (k/µL)	208.36 (87.21)	215.97 (69.31)	239.52 (103.72)**	249.66 (69.4)	261.39 (96.53)	263.8 (62.35)
PT (s)	14.59 (1.93)	14.29 (1.85)	15.49 (2.65)***	14.37 (2.17)	14.01 (1.35)	13.34 (1.1)
WBC (k/µL)	7.96 (3.75)**	6.89 (2.97)	8.41 (4.14)**	7.03 (2.51)	8.39 (3.48)**	6.99 (2.43)

Continued

Table 2 Continued

	During hospitalization		At follow-up		Non-hospitalized at follow-up	
	I-DM (n=292, 21.19%)	Non-I-DM (n=1086)	P-DM (n=128, 14.75%)	Non-P-DM (n=740)	P-DM (n=39, 4.15%)	Non-P-DM (n=900)
TEMP (°F)	98.75 (0.86)**	98.55 (0.8)	98.21 (0.64)	98.11 (0.46)	98.15 (0.28)	98.16 (0.43)
TnT (ng/mL)	0.133 (0.437)***	0.022 (0.026)	0.20 (0.533)***	0.029 (0.079)	0.021 (0.015)*	0.013 (0.011)
SBP (mm Hg)	129.39 (20.8)	129.98 (19.36)	126.67 (17.25)	131.29 (20.01)	125.08 (14.25)	129.6 (16.47)
BUN (mg/dL)	26.31 (18.27)***	18.65 (10.23)	23.81 (18.99)***	15.73 (6.86)	13.34 (4.99)	13.4 (4.43)
Outcomes, n (%)						
IMV	102 (34.9%)***	50 (4.6%)	29 (22.7%)***	25 (3.4%)	–	–
In-hospital death	85 (29.1%)***	66 (6.1%)	–	–	–	–
In-hospital steroid usage	122 (41.8%)***	214 (19.7%)	44 (34.4%)**	164 (22.2%)	3 (7.7%)	47 (5.2%)

*P<0.05, **p<0.01, ***p<0.001 between diabetes and no diabetes within each group.
Laboratory data were obtained from hospitalization or initial outpatient visit.
ALT, alanine aminotransferase; BMI, body mass index; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; Cr, creatinine; CRP, C-reactive protein; DDIM, D-dimer; FER, ferritin; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; I-DM, in-hospital diabetes mellitus; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; Lymph, lymphocyte count; P-DM, persistent diabetes mellitus; PLT, platelet count; PT, prothrombin time; SBP, systolic blood pressure; TEMP, temperature; TnT, troponin T; WBC, white blood cell.

(p<0.05). IMV (22.7% vs 3.4%, p<0.001) and steroid use (34.4% vs 22.2%, p<0.01) in the P-DM group were significantly higher compared with those without P-DM.

At follow-up for the non-hospitalized cohort, there were no significant differences in demographics and major comorbidities (except HTN) between the with and without P-DM groups (p>0.05). Only some laboratory values (HbA1c, glucose, LDL, CRP, Lymph, WBC, and TnT) were significantly different between groups (p<0.05). In-hospital steroid use was comparable between groups (7.7% vs 5.2%, p>0.05).

Features of patients without COVID-19 with and without I-DM

Table 3 shows characteristics of patients without COVID-19 with history of prediabetes with and without I-DM during hospitalization, hospitalized with and without P-DM at follow-up, and non-hospitalized patients with and without P-DM at follow-up.

During hospitalization, patients with I-DM were older, more male, more white, and had higher rates of CHF but lower rates of HTN than those without I-DM (all p<0.05). There were differences in most lab values (HbA1c, admission glucose level, HDL, LDL, LDH, Cr, ALT, PLT, PT, WBC, TnT, and BUN, all p<0.05) between groups. The rates of IMV (16.9% vs 1.1%, p<0.001), in-hospital mortality (10.4% vs 0.9%, p<0.001), and in-hospital steroid use (23.7% vs 4.5%, p<0.001) were higher among patients with I-DM.

Hospitalized patients with P-DM at follow-up were more likely to be male and have CHF than those without P-DM (p<0.05). Many lab values (HbA1c, glucose, HDL, CRP, FER, BNP, Cr, ALT, WBC, and BUN, all p<0.05) were different between P-DM and non P-DM groups. Hospitalized patients with P-DM at follow-up had higher rates of IMV (9.3% vs 1.0%, p<0.001) and in-hospital steroid use (13.7% vs 5.3%, p<0.01).

Non-hospitalized patients with P-DM at follow-up were similar in demographics and comorbidities compared with those without P-DM. Those with P-DM had higher HbA1c, glucose, ALT, Lymph, PT, and WBC levels but lower HDL and BUN levels than those without P-DM (all p<0.05).

Features of hospitalized patients with I-DM and P-DM by COVID-19 status

Table 4 shows characteristics of patients with and without COVID-19 with I-DM during hospitalization and with P-DM at follow-up for hospitalized and non-hospitalized groups. Hospitalized patients with COVID-19 with I-DM were younger, more female, had more Hispanic and fewer white patients, more CKD compared with hospitalized controls with I-DM (p<0.05), had worse laboratory test data (FER, ALT, Lymph, WBC, TnT (p<0.05)), higher IMV (34.9% vs 14.6%, p<0.001), steroid use (41.8% vs 23.7%, p<0.001), and mortality rate (29.1% vs 10.4%, p<0.001) compared hospitalized patients without COVID-19 with I-DM.

Table 3 Characteristics of patients without COVID-19 with history of prediabetes during (A) hospitalization, (B) hospitalized patients at follow-up, and (C) non-hospitalized patients at follow-up

	During hospitalization		At follow-up		Non-hospitalized at follow-up	
	I-DM (n=249, 6.02%)	Non-I-DM (n=3885)	P-DM (n=204, 7.51%)	Non-P-DM (n=2511)	P-DM (n=55, 4.10%)	Non-P-DM (n=1287)
Demographics, n (%)						
Age, mean years (±SD)	67.8 (17.9)***	63.5 (17.8)	65.6 (17.3)	64.8 (16.8)	54.9 (10.2)	55.0 (15.3)
Male	139 (55.8%)***	1641 (42.2%)	110 (53.9%)***	1035 (41.2%)	20 (36.4%)	396 (30.8%)
Hispanic	82 (32.9%)	1456 (37.5%)	71 (34.8%)	954 (38.0%)	22 (40.0%)	465 (36.1%)
White	43 (17.3%)*	452 (11.6%)	22 (10.8%)	273 (10.9%)	4 (7.3%)	92 (7.1%)
Black	79 (31.7%)	1397 (36.0%)	74 (36.3%)	927 (36.9%)	13 (23.6%)	470 (36.5%)
Asian	9 (3.6%)	98 (2.5%)	9 (4.4%)	64 (2.5%)	2 (3.6%)	46 (3.6%)
Other	36 (14.5%)	482 (12.4%)	28 (13.7%)	293 (11.7%)	14 (25.5%)	214 (16.6%)
Comorbidities, n (%)						
BMI (kg/m^2)	29.02 (6.7)	29.14 (6.04)	30.71 (8.01)	28.89 (6.42)	31.1 (14.3)	30.75 (4.97)
CHF	21 (8.4%)*	180 (4.6%)	22 (10.8%)*	157 (6.3%)	0 (0.0%)	13 (1.0%)
CKD	33 (13.3%)	622 (16.0%)	32 (15.7%)	473 (18.8%)	3 (5.5%)	128 (9.9%)
Hypertension	113 (45.4%)*	2058 (53.0%)	101 (49.5%)	1416 (56.4%)	29 (52.7%)	602 (46.8%)
COPD/Asthma	41 (16.5%)	753 (19.4%)	38 (18.6%)	551 (21.9%)	13 (23.6%)	316 (24.6%)
Retinopathy	–	–	0 (0.0%)	–	0 (0.0%)	–
Peripheral neuropathy	–	–	0 (0.0%)	–	0 (0.0%)	–
Lab values, mean (±SD)						
HbA1c (%)	6.07 (0.66)***	5.77 (0.24)	6.27 (0.91)***	5.7 (0.29)	6.59 (0.46)***	5.81 (0.24)
Glucose (mg/dL)	154.18 (75.88)***	106.35 (20.0)	129.84 (54.04)***	98.34 (16.98)	93.48 (59.04)***	82.71 (41.78)
HDL (mg/dL)	44.38 (11.43)***	50.53 (12.19)	41.74 (10.17)***	50.11 (12.33)	45.05 (10.29)***	50.99 (11.24)
LDL (mg/dL)	91.51 (32.89)**	102.88 (32.29)	95.71 (34.43)	100.25 (31.53)	111.0 (34.78)	114.72 (31.11)
CRP (mg/dL)	18.8 (42.46)	5.16 (7.91)	5.73 (6.05)**	2.93 (4.58)	2.7 (0.0)	1.82 (1.67)
FER (ng/mL)	435.22 (406.67)	180.2 (231.83)	317.89 (358.52)***	140.57 (178.31)	140.97 (102.1)	90.83 (83.79)
LDH (U/L)	375.58 (242.51)*	254.04 (92.06)	244.3 (48.13)	258.32 (95.18)	182.0 (0.0)	197.83 (42.68)
BNP (pg/mL)	708.88 (1140.4)	1173.64 (2969.75)	793.28 (1244.35)*	387.38 (757.36)	na	200.7 (451.42)
Cr (mg/dL)	1.31 (0.65)***	1.02 (0.4)	1.14 (0.46)***	0.94 (0.3)	0.88 (0.17)	0.87 (0.18)
DDIM (µg/mL FEU)	2.96 (5.92)	3.54 (5.31)	1.56 (1.14)	1.71 (1.82)	na	0.3 (0.04)
ALT (U/L)	35.99 (38.34)**	26.21 (26.41)	26.51 (16.42)***	21.78 (12.43)	32.28 (19.0)***	21.45 (9.38)
Lymph (k/µL)	1.75 (1.16)	1.68 (0.79)	1.85 (0.93)	1.9 (0.79)	2.36 (0.7)*	2.1 (0.59)
PLT (k/µL)	221.51 (74.91)**	236.48 (71.87)	244.2 (75.64)	244.33 (67.59)	265.81 (65.73)	262.19 (60.7)
PT (s)	14.81 (2.6)**	14.19 (1.76)	14.43 (1.76)	14.43 (2.25)	47.3 (0.0)*	13.38 (1.0)
WBC (k/µL)	9.65 (5.26)***	8.21 (3.63)	8.86 (3.36)***	7.02 (2.46)	7.1 (1.92)*	6.37 (1.63)

Continued

Table 3 Continued

	During hospitalization		At follow-up		Non-hospitalized at follow-up	
	I-DM (n=249, 6.02%)	Non-I-DM (n=3885)	P-DM (n=204, 7.51%)	Non-P-DM (n=2511)	P-DM (n=55, 4.10%)	Non-P-DM (n=1287)
TEMP (°F)	98.09 (0.55)*	98.17 (0.49)	98.18 (0.57)	98.17 (0.55)	98.3 (0.63)	98.2 (0.33)
TNT (ng/mL)	0.027 (0.034)*	0.042 (0.162)	0.048 (0.160)	0.025 (0.040)	na	0.010 (0.0)
SBP (mm Hg)	137.14 (23.75)*	132.57 (18.91)	129.39 (19.58)	130.1 (18.03)	131.17 (26.79)	130.6 (13.4)
BUN (mg/dL)	24.52 (13.89)***	16.76 (7.42)	18.96 (10.42)***	15.28 (5.79)	12.48 (4.15)*	13.67 (3.79)
Outcomes, n (%)						
IMV	42 (16.9%)***	42 (1.1%)	19 (9.3%)***	26 (1.0%)	–	–
In-hospital death	26 (10.4%)***	35 (0.9%)	–	–	–	–
In-hospital steroid usage	59 (23.7%)***	175 (4.5%)	28 (13.7%)***	133 (5.3%)	0 (0.0%)	7 (0.5%)

*P<0.05, **p<0.01, ***p<0.001 between diabetes and no diabetes within each group.
Laboratory data were obtained from hospitalization or initial outpatient visit.
ALT, alanine aminotransferase; BMI, body mass index; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; Cr, creatinine; CRP, C-reactive protein; DDIM, D-dimer; FER, ferritin; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; I-DM, in-hospital diabetes mellitus; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; Lymph, lymphocyte count; na, not available; P-DM, persistent diabetes mellitus; PLT, platelet count; PT, prothrombin time; SBP, systolic blood pressure; TEMP, temperature; TnT, troponin T; WBC, white blood cell.

Hospitalized patients with COVID-19 who developed P-DM were younger (p<0.01) and more of 'other' races but otherwise showed no significant differences in demographics, race, ethnicity, and major comorbidities compared with controls with I-DM. Hospitalized patients with COVID-19 with P-DM had worse laboratory test data (glucose, FER, LDH, Cr, ALT, Lymph, PT, and TNT, all p<0.05). Hospitalized patients with COVID-19 with P-DM had higher IMV (22.7% vs 9.3%, p<0.01) and steroid use (34.4% vs 13.7%, p<0.001) compared hospitalized controls with P-DM.

Non-hospitalized patients with COVID-19 with P-DM were less obese (p<0.05), had worse laboratory test values (glucose and HDL (p<0.05)), and more steroid use (7.7% vs 0%, p<0.001), but otherwise showed no significant differences in demographics, race, ethnicity, and major comorbidities compared with non-hospitalized controls with P-DM.

Risk factors of I-DM and P-DM

Predictive models were used to identify clinical variables that predict I-DM and P-DM (figure 2). IMV (HR 4.6 (95% CI 3.5 to 6.1), p<0.005), in-hospital steroid treatment (HR 2.88 (2.2 to 3.8), p<0.005), SARS-CoV-2 infection status (HR 1.8 (1.4 to 2.3), p<0.005), and HbA1c (HR 1.7 (1.6 to 1.8), p<0.005) were significant predictors of I-DM.

I-DM (HR 23.2 (95% CI 16.1 to 33.4), p<0.005), IMV (HR 2.4 (1.6 to 3.8), p<0.005), and HbA1c (HR 1.3 (1.1 to 1.4), p<0.005) were significant predictors of P-DM at follow-up.

DISCUSSION

This study investigated the incidence of progression from prediabetes to diabetes in patients with COVID-19 compared with patients without COVID-19. The major findings are: (i) 21.19% of hospitalized patients with COVID-19 with history of prediabetes developed I-DM compared with 6.02% of non-COVID-19 propensity-matched counterparts, (ii) of the hospitalized patients with COVID-19 with history of prediabetes at 5-month follow-up, 14.75% developed persistent diabetes compared with 4.15% of the non-hospitalized counterparts, (iii) non-hospitalized patients with and without COVID-19 with history of prediabetes had similar persistent diabetes incidence (4.15% and 4.1%), (iv) critical illness (HR 4.6), in-hospital steroid treatment (HR 2.88), SARS-CoV-2 infection (HR 1.8), and HbA1c (HR 1.7) were significant risk factors for developing I-DM, and (v) I-DM (HR 23.2), IMV (HR 2.4), and HbA1c (HR 1.3) were significant risk factors for developing persistent diabetes.

Several commentaries, case, and cohort studies have reported that SARS-CoV-2 infection could trigger new-onset diabetes in COVID-19 survivors.[14–19] In particular, a cohort study on veterans reported an association between SARS-CoV-2 infection and persistent postacute diabetes

Table 4 Characteristics of patients with prediabetes with (A) I-DM during hospitalization, (B) hospitalized patients with P-DM at follow-up, and (C) non-hospitalized patients at P-DM follow-up

	I-DM during hospitalization		P-DM at follow-up		P-DM non-hospitalized at follow-up	
	COVID-19 (n=292, 21.19%)	Non-COVID-19 (n=249, 6.02%)	COVID-19 (n=128, 14.75%)	Non-COVID-19 (n=204, 7.51%)	COVID-19 (n=39, 4.15%)	Non-COVID-19 (n=55, 4.10%)
Demographics, n (%)						
Age, mean years (±SD)	66.0 (16.8)*	67.8 (17.9)	61.7 (18.1)*	65.6 (17.3)	56.4 (17.0)	54.9 (10.2)
Male	134 (45.9%)*	139 (55.8%)	57 (44.5%)	110 (53.9%)	14 (35.9%)	20 (36.4%)
Hispanic	127 (43.5%)*	82 (32.9%)	57 (44.5%)	71 (34.8%)	15 (38.5%)	22 (40.0%)
White	29 (9.9%)*	43 (17.3%)	12 (9.4%)	22 (10.8%)	1 (2.6%)	4 (7.3%)
Black	101 (34.6%)	79 (31.7%)	48 (37.5%)	74 (36.3%)	16 (41.0%)	13 (23.6%)
Asian	6 (2.1%)	9 (3.6%)	3 (2.3%)	9 (4.4%)	3 (7.7%)	2 (3.6%)
Other	29 (9.9%)	36 (14.5%)	8 (6.2%)*	28 (13.7%)	4 (10.3%)	14 (25.5%)
Comorbidities, n (%)						
BMI (kg/m^2)	29.8 (7.52)	29.02 (6.7)	29.07 (6.65)	30.71 (8.01)	25.81 (3.0)*	31.1 (14.3)
CHF	17 (5.8%)	21 (8.4%)	6 (4.7%)	22 (10.8%)	1 (2.6%)	0 (0.0%)
CKD	58 (19.9%)*	33 (13.3%)	21 (16.4%)	32 (15.7%)	2 (5.1%)	3 (5.5%)
Hypertension	157 (53.8%)	113 (45.4%)	63 (49.2%)	101 (49.5%)	26 (66.7%)	29 (52.7%)
COPD/Asthma	53 (18.2%)	41 (16.5%)	27 (21.1%)	38 (18.6%)	9 (23.1%)	13 (23.6%)
Retinopathy	–	–	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Peripheral neuropathy	–	–	2 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lab values, mean (±SD)						
HbA1c (%)	5.9 (0.58)	6.07 (0.66)	6.15 (0.78)	6.27 (0.91)	6.4 (1.05)	6.59 (0.46)
Glucose (mg/dL)	142.09 (51.54)	154.18 (75.88)	119.7 (44.06)*	129.84 (54.04)	149.48 (78.96)*	93.48 (59.04)
HDL (mg/dL)	46.31 (14.81)	44.38 (11.43)	40.19 (12.94)	41.74 (10.17)	37.79 (14.32)*	45.05 (10.29)
LDL (mg/dL)	82.64 (26.76)	91.51 (32.89)	88.68 (34.99)	95.71 (34.43)	111.96 (44.82)	111.0 (34.78)
CRP (mg/dL)	8.65 (6.38)	18.8 (42.46)	7.85 (6.9)	5.73 (6.05)	8.4 (7.68)	2.7 (0.0)
FER (ng/mL)	1023.64 (1072.69)*	435.22 (406.67)	1017.36 (1398.92)*	317.89 (358.52)	1535.73 (1937.81)	140.97 (102.1)
LDH (U/L)	396.88 (199.97)	375.58 (242.51)	409.31 (228.46)*	244.3 (48.13)	259.33 (80.74)	182.0 (0.0)
BNP (pg/mL)	613.89 (1090.68)	708.88 (1140.4)	406.79 (580.94)	793.28 (1244.35)	129.5 (104.5)	na
Cr (mg/dL)	1.6 (1.24)	1.31 (0.65)	1.25 (0.98)*	1.14 (0.46)	0.95 (0.3)	0.88 (0.17)
DDIM (µg/mL FEU)	2.25 (2.42)	2.96 (5.92)	2.96 (2.72)	1.56 (1.14)	4.32 (3.78)	na
ALT (U/L)	34.9 (24.5)*	35.99 (38.34)	39.88 (46.09)*	26.51 (16.42)	27.58 (15.76)	32.28 (19.0)
Lymph (k/µL)	1.15 (0.71)***	1.75 (1.16)	1.55 (0.87)**	1.85 (0.93)	2.21 (0.83)	2.36 (0.7)
PLT (k/µL)	208.36 (87.21)	221.51 (74.91)	239.52 (103.72)	244.2 (75.64)	261.39 (96.53)	265.81 (65.73)
PT (s)	14.59 (1.93)	14.81 (2.6)	15.49 (2.65)**	14.43 (1.76)	14.01 (1.35)	47.3 (0.0)

Continued

Table 4 Continued

	I-DM during hospitalization		P-DM at follow-up		P-DM non-hospitalized at follow-up	
	COVID-19 (n=292, 21.19%)	Non-COVID-19 (n=249, 6.02%)	COVID-19 (n=128, 14.75%)	Non-COVID-19 (n=204, 7.51%)	COVID-19 (n=39, 4.15%)	Non-COVID-19 (n=55, 4.10%)
WBC (k/µL)	7.96 (3.75)***	9.65 (5.26)	8.41 (4.14)	8.86 (3.36)	8.39 (3.48)	7.1 (1.92)
TEMP (°F)	98.75 (0.86)***	98.09 (0.55)	98.21 (0.64)	98.18 (0.57)	98.15 (0.28)	98.3 (0.63)
TnT (ng/mL)	0.133 (0.437)*	0.027 (0.034)	0.20 (0.533)*	0.048 (0.160)	0.021 (0.015)	na
SBP (mm Hg)	129.39 (20.8)**	137.14 (23.75)	126.67 (17.25)	129.39 (19.58)	125.08 (14.25)	131.17 (26.79)
BUN (mg/dL)	26.31 (18.27)	24.52 (13.89)	23.81 (18.99)	18.96 (10.42)	13.34 (4.99)	12.48 (4.15)
Outcomes, n (%)						
IMV	102 (34.9%)***	42 (16.9%)	29 (22.7%)**	19 (9.3%)	–	–
In-hospital death	85 (29.1%)***	26 (10.4%)	–	–	–	–
In-hospital steroid usage	122 (41.8%)***	59 (23.7%)	44 (34.4%)***	28 (13.7%)	3 (7.7%)	0 (0.0%)

*P<0.05, **p<0.01, ***p<0.001 between patients with and without COVID-19 within each group.
Laboratory data were obtained from hospitalization or initial outpatient visit.
ALT, alanine aminotransferase; BMI, body mass index; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; Cr, creatinine; CRP, C-reactive protein; DDIM, D-dimer; FER, ferritin; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; I-DM, in-hospital diabetes mellitus; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; Lymph, lymphocyte count; na, not available; P-DM, persistent diabetes mellitus; PLT, platelet count; PT, prothrombin time; SBP, systolic blood pressure; TEMP, temperature; TnT, troponin T; WBC, white blood cell.

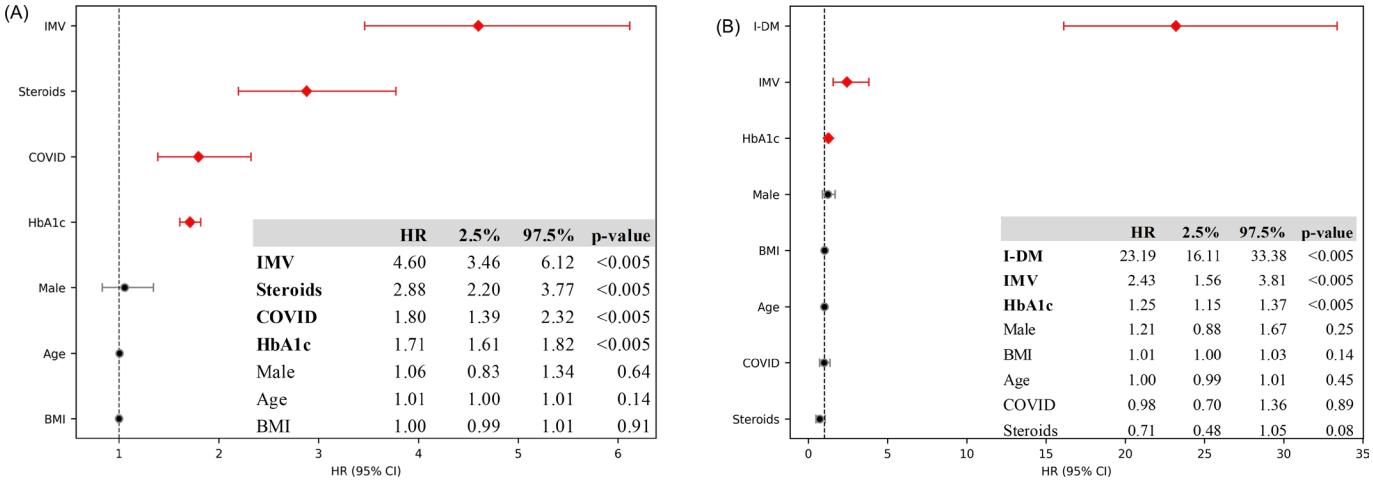
in patients who survived the first 30 days of COVID-19 (March 1, 2020 and September 30, 2021).[18] Guo *et al* reported on the incidence trends of new-onset type 1 diabetes (T1D) and T2D in children and adolescents in Florida before and during the COVID-19 pandemic. The age-adjusted incidence of both T1D and T2D increased post-19 for children and adolescents.[16] However, there have been no studies on prediabetic risk of new-onset T2D. We extended previous studies by investigating patients with prediabetes who were likely at greater risk, including a longer follow-up period and identifying risk factors, among others. Indeed, SARS-CoV-2 infection conferred a much greater risk for developing I-DM and P-DM in patients with prediabetes. The higher incidence could be caused by the virus itself, steroid treatment, or stress hyperglycemia related to hospitalization. These and other risk factors are likely intertwined and interdependent and thus we developed predictive models with adjustment of covariates.

Predictive models identified critical illness, HbA1c, steroid treatment and SARS-CoV-2 infection status to be significant predictors of I-DM among all hospitalized patients. Patients with a critical illness, measured by IMV as a surrogate of disease severity, were 4.6 times more likely to develop I-DM. Steroid treatment was also strongly associated with I-DM, consistent with the effects of steroids on impairing insulin sensitivity and enhancing hepatic gluconeogenesis.

It is not surprising that elevated HbA1c is associated with higher risk of progression from prediabetes to DM, although SARS-CoV-2 infection, IMV, and steroid treatment were stronger predictors. SARS-CoV-2 infection status was also a predictor of I-DM, with patients with COVID-19 being 1.8 times more likely to develop I-DM after adjusting for covariates. This is consistent with an enhanced inflammatory response demonstrated by elevated serum markers in patients with COVID-19 which can impair insulin sensitivity and insulin secretion.[20] In addition, there could be beta-cell failure or direct damage to hepatocytes due to the toxic effects of inflammatory cytokines.[21]

Predictive models identified I-DM, critical illness, and HbA1c, but not SARS-CoV-2 infection, to be significant predictors of P-DM. I-DM and IMV by far are the dominant risk factors suggesting that the stress burden from critical illness may result in delayed or incomplete resolution of increased insulin resistance. While SARS-CoV-2 infection was not an independent predictor of P-DM, it does contribute to I-DM which was by far the strongest independent predictor of P-DM.

Several reports suggest that the SARS-CoV-2 might directly cause diabetes, either directly by destroying insulin producing β-cells or indirectly by infecting adipose cells which produce inflammatory adipokines and enhance insulin resistance.[21] This has been observed clinically as larger-than-expected doses of insulin are frequently needed to manage glucose levels in hospitalized patients with COVID-19.[22 23] Moreover, many



	HR	2.5%	97.5%	p-value
IMV	4.60	3.46	6.12	<0.005
Steroids	2.88	2.20	3.77	<0.005
COVID	1.80	1.39	2.32	<0.005
HbA1c	1.71	1.61	1.82	<0.005
Male	1.06	0.83	1.34	0.64
Age	1.01	1.00	1.01	0.14
BMI	1.00	0.99	1.01	0.91

	HR	2.5%	97.5%	p-value
I-DM	23.19	16.11	33.38	<0.005
IMV	2.43	1.56	3.81	<0.005
HbA1c	1.25	1.15	1.37	<0.005
Male	1.21	0.88	1.67	0.25
BMI	1.01	1.00	1.03	0.14
Age	1.00	0.99	1.01	0.45
COVID	0.98	0.70	1.36	0.89
Steroids	0.71	0.48	1.05	0.08

Figure 2 Feature importance of (A) prediction of in-hospital diabetes mellitus (I-DM) with demographics, IMV, body mass index (BMI), hemoglobin A1c (HbA1c), steroid use, and COVID-19 status from hospitalized patients with and without COVID-19 as inputs. (B) Prediction of persistent diabetes mellitus (P-DM) with the same inputs plus I-DM were used. Red colors/bold indicate statistical significance (p<0.05).

patients with prediabetes have underlying medical conditions and comorbidities[8] that render them susceptible to developing new-onset T2D after SARS-CoV-2 infection compared with the general population.

However, there have been more recent studies suggesting that the diabetogenic effect of COVID-19 is not as prevalent as previously reported and that stress hyperglycemia could explain a portion of new diabetes diagnoses.[19] Lockhart *et al* included additional adjustments for disease severity and comorbidities which normalized insulin requirements in critically ill patients with and without COVID-19,[17] although the study sample size was relatively small. The lack of longitudinal follow-up in prior studies also warrants caution in interpretation. Cromer *et al* found that among 64 COVID-19 survivors with newly diagnosed T2D over nearly 1 year of follow-up, over 40% of COVID-19 survivors with newly diagnosed DM showed regression to normoglycemia or prediabetes. Although the rate of P-DM was higher in patients with COVID-19 than patients without COVID-19 in our study, many who developed I-DM did not have P-DM at follow-up. This suggests that beta-cells had not been permanently injured, but instead that transient mechanisms associated with inflammatory responses resulted in stress hyperglycemia which can resolve in the many patients after acute SARS-CoV-2 infection. Furthermore, rates of P-DM were similar at follow-up between non-hospitalized patients with COVID-19 and patients without COVID-19. This suggests that mild COVID-19 does not cause sufficient inflammatory and metabolic burden to result in increased progression from prediabetes to DM.

Limitations

There are several limitations to our analysis. Patients who did not return to our health system could not be studied. There may be a selection bias towards patients established in our health system with regular follow-up visits and lab measurements. However, based on our findings, we would suspect that patients new to the health system or who do not receive routine medical care are actually at greater risk of developing frank diabetes following COVID-19 due to lack of regular health maintenance and would benefit more from close monitoring. We followed patients for ~5 months after diagnosis, but a longer follow-up study is needed. We did not determine the type of diabetes in patients with P-DM to ascertain if there was pancreatic islet injury leading to development of T1D as these data were not available. We only included patients with confirmed prediabetes status based on HbA1c and glucose, but it is possible some patients could have been misclassified due to underdiagnosis or inaccurate EMR coding. It is also possible that there are diabetogenic effects of non-diabetes medications contributing towards the rates of P-DM observed at follow-up that were not fully accounted for, as the matching process included select comorbidities and did not consider active patient medication lists. There may be additional confounders that were not accounted for in our analyses. Our database was limited to patient data from within our health system and did not contain information from other health systems. Thus, some data, such as smoking status, vaccination status, or illness duration, were not available and not included in our models.

CONCLUSIONS

Hospitalized, but not non-hospitalized, patients with COVID-19 with history of prediabetes have a markedly higher risk for developing I-DM and P-DM after SARS-CoV-2 infection compared with COVID-19-negative counterparts. Critical illness, steroid treatment, HbA1c, and SARS-CoV-2 infection are independent risk factors for developing I-DM. I-DM, critical illness, and HbA1c are independent risk factors for developing P-DM. Patients with prediabetes with severe COVID-19 disease

may require diligent monitoring for resolution of stress hyperglycemia and possible progression to persistent frank diabetes.

Contributors SHW and AYX researched data, performed data analysis and interpretation, and wrote, reviewed, and edited the manuscript. TQD supervised the data analysis, interpretation, and reviewed and edited the manuscript. All authors contributed to revisions and final approval of the submitted manuscript. TQD is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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ORCID iDs
Alexander Y. Xu http://orcid.org/0000-0002-6341-1822
Stephen H. Wang http://orcid.org/0000-0002-6212-2906
Tim Q. Duong http://orcid.org/0000-0001-6403-2827

REFERENCES

1 Metwally AA, Mehta P, Johnson BS, *et al*. COVID-19-induced new-onset diabetes: trends and Technologies. *Diabetes* 2021;70:2733–44.
2 Chandrashekhar Joshi S, Pozzilli P. COVID-19 induced diabetes: a novel presentation. *Diabetes Res Clin Pract* 2022;191:110034.
3 van der Heide V, Jangra S, Cohen P, *et al*. Limited extent and consequences of pancreatic SARS-Cov-2 infection. *Cell Rep* 2022;38:110508.
4 Huang C, Wang Y, Li X, *et al*. Clinical features of patients infected with 2019 novel Coronavirus in Wuhan, China. *Lancet* 2020;395:497–506.
5 Wang D, Hu B, Hu C, *et al*. Clinical characteristics of 138 hospitalized patients with 2019 novel Coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020;323:1061.
6 Guo T, Fan Y, Chen M, *et al*. Cardiovascular implications of fatal outcomes of patients with Coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020;5:811–8.
7 Shi S, Qin M, Cai Y, *et al*. Characteristics and clinical significance of myocardial injury in patients with severe Coronavirus disease 2019. *Eur Heart J* 2020;41:2070–9.
8 Kolluru GK, Bir SC, Kevil CG. Endothelial dysfunction and diabetes: effects on angiogenesis, vascular remodeling, and wound healing. *Int J Vasc Med* 2012;2012:918267.
9 Hoogenboom WS, Pham A, Anand H, *et al*. Clinical characteristics of the first and second COVID-19 waves in the Bronx, New York: a retrospective cohort study. *Lancet Reg Health Am* 2021;3:100041.
10 Hoogenboom WS, Fleysher R, Soby S, *et al*. Individuals with sickle cell disease and Sickle cell trait demonstrate no increase in mortality or critical illness from COVID-19 - a fifteen hospital observational study in the Bronx, New York. *Haematologica* 2021;106:3014–6.
11 Lu JQ, Lu JY, Wang W, *et al*. Clinical predictors of acute cardiac injury and normalization of troponin after hospital discharge from COVID-19. *EBioMedicine* 2022;76:103821.
12 Dell'Aquila K, Lee J, Wang SH, *et al*. n.d. Incidence, characteristics, risk factors and outcomes of diabetic Ketoacidosis in COVID-19 patients: comparison with influenza and pre-pandemic data. *Diabetes Obesity Metabolism*;2023:1–13.
13 Hou W, Zhao Z, Chen A, *et al*. Machining learning predicts the need for escalated care and mortality in COVID-19 patients from clinical variables. *Int J Med Sci* 2021;18:1739–45.
14 Rubino F, Amiel SA, Zimmet P, *et al*. New-onset diabetes in COVID-19. *N Engl J Med* 2020;383:789–90.
15 Birabaharan M, Kaelber DC, Pettus JH, *et al*. Risk of new-onset type 2 diabetes in 600 055 people after COVID-19: a cohort study. *Diabetes Obes Metab* 2022;24:1176–9.
16 Guo Y, Bian J, Chen A, *et al*. Incidence trends of new-onset diabetes in children and adolescents before and during the COVID-19 pandemic: findings from Florida. *Diabetes* 2022;71:2702–6.
17 Lockhart SM, Griffiths H, Petrisor B, *et al*. The excess insulin requirement in severe COVID-19 compared to non-COVID-19 viral pneumonitis is related to the severity of respiratory failure and pre-existing diabetes. *Endocrinol Diabetes Metab* 2021;4:e00228.
18 Xie Y, Al-Aly Z. Risks and burdens of incident diabetes in long COVID: a cohort study. *Lancet Diabetes Endocrinol* 2022;10:311–21.
19 Cromer SJ, Colling C, Schatoff D, *et al*. Newly diagnosed diabetes vs. pre-existing diabetes upon admission for COVID-19: associated factors, short-term outcomes, and long-term Glycemic phenotypes. *J Diabetes Complications* 2022;36:108145.
20 Emamalipour M, Seidi K, Jahanban-Esfahlan A, *et al*. Implications of resistin in type 2 diabetes mellitus and coronary artery disease: impairing insulin function and inducing pro-inflammatory Cytokines. *J Cell Physiol* 2019;234:21758–69.
21 Sathish T, Tapp RJ, Cooper ME, *et al*. Potential metabolic and inflammatory pathways between COVID-19 and new-onset diabetes. *Diabetes Metab* 2021;47:101204.
22 Wu L, Girgis CM, Cheung NW. COVID-19 and diabetes: insulin requirements parallel illness severity in critically Unwell patients. *Clin Endocrinol (Oxf)* 2020;93:390–3.
23 Kapoor R, Timsina LR, Gupta N, *et al*. Maintaining blood glucose levels in range (70–150 mg/dL) is difficult in COVID-19 compared to non-COVID-19 ICU patients—a retrospective analysis. *J Clin Med* 2020;9:3635.