# Newly diagnosed diabetes vs. pre-existing diabetes upon admission for COVID-19: Associated factors, short-term outcomes, and long-term glycemic phenotypes

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## A B S T R A C T

*Aims:* High rates of newly diagnosed diabetes mellitus (NDDM) have been reported in association with coronavirus disease-2019 (COVID-19). Factors associated with NDDM and long-term glycemic outcomes are not known.
*Methods:* Retrospective review of individuals admitted with COVID-19 and diabetes mellitus (DM; based on labs, diagnoses, outpatient insulin use, or severe inpatient hyperglycemia) between March and September 2020, with follow-up through July 2021.
*Results:* Of 1902 individuals admitted with COVID-19, 594 (31.2%) had DM; 77 (13.0%) of these had NDDM. Compared to pre-existing DM, NDDM was more common in younger patients and less common in those of non-Hispanic White race/ethnicity. Glycemic parameters were lower and inflammatory markers higher in patients with NDDM. In adjusted models, NDDM was associated with lower insulin requirements, longer length of stay, and intensive care unit admission but not death. Of 64 survivors with NDDM, 36 (56.3%) continued to have DM, 26 (40.6%) regressed to normoglycemia or pre-diabetes, and 2 were unable to be classified at a median follow-up of 323 days.
*Conclusions:* Diabetes diagnosed at COVID-19 presentation is associated with lower glucose but higher inflammatory markers and ICU admission, suggesting stress hyperglycemia as a major physiologic mechanism. Approximately half of such individuals experience regression of DM.

## 1. Introduction

Many reports suggest that newly diagnosed diabetes mellitus (NDDM), or hyperglycemia without known prior diagnosis of diabetes mellitus (DM) is common at the time of admission for coronavirus disease-2019 (COVID-19),[1–5] as well as in the months following COVID-19.[6,7] NDDM at the time of COVID-19 admission is often termed "new-onset diabetes," although documentation of normoglycemia prior to admission is rare; it is unclear whether diabetes diagnosis at the time of presentation for COVID-19 is merely newly recognized or represents a

different stage or phenotype of dysglycemia. It is not known whether specific patient characteristics are associated with NDDM or whether these cases represent insulin resistant or deficient forms of diabetes, pre-existing but undiagnosed or truly "new-onset diabetes," or merely transient stress hyperglycemia in the setting of acute infection. Longitudinal follow-up of patients with newly diagnosed diabetes in association with COVID-19 is needed to better understand this presentation and its long-term prognosis. Pre-existing DM at the time of COVID-19 infection has been associated with higher rates of hospitalization, intensive care unit (ICU) admission, mechanical ventilation, and death

in numerous studies.[8–15] Similarly, hyperglycemia in patients admitted with COVID-19 who do not have known pre-existing diabetes may be associated with adverse outcomes,[1–3,5] as in patients hospitalized for other, non-COVID-19 acute illnesses.[16,17]

Here we report on 594 individuals admitted with COVID-19 and diabetes, describing the characteristics and long-term follow-up of 77 individuals with newly diagnosed diabetes at the time of admission for COVID-19.

## 2. Materials and methods

### 2.1. Study population and data source

Using electronic health record (EHR) data, we reviewed all adults ≥18 years of age admitted to a single academic tertiary care hospital (Massachusetts General Hospital, Boston, MA) for COVID-19 between March 1, 2020 and September 27, 2020 with evidence of DM. Evidence of DM was defined by any of the following criteria: hemoglobin A1c (HbA1c) ≥ 6.5% (48 mmol/mol) prior to or during admission; 2 international classification of disease (ICD) codes for any form of diabetes mellitus prior to or during admission; use of insulin as an outpatient prior to admission; or occurrence of severe hyperglycemia (≥300 mg/dL (16.7 mmol/L)), on two hospital days during the admission for COVID-19. The threshold of 300 mg/dL (16.7 mmol/L) was chosen as it is beyond the usual range of stress hyperglycemia in individuals without underlying diabetes,[18] suggesting significant underlying pathology, and due to the desire to ensure high specificity for diabetes compared to previous studies.

### 2.2. Outcomes and covariates

The primary outcome was presence of NDDM. All individuals meeting criteria for DM underwent extensive chart review, including records from outside hospitals when available, to determine if their diabetes was newly diagnosed, or truly unknown prior to admission. This designation relied on patient or family report upon admission as well as review of all available historical laboratory data, medications, and clinical notes from all linked institutions and with no date restrictions. If a patient (1) did not report a history of diabetes, (2) had no clinical notes reporting a diagnosis of diabetes in any available health system record, (3) had no HbA1c values ≥6.5% (48 mmol/mol), (4) had no random glucose values greater than 200 mg/dL (11.1 mmol/L), and (5) had never taken a non-metformin diabetes medication, they were classified as having "newly diagnosed diabetes" (NDDM). Metformin use alone was not considered diagnostic of diabetes in the absence of other evidence (patient self-report, clinical notes, diagnostic codes, HbA1c or glucose values) as it may be used in other conditions such as pre-diabetes and polycystic ovarian syndrome. However, if any one of these criteria were met, suggesting some evidence by which diabetes may have been known prior to admission, the patient was included in the "pre-existing diabetes" group. Each chart was reviewed by a single investigator, trained on chart extraction using standardized criteria; approximately 15% of charts were re-reviewed by the first author to ensure concordance.

Longitudinal outcomes, including diabetes type, glycemic trajectory, and diabetes persistence vs. regression in the months following their COVID-19 admission, were also obtained through chart review, with a most recent follow-up date of July 1, 2021. Diabetes persistence was defined by HbA1c ≥ 6.5% (48 mmol/mol), use of any diabetes medications, or discussion of diabetes diagnosis or treatment plans in clinical notes at their most recent medical appointment during follow-up (e.g., if a patient took no medications but clinical notes continued to report lifestyle interventions for the treatment of diabetes, he or she was considered to have persistent diabetes). Regression to pre-diabetes at follow-up was defined by HbA1c 5.7–6.4% (39–46 mmol/mol) [19] with neither use of diabetes medications nor discussion of diabetes diagnosis

or treatment in clinical notes at most recent follow-up. Missing data (e. g., HbA1c) during longitudinal follow-up are noted among the outcomes reported in Fig. 1.

Secondary outcomes included glucose metrics (median glucose, occurrence of hypoglycemia <70 mg/dL or hyperglycemia >180 mg/dL) during the first three days of hospitalization, mean total daily dose (TDD) of insulin during the first three days of hospitalization, length of stay (LOS), diabetic ketoacidosis (DKA) during admission (defined by elevated urine or serum ketones, elevated anion gap, low bicarbonate or pH, and glucose greater than 250 mg/dL (13.9 mmol/L)), ICU admission, and death. We focused on glycemic outcomes during the first three days of hospital admission to capture the patient's presenting physiology.

Race and ethnicity were recorded in the EHR based on patient self-report and were coded as non-Hispanic White, non-Hispanic Black, Hispanic, non-Hispanic Asian, and Other or unknown race. Detailed insurance information in the EHR was categorized as private/commercial, Medicare, Medicaid, or uninsured. Comorbidities and diabetes medication use were recorded based on ever receiving an ICD diagnosis for the comorbidity or ever taking the medication prior to admission. Laboratory results and vital signs reported represent the first recorded values upon presentation. As laboratory results were collected based on routine clinical care, some individuals did not receive all examined tests; rates of missing results are reported for all tests with >15% missing values (Table 1). Data on glucocorticoid use was not recorded as this was not included in the standard of care for COVID-19 at the time of study design; in addition, >90% of individuals in this sample were admitted prior to the publication of the RECOVERY trial demonstrating the utility of dexamethasone in the management of COVID-19.[20]

### 2.3. Statistical analysis

Baseline characteristics of those with pre-existing and newly diagnosed diabetes are reported using median and interquartile range for continuous variables and using proportions for categorical variables. Differences between groups were assessed using Wilcoxon rank sum test for continuous variables and Fisher's exact test for categorical variables, with a significance threshold of 0.05. Logistic and linear regression models were used to examine the association of age, sex, race/ethnicity, and body mass index (BMI) with NDDM, and the association of age, sex, race/ethnicity, BMI, and NDDM with secondary outcomes (mean TDD insulin on first three days of hospitalization, LOS, DKA, ICU admission, and death). All analyses were conducted using R version 4.0.2 (R foundation; Vienna, Austria).

## 3. Results

### 3.1. Baseline characteristics

Of 1902 individuals admitted with COVID-19 between March 1, 2020 and September 27, 2020, 632 individuals with likely diabetes were reviewed, of whom 594 (31.2% of all admissions, 94% of likely diabetes cases) met inclusion criteria for DM. Of these, 77 individuals (4.0% overall, 13.0% of those with DM) had NDDM based on review of all available records. Thirty-three (42.9%) individuals with NDDM had evidence of pre-diabetes prior to admission. Baseline characteristics, laboratory data, and vital signs on admission are presented in Table 1. Of those with pre-existing diabetes (*n* = 594), 479 (92.8%) had type 2 diabetes, 11 (2.1%) had type 1 diabetes, 13 (2.5%) had gestational diabetes, 7 (1.4%) had secondary (steroid-induced, post-transplant, etc.) diabetes, and 3 (0.6%) had pancreatic diabetes.

Compared to patients with pre-existing DM at the time of admission, patients with NDDM were younger, less likely to be of non-Hispanic White race/ethnicity, less likely to have Medicare insurance, and more likely to have Medicaid insurance in univariate analyses (Table 1). Fewer individuals with NDDM were diagnosed with hypertension,
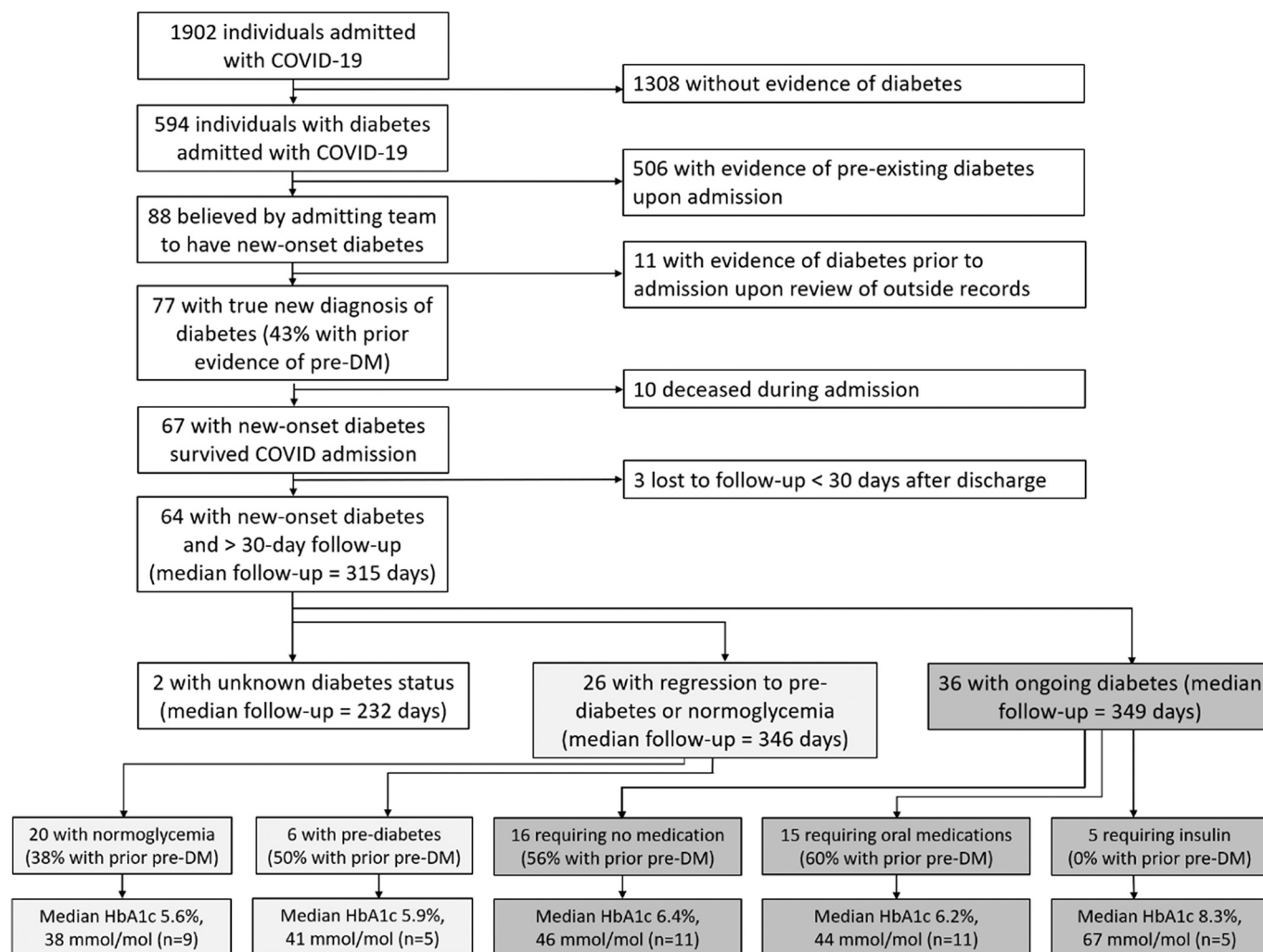
**Fig. 1.** Flow diagram: Long-term follow-up and outcomes for patients with newly diagnosed DM.

coronary artery disease, heart failure, and chronic kidney disease in the NDDM group. Glycemic parameters on admission (random/first glucose upon admission, HbA1c) were lower, but inflammatory markers and markers of COVID-19 severity (including C-reactive protein, ferritin, lactate dehydrogenase, aspartate and alanine aminotransferase) were higher in those with NDDM, compared to those with pre-existing DM. No differences in admission vital signs were seen between groups.

### 3.2. Predictors of NDDM and short-term clinical outcomes

In univariate analyses, individuals with NDDM were less likely to experience hyperglycemia (>180 mg/dL) during the first three days of admission and had lower insulin requirements on the first three days of admission, longer length of stay, and higher risk of ICU admission compared to individuals with pre-existing DM (Table 2). In multivariable models, younger age, but not sex, race/ethnicity, or BMI, was associated with NDDM, as compared to pre-existing diabetes (Table 3). In both univariate analyses and in models adjusted for age, sex, race/ethnicity, and BMI, NDDM was associated with lower insulin requirements on the first three days of hospitalization (beta (95% confidence interval (CI)): −12.67, [−20.53, −4.82] units), longer length of stay (beta (95% CI): 8.69 [4.35, 13.04] days), and higher likelihood of ICU admission (odds ratio (95% CI): 4.42 [2.56, 7.90]) compared to individuals with pre-existing diabetes. NDDM was not associated with occurrence of DKA or death in multivariable models, compared to individuals with pre-existing diabetes.

### 3.3. Classification and long-term glycemic outcomes of NDDM

Of the 77 individuals with NDDM, ten individuals died during the initial COVID-19 admission, and three were lost to follow-up within 30 days of admission (Fig. 1). Five patients with NDDM (6.5%) had DKA during admission, compared to 57 (11.0%) with pre-existing DM; however, only one was found to have positive pancreatic autoantibodies, while one other had antibody-negative type 1 diabetes vs. pancreatic diabetes based on negative autoantibodies, low c-peptide, and insulin dependence in a young patient with chronic pancreatitis. All other individuals with NDDM (n = 62 of 64 survivors with at least 30 days of follow-up) were diagnosed with type 2 diabetes.

At a median of 323 days (interquartile range 205–385 days) of follow-up, 36 (56.3%) of the 64 survivors with NDDM continued to have evidence of DM, 26 (40.6%) regressed to normoglycemia or pre-diabetes, and two were unable to be classified (Fig. 1). Of the 36 with evidence of diabetes at follow-up, 16 (44.4%) had diet-controlled DM with median HbA1c 6.4 (46 mmol/mol; IQR 6.1, 6.8%). Fifteen (41.7%) used non-insulin medications only (14 metformin monotherapy, 1 metformin and semaglutide) with median HbA1c 6.2% (44 mmol/mol; IQR 6.1, 6.8%). Although 25 (39.1%) of the 64 survivors were discharged on insulin, often to inpatient rehabilitation facilities, only 5 (7.8% of survivors with NDDM, 13.9% of those with NDDM and persistent diabetes) required insulin, with or without oral meds, at follow-up, with median HbA1c 8.3% (67 mmol/mol; IQR 7.5, 8.4%). Of the subset of individuals with NDDM who also had pre-existing pre-

**Table 1**

Baseline characteristics, by newly diagnosed vs. pre-existing diabetes status.

| | Pre-existing DM (*n* = 517) | | Newly diagnosed DM (*n* = 77) | | *P* value[a] |
|---|---|---|---|---|---|
| | N or median | % or IQR | N or median | % or IQR | |
| Age (years), median (IQR) | 64.03 | (55.54, 74.46) | 54.12 | (45.35, 63.34) | <0.01 |
| Male, n (%) | 308 | 59.57% | 50 | 64.94% | 0.39 |
| Race, n (%) | | | | | 0.03 |
|   Non-Hispanic White | 192 | 37.14% | 17 | 22.08% | |
|   Non-Hispanic Black | 69 | 13.35% | 9 | 11.69% | |
|   Hispanic | 172 | 33.27% | 30 | 38.96% | |
|   Non-Hispanic Asian | 25 | 4.84% | 5 | 6.49% | |
|   Other, Unknown | 59 | 11.41% | 16 | 20.78% | |
| Insurance type, n (%) | | | | | <0.01 |
|   Private/commercial | 224 | 42.9% | 40 | 52.6% | |
|   Medicare | 181 | 35.0% | 5 | 6.6% | |
|   Medicaid | 98 | 19.0% | 27 | 35.5% | |
|   Uninsured | 14 | 2.7% | 4 | 5.3% | |
| BMI, kg/m$^2$ | 30.15 | (26, 34.4) | 30.2 | (26.23, 33.9) | 0.97 |
| Obese, n (%) | 255 | 50.8% | 38 | 54.29% | 0.61 |
| Diabetes medication ever use, n (%) | | | | | |
|   Insulin | 215 | 41.59% | 0 | 0% | <0.01 |
|   Metformin | 338 | 65.38% | 2 | 2.60% | <0.01 |
|   Sulfonylurea | 137 | 26.50% | 0 | 0% | <0.01 |
|   DPP4 inhibitors | 60 | 11.61% | 0 | 0% | <0.01 |
|   GLP1-RA | 82 | 15.86% | 0 | 0% | <0.01 |
|   Any non-insulin diabetes medication | 390 | 75.44% | 2 | 2.60% | <0.01 |
| Comorbidities, n (%) | | | | | |
|   Hypertension | 390 | 75.44% | 22 | 28.57% | <0.01 |
|   CAD | 75 | 15.34% | 2 | 3.7% | 0.02 |
|   Heart failure | 116 | 23.72% | 3 | 5.56% | <0.01 |
|   COPD | 127 | 25.97% | 8 | 14.81% | 0.10 |
|   CKD | 157 | 32.11% | 4 | 7.41% | <0.01 |
| Laboratory values on admission, median (IQR)[b] | | | | | |
|   HbA1c (%) | 7.7 | (6.7, 9.0) | 6.7 | (6.4, 7.3) | <0.01 |
|   HbA1c (mmol/mol) | 61 | (50, 75) | 50 | (48, 57) | <0.01 |
|   Glucose (mg/dL) | 184 | (137, 256) | 143.5 | (129.6, 183.08) | <0.01 |
|   Absolute lymphocyte count (K/μL) | 14.33 | (8.58, 22.03) | 13.57 | (8.45, 19.56) | 0.56 |
|   Creatinine (mg/dL) | 1.04 | (0.82, 1.68) | 0.9 | (0.78, 1.11) | 0.01 |
|   CRP (mg/dL) | 74.8 | (31.23, 145.68) | 128.5 | (65, 196.8) | <0.01 |
|   ESR (mm/h)[b] | 44 | (28, 65) | 41.5 | (27, 67.25) | 0.76 |
|   Ferritin (μg/L)[b] | 504 | (233, 986.25) | 856 | (491.5, 1387.5) | <0.01 |
|   LDH (U/L)[b] | 318 | (241.5, 418) | 439.5 | (326, 598) | <0.01 |
|   Albumin (g/dL) | 3.6 | (3.2, 3.9) | 3.5 | (3.08, 3.75) | 0.13 |
|   Total protein (g/dL) | 7.4 | (6.9, 7.8) | 7.4 | (6.93, 7.79) | 0.93 |
|   AST (U/L) | 40 | (27, 62) | 57.5 | (41, 88.75) | <0.01 |
|   ALT (U/L) | 29 | (18, 47) | 38.5 | (28, 74.5) | <0.01 |
|   Alkaline phosphatase (U/L) | 88.5 | (68, 121) | 85 | (65.63, 103.95) | 0.09 |
|   Troponin T (ng/L)[b] | 25.5 | (12, 55.5) | 13 | (7.25, 17.88) | <0.01 |
| Vital signs on admission, median (IQR) | | | | | |
|   Temperature (°C) | 97.8 | (97.3, 98.4) | 97.6 | (97.3, 98.1) | 0.12 |
|   Heart rate (beats/min) | 81 | (72, 94) | 87 | (75, 97) | 0.10 |
|   SBP (mmHg) | 128 | (114, 139) | 125 | (110, 141) | 0.38 |
|   DBP (mmHg) | 67 | (60, 74) | 70 | (63, 80) | 0.05 |
|   RR (breaths/min) | 18 | (18, 20) | 20 | (18, 20) | 0.42 |
| Criteria for DM[c] | | | | | |
|   HbA1c ≥ 6.5% (48 mmol/mol) | 391 | 75.6% | 53 | 68.8% | 0.21 |
|   2 ICD codes for DM[d] | 302 | 58.4% | 8 | 10.4% | <0.01 |
|   Insulin prior to admission | 215 | 41.6% | 0 | 0% | <0.01 |
|   Glucose ≥300 mg/dL on two hospital days | 191 | 36.9% | 35 | 45.5% | 0.17 |

IQR = interquartile range; DPP4 = dipeptidyl peptidase 4; GLP1-RA = glucagon-like peptide-1 receptor agonist; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease; HbA1c = hemoglobin A1c; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; IL-6 = interleukin-6; LDH = lactate dehydrogenase; AST = aspartate aminotransferase; ALT = alanine aminotransferase; SBP = systolic blood pressure; DBP = diastolic blood pressure; RR = respiratory rate; DM = diabetes mellitus.

[a] Tested using Wilcoxon rank sum test for continuous variables and with Fisher's exact test for categorical variables.

[b] Fewer than 15% of values were missing for each laboratory test, unless marked here. Patient results were missing (not collected) for 22.7% of ESR values, 16.2% of ferritin values, 15.2% of LDH values, and 29.3% of troponin T values.

[c] Detailed criteria for DM diagnosis: HbA1c ≥ 6.5% (48 mmol/mol) *prior to or during admission*; 2 international classification of disease (ICD) codes for any form of diabetes mellitus *prior to or during admission*; use of insulin as an outpatient *prior to admission*; or occurrence of severe hyperglycemia (≥300 mg/dL (16.7 mmol/L)) on two hospital days *during the admission* for COVID-19.

[d] Includes ICD codes placed during admission.

diabetes (*n* = 33), there were 28 survivors of hospitalization. Of these, 18 (64%) had persistent diabetes, 3 (11%) continued to have pre-diabetes, and 7 (25%) regressed to normoglycemia during follow-up, similar to those without known pre-diabetes (*p* = 0.27). Among all 64 survivors with at least 30 days of follow-up, 41 (64.1%) had an HbA1c assessed during follow-up, and 33 (80.5%) of these had an HbA1c ≤ 7%

**Table 2**
Clinical outcomes, by newly diagnosed vs. per-existing diabetes status.

| | Pre-existing DM (n = 517) | | Newly Diagnosed DM (n = 77) | | P value[a] |
|---|---|---|---|---|---|
| | N or median | % or IQR | N or median | % or IQR | |
| Median glucose (HD 1–3), median (IQR) | 174.56 | (139.33, 212.61) | 172.11 | (142.49, 192.28) | 0.48 |
| Hypoglycemia HD 1–3, n (%) | 38 | 7.35% | 2 | 2.6% | 0.15 |
| Hyperglycemia >180 mg/dL HD 1–3, n (%) | 336 | 64.99% | 31 | 40.26% | <0.01 |
| Median TDD Insulin (HD 1–3), median (IQR) | 3.33 | (0, 23) | 0 | (0, 2.67) | <0.01 |
| Length of stay (LOS), median (IQR) | 8 | (4, 17) | 20 | (8, 37) | <0.01 |
| Diabetic ketoacidosis (DKA), n (%) | 57 | 11.03% | 5 | 6.49% | 0.32 |
| ICU admission, n (%) | 187 | 36.17% | 56 | 72.73% | <0.01 |
| Death, n (%) | 100 | 19.34% | 12 | 15.58% | 0.53 |

IQR = interquartile range; HD = hospital day; TDD = total daily dose; ICU = intensive care unit.

[a] Tested using Wilcoxon rank sum test for continuous variables and with Fisher's exact test for categorical variables.

(53 mmol/mol).

## 4. Discussion

In this report, we describe the presentation and outcomes of individuals with NDDM at the time of COVID-19 admission. NDDM was present in 4.0% of all patients admitted with COVID-19 to our institution between March and September 2020, and 13.0% of hospitalized patients with DM and COVID-19. Compared to pre-existing diabetes, NDDM was more common in younger individuals, those of non-White race/ethnicity, and those with higher inflammatory markers. NDDM was associated with lower insulin requirements, longer LOS, and admission to the ICU, but not with death. More than a third of NDDM patients had known pre-diabetes prior to admission, yet almost half regressed to pre-diabetes or normoglycemia at follow-up, and the majority had HbA1c ≤ 7% (54 mmol/mol) at follow-up.

Compared to many reports of high rates of "new-onset diabetes" early in the pandemic,[1–5,21] the rate of NDDM in this study was low. This may be due to the rigorous assessment in our study – for example, 10 individuals in this cohort were believed to have NDDM by their admitting teams but were found to have evidence of prior hyperglycemia upon detailed chart review, including review of outside hospital records. Alternatively, low rates may be due to the stricter definition of NDDM, as compared to some studies which used fasting blood glucose >125–140 mg/dL or any glucose >140–180 mg/dL during admission to diagnose new-onset diabetes or new-onset hyperglycemia in their study population;[1,3–5,22] these other studies may therefore be capturing mild stress hyperglycemia, which was not considered NDDM in our study. We believe that what the literature has often termed "new-onset diabetes" at the time of COVID-19 likely frequently represents stress hyperglycemia at the time of acute inflammatory illness; while we aimed to improve specificity for diabetes diagnosis by raising the glycemic threshold required for diagnosis, 31% of our cohort with newly diagnosed diabetes by any criteria and at least 30-days of follow-up reverted to normoglycemia, suggesting a true diagnosis of stress hyperglycemia rather than new-onset diabetes. In further support of this, of the 13 individuals who met NDDM criteria based solely on severe inpatient hyperglycemia, of whom 9 survived, only one (11%) continued to have evidence of persistent diabetes during follow-up, suggesting that individuals meeting lower inpatient hyperglycemia thresholds may have even lower rates of persistent diabetes after recovery from COVID-19. In our study, individuals with NDDM had, on average, lower glucose levels and HbA1c on admission than those with pre-existing DM. Although

**Table 3**
Regression models in all patients with DM, predicting (A) NDDM, (B) mean TDD of insulin dose during the first three days of hospitalization, (C) LOS, (D) DKA, (E) ICU admission, and (F) death.

| | Model 1: NDDM | | Model 2: Mean TDD of insulin on hospital days 1–3 | | Model 3: LOS | | Model 4: DKA | | Model 5: ICU Admission | | Model 6: Death | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | OR (95% CI) | p value | Beta (95% CI) | p value | Beta (95% CI) | p value | OR (95% CI) | p value | OR (95% CI) | p value | OR (95% CI) | p value |
| Age (per year) | 0.96 (0.94, 0.98) | <0.01 | −0.22 (−0.41, −0.03) | 0.02 | −0.02 (−0.12, 0.09) | 0.77 | 0.99 (0.97, 1.01) | 0.36 | 1.00 (0.99, 1.01) | 0.76 | 1.06 (1.04, 1.08) | <0.01 |
| **Sex** | | | | | | | | | | | | |
| Female | Ref | | Ref | | Ref | | Ref | | Ref | | Ref | |
| Male | 1.22 (0.72, 2.11) | 0.46 | 4.21 (−1.02, 9.43) | 0.11 | 4.65 (1.76, 7.54) | <0.01 | 0.99 (0.57, 1.74) | 0.96 | 1.11 (0.78, 1.58) | 0.57 | 1.56 (0.97, 2.54) | 0.07 |
| **Race** | | | | | | | | | | | | |
| Non-Hisp. White | Ref | | Ref | | Ref | | Ref | | Ref | | Ref | |
| Non-Hisp. Black | 1.16 (0.46, 2.78) | 0.74 | −2.43 (−10.70, 5.84) | 0.56 | 4.35 (−0.23, 8.92) | 0.06 | 0.67 (0.21, 1.79) | 0.46 | 1.25 (0.71, 2.20) | 0.43 | 0.82 (0.39, 1.64) | 0.58 |
| Hispanic | 1.34 (0.69, 2.70) | 0.39 | 1.67 (−4.80, 8.13) | 0.61 | 0.41 (−3.17, 3.99) | 0.82 | 1.29 (0.65, 2.60) | 0.47 | 1.41 (0.91, 2.19) | 0.13 | 0.71 (0.39, 1.26) | 0.25 |
| Non-Hisp. Asian | 1.71 (0.45, 5.28) | 0.38 | 1.00 (−11.16, 13.16) | 0.87 | 10.12 (3.39, 16.85) | <0.01 | 1.19 (0.26, 3.89) | 0.80 | 1.35 (0.58, 3.05) | 0.48 | 0.46 (0.13, 1.33) | 0.19 |
| Other, unknown race | 1.85 (0.79, 4.21) | 0.15 | 2.24 (−6.25, 10.73) | 0.60 | −0.75 (−5.45, 3.95) | 0.75 | 1.67 (0.70, 3.82) | 0.23 | 1.43 (0.80, 2.55) | 0.22 | 0.65 (0.30, 1.34) | 0.26 |
| BMI (per 1 kg/m²) | 0.98 (0.94, 1.02) | 0.30 | 0.65 (0.30, 1.01) | <0.01 | 0.21 (0.01, 0.41) | 0.04 | 1.00 (0.96, 1.03) | 0.88 | 1.02 (1.00, 1.05) | 0.10 | 1.01 (0.98, 1.04) | 0.50 |
| **Diabetes onset** | | | | | | | | | | | | |
| Pre-existing | | | Ref | | Ref | | Ref | | Ref | | Ref | |
| NDDM | | | −12.52 (−20.42, −4.61) | <0.01 | 8.39 (4.02, 12.77) | <0.01 | 0.43 (0.13, 1.12) | 0.12 | 4.34 (2.51, 7.76) | <0.01 | 1.13 (0.49, 2.39) | 0.76 |

NDDM = newly diagnosed diabetes mellitus; TDD = total daily dose; LOS = length of stay; DKA = diabetic ketoacidosis; ICU = intensive care unit; OR = odds ratio; CI = confidence interval; Ref = reference; BMI = body mass index.

multiple studies have reported high rates of severe diabetes outcomes (e. g., DKA) in those with "new-onset diabetes,"[23–26] no study has compared these outcomes directly between patients with COVID-19 and pre-existing diabetes vs. those with COVID-19 and NDDM. We observed comparable rates of DKA in pre-existing diabetes compared to NDDM. One study found relatively higher glycemic levels in those with COVID-19 and "new-onset diabetes", but this was compared to individuals with "new-onset diabetes" *without* infection with COVID-19.[27]

NDDM was more common among younger individuals and less common in those of non-Hispanic White race/ethnicity. This may represent decreased access to care among younger individuals and those who are underinsured or have limited English proficiency. Indeed, there were two main patterns of NDDM noted in this study: mild hyperglycemia occurring in those with pre-existing pre-diabetes and more severe hyperglycemia in patients with minimal medical care prior to admission for COVID-19. This suggests the term "newly diagnosed diabetes" may be more appropriate than "new-onset diabetes," as it is unclear in many cases whether the diabetes is truly new-onset or merely newly recognized. Additionally, given this finding, we believe it is possible that infection with COVID-19 may not directly cause diabetes, but instead may push patients with pre-diabetes into frank diabetes and push patients with undiagnosed diabetes into extremis, as suggested by some experts.[28] To our knowledge, support for this observation has not been previously supported with primary data.

Finally, individuals with NDDM had higher inflammatory markers and more frequently required admission to the ICU than those with pre-existing diabetes, suggesting that the inflammatory response itself may be a contributor to NDDM. In support of this, most cases of NDDM were marked by inpatient hyperglycemia which generally regressed after resolution of acute illness, with only 7.8% requiring insulin after a median follow-up of almost one year. Similar to these results, a recent study in Italy reported high rates of "new-onset diabetes" in patients admitted with COVID-19 (27% of all admitted patients, 43% of all with diabetes), yet reported that 63% of these individuals regressed to normoglycemia, 35% continued to have evidence of hyperglycemia, and only 2% were diagnosed with overt diabetes 6 months after discharge.[22] A second study, also from Italy, evaluated patients admitted with COVID-19 to a single center, including 154 with pre-existing diabetes and 39 with a new diagnosis of diabetes, finding that fasting glucose regressed to pre-admission levels after discharge.[29] Inflammatory markers, including C-reactive protein, ferritin, and lactate dehydrogenase were elevated in patients with diabetes compared to those without diabetes but was not compared between those with pre-existing vs. newly diagnosed diabetes. Although previous studies and our findings do not directly examine physiology, the association of NDDM with high inflammatory markers and ICU care, and the improvement of hyperglycemia after discharge, suggest that this phenomenon may be related to acute inflammation and insulin resistance which resolves over time, rather than autoimmunity or direct injury to beta cells. However, the high rates of DKA in patients with both "new-onset diabetes" and pre-existing DM in many studies suggest that mechanisms of acute insulin deficiency may also be at play, as proposed by several investigators.[30–32]

To our knowledge, this is one of the first studies to describe longitudinal follow-up among patients with NDDM at the time of COVID-19 admission. Its strengths include validation of diabetes type and outcomes by thorough chart review. However, the study is limited by its observational design with patients receiving different length and intensity of follow-up. Similarly, the absence of medical care prior to admission for some patients may have caused misclassification of patients with pre-existing, undiagnosed DM; this is a significant limitation affecting all studies related to "new-onset diabetes" and COVID-19, as COVID-19 may lead individuals with limited access to healthcare to present to care for the first time. Further, an inpatient admission is often not the ideal moment to assess diabetes status as both factors occurring before and during hospitalization can affect glycemic parameters; some individuals here were included based on persistent inpatient severe

hyperglycemia ($>300$ mg/dL (16.7 mmol/L) on two distinct hospital days), which may not represent a true diagnosis of DM; however, we chose to use this criterion to increase specificity based on numerous studies demonstrating the association of new-onset (or newly recognized) hyperglycemia with COVID-19 outcomes.[1–5] Another limitation of this study is the inability to report whether patients received dexamethasone while hospitalized; however, as the surge in Massachusetts occurred in spring 2020, the majority of patients included in this analysis were admitted prior to the announcement of findings from the RECOVERY trial which demonstrated the benefits of dexamethasone therapy for COVID-19–521 (87.7%) before the press release, 524 (88.2%) before publication of the preprint, and 548 (92.3%) before publication of the preliminary results in the New England Journal of Medicine,[20] with equal distribution of pre-existing and newly diagnosed diabetes before and after these dates (92% vs. 91% before publication, respectively; $p = 0.65$). Further, the selection of a high glucose cutoff (greater than 300 mg/dL required on two hospital days) of inpatient hyperglycemia will only include individuals with extreme hyperglycemia, whether due to underlying physiology, acute stress, or significant steroid-induced hyperglycemia, rather than those who experienced more modest steroid-induced hyperglycemia. Finally, the assessment of patients at a single academic center may limit the generalizability and external validity of these findings; the CoviDIAB project, which established a global registry to study "new-onset diabetes" associated with COVID-19, will provide crucial insights to study this phenomenon further.[33]

New diagnosis of DM at the time of admission for COVID-19 represented 13.0% of all cases of DM admitted with COVID-19, was more common in younger individuals and less common in those of non-Hispanic White race/ethnicity and was associated with increased inflammatory markers and ICU admission, but not with death. Among those with follow-up data available, NDDM in the setting of COVID-19 generally had a mild glycemic course after discharge, marked by improvement in glycemia and even remission of diabetes in many instances, suggesting that stress-related insulin resistance, rather than direct beta cell injury, may be the primary driver of NDDM upon COVID-19 admission. Further studies are needed to confirm these findings and explore mechanisms driving acute hyperglycemia related to COVID-19.

## Author contributions

SJC, CC, MSP, and DJW contributed to the conception and design of the study. SJC, CC, DS, ML, MIS, and DJS contributed to data collection. SJC carried out statistical analyses. SJC drafted the manuscript, with critical revisions by MSP, DJW, and all authors. All authors give approval of the manuscript version to be submitted. Guarantor: SJC.

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## Declaration of competing interest

SJC reports employment of a close family member by Johnson & Johnson. MSP reports an investigator-initiated grant funded by Vertex Pharmaceuticals for unrelated studies. DJW reports serving on data monitoring committees for Novo Nordisk. CC, DS, ML, MIS, and DJS report no conflicts of interest.

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