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Association of glycemic control with Long COVID in patients with type 2 diabetes: findings from the National COVID Cohort Collaborative (N3C)

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ABSTRACT

Introduction Elevated glycosylated hemoglobin (HbA1c) in individuals with type 2 diabetes is associated with increased risk of hospitalization and death after acute COVID-19, however the effect of HbA1c on Long COVID is unclear.

Objective Evaluate the association of glycemic control with the development of Long COVID in patients with type 2 diabetes (T2D).

Research design and methods We conducted a retrospective cohort study using electronic health record data from the National COVID Cohort Collaborative. Our cohort included individuals with T2D from eight sites with longitudinal natural language processing (NLP) data. The primary outcome was death or new-onset recurrent Long COVID symptoms within 30–180 days after COVID-19. Symptoms were identified as keywords from clinical notes using NLP in respiratory, brain fog, fatigue, loss of smell/taste, cough, cardiovascular and musculoskeletal symptom categories. Logistic regression was used to evaluate the risk of Long COVID by HbA1c range, adjusting for demographics, body mass index, comorbidities, and diabetes medication. A COVID-negative group was used as a control.

Results Among 7430 COVID-positive patients, 1491 (20.1%) developed symptomatic Long COVID, and 380 (5.1%) died. The primary outcome of death or Long COVID was increased in patients with HbA1c 8% to <10% (OR 1.20, 95% CI 1.02 to 1.41) and ≥10% (OR 1.40, 95% CI 1.14 to 1.72) compared with those with HbA1c 6.5% to <8%. This association was not seen in the COVID-negative group. Higher HbA1c levels were associated with increased risk of Long COVID symptoms, especially respiratory and brain fog. There was no association between HbA1c levels and risk of death within 30–180 days following COVID-19. NLP identified more patients with Long COVID symptoms compared with diagnosis codes.

Conclusion Poor glycemic control (HbA1c≥8%) in people with T2D was associated with higher risk of Long COVID symptoms 30–180 days following COVID-19. Notably, this risk increased as HbA1c levels rose. However, this association was not observed in patients with T2D without a history of COVID-19. An NLP-based definition of Long COVID identified more patients than diagnosis codes and should be considered in future studies.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Type 2 diabetes is associated with increased risk of hospitalization and death following acute COVID-19 infection, and patients with poor glycemic control have worse outcomes compared to those with controlled diabetes. However, the effect of glycemic control on Long COVID is unclear.

WHAT THIS STUDY ADDS

⇒ This study demonstrates that poor glycemic control increases the risk of developing new-onset recurrent Long COVID symptoms, especially respiratory and brain fog symptoms, 30–180 days following COVID infection.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Clinicians should be aware of the increased risk of Long COVID in patients with poor glycemic control, especially respiratory and brain fog symptoms. Additionally, this study highlights that only textual data from clinical notes contained sufficient information to capture Long COVID in these patients, indicating the potential insensitivity of diagnosis codes in identifying Long COVID.

INTRODUCTION

Since the beginning of the COVID-19 pandemic in November 2019, over 750 million individuals globally have been infected with SARS-CoV-2, resulting in over 7 million associated deaths.[1] The burden of disease from COVID-19 lasts beyond the acute phase, with 42% of COVID-19 survivors reporting at least one persistent symptom following acute infection.[2] Long COVID is a multisystem condition consisting of ongoing, relapsing, or new symptoms present 30 or more days after infection with SARS-CoV-2.[3–5] These symptoms include,

but are not limited to, loss of smell/taste, fatigue, brain fog, cough, dyspnea, and muscle aches.[3–6]

Type 2 diabetes (T2D) is associated with increased mortality and morbidity in patients with acute COVID-19 infection, including higher risk of hospitalization, intensive care unit admission and death.[7–9] People with T2D are at a greater risk of coexisting comorbidities, further potentiating the increased risk of health complications.[10] The severity of acute COVID-19 is also associated with glycemic control; increased glycosylated hemoglobin (HbA1c) or blood glucose levels are correlated with higher risk of death, hospitalization, and use of invasive ventilation or extracorporeal membrane oxygenation.[7 11 12] Some studies have shown that HbA1c>8% is associated with greater all-cause mortality and higher incidence of cardiovascular events as well.[13 14] In addition to acute outcomes, diabetes has also been associated with development of long-term sequelae after COVID-19. A machine learning model trained on patients from the National COVID Cohort Collaborative (N3C) database found that patients with pre-existing diabetes have an OR of 1.49 of developing Long COVID compared with those without diabetes.[15] However, Heald *et al*,[16] which based the definition of Long COVID on diagnosis codes, did not show a relationship between HbA1c and Long COVID in people with T2D.

Although Long COVID is widely recognized as a medical condition, it is challenging to identify cases in epidemiologic studies due to ambiguous definitions of the entity and underdiagnosis by clinicians. The International Classification of Diseases Tenth Revision (ICD-10) code U09.9 ('Post COVID-19 condition, unspecified') was initially released in October 2021, but it is not used equally across all demographics and backgrounds, and may not accurately identify the true affected population.[4 17 18] By some estimates, U09.9 diagnosis has a positive predictive value of only 40% for the WHO definition of Long COVID.[4] There have been attempts at defining Long COVID by evaluating symptoms occurring in the months following acute COVID-19 infection, rather than relying on the U09.9 code. These studies typically rely on in-person surveys[3] or ICD-10 codes for identifying symptoms.[5] However, in-person surveys are labor intensive and impractical for large cohorts and, as many of the symptoms of Long COVID are nonspecific, they may be undercaptured with diagnosis codes.[4 19] Natural language processing (NLP) is an artificial intelligence technique that can be used to identify key phrases (ie, symptoms) in clinical notes from the electronic health record (EHR). NLP avoids the manual process of assigning diagnosis codes and may be more thorough and reliable than ICD-10 codes[20] for identifying symptoms of Long COVID.[4 6 21 22] In this analysis, we conducted a retrospective cohort study using NLP data from the N3C to evaluate the association between HbA1c levels and the development of Long COVID or death in people with T2D in the 30–180 days following COVID infection.

METHODS

Study design

We conducted a retrospective cohort study using the N3C, a research database of EHR data from over 80 US healthcare systems. A description of the N3C and the characteristics of the population in the database has been previously published.[23 24] We used a subset of N3C EHR records from eight healthcare sites that applied NLP to extract symptom keywords from clinical notes.[25] Our study population included adult patients with: (1) an index date, defined by a COVID-19 diagnosis code or SARS-CoV-2 laboratory test between January 1, 2021 and June 30, 2022, (2) a preindex diagnosis of T2D, (3) at least one HbA1c measurement between 6 months prior to and 7 days after their index date, (4) at least two clinical notes analyzed by NLP in the 30–180 days prior to index date and (5) at least three healthcare visits or death in 30–180 days after the index date.[26] Patients who died within 30 days of COVID-19 diagnosis were excluded (figure 1). We preconditioned cohort selection on survival at 30 days because this was the point at which a diagnosis of Long COVID can be made. The Stony Brook University Office of Research Compliance determined that the study met criteria for exemption under 45 CFR 46.104(d)(4), IRB2021-00098. The data that support the findings of this study are available from the N3C but restrictions apply to the availability of these data, which were used under license for the current study and therefore are not publicly available. Data are, however, available from the authors on reasonable request and with permission of the N3C.

COVID-positive and COVID-negative cohorts

The COVID-positive cohort was defined by either a positive laboratory test for SARS-CoV-2 or diagnostic code for COVID-19 between January 1, 2021 and June 30, 2022. To assess the incidence and correlation of Long COVID-like symptoms or death with patient factors in the absence of COVID-19, we also ran the analysis in a COVID-negative cohort. The COVID-negative cohort was defined by at least one negative SARS-CoV-2 test between January 1, 2021 and June 30, 2022 and no positive test or diagnosis.[27] The index date was defined as the earliest COVID-19 diagnosis date for the COVID-positive group, and the date of a negative laboratory test for SARS-CoV-2 for the COVID-negative group. For COVID-negative patients who had multiple SARS-CoV-2 tests, each test was included as an independent index date, with statistical weighting inversely proportional to the number of tests an individual received. As an example, if an individual had four negative tests, each was assigned a weight of 0.25, and if a person had two tests each was given a weight of 0.5.

Outcomes and covariates

The primary endpoint was a composite outcome of either Long COVID or death in the 30–180 days following COVID-19 diagnosis. Long COVID was defined as the

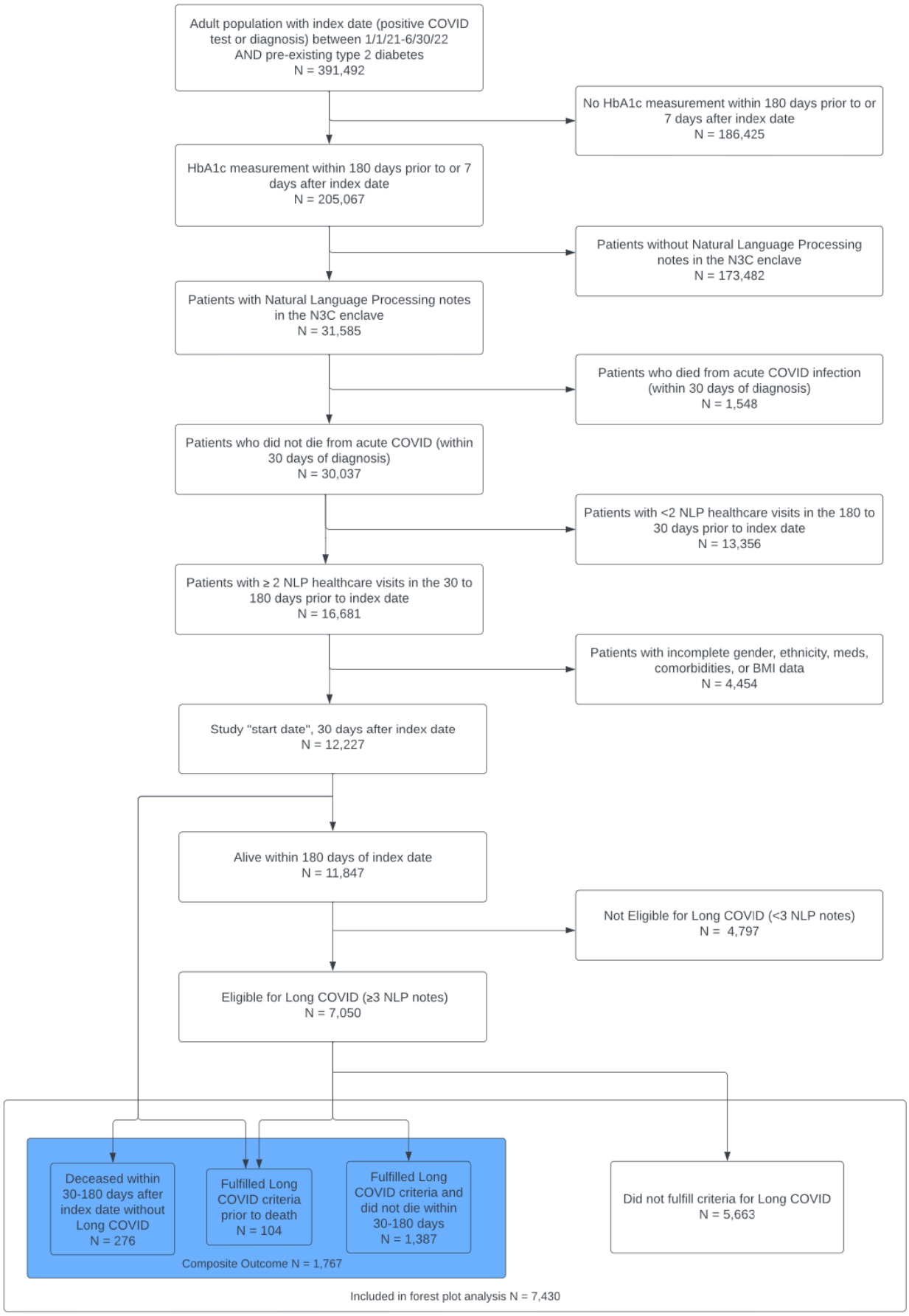

Figure 1 Cohort flow diagram. BMI, body mass index; N3C, National COVID Cohort Collaborative; NLP, natural language processing.

presence of at least one new-onset recurrent symptom category identified by NLP, requiring: (1) three separate dates with any symptom (eg, dyspnea) within a category (eg, respiratory symptoms) in the 30–180 days after index date, and (2) no symptoms within that category in the 30–180 days prior to index date. For patients who had a Long COVID symptom (eg, dyspnea) in the 30–180 days prior to the index date, they could still be diagnosed with Long COVID based on postindex incidence of a new symptom category (eg, brain fog).[4 5] As an example, a patient would need to have any respiratory symptom on three dates in the 30–180 days following COVID-19 and could not have had any respiratory symptom in the 30–180 days prior to index date (online supplemental figure 1a).

Symptoms were based on key terms identified from EHR notes in the N3C NLP dataset.[6] From the list of available symptoms, compiled from 1849 NLP key terms, we divided relevant Long COVID-associated symptoms into seven categories, 'brain fog', 'respiratory symptoms', 'loss of taste/smell', 'musculoskeletal symptoms', 'fatigue', 'cough', and 'cardiovascular symptoms', based on prior symptoms-based definitions of Long COVID[4–6 28 29] (online supplemental figure 1b). Death was included in our composite outcome to prevent bias associated with competing endpoints.[30 31]

The HbA1c measurements and body mass index (BMI), within 6 months prior to or up to 7 days after, that were closest to the index date were included. HbA1c was stratified by range, <6.5%, 6.5 to <8%, 8 to <10%, and ≥10%, and values less than 2% were excluded. We included demographics and comorbidities in the prior year, and diabetes medications within 90 days prior to the index date. Insulin use associated with inpatient encounters was excluded. Gender, age, race and ethnicity information was determined by a combination of observed and self-reported data across sites in the N3C.[23 24]

Statistical plan

Statistical analyses were conducted using Python V.3.6.10 and R V.3.5.1 and data release V.141 (September 14, 2023) under Data Use Request RP-7958530 in Palantir's Foundry platform (2021, Denver, Colorado), a secure analytics enclave housing the N3C data. For the primary analysis, multivariate logistic regression was used to estimate the association of HbA1c with the risk of developing symptomatic Long COVID or death in the 30–180 days following the index date. The model was adjusted for demographics, BMI, comorbidities and diabetes medications. Associations were assessed as adjusted ORs.

We performed a series of sensitivity analyses for our primary analysis (online supplemental section 2): (1) 1-year window: an analysis was performed including symptoms within a year prior to and a year following index date (instead of 6 months) (online supplemental figure 2A); (2) lower threshold: the threshold for the required number of postindex date visits and number of dates with a symptom for Long COVID criteria was set at 2 (instead of 3) (online supplemental figure 2B); (3) symptom interval: Long COVID was defined by death or new-onset symptoms occurring ≥30 days apart from one another (online supplemental figure 2C); (4) matched cohort: using Matchit package V.4.4.0, we performed a 1:1 matching of COVID-positive and negative patients based on index month and year, age, gender, race, ethnicity and HbA1c range, to assess the impact of defining our COVID-negative cohort using a weighted average system compared with cohort matching (online supplemental figure 2D).

We conducted a secondary analysis using a subgroup of patients who met the visit utilization criteria (two preindex visits and three postindex visits in the 30–180 days' window) via both NLP and diagnosis codes, to evaluate the impact of defining Long COVID with NLP compared with diagnosis codes (online supplemental section 3). Three groups were compared: (1) Long COVID based on NLP symptoms, (2) Long COVID based on symptom-coded diagnoses, (3) Long COVID based on the U09.9 diagnosis code[32] in the 30–180 days following index date.

A series of additional analyses in the online supplemental section were conducted as well. To demonstrate the 30–180 day risk of death or Long COVID separately, rather than joined as a composite outcome, analyses were run with the two outcomes independently (online supplemental section 4A,B). The biases associated with our eligibility criteria, and the impact of our post-COVID visit requirements on outcomes, were analyzed in online supplemental section 5. Online supplemental section 6 demonstrated the multivariate analyses for each Long COVID symptom independently, and online supplemental section 7 included prior vaccination (any COVID vaccine prior to index date) as a covariate in the analysis.

RESULTS

There were 7430 COVID-positive patients with T2D eligible for inclusion in the analysis (figure 1). Demographics, comorbidities, and diabetes medication characteristics of the cohort are shown in table 1. Within the COVID-positive population, 54.3% were women, and mean age was 62 years with an SD of 14.4. The cohort was 59.9% White, 17.8% Black or African American, and 23.3% Hispanic or Latino. The COVID-positive group had a mean HbA1c of 7.3% with an SD of 1.8% and median of 6.9% (table 1), while the negative group had a mean, SD and median of 7.1%, 1.8% and 6.7%, respectively. The overall rate of the composite outcome (Long COVID or death) within the COVID-19-positive group was 23.8% (n=1767). The rate of death was 5.1% (n=380) and the rate of Long COVID was 20.1% (n=1491); 104 of these patients (1.4%) met criteria for Long COVID prior to death. Of the 380 individuals who died during the study period, 157 did not meet the post-COVID visit count criteria for Long COVID (<3 healthcare visits). However, 104 of the remaining 223 individuals (46.2%) were diagnosed with Long COVID—a rate significantly

Table 1 Baseline cohort characteristics of COVID-19-positive population

	HbA1c bins				
HbA1c	<6.5	6.5 to <8	8 to <10	>10	Total
Total	2734 (100%)	2689 (100%)	1350 (100%)	657 (100%)	7430 (100%)
Outcomes					
Composite outcome	671 (24.5%)	595 (22.1%)	326 (24.1%)	175 (26.6%)	1767 (23.8%)
Long COVID	552 (20.2%)	495 (18.4%)	290 (21.5%)	154 (23.4%)	1491 (20.1%)
Death	156 (5.7%)	134 (5%)	58 (4.3%)	32 (4.9%)	380 (5.1%)
No outcome	2063 (75.5%)	2094 (77.9%)	1024 (75.9%)	482 (73.4%)	5663 (76.2%)
Symptoms					
Fatigue	165 (6%)	161 (6%)	82 (6.1%)	47 (7.2%)	455 (6.1%)
Respiratory	193 (7.1%)	158 (5.9%)	113 (8.4%)	57 (8.7%)	521 (7%)
Cough	147 (5.4%)	161 (6%)	77 (5.7%)	39 (5.9%)	424 (5.7%)
Smell/taste	<20	<20	<20	<20	30 (0.4%)
Brain fog	114 (4.2%)	76 (2.8%)	63 (4.7%)	33 (5%)	286 (3.8%)
Cardiovascular	133 (4.9%)	100 (3.7%)	62 (4.6%)	39 (5.9%)	334 (4.5%)
Musculoskeletal	47 (1.7%)	50 (1.9%)	30 (2.2%)	<20	140 (1.9%)*
BMI					
<18.5	34 (1.2%)	<20	<20	21 (3.2%)	83 (1.1%)
18.5 to <25	494 (18.1%)	350 (13%)	181 (13.4%)	103 (15.7%)	1128 (15.2%)
25 to <30	752 (27.5%)	730 (27.1%)	336 (24.9%)	162 (24.7%)	1980 (26.6%)
30–35	678 (24.8%)	741 (27.6%)	349 (25.9%)	151 (23%)	1919 (25.8%)
35 to <40	401 (14.7%)	423 (15.7%)	261 (19.3%)	109 (16.6%)	1194 (16.1%)
>40	375 (13.7%)	430 (16%)*	210 (15.6%)*	111 (16.9%)	1126 (15.2%)
Age					
<40	247 (9%)	105 (3.9%)	98 (7.3%)	94 (14.3%)	544 (7.3%)
40 to <50	269 (9.8%)	239 (8.9%)	169 (12.5%)	105 (16%)	782 (10.5%)
50 to <60	497 (18.2%)	488 (18.1%)	329 (24.4%)	190 (28.9%)	1504 (20.2%)
60 to <70	718 (26.3%)	790 (29.4%)	366 (27.1%)	158 (24%)	2032 (27.3%)
70 to <80	673 (24.6%)	751 (27.9%)	268 (19.9%)	78 (11.9%)	1770 (23.8%)
>80	330 (12.1%)	316 (11.8%)	120 (8.9%)	32 (4.9%)	798 (10.7%)
Gender					
Female	1572 (57.5%)	1406 (52.3%)	680 (50.4%)	378 (57.5%)	4036 (54.3%)
Male	1162 (42.5%)	1283 (47.7%)	670 (49.6%)	279 (42.5%)	3394 (45.7%)
Ethnicity					
Non-Hispanic or Latino	2118 (77.5%)	2106 (78.3%)	1006 (74.5%)	468 (71.2%)	5698 (76.7%)
Hispanic or Latino	616 (22.5%)	583 (21.7%)	344 (25.5%)	189 (28.8%)	1732 (23.3%)
Race					
White	1647 (60.2%)	1689 (62.8%)	783 (58%)	328 (49.9%)	4447 (59.9%)
Black	484 (17.7%)	403 (15%)	264 (19.6%)	168 (25.6%)	1319 (17.8%)
Other	603 (22.1%)	597 (22.2%)	303 (22.4%)	161 (24.5%)	1664 (22.4%)
Comorbidities					
Heart disease	1125 (41.1%)	1034 (38.5%)	515 (38.1%)	222 (33.8%)	2896 (39%)
Mild liver disease	382 (14%)	345 (12.8%)	159 (11.8%)	84 (12.8%)	970 (13.1%)
Severe liver disease	133 (4.9%)	82 (3%)	38 (2.8%)	23 (3.5%)	276 (3.7%)
Kidney disease	975 (35.7%)	864 (32.1%)	486 (36%)	203 (30.9%)	2528 (34%)
Cancer	521 (19.1%)	498 (18.5%)	168 (12.4%)	63 (9.6%)	1250 (16.8%)

Continued

Table 1 Continued

	HbA1c bins				
Dementia	93 (3.4%)	88 (3.3%)	46 (3.4%)	20 (3%)	247 (3.3%)
Lung disease	1065 (39%)	836 (31.1%)	411 (30.4%)	176 (26.8%)	2488 (33.5%)
Cerebrovascular disease	327 (12%)	257 (9.6%)	120 (8.9%)	61 (9.3%)	765 (10.3%)
Diabetes medications					
Metformin	858 (31.4%)	1308 (48.6%)	612 (45.3%)	269 (40.9%)	3047 (41%)
Sulfonylurea	169 (6.2%)	393 (14.6%)	274 (20.3%)	104 (15.8%)	940 (12.7%)
Insulin	289 (10.6%)	411 (15.3%)	305 (22.6%)	213 (32.4%)	1218 (16.4%)
DPP-4 inhibitors	137 (5%)	270 (10%)	141 (10.4%)	66 (10%)	614 (8.3%)
SGLT-2 inhibitors	141 (5.2%)	417 (15.5%)	306 (22.7%)	99 (15.1%)	963 (13%)
GLP-1 agonists	217 (7.9%)	423 (15.7%)	335 (24.8%)	138 (21%)	1113 (15%)
TZDs	30 (1.1%)	86 (3.2%)	53 (3.9%)	<20	180 (2.4%)*

Data are presented as n (%), with percentages representing the percent of the HbA1c bin. Cells with <20 data points were reported as <20 to prevent reidentification.
*Indicates rounded/obfuscated values to prevent reidentification.
BMI, body mass index; HbA1c, glycosylated hemoglobin; TZDs, thiazolidinediones.

higher than the baseline Long COVID rate of approximately 20%. Additionally, 104 of the 1491 individuals with Long COVID died (7%) in the 30–180 days' window, a rate much greater than those who did not have Long COVID (119 died out of 5782, or 2.1%). Of COVID-positive individuals with Long COVID, the most frequent symptom category was respiratory (34.9%) or cough (28.4%), followed by fatigue (30.5%), cardiovascular (22.4%), brain fog (19.2%), musculoskeletal (9.6%), and loss of smell/taste (2.0%). Fatigue and respiratory symptoms occurred in combination most frequently, followed by cardiorespiratory symptoms.

The primary outcome of Long COVID (or Long COVID-like symptoms in the COVID-negative group) or death for each HbA1c range in the COVID-positive and COVID-negative cohorts is shown in figure 2. In the COVID-positive group, the risk was greater in patients with HbA1c ranges of 8% to <10% (OR 1.20, 95% CI 1.02 to 1.41) and ≥10% (OR 1.40, 95% CI 1.14 to 1.72) compared with those with an HbA1c range of 6.5% to <8%. Risk was also greater in patients with severe liver disease, cancer, dementia, and outpatient insulin use. Risk was lower in those on metformin, GLP-1 analogs, SGLT-2 inhibitors, and younger age. Patients who had been hospitalized during their acute COVID-19 infection (20%, 1500 of 7430) had a significantly greater risk of death at 30–180 days (OR 3.14, 95% CI 2.51 to 3.93), symptomatic Long COVID (OR 1.73, 95% CI 1.51 to 1.99), and composite outcome of death or Long COVID (OR 2.08, 95% CI 1.83 to 2.37), compared with non-hospitalized individuals with COVID and diabetes. In the COVID-positive cohort, the risk of Long COVID (excluding death as an endpoint) was greater in HbA1c ranges of 8% to <10% and ≥10% (online supplemental figure 4A), while there was no difference in risk of death between HbA1c ranges (online supplemental figure 4B). The results from the sensitivity analyses, accounting for different criteria for utilization, number of, and interval between, symptoms to define the outcome, and study duration showed a similar trend in the association between HbA1c level and development of Long COVID/Long COVID-like symptoms or death (online supplemental section 2). In the COVID-negative group, there was no statistically significant difference in risk of either death or new-onset Long COVID-like symptoms between any HbA1c range. An assessment of the biases associated with our selection criteria suggested that we over-represented those who are older, Hispanic, or have lower BMI (online supplemental section 5).

An analysis of Long COVID symptoms in COVID-positive patients by each symptom category demonstrated a greater risk in patients with HbA1c≥8% for respiratory and brain fog symptoms only (table 2, online supplemental section 6). There was no difference in risk by HbA1c for other symptom categories. Risk of developing new-onset respiratory, cough, or brain fog symptoms, as well as Long COVID itself, was greater in the COVID-positive cohort compared with the COVID-negative group (online supplemental table 6H). Vaccination prior to index date was associated with a lower risk of Long COVID (OR 0.81) in the COVID-positive group (online supplemental section 7). The risk of Long COVID was similar in both vaccinated and unvaccinated groups, with an OR of 1.18 and 1.27, respectively, in patients with HbA1c between 8% and 10%, and OR of 1.36 and 1.30 in patients with HbA1c≥10% compared with patients with HbA1c between 6.5% and 8%.

The results of the secondary analysis showed the rates of Long COVID diagnosis and risk by HbA1c range using (1) NLP keywords, (2) symptom diagnosis codes or (3) the U09.9 code, to define Long COVID (online supplemental section 3). There were 6822 patients with

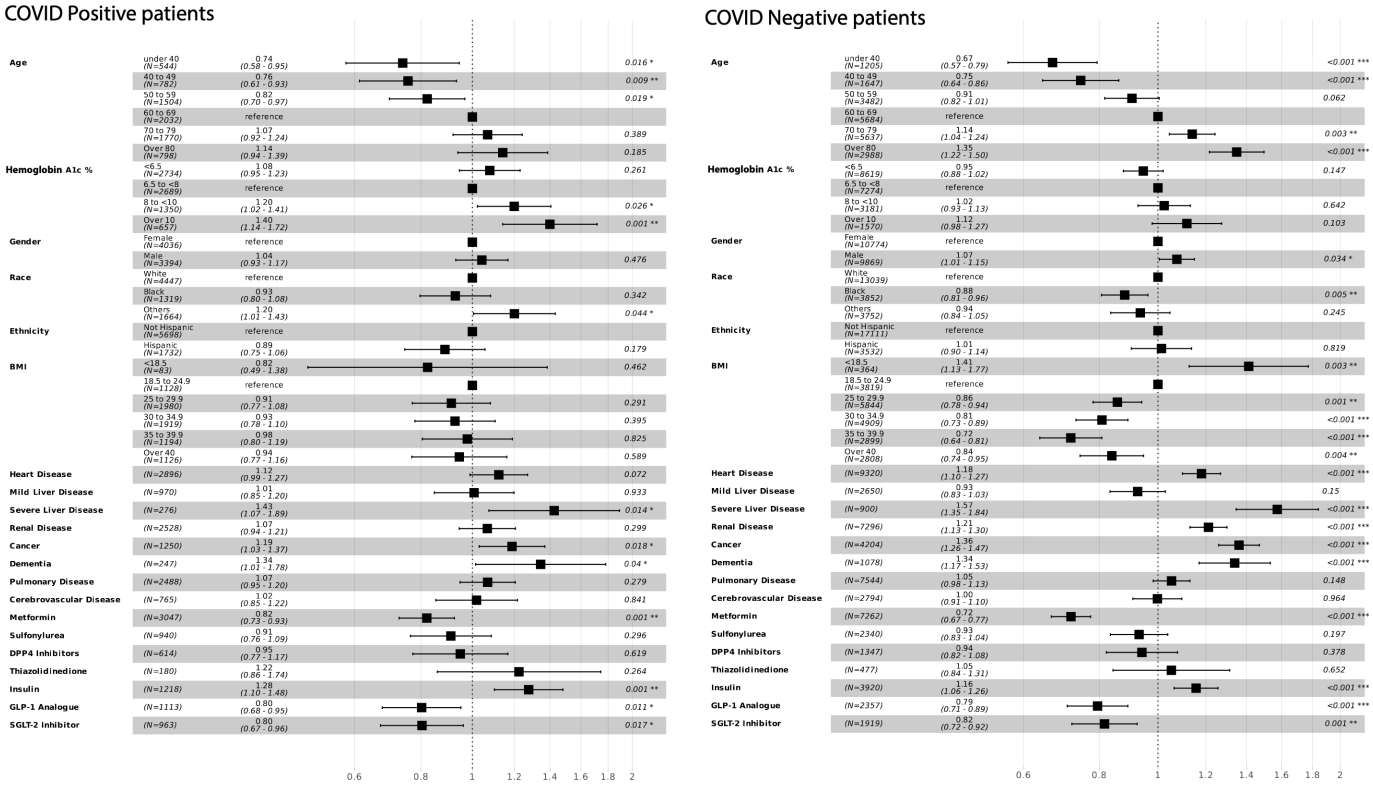

Figure 2 Forest plots showing adjusted ORs and their 95% CIs for Long COVID or death in COVID-positive and COVID-negative patients with type 2 diabetes. Multivariate analysis adjusted for age, gender, race, ethnicity, comorbidities, diabetes medication, glycosylated hemoglobin (HbA1c) range, and body mass index (BMI). *p<0.05, **p<0.01, ***p<0.001.

utilization data that met eligibility for inclusion, with similar demographic composition to the population in the primary analysis. Based on the different methods for defining Long COVID diagnosis, the rate of Long COVID among COVID-positive patients was 2.6% using the U09.9 code, 8.7% using symptom diagnosis codes, and 20.4% using NLP keywords. The association of HbA1c with the development of Long COVID was only seen when using the NLP definition of Long COVID; the two diagnosis code methods failed to show a difference in Long COVID diagnosis rates between HbA1c groups (online supplemental section 3C). Comparing those diagnosed with Long COVID by NLP keywords or symptom diagnosis codes, 65.1% were detected by NLP, 18.5% were detected by symptom diagnosis codes, and 16.4% were detected by both methods (online supplemental section 3A). A Venn diagram comparing the number of patients diagnosed with Long COVID by the three different methods showed

Table 2 Multivariable analysis of the OR of developing Long COVID symptoms, stratified by HbA1c range

	OR (CI) of Long COVID symptom occurrence in COVID-positive patients by HbA1c bin compared with COVID-positive reference HbA1c (6.5% to <8%)			
Symptom category	<6.5%	6.5% to <8%	8% to <10%	>10%
Respiratory	1.23 (0.98 to 1.54)	Reference	1.59 (1.23 to 2.05)	1.72 (1.24 to 2.39)
Cough	0.88 (0.69 to 1.1)	Reference	0.99 (0.74 to 1.3)	1.11 (0.77 to 1.6)
Fatigue	0.99 (0.78 to 1.25)	Reference	1.07 (0.81 to 1.41)	1.33 (0.93 to 1.88)
Brain fog	1.32 (0.97 to 1.8)	Reference	1.86 (1.31 to 2.6)	2.02 (1.31 to 3.1)
MSK	0.92 (0.61 to 1.4)	Reference	1.12 (0.7 to 1.8)	1.28 (0.71 to 2.3)
Cardiovascular	1.30 (0.99 to 1.71)	Reference	1.15 (0.83 to 1.61)	1.47 (0.99 to 2.18)
Smell/taste	2.17 (0.85 to 5.6)	Reference	1.60 (0.53 to 4.9)	2.00 (0.50 to 8.1)
Long COVID (any symptom)	1.08 (0.94 to 1.24)	Reference	1.26 (1.07 to 1.49)	1.44 (1.17 to 1.79)

ORs are relative to reference HbA1c (6.5% to <8%). Results were based on multivariate analyses adjusting for age, race, gender, ethnicity, body mass index (BMI), comorbidities, and diabetes medications. 95% CIs shown in parenthesis. See online supplemental section 6 for the forest plots associated with the ORs in the table.
HbA1c, glycosylated hemoglobin; MSK, musculoskeletal.

that there were approximately 2.3× and over 7× as many patients diagnosed by the NLP method compared with using symptom diagnosis codes or the U09.9 diagnosis code, respectively (online supplemental section 3B). See online supplemental section 3 for data on each symptom category and for a comparison of diagnosis methods.

CONCLUSION

This is the first NLP-based study on the association between glycemic control and development of Long COVID or death in people with T2D following COVID-19 infection, using a large national database. We found that among patients with COVID-19 and T2D, poor glycemic control is associated with an increased risk of developing Long COVID symptoms or death in the 30–180 days following COVID-19, and the risk increases with higher HbA1c levels. This association is not present in COVID-negative patients, suggesting that the development of new-onset Long COVID-like symptoms is not independently correlated with poorly controlled diabetes or contemporary exposures, but rather represents persistent sequelae associated with COVID-19 infections. The outcome driving the results of the COVID cohort is primarily Long COVID, as there was no difference in the risk of death by HbA1c level. Sensitivity analyses also suggest that our results are relatively insensitive to unmeasured confounding or to changes in criteria for defining Long COVID. While there is mixed evidence regarding the role of diabetes in the risk of Long COVID, hyperglycemia and insulin resistance leading to viral persistence in tissues, immune dysregulation and chronic inflammation, and endothelial dysfunction, have been proposed as mechanisms in the development of long-term symptoms.[15 33 34]

For people with T2D, our findings suggest that patients with hyperglycemia have a higher burden of persistent symptoms after COVID-19, particularly respiratory symptoms and brain fog. Our findings are in contrast with a recently published study, Heald *et al*,[16] which did not find any relationship between glycemic control and likelihood of developing Long COVID. However, the difference in findings may be accounted for by several methodological differences. The analysis in the paper by Heald *et al* included a comparison group of people without a diagnosis of T2D in the regression analysis, where differences in HbA1c may not have had any effect on the outcome. Additionally, the diagnosis of Long COVID was based on Long COVID diagnosis codes rather than symptoms from clinical notes. Of note, we also found no association between HbA1c and Long COVID when using Long COVID diagnosis codes.

Our results are consistent with other studies showing negative outcomes associated with poor glycemic control in patients with diabetes, including increased mortality during acute COVID-19 infection,[7 8 12] all-cause mortality,[13 35] myocardial infarction and microvascular complications.[14 36] Our findings are also in line with the recommendations from the American Diabetes Association of an HbA1c target of <7% to 7.5% for 'healthy' patients and <8% for those with chronic comorbidities, and the American College of Physicians' recommended target of 7% to 8%.[37 38] Despite the concern that better glycemic control may be associated with other health-seeking behaviors such as vaccination, we found that after adjusting for vaccination status, and that in both vaccinated and unvaccinated cohorts, patients with higher HbA1c still had an increased risk of Long COVID (online supplemental section 7). Although vaccination was associated with a lower risk of Long COVID, as seen in other studies,[39] patients in our cohort who were vaccinated were more likely to be older, have well-controlled HbA1c, have normal BMI and use SGLT-2i, GLP-1 agonists and DPP-4i. In a separate analysis, we also found higher HbA1c was associated with increased risk of Long COVID during the Omicron variant era, indicating that for the contemporary variant periods, there is still concern for risk of Long COVID with increased HbA1c.

Interestingly, we found that metformin, SGLT-2 inhibitors and GLP-1 agonists were associated with a lower risk of Long COVID and death in the 6 months following COVID infection, which has also been seen in other studies.[9 40] Metformin has been shown to decrease the risk of Long COVID, with hypothesized mechanisms of action including reduction in oxidative stress and inflammation, and prevention of senescent phenotype induction by SARS-CoV-2.[41] The role of other hypoglycemic agents in mitigating Long COVID is under investigation.[42] Insulin use was associated with an increased risk of Long COVID or death, and may be a marker for more severe or longer duration of diabetes and hyperglycemia, a trend noted in previous studies as well.[9]

Surprisingly, in COVID-negative patients, higher BMIs were associated with a reduced risk of Long COVID-like symptoms or death following a negative COVID test. This trend was not observed in the COVID-positive cohort. One possible explanation for this paradoxical finding may be that higher BMI individuals may be more likely to be on GLP-1 or SGLT-2 medications which reduce symptoms and death. The 'obesity paradox' has been noted in several studies, which found patients with elevated BMI have lower all-cause and cardiovascular mortality compared with patients of normal weight.[43]

Long COVID is a challenging disease to study using large-scale EHR data, as the diagnosis code for Long COVID (U09.9) and symptom codes that may suggest Long COVID are underused in clinical practice. The difference in rate and overlap of patients with Long COVID diagnoses based on different methods for defining Long COVID demonstrates the limitation with using coding-based definitions as the gold standard. Our results suggest that NLP may be a more effective and sensitive tool for defining Long COVID both compared with approaches that use symptom

diagnosis codes or the U09.9 code (online supplemental section 3A).[4 16] This is consistent with other NLP-based studies, which have shown better success in analyzing Long COVID with NLP compared with ICD-10 coding.[4 6 21 22] Given the limitations in EHR coding, we would advocate that future studies consider using NLP-based definitions of Long COVID to define cohorts or outcomes. While it is challenging to create and validate NLP data pipelines in clinical data, this study serves as a use case that highlights why text data from clinical notes are important for studying emerging diseases with heterogeneous presentations such as Long COVID.

Our study had several limitations. Based on our definition, we excluded patients who had pre-existing Long COVID-like symptoms that worsened after COVID-19 infection, which may decrease the sensitivity in identifying Long COVID. The study cohort represents a subset of the N3C patients where NLP analyses were conducted and allowed for this analysis, and thus may be biased toward patients who were seen at primarily academic centers. Evaluating the effect of vaccines with EHR data is also challenging because of significant missingness in vaccination data, limiting the reliability of analyses. Furthermore, we suspect the positive effect of vaccination may be partially confounded by health-seeking behavior, as individuals who are more proactive about their health may be more likely to get vaccinated. While documentation of symptoms in clinical text is superior to coding of symptom diagnoses, providers may not document all symptoms that a patient experiences or persistence of symptoms that have been recorded in previous records. Additionally, the widespread use of testing at home makes ascertainment challenging; patients in the COVID-negative control group may have had COVID-19 infection if testing was not done in a health center and recorded in the EHR.

This study shows that in people with T2D, poorer glycemic control with HbA1c≥8% increases the risk of developing Long COVID after COVID-19 infection, specifically with respiratory symptoms and brain fog. NLP was a more effective method for capturing symptoms compared with diagnosis codes, and future studies should consider using NLP-based definitions to study Long COVID.

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Contributors SS, RW, and RM conceived the study. SS and YJY performed the analysis. JEBR and RW provided clinical expertise and reviewed/edited the manuscript. RM, MAH, TS, ZB-D, JDH and DB provided statistical or analytical expertise and reviewed/edited the manuscript. CB provided expertise on diabetes and obesity. SS drafted the manuscript and is the guarantor of this work, and as such had full access to all the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis.

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