Glycemic Control and Clinical Outcomes in U.S. Patients With COVID-19: Data From the National COVID Cohort Collaborative (N3C) Database

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OBJECTIVE

The purpose of the study is to evaluate the relationship between HbA_{1c} and severity of coronavirus disease 2019 (COVID-19) outcomes in patients with type 2 diabetes (T2D) with acute COVID-19 infection.

RESEARCH DESIGN AND METHODS

We conducted a retrospective study using observational data from the National COVID Cohort Collaborative (N3C), a longitudinal, multicenter U.S. cohort of patients with COVID-19 infection. Patients were ≥18 years old with T2D and confirmed COVID-19 infection by laboratory testing or diagnosis code. The primary outcome was 30-day mortality following the date of COVID-19 diagnosis. Secondary outcomes included need for invasive ventilation or extracorporeal membrane oxygenation (ECMO), hospitalization within 7 days before or 30 days after COVID-19 diagnosis, and length of stay (LOS) for patients who were hospitalized.

RESULTS

The study included 39,616 patients (50.9% female, 55.4% White, 26.4% Black or African American, and 16.1% Hispanic or Latino, with mean ± SD age 62.1 ± 13.9 years and mean ± SD HbA_{1c} 7.6% ± 2.0). There was an increasing risk of hospitalization with incrementally higher HbA_{1c} levels, but risk of death plateaued at HbA_{1c} >8%, and risk of invasive ventilation or ECMO plateaued >9%. There was no significant difference in LOS across HbA_{1c} levels.

CONCLUSIONS

In a large, multicenter cohort of patients in the U.S. with T2D and COVID-19 infection, risk of hospitalization increased with incrementally higher HbA_{1c} levels. Risk of death and invasive ventilation also increased but plateaued at different levels of glycemic control.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has claimed >4 million lives worldwide since the first reported case of coronavirus disease 2019 (COVID-19) in December 2019 (1). Diabetes has been implicated as a risk factor for increased mortality and morbidity in patients with COVID-19 infection, with a higher prevalence of diabetes reported in patients with severe outcomes, including

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hospitalization, intensive care unit (ICU) admission, or death (2,3). Several studies suggest a relationship between poor glycemic control and severity of COVID-19 outcomes (4–7). One study from a health maintenance organization in Israel reported a J-shaped association between preinfection glucose and risk for severe COVID-19 in patients with known diabetes, with the lowest risk in patients with a fasting blood glucose (FBG) of 106–125 mg/dL (8). Large population-based cohort studies in the U.K. also demonstrated increased mortality in COVID patients with HbA_{1c} >58 mmol/mol (7.5%) (9) and a J-shaped relationship with lowest risk for patients with type 2 diabetes (T2D) at HbA_{1c} 48–53 mmol/mol (6.5–7.0%), with increased risk at <48 mmol/mol (6.5%) and incrementally increasing risk of mortality with higher HbA_{1c} levels (10). A recent meta-analysis reported that HbA_{1c} measures prior to or at hospital admission were linearly associated with increased COVID-19 mortality, with HbA_{1c} as a continuous variable (11,12), and an increased odds ratio (OR) with a cutoff of 7.5% for HbA_{1c} (12). However, some studies reported no significant relationship between glycemic control and COVID-19–related mortality. While the CORONAvirus SARS-CoV-2 and Diabetes Outcomes (CORONADO) prospective study from 53 French hospitals showed poorer composite outcomes for hyperglycemia, it did not demonstrate an association between HbA_{1c} and mortality in patients with COVID-19 (13). A three-hospital medical center in New York City with a majority Black patient population also showed no significant association between HbA_{1c} and risk of death related to the virus (14).

According to the 2020 Census statistics, the U.S. population is racially and ethnically diverse, with Black or African American and Asian race alone or in combination comprising 14.2% and 7.2% of the population, and 18.3% reporting Hispanic or Latino ethnicity (15), respectively. Current large studies conducted in countries with more readily accessible population-level data are demographically different from the U.S., and to our knowledge, studies of the relationship between HbA_{1c} and COVID-19 outcomes in the U.S. are currently limited to single health systems or studies with a relatively small sample size. A U.S. retrospective study of 451 patients with diabetes and hyperglycemia at 88 hospitals showed a longer length of stay (LOS) and higher mortality (4), and a small single-site study showed a statistically significant increase in hospital and ICU LOS with shorter ventilator-free days in patients with HbA_{1c} >6% (16).

In this study, we use data from the National COVID Cohort Collaborative (N3C), a multisite partnership that aggregates and harmonizes electronic health record (EHR) data across clinical organizations and health system entities in the U.S. to create a longitudinal, multicenter cohort of patients with COVID-19 infection (17,18). Our study goal was to evaluate the relationship between HbA_{1c} and outcomes in patients with T2D with acute COVID-19 infection in the U.S., including mortality, invasive ventilation or extracorporeal membrane oxygenation (ECMO), hospitalization, and inpatient LOS.

RESEARCH AND DESIGN METHODS

Study Design and Population

We conducted a retrospective cohort study using EHR data from U.S. health care systems contributing to the N3C Data Enclave. A description of the rationale, design, infrastructure, and deployment of N3C has been published previously (17), as well as characterizations of the adult (18) and pediatric (19) populations. N3C includes EHR-derived patient data dating back to 1 January 2018 from patients with either positive laboratory tests for SARS-CoV-2 or diagnostic codes for COVID-19 (17,18). Data are continuously provided to N3C from health care systems in their respective native data model, mapped to the Observational Medical Outcomes Partnership (OMOP) common data model (https://ohdsi.github.io/TheBookOfOhdsi/), and made available for authorized research after passing quality checks.

The current study population included adults at least 18 years of age with any prior diagnosis of T2D and at least one HbA_{1c} measured within 1 year before and up to 7 days after the first diagnosis of COVID-19 infection. T2D diagnosis was defined by the presence of an ICD-10 diagnosis code for T2D prior to the date of COVID-19 diagnosis. Deidentified data were accessed and analyzed using Palantir (2021, Denver, CO), a secure analytics platform within the N3C data enclave. The Stony Brook University Office of Research Compliance determined that the study did not constitute human subjects research.

Measures and Outcomes

The study's primary outcome was mortality within 30 days of the index date, which we defined as the date of the first COVID-19 diagnosis by either a positive SARS-CoV-2 PCR test or diagnosis code. For patients who had died but were missing a recorded date of death in the data, the date used for analysis was the date of the last measurement, medication start date, or condition record for the patient. Secondary outcomes included treatment with invasive ventilation or ECMO, hospitalization, and LOS for a subgroup of patients who were hospitalized. Hospitalization was defined as an inpatient visit with a start date up to 7 days before or 30 days after the index date. Patients who died were excluded from the LOS analysis. Concepts for invasive ventilation or ECMO were identified using templates from the N3C Knowledge Store, a resource in the N3C Data Enclave that is created and validated by N3C domain experts (18,20). Invasive ventilation was defined by a condition, procedure, or observation for invasive ventilation or ECMO during the visit.

Concepts for diabetes, HbA_{1c}, preexisting comorbidities, and medications prior to the COVID-19 diagnosis were identified using code sets developed by the Diabetes and Obesity Domain Team or templates from the N3C Knowledge Store (18–21). The most recent HbA_{1c} measurement within 365 days before or 7 days after the index date was included, and HbA_{1c} data were categorized as <6%, 6 to <7%, 7 to <8%, 8 to <9%, 9 to <10%, and >10%. HbA_{1c} values <4% were excluded from the analysis. To adjust for confounders that could affect adverse outcomes or HbA_{1c} levels, we included known comorbidities that contribute to COVID-19 mortality risk and medications that affect HbA_{1c} level (22,23). Comorbidities were defined using the updated Charlson Comorbidity Index (24), and information about medications was included for patients with at least one medication record in the 90 days prior to the COVID-19 diagnosis. Demographic information and BMI were also included in the analysis. Groupings of comorbidities were selected using N3C

Knowledge Store templates for Charlson Comorbidity Index categories and included myocardial infarction, congestive heart failure (CHF), peripheral vascular disease, stroke, dementia, pulmonary disease, mild and severe liver disease, renal disease, cancer, and HIV. For data quality assurance, sites reporting a <1% rate for an outcome of interest were excluded from the analysis.

Statistical Analysis

Statistical analysis was conducted using Python 3.6 and R 3.5.1 in the Palantir platform in the N3C Data Enclave. A Cox proportional hazard model was used to analyze hazard ratios (HRs) for mortality. Multivariable logistic regression was used to evaluate hospitalization and invasive ventilation outcomes, and multivariable linear regression was used to analyze LOS outcomes. All models were fully adjusted for demographic covariates, BMI, comorbidities, and medications. Across all analyses, an HbA_{1c} of 6 to <7% served as the reference category. *P* values <0.05 were considered statistically significant. Analyses were conducted using data with a release date of 22 July 2021.

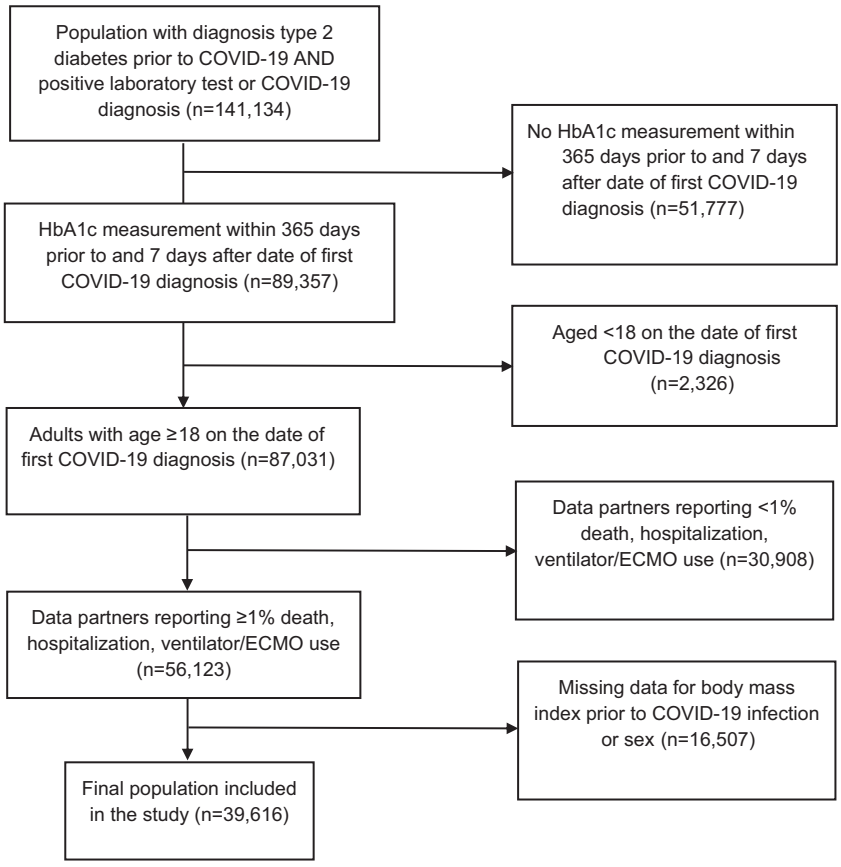

Figure 1—Study flow diagram of the cohort.

RESULTS

There were 39,616 individuals across 35 sites who were eligible for inclusion in the analysis (Fig. 1). The demographic and clinical characteristics of the cohort are reported in Table 1. Of the study population, 50.9% were women, and mean ± SD age was 62.1 ± 13.9 years. The cohort was 55.4% White, 26.4% Black or African American, and 16.1% Hispanic or Latino. The overall rate of mortality was 5.7% (*n* = 2,242), and rate of invasive ventilation or ECMO was 7.0% (*n* = 2,779). The overall rate of hospitalization was 49.0% (*n* = 19,401) with a mean ± SD LOS of 11.7 ± 18.1 days. The mean ± SD of HbA_{1c} measurements was 7.6% ± 2.0, and the most recent HbA_{1c} level was measured within 90 days of the COVID-19 diagnosis for 65.5% and within 180 days for 85.9% of individuals.

The results from the Cox proportional hazards model for death are shown as HRs with 95% CIs in Fig. 2. Relative to a HbA_{1c} level of 6 to <7% in the fully adjusted survival model, the HR for death was significantly increased with HbA_{1c} levels 7 to <8% (HR 1.17, 95% CI 1.04–1.32), 8 to <9% (HR 1.40, 95% CI 1.22–1.60), 9 to <10% (HR 1.37, 95% CI 1.15–1.63), and >10% (HR 1.46, 95% CI 1.24–1.71).

Additional demographic risk factors for death included increasing age, male sex, and Hispanic or Latino ethnicity. Individuals with BMI <25 kg/m^2 or >40 kg/m^2, history of CHF, dementia, severe liver disease, or renal disease, and with insulin prescription within the prior 90 days had higher risk of death. With the exception of thiazolidinediones and dipeptidyl peptidase 4 (DPP-4) inhibitors, noninsulin diabetes medications were associated with a decreased risk of mortality.

The results from the multivariable logistic regressions for hospitalization and invasive ventilation or ECMO outcomes are shown as odds ratios (ORs) with 95% CIs in Fig. 3. The adjusted ORs for hospitalization increased incrementally with each HbA_{1c} category >6% to <7%, with an OR of 2.32 (95% CI 2.15–2.50) for HbA_{1c} >10%. Odds of invasive ventilation or ECMO also increased incrementally with each HbA_{1c} category >6 to <7% and plateaued with HbA_{1c} 9 to <10 (OR 1.59, 95% CI 1.36–1.85) and >10% (OR 1.60, 95% CI 1.40–1.83). There were higher odds of hospitalization in Black or African American and Asian or Pacific Islander racial groups, but increased odds of invasive ventilation or ECMO were only seen in the Asian or Pacific Islander group. Hispanic or Latino ethnicity was associated with higher odds of both hospitalization and invasive ventilation or ECMO. The relationship between BMI and hospitalization was U shaped, with an increased risk at both BMI <25 kg/m^2 and >40 kg/m^2 relative to patients with a BMI between 30 and 34.99 kg/m^2. For the subgroup of patients who required hospitalization, HbA_{1c} level did not significantly affect LOS. There was, however, a significant increase in LOS in patients with a BMI <20 kg/m^2, Hispanic or Latino ethnicity, renal disease, cancer, and use of insulin or a glucagon-like peptide 1 (GLP-1) receptor agonist within 90 days of the COVID-19 diagnosis. The relationship between age and LOS was U shaped, with shorter hospitalization days in the <40 and >80 age-groups, and longest LOS in the 60–69 group (Supplementary Figure 1).

Table 1—Baseline cohort characteristics and death within 30 days of COVID-19 diagnosis

	Population (n = 39,616)	Deaths (n = 2,242)	P value
Sex			<0.01
Male	19,431 (49.1)	1,310 (58.4)	
Female	20,185 (50.9)	932 (41.6)	
Age (years)			<0.01
<40	2,728 (6.9)	21 (1.0)	
40–49	4,352 (11.0)	70 (3.1)	
50–59	8,550 (21.6)	236 (10.5)	
60–69	11,128 (28.1)	524 (23.4)	
70–79	8922 (22.5)	801 (35.7)	
≥80	3,936 (9.9)	590 (26.3)	
Race			0.64
White	21,946 (55.4)	1,268 (56.6)	
Black or African American	10,467 (26.4)	569 (25.4)	
Asian or Pacific Islander	1,098 (2.8)	68 (3.0)	
Other/missing data	6,105 (15.4)	337 (15.0)	
Ethnicity			<0.01
Non-Hispanic or Latino	31,084 (78.5)	1,720 (76.7)	
Hispanic or Latino	6,396 (16.1)	363 (16.2)	
Missing data	2,136 (5.4)	159 (7.1)	
BMI (kg/m^2)			<0.01
<20	822 (2.2)	96 (4.3)	
20–24.9	4,526 (11.4)	374 (16.7)	
25–29.9	10,224 (25.8)	639 (28.5)	
30–34.9	10,111 (25.5)	521 (23.2)	
35–39.9	6,794 (17.1)	325 (14.5)	
≥40	7,139 (18.0)	287 (12.8)	
Preexisting comorbidities			
Myocardial infarction	5,375 (13.6)	510 (22.7)	<0.01
CHF	9,475 (23.9)	972 (43.4)	<0.01
Peripheral vascular disease	8,427 (21.3)	712 (31.7)	<0.01
Stroke	7,060 (17.8)	628 (28.0)	<0.01
Dementia	1,878 (4.7)	290 (12.9)	<0.01
Pulmonary disease	12,638 (31.9)	830 (37.0)	<0.01
Mild liver disease	6,078 (15.3)	347 (15.4)	0.84
Severe liver disease	1,185 (3.0)	123 (5.5)	<0.01
Renal disease	12,300 (31.0)	1,185 (52.8)	<0.01
Cancer	5,754 (14.5)	476 (21.2)	<0.01
HIV	444 (1.1)	<20*	0.07
Medications			
Metformin	10,408 (26.3)	257 (11.5)	<0.01
GLP-1 receptor agonist	3,160 (7.9)	80 (3.6)	<0.01
DPP-4 inhibitor	2,172 (5.5)	97 (4.3)	0.015
Sodium–glucose cotransporter 2 inhibitor	2,122 (5.4)	44 (2.0)	<0.01
Sulfonylurea	3,653 (9.2)	134 (5.9)	<0.01
Thiazolidinedione	503 (1.3)	<20*	<0.01
Insulin	11,172 (28.2)	770 (34.3)	<0.01
Severity of illness			
Hospitalization	19,401 (49.0)	2,067 (92.2)	<0.01
Invasive ventilation or ECMO	2,779 (7.0)	1,160 (51.7)	<0.01

Data are presented as n (%). *Cells with <20 data points were reported as <20 to avoid risk of reidentification.

CONCLUSIONS

In this analysis of a large, multicenter, U.S. cohort of patients with T2D and COVID-19 infection, we analyzed the relationship between HbA_{1c} and acute COVID-19–related outcomes. Compared with patients with an HbA_{1c} of 6% to <7%, mortality increased in parallel with rising HbA_{1c} but the amount of increased risk plateaued at >8%. This was consistent with prior results showing increased mortality associated with HbA_{1c} >7.5%, but contrasted with results from Holman et al. (10), which showed increasing risk at each HbA_{1c} level >6.5–7.0%. The variability in findings may reflect differences in our cohort and inclusion of certain covariates, such as noncardiovascular comorbidities and medications for diabetes treatment prior to COVID-19 infection (10). Similarly, we found an increased odds of invasive ventilation and ECMO, with a plateau in the relative increase

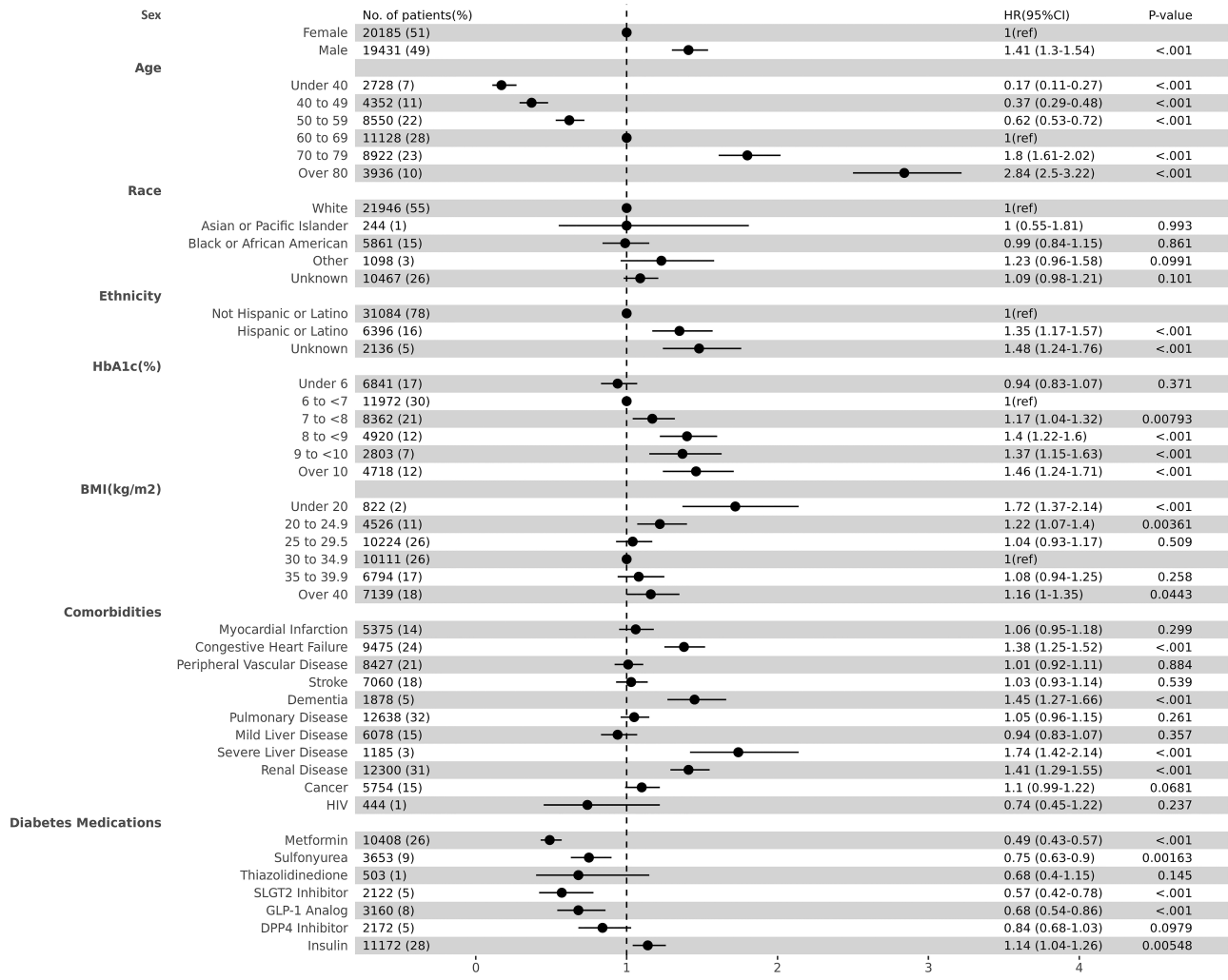

Figure 2—Forest plots showing adjusted HRs for death in patients with diabetes within 30 days of COVID-19 diagnosis (n = 39,616). SGLT2, sodium–glucose cotransporter 2.

at HbA_{1c} >9%. Our findings suggest that while worse glycemic control affects risk of certain outcomes, such as hospitalization for COVID-19, the effect plateaus at certain levels of glycemia for more severe outcomes such as invasive ventilation or ECMO and death. This analysis on the impact of increasing HbA_{1c} on COVID-19 mortality and ventilation or ECMO outcomes does not reflect the traditional dose-dependent exposure risk of glycemia established in the literature for long-term microvascular complications (25,26). Our findings suggest that in the context of acute infection with COVID-19, there are possibly glycemic thresholds of risk for severe outcomes. While factors such as inflammation and cardiovascular events have been proposed (27–30), it is difficult to elucidate the underlying mechanisms for increased risk and the plateau at higher HbA_{1c} levels. Although prior studies have shown an association between increasing HbA_{1c} and level of inflammatory markers, the HbA_{1c} levels studied were lower than the HbA_{1c} level at which risk plateaued in our study (31–33). In the UK Prospective Diabetes Study (UKPDS) 35 study by Stratton et al. (26), there was a plateau in the risk of increasing glycemia on long term macrovascular complications at higher HbA_{1c} levels that contrasted with the linearly increased risk of microvascular complications.

In contrast to prior published studies, the diversity of our cohort was more comparable to the general population in the U.S. As seen previously, there was an increased risk of hospitalization and death in acute COVID-19 infection for patients who identify as Hispanic or Latino (34). Patients who identify as Black or African American had a significantly higher rate of hospitalization but no difference in LOS, mortality, or need for invasive ventilation for ECMO. To evaluate for the interaction between race and HbA_{1c}, we analyzed mortality risk in subpopulations of Black and Caucasian patients to evaluate for race-associated effects, and while subtle differences were seen for each race, we did not find any meaningful difference in the curves in each subpopulation. Interestingly, while Asian and Pacific Islander race was associated with higher odds of hospitalization and invasive ventilation or ECMO, risk of death was not significantly increased.

Regarding comorbid disease, there was increased risk of all adverse outcomes in patients with CHF and renal disease and increased risk of hospitalization and death for those with advanced liver disease and dementia. Individuals

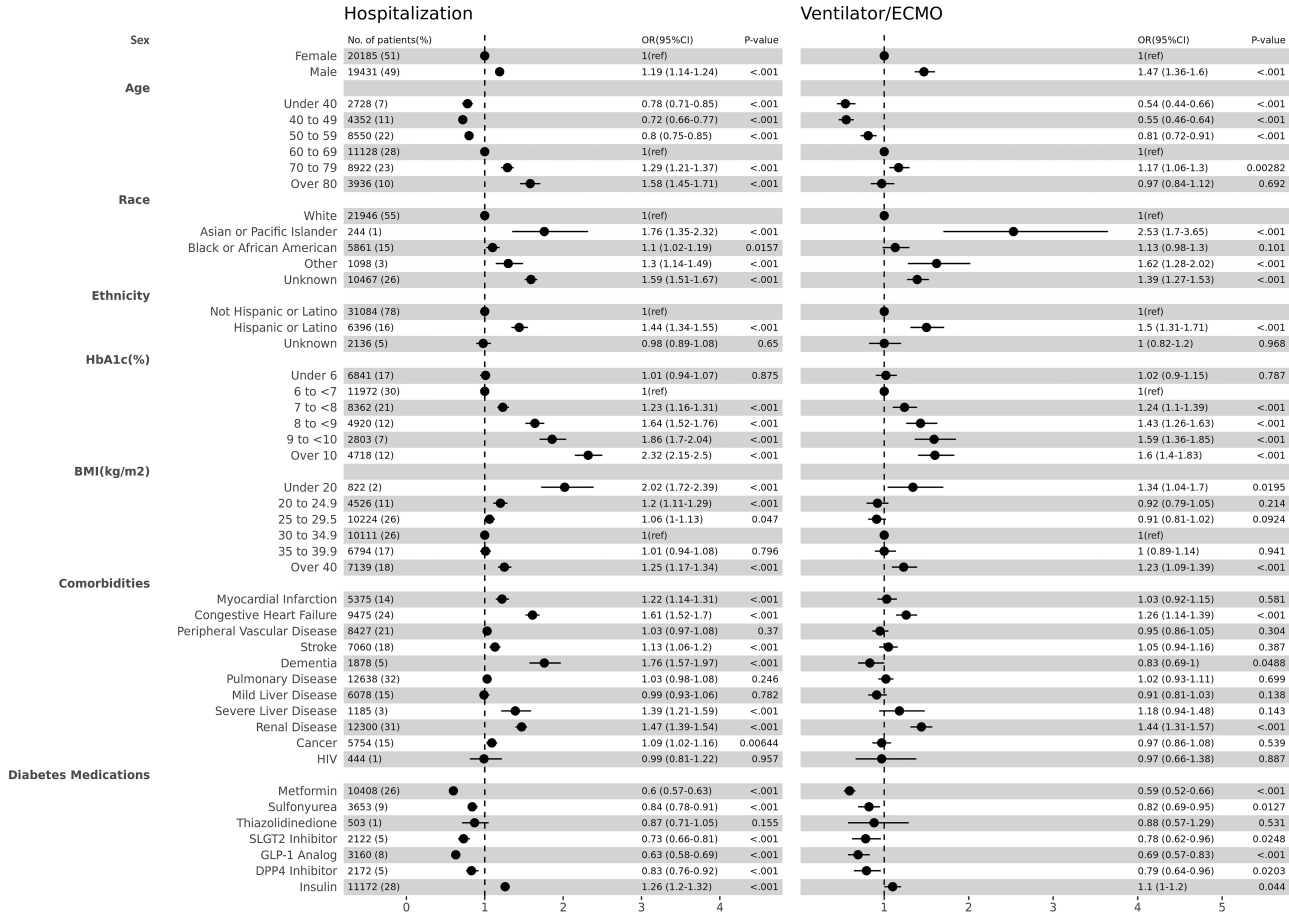

Figure 3—Forest plots showing adjusted ORs for hospitalization and invasive ventilation or ECMO in patients with diabetes within 30 days of COVID-19 diagnosis (*n* = 39,616).

with dementia had significantly lower odds of invasive ventilation or ECMO, which may reflect greater emphasis on palliative practices for this population. Relative to patients with a BMI between 30 and 34.99 kg/m^2, those with a BMI $<$20 kg/m^2 were at much higher risk for all adverse outcomes, which may be reflective of a frailer population with poor nutritional status. Patients with BMI $>$40 kg/m^2 had increased risk of hospitalization, ventilation or ECMO, and death. Noninsulin diabetes medications, with the exception of DPP-4 inhibitors for mortality and thiazolidinediones for all outcomes, were associated with lower risk of mortality, hospitalization, and invasive ventilation. These findings align with previously reported N3C data studying the protective effects of sodium–glucose cotransporter 2 inhibitors and GLP-1 receptor agonists versus DPP-4 inhibitors (21), and metformin (35–37).

Our study had several limitations, including the inability to delineate the duration of diabetes of our cohort. It has long been recognized that diabetes duration confers a higher risk of both micro- and macrovascular complications (26,38), which could potentially impact the risk for COVID-19 outcomes. Although we were able to look at associations between glycemic control and acute COVID-19 infection, causal analyses are difficult to establish with the limitations of the database and our current analysis. The study cohort may also be biased toward patients with more severe illness, with a relatively high hospitalization rate of 49.0%, as the data sources for the N3C Data Enclave are primarily from academic medical centers. A limitation in using EHR data is that the data are only available if the patient was seen by a provider who uses the reporting EHR system. In our study, we excluded patients who did not have an HbA_{1c} reported (36.6%), which could represent a heterogeneous population of patients who are followed by another health system or provider, those without HbA_{1c} measurements due to poor follow-up, or patients with new diagnosis of T2D. While our study cohort is more representative of the demographics of the U.S. population than prior studies, there are some differences, with Black and African American individuals comprising 26.4% of the study cohort and 14.2% of the general population, and Asian and Pacific Island individuals comprising 2.8% of the cohort and 7.2% of the U.S. population. Additionally, unlike studies where cause of death was confirmed by death certificate, we were unable to assess COVID-19–specific mortality.

Despite these limitations, this study represents the largest multicenter U.S. cohort study of HbA_{1c} and COVID-19 outcomes to date. We report that risk of hospitalization increased with incrementally

higher HbA_{1c} levels. Risk of death and invasive ventilation also increased relative to those with good glycemic control, but this effect plateaued at different levels of glycemia.

APPENDIX

N3C Consortium. Tellen Bennett, Elena Casiraghi, Christopher Chute, Peter DeWitt, Michael Evans, Kenneth Gersing, Andrew Girvin, Melissa Haendel, Jeremy Harper, Janos Hajagos, Stephanie Hong, Jared Huling, Emily Pfaff, Jane Reusch, Til Sturmer, Kenneth Wilkins, and Jacob Wooldridge.

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