



Excess Mortality in COVID-19-Positive Versus COVID-19-Negative Inpatients With Diabetes: A Nationwide Study

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Diabetes is a major risk factor for death in those with coronavirus disease 2019 (COVID-19) infection (1). However, even those with diabetes who do not have a COVID-19 infection have an increased risk for mortality compared with those without diabetes (2). In the current study, we focused on hospitalized patients with diabetes and compared those who tested positive for COVID-19 infection to those who tested negative. Our aim was to identify the excess risk of mortality that COVID-19 infection adds among inpatients with diabetes and to assess if this increased mortality can be explained by underlying comorbidities/complications or if it is more closely related to the COVID-19 disease.

For this cohort study, we used data from the Veterans Affairs (VA) Central Data Warehouse. We focused only on inpatients with diabetes who were evaluated for COVID-19 infection from 3 March 2020 to 21 May 2020 and for whom we were able to extract the available covariates. To avoid inaccurate diagnoses of diabetes, such as stress-induced hyperglycemia, we included only those who had diabetes prior to 1 January 2019. Diabetes was defined by ≥ 2 ICD-9/ICD-10 codes within 2 years prior to 1 January 2019 from inpatient

or outpatient visits on separate days or prescription for diabetes medications within the current year (3). Prescriptions for metformin are sometimes provided to people with prediabetes and, therefore, may not always be a reliable indicator of diabetes diagnosis.

Subjects were characterized as positive for COVID-19 infection by either a confirmed positive laboratory test (90.68%) or by clinical case review (9.32%), based on Centers for Disease Control and Prevention recommendations: 1) at least one of the symptoms of cough, shortness of breath, or difficulty breathing; 2) severe respiratory illness, with clinical or radiographic evidence of pneumonia and/or acute respiratory distress syndrome; and 3) no alternative, more likely diagnosis (4). COVID-19 testing was not performed universally in all patients but only in high-risk individuals and those with signs or symptoms suggestive of COVID-19 infection, as clinically indicated. We defined mortality as death from any cause up to 30 days after subjects were evaluated for COVID-19 (through 21 June 2020). Covariates studied were, among others, demographics, comorbidities/complications (coronary artery disease, cancer, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary

disease, cerebrovascular accident, hypertension, dyslipidemia, liver disease, diabetic neuropathy, peripheral vascular disease, and diabetic retinopathy, based on ICD-9/ICD-10 codes reported within the last 2 years), diabetes medications (defined as insulin only, noninsulin, insulin and noninsulin, or none), and the Charlson comorbidity index (CCI) score.

Three weighted Poisson regression models (SAS proc GENMOD) quantified relative mortality rate as a function of COVID-19 status ([mortality rate in COVID-19-positive patients]/[mortality rate in COVID-19-negative patients]). The dependent variable was mortality. Each analysis contained COVID-19 status (positive vs. negative) with or without additional independent variables. The regressions were weighted by the stabilized inverse probability of having COVID-19 (5). The study was approved by the University of Maryland Institutional Review Board and the Baltimore VA research committee.

Our cohort included 6,014 inpatients with diabetes, either COVID-19 positive ($n = 698$) or negative ($n = 5,316$). 26.6% of the hospitalized patients with diabetes were evaluated for COVID-19 infection. The crude mortality rate was 25.2% for COVID-19-positive vs. 7.3%

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Table 1—Mortality rates and rate ratios of the mortality rates among COVID-19-positive and COVID-19-negative subjects

Model	MR COVID-19-positive	MR COVID-19-negative	RR of MR COVID-19-positive vs. COVID-19-negative (95% CI)
Unadjusted	25.2%	7.3%	3.46 (2.90–4.14)
Model 1	21.9%	6.0%	3.67 (3.09–4.37)
Model 2	28.3%	7.8%	3.62 (3.04–4.32)

Model 1 was adjusted for age, sex, race, BMI, HbA_{1c}, and CCI. Model 2 was adjusted for model 1 and for smoking history, diabetes medications, ACE inhibitor/angiotensin receptor blocker therapy, coronary artery disease, cancer, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease, cerebrovascular accident, hypertension, dyslipidemia, liver disease, neuropathy, peripheral vascular disease, and retinopathy. MR, mortality rate; RR, relative rate.

for COVID-19-negative subjects. No statistically significant interactions between the different covariates collected with COVID-19 infection and mortality were found (data not shown). In the unadjusted model (Table 1), those who tested positive for COVID-19 infection were 3.46 times more likely to die than those who tested negative (relative ratio [RR] 3.46, 95% CI 2.90–4.14). Following adjustment for age, sex, race, BMI, HbA_{1c}, and CCI (model 1), COVID-19-positive patients still had a higher mortality risk than COVID-19-negative subjects (RR 3.67, 95% CI 3.09–4.37). The results remained almost unchanged in the fully adjusted model (model 2) when we adjusted for multiple covariates (RR 3.62, 95% CI 3.04–4.32).

Our study is one of few nationwide studies evaluating COVID-19 infection in patients with diabetes. Additional strengths are adjustment for multiple covariates and comorbidities/complications as well as the adequate observation period (30 days) to determine the mortality outcome. Finally, we included only subjects with a history of diabetes, excluding those who may have developed COVID-19 stress-induced hyperglycemia. Limitations include that this was a retrospective cohort study, including mainly male subjects, and important confounding factors may not have been ascertained in

our analysis. As some patients with prediabetes are treated with metformin, we may have included them as having diabetes. Additionally, we may have misclassified subjects with true COVID-19 infection, as COVID-19 testing was not performed in all inpatients. Our data were collected early in the pandemic; therefore, the mortality rates in the later phases of the COVID-19 pandemic may have changed, as our knowledge about COVID-19 infection has increased and more treatment options are available.

In summary, we report that hospitalized patients with diabetes who were positive for COVID-19 infection were 3.6 times more likely to die than those who were negative for COVID-19 infection, a result that was not materially influenced by differences in demographics or comorbidities.

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