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Original Research

Association Between Diabetes and Mortality Among Adult Patients Hospitalized With COVID-19: A Cohort Study of Hospitalized Adults in Ontario, Canada, and Copenhagen, Denmark

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Key Messages

- Diabetes has been reported to be a risk factor associated with a more severe course of COVID-19.
- The association between diabetes and adverse clinical outcomes has not been sufficiently characterized.
- After controlling for several confounders, diabetes was only weakly associated with 30-day risk of death in hospitalized patients.

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ABSTRACT

Objectives: Diabetes has been reported to be associated with an increased risk of death among patients with COVID-19. However, the available studies lack detail on COVID-19 illness severity and measurement of relevant comorbidities.
Methods: We conducted a multicentre, retrospective cohort study of patients 18 years of age and older who were hospitalized with COVID-19 between January 1, 2020, and November 30, 2020, in Ontario, Canada, and Copenhagen, Denmark. Chart abstraction emphasizing comorbidities and disease severity

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was performed by trained research personnel. The association between diabetes and death was measured using Poisson regression. The main outcome measure was in-hospital 30-day risk of death.
Results: Our study included 1,133 hospitalized patients with COVID-19 in Ontario and 305 in Denmark, of whom 405 and 75 patients, respectively, had pre-existing diabetes. In both Ontario and Denmark, patients with diabetes were more likely to be older; have chronic kidney disease, cardiovascular disease, and higher troponin levels; and be receiving antibiotics, when compared with adults without diabetes. In Ontario, 24% (n=96) of adults with diabetes died compared with 15% (n=109) of adults without diabetes. In Denmark, 16% (n=12) of adults with diabetes died in hospital compared with 13% (n=29) of those without diabetes. In Ontario, the crude mortality ratio among patients with diabetes was 1.60 (95% confidence interval [CI], 1.24 to 2.07) and in the adjusted regression model it was 1.19 (95% CI, 0.86 to 1.66). In Denmark, the crude mortality ratio among patients with diabetes was 1.27 (95% CI, 0.68 to 2.36) and in the adjusted model it was 0.87 (95% CI, 0.49 to 1.54). Meta-analysis of the 2 rate ratios from each region resulted in a crude mortality ratio of 1.55 (95% CI, 1.22 to 1.96) and an adjusted mortality ratio of 1.11 (95% CI, 0.84 to 1.47).
Conclusion: The presence of diabetes was not strongly associated with in-hospital COVID-19 mortality independent of illness severity and other comorbidities.

Motd clés:
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RÉSUMÉ

Objectifs : Le diabète a été associé à une augmentation du risque de mortalité chez les patients atteints de la COVID-19. Toutefois, les études disponibles ne fournissent pas suffisamment de détails sur la gravité de la maladie à coronavirus 2019 et la mesure des comorbidités pertinentes.
Méthodes : Nous avons mené une étude de cohorte rétrospective multicentrique auprès de patients atteints de la COVID-19 > 18 ans qui ont été hospitalisés entre le 1er janvier 2020 et le 30 novembre 2020 en Ontario, au Canada, et à Copenhague, au Danemark. L'extraction des données inscrites aux dossiers, qui mettent en relief les comorbidités et la gravité de la maladie, a été réalisée par le personnel de recherche qualifié. L'association entre le diabète et la mortalité a été mesurée à l'aide de la régression de Poisson. Le critère d'évaluation principal était le risque de mortalité à l'hôpital dans les 30 jours.
Résultats : Notre étude portait sur 1133 patients hospitalisés atteints de la COVID-19 en Ontario et sur 305 patients hospitalisés atteints de la COVID-19 au Danemark, dont 405 et 75 patients, et ce respectivement, avaient un diabète préexistant. Tant en Ontario qu'au Danemark, les patients diabétiques étaient plus susceptibles que les adultes non diabétiques d'être des personnes âgées, d'avoir une insuffisance rénale chronique, une maladie cardiovasculaire et des concentrations plus élevées de troponine, et de recevoir des antibiotiques. En Ontario, 24 % (n = 96) des adultes diabétiques comparativement à 15 % (n = 109) des adultes non diabétiques sont morts. Au Danemark, 16 % (n = 12) des adultes diabétiques comparativement à 13 % (n = 29) des adultes non diabétiques sont morts à l'hôpital. En Ontario, le taux brut de mortalité chez les patients diabétiques était de 1,60 (intervalle de confiance [IC] à 95 %, de 1,24 à 2,07) et, dans le modèle de régression ajusté, il était de 1,19 (IC à 95 %, de 0,86 à 1,66). Au Danemark, le taux brut de mortalité chez les patients diabétiques était de 1,27 (IC à 95 %, de 0,68 à 2,36) et, dans le modèle de régression ajusté, il était de 0,87 (IC à 95 %, de 0,49 à 1,54). La méta-analyse des 2 taux de chacune des régions a permis d'établir un taux brut de mortalité de 1,55 (IC à 95 %, de 1,22 à 1,96) et un taux de mortalité ajusté de 1,11 (IC à 95 %, de 0,84 à 1,47).
Conclusion : La présence du diabète n'était pas fortement associée à la mortalité à l'hôpital des patients atteints de la COVID, et ce, indépendamment de la gravité de la maladie et des autres comorbidités.

Introduction

Since January 2020, over 450 million people worldwide have been infected with the severe acute respiratory syndrome coronavirus-2, and more than 5 million people have died. Reported risk factors for contracting COVID-19 include male sex; older age; living in congregate settings, such as a long-term care facility or shelter; or having social, economic, or personal barriers that limit health-care access (1,2). Reported risk factors associated with experiencing a more severe course of COVID-19 include older age, male sex, diabetes mellitus, hypertension, obesity, cardiac disease, and chronic kidney disease (3–5).

Much attention has focussed on diabetes and COVID-19 given its reported association with a worse prognosis, including an increased risk of intensive care unit admission (3,6–9), mechanical ventilation (3,10), and mortality (4,11–14). Within these studies, there is considerable variability in the measured strength of the association between diabetes and adverse clinical outcomes. Uncertainty remains about whether diabetes itself increases the risk of adverse outcomes given its inherent pro-inflammatory state, or whether the association is a result of related comorbid conditions (given that diabetes is an independent predictor of microvascular and macrovascular disease) or differences in care processes (15–17). From a patient's perspective, it is not known whether someone with diabetes, but without complications or comorbidities, carries a comparable risk of severe clinical outcomes from COVID-19 as a person with diabetes and late-stage complications such as advanced kidney or cardiovascular disease.

Existing studies describing the relationship between diabetes and COVID-19 severity have typically included single-centre or regional data and patients with varying illness severity. The main objective of our study was to better understand the association between diabetes and death among patients hospitalized with COVID-19.

Methods

Study setting and data source

We conducted a retrospective (Ontario) and prospective (Denmark) cohort study at 10 hospitals in Ontario, Canada, and 8 in Copenhagen, Denmark. The sites represented a convenience

Table 1
Baseline characteristics of patients who were hospitalized with COVID-19 at 10 hospitals in Ontario, Canada

Variable	Diabetes (n=405)	No diabetes (n=728)
Age, years, mean (SD)	69.9 (14.0)	62.8 (19.8)
Age group, years, n (%)		
<50	32 (7.9)	190 (26.0)
50–59	54 (13.3)	114 (15.7)
60–69	98 (24.2)	124 (17.0)
70–79	112 (27.7)	124 (17.0)
80–89	82 (20.2)	117 (16.1)
≥90	27 (6.7)	59 (8.1)
COVID-19 positivity date, n (%)		
On/before April 25, 2020	243 (60)	421 (57.8)
After April 25, 2020	162 (40)	307 (42.2)
Nosocomial COVID-19, n (%)	55 (13.6)	86 (11.8)
Sex, n (%)		
Female	171 (42.2)	308 (42.3)
Limited English proficiency, n (%)	50 (12.3)	76 (10.4)
Admission location, n (%)		
Home	252 (62.2)	460 (63.2)
LTC	91 (22.5)	120 (16.5)
Hospital (transfer)	49 (12.1)	79 (10.9)
No fixed home address	13 (3.2)	69 (9.5)
Comorbidities, n (%)		
Hypertension	316 (78.0)	326 (44.8)
Heart failure	85 (20.9)	76 (10.4)
Smoking	97 (23.9)	148 (20.3)
Cardiovascular diagnosis	130 (32.1)	135 (18.5)
COPD	85 (20.9)	122 (16.8)
CKD	112 (27.7)	59 (8.1)
Creatinine, n (%)		
0–100 μmol/L	153 (37.8)	466 (64.0)
101–200 μmol/L	138 (34.1)	142 (19.5)
>200 μmol/L	78 (19.3)	37 (5.1)
Missing	36 (8.9)	83 (11.4)
A1C%, mean (SD)	7.8 (2.3)	5.6 (0.4)
NA, %	243 (60.0)	663 (91.1)
Lymphocyte, 10^9 cells/L, mean (SD)	1.1 (0.8)	1.2 (0.8)
NA, %	43 (10.6)	80 (10.9)
Ferritin, μg/L, mean (SD)	938 (1,444)	972 (2,096)
NA, %	198 (48.9)	313 (42.9)
Presence of CXR, n (%)	345 (85.2)	597 (82.0)

A1C, glycated hemoglobin; *ABG*, arterial blood gas; *COPD*, chronic obstructive pulmonary disease; *CKD*, chronic kidney disease; *CXR*, chest x-ray; *LTC*, long-term care; *NA*, not available; *SD*, standard deviation.

Table 2
Baseline characteristics of patients who were hospitalized with COVID-19 at 8 hospitals in Copenhagen, Denmark

Variable	Diabetes (n=75)	No diabetes (n=230)
Age, years, mean (SD)	70.3 (13.0)	68.1 (13.9)
Age group, years, n (%)		
50–59	16 (21.3)	67 (29.1)
60–69	16 (21.3)	51 (22.2)
70–79	23 (30.7)	52 (22.6)
80–89	17 (22.7)	49 (21.3)
≥90	3 (4.0)	11 (4.8)
COVID-19 positivity date		
On/before April 25, 2020	47 (62.7)	139 (60.4)
After April 25, 2020	28 (37.3)	91 (39.6)
Nosocomial COVID-19, n (%)	14 (18.7)	36 (15.7)
Sex, n (%)		
Female	29 (38.7)	102 (44.3)
Admission location, n (%)		
Home	61 (81.3)	194 (84.3)
LTC/hospital	14 (18.7)	36 (15.7)
Comorbidities, n (%)		
Hypertension	47 (62.7)	126 (54.8)
Heart failure	10 (13.3)	24 (10.4)
Smoking	43 (57.3)	127 (55.2)
CVD	14 (18.7)	37 (16.1)
COPD	13 (17.6)	33 (14.3)
CKD	17 (22.7)	29 (12.6)
Creatinine, n (%)		
0–100 μmol/L	46 (61.3)	179 (77.8)
101–200 μmol/L	21 (28.0)	32 (13.9)
>200 μmol/L	8 (10.7)	16 (7.0)
A1C%, mean (SD)	7.2 (1.8)	5.9 (0.5)
Lymphocyte, 10^9 cells/L, mean (SD)	1.6 (1.7)	1.2 (1.0)
Ferritin, μg/L, mean (SD)	937 (1,217)	947 (1,064)
Presence of CXR, n (%)	71 (94.7)	218 (94.8)

A1C, glycated hemoglobin; *CKD*, chronic kidney disease; *COPD*, chronic obstructive pulmonary disease; *CXR*, chest x-ray; *LTC*, long-term care; *SD*, standard deviation.

sample of hospitals where the study team members worked. The electronic medical record was the primary source of data collection, and manual data collection was performed by trained research personnel. Our study was approved by the institutional research ethics board at each participating institution. For data privacy reasons, we were unable to combine the data from Ontario and Denmark into a single data set and thus we report results separately.

Study population

The cohort included adults ≥18 years of age and hospitalized with COVID-19 between January 1, 2020, and November 30, 2020. Consecutive patients hospitalized with COVID-19 were identified using Departments of Infection Prevention and Control at each hospital and through access to a central repository where their laboratory results for severe acute respiratory syndrome coronavirus-2 were reported. Patients were classified as having diabetes mellitus by 1 of the following at hospital presentation: a glycated hemoglobin (A1C) of ≥6.5%; current use of at least 1 oral or injectable diabetes medication; or chart review with a physician's note indicating the patient had diabetes. We were not able to distinguish between type 1 and type 2 diabetes or classify diabetes by severity.

Data collection

Patients' demographics included age, sex, English proficiency, and place of residence before the hospitalization. English proficiency was extracted from the medical records as reported by the patients or as noted in their registration log at the hospital. Place of residence before the hospitalization was indicated in the admission or discharge summary and included home, homeless/no fixed home address, long-term care, and transfer from another hospital. Pre-existing medical conditions previously shown to be associated with mortality from COVID-19 (cardiovascular disease, pulmonary disease, smoking status, renal failure) were identified based on the admission and discharge note in the patients' past medical history section (18). We also included in-hospital laboratory results (complete blood count and markers previously shown to be associated with severity of illness at presentation, such as D-dimer, C-reactive protein [CRP], and troponin), imaging tests (using the first available of chest x-ray [CXR], computed tomography of the chest, echocardiogram, Doppler ultrasound), medications taken before admission to hospital, and clinical outcomes (admission to hospital, intubation, and in-hospital death). These variables were collected by trained research personnel from the medical electronic records. Our proxies for disease severity included markers known to be associated with worse clinical outcomes, including CRP, troponin, creatinine, D-dimer, abnormal CXR, and need for supplemental oxygen (19). Text mapping using the publicly available CHARTextract natural language processing tool was used to characterize the

Table 3
Markers of illness severity (Ontario, Canada)

Variable	Diabetes (n=405)	No diabetes (n=728)
CRP, mg/L		
0–14.9	23 (5.7)	75 (10.3)
15–100	105 (25.9)	167 (22.9)
>100	90 (22.2)	138 (18.9)
Missing	187 (46.2)	348 (47.8)
CRP, mg/L, median (IQR)	79.3 (37.2–151.1)	65.5 (20–135.3)
D-dimer group		
<ULN	26 (6.4)	74 (10.2)
ULN–2×ULN	61 (15.1)	111 (15.2)
>2×ULN	137 (33.8)	199 (27.3)
Missing	181 (44.7)	344 (47.3)
Troponin group		
<ULN	151 (37.3)	294 (40.4)
ULN–2×ULN	66 (16.3)	89 (12.2)
>2×ULN	84 (20.7)	99 (13.6)
Missing	104 (25.7)	246 (33.8)
Oxygen requirement	57 (14.1)	98 (13.5)
NA	303 (74.8)	537 (73.7)
Presence of ABG	72 (17.8)	102 (14.0)
CXR results		
Normal	59 (14.6)	137 (18.8)
Abnormal	227 (56.1)	371 (50.9)
Missing	61 (15.1)	134 (18.4)
Unknown	39 (9.6)	63 (8.7)

ABG, arterial blood gas; *CRP*, C-reactive protein; *CXR*, chest x-ray; *IQR*, interquartile range; *NA*, not available; *ULN*, upper limit of normal.
Note: Data expressed as number (%), unless noted otherwise.

findings on each imaging report. Specifically, we used "regular expression" natural language processing to classify the CXR results as abnormal, as this is a commonly used approach. We first identified common words and phrases that we expected to be closely associated with normal CXRs ("normal chest x-ray" or "clear") and others closely associated with COVID-19 pneumonia (e.g. "bibasilar" or "opacification"). We then labelled a subset of the CXRs as being "normal" vs "abnormal," based on review of the full CXR report by 2 of the authors with experience caring for patients hospitalized with COVID-19 (M.F. and K.L.Q.). We then provided the words and phrases to CHARTextract, a tool developed by our research team (https://lks-chart.github.io/chartextract-docs), to identify how well these words discriminated between normal and abnormal CXRs and iteratively updated the included words and phrases.

Table 4
Markers of illness severity (Copenhagen, Denmark)

Variable	Diabetes (n=75)	No diabetes (n=230)
CRP group, mg/L		
0–14.9	13 (17.3)	41 (17.8)
15–100	44 (58.7)	135 (58.7)
>100	16 (21.3)	47 (20.4)
Missing	2 (2.7)	7 (3.0)
CRP, mg/L, median (IQR)	48 (23–89)	56 (23–96)
D-dimer group		
<ULN	6 (8.0)	34 (14.8)
ULN–2×ULN	21 (28.0)	48 (20.9)
>2×ULN	22 (29.3)	69 (30.0)
Missing	26 (34.7)	79 (34.3)
Troponin group		
<ULN	24 (32.0)	72 (31.3)
ULN–2×ULN	7 (9.3)	35 (15.2)
>2×ULN	18 (24.0)	30 (13.0)
Missing	26 (34.7)	93 (40.4)
Oxygen requirement	41 (54.7)	124 (53.9)
Presence of ABG	57 (76.0)	154 (67.0)
CXR results		
Normal	1 (1.3)	1 (0.4)
Abnormal	17 (22.7)	49 (21.3)
Missing	57 (76.0)	180 (78.3)

ABG, arterial blood gas; *CRP*, C-reactive protein; *CXR*, chest x-ray; *IQR*, interquartile range; *ULN*, upper limit of normal.
Note: Data expressed as number (%), unless noted otherwise.

Table 5
Patterns of care in hospital (Ontario, Canada)

Variable	Diabetes (n=405)	No diabetes (n=728)
CT of thorax	97 (23.9)	155 (21.3)
Echocardiogram	43 (10.6)	59 (8.1)
Doppler ultrasound	47 (11.6)	68 (9.3)
Antibiotic received	304 (75.1)	492 (67.6)
Antiviral received	52 (12.8)	114 (15.7)
Steroid received	92 (22.7)	145 (19.9)
Biologic received	3 (0.7)	9 (1.2)

CT, computed tomography.
Note: Data expressed as number (%).

Patient follow-up

Measurements began on the date of hospitalization for COVID-19 (the index date) and follow-up continued until death, discharge from hospital, or 30 days from the index date. This specification of the follow-up period was the same as that used in the in-hospital COVID-19 clinical trials (20–22). Our primary outcome was within-hospital 30-day risk of death.

Data analysis

Descriptive statistics were used to compare baseline characteristics between the 2 groups. The association between diabetes and death was measured using Poisson regression that included patient-level characteristics such as age, sex, admission location, comorbid conditions (heart failure, cerebrovascular disease, hypertension, chronic obstructive pulmonary disease/asthma, smoking), and proxies for illness severity (CRP, troponin, creatinine, CXR findings). A separate Poisson regression model was performed for the Ontario and Danish data and the results were meta-analyzed to provide an overall rate ratio for mortality.

Results

Our study included 1,438 hospitalized patients with COVID-19, including 1,133 (78.8%) from Canada and 305 (21.2%) from Denmark. Four hundred eighty patients (33.4%) had diabetes, including 405 from Canada and 75 from Denmark (Tables 1 and 2). In Canada, people with diabetes were older and had more comorbidities (e.g. chronic kidney disease, cardiovascular disease, heart failure, hypertension) than those who did not have diabetes (Table 1). They were more likely to be from a long-term-care home

Table 6
Patterns of care in hospital (Copenhagen, Denmark)

Variable	Diabetes (n=75)	No diabetes (n=230)
CT of thorax	14 (18.7)	50 (21.8)
Echocardiogram	75 (100.0)	230 (100.0)
Antibiotic received	63 (84.0)	166 (72.2)
Antiviral received	12 (16.0)	45 (19.6)
Biologic received	0 (0)	0 (0)

CT, computed tomography.
Note: Data expressed as number (%).

Table 7
Univariate and multivariable model for association between diabetes and death (Ontario, Canada)

Variable	Univariate		Multivariable	
	MR	95% CI	MR	95% CI
Diabetes	1.60	1.24–2.07	1.19	0.86–1.66
Age, years (ref: <60)				
60–69	3.30	1.78–6.15	2.24	1.12–4.51
70–79	4.64	2.6–8.26	2.90	1.45–5.78
80–89	7.39	4.25–12.85	4.46	2.27–8.75
≥90	11.89	6.83–20.69	5.96	2.78–12.79
Sex (male)	1.09	0.84–1.41	1.17	0.86–1.59
Admission location (ref: home)				
Shelter	0.15	0.04–0.6	0.47	0.14–1.65
Long-term care	2.06	1.6–2.66	1.13	0.8–1.59
Heart failure	1.81	1.36–2.4	0.97	0.65–1.43
CVD	2.12	1.64–2.74	1.28	0.92–1.77
Smoking	0.96	0.68–1.36	0.91	0.63–1.3
COPD/asthma	0.97	0.69–1.36	0.86	0.6–1.24
HTN	2.37	1.72–3.25	1.10	0.75–1.62
Creatinine (ref: 0–100)				
101–200 μmol/L	2.36	1.76–3.17	1.43	0.99–2.06
>200 μmol/L	2.99	2.14–4.19	1.53	0.91–2.55
Missing	1.11	0.43–2.84	1.37	0.4–4.73
CRP (ref: 0–14.9)				
>100 mg/L	6.16	2.56–14.82	3.73	1.21–11.48
15–100 mg/L	3.20	1.31–7.85	2.65	0.86–8.2
Missing	3.32	1.38–8	2.77	0.91–8.4
Troponin (ref: <ULN)				
ULN–2×ULN	1.84	1.28–2.65	1.00	0.64–1.55
>2×ULN	2.92	2.16–3.94	1.53	0.98–2.41
Missing	0.70	0.45–1.09	0.71	0.42–1.2
CXR results (ref: normal or unknown)				
Abnormal	1.59	1.15–2.2	1.28	0.88–1.87
Missing	0.97	0.61–1.55	1.22	0.73–2.04

CI, confidence interval; *COPD*, chronic obstructive pulmonary disease; *CRP*, C-reactive protein; *CVD*, cardiovascular disease; *CXR*, chest x-ray; *HTN*, hypertension; *MR*, mortality ratio; *ref*, reference; *ULN*, upper limit of normal.
Note: In Ontario, 24% (96 of 405) of adults with diabetes died compared with 15% (109 of 728) of adults without diabetes.

and have greater severity of illness at presentation to hospital (e.g. higher CRP and D-dimer, abnormal CXR) (Table 3). They also had higher troponin and creatinine values compared with patients without diabetes. In Denmark, patients with diabetes also were older and had more comorbidities than those without diabetes (Table 2). They had higher creatinine and troponin values at time of presentation as well. In Denmark, CRP and D-dimer levels were similar between those with diabetes and those without, and both groups were equally likely to have an abnormal CXR (Table 4).

In both Canada and Denmark, people with diabetes were more likely to receive an antibiotic and less likely to receive an antiviral medication (Tables 5 and 6). In Canada, steroid use was uncommon and occurred at a similar frequency for the 2 groups. There was no clear difference in the number of patients with and without diabetes who received a computed tomography of the thorax, echocardiogram, or Doppler ultrasound of the lower extremities (Table 5). In Denmark, all patients received an echocardiogram, none received a biologic, and data on Doppler studies and steroid administration were not collected (Table 6).

In Canada, 24% (n=96) of adults with diabetes died compared with 15% (n=109) of adults without diabetes. In Canada, the crude mortality ratio for patients with diabetes vs those without diabetes was 1.60 (95% confidence interval [CI], 1.24 to 2.07). After adjustment for patient-level characteristics (Table 7), the mortality ratio was 1.19 (95% CI, 0.86 to 1.66). In Denmark, 16% (n=12) of adults with diabetes died in hospital compared with 13% (n=29) of those without diabetes. In the Danish patient population, the crude mortality ratio was 1.27 (95% CI, 0.68 to 2.36), but, after control of confounders, the adjusted mortality ratio was 0.87 (95% CI, 0.49 to 1.54) (Table 8). Meta-analysis of the 2 rate ratios from each region demonstrated a crude mortality ratio of 1.55 (95% CI, 1.22 to 1.96) and an adjusted mortality ratio of 1.11 (95% CI, 0.84 to 1.47).

Discussion

After control of confounding, diabetes was only weakly associated with within-hospital 30-day risk of death, with no consistent pattern in Canada and Denmark, but we acknowledge that the confidence intervals were wide, which limits strong conclusions. Multiple studies assessing whether diabetes was associated with an increased risk of mortality lacked information on severity of illness on presentation (e.g. CXR findings) or lab values associated with a worse prognosis (e.g. troponin, D-dimer, creatinine). The strongest predictor of respiratory failure and mortality among COVID-19 patients, aside from age, is illness severity at presentation (19). Studies that fail to account for these important confounders may overestimate the independent effect of diabetes on COVID-19 outcomes.

Patients with diabetes tended to have both more severe illness (e.g. higher CRP, worse CXR findings) and worse prognostic signs in both countries that we studied. It is unknown whether patients with diabetes are sicker on presentation because of delays in seeking care causing selection bias, association between diabetes and other factors that may influence severity such as race or socioeconomic deprivation, or the direct influence of diabetes. The higher illness severity may explain why patients with diabetes were more likely to receive antibiotics while in hospital, although subsequent trials have identified that antibiotics are ineffective against COVID-19 (20). The higher use of antibiotics in patients with diabetes may also be explained by their inherent immunocompromised state and their susceptibility to bacterial co-infection.

Our study has limitations. First, although we had complete data for A1C in the Danish data set, there was a high degree of missingness in the Ontario data set. As a result, there may have been some

Table 8
Univariate and multivariable model for association between diabetes and death (Copenhagen, Denmark)

Variable	Univariate		Multivariable	
	MR	95% CI	MR	95% CI
Diabetes	1.27	0.68–2.36	0.87	0.49–1.54
Age, in years (ref: <60)				
60–69	5.00	0.57–43.45	4.45	0.54–36.89
70–79	15.5	2.07–115.39	14.71	2.11–102.34
80–89	21.4	2.91–157.02	14.98	2.18–103.02
≥90	29.6	3.72–235.95	17.75	2.28–138.06
Sex (male)	2.05	1.07–3.95	1.34	0.68–2.63
Admission location (ref: home)				
Long-term care	1.87	1–3.48	1.92	1.02–3.59
Heart failure	2.57	1.39–4.77	0.64	0.33–1.25
CVD	2.58	1.46–4.58	1.89	0.94–3.79
Smoking	1.12	0.63–2	0.68	0.32–1.47
COPD/asthma	0.86	0.44–1.68	1.07	0.48–2.36
HTN	1.84	0.98–3.48	0.66	0.3–1.44
Creatinine (ref: 0–100)				
101–200 μmol/L	4.25	2.27–7.93	3.96	1.8–8.68
>200 μmol/L	4.69	2.24–9.81	2.17	0.92–5.09
Missing	4.69	0.88–24.93	2.55	0.44–14.62
CRP (ref: 0–14.9)				
>100 mg/L	7.29	1.76–30.19	4.93	1.28–19
15–100 mg/L	3.17	0.76–13.11	2.61	0.71–9.59
Missing	3.00	0.3–29.87	1.6	0.22–11.71
Troponin (ref: <ULN)				
ULN–2×ULN	3.81	0.95–15.25	1.52	0.39–5.95
>2×ULN	6.00	1.7–21.19	1.00	0.28–3.62
Missing	6.45	2–20.83	3.88	1.08–13.97
CXR results (ref: normal or unknown)				
Abnormal	0.48	0.11–2.07	3.15	0.97–10.2
Missing	0.20	0.048–0.85	1.13	0.42–3.05

CI, confidence interval; *COPD*, chronic obstructive pulmonary disease; *CRP*, C-reactive protein; *CVD*, cardiovascular disease; *CXR*, chest x-ray; *HTN*, hypertension; *MR*, mortality ratio; *ref*, reference; *ULN*, upper limit of normal.
Note: In Denmark, 16% (12 of 75) of adults with diabetes died in hospital compared with 13% (29 of 230) of those without diabetes.

patients in the Ontario data set with undiagnosed diabetes, but we believe this to be rare because our definition of diabetes included not only an A1C measurement but also a previous diagnosis of diabetes or use of medication for diabetes. Second, we did not capture the proportion of patients with type 1 diabetes vs type 2 diabetes; we estimate that approximately 90% of patients had type 2 diabetes based on other published literature (23). Third, we lacked data on other important comorbid conditions such as elevated body mass index (BMI). One meta-analysis identified that the relative risk of mortality was 3.52 in those with a BMI of ≥25 kg/m^2 and thus an important risk factor for COVID-19 outcomes (24). Residual confounding related to BMI would mean that we overestimated the relationship between diabetes and mortality, which was already weak after adjustment for confounders. Fourth, we also lacked other variables such as symptom severity related to dyspnea and their respiratory rate. In addition, because we lacked A1C measurements for all patients, we were unable to estimate the relationship between diabetes severity and inpatient mortality. This issue is important because studies have suggested that higher A1C levels are associated with worse outcomes (25). Fifth, this study was conducted in 2 high-income countries (Denmark and Canada) with socialized health-care systems; the results may thus not be generalizable to areas of low-income and/or private-paying systems. Unfortunately, our data set lacked important social determinants of health such as income, race or ethnicity, and education level. Sixth, our study was relatively small. Another limitation of our study is the potential for collider bias, because we restricted our work to adults hospitalized with COVID-19, and patients with diabetes may be hospitalized with a lower risk profile than those without diabetes. This selection bias would lead to underestimation of the effect of diabetes on COVID-19 mortality. However, because our unadjusted findings suggest an increased risk of inpatient mortality among adults with COVID-19 compared with adults without diabetes and this effect was attenuated in our multivariable model, collider bias alone could not explain our null findings. Nonetheless, given our small study size, our finding that diabetes itself may not be a strong risk factor for death within 30 days of hospitalization warrants corroboration from other patient populations.

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Author Disclosures

Conflicts of interest: M.F. is a consultant for Proof Dx, a start-up company developing a point-of-care diagnostic test for COVID-19 using CRISPR. B.A.P. has received speaker honoraria from Abbott, Medtronic, Insulet, and Novo Nordisk; has served as an advisor to Insulet, Sanofi, Vertex, and Abbott; and has received research support to his research institute from Novo Nordisk and the Bank of Montreal.

Author Contributions

All authors were involved in the study concept and design, acquisition of data, critical revision of the manuscript, statistical analysis, and analysis/interpretation of data. O.B. and M.F. drafted the manuscript.

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