Journal Pre-proof

The association between diabetes and mortality among adult patients hospitalized with COVID-19: Cohort Study of Hospitalized Adults in Ontario, Canada and Copenhagen, Denmark

Orly Bogler, MD, Afsaneh Raissi, Michael Colacci, MD, Andrea Beaman, BScPhm, PharmD, RPh, Tor Biering-Sørensen, MD, PhD, MPH, Alex Cressman, MD, MSc, Allan Detsky, MD, PhD, Alexi Gosset, BA, Mats Højbjerg Lassen, MD, Chris Kandel, MD, PhD, Yaariv Khaykin, MD, David Barbosa, Lauren Lapointe Shaw, MD, PhD, Derek R. MacFadden, MD, ScD, Alexander Pearson, MD, Bruce Perkins, MD, MPH, BSc, Kenneth J. Rothman, DrPH, Kristoffer Grundtvig Skaarup, MD, Rachael Weagle, MD, MPH, Chris Yarnell, MD, Michelle Sholzberg, MDCM, MSc, Bena Hodzic-Santor, MD Candidate, Erik Lovblom, Jonathan Zipursky, MD, Kieran L. Quinn, MD, PhD, Mike Fralick, MD, SM, PhD

PII: S1499-2671(23)00038-2

DOI: https://doi.org/10.1016/j.jcjd.2023.02.005

Reference: JCJD 1638

To appear in: *Canadian Journal of Diabetes*

Received Date: 13 July 2022

Revised Date: 9 February 2023

Accepted Date: 17 February 2023

Please cite this article as: Bogler O, Raissi A, Colacci M, Beaman A, Biering-Sørensen T, Cressman A, Detsky A, Gosset A, Lassen MH, Kandel C, Khaykin Y, Barbosa D, Shaw LL, MacFadden DR, Pearson A, Perkins B, Rothman KJ, Skaarup KG, Weagle R, Yarnell C, Sholzberg M, Hodzic-Santor B, Lovblom E, Zipursky J, Quinn KL, Fralick M, The association between diabetes and mortality among adult patients hospitalized with COVID-19: Cohort Study of Hospitalized Adults in Ontario, Canada and Copenhagen, Denmark, *Canadian Journal of Diabetes* (2023), doi: https://doi.org/10.1016/j.jcjd.2023.02.005.

The association between diabetes and mortality among adult patients hospitalized with COVID-19: Cohort Study of Hospitalized Adults in Ontario, Canada and Copenhagen, Denmark

Orly Bogler, MD[1,2], Afsaneh Raissi[2], Michael Colacci, MD[1], Andrea Beaman BScPhm, PharmD, RPh[3], Tor Biering-Sørensen MD, PhD, MPH[4], Alex Cressman, MD, MSc[1], Allan Detsky, MD, PhD[1,2], Alexi Gosset, BA[1,2], Mats Højbjerg Lassen, MD[4], Chris Kandel, MD, PhD[5], Yaariv Khaykin, MD[6], David Barbosa[6], Lauren Lapointe Shaw, MD, PhD[7], Derek R. MacFadden, MD, ScD[8], Alexander Pearson, MD[9], Bruce Perkins, MD, MPH[2], BSc, Kenneth J. Rothman, DrPH[11], Kristoffer Grundtvig Skaarup, MD[4], Rachael Weagle[12], MD, MPH, Chris Yarnell, MD[13], Michelle Sholzberg, MDCM, MSc[1,10], Bena Hodzic-Santor MD Candidate[1,2], Erik Lovblom[2], Jonathan Zipursky, MD[1], Kieran L. Quinn, MD, PhD[1,2,14], and Mike Fralick[1,2], MD, SM, PhD

KQ and MF were co-senior authors

Affiliations

1. Department of Medicine, University of Toronto, Temerty Faculty of Medicine, Toronto, ON, Canada.
2. Sinai Health System, Department of Medicine, University of Toronto, Toronto, ON, Canada
3. Trillium Health Partners, Mississauga, ON, Canada.
4. Department of Cardiology, University of Copenhagen, Denmark
5. Michael Garron Hospital, Toronto, ON, Canada
6. Department of Medicine, Southlake Regional Health Centre, Newmarket, ON, Canada
7. University Health Network, Toronto, ON, Canada.
8. The Ottawa Hospital Research Institute, Ottawa, ON, Canada.
9. Department of Medicine, University of Ottawa, Ottawa, ON, Canada.
10. St Michael's Hospital, Unity Health Toronto, Toronto, Ontario, Canada
11. Department of Epidemiology, School of Public Health, Boston University, Boston, Massachusetts, USA.
12. Department of Family Medicine, University of Ottawa, Ottawa, ON, Canada.
13. Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Ontario, Canada.
14. Interdepartmental Division of Palliative Care, Sinai Health System and University of Toronto, Toronto, ON, Canada.

Correspondence: Michael Fralick, MD, PhD, SM, FRCPC
Sinai Health System

60 Murray Street
M5T 3L9
email: mike.fralick@mail.utoronto.ca
words: 2,474 figures: 2 tables: 2

Study concept and design: All authors
Acquisition of data: All authors
Analysis/interpretation of data: All authors
Drafting of the manuscript: Bogler O, Fralick M
Critical revision of the manuscript: All authors
Statistical analysis: All authors
Obtained funding: This research is supported by Sinai Health Department of Medicine Research fund.
Conflicts of interest: None

The association between diabetes and mortality among adult patients hospitalized with COVID-19: Cohort Study of Hospitalized Adults in Ontario, Canada and Copenhagen, Denmark

Orly Bogler, MD[1,2], Afsaneh Raissi[2], Michael Colacci, MD[1], Andrea Beaman BScPhm, PharmD, RPh[3], Tor Biering-Sørensen MD, PhD, MPH[4], Alex Cressman, MD, MSc[1], Allan Detsky, MD, PhD[1,2], Alexi Gosset, BA[1,2], Mats Højbjerg Lassen, MD[4], Chris Kandel, MD, PhD[5], Yaariv Khaykin, MD[6], David Barbosa[6], Lauren Lapointe Shaw, MD, PhD[7], Derek R. MacFadden, MD, ScD[8], Alexander Pearson, MD[9], Bruce Perkins, MD, MPH[2], BSc, Kenneth J. Rothman, DrPH[11], Kristoffer Grundtvig Skaarup, MD[4], Rachael Weagle[12], MD, MPH, Chris Yarnell, MD[13], Michelle Sholzberg, MDCM, MSc[1,10], Bena Hodzic-Santor MD Candidate[1,2], Erik Lovblom[2], Jonathan Zipursky, MD[1], Kieran L. Quinn, MD, PhD[1,2,14], and Mike Fralick[1,2], MD, SM, PhD

KQ and MF were co-senior authors

Affiliations

1. Department of Medicine, University of Toronto, Temerty Faculty of Medicine, Toronto, ON, Canada.
2. Sinai Health System, Department of Medicine, University of Toronto, Toronto, ON, Canada
3. Trillium Health Partners, Mississauga, ON, Canada.
4. Department of Cardiology, University of Copenhagen, Denmark
5. Michael Garron Hospital, Toronto, ON, Canada
6. Department of Medicine, Southlake Regional Health Centre, Newmarket, ON, Canada
7. University Health Network, Toronto, ON, Canada.
8. The Ottawa Hospital Research Institute, Ottawa, ON, Canada.
9. Department of Medicine, University of Ottawa, Ottawa, ON, Canada.
10. St Michael's Hospital, Unity Health Toronto, Toronto, Ontario, Canada
11. Department of Epidemiology, School of Public Health, Boston University, Boston, Massachusetts, USA.
12. Department of Family Medicine, University of Ottawa, Ottawa, ON, Canada.
13. Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Ontario, Canada.
14. Interdepartmental Division of Palliative Care, Sinai Health System and University of Toronto, Toronto, ON, Canada.

Correspondence: Michael Fralick, MD, PhD, SM, FRCPC
Sinai Health System

60 Murray Street
M5T 3L9
email: mike.fralick@mail.utoronto.ca
words: 2,474 figures: 2 tables: 2

Study concept and design: All authors
Acquisition of data: All authors
Analysis/interpretation of data: All authors
Drafting of the manuscript: Bogler O, Fralick M
Critical revision of the manuscript: All authors
Statistical analysis: All authors
Obtained funding: This research is supported by Sinai Health Department of Medicine Research fund.
Conflicts of interest: None

Key Messages:

- Diabetes has been a reported risk factor associated with experiencing a more severe course of COVID-19
- However, this 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

Abstract (wordcount: 238)

Importance: Diabetes has been reported to be associated with an increased risk of death among patients with COVID-19. However, available studies lack detail on COVID illness severity and measurement of relevant comorbidities.

Design, Setting, and Participants: We conducted a multicenter, retrospective cohort study of patients over the age of 18 years who were hospitalized with COVID-19 between January 1, 2020 and November 30, 2020 in Ontario, Canada and Copenhagen, Denmark. Chart abstraction emphasizing co-morbidities and disease severity was performed by trained research personnel. The association between diabetes and death was measured using Poissson regression.

Main Outcomes and Measures: within hospital 30-day risk of death.

Results: Our study included 1133 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, higher troponin levels, and to receive antibiotics compared with adults who did not have 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) among those without diabetes. In Ontario, the crude mortality rate ratio among patients with diabetes was 1.60 [1.24 – 2.07 95% CI] and in the adjusted regression model was 1.19 [0.86 – 1.66 95% CI]. In Denmark, the crude mortality rate ratio among patients with diabetes was 1.27 (0.68 – 2.36 95% CI) and in the adjusted model was 0.87 (0.49 – 1.54 95% CI)]. Meta-analysis of the two rate ratios from each region resulted in a crude mortality rate ratio of 1.55 (95% CI 1.22,1.96) and an adjusted mortality rate ratio of 1.11 (95% CI 0.84, 1.47).

Conclusions: Presence of diabetes was not strongly associated with in-hospital COVID mortality independent of illness severity and other comorbidities.

INTRODUCTION

Since January 2020, over 450 million people worldwide have been infected with the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2), and more than 5 million people have died. Reported risk factors for contracting Coronavirus Disease 2019 (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 healthcare 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 focused on diabetes and COVID-19 given its reported association with a worse prognosis, including an increased risk of intensive care unit (ICU) 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 perspective, it is not known if 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 center or regional data and patients with varying illness severity.

The main objective of our study was to 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 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 one single dataset and thus we report results separately.

Study population

The cohort included adults 18 years or older hospitalized with COVID-19 between January 1, 2020, and November 30, 2020. Consecutive patients hospitalized with COVID-19 were identified using Infection Prevention and Control departments at each hospital and through access to a central repository where SARS-CoV-2 laboratory results were reported. Patients were classified as having diabetes mellitus by one of the following at hospital presentation: hemoglobin A1C $\geq$ 6.5%, current use of at least one 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

Patient 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, long-term care, 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 (completed blood count, markers previously shown to be associated with severity of illness at presentation such as D-dimer, C-reactive protein [CRP], troponin), imaging tests (using the first available of chest x-ray [CXR], CT chest, echocardiogram, and 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: 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 findings on each imaging report. Specifically, we used “regular expression” NLP to classify the chest x-ray results as abnormal as this is one of the most commonly used approaches. We first identified common words and phrases that we expected to be highly associated with normal chest x-rays (“normal chest x-ray”, “clear”) and others that would be highly associated with COVID pneumonia (e.g., “bi-basilar”, “opacification”). We then labeled a subset of the chest x-rays as

being “normal” versus “abnormal” based on review of the full chest x-ray report by two clinicians who have experience caring for patients hospitalized with COVID-19 (MF, & KQ). 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 chest x-rays and iteratively updated the included words and phrases.

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 two groups. The association between diabetes and death was measured using Poisson regression that include patient level characteristics including age, sex, admission location, comorbid conditions (heart failure, cerebrovascular disease [CVD], hypertension [HTN], COPD/asthma, and smoking), and

proxies for illness severity (CRP, troponin, creatinine, and chest x-ray findings). A separate Poisson regression model was performed in 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 Ontario and 305 (21.2%) from Denmark. 480 patients (33.4%) had diabetes, 405 from Ontario and 75 from Denmark. In Ontario, people with diabetes were older and had more comorbidities (e.g., chronic kidney disease, cardiovascular disease, heart failure and hypertension) than those who did not have diabetes (Table 1a). They were also more likely to be from a long-term care home and have higher severity of illness at presentation to hospital (e.g., higher CRP and D-dimer, abnormal chest x-ray) (Table 2a). 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 1b). They had a higher creatinine and troponin 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 2b).

In both Ontario and Denmark, people with diabetes were more likely to receive an antibiotic and less likely to receive an anti-viral medication (Tables 3a and 3b). In Ontario, steroid use was uncommon and occurred at a similar frequency for the two groups. There was also no clear difference in the number of patients with and without diabetes who received a CT thorax, echocardiogram, or doppler ultrasound of the lower extremities (Table 3a). In Denmark, all

patients received an echocardiogram, none received a biologic, and data on doppler studies and steroid administration was not collected (Table 3b).

In Ontario, 24% (n=96) of adults with diabetes died compared with 15% (n=109) of adults without diabetes. In Ontario, the crude mortality ratio for patients with diabetes, compared with non-diabetic, was 1.60 (95% CI 1.24 – 2.07). After adjustment for patient-level characteristics (Table 4), the mortality ratio was 1.19 [95% CI 0.86 – 1.66]. In Denmark, 16% (n=12) of adults with diabetes died in hospital compared with 13% (n=29) among those without diabetes. In the Danish patient population, the crude mortality ratio was 1.27 (95% CI 0.68 – 2.36), but after control of confounders the adjusted mortality ratio was 0.87 [95% CI 0.49 – 1.54] (Table 4

). Meta-analyzing the two rate ratios from each region resulted in a crude mortality rate ratio of 1.55 (95% CI 1.22,1.96) and an adjusted mortality rate ratio of 1.11 (95% CI 0.84, 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., chest x-ray 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 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 outcomes.

Patients with diabetes tended to have both more severe illness (e.g., higher CRP, worse chest x-ray findings) and worse prognostic signs in both countries that we studied. It is unknown if 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, though 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 immune-compromised state and their susceptibility to bacterial co-infection.

Our study has important limitations. First, while we had complete data for hemoglobin A1C in the Danish dataset, there was a high degree of missingness in the Ontario dataset. As a result, there may have been some patients in the Ontario dataset with undiagnosed diabetes, but we believe this to be rare because our definition of diabetes included not only an A1C measurement but also a prior diagnosis of diabetes or use of medication for diabetes. Second, we did not capture the proportion of patients with type 1 diabetes versus 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 BMI. A prior meta-analysis identified that the relative risk of mortality was 3.52 in those with BMI $\geq$ 25 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 hemoglobin A1C measurements for all patients, we were unable to estimate the relationship

between diabetes severity and inpatient mortality. This issue is important because prior studies suggest that higher A1C levels are associated with worse outcomes(25). Fifth, this study was conducted in two high-income countries (Denmark and Canada) with socialized healthcare systems; the results may thus not be generalizable to areas of low-income and/or private-paying systems. Unfortunately, our dataset 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 our study was restricted 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 suggested 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.

Table 1a. Baseline characteristics of patients over the age of 18 years who were hospitalized with COVID-19 at 10 hospitals in Ontario, Canada

Variable	Strata	Diabetes (n=405)	No Diabetes (n=728)
Age Mean(SD)	Age	69.9 (14.0)	62.8 (19.8)
Age group (n, %)	<50 years	32 (7.9)	190 (26.0)
	50-59 years	54 (13.3)	114 (15.7)
	60-69 years	98 (24.2)	124 (17.0)
	70-79 years	112 (27.7)	124 (17.0)
	80-89 years	82 (20.2)	117 (16.1)
	90+ Years	27 (6.7)	59 (8.1)
COVID Positivity Date	On/Before April 25th, 2020	243 (60)	421 (57.8)
	After April 25th, 2020	162 (40)	307 (42.2)
Nosocomial COVID (%)		55 (13.6)	86 (11.8)
Sex (n, %)	Female	171 (42.2)	308 (42.3)
Limited English Proficiency (%)		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 Dx	130 (32.1)	135 (18.5)
	COPD	85 (20.9)	122 (16.8)
	CKD	112 (27.7)	59 (8.1)
Creatinine, µmol/L (%)	0-100	153 (37.8)	466 (64.0)
	101-200	138 (34.1)	142 (19.5)
	>200	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)		1.133 (0.8)	1.196 (0.8)
	NA (%)	43 (10.6)	80 (10.9)
Ferritin, µg/L, Mean (SD)		937.932 (1443.5)	972 (2096.2)
	NA (%)	198 (48.9)	313 (42.9)
Presence of CXR (%)		345 (85.2)	597 (82.0)

SD = standard deviation; LTC = long term care; COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease; WBC = white blood cell; CXR = chest x-ray

Table 1b. Baseline characteristics of patients over the age of 18 years who were hospitalized with COVID-19 at 8 hospitals in Copenhagen, Denmark

Variable	Strata	Diabetes (n=75)	No Diabetes (n=230)
Age (Mean, SD)	Age (Mean SD)	70.3 (13.0)	68.1 (13.9)
Age group (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 Positivity Date	On/Before April 25th, 2020	47 (62.7)	139 (60.4)
	After April 25th, 2020	28 (37.3)	91 (39.6)
Nosocomial COVID (%)		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)
	Cerebrovascular Dx	14 (18.7)	37 (16.1)
	COPD	13 (17.6)	33 (14.3)
	CKD	17 (22.7)	29 (12.6)
Creatinine, µmol/L (%)	0-100	46 (61.3)	179 (77.8)
	101-200	21 (28.0)	32 (13.9)
	>200	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)		936.7 (1216.7)	947.3 (1064.2)
Presence of CXR (%)		71 (94.7)	218 (94.8)

SD = standard deviation; LTC = long term care; COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease; WBC = white blood cell; CXR = chest x-ray

Table 2a. Markers of Illness Severity (Ontario)

Variable	Strata	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)
Median CRP (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 CXR (%)	59 (14.6)	137 (18.8)
	Abnormal CXR (%)	227 (56.1)	371 (50.9)
	Missing CXR (%)	61 (15.1)	134 (18.4)
	Unknown CXR (%)	39 (9.6)	63 (8.7)

CRP = c-reactive protein; IQR = interquartile range; ULN = upper limit of normal; ABG = arterial blood gas; CXR = chest x-ray

Table 2b. Markers of Illness Severity (Denmark)

Variable	Strata	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)
Median CRP, mg/L (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 CXR (%)	1 (1.3)	1 (0.4)
	Abnormal CXR (%)	17 (22.7)	49 (21.3)
	Missing CXR (%)	57 (76.0)	180 (78.3)

CRP = c-reactive protein; IQR = interquartile range; ULN = upper limit of normal; ABG = arterial blood gas; CXR = chest x-ray

Table 3a. Patterns of care in hospital (Ontario).

Variable	Diabetes (n=405)	No Diabetes (n=728)
CT 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)

Table 3b. Patterns of care in hospital (Denmark)

Variable	Diabetes (n=75)	No Diabetes (n=230)
CT 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)

Table 4a. Univariate and multivariable model for the association between diabetes and death (Ontario).

	Univariate		**Multivariable**	
Variable	**MR**	**95% CI**	**MR**	**95% CI**
Diabetes	1.60	1.24 – 2.07	1.19	0.86 – 1.66
Age (ref < 60 years)				
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
LTC	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 (µmol/L) (Ref 0-100)				
- 101-200	2.36	1.76 – 3.17	1.43	0.99 – 2.06
- >200	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	6.16	2.56 – 14.82	3.73	1.21 – 11.48
- 15-100	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

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

Table 4b. Univariate and multivariable model for the association between diabetes and death (Denmark).

	Univariate		**Multivariable**	
Variable	**MR**	**95% CI**	**MR**	**95% CI**
Diabetes	1.27	0.68 – 2.36	0.87	0.49 – 1.54
Age (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)				
LTC	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 (µmol/L) (Ref 0-100)				
- 101-200	4.25	2.27 – 7.93	3.96	1.8 – 8.68
- >200	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	7.29	1.76 – 30.19	4.93	1.28 – 19
- 15-100	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/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

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

References

1. Pijls BG, Jolani S, Atherley A, Derckx RT, Dijkstra JIR, Franssen GHL, et al. Demographic risk factors for COVID-19 infection, severity, ICU admission and death: a meta-analysis of 59 studies. BMJ Open. 2021;11(1):e044640.
2. Karmakar M, Lantz PM, Tipirneni R. Association of Social and Demographic Factors With COVID-19 Incidence and Death Rates in the US. JAMA Network Open. 2021;4(1):e2036462-e.
3. Guan W-j, Ni Z-y, Hu Y, Liang W-h, Ou C-q, He J-x, et al. Clinical characteristics of coronavirus disease 2019 in China. New England journal of medicine. 2020;382(18):1708-20.
4. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239-42.
5. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet. 2020;395(10229):1054-62.
6. Shi Q, Zhang X, Jiang F, Zhang X, Hu N, Bimu C, et al. Clinical Characteristics and Risk Factors for Mortality of COVID-19 Patients With Diabetes in Wuhan, China: A Two-Center, Retrospective Study. Diabetes Care. 2020;43(7):1382-91.
7. Roncon L, Zuin M, Rigatelli G, Zuliani G. Diabetic patients with COVID-19 infection are at higher risk of ICU admission and poor short-term outcome. Journal of Clinical Virology. 2020;127:104354.
8. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clinical Research in Cardiology. 2020;109(5):531-8.
9. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. Jama. 2020;323(20):2052-9.
10. Sun Y, Guan X, Jia L, Xing N, Cheng L, Liu B, et al. Independent and combined effects of hypertension and diabetes on clinical outcomes in patients with COVID-19: A retrospective cohort study of Huoshen Mountain Hospital and Guanggu Fangcang Shelter Hospital. Journal of Clinical Hypertension. 2021;23(2):218-31.
11. Barron E, Bakhai C, Kar P, Weaver A, Bradley D, Ismail H, et al. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. The Lancet Diabetes & Endocrinology. 2020;8(10):813-22.
12. Holman N, Knighton P, Kar P, O'Keefe J, Curley M, Weaver A, et al. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. The Lancet Diabetes & Endocrinology. 2020;8(10):823-33.
13. Zhu L, She ZG, Cheng X, Qin JJ, Zhang XJ, Cai J, et al. Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. Cell Metabolism. 2020;31(6):1068-77.e3.

14. Dennis JM, Mateen BA, Sonabend R, Thomas NJ, Patel KA, Hattersley AT, et al. Type 2 Diabetes and COVID-19-Related Mortality in the Critical Care Setting: A National Cohort Study in England, March-July 2020. Diabetes Care. 2021;44(1):50-7.
15. Apicella M, Campopiano MC, Mantuano M, Mazoni L, Coppelli A, Del Prato S. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. The Lancet Diabetes & Endocrinology. 2020;8(9):782-92.
16. Lim S, Bae JH, Kwon HS, Nauck MA. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. Nature Reviews Endocrinology. 2021;17(1):11-30.
17. Drucker DJ. Coronavirus Infections and Type 2 Diabetes-Shared Pathways with Therapeutic Implications. Endocrine Reviews. 2020;41(3):01.
18. Gao Y-d, Ding M, Dong X, Zhang J-j, Kursat Azkur A, Azkur D, et al. Risk factors for severe and critically ill COVID-19 patients: A review. Allergy. 2021;76(2):428-55.
19. Argenziano MG, Bruce SL, Slater CL, Tiao JR, Baldwin MR, Barr RG, et al. Characterization and clinical course of 1000 patients with coronavirus disease 2019 in New York: retrospective case series. BMJ. 2020;369:m1996.
20. Abaleke E, Abbas M, Abbasi S, Abbott A, Abdelaziz A, Abdelbadiee S, et al. Azithromycin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. The Lancet. 2021;397(10274):605-12.
21. Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results. New England Journal of Medicine. 2020;384(6):497-511.
22. Fralick M, Colacci M, Munshi L, Venus K, Fidler L, Hussein H, et al. Prone positioning of patients with moderate hypoxia due to COVID-19: A multicenter pragmatic randomized trial [COVID-PRONE]. medRxiv. 2021:2021.11.05.21264590.
23. Verma AA, Hora T, Jung HY, Fralick M, Malecki SL, Lapointe-Shaw L, et al. Characteristics and outcomes of hospital admissions for COVID-19 and influenza in the Toronto area. Canadian Medical Association Journal. 2021;193(12):E410-E8.
24. Seidu S, Gillies C, Zaccardi F, Kunutsor SK, Hartmann-Boyce J, Yates T, et al. The impact of obesity on severe disease and mortality in people with SARS-CoV-2: A systematic review and meta-analysis. Endocrinology, Diabetes & Metabolism. 2021;4(1):e00176.
25. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;584(7821):430-6.