



# Infection Rates and Impact of Glucose Lowering Medications on the Clinical Course of COVID-19 in People with Type 2 Diabetes: A Retrospective Observational Study

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**Purpose:** Diabetes is a risk factor for COVID-19 severity, but the role played by glucose lowering medications (GLM) is still unclear. The aim of this study was to assess infection rates and outcomes of COVID-19 (hospitalization and mortality) in adults with diabetes assisted by the Local Health Unit of Padua (North-East Italy) according to the ongoing GLM.

**Patients and Methods:** People with diabetes were identified using administrative claims, while those with SARS-CoV-2 infection were detected by cross referencing with the local COVID-19 surveillance registry. A multivariate logistic regression model was used to verify the association between GLM classes and the outcome.

**Results:** SARS-CoV-2 infection rates were marginally but significantly higher in individuals with diabetes as compared to those without diabetes (RR 1.04,  $p = 0.043$ ), though such relative 4% increase may be irrelevant from a clinical and epidemiological perspective. 1923 individuals with GLM-treated diabetes were diagnosed with COVID-19; 456 patients were hospitalized and 167 died. Those treated with insulin had a significantly higher risk of hospitalizations for COVID-19 (OR 1.48  $p < 0.01$ ) as were those treated with sulphonylureas/glinides (OR 1.34,  $p = 0.02$ ). Insulin use was also significantly associated with higher mortality (OR 1.90,  $p < 0.01$ ). Use of metformin was significantly associated with lower death rates (OR 0.62,  $p = 0.02$ ). The association of other GLM classes with the outcome was not significant.

**Conclusion:** Diabetes does not appear to modify the risk of SARS-CoV-2 infection in a clinically meaningful way, but strongly increases the rates of hospitalization and death. Insulin use was associated with worse outcomes, whereas metformin use was associated with lower mortality.

**Keywords:** diabetes mellitus, SARS-CoV-2, antidiabetic drugs, metformin, hospitalization, odds ratio, administrative claims, Veneto

## Introduction

SARS-CoV-2 belongs to Coronaviridae family and first manifested in humans at the end of 2019 in China and rapidly spread around the world, causing the COVID-19 (Coronavirus Disease 2019) pandemic.<sup>1</sup> The Coronaviridae family was responsible for two prior epidemics due to particularly aggressive coronavirus strains: the Severe Acute Respiratory Syndrome (SARS) in 2002, and the Middle East Respiratory Syndrome (MERS) in 2012.<sup>2</sup> Coronavirus infection usually presents with flu-like manifestations including fatigue, cough, fever, and mild respiratory symptoms. In some cases, the symptoms can be severe with pneumonia, acute respiratory distress syndrome (ARDS), renal failure, and thromboembolic events.<sup>3,4</sup>

A key component that allows the virus to enter the target cell is the ACE2 receptor (Angiotensin-Converting enzyme 2), which is overexpressed in alveolar type II cells.<sup>5</sup> Once in the host, SARS-CoV-2 triggers an uncontrolled and excessive immune response, characterized by the massive release of inflammatory mediators and cytokines, generating the so-called “cytokine storm”, commonly seen in severe COVID-19.<sup>5</sup>

Coronavirus infection is particularly dangerous for some groups of the population, like elderly people or individuals with chronic comorbidities, such as hypertension, respiratory diseases, cancer, obesity and diabetes.<sup>6</sup> The prevalence of diabetes in people with COVID-19 appears to be comparable to the prevalence of diabetes in the general population with a sex and age distribution.<sup>7</sup> Yet, studies showed that people with diabetes and COVID-19 are more likely to have a worse outcome than the non-diabetic counterparts, including higher risk of hospitalization and death.<sup>8</sup> Several factors can explain why diabetes and coronavirus infection affect each other. First, diabetes is associated with a proinflammatory state which amplifies the cytokine storm.<sup>9</sup> Impaired glycemic control affects both the innate and the adaptive immune systems making the first line of defense less effective to counter infections.<sup>10</sup> In parallel, glucose lowering medications (GLM) may alter the response to coronavirus infection. Metformin, for example, seems to reduce mortality in COVID-19 patients,<sup>11</sup> while the evidence on DPP4i (Dipeptidyl-Peptidase-4 inhibitors) is conflicting<sup>12,13</sup> and insulin appears to be associated with higher mortality rates.<sup>14</sup>

The aim of this study was to analyze rates of infection and the clinical course of COVID-19 in terms of hospitalizations and mortality in adults assisted by the Padua’s Local Health Unit in North-East Italy, and according to the ongoing GLM regimen.

## Materials and Methods

### Data Source

This retrospective population-based cohort study was conducted between 1st March 2020 and 31st December 2020 in the Padova Local Health Unit (LHU) that covers an overall population of 936,000 persons (20% of the Veneto Region population in the Northeast Italy). A COVID-19 surveillance registry of the LHU was linked to claims databases. This local COVID-19 surveillance registry includes information on demographics and hospitalization records of residents who tested positive for SARS-CoV-2 RNA by polymerase chain reaction (PCR) on nasopharyngeal/throat swabs and related outcomes. In Italy, the National Health Systems (NHS) is publicly funded to offer complete health-care services to residents, irrespective of social class or employment. Each resident is identified by a personal identification number and is assisted by general practitioners provided under the Italian NHS. After clinical certification by a specialist, subjects affected by chronic diseases, including diabetes are exempted to pay a fee (co-payment) for specific medicines, exams and medical visits. The LHU pharmaceutical prescription database contains the drug name and anatomic therapeutic chemical (ATC) classification code, quantity, and the date of medicine dispensation, reimbursed by the NHS and no information is included on therapeutics administered within the hospital. The database with information retrieved from hospitals includes the dates of admission, discharge, death, the primary diagnosis, and up to five co-existing clinical conditions and the procedures received. The diagnoses, consistently coded according to the 9th International Code of Diseases (ICD-9-CM) and standardized in all Italian hospitals, are recorded by the hospital specialists responsible of patients care and are validated by the hospital administration for obtaining NHS reimbursement. Patient unique identification code allows linkage of these databases. To ensure privacy, each patient identification code, which allows linkage, was automatically converted by LHU administration into an anonymous code before starting any analysis. In accordance with Italian legislation, this retrospective observational study, using anonymous data from administrative databases, not involving direct access by investigators to individual patients’ data, was approved by the Ethics Committee of the Padua Province (protocol no. 5141, approved on 23/09/2021). In agreement with National regulations (det. AIFA 20/03/2008 on observational research), given the retrospective database nature of the study, a waiver was applied to the need of informed consent.

### Study Population

A diagnosis of diabetes was made by three sources: hospitalizations for diabetes (with ICD-9-CM code as main and secondary diagnosis: 250-XXX), consumption of GLM (with ATC classification = A10-XXX), co-payment exemption

(code 013-XXX). Those testing positive for SARS-CoV-2 were subsequently identified by cross-referencing the “COVID-19 patients database” of the Hygiene, Workplace Safety and Epidemiological Service of Padua, a database containing information on patients diagnosed with SARS-CoV-2.

To evaluate the prevalence of SARS-CoV-2 infection, we retained only individuals with diabetes who met the following inclusion criteria: age  $\geq 18$ , assisted by the Padua’s LHU and known SARS-CoV-2 status. To evaluate the clinical course of COVID-19 the patients had to have, in addition to criteria defined above, also the consumption of at least 1 pack of GLM in the observation period and at least 2 packages of GLM in the previous year (01/03/2019–29/02/2020). Age of patients was calculated as of March 1, 2020.

## Data Collection and Processing

To evaluate the risk of SARS-CoV-2 infection for the diabetic population, a comparison was made between the prevalence of diabetes among individuals who had a confirmed SARS-CoV-2 infection until 31/12/2020 and the whole population of the Padua’s LHU ( $n = 776,388$  in 2020). Outcome analysis was performed according to the ongoing GLM regimen. In order to evaluate outcome differences across treatments, each individual has been assigned to one or more of the following groups: 1) insulin, 2) metformin, 3) sulphonylureas/glinides, 4) acarbose/pioglitazone (combined because of low numbers), 5) DPP4 inhibitors, 6) GLP-1 receptor agonists, 7) SGLT2 inhibitors. In order to be assigned to a group, the patient had to have the consumption of at least one package of the drug included in that group in the observation period, between 01/01/2019 and the date of COVID-19 positivity. The ATC codes used to determine the treatment groups are listed in [Supplementary Table 1](#).

Hospitalization for COVID-19 patients was retrieved by the ICD-9-CM codes related to respiratory system diseases, Coronavirus infection, and cardiovascular diseases (acute myocardial infarction, heart failure, angina pectoris, ischemic heart disease, stroke, thrombotic events). Three months was chosen as the time window between infection and hospitalization to ensure a possible link between the two events. A follow-up of at least 3 months from the date of SARS-CoV-2 positivity was available for each patient. The ICD-9-CM codes considered are presented in [Supplementary Table 2](#). Information on the death status of patients has been taken from the regional population registry (AUR).

The analysis was adjusted for the following confounding factors: age, sex, comorbidities, estimated duration of diabetes (calculated as the period between the date of the first record related to diabetes in the administrative claims and the date of positivity to SARS-CoV-2). The following comorbidities were identified by co-payment exemption codes or by tracer drugs (ie, drugs typically use to treat medical conditions): hypertension, dyslipidemia, cardiovascular diseases (heart failure, arrhythmias, atrial fibrillation, ischemic heart disease), renal failure, cancer, COPD and/or other chronic respiratory disease, primary and secondary immunodeficiency. Criteria used to define comorbidities taken in consideration are presented in [Supplementary Table 3](#).

## Statistical Analysis

The study sample was described using absolute frequencies and percentages for the categorical variables and by means and standard deviation for continuous variables.

We compared clinical variables in relation to occurrence or non-occurrence of the outcomes of interest (hospitalization and mortality). For continuous variables, we performed Student’s *t*-test for two independent samples or, if not applicable, we used the Wilcoxon rank sum test (two-sample Wilcoxon rank-sum test). For categorical variables, we used the Pearson’s chi-square test or the Fisher’s exact test, as appropriate.

A multivariate logistic regression model was adapted to verify the association between the outcome (dependent variable) and the GLM classes. For the control of potential confounders, all covariates deemed clinically relevant were included in the model: age, sex, comorbidities defined above, disease duration. The verification of the goodness-of-fit of the model was performed by means of the Hosmer-Lemeshow test.

In all analyses, a *P* value  $< 0.05$  was considered significant. The data were analyzed with Stata software version 14 (Stata Corporation, College Station, TX, USA).

## Results

### Infection Rates

The total population assisted by the LHM of Padua in 2020 was 776,388 adults, of whom, 54,009 had a claim-based diagnosis of diabetes with a resulting prevalence of 7.0%. The total number of patients affected by SARS-CoV-2 in the Padua's LHM in 2020 was 40,798, of whom 2953 were also affected by diabetes. The resulting prevalence of diabetes in people with SARS-CoV-2 infection was 7.2% (RR = 1.04 [1.00–1.08])  $p = 0.043$ .

### Hospitalization Rates by Ongoing Therapies

Of 2953 patients with diabetes identified by inclusion criteria, 1923 patients with diabetes and diagnosed with SARS-CoV-2 infection were on a GLM and were included in the analysis to evaluate disease course according to the GLM regimen. Each patient has been assigned to one or more groups according to the use of GLM classes. The average number of GLM classes per patient was 1.77, in agreement with the notion that most people with diabetes require more than one GLM. The average age was 69.2 years, and the 59.8% were men. Almost 90% of subjects had at least one comorbidity and, on average, patients were affected by two concomitant diseases, the most common being hypertension (74.8%), dyslipidemia (62.7%) and cardiovascular diseases like heart failure, arrhythmias, atrial fibrillation, and ischemic heart disease (49.7%). On average, the duration of diabetes was 11.5 years, with a maximum for patients on insulin treatment (14.3 years). A total of 456 hospitalizations with diagnoses attributable to COVID-19 or to cardiovascular/thrombotic events were detected (23.7%). The vast majority of patients (95.8%) were hospitalized for SARS-CoV-2 related diagnoses, while the remainder were due to heart failure, angina, ischemic heart disease, stroke, or thrombotic events. Deaths for any cause were 167 (8.7%). Baseline characteristics of these individuals are presented in [Table 1](#).

The analysis of hospitalization outcome as a function of therapy is shown in [Table 2](#). According to the logistic regression model, male gender was associated with hospitalization (OR 1.81,  $p < 0.01$ ) and the risk of hospitalization increased with age (50–59 years OR 3.55  $p < 0.01$ ; >80 years OR 9.98  $p < 0.01$ ). Chronic kidney disease was significantly associated with higher risk of hospitalization (OR 2.37,  $p < 0.01$ ) while other comorbidities were not. Patient treated with insulin had a significantly higher risk of hospitalizations for COVID-19 (OR 1.48  $p < 0.01$ ) as did those treated with sulphonylureas/glinides (OR 1.34,  $p = 0.02$ ). The association between other drug groups with the outcome was not statistically significant.

### Mortality by Ongoing Therapies

The analysis of death as a function of GLM is shown in [Table 3](#). Male gender was associated with an increased risk of death (OR 1.66,  $p = 0.01$ ); advanced age was also associated with mortality, especially for patients aged >70 years (70–79 years OR 12.72,  $p = 0.02$ ; >80 years OR 82.06,  $p < 0.01$ ). Patient treated with insulin displayed a significantly higher risk of death for all causes (OR 1.90,  $p < 0.01$ ) while patient treated with Metformin showed a significantly lower risk of death (OR 0.62,  $p = 0.02$ ). The association of other drug groups with the outcome was not statistically significant.

## Discussion

Diabetes has emerged as one of the comorbidities that worsen the prognosis for people infected by SARS-CoV-2 and it is also related to a higher rate of death.<sup>8</sup> In addition to confirming this finding, we herein evaluated the potential role of different GLM classes on the clinical course of the coronavirus infection in people with diabetes. Overall, we obtained results that were partly consistent with prior evidence.

A minor excess in the rate of SARS-CoV-2 infection was found, with a 4% relative rate increase. Though statistically significant (due to large sample size), such difference could be considered quantitatively irrelevant from a clinical and epidemiological perspective. In addition, this analysis does not unequivocally lead to the conclusion that diabetes increases the likelihood of SARS-CoV-2 infection because exposure to an infectious agent may be a function of different components (environmental, behavioral, etc.) that have not been considered in this study. A previous analysis of SARS-CoV-2 cases in the Veneto population up to July 2020 identified a rate ratio for ascertained infection of 1.31 among people with versus those without diabetes.<sup>15</sup> The different result obtained in our study, which indicates much a smaller, if

**Table 1** Baseline Characteristics of the Positive Diabetic Population Treated with Hypoglycemic Drugs

	Total	Insulin	Metformin	Sulphonylureas, Glinides	Acarbose, Pioglitazone	DPP4i	GLP-1 RA	SGLT2i
N. of subjects by group of treatment (n)/(%)	1923	611 (31.8%)	1462 (76.0%)	455 (23.7%)	82 (4.3%)	348 (18.1%)	216 (11.2%)	230 (12.0%)
Age, median (years)	69.2	67.2	69.7	72.1	68.3	73.5	62.9	64.2
Sex, Male (n)/(%)	1150 (59.8%)	346 (56.6%)	887 (60.7%)	265 (58.2%)	49 (59.8%)	207 (59.5%)	137 (63.4%)	159 (69.1%)
Duration of diabetic disease, median	11.5	14.3	10.9	12.9	11.8	13	10.3	11
<b>Comorbidities (n)/(%)</b>								
Hypertension	1439 (74.8%)	435 (71.2%)	1120 (76.6%)	347 (76.3%)	58 (70.7%)	267 (76.7%)	169 (78.2%)	181 (78.7%)
Dyslipidemia	1205 (62.7%)	365 (59.7%)	926 (63.3%)	295 (64.8%)	54 (65.9%)	236 (67.8%)	140 (64.8%)	174 (75.7%)
Other CV diseases	955 (49.7%)	329 (53.8%)	728 (49.8%)	241 (53.0%)	36 (43.9%)	216 (62.1%)	97 (44.9%)	125 (54.3%)
Renal failure	47 (2.4%)	31 (5.1%)	17 (1.2%)	8 (1.8%)	2 (2.4%)	18 (5.2%)	4 (1.9%)	4 (1.7%)
Primary immunodeficiencies	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Acquired immunodeficiencies	54 (2.8%)	30 (4.9%)	36 (2.5%)	11 (2.4%)	3 (3.7%)	13 (3.7%)	4 (1.9%)	10 (4.3%)
Cancer	234 (12.2%)	68 (11.1%)	195 (13.3%)	56 (12.3%)	3 (3.7%)	41 (11.8%)	17 (7.9%)	34 (14.8%)
Chronic respiratory diseases	86 (4.5%)	35 (5.7%)	62 (4.2%)	32 (7.0%)	2 (2.4%)	19 (5.5%)	10 (4.6%)	9 (3.9%)
Patients with >1 comorbidities (n)/(%)	1723 (89%)	523 (85.6%)	1339 (91.6%)	420 (92.3%)	69 (84.2%)	323 (92.8%)	196 (90.7%)	215 (93.5%)
<b>Hospitalizations (n)/(%)</b>								
For SARS-CoV-2 infections	437 (95.8%)	161 (94.7%)	320 (97.0%)	128 (97.0%)	21 (100.0%)	95 (96.9%)	42 (93.3%)	43 (93.5%)
For thrombotic/CV disease	19 (4.2%)	9 (5.3%)	10 (3.0%)	4 (3.0%)	0 (0.0%)	3 (3.1%)	3 (6.7%)	3 (6.5%)
Total	456 (23.7%)	170 (27.8%)	330 (22.6%)	132 (29.0%)	21 (25.6%)	98 (28.2%)	45 (20.8%)	46 (20.0%)
Deaths (n)/(%)	167 (8.7%)	77 (12.6%)	104 (7.1%)	49 (10.8%)	6 (7.3%)	45 (12.9%)	10 (4.6%)	13 (5.7%)

**Abbreviations:** DPP4i, Dipeptidyl-Peptidase-4 inhibitors; GLP-1 RA, Glucagon-like peptide-1 receptor agonists; SGLT2i, Sodium-glucose cotransporter 2 inhibitors; CV, Cardiovascular.

**Table 2** Analysis of Hospitalization as a Function of Hypoglycemic Therapy

	OR	95% C.I. Lower Limit	95% C.I. Upper Limit	P value
Sex (M vs F)	1.81	1.42	2.29	<0.01
Age Class (ref 18–49)				
50–59	3.55	1.60	7.91	<0.01
60–69	3.92	1.80	8.57	<0.01
70–79	5.53	2.52	12.12	<0.01
Over 80	9.98	4.52	22.04	<0.01
Insulin	1.48	1.15	1.92	<0.01
Metformin	0.85	0.64	1.12	0.25
Sulphonylureas/Glinides	1.34	1.04	1.73	0.02
Acarbose/Pioglitazone	1.12	0.66	1.91	0.68
DPP4i	1.02	0.76	1.36	0.90
GLP-1 RA	1.09	0.75	1.58	0.65
SGLT2i	0.89	0.62	1.29	0.54
Hypertension	1.11	0.83	1.49	0.47
Dyslipidemia	0.98	0.77	1.25	0.88
Other CV diseases	1.23	0.95	1.58	0.12
Renal failure	2.37	1.27	4.43	0.01
Acquired immunodeficiencies	1.41	0.76	2.61	0.28
Cancer	0.75	0.53	1.06	0.10
Chronic respiratory diseases	1.36	0.84	2.20	0.22
Duration of diabetic disease	0.99	0.97	1.01	0.30

**Abbreviations:** DPP4i, Dipeptidyl-Peptidase-4 inhibitors; GLP-1 RA, Glucagon-like peptide-1 receptor agonists; SGLT2i, Sodium-glucose cotransporter 2 inhibitors; CV, Cardiovascular.

**Table 3** Analysis of Death as a Function of Hypoglycemic Therapy

	OR	95% C.I. Lower Limi	95% C.I. Upper Limit	P value
Sex (M vs F)	1.66	1.14	2.42	0.01
Age class (ref 18–49)				
50–59	0.58	0.03	9.82	0.70
60–69	8.01	0.99	64.96	0.05
70–79	12.72	1.58	102.68	0.02
Over 80	82.06	10.19	660.50	<0.01
Insulin	1.90	1.28	2.84	<0.01
Metformin	0.62	0.41	0.93	0.02

(Continued)

**Table 3** (Continued).

	OR	95% C.I. Lower Limi	95% C.I. Upper Limit	P value
Sulphonylureas/Glinides	1.20	0.80	1.79	0.38
Acarbose/Pioglitazone	0.96	0.38	2.42	0.93
DPP4i	1.17	0.76	1.79	0.48
GLP-1 RA	1.33	0.64	2.77	0.45
SGLT2i	1.28	0.65	2.53	0.48
Hypertension	1.21	0.73	2.00	0.46
Dyslipidemia	0.72	0.49	1.06	0.10
Other CV diseases	1.55	1.00	2.41	0.05
Renal failure	1.39	0.56	3.45	0.47
Acquired immunodeficiencies	10.13	4.67	21.99	<0.01
Cancer	0.13	0.05	0.34	<0.01
Chronic respiratory diseases	0.96	0.46	2.01	0.91
Duration of diabetic disease	0.98	0.95	1.01	0.19

**Abbreviations:** DPP4i, Dipeptidyl-Peptidase-4 inhibitors; GLP-1 RA, Glucagon-like peptide-1 receptor agonists; SGLT2i, Sodium-glucose cotransporter 2 inhibitors; CV, Cardiovascular.

any, incremental risk of infection associated with diabetes may be due to the extended period of observation, when variants of the initial viral strain began to circulate.<sup>16</sup>

In parallel, we confirm a strikingly increased risk of hospitalization for SARS-CoV-2 related causes and death among individuals with diabetes as compared to those without. This finding is in line with prior evidence from several countries and health-care settings.<sup>17</sup> We then assessed hospitalization and death outcomes in relation to the use of GLM classes. Insulin users had a higher risk of been hospitalized in comparison to insulin non-users (OR 1.48  $p < 0.01$ ) as did those treated with sulphonylureas or glinides (OR 1.34,  $p = 0.02$ ). These findings are supported by prior studies in the literature<sup>14,18</sup> but should be correctly interpreted according to the clinical characteristics of insulin-treated patients and the intrinsic limitations of this study. First, people with diabetes who require insulin are typically considered frailer as compared to those who do not require insulin, even after adjustment for confounders as we did in our study. Subjects treated with insulin are usually older and affected by more comorbidities when compared to non-insulin treated ones. These features tend to predispose patients to hospitalization and, if not comprehensively accounted for, represent a bias in the outcome analysis of our study as in others. Furthermore, in this observational study, clinical features such as BMI, glycated hemoglobin, blood pressure, lipid levels, were not available, thereby limiting the possibility to adjust for covariates that can affect the outcome. Similar considerations can be made for individuals on sulphonylureas/glinides: these patients were older (72.1 years compared to 69.2 years, see Table 1) and likely in a more advanced state of disease with characteristics making them fragile.<sup>19</sup> Though patients with diabetes or other metabolic disorders were always considered to be more at risk of disease progression, hospital admission capacity varied during the various phases of the pandemic, thereby affecting the rates of hospitalization in various groups. Further information on COVID-19 severity and medications used in the hospital were not available.

The analysis of mortality as a function of GLM therapy also identified insulin use was associated with a higher mortality risk (OR 1.90,  $p < 0.01$ ). The same considerations as before can be made. Another interesting result is that metformin use appeared to be protective against mortality. This effect is observed in other studies<sup>14</sup> but the possibility of bias should be acknowledged. Metformin users, contrary to what happens with insulin and sulphonylureas, have a lower risk of death compared to other treatments. This can be explained by considering the intrinsic characteristics of

metformin users: they are usually younger and healthier because metformin is the first-line drug treatment for type 2 diabetes and is contraindicated in the presence of advanced end-organ renal, cardiac, pulmonary, and hepatic damage.

As a notable exception compared the literature, the nationwide observational cohort study in UK conducted on almost 3 million people reported that use of sulphonylureas or meglitinides was associated with a significantly lower rate of COVID-19 related death. The authors attributed this spurious effect to the fact that those patients had a less severe disease compared to others, and conclude that these findings are likely to be due to confounding by indication.<sup>20</sup>

Notably, in the primary secondary analysis of the COVID-OUT trial, patients randomized to metformin had a significantly lower rate of emergency department visit, hospitalization, or death (hazard ratio 0.58; 95% C.I. 0.35 to 0.94),<sup>21</sup> providing for the first time a high-quality validation of the findings of several observational studies, including ours.

Survival analysis should be anyway weighted carefully in view of potential confounders. For example, we found a lower short-term mortality among infected patients with cancer, the reason for which is unknown. Patients with cancer may have sought medical treatment more promptly than others after the onset of symptoms, or may be protected by some medications used to treat cancer, such as androgen-deprivation drugs.<sup>22</sup>

## Conclusion

We found that diabetes is associated with a marginal and clinically negligible propensity towards excess SARS-CoV-2 infection, but strongly increases the risk of hospitalization and death. Since these data refer to 2020, when infection was due to SARS-CoV-2 variants now extinct, the relevance of such finding is unclear. With regard to diabetes treatments, we found that users of insulin and sulphonylureas had worse outcomes, whereas metformin users displayed reduced mortality. While we cannot rule out confounding due to unmeasured factors, these data are re-assuring on the risk of COVID-19 outcomes in patients who are infected while on being metformin treatment and suggest a possible benefit of metformin against COVID-19 outcomes.

## Disclosure

Professor Angelo Avogaro reports grants and/or personal fees from Mundipharma, Astrazeneca, Lilly, Novo Nordisk, Amarin, Sanofi, Servier, and Amgen, outside the submitted work. Prof. Dr. Gian Paolo Fadini reports personal fees and/or grants from Abbott, AstraZeneca, Boehringer, Lilly, Novo Nordisk, Sanofi, Servier, and Takeda, outside the submitted work. The author reports no other conflicts of interest in this work.

## References

1. Hui DS, I Azhar E, Madani TA. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health — the latest 2019 novel coronavirus outbreak in Wuhan, China. *Int J Infect Dis.* 2020;91:264–266. doi:10.1016/j.ijid.2020.01.009
2. Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. *Nat Rev Microbiol.* 2019;17(3):181–192. doi:10.1038/s41579-018-0118-9
3. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. *JAMA.* 2020;324(8):782–793. doi:10.1001/jama.2020.12839
4. Harrison AG, Lin T, Wang P. Mechanisms of SARS-CoV-2 transmission and pathogenesis. *Trends Immunol.* 2020;41(12):1100–1115. doi:10.1016/j.it.2020.10.004
5. Pollard CA, Morran MP, Nestor-Kalinowski AL. The COVID-19 pandemic: a global health crisis. *Physiol Genomics.* 2020;52(11):549–557. doi:10.1152/physiolgenomics.00089.2020
6. Goldstein JR, Lee RD. Demographic perspectives on the mortality of COVID-19 and other epidemics. *Proc Natl Acad Sci U S A.* 2020;117(36):22035–22041. doi:10.1073/pnas.2006392117
7. Fadini GP, Morieri ML, Longato E, Avogaro A. Prevalence and impact of diabetes among people infected with SARS-CoV-2. *J Endocrinol Invest.* 2020;43(6):867–869. doi:10.1007/s40618-020-01236-2
8. Varikasuvu SR, Dutt N, Thangappazham B, Varshney S. Diabetes and COVID-19: a pooled analysis related to disease severity and mortality. *Prim Care Diabetes.* 2021;15(1):24–27. doi:10.1016/j.pcd.2020.08.015
9. Sun B, Huang S, Zhou J. Perspectives of antidiabetic drugs in diabetes with coronavirus infections. *Front Pharmacol.* 2021;11. doi:10.3389/fphar.2020.592439
10. Jafar N, Edriss H, Nugent K. The effect of short-term hyperglycemia on the innate immune system. *Am J Med Sci.* 2016;351(2):201–211. doi:10.1016/j.amjms.2015.11.011
11. Lukito AA, Pranata R, Henrina J, Lim MA, Lawrensia S, Suastika K. The effect of metformin consumption on mortality in hospitalized COVID-19 patients: a systematic review and meta-analysis. *Diabetes Metab Syndr.* 2020;14(6):2177–2183. doi:10.1016/j.dsx.2020.11.006
12. Solerte SB, D'Addio F, Trevisan R, et al. Sitagliptin treatment at the time of hospitalization was associated with reduced mortality in patients with type 2 diabetes and COVID-19: a multicenter, case-control, retrospective, observational study. *Dia Care.* 2020;43(12):2999–3006. doi:10.2337/dc20-1521



13. Fadini GP, Morieri ML, Longato E, et al. Exposure to dipeptidyl-peptidase-4 inhibitors and COVID -19 among people with type 2 diabetes: a case-control study. *Diabetes Obes Metab.* 2020;22(10):1946–1950. doi:10.1111/dom.14097
14. Schlesinger S, Neuenschwander M, Lang A, et al. Risk phenotypes of diabetes and association with COVID-19 severity and death: a living systematic review and meta-analysis. *Diabetologia.* 2021;64(7):1480–1491. doi:10.1007/s00125-021-05458-8
15. Bonora E, Fedeli U, Schievano E, et al. SARS-CoV-2 and COVID-19 in diabetes mellitus. Population-based study on ascertained infections, hospital admissions and mortality in an Italian region with ~5 million inhabitants and ~250,000 diabetic people. *Nutr Metab Cardiovasc Dis.* 2021;31(9):2612–2618. doi:10.1016/j.numecd.2021.06.010
16. Webster P. COVID-19 timeline of events. *Nat Med.* 2021;27(12):2054–2055. doi:10.1038/s41591-021-01618-w
17. Kumar A, Arora A, Sharma P, et al. Is diabetes mellitus associated with mortality and severity of COVID-19? A meta-analysis. *Diabetes Metab Syndr.* 2020;14(4):535–545. doi:10.1016/j.dsx.2020.04.044
18. Yu B, Li C, Sun Y, Wang DW. Insulin treatment is associated with increased mortality in patients with COVID-19 and type 2 diabetes. *Cell Metab.* 2021;33(1):65–77.e2. doi:10.1016/j.cmet.2020.11.014
19. Boye KS, Tokar Erdemir E, Zimmerman N, et al. Risk factors associated with COVID-19 hospitalization and mortality: a large claims-based analysis among people with type 2 diabetes mellitus in the United States. *Diabetes Ther.* 2021;12(8):2223–2239. doi:10.1007/s13300-021-01110-1
20. Khunti K, Knighton P, Zaccardi F, et al. Prescription of glucose-lowering therapies and risk of COVID-19 mortality in people with type 2 diabetes: a nationwide observational study in England. *Lancet Diabetes Endocrinol.* 2021;9(5):293–303. doi:10.1016/S2213-8587(21)00050-4
21. Bramante CT, Huling JD, Tignanelli CJ, et al. Randomized trial of metformin, ivermectin, and fluvoxamine for Covid-19. *N Engl J Med.* 2022;387(7):599–610. doi:10.1056/NEJMoa2201662
22. Montopoli M, Zumerle S, Vettor R, et al. Androgen-deprivation therapies for prostate cancer and risk of infection by SARS-CoV-2: a population-based study (N = 4532). *Ann Oncol.* 2020;31:1040–1045. doi:10.1016/j.annonc.2020.04.479

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