Impact of Comorbidities and Glycemia at Admission and Dipeptidyl Peptidase 4 Inhibitors in Patients With Type 2 Diabetes With COVID-19: A Case Series From an Academic Hospital in Lombardy, Italy

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OBJECTIVE

Diabetes may unfavorably influence the outcome of coronavirus disease 19 (COVID-19), but the determinants of this effect are still poorly understood. In this monocentric study, we aimed at evaluating the impact of type 2 diabetes, comorbidities, plasma glucose levels, and antidiabetes medications on the survival of COVID-19 patients.

RESEARCH DESIGN AND METHODS

This was a case series involving 387 COVID-19 patients admitted to a single center in the region of Lombardy, the epicenter of the severe acute respiratory syndrome coronavirus 2 pandemic in Italy, between 20 February and 9 April 2020. Medical history, pharmacological treatments, laboratory findings, and clinical outcomes of patients without diabetes and patients with type 2 diabetes were compared. Cox proportional hazards analysis was applied to investigate risk factors associated with mortality.

RESULTS

Our samples included 90 patients (23.3%) with type 2 diabetes, who displayed double the mortality rate of subjects without diabetes (42.3% vs. 21.7%, $P < 0.001$). In spite of this, after correction for age and sex, risk of mortality was significantly associated with a history of hypertension (adjusted hazard ratio [aHR] 1.84, 95% CI 1.15–2.95; $P = 0.011$), coronary artery disease (aHR 1.56, 95% CI 1.04–2.35; $P = 0.031$), chronic kidney disease (aHR 2.07, 95% CI 1.27–3.38; $P = 0.003$), stroke (aHR 2.09, 95% CI 1.23–3.55; $P = 0.006$), and cancer (aHR 1.57, 95% CI 1.08–2.42; $P = 0.04$) but not with type 2 diabetes ($P = 0.170$). In patients with diabetes, elevated plasma glucose (aHR 1.22, 95% CI 1.04–1.44, per mmol/L; $P = 0.015$) and IL-6 levels at admission (aHR 2.47, 95% CI 1.28–4.78, per 1-SD increase; $P = 0.007$) as well as treatment with insulin (aHR 3.05, 95% CI 1.57–5.95; $P = 0.001$) and β-blockers (aHR 3.20, 95% CI 1.50–6.60; $P = 0.001$) were independently associated with increased mortality, whereas the use of dipeptidyl peptidase 4 inhibitors was significantly and independently associated with a lower risk of mortality (aHR 0.13, 95% CI 0.02–0.92; $P = 0.042$).

CONCLUSIONS

Plasma glucose levels at admission and antidiabetes drugs may influence the survival of COVID-19 patients affected by type 2 diabetes.

PATHOPHYSIOLOGY/COMPLICATIONS

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The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for the acute respiratory syndrome known as coronavirus disease 19 (COVID-19), first emerged at the end of 2019 in Wuhan, China (1).

After its subsequent global spread, COVID-19 was officially declared a pandemic by the World Health Organization on 11 March 2020 (2). The first confirmed case of COVID-19 in Italy was diagnosed in Lombardy on 20 February 2020. Within a few weeks, several other cases, including a substantial number of critically ill patients, started being diagnosed in the surrounding geographical area (3).

According to the latest report of the Italian National Institute of Health (Istituto Superiore di Sanità), updated on 22 July 2020, 34,142 patients with a diagnosis of SARS-CoV-2 infection died in Italy, 16,776 (49.1%) of them in the region of Lombardy alone (4).

There is convincing evidence that diabetes may unfavorably influence the prognosis of patients with COVID-19 (5,6), as was previously reported in patients with diabetes affected by the closely related coronavirus-induced severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) (7,8). This is to be expected, as diabetes is one of the leading causes of morbidity and mortality worldwide and is itself known to prompt a dysregulation in the body's immune response (9–12). Conversely, infections are an important cause of morbidity and death in patients with diabetes (13).

The dynamics of increased mortality in COVID-19 patients with diabetes are currently being investigated. Data from Wuhan indicate that COVID-19 patients with diabetes had worse outcomes, mainly attributable to older age and coexisting hypertension (14). Some reports showed an association between metabolic control and survival (15,16), while others found insulin therapy to correlate with worse clinical outcome (17). By contrast, other studies showed no impact of diabetes on the severity of illness and mortality after adjustment for confounding variables (14,18,19). Heterogeneity of study populations may have at least in part influenced the inconsistent results of literature.

In this single-center study carried out in a large research hospital in the south of Milan (Italy), we aimed at evaluating the relationship between diabetes and COVID-19 infection outcome, specifically analyzing the baseline comorbidities, the clinical features, and the possible impact of antidiabetes medications on risk of mortality in this clinical setting.

RESEARCH DESIGN AND METHODS

Study Design

This is a large case series involving 387 patients with diagnosis of COVID-19 infection admitted to the Humanitas Clinical and Research Hospital, IRCCS, between February 20 and 9 April 2020. The institutional ethics committee approved this study, and patients gave standard written informed consent to the use of their anonymized clinical data for research purposes.

Inclusion criteria were *1*) age >18 years, *2*) nasopharyngeal swab positive for SARS-CoV-2, *3*) chest computed tomography (CT) scan suggestive for viral pneumonia, *4*) fever and/or respiratory symptoms at the admission, and *5*) completed hospital stay before end of study (discharged or deceased). Failure to meet any of the previous criteria was cause for exclusion from the study.

As primary end point of this study, we evaluated the predictive factors of COVID-19–related mortality in patients with type 2 diabetes; as secondary end point, we explored the determinants of mortality in the entire population of COVID-19 patients with diabetes and patients without diabetes. For this purpose, comorbidities, laboratory parameters, prescribed medications, and antidiabetes therapy were evaluated.

Some of the enrolled patients have already been involved in other studies evaluating different end points from the current study (20–23).

Data Collection

We collected the following data from our electronic medical records system (wHospital): demographic information, medical and medication history, laboratory tests at admission, chest CT scans, inpatient treatment plan (including maximal supportive oxygen therapy), and clinical outcomes (discharged alive or deceased during hospital stay). Throughout this collection process, we were able to retrieve >95% of the required data for our entire study population.

At the admission, the nasopharyngeal specimens were obtained from the patients and stored in a viral-transport medium, and total RNA was then extracted and examined by RT-PCR according to the manufacturer's procedure kit (Enlight).

Chest CT scans were evaluated by an experienced team of radiologists and classified as typical for COVID-19 based on radiological findings as previously described (24).

We also collected data from medical records about the following clinical conditions: hypertension, coronary artery disease (CAD), stroke, past or active cancer, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD) associated with stages 3–5 kidney failure as defined by estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 (calculated by Chronic Kidney Disease Epidemiology Collaboration equation), and obesity (defined as BMI ≥30 kg/m^2).

The following laboratory tests at admission were assessed for each patient: glycemia (mmol/L), creatinine (mg/dL), lymphocyte count ($\times 10^3/mm^3$), interleukin-6 (IL-6) (pg/mL), D-dimer (ng/mL), lactate dehydrogenase (LDH) (units/L), ferritin (ng/mL), C-reactive protein (CRP) (mg/dL), and procalcitonin (PCT) (ng/mL).

Procedures

According to the guidelines of the Italian Society of Infectious Disease (25) and to the internal protocol of our hospital, all patients admitted with COVID-19 were treated with a standard therapy consisting of hydroxychloroquine, enoxaparin, antiviral agents (lopinavir/ritonavir), and antibiotics. Steroids were used as a second-line therapy in patients unresponsive to therapy or with disease progression despite treatment with hydroxychloroquine and antiviral agents.

At admission, all oral antidiabetes drugs were discontinued, with the exception of the dipeptidyl peptidase 4 inhibitors (DPP4-I) because of their acceptable safety profile (26), and the patients were prescribed a basal-bolus insulin scheme.

Statistical Analysis

We summarized all continuous variables calculating the mean or median with respective SDs or interquartile ranges (IQR). Categorical variables were expressed both in absolute numbers and their relative prevalence in percentages (%). Differences between groups were analyzed using the χ^2 test or Fischer

Table 1—Demographic, clinical characteristics, laboratory parameters, medications, and outcomes in 385 hospitalized patients with COVID-19 stratified according to the presence of diabetes

	No diabetes (n = 295)	Diabetes (n = 90)	P
Male/female sex	193 (65.4)/102 (34.6)	65 (72.2)/25 (27.8)	0.230
Age (years)	63 (52–74)	71 (64–78)	<0.001
Comorbidities			
Hypertension	121 (41)	69 (76.7)	<0.001
Obesity (BMI >30 kg/m^2)	99 (33.7)	43 (47.8)	0.117
CAD	50 (16.9)	35 (38.9)	<0.001
CKD	15 (5.1)	17 (18.9)	<0.001
COPD	20 (6.8)	14 (15.6)	0.010
Stroke	12 (4.1)	15 (16.7)	<0.001
Cancer	43 (14.6)	19 (21.1)	0.140
Laboratory findings			
Glycemia (mmol/L)	5.7 ± 1.4	9.1 ± 3.4	<0.001
Creatinine (mg/dL)	0.95 ± 1.1	1.48 ± 1.9	0.001
eGFR (mL/min/1.73 m^2)	90.1 ± 26.4	72.4 ± 31.2	<0.001
Lymphocytes (×10^3/mm^3)	1.1 ± 0.5	1 ± 0.5	0.924
IL-6 (pg/mL)	60 ± 99	85 ± 67	0.125
D-dimer (ng/mL)	1,090 ± 2,721	928 ± 1,681	0.621
LDH (units/L)	338 ± 152	333 ± 131	0.792
Ferritin (ng/mL)	634 ± 579	591 ± 505	0.574
CRP (mg/dL)	9.4 ± 7.7	11 ± 7.5	0.900
PCT (ng/mL)	0.51 ± 1.2	0.49 ± 0.8	0.905
Medications			
Lipid-lowering drugs	43 (14.6)	29 (32.2)	<0.001
Antiplatelet/anticoagulant	66 (22.4)	41 (45.6)	<0.001
ACE-I/ARB	72 (24.4)	40 (44.4)	<0.001
Calcium channel blockers	26 (8.8)	28 (31.1)	<0.001
β-Blockers	63 (21.3)	33 (36.6)	0.003
Diuretics	30 (10.1)	25 (27.7)	<0.001
O_2 therapy			
Supplemental O_2	156 (52.8)	40 (44.4)	0.168
Noninvasive mechanical ventilation	38 (12.9)	24 (26.7)	0.002
Invasive ventilation	25 (8.5)	5 (5.6)	0.366
Length of hospitalization (days)	8 (6–12)	9 (6–11.75)	0.600
Mortality	64 (21.7)	38 (42.3)	<0.001

Categorical data n (%), and continuous data are means ± SD or median (IQR).

exact test for categorical variables and Student t test or Mann-Whitney U test for continuous variables, as appropriate.

For exploration of the risk factors associated with mortality in the entire population and in the subgroup of patients with type 2 diabetes, a Cox proportional hazards regression model was applied, crude and adjusted for age and sex. We then conducted a separate multivariate Cox analysis to test the independent impact of age ≥70 years, glycemia, CRP, D-dimer, and IL-6 on mortality in the entire population and in the subgroup of patients with type 2 diabetes. The cumulative rates of death were plotted by application of the Kaplan-Meier method.

Statistical analyses were performed with SPSS 13.0. A P value <0.05 was considered statistically significant.

RESULTS

Clinical Characteristics at Admission

Among the 498 consecutive patients admitted to our hospital during the study period, 387 (median age 66 years [IQR 54–76]), 258 male [66.7%]) fulfilled the inclusion criteria of this study and were enrolled.

According to their medical history, 90 (23.3%) patients in the study cohort had preexisting type 2 diabetes, 2 had type 1 diabetes (0.5%), and the remaining 295 (76.2%) did not have diabetes. Patients with type 1 diabetes were excluded from the analysis, eluding the purpose of our study focused on type 2 diabetes. Descriptive characteristics of the study population are reported in Table 1.

Patients with type 2 diabetes were older (median age 71 years old [IQR 64–78] vs. 63 years old [IQR 52–74], P < 0.001); had a higher prevalence of hypertension (76.7% vs. 41.0%, P < 0.001), CAD (38.9% vs. 16.9%, P < 0.001), CKD (18.9% vs. 5.1%, P < 0.001), COPD (15.6% vs. 6.8%, P = 0.010), and stroke (16.7% vs. 4.1%, P < 0.001); had higher plasma glucose (9.1 ± 3.4 vs. 5.7 ± 1.4 mmol/L, P < 0.001), higher serum creatinine (1.48 ± 1.9 vs. 0.95 ± 1.1 mg/dL, P = 0.001), and lower eGFR (72.4 ± 31.2 vs. 90.1 ± 26.4 mL/min/1.73 m^2, P < 0.001); and were more likely to take lipid-lowering medications (P < 0.001), antiplatelet/anticoagulant (P < 0.001) and antihypertensive drugs (P from 0.003 to <0.001) compared with patients without diabetes, without any significant differences in regard to sex, inflammatory parameters, and prevalence of obesity and cancer.

In patients with type 2 diabetes, metformin was the most frequently administered antidiabetes medication, prescribed to 76.0% of the patients, followed by insulin (32.0%), DPP4-I (12.2%), sulfonylureas (11.1%), glucagon-like peptide 1 receptor agonists (GLP-1 RA) (6.7%), sodium–glucose cotransporter 2 inhibitors (SGLT2-I) (5.6%), and pioglitazone (1.1%).

Outcomes

All of the COVID-19 patients received a treatment comprising hydroxychloroquine, enoxaparin, antiviral agents (lopinavir/ritonavir), and antibiotics. A total of 102 (26.4%) patients were also treated with steroids, with no difference between patients without diabetes and patients with diabetes (P = 0.093).

A total of 196 (50.9%) patients received supplemental O_2 during hospitalization, without significant difference between patients with diabetes and patients without diabetes (P = 0.168), while escalation to noninvasive mechanical ventilation occurred in 62 (16%) patients and was more frequent in patients with diabetes versus patients without diabetes (26.7% vs. 12.9%, P = 0.002). Invasive ventilation was required for 30 (7.7%) patients, without significant difference between the two groups (P = 0.366) (Table 1). The overall median length of stay was 8 days (range 1–31), with a comparable duration in the two groups (P = 0.600) (Table 1). The in-hospital mortality rate in patients with type 2 diabetes was double that of patients without diabetes (42.3% vs. 21.7%, P < 0.001) (Table 1).

The Kaplan-Meier survival curve of patients stratified by diabetes is shown in Fig. 1 (P = 0.002).

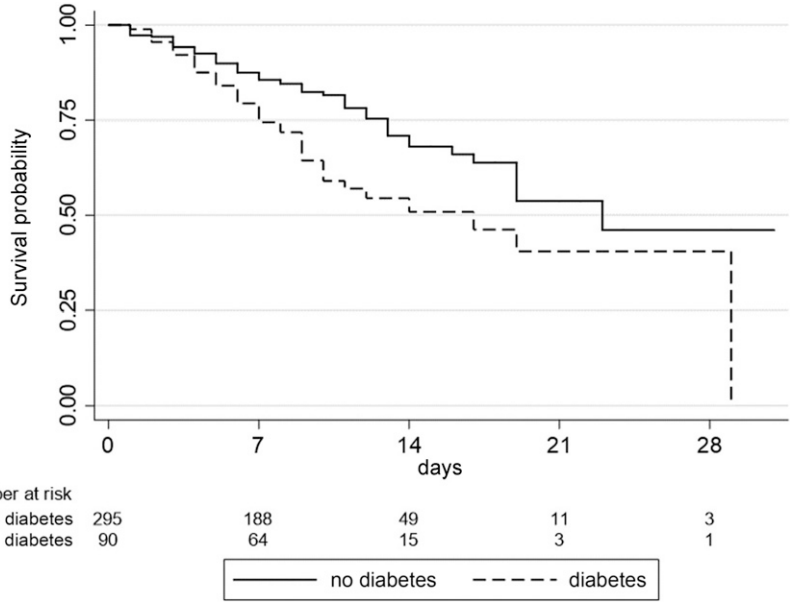

Figure 1—Survival curve of COVID-19 patients stratified by the presence of diabetes ($P = 0.002$).

Risk Factors Associated With Mortality in the Entire Study Population

In the univariate Cox analysis, age ≥70 years, diabetes, hypertension, CAD, CKD, stroke, cancer, and treatment with lipid-lowering drugs, calcium channel blockers, β-blockers, and diuretics, as well as all biochemical laboratory parameters except ferritin, were associated with a higher mortality rate (Table 2). After adjustment for age and sex, hypertension (adjusted hazard ratio [aHR] 1.84, 95% CI 1.15–2.95; $P = 0.011$), CAD (aHR 1.56, 95% CI 1.04–2.35; $P = 0.031$), CKD (aHR 2.07, 95% CI 1.27–3.38; $P = 0.003$), stroke (aHR 2.09, 95% CI 1.23–3.55; $P = 0.006$), cancer (aHR 1.57, 95% CI 1.08–2.42; $P = 0.042$), glycemia (aHR 1.007, 95% CI 1.004–1.010, per mmol/L; $P < 0.001$), creatinine (aHR 1.17, 95% CI 1.08–1.27, per mg/dL; $P < 0.001$), IL-6 (aHR 3.22, 95% CI 2.05–5.05, per 1-SD increase; $P < 0.001$), D-dimer (aHR 2.25, 95% CI 1.66–3.04, per 1-SD increase; $P = 0.001$), LDH (aHR 1.68, 95% CI 1.32–2.13, per 1-SD increase; $P < 0.001$), CRP (aHR 1.06, 95% CI 1.03–1.08, per mg/dL; $P < 0.001$), and PCT (aHR 1.07, 95% CI 1.03–1.10, per ng/mL; $P < 0.001$) retained a significant and independent association with a higher mortality risk, whereas the association with type 2 diabetes was lost (Table 2).

In the multivariate analysis including biochemical laboratory parameters, age ≥70 years (HR 7.24, 95% CI 2.76–19.00; $P < 0.001$), high glycemia (HR 1.006, 95% CI 1.001–1.011, per mmol/L; $P = 0.017$), high IL-6 (HR 2.58, 95% CI 1.44–4.63, per 1-SD increase; $P = 0.001$), and D-dimer (HR 2.03, 95% CI 1.08–3.80, per 1-SD increase; $P = 0.027$) were significantly associated with higher risk of mortality (Table 2).

Risk Factors Associated With Mortality in Patients With Type 2 Diabetes

In the univariate Cox analysis, age ≥70 years, CAD, CKD, treatments with β-blockers or insulin, lower lymphocyte count, and higher IL-6, LDH, CRP, and PCT levels were associated with higher mortality, whereas the use of metformin or DPP4-I was associated with a lower mortality rate (Table 2). After adjustment for sex and age, β-blockers (aHR 3.21, 95% CI 1.50–6.60; $P < 0.001$), insulin (aHR 3.05, 95% CI 1.57–5.95; $P < 0.001$), lower lymphocyte count (aHR 0.27, 95% CI 0.11–0.64, per $10^3/mm^3$; $P = 0.003$), higher IL-6 (aHR 2.02, 95% CI 1.15–3.56, per 1-SD increase; $P = 0.015$), and LDH (aHR 1.56, 95% CI 1.05–2.33, per 1-SD increase; $P = 0.029$) were still significantly associated with higher mortality, whereas the use of DPP4-I was independently associated with a significant reduction of mortality risk (aHR 0.13, 95% CI 0.02–0.92; $P = 0.042$) (Table 2). With regard to comorbidity, there was a trend of association between CKD and mortality risk after adjustment for age and sex (aHR 2.06, 95% CI 1.01–4.21; $P = 0.056$) (Table 2).

In the multivariate analysis including biochemical parameters, higher glycemia (HR 1.22, 95% CI 1.04–1.44, per mmol/L; $P = 0.015$) and IL-6 (HR 2.47, 95% CI 1.28–4.78, per 1-SD increase; $P = 0.007$) were independent risk factors for mortality (Table 2).

In Table 3, we report the clinical features of patients with type 2 diabetes grouped by glucose-lowering drugs. The group treated with insulin was more likely to have higher levels of IL-6 ($P = 0.026$) and PCT ($P = 0.034$), a greater prevalence of CKD ($P = 0.014$), and requirement of invasive ($P = 0.019$) or noninvasive ($P = 0.010$) mechanical ventilation. Fewer patients in this group were prescribed ACE inhibitors (ACE-I)/angiotensin receptor blockers (ARB) ($P = 0.012$), metformin ($P = 0.006$), or DPP4-I ($P = 0.012$) than in the group not treated with insulin. DPP4-I users needed noninvasive mechanical ventilation less frequently ($P = 0.029$) compared with the nonusers. Notably, none of the DPP4-I users were taking insulin ($P = 0.006$ vs. non–DPP4-I users). No significant differences in age, glycemia, comorbidities, or inflammatory parameters were found between DPP4-I users and nonusers.

CONCLUSIONS

Our study focused on a SARS-CoV-2–positive population admitted to a single hospital located in the epicenter of the COVID-19 pandemic in Italy.

Prevalence of type 2 diabetes in this cohort was 23.3%, which is higher than that previously reported in publications from China (5,6,17) and similar to that in Europe (27,28) but lower than data from the U.S. (29–31). Compared with subjects without diabetes of this study, the subset of patients with type 2 diabetes was older and burdened by a higher prevalence of comorbidities (i.e., hypertension, CAD, CKD, and stroke) and related polypharmacy, with many patients taking multiple medications (including antihypertensive, lipid-lowering, and antiplatelet/anticoagulants drugs).

These patient characteristics reflect Italian demographics, as Italy now hosts one of the oldest populations worldwide (databank.worldbank.org). This trend might also partly account for the mortality rates observed in our study.

Patients with type 2 diabetes were twice as likely to die compared with patients without diabetes, which is in accordance with findings in previous

Table 2—Results of Cox regression analysis evaluating the determinants of COVID-related mortality risk in the entire population of 385 patients and in the subgroup of 90 patients with type 2 diabetes

	All patients (n = 385)		Patients with type 2 diabetes (n = 90)	
	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[a]	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[a]
Age ≥70 years	5.73 (3.54–9.26)*		2.76 (1.30–5.86)*	
Sex (female vs. male)	0.94 (0.62–1.43)		1.06 (0.51–2.18)	
Diabetes	1.84 (1.23–2.76)*	1.33 (0.88–2.0)	—	—
Hypertension	3.02 (1.92–4.76)*	1.84 (1.15–2.95)*	2.33 (0.91–5.97)	2.20 (0.85–5.70)
Obesity (BMI >30 kg/m^2)	1.12 (0.69–1.82)	1.33 (0.81–2.18)	1.3 (0.6–2.7)	1.61 (0.72–3.60)
CAD	2.58 (1.74–3.83)*	1.56 (1.04–2.35)*	1.93 (1.01–3.68)*	1.75 (0.90–3.38)
CKD	3.10 (1.90–5.05)*	2.07 (1.27–3.38)*	2.2 (1.09–4.47)*	2.06 (1.01–4.21)
Stroke	3.04 (1.81–5.13)*	2.09 (1.23–3.55)*	1.75 (0.84–3.61)	1.54 (0.74–3.23)
COPD	1.41 (0.81–2.46)	0.95 (0.54–1.66)	1.53 (0.7–3.35)	1.18 (0.52–2.67)
Cancer	2.58 (1.70–3.93)*	1.57 (1.08–2.42)*	1.67 (0.82–3.41)	1.16 (0.54–2.47)
Lipid-lowering drugs	1.8 (1.2–2.7)*	1.1 (0.7–1.8)	1.3 (0.6–2.6)	1.3 (0.6–2.6)
Antiplatelet/anticoagulant	1.4 (0.9–2.2)	0.8 (0.5–1.2)	1.1 (0.5–2.2)	1 (0.5–2.0)
ACE-I/ARB	1.2 (0.8–1.9)	0.8 (0.5–1.3)	0.8 (0.4–1.6)	0.7 (0.3–1.4)
Calcium channel blockers	1.8 (1.1–2.9)*	1.3 (0.8–2.0)	1.8 (0.9–3.6)	1.7 (0.8–3.6)
β-Blockers	1.6 (1–2.4)*	1.2 (0.8–1.9)	3.1 (1.5–6.4)*	3.21 (1.5–6.6)*
Diuretics	2 (1.2–3.1)*	1.3 (0.8–2.0)	1.6 (0.8–3.3)	1.4 (0.7–2.9)
Insulin			3.34 (1.74–6.41)*	3.05 (1.57–5.95)*
Metformin			0.43 (0.21–0.85)*	0.55 (0.27–1.11)
Sulfonylureas			0.34 (0.08–1.42)	0.28 (0.06–1.20)
DPP4-I			0.14 (0.02–1.01)	0.13 (0.02–0.92)*
SGLT2-I			NA†	NA†
GLP-1 RA			NA†	NA†
Pioglitazone			NA†	NA†
Glycemia (mmol/L)	1.007 (1.003–1.010)*	1.007 (1.004–1.010)*	1.003 (0.998–1.008)	1.004 (0.999–1.010)
Creatinine (mg/dL)	1.2 (1.1–1.3)*	1.17 (1.08–1.27)*	1 (0.9–1.2)	1.09 (0.96–1.24)
Lymphocytes (×10^3/mm^3)	0.60 (0.40–0.89)*	0.74 (0.5–1.1)	0.28 (0.13–0.61)*	0.27 (0.11–0.64)*
IL-6 (per 1-SD increase)	3.23 (2.16–4.84)*	3.22 (2.05–5.05)*	2.1 (1.21–3.64)*	2.02 (1.15–3.56)*
D-dimer (per 1-SD increase)	2.49 (1.86–3.34)*	2.25 (1.66–3.04)*	1.54 (0.96–2.46)	1.32 (0.81–2.14)
LDH (per 1-SD increase)	1.62 (1.27–2.05)*	1.68 (1.32–2.13)*	1.53 (1.01–2.33)*	1.56 (1.05–2.33)*
Ferritin (per 1-SD increase)	1.33 (0.96–1.85)	1.42 (0.99–2)	1.58 (0.92–2.7)	1.71 (0.96–3.04)
CRP (mg/dL)	1.05 (1.03–1.08)*	1.06 (1.03–1.08)*	1.04 (1.00–1.08)*	1.04 (0.99–1.09)
PCT (ng/mL)	1.08 (1.06–1.11)*	1.07 (1.03–1.1)*	1.08 (1.02–1.15)*	1.28 (0.97–1.69)

	Multivariate HR (95% CI)	
	All patients	Patients with type 2 diabetes
Age ≥70 years	7.24 (2.76–19.00)*	3.23 (0.70–14.88)
Glycemia (mmol/L)	1.006 (1.001–1.011)*	1.22 (1.04–1.44)*
IL-6 (per 1-SD increase)	2.58 (1.44–4.63)*	2.47 (1.28–4.78)*
D-dimer (per 1-SD increase)	2.03 (1.08–3.80)*	1.89 (0.81–4.39)
CRP (mg/dL)	0.98 (0.92–1.05)	0.93 (0.85–1.01)

HR, hazard ratio; NA, not assessed. [a]Adjusted for age and sex. *$P < 0.05$. †Not assessed because of small numbers (SGLT2-I n = 5, GLP-1 RA n = 6, pioglitazone n = 1).

studies (5,6,27,28,31). However, the significant association between type 2 diabetes and mortality was lost after adjustment of models for age and sex, whereas cardiovascular diseases, CKD, and cancer were shown to be independent risk factors of mortality. These findings suggest that comorbidities not necessarily related to diabetes may be important predictors of mortality more than diabetes itself in patients with COVID-19. Nonetheless, it is reasonable to hypothesize that an altered glucose metabolism may have influenced the outcome of our patients with COVID-19. In fact, the analysis of biochemical predictors of mortality in the overall study population revealed that an initial higher plasma glucose level was significantly and independently correlated with a lower survival of COVID-19 patients. This finding is consistent with the result of a recent study showing that hyperglycemia at hospital admission was an independent factor associated with severe prognosis in subjects hospitalized for COVID-19 (32). One could argue that patients presenting with higher blood glucose levels at admission were those with already more

Table 3—Clinical features of 90 patients with type 2 diabetes stratified by glucose-lowering drugs

	Insulin		Metformin		DPP4-I		Sulfonylureas	
	Yes	No	Yes	No	Yes	No	Yes	No
n	29	61	69	21	11	79	10	80
Sex (male)	21 (72.4)	44 (72.1)	50 (72.5)	15 (71.4)	10 (90.9)	55 (69.6)	6 (60)	59 (73.8)
Age (years)	72 ± 10	70 ± 13	**69 ± 13**	**75 ± 8**	70 ± 13	71 ± 12	75 ± 8	70 ± 12
Glycemia (mmol/L)	9.5 ± 4.3	8.9 ± 3.0	9.0 ± 3.2	9.4 ± 4.2	9.8 ± 3.2	9.0 ± 3.5	8.4 ± 2.8	9.2 ± 3.5
Creatinine (mg/dL)	1.8 ± 2.3	1.3 ± 1.7	1.8 ± 2.5	1.3 ± 1.7	0.9 ± 0.4	1.5 ± 2	**0.7 ± 0.2**	**1.5 ± 2**
Lymphocytes ($\times 10^3/mm^3$)	0.97 ± 0.5	1.13 ± 0.6	1.1 ± 0.6	1.0 ± 0.5	1.2 ± 0.3	1.0 ± 0.6	1.0 ± 0.5	1.1 ± 0.6
IL-6 (pg/mL)	**120 ± 80**	**72 ± 57**	77 ± 60	114 ± 84	56 ± 41	90 ± 69	72 ± 38	88 ± 70
D-dimer (ng/mL)	2,459 ± 8,150	969 ± 1,946	985 ± 1,862	3,102 ± 9,878	468 ± 176	1,574 ± 5,172	510 ± 330	1,554 ± 5,136
LDH (units/L)	318 ± 97	365 ± 180	316 ± 107	391 ± 183	290 ± 88	340 ± 136	293 ± 60	338 ± 137
Ferritin (ng/mL)	797 ± 846	550 ± 414	586 ± 465	778 ± 915	467 ± 449	649 ± 608	757 ± 512	615 ± 602
CRP (mg/dL)	12.1 ± 9.1	11.2 ± 7.8	11.5 ± 8.1	11.6 ± 8.8	9.2 ± 6.7	11.8 ± 8.4	**17.1 ± 8.0**	**10.8 ± 8.0**
PCT (ng/mL)	**1.9 ± 6.2**	**0.4 ± 0.8**	0.9 ± 4.0	0.7 ± 1.0	0.3 ± 0.3	1.0 ± 3.8	0.3 ± 0.2	1.0 ± 3.8
Hypertension	23 (79.3)	46 (75.4)	50 (72.5)	19 (90.5)	6 (54.6)	63 (79.8)	8 (80)	61 (76.3)
Obesity (BMI >30 kg/m^2)	15 (51.7)	28 (45.9)	33 (47.8)	10 (47.6)	3 (27.3)	40 (50.6)	5 (50)	38 (47.5)
CAD	15 (51.7)	20 (32.8)	**22 (31.9)**	**13 (61.9)**	6 (54.6)	29 (36.7)	2 (20)	33 (41.3)
CKD	**9 (31.0)**	**8 (13.1)**	**8 (11.6)**	**9 (42.9)**	2 (18.2)	15 (19.0)	0	17 (21.39
COPD	5 (17.2)	9 (14.8)	10 (14.5)	4 (19.1)	2 (18.2)	12 (15.2)	2 (20)	12 (15.0)
Stroke	4 (13.8)	11 (18.0)	11 (15.9)	4 (19.1)	0	15 (19.0)	0	15 (18.8)
Cancer	9 (31.0)	10 (16.4)	13 (18.8)	6 (28.6)	0	19 (24.1)	4 (40)	15 (18.8)
Mortality	**19 (65.5)**	**19 (31.2)**	**25 (36.2)**	**13 (61.9)**	**1 (9.1)**	**37 (46.8)**	3 (30)	35 (43.8)
Length of stay (days)	**7.3 ± 4.3**	**10.5 ± 5.3**	10.0 ± 5.4	7.5 ± 3.8	**12.7 ± 5.2**	**9.0 ± 5.1**	12.5 ± 7.8	9.1 ± 4.7
No O_2 support	**2 (6.9)**	**16 (26.2)**	**18 (26.1)**	**0**	2 (18.2)	16 (20.3)	**1 (10)**	**17 (21.3)**
O_2 supplemental	10 (34.5)	30 (49.2)	32 (46.4)	8 (38.1)	6 (54.5)	34 (43)	5 (50)	35 (43.8)
Noninvasive mechanical ventilation	**13 (44.8)**	**12 (19.7)**	**15 (21.7)**	**10 (47.6)**	**2 (18.2)**	**23 (29.1)**	3 (30)	22 (27.5)
Invasive ventilation	**4 (13.8)**	**3 (4.9)**	**4 (5.8)**	**3 (14.3)**	1 (9.1)	6 (7.6)	1 (10)	6 (7.5)
Lipid lowering	8 (28.6)	21 (35.6)	20 (30.3)	9 (42.9)	3 (30)	26 (33.8)	1 (10)	28 (36.4)
Antiplatelet/anticoagulant	17 (60.7)	24 (40.7)	28 (42.4)	13 (61.9)	6 (60)	35 (45.5)	2 (20)	39 (50.6)
ACE-I/ARB	**7 (26.9)**	**33 (57.9)**	31 (48.4)	9 (47.4)	4 (40)	36 (49.3)	5 (50)	35 (47.3)
Calcium channel blockers	12 (46.2)	16 (28.1)	**17 (26.6)**	**11 (57.9)**	3 (30)	25 (34.2)	1 (10)	27 (36.5)
β-Blockers	13 (50)	20 (35.1)	24 (37.5)	9 (47.4)	4 (40)	29 (39.7)	3 (33)	30 (40.5)
Diuretics	10 (38.5)	15 (26.3)	**17 (26.6)**	**8 (42.1)**	2 (20)	23 (31.5)	0	25 (33)
Insulin	—	—	**11 (15.9)**	**18 (85.7)**	**0**	**29 (36.7)**	2 (20)	27 (33.8)
Metformin	**11 (37.9)**	**58 (95.1)**	—	—	10 (90.9)	59 (74.7)	8 (80)	61 (76.3)
Sulfonylureas	2 (6.9)	8 (13.1)	8 (11.6)	2 (9.5)	0	10 (12.7)	—	—
DPP4-I	**0**	**11 (18.0)**	10 (14.5)	1 (4.7)	—	—	0	11 (13.8)
SGLT2-I	2 (6.9)	3 (4.9)	4 (5.8)	1 (4.8)	0	5 (6.3)	0	5 (6.3)
GLP-1 RA	2 (6.9)	4 (6.6)	6 (8.7)	0	0	6 (7.6)	1 (10)	5 (6.3)
Pioglitazone	0	1 (1.6)	1 (1.5)	0	0	1 (1.3)	0	1 (1.3)

Statistically significant data ($P < 0.05$) appear in boldface type.

severe SARS-CoV-2 infection, consistent with theories suggesting that inflammatory mediators may promote altered glucose homeostasis (12,33,34). As previously suggested, there is a bidirectional link between glucose metabolism and immune system (35), and our findings may equally reflect a direct effect of altered glucose homeostasis on the immune response to SARS-CoV-2, thereby influencing the outcome of COVID-19.

This study provided novel and insightful information on mortality trends in COVID-19 patients with type 2 diabetes. After adjustment for age and sex, cardiovascular comorbidities and cancer were no longer significantly associated with mortality in this subgroup. These results may suggest that chronic comorbidities present at admission are more related to advanced age of patients—rather than being correlated with type 2 diabetes. Nonetheless, we cannot completely exclude that vascular complications of diabetes may have predisposed the patients to an unfavorable progression of SARS-CoV-2 infection. Consistent with findings observed in other clinical settings (33,34), CKD tended to be associated with lower survival in patients with COVID-19, possibly because the vascular complications made patients more fragile by reducing their systemic functional reserve. This hypothesis is further supported by the

higher mortality observed in β-blockers users; β-blockers are routinely prescribed in patients at higher cardiovascular risk.

Some studies suggested that diabetes, along with obesity, may promote an imbalance of the immune system favoring the rapid progression of pneumonia in infection triggered by other coronaviruses (7,8). A similar relationship appears to be emerging in COVID-19 (36,37). In particular, among patients with diabetes, nonsurvivors presented more abnormal inflammatory indexes, i.e., low lymphocyte count and higher IL-6, ferritin, CRP, PCT, and LDH levels (Supplementary Table 1), which are known to be associated with a poor prognosis in COVID-19 (1).

Another observation emerging from our study concerns the possible role played by antidiabetes medications in the clinical evolution of SARS-CoV-2 infection. One-third of patients with type 2 diabetes were on insulin therapy at admission, and these patients had a more severe evolution of COVID-19 with a more than tripled risk of mortality. Remarkably, the effect of insulin on mortality was independent of patients' age and possibly reflected the direct effects of this therapy on immune response to SARS-CoV-2 infection (35). Nevertheless, the worse outcome in insulin users may be related to a more severe, poorly controlled, and long-standing underlying diabetes in which this treatment is usually prescribed (38).

A novel finding of this study was the better outcome in COVID-19 patients taking DDP4-I. Specifically, patients taking DPP4-I showed less severe pneumonia, as suggested by the lower use of noninvasive mechanical ventilation, and lower mortality risk. These findings are consistent with literature suggesting that DPP-4/CD26 may interact with the S1 domain of the viral spike glycoprotein (39), which has been established as SARS-CoV-2's molecular link with the ACE-2 receptor expressed on the cells surface (40). The DPP4 inhibition may play a role in antagonizing the DPP4/CD26 inflammatory pathway, reducing COVID-19 virulence, and preventing the dangerous cytokine storm started at pulmonary levels, which is involved in disease progression (41,42).

Study Limitations

This study has some limitations, which are partly related to its retrospective nature. Firstly, data from patients who were still hospitalized during the study observation ("open case") were not included in our analysis. Their inclusion would have probably increased the statistical robustness of our findings. Secondly, the small number of patients taking DPP4-I did not allow reliable analysis of the independent effects of these drugs on clinical outcome of COVID-19. Although age, sex, glycemia, and comorbidities were not significantly different between DPP4-I users and nonusers, we cannot exclude possible confounding factors related to the specific setting in which these drugs are prescribed. For instance, the lack of concurrent insulin therapy among DPPI-4 users may have influenced the lower mortality in this subgroup of COVID-19 patients. However, the better clinical outcome in DPP4-I users may add a positive contribution to the current debate on their effectiveness, supporting the need for further investigations. Thirdly, the lack of glycated hemoglobin measurements at admission and information on glucose homeostasis during hospitalization prevents us from providing more reliable evidence on the effect that glycemic control may have on clinical outcomes of COVID-19 and survival of patients, as previously reported (15). Finally, our data were sourced from a single center, in a metropolitan area, and may not be representative of the entire Italian population.

Conclusion

This study provides evidence that glucose level at hospital admission and ongoing antidiabetes drugs may influence the outcome of COVID-19 in patients with type 2 diabetes. Our results reinforce the role of diabetologists in the multidisciplinary management of patients with COVID-19.

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