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

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OBJECTIVE

Poor outcomes have been reported in patients with type 2 diabetes and coronavirus disease 2019 (COVID-19); thus, it is mandatory to explore novel therapeutic approaches for this population.

RESEARCH DESIGN AND METHODS

In a multicenter, case-control, retrospective, observational study, sitagliptin, an oral and highly selective dipeptidyl peptidase 4 inhibitor, was added to standard of care (e.g., insulin administration) at the time of hospitalization in patients with type 2 diabetes who were hospitalized with COVID-19. Every center also recruited at a 1:1 ratio untreated control subjects matched for age and sex. All patients had pneumonia and exhibited oxygen saturation <95% when breathing ambient air or when receiving oxygen support. The primary end points were discharge from the hospital/death and improvement of clinical outcomes, defined as an increase in at least two points on a seven-category modified ordinal scale. Data were collected retrospectively from patients receiving sitagliptin from 1 March through 30 April 2020.

RESULTS

Of the 338 consecutive patients with type 2 diabetes and COVID-19 admitted in Northern Italy hospitals included in this study, 169 were on sitagliptin, while 169 were on standard of care. Treatment with sitagliptin at the time of hospitalization was associated with reduced mortality (18% vs. 37% of deceased patients; hazard ratio 0.44 [95% CI 0.29–0.66]; $P = 0.0001$), with an improvement in clinical outcomes (60% vs. 38% of improved patients; $P = 0.0001$) and with a greater number of hospital discharges (120 vs. 89 of discharged patients; $P = 0.0008$) compared with patients receiving standard of care, respectively.

CONCLUSIONS

In this multicenter, case-control, retrospective, observational study of patients with type 2 diabetes admitted to the hospital for COVID-19, sitagliptin treatment at the time of hospitalization was associated with reduced mortality and improved clinical outcomes as compared with standard-of-care treatment. The effects of sitagliptin in patients with type 2 diabetes and COVID-19 should be confirmed in an ongoing randomized, placebo-controlled trial.

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Coronavirus disease 2019 (COVID-19) is a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which since late 2019 has spread globally and severely threatened public health and economic systems, with a particularly acute burden for patients with type 2 diabetes (1–4). SARS-CoV-2 is transmitted through droplet, contact, and airborne routes, and the virus exploits ACE2 as its host receptor (5). Recent studies have suggested that SARS-CoV-2 may also bind dipeptidyl peptidase 4 (DPP-4 or CD26) when entering cells of the respiratory tract (6,7). Based on the modeling of SARS-CoV-2 structure and receptors, it has been also postulated that DPP-4 may facilitate the SARS-CoV-2 entry into target cells, due to its high homology with Middle East respiratory syndrome coronavirus (7). The interplay between the SARS-CoV-2 spike glycoprotein S1 and human DPP-4 may represent a potential factor that promotes SARS-CoV-2 hijacking and virulence (7–9), and inhibition of this interaction may thus have the potential to improve clinical outcomes of COVID-19. Sitagliptin is an oral and highly selective DPP-4 inhibitor with glucose-lowering effects, and it was approved by the Food and Drug Administration in 2006 as an antidiabetic drug (10–13) due to its efficacy in increasing the bioavailability of glucagon-like peptide 1 (GLP-1). This molecule is also known for its immunoregulatory and anti-inflammatory effects; indeed, sitagliptin has been shown to inhibit hepatitis C virus replication, to suppress chemokine release, and to reduce interleukin-6 production (14–17). Interestingly, sitagliptin showed high selectivity for DPP-4 and may have favorable effects on β-cells by exerting an anti-inflammatory function (16,18). Based on all of the aforementioned premises, DPP-4 inhibition has been suggested to be of potential benefit for patients with COVID-19, particularly in those with type 2 diabetes (19–22). Interestingly, while type 2 diabetes does not increase susceptibility to SARS-CoV-2 infection, type 2 diabetes has been associated with worse outcomes of COVID-19 (23). Type 2 diabetes increases the mortality risk in patients with COVID-19 (5,23), particularly in those with more severe disease (24). In patients with type 2 diabetes and COVID-19, poorly controlled blood glucose levels are associated with markedly higher mortality as compared with subjects with better metabolic control (23). Therefore, we examined whether sitagliptin, the DPP-4 inhibitor with higher selectivity for CD26, may be beneficial in treating COVID-19, particularly in patients with type 2 diabetes who appear to be at high risk of mortality and of cardiorenal (25–31) or cerebrovascular complications (1,4). In the current study, we report several clinical and biochemical outcomes in patients with type 2 diabetes hospitalized for COVID-19 and treated or not with sitagliptin as an add-on therapy to the standard of care in a multicenter, case-control, retrospective, observational study.

RESEARCH DESIGN AND METHODS

Patients and Study Design

Patients with type 2 diabetes, as defined by the most recent American Diabetes Association guidelines (32), who were hospitalized for a laboratory-confirmed SARS-CoV-2 infection were included in this multicenter, case-control, retrospective, observational study. Near-normal hepatic function (up to fourfold increase in AST and ALT values) and an estimated glomerular filtration rate (eGFR) $\geq$30 mL/min/1.73 m^2 were required in order for patients to be included. Given the pandemic evolution, the use of DPP-4 inhibitor sitagliptin in patients with type 2 diabetes as add-on therapy to standard of care was considered by the treating physician in view of the clinical practice, based on the clinical evaluation of the moment, and according to several reports released from the pandemic areas (20–22). Also, the Italian Society for the Study of Diabetes issued a statement on the potential benefit for the use of DPP-4 inhibitors in patients with type 2 diabetes and COVID-19 on top of the insulin treatment, as standard of care, during hospitalization for COVID-19 (33). Every center also recruited at a 1:1 ratio untreated control subjects matched for age and sex. Data collection and analysis were performed retrospectively and covered by an appropriate Institutional Review Board approval at the central institution (SIDIACO-RETRÒ; Luigi Sacco Hospital, University of Milan). Current treatment for type 2 diabetes, including the use of the DPP-4 inhibitor sitagliptin, was stopped at hospital admission, and all patients were switched to insulin treatment (intravenously or subcutaneously) as standard of care. The use of insulin treatment in patients with type 2 diabetes and admitted to hospital for critical clinical conditions has been already included as a standard protocol in most hospitals throughout the country according to the guidelines of the Italian Society for the Study of Diabetes and supported by the European Association for the Study of Diabetes (34). Standard of care comprised insulin injection administered according to the "modified Yale insulin infusion protocol." The glycemic target was between 140 and 180 mg/dL, with withholding of insulin once blood glucose level approached 100 mg/dL. For 2 months (from 1 March through 30 April 2020), 338 consecutive adult inpatients who were hospitalized for SARS-CoV-2 infection and had type 2 diabetes were analyzed, and a defined outcome (death or discharge) was considered the primary end point of the study. Of the 338 patients included in the study, 169 were treated with sitagliptin and 169 were not. Sitagliptin was administered at an adjusted dosage for eGFR (i.e., 100 mg once daily if eGFR $\geq$45 mL/min/1.73 m^2, or 50 mg if eGFR was 30–45 mL/min/1.73 m^2). Patients included in

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the study did not take other glucose-lowering medications during their hospitalization. Patients were enrolled in seven academic medical centers in Northern Italy, the area with the highest prevalence of COVID-19 worldwide (35), and clinical outcomes were collected retrospectively. Nearly 23% of the patients who were hospitalized in the different clinical centers for COVID-19 between 1 March and 30 April had diabetes, and around one-third of those patients with type 2 diabetes and COVID-19, comprising pneumonia, fever, and laboratory test for COVID-19, were eligible to be included in this study. Given the emergency conditions, data on clinical and laboratory parameters may not be available in all patients; therefore, analyses were based on nonmissing data.

Outcome Measures

Glycometabolic control was assessed by measuring fasting blood glucose levels daily and blood glucose level at least three times per day, although frequency may have been different among centers according to the local protocol and hospital guidelines. Mean glycemia level was calculated based on the available measurements of blood glucose collected daily during the hospitalization. Demographic and clinical characteristics at hospital admission are reported in Table 1. We first evaluated hospital discharge and death as primary end points. Next, we also assessed the proportion of patients within the two groups experiencing relevant clinical events, such as admission to the intensive care unit, the use of mechanical ventilation, and the need for extracorporeal membrane oxygenation (ECMO) at hospital admission and at follow-up. We also analyzed the proportion of patients within the two groups who displayed clinical improvement, as defined by hospital discharge and/or a reduction of at least two points from baseline on a modified ordinal score comprising seven major points as follows and already reported (36): *1*) not hospitalized with resumption of normal activities; *2*) not hospitalized, but unable to resume normal activities; *3*) hospitalized, not requiring supplemental oxygen; *4*) hospitalized, requiring supplemental oxygen; *5*) hospitalized, requiring noninvasive mechanical ventilation; *6*) hospitalized, requiring invasive mechanical ventilation or ECMO; and *7*) death.

Statistical Analysis

Continuous variables are presented as means with SEs, and categorical variables are presented as proportions. Independent sample *t* tests and χ^2 test/Fisher exact test were used as appropriate to compare continuous variables and categorical variables, respectively. Two-tailed *P* values of <0.05 were considered statistically significant. Univariable and multivariable logistic regression methods were used to model the relationships between risk factors and outcomes of interest (Stata version 12; StataCorp, College Station, TX). Log-rank (Mantel-Cox) test was used in the time to clinical end point analysis between the two groups (GraphPad Prism version 7.0; GraphPad Software, Inc., San Diego, CA).

Data and Resource Availability

All requests for raw and analyzed data will be reviewed to verify if the request is subject to any intellectual property or confidentiality obligations. Any data and materials that can be shared will be released via a Material Transfer Agreement.

RESULTS

Patient Characteristics

A total of 169 patients with type 2 diabetes and diagnosed with COVID-19 infection were treated with the DPP-4 inhibitor sitagliptin as an add-on therapy to standard of care, while 169 patients

Table 1—Baseline demographic and clinical characteristics of patients

Characteristic	Standard of care	Sitagliptin	*P* value
Age (years)	69 ± 1.0	69 ± 0.9	0.83
Patients ≥70 years of age, *n* (%)	90 (53)	92 (54)	0.91
Male sex, *n* (%)	115 (68)	123 (73)	0.40
Duration of diabetes (years)	8.7 ± 1.2	9.2 ± 0.8	0.73
Coexisting conditions, *n* (%)			
Cardiovascular disease	53 (38)	65 (40)	0.63
Chronic kidney disease	34 (28)	34 (21)	0.26
Hypertension	80 (67)	118 (74)	0.23
Cancer	17 (14)	27 (17)	0.62
Glucose-lowering medications, *n* (%)			
Metformin	63 (39)	79 (44)	0.16
Insulin	48 (30)	39 (22)	0.15
Other oral antidiabetic agents	50 (31)	61 (34)	0.25
Antihypertensive drugs, *n* (%)			
ACE inhibitors	29 (50)	38 (38)	0.13
β-Blockers	34 (56)	32 (33)	0.007
Diuretics	30 (52)	36 (38)	0.13
Antiplatelet drugs, *n* (%)	29 (49)	39 (40)	0.32
Anticoagulant drugs, *n* (%)	52 (77)	74 (68)	0.17
Respiratory rate (breaths/min)	25.8 ± 0.7	23.7 ± 0.6	0.04
Clinical score (0–7)	4.4 ± 0.1	4.4 ± 0.08	0.88
BMI (kg/m^2)	30 ± 0.6	29 ± 0.4	0.18
HbA_{1c} (%)	7.5 ± 0.1	7.5 ± 0.1	0.66
HbA_{1c} (mmol/mol)	58.6 ± 1.2	58.6 ± 1.3	0.98
Glycemia (mg/dL)	188 ± 6.8	180 ± 6.7	0.38
Serum creatinine (mg/dL)	1.4 ± 0.08	1.2 ± 0.08	0.10
Lymphocyte count ($\times 10^{-9}$/L)	0.9 ± 0.06	1.1 ± 0.17	0.13
CRP (mg/L)	19 ± 2.3	14 ± 0.7	0.01
D-dimer (μg/mL)	6,377 ± 1,928	5,835 ± 1,391	0.82
Interleukin-6 (ng/L)	95 ± 9.7	89 ± 10.7	0.71
LDH (units/L)	423 ± 43	387 ± 16	0.43
Ferritin (μg/mL)	601 ± 48	688 ± 97	0.43
AST (units/L)	42 ± 3.0	43 ± 2.6	0.79
ALT (units/L)	38 ± 2.4	40 ± 2.9	0.74
Procalcitonin (ng/mL)	12.7 ± 4.4	8.3 ± 3.3	0.42
Oxygen saturation (%)	92 ± 0.7	92 ± 0.5	0.31

Data are mean ± SEM unless otherwise indicated. Other oral antidiabetic agents are metformin, sulfonylureas, GLP-1-receptor agonists, DPP-4 inhibitors, sodium–glucose cotransporter 1 inhibitors, glinides, and thiazolidinediones. LDH, lactate dehydrogenase.

Table 2—Clinical outcomes in patients evaluated at follow-up (30 days)

Characteristic	Standard of care	Sitagliptin	*P* value
Mortality, *n* (%)	63 (37)	31 (18)	0.0001
Clinical score reduction, *n* (%)			
≥2 points	50 (34)	72 (52)	0.0005
<2 points	67 (46)	36 (26)	0.0005
Overall improvement of clinical score, *n* (%)	55 (38)	83 (60)	0.0001
Hospital discharge at day 30, *n*	89	120	0.0008
EIR (IU/day)	31 ± 2.8	30 ± 3.8	0.83
Glycemia (mg/dL)	170 ± 9	139 ± 4	0.002***
Serum creatinine (mg/dL)	1.3 ± 0.1	1.0 ± 0.07	0.008*
Lymphocyte count ($\times 10^{-9}$/L)	1.1 ± 0.07	1.6 ± 0.2	0.03^
CRP (mg/L)	7.1 ± 0.9	3.7 ± 0.5	0.001***^^^
D-dimer (μg/mL)	3,507 ± 1,082	2,693 ± 561	0.50*
Interleukin-6 (ng/L)	81 ± 11	72 ± 10	0.55
LDH (units/L)	302 ± 21	370 ± 18	0.01^
Ferritin (μg/mL)	440 ± 43	411 ± 49	0.66*^
AST (units/L)	42 ± 4.6	28 ± 1.6	0.005***
ALT (units/L)	48 ± 5.5	43 ± 3.4	0.41
Procalcitonin (ng/mL)	8.9 ± 2.9	1.4 ± 0.5	0.01*
Oxygen saturation (%)	92 ± 1.0	96 ± 0.7	0.004***

Data are mean ± SEM unless otherwise indicated. EIR, exogenous insulin requirement; LDH, lactate dehydrogenase; IU, international units. Baseline vs. follow-up sitagliptin: *$P < 0.05$; ***$P < 0.001$. Baseline vs. follow-up standard of care: ^$P < 0.05$; ^^^$P < 0.001$.

with type 2 diabetes and COVID-19 receiving standard-of-care treatment only were considered. Baseline demographic and clinical characteristics of the two groups of patients are reported in Table 1. The mean age was 69 years in the sitagliptin-treated group and in the control group. No major differences were observed between the two groups with regard to other demographic characteristics. All patients were admitted to the hospital with respiratory symptoms and fever. Type 2 diabetes was a known diagnosis in 322 (95%) patients, while in 16 patients (5%), type 2 diabetes was diagnosed during hospitalization through routine metabolic screening. No differences were observed with regard to duration of diabetes, renal function, vital signs, use of glucose-lowering medication, laboratory tests, and comorbidities such as cardiovascular disease (38% vs. 40%), cancer (14% vs. 17%), or hypertension (67% vs. 74%) in the two groups at baseline (Table 1). Assessment of clinical score at admission to the hospital did not show any differences between the two groups (Table 1), nor was it different when analyzed by the use of different glucose-lowering therapy at admission. Serum glucose at hospital admission was comparable between the two groups as well (Table 1). Overall, characteristics at admission to hospital were comparable in the two groups. Patients were switched from current treatment for type 2 diabetes, which included mostly metformin, but also insulin, sulfonylureas, DPP-4 inhibitors, sodium–glucose cotransporter 2 inhibitors, GLP-1 receptor agonists, glinides, and thiazolidinediones, to insulin treatment (intravenously or subcutaneously) at hospital admission as standard of care (Table 1). No difference was evident in antihypertensive treatment between groups or for other medications such as diuretics, anticoagulants, and antiplatelet drugs, while a higher proportion of patients in the standard-of-care group was receiving β-blockers (Table 1). With regard to other treatments, hydroxychloroquine was initiated in 252 patients and antiviral agents in 171 patients during hospitalization, similarly distributed within the two groups.

Mortality

The use of sitagliptin at the time of hospitalization was associated with a reduced mortality (Table 2). A total of 31 out of 169 (18%) patients died in the sitagliptin-treated group as compared with 63 out of 169 (37%) patients in the control group ($P = 0.0001$). Treatment with sitagliptin in patients with type 2 diabetes and COVID-19 was thus associated with a decreased odds ratio (OR) for in-hospital death (OR 0.37 [CI 0.23–0.62]; $P = 0.0001$), which was confirmed after adjustment for clinically relevant factors (age, sex, comorbidities, and ongoing treatments), as shown in Table 3. A time to clinical end point (death/discharge) analysis also confirmed better outcomes in the sitagliptin-treated patient group as compared with the standard-of-care group in the overall population studied (hazard ratio [HR] 0.44 [95% CI 0.29–0.66]; $P = 0.0001$) (Fig. 1*A*). Given the importance that the glycometabolic control may have in increasing the mortality rate, we analyzed the mean blood glucose level measured during the hospitalization and demonstrated that it was lower in the sitagliptin-treated patients as compared with the standard-of-care group (Fig. 1*B*). After grouping patients for mean glucose level quartiles, we observed in a time to clinical end point (death/discharge) analysis that better glycometabolic control during hospitalization was associated with better outcomes (Supplementary Fig. 1). Finally, we also found no difference between the groups as far as units of insulin required received daily (Table 2).

Table 3—Multivariable analysis of factors associated with mortality in patients with type 2 diabetes and COVID-19 treated with sitagliptin or with standard-of-care therapy

	OR (95% CI)	*P* value
Treatment with sitagliptin	0.23 (0.12–0.46)	0.0001
Sex (male)	1.05 (0.51–2.16)	0.88
Age (years)	1.07 (1.04–1.11)	0.0001
Cancer	1.74 (0.78–3.88)	0.17
Cardiovascular disease	2.5 (1.30–4.81)	0.006
Chronic kidney disease	1.12 (0.54–2.35)	0.74
Use of hydroxychloroquine	1.47 (0.55–3.87)	0.43
Use of antiviral agents	0.91 (0.44–1.85)	0.79

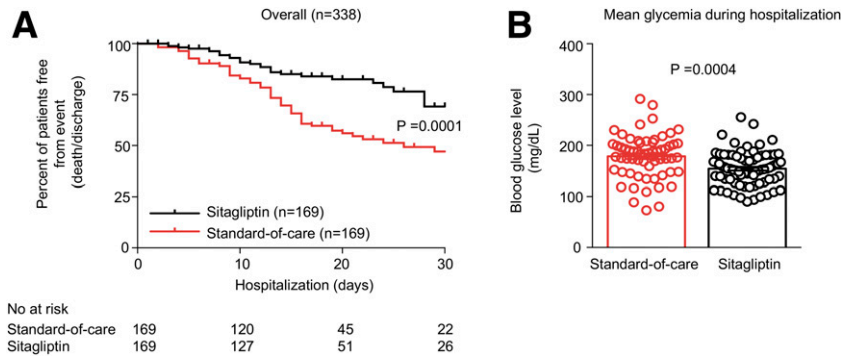

Figure 1—Mortality in patients with type 2 diabetes and COVID-19 treated with sitagliptin or receiving standard of care. *A*: Time to clinical end point (death/hospital discharge) in sitagliptin-treated patients and in the standard-of-care group. *B*: Bar graph representing mean blood glucose levels measured during the hospitalization in the two groups. Data are represented as mean ± SEM. No, number of patients.

Clinical Outcomes

Patients treated with sitagliptin add-on therapy at the time of hospitalization showed significant improvement in clinical outcomes (Tables 2 and 4). With regard to relevant clinical parameters, the use of sitagliptin was associated with a decreased risk for the need of mechanical ventilation as compared with treatment with the standard of care (HR 0.27 [CI 0.11–0.62]; $P = 0.003$) (Table 4). A reduced risk for the need of intensive care unit was also observed to a lesser extent in the sitagliptin-treated group as compared with the standard-of-care group (HR 0.51 [CI 0.27–0.95]; $P = 0.03$), while no difference was evident in the requirement of ECMO (HR 1.15 [CI 0.41–3.17]). With regard to the clinical improvement as defined by a reduction of two points or more in the modified seven-point category scale at day 30 of follow-up, this was available in 139 sitagliptin-treated patients and in 145 patients of the standard-of-care group. A total of 72 patients (52%) in the sitagliptin-treated group were rated with a decrease of at least two points, while only 50 (34%) were found to be clinically improved in the standard-of-care group (Table 2 and Supplementary Fig. 2). Moreover, worsening of clinical outcomes, as defined by any increase in the clinical score compared with baseline, was observed in a higher number of standard-of-care-treated patients (67 [46%]) as compared with those receiving sitagliptin (36 [26%]) (Table 2 and Supplementary Fig. 2). A more comprehensive analysis also showed that treatment of sitagliptin at the time of hospitalization was associated with an overall clinical improvement as compared with patients in the standard-of-care group (Table 2). A greater number of patients treated with sitagliptin were discharged from the hospital at day 30 as compared with the number of discharged patients in the standard-of-care group (Table 2). No sitagliptin-related severe adverse events were registered in patients enrolled in the sitagliptin-treated group.

Laboratory Analysis

A reduction in inflammatory parameters such as procalcitonin and CRP was detected (Table 2). Lymphocyte counts of sitagliptin-treated patients were increased compared with baseline and compared with patients treated with standard of care (Table 2). Finally, an improvement in glycemic control was evident at follow-up in patients treated with sitagliptin as compared with patients receiving standard-of-care insulin treatment only (Table 2).

Subgroup Analysis

A subanalysis in patients who were ≥70 years of age confirmed a lower mortality (29% vs. 51%) and better outcomes in a time to clinical end point analysis in the sitagliptin-treated group as compared with those in the standard-of-care group (HR 0.54 [CI 0.34–0.85]; $P = 0.009$) (Fig. 2). A time to clinical end point analysis comparing males versus females in the sitagliptin-treated group as compared with those in the standard-of-care group did not show any difference in the clinical outcomes within the group of treatment (Fig. 2). However, we must highlight that both males and females in the standard-of-care group had the worst outcome (sitagliptin males vs. standard-of-care males: $P = 0.001$, HR 0.44 [CI 0.27–0.73]; sitagliptin females vs. standard-of-care females: $P = 0.03$, HR 0.42 [CI 0.20–0.87]). A subanalysis in patients who had a glycated hemoglobin (HbA_{1c}) below the median (7.5%) demonstrated a better outcome in both the sitagliptin-treated patients and the standard-of-care group (Fig. 2). An HbA_{1c} value above the median of 7.5% was associated with worst outcomes, particularly in patients treated with standard of care (sitagliptin vs. standard of care, HR 0.29 [CI 0.14–0.63]; $P = 0.0003$). A stratification of patients based on the BMI, measured at baseline, also confirmed better outcomes in those treated with sitagliptin and in those who had a BMI below the median of 29 kg/m^2 (HR 0.40 [CI 0.16–0.99]; $P = 0.03$) (Fig. 2). Higher BMI was associated with worst outcomes in the standard-of-care group (sitagliptin vs. standard of care, HR 0.21 [CI 0.09–0.45]; $P = 0.0002$). No interaction between treatment and any of the subgroup variable was observed. Finally, the preadmission therapy with metformin, insulin, or other glucose-lowering agents did not have any effect on clinical outcomes (Supplementary Fig. 1*B*).

CONCLUSIONS

The COVID-19 pandemic has severely affected most of the communities in

Table 4—HRs calculated for the secondary clinical outcomes (need for intensive care unit, mechanical ventilation, and ECMO)

Secondary end points	*N* at risk (*N* with end point), sitagliptin vs. standard of care	HRs (95% CI) for sitagliptin vs. standard of care	*P* value
Intensive care	118 (15) vs. 102 (25)	0.51 (0.27–0.95)	0.03
Mechanical ventilation	118 (6) vs. 102 (17)	0.27 (0.11–0.62)	0.003
ECMO	118 (8) vs. 102 (7)	1.15 (0.41–3.17)	0.77

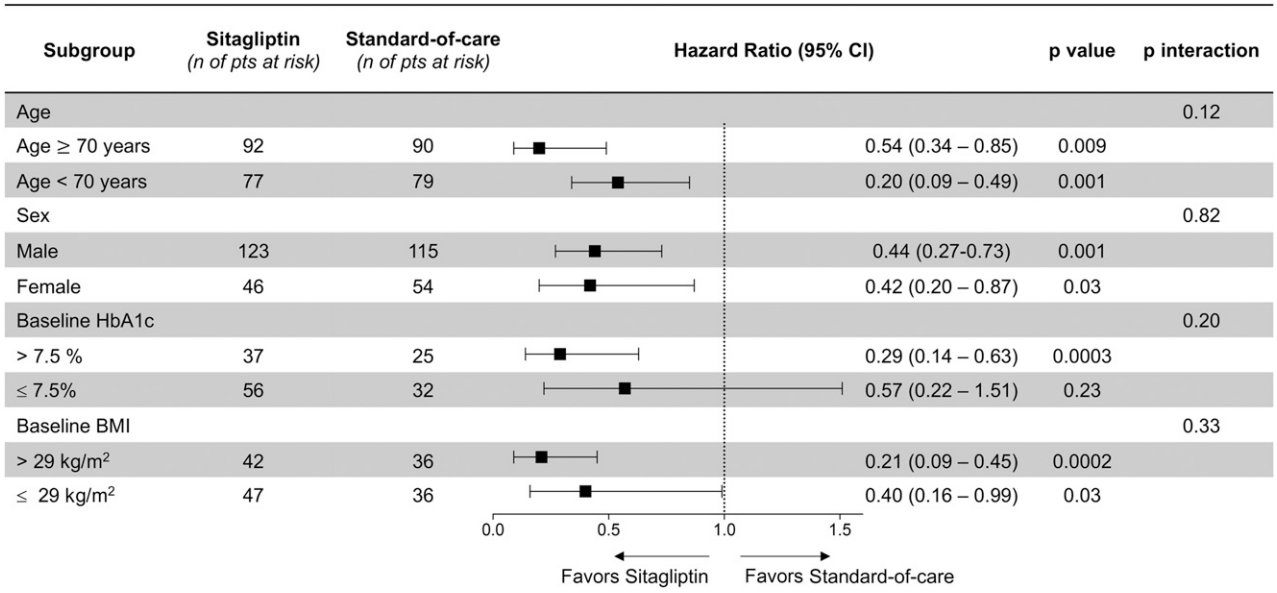

Figure 2—Subgroup analysis in patients (pts) with type 2 diabetes and COVID-19 treated with sitagliptin or receiving standard of care. Forest plots of subgroup analyses exploring the effect of treatment with sitaliptin/standard of care in patients with type 2 diabetes and COVID-19. Subgroups include age (≥70 or <70 years), sex (males or females), baseline HbA_{1c} (>7.5% or ≤7.5%), and baseline BMI (>29 kg/m^2 or ≤29 kg/m^2).

Northern Italy, where the overall mortality was ∼200 times higher than that observed in the same period of time in previous years (37,38). Particularly burdened have been our fragile population of patients with type 2 diabetes. No clearly effective treatment for COVID-19 was available during the coronavirus outbreak; we therefore performed a multicenter, case-control, retrospective, observational clinical study in which we analyzed data from patients with type 2 diabetes hospitalized for COVID-19 treated with the highly selective DPP-4 inhibitor sitagliptin (39–41) as an add-on therapy to standard of care at the time of hospitalization. All patients had pneumonia and oxygen saturation <95% when breathing ambient air or were receiving oxygen support. The primary end points were discharge from the hospital/death and improvement of clinical outcomes, defined as an increase in at least two points on a seven-category modified ordinal scale. Data were collected retrospectively from patients receiving sitagliptin from 1 March through 30 April 2020. Of the 338 patients with type 2 diabetes and COVID-19 enrolled in Northern Italy hospitals, 169 were on sitagliptin, while 169 were receiving the standard of care. The use of sitagliptin at the time of hospitalization was associated with a reduced mortality and with an improvement in the clinical outcomes as compared with the standard-of-care treatment alone. DPP-4 inhibitors may be beneficial for COVID-19 in multiple aspects. First, sitagliptin may prevent SARS-CoV-2–related detrimental effects as the binding site for SARS-CoV-2 spike protein S1 identified through cryo-electron microscopy structure analysis of ACE2 (42) has high homology with the DPP-4 sequence, thus suggesting that DPP-4 may facilitate SARS-CoV-2 entry into cells (7). Thus, the use of DPP-4 inhibitors may reduce SARS-CoV-2 virulence, thereby preventing the ensuing multiorgan failure and acute and chronic injury to the lungs, as well as impeding the cytokine storm caused by pulmonary damage. Secondly, modulation of DPP-4 expression on immune cells by sitagliptin may induce broad anti-inflammatory and immunoregulatory effects (15,43). The cytokine storm that follows viral entry is also a primary factor in inducing progression of extrapulmonary multiple-organ failure until death, and immunomodulators may be effective in restoring homeostasis of the immune response following coronavirus infection to improve patient prognosis. DPP-4 is a mediator of inflammatory signaling, and the DPP-4 inhibitor sitagliptin may efficiently antagonize the inflammation associated with SARS-CoV-2 (15,43). Sitagliptin may specifically reduce the excessive and prolonged cytokine responses observed in COVID-19. A potential immunomodulatory effect of sitagliptin was suggested in our study by a reduction in plasma CRP and procalcitonin during follow-up in sitagliptin-treated patients as compared with the patients in the standard-of-care group. Thirdly and lastly, sitagliptin may improve glycometabolic control, which would likely benefit antagonism of the clinical progression of COVID-19. Recently, poor glucose control has been associated with worse outcomes in patients with type 2 diabetes and COVID-19 (44,45). In our study, only mild changes in fasting glycemia were observed, and the majority of deaths observed occurred in patients >70 years of age and with coexisting pathologies. Age-dependent cellular and humoral immunity alterations could favor increased viral replication and a more prolonged inflammatory response potentially responsible for poor mortality outcome (46), and some of these changes may be reversed by the DPP-4 inhibitor sitagliptin. Interestingly, DPP-4 inhibitors upregulate soluble DPP-4 plasma levels, but this is dissociated from the extent of the inflammatory effect and may account as another potential mechanism by which sitagliptin may exert a positive effect (47). We acknowledge that our study has several shortcomings, including the nonrandomized uncontrolled design, a slight increase in some of the inflammatory markers detected at baseline in the standard-of-care group as compared with the sitagliptin-treated patients, and the lack of some clinical data that were not

available for all patients included in the analysis. In particular, data for mechanical ventilation, intensive care unit, and ECMO as secondary end points were missing in 51 sitagliptin-treated patients and 67 standard-of-care patients. Interestingly, the use of sitagliptin at the time of hospitalization was associated with reduced mortality, which approached that of individuals without type 2 diabetes, and it was consistent across all of the centers involved. In conclusion, in patients with type 2 diabetes and COVID-19, sitagliptin treatment as add-on therapy to standard of care at the time of hospitalization was associated with better clinical outcomes, a greater number of patients treated with sitagliptin discharged from the hospital at day 30, and reduced mortality as compared with standard of care. The effects of sitagliptin in patients with type 2 diabetes and COVID-19 should be confirmed in an ongoing, randomized, placebo-controlled trial that contains extended primary and secondary end points, as compared with those reported in this study, including the measurement of DPP-4 level in biological samples collected and multiple time points of assessment (NCT04365517). Given the beneficial effects observed in lowering mortality rate and improving clinical outcomes, sitagliptin may also be considered for further testing in patients with COVID-19 and without type 2 diabetes.

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