Diabetes Ther (2021) 12:2857–2870
https://doi.org/10.1007/s13300-021-01133-8

ORIGINAL RESEARCH

Lower COVID-19 Mortality in Patients with Type 2 Diabetes Mellitus Taking Dipeptidyl Peptidase-4 Inhibitors: Results from a Turkish Nationwide Study

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Received: June 2, 2021 / Accepted: July 28, 2021 / Published online: August 16, 2021

ABSTRACT

Introduction: To investigate the effect of pre-existing treatment with dipeptidyl peptidase-4 inhibitors (DPP-4is) on COVID-19-related hospitalization and mortality in patients with type 2 diabetes mellitus (T2DM).

Methods: A multicenter, retrospective cohort study was conducted using patient data extracted from the Turkish National Electronic Data-

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base. All patients who tested positive for COVID-19 (PCR test) between 11 March through to 30 May 2020 were screened for eligibility (n = 149,671). Following exclusion of patients based on pre-determined inclusion criteria, patients with T2DM using a DPP-4i or glucose-lowering medications other than a DPP-4i were compared for mortality and hospitalization. The propensity score method was used to match age, gender, micro- and macrovascular complications, and medications in the two groups. Independent associates of mortality were analyzed using multivariable analysis on the whole T2DM population.

Results: A total of 33,478 patients with T2DM who tested postive for COVID-19 who met the inclusion criteria were included in the analysis. Median (interquartile range) age was 54 (22) years and 42.4% were male. Of these, 9100 patients using DPP-4is (n = 4550) or other glucose-lowering drugs (n = 4550) were matched in two groups. After matching, analysis revealed a lower mortality in the DPP-4i group (9.5 vs. 11.8%; $p < 0.001$). In the multivariable model, the use of DPP-4is (odds ratio [OR] 0.57, 95% confidence interval [CI] 0.35–0.91; p = 0.02) was associated with lower mortality in the whole sample, while age, male gender, computed tomography finding of COVID-19, obesity, low glomerular filtration rate, and an insulin-based regimen also predicted increased risk of death. There was no association between the preexisting treatment with DPP-4is and COVID-19-related hospitalization in the matched analysis or multivariate model. The rate of admission to the intensive care unit and/or mechanical ventilation favored the DPP-4i group (21.7 vs. 25.2%; p = 0.001), although this association became saturated in the multivariate analysis (OR 0.65, 95% CI 0.39–1.08; p = 0.099).

Conclusions: The results of this study demonstrate an association between DDP-4i use and reduced mortality in people with T2DM who tested PCR positive for COVID-19.

Keywords: Type 2 diabetes mellitus; COVID-19; Hospitalization; Intensive care unit admission; Mechanical ventilation; Mortality; DPP-4 inhibitor; Anti-diabetic agents

Key Summary Points

A multicenter, retrospective study was conducted to explore the association of preexisting use of dipeptidyl peptidase-4 inhibitors (DPP-4is) with COVID-19-related outcomes in patients with type 2 diabetes mellitus (T2DM).

The use of DPP-4is in patients with T2DM who tested positive for COVID-19 was independently associated with lower mortality.

The rate of COVID-19-related hospitalization was similar between patients on DPP-4 inhibitors and those on other regimens.

Less frequent intensive care unit admission and/or mechanical ventilation were also observed among patients using DPP-4 inhibitors.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has caused serious death tolls world-wide since the beginning of the pandemic. People with chronic non-communicable diseases are more vulnerable

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to the adverse outcomes of COVID-19 [1–4]. One of the best examples is the well-established link between obesity and COVID-19 mortality and morbidity [5]. Diabetes is also one of the most significant chronic diseases that increases the severity of COVID-19 and the associated risk of mortality [3, 4]. Good glycemic control is a key element for improved COVID-19 outcomes [6, 7]. However, the effects of different glucose-lowering medications on COVID-19 outcomes have not been clearly identified so far. Therefore, it is important to identify the best treatment options for glycemic regulation that would also improve COVID-19-related outcomes [8].

Dipeptidyl peptidase-4 inhibitors (DPP-4is) are a class of medications that have particularly attracted scrutiny due to their anti-inflammatory, anti-fibrotic, and anti-adipogenic properties, and which may be involved in preventing viral entry and progression to hyper-inflammation response in severe COVID-19 cases [9, 10]. The results of clinical studies, and even their meta-analyses, conducted to date are inconsistent. In this context, to reach robust conclusions, further studies with a large sample size are required. Although DPP-4is have been on the market for a long time and are widely prescribed, the total number of users in COVID-19 studies and meta-analyses published so far has remained low.

In the study reported here, we identified a large sample of patients using DPP-4is from the previously published studies with the Turkish National Database of COVID-19 patients with diabetes [11, 12]. The aim of our study was to search for any association between preexisting treatment with DPP-4is and mortality and other COVID-19-related clinical outcomes related to the use of other anti-diabetic agents in patients with type 2 diabetes mellitus (T2DM).

METHODS

Study Design and Participants

The patient data used in this population-based retrospective cohort study were generated from the Turkish Ministry of Health National Electronic Database. This database is mandated to record all real-time reverse transcription (RT)-PCR-positive tests for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in the national case-based surveillance system, integrated with the Public Health Management Database and the Laboratory Information Management system, which store data on COVID-19 patients.

Data on all patients with a confirmed diagnosis of COVID-19 between 11 March through to 30 May 2020 in the database were extracted and evaluated (n = 149,671). After exclusion of patients without diabetes (n = 105,705), those with type 1 diabetes mellitus (n = 370), and unclassified patients (n = 715), a total of 42,881 patients with T2DM were identified. Among these, patients with missing glycosylated hemoglobin (HbA1c) data (n = 9403) were subsequently excluded. Of the remaining patients with T2DM (n = 33,478), 6846 (20.5%) were taking DPP-4is and 26,632 (79.5%) were on other glucose-lowering regimes. Matching between the DPP-4i user and non-user groups was done according to age, gender, micro- and macro-vascular complications, and medications with angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs), statin, insulin, metformin, and other oral anti-diabetic drugs (OADs). A tolerance level of $\pm$ 5 years of age was chosen. The final sample (n = 9100) included 4550 patients in each group. The flow diagram of the study population is presented in Fig. 1.

This study was approved by the COVID-19 Investigation Review Board under the Bioethics Committee of Ministry of Health, which waived the requirement of informed consent due to the retrospective study design and anonymity of the national database (IRB no: 95741342-020:186404/28.10.2020). The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments.

Data Collection

Sociodemographic characteristics (gender, age, body mass index [BMI], smoking), comorbid conditions, macrovascular and microvascular complications, and medications were recorded from the COVID-19 registry. Laboratory results

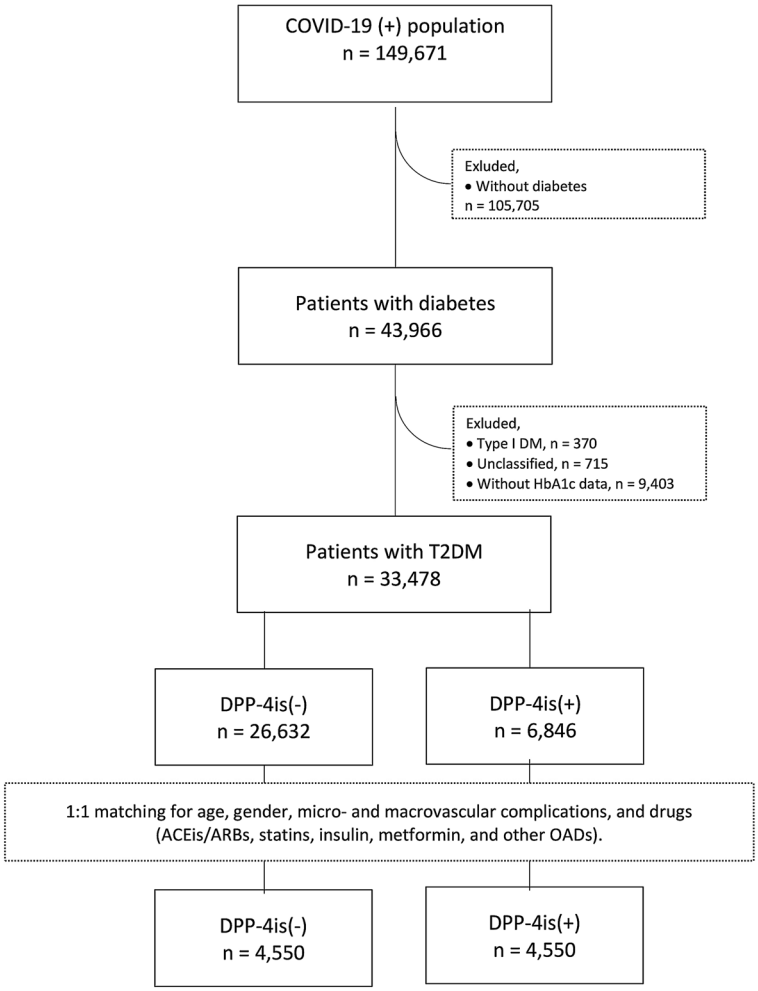

Fig. 1 Flow chart of patient inclusion and exclusion in this population-based retrospective cohort study. *ACEis* Angiotensin-converting enzyme inhibitors, *ARBs* angiotensin receptor blockers, *COVID-19* coronavirus disease 19, *DM* diabetes mellitus, *HbA1c* glycosylated hemoglobin, *OADs* oral anti-diabetic drugs, *T2DM* type 2 DM

obtained were HbA1c, low-density lipoprotein (LDL)-cholesterol, glomerular filtration rate (GFR), alanine and aspartate aminotransferases, C-reactive protein, and lymphocyte count. Chest computerized tomography (CT) results were recorded as positive (consistent with COVID-19 radiological findings) or negative for COVID-19.

Definitions

A diagnosis of T2DM was based on relevant International Classification of Diseases System-Tenth Revision (ICD-10) codes, having any HbA1c $\geq$ 6.5% (48 mmol/mol), or monthly refill of anti-diabetic medications following the diagnosis of T2DM. Hypertension, dyslipidemia, chronic obstructive pulmonary disease, asthma, heart failure, cardiovascular diseases, and cancer were defined based on the ICD-10 codes. Obesity was defined as BMI $\geq$ 30 kg/m^2. Smoking was defined as currently smoking at the time of the COVID-19 diagnosis. Diabetic retinopathy was defined as having an intravitreal injection or laser photocoagulation in addition to an ICD-10 code for T2DM. Diabetic neuropathy diagnosis was based on the ICD-10 codes of diabetic neuropathy. The estimated

GFR (eGFR) was calculated by using the CKD-EPI equation [13]. Patients who did not have an ICD-10 code for type 1 or type 2 diabetes mellitus in the previous 12 months or patients who had an HbA1c $< 6.5\%$ in the absence of any anti-hyperglycemic prescription were defined as non-diabetic. An insulin-based regimen was defined as the prescription of an insulin type with/without OADs. Renin-angiotensin system (RAS) blocker use was defined as receiving any ACEi or ARB.

Study Outcomes

The study outcomes were mortality, hospitalization, and admission to the intensive care unit (ICU) and/or mechanical ventilation due to COVID-19.

Statistical Analyses

Numerical data were expressed as the median with interquartile range and categorical variables as count (n) with percentage. Normality of the distribution was assessed using the Kolmogorov–Smirnov test. Differences between the variables in the whole sample and the propensity score matched (PSM) groups were assessed using the Chi-square test for categorical variables and the Student's t test or the Mann–Whitney U test, as appropriate.

Univariate analyses were performed to evaluate the potential variables associated with hospitalization or mortality in the whole sample and PSM groups. Using the same approach, multivariable logistic regression analysis was performed to explore the potential independent association of taking DPP-4is and mortality outcome. Odds ratios (ORs) were reported with 95% confidence intervals (CIs). Statistical significance was set at $p \leq 0.05$. All data were analyzed using Statistical Package for the Social Sciences (SPSS) for Windows 25.0 (SPSS IBM Corp., Armonk, NY, USA).

RESULTS

The demographic and clinical characteristics of patients with T2DM included in this study (n = 33,478) are presented in Table 1. Of these 33,478 patients, 6846 (20.5%) were taking DPP-4is. Compared to patients in the non-DPP-4i group, those in the DPP-i group were significantly older, more frequently male, less frequently smokers, and less educated; had a higher frequency of pulmonary involvement, higher BMI, higher blood glucose and HbA1c levels on admission; and had lower LDL-cholesterol levels, lower GFR, and higher rates of co-morbidities and complications. The percentage of patients with eGFR < 60 ml/min/1.73 m^2 was higher in the group on DPP-4is; the patients in this group were also more frequently on an injectable regimen, other OAD, RAS blockers, statins, and acetylsalicylic acid.

The comparison of variables after matching is presented in Table 2. After matching, patients in the group taking DPP-4is were still significantly less educated and had higher BMI, higher blood glucose and HbA1c levels on admission. The rate of microvascular and macrovascular complications, and the treatments were also matched. However, after matching, median eGFR was higher, and the percentage of patients with eGFR < 60 ml/min/1.73 m^2 was significantly lower in the group taking DPP-4is; dyslipidemia and obesity were also more frequent in this grouup, while the rate of asthma/chronic obstructive pulmonary disease (COPD) and cancer were lower.

Outcomes

Mortality in the overall sample was 7.7% (n = 2565). Hospitalization and ICU admission and/or intubation were 55.6 and 20.6%, respectively (Table 1).

After matching, event rates for two of the three outcomes favored the group on DPP-4is. Of the patients receiving DPP-4is, 9.5% died, as compared with 11.8% of those on other glucose-lowering medications ($p < 0.001$) (Table 2), indicating a significantly lower mortality in patients receiving DPP-4is.

Table 1 Demographic and clinical characteristics of the entire study population and of subgroups according to dipeptidyl peptidase-4 inhibitor use

Demographic and clinical characteristics	Total cohort (n = 33,478)	DPP-4i (−) cohort (n = 26,632; 79.5%)	DPP-4i (+) cohort (n = 6846; 20.5%)	p
Age (years), median [IQR]	54 [22]	52 [24]	60 [16]	< 0.001*
Gender, male, n (%)	14,209 (42.4)	10,992 (41.3)	3217 (42.0)	< 0.001*
Smoking (current smoker, n, %)	3612 (16.2)	3005 (16.7)	607 (13.9)	< 0.001*
Education (≥ 9 years), n (%)	1309 (29.7)	1183 (31.3)	126 (13.9)	< 0.001*
BMI (kg/m^2), median [IQR]	29.76 [7.14]	29.4 [7.3]	30.8 [6.7]	< 0.001*
Laboratory values				
Glucose (mg/dL), median [IQR]	147 [90]	116 [55]	179 [108]	< 0.001*
HbA1c (%), median [IQR]	7.18 [2.21]	6.4 [1.6]	8.1 [2.7]	< 0.001*
HbA1c (mmol/mol), median [IQR]	53.0 [26.2]	46.5 [17.0]	65.0 [29.5]	< 0.001*
HbA1c > 7% (53 mmol/mol), n (%)	4068 (60.3)	1421 (48.6)	2647 (69.2)	< 0.001*
LDL-cholesterol (mg/dL), median [IQR]	108.8 [48.7]	117.5 [52.3]	112.4 [54.0]	< 0.001*
eGFR (ml/min/1.73 m^2), median [IQR]	83.1 [39.6]	84.9 [37.9]	77.3 [41.7]	< 0.001*
eGFR < 60, n (%)	2187 (18.8)	1474 (16.8)	713 (25.1)	< 0.001*
AST > ULN, n (%)	1061 (21.1)	796 (20.8)	265 (21.9)	0.448
ALT > ULN, n (%)	1048 (20.6)	827 (21.4)	221 (18.1)	0.013*
CRP > ULN, n (%)	6460 (70.0)	4830 (67.4)	1630 (78.7)	< 0.001*
Lymphopenia, Lym# < 1000, n (%)	3810 (19.9)	29.05 (19.7)	905 (20.8)	0.103
Chest CT on admission consistent with COVID-19, n (%)	10,900 (34.5)	8129 (32.6)	2771 (41.9)	< 0.001*
Comorbid conditions, n (%)				
Hypertension	22,897 (68.4)	17,036 (64.0)	5861 (85.6)	< 0.001*
Dyslipidemia	14,923 (44.6)	10,021 (37.6)	4902 (71.6)	< 0.001*
Obesity	2112 (49.5)	1466 (47.6)	646 (54.6)	< 0.001*
Asthma/COPD	11,112 (33.2)	8571 (32.2)	2541 (37.1)	< 0.001*
Heart failure	2992 (8.9)	2048 (7.7)	944 (13.8)	< 0.001*
Cancer	2402 (7.2)	1846 (6.9)	556 (8.1)	0.001*
Microvascular complications	6120 (18.3)	3445 (12.9)	2675 (39.1)	< 0.001*
Macrovascular complications	11,864 (35.4)	8502 (35.9)	3362 (49.1)	< 0.001*

Table 1 continued

Demographic and clinical characteristics	Total cohort (n = 33,478)	DPP-4i (−) cohort (n = 26,632; 79.5%)	DPP-4i (+) cohort (n = 6846; 20.5%)	p
Treatments, n (%)				
Insulin-based regimen	7705 (23.0)	4130 (15.5)	3575 (52.2)	< 0.001*
Metformin	16,517 (49.3)	11,850 (44.5)	4667 (68.2)	< 0.001*
Other OADs (SU, acarbose, glinid, piog., SGLT2i)	8348 (24.9)	3692 (13.9)	4656 (68.0)	< 0.001*
RAS blocker	15,746 (47.0)	11,191 (42.0)	4555 (66.5)	< 0.001*
Statin	8648 (25.8)	5111 (19.2)	3537 (51.7)	< 0.001*
Acetylsalicylic acid	10,219 (30.5)	7065 (26.5)	3154 (46.1)	< 0.001*
Outcomes, n (%)				
Death	2565 (7.7)	1886 (7.1)	679 (9.9)	< 0.001*
Hospitalization	18,621 (55.6)	14,054 (52.8)	4567 (66.7)	< 0.001*
ICU admission and/or Mechanical ventilation	3832 (20.6)	2796 (19.9)	1036 (22.7)	< 0.001*

DPP-4i Dipeptidyl peptidase-4 inhibitor, *BMI* body mass index, *HbA1c* glycosylated hemoglobin, *LDL-C* low-density lipoprotein cholesterol, *eGFR* estimated glomerular filtration rate, *AST* aspartate aminotransferase, *ULN* upper limits of normal, *ALT* alanine aminotransferase, *CRP* C-reactive protein, *Lym#* lymphocyte count, *CT* computed tomography, *COVID-19* coronavirus disease 2019, *COPD* chronic obstructive pulmonary disease, *OAD* oral anti-diabetic drug, *SU* sulfonilurea, *piog.* pioglitazone, *SGLT2i* sodium/glucose cotransporter-2 inhibitor, *RAS* renin angiotensin system, *ICU* intensive care unit, *IQR* interquartile range

*Statistically significant difference at $p \leq 0.05$

Hospitalization was recorded for 66.3% of patients receiving DPP-4is and 65.7% of patients on other glucose-lowering regimens (p = 0.595); this outcome was not significantly different between the two groups. The analysis of the outcome of ICU admission and/or mechanical ventilation showed that the latter were significantly lower in patients receiving DPP-4is compared with the patients on other glucose-lowering regimens (21.7 vs. 25.2%; p = 0.001).

Multivariate regression analysis for mortality of patients with T2DM was performed in the original cohort of 33,478 patients (Table 3). This analysis showed that preexisting use of DPP-4is (OR 0.57, 95% CI 0.35–0.91; p = 0.02) was an independent associate of mortality, along with age (OR 1.08, 95% CI 1.05–1.10; $p < 0.001$), male gender (OR 2.09, 95% CI 1.37–3.19; p = 0.001), CT finding of COVID-19 (OR 1.60, 95% CI 1.08–2.37; p = 0.019), obesity (OR 1.87, 95% CI 1.22–2.84; p = 0.004), chronic kidney disease (OR 3.21, 95% CI 1.55–6.65; p = 0.002) and using insulin-based regimens (OR 2.39, 95% CI 1.51–3.80; $p < 0.001$).

DISCUSSION

The findings from this sizeable COVID-19 registry study indicate that preexisting treatment with DPP-4is may be associated with a reduction in mortality in patients with T2DM. The nearly 50% lower mortality observed in this group is also reassuring in terms of their safety during the COVID-19 pandemic. Although the rate of hospitalization was similar between the

Table 2 Demographic and clinical characteristics of patients with type 2 diabetes mellitus grouped by DPP-4i use after case–control matching

Demographic and clinical characteristics	Total (n = 9100)	DPP-4i (−) (n = 4550)	DPP-4i (+) (n = 4550)	p
Age (years), median [IQR]	60 [16]	61 [17]	60 [16])	0.122
Gender, male, n (%)	4460 (49.0)	2230 (49.0)	2230 (49.0)	1.000
Smoking (current smoker), n (%)	851 (14.5)	432 (14.6)	419 (14.4)	0.856
Education (9 years and over), n (%)	208 (17.2)	115 (19.1)	93 (15.3)	0.079*
BMI (kg/m^2), median [IQR]	30.1 [6.5]	29.4 [6.4]	30.8 [6.6]	0.003*
Laboratory values				
Glucose (mg/dL), median [IQR]	156 [103]	144 [104]	174 [99]	< 0.001*
HbA1c (%), median [IQR]	7.4 [2.5]	7.0 [2.2]	7.8 [2.5]	< 0.001*
HbA1c (mmol/mol), median (IQR)	57.4 [27.0]	53.0 [24.1]	61.8 [27.3]	< 0.001*
HbA1c > 7% (53 mmol/mol), n (%)	4068 (60.3)	1421 (48.6)	2647 (69.2)	< 0.001*
LDL-cholesterol (mg/dL), median [IQR]	114 [53]	113 [51]	115 [53]	0.727
eGFR (ml/min/1.73 m^2), median [IQR]	76.2 [43.9]	73.1 [46.2]	78.4 [40.1]	< 0.001*
eGFR< 60, n (%)	1024 (28.2)	582 (31.7)	442 (24.6)	< 0.001*
AST > ULN, n (%)	372 (22.4)	188 (21.7)	184 (23.1)	0.491
ALT > ULN, n (%)	333 (19.6)	188 (21.0)	145 (18.1)	0.130
CRP > ULN, n (%)	2170 (77.9)	1117 (77.4)	1053 (78.3)	0.550
Lymphopenia, Lym# < 1000, n (%)	1209 (21.5)	620 (22.4)	589 (20.6)	0.095
Chest CT on admission consistent with COVID-19, n (%)	3542 (40.4)	1736 (39.8)	1806 (41.1)	0.201
Comorbid conditions, n (%)				
Hypertension	7725 (84.9)	3865 (84.9)	3860 (84.8)	0.884
Dyslipidemia	5893 (64.8)	2786 (61.2)	3107 (68.3)	< 0.001*
Obesity	726 (51.5)	314 (47.9)	412 (54.7)	0.010*
Asthma/COPD	3459 (38.0)	1793 (39.4)	1666 (36.6)	0.006*
Heart failure	1312 (14.4)	668 (15.1)	624 (13.7)	0.056
Cancer	820 (9.0)	445 (9.8)	375 (8.2)	0.010*
Microvascular complication	2956 (32.5)	1478 (32.5)	1478 (32.5)	1.000
Macrovascular complications	4490 (49.3)	2245 (49.3)	2245 (49.3)	1.000
Treatments, n (%)				
Insulin-based regimen	3634 (39.0)	1817 (39.0)	1817 (39.0)	1.000
Metformin	6230 (68.5)	3115 (68.5)	3115 (68.5)	1.000

Table 2 continued

Demographic and clinical characteristics	Total (n = 9100)	DPP-4i (−) (n = 4550)	DPP-4i (+) (n = 4550)	p
Other OADs (SU, acarbose, glinid, piog., SGLT2i)	5098 (56.0)	2549 (56.0)	2549 (56.0)	1.000
RAS blocker	6064 (66.6)	3032 (66.6)	3032 (66.6)	1.000
Statin	4254 (46.7)	2127 (46.7)	2127 (46.7)	1.000
Acetylsalicylic acid	4054 (44.5)	2015 (44.3)	2039 (44.8)	0.614
Outcomes, n (%)				
Death	968 (10.6)	537 (11.8)	431 (9.5)	< 0.001*
Hospitalization	6006 (66.0)	2991 (65.7)	3015 (66.3)	0.595
ICU admission and/or mechanical ventilation	1405 (23.5)	751 (25.2)	654 (21.7)	0.001*

The parameters of gender, micro- and macro-vascular complications, ACEis/ARBs, statins, insulin, metformin and other OADs were 1:1 matched; age was matched with ± 5 years tolerance

*Statistically significant difference at $p \leq 0.05$

DPP-4i dipeptidyl peptidase-4 inhibitor, *BMI* body mass index, *HbA1c* glycosylated hemoglobin, *LDL-C* low-density lipoprotein cholesterol, *eGFR* estimated glomerular filtration rate, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *CRP* C-reactive protein, *CT* computed tomography, *COVID-19* coronavirus disease 2019, *COPD* chronic obstructive pulmonary disease, *OAD* oral anti-diabetic drug, *SU* sulfonylurea, *piog.* pioglitazone, *SGLT2i* sodium/glucose cotransporter-2 inhibitor, *RAS* renin angiotensin system, *ICU* intensive care unit, *IQR* interquartile range, *Lym#* lymphocyte count, *ULN* upper limits of normal

group on DPP-4is and the group on other glucose-lowering medications, patients on DPP-4is in our study clearly had a lower rate of ICU admission and/or mechanical ventilation.

DPP-4 (or CD26) is a transmembrane glycoprotein expressed ubiquitously in various tissues, including the immune cells, endothelium, liver, kidney, and pneumocytes [14]. Apart from its role in glucose and insulin metabolism, the DPP-4 receptor also interacts with the spike glycoprotein of SARS-CoV-2 virus to facilitate its invasion into respiratory cells [15]. Therefore, the upregulation of the DPP-4 receptor, a common feature of people with chronic diseases, might be another reason for the increased COVID-19 severity in these people [16]. It has been shown that DPP-4 receptor antibodies can prevent coronavirus infection by preventing the entry of viral particles into the human bronchial epithelial cells [17, 18]. The results of these two in vitro studies are exciting as they imply that DPP-4is have the potential to reduce the severity of COVID-19 infection by their antiviral and anti-inflammatory effects [19, 20].

Although the preclinical data on the benefit of DPP-4 inhibition in COVID-19 prognosis are promising, no evidence from randomized controlled clinical studies is currently available. Thus, at the present time clinical evidence is mainly observational. Two recent retrospective studies performed in different regions of Italy reported that preexisting treatment with DPP-4is in patients with T2DM was associated with improved COVID-19 outcomes, including reduced mortality [21, 22]. One of these studies was a multicenter, case–control study that analyzed 164 patients on sitagliptin; the authors reported a 56% reduction in mortality due to COVID-19 [21]. The other single-center study included 101 patients with T2DM, of whom 11 were receiving DPP-4is; these authors reported an 87% reduction in COVID-19 mortality [22]. However, several other studies of a similar

Table 3 Multivariate regression analysis for mortality of patients with type 2 diabetes mellitus (n = 33,478)

Variable	Odds ratio	95% Confidence interval	p
Age	1.08	1.05–1.10	< 0.001*
Gender (male)	2.09	1.37–3.19	0.001*
CT findings of COVID-19	1.60	1.08–2.37	0.019*
Hypertension	0.71	0.30–1.66	0.429
Dyslipidemia	1.06	0.64–1.77	0.815
Obesity	1.87	1.22–2.84	0.004*
Asthma/COPD	1.13	0.75–1.71	0.555
Heart failure	1.14	0.68–1.88	0.625
Chronic kidney disease	3.21	1.55–6.65	0.002*
Microvascular complications	0.59	0.28–1.23	0.159
Macrovascular complications	0.97	0.58–1.61	0.903
Cancer	1.30	0.76–2.25	0.339
RAS blocker ± combinations	0.75	0.44–1.27	0.282
Statins	1.13	0.69–1.85	0.632
Acetylsalicylic acid	1.02	0.66–1.59	0.928
Insulin-based regimens	2.39	1.51–3.80	< 0.001*
HbA1c	1.04	0.98–1.11	0.151
DPP4i-based regimens	0.57	0.35–0.91	0.020*

CT computed tomography, *COVID-19* coronavirus disease 2019, *COPD* chronic obstructive pulmonary disease, *RAS* renin angiotensin system, *HbA1c* glycosylated hemoglobin, *DPP-4i* Dipeptidyl peptidase-4 inhibitor, *OR* odds ratio
*Statistically significant difference at $p \leq 0.05$

design did not confirm the benefits of DPP-4is on the COVID-19 outcomes [23–29].

Because of the small number of patients, lack of randomization, and insufficient reporting of secondary outcomes in published studies [30], several authors have performed meta-analyses. One meta-analysis of six studies (heterogeneity [I^2]: 54%) and another of seven studies (I^2: 55%) published in December 2020 and January 2021, respectively, revealed no significant difference in the risk for the development of a fatal or severe course of illness with the use of DPP-4is in patients with COVID-19 [31, 32]. Two subsequent meta-analyses with very low heterogeneity, published in February 2021 and March 2021 and included nine and ten studies, respectively, came to similar conclusions [33, 34], with the exception of some benefits of in-hospital use of DPP-4is. More recently, Rakhmat et al. published a meta-analysis of nine studies and reported that taking DPP-4is was associated with lower mortality in COVID-19 patients with diabetes mellitus [35]. Their dataset included a total of 4477 patients with diabetes mellitus, of whom 31% were on DPP-4is; the use of DPP-4is was associated with 24% lower mortality in COVID-19 patients [35]. The present analysis included a dataset of 4550 DPP-4i users and an equal number of non-users with full outcome information starting from the day

of the PCR-positive COVID-19 diagnosis, making the study larger than any meta-analysis previously published. Our results confirm the findings of a few previous studies and of one of the six meta-analyses that provided evidence of reduced mortality due to COVID-19 in patients with diabetes mellitus who are receiving DPP-4is alone or in any combination. Propensity score matching and multivariate logistic regression allowed us to rule out the potential confounding effects of age, gender, micro- and macro-vascular complications, anti-hyperglycemic medications, RAS blockers, and statins. Obesity has been linked to increased COVID-19 mortality; however, patients in the group taking DPP-4is in our study showed lower mortality than those in the group taking other glucose-lowering medications despite their median BMI being higher and obesity diagnosis more prevalent. Moreover, the odds of lower mortality in patients taking DPP-4is was not small, nearly 50%, suggesting a clinically meaningful finding.

The association of DPP-4i use and hospitalization due to COVID-19 is less known. The rate of hospitalization did not favor DPP-4is over other anti-hyperglycemics in the present study. This finding is in line with a recent report by Fadini et al. [24], but none of the studies mentioned above evaluated this outcome. The lack of any modification in the rate of hospitalization in users of DPP-4is despite a clear association with reduced mortality is difficult to explain. One explanation may be that DPP-4is might modify the disease course prominently in more severe cases but only have a minor impact on a less progressive clinical picture. Another potential explanation may be the overall high hospitalization rate in our dataset because many individuals were indeed not selectively hospitalized during the initial months of the pandemic. Since our dataset did not allow discrimination of causes of hospitalization, this outcome needs to be elucidated in future studies.

This study has a number of limitations. As with any retrospective cohort study, it is not possible to draw causal inferences between the preexisting treatment with anti-hyperglycemic agents and the outcomes of COVID-19. One of the main limitations could be that the testing protocol for COVID-19 was not universal and that many of the mild cases would have gone undetected. Therefore, only moderate to severe cases of COVID-19 would have been detected by PCR testing. This may partly explain the finding that while two thirds of the cohort were admitted to hospital there was no difference in the rate of hospitalization between the two groups we studied. Also, since the data were collected from the electronic medical health records of the Turkish Ministry of Health, the absence of some data cannot be ignored. Moreover, the potential effects of unmeasured confounding factors cannot be excluded. It should be noted that no imputation was done during our analyses.

There are also some strengths of the present study, including the largest sample with DPP-4i users so far published, 1:1 matching with control patients with diabetes mellitus, nationwide representation, multicenter design, exclusion of unconfirmed (PCR negative) COVID-19 cases, and the availability of full information on the most relevant COVID-19-related outcomes. Countrywide administration of centrally guided outpatient and inpatient protocols by the Ministry of Health is another strength because standardized protocols may reduce the confounding of the results by the level or the quality of care following COVID-19 diagnosis.

CONCLUSION

In conclusion, we observed a lower mortality rate and lower rates of ICU admission and/or mechanical ventilation among COVID-19 patients with T2DM who had preexisting treatment with DPP-4is compared with non-DPP-4i users. The rate of hospitalization did not favor DPP-4is in the same population. Age, male gender, CT findings of COVID-19, obesity, chronic kidney disease, and insulin-based regimen were the other independent risk factors for COVID-19 mortality in our study.

ACKNOWLEDGEMENTS

We owe a debt of gratitude to all healthcare professionals who have devoted their lives to combating COVID-19 and have provided these data.

Funding. No funding or sponsorship was received for this study or publication of this article.

Authorship. All named authors meet the International Committee of Medical Journal Editors required criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authors' Contributions. RE, AS, IS and IT were involved in the conception and design of the study. Staff from the Ministry of Health (NA, OC, and MC) were responsible for the data download and verification. ID and CH cleaned the data and performed the analyses. ID, CH, and IT prepared the figures and tables. AS and RE drafted the manuscript. IS reviewed and made critical contributions to the final draft. All authors were involved in the interpretation, critically reviewed the first draft, and approved the final version.

Disclosures. All of the authors (Rıfat Emral, Cem Haymana, İbrahim Demirci, İlker Taşçı, Mustafa Şahin, Erman Çakal, Naim Ata, Uğur Ünlütürk, Tevfik Demir, Derun Ertuğrul, İbrahim Şahin, Ayşegül Atmaca, Osman Celik, Murat Caglayan, Kazim Yalcin Arga, Selçuk Dağdelen, Serpil Salman, İlhan Satman, Alper Sönmez) declare that they have nothing to disclose.

Compliance with Ethics Guidelines. This study was approved by the COVID-19 Investigation Review Board under the Bioethics Committee of Ministry of Health, which waived the requirement of informed consent due to the retrospective study design and anonymity of the national database (IRB no: 95741342-020:186404/28.10.2020). The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments.

Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available due to being a part of the national registry data of the Turkish Ministry of Health.

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