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Original research

Factors influencing on development of COVID-19 pneumonia and association with oral anti-diabetic drugs in hospitalized patients with diabetes mellitus



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ARTICLE INFO

Article history:

Received 18 May 2021

Received in revised form 24 July 2021

Accepted 1 August 2021

Available online 4 August 2021

Keywords:

COVID-19

Oral anti-diabetic

Drugs

Diabetes mellitus

Pneumonia

ABSTRACT

Background: Diabetes mellitus (DM) increases mortality and morbidity in patients with coronavirus disease (COVID-19). In this study, it was aimed to assess factors influencing on COVID-19 pneumonia in hospitalized patients with diabetes and association with oral anti-diabetic drugs.

Materials and methods: This cross-sectional study included 432 patients with type 2 diabetes mellitus diagnosed with COVID-19. Data regarding clinical characteristics, demographic characteristics, intensive care unit (ICU) rate in patients admitted to ICU, laboratory results on day 1 and 7, thoracic computed tomography (CT) findings and oral anti-diabetic drugs used were extracted from medical records. In all patients, 75-days mortality was recorded. Data were assessed independently.

Results: There was pneumonia in 386 (89.4%) of 432 patients with diabetes. The risk for pneumonia was markedly higher in patients on DPP-4 inhibitors; however, there was no significant among other oral anti-diabetic groups and subgroups. In addition, elevated CRP was linked to the increased risk for pneumonia. Only patients in the pneumonia group had SGLT-2 inhibitor use. During follow-up, 91 patients died. In Cox regression analysis, low Glasgow Coma Scale score, and increased lactate dehydrogenase levels were identified as significant independent risk factors for mortality.

Conclusion: The study indicated that DPP-4 inhibitor used and elevated CRP level were associated with pneumonia development. Only patients in the pneumonia group had SGLT-2 inhibitor use. No oral anti-diabetics was found to be associated with COVID-19 related death.

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1. Introduction

Patients with diabetes mellitus (DM) are susceptible to various infections and sepsis [1]. Clinical experiences showed that the susceptibility is associated with fatal infections and adverse clinical outcomes due to factors including severe activation of pro-inflammatory cascade, impaired immune response and cellular dysfunction resulting from metabolic disorders and hyperglycemia [2–4].

The Coronavirus disease 2019 (COVID-19), which affected 118 million people and caused more than 2.5 million deaths worldwide, has become an important clinical issue for patients with DM [5,6]. Many studies showed that DM caused an increase in the mortal-

ity in patients with COVID-19 pneumonia as similar to previous coronavirus outbreaks (SARS-CoV and MERS-CoV) [7,8]. However, mechanism underlying increased mortality has not been fully elucidated [9].

It is thought that patients with diabetes mellitus are more susceptible to COVID-19 pneumonia due to multiple immune disorders. However, it is controversial whether treatments for DM and clinical-laboratory differences have effect on the development of COVID-19 pneumonia in patients with diabetes [10]. In the present study, it was aimed to assess factors affecting development of COVID-19 pneumonia and its relationship with oral anti-diabetic drugs in hospitalized patients with diabetes.

2. Materials and methods

The single-center, cross-sectional study was conducted at Kayseri City Training and Research Hospital. The study included 432 diabetes mellitus patients with the diagnosis of COVID-19 who

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were admitted to pandemic clinics between 1 March 2020 and 15 September 2020. The study was approved by Ethics Committee on Clinical Trials of Kayseri City Training and Research Hospital (195/2020). The study was conducted in accordance to tenets of Helsinki Declaration.

2.1. Subjects

The study included patients with type 2 diabetes mellitus (aged >18 years) with diagnosis of COVID-19. The cases in which SARS-CoV-2 RNA was detected in upper respiratory tract samples using a SARS-CoV-2 nucleic acid detection in accordance manufacturer's instructions (Shanghai BioGerm Medical Biotechnology Co., Ltd.) were considered as PCR positive for SARS-CoV-2. The diagnosis of COVID-19 was made if SARS-CoV-2 PCR was positive or if there were compatible COVID-19 symptoms (loss of taste or smell, dyspnea, etc.) with typical ground glass appearance on thoracic computed tomography (CT) scan in the setting of an exposure risk and in the absence of other identifiable causes. The patients with diabetes was defined as patients using oral anti-diabetic drugs and having diagnosis of type 2 DM in medical records. The patients on oral anti-diabetic treatment for at least 3 months were included. In all patients, data regarding demographic characteristics (age, gender), clinical findings (comorbidities including hypertension, coronary artery disease, chronic obstructive pulmonary disease, asthma, chronic renal failure, congestive heart failure, hyperlipidemia, cerebrovascular disease, hypothyroidism), macro (coronary and peripheral artery disease and cerebrovascular disease) and microvascular complications (nephropathy, retinopathy and neuropathy), laboratory findings (C-reactive protein [CRP], blood urea nitrogen [BUN], creatinine, lactate dehydrogenase [LDH], ferritin, glomerular filtration rate [GFR], white blood cell [WBC] count), neutrophil count, lymphocyte count, platelet count, fibrinogen, activated partial thromboplastin time [aPTT], D-dimer, prothrombin time (PT), INR, HbA1c), severity scores (Glasgow Coma Scale, APACHE-II) and need for mechanical ventilation in patients admitted to intensive care unit (ICU), thoracic CT scan findings and oral anti-diabetic drugs used (active substance, subgroups, duration of use) were recorded. For routine laboratory tests, blood samples drawn on day 1 and 7 of admission were used. The severity scores within one hour after ICU admission were used.

The first hospitalization was assessed in patients with multiple hospitalizations. The patients re-hospitalized on the day or next day of discharge, hospitalizations were combined in one hospitalization.

The patients were stratified into 2 groups as patients with and without pneumonia according to thoracic CT scan findings. Data were compared between two groups. In all patients, 75-days mortality was recorded. Mortality-related markers were compared between survivors and non-survivor.

The patients aged <18 years and >80 years, those with autoimmune disease or chronic infection and those with malignancy were excluded. In addition, the patients with diagnosis of DM on medical records but not using oral anti-diabetic drugs or those on oral anti-diabetic drugs less than 3 months were also excluded.

2.2. Statistical analysis

Statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Data are presented as mean \pm standard deviation (SD), the median (interquartile range) or count (percent). The normality and the homogeneity of the data were evaluated by Shapiro–Wilk test and Levene test, respectively. Comparisons between groups for continuous variables were performed using the Student t test (normal distribution) or the Mann–Whitney

U test (non-normal distribution). Fisher test or the χ^2 test was used for all categorical data. Logistic regression analysis was used to determine the relative risks of developing pneumonia. Only the variables with a statistically significant association in the simple logistic regression model were included in the multiple logistic regression model. Odds ratios (OR) and 95% confidence intervals (CI) were determined. Cox regression models were used to predict death. A p value <0.05 were considered as statistically significant.

3. Results

3.1. Patients characteristics

In the study, 432 type 2 diabetes mellitus patients with diagnosis of COVID-19 were assessed. Of the patients 197 (45.6%) were men (Table 1). Overall, 382 patients (88.4%) had a comorbid condition. The hypertension was most common comorbid disease (74.1%); followed by hyperlipidemia (51.6%). The biguanides were the most commonly used oral anti-diabetic drugs (89.6%); followed by DPP-4 (dipeptidyl peptidase 4) inhibitors (56.9%). Of the patients, 161 (37.3%) were admitted to intensive care unit.

3.2. Clinical and laboratory findings associated with pneumonia

The patients were stratified into 2 groups according to presence of diffuse ground glass areas on thoracic CT scan: patients with or without pneumonia. There was pneumonia in 386 patients (89.4%). Table 1 presents demographic and clinical characteristics of patients with or without pneumonia. Mean age was 63.6 ± 10.1 years in patients with pneumonia whereas 59.6 ± 11.1 years in patients without pneumonia. There was no significant difference in gender distribution and comorbid conditions between groups; however, mean age was significantly higher in patients with pneumonia than those without ($p = 0.011$). The ICU admission rate was higher in patients with pneumonia ($p < 0.001$). In additions, 75-days mortality was significantly higher in patients with pneumonia when compared to those without pneumonia (23.12% vs. 2.2%, $p = 0.001$).

The DPP-4 inhibitor and SGLT-2 (sodium–glucose-cotransporter 2) inhibitor use was significantly more common among diabetes mellitus patients with pneumonia ($p = 0.01$ and $p = 0.006$, respectively) (Table 1); however, no significant difference was detected in the DPP-4 inhibitor (linagliptin, sitagliptin, vildagliptin, saxagliptin) and SGLT-2 inhibitor subgroups (dapagliflozin, empagliflozin) ($p > 0.05$; Table A1). The main combination of oral anti-diabetic drugs was DPP-4 inhibitor + biguanides in the whole group, however there was no significant difference between groups according to pneumonia ($p = 0.948$) (Table 1).

Mean fasting glucose level, CRP, LDH and fibrinogen levels were significantly higher in pneumonia group than patients without pneumonia ($p = 0.005$, $p < 0.001$, $p = 0.017$ and $p = 0.002$; respectively). Other parameters including HbA1C were not different between groups ($p > 0.05$; Table A2).

To identify risk for pneumonia, univariate and multivariate logistic regression analysis was performed and only the variables with a statistically significant association in the simple logistic regression model were included in the multiple logistic regression model (Table 2). SGLT-2 inhibitor use was not included in the regression analysis, because only patients in the pneumonia group had SGLT-2 inhibitor use. In age and gender adjusted model, the logistic regression showed that CRP elevation was associated with pneumonia development (Odd ratio [OR]: 1.030; 95% CI: 1.006–1.053; $p = 0.012$). The risk for pneumonia was significantly increased in patients on DPP-4 inhibitor (OR: 4.628; 95% CI: 1.189–18.013; $p = 0.027$).

Table 1
Demographic and clinical findings of patients who with pneumonia and without pneumonia.

	Total n = 432	No pneumonia n = 46	Pneumonia n = 386	p
Age, year	63.3 ± 10.3	59.6 ± 11.1	63.6 ± 10.1	0.011
Male gender	197 (45.6)	22 (47.8)	175 (45.3)	
Female gender	235 (54.4)	24 (52.2)	211 (54.7)	0.749
Duration of diabetes, year	6.2 ± 2.9	5.5 ± 3.2	6.2 ± 2.8	0.122
Microvascular complications	204 (47.2)	17 (37)	187 (48.4)	0.140
Macrovascular complications	155 (35.9)	13 (28.3)	142 (36.8)	0.254
Comorbidities	382 (88.4)	39 (84.8)	343 (88.9)	0.462
Hypertension	320 (74.1)	32 (69.6)	288 (74.6)	0.460
Asthma	38 (8.8)	4 (8.7)	34 (8.8)	0.980
Chronic obstructive pulmonary disease	45 (10.4)	5 (10.9)	40 (10.4)	0.915
Coronary artery disease	123 (28.5)	9 (19.6)	114 (29.5)	0.157
Chronic kidney disease	20 (4.6)	2 (4.3)	18 (4.7)	0.923
Hyperlipidemia	223 (51.6)	20 (43.5)	203 (52.6)	0.242
Cerebrovascular disease	24 (5.6)	3 (6.5)	21 (5.4)	0.762
Hypothyroidism	29 (6.7)	2 (4.3)	27 (7.0)	0.498
Anti-hypertensive treatment				
Angiotensin-converting enzyme inhibitors	105 (24.3)	12 (26.1)	93 (24.1)	0.766
Angiotensin II receptor blockers	120 (27.8)	12 (26.1)	108 (28)	0.787
Beta blockers	119 (27.5)	13 (28.3)	106 (27.5)	0.909
Diuretics	166 (38.4)	23 (50)	143 (37)	0.088
Diabetes treatment				
Oral antidiabetics only	242 (56)	30 (65.2)	212 (54.9)	0.184
Oral antidiabetics + insulin	190 (44)	16 (34.8)	174 (45.1)	
Oral antidiabetic drugs				
DPP-4 Inh	246 (56.9)	18 (39.1)	228 (59.1)	0.010
Sulfonylureas	66 (15.3)	6 (13.0)	60 (15.5)	0.656
Biguanides	379 (89.6)	44 (95.7)	335 (88.9)	0.154
SGLT-2 Inh	56 (13.0)	0 (0.0)	56 (14.5)	0.006
Glitazones	27 (6.3)	4 (8.7)	23 (6.0)	0.468
Combinations of oral antidiabetic drugs				
DPP-4 Inh + biguanides	133 (30.8)	14 (30.4)	119 (30.8)	0.948
DPP-4 Inh + sulfonylureas	1 (0.2)	0	1 (0.3)	–
DPP-4 Inh + SGLT-2 Inh	2 (0.5)	0	2 (0.5)	–
DPP-4 Inh + glitazones	2 (0.5)	0	2 (0.5)	–
Biguanides + sulfonylureas	18 (4.2)	4 (8.7)	14 (3.6)	–
Biguanides + SGLT-2 Inh	7 (1.6)	0	7 (1.8)	–
Biguanides + glitazones	10 (2.3)	2 (4.3)	8 (2.1)	–
Biguanides + DPP-4 Inh + sulfonylureas	25 (5.8)	2 (4.3)	23 (6)	–
Biguanides + DPP-4 Inh + SGLT-2 Inh	27 (6.25)	0	27 (7)	–
Biguanides + DPP-4 Inh + glitazones	3 (0.7)	1 (2.2)	2 (0.5)	–
Biguanides + sulfonylureas + SGLT-2 Inh	2 (0.5)	0	2 (0.5)	–
Biguanides + sulfonylureas + glitazones	3 (0.7)	0	3 (0.8)	–
Biguanides + SGLT-2 Inh + glitazones	1 (0.2)	0	1 (0.3)	–
Biguanides + DPP-4 Inh + sulfonylureas + SGLT-2 Inh	8 (1.9)	0	8 (2.1)	–
Biguanides + DPP-4 Inh + sulfonylureas + glitazones	2 (0.5)	0	2 (0.5)	–
Biguanides + DPP-4 Inh + glitazones + SGLT-2 Inh	4 (0.9)	0	4 (1)	–
Biguanides + DPP-4 Inh + sulfonylureas + glitazones + SGLT-2 Inh	1 (0.2)	0	1 (0.3)	–
Intensive care unit	161 (37.3)	4 (8.7)	157 (40.7)	<0.001
Mechanical ventilation	90 (55.9)	2 (50)	88 (56.1)	0.810
Mortality 75th day	91 (21.0)	1 (2.1)	90 (23.3)	0.001

DPP-4 Inh, dipeptidyl peptidase 4 inhibitors; SGLT-2 Inh, sodium glucose co-transporter type 2 inhibitors. We provided the significant values as bold.

3.3. Clinical and laboratory findings associated with mortality

Overall, 91 patients died during follow-up. Table 3 presents demographic and clinical characteristics of non-survivors. Mean age was significantly higher in non-survivors when compared to survivors ($p < 0.001$). The presence of pneumonia and comorbidity was significantly lower in survivors when compared to non-survivors (87.1% vs. 97.8%, $p = 0.02$ and 86.5% vs. 95.6%, $p = 0.016$, respectively). The presence of hypertension, asthma, coronary artery disease, congestive heart failure and chronic renal failure were found to be associated with increased mortality ($p < 0.05$). There was no significant difference in mortality among oral anti-diabetic drugs ($p > 0.05$); however, duration of diabetes was longer in non-survivors when compared to survivors (7.4 ± 2.6 vs. 5.8 ± 2.8 ; $p < 0.001$). Mean APACHE score was 18.1 ± 13.5 while mean GCS score was 10.9 ± 4.7 in non-survivors. The high APACHE II score and low GCS score were associated with mortality ($p = 0.026$ and $p < 0.001$, respectively).

The blood parameters on day 1 and 7 of admission were compared between survivors and non-survivors (Table 4). On day 1 and 7, mean CRP, BUN, LDH, ferritin, D-dimer levels and neutrophil count were significantly higher in non-survivors compared to survivors ($p < 0.001$). Again, mean GFR values on day 1 and 7 were found to be significantly lower in non-survivors ($p < 0.001$). Mean fibrinogen level was significantly higher on day 1 in non-survivors ($p = 0.012$); however, no significant difference was found between non-survivors and survivors on day 7 ($p > 0.05$). The mean creatinine level on day 7 was significantly higher in non-survivors ($p < 0.001$) but no significant difference was observed on day 1 ($p > 0.05$).

To identify risk factors for mortality, Cox regression analysis was performed on all parameters found to be significant in Tables 3 and 4 (Table 5). Elevated LDH levels were identified as independent risk factors for mortality (OR: 1.001; 95% CI: 1.00–1.001; $p = 0.009$). In addition, high GCS scores were found to be associated with reduction in risk for mortality (OR: 0.901; 95% CI:

Table 2
Results of multiple logistic regression analysis for risk factors associated with pneumonia in age and gender adjusted model.

Risk factors	OR	95% CI	p
Univariate analysis			
Hypertension	1.286	0.659–2.509	0.461
Angiotensin-converting enzyme inhibitors	0.899	0.447–1.808	0.766
Angiotensin II receptor blockers	1.101	0.550–2.205	0.787
Chronic obstructive pulmonary disease	0.948	0.354–2.537	0.915
Asthma	1.014	0.343–2.999	0.980
Duration of diabetes	1.086	0.978–1.205	0.123
Fasting glucose level	1.007	1.002–1.012	0.005
HbA1C	1.166	0.728–1.867	0.522
DPP-4 Inh	2.245	1.200–4.198	0.011
C-reactive protein	1.036	1.020–1.051	<0.001
Lactate dehydrogenase	1.009	1.003–1.014	0.001
Fibrinogen	1.001	1.000–1.001	0.003
Biguanides	0.363	0.085–1.550	0.171
Blood urea nitrogen	1.021	0.993–1.051	0.139
Multiple analysis			
Fasting glucose level	1.007	0.997–1.016	0.154
DPP-4 Inh	4.628	1.189–18.013	0.027
C-reactive protein	1.030	1.006–1.053	0.012
Lactate dehydrogenase	1.002	0.995–1.009	0.536
Fibrinogen	1.000	1.000–1.001	0.374

SGLT-2 Inh, sodium glucose co-transporter type 2 inhibitors; DPP-4 Inh, dipeptidyl peptidase 4 inhibitors; OR, odds ratio; CI, confidence interval. We provided the significant values as bold.

0.831–0.976; p = 0.011). No other parameter was found to be associated with risk for mortality.

4. Discussion

We investigated association between pneumonia development and clinical data by selecting a specific study population including 432 type 2 diabetes mellitus patients with a diagnosis of COVID-19. Our results indicate that only DPP-4 inhibitor use and elevated CRP levels were independent risk factors for development of pneumonia in diabetes mellitus patients with COVID-19. In addition, in Cox regression analysis, low GCS score and elevated LDH levels were linked with 75-days mortality.

In coronavirus infections, initial response is created by sub-mucosal mast cells of respiratory tract [11]. The mast cell degranulation is regulated by stromal cell-derived factor-1 (SDF-1) which is inactivated by DPP-4 [12]. However, growing evidence shows mast cells release bioactive molecules which exacerbate clinical course of disease while neutralizing these pathogens [11,13]. The dual activity of mast cells in viral infection has led debates about COVID-19 pneumonia and DPP-4 inhibitors [14–17].

In our study, DPP-4 inhibitor use was found to be associated with pneumonia development in diabetes mellitus patients with

Table 4
Laboratory findings associated with death on day 1 and on day 7 in patients who had COVID-19.

	Laboratory measures of on 1th day			Laboratory measures of on 7th day		
	Non-survivor n = 91	Survivor n = 341	p	Non-survivor n = 91	Survivor n = 341	p
C-reactive protein, mg/dL	110.2 ± 94.7	60.7 ± 65.8	<0.001	91.3 ± 76.3	35.5 ± 45.5	<0.001
Blood urea nitrogen, mg/dL	35.4 ± 22.9	19.0 ± 11.3	<0.001	50.5 ± 33.9	21.2 ± 13.4	<0.001
Creatinine, mg/dL	2.4 ± 15.8	1.6 ± 1.2	0.637	1.8 ± 1.6	0.9 ± 0.8	<0.001
Lactate dehydrogenase, U/L	560.0 ± 453.0	306.3 ± 155.5	<0.001	618.1 ± 301.6	285.1 ± 108.5	<0.001
Ferritin, ng/mL	880.8 ± 1369	305.2 ± 363.5	<0.001	793.5 ± 479.6	432.2 ± 427.2	<0.001
Glomerular filtration rate, mL/min	53 ± 26.3	76.5 ± 25.1	<0.001	55.5 ± 33.5	82.6 ± 33.5	<0.001
Neutrophil, ×10 ³ /μL	9.9 ± 14.7	5.6 ± 3.9	<0.001	10.7 ± 5	5.5 ± 2.9	<0.001
Lymphocyte, ×10 ³ /μL	1.8 ± 3.8	1.5 ± 1.0	0.334	2.0 ± 5.5	2.7 ± 15	0.724
Platelet ×10 ³ /μL	218.6 ± 96.6	225.2 ± 83.9	0.525	256.9 ± 92.7	313.3 ± 256	0.109
Fibrinogen, mg/L	5985 ± 1822	5312 ± 1764	0.012	5568 ± 1956	5231 ± 1794	0.304
Activated partial thromboplastin time, s	34.8 ± 18.5	32.3 ± 32.7	0.539	90.7 ± 401.0	85.1 ± 509.3	0.945
D-dimer, ng/mL	2669 ± 3325	1147 ± 1572	<0.001	3340 ± 3547	1110 ± 1580	<0.001
Prothrombin time, s	16.1 ± 5.7	14.3 ± 7.0	0.045	17.1 ± 7.9	14.6 ± 5.6	0.014
INR	1.2 ± 0.4	1.1 ± 0.5	0.047	1.3 ± 0.6	1.1 ± 1.1	0.380

Table 3
Characteristics associated with death in patients who had COVID-19.

	Non-survivor n = 91	Survivor n = 341	p
Age mean	67.9 ± 8.2	61.9 ± 10.4	<0.001
Male gender	49 (53.8)	148 (43.4)	0.077
Female gender	42 (46.2)	193 (56.6)	
Duration of diabetes, year	7.4 ± 2.6	5.8 ± 2.8	<0.001
Bilateral diffuse infiltration (pneumonia)	89 (97.8)	297 (87.1)	0.002
Comorbidities			
Hypertension	87 (95.6)	295 (86.5)	0.016
Asthma	75 (82.4)	245 (71.8)	0.044
Chronic obstructive pulmonary disease	3 (3.3)	35 (10.3)	0.037
Coronary artery disease	11 (12.1)	34 (10.0)	0.564
Congestive heart failure	34 (37.4)	89 (26.1)	0.037
Chronic kidney disease	12 (13.2)	16 (4.7)	0.007
Hyperlipidemia	8 (8.8)	12 (3.5)	0.047
Cerebrovascular disease	51 (56.0)	172 (50.4)	0.348
Hypothyroidism	7 (7.7)	17 (5.0)	0.309
Oral antidiabetic drugs	7 (7.7)	22 (6.5)	0.642
DPP-4 Inh	56 (61.5)	190 (55.7)	0.342
Sulfonylureas	14 (15.4)	52 (15.2)	1.000
Biguanides	74 (88.1)	305 (90.0)	0.689
SGLT-2 Inh	14 (15.4)	42 (12.3)	0.482
Glitazones	7 (7.7)	20 (5.9)	0.475
APACHE II score on admission mean ± SD	18.1 ± 13.5	13.6 ± 10.7	0.026
GCS score on admission mean ± SD	10.9 ± 4.7	14.7 ± 0.6	<0.001
Fasting glucose level, mg/dL	253 ± 129	192 ± 85.6	<0.001
Duration of biguanide use, year	7.0 ± 2.6	5.7 ± 2.7	<0.001
HbA1C mean ± SD^a	8.4 ± 1.4	8.2 ± 2.0	0.665

DPP-4 Inh, dipeptidyl peptidase 4 inhibitors; SGLT-2 Inh, sodium glucose co-transporter type 2 inhibitors; APACHE II, acute physiology, assessment and chronic health evaluation; GCS, glasgow coma scale; HbA1C, hemoglobin A1c. We provided the significant values as bold.

^a n = 6 for no pneumonia group and n = 99 for pneumonia group.

diagnosis of COVID-19, which differs from results reported by studies in the literature. In previous studies comparing patients using or not using DPP-4 inhibitor, it was reported that the need for mechanical ventilation was less common among patients on DPP-4 inhibitor [18,19]. Among these, in the study on 90 patients by Mirani et al., only 12% were on DPP-4 inhibitor [18]; the number of patients was smaller than that in our study. In the study by Solerte et al., only sitagliptin was investigated [19]. In a study by Kim et al., no significant association was found between DPP-4 inhibitor use and severity of pneumonia [20]. However, above-mentioned studies excluded COVID-19 patients without pulmonary involvement on thoracic CT scans; thus, they are inadequate to assess factors predisposing to pneumonia.

Table 5
Results of Cox regression analysis for risk factors associated with death. We provided the significant values as bold.

Risk factors	OR	95% CI	p
Duration of diabetes	0.996	0.813–1.220	0.968
Asthma	0	0	0.989
Coronary artery disease	0.512	0.200–1.312	0.163
Chronic kidney disease	0	0	0.981
Age	0.988	0.932–1.048	0.694
APACHE II	1.000	0.963–1.039	0.983
GCS	0.901	0.831–0.976	0.011
Fasting glucose level	1.003	1.000–1.006	0.097
C-reactive protein	1.000	0.997–1.004	0.833
Blood urea nitrogen	1.017	0.997–1.037	0.093
Lactate dehydrogenase	1.001	1.000–1.001	0.009
Ferritin	1.000	0.999–1.000	0.501
D-dimer, ng/mL	1.000	1.000–1.000	0.718
Fibrinogen	1.000	1.000–1.000	0.712

OR, odds ratio; CI, confidence interval; APACHE II, acute physiology assessment and chronic health evaluation; GCS, glasgow coma scale. We provided the significant values as bold.

For DPP-4 use, the mechanisms underlying risk for potential infection haven't been fully elucidated. A membrane-bound form of DPP-4, namely CD26, is present in several cell types including T lymphocytes, B lymphocytes, natural killer cells and macrophages [21]. The CD26 is N-terminal dipeptide that cleaves a protease from polypeptides and involved in some biological processes that may potentially modify immune function [12]. Thus, the CD26/DPP4-mediated cleavage of immunoregulatory substrates such as regulatory peptides, neuropeptides and chemokines may influence on immune activity or function [22]; thereby, CD26 inhibition by DPP-4 inhibitors may alter immune function.

In a meta-analysis, all-causes infections showed a significant increase with sitagliptin therapy but no significant increase was found with vildagliptin therapy [23]. However, no significant increase was observed in risk for respiratory tract infections with DPP-4 inhibitors when results from several safety analyses of clinical trials on sitagliptin and vildagliptin were compared with placebo [24]. In a study on association between oral anti-diabetics and community-acquired pneumonia, no increase was observed in risk for pneumonia by DPP-4 inhibitor use [25]. A case-control study on Vigibase database of World Health Organization (WHO), it was found that reports of infections were increased after introduction of DPP-4 inhibitors [26]. Kawasaki et al. demonstrated that sitagliptin diminished pulmonary damage caused by LPS in rats [27]. There is no evidence for similar findings in human lung. Thus, it is unknown whether DPP-4 inhibition will affect immune function or whether it will increase risk for infection in human. Based on our current results, the finding of the increased risk for pneumonia in diabetes mellitus patients with COVID-19 using DPP-4 inhibitor indicate potential role of DPP-4 in COVID-dipeptide 19 pneumonia.

DPP-4 was previously defined as a functional receptor for MERS-CoV [28,29]. In some studies, it was shown that there was correlation between DPP-4 and angiotensin converting enzyme (ACE)-2 [30,31]. This has led the hypothesis that SARS-CoV-2 might use DPP-4 as a functional receptor in addition to ACE-2 [30,32]. In a study quantifying DPP-3 levels in COVID-19 patients, Schlicht et al. found that DPP-4 levels were found to be decreased as similar to MERS-CoV [33], supporting the hypothesis.

In our study, only patients in pneumonia group were receiving SGLT-2 inhibitor. Therefore we could not clearly reveal the role of SGLT-2 inhibitor's role in COVID-19. In a retrospective cohort study, it was reported that SGLT-2 inhibitor use did not predispose COVID-19 development [34]. However, data regarding SGLT-2 inhibitors are limited; thus, our study will add literature in this context. Further randomized, controlled studies are needed to understand the role of SGLT-2 inhibitor roles in COVID-19. In addition, although

advanced age and elevated CRP, LDH and fibrinogen levels were found to be associated with pneumonia, only CRP elevation resulted in increased risk for pneumonia in multiple analysis. This finding is in agreement with literature [35].

In studies about mortality, data regarding DPP-4 inhibitor are controversial. Some authors reported better outcomes in COVID-19 patients using DPP-4 inhibitor [19] while other authors reported inconclusive results on the issue [35–39]. In another study, it was reported in-hospital DPP-4 use decreased mortality but pre-hospital use had no association with mortality [40]. Our results are supportive for previous studies, without significant increase in mortality by DPP-4 inhibitor use.

Many studies have defined markers for mortality in COVID-19. The parameters consistent with literature including comorbidity, asthma, coronary artery disease, chronic renal failure, advanced age, high APACHE II score and low GCS score were more common among non-survivors [39,41,42]. In addition, fasting glucose level and duration of diabetes was linked with death. In our study, non-survivor patients had higher duration of biguanide use. This may be secondary to prolonged diabetes mellitus duration since, as presented in our study, metformin is most commonly used oral anti-diabetic agent worldwide and it is generally used as first-line treatment [43,44].

To determine alteration in mortality-related factors during course of disease, we assessed blood parameters on day 1 and 7. In agreement with literature, elevated CRP, BUN, LDH, ferritin, D-dimer and neutrophil count and low GFR level were found to be associated with mortality [20,39,42,45,46]. Mean fibrinogen level was significantly higher on day 1 in non-survivors; however, no significant difference was found between non-survivors and survivors on day 7. This may be affected by COVID-19 treatment initiated at hospital admission. Similarly, the mean creatinine level on day 7 was significantly higher in non-survivors but no significant difference was observed on day 1. The change in creatinine levels on day 7 can be explained by COVID-19 progression and nephrotoxic effects of available treatments [47,48]. However, in our study, only elevated LDH levels were identified as significant independent risk factors for mortality in agreement with previous studies [20,35,42].

The all studies including ours delineate a complex picture for interaction between DM and COVID-19 pneumonia. Diabetes mellitus leads immune disorder and various metabolic disorders. Together with effects of DM on immune system DM therapies may alter response to and clinical outcomes of COVID-19 pneumonia. On contrary to other studies, our study emphasizes factors influencing on development of COVID-19 pneumonia in patients with diabetes. This paves the way for protective measures that may be implemented in diabetes mellitus patients with well-known predisposition to infections. However, further randomized, controlled studies are needed to better understand factors involved in the development of pneumonia in diabetes mellitus patients with a diagnosis of COVID-19.

This study has some limitations. Due to deficiencies of infrastructure and training of healthcare providers, the documentation about history of COVID-19 exposure and laboratory tests were incomplete. In particular, HbA1c values were missing in a considerable proportion of subjects; thus, our analysis regarding association between degree of glycemic control and severity and mortality of COVID-19 was limited. Although we had age adjusted regression analysis, we could not totally exclude age effect on relationship between pneumonia and oral anti-diabetics.

5. Conclusion

The DPP-4 inhibitor uses and elevated CRP level increased risk for pneumonia in diabetes mellitus patients with a diagnosis of COVID-19. Only patients in the pneumonia group had SGLT-2

inhibitor use. No oral anti-diabetics were found to be associated with COVID-19 related death.

Research funding

During this study, any pharmaceutical company that has a direct connection with the subject of the research, a company that provides and/or produces medical tools, equipment, and materials, or any commercial company, during the evaluation process of the study, financial and/or no moral support was received.

Author contributions

All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Disclosure

Regarding this study, the authors and/or their family members do not have a scientific and medical committee membership or relationship with their members, consultancy, expertise, working status in any company, shareholding, or similar situations with a potential conflict of interest.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A

Table A1

Subgroup analysis for DPP-4 inhibitors and SGLT-2 inhibitors in patients with and without pneumonia.

DPP-4 inhibitors sub-groups	Total	No pneumonia	Pneumonia	p
	n = 246	n = 18	n = 228	
Linagliptin	53 (21.5)	2 (11.1)	51 (22.4)	0.521
Saxagliptin	2 (0.8)	0 (0.0)	2 (0.9)	
Sitagliptin	98 (39.8)	7 (38.9)	91 (39.9)	
Vildagliptin	93 (37.8)	9 (50.0)	84 (36.8)	
SGLT-2 inhibitors sub-groups	Total	No pneumonia	Pneumonia	p
	n = 56	n = 0	n = 56	
Dapagliflozin	25 (44.6)	0 (0.0)	25 (44.6)	
Empagliflozin	31 (55.4)	0 (0.0)	31 (55.4)	

DPP-4 Inh, dipeptidyl peptidase 4 inhibitors; SGLT-2 Inh, sodium glucose co-transporter type 2 inhibitors.

Table A2

Laboratory findings of patients who with pneumonia and without pneumonia.

Laboratory measures of on admission day	No pneumonia	Pneumonia	P
	n = 46	n = 386	
Fasting glucose level, mg/dL	164 ± 59.6	209 ± 101	0.005
HbA1C, % ^a	7.8 ± 1.4	8.3 ± 1.9	0.524
C-reactive protein, mg/dL	7 (16.45)	55.3 (85.43)	<0.001
Blood urea nitrogen, mg/dL	19.5 (9.25)	19 (16)	0.136
Creatinine, mg/dL	0.99 (0.26)	1.1 (0.69)	0.532
Lactate dehydrogenase, U/L	235 (102.3)	321 (226)	0.017
Ferritin, ng/mL	117 (379)	226 (437)	0.505
Glomerular filtration rate, mL/min	76.5 ± 24.5	71 ± 27.3	0.366

Table A2 (Continued)

Laboratory measures of on admission day	No pneumonia	Pneumonia	P
	n = 46	n = 386	
White blood cell count, ×10 ⁹ /L	5.6 (2.9)	7.6 (6.1)	0.30
Neutrophil (PMN), ×10 ³ /μL	2.8 (3.3)	5.8 (5.9)	0.071
Lymphocyte, ×10 ³ /μL	1.8 (1.3)	1.2 (0.8)	0.412
Platelet ×10 ³ /μL	214.6 ± 52.5	224.8 ± 89.8	0.452
Fibrinogen, mg/L	4022 ± 1219	5563 ± 1792	0.002
Activated partial thromboplastin time (aPTT), s	30.6 ± 12.6	33.0 ± 30.5	0.753
D-dimer, ng/mL	660 (547)	1090 (1500)	0.346
Prothrombin time (PT), s	12.9 (2)	14 (2.5)	0.075

^a n = 6 for no pneumonia group and n = 99 for pneumonia group HbA1C: hemoglobin A1c.

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