ORIGINAL ARTICLE

Eastern Journal of Medicine
East J Med 28(1): 59-67, 2023
DOI: 10.5505/ejm.2023.57984

The Impact of Diabetes Mellitus on the Course of COVID-19 Pneumonia

Dilek Bulut[1*], Merve Sefa Sayar[2]

[1]Department of Infectious Diseases and Clinical Microbiology, Diskapi Yildirim Beyazit Training and Research Hospital, Ankara, Turkey
[2]Department of Infectious Diseases and Clinical Microbiology, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey

ABSTRACT

Diabetes mellitus (DM) is one of the most commonly encountered chronic diseases throughout the world. We aimed to reveal the association between such a common disease and COVID-19-related pneumonia posing a global threat, and its impact on the course of the disease.

In our study, 125 patients diagnosed and treated due to COVID-19 pneumonia were analyzed in our hospital within two months. While 25 patients were in the group with DM,there was no comorbidity in 100 patients.The main goal of our study was to evaluate isolatedly the effect of DM on COVID-19 pneumonia when other comorbidities were excluded. For this purpose, we compared the demographic characteristics, symptoms, and signs of the disease, laboratory parameters, computerized tomography(CT) findings, and some data about the clinical course of the disease between two patient groups.

Based on the findings of the analyzes, those in the case group were seen to be older. Such respiratory symptoms as cough and shortness of breath were found to be more common in the case group.Inflammatory parameters, such as c-reactive protein (CRP), white blood cell count (WBC), neutrophil count, and D-dimer were also higher in the case group. As well as the poor progression of the disease, the requirements for intensive care unit (ICU) andoxygen (O2), hospitalization period, and mortality rates were also higher among diabetic patients.

The existence of DM poses a risk in terms of requiring care in ICU, severe pace ofthe disease, and higher mortality in those with COVID-19 pneumonia.

Keywords: Diabetes Mellitus, Coronavirus, COVID-19, Pneumonia, Prognosis

Introduction

Most of the coronaviruses are enveloped viruses of the ribonucleic acid (RNA) genome leading to mild upper respiratory tract infections, especially in individuals with healthy immune systems (1, 2). In December 2019, a new beta-coronavirus was identified in Wuhan, the largest and the most populous city in the Province of Hubei in China, currently called COVID-19 (3). Spreading rapidly, the condition was declared as a pandemic by the World Health Organization (WHO) on March 11, 2020 (4). The virus, affecting almost all countries in various degrees and leading to a global problem in many areas such as sociological, economic, and health, was declared for the first time in our country on 10th March 2020. A total of 163.942 cases and 4.540 deaths related to COVID-19 were recorded in Turkey from the first cases of COVID-19 declared on 10th March 2020 until the date our study was completed on 31st May 2020 (5).

Although the condition is dealt with mildly by most patients, COVID-19 disease results in pneumonia, acute respiratory distress syndrome (ARDS), multiple organ failure, and death, especially in some patient groups (6). In the literature, numerous studies report that the complications and mortality led by COVID-19 progress at a higher rate among those with certain risk factors, such as diabetes mellitus (DM), obesity and hypertension (HT) (7-12).

DM is one of the most commonly encountered chronic conditions with multiple systemic complications (13). In another study performed in the USA, 10.5% of the total population, and 26.8% of the population aged 65≤ at the risk of death due to COVID -19 disease are stated to have DM (14). It is important to reveal the association between DM, which is witnessed so

***Corresponding Author:** Dilek Bulut, Infectious Diseases and Clinical Microbiology Specialist, Department of Infectious Diseases and Clinical Microbiology, Dışkapı Training and Research Hospital, Ankara, Turkey
E-mail: dilekerdim@hotmail.com, Telephone Number: +90 (507) 741 82 36
ORCID ID: Dilek Bulut: 0000-0001-5874-174X, **Merve Sefa Sayar:** 0000-0002-0436-4122
Received: 14.07.2021, **Accepted:** 18.08.2022

commonly and causes mortality and morbidity due to its complications, and COVID-19 disease, which is considered a global threat. DM is known to impair the outcomes of severe acute respiratory syndrome coronavirus (SARS-CoV), hemagglutinin type-1 and neuraminidase type-1 (H1N1), and other similar viral infections leading to ARDS (15, 16). Additionally, considering the transmission rate of SARS-CoV-2 and global prevalence of DM, creating a parallel disease spectrum in the respiratory tract, such an interaction is alarming and so the correlation between DM and COVID-19 disease is an important issue for health authorities. In this respect, it is significant tounderstand the relationship between DM and COVID-19 pneumonia in terms of optimal care in DM patients, measures to reduce mortality and morbidity, improvement of novel treatment and care strategies and development of different clinical severity scores in patients with DM.

With the present study, we aimed to investigate whether DM affects the length of hospitalization in the wards and ICU, disease severity and treatment modalities administered to patients with COVID-19 pneumonia.Thus, our study aims at providing better care for COVID-19 patients with DM, increasing the awareness in early intervention, and contributingto the essential scientific discussions on measures to be taken in terms of antiviral or additional treatments.

Material and Method

The present report is a retrospective case-control study where 125 patients diagnosed with COVID-19 pneumonia were investigated between 1st April-31st May 2020 in Van Training and Research Hospital. Of 125 study participants, while 100 constituted the non-diabetic control group, 25 were grouped as the case or patient group diagnosed with DM. Moreover, in order to rule out the effects of other comorbidities, those with additional comorbidities were not included in both groups.

Patients' demographic characteristics, symptoms and findings, readings of laboratory investigations, images and reports of chest tomography, length of hospitalization, and the requirement for ICU were created by scanning retrospectively the patients' files and from the pre-created hospital system.In addition, several data with no access were obtained through direct contact with the patients or their families.

The inclusion criteria were composed of the following:

1- Being over 18 years of age,
2- The determination of SARS-CoV-2 through the reverse transcription-polymerase chain reaction (RT-PCR) test taken from the respiratory tract swabs based on the guidelines of The Turkish Ministry of Health meeting the definition of probable cases,
3- The existence of significant involvement in chest tomography suggesting Covid-19 pneumonia,
4- No additional diseases other than DM in the case group with DM,
5- No additional diseases in the control group without DM,

For patients' respiratory tract samples, the oropharyngeal swab samples were first taken and then the nasal samples were obtained using the same swab under the guidelines by The Turkish Ministry of Health. The swap samples were delivered to the laboratory through the cold-chain transport and examined using RT-PCR for SARS-CoV-2.

Computerized tomography (CT) imaging scores created by Guo et al. were used to measure the severity of involvement in the lungs of those with COVID-19 pneumonia and the values of CT score were obtained using the scoring system below (12).

Distribution of performance scores among the cases:

(1) unilateral patchyshadows or ground-glass opacity in five cases,

(2) bilateral patchy shadows or ground-glass opacity in seven,

(3) diffuse changes for (1) or (2) in two,

(4) unilateral solid shadow, strip shadow in two,

(5) bilateral solid shadow, strip shadow in four,

(6) unilateral pleural effusion in two,

(7) bilateral pleural effusion in four,

(8) an increase or enlargement in mediastinal lymph nodes in one case.

This study was reviewed and approved by the medical ethics committee of Van Traning and Research Hospital (approval number: 2020/10).

Statistical Analysis: The visual (histogram) and analytical methods (the Kolmogorov-Smirnov and Shapiro-Wilk tests) were used to evaluate the normal distribution of continuous data. For the descriptive statistical findings, continuous data were reported as median (min-max) in those with

no normal distribution and as mean±standard deviation (SD) in those with normal distribution, while thecategorical data were reported as numbers (percentage).While evaluating the statistical difference between the averages and medians in continuous data, the *t*-test and Mann-Whitney U test were used for independent samples, respectively. In assessing the statistical significance in categorical data, the chi-square and Fisher's exact tests were utilized. However, the Pearson's correlation analysis was used to evaluate the correlation between groups. The statistical significance level was set as 0.05 and the statistical analyses of the study findings were evaluated through the Statistical Package for the Social Sciences software for Windows, version 27.0 (SPSS Inc., Chicago, IL,USA).

Results

As to the demographic characteristics of 125 study participants diagnosed with COVID-19 pneumonia, 41.6% were female and 58.4% were male. While the mean age was measured as 60.2±10.8 years in the case group with DM, the rate was 36 ±13.3 years in the non-diabetic control group and there was a statistically significant difference between both groups ($p<0.05$) (Table 1). Except for DM, no comorbid diseases, another demographic feature, was also present in both groups.

The three most common symptoms were detected as cough (84%), fever (64%) and shortness of breath (52%) in the case group, and cough (39%), myalgia (34%) and fever (20%) in the control group. Compared the two groups statistically in terms of symptoms, a difference was observed in terms of the percentages of cough, fever and shortness of breath seen in the diabetic group and the difference was significantly higher those with DM ($p<0.05$) (Table 2).

Among the laboratory parameters examined in the study, there was a statistically significant difference between both groups in terms of the values of gamma-glutamyl transferase (GGT), C-reactive protein (CRP), white blood cell (WBC) count, neutrophil count, mean platelet volume (MPV), D-dimer and albumin. However, the mean values of GGT were also determined as 50.8±43.5 and 22.7±18.8 in the case and control groups ($p<0.05$), respectively. Even so, while the medians of CRP in the case and control groups were measured as 30 (1-250) and 4.7 (0-298) ($p<0.05$), the mean values of WBC were detected to be 7985.6±3286.0 and 6527.1±2803.2 in the case and control groups ($p<0.05$), respectively.The mean values of the absolute neutrophil count were 5743.2±3379.1 and 4398.5±2413.3 in the case and control groups ($p<0.05$), respectively. However, in terms of MPV, the mean values in the case and control groups were detected as 10.4±1.4 and 9.8±1.2 ($p <0.05$), respectively. While detected to be 717.3±889.6 in the case group, the mean value of D-dimer was found as 200±258.5 in the control group ($p<0.05$). As the median values, albumin was also measured to be 3.7±0.4 in the case group and 4.3±0.3 in the control group ($p<0.05$) (Table 3).

Since COVID-19 pneumonia was considered the inclusion criteria for the study, typical changes consistent with COVID-19 pneumonia were sought in lung tomography of all patients in the study. When both groups were compared based on the tomography scores to predict the severity of lung involvement, a statistically significant difference was seen to be present between the severity scores of both groups ($p<0.05$). While the median value of chest CT scores was 10 (7-17) in the case group with COVID-19 pneumonia and DM, the value was found as 6 (5-12) in the control group without DM. Chest CT scores were significantly higher in the case group (Table 4).

Given the clinical pace of the disease and the outcomes of treatment regimes, there was a statistically significant difference between both groups in terms of ICU requirement, need for O_2 and steroids, number of deaths, and the total duration of hospitalization. Of 25 patients in the case group, seven were detected to need caring in ICU, accounting for 5.6% of thewhole study participants. All of the patients in the control group were detected not to need caring in ICU. When the case group's requirement for caring in ICU was compared with that of the control group, a statistically significant difference was found in favor of the case group with DM ($p<0.05$). Forty percent of the diabetic case group and 6% of the control group were detected to need O_2, and the requirement for O_2 in the case group was seen to be statistically significant, compared to that of the controls ($p<0.05$). While two of 25 COVID-19 patients with DM died, no deaths were observed among those in the control group. The mortality rate was found to be 1.3% among the entire study participants, and there was a significant difference in terms of deathsbetween both groups ($p<0.05$).The median values of total hospitalization were found as 10 days (2-30) and 7 days (2-20) in the case and control groups, and the difference was statistically significant ($p<0.05$)

Table 1. Demographic Features

		DM/Yes n (%)	DM/No n (%)	Total n (%)	p
Gender	Male	14 (56%)	38 (38%)	52 (41.6%)	0.102†
	Female	11 (44%)	62 (62%)	73 (58.4%)	
Age (yrs) Mean±SD		60.2±10.8	36.0±13.3	40.8±16.1	0.001*

CI: Confidence interval, DM: Diabetes mellitus, SD: Standard deviation,
*t test for independent variables †Chi-square test

Table 2. The distribution of Symptoms In The Study Groups

Existence of symptoms	DM/Yes n (%)	DM/No n (%)	Total n (%)	p
Fever	16 (64%)	20 (20%)	36 (28.8%)	0.001†
Coughing	21 (84%)	39 (39%)	60 (48%)	0.001†
Headache	7 (28%)	15 (15%)	22 (17.6%)	0.127*
Myalgia	12 (48%)	34 (34%)	46 (36.8%)	0.194†
Sorethroat	6 (24%)	17 (17%)	23 (18.4%)	0.401*
Impairedtaste/smell	2 (8%)	8 (8%)	10 (8%)	1.000*
Shortness of breath	13 (52%)	10 (10%)	23 (18.4%)	0.001*

CI: Confidence interval, DM: Diabetes mellitus *Fisher's test †Chi-square test

(Table 5). Whether there was a correlation between mean fasting glucose and HbA1c values of 25 patients in the case group and ICU requirement, need for O_2 and the total duration of hospitalization was also examined, no significant difference was found.

Discussion

It is a known fact that DM leads to the predisposition to various infections and results in poor clinical outcomes (17-19). In many studies conducted previously, it is seen that commonly encountered comorbidities in societies, such as DM and HT, impair the pace of COVID-19 pneumonia and bring about higher mortality (7-11). However, the number of studies evaluating isolatedly the effects of DM without looking at the effects of other comorbidities is limited.

In our study, we attribute the advanced age of our diabetic case group with COVID-19 pneumonia to excluding additional comorbidities out of the criteria in both groups, and this finding is compatible with that in the study by Guo et al. In the aforementioned study where additional comorbidities were excluded from the study samples, although there was a significant difference inage levels between the groups, DM was predicted to increase significantly the risk of progression of COVID-19 pneumonia (12).

In our study, such symptoms as cough, fever, shortness of breath, and myalgia, were detected as the most common maladies in patients with COVID-19 pneumonia, and such a finding was in line with that found in the general population in other studies (20-22). In the literature, the predominance of such symptoms as cough, fever, and shortness of breath has been reported to be effective in predicting the requirement for staying in ICU and more severe course of the disease, and such symptoms are encountered higher in the diabetic population (23). We consider that the higher prevalence of symptoms such as cough, fever and shortness of breath in our diabetic case group was associated with the higher rate of lung involvement in the case group. In addition, these symptoms may also be the precursor of a more severe pace of the disease.

Dysfunctional pro-inflammatory cytokine responses are likely to be another underlying cause of severe COVID-19 pneumonia in the diabetic population (3, 24, 25). In diabetic patients, the levels of pro-inflammatory cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) are higher (25). Different markers, such as CRP, D-dimer and fibrinogen, have also been found to be increased in DM patients contracting COVID-19 disease (3). In our study, the detection of higher rates of such parameters as CRP, D-dimer, WBC, and absolute neutrophil count as the indicators of

Table 3. Comparison of Laboratory Parameters Between Study Groups

Laboratory parameters	DM/Yes	DM/No	Total	p
AST (U/L) Mean±SD	26.4±13.8	23.5±22.4	24.1±20.9	0.536*
ALT (U/L) Mean±SD	28.2±19.2	22.0±25.4	23.2±24.3	0.253*
ALP (U/L) Mean±SD	83.0±23.2	73.2±25.7	75.2±25.5	0.084*
GGT (U/L) Mean±SD	50.8±43.5	22.7±18.8	28.3±27.9	0.004*
LDH (U/L) Mean±SD	236.6±63.0	215.4±73.5	219.6±71.8	0.188*
Creatinine (mg/dl) Median (Min-Max)	0.9 (0.5-89)	0.9 (0.5-1.4)	0.9 (0.5-89)	0.565†
CRP (mg/L) Median (Min-Max)	30 (1-250)	4.7 (0-298)	6.1 (0-298)	0.001†
PCT (ng/mL) Mean±SD	0.1±0.1	0.2±0.9	0.2±0.9	0.801*
WBC (10 ^9/L) Mean±SD	7985.6±3286.0	6527.1±2803.2	6818.8±2950.7	0.026*
Lymphocyte (10 ^9/L) Mean±SD	1663.6±830.5	1592.6±620.4	1606.8±664.6	0.635*
Neutrophil (10 ^9/L) Mean±SD	5743.2±3379.1	4398.5±2413.3	4667.4±2674.2	0.024*
Hb (g/dL) Mean±SD	14.3±1.7	14.7±1.7	14.6±1.7	0.295*
Platelet (10 ^3/uL) Mean±SD	201800.0±45409.3	222950.0±66186.1	218720.0±62997.3	0.134*
MPV (%) Mean±SD	10.4±1.4	9.8±1.2	9.9±1.3	0.039*
Ferritin (ng/ml) Median (Min-Max)	195 (16-1638)	133.7 (1.1-1828)	138.3 (1.1-1828)	0.131†
D-Dimer (ng/ml) Mean±SD	717.3±889.6	200.0±258.5	303.4±499.7	0.008*
Troponin (ng/mL) Mean±SD	0.1±0.1	0.1±0.1	0.1±0.1	0.327*
CK (U/L) Mean±SD	135.3±108.7	123.8±116.2	126.1±114.4	0.656*
Albumin (g/dl) Mean±SD	3.7±0.4	4.3±0.3	4.2±0.4	0.001*

SD: Standard deviation, Min:Minimum, Max:Maximum, ALP: Alkaline phosphatase, AST: Aspartate aminotransferase, CK: Creatinekinase, CRP: C-reactive protein, DM: Diabetes mellitus, GGT: Gamma-glutamyl transferase, Hb: Hemoglobin, LDH: Lactatedehydrogenase, MPV: Mean platelet volume, PCT: Procalcitonin, WBC:White blood cell, *t test for independent variables, †A non-parametric test was used since creatinine, ferritin and CRP were not compatible with normal distribution

inflammation in our COVID-19 pneumonia patients with DM was considered to be associated with the higher risks of inflammation responses and the table of macrophage activation syndrome (MAS) in the case group.

Table 4. Comparison of Scores of Lung Tomography Between The Study Groups

Scores of lung tomography	DM/Yes	DM/No	Total	p
Median (min-max)	10.0 (7.0-17.0)	6.0 (5.0-12.0)	6.0 (5.0-17.0)	0.001*

Min:Minimum, Max:Maximum DM: Diabetes mellitus, SD: Standard deviation
*Mann-Whitney U test

Table 5. The Course of the COVID-19 Pneumonia In The Study Groups

ClinicalSpectrum		DM/Yes		DM/No		Toplam		p
		n	%	n	%	n	%	
Requirement for ICU	Yes	7	28.0	-	-	7	5.6	0.001†
	No	18	72.0	100	100.0	118	94.4	
Requirement for O2	Yes	10	40.0	6	6.0	16	12.8	0.001*
	No	15	60.0	94	94.0	109	87.2	
Requirement for stereoids	Yes	10	40.0	9	9.0	19	15.2	0.001*
	No	15	60.0	91	91.0	106	84.8	
Final Status	Exitus	2	8.0	-	-	2	1.6	0.039*
	Healthy	23	92.0	100	100.0	123	98.4	
Duration of Stay in Hospital Median (Min-Max)		10.0 (2.0-30.0)		7.0 (2.0-20.0)		7.0 (2.0-30.0)		0.032†

CI: Confidence interval, DM: Diabetes mellitus, ICU: Intensive care unit, O_2: Oxygen, SD: Standard deviation, *Fisher's test †Chi-square test

During the inflammatory storm, the level of D-dimer increases significantly, meaning a plasmin-associated issue that activates the inflammation process at the early stage. However, as the inflammation progresses, the hypoxia-induced molecular thrombin is also activated directly and the activation of monocyte-macrophages also secrete a bit tissue factor and so leading to exogenous coagulation (12). Such a condition leads to a general tendency to coagulation, or even extensive disseminated intravascular coagulation (DIC). In our study, the level of D-dimer was found to be significantly higher in the case group with DM. We attributed this increase was the signs of poor progression of the disease among COVID-19 patients and the inflammatory response would be more severe. These findings reveal that COVID-19 pneumonia patients with DM are prone to creating an inflammatory storm leading to the rapid deterioration of their clinics.

Various biochemical parameters, such as lactate dehydrogenase (LDH), alanine transaminase (ALT), gamma glutamyl transferase (GGT) and troponin have been reported to be increased in those with COVID-19 pneumonia in various studies and these biomarkers are also known as important markers indicating myocardial, kidney and liver damages (12, 26). In our study, although the value of GGT was found to be significantly higher in the case group with DM, no significant difference was observed in the levels of ALT, aspartate aminotransferase (AST), troponin and LDH. The existence of higher enzyme levels in the diabetic case group was important in terms of showing that organ damage would be more severe, compared with those in the control group. Furthermore, the fact that we found a lower level of albumin in the case group than the non-diabetic controls reveals that DM patients are more likely to be malnourished.

In our study, we consider that the existence of more severe lung involvements and higher CT scores in the case group arose from more severe lung damages due to the viral respiratory pathogens in DM patients (15, 19, 27, 28). Although there are many other mechanisms involved in such an outcome, the most prominent culprithas been attributed to the following entity: Patients with DM have a low respiratory function as revealed by various animal studies reporting that alveolar-capillary microangiopathy and interstitial fibrosis are induced by the glycolysis of lung tissue collagen in themodels of DM (29, 30). In another study, the expression of angiotensin-converting enzyme-2 (ACE-2) was shown to increase in the lungs, kidneys, heart, and pancreas in rodent DM models (31, 32). ACE-2 is a type-1 integral membrane glycoprotein expressed in epithelial cells of cardiovascular, pulmonary, renal, brain, and intestinal tissues (24, 33, 34). ACE-2

increases the anti-inflammatory and anti-cytokine activity by lowering the levels of proinflammatory cytokines (35). SARS-CoV-2 uses ACE-2 for binding to pneumocytes (33). The increased expression of ACE-2 in DM patients may support the increased cellular binding of SARS-CoV-2 (36-38). The findings from our study and parallel studies support the hypothesis stating that the diabetic population is susceptible to SARS-CoV-2 infection.Besides, the outcomes compatible with our results that were reported in some studies also supportthe abovementioned mechanisms we emphasized that diabetic patients are at highersevereriskof COVID-19 disease (11, 12).

As consistent with our findings, the parameters reported in previous studies, such as requirements for the care in ICU and O_2, and the higher rate of mortality demonstrating the severe pace of the disease, were significantly higher in the diabetic population with COVID-19 pneumonia (6, 12, 19, 22, 39, 40). The mechanisms that were associated with higher mortality and more severe clinical presentation in DM patients may also be associated with lung dysfunction and severe inflammation emphasized in the abovementioned statements.DM inhibits neutrophil chemotaxis, phagocytosis, and intracellular killing of microorganisms. The adaptive immunity disorder characterized by the delayed type-1 T helper (Th1) cell-mediated immunity and the delayed hyperinflammatory response is alsoobserved in DM patients (41). The risk of respiratory tract infections is higher among diabetic individuals, especially due to the innate immune system (24, 42). Even transient hyperglycemia can temporarily affect the innate immune responses to infections (43). Another study has also suggested that ACE-2 may be the key pathway of COVID-19 severity in diabetic individuals (42). Additionally, people with DM are affected by a low-grade chronic inflammation to trigger a cytokine storm, seeming to be the ultimate cause of deaths in severe cases of COVID-19 pneumonia (44).

Another marker predicting mortality in diabetic patients has also been reported as hyperglycemia [19]. Hyperglycemia led by DM has beenassociated with abnormal glycosylation and glycosylation-related dysfunction in immunoglobulins (22). In our study, no correlation existed between the criteria predicting the regulation of DM and the disease severity. We consider that this issue was due to the insufficient number of cases for evaluating such a correlation.In addition, there were no dataavailable to evaluate the type of DM, disease duration, presence of related complications and glycemic control developing during the infection in DM patients.

Since the significant age difference between both groups resulted in the inhomogeneity of the groups, the difference can be seen as the most important limitation of our study. Under the design of our study, since we planned the study to determine the isolated effect of DM on COVID-19, the control group consisted of younger patients without additional diseases, while the case group was composed of those at an advanced age. As another limitation, since our study was with a retrospective design, there were no data available to evaluate the type of DM, disease duration, presence of related complications and glycemic outcomes during the infection in DM patients. Also, the effects of these dataon the pace of COVID-19 pneumonia could not be evaluated. Due to the low mortality rate in the case group, further analyzes could not also be performed to determine the effects of mortality as a risk factor. Finally, we attribute the lack of correlation between the criteria regulating DM and the severity of the disease to the low number of study participants. This issue was also another reason not allowing some further analysis to be performed.

In summary, our study findings demonstrated that COVID-19 pneumonia patients with DM had more severe symptoms and higher pulmonary involvement,and the clinical pace was poorer in such patients. Based on these findings, clinicians should not be late in administering the treatment to COVID-19 patients with DM by taking the possibility of rapid deterioration in the clinics of these patients into consideration. In addition, optimalclinical care and additional support treatments are of vital importance in treating such patients.

References

1. Adachi S, Koma T, Nomaguchi M, Adachi A. Commentary: Origin and evolution of pathogenic coronaviruses. Frontiers in Immunology. 2020; 11: 811.
2. Yilmaz NK, Swanstrom R, Schiffer CA. Improving viral protease inhibitors to counter drug resistance. Trends in microbiology 2016; 24: 547-557.
3. Maddaloni E, Buzzetti R. Covid-19 and diabetes mellitus: unveiling the interaction of two pandemics. Diabetes/Metabolism Research and Reviews. 2020:e33213321.

4. Team EE. Note from the editors: novel coronavirus (2019-nCoV). Eurosurveillance 2020; 25: 2001231.
5. T.C. Sağlık Bakanlığı Halk Sağlığı Genel Müdürlüğü (2020). COVID-19 (SARS CoV2 ENFEKSİYONU) REHBERİ (Bilim Kurulu Çalışması), April 14, 2020 [Available from: https://covid19.saglik.gov.tr/TR-66393/covid-19-salgin-yonetimi-ve-calisma-rehberi.html.
6. Huang I, Lim MA, Pranata R. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia–a systematic review, meta-analysis, and meta-regression. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020.
7. Guan W, Ni Z, Hu Y, et al. China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019; 1708-1720.
8. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. Jama 2020; 323: 1775-1776.
9. Stovall M, Smith SA, Langholz BM, et al. Dose to the contralateral breast from radiotherapy and risk of second primary breast cancer in the WECARE study. International Journal of Radiation Oncology* Biology* Physics 2008; 72: 1021-1030.
10. Park S-Y, Kim J-H, Kim H-J, et al. High prevalence of asthma in elderly women: findings from a Korean national health database and adult asthma cohort. Allergy, asthma & immunology research 2018; 10: 387-396.
11. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The lancet. 2020.
12. Guo W, Li M, Dong Y, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes/metabolism research and reviews. 2020:e3319.
13. Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas. Diabetes research and clinical practice 2019; 157: 107843.
14. Control CfD, Prevention. National diabetes statistics report, 2020. Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services. 2020.
15. Booth CM, Matukas LM, Tomlinson GA, et al. Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. Jama 2003; 289: 2801-2809.
16. Allard R, Leclerc P, Tremblay C, Tannenbaum T-N. Diabetes and the severity of pandemic influenza A (H1N1) infection. Diabetes care. 2010; 33: 1491-3.
17. Knapp S. Diabetes and infection: Is there a link?-A mini-review. Gerontology 2013; 59: 99-104.
18. Joshi N, Caputo GM, Weitekamp MR, Karchmer A. Infections in patients with diabetes mellitus. New England Journal of Medicine 1999; 341: 1906-1912.
19. Yang J, Feng Y, Yuan M, et al. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. Diabetic medicine 2006; 23: 623-8.
20. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. Jama 2020; 323: 1061-1069.
21. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet 2020; 395: 497-506.
22. Yan Y, Yang Y, Wang F, et al. Clinical characteristics and outcomes of patients with severe covid-19 with diabetes. BMJ Open Diabetes Research and Care 2020; 8: e001343.
23. Jain V, Yuan J-M. Predictive symptoms and comorbidities for severe COVID-19 and intensive care unit admission: a systematic review and meta-analysis. International Journal of Public Health. 2020:1.
24. Ceriello A. Management of diabetes today: An exciting confusion. Diabetes Research and Clinical Practice 2020; 162: 108129.
25. Geerlings SE, Hoepelman AI. Immune dysfunction in patients with diabetes mellitus (DM). FEMS Immunology & Medical Microbiology 1999; 26: 259-265.
26. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet 2020; 395: 507-513.
27. Hulme KD, Gallo LA, Short KR. Influenza virus and glycemic variability in diabetes: a killer combination? Frontiers in Microbiology 2017; 8: 861.
28. Alfaraj SH, Al-Tawfiq JA, Memish ZA. Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection during pregnancy: Report of two cases & review of the literature 2019.
29. Yang J, Tan Y, Zhao F, et al. Angiotensin II plays a critical role in diabetic pulmonary fibrosis most likely via activation of NADPH oxidase-mediated nitrosative damage. American Journal of Physiology-Endocrinology and Metabolism 2011; 301: 132-144.
30. Popov D, Simionescu M. Alterations of lung structure in experimental diabetes, and diabetes associated with hyperlipidaemia in hamsters. European Respiratory Journal 1997; 10: 1850-1858.
31. Roca-Ho H, Riera M, Palau V, Pascual J, Soler MJ. Characterization of ACE and ACE2 expression within different organs of the NOD

mouse. International journal of molecular sciences 2017; 18: 563.

32. Wysocki J. Ye M, Soler MJ, Gurley SB, Xiao HD, Bernstein KE, Coffman TM, Chen S, Batlle D. ACE and ACE2 activity in diabetic mice Diabetes 2006; 55: 2132-2139.
33. Shi Y, Wang Y, Shao C, et al. COVID-19 infection: the perspectives on immune responses. Nature Publishing Group; 2020.
34. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020.
35. Rossi GP, Sanga V, Barton M. Potential harmful effects of discontinuing ACE-inhibitors and ARBs in COVID-19 patients. Elife. 2020; 9: e57278.
36. Liu F, Long X, Zou W, et al. Highly ACE2 expression in pancreas may cause pancreas damage after SARS-CoV-2 infection. medrxiv. 2020.
37. Lukassen S, Chua RL, Trefzer T, et al. SARS-CoV-2 receptor ACE 2 and TMPRSS 2 are primarily expressed in bronchial transient secretory cells. The EMBO journal 2020; 39: e105114.
38. Lin W, Hu L, Zhang Y, et al. Single-cell Analysis of ACE2 Expression in Human Kidneys and Bladders Reveals a Potential Route of 2019-nCoV Infection. bioRxiv. 2020.
39. Roncon L, Zuin M, Rigatelli G, Zuliani G. Diabetic patients with COVID-19 infection are at higher risk of ICU admission and poor short-term outcome. Journal of Clinical Virology 2020; 104354.
40. Cao J, Hu X, Cheng W, et al. Clinical features and short-term outcomes of 18 patients with corona virus disease 2019 in intensive care unit. Intensive care medicine 2020; 1-3.
41. Hodgson K, Morris J, Bridson T, et al. Immunological mechanisms contributing to the double burden of diabetes and intracellular bacterial infections. Immunology. 2015; 144: 171-185.
42. Holt RIG. Diabetic Medicine in lock-down. Diabet Med 2020; 37: 907-908.
43. Jafar N, Edriss H, Nugent K. The effect of short-term hyperglycemia on the innate immune system. The American journal of the medical sciences 2016; 351: 201-211.
44. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet (London, England) 2020; 395: 1033.