



COVID-19 pneumonia in patients with impaired fasting glucose, newly diagnosed diabetes and pre-existing diabetes: a tertiary center experience

Banu Boyuk ¹, Seydahmet Akin,¹ Nazire Aladag,¹ Arzu Isik,¹ Hande Erman ¹, Yasemin Ozgur,¹ Meryem Topal,¹ Nevra Karademir,¹ Busra Tomar Uysal,¹ Bahar Ozbilgehan,¹ Dilan Kabaca,¹ Canan Kalmaz,¹ Seyma Arslan,² Ozcan Keskin¹

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¹Internal Medicine, Istanbul Kartal Dr. Lufti Kırdar City Hospital, Istanbul, Turkey
²Public Health, Istanbul Universitesi Istanbul Tıp Fakültesi, Istanbul, Turkey

Correspondence to
Dr Banu Boyuk, Internal Medicine, Istanbul Doctor Lufti Kırdar Kartal Training and Research Hospital, Istanbul 34865, Turkey; banuilk@gmail.com

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ABSTRACT

COVID-19 infection is known to increase mortality in patients with diabetes. We aim to demonstrate the differences in disease course and clinical outcomes of patients with COVID-19 regarding the presence of impaired fasting glucose, pre-existing diabetes mellitus (DM) or new-onset DM. 236 patients with positive reverse transcription-PCR tests for SARS-CoV-2 were included in this single-center, retrospective observational study between March 2020 and May 2021. Laboratory results, comorbidities, medications and imaging findings were noted. Logistic regression was used to estimate associated factors for admission to the intensive care unit (ICU). 43 patients with normal glucose, 53 with impaired fasting glucose, 60 with newly diagnosed DM, and 80 with pre-existing DM were classified. Patients with pre-existing DM had higher fasting glucose and glycated hemoglobin than the other groups ($p < 0.001$ for all). Patients with newly diagnosed DM were more likely to need dexamethasone 6 mg ($p = 0.001$). In both newly diagnosed diabetes and impaired fasting glucose groups, 250 mg methylprednisolone was needed at higher rates ($p = 0.002$). Newly diagnosed DM had higher rates of intubation (21.6%) and more mortality (20.0%) ($p = 0.045$ and $p = 0.028$, respectively). Mortality and hospitalization in the ICU were lower in the group receiving antidiabetic treatment. The risk of ICU attendance was higher in patients with impaired fasting glucose (HR=1.71, 95% CI: 0.48 to 6.08) and newly diagnosed DM (HR=1.88, 95% CI: 0.57 to 6.17), compared with pre-existing DM and non-diabetics. Newly diagnosed DM and impaired fasting glucose are associated with increased mortality and intubation in inpatients with COVID-19.

INTRODUCTION

While diabetes mellitus (DM), the pandemic of our age, has been showing its effects globally without slowing down, the SARS-CoV-2 pandemic, which started in Wuhan, China, in February 2020, has started to affect all populations devastatingly. Although temporary

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Diabetes mellitus (DM) predisposes to a particularly severe course of COVID-19. However, limited data are available on the course of COVID-19 in patients with different glucose statuses.

WHAT THIS STUDY ADDS

⇒ Newly diagnosed DM was associated with increased mortality and intubation rates in COVID-19 pneumonia. The risk of intensive care unit attendance was higher in patients with impaired fasting glucose and newly diagnosed DM, compared with pre-existing DM and non-diabetics.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ Among patients with diabetes, patients with newly diagnosed diabetes and impaired fasting glucose are at risk of severe COVID-19 pneumonia. For this reason, it is important to diagnose patients according to fasting blood glucose and glycated hemoglobin values in determining high-risk individuals.

successes have been achieved in the struggle, the pandemic still shows its effects around the world. As of September 2021, over 230 million cases and over 4,700,000 deaths have been reported worldwide on the WHO website. In Turkey, on the same date, the number of cases was recorded as 6,960,297 and the number of deaths as 62,524.¹

Although there is no specific effective drug treatment for the disease, it is hoped that the vaccines developed will slow down the pandemic.² Infection is more fatal in patients with COVID-19 with DM, chronic obstructive pulmonary disease, cardiovascular diseases, hypertension, malignancies and other comorbidities.³ In many publications, it has been reported that the mortality rate due to COVID-19 is at least twice as high in patients

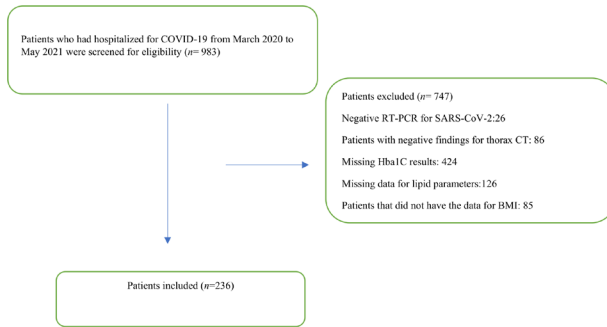


Figure 1 Study flow diagram. BMI, body mass index; HbA1c, glycated hemoglobin; RT-PCR, reverse transcription-PCR.

with diabetes compared with non-diabetics, and the disease is more severe.⁴ The high tendency of infection in patients with diabetes, the effects of antidiabetic drugs on the inflammation process, the increased use of steroids in the treatment, and the fact that diabetes has not yet been diagnosed in some patients make the treatment process of COVID-19 much more complicated. There is insufficient information showing the course of the disease in patients with impaired fasting glucose (IFG) and newly diagnosed diabetes.⁵

Investigating whether the course of COVID-19 is altered in patients with different glucose statuses will help in clarifying patient groups at risk of severe COVID-19 infection. Therefore, we aimed to compare the COVID-19 outcomes of hospitalized patients with impaired fasting blood glucose, pre-existing diabetes and new-onset diabetes.

MATERIALS AND METHOD

Study design and participants

Patients who were hospitalized with COVID-19 pneumonia in the internal medicine pandemic clinic between March 2020 and May 2021 were included in the single-center, retrospective observational study. Of 983 patients with SARS-CoV-2, 236 were appropriate for the study (figure 1). Patients with COVID-19 pneumonia, confirmed by positive real-time reverse transcription-PCR tests for SARS-CoV-2 and radiographic imaging were eligible for enrollment. Demographic characteristics, comorbid disease, medications, symptoms, biochemical parameters, imaging study findings, treatments given during hospitalization, and clinical parameters (mortality, admission to intensive care unit (ICU), intubation) of all patients were recorded from electronic medical records. All patients with COVID-19 were defined as mild-moderate and severe according to criteria of the WHO. Treatment options were assessed in line with the clinical severity definition according to the WHO and Turkish Health Ministry treatment recommendations.^{6,7}

Laboratory parameters including complete blood count, biochemical tests (fasting plasma glucose, glycated hemoglobin (HbA1c), kidney and liver function tests, lactate dehydrogenase, albumin, ferritin, high-sensitive troponin T, D-dimer, and lipid profiles), procalcitonin, and C reactive protein were used. In our study, a semiquantitative CT severity scoring recommended by the Radiological Society of North America was used.⁸ Considering the severity of radiologic involvement, the score was calculated separately for 6 lung zones as follows: 1, <0%–25% involvement; 2,

25–50% involvement; 3, 50–75% involvement; 4, 75–100% involvement. The overall CT score was calculated as the sum of the individual zonal scores, and the maximum score was 24. A score of 1–6 represents mild radiological involvement, 7–11 represents moderate radiological involvement and >12 represents severe radiological involvement. Patients were divided into four categories based on initial laboratory measurement and history of diabetes at hospitalization: normal glucose (patients with fasting glucose levels below 100 mg/dL), IFG (patients with glucose levels between 100 mg/dL and 125 mg/dL), newly diagnosed DM (patients presenting with fasting glucose \geq 126 mg/dL and no previous diagnosis of DM) and pre-existing DM (previously diagnosed with fasting glucose \geq 126 mg/dL or use of antidiabetic medication).

Statistical analysis

Continuous data are expressed as mean \pm SD. Count data are reported as frequencies and percentages. Pearson's χ^2 or the Fisher's exact test was used to determine differences for categorical variables (demographics, history of diseases, clinical symptoms, and treatment and clinical outcomes), and a general linear model was used to determine differences for continuous variables (eg, laboratory measurements). All variables were adjusted for age and sex. Logistic regression was used to estimate HRs for admission to the ICU among patients with different glucose statuses (normal glucose, IFG, newly diagnosed diabetes, and pre-existing diabetes). Three models were used: model 1 adjusted for age and sex; model 2 adjusted for variables in model 1 as well as admission to the ICU, using antihypertensive medications, and using lipid-lowering agents; model 3 adjusted for variables in model 2, as well as using glucose-lowering drugs before hospital admission and during hospitalization, and using corticosteroids. The SPSS statistics V.24.0 software package (IBM) was used for statistical analysis of the data. Two-sided $p < 0.05$ was considered statistically significant.

RESULTS

Demographics, symptoms, laboratory, and radiologic characteristics of patients with COVID-19 with different glucose categories

In this study, a total of 236 patients were included, including 43 patients with normal glucose, 53 with IFG, 60 with newly diagnosed diabetes, and 80 with DM, according to the diagnosis and classification of DM. The general characteristics, laboratory findings and the severity of thorax CT findings of the study population are shown in table 1. Patients with pre-existing diabetes, newly diagnosed diabetes, and normal glucose were slightly older compared with patients with IFG ($p=0.018$). The mean diastolic blood pressure of patients with newly diagnosed diabetes was statistically higher than the groups with pre-existing DM, normal glucose, and IFG ($p=0.016$) (table 1). The laboratory and radiologic findings of the patients with COVID-19 are presented in table 1. Patients with known DM had higher fasting glucose and HbA1c values than the other groups ($p < 0.001$ for all). In patients with newly diagnosed DM, the alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were statistically significantly higher than in the other groups ($p=0.015$ and $p=0.049$, respectively). Patients with

Table 1 Clinical, laboratory and thorax CT findings of patients with COVID-19 infection according to presence of pre-existing DM, new-onset DM or impaired fasting glucose

	Normal FBG n=43	Impaired FBG n=53	New-onset DM n=60	Pre-existing DM n=80	P value
Age, y	63.02±2.39	57.87±2.21	62.12±2.14	66.33±1.30	0.018
Male, n (%)	25 (58.1)	34 (64.2)	36 (60.0)	42 (52.5)	0.590
BMI, kg/m ²	27.57±4.10	26.95±3.35	27.90±4.09	27.55±3.88	0.847
SBP (mm Hg)	120.70±14.37	116.79±14.2	121.20±13.82	120.76±11.52	0.157
DBP (mm Hg)	70.70±8.83	70.85±7.83	74.53±7.45	72.85±7.06	0.016
Laboratory findings, n (%)					
FBG, mg/dL	88.19±7.37	111.51±7.63	171.95±48.85	213.00±99.65	<0.001
HbA1c, %	5.52±0.40	5.66±0.46	6.64±1.29	8.40±2.32	<0.001
Creatinine (mg/dL)	1.29±1.42	1.08±0.63	1.04±0.72	1.39±1.42	0.258
AST, U/L	34.77±21.35	38.57±26.69	55.13±54.95	37.06±22.80	0.015
ALT, U/L	25.02±17.54	35.42±27.92	46.87±50.93	34.26±32.7	0.049
LDH (U/L)	337.17±155.97	350.45±156.09	376.29±171.09	334.01±140.12	0.437
Albumin (g/dL)	33.88±8.20	34.12±5.98	35.37±4.74	34.49±4.52	0.323
Ferritin (ng/mL)	658.70±743.32	799.66±651.42	801.18±695.14	666.15±664.78	0.870
Procalcitonin (µg/L)	6.05±36.23	1.24±5.12	1.08±6.01	0.40±1.04	0.141
CRP, mg/L	72.30±59.28	108.67±78.77	110.44±78.12	95.85±81.76	0.084
Hs-TnT (ng/mL)	0.02±0.02	0.03±0.05	0.03±0.05	0.03±0.05	0.418
Hemoglobin, g/dL	12.28±2.15	12.42±2.25	12.87±2.27	12.29±1.86	0.576
Platelets ×10 ⁹ /L	234.09±108.32	203.02±86.05	214.43±99.49	264.24±124.01	0.004
WBC, ×10 ⁹ /L	8.18±4.01	7.43±3.61	7.69±4.13	8.49±4.64	0.542
Lymphocyte, ×10 ⁹ /L	1.29±0.97	1.05±0.64	0.95±0.62	1.11±0.70	0.102
D-dimer, ng/mL	2210.12±3392.35	1333.04±1167.63	1434.58±1586.33	1656.45±2504.06	0.245
T. cholesterol, mg/dL	157.46±40.71	158.64±58.36	176.10±69.11	178.71±58.38	0.162
LDL-C, mg/dL	123.37±64.78	119.64±65.44	147.30±76.55	180.68±179.21	0.040
HDL-C, mg/dL	69.28±40.08	84.27±47.52	72.83±46.09	75.50±42.82	0.886
TG, mg/dL	67.81±64.75	55.66±51.89	83.43±88.95	72.48±77.02	0.567
Thorax CT findings, n (%)					
Low	13 (33.3)	7 (14.6)	14 (25.0)	20 (27.0)	0.090
Medium	14 (35.9)	22 (45.8)	16 (28.6)	17 (23.0)	0.090
Severe	12 (39.8)	19 (39.6)	26 (46.4)	37 (50.0)	0.090

Statistical significance: p<0.05.
 ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CRP, C reactive protein; DBP, diastolic blood pressure; DM, diabetes mellitus; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; hs-TnT, high-sensitive troponin T; LDH, lactate dehydrogenase; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; T. cholesterol, total cholesterol; TG, triglycerides; WBC, white blood cell.

pre-existing DM had higher platelet and low-density lipoprotein levels than patients with normal glucose, IFG, and newly diagnosed DM ($p=0.004$ and $p=0.040$, respectively). There was no statistically significant difference between the groups in terms of severity of radiological involvement ($p=0.09$) (table 1).

Comorbidities and medications were demonstrated in table 2. The incidences of coronary artery disease and hypertension in patients with pre-existing DM were statistically different compared with the other groups ($p=0.037$ and $p<0.001$, respectively). The frequency of chronic kidney disease in patients with normal glucose levels was statistically higher than in the other groups ($p=0.006$). The use of antidiabetic drugs was only available in patients with known diabetes. The most commonly used antihypertensive drugs in patients with DM were calcium channel blockers ($p=0.01$). The frequency of those receiving statin therapy was statistically significantly higher in the group with pre-existing DM than in the other groups ($p=0.033$). There was

no use of warfarin in patients with newly diagnosed DM and pre-existing DM (table 2).

Treatments and outcomes of patients with COVID-19 with different glucose categories

In patients with newly diagnosed DM, the number of those who received favipiravir treatment was statistically significantly higher than in the other groups ($p=0.027$). Patients with newly diagnosed DM were more likely to need dexamethasone 6 mg ($p=0.001$). In both newly diagnosed diabetes and IFG groups, 250 mg methylprednisolone was needed at higher rates than the other groups ($p=0.002$). Newly diagnosed DM had higher rates of intubation (21.60%) and had more mortality (20.0%) ($p=0.045$ and $p=0.028$, respectively) (table 3). When we further compare the clinical outcomes of pre-existing DM and new-onset DM group, we observed lower intubation and mortality rates in pre-existing diabetes ($p=0.007$ and $p=0.016$, respectively)

Table 2 Distribution of comorbidities and pre-existing medications of patients with COVID-19

	Normal FG n=43		IFG n=53		New-onset DM n=60		Pre-existing DM n=80		P value
	n	%	n	%	n	%	n	%	
Comorbidities									
CAD	8	18.60	9	17.00	13	21.70	29	36.30	0.037
Respiratory disease	7	16.30	6	11.30	3	5.00	8	10.00	0.294
Hyperlipidemia	1	2.30	2	3.80	6	10.00	11	13.80	0.061
CKD	9	20.90	8	15.10	1	1.70	10	12.50	0.006
Thyroid disease	6	14.00	6	11.30	3	5.00	7	8.80	0.424
Malignancies	3	7.00	4	7.50	5	8.30	5	6.30	0.972
Neurologic disease	9	20.90	6	11.30	8	13.30	6	7.50	0.188
Hypertension	20	46.50	22	41.50	25	41.70	65	81.30	<0.001
Drug usage									
Beta-blockers	4	9.30	6	11.30	5	8.30	21	26.00	0.60
ACE inhibitors	4	9.30	7	13.20	9	15.00	14	17.50	0.640
ARB	7	16.30	10	18.90	7	11.70	16	20.00	0.580
CCB	9	20.90	8	15.10	3	5.00	21	26.30	0.010
Alpha-blockers	2	4.70	2	3.80	0	0	4	5.00	0.179
Thiazides	0	0	1	1.90	1	1.70	4	5.00	0.256
Furosemide	3	7.00	1	1.90	3	5.00	5	6.30	0.580
Metformin	0	0	0	0	0	0	34	43.0	<0.001
Pioglitazone	0	0	0	0	0	0	2	2.50	<0.001
Sulfonylurea	0	0	0	0	0	0	10	12.5	<0.001
DPP4 inhibitors	0	0	0	0	0	0	12	15.0	<0.001
SGLT2 inhibitors	0	0	0	0	0	0	6	7.5	<0.001
Insulin	0	0	0	0	0	0	23	28.8	<0.001
Statins	2	4.7	0	0	4	6.7	8	10.1	0.033
L-thyroxine	1	2.3	2	3.8	0	0	2	2.5	0.362
Clopidogrel	0	0.0	3	5.7	2	3.3	4	5.0	0.251
NOAC	2	4.7	0	0	1	1.7	6	7.5	0.058
Warfarin	1	2.3	3	5.7	0	0	0	0	0.046

Statistical significance: $p < 0.05$.
 ARB, angiotensin receptor blocker; CAD, coronary artery disease; CCB, calcium channel blocker; CKD, chronic kidney disease; DM, diabetes mellitus; DPP4, dipeptidyl peptidase 4; FG, fasting glucose; IFG, impaired fasting glucose; NOAC, new oral anticoagulant; SGLT2, sodium glucose co-transporter-2.

(online supplemental file 1)online supplemental table 1. The frequencies of mortality and ICU admission rates were lower in the group receiving antidiabetic treatment ($p=0.05$ and $p=0.045$, respectively) (table 4).

Risk rates of hospitalization in the ICU of patients with COVID-19 by different glucose categories

After adjusting for age, sex, antihypertensive drug use, anti-lipid drug use, and intubation, the risk of hospitalization in

Table 3 Distribution of patients with COVID-19 infection according to medication

	Normal FG n=43	IFG n=53	New-onset DM n=60	Pre-existing DM n=80	P value
Medication, n (%)					
Favipiravir	41 (95.3)	53 (100.0)	58 (96.7)	72 (90.0)	0.027
Plaquenil	8 (18.6)	9 (17.0)	10 (16.7)	17 (21.3)	0.895
Colchicine	12 (27.9)	24 (45.3)	23 (38.3)	22 (27.5)	0.129
Enoxaparin	39 (90.7)	51 (96.2)	58 (96.7)	70 (87.5)	0.123
Dexamethasone 6 mg	29 (67.4)	48 (90.6)	56 (93.3)	62 (77.5)	0.001
Pulse 250 mg methylprednisolone	7 (16.3)	22 (41.5)	25 (41.7)	16 (20.0)	0.002
Antibiotic	16 (38.1)	25 (47.2)	28 (46.7)	34 (42.5)	0.787
Clinical outcome, n (%)					
Mortality	5 (12.5)	5 (9.6)	12 (20.0)	4 (5.4)	0.045
ICU admittance	5 (11.6)	8 (15.1)	12 (20.0)	6 (7.5)	0.078
Intubation	4 (10.0)	6 (11.3)	13 (21.6)	4 (5.4)	0.028

Statistical significance: $p < 0.05$.
 DM, diabetes mellitus; FG, fasting glucose; ICU, intensive care unit; IFG, impaired fasting glucose.

Table 4 Association of antidiabetic drug use with mortality and intubation in COVID-19 in pre-existing diabetes

	Antidiabetic drug usage		P value
	Presence n=6	Absence n=47	
Mortality, n (%)	3 (4.9)	23 (14.1)	0.050
Intubation, n (%)	3 (4.9)	24 (14.7)	0.045

Statistical significance: $p < 0.05$.

the ICU was increased in patients with IFG (HR=1.71, 95% CI: 0.48 to 6.08) and newly diagnosed DM (HR=1.88, 95% CI: 0.57 to 6.17), compared with patients with normal glucose (model 2). The situation did not change after adjusting for age, sex, antihypertensive treatment, antidiabetic treatment, anti-lipid treatment, corticosteroid use, and intubation (model 3) (table 5).

DISCUSSION

The main result of our study was that mortality and intubation rates in patients hospitalized with COVID-19 were significantly higher in patients with newly diagnosed diabetes and those with IFG than in the non-diabetic group. In the data from China at the beginning of the pandemic, it was reported that a mortal course due to COVID-19 was associated with one or more comorbid conditions. In these studies, it was reported that the increase in pandemic-related mortality in patients with diabetes was 2–4 times higher.^{9 10} The existence of the same relationship was confirmed in many publications.^{11 12} On the other hand, surprising results were obtained in some large studies on DM. In the multicenter Coronavirus SARS-CoV-2 and Diabetes Outcomes (CORONADO) Study conducted in France, a relationship was shown between disease prognosis and glucose levels at the onset of the disease, but not past glucose levels.¹³ Again, recent studies showed that fasting blood glucose at presentation was an independent predictor of critical illness,¹⁴ death,¹⁵ or poor outcome in patients hospitalized with COVID-19, regardless of a previous diagnosis of DM. In the study of Alonso *et al* from Mexico, in which the records of 1,280,806 patients with COVID-19 were evaluated, the prevalence of DM was found as 12.97%. It has been reported that the prognosis is worse in patients with type 2

DM who have metabolic syndrome (MetS) components at the onset of the COVID-19 infection.¹⁶

The mechanisms that worsen the clinical course of COVID-19 are thought to be activation of the renin-angiotensin system (RAS), systemic inflammation, and hypercoagulability. It is thought that insulin resistance, which forms the basis of MetS, plays a triggering role in the proinflammatory and procoagulant processes.¹⁷ In line with this information, we can attribute the more severe clinical course of infection in patients with newly diagnosed diabetes in our study to the fact that the patients had not yet received antidiabetic treatment and those pathologic mechanisms were active due to high insulin resistance. Although many studies are investigating the relationship between COVID-19 and DM, insufficient publications are addressing the relationship between patients with pre-diabetes and IFG. In a multicenter retrospective cohort study, Zhang *et al* investigated the relationship between disease mortality and newly diagnosed DM and IFG at the time of hospitalization in 312 patients with COVID-19 hospitalized in 5 hospitals in Wuhan between January 1 and March 17, 2020.¹⁸ Compared with patients with normal fasting glucose, more mechanical ventilation (5 (3%), 6 (10%), 21 (25%)), and more mortality (4 (2%), 9 (15%)), 20 (24%)) were reported in patients with IFG and in patients with DM. Supporting the results of our study, Zhu *et al* showed the relationship between good glycemic control and lower mortality in patients with COVID-19.¹⁹ Wu *et al* showed a relationship between the presence of DM and the development of acute respiratory distress syndrome in a study on 201 patients in Wuhan.²⁰

The relationship between hyperglycemia and poor prognosis in the course of COVID-19 has not yet been clarified. There may be a bidirectional relationship between hyperglycemia and COVID-19 whereby COVID-19 can precipitate hyperglycemia and the presence of hyperglycemia may worsen the severity of COVID-19.^{21 22} As for other reasons, impaired immune response, a procoagulant state, the increased inflammatory process, and metabolic disorders are thought to play a role in patients with diabetes or patients with IFG.^{23–25} Hyperglycemia and DM, being riskier in terms of coinfection and sepsis, may also be a factor that negatively affects prognosis. Suppression of cytokine production, defects in phagocytosis, and dysfunction of immune cells are shown as causes of susceptibility to

Table 5 The risk of ICU attendance of patients with COVID-19 infection according to presence of DM and IFG

	Normal FG n=40			IFG n=53			New-onset DM n=57			Pre-existing DM n=73		
	5	Lower limit	Upper limit	8	Lower limit	Upper limit	12	Lower limit	Upper limit	6	Lower limit	Upper limit
ICU attendance	HR			HR			HR			HR		
Model 1	1.00	1.00	1.00	1.555	0.451	5.364	1.948	0.609	6.229	0.461	0.123	1.732
Model 2	1.00	1.00	1.00	1.710	0.480	6.087	1.882	0.573	6.174	0.469	0.122	1.801
Model 3	1.00	1.00	1.00	1.715	0.481	6.112	1.962	0.596	6.457	0.469	0.122	1.799

Model 1: evaluation by age and gender.

Model 2: evaluation according to age, gender, use of antihypertensive and lipid-lowering drug and intubation status.

Model 3: evaluation according to age, gender, use of antihypertensive, lipid-lowering drug and corticosteroid and intubation status.

DM, diabetes mellitus; FG, fasting glucose; ICU, intensive care unit; IFG, impaired fasting glucose.

infection in patients with diabetes.²⁶ Limited data suggested a link between COVID-19 and endocrine status. It was hypothesized that stress during severe COVID-19 leads to hypothalamic–pituitary axis activation and as a result elevates serum cortisol secretion.²⁷ On the other hand, comorbidities such as hypertension, obesity, cardiovascular causes, and kidney damage accompanying diabetes may be associated with the composite endpoints and mortality in COVID-19.

In our study, when the patients who did and did not receive antidiabetic treatment were compared, the mortality of the group that received treatment was found to be significantly lower. When compared in terms of intubation, we found a significantly decreased rate of intubation in the group that received antidiabetic treatment. This result suggested that patients who had COVID-19 while under treatment for DM had a better prognosis than those whose diabetes was newly diagnosed and did not use medication. Considering that the use of aspirin, statins, and RAS blockers in conjunction with the treatment of DM is more common, these drugs may have positive effects on the endothelium, as well as their anti-inflammatory and antithrombotic effects. Further analysis of clinical outcomes between patients with new-onset DM and pre-existing DM in the current study revealed that mortality and intubation rates were higher in patients with new-onset DM despite lower HbA1c values. Recent studies reported that newly diagnosed DM was associated with poor outcome in COVID-19 when compared with pre-existing diabetes or no diabetes.^{28 29} In the case of pre-diabetes and newly diagnosed diabetes, glycemic variability becomes greater and more frequent, irrespective of HbA1c. Glycemic oscillations play an important role in endothelial dysfunction which further induces cytokine production.³⁰ The most important finding of our study was that patients with newly diagnosed diabetes had a worse prognosis than patients in the other groups. After the influenza pandemic, it was previously hypothesized that glycemic variability augments the severity of influenza through effecting pulmonary endothelial cells.³¹ Similarly, glycemic variability in patients with newly diagnosed DM may contribute to severity of COVID-19 pneumonia. On the other hand, the age of the patients, the delayed diagnosis of DM, and the presence of comorbid diseases may play a role in this result. In our study, the rates of use of favipiravir, dexamethasone, and pulse steroid treatment were found to be higher in patients with newly diagnosed DM compared with the other groups. When evaluated in terms of drug groups, more antiviral and steroids were used in patients with newly diagnosed diabetes, which was attributed to the more severe clinical course of this group.

The mean values of ALT and AST in patients with newly diagnosed DM were statistically significantly higher than in the other groups. The prognostic value of abnormal liver function tests in COVID-19 is not well known. Recently, it was found that high AST and ALT values were associated with increased disease severity and mortality.^{32–35} The underlying mechanism of elevated liver function tests in COVID-19 infection is thought to be related to hyper-inflammatory state and thrombotic microangiopathy.³² In our study, in addition to potential causes of elevated liver enzymes, such as fatty liver and medications, the

hyperinflammatory state may contribute to the elevation of ALT and AST in patients with newly diagnosed DM.

The higher mean diastolic blood pressure of patients with newly diagnosed diabetes may be related to the worse prognosis in this group. Consistent with the results of our study, many studies showed that hypertension was a poor prognosis criterion in the course of COVID-19.^{36 37}

This is a pilot study for hospitalized patients for COVID-19 pneumonia. The results cannot be generalized due to single-centered and retrospective design of the study. The second important limitation was that there were treatment changes between the periods of the pandemic. Treatment protocol differences such as the fact that hydroxychloroquine was used in the first wave but was not preferred in the third wave, that favipiravir was started very early in the second wave, and that steroids were used more intensively in the third wave also affected the treatment of patients with DM. In previous studies, new hyperglycemia has been observed in patients treated with prednisolone in 14% of general medical admissions even in a short period of time.^{38 39} However, it must be noted that both plasma glucose levels and other laboratory investigations were recorded on admission. Therefore, plasma glucose values of our patients were not affected by treatment with glucocorticoids. Third, the groups we defined as IFG and newly diagnosed DM were formed after patients were already infected, thus perhaps not reflecting baseline pre-infection blood glucose concentrations. Nevertheless, the prominent features of our study are that few studies in the literature have compared these four groups, the patient population consists of patients who were followed with a similar treatment approach, and that all patients were inpatients with COVID-19 pneumonia.

CONCLUSION

We showed that newly diagnosed DM was associated with increased mortality and intubation rates in COVID-19 pneumonia. In addition, we found that patients with pre-existing diabetes who used antidiabetic therapy had less ICU admissions and mortality due to COVID-19 pneumonia. Our study is important in terms of showing the positive results of an early diagnosis of DM and early initiation of antidiabetic treatment. Similar studies with a larger number of patients followed up with the same treatment protocol for the same period of the pandemic will help us better understand this issue.

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ORCID iDs

Banu Boyuk <http://orcid.org/0000-0001-7794-4411>

Hande Erman <http://orcid.org/0000-0001-7213-9624>

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