RESEARCH ARTICLE
Eurasian J Bio Chem Sci, 5(2):69-76, 2022
https://doi.org/10.46239/ejbcs.1114089

EJBCS

Eurasian Journal of Biological and Chemical Sciences

Journal homepage: www.dergipark.org.tr/ejbcs

Biochemical laboratory findings on COVID-19 patients: pathogen-disease relationship

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Received : 09/05/2022
Accepted : 15/06/2022

Abstract: The COVID-19 process, which started in Wuhan, China, is one of the most significant viral diseases characterized by high mortality and catching millions of people around the world since it appears. In this study, a total of 189 patients, 85 outpatients, and 104 inpatients were diagnosed with COVID-19 with positive PCR tests examined, admitted to the COVID 1-2-3 services of the Faculty of Medicine of Kafkas University between November 1 and November 16, 2020, has been examined. The relationship between laboratory findings and pathogen disease in the diagnosis, treatment and course of the disease has been tried to be revealed. The majority of patients with fever, reflux diabetes and tumours are over the age of 65 (61.7%), and 68 (36.2%) of them are women and 120 (63.8%) are men. Demographic characteristics of the patients, biochemical parameters such as serum ferritin, iron, troponin T, D-dimer levels, and hemogram and coagulation results were evaluated. Findings will contribute to clinicians and biochemists about the prognosis and mortality of COVID-19, its course in some other diseases, and the ways to be followed in treatment.

Keywords: COVID-19, biochemical parameters, chronic diseases.

COVID-19 hastalarında biyokimyasal laboratuvar bulguları: patojen ve hastalık ilişkisi

Özet: Çin'in Wuhan kentinde başlayan COVID-19 süreci; ortaya çıkışından bu yana dünya üzerinde milyonlarca insanın yakalandığı ve yüksek mortalite ile karakterize edilen en önemli viral hastalıklarının başında yer almaktadır.1-16 Kasım 2020 zaman aralığında Kafkas Üniversitesi Tıp Fakültesi Covid 1-2-3 servislerine başvuran PCR testleri pozitif çıkan Covid-19 tanısı almış ayakta tedavi edilen 85, yatarak tedavi edilen 104 hasta olmak üzere 189 hasta alındı. Hastalığın tanı, tedavi ve seyrinde laboratuvar bulgularının patojen hastalık ilişkisi ortaya konmaya çalışıldı. Araştırmada ateş, reflü, diyabet ve tümörlü hastaların büyük çoğunluğunu 65 yaşın üzerinde (%61.7) olup bunların 68 (%36.2)'i kadın, 120 (%63.8)'si erkekti. Hastaların demografik özellikleri, serum ferritin, demir, troponin T, D-dimer düzeyleri gibi biyokimyasal parametreler ile hemogram ve koagülasyon sonuçları değerlendirildi. Bulgular; Covid-19'un prognozu ve mortalitesi ve diğer bazı hastalıklardaki seyri hakkında klinisyenlere ve biyokimyacılara tedavide izlenecek yollarda katkı sağlayacaktır.

Anahtar Kelimeler: Covid-19, biokimyasal parametreler, kronik hastalıklar.

1. Introduction

Coronaviruses causing COVID-19 are of the Orthocoronavirinae subfamily in the Coronaviridae family. They are enveloped (zoonotic) RNA viruses that can infect humans and a wide variety of animal species (Mac-Lachlan and Dubovi 2017). They are included in the same virus family as SARS CoV and MERS CoV. The subtypes circulating in humans (HCoV-229E, HCoV-OC43, HCoV-NL63 and HKU1-CoV) constitute a large virus family that mostly causes the common cold (Inal 2016). SARS-CoV-2 shares 79.6% of its genome sequences with SARS-CoV. Thanks to the spike (S) glycoprotein encoded, both viruses enter the host cell by binding to the transmembrane serine protease (TMPRSS) and ACE2 (angiotensin converting enzyme (Inal 2016) receptors released from the host cell

membrane. Once inside the cell, SARS-CoV-2 causes cellular death and injury in the airway epithelial cells through various processes such as pyroptosis. Increased proteases and reactive oxygen species cause further damage and hyperinflammation (Lu 2020; Lan et al. 2020). SARSCoV-2 has been found to show quite high affinity to the ACE2 receptor. Several organs and especially the lung possess ACE2 receptors on cell surfaces (Xu et al. 2020). The new type of coronavirus has been shown to bind to the ACE2 receptor ten times more strongly (Qi et al. 2020; Kappert et al. 2020).

Many studies have been conducted to identify the predictors of laboratory findings related to the course of the disease since the start of the coronavirus disease pandemic in 2019. The oxygen level decreases due to the virus-related alveolar collapse in most of the studies, but the condition advances with shortness of breath since CO2 exchange continues (Dreher et al. 2020; Kappert) et al. 2020; Wang. Et al.2020) In other words, all tissues and organs, and especially the lung, are affected by the pathogen. In addition to the physiological, clinical, hematological and homeostasis-related findings, biochemical parameters also provide partial but important information about the course of the disease in order to determine the pathogen's effects. These chemical markers not only reflect the severity of the disease, but also shed light on the prognosis and the pathological mechanisms.

The elevation of proinflammatory cytokines in the disease indicates that the serum concentration acute phase proteins are the cause of the increased CRP in particular (Ruan et al 2020; Banerjee et al. 2020)). while high ferritin levels indicate advanced disease and increased mortality (Chan et al. 2020; Guo et al. 2020). Cardiovascular disease (CVD), diabetes mellitus type 2 (DMT2), hypertension, malignancy and chronic obstructive pulmonary disease (COPD) can be present among Covid-19 patients. This is due to the fact that there may be oxidative species (ROS) formed during reactive release with an imbalance in the endogenous antioxidant capacity (Wang et al. 2010). However, increased coagulation abnormalities and a high incidence of thrombotic events together with changes in the activated partial thromboplastin time (aPTT) and prothrombin time, increased D-dimer levels, and thrombocytopenia have been found in these patients (Yılmaz and Eren 2020).

One of the most striking laboratory results in COVID-19 is high serum ferritin levels. Understanding how iron metabolism and viral infection interact may be important in developing new methods of keeping the disease under control. The extracellular iron found in normal healthy lungs is reported to cause oxidative damage and make the organism particularly vulnerable to viral infections (Memikoğlu and Genç 2021). COVID-19 has been reported to potentially cause long-term and progressive hypoxia by binding to the heme groups in the hemoglobin in erythrocytes, in addition to multi-organ damage by decreasing the oxygen saturation (Khot and Nadkar 2020).

The iron-related severe fatigue seen in the patients at the onset and later stages of COVID-19 can be considered a hypoxic state due to the decrease in oxygen. Biochemical examinations of 99 patients with coronavirus have revealed a significant increase in serum ferritin, erythrocyte sedimentation rate, C-reactive protein, albumin, and lactate dehydrogenase index values, while most of the hemoglobin and neutrophil counts were decreased. This clinical picture indicates that the pneumonia is associated with hemoglobin (Guo et al. 2020). The aim of this study was to understand how the iron metabolism and viral infection interact, in order to possibly guide the development of other studies and new methods, take the disease under control, and make new recommendations. A total of 189 patients with positive COVID-19 PCR tests were included in the study. These patients' demographic characteristics, laboratory values, and the relationship of the pathogen with oxygen and iron were investigated. Based on these data, we tried to determine whether there was a significant relationship between the biochemical values of the patients and compensation, and whether these parameters could be used as prognostic indicators.

2. Materials and Method

The records of 189 patients attending the Kafkas University Faculty of Medicine Research Hospital's COVID department and intensive care unit during the 1-16 November, 2020 period were retrospectively reviewed. Taking the WHO guidelines into account, patients diagnosed with SARS-CoV-2 RNA with the polymerase chain reaction (PCR) test were included in the study with a diagnosis of COVID-19, regardless of whether they had symptoms or not. The study was conducted according to the Helsinki Declaration. Approval for the study was obtained from the Kafkas University Faculty of Medicine's Non-Interventional Research Ethics Committee, dated April 04, 2021 and numbered 80576354-050-991/62. The patients were divided into two groups as inpatients and outpatients. Thorax CT and a PCR test were performed in every patient. The patients who were positive and whose vital functions had been adversely affected by the COVID-19 symptoms were hospitalized and COVID-19 treatment was started. Asymptomatic patients who were diagnosed with COVID-19 and did not have direct chest x-ray or lung tomography images and also did not have pneumonia were followed up as outpatients.

Roche Cobas C501 brand device with urea (kinetic test, ureaz and glutamate dehydrogenase), creatinine (Jaffe method), lactate dehydrogenase(LDH), aspartate aminotransferase(AST), alanine aminotransferase (ALT) (absorbance), gamma glutamyltransferase(GGT) (enzymatic colorimetric), alkaline phosphatase(ALP) (colorimetric), bilirubin (diazo method), CK, Ca, Mg, P, Hb (photometric), albumin, D-dimer (immunoturbidimetric), C-reactive protein(CRP) (turbidimetric), Na, Cl (ion selective electrode (ISE)), ferritin (electrochemiluminescence), troponin (electrochemiluminescence). Coagulation markers were measured with the Ceveron Alpha device, using the activated partial thromboplastin time(APTT), prothrombin time(PT): clotting test method. Hemogram was performed

with Abxpentra Dx 120 and leukocytes, red blood cell (RBC) and defined platelet(PLT) with double hydrodynamic sequential system (DHSS) cytometry, impedance and absorbance methods.

2.1. Statistical Analysis

The descriptive data (mean, standard deviation, minimum, maximum, percentage) of the variables were calculated. The Mann-Whitney U test was used for two independent groups and the Kruskal-Wallis test for more than two independent groups as the nonparametric test for the intragroup comparison of the parameters not showing a normal distribution. A confidence interval of 95% and a statistical significance level of $p<0.05$ were used.

3. Results

A total of 189 patients diagnosed with COVID-19, including 85 outpatients and 104 inpatients were included in the study. Most of the patients (61.7%) were aged over 65 years; 68 (36.2%) were female and 120 (63.8%) were male (Table 1).

Table 1. Demographic characteristics of patients

Variable			
Age	35-49 years	35 - 49 years	50 - 64 years
Number(n)	23	14	49
Percentage (%)	12.2	7.4	26.1
Gender			Total
Famale	68	121	189
Male	36.2	63.8	100.0

Table 2. Chronic disease distribution of patients

Variable	**None**	**Present**	**Total**		**None**	**Present**	**Total**
Tumor				**Cough**			
Number	182	6	188	Number	116	72	188
Precentage(%)	96.8	3.2	100.0	Precentage(%)	61.7	38.3	100.0
Dabet				**Fever**			
Number	152	36	188	Number	185	3	188
Precentage(%)	80.9	19.1	100.0	Precentage(%)	98.4	1.6	100
HT				**KH**			
Number	147	39	186	Number	165	23	188
Precentage(%)	79.0	21.0	100.0	Precentage(%)	87.8	12.2	100.0
Variable	None	Present	Total		None	Present	Total
Tumor				**Cough**			

A tumor was present in 3.2% 0f the patients in 19.1% HT in 21.0%, cardiac failure in 12.2% symptoms consistent with gastrointestinal reflux in 18.6%, acough in 38.3% and fever (above 37.4 degrees 0C) in 1.6% (Table 2). The blood biochemical parameters, hemogram and coagulation results evaluated in the study are given in Table 3 and 4.

Table 3 Biochemical laboratory results

Variable	**n**	**Mean**	**Sd**	**Median**	**Min**	**Max**
Albumin	12	4.09	0.77	4.09	2.83	5.59
Urea	184	44.48	23.18	39.00	0.89	152.00
Creatinine	182	1.05	0.77	0.92	0.38	10.07
ALP	112	85.71	28.61	80.00	40.00	192.00
ALT	184	31.79	45.87	21.00	5.00	526.00
AST	184	32.23	26.13	26.00	11.00	213.00
D-bilirubin	181	0.22	0.28	0.16	0.00	2.40
GGT	135	45.99	52.82	31.00	6.00	440.00
LDH	178	299.97	114.28	273.00	108.00	814.00
CK	170	110.53	109.59	75.50	0.50	855.00
LDH	178	299.97	114.28	273.00	108.00	814.00
Ca	178	9.05	0.67	9.00	7.20	12.50
Mg	16	1.88	0.35	1.91	1.09	2.54
P	30	3.99	0.65	4.19	2.06	5.09
Na	185	135.58	13.62	137.00	9.80	154.00
Cl	175	101.36	11.26	102.20	4.31	117.70

Table 4. Hemogram and coagulations tests

Variable	n	Mean	Sd	Median	Min	Max
RBC	184	5.02	0.59	5.02	3.49	6.90
WBC	184	5.97	2.69	5.25	2.10	20.50
HGB	184	14.68	1.76	14.70	9.60	19.30
HCT	184	43.56	4.98	43.60	30.90	60.70
MCV	184	86.98	5.97	87.00	65.00	107.00
MCH	184	29.28	2.51	29.30	19.90	38.60
MCHC	184	33.64	1.49	33.60	28.50	36.70
RDV	184	14.41	1.95	14.00	4.00	22.40
Hb	184	14.68	1.76	14.70	9.60	19.30
NEU	183	4.61	6.48	3.20	1.00	58.00
LYM	184	1.95	3.65	1.30	0.37	34.10
MON	183	0.86	1.64	0.50	0.10	12.10
BAS	106	0.06	0.17	0.02	0.00	1.60
EOS	147	0.13	0.33	0.10	0.00	3.70
NEU%	182	60.99	12.38	62.75	0.00	89.30
PLT	184	210.92	96.27	198.00	13.80	602.00
PDW	184	23.15	35.50	16.00	10.00	236.00
Activated PTT	175	34.71	19.15	31.40	12.00	262.20
Ferritin	175	384.23	331.27	296.20	6.01	2000.00
D-Dimer	81	2309.95	4179.33	736.00	205.00	18800.00
PT(SN)	176	12.75	3.69	12.20	1.01	40.90

Table 5. Relationship between fever, reflu, diabetes and tumor laboratory findings

		Temperature				Reflux				Diabetes				Tumor			
		None		Present		None		Present		None		Present		None		Present	
Parameters		Hospitalization	Discharged	Hospitalization	Discharged	Hospitalization	Discharged	Hospitalization	Discharged	Hospitalization	Discharged	Hospitalization	Discharged	Hospitalization	Discharged	Hospitalization	Discharged
CRP	r	.203*	.152*	0.87	1.000	.246*	.226*	0.07	-0.005	.250*	.187*	-0.03	0.01	.261*	.202*	-0,68	-0.41
	p	0.01	0.05	0.33	N/A	0.00	0.01	0.69	0.98	0.00	0.03	0.86	0.94	0.00	0.01	0.14	0.42
Ferritin	r	0.03	0.02	-0.87	-0.50	0.06	0.08	-0.09	-0.19	0.07	0.03	-0.09	0.07	0.05	0.05	-0.72	-0.76
	p	0.70	0.75	0.33	0.67	0.46	0.34	0.62	0.30	0.39	0.76	0.62	0.70	0.49	0.53	0.11	0.08
D-Dimer	r	0.18	0.17	N/A	N/A	0.18	0.17	0.15	0.06	0.20	0.22	0.04	-0.20	0.13	0.13	0.87	0.87
	p	0.11	0.13	N/A	N/A	0.15	0.17	0.62	0.84	0.11	0.07	0.90	0.54	0.25	0.26	0.33	0.33
WBC	r	0.09	0.10	0.00	-0.50	0.07	0.10	0.14	0.10	0.09	0.12	0.01	-0.04	0.11	0.12	-0.48	-0.53
	p	0.24	0.18	1.00	0.67	0.42	0.22	0.42	0.56	0.29	0.15	0.94	0.84	0.13	0.11	0.34	0.28
RBC	r	-.181*	-0.14	0,00	0.50	-.212*	-.170*	-0.03	0.05	-.177*	-0.09	-0.18	-0.30	-.186*	-0.14	0.09	-0.20
	p	0.02	0.07	1.00	0.67	0.01	0.04	0.89	0.78	0.03	0.27	0.30	0.09	0.01	0.07	0.87	0.70
HGB	r	-0.14	-0.06	-0.87	-0.50	-.164*	-0.08	-0.07	-0.01	-.164*	-0.05	-0.01	-0.04	-.158*	-0.07	0.48	0.09
	p	0.06	0.45	0.33	0.67	0.05	0.32	0.69	0.97	0.05	0.53	0.94	0.82	0.04	0.36	0.34	0.87
PT (Sec)	r	0.06	0.13	1.000	0.87	0.08	.166*	0.02	0.06	0.02	0.08	0.22	0.32	0.03	0.09	0.72	.971*
	p	0.44	0.10	N/A	0.33	0.36	0.05	0.90	0.75	0.83	0.34	0.21	0.07	0.73	0.26	0.11	0.00
PT (%)	r	0.03	-0.04	-1.000	-0.87	0.03	-0.08	-0.02	-0.05	0.09	0.03	-0.21	-0.32	0.05	-0.02	-0.15	-0.41
	p	0.66	0.60	N/A	0.33	0.74	0.37	0.91	0.79	0.26	0.77	0.23	0.07	0.55	0.82	0.78	0.42
PT (INR)	r	-0.02	0.02	1.000	0.87	-0.02	0.05	0.02	0.06	-0.08	-0.05	0.23	0.32	-0.03	0.00	0.15	0.41
	p	0.77	0.80	N/A	0.33	0.85	0.59	0.90	0.75	0.33	0.56	0.20	0.07	0.66	0.97	0.78	0.42

Table 5 shows the Mann-Whitney U test analysis results for the association between reflux, diabetes and tumor and the C-reactive protein, Ferritin, D-Dimer, white blood cells (WBC), red blood cells(RBC), hemoglobin (HGB), prothrombin time (PT) (Sec), PT (%) and PT (INR) values. A significant relationship was present between reflux and the PT (Sec) value (p=0.014). The median PT (Sec) value was 12.25 (1.01-39.50) in the absence of reflux and 12 (11-21.80) in the presence of reflux. A significant relationship was also found between reflux and the PT (%) value (p=0.032). The median PT (%) was 89.3 (0.88-120.8) in the absence of reflux and 95 (45.50-108) in the presence of reflux. The relationship between reflux and the PT (INR) variable was found to be significant (p=0.03). No significant relationship was found between fever, diabetes, and tumor presence and the CRP, Ferritin, D-Dimer, WBC, RBC, HGB, PT (Sec), PT (%), and PT (INR) values.

4. Discussion

The COVID-19 pandemic threatens the population's health, weakens the economy, and destabilizes the society worldwide (Legido et al. 2020). Although various treatment methods are used in COVID-19 patients, there is no currently proven definitive treatment and the search for an effective treatment continues. The oxygen level decreases due to the virus-related alveolar collapse, but the severity of the shortness of breath increased since the CO_2 exchange continues (Dreher et al. 2020). This means that the organism is exposed to oxygen saturation. Respiratory distress has been accepted as an oxygen saturation level below 93% in our country. Detection of decreased oxygen saturation, platelet count, and lymphocyte count, in addition to increased CRP, ESR, prothrombin time, and D-iron in the early stage of viral infections could save lives. Our results indicate that normal or low WBC is generally associated with lymphopenia but a lymphocyte count below 1000/mcL can be associated with more serious diseases. The platelet count is usually normal or slightly low. Diffuse alveolar and endothelial damage associated with thrombus has been reported in the pulmonary small arteries in this condition (Kuno et al. 2020). CRP and ESR are generally high. The prothrombin time and D-dimer elevation can be associated with serious diseases, and have been found to high in diabetes patients (Khot and Nadkar 2020). The most common comorbid disease was found to be cardiovascular disease with 28.2% of the cases having hypertension, 8.6% coronary artery disease, and 6.9% heart failure (HF) in a study from the United States of America including 8438 COVID-19 (Palmieri et al. 2020). We similarly found COVID-19 to affect the cardiovascular system, directly or indirectly. The morbidity and mortality seem to increase when COVID-19 is accompanied by CVD. The mean age of the 59304 COVID-19 patients who died was 80 years and the death rate was higher in men in the December 2020 report from Italy, the country with the highest death rate (Drakesmith and Prentice, 2008). Besides, some studies report those elderly men are more likely to be infected and rapidly develop acute respiratory distress syndrome (ARDS), creating a life-threatening situation (Guo et al. 2020).

Iron is important for both biological and physiological events. In case of disease, both the pathogen and the infected person need iron. RNA gains active multi-reactive capacity and the ability to catalyze new chemical reactions in limited oxygen respiration or in the presence of iron in the environment in disease states. People with congenitally or acquired strong immune systems can carefully regulate the iron metabolism to limit the presence of iron at times of infection. Iron can increase virulence and pro-oxidant reactions and contribute to oxidative stress in the lungs. The result is peroxidation, which leads to cellular damage in the blood and tissues. Viruses target the same channel used for iron transfer during pH-dependent cellular entry into the intracellular acidic compartments. The inflammatory effect has been seen to cause disturbed gas exchange between the alveoli and blood vessels, leading to pulmonary fibrosis and organ failure, in the pathogenesis (Drakesmith and Prentice 2008). The incidence of oxidative stress and acute respiratory distress syndrome (ARDS) in COVID-19 patients has been reported as 17-29% and the rate for intensive care need in these patients as 23-32% (Goh et al. 2020). ARDS patients are exposed to severe oxidative stress during this process. COVID-19 glycoproteins bind to the heme in the erythrocyte and the toxic oxidative iron within the specific structure is separated. Free iron circulates freely when outside the cell. Hemoglobin can no longer bind to oxygen without the iron ion. In other words, erythrocytes lose their biological activity when hemoglobin deteriorates. Erythrocytes circulate without oxygen only with the porphyria-related COVID-19 virus. The insufficient oxygen in the tissues causes severe hypoxia and a decrease in blood oxygen saturation. When the iron ion is released from the heme structure of millions of erythrocytes in patients carrying the pathogen, this iron increases prooxidant reactions and causes oxidative stress in the lung (Thell 2003). In contrast, there is oxidant-antioxidant balance in the organism under normal conditions. One of these defense systems consists of the small macrophages that circulate and clean free radicals such as this oxidative iron, while endogenous antioxidant enzymes constitute another (Güven and Kaya, 2005). The transferrin iron saturation is reported to increase to high levels in viral pneumonia and accordingly a deterioration to be present in the level of antioxidant protection. (Thomas and Thomas 2017). The presence of excess iron outside healthy lung cells decreases the defenses against viral infections. In the presence of severe oxygen deficiency in patients with COVID-19, the RBC values in the patient's circulation provide direct or indirect information about the severity of the disease (Ruddell et al. 2009). Whether serum ferritin, which indicates the status of iron storage in humans, is released from the cell with an active mechanism or by cell leakage is not certain. However, while many studies report that it can function as a proinflammatory cytokine responsible for cell damage (Guo et al. 2020). It also protects the cells during the oxidation of Fe (II) to Fe (III). Besides, after SARS-CoV-2 enters the host cell, it encodes the production of structural and non-structural proteins during the viral replication stage and invades hemoglobin, which is one of the non-structural proteins, and removes the iron atom, and

also prevents the transport of the oxygen by binding to the relevant region. Such hemoglobin types are considered risky hemoglobins. This clinical picture may explain the rapidly developing hypoxia. Theoretically speaking, the viral load would be primarily responsible for the severity of the disease, since patients with certain diseases have risky hemoglobin (Liu et al. 2020).

While C-reactive protein (CRP) values were observed to increase in patients with a ground glass image by thorax CT in the lungs infected with COVID-19 after detecting a positive PCR test in the blood, lymphopenia together with increased creatinine phosphokinase (CPK), ferritin, D-iron (>1 mcg/ml), and prothrombin time values were found, possibly as a result of kidney damage (Kappert et al. 2020). The similar situation in our study strengthens the view that the CRP value can be considered an indicator of disease severity. Wang et al. (2020) have reported that increased severity of the disease is associated with increased iron levels. The biochemistry laboratory results of 63 COVID-19 patients have revealed that the blood iron values were parallel to the classification of the disease severity in the patients as light, moderate, severe and critical (Sun et al. 2020). Increased iron concentrations in the body cause tissue damage, inflammation, and impaired organ function. The pathological changes caused by the irregularities in serum ferritin are also important (Lan et al. 2020). Certain biochemical values are reported to undergo more significant changes in covid-19 patients with diabetes mellitus and reach the level of hyperferritinemia syndrome (Mehta et al. 2020). and this could increase the mortality rate due to immunosuppression (Mehta et al. 2020; Shoenfeld 2020). Monitoring of the serum iron level is recommended in other studies and regulators of iron homeostasis such as serum ferittin and hepadin are stated as a possible reason for the elevated serum ferritin. It can therefore be said that D-iron and ferritin have a strong correlation with the diagnosis and disease severity (Kurz et al. 2011). The infection symptoms and signs and the test values in the diabetic COVID-19 patients in our study were similar to classic COVID-19 cases.

Advanced age itself is seen to be a factor in decreasing the immune response and the prevalence of this weakened state increases markedly in this age group. Considering the data obtained in the study and the age of the patients, it is necessary to address the possible COVID-19 biochemical parameters that increase disease severity singly or in combination, analyze by which mechanisms the negative effects occur, and implement the relevant practices in diagnosis and treatment. For example, markers such as iron should be investigated in addition to the possible mechanisms mediated by ACE2. These findings could be very important and provide clues to clinicians and biochemists about the prognosis and mortality of COVID-19. We therefore recommend conducting specific studies that further reveal the metabolic pathways of virus-iron interaction and focusing on decreasing the iron levels to enable more specific treatment in viral infections. Hypercoagulopathy and thrombosis were common in this infection and the major reason for many complications seen in COVID-19. Creatine kinase, cardiac troponins, myoglobin were used to assess cardiac status; aspartat aminotransferase, albumin, lactate dehydrogenase were used broadly to assess liver function and fibrin degradation products, activated partial thromboplastin time and D-dimer were used to determine the thrombotic state.

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