ORIGINAL ARTICLE

Eastern Journal of Medicine

East J Med 27(1): 146-154, 2022
DOI: 10.5505/ejm.2022.00086

Relationship Between Inflammatory Parameter and Mortality in Intensive Care Patients with COVID-19

Necla Dereli[1], Munire Babayigit[1*], Filiz Koç[2], Özlem Özbek[1], Gokhan Yildiz[3], Merve Karasahin[1], Ozge Gursozlu[1], Nur Sena Çakar[1]

[1]Department of Anesthesiology and Reanimation, Kecioren Training and Research Hospital, Ankara, Turkey
[2]Department of Clinical Microbiology and Infectious Diseases, Kecioren Training and Research Hospital, Ankara, Turkey
[3]Department of Algology, Ankara City Hospital, Ankara, Turkey

ABSTRACT

We aimed to examine the relationship between hypoxemia, inflammatory parameters, cytokine storm and mortality in the COVID-19 Intensive Care Unit.

COVID-19 patients followed in intensive care unit between 21 March and 1 June 2020 were retrospectively analyzed. Inflammatory parameters (CRP, ferritin, D Dimer, leukocyte and lymphocyte, LDH…) were measured in blood samples taken simultaneously. The relationship of these parameters with mortality was evaluated.

Of the 30 patients, 11 (36.7%) were female, 19 (63.3%) were male. When living (Group 1) and dead (Group 2) patient groups were compared, a statistically significant difference was found between the groups in terms of mean age ($p = 0.013$). It was observed that PaO2 / FiO2 ratios were lower in Group 2 in all measurements starting from the day of hospitalization in intensive care. While there was no difference between CRP and procalcitonin values in the first week, the 12th and last day measurements were found to be statistically significantly higher in Group 2 (respectively $p2 = 0.050$, $p2 = 0.016$; $p2 = 0.050$, $p2 < 0.001$).

When the patients with severe pneumonia treated in the intensive care unit with the diagnosis of COVID-19 were examined, it was observed that the patients who died were more hypoxic at the intensive care entrance and on the 3rd day compared to the survivors, the level of hypoxemia did not affect the cytokine storm, and there was no difference in mortality between those who experienced cytokine storm and those who did not.

Keywords: COVID-19, intensive care unit, inflammation, mortality

Introduction

In severe pneumonia caused by human coronaviruses (hCoVs), rapid virus replication and increase in proinflammatory cytokine / chemokine response cause ALI (Acute Lung Injury) and ARDS (Acute Respiratory Distress Syndrome). Since ALI and ARDS have high morbidity and mortality, coronaviruses with high pathogenicity pose a threat to public health. During the epidemic between 2002 and 2003, SARS-CoV infected 8400 people, and the mortality was 9.6% (1,2). More recently, MERS-CoV had a mortality rate of approximately 36% (3,4).

Current statistics show that 14% of COVID-19 related pneumonia cases are severe and 5% of infected patients are critically ill patients in need of intensive care (5). Mortality rates in severe and critically ill patients are remarkable, and 66% of critically ill patients die (6). Due to the limited resources of critical care, it is necessary to identify simple but reliable predictors of survival in COVID-19 patients. Since COVID-19 mainly affects the respiratory system, measurements reflecting respiratory function will be more relevant to the results. In various studies on COVID-19, it has been shown that hypoxemia is an independent risk factor for mortality, and there is a relationship between the severity of the disease and some inflammatory parameters and cytokine storm in various studies (7). Findings as a result of studies on this subject will help to understand the risk factors associated with the severity of SARS-CoV-2 disease. Therefore, we aimed to examine the relationship between hypoxemia, inflammatory parameters, cytokine storm and mortality in the our COVID-19 Intensive Care Unit.

***Corresponding Author:** Münire Babayiğit, Anesteziyoloji ve Reanimasyon Kliniği, Keçiören Eğitim ve Araştırma Hastanesi, Ankara
Eposta: mnroksuz@hotmail.com, Fax +903122130034
ORCID ID: Necla Dereli: 0000-0003-3019-315X, **Munire Babayigit:** 0000-0002-5090-3262, **Filiz Koç:** 0000-0001-9469-1153, **Özlem Özbek:** 0000-0002-3222-1970, **Gokhan Yildiz:** 0000-0001-5905-938X, **Merve Karasahin:** 0000-0003-3808-9402, **Ozge Gursozlu:** 0000-0003-1994-6026, **Nur Sena Çakar:** 0000-0002-1191-7530
Received: 16.03.2021, **Accepted:** 06.10.2021

Materials and Methods

The files of 30 patients over the age of 18 who were treated with the diagnosis of COVID-19 (whose diagnosis was confirmed with nasopharyngeal reverse-transcriptase-poly merasechain-reaction test) in Anesthesia Intensive Care Unit of Kecioren Training and Research Hospital, between 21 March 2020 and 01 June 2020 were examined. Patients with PCR test (-) and those staying in the intensive care unit for less than 24 hours were excluded from the study. The patients included in the study were divided into two groups as Group 1 = Survivors and Group 2 = Non-survivors. Demographic data of the patients were reviewed. Arterial blood gas samples and inflammatory markers (CRP, ferritin, D-Dimer, leukocyte and lymphocyte, LDH ...) were recorded when the patients were admitted to intensive care unit and during their treatment. Hypoxemia levels (PaO2/FIO2) and inflammatory parameters (CRP, ferritin, LDH, procalcitonin, D-dimer) at the time of admission to intensive care were compared with the levels and parameters during the treatment process. It was investigated whether there was a parallelism between hypoxemia level and inflammatory parameters, and whether there was any difference between the clinical course and mortality rates of patients who entered and did not enter cytokine storm.

Statistical Analysis: Continuous variables were expressed as mean standard deviation, categorical data as numbers and percentages. In the intergroup analysis of continuous variables, normality analyzes were performed using the Kolmogorov-Smirnov Goodness of Fit Test. Since the data did not conform to normal distribution, Mann Whitney U Test was used for intergroup analyzes and Wilcoxon Ordered Signs Test was used for in-group analyzes. Friedman Test was used in three or more group comparisons. The Wilcoxon Ordered Signs Test was used as an advanced analysis test to test in which group the difference arose in the intergroup evaluations. Comparisons of categorical data were made using the Chi-Square Test. Analyzes were made with IBM SPSS (Statistics Package Program for Social Sciences) version 24.0 (IBM Corporation, Armonk, NY, USA). Statistical significance level was taken as $p < 0.05$.

Results

11 out of 30 (36.7%) patients who were followed up in the intensive care unit due to severe COVID-19 died despite the treatments performed. While a statistically significant difference was found between the groups in terms of mean age(72.18 ± 17.04 in ex-patients,58. 95 ± 10.41 in survivors; $p = 0.013$), no significant difference was found in terms of body mass index (BMI) values and gender ratios ($p > 0.05$). While the Nutric score value of 47.4% of the patients in group 1 was "0", the Nutric score value of 63.6% of the patients in group 2 was found to be "4" ($p < 0.05$) (Table 1).

When the comorbidities of the patients were examined in terms of COPD, DM, CAD, CVA, CKF, asthma and hypertension, no statistically significant difference was found between the groups (Table 2).

When evaluated according to ACE inhibitor, anticoagulant, antiaggregant intake as chronic treatment and hydroxychloroquine intake during hospital treatment, no statistically significant difference was found between the two groups (Table 3).

When PaO2/FiO2 ratios were compared between the groups, a statistically significant difference was found in the measurements on the day of ICU admission, the 3rd day, and the last days ($p2 = 0.025$, $p2 = 0.042$, $p2 = 0.001$, Table 4). However, it was observed that PaO2/FiO2 ratios were lower in Group 2 in all measurements starting from the day of hospitalization in intensive care.

While there was no difference between CRP and procalcitonin values in the first week, the 12th and last day measurements were found to be statistically significantly higher in Group 2 (respectively $p2 = 0.050$, $p2 = 0.016$; $p2 = 0.050$, $p2 < 0.001$, Table 4).

There was no statistically significant difference between the two groups in all measurements between ferritin and D-Dimer values.

When the lactate values were examined, it was found that it started to increase in Group 2 as of the 4th day and was statistically significantly higher in Group 2 (respectively $p2 = 0.014$, $p2=0.021$, $p2=0.002$, Table 4.

No significant difference was found between the age, BMI average and gender, nutricscore and mortality rates of those who experienced cytokine storm and those who did not ($p > 0.05$) (Table 5).

When the laboratory data of the patients with cytokine storm during the cytokine storm period were compared with the data on the day of admission to ICU, it was observed that the SOFA score, CRP, procalcitonin, ferritin lactate, D-

Table 1. Comparison of Groups In Terms of Some Socio-Demographic and Clinical Characteristics

	Group 1 (Survivors) (n=19)	Group 2 (Non-Survivors) (n=11)	Total (n=30)	p
Age (Avg±Sd)	58,95±10,41	72,18±17,04	63,80±14,47	0.013*
BMI (Avg±Sd)	29,89±4,42	31,49±6,14	30,48±5,07	0.416*
Gender (n, %)				
Female	5 (%26,3)	6 (%54,5)	11 (%36,7)	0.238**
Male	14 (%73,7)	5 (%45,5)	19 (%63,3)	
Nutric score (n, %)				
0	9 (%47,4)	0 (%0,0)	9 (%30,0)	
1	1 (%5,3)	1 (%9,1)	2 (%6,7)	0.002**
3	8 (%42,1)	3 (%27,3)	11 (%36,7)	
4	1 (%5,3)	7 (%63,6)	8 (%26,7)	
Total	19 (100,0)	11 (100,0)	30 (100,0)	
* T-Test				
** Chi-Square Test				

BMI: Body Mass Index

Table 2. Comparison of Groups According To Comorbid Disease Rates

Comorbidity	Group 1 (Survivors) (n=19)	Group 2 (Non-Survivors) (n=11)	Total (n=30)	p
COPD (n, %)				
No	17 (%89,5)	8 (%72,7)	25 (%83,3)	0.327*a
Yes	2 (%10,5)	3 (%27,3)	5 (%16,7)	
Asthma (n, %)				
No	16 (%84,2)	9 (%81,8)	25 (%83,3)	1.000*a
Yes	3 (%15,8)	2 (%18,2)	5 (%16,7)	
Hypertension (n, %)				
No	12 (%63,2)	4 (%36,4)	16 (%53,3)	0.257*a
Yes	7 (%36,8)	7 (%63,6)	14 (%46,7)	
DM (n, %)				
No	14 (%73,7)	6 (%54,5)	20 (%66,7)	0.425*a
Yes	5 (%26,3)	5 (%45,5)	10 (%33,3)	
CAD (n, %)				
No	16 (%84,2)	8 (%72,7)	24 (%80,0)	0.641*a
Yes	3 (%15,8)	3 (%27,3)	6 (%20,0)	
CVA (n, %)				
No	19 (%100,0)	10 (%90,9)	29 (%96,7)	0.367*a
Yes	0 (%0,0)	1 (%9,1)	1 (%3,3)	
CKF (n, %)				
No	18 (%94,7)	11 (%100,0)	29 (%96,7)	1.000*a
Yes	1 (%5,3)	0 (%0,0)	1 (%3,3)	
Total	19 (100,0)	11 (100,0)	30 (100,0)	
* Chi-Square Test (aFisher's Exact Test)				

COPD: Chronic obstructive pulmonary disease; DM: diabetes mellitus, CAD: Coronary artery disease, CVA: Cerebrovascular disease, CKF: Chronic Kidney Failure

Table 3. Comparison of The Groups According To Their Drug Use

	Group 1 (Survivors) (n=19)	Group 2 (Exs) (n=11)	Total (n=30)	p
ACE inh. (n, %)				
Not Used	15 (%83,3)	10 (%100,0)	25 (%83,3)	0.533*a
Used	3 (%16,7)	0 (%0,0)	5 (%16,7)	
Hydroxychloroquine (n, %)				
Not Used	1 (%6,3)	3 (%27,3)	4 (%14,8)	0.273*a
Used	15 (%93,8)	8 (%72,7)	23 (%85,2)	
Anticoagulant (n, %)				
Not Used	14 (%77,8)	9 (%90,0)	23 (%82,1)	0.626*a
Used	4 (%22,2)	1 (%10,0)	5 (%17,9)	
Antiagregan (n, %)				
Not Used	17 (%94,4)	9 (%90,0)	26 (%92,9)	1.000*a
Used	1 (%5,6)	1 (%10,0)	2 (%7,1)	
Total	18 (100,0)	10 (100,0)	28 (100,0)	

* Chi-Square Test (aFisher's Exact Test)

Dimer values were significantly increased and the PaO2 / FiO2 ratio and LDH values did not change (p1: 0.020, p1 : 0.007, p1: 0.018, p1: 0.008 p1: 0.021, p1: 0.011, p1: 0.307, p1: 0.646, Table 6).

Discussion

Hypoxia is the primary pathophysiological feature of COVID-19 and is the main cause of mortality in severe COVID-19 patients. It is found in all stages of the disease. There are determinants of hypoxemia at systemic, organ and cellular levels, and factors that trigger hypoxia increase the effect of hypoxemia (8).

In ARDS in Covid-19 patients, tissue inflammation disrupts oxygen delivery and changes in ventilation / perfusion ratio due to bilateral interstitial infiltrates aggravate hypoxemia (9,10).

In a study in which 140 COVID-19 pneumonia patients were examined, it was shown that hypoxemia was an independent risk factor for hospital mortality, and 90.5% cut-off value of oxygen saturation could be used in surveillance estimation with 84.6% sensitivity and 97.2% specificity (11). In another multicenter study of 1629 cases in the United States, advanced age, low oxygen saturation (88%), increased procalcitonin and lactic acid levels were shown to be the most important risk factors for hospital mortality (12).

In this study, the hypoxemia levels of severe COVID-19 patients were monitored with PaO2 / FiO2 ratio when they were admitted to intensive care and during their treatment. When PaO2 / FiO2 ratios were compared between the living and dead patient groups, a statistically significant difference was found in the measurements on the day of intensive care hospitalization, on the 3rd day and on the last day. In addition, it was observed that PaO2 / FiO2 ratios in Group 2 (the patient group with death) were lower in all measurements from the day of hospitalization to the intensive care unit compared to Group 1. Our results are consistent with studies showing that hypoxemia is a risk for hospital mortality.

ARDS, which occurs in severe cases of COVID-19, may eventually lead to end organ dysfunction and failure. Classical ARDS findings are severe respiratory distress with decreased compliance. ARDS in COVID-19 patients is different from other forms of ARDS. Patients with this atypical form of ARDS have more compliance than expected, the significant shunt increase may be secondary to hypoxic pulmonary vasoconstriction and hypercoagulable state. Hypercoagulable state may cause microvascular thrombus formation in the pulmonary circulation in patients with COVID-19.

Patients with COVID-19 with severe respiratory failure have thrombogenesis as well as increased cytokine release followed by widespread inflammation causing end organ damage (cytokine release syndrome / CRS or cytokine storm) (13-17). This uncontrolled inflammatory response in COVID-19 is at the center of clinical adverse

outcomes as previously in SARS and MERS and cause mortality and morbidity (18).

In this study, COVID-19 patients who entered cytokine storm and those who did not were compared. The relationship between hypoxemia level and inflammatory parameters and cytokine release was examined. It was found that there was no hypoxemia and no change in LDH level during cytokine storm. When the laboratory data during the cytokine storm period of the patients who entered the cytokine storm were compared with the data on the admission day to ICU, it was found that the SOFA score, CRP, procalcitonin, lactate, D-Dimer values increased significantly, PaO2 / FiO2 ratio and LDH values did not change. There was no significant difference in mortality between patients who entered cytokine storm and those who did not. This difference may be due to the small number of our patients or the use of Interleukin 6 antagonists in our patients (9 out of 12 patients).

The most common laboratory findings at the time of diagnosis in COVID-19 are lymphocytopenia (83.2%), thrombocytopenia (36.2%) and leukopenia (33.7%) (19-21). It has been reported that there is an increase in various infectious parameters such as CRP, ALT, AST and D-dimer. If bacterial infection is not involved at the time of initial diagnosis, procalcitonin levels are normal (22-24).

D-Dimer, serum ferritin, troponin I, LDH, Pa02 <90 mmHg and IL-6 levels that are high at the time of diagnosis of COVID-19 or increased during follow-up are defined as "poor prognostic factors" associated with severe disease and mortality (23-25).

In a study involving ninety-nine patients, it was reported that the common symptoms of COVID-19 patients are increased neutrophilia 38%, lymphopenia 35%, and systemic inflammatory proteins IL-6 52% and CRP 84% (25). In another study conducted with 41 patients, admission to the intensive care unit and mortality were associated with neutrophilia and lymphopenia (24). In a third cohort study, in 85 patients who died from COVID-19, significant leukopenia was reported as 11.8%, lymphopenia 77.6%, thrombocytopenia 41.2%, anemia 48.2%, hypofibrinogenemia 22.4%, and hypoalbuminemia 78.8% (26).

Increased levels of C-reactive protein, ferritin, and cytokines and lymphopenia may guide the clinician to diagnose cytokine release syndrome in COVID 19 patients. It has been shown that the increase in CRP levels correlates with the size of the lesions in the lungs and can predict the severity of the disease (27).

In our study, CRP, ferritin and D-dimer were used as inflammatory markers. Procalcitonin monitoring was performed to rule out bacterial infection. While there was no difference in CRP and procalcitonin values between the two groups in the first week, the 12th and last day measurements were found to be statistically significantly higher in Group 2. Consistent with studies suggesting that CRP is the criteria of the severity of the disease and mortality, CRP was found to be higher in the non-survivor group in our study. There was no statistically significant difference between the two groups in all measurements of ferritin and D-dimer values. When the lactate values were examined, it was found that it started to increase in Group 2 as of the 4th day and remained statistically significantly higher in the following days.

In conclusion, when our patients who were treated in our intensive care unit with the diagnosis of COVID-19 were examined, it was observed that lactate and CRP values were high in patients with death, there was no difference in mortality between those who experienced cytokine storm and those who did not, and there was no increase in hypoxemia on days when cytokine storm occurred. Although the low number of patients is a limitation in our study, we believe that it will be a guide for future studies.

Table 4. Comparison of Oxygenation and Inflammatory Parameters of Covid-19 Cases Followed In Intensive Care Between Groups and Within Groups

	Day of intensive care hospitalization (n=30)	1. Day (n=28)	2. Day (n=25)	3. Day (n=22)	4. Day (n=21)	5. Day (n=18)	12. Day (n=14)	Last Day (n=25)	p1
	Median (min-max)	Median (min-max)	Median (min-max)	Median (min-max)	Median (min-max)	Median (min-max)	Median (min-max)	Median (min-max)	
PaO2/FiO2 (Group 1)	186 (63-295)	205 (57-280)	205 (95-317)	185 (87-260)	183 (85-285)	175 (75-290)	159 (131-266)	235 (180-280)	0.025*
PaO2/FiO2 (Group 2)	132 (50-220)	150 (65-320)	134 (66-250)	119 (87-165)	133 (70-210)	162 (65-220)	119 (0-260)	100 (50-275)	0.726*
	p2=0.025**	p2=0.090**	p2=0.200**	p2=0.042**	p2=0.156**	p2=0.441**	p2=0.365**	p2=0.001**	
CRP (Group 1)	146 (9-354)a	145 (5,9-380)a	128 (3,5-428)a	152 (2,1-454)a	89 (1,5-439)a	119 (0,9-413)a	13 (0,4-217)a	37 (0,4-283)a	0.007*
CRP (Group 2)	78 (13-237)	101,5 (21-284)	176 (36-269)	154 (57-203)	131 (43-263)	97 (16,1-342)	95(11-248)	207 (13-366)	0.579*
	p2=0.435**	p2=0.760**	p2=1.000**	p2=0.789**	p2=0.751**	p2=0.892**	p2=0.050**	p2=0.016**	
Procalcitonin (Group 1)	0,13 (0,01-1,4)	0,11 (0,02-1,38)	0,14 (0,03-1,20)	0,15 (0,01-0,70)	0,16 (0,01-3,90)	0,38 (0,03-2,7)	0,10 (0,02-0,77)	0,06 (0,01-0,57)	0.006*
Procalcitonin (Group 2)	0,14 (0,01-1,5)a	0,28 (0,03-0,97)	0,20 (0,03-43)	0,11 (0,06-21)	0,49 (0,12-10)	0,85 (0,13-9,2)a	0,38 (0,08-3,4)	1,10 (0,08-18)	0.037*
	p2=0.435**	p2=0.760**	p2=1.000**	p2=0.789**	p2=0.751**	p2=0.892**	p2=0.050**	p2<0.001**	
Ferritin (Group 1)	665 (77-1659)	713 (119-1933)	830 (154-1936)a	865 (210-1650)a	865 (190-2112)a	919 (281-1650)a	517 (120-1385)a	534,5 (120-2012)a	0.004*
Ferritin (Group 2)	727 (44-1557)	764 (40-1560)	773 (56-1384)	655 (95-9160)	592 (123-1611)	623 (197-1511)	915 (219-11394)	932,5 (197-1650)	0.403*
	p2=0.954**	p2=0.727**	p2=0.881**	p2=0.823**	p2=0.501**	p2=0.107**	p2=0.463**	p2=0.245**	
LDH (Group 1)	371 (212-886)	396 (209-680)a	371 (8,9-545)	368 (205-490)	357 (194-564)	388 (207-473)a	353 (209-460)	235 (180-372)a	0.029*
LDH (Group 2)	455 (195-1523)	513 (208-969)	435 (200-874)	460 (218-770)	495 (240-1034)	494 (277-669)	373 (256-928)	432 (209-1184)	0.366*
	p2=0.438**	p2=0.339**	p2=0.351**	p2=0.181**	p2=0.113**	p2=0.135**	p2=0.286**	p2=0.002**	

Lactate (Group 1)	0,90 (0,15-2,31)	1,06 (0,59-1,80)	0,90 (0,25-1,91)	1,04 (0,16-1,60)	0,96 (0,40-1,50)	1,00 (0,20-1,49)	1,10 (0,30 - 1,40)	0,82 (0,18-1,32)	0.034*
Lactate (Group 2)	1,22 (0,28-4,97)	1,00 (0,72-1,18)	1,30 (0,80-1,8)	1,55 (0,70-4,5)	1,63 (0,90-4,8)	1,50 (0,90-4,9)	1,60 (1-6,20)	1,95 (0,57-13)	0.089*
	p2=0.368**	p2=0.603**	p2=0.204**	p2=0.052**	p2=0.014**	p2=0.021**	p2=0.072**	p2=0.002**	
D-dimer (Group 1)	770 (490-6090)	875 (350-9520)	1065 (400-6940)	1275 (320-5370)	960 (370-6740)	1240 (172-4160)	2090 (630-6430)	930 (470-3590)	0.065*
D-dimer (Group 2)	760 (510-2840)	975 (500-9130)	2380 (680-4360)	1710 (700-4270)	1655 (840-15440)	1320 (4,7-10660)	4390 (940-8890)	2190 (510-10550)	0.620*
	p2=0.918**	p2=0.846**	p2=0.738**	p2=0.504**	p2=0.392**	p2=0.892**	p2=0.125**	p2=0.137**	

* Friedman Test (Post hoc:aWilcoxonSignedRanks Test)
** Mann Whitney U Test

Table 5. Comparison of Patients With And Without Cytokine Storm In Terms of Some Socio-Demographic and Clinical Characteristics

	With cytokine storm (n=12)	Without cytokine storm (n=18)	p1
Age (Avg±Sd)	59,67±13,25	66,56±14,95	0.207*
BMI (Avg±Sd)	30,94±5,84	30,17±4,64	0.694*
Gender (n, %)			
Female	4 (%33,3)	7 (%38,9)	0.757**
Male	8 (%66,7)	11 (%61,1)	
Nutric score (n, %)			
0	6 (%50,0)	3 (%16,7)	
1	0 (%0,0)	2 (%11,1)	0.186**
3	4 (%33,3)	7 (%38,9)	
4	2 (%16,7)	6 (%33,3)	
Mortality (n, %)			
Alive	8 (%66,7)	11 (%61,1)	0.757**
Ex	4 (%33,3)	7 (%38,9)	

* T Test
** Chi-Square Test
BMI: Body Mass Index

Table 6. Comparison of Cytokine Levels During Cytokine Storm - ICU Admission Day

	ICU admission day (n=12)	Cytokine storm day (n=12)	p1
	Median (min-max)	Median (min-max)	
PaO2/FiO2	143,5 (63-295)	128,5 (63-250)	0.307*
SOFA	3 (1-5)	7 (2-11)	0.020*
CRP	137,5 (9-354)	255 (5,9-354)	0.007*
Procalcitonin	0,20 (0,01-0,80)	0,39 (0,07-43)	0.018*
Ferritin	691 (77-1659)	1153 (241-2786)	0.008*
LDH	483,5 (291-854)	455,5 (240-969)	0.646*
Lactate	1,04 (0,29-1,80)	1,30 (0,72-4,80)	0.021*
D-dimer	750 (490-2330)	1170 (610-10660)	0.011*
* Wilcoxon Signed Ranks Test			

References

1. Perlman S, Netland J. Coronaviruses post-SARS: update on replication and pathogenesis. Nat Rev Microbiol 2009; 7: 439-450.
2. https://www.who.int/csr/sars/country/2003_07_11/en/. (Accessed date: 01.03.2021).
3. http://www.who.int/csr/disease/coronavirus_infections/MERS_CoV_RA_20140613.pdf WUoM-CTfAtHaIRfA-RGLaoMAf (Accessed date: 01.03.2021).
4. WHO: Middle East respiratory syndrome coronavirus (MERS-CoV). http://www.who.int/emergencies/mers-cov/en/ (Accessed date: 02.03.2021)
5. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. Jama. 2020 2648.
6. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State JAMA 2020; 323: 1612-1614.
7. 7- Chen G, Zhao J, NingQ. Clinical and immunological features of severe and moderate coronavirus disease 2019 J Clin Invest 2020; 130: 2620-2629.
8. 8- Serebrovska ZO, Chong EY, Serebrovska TV, TumanovsLV,Xi L.Hypoxia, HIF-1α, and COVID-19: from pathogenic factors to potential therapeutic targets Acta Pharmacol Sin 2020; 41: 1539-1546.
9. 9- Lazzeri M, Lanza A, Bellini R, et al. Respiratory physiotherapy in patients with COVID-19 infection in acute setting: a Position Paper of the Italian Association of Respiratory Physiotherapists (ARIR). Monaldi Arch Chest Dis 2020; 90.
10. He G, Han Y, Fang Q, et al. Clinical experience of high-flow nasal cannula oxygen therapy in severe corona virus disease 2019 (COVID-19) patients. Zhejiang Da Xue Xue Bao Yi Xue Ban 2020; 49: 232-239.
11. Xie J, Covassin N,Fan Z, et al. Association Between Hypoxemia and Mortality in Patients With COVID-19 Mayo Clin Proc. n June 2020; 95: 1138-1147.
12. Bahl A, Van Baalen MN,Ortiz L, et al. Early predictors of in- hospital mortality in patients with COVID- 19 in a large American cohort Internal and Emergency Medicine 2020; 15: 1485-1499.
13. Rahmati L, Moosavi MS. Cytokine-Targeted Therapy in Severely ill COVID-19 Patients: Options and Cautions EJMO 2020; 4: 179-180.
14. Tufan A, Güler AA, Matucci-Cerinic M.COVID-19, immune system response, hyperinflammation and repurposing antirheumatic drugs Turk J Med Sci 2020; 50: 620-632.
15. 15- Ye Q, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. J Infect 2020; 80: 607-613.
16. 16-Castelli V, Cimini A, Ferri C. Cytokine Storm in COVID-19: "when you come out of thestorm, youwon't be the same person whowalked in". Front Immunol 2020; 11: 2132.
17. 17-Soy M, Keser G, Atagündüz P, Tabak F, Atagündüz I, Kayhan S. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. Clin Rheumatol 2020; 39: 2085-2094.
18. Felsenstein S, Herbert JA, McNamara PS, Hedrich CM. COVID-19: Immunology and

treatment options. ClinImmunol 2020; 215: 108448.

19. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of corona-virus disease 2019 in China. N Engl J Med 2020; 382: 1708-1720.
20. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical Features of 69 Cases with Coronavirus Disease 2019 in Wuhan, China. Clin Infect Dis 2020; ciaa272.
21. Wang C, Horby P, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet 2020; 395: 470-473
22. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respir-atory distress syndrome and death in patients with coronavirus disease 2019 pneumo-nia in Wuhan, China. JAMA Intern Med 2020; e200994.
23. 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. Lancet 2020; 395: 1054-1062.
24. 24- Huang C, Wang Y, Li X, et al. Clinical featrures of patients infected with 2019 novel coronavirus in Wuhan China. Lancet 2020; 395: 497.
25. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descrip tive study. Lancet 2020; 395: 507-513.
26. Du Y, Tu L, Zhu P, et al. Clinical Features of 85 Fatal Cases of COVID-19 from Wuhan. A Retrospective Observational Study. Am J Respir Crit Care Med 2020; 201: 1372-1379.
27. Celikel Acar B. Cytokine Release Syndrome and Treatment in COVID-19. Turkish J Pediatr Dis 2020; 14: 55-59.