




RESEARCH
ARTICLE

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The Risk Factors Affecting Length of Stay and Mortality in Covid 19 Patients: Laboratory Parameters, Comorbidities, and Demographic Characteristics

ABSTRACT

Objective: Covid 19 can cause fatal pneumonia and serious complications. In the course of the disease the levels of different biochemical parameters increased and these parameters provide important information about the prognosis of the disease. The aim of this study was to investigate the relationship between biochemical parameters and length of stay and mortality in Covid 19 patients.

Methods: In this retrospective study, a total of 767 Covid 19 patients hospitalized in our hospital were included. The demographic characteristics, length of stay, comorbid diseases and biochemical parameters of the patients were scanned from the hospital's database and patient files and recorded. Patients were grouped according to the length of stay; 1st Group: 7 days and less, 2nd Group: 8-10 days, 3rd Group: 11-13 days, and 4th Group: 14 days and more.

Results: The mean CRP level was significantly higher in group 4 compared to group 1 (p = 0.002). The mean levels of LDH, PRO_BNP, and procalcitonin were significantly higher in group 4 compared to group 1 and group 2 (p < 0.001, p = 0.026, p = 0.007, respectively). The mean level of fibrinogen was significantly higher in group 4 compared to group 2 (p = 0.011). Presence of DM and HT as comorbidities (p = 0.022, p = 0.006) and high levels of LDH and ferritin (p < 0.001, p = 0.041) significantly increased the risk of death.

Conclusions: The results of our study show that positive correlation between the levels of CRP, LDH, PCT, PROBNP, and fibrinogen the prolongation of hospitalization in Covid 19 patients and these parameters can be associated with the severity disease. These results show that increased levels of LDH and ferritin, age, prolongation of hospitalization, and the presence of HT and DM increase mortality rate and can be specific parameters in terms of prognosis.

Keywords: Covid 19, Laboratory Tests, Mortality, Comorbidity Diseases, CRP, LDH.

Covid 19 Hastalarında Kalış Süresini ve Mortaliteyi Etkileyen Risk Faktörleri: Laboratuvar Parametreleri, Komorbiditeler ve Demografik Özellikler

ÖZET

Amaç: Covid 19, ölümcül pnömoniye ve ciddi komplikasyonlara neden olabilen güncel pandemik hastalıktır. Hastalığın farklı evrelerinde farklı biyokimyasal parametrelerin düzeyinde artış görülmekte ve bu parametreler hastalığın seyri konusunda önemli bilgiler vermektedir. Bu çalışmada, Covid 19 hastalarındaki yatış süresi ve mortalite oranı ile biyokimyasal parametreler arasındaki ilişkinin araştırılması amaçlanmıştır.

Gereç ve Yöntem: Bu retrospektif çalışmaya, hastanemizde yatan toplam 767 Covid 19 hastası dahil edildi. Hastanenin veri tabanı ve hasta dosyaları incelenerek hastaların demografik özellikleri, yatış süreleri, ek hastalıkları ve biyokimyasal parametreler taranarak kaydedildi. Hastalar yatış gününe göre, 1. Grup: 7 gün ve altı, 2. Grup: 8-10 gün arası 3. Grup: 11-13 gün arası, 4. Grup: 14 gün ve üzeri olmak üzere toplam 4 gruba ayrıldı. Hastaların demografik özellikleri, laboratuvar bulguları, ek hastalıkları ve mortalite oranları bu gruplara göre düzenlenerek istatistiksel analiz yapıldı.

Bulgular: Hastaların 459 (60%)'u erkek 308 (40%)'i kadındı. Grup 4 hastalarındaki CRP düzeyi, grup 1'deki hastalara göre istatistiksel anlamlı olarak yüksekti (p=0.002). Grup 4 hastalarındaki LDH, PRO_BNP ve prokalsitonin düzeyi hem grup 1 hemde grup 2'ye göre istatistiksel anlamlı olarak yüksekti (sırasıyla p<0.001, p=0.026, p=0.007). Fibrinojen düzeyi, grup 4 deki hastalarda grup 2'deki hastalara göre anlamlı olarak yüksekti (p=0.011). DM, HT, LDH ve ferritin düzeyi yüksekliği ölüm riskinin anlamlı olarak artırmıştı (sırasıyla p=0.022, p=0.006, p<0.001, p=0.041). Benzer olarak yaş ve yatış gününün uzaması ölüm riskini anlamlı olarak artırmıştı (p<0.001).

Sonuç: Çalışmamızın sonuçları, Covid 19 hastalarının yatış süresinin uzamasıyla CRP, LDH, PCT, PROBNP ve fibrinojen düzeyinin doğru orantılı olarak arttığını ve hastalığın şiddetliye ilişkili olabileceğini göstermektedir. Yine bu sonuçlar, LDH ve ferritin düzeyinin, yaş, yatış gününün uzaması, HT, DM gibi ek hastalıkların varlığının mortalite oranını artırdığını ve prognoz açısından daha spesifik parametreler olduğunu göstermektedir.

Anahtar Kelimeler: Covid 19, Laboratuvar Testleri, Mortalite, Ek Hastalıklar, CRP, LDH.

INTRODUCTION

The new type of corona virus 19 (Covid 19) is the pandemic disease that can cause severe pneumonia characterized by acute respiratory distress syndrome (ARDS) and goes on affecting the whole world (1). Severity of Covid 19 is mild or moderate in 80% of the patients. However, 20% of the patients needs to be hospitalized due to the increasing oxygen demand and 5% of them are hospitalized in the intensive care units (ICU) due to severe pneumonia(1).

Various laboratory tests including hematological, biochemical and immunological parameters provide important clinical data in the diagnosis, treatment, prognosis and monitoring of Covid 19 disease (2,3). In addition, these tests are very important parameters in differentiating the severity of the disease and predicting the mortality risk (4). The anti-inflammatory parameters including interleukins, serum reactive protein (CRP), lactatedehydrogenase (LDH), ferritin, procalcitonin (PCT), and D dimer are the most important ones among these tests(2). In several studies, it has been shown that especially an increased level of CRP is directly proportional to the severity of the disease and is a good diagnostic marker that can detect severe Covid 19 disease at an early stage(5-7). PCT is a propeptide of calcitonin devoid of hormonal activity. Although the blood PCT levels are within the normal range in mild Covid 19 patients, it can rise up to 5 times higher than the normal level in severe cases(8). D dimer and fibrinogen levels, which are indicators of hypercoagulation, increase significantly more in severe Covid 19 patients compared to other patients. Especially, an increased level of D dimer is associated with the risk of developing ARDS, hospitalization in ICU and mortality rate (2). It has also been shown that ProBNP, which is an indicator of cardiac pathology, increased in severe patients and associated with poor prognosis(9). LDH level has been shown to be an important indicator of respiratory failure as well as liver failure (10). In several studies, it has been shown that ferritin levels increase approximately 5 times more in severe Covid 19 patients compared to patients with a milder course of disease(3).

Age, gender and comorbidities are among the most important parameters that increase the severity and mortality rate of Covid 19 (10). In several studies, it has been shown that the average age of critically ill Covid 19 patients was 63 and the majority of the cases were males (11). The presence of comorbid diseases, including cancer, immune-suppressive diseases, lung and heart diseases, and especially diabetes mellitus (DM) and hypertension (HT) is associated with an increase in the severity and mortality rate of Covid 19 (12).

The aim of this study is to investigate the effects of demographic characteristics, laboratory findings and comorbidity diseases of Covid 19

patients hospitalized in our hospital on mortality and length of stay in hospital.

MATERIAL AND METHODS

Ethical Approval: Ethical approval for the study was obtained from the Clinical Ethics Committee of Inonu University School of Medicine (No:2020/188).

Study Population: This study included 767 Covid 19 patients hospitalized in the wards and intensive care units (ICU) of Malatya Training and Research Hospital, between March 15 and November 15, 2020. Data were scanned retrospectively from the hospital's database and patient files. Patients with active tuberculosis or hepatitis B and C, suspected or proven bacterial infection focus, those with active diverticulitis or gastrointestinal system perforation, and pregnant women were excluded from the study. Demographic characteristics, comorbidities, laboratory parameters including CRP, PCT, ferritin, LDH, D-dimer, fibrinogen, international normalized ratio (INR), and ProBNP, hospital stay and survival status of the patients were recorded.

Study Design: The patients were divided into 4 groups according to length of stay in the hospital; namely Group 1: 7 days and less, Group 2: 8-10 days, Group 3: 11-13 days, Group 4: 14 days and more. The demographic characteristics, laboratory findings, comorbidities and mortality rates of the patients were statistically analyzed according to these groups.

Statistical Analysis: Data were summarized by median (min-max) and numbers (percentage). Conformity to normal distribution was evaluated by using the Kolmogorov-Smirnov test. The Pearson chi-square and Kruskal Wallis tests were used for statistical analysis, where appropriate. Conover test was used in multiple comparisons. Logistic regression analysis was applied to estimate the odds ratio. The data were analyzed by using IBM SPSS Statistics 26.0 program. A value of $p < 0.05$ was considered statistically significant.

RESULTS

459 (60%) of the patients were males and 308 (40%) were females. The CRP levels of the patients in group 4 were significantly higher compared to the patients in group 1 ($p = 0.002$). The mean LDH, PRO_BNP and PCT levels of the patients in group 4 were significantly higher compared to both group 1 and group 2 ($p < 0.001$, $p = 0.026$, $p = 0.007$, respectively). The fibrinogen levels of the patients in group 4 was significantly higher compared to the patients in group 2 ($p = 0.011$). There was no significant difference between the groups in terms of age and D dimer and fibrinogen levels ($p > 0.05$) (Table 1).

Discharge rate was found to be significantly lower in group 4 compared to group 1 and group 2

(p <0.001). The rate of patients with chronic obstructive disease (COPD) was significantly higher in group 4 and group 2 compared to group 1

(p = 0.017). There was no difference between the groups in terms of other comorbid diseases (p> 0.05) (Table 1).

Table 1. Demographic characteristics and laboratory values of the patients according to the length of stay in hospital

		Length of stay in hospital				p-value
		7 days and less	8-10 days	11-13 days	14 days and longer	
		Median (Min-Max)	Median (Min-Max)	Median (Min-Max)	Median (Min-Max)	
Age		68 (18-104) ^a	72 (19-101) ^a	68 (19-95) ^a	70 (21-92) ^a	0.064
CRP		6.76 (0.02-49.67) ^a	8.02 (0.02-55.46) ^{a,b}	8.05(0.02-31.77) ^{a,b}	10.9 (0.03-37.15) ^b	0.002
LDH		358 (146-1386) ^a	372 (127-2889) ^a	385.5 (176-1241) ^{a,b}	454 (190-1369) ^b	<0.001
FERITIN		421.9 (7.6-1869) ^a	428.1 (1.09-2000) ^a	471.9 (32.14-1987) ^a	433.95 (16.64-1992) ^a	0.938
FIBRINOGEN		491.4 (235.3-1394) ^{ab}	460.6 (54.1-1477) ^a	487.75 (15.7-902.1) ^{a,b}	563.3 (53.6-6325) ^b	0.011
D-DIMER		0.6 (0.06-40.6) ^a	0.73 (0.04-36.4) ^a	0.68 (0.06-35.5) ^a	0.77 (0.01-31.3) ^a	0.085
INR		1.17 (0.85-10.9) ^a	1.16 (0.88-66.3) ^a	1.16 (0.88-6.59) ^a	1.19 (0.96-11.6) ^a	0.289
PRO_BNP		392.7 (21.82-30342) ^a	466.7(1.23-30470) ^{ab}	628.05 (10.49-18601) ^{b,c}	641.7 (9.23-21851) ^c	0.026
PROCALCITONIN		0.10 (0.02-24.6) ^a	0.11 (0.02-97.16) ^a	0.14 (0.03-9.02) ^{ab}	0.17 (0.02-24.51) ^b	0.007
		Count (Percent)	Count (Percent)	Count (Percent)	Count (Percent)	
Gender	Male	115 (61.80%) ^a	154 (55.40%) ^a	90 (60.80%) ^a	100 (64.50%) ^a	0.255
	Female	71 (38.20%) ^a	124 (44.60%) ^a	58 (39.20%) ^a	55 (35.50%) ^a	
Prognosis	Discharge	163 (87.60%) ^a	232 (83.50%) ^a	116 (78.40%) ^{ab}	101 (65.20%) ^b	<0.0001
	Dead	23 (12.40%) ^a	46 (16.50%) ^a	32 (21.60%) ^{ab}	54 (34.80%) ^b	
CRF	No	183 (98.40%) ^a	276 (99.30%) ^a	145 (98.00%) ^a	149 (96.10%) ^a	0.133
	Yes	3 (1.60%) ^a	2 (0.70%) ^a	3 (2.00%) ^a	6 (3.90%) ^a	
Alzheimer	No	182 (97.80%) ^a	276 (99.30%) ^a	147 (99.30%) ^a	153 (98.70%) ^a	0.501
	Yes	4 (2.20%) ^a	2 (0.70%) ^a	1 (0.70%) ^a	2 (1.30%) ^a	
DM	No	174 (93.50%) ^a	257 (92.40%) ^a	139 (93.90%) ^a	144 (92.90%) ^a	0.939
	Yes	12 (6.50%) ^a	21(7.60%) ^a	9 (6.10%) ^a	11 (7.10%) ^a	
COPD	No	152 (81.70%) ^a	196 (70.50%) ^b	104 (70.30%) ^{a,b}	106 (68.40%) ^b	0.017
	Yes	34 (18.30%) ^a	82 (29.50%) ^b	44 (29.70%) ^{a,b}	49 (31.60%) ^b	
HT	No	178 (95.70%) ^a	267 (96.00%) ^a	1481 (100.00%) ^a	149 (96.10%) ^a	0.101
	Yes	8 (4.30%) ^a	11 (4.00%) ^a	1 (0.00%) ^a	6 (3.90%) ^a	
CHF	No	179 (96.20%) ^a	267 (96.00%) ^a	139 (93.90%) ^a	145 (93.50%) ^a	0.510
	Yes	7 (3.80%) ^a	11 (4.00%) ^a	9 (6.10%) ^a	10 (6.50%) ^a	
CAD	No	181 (97.30%) ^a	272 (97.80%) ^a	139 (93.90%) ^a	153 (98.70%) ^a	0.060
	Yes	5 (2.70%) ^a	6 (2.20%) ^a	9 (6.10%) ^a	2 (1.30%) ^a	
Arrhythmia	No	181 (97.30%) ^a	271 (97.50%) ^a	143 (96.60%) ^a	147 (94.80%) ^a	0.482
	Yes	5 (2.70%) ^a	7 (2.50%) ^a	5 (3.40%) ^a	8 (5.20%) ^a	

a, b,c: Different characters in each row show a statistically significant difference (p <0.05). **CRF:** Chronic renal failure, **DM:** Diabetes mellitus, **COPD:** Chronic obstructive pulmonary disease, **HT:** Hypertension, **CHF:** Chronic heart failure, **CAD:** Coroner artery disease.

The effects of the laboratory findings, comorbid diseases, age and length of stay on mortality are shown in Table 2. DM and HT significantly increased the risk of death (p = 0.022, p = 0.006, respectively). Other comorbid diseases had no effect on mortality (p> 0.05). We found that,

only high levels of LDH and ferritin increased the risk of death significantly (p <0.001, p = 0.041, respectively). It was also found that, advanced age and prolonged stay in the hospital significantly increased the risk of death (p <0.001).

Table 2. The effects of the laboratory findings, comorbid diseases, age and length of stay on risk of mortality

Variables	Odds Ratio	95% C.I.for EXP(B)		p-value
		Lower	Upper	
DM	2.454	1.135	5.306	0.022
COPD	1.215	0.765	1.931	0.409
HT	4.724	1.545	14.447	0.006
CHF	1.664	0.678	4.087	0.267
CAD	2.032	0.710	5.816	0.186
Arrhythmia	2.509	0.901	6.981	0.078
CRP	1.013	0.983	1.044	0.388
LDH	1.003	1.002	1.004	<0.0001
Ferritin	1.001	1.000	1.001	0.041
DDimer	1.011	0.968	1.057	0.619
INR	0.996	0.850	1.167	0.957
Procalcitonin	1.097	0.993	1.212	0.070
Age	1.055	1.033	1.077	<0.0001
Length of stay in hospital	1.077	1.037	1.118	<0.0001
Constant	0.003			<0.0001

DM: Diabetes mellitus, **COPD:** Chronic obstructive pulmonary disease, **HT:** Hypertension, **CHF:** Chronic heart failure, **CAD:** Coroner artery disease.

DISCUSSION

The clinical prognosis of Covid 19 disease is divided into three different phases, namely, early infection, pulmonary, and anti-inflammatory phases, and each phase has a typical biochemical marker (2). The early infection phase begins with infiltration of the virus into the lung parenchyma, with symptoms characterized by fever and cough similar to typical upper respiratory tract infection. The most important laboratory finding during this phase is lymphopenia. In the pulmonary phase, lung infection develops in the form of viral pneumonia and increased levels of CRP are prominent as well as lymphopenia and elevation of transaminases. The inflammatory phase is characterized by ARDS caused by systemic inflammation or cytokine storm. During this phase, patients are usually treated in the ICU. During this period, cardiac and kidney damages caused by the complications of Covid 19 are quite common. In addition, increased levels of CRP, PCT, D dimer, LDH, fibrinogen, ferritin, ProBNP, and creatinine are observed at the forefront, during this phase (2). The increased levels of these parameters are directly associated with the severity of the disease, the mortality rate and the length of stay in the hospital (13, 14).

In many studies, there are contradictory reports regarding which parameters are more specific in determining both the severity of the disease and the risk of mortality. For example, in a study examining the biochemical parameters in mild, moderate and severe Covid 19 cases, it was found that CRP and LDH levels increased 3 days after hospitalization in patients with severe disease and the CRP levels decreased dramatically within 6-9 days, and then there was no difference between the patients. In the same study, it was found that LDH levels were still significantly higher within 6-9 days, and LDH was suggested to be a more important indicator of treatment response (15). In other studies, it has been shown that liver enzymes including ALT and AST are elevated in severe patients, but LDH is a more important parameter in detecting disease severity and poor prognosis (14, 16). In a study conducted in China, it was found that CRP and PCT levels were higher in patients with severe disease compared to patients with mild and moderate disease. However only the CRP was suggested to be an independent risk factor in detecting the severity of the disease (17, 18). In another study, it was suggested that PCT may be a more specific parameter in determining the prognosis (19). In a meta-analysis, it was found that many biochemical parameters increased in patients with severe Covid 19, however, high levels of ferritin as well as interleukins were found to be more important parameters in distinguishing severe and fatal Covid 19 patients (20). Similarly, in our study, we found that CRP, LDH, PROBNP, PCT and fibrinogen levels were statistically significantly higher in group 4 patients compared to group 1 and

group 2 patients; prolongation of the length of stay in the hospital was associated with the severity of the disease ($p < 0.05$). LDH and ferritin levels were independent risk factors, increasing the mortality rate ($p < 0.05$ for both). This finding supports studies suggesting that LDH and ferritin levels were more specific parameters. Similar to other studies, in our study, although many parameters increased, only a few of them affected the prognosis. This may be due to the personal characteristics of the patients, the type of comorbidities, and the rate and severity of complications. In addition, the fact that the patients in our sample were divided into groups according to the total length of stay in the hospital, but not according to being hospitalized in the ICU or wards may have affected our findings.

In a meta-analysis, in which more than 1000 Covid 19 patients were included and a total of 61 studies were reviewed, it was found that severe disease was more common and the mortality rate was higher in male patients. In addition, in the same study, it was shown that the severity of the disease and the mortality rate were higher in elderly people and comorbidities such as HT, cardiovascular disease, chronic renal failure, and COPD increase the severity of the disease, the rate of ICU admission, and mortality (21). In a different meta-analysis, it was found that rate of comorbidities was higher in patients with severe disease and HT and DM were the most commonly seen diseases (22). Similarly, in a study conducted on 32583 patients in Mexico, HT and DM were shown to be the most common comorbidities and affected the severity of the disease (10). In our study, the number of male patients was higher than female patients (60%) and the average age of the patients was 69.5. The rate of male patients was highest in group 4 (64.50%). Advanced age and prolongation of stay in the hospital were indicators of disease severity and significantly increased the mortality rate. At least one comorbidity was present in 51.5% of the patients and the most common comorbidity was COPD. The number of individuals with COPD was statistically significantly higher in group 4 compared to group 1 ($p < 0.0001$). In addition, we found that HT was present in 26 patients and DM was present in 53 patients. However, in the risk analysis, it was determined that HT and DM increased the mortality rate statistically significantly. Unlike other studies, in our study, although the number of patients with HT and DM was less, both increased the mortality risk significantly. This finding suggests that HT may be an important risk factor, even though it is seen less frequently, and the increased risk should be considered in the treatment and monitoring of these patients.

CONCLUSIONS

The results of our study show that CRP, LDH, PCT, PROBNP, and fibrinogen levels

increased in direct proportion with the prolongation of hospital stay in Covid 19 patients and these parameters may be associated with the severity of the disease. In addition, these results show that LDH and ferritin levels, age, length of stay in

hospital, presence of comorbid diseases including HT and DM increase mortality rate and may be specific parameters in terms of prognosis.

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