



Evaluation of the Effect of Biomarker Levels Associated with Disease Severity on Mortality in COVID-19 Patients in the Gaziantep Region of Turkey

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ABSTRACT

This study aimed to investigate the effect of clinical and some specific laboratory parameters on the prognosis and mortality of critically ill COVID-19 patients who need to be followed in the intensive care unit (ICU). This is a retrospective cohort study. A total of 180 patients treated in the ICU were included in the study. The data of clinical and levels of D-dimer, cardiac troponin I (cTnI), Ferritin, and CK-MB were researched. The multivariate and univariate logistic regression models were employed to investigate the risk factors affiliated with in-hospital death. There was a significant difference in mortality between women and men ($p=0.002$). Hypertension was the most common comorbid disease, mortality was detected to be significantly greater in patients over 65 years of age. The serum D-dimer, cTnI, CK-MB, and ferritin levels were found to be higher in patients at risk. In the multivariate logistic regression model, we detected that ferritin above 300 $\mu\text{g/l}$ ($p=0.05$) alongside cancer was associated with mortality. This study showed that advanced age is an important risk factor as well as the mortality of patients with cancer –especially those with a ferritin value above 300 $\mu\text{g/l}$ and patients with a high cTnI value.

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Türkiye'nin Gaziantep Bölgesinde COVID-19 Hastalarında Hastalık Şiddetiyle İlişkili Biyobelirteç Düzeylerinin Mortalite Üzerine Etkisinin Değerlendirilmesi

ÖZET

Bu çalışma, yoğun bakım ünitesinde (YBÜ) takip edilmesi gereken kritik COVID-19 hastalarının prognoz ve mortalitesi üzerine klinik ve bazı özellikli laboratuvar parametrelerinin etkisini araştırmayı amaçlamıştır. Bu retrospektif bir kohort çalışmasıdır. Yoğun bakımda tedavi edilen toplam 180 hasta çalışmaya dahil edildi. D-dimer, kardiyak troponin I (cTnI), Ferritin ve CK-MB klinik verileri ve düzeyleri araştırıldı. Hastane içi ölümlle ilişkili risk faktörlerini araştırmak için çok değişkenli ve tek değişkenli lojistik regresyon modelleri kullanıldı. Kadınlar ve erkekler arasında mortalite açısından anlamlı fark vardı ($p=0,002$). Hipertansiyon en sık görülen komorbid hastalıktı, mortalite 65 yaş üstü hastalarda anlamlı olarak daha yüksek saptandı. Risk altındaki hastalarda serum D-dimer, cTnI, CK-MB ve ferritin düzeyleri daha yüksek bulundu. Çok değişkenli lojistik regresyon modelinde, kanserle birlikte 300 $\mu\text{g/l}$ 'nin ($p=0.05$) üzerindeki ferritin mortalite ile ilişkili olduğunu saptandı. Bu çalışma kanserli hastalarda, özellikle ferritin değeri 300 $\mu\text{g/l}$ 'nin üzerinde olanlarda ve cTnI değeri yüksek olan hastalarda, ileri yaşın mortalitesi kadar önemli bir risk faktörü olduğunu göstermiştir. Serum D-dimer, cTnI, CK-MB ve ferritin düzeyleri yüksek olan hastalarda mortalite anlamlı olarak daha yüksekti.

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INTRODUCTION

COVID-19(Coronavirus disease 2019), a member of the family Coronaviridae, was first observed in December 2019 in Wuhan, China. Severe acute respiratory syndrome, which soon turned into a worldwide spreading COVID-19 pandemic, is an infection brought about by Coronavirus-2 (SARS-CoV-2) (Doruk et al. 2021).

In SARS-CoV-2 disease, the virus mainly binds to the receptor of the angiotensin-converting enzyme 2 (ACE2), which belongs to the cell membrane and is expressed in the lung. The circulatory system also becomes a target of the virus because it expresses ACE2. Interstitial pneumonia in COVID-19, which often causes pneumonia in the lungs, is affiliated with a poor prognosis (Bayrakçı 2022).

The level of cardiac troponin was found to be significantly greater in severely infected patients hospitalized in the intensive care unit (ICU) or who died. Myocardial damage recognized by an increased level of troponin occurs in COVID-19 patients due to non-ischemic myocardial processes, including severe acute respiratory syndrome, particularly with sepsis, hypoxia, pulmonary thrombosis, systemic inflammation, and embolism (Imazio et al. 2020).

It is noted that hypertension, diabetes, cerebrovascular disease, and ischemic heart disease are significantly more frequent in people requiring intensive care or dying from COVID-19. Myocardial damage and dysfunction caused by SARS-CoV-2 are common in COVID-19 patients followed up in ICU, evidenced by the frequent occurrence of troponin elevation and electrocardiographic abnormalities (Salazar et al. 2020).

The clinical signs of COVID-19 are aggravated by the propagation of disseminated intravascular coagulation (DIC), thrombosis, and cytokine storms. Coagulation/fibrinolytic abnormality, which is very often noted in COVID-19, is associated with an increase in D-dimer and plays a significant role in the prognosis. However, assessing the D-dimer value by a physician is important in supporting examination findings (Asakura et al. 2021).

An increase in the levels of cardiac biomarkers is observed in COVID-19 patients, including high-sensitive cardiac troponin I (cTnI), NT-proB-type Natriuretic Peptide (Pro-BNP), myoglobin (MB), creatinine kinase-MB (CK-MB), as well as D-dimer. In particular, the incidence of COVID-19 increases in cancer patients (Huang et al. 2021).

This study was designed to investigate the effect of D-dimer, cTnI, Ferritin, and CK-MB levels on the

mortality of critically ill COVID-19 patients who need to be followed up in the ICU.

MATERIALS and METHODS

The study retrospectively analyzed the hospital archives of COVID-19 patients who were admitted to the ICU of Gaziantep Ersin Arslan Educational Research Hospital between May 1 and July 1, 2021. The study included 18-year-old and older patients who were admitted to intensive care with a diagnosis of COVID-19, whose cTnI, D-dimer, and CK-MB were examined within the first day in the ICU.

Demographic data, medical history, clinical data, chronic medication, laboratory findings, comorbidities, intubation status and duration, complications, mortality, and data on mortality and low-dose computed tomography of the lung (LDCT) findings were present in the patient's electronic medical record. The following-up period ended with the patient's discharge or death. The data obtained by the study team during the application hospital stay were collected retrospectively.

cTnI levels were determined by the Abbott cTnI ADV microparticle enzyme immunoassay on the Architect i2000SR Immunoassay Analyzer (Abbott Diagnostics, Chicago, Ill., USA). The normal cTnI level was accepted as ≤ 34.2 ng/L in men and ≤ 15.6 ng/L in women according to the laboratory reference data of our hospital. High values than these were considered to be the abnormal cTnI level.

The measurement of CK-MB activity was performed using the Abbott Architect c 8000 devices using the immune inhibition method (Abbott Diagnostics, Chicago, Ill., USA). A 25 U/L was accepted as the upper limit of the normal.

The D-dimer activity was measured in the plasmas of patients by using the immunoturbidimetric method on the STA Compact Max device (Stago, France). The threshold value we used to detect the negative D-dimer's negative and positive predictive values was 00 mg/dl.

Ferritin measurements were made from the serum obtained via centrifuging the blood samples at 4000 rpm for 10 minutes, using the enzyme immune assay method (Beckman Coulter DXI 800 device of SRT company's original kit). The threshold value we used to determine the negative and positive predictive values of ferritin levels was 360 µg/L.

The serums were analyzed with the Enzyme Immune Assay (EIA) method in the CBC laboratory using the kit of Bio Merieux Company (Ferritin EIA).

Statistical analysis was conducted employing the SPSS 15.0 software. Also, continuous and categorical variables were indicated as median, mean, and n (%), respectively. The suitability of the variables for normal distribution was analyzed employing the figures (probability and histogram graphs) and analytical methods (Shapiro-Wilk tests/Kolmogorov-Smirnov).

According to the Kolmogorov-Smirnov test, the data where the p-value was above 0.05 was considered to show normal distribution. The differentiation between the groups was compared using the Chi-square, Fisher, and the comparison of numerical data that was not normally distributed was done with the Mann-Whitney U test. The multivariate and univariate logistic regression models were employed to investigate the risk factors affiliated with in-hospital death. A p-value of 0.05 ($p \leq 0.05$) was regarded to be statistically significant.

To be able to conduct the study, necessary permission

was taken from the Ethics Committee for Non-Interventional Clinical Research of Gaziantep University (No: 2022/75).

RESULTS and DISCUSSION

A total of 180 patients, 81 (45.3%) of whom were female and 99 (54.7%) of whom were male, were enrolled in the study. The patient's median age was 64 years. The average age was 63.9 ± 14.7 years (Range 20-94). The difference between men and women in terms of age was compared by the Mann-Whitney U test since age did not show a normal distribution. There was a significant differentiation between women and men ($p=0.002$). The median age was 61 years for males and the average median age was 60.8 ± 15 years (Range 20-91). The median age was 67 years for women and the average median age was 68.4 ± 12.7 years (Range 43-94) (Table 1).

Table 1. Demographic data of the study
Çizelge 1. Çalışmanın demografik verileri

Parameters	n	Std Dev	CI 95%
Gender	180		
Male	99 (54.7%)		
Female	81 (45.3%)		
Age	63.9 ± 14.7 (20-94)	14.7	2.16
<65 years	94	0.22	0.07
>65 years	86	0.49	0.03
Hospitalized stay	8.9 ± 6.8 (1-37)	7.05	1.03
Mortality	96		

The diagnosis result of COVID-19 was verified by PCR in 149 (82.8%) patients and by clinical and radiological findings in 31 (17.2%) patients. We did find no differentiation between men and women in terms of PCR positivity ($p=0.412$).

During diagnosis, a comorbid disease was present in 135 (75%) of the patients. Hypertension was the most common comorbid disease in 35 (19.4%) patients. This was followed by the diagnosis of type 2 diabetes mellitus, which was detected in 28 (15.6%) patients, and cancer, which was detected in 10 (5%) patients. (Table 2).

The median intensive care hospitalization time of the patients was 8.9 days and the average hospitalization time was 8.9 ± 6.8 (Range 1-37). Of the patients who were followed up, 94 (53.3%) died, and 76 (44.7%) patients were discharged. There was no difference in gender between patients who died and survived ($p=0.170$). Assessed for comorbid diseases, no statistical difference was detected in the presence of comorbid diseases such as type 2 DM and hypertension ($p=0.089$, $p=0.182$, and $p=0.532$, respectively). However, the presence of cancer made a significant difference ($p=0.036$). Of the 10 patients with cancer, only one was able to be discharged, while all the other

patients died.

Advanced age is an important cause of mortality between the mortality reasons of patients. When patients were categorized as over and below 65 years of age, mortality was detected to be significantly greater in patients over 65 years of age. Also, 48 (63.15%) of the 76 patients over the age of 65 died, and 46 (46.15%) of the 104 patients under the age of 65 died. The age differences between those discharged from the hospital and dead patients were statistically significant ($p=0.003$).

This study shows that 48.33% of COVID-19 patients have an elevated cTnI level on the first day of hospitalization. According to our study, 60 out of 87 (68.96%) of the patients with a high cTnI level (1.49) died.

In this study, founded that the CK-MB values of 22 of the patients in the ICU due to COVID-19 were above the normal value. Of these 22 patients, 19 (86.36%) cases resulted in mortality.

In this study, the D dimer level of 129 patients was above 1.0 and the average D dimer was 5.01. Of these 129 patients, 76 ended up with mortality. D-dimer concentrations were significantly higher in the

decedent patients (5.41µg/mL) than in discharged patients (1.86µg/mL). D-dimer concentrations were above 15µg/mL in 14 of the 96 dead patients (14.58%) and in 3 of the 84 recovered patients (3.5%).

Mortality was significantly higher in 72 (60%) of 120 patients with serum ferritin above 300 µg/L, while 22 (44%) of 50 patients with ferritin under 300 µg/L died (p=0.041).

Table 2. Statistical analysis of the study
Çizelge 2. Çalışmanın istatistiksel analizi

Parameters	n	Mean	Hospital Stay		Mortality	
				p<	%	p<
Gender						
Male	99	55%			57.5%	
Female	81	45%			48.1%	
Ages		63.9				
<65 years	94	52.2%			47.8%	
>65 years	88	47.8%	>20 days	0.004	57.9%	0.006
Comorbidity						
Yes	135	75%			56.2%	0.08
Hypertension	33	18.3%			51.5%	0.06
Diabetes Mellitus	19	10.5%			63.1%	
Hypertension and Diabetes Mellitus	29	16.2%	>25 days	0.005	55.1%	
Malignity	11	6.1%			72.7%	
Other	43	23.9%			53.4%	0.04
No	45	25%	<10 days	0.03	44.4%	
Data from the laboratory						
CKMB (ng/ml)		3.95±2.15				0.07
Troponin (ng/L)		0.82±0.37				0.5
D-Dimer (µg/L)		3.48±1.01				0.05
Ferritin (µg/L)		784±50.8				0.08

*Mann Whitney U test was used with a 95% Confidence Interval (CI) for statistical analysis

In the multivariate logistic regression model, we found that ferritin above 300 µg/L (p=0.05) alongside cancer was associated with mortality

This research is a retrospective cohort research that demonstrates the strength of predicting the clinical progress and prognosis of patients with elevated levels of cardiac cTnI and D-dimer detected on the first day of patients admitted to ICU due to COVID-19.

In this study, 96 of the 180 patients died during follow-up and treatment.

This study shows that 48.33% of COVID-19 patients have an elevated cTnI level on the first day of hospitalization. Patients with elevated troponin-I levels were older and had greater rates of congestive heart disease and cardiovascular risk factors (dyslipidemia, hypertension, diabetes, peripheral vascular disease, chronic kidney disease, cerebrovascular disease). Cardiac troponins are used in routine practice as sensitive and specific biomarkers to diagnose myocardial damage in diseases such as acute coronary syndromes or acute myocarditis (Thygesen et al. 2010).

Elevation of cardiac troponins is seen as a prognostic marker for predicting the negative consequences of heart failure, even without coronary artery stenosis (Kociol et al. 2010). In addition, cardiac troponin

uprising has been revealed in many non-myocardial ischemic conditions such as sepsis syndrome, pulmonary embolism, subarachnoid hemorrhage, and renal failure, and has been considered prognostic biomarkers with several clinical outcomes (Freda et al. 2002). In this study, cTnI elevation was strongly associated with poor in-hospital prognosis, including clinical course of patients, need for ICU, and all-cause mortality. Cordeanu et al. revealed that 34% of their patients had a high level of Troponin-I and had a four-fold enhanced risk of death in these patients in comparison with patients with a normal level of troponin-I (Cordeanu et al. 2020).

According to this study, 60 out of 87 (68.96%) of the patients with a high cTnI level (1.49) died. Patients hospitalized in ICU due to COVID-19 and with troponin levels above 1.00 had a high mortality rate.

Majure et al. (2021) conducted a study where troponin was an estimator of death, involving 6247 patients infected with COVID-19, and reported significantly increased mortality rates in the group of patients with high troponin quantity in comparison with patients with normal troponin levels.

Shi et al. (2020) conducted a study on 671 patients with verified COVID-19, the myocardial injury prevalence determined by hs-troponin I above the 99th percentile

was found to be 15.8%. Both cardiac troponin I >0.026 ng/ml (hazard ratio, 4.56, $p = .02$) and CK-MB >2.2 ng/ml (hazard ratio, 6.62, $p <.001$) was separately associated with an increase in in-hospital mortality.

We found that the CK-MB value of 22 of the patients in the ICU due to COVID-19 was above the normal value. Of these 22 patients, 19 (86.36%) cases resulted in mortality. This shows that the elevation of cTn and CK-MB quantities in COVID-19 intensive care patients is associated with mortality.

COVID-19 mortality rates vary according to age and gender all over the world. Even if the majority of infections in China and Germany affect young age groups, it particularly strains the elderly population. The mortality rate in China is reported as 2.3%. The proportion of people over 80 is only 3%. The elderly people in Italy are even more seriously affected. Of them, 37.6% are aged 70 and over, and the mortality rate of 7.2% is significantly higher than in China. Mortality in this group increases significantly with age. Also, 12.5% of the 70-79 age group die, 19.7% of the 80-89 age group die, and 22.9% of the very old (≥ 90 years) group die (4, 5, 6). In the study conducted by Li et al. on 425 patients, there were no patients under the age of 15. Fifty-six percent of the patients were male and the majority of them were 45 years of age or older. In later studies, it was also observed that the disease was more severe in older age and male patients (Bornstein et al. 2020).

A total of 180 patients who received inpatient treatment in intensive care between 1 May 2021 and 1 July 2021 in this hospital were assessed. Firstly, a demographic analysis of these patients was done. When the age of the patients is evaluated, a statistically significant relationship of age is observed between the deceased patients and the recovered patients ($p < 0.05$). Mortality in this group increases significantly with age. Also, 12.5% died in the 70-79 age group, 19.7% died in the 80-89 age group, and 22.9% died in the very old (≥ 90 years) age group. Seventy-six of the deceased patients were over the age of 65 years and the average age was 80.71 years. The number of recovered patients was 84, and the average age was 60.22 years. Advanced age is an important cause of mortality when considering the mortality of patients. Mortality is significantly greater in patients over 65 years old when patients are categorized as over and below 65 years of age. Of the 76 patients over the age of 65, 48 patients (63.15%) died, while 46 (46.15%) of the 104 patients under the age of 65 died.

According to this study, 96 patients out of 180 died and 57 (59.37%) of the deceased patients were male. This shows us that high age and male gender were found to be associated with mortality and the need for intensive care in patients with COVID-19.

Diabetes and hypertension are the most common

comorbidities for people with COVID-19 who require hospitalization in ICU. In a study comprising 5,700 patients, conducted by Richardson S. et al., the median age was reported as 63-year-old, and the most frequent comorbidities were diabetes (1808; 33.8%), obesity (1737; 41.7%), and hypertension (3026; 56.6%) (Richardson et al. 2020). Recent studies show that COVID-19 patients with hypertension have a greater risk of mortality in general compared to non-hypertensive patients (Zuin et al. 2020).

Retrospective cohort research comprised 126 COVID-19 patients with pre-existing hypertension, as well as 125 COVID-19 patients of similar age and gender without hypertension, and reported that myocardial damage after hypertension is a worse prognosis factor and is straightforwardly linked with higher mortality in COVID-19 (Yang et al. 2020).

In this study, the comorbid disease was present in 135 (75%) of the patients in the course of diagnosis. Hypertension was the most common comorbid disease in 67 (49.52%) patients. This was followed by the diagnosis of type 2 diabetes mellitus, which was detected in 38 (28.14%) patients, and cancer, which was detected in 10 (7.40%) patients. Seventy-six (56.29%) of the 135 patients who were followed up due to COVID-19 died, also only 15 (33.33%) of the 45 patients who did not have additional disease died. Comorbidity significantly increases mortality in patients in intensive care due to COVID-19.

The elevation of the D-dimer indicates a state of hypercoagulation in patients with COVID-19. D-dimer, a fibrin degradation product, is observed to be high in the blood serum of patients with COVID-19. The elevation of D-dimer in COVID-19 is the most sensitive marker among coagulation parameters and indicates a higher risk of developing thrombosis.

Zhang et al. (2020) emphasized that D-dimer levels (>2 mg/dl) are an important indicator in determining mortality in COVID-19 patients with pneumonia.

Guan et al. (2020) reported the results of a large retrospective study that for the first time demonstrated the correlation between abnormal D-dimer levels and disease severity in COVID-19 patients. They set a cut-off point at a D-dimer level of more than 0.5 mg/L and revealed that a significantly bigger ratio of individuals with the novel coronavirus with severe symptoms exhibits abnormally high D-dimer levels than the patients with moderate or mild symptoms ($p = 0.002$).

In addition, Tang et al. (2020) revealed that patients with COVID-19 at severe disease levels showed nearly 3.5 times higher D-dimer quantities than those with moderate or mild disease.

According to this study, D-dimer levels of patients in intensive care were significantly higher than normal. The reason for this is immobilization, comorbidities,

and intense viral inflammation, and therefore we think that vascular occlusions and microthrombi are more common in patients who are followed up in intensive care.

Also, in-hospital mortality was linked with elevated D-dimer levels, demonstrating that the test could be used as a single helpful biomarker for clinical outcomes in COVID-19 patients.

When COVID-19 infection causes an "inflammatory storm", not only the associated cytokines are greatly elevated, but also some inflammatory biological markers including serum ferritin, CRP, PCT, and SAA are increased. CRP, Ferritin, PCT, and SAA levels increased significantly in the severe and critical COVID-19 cases than in moderate cases (Qin et al. 2020).

Zhou et al. (2020) reported that mortality increases in COVID-19 patients with higher serum ferritin levels.

We found that patients with serum ferritin above 300 µg/L had significantly higher mortality, 72 (60%) of 120 patients with high ferritin died, while 22 (44%) of 50 patients with ferritin under 300 µg/L died ($p=0.041$).

The outcomes of this study can make significant contributions to clinical practice. Assessing the level of ferritin can contribute to the early identification of patients who need to be remedied in a more screened environment due to the high risk of a bad result. In addition, the assessment of ferritin could allow making treatment decisions to prevent complications and/or death.

In this study, we aimed to determine the determinants of biochemical parameters that may have an impact on the need for treatment, as well as mortality in the ICU, of patients receiving inpatient treatment with a COVID-19 diagnosis.

The study was conducted under some limitations. Although a sufficient number of patients were involved in the research, it was still a retrospective study, the data were collected from a single center, and the processes of comorbid diseases could not be detailed, which constituted the limitations of the study.

CONCLUSION

Consequently, COVID-19 is a disease whose activity is still very high and continues to spread rapidly. Scientists are continuing to look for markers that can help in the early detection of this disease and determining the prognosis.

We believe that the biochemical parameters mentioned in this study are important in determining the prognosis of the disease and may be useful in terms of the need for patients to be referred to the intensive care unit after the initial examination in the emergency department.

As a result, given the numerous potential causes of abnormal cTnI levels, normal troponin levels may be more valuable for clinicians. In this research, we found out that the normal troponin quantity on the first day of hospitalization had a high negative predictive accuracy (99.3-91.7%) in the male and female gender for mortality. Such a powerful biomarker can be used during the admission of patients to the hospital to evaluate and conduct further treatment in high-risk people.

As a consequence, hematological and biochemical parameters can be used as predictive markers during the treatment process, both during the application for diagnostic purposes and in determining the severity and prognosis of the disease, as well as during the follow-up of treatment.

Advanced age and comorbidities in COVID-19 patients are linked with a poor prognosis in critical patients with COVID-19. Also, a greater number of comorbidities are affiliated with the higher disease severity of COVID-19. It can help determine the patients at high mortality risk in the COVID-19 pandemic as a model that summarizes the sum of CCI, age, and comorbidities.

Author's Contribution

The authors declare that they have contributed equally to the article.

Statement of Conflict of Interest

Authors have no conflict of interest to declare.

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