

Comparison of Brain Natriuretic Peptide and Other Laboratory Parameters of Those Who Died from Coronavirus Disease and Those Who Were Discharged

Koronavirüs Hastalığı Nedeniyle Ölenlerle Taburcu Olanların Beyin Natriüretik Peptit ve Diğer Laboratuvar Parametrelerinin Karşılaştırılması

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ABSTRACT

Objective: In this study, we aim to compare the brain natriuretic peptide (BNP) of patients who were diagnosed with COVID-19 infection, who were hospitalized and discharged, and those who died.

Materials and Methods: The study was conducted on 474 patients diagnosed with COVID-19 disease. Information of 56 patients who died and 418 patients with COVID-19 who were discharged were obtained from the hospital information management system (HIMS) and analyzed retrospectively. The relationship between BNP, white blood cell (WBC), neutrophil (NEU), lymphocyte (LYM), platelet (PLT), Procalcitonin (PCT), High Sensitive Troponin I (hs Tn I), D-dimer and C-Reactive Protein (CRP) levels in deceased patients and discharged patients researched.

Results: There was no statistically significant difference in mortality between women and men ($p=0.385$). There was no statistically significant difference in BNP, WBC, NEU, LYM, platelet, PCT and hs Tn I values between those who died and those who were discharged. D-dimer and CRP values of those who died and discharged were statistically significant ($p<0.031$ and 0.020 , respectively).

Conclusions: Increased levels of CRP and D-dimer were found to be associated with mortality. More comprehensive studies are needed on this subject.

Keywords: Brain Natriüretik Peptide, C-Reactive Protein, Coronavirus infections, D-dimer

ÖZ

Amaç: Bu çalışmada amacımız, COVID-19 enfeksiyonu teşhisi alıp hastanede yatıp taburcu olanlar ile ölen hastaların beyin natriüretik peptidini (BNP) karşılaştırmaktır.

Materyal ve Metot: Çalışma COVID-19 hastalığı teşhisi konan 474 hasta üzerinde gerçekleştirildi. Ölen 56 hasta ile taburcu olan 418 COVID-19 hastasının bilgileri hastane bilgi yönetim sisteminden (HBYS) alındı ve geriye dönük olarak analiz edildi. Ölen hastalar ile taburcu olan hastalarda BNP, beyaz küre hücresi (WBC), nötrofil (NEU), lenfosit (LYM), trombosit (PLT), Procalcitonin (PCT), Yüksek Duyarlı Troponin I (hs Tn I), D-dimer ve C-Reaktif Protein (CRP) düzeyleri arasındaki ilişki araştırıldı.

Bulgular: Kadınlar ile erkekler arasında mortalite açısından istatistiksel olarak anlamlı bir fark yoktu ($p=0,385$). Ölenler ile taburcu olanlar arasında BNP, WBC, NEU, LYM, trombosit, PCT ve hs Tn I değerlerinde istatistiksel olarak anlamlı fark yoktu. Ölenler ile taburcu olanların D-dimer ($p<0,031$) ve CRP ($p<0,020$) değerleri istatistiksel olarak anlamlı bulundu.

Sonuç: Artan CRP ve D-dimer düzeylerinin mortalite ile ilişkili olduğu bulundu. Bu konuda daha kapsamlı çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Beyin Natriüretik Peptid, C-reactive protein, D-dimer, coronavirus enfeksiyonları

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Yayın Bilgisi / Article Info:

Gönderi Tarihi/ Received: 26/01/2023

Kabul Tarihi/ Accepted: 05/10/2023

Online Yayın Tarihi/ Published: 18/12/2023

INTRODUCTION

COVID-19 appeared for the first time in Wuhan City, China. COVID-19 infection has been classified as a pandemic by WHO.¹ Common symptom of COVID-19 are fever, cough, shortness of breath, muscle aches, diarrhea, loss of smell and taste, and fatigue in most patients.² Approximately 15% of affected patients have acute respiratory distress syndrome (ARDS).³ In the literature, patients with pre-existing Cardiovascular Diseases (CVD) and infected with COVID-19 have a more severe and higher mortality rate.⁴

Neutrophils, lymphocytes, and platelets are important blood cells that play a role in inflammation-related diseases. Today, it is used in many infectious and tumoral formations.⁵

C-reactive protein (CRP) is an acute phase reactant (APR). CRP was first detected in the serum of patients with pneumococcal pneumonia. APR concentration was increased in serum due to tissue damage and inflammation. Due to these properties, the increase in serum CRP levels a few hours after inflammation has led to this being one of the first biomarkers considered in COVID-19.⁶

The systemic values of D-dimer are used to evaluate the circulating fibrin cycle, and even a single measurement is sufficient to obtain information about the fibrinolytic status. D-dimer is generally used to evaluate coagulation and fibrinolysis activation.⁷

Procalcitonin (PCT) production, an undetectable or meagre amount of detectable protein in the blood of healthy individuals, can be stimulated by bacterial endotoxins, exotoxins, and some cytokines. It has been found that the most common increase in the serum in sepsis. Its early rise can be detected in a short time and quickly. This feature is a valuable parameter in the diagnosis and follow-up of sepsis.⁸

Troponins are found in skeletal and cardiac muscle structures together with tropomyosin. Troponins are structural proteins that regulate skeletal and cardiac muscle contraction.⁹

Cardiac complications are a common occurrence among hospitalized patients with COVID-19. BNP is secreted from the ventricle due to the tension of myocyte cells in the atrium and ventricle walls of the heart.¹⁰ Natriuretic peptides are important biomarkers of myocardial stress. Natriuretic peptides are also frequently elevated in patients with severe respiratory disease. Typically, elevated cardiac filling pressures or elevation of BNP or NT-proBNP in the absence of clinical heart failure are associated with worse outcomes in patients with ARDS.¹¹

This study aimed to determine the predictive value of BNP levels in people who recovered from COVID-19 infection and died.

MATERIALS AND METHODS

Ethical Approval: The study was approved by the Sakarya University Ethical Committee (Date: 04/09/2020, decision no: E.7734). And institutional permissions (Date: 02.06.2020) were obtained. In line with the Helsinki Declaration, the nurses were informed about the study, and their informed consent was obtained. After obtaining verbal consent from the nurses who volunteered to participate in the study, they were included in the study.

Study Group: A total of 474 patients who applied to our hospital's pandemic outpatient clinics and were diagnosed with COVID-19 and hospitalized in the COVID-19 service were included in this study. Of these patients, information on 56 patients who died due to COVID-19 and 418 patients who recovered were obtained from the hospital information management system and analyzed retrospectively. Diagnosis of COVID-19; clinical findings and computed tomography and SARS-CoV-2 RT-PCR. In our study, BNP, WBC, neutrophil (NEU), lymphocyte (LYM), platelet (PLT), D-dimer, C-reactive protein (CRP), Procalcitonin (PCT), and High Sensitive Troponin I (hs Tn I) parameters were evaluated.

Sample Collection, Nucleic Acid Isolation and Reverse Transcriptase PCR Reaction: Combined nasopharyngeal and oropharyngeal swab samples were placed in a viral transport medium immediately after taking with a dacron swab and were stored at 2-8°C and transported to the laboratory. The samples were sent to the laboratory following the infection prevention and control procedures, paying attention to the triple transport system and cold chain rules. After the samples were accepted in the microbiology laboratory, the samples were taken to the 3rd-level bio-safe negative pressure room. Bio-Speedy® Viral Nucleic Acid Isolation Kit (bioeksen, Türkiye) was used for total nucleic acid isolation from samples. The isolation procedure was carried out with the manufacturer's recommendations.

Bio-Speedy® COVID-19 RT-qPCR Detection Kit (Bioeksen, Türkiye) was used for the RT-PCR study. PCR amplification and evaluation of results were performed following the manufacturer's recommendations.

Complete Blood Count, Biochemistry and Coagulation Parameters Analyses: CELLDYN 3700 (Abbott, USA) device for hemogram tests, DIAGON COAG XL (DIAGON, Hungary) device for D-dimer tests, Architect i2000 (Abbott, USA) device for hs

Tn I, and BNP tests, Cobas e 411 (Roche, USA) and BN II (Siemens, Germany) device were used for CRP tests.

Statistical analysis: Descriptive analyses were performed to provide information on the general characteristics of the study population. The distribution of data is too skewed to use a parametric test. Accordingly, the Mann-Whitney U test was used to compare the numeric variables. The numeric variables were presented as the median [interquartile range]. The chi-square test was used to compare the categorical variables between the two groups. The categorical variables were presented as the frequency (% percentage). The p-value of 0.05 was considered significant. Analyses were performed using SPSS statistical software (IBM SPSS Statistics, Version 23.0.)

RESULTS

Of the 474 patients in the study, 301 (63.5%) were

male, and 39 (13%) of them died, while 262 (87.2%) were discharged. In addition, of 474 patients, 173 were women (36.5), and 17 (9.8%) of them died, while 156 (90.2%) were discharged. There was no statistically significant difference in mortality rate between women and men (p=0.385). There was no statistically significant difference in BNP, WBC, NEU, LYM, PLT, PCT and hs Tn I values of the patients who died and were discharged (p>0.05). A statistically significant difference was found between the D-dimer (died group: 3175 [6695], discharged group: 1925 [3907]) (p<0.031) and CRP (died group: 111.5 [115.65], discharged group: 95.05 [113.1]) (p<0.020) values of patients who died and were discharged (Table 1).

It was found to be statistically significantly higher in the group of patients who died and were discharged (p<0.05). Box plot comparison of CRP values of died and discharged patients is presented in Figure 1.

Table 1. Evaluated parameters of the patients included in the study (n=474).

Parameters	Ex (n=418) Median [IR]	Discharge (n=56) Median [IR]	p
Age	73.5 [15.5]	70 [16]	0.099
Female (n=173), n(%)	17 (9.8)	156 (90.2)	0.385
Male (n=301), n(%)	39 (13)	262 (87)	0.385
BNP (ng/L)	113.15 [447]	169.85 [388.2]	0.324
WBC (K/ μ L)	13.6 [7.1065]	12.1 [7.94]	0.354
NEU (K/ μ L)	12.95 [6.6695]	10.8 [7.56]	0.141
LYM (K/ μ L)	0.5895 [0.517]	0.5085 [0.513]	0.068
PLT (K/ μ L)	201 [123]	207 [120]	0.470
CRP (mg/dL)	111.5 [115.65]	92.05 [113.1]	0.020
D-Dimer (μ gFEU/L)	3175 [6695]	1925 [3907]	0.031
PCT (ng/ml)	0.445 [1.386]	0.3635 [1.487]	0.364
Hs Tn I (ng/L)	55.8 [271.8]	113.9 [552]	0.283

IR: Interquartile range; BNP: Brain natriuretic peptide; WBC: White blood cell; NEU: Neutrophil; LYM: Lymphocyte; PLT: Platelet; PCT: Procalcitonin; hs Tn I: High sensitive troponin I and CRP: C-Reactive protein (CRP, p=0.020, D-Dimer, p=0.031).

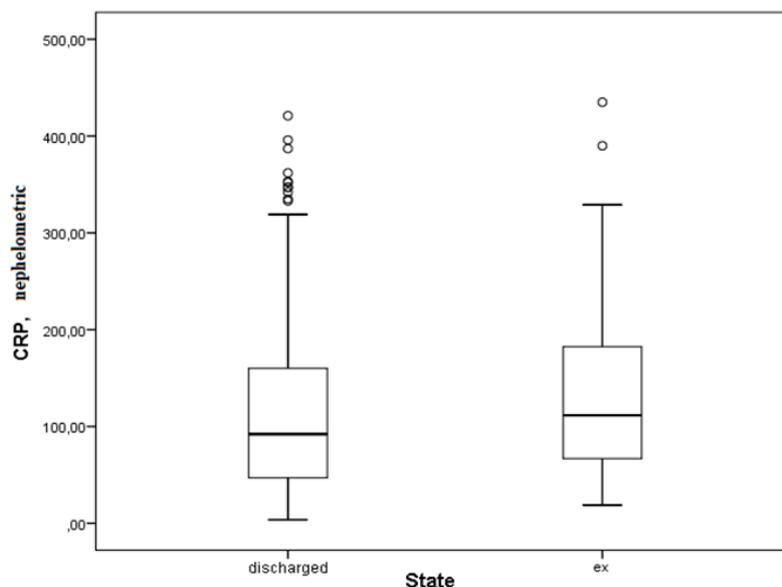


Figure 1. Comparison of the CRP values of those who died and those who were discharged patients.

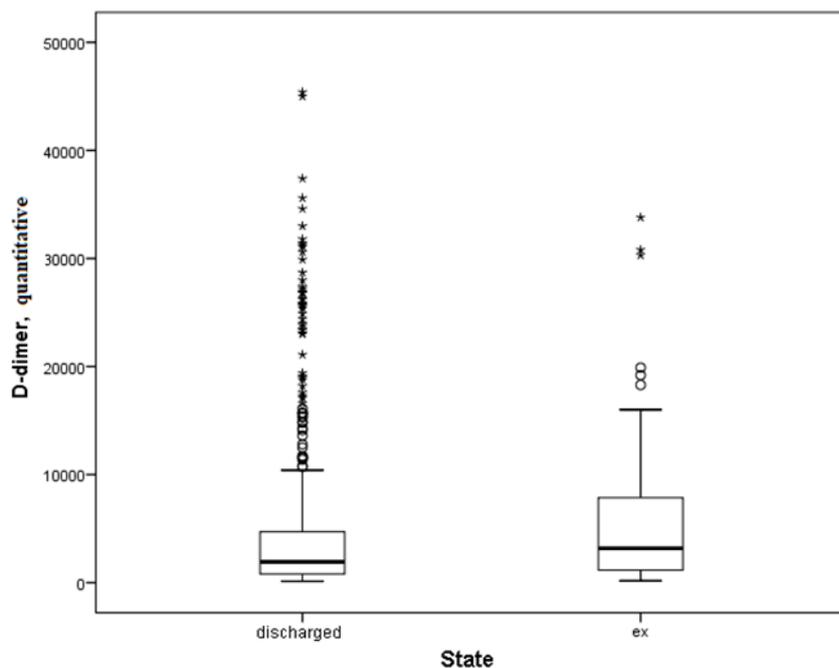


Figure 2. Comparison of the D-dimer values of those who died and those who were discharged patients.

It was found to be statistically significantly higher in the group of patients who died and were discharged ($p < 0.05$). Box plot comparison of D-dimer values of died and discharged patients is presented in Figure 2.

DISCUSSION AND CONCLUSION

Considering the pathogenesis of COVID-19 disease, it is seen that it affects the respiratory tract and cardiovascular system and causes abnormalities in some blood parameters. In the study conducted by Yang et al. BNP, CRP, D-dimer, PCT, hsTn I, WBC, neutrophil, lymphocyte and thrombocyte parameters were determined in patients who were discharged after recovering from COVID-19 infection and died due to this disease. BNP, PCT, and CRP are the leading indicators of inflammatory severity in ICU cases. Deaths corresponding to worsening sepsis in these patients were significantly increased or detected at relatively high levels, which can lead to life-threatening organ dysfunction.¹² In our study conducted on patients discharged and who died with clinically severe COVID-19, elevated BNP, hs Tn I, and D-dimer levels were detected. In their study on COVID-19 patients, Tao et al. determined that $CRP > 77.35$ mg/L, $PCT > 0.20$ μ g/L, and $LDH > 481$ U/L are independent risk factors associated with death events. CRP, PCT and LDH levels were high in patients who died from COVID-19; found that it gradually decreased to normal levels in the dischar-

ged group. Therefore, monitoring of laboratory parameters has shown that it can predict prognosis in severe patients in clinical practice. They reported that the increased incidence of harmful arrhythmias and myocardial complications during illness in patients with high BNP and TnT levels played a more significant role in the fatal outcome of COVID-19 compared to the presence of underlying cardiovascular disease.¹³ It revealed many risk factors associated with poor prognoses, such as assessment scores and high CRP, PCT, and LDH. Elevated CRP, PCT, and LDH values were elevated in patients who died but gradually returned to normal levels in patients discharged. Therefore, monitoring these laboratory parameters is essential in predicting prognosis in clinical practice for severe patients.^{14,15}

When Bonetti et al. compared the laboratory parameters of patients hospitalized with COVID-19 and discharged patients, they found that CK, LDH, troponin, D-dimer and CRP levels increased in patients who died.¹⁶ In patients who died from COVID-19, LDH, BNP, Hs-cTnT, Many laboratory indicators, such as D -dimer, CRP, and PCT, were significantly increased compared to recovered patients.¹⁷ Tan et al. reported that CRP levels were significantly increased in 65.0% of hospitalized patients and PCT levels were significantly increased in 5.7%, and cox proportional risk model analysis showed that CRP and PCT were used to predict severity in COVID-19 patients. He reported that these parameters can be

used as independent factors.¹⁸ COVID-19 patients have severe and adverse outcomes. In our study, in parallel with other studies, high values were obtained in other parameters, especially D-dimer and CRP. This shows that COVID-19 affects the whole body, especially the circulatory and respiratory systems.

In a study by Guan W. on 1099 people without the disease, PCT was shown to be low (<0.5 µg/L) in 96% of cases.¹⁹ Huang et al. in their study found that high CRP, PCT, D-dimer and LDH levels are risk factors for poor prognosis in COVID-19.²⁰ Infection markers, CRP, LDH, and PCT, and D-dimer, which is one of the coagulation function tests, are positive with COVID-19 severity.²¹ A meta-analysis showed that increased PCT values were associated with a ~5-fold higher risk of severe COVID-19.²² In a study conducted with COVID-19 patients, it was reported that high CK levels might be the only initial application of these patients. Total CK should be requested at the time of admission for each patient.²³ In our study, we found that BNP, CRP, D-dimer, PCT, and hs Tn I values were higher in patients who died due to COVID-19 infection than those who were discharged. In our study, it was determined that BNP, CRP, D-dimer, PCT and hs Tn I values were higher in patients who died due to COVID-19 infection compared to those who were discharged.

Terpos et al. reported in a study they conducted on COVID-19 patients that high CK levels may be the only first admission of these patients and total CK should be requested for each patient at the time of admission.²⁴ Pan et al. in their study of severe COVID-19 patients, found that neutrophils increased significantly, while lymphocytes, monocytes, and hematocrit decreased significantly.²⁵ Liao et al. in their study of severe COVID-19 patients, found that neutrophils increased significantly, while lymphocytes, monocytes, and hematocrit decreased significantly.²⁶ Ozdin et al. found an increase in neutrophil-lymphocyte ratios in their study on COVID-19 patients.²⁷ Shi et al. found that 11.4% of severe COVID-19 cases had leukocytosis and rates were higher than mild-to-moderate cases and that COVID-19 caused disseminated intravascular coagulation (DIC) with severe thrombocytopenia. they have done.²⁸ D-dimer elevation and thrombocytopenia, indicating activation of hemostasis and fibrinolysis, are associated with higher mortality in COVID-19 patients.^{29,30} In our study, it was determined that WBC and Neutrophil values increased, while lymphocyte values decreased in patients who died from COVID-19 infection compared to those who were discharged. In our study, it was found that patients who died due to COVID-19 infection had a decrease in platelet values compared to those who were discharged. In our

study, it was determined that there was a decrease in platelet values in patients who died due to COVID-19 infection.

Factors such as body mass index, cardiovascular disease status, end-stage renal disease and diabetes can affect BNP levels. The fact that the patients we included in the study consisted of patients diagnosed with COVID-19 and it was a retrospective study makes it difficult to reach these data. All these situations constitute the limitations of our study.

In conclusion, according to the results of our study, it was determined that advanced age, BNP, D-dimer, CRP, hs Tn I, WBC, neutrophil, lymphocyte and platelet increase were associated with mortality. These laboratory parameters are important in patient follow-up. More comprehensive studies are needed on this subject.

Ethics Committee Approval: The study was approved by the Sakarya University Ethical Committee (Date: 04/09/2020, decision no: E.7734). And institutional permissions (Date: 02.06.2020) were obtained. In line with the Helsinki Declaration, the nurses were informed about the study, and their informed consent was obtained. After obtaining verbal consent from the nurses who volunteered to participate in the study, they were included in the study.

Conflict of Interest: No conflict of interest was declared by the authors.

Author Contributions: Concept – MO; Supervision –MO, MK, SY, EÇ, İK, AO; Materials –MO; Data Collection and/or Processing –MO; Analysis and/ or Interpretation –MO, MK, SY, EÇ, İK, AO; Writing – MO, MK.

Peer-review: Externally peer-reviewed.

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