JoCASS
Çukurova Anestezi ve Cerrahi Bilimler Dergisi
2018 Adana

REDEFINITION OF BNP AS A PROGNOSTIC BIOMARKER IN INTENSIVE CARE AT COVID-19 INFECTION

COVID-19 ENFEKSİYONUNDA YOĞUN BAKIMDA BNP'NİN PROGNOSTİK BİR BİYOBELİRTEÇ OLARAK YENİDEN TANIMLANMASI

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Geliş Tarihi/Received: 30.05.2022 Kabul Tarihi-Accepted: 26.06.2022 Available Online Date/Çevrimiçi Yayın Tarihi: 31.08.2022
Cite this article as: Turgay Yıldırım Ö, Ayyıldız A, Yıldırım S. Redefinition of BNP as a prognostic biomarker in intensive care at COVID-19 infection.
J Cukurova Anesth Surg. 2022;5(2):116-127.
Doi: 10.36516/jocass.1123404

Abstract
Aim: Coronavirus disease 2019 (COVID-19) has caused a global pandemic and increased mortality has forced researchers to identify prognostic factors to identify patients at higher risk of mortality. In this study, we aimed to investigate the usability of Brain natriuretic peptide (BNP) as a predictor of mortality in critically ill patients hospitalized in the intensive care unit.
Methods: This retrospective study included 50 patients diagnosed with COVID-19 and followed in the intensive care unit. Patients with known heart failure who were found to have heart failure on echocardiography during follow-up were excluded from the study.
Results: The patients were divided into two groups based on their mortality status during hospitalization in the intensive care unit. These groups were found to be statistically similar in terms of chronic disease, gender, and age (p>0.05). Non-survivor group had higher levels of BNP at the admission to intensive care unit when compared to survivor group (93.2 pg/mL (43.5-357.3) vs. 62.9 (25.0-147.1), p=0.004, respectively). Regression analysis revealed that higher BNP levels and lower lymphocyte counts can be used as a predictor of mortality for these patients. ROC curve analysis indicated that best cut-off value for predicting in-hospital death for BNP was 85.6 pg/mL with a sensitivity of 73.1% and a specificity of 70.8%.
Conclusions: High BNP levels at admission to the intensive care unit can be used as an in-hospital mortality indicator in COVID-19 patients followed up in the intensive care unit.

Keywords: Brain natriuretic peptide, COVID-19, prognosis, mortality, intensive care

Öz
Amaç: Coronavirus hastalığı 2019 (COVID-19), küresel bir pandemiye neden olmuş ve artan ölüm oranları, araştırmacıları daha yüksek ölüm riski altındaki hastaları belirlemek için prognostik faktörleri araştırmaya zorlamıştır. Biz bu çalışmada, yoğun bakım ünitesinde yatan kritik hastalarda, beyin natriüretik peptidinin (BNP) mortalitenin bir belirleyicisi olarak kullanılabilirliğini araştırmayı amaçladık.
Yöntemler: Bu retrospektif çalışmaya COVID-19 tanısı konan ve yoğun bakım ünitesinde takip edilen 50 hasta dahil edilmiştir. Bilinen kalp yetmezliği olan ve takiplerinde ekokardiyografide kalp yetmezliği saptanan hastalar çalışma dışı bırakılmıştır.
Bulgular: Hastalar yoğun bakım ünitesinde yatışları sırasındaki mortalite durumlarına göre iki gruba ayrıldı. Bu gruplar kronik hastalık, cinsiyet ve yaş açısından istatistiksel olarak benzerdi (p>0.05). Mortalite ile seyreden grup, hayatta kalan grupla karşılaştırıldığında yoğun bakım ünitesine kabulde daha yüksek BNP seviyelerine sahipti (mortalite ile seyreden grup 93,2 pg/mL (43,5-357,3) ve hayatta kalan grup 62,9 (25,0-147,1), p=0.004). Regresyon analizi, daha yüksek BNP düzeylerinin ve daha düşük lenfosit sayılarının bu hastalarda mortalitenin bir göstergesi olarak kullanılabileceğini ortaya koydu. ROC eğrisi analizi, BNP için hastane içi ölümü öngörmede en iyi eşik değerinin %73,1 duyarlılık ve %70,8 özgüllük ile 85,6 pg/mL olduğunu gösterdi.
Sonuç: Yoğun bakım ünitesinde takip edilen COVID-19 hastalarında yoğun bakıma kabuldeki yüksek BNP seviyeleri hastane içi mortalite göstergesi olarak kullanılabilir.

Anahtar Kelimeler: Beyin natriüretik peptidi, COVID-19, prognoz, mortalite, yoğun bakım

Introduction

Coronavirus disease 2019 (COVID-19) has spread around the world since its emergence from Wuhan province of China in December 2019 and has been declared a global pandemic by the World Health Organization as of March 11, 2020 [1,2]. COVID-19 can cause simple upper respiratory infections, as well as affect the respiratory system in a wide spectrum, ranging from advanced lung diseases and acute respiratory distress syndrome [3–5]. Apart from the respiratory system involvement, COVID-19 may cause cardiac injury, thromboembolic complications, multiorgan failure and other serious complications [6–12]. Knowing which patient will have a worse prognosis and higher risk of death at the first hospitalization will affect our early approach to the patient.

Brain natriuretic peptide (BNP) is a biomarker secreted from the heart due to increased wall tension [13]. It is an established biomarker that is used in the diagnosis of reduced ejection fraction and preserved ejection fraction heart failure and higher levels show poor prognosis in these patients [14,15]. Recent studies showed that N terminal pro BNP might be associated with mortality in patients with COVID-19 [16,17]. BNP also shown to be higher in severe patients compared to mild to moderate patients [18]. With this study we aim to investigate the prognostic value of BNP on mortality among patients who are already at intensive care unit due to severe COVID-19 pneumonia.

Materials and Methods

- *Study design and participants*

For this retrospective study, the patients were recruited at Eskişehir City Hospital intensive care unit from 15.11.2020 to 15.01.2021. All patients were diagnosed as COVID-19 and the diagnosis were confirmed by thorax computerized tomography and polymerase chain reaction for COVID-19. Patients with a history of heart failure, with missing medical data, patients without BNP values at the admission to the intensive care unit and pediatric population were excluded from the study. Transthoracic echocardiography was performed in patients with clinical suspicion of heart failure, and patients with heart failure were excluded.

The patients were treated according to the algorithms in the guidelines prepared by the scientific committee of the Ministry of Health of our country and constantly updated with new literature. The patients we followed in intensive care unit were severe COVID-19 pneumonia, acute respiratory distress syndrome (ARDS) due to COVID-19 infection, sepsis due to COVID-19 and septic shock. Hypoxemic respiratory failure patients were gradually oxygenated (nasal cannula - simple mask - mask with reservoir - high flow nasal cannula- Continious Positive Airway Pressure - invasive mechanical ventilation). Lung protective mechanical ventilator strategies were applied to patients who developed ARDS.

The study was approved by Ministry of Health and local ethics committee.

- *Data collection*

The data set were collected retrospectively and evaluated by two physicians independently to double-check the data. Demographic and clinical information was gained form hospital medical records. The BNP and other laboratory values were obtained from the laboratory results at the admission to the intensive care unit.

The data was summarized at the first three columns of Table 1. Gender, hypertension, diabetes mellitus, respiratory comorbidities, cerebrovascular diseases and chronic renal failure variables are categorical; therefore their percentages in the total data set are reported in parenthesis after the number of patients with the aforementioned characteristic. Our variable of interest

(BNP) and the remaining are all continuous variables. The continuous variables in the data set are reported as “median ± standard deviation” if they are normally distributed, and “median (interquartile range)” if they are non-normally distributed.

- *Comparison of two groups*

The intermediate step in this investigation of BNP and other indicators on the mortality of COVID-19 patients is the comparison of these indicators among the survivor and non-survivor groups. For this purpose three methods are adopted depending on the classification of the variable taken into account [19]. The chi-square test is used to investigate the association among the groups for categorical variables. The independent samples t test is employed to compare the means of the two independent groups for normally distributed continuous variables. Finally, the Mann-Whitney U test is implemented to test whether two groups have the same distribution for non-normally distributed continuous variables.

Although the distinction between categorical and continuous variables are obvious, whether a continuous variable is identically and/or normally distributed is distinguished via Levene and Shapiro-Wilk tests [20]. In other words homogeneity of variances is tested by Levene test and distribution of the variable for normality is tested by Shapiro-Wilk test.

The results used for comparison of the two independent samples are reported in the last column of Table 1. Since there are three different tests employed, only the p-values of the testes are listed. To sum up a p-value of less than 5% (0.05) indicates statistical significance, which in turn means there is a significant difference between survivor and non-survivor groups for whichever variable was under consideration.

- *Logistic regression*

The aforementioned chi-square, independent samples t and Mann Whitney U tests are useful for exploratory investigations and in situations where the number of predictor variables of interest is limited. However they can be cumbersome when multiple explanatory variables are being considered and are not well suited to situations where the explanatory variables may take on a large number of possible values [21]. A popular method when such cases emerge is logistic regression; it has the suppleness and strengths of regression model (it is a multivariate analysis, can take many types of variables such as categorical and continuous, and has predictive ability) as well as the capability to consider a binary dependent variable.

Logistic regression is a modeling approach that can be used to describe the relationship of several explanatory variables to a dichotomous dependent variable [22]. In this study the explanatory variables are listed in the Table 1 as the row names. The dependent variable is mortality or the binary variable that shows whether the patient survived COVID-19 or not. In logistic regression rather than the coefficients of the explanatory variables their odd ratios (OR) are considered. The odds ratio represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure [23]. A simplistic approach to the OR is using it as a tool to determine whether a particular exposure or variable affects a particular outcome, and to compare the magnitude of variables for that outcome:

- OR=1 Exposure/variable does not affect odds of outcome,
- OR>1 Exposure/variable associated with higher odds of outcome, and
- OR<1 Exposure/variable associated with lower odds of outcome.

Although the same approach is suitable for logistic regression, the distance of OR to 1 (where 1 indicates variable has no effect on the outcome, the dependent variable) is a better measure to see how mortality of COVID-19 patient is affected by the change in variable under consideration.

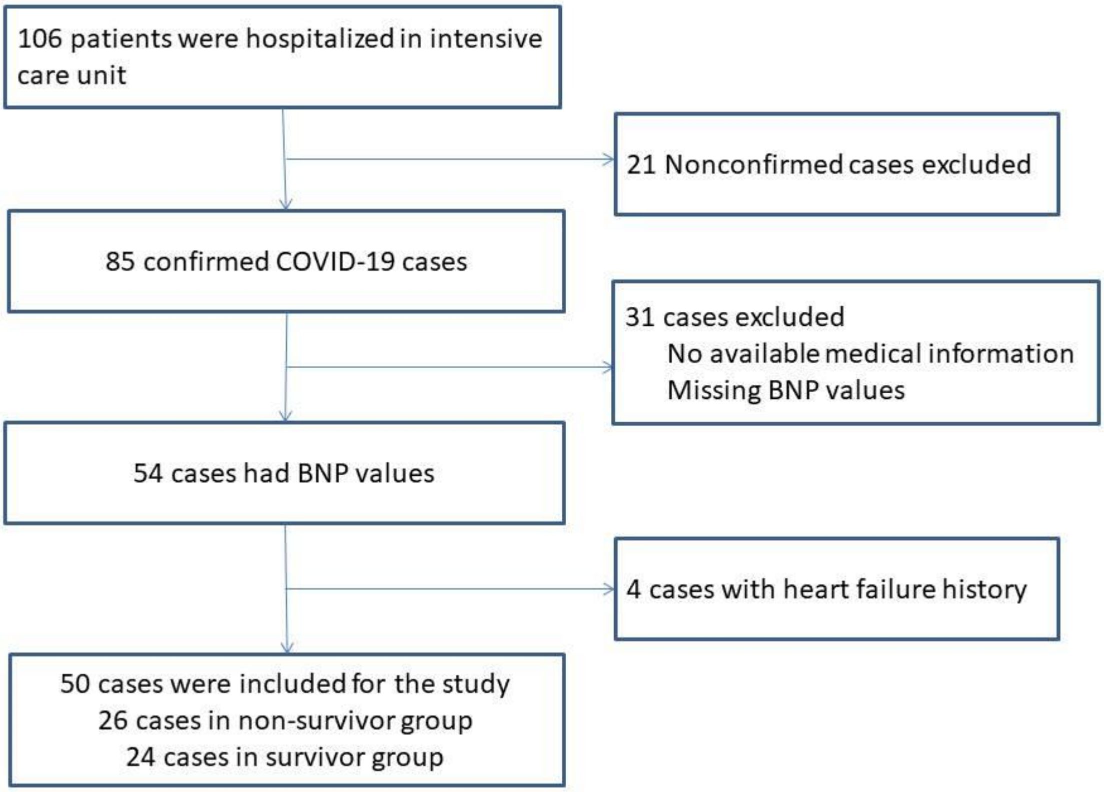

Figure 1. Flowchart of patient recruitment

- *Receiver operating characteristic*

The receiver operating characteristic (ROC) curve constructed by plotting the false positive rate (FPR) which is "1-specificity" against the true positive rate (TPR) which is the "sensitivity" at various threshold settings. It depicts relative tradeoffs between benefits (true positives) and costs (false positives) of a binary prediction or classification[24]. The area under a given ROC curve or AUC measures the performance across the aforementioned threshold settings.
Furthermore ROC curve is a useful tool for finding the optimal threshold setting which also known as best cut-off value. The best cut-off value dichotomizes the values of the explanatory variable in a regression setting; therefore, it provides decision/prediction point regarding which group each observation falls into. Finally, to determine the best cut-off value "Youden's J statistic" as well as "least-distance-to-(0,1)" criteria, which are very well documented in [25], are employed in this study.

Results

- *Patient characteristics*

106 patients were hospitalized at intensive care unit for prediagnosis of COVID-19. According to the results of consecutive 2 negative PCR results, 21 cases were excluded from the study. From the remaining patients, 31 cases were excluded because they do not have BNP values at the admission to the intensive care unit and they do not have sufficient medical information and 4 cases were excluded due to known history of heart failure (Figure 1).
The mean age of the study population was 67.8±13.7 and 54% (n=27) was female.

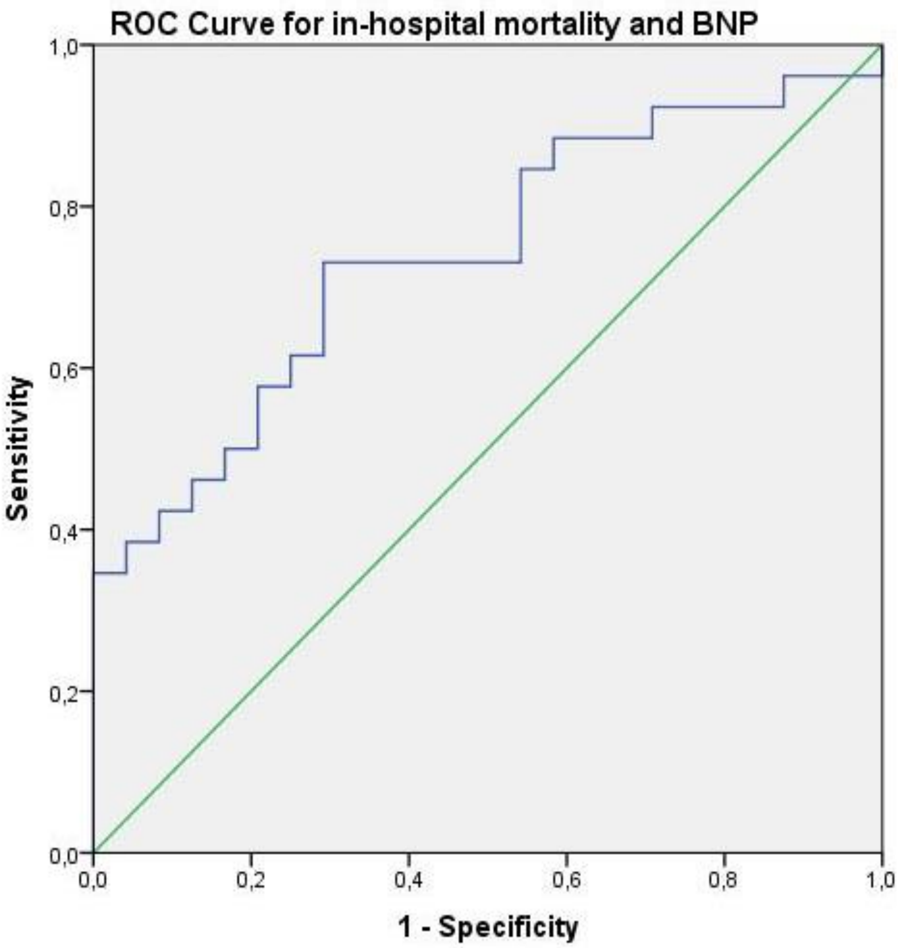

Figure 2. ROC curve of BNP for prediction of in-hospital mortality

The patients were divided into two groups according to the in-hospital mortality status. 52% of the cases who died during intensive care stay are included in the non-survivor group, and the remaining 48% of the patients were discharged from intensive care unit. Non-survivor group and survivor groups were similar in terms of age (71.1±11.1 and 64.1±15.4, p=0.067, respectively), gender (42.3% were female and 66.7 were female, p=0.084, respectively)and with similar comorbidities of hypertension (34.6% (n=9) vs 33.3% (n=8), p=0.924), diabetes mellitus (26.9% (n=7) vs 33.3 (n=8), p=0.621), respiratory diseases (34.6% (n=9) vs 25.0% (n=6), p=0.459), cerebrovascular diseases (0% (n=0) vs 4.1% (n=1), p=0.293) and chronic renal diseases (11.5% (n=3) vs 0% (n=0), p=0.086) (Table 1).

- *Laboratory results*

Median BNP value of the study population was 93.2 (43.5-357.3). Non-survivor group had higher levels of BNP at the admission to intensive care unit when compared to survivor group (93.2 (43.5-357.3) vs 62.9 (25.0-147.1), p=0.004, respectively)
Results of the comparison of the non-survivor and survivor group showed statistically significant difference among troponin-I (26.4 (12.3-81.6) vs. 8.6 (5.4-13.8), p=0.001) values. Other laboratory values showed no significant difference between groups.

Table 1. Baseline characteristics and laboratory results of the patients with COVID-19.

	Patients, no. (%)	Mortality		P value
	All (n=50)	Non-survivor (n=26)	Survivor (n=24)	
Age, mean±SD, y	67.8±13.7	71.1±11.1	64.1±15.4	0.067
Female	27 (54%)	11 (42.3%)	16 (66.7%)	0.084
Hypertension	17 (34%)	9 (34.6%)	8 (33.3%)	0.924
Diabetes Mellitus	15 (30%)	7 (26.9%)	8 (33.3%)	0.621
Cardiovascular diseases	6 (12%)	5 (19.2%)	1 (4.1%)	0.101
Respiratory comorbidities	15 (30%)	9 (34.6%)	6 (25.0%)	0.459
Cerebrovascular diseases	1 (2%)	0 (0%)	1 (4.1%)	0.293
Chronic renal failure	3 (6%)	3 (11.5%)	0 (0%)	0.086
B-type natriuretic peptide, pg/mL	93.2 (43.5-357.3)	194.4 (60.8-958.3)	62.9 (25.0-147.1)	0.004
Hemoglobin, g/dL	12.5±2.1	12.7±2.1	12.2±2.0	0.362
Leukocytes x10^3/µL	10.9 (7.1-14.8)	11.6 (7.1-15.4)	10.8 (7.0-14.5)	0.846
Neutrophil x10^3/µL	9.3 (6.0-12.5)	10.1 (6.0-12.9)	8.8 (5.9-12.1)	0.600
Lymphocyte x10^3/µL	0.82 (0.53-1.19)	0.73 (0.53-1.05)	0.83 (0.51-1.55)	0.290
Platelets x10^3/µL	246.8±84.4	243.7±91.0	247.6±76.5	0.871
Glucose, mg/dL	146.5 (122.7-255.0)	144.5 (122.5-242.7)	149.0 (122.5-269.2)	0.930
Creatinine, mg/dL	0.84 (0.72-1.13)	0.88 (0.74-1.9)	0.77 (0.69-1.05)	0.090
C-reactive protein, mg/dL	109.4 (57.2-193-2)	122.0 (59.6-191.5)	109.4 (50.8-254.4)	0.764
Troponin I, pg/mL	13.8 (6.6-37.4)	26.4 (12.3-81.6)	8.6 (5.4-13.8)	0.001
D-dimer	1.7 (0.97-5.3)	1.68 (1.12-5.60)	2.26 (0.73-5.12)	0.771

Abb: SD; standard deviation, y; years

The demographic and laboratory values of the patient groups were given at Table 1.

- *Regression analysis*

The association of the variables, especially BNP, to mortality is further investigated by logistic regression. The findings of the regression are reported at Table 2; which depict that BNP and lymphocyte counts are independently associated with mortality. In other words the p-values associated with these two variables are below 5% significance level ($p<0.05$). The odds ratio of lymphocyte count suggests 0.1 unit ($x10^3/\mu L$) increase lowers the odds ratio of mortality by 9% ($0.1\times (0.104-1)\times 100=-8.96$). A 10 unit (pg/mL) increase in BNP in turn increases the odds of mortality by 8% ($10\times (1.008-1)\times 100=8$). In this study it is obvious that lymphocyte is associated with lower odds of mortality, while BNP associated with higher odds of mortality.
Finally another logistic regression where the only explanatory variable is BNP, also supports the finding that BNP is significantly ($p=0.0316$ in this case) associated with in-hospital mortality for COVID-19 patients under intensive care.
The other explanatory variables such as chronic diseases (such as hypertension, diabetes mellitus, respiratory comorbidities, and cardiovascular diseases) have no significant impact on the mortality of the COVID-19 patients once the BNP and lymphocyte are controlled for.

Table 2. Binary logistic regression analysis on the risk factors associated with mortality in COVID-19 patients followed at intensive care unit.

Variable	Odds Ratio	95% Confidence Interval	p-value
Age	0.989	0.903-1.083	0.809
Gender	0.278	0.038-2.039	0.208
Hypertension	9.073	0.621-132.515	0.107
Diabetes Mellitus	3.204	0.082-124.566	0.533
Respiratory comorbidities	0.462	0.071-3.019	0.420
Cardiovascular diseases	0.003	0.000-9.457	0.156
B-type natriuretic peptide	1.008	1.001-1.015	0.028
Hemoglobin	1.553	0.956-2.523	0.075
Neutrophil	0.849	0.659-1.095	0.208
Lymphocyte	0.104	0.013-0.826	0.032
Platelets	1.013	0.999-1.026	0.062
Glucose	1.010	0.993-1.028	0.249
Creatinine	1.168	0.038-35.809	0.929
C-reactive protein	0.993	0.982-1.004	0.209
Troponin I	0.989	0.977-1.002	0.097
D-dimer	1.017	0.850-1.217	0.855
Constant	0.114		0.752

Moreover demographic variables such as age and gender are found out to be unassociated with mortality as well. Finally platelets, hemoglobin and troponin-I values have extremely weak ($0.05 \leq p < 0.10$), almost non-existent, association with mortality.

- *Receiver operator characteristic (ROC) curve for prediction in-hospital death*

The previous finding support that BNP is associated with mortality of COVID-19 patients. In this regard, the next question is what values of the BNP predict mortality (with better precision). The answer to this question is easily answered by receiver operation characteristic (ROC) curve. Figure 2 shows the ROC curve of BNP for prediction of in-hospital mortality for intensive care patients. The area under the curve was 0.740 (95% confidence interval 0.603-0.878, p=0.004) which is an acceptable value and indicates that BNP can predict the mortality of the patients. Finally, the best cut-off value for predicting in-hospital death was 85.6 pg/mL with a sensitivity of 73.1% and a specificity of 70.8%. Both "Youden's J statistic" and "least-distance-to-(0,1)" criterion produce the value 85.6 pg/mL for the best cut-off value. In other words optimal choice for predicting which group the COVID-19 patients will fall into is to see whether BNP values are higher or lower than 85.6 pg/mL.

Discussion

This study showed that BNP can use as a reliable biomarker for predicting mortality among severe COVID-19 patients who are followed at intensive care unit. 85.6 pg/mL can be used as a cut-off value for mortality among these patients.

Although COVID-19 originally originated in China, it has now become a global pandemic and has become a common problem of the world that needs to be solved [1,2]. This is not the first pandemic that humanity has faced. For example, the Spanish flu in 1918 also caused a global pandemic, with an estimated 40 to 100 million deaths. The Asian flu, which emerged later in 1957, killed 1.1 million people. The emergence of the vaccine for this virus and the widespread production of the vaccine subsequently prevented the Asian flu pandemic from taking more lives [26]. Likewise, after the spread of COVID-19, scientists shared every finding and every treatment applied with other scientists, allowing the whole world to recognize the disease, globally discuss the reliability and usefulness of the methods tried in terms of diagnosis, prognosis and treatment. One of the issues emphasized was the presence of a biomarker that could predict the course of the disease when the patient applied. In addition to the many biomarkers that have been proposed in this regard, another biomarker that has been emphasized is BNP. When severe/critical patients diagnosed with COVID-19 and mild patients are compared, BNP values are found to be higher in patients with severe prognosis [18]. In another study conducted on COVID-19 patients who were admitted to the hospital and followed up for 7 days, it was found that high BNP levels predict mechanical ventilation need and mortality [27]. Before COVID-19, BNP was already proposed as a prognostic marker for pneumonia [28]. But previous studies mostly aimed to differentiate severe cases and mild cases. Our study aimed to examine the effect of BNP on mortality in critically-ill COVID-19 patients. In other words, our aim was not to identify severe COVID-19 patients, but to aim whether BNP is a predictive factor for mortality in patients who are already in critical condition and followed in intensive care unit. The results of our study suggested that BNP values are higher at admission to the intensive care unit for patients who died compared to survivor group. Also regression analysis showed that BNP can be used as a predictor of mortality at COVID-19 patients. Before our study, many biomarkers other than BNP have been shown as an indicator of severity for COVID-19 and are used in practice. Examples of these markers are troponin-I, D-dimer, C-reactive ptotein and atherogenic index of plasma. But these biomarkers are indicative of the need for intensive care or mortality in COVID-19 patients [29–31]. Studies conducted generally enable these biomarkers to distinguish severe patients at the first admission to the hospital. The results of our study show that high BNP, troponin-I and low lymphocytes help to differentiate mortality risk in critically ill patients. But regression analysis suggests that only BNP and lymphocyte count may be used as a predictor of mortality for critically-ill patients. Interestingly, D-dimer levels did not differ statistically when the survivor and non-survivor groups were compared. D-dimer was shown to be elevated in patients who required intensive care unit admission, had ARDS during admission or had in-hospital mortality [2,32–34]. Our results showed otherwise most probably due to clinical severity of our patients. The difference in the results of our study may have emerged, as other studies compared all patients who were admitted to the hospital without making separate evaluations of patients in the service or intensive care unit in the study groups.

In individuals with a history of cardiac disease and diagnosed with COVID-19, the BNP was found to be not predictive of death, mechanical ventilation and thromboembolic events [35]. Coexistence of pneumonia and heart failure are factors that increase the risk of mortality. Pneumonia is a predictor of mortality in heart failure patients [36]. Therefore, we chose to exclude heart failure patients from our study. Finding different results from the study of Andreini et al. may be due to this difference in patient selection [35].

High BNP values are indicators of mortality in pneumonia patients [37]. In addition, high BNP levels show poor prognosis in patients with sepsis and septic shock [38,39]. The effect of hypoxia on pulmonary artery pressure in pneumonia patients increases ventricular wall tension, and this may explain the elevation of BNP in pneumonia patients independent of heart failure [16,40]. High pulmonary artery pressure is also seen in COVID-patients, which is an indicator of poor prognosis and mortality [41,42]. This mechanism may explain the elevation of BNP levels in critically ill patients that resulted in mortality in our study.

- *Limitations*

Some limitations exist in our study. First, our study is a single center and single intensive care experience. Secondly, the number of patients is small. A multicentric prospective study with higher number of patients would give more reliable results. Third, we excluded patients with a history of heart failure but we only performed transthoracic echocardiography to whom with a suspicion of heart failure. It would be better to perform all patients transthoracic echocardiography because we may have failed to exclude these patients who are clinically silent without symptoms of heart failure.

Conclusion

Predicting which patients will have a poor prognosis in a disease such as COVID-19 is vital for these patients. With this study, we aim to investigate whether we can predict mortality with simple blood parameters during the admission to the intensive care unit. We found out that BNP tends to be higher in intensive care patients with COVID-19 with in-hospital mortality. Binary logistic regression confirms that BNP has a significant association with the mortality of COVID-19 patients. Additionally, BNP can be used as a predictor of mortality with a cut-off value of 85.6 pg/mL with a sensitivity of 73.1% and a specificity of 70.8% at these patients.

Author contributions

All authors contributed to the study conception and design. All authors read and approved the final manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

Authors declared no financial support.

Ethical approval

This study, in which patients participated on a voluntary basis, was conducted in accordance with all ethical procedures /standards and the Declaration of Helsinki.
Approval numbered 2021/06-160 was obtained from Eskişehir Osmangazi University Non-Interventional Clinical Research Ethics Committee.

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