PROGNOSTIC VALUE OF NT-PROBNP AND SOME COAGULATION MARKERS IN SEVERE COVID-19 PATIENTS

ŞİDDETLİ COVID-19 HASTALARINDA NT-PROBNP VE BAZI KOAGÜLASYON BELİRTEÇLERİNİN PROGNOSTİK DEĞERİ

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ABSTRACT

Objective: The aim of our study is to examine the effect of N-terminal fragment of the pro-brain natriuretic peptide (NT-proBNP) and some coagulation markers (D-dimer, fibrinogen and International Normalized Ratio (INR)) on mortality in COVID-19 patients over the age of 18.

Materials and Methods: In the study, the relationship between D-dimer, fibrinogen, and INR with NT-proBNP in 1614 patients diagnosed with COVID-19 was evaluated retrospectively, considering the survival status of the patients. The patients were divided into two groups as 18-65 years old and over 65 years old.

Results: Among 1614 patients, 213 NT-proBNP and D-dimer levels were measured; NT-proBNP and fibrinogen levels were measured 161; there were 233 patients whose NT-proBNP and INR levels were measured. NT-proBNP levels were significantly higher in all patients who died. High D-dimer level in 96.7% of deaths in NT-proBNP~D-dimer group, high fibrinogen level in 80.2% of deaths in NT-proBNP~fibrinogen group; high INR levels were detected in 82.8% of the deaths in the NT-proBNP~INR group.

Conclusion: The results of our study showed that high NT-proBNP and high coagulation marker levels (D-dimer, fibrinogen, INR) may have an effect on mortality in patients who died due to COVID-19.

Keywords: Cardiac Dysfunction, Coagulation Markers, COVID-19, D-dimer, Fibrinogen, INR, NT-proBNP.

ÖZET

Amaç: Çalışmamızın amacı, 18 yaş üstü COVID-19 hastalarında NT-proBNP ile bazı pıhtılaşma belirteçlerinin (D-dimer, fibrinojen ve INR) mortalite üzerine etkisini incelemektir.

Gereç ve Yöntem: Çalışmada COVID-19 tanısı alan 1614 hastada D-dimer, fibrinogen ve INR ile NT-proBNP arasındaki ilişki, hastaların hayatta kalıp kalmama durumları göz önünde bulundurularak retrospektif olarak değerlendirildi. Hastalar 18-65 yaş ve 65 yaş üstü olmak üzere iki gruba ayrıldı.

Bulgular: 1614 hasta arasında NT-proBNP ve D-dimer düzeyleri ölçülmüş 213; NT-proBNP ve fibrinojen düzeyleri ölçülmüş 161; NT-proBNP ve INR düzeyleri ölçülmüş 233 hasta vardı. NT-proBNP seviyeleri, ölen tüm hastalarda anlamlı olarak yüksekti. NT-proBNP~D-dimer grubunda ölenlerin % 96,7'sinde yüksek D-dimer düzeyi, NT-proBNP~Fibrinojen grubunda ölenlerin %80,2'sinde yüksek fibrinojen düzeyi; NT-proBNP~INR grubunda ölenlerin %82.8'inde yüksek INR seviyeleri tespit edildi.

Sonuç: Çalışmamızın sonuçları, COVID-19 nedeniyle ölen hastalarda yüksek NT-proBNP ile yüksek pıhtılaşma belirteç düzeylerinin (D-dimer, fibrinojen, INR) mortalite üzerine etkisi olabileceğini gösterdi.

Anahtar Kelimeler: COVID-19, D-dimer, Fibrinojen, INR, Kardiyak Disfonksiyon, Koagülasyon Belirteçleri, NT-proBNP.

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INTRODUCTION

COVID-19, a illness that causes severe acute respiratory syndrome belonging to the coronavirus family, is one of the devastating epidemics that led to a pandemic in the 21st century, and it is reported that it can cause significant morbidity and mortality (Abdeen et al., 2021). Studies show that cardiac damage, as manifested by cardiac biomarker elevation, is detected in the majority of COVID-19 patients and is related with increased mortality (Qin et al., 2020). Natriuretic peptides are biomarkers of myocardial damage and typically elevated in patients with severe respiratory disease in raised cardiac stress or clinical heart failure (Abdeen et al., 2021). NT-proBNP represents changes in intracardial pressure, particularly atrial pressure, and therefore it is also used as an important indicator of cardiac function (He et al., 2020). In particular, natriuretic peptides have been found to function as a predictor of cardiac risk in patients with severe COVID-19, and high NT-proBNP concentrations are related to severity of COVID-19 (Mahajan et al., 2020). In connection with this, there are studies showing hypercoagulability, pulmonary intravascular coagulation, microangiopathy, and arterial thrombosis in COVID-19 (Gerotziafas et al., 2020). About 20% of COVID-19 patients and nearly all, severe COVID-19 cases have severe coagulation abnormalities (Zhai et al., 2020). Abnormal coagulation and cardiac biomarkers is reported to be risk for mortality in COVID-19 (Yang et al., 2021).

Our aim of this study is to evaluate the levels of NT-proBNP and some coagulation markers in patients who died and survived after being diagnosed with COVID-19 in our hospital, and to examine the effects of these parameters on mortality.

MATERIALS AND METHODS

We planned this research as a descriptive and cross-sectional analytical study. Before starting the study, we received approval from the Republic of Türkiye Ministry of Health. In addition, we received approval for the study by the Health Sciences Non-Interventional Clinical Research Ethics Committee of Inonu University.

The study was carried out by retrospectively scanning the files of COVID-19 patients who applied to our center between Inonu University Turgut Ozal Medical Center 01.03.2020 - 01.11.2020. When the data of COVID-19 patients with NT-proBNP, D-dimer, fibrinogen, INR values from the hospital data recording system were examined, a total of 1614 patient results were obtained. NT-proBNP, a cardiac marker, and D-dimer, fibrinogen, and INR levels, which are coagulation parameters, were categorically classified in pairs (patients whose NT-proBNP~D-dimer, NT-proBNP~Fibrinogen and NT-proBNP~INR results were examined). In this classification, patients were evaluated according to their survival status. There were 213 patients with NT-proBNP~D-dimer results, 161 patients with NT-proBNP~Fibrinogen levels, and 233 patients with NT-proBNP~INR levels. Evaluation was made separately for all three group.

NT-proBNP levels were studied in Siemens brand-Immulite 2000 autoanalyzer using the chemiluminescence immunoassay method. The reference range for serum NT-proBNP measurements was 0-110 pg/mL. D-dimer, fibrinogen and INR levels were analyzed by turbidimetric method in Sysmex brand-CS-2500 autoanalyzer. Reference ranges were accepted as 0-0.55 mg/L for serum D-dimer, 150-350 mg/dL for fibrinogen and 0.8-1.2 for INR.

Statistical Analysis

While evaluating the findings obtained in the investigate, SPSS (Statistical Package for Social Sciences) for Windows 20.00 program was used for statistical analysis. Descriptive statistics for continuous variables are summarized as mean and standard deviation, and descriptive statistics for categorical data are summarized in tables as frequency and percentage. Pearson Chi-Square test was used to compare the categorical data. Bonferroni correction was applied for pairwise comparisons when there was difference between groups. The normality of the numerical data was tested with the Kolmogorov-Smirnov test. Since all the numerical variables in the study were not normally distributed, the linear relationship between the numerical variables was determined by Spearman's correlation coefficient. The significance level for all tests was accepted as 0.01.

RESULTS

NT-proBNP~D-dimer

There were 213 patients in the NT-proBNP~D-dimer group, of which 53.5% (n=114) were male and 61.5% (n=131) were 65 years old and over; 93.9% (n=200) had high NT-proBNP levels and 92% (n=196) had high D-dimer levels. We observed that 42.7% (n=91) of 213 patients in this group died. Of the 91 patients who died in this group, 57.1% (n=52) were male, 64.8% (n=59) were 65 years old and over, and 100% (n=91) had high NT-proBNP levels. While there was a significant difference in mortality in NT-proBNP and D-dimer levels (p<0.01), there was no difference in gender and age levels (p>0.01) (Table 1).

Since both NT-proBNP and D-dimer values did not show normal distribution according to Kolmogorov-Smirnov test from data obtained from 213 patients (p<0.001), Spearman's rho correlation coefficient was calculated for the linear relationship between these two parameters (r=0.547; p<0.001). There was a moderately positive and statistically significant linear relationship between NT-proBNP and D-dimer values.

Table 1. NT-proBNP, D-dimer Levels, Age, and Gender Distribution by Death/Survival Status

	Total	Survivor	Non-Survivor	χ^2	p value
Gender					
Female	99 (46.5%)	60 (49.2%)	39 (42.9%)	0.838[a]	0.360
Male	114 (53.5%)	62 (50.8%)	52 (57.1%)		
Age					
18-65	82 (38.5%)	50 (41%)	32 (35.2%)	0.745[a]	0.388
≥65	131 (61.5%)	72 (59%)	59 (64.8%)		
NT-proBNP Levels (pg/mL)					
Normal	13 (6.1%)	13 (10.7%)	0 (0%)	10.327[b]	**0.00****
High	200 (93.9%)	109 (89.3%)	91 (100%)		
D-dimer Levels (mg/L)					
Normal	17 (8%)	14 (11.5%)	3 (3.3%)	4.747[b]	**0.029***
High	196 (92%)	108 (88.5%)	88 (96.7%)		
Total	**213**	**122**	**91**		

[a]*Chi Square Test* [b]*Fisher's Exact Test* *p<0.05 **p<0.01*

NT-proBNP~Fibrinojen

There were 161 patients in the NT-proBNP~Fibrinogen group. 52.8% (n=85) of this group were male; 58.4% (n=94) were 65 years or older; 97.5% (n=157) had high NT-proBNP levels and 83.2% (n=134) had high fibrinogen levels. Considering the death/survival status, it was seen that 50.31% (n=81) of 161 patients in the group died. Of the 81 patients who died in this group, 55.6% (n=45) were male; 64.0% (n=52) were 65 years or older; 100% (n=81) had high NT-proBNP level and 80.2% (n=65) had high fibrinogen level. There was no difference in terms of gender, age, NT-proBNP and fibrinogen levels according to survival status (p>0.01), (Table 2).

Since both NT-proBNP and fibrinogen values in this group did not show normal distribution according to Kolmogorov-Smirnov test (p<0.01), Spearman's rho correlation coefficient was calculated for the linear relationship between these two parameters (r=0.195; p<0.01). There was a very weak significant linear relationship between NT-proBNP and fibrinogen values.

Table 2. NT-proBNP, Fibrinogen Levels, Age, and Gender Distribution by Death/Survival Status

	Total	Survivor	Non-Survivor	χ^2	p value
Gender					
Female	76 (47.2%)	40 (50%)	36 (44.4%)	0.498[a]	0.360
Male	85 (52.8%)	40 (50%)	45 (55.6%)		
Age					
18-65	67 (41.6%)	38 (47.5%)	29 (35.8%)	2.267[a]	0.132
≥65	94 (58.4%)	42 (52.5%)	52 (64%)		
NT-proBNP Levels (pg/mL)					
Normal	4 (2.5%)	4 (5.0%)	0 (0%)	4.153[b]	0.059
High	157 (97.5%)	76 (95%)	81 (100%)		
Fibrinogen Levels (mg/dL)					
Normal	27 (16.8%)	11 (13.8%)	16 (19.8%)	9.882[a]	0.419
High	134 (83.2%)	69 (86.2%)	65 (80.2%)		
Total	**161**	**80**	**81**		

[a]Chi Square Test [b]Fisher's Exact Test *p<0.05 **p<0.01

NT-proBNP~INR

There were 233 patients in the NT-proBNP~INR group, 51.9% (n=121) of them were male, 60.9% (n=142) of them were 65 years or older, 94% (n=219) of them had high NT-proBNP levels and 60.3% (n=141) of them had high INR levels. Considering the death/survival status, it was seen that 39.9% (n=93) of 233 patients in the group died. 55.9% (n=52) of the 93 patients who died in this group were male; 66.7% (n=62) were 65 years or older; 98.9% (n=92) of them had high NT-proBNP levels and 82.8% (n=77) of them had high INR levels, and their INR levels were higher than those with normal INR levels (p<0.01). There was a difference in NT-proBNP and INR levels (p<0.01), but there was no difference in terms of gender, age (Table 3).

Table 3. NT-proBNP, INR Levels, Age, and Gender Distribution by Death/Survival Status

		Survivor	Non-Survivor	χ^2	p value
Gender					
Female	112 (48.1%)	71 (50.7%)	41 (44.1%)	0.983[a]	0.321
Male	121 (51.9%)	69 (49.3%)	52 (55.9%)		
Age					
18-65	91 (39.1%)	60 (42.9%)	31 (33.3%)	76.845[a]	0.144
≥65	142 (60.9%)	80 (57.1%)	62 (66.7%)		
NT-proBNP Levels (pg/mL)					
Normal	14 (6.0%)	13 (9.3%)	1 (1.1%)	6.670[b]	**0.021***
High	219 (94.0%)	127 (90.7%)	92 (98.9%)		
INR Levels					
Normal	92 (39.7%)	76 (54.7%)	16 (17.2%)	32.695[a]	**0.001****
High	141 (60.3%)	64 (45.3%)	77 (82.8%)		
Total	**233**	**140**	**93**		

[a]Chi Square Test [b]Fisher's Exact Test *p<0.05 **p<0.01

Since both NT-proBNP and INR values from the data obtained from 233 patients were not with normal distribution according to the Kolomogrov-Smirnov test (p<0.01), Spearman's rho correlation coefficient was calculated for the linear relation between this two parameters (r=0.467; p<0.01). There was a statistically significant linear relationship between NT-proBNP and INR values at a moderate level with positive direction.

DISCUSSION

In this study we examined potential relationship between mortality and plasma NT-proBNP, coagulation markers which are D-dimer, fibrinogen, and INR in patients with COVID-19. In studies, they found a lower survival rate in patients with high NT-proBNP levels and defined high NT-proBNP levels as an independent risk factor for death in severe COVID-19 patients and stated that it was associated with prognosis (Gao et al., 2020; Qin et al., 2020; Tuo et al., 2021). Han et al. investigated the relationship between heart damage and disease severity in patients with COVID-19 and found that high concentrations of NT-proBNP were associated with disease severity and mortality (Han et al., 2020). It has been stated that there may be many factors contributing to increasing of NT-proBNP levels in patients with COVID-19, as well as the virus itself may increase the level of NT-proBNP in patients with COVID-19 (Gao et al., 2020). Similar to studies in the literature, we found that patients with high NT-proBNP levels had a significantly lower survival rate than those with normal levels.

It has been determined that one of the parameters that can be an indicator of the severity and mortality rate of COVID-19 is D-dimer, and it has been emphasized that D-dimer may be an indicator of increased thrombus formation in early myocardial infarction and acute coronary syndrome (Dyah et al., 2021). Inciardi et al. examined D-dimer, NT-proBNP levels in 99 patients with COVID-19 and found numerically higher levels at hospitalization in non-survivors compared to survivors (Inciardi et al., 2020). Wu et al. planned a cohort study of 201 patients with COVID-19 pneumonia. They stated that advanced age and coagulation dysfunction (higher D-dimer) are among the risk factors associated with the development of acute respiratory distress syndrome (ARDS) and death from ARDS. Older age has been associated with a greater risk of developing ARDS and death, possibly due to weak immune response (Wu et al., 2020). Tang et al. emphasized that coagulopathy may develop in patients with COVID-19 and that abnormal coagulation parameters are mostly related to the severity of the disease, with elevations in D-dimer and fibrin degradation products (FDPs) (Tang et al., 2020). Another study reported that high D-dimer, the most common coagulation disorder in COVID-19, is an independent risk factor for death (Colling & Kanthi, 2020). Zhou et al. emphasized that especially patients with D-dimer value higher than 1000 ng/mL are nearly 20 times more likely to die from infection than patients with lower D-dimer values (Zhou et al., 2020).

Colling and Kanthi noted that most patients with COVID-19 have a normal or shortened activated partial thromboplastin time (aPTT) and a normal or slightly prolonged prothrombin time (PT), but unlike D-dimer, these laboratory findings do not reliably correlate with disease severity. It was stated that both the initial measurement of coagulation parameters and their follow-up during the disease can help in estimating the severity of the disease. They reported that high D-dimer, FDPs levels and low fibrinogen levels were associated with death at admission (Colling & Kanthi, 2020). Dyah et al. also stated that high NT-proBNP and D-dimer levels may be predictive markers for the severity of COVID-19 and survival of patients (Dyah et al. 2020). In the study of Zhou et al. in which they included 191 patients, it was stated that 59% (n=81) of 137 patients who survived in the 45-58 age range and 70.0% (n=38) of the 54 patients who died between the ages of 63-76 years were male. D-dimer levels were found to be high in 42% (72/172) of a total of 191 patients. While the rate of patients with high D-dimer levels and surviving was 24.0% (28/118), the rate of patients with high D-dimer levels and died was 81.0% (44/54). Also 6.0% of the total 191 patients (11 /182) have been reported to have high levels of prothrombin time. While the rate of patients with high prothrombin time levels and surviving was 3.0% (4/128), the rate of patients with high prothrombin time levels and died was reported as 13.0% (7/54) (Zhou et al., 2020). While this study was compatible with our results in terms of gender, age and D-dimer results, it was not in terms of prothrombin time (Dyah et al., 2021). In their study of 193 severe COVID-19 patients, Yan et al. found that those who died were significantly older when survival and death were compared. They reported that the D-dimer and prothrombin time levels of the deceased patients were significantly higher, and that there was no significant difference in the fibrinogen level between the survivors and the deceased (Yan et al., 2020). The results in this study were similar to the results of our study.

The literature to date shows that COVID-19 is associated with cardiovascular diseases and coagulation disorders. Our study also showed that advanced age, high serum NT-proBNP, D-dimer, INR levels were important determinants of mortality in patients.

CONCLUSION

In our study, we observed that patients with high levels of NT-proBNP, D-dimer, and INR had a significantly lower survival rate than patients with normal levels. Although patients with high fibrinogen levels had a weaker survival rate associated to those with normal levels, there was no statistically significant difference between the groups. As a result, when our study was examined in terms of death/survival status, there was no significant difference in terms of gender, age, and fibrinogen levels in COVID-19 patients; there were significant differences in the levels of NT-proBNP, D-dimer, and INR. Therefore, we think that close monitoring of fluctuating levels of the myocardial biomarker NT-proBNP and early intervention in patients with high levels of this marker will help clinicians reduce COVID-19 complications and mortality. Since the precise mechanism of cardiac injury in patients with COVID-19 remains unclear, we think that our data will guide further studies that will uncover this mechanism, based on our study.

Author Contributions
Plan, design: NB, MD; **Material, methods and data collection:** NB, MD; **Data analysis and comments:** NB, MD, MÇT; **Writing and corrections:** NB, MD.

Conflict of interest
There is no competing interest.

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