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Original Article

The Relationship Between NT-proBNP Levels and Prognosis of the Patients Hospitalized in the Internal Medicine Clinic

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ABSTRACT

Objective: N-terminal pro-B-type Natriuretic Peptide (NT-proBNP) is an important biomarker used in the diagnosis of heart failure. However, recent studies have shown that NT-proBNP is associated not only with cardiovascular diseases but also with other conditions such as pneumonia, renal failure, and malignancies. This study aims to investigate the impact of NT-proBNP on the prognosis of patients hospitalized in the internal medicine department.

Methods: A retrospective evaluation was conducted on 971 patients hospitalized between January 2022 and October 2023. Patients were divided into two groups: those who were discharged and those who were transferred to the Intensive Care Unit (ICU) or deceased, and their relationships with NT-proBNP levels were examined.

Results: Patients with high NT-proBNP levels had a significantly higher risk of being transferred to the ICU or dying (Discharged vs. ICU/Deceased: 3732.15±7297 vs. 10923±12572; p<0.001). ROC analysis identified a cutoff value of >1826 pg/ml, above which the risk of ICU admission or death was found to be 5.44 times higher (OR: 5.44). When analyzed separately in patients with and without cardiac symptoms, the prognostic impact of NT-proBNP levels was significant in both groups (p<0.001).

Conclusion: NT-proBNP can be used as an effective biomarker for predicting prognosis in both cardiac and non-cardiac diseases in patients hospitalized in internal medicine clinics.

INTRODUCTION

N-terminal pro-B-type Natriuretic Peptide (NT-proBNP) is a biologically inactive protein that is produced in the heart chambers and released along with BNP during the breakdown of the proBNP protein.[1] BNP, which increases with the stretching of the heart muscle, is a peptide that regulates cardiovascular homeostasis by reducing renin and aldosterone secretion through diuresis and vasodilation.[2] These two molecules (BNP and NT-proBNP) are released into the bloodstream in nearly equal amounts during the breakdown of proBNP. However, because BNP has a relatively short biological half-life (approximately 20 minutes), whereas NT-proBNP has a longer half-life (approximately 60–120 minutes) and remains in circulation longer, NT-proBNP is a more easily measurable biomarker for the diagnosis and monitoring of heart failure compared to BNP.[3,4]

Various studies have shown that NT-proBNP is associated not only with heart failure but also with other conditions such as pneumonia, cerebrovascular events, malignancy, and end-stage renal failure.[5-10] These findings suggest that NT-proBNP is closely related to overall health status in addition to cardiovascular diseases.

Studies investigating the association of NT-proBNP with clinical conditions beyond cardiovascular diseases suggest that this biomarker has a broad range of applications for integration into clinical practice.[11,12] It has also been shown that NT-proBNP levels increase in conditions involving heightened inflammatory responses and acute phase reactants.[13] The aim of this study is to evaluate the relationship between NT-proBNP and the discharge status of patients hospitalized in the internal medicine ward, independent of comorbidities and reasons for admission. This examination aims to demonstrate the potential utility of NT-proBNP as a marker for determining the prognosis of patients in the ward and to integrate it more effectively into clinical practice, thereby contributing to future re-

search that will explore the significance of NT-proBNP in medical applications.

MATERIALS AND METHODS

This study was conducted retrospectively by evaluating patients who were hospitalized and followed up in the Internal Medicine ward between January 2022 and October 2023, and whose NT-proBNP values were measured. The study was approved by the institutional ethics committee (approval no: 116; 26/10/2023) and complied with the Declaration of Helsinki and good clinical practice guidelines.

Serum NT-proBNP levels, discharge status, primary diagnosis, and comorbidities were added to the study form by scanning the hospital information systems. The patients included in the study were evaluated in two groups. Group 1 consisted of patients who were discharged from the Internal Medicine ward in good health (control group), while Group 2 included patients who were transferred to the Intensive Care Unit or who died in the ward (study group). The NT-proBNP values and discharge statuses of patients in both groups were compared. Patients who left the ward voluntarily by signing a treatment refusal form or were referred to an inpatient ward other than the Intensive Care Unit were not included in the study due to the uncertainty of their prognostic status.

Statistical Analysis

The data were analyzed using the SPSS 25.0 software package. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess the normality of the data distribution. Descriptive statistical methods (mean, standard deviation, median, IQR, frequency, percentage) were used to evaluate the study data. The Independent t-test was used for the comparison of two groups with parametric distribution, while the Mann-Whitney U test was used for the comparison of two groups with non-parametric distribution. ROC analysis was used to determine the cutoff value. The Chi-square test was used for the analysis of categorical data. Statistical significance was evaluated at the level of $p<0.05$ for all values.

RESULTS

A total of 971 patients with a mean age of 68±17.69 years were included in the study. When the prognoses of the patients after hospitalization were examined, it was observed that 814 patients were discharged from the ward, 151 patients were transferred to the Intensive Care Unit, and 6 patients passed away. Due to the relatively low number of deceased patients, these patients were combined with those transferred to the Intensive Care Unit, forming a group of 157 patients. The relationship between the patients' NT-proBNP levels and their prognosis is presented in Table 1.

In Table 1, it is evident that there is a significant difference between the group of patients who were discharged and those who were either transferred to the ICU or deceased. The NT-proBNP levels of patients who were discharged and returned home were significantly lower compared to the other patient group (Discharged–ICU or Deceased: 3732.15±7297–10923±12572; $p<0.001$).

In Table 2, the distribution of previous diseases that are thought to potentially affect the NT-proBNP levels in the 971 patients is presented. The patients were divided into two groups: those with cardiac findings, such as a history of hypertension, coronary artery disease, and heart failure (659 patients), and those with no history of cardiac disease until the time of admission (312 patients). The NT-proBNP values were compared based on their discharge

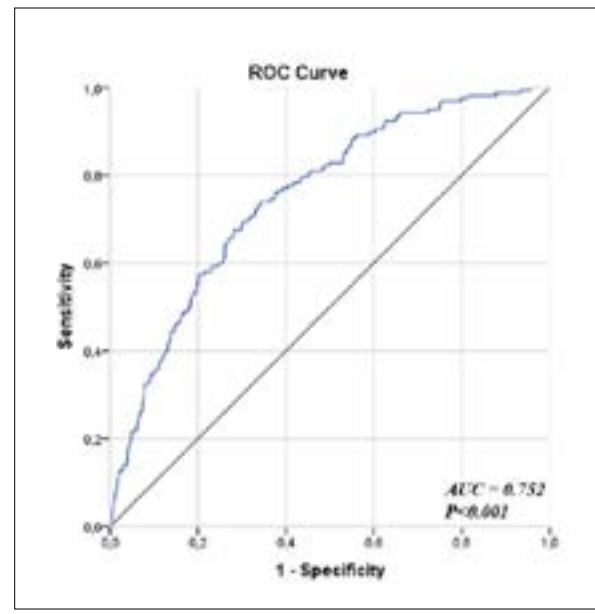

Figure 1. ROC curve regarding the effect of NT-proBNP levels on the prognosis of paitents.

Table 1. Effects of NT-proBNP values on post-hospitalization prognosis

	Dischaged (n:814)	ICU/Deceased (n:157)	p-value
NT-proBNP			
Mean±SD	3732.15±7297	10923±12572	<0.001
Median(IQR)	931 (2302)	5138(13788)	

Table 2. Chronic Diseases of Patients, Their Numbers, and Percentages

Condition	Number of Patients	Percentage (%)
Hypertension	580	59.70
Coronaryarterydisease	226	23.30
Heartfailure	186	19.20
Diabetesmellitus	370	38.10
Chronickidneydisease	194	20.00
Acutekidneyfailure	167	17.20
Liverfailure	31	3.20
COPD orAsthma	133	13.70
Pneumonia	125	12.90
Pulmonaryembolism	18	1.90
Malignancy	108	11.10
Pancreatitis	70	7.20
Anemia	93	9.60
Cerebrovascular accident	102	10.50
Dementia	111	11.40
Hypothyroidism	66	6.80
Hyperthyroidism	11	1.10
Rheumatologic diseases	33	3.40

Table 3. The effects of NT-proBNP levels on the prognosis after hospitalization in patients with and without cardiac complaints

	Cardiacproblem (-)			Cardiac problem (+)		
	Dischaged (n:272)	ICU/Deceased (n:40)	p Value	Dischaged (n:542)	ICU/Deceased (n:117)	p Value
Mean±SD	1275±3870	6754±9768	<0.001	4967±8243	12348±13131	<0.001
Median(IQR)	249 (793)	2330 (4922)		1547 (4349)	7435(18219)	

status from the ward (Table 3).

As seen in Table 3, NT-proBNP levels in discharged patients, regardless of whether they had cardiac findings or not, were significantly lower compared to those who were transferred to the ICU or who died (p<0.001). ROC analysis was performed to determine a cutoff value for NT-proBNP to ensure its usability in the clinic. The ROC curve resulting from the analysis is shown in Figure 1.

Table 4 presents the ROC curve analysis. The area under the ROC curve (AUC) was calculated to be 0.752. This value indicates that NT-proBNP has good discriminative ability as a prognostic marker. The cutoff value determined from the ROC curve analysis was found to be >1826. NT-proBNP levels above this value were associated with a high-risk prognosis. According to the analysis results, the sensitivity was calculated as 73.89%, and the specificity as 65.81%.

When patients were evaluated based on whether their NT-proBNP levels were above or below the cutoff value of 1826 pg/ml, it was observed that this had a significant impact on their discharge outcomes (Table 5).

When the discharge outcomes of patients are reviewed based on the determined cutoff value, it is observed that 41 patients, representing 7.1% of the 577 patients with a cutoff value of ≤1826, were in the ICU-deceased group. However, when the cutoff value is >1826, this rate significantly increases to 29.4% (116 out of 394 patients) (χ^2(1,

Table 4. ROC Curve Analysis Table

Area Under the ROC Curve (AUC)	0.752
Standard Error	0.0203
95% ConfidenceInterval	0.724to 0.779
z-value	12.409
p<0.0001	
Youden Index J	0.3969
Cutoff Point	>1826
Sensitivity	73.89
Specificity	65.81

Table 5. The Impact of the Determined Cut-off Value on Patient Discharge

NT-proBNP	Dischaged	ICU/Deceased	p
Cut-off ≤ 1826	536	41	<0.0001
Cut-off> 1826	278	116	

N=971)=81.17, p<0.00001). Additionally, the risk of ICU admission or mortality before discharge for patients with an NT-proBNP value>1826 pg/ml was found to be approximately 5.44 times higher than others (OR=5.44).

DISCUSSION

BNP is a protein that has been shown to increase when the heart ventricle walls are stretched or under pressure as a result of physiological and biochemical processes in many diseases, particularly heart failure.[7-10] This suggests that NT-proBNP may have a wide application area in its integration into clinical practice. In our study, the NT-proBNP levels measured at the time of hospital admission in patients who were subsequently discharged in good health from the internal medicine ward were significantly lower than the NT-proBNP levels at the time of admission of patients who were transferred to intensive care or who deceased after their condition became critical while hospitalized in the internal medicine clinic. Since this relationship has been demonstrated in both patients with and without previous cardiac complaints, it gives important messages in terms of the prognosis of patients.

In a study conducted by Fonarow and colleagues involving 48,629 individuals, it was found that BNP levels measured at hospital admission significantly predicted in-hospital mortality in patients with acute decompensated heart failure. The study divided BNP levels into four groups, and the in-hospital mortality rates were found to be 1.9% in those with BNP ≤430 pg/ml, while it was 6.0% in those with BNP ≥1,730 pg/ml. Consequently, the routine assessment of BNP levels has been shown to provide valuable prognostic information for risk stratification and management of these patients.[14] Similar to this study, there are various studies in the literature that examine the relationship between NT-proBNP levels and prognosis. While many studies focus on patients with heart failure symptoms, research exploring the relationship between NT-proBNP and other chronic diseases has also begun to emerge.

According to the results of a study conducted by Waldum and colleagues involving 2,076 patients, the risk of cardiovascular mortality significantly increases as NT-proBNP levels rise in heart failure patients with impaired renal function. Specifically, it was found that 59.1% of patients with impaired renal function had NT-proBNP levels above 2180 pg/ml, and the 2-year survival rate for this group was 57%; this rate was significantly lower than the 85% survival rate observed in patients with normal renal function.[15]

In another study by Nowak and colleagues, the potential of NT-proBNP, MR-proANP, and BNP to predict short- and long-term mortality in patients with community-acquired pneumonia was compared, and all three natriuretic peptides were found to be effective. NT-proBNP was shown to be an independent predictor of both short- and long-term mortality (hazard ratio: 1.004, 95% CI: 1.00–1.01, p=0.001, per 300 pg/ml increase). These findings suggest that NT-proBNP levels provide simple and robust predictions in patients with community-acquired pneumonia and that its prognostic accuracy is comparable to the pneumonia severity index.[13] While the relationship between NT-proBNP levels and prognosis in this study shows similarities to ours, the focus on patients diagnosed solely with community-acquired pneumonia differentiates this study from ours.

Another study conducted by Idris et al.[8] on a group of 125 patients showed that NT-proBNP levels had significant effects on 1-year mortality in patients with acute stroke. NT-proBNP levels in deceased patients (980.2±1249.9 pmol/L) were significantly higher than in survivors (125.4±244.9 pmol/L), suggesting the possibility of occult cardiac dysfunction, although the patients did not have obvious complaints of heart failure. Cox regression analysis performed in the study evaluated 1-year mortality using variables such as age, gender, creatinine, urea, ALT, alkaline phosphatase, and NT-proBNP. According to the results of the analysis, the most significant variable for 1-year mortality was log NT-proBNP (Wald 17.9, p<0.0001). Fifteen of 57 patients with a median NT-proBNP value above 42 pmol/L died within 1 year, whereas only 1 of 57 patients with a median value below this value died (p<0.001). Although this study is specific to ischemic stroke patients, unlike other studies, it consists of patients without significant heart failure.

In a study conducted by Benmachiche and colleagues involving 3,833 individuals, the in-hospital mortality rate and length of stay were found to be higher in the fifth quintile group with the highest NT-proBNP levels compared to other groups (20.3% vs. 6.5% and 20.8±24.0 days vs. 14.9±26.5 days, both p<0.001). After multivariate adjustment, the hazard ratio (HR) for in-hospital mortality in the fifth quintile group was determined to be 1.97 (1.57-2.46), and the adjusted length of stay was 20.4±1.0 days (p<0.001). As a result, patients with high NT-proBNP levels were found to be at a higher risk of in-hospital mortality and longer hospital stays, independent of their clinical characteristics.[11] The difference between this study and other studies is that NT-proBNP levels were not only limited to patients with heart failure or cardiac symptoms but

also included 2,177 other patients without any cardiac or pulmonary disease findings.

This study aligns with ours in that it includes not only patients with heart failure symptoms but also a significant number of patients without heart failure. Similarly, in our study, NT-proBNP levels were statistically significantly lower in patients who were discharged in good health compared to those in the other group, regardless of whether they had known heart failure or not.

In a study conducted by Kotanidou and colleagues, NT-proBNP levels were found to be a significant biomarker for predicting ICU mortality in 233 consecutive patients with non-cardiac critical illness. The study demonstrated that NT-proBNP levels at ICU admission were significantly higher in non-survivors. Additionally, it was shown that this biomarker was effective in predicting ICU mortality independent of APACHE II scores and cytokine levels.[12] While this study, like ours, includes all patient groups, our study focuses on patients discharged from the internal medicine ward, whereas their study addresses the impact on the prognosis of ICU patients.

When the results of these studies and ours are evaluated together, it can be said that NT-proBNP levels are important for determining the need for ICU admission, as in our study, and for predicting prognosis in the ICU. In some studies, NT-proBNP values have been divided into quintiles to indicate the severity of illness, while in others, the risk has been determined based on the degree of increase in proBNP levels.[12-15]

In our study, through ROC analysis aimed at determining the risk of ICU admission or discharge, we identified NT-proBNP>1826 pg/ml as the cutoff value with 73.89% sensitivity and 65.81% specificity. According to this cutoff value, the risk of ICU admission or death before discharge was found to be approximately 5.44 times higher in patients with NT-proBNP levels>1826 pg/ml (OR=5.44).

Although NT-proBNP levels are typically used as indicators of heart failure and other cardiac conditions, they can also increase in various non-cardiac diseases. These increases are due to non-cardiac factors and may be associated with different mechanisms. Sepsis is a condition characterized by organ dysfunction resulting from the body's excessive response to infection. In septic shock, elevated inflammatory cytokines and increased vascular permeability place additional stress on the heart, leading to increased NT-proBNP levels.[16,17]

In both acute and chronic renal failure, NT-proBNP levels can rise significantly. This increase results from impaired clearance of NT-proBNP through the kidneys or fluid accumulation due to renal failure, which subsequently impacts the heart and leads to elevated circulating levels.[15-18]

In patients with COPD, chronic hypoxia places stress on the right ventricle and can lead to pulmonary hypertension. Similarly, during a pulmonary embolism, the sudden increase in pressure on the right ventricle can increase NT-proBNP release.[19,20]

In cancer patients, NT-proBNP levels may rise due to the systemic effects of the malignancy itself and the cardiotoxic effects of chemotherapeutic agents. This increase is associated with mechanisms such as inflammation, oxidative stress, and direct cardiac damage.[9,21]

Our study is different from others in that it includes not only cardiac-related conditions but also other chronic diseases, and it evaluates these conditions as a whole. However, there are some limitations to this study. The retrospective nature of our data set and the limited sample size are considered weaknesses of the study.

Conclusion

In conclusion, this study demonstrates that NT-proBNP levels can be used to determine prognosis not only in cardiac diseases but also in patients admitted to internal medicine wards for various other reasons. The identified NT-proBNP cutoff value of >1826 pg/ml provides high accuracy in predicting the need for intensive care or the risk of mortality. These findings support the broader use of NT-proBNP in clinical practice.

Ethics Committee Approval

The study was approved by the Health Sciences University Istanbul Fatih Sultan Mehmet Training and Research Hospital Ethics Committee (Date: 26.10.2023, Decision No: 116).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: A.Ö., N.O.; Design: M.K., Y.S.; Supervision: Y.S., M.S.; Fundings: A.Ö., N.O.; Data collection &/or processing: M.K., N.O.; Analysis and/or interpretation: Y.S., A.Ö.; Literature search: M.S., N.O.; Writing: M.K., Y.S.; Critical review: A.Ö., N.O.

Conflict of Interest

None declared.

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Dahiliye Kliniğinde Yatan Hastaların NT-proBNP Değeri ile Prognoz Arasındaki İlişki

Amaç: N-terminal pro-B-tipi Natriüretik Peptid (NT-proBNP), kalp yetmezliği tanısında kullanılan önemli bir biyomarkerdir. Ancak son çalışmalar, NT-proBNP'nin yalnızca kardiyovasküler hastalıklarla değil, aynı zamanda pnömoni, böbrek yetmezliği ve maligniteler gibi diğer durumlarla da ilişkili olabileceğini göstermektedir. Bu çalışma, NT-proBNP'nin iç hastalıkları servisinde yatan hastaların prognozu üzerindeki etkisini araştırmayı amaçlamaktadır.

Gereç ve Yöntem: Ocak 2022-Ekim 2023 tarihleri arasında yatan 971 hasta retrospektif olarak değerlendirildi. Hastalar, taburcu edilenler ve Yoğun Bakım Ünitesi'ne sevk edilen ya da vefat edenler olarak iki gruba ayrıldı ve NT-proBNP seviyeleri ile ilişkileri incelendi.

Bulgular: NT-proBNP seviyeleri yüksek olan hastaların Yoğun Bakım Ünitesi'ne sevk edilme veya ölüm riski anlamlı derecede yüksek bulundu (Taburcu–YBU veya Ex: 3732.15±7297–10923±12572; p<0.001). ROC analizi sonucunda belirlenen kestirim değeri >1826 pg/ml idi ve bu değerin üzerinde olan hastalarda yoğun bakıma gitme veya ölüm riskinin 5.44 kat daha yüksek olduğu görüldü (OR: 5.44). Kardiyak bulgusu olan ve olmayan hastalarda ayrı ayrı değerlendirildiğinde, NT-proBNP düzeylerinin prognoz üzerindeki etkisinin her iki grupta da belirgin olduğu saptandı (p<0,001).

Sonuç: NT-proBNP, hem kardiyak hem de kardiyak olmayan hastalıkların prognozunu belirlemede etkili bir biyomarker olarak iç hastalıkları kliniğinde yatan hastaların prognozunu öngörmede kullanılabilir.

Anahtar Sözcükler: NT-proBNP; prognoz; risk belirleme; yatan hastalar.