

# Effect of renal failure on N-terminal Pro-Brain natriuretic peptide in patients admitted to emergency department with acute dyspnea

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## ABSTRACT

**Objective:** Preexisting renal failure diminishes the excretion of N-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP), therefore limits the diagnostic value of this peptide for concomitant heart failure. The aim of this study was to evaluate the association between NT-proBNP and the stages of renal dysfunction in a typical population attended to emergency department with acute dyspnea.

**Methods:** In this cross-sectional study, all consecutive patients with acute dyspnea underwent clinical evaluation, laboratory assessment of NT-proBNP, and echocardiographic examinations. Among subjects, 54.5% were diagnosed as heart failure. Grouping variables according to renal function capacity and ejection fraction, independent variables were compared with Kruskal-Wallis or ANOVA with posthoc tests. Correlation and linear regression analysis were done to analyze the variables associated with NT-proBNP. The diagnostic performance of NT-proBNP was evaluated by receiver-operating characteristic (ROC) curve.

**Results:** Serum median NT-proBNP level in patients with severe renal impairment was significantly higher than moderate and mildly decreased renal functions ( $p=0.001$ ). In patients with moderate and severe left ventricular failure, NT-proBNP was significantly higher compared with normal subjects (LVEF>50%) ( $p=0.040$ , and  $0.017$ , respectively). Renal dysfunction was associated in 56% of patients with heart failure. The area under the ROC curve of NT-proBNP for identifying left ventricular failure in patients with renal failure (eGFR<90 mL/min/1.73 m<sup>2</sup>) was 0.649 and reached significant difference (95% CI:0.548-0.749,  $p=0.005$ ).

**Conclusion:** In addition to NT-proBNP measurement in clinical judgement of heart failure, renal functions have to be taken into consideration to avoid misdiagnosis (*Anadolu Kardiyol Derg 2014; 14: 519-24*).

**Key words:** diagnostic accuracy, heart failure, natriuretic peptides, regression analysis, renal failure

## Introduction

Brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) are mainly produced and secreted from myocytes of the heart which act like an endocrine gland due to volume overload and left ventricular overtension. They regulate blood pressure and volume which directly affects kidneys (1), therefore natriuretic peptides are widely used as cardiac biomarkers for the evaluation of left ventricular function and the diagnosis of heart failure (2). In patients presenting with acute dyspnea and/or peripheral edema, NT-proBNP increases in response to increased myocardial wall stress (3, 4).

NT-proBNP is believed to be cleared from blood through renal excretion alone, therefore, more affected by renal function and age than BNP which is cleared from blood by natriuretic peptide C receptor and degraded by neutral endopeptidase (1, 5). They are

also affected by body mass index and gender (6). As a biochemical marker, NT-proBNP has a longer half-life with high blood concentrations compared to BNP which is a preferred factor in laboratories. These markers were also detected for their relationship with the extracellular volume, however the results are controversial (7).

Preexisting renal failure diminishes the excretion of NT-proBNP and BNP, therefore limits the diagnostic value of these peptides for heart failure (8). Because heart failure and renal failure are commonly associated with each other and the prevalence is higher in advanced ages, the diagnosis or exclusion of heart failure becomes more important in these populations (9).

In the emergency departments, natriuretic peptides are used for unexplained dyspnea to support the heart failure diagnosis with clinical evaluation. In the PRIDE study (10), authors concluded that NT-proBNP testing was more valuable than BNP in patients with congestive heart failure irrespective of renal func-

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tion. However, natriuretic peptides still remain to be debated to diagnose or monitor cardiac dysfunction accompanying renal dysfunction (11).

In this study, we aimed to evaluate the diagnostic value of NT-proBNP for outpatients attended to the emergency department with acute dyspnea and to understand the effect of renal functions on NT-proBNP concentrations.

## Methods

### Study design and population

This cross-sectional study was held in Tepecik Research and Training Hospital, a tertiary Hospital in Izmir, Turkey, in a time period between Jan 2008-May 2009.

Eligible subjects were selected from consecutive patients admitted to our emergency department in whom NT-proBNP was analyzed and left ventricular ejection fraction was obtained for symptoms of severe dyspnea and chest pain. Some patients were initially identified but were not enrolled until they were examined echocardiographically. Patients presenting with dyspnea after a trauma or malignancy and patients who refused to participate in the study were excluded. Data were collected with a questionnaire prepared including their health history, medications etc. The study protocol was approved by the institutional review board committee and written informed consent was obtained from all participants.

### Study protocol

All subjects were examined by physicians on the first day of admission to the emergency department including physical examination, chest X-ray, ECG, echocardiography and biochemical examinations. Patients with systolic blood pressure (BP)  $\geq 140$  mm Hg and/or diastolic BP  $\geq 90$  mm Hg and/or patients who are under treatment with antihypertensives were defined as having hypertension.

Data from the questionnaire, clinical findings, medications, signs, symptoms, biochemical data were tabulated. All patients were assessed with respect to New York Heart Association (NYHA) functional class according to their medical history and physical examination.

All patients were categorized into 4 groups according to the stages of eGFR following the KDIGO guideline (12); No renal failure ( $\geq 90$  mL/min/1.73 m<sup>2</sup>), mildly decreased (60-89 mL/min/1.73 m<sup>2</sup>), moderately decreased (30-59 mL/min/1.73 m<sup>2</sup>), severely decreased renal function ( $<30$  mL/min/1.73 m<sup>2</sup>).

Patients were also classified according to left ventricle ejection fractions as preserved (LVEF $>50\%$ ), moderately reduced (LVEF 35-50%), and severely reduced (LVEF $<35\%$ ).

The severity of cardiac failure was classified in stages I-IV by the New York Heart Association.

### Baseline laboratory and clinical examinations

CK-MB mass and Troponin I were detected on the analyzer (Dade Behring, Siemens Diagnostics, Marburg, Germany).

Biochemical test results related to NT-proBNP and renal functions (blood urea nitrogen, creatinine, hemoglobin, pO<sub>2</sub>) were also collected that were studied with fresh sera on the first day of admission. Blood pressure was measured with manual sphygmomanometer.

### Renal function assessment

Serum creatinine, BUN was determined on the first day of admission on Olympus AU640 (Olympus, Hamburg, Germany). Estimated glomerular filtration rate (eGFR) was calculated by the modification of diet in renal disease method (13).

### NT-proBNP assessment

Serum NT-proBNP was determined by a sandwich enzyme immunoassay method on analyzer (Dade Behring, Siemens Diagnostics, Marburg, Germany) and expressed as pg/mL. The recommended clinical thresholds to rule out heart failure were 125 pg/mL for patients younger than 75 years, and 450 pg/mL for patients 75 years and older. Intra and interassay CV's were 1.5% and 4.1% respectively.

### Echocardiography

Echocardiographic examinations were performed according to American Society of Echocardiography recommendations (14) with a Vingmed ultrasound system (Vingmed System 7, General Electric, Horten, Norway) and a 2.5 MHz transducer. Measurements were made on 3 representative beats and the results were averaged. Standard echocardiographic analysis included two-dimensional and Doppler flow measurements. Left ventricle ejection fraction calculation was based on LV end-diastolic and end-systolic measurements.

### Statistical analysis

Normality of data was evaluated with Kolmogorov-Smirnov test and with histograms. Gaussian distributed data were written as mean $\pm$ standard deviation, non-normal distributed ones as medians with interquartile range (IQR), and categorical data were presented as a proportion (%). Categorical variables were analyzed by chi-square test. Parametric analyses were performed with ANOVA with a posthoc Tukey test. Natural logarithmic transformation of NT-proBNP values resulted in a dataset with a normal distribution. Non-parametric data were compared with Kruskal-Wallis, finding significant, Mann-Whitney U test was used for independent pairs.

Correlation and linear regression analyses were used to analyze the variables associated with NT-proBNP. Spearman's correlation test for normal, Pearson's correlation for skewed distribution were used. The relationship between NT-proBNP and renal dysfunction was tested with the area under the receiver-operating characteristic (ROC) curve. P $<0.05$  value was considered as statistically significant. Statistical analyses were performed using statistical package for Windows version 15.0, SPSS Inc. (Chicago, Illinois).

## Results

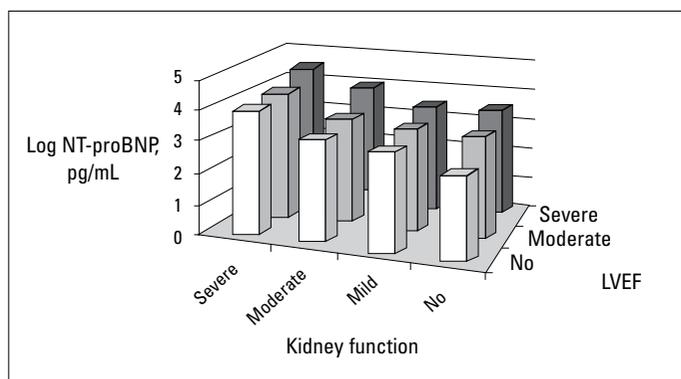
In this study, we evaluated the relationship of NT-proBNP and severity of renal failure and left ventricle ejection fraction in

totally 132 patients who were older than 45 years of age with a mean age of 73 years.

**Renal function and NT-proBNP assessment**

Demographic, clinical and laboratory data of the patients were summarized in Table 1. Gender difference was not observed for NT-proBNP evaluating the patients according to their renal functions (p=0.267).

Serum median NT-proBNP level in patients with severe renal impairment [12200 (729-53408) pg/mL] was significantly higher than moderate [2889 (64-47067) pg/mL, p<0.001], mildly decreased renal functions [2065 (48-17959) pg/mL, p<0.001] and patients with normal GFR [1466 (35-6420) pg/mL, p<0.001].



**Figure 1. Relationship of renal function and the degree of left ventricular ejection fraction**

The intersection between cardiac and renal dysfunctions showed an increasing trend in LVEF- left ventricle ejection fractions; NT - proBNP concentrations

**Cardiac function and NT-proBNP assessment**

Table 2, showing the demographic characteristics and laboratory data of patients were classified according to left ventricular ejection fractions. Patients with lower left ventricular ejection fractions were characterized by significantly higher NT-proBNP than those with preserved left ventricle functions. NT-proBNP concentrations in all heart failure patients according to the groups of renal dysfunctions and subgroups with LVEFs were showed in Figure 1.

**Factors affecting NT-proBNP values**

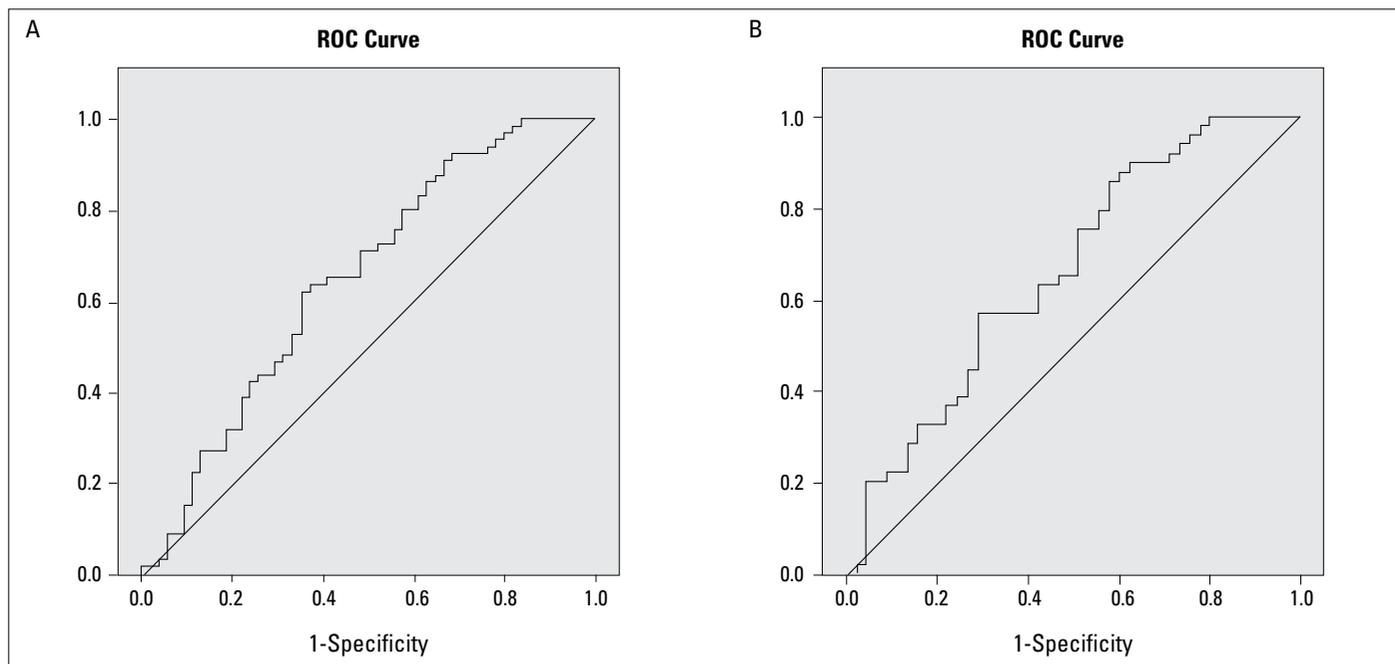
Correlation between NT-proBNP concentrations and clinical, laboratory data were showed in Table 3. NT-proBNP concentrations were positively correlated with age (r=0.202, p=0.020), CK-MB (r=0.322, p<0.001), and Troponin I (r=0.331, p<0.001). Negative correlations were observed with eGFR (r=-0.432, p<0.001) and EF (r=-0.222, p<0.001).

Multiple linear regression analyses demonstrated that with NT-proBNP levels as the dependent variable, NT-proBNP levels were positively correlated with age (β=0.183, p=0.040), negatively correlated with EF (β=-0.211, p=0.015) (Table 3). Multivariate linear regression analysis showed that NT-proBNP is the most significant predictor for eGFR.

NT-proBNP showed an increasing trend with increasing age. Separating patients into subgroups with a cut-off age of 75 years, significant difference was observed (p=0.049) (Table 4).

**Renal function and ROC analysis of NT-proBNP**

The area under the ROC curve of NT-proBNP levels in patients with renal dysfunction (eGFR<90 mL/min/1.73 m<sup>2</sup>, n=120)



**Figure 2. Receiver operating characteristic curve of NT-proBNP for diagnosis of heart failure renal failure** A) Receiver operating (ROC) curve analysis of serum NT-proBNP levels for the diagnostic value of heart failure in patients with eGFR<90 mL/min/1.73 m<sup>2</sup> (n=120). AUC was determined as 0.649 with a cut-off value of 3889 pg/mL with a sensitivity of 68.3% and specificity 75.0%. B) Receiver operating (ROC) curve analysis of serum NT-proBNP levels for the diagnostic value of heart failure in patients with renal failure [30<eGFR <90 mL/min/1.73<sup>2</sup> (n=94)]. Cut-off value of serum NT-proBNP is 3670 pg/mL with a sensitivity of 68.3% and specificity of 60.4% and area under the curve is 0.662.

**Table 1. Demographic, clinical characteristics and laboratory data of patients classified according to eGFR**

Characteristics	Total Group	Normal eGFR ≥90	Mild 60≤eGFR<90	Moderate 30≤eGFR<60	Renal failure eGFR<30	P	F	Chi-square
n	132	12	42	52	26			
Age, years	73±10.8	64±9.8	74±10.9*	74±10.4*	74±10.3*	0.023	3.301	
Gender, male	52%	67%	60%	42%	54%	0.267		
Heart failure	55%	50%	50%	54%	65%	0.642		
Hypertension	69%	67%	67%	70%	65%	0.840		
Previous Myocardial Infarction	16%	8%	13%	18%	17%	0.863		
Chronic Obstructive Pulmonary Disease	33%	40%	36%	28%	35%	0.809		
NYHA II	35%	26%	37%	44%	22%			
III	43%	47%	45%	42%	65%	0.042		
IV	10%	5%	11%	10%	13%			
Diuretics	65%	50%	72%	63%	64%	0.567		
ACE	51%	70%	56%	54%	27%	0.007		
Digoxin	19%	20%	25%	17%	14%	<0.001		
Beta blocker	14%	10%	14%	19%	5%	0.217		
PO <sub>2</sub>	94±3.8	95±2.0	94±3.9	93±3.8	94±4.4	0.620	0.594	
Blood pressure, mm Hg systolic	144±32.6	136±32.5	138±24.7	152±36.7	141±34.6	0.438	1.453	
Blood pressure, mm Hg diastolic	82±14.7	78±11.9	78±9.2	88±15.8	78±17.5	0.093	4.756	
EF (%)	48±11.1	47±11.2	49±11.8	48±11.8	48±8.7	0.952	0.170	
eGFR, mL/min/1.73 m <sup>2</sup>	56±28.9	115±26.9	73±9.0*	46±8.0*	19±6.7*	<0.001	182.2	
Creatinine, mg/dL, median (IQR)	1.20 (0-11.0)	1.00 (0.7-1.2)	1.20 (1.0-2.1)	1.30 (1.0-2.1)	2.85 (1.9-11.0)*	<0.001		71.04
NT-proBNP, pg/mL, median (IQR)	3602 (35-53408)	1466 (35-6420)	2065 (48-17959)	2889 (64-47067)	12200* (729-53408)	<0.001		26.58
Troponin-I, ng/mL	0.01 (0-67)	0.02 (0-0.19)	0.0 (0-0.62)	0.0 (0-60)	0.08 (0-67)	0.015		10.42
CK-MB, ng/mL	1.6 (0-338)	1.1 (0-2.9)	1.6 (0-17.6)	1.3 (0-29)	2.7 (0-338)	0.091		6.459
Hemoglobin, g/dL	11.9 (2.03)	12.5±1.13	12.5±2.27	11.9±1.77	10.7±1.94	0.003	5.166	

CK-MB-MB isoenzyme of creatine kinase; eGFR-estimated glomerular filtration rate; NT-proBNP-N-terminal brain natriuretic peptide; NYHA-New York Heart Association. Data are expressed as mean±SD, percentages, or median values (quartile 1, quartile 3).  $\chi^2$  test was used for categorical data. ANOVA was used with a posthoc Tukey test for Gaussian distributed variables. Kruskal-Wallis test (with a posthoc Mann-Whitney U test) was used for non-Gaussian variables. \*p<0.05, compared to eGFR≥90 group. Posthoc Tukey test results for age: p=0.021, 0.023, 0.027 respectively comparing the mild, moderate and renal failure groups with normal eGFR group. A p value<0.001 was determined.

was 0.649 and reached to a significant difference (95% CI:0.548-0.749, p=0.005) (Fig. 2A) (Table 5). At optimal cut-off value of 3839 pg/mL, NT-proBNP yielded sensitivity 68.3%, specificity 75.0%, accuracy 71.6% and negative predictive value 70.3%. Figure 2B shows the ROC curve for diagnosis of heart failure in a different renal dysfunction stage (30<eGFR<90 mL/min/1.73 m<sup>2</sup>, n=94).

The area under the ROC curve of NT-proBNP levels in renal failure (eGFR<30 mL/min/1.73 m<sup>2</sup>, n=26) and clinical diagnosis of heart failure was 0.510 and not significant (95% CI: 0.263-756, p=0.936).

## Discussion

Heart failure with a concomitant renal failure is a leading cause of morbidity and mortality which is termed as cardiorenal

syndrome. In the present study, with a population attended to the emergency service with acute dyspnea and age ranged from 46 to 99 years, NT-proBNP concentrations correlated negatively with eGFR values and with the progression in renal insufficiency, NT-proBNP concentrations found as elevated to the very high concentrations. At higher cut-off values than intended by the manufacturer, NT-proBNP is a valuable marker in high-risk patients when renal functions and age were also taken into consideration.

Renal failure accompanying to the heart failure reduces the usefulness of cardiac biomarkers and the cutpoints recommended are lower to exclude heart failure accompanying to the lower GFR (<60 mL/min 1.73 m<sup>2</sup>) (15). Regarding the elevation in NT-proBNP values due to renal dysfunction, Cui et al. (16) showed higher values in elderly patients irrespective to the heart failure. Comparing the diagnostic performance of

**Table 2. Demographic characteristics and laboratory data of patients classified according to left ventricular ejection fraction**

	EF >50% preserved	EF 35-50% moderate	EF <35% severe	P	F
n	60	56	16		
Age, years	74±9.7	72±11.8	68±9.3	0.074	2.65
Gender, male %	35.0%	58.9%	87.5%	<0.001	
NT-proBNP, pg/mL median (IQR)	2149 (35-53408)	3839 (119-34383)*	5130 (989-47067)*	0.007	5.233
GFR, mL/min/ 1.73 m <sup>2</sup>	57±30.5	53±28.6	61±24.4	0.554	0.533

Data are expressed as mean±SD or median (IQR)  
eGFR, estimated glomerular filtration rate; EF, left ventricular ejection fraction; NT-proBNP-N-terminal brain natriuretic peptide. ANOVA and posthoc Tukey test was used for log-transformed NT-proBNP value comparison  
\*Comparing the moderate and severe group NT-proBNP levels with the preserved group, p values are 0.040, 0.017, respectively

**Table 5. Predictive values of NT-proBNP**

Condition	Cut-off, pg/mL	ROC area (95%CI)	P	Sensitivity	Specificity	Accuracy	PPV	NPV
eGFR<90	3839	0.649 (0.548-0.749)	0.005	68.3%	75.0%	71.6%	73.2%	70.3%
30<eGFR<90	3670	0.662 (0.551-0.772)	0.007	68.3%	60.4%	63.8%	57.1%	71.1%

CI - confidence interval, eGFR - estimated glomerular filtration rate (mL/min/1.73 m<sup>2</sup>), NPV - negative predictive value, NT - proBNP-N - terminal brain natriuretic peptide, PPV - positive predictive value, ROC - receiver operator characteristics

NT-proBNP with ROC curves, they suggested that those very high concentrations of NT-proBNP might be useful to assess the severity of renal dysfunction in elderly. In the current study, we determined a cut-off value of 3839 pg/mL for NT-proBNP in patients with renal impairment with a positive predictive value of 73.2% and negative predictive value of 70.3% in diagnosis of heart failure.

In the PRIDE study, NT-proBNP was evaluated with a cut-off value of 300 pg/mL that had a negative predictive value of 99% in diagnosis of heart failure, however they excluded the patients with severe renal failure (17). For those reasons NT-proBNP was concluded to be of diagnostic value in heart failure in the state of normal renal functions (18). In the current study we included patients regardless of their renal functions and in the study population with heart failure, 56% had eGFR lower than 60 mL/min/1.73 m<sup>2</sup>.

In a study by Luchner et al. (15), NT-proBNP showed a high negative predictive value to rule-out the left ventricular dysfunction with remarkable specificity and sensitivity. They concluded that renal functions had to be determined to prevent misdiagnosis of heart failure. Interestingly those authors observed unhealthy heart and renal functions classified as falsely positive or falsely negative in their study group.

Cardiac troponins are components that release into the blood due to the myocardial injury. In a comprehensive study, troponin T and troponin I were found as elevated with kidney failure which correlated with the disease severity in the absence of acute coronary syndrome (19). Those patients were associated with poor survival for which the reason may be due to subclinical myocardial damage although they revealed no signs

**Table 3. Correlation between NT-proBNP concentrations and clinical, laboratory data**

Variable	Univariate		Multivariate	
	r	P	β	P
eGFR, mL/min/1.73 m <sup>2</sup>	-0.432	<0.001	-0.392	<0.001
Age, years	0.202	0.020	0.183	0.040
EF, %	-0.222	0.010	-0.211	0.015
CK-MB, ng/mL	0.322	<0.001	-0.327	0.744
Troponin I, ng/mL	0.331	<0.001	0.870	0.386

CK-MB-MB isoenzyme of creatine kinase, EF - left ventricular ejection fraction, eGFR - estimated glomerular filtration rate, NT-proBNP-N - terminal brain natriuretic peptide

**Table 4. Median NT-proBNP concentrations of subgroups according to ages**

	age ≥75 (n=66)	age<75 (n=66)	P
NT-proBNP, pg/mL	4540 (48-47100)	2095 (35-53408)	0.049

NT-proBNP-N-terminal brain natriuretic peptide

of cardiac injury. Similar to the study by Cui et al (16), we found a moderate correlation between NT-proBNP and CK-MB, Troponin I respectively suggested to be elevated because of myocardial damage contributed to the elevation of NT-proBNP.

In their study, Wang et al. (20) examined the diagnostic value of NT-proBNP and BNP to discriminate left ventricular failure in acute exacerbation of chronic bronchitis in patients with no history of heart failure for which NT-proBNP showed a superior diagnostic performance than BNP. At a cut-off value of 935 pg/mL, they demonstrated high sensitivity (94.4%) and negative predictive value (97.6%). The independent effects of pulmonary pressure, atrial fibrillation and renal function on NT-proBNP concentrations were also observed similar to another study (21).

To diagnose heart failure, knowledge of the non-cardiac factors which influences NT-proBNP is crucial. Anemia is one of the independent factor affects the natriuretic peptides which is common in heart and renal failure. In CKD, anemia is mainly caused by the reduced erythropoietin production (22).

### Study limitations

In this study we studied with a small group of patients and did not follow-up patients for their survival. Therefore, studies with a larger group of patients needed to confirm the present results.

### Conclusion

A significant inverse relationship was observed between renal function and NT-proBNP concentration in patients with

acute dyspnea regardless of the final diagnosis. This may be the result of volume overload and the myocardial injury. Despite its low specificity in diagnosis for left ventricular failure, this biochemical marker is an easy diagnostic parameter to assess with only one tube of venous blood in clinical practice especially for outpatients. Our results indicate that NT-proBNP may be a suitable marker to rule out heart failure in high-risk patients when interpreted with renal functions.

**Conflict of interest:** None declared.

**Peer-review:** Externally peer-reviewed.

**Authorship contributions:** Concept - A.Ç., I.Ç.; Design - A.Ç., I.Ç., S.Ç.; Supervision - A.Ç., S.Ç.; Resource - A.Ç., I.Ç.; Materials - A.Ç., I.Ç., Y.G.; Data collection&/or Processing - A.Ç., B.G.; Analysis &/or interpretation - S.Ç., Ö.Ö.; Literature search- S.Ç., A.Ç.; Writing - S.Ç., Ö.Ö.; Critical review - S.Ç., Ö.Ö.

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