doi: 10.53446/actamednicomedia.1109613

Acta Medica Nicomedia

Cilt: 6 Sayı: 1 Şubat 2023 / Vol: 6 Issue: 1 February 2023
https://dergipark.org.tr/tr/pub/actamednicomedia

Research Article | Araştırma Makalesi

ASSOCIATION OF N-TERMINAL PROHORMONE BRAIN NATRIURETIC PEPTIDE LEVEL AND ECHOCARDIOGRAPHIC LEFT VENTRICULAR SYSTOLIC OR DIASTOLIC DYSFUNCTION IN NON-ACUTE DYSPNEA

AKUT OLMAYAN DİSPNEDE N-TERMİNAL PROHORMON BEYİN NATRİÜRETİK PEPTİT SEVİYESİ İLE EKOKARDİYOGRAFİK SOL VENTRİKÜL SİSTOLİK VEYA DİYASTOLİK İŞLEV BOZUKLUĞU İLİŞKİSİ

Pelin Karaca Ozer[1*], Elif Ayduk Govdeli[1]

[1]Istanbul University, Istanbul Medical Faculty, Department of Cardiology, Istanbul, Türkiye.

ABSTRACT

Objective: The aim of the study was to evaluate serum N-terminal prohormone brain natriuretic peptide (NT-proBNP) level and evidence of left ventricular (LV) systolic dysfunction (SD) or diastolic dysfunction (DD) in non-obese patients with non-acute dyspnea.

Methods: This study retrospectively evaluated the serum NT-proBNP level and LV SD or DD from transthoracic echocardiography (TTE) in patients with non-acute dyspnea between October 2020 and October 2021. The normal limit for the serum NT-proBNP level (125 pg/ml) was used as the cut-off value.

Results: Ultimately, 435 patients were included in the study. In 61% of the patients (n=264), the NT-proBNP level was elevated (≥ 125 pg/ml). There was no evidence of SD or DD in 56% of the patients (n=147) with ≥ 125 pg/ml. The patients whose NT-proBNP ≥ 125 but who had no SD or DD had a significantly higher H2FPEF score ≥ 6, atrial fibrillation, malignancy, previous COVID-19, and need for hospitalization than the patients whose NT-proBNP < 125 and who had no SD or DD (13% vs. 4%; 5% vs. 1%; 16% vs. 9%; 29% vs. 5%; and 25% vs. 11%, respectively). An NT-proBNP value < 752.1 pg/ml excluded SD with 72.5% sensitivity and 83.1% specificity and < 350.3 pg/ml excluded DD with 71.3% sensitivity and 75.5% specificity.

Conclusion: A high NT-proBNP value does not always indicate SD or DD. NT-proBNP measurement may detect not only overt heart failure but also subclinical LV dysfunction in various clinical entities, in addition to adding prognostic significance in non-acute dyspnea.

Keywords: Dyspnea, heart failure, NT-proBNP

ÖZ

Amaç: Bu çalışmanın amacı, akut olmayan nefes darlığı şikayeti olan, obez olmayan hastalarda serum N-terminal prohormon beyin natriüretik peptit (NT-proBNP) düzeyinin ve sol ventrikül (SV) sistolik disfonksiyonunun (SD) veya diyastolik disfonksiyonunun (DD) kanıtlarını değerlendirmektir.

Yöntem: Bu çalışmada, Ekim 2020 ile Ekim 2021 arasında akut olmayan nefes darlığı şikayeti ile başvuran hastalarda transtorasik ekokardiyografi (TTE) ile değerlendirilen SV SD veya DD varlığı ile serum NT-proBNP düzeyi geriye dönük olarak değerlendirildi. Serum NT-proBNP düzeyi için normal sınır (125 pg/ml) cut-off değeri olarak kullanıldı.

Bulgular: Toplamda 435 hasta çalışmaya dahil edildi. Hastaların %61'inde (n=264), NT-proBNP düzeyi yüksekti (≥ 125 pg/ml). ≥ 125 pg/ml olan hastaların %56'sında (n=147) SD veya DD kanıtı yoktu. NT-proBNP'si artmış ancak SD veya DD'si olmayan hastalarda, H2FPEF skoru ≥ 6, atriyal fibrilasyon, malignite, önceki COVID-19 ve hastaneye yatış ihtiyacı olan hastalar, NT-proBNP'si normal olan ve SD veya DD olmayan hastalara göre anlamlı olarak daha yüksekti (sırasıyla %13'e karşı %4; %5'e karşı %1; %16'ya karşı %9; %29'a karşı %5; ve %25'e karşı %11). NT-proBNP değerinin < 752,1 pg/ml oluşu SD'u %72,5 duyarlılık ve %83,1 özgüllük ile ve < 350,3 pg/ml oluşu DD'u %71,3 duyarlılıkla ve %75,5 özgüllük ile dışladı.

Sonuç: Yüksek bir NT-proBNP değeri her zaman SD veya DD'yi göstermez. NT-proBNP ölçümü, akut olmayan dispnede prognostik önem eklemenin yanı sıra, çeşitli klinik durumlarda sadece aşikar kalp yetersizliğini değil, aynı zamanda subklinik SV disfonksiyonunu da saptayabilir.

Anahtar Kelimeler: Dispne, kalp yetersizliği, NT-proBNP

*** Corresponding author/İletişim kurulacak yazar:** Pelin Karaca Ozer; Istanbul University, Faculty of Medicine, Department of Cardiology. Topkapi Mahallesi, Turgut Ozal Millet Caddesi, 34093, Fatih/Istanbul, Türkiye.
Phone/Telefon: +90 (539) 717 05 01 **e-mail/e-posta:** pkaracaozer@gmail.com
Submitted/Başvuru: 27.04.2022 • **Accepted/Kabul:** 19.10.2022 • **Published Online/ Online Yayın:** 28.02.2023

Introduction

Measurement of natriuretic peptides (NPs) is important for clinical decision-making when evaluating patients with suspected heart failure (HF).[1,2]

Studies of the role of NPs had shown that they are valuable in excluding the presence of HF due to their high sensitivity. However, the low specificity of the test that measures NPs limits its usefulness.[2,3] In addition, the lack of a precise reference range for the NP level indicative of HF creates difficulties in assessing the diagnostic utility of the test.[4]

Cut-off points for NPs have been recommended in guidelines, including the most recently published HF guidelines.[5,6] However, the frequent absence of echocardiographic HF with elevated brain NP (BNP) in outpatient clinics suggests that it is necessary to continue to evaluate the impact of clinical factors on decision cut-off points.

The diagnostic value of serum N-terminal prohormone brain natriuretic peptide (NT-proBNP), the decision cut-off points that maximize its diagnostic value, how it performs in daily practice in patients with non-acute dyspnea, and the interpretation of its high level in patients without HF are the areas of interest in this study.

Methods

This is a single-center, cross-sectional study conducted retrospectively on 435 non-obese patients who visited cardiology outpatient clinic between October 2020 and October 2021 with the complaint of dyspnea, whose NT-proBNP levels were measured and who underwent transthoracic echocardiography (TTE).

Patients with acute dyspnea and emergency presentations such as acute coronary syndrome, myocarditis, acute pulmonary embolism, and pneumonia; patients with explainable cardiac dyspnea such as moderate to severe valvular heart disease, cardiomyopathy; and patients with chronic renal failure and a body mass index (BMI) > 35 kg/m^2 were excluded from this study.

The study protocol was implemented according to the principles of the Declaration of Helsinki and was approved by the local Ethics Committee (approval number: 2067; 12/2021).

Conventional Echocardiographic Analysis

Examinations were performed using Vivid 7 (GE), IE33 (Philips), or Vivid T8 (GE) echo devices, with a middle-range frequency (3-8 MHz) broadband transducer to evaluate parasternal and apical images (2D, M-mode, Doppler echo), with the patient placed in the left lateral decubitus position. Images were obtained using the techniques recommended by the American Society of Echocardiography guidelines.[7]

LV systolic dysfunction (SD) was defined as LV ejection fraction (EF) < 50%. The presence or absence of diastolic dysfunction (DD) in patients with a normal LVEF are based on the assessment of four variables. These variables and their cutoff values include: Septal e' < 7 cm/sec or lateral e' < 10 cm/sec, average E/e' > 14, left atrial volume index (LAVI) > 34 mL/m^2, and peak TR velocity > 2.8 m/sec. DD is present if more than half of the available variables are abnormal (> 50% positive) according to the guidelines for the evaluation of LV diastolic function by TTE.[8]

Calculating H_2FPEF Score

(1) BMI > 30 kg/m^2 (H); (2) the use of ≥ 2 antihypertensive medications (H); (3) the presence of atrial fibrillation (AF) (F); (4) pulmonary hypertension defined as systolic pulmonary artery pressure (sPAP) > 35 mmHg (P); (5) an age > 60 years (E); and (6) elevated filling pressures evident from E/e' > 9 (F). The presence of paroxysmal or persistent AF yields 3 points, a BMI > 30 kg/m^2 yields 2 points, and all the other criteria listed above yield 1 point.[9]

Natriuretic Peptide Measurements

The same assay kits were used to measure each peptide in each patient. Specifically, NT-proBNP was measured using the Roche Elecys proBNP test (Roche Diagnostics, Indianapolis, IN). NT-proBNP levels were evaluated retrospectively from medical records.

Statistical Analysis

All statistical tests were conducted using the Statistical Package for the Social Sciences 26.0 for Windows (SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test was used to analyze the normality of the data. Continuous data are expressed as mean ± standard deviation (SD), and categorical data are expressed as percentages. A chi-square or Fisher's exact test was used to assess the differences in categorical variables between the groups. A Student's t-test or the Mann–Whitney U test was used to compare unpaired samples as needed. The relationships among the parameters were assessed using Pearson's or Spearman's correlation analysis according to the normality of the data. The primary analysis used ANOVA to compare all reported data for parametric variables, whereas the Kruskal–Wallis test was used for comparison among non-parametric variables between groups. Univariate and multivariate logistic regression analyses were used to identify the independent variables of hospitalization. The results of the univariate and multivariate regression analyses are presented as odds ratios with 95% confidence intervals (CIs). For the pro-BNP levels, receiver operating characteristic (ROC) curves were obtained, and the optimal values with the greatest total sensitivity and specificity in the exclusion of SD or DD were selected. Significance was assumed at a two-sided $p < 0.05$.

Results

A total of 435 patients were included in this study, the mean age of whom was 58±9.7 years. Sixty-one percent

(n=264) of them had an NT-proBNP level ≥ 125 pg/ml and thirty- nine percent (n=171) of them had an NT-proBNP level < 125 pg/ml. There were no statistically significant differences between the two groups in terms of age, gender, and BMI.

DD and SD were more frequent in the patients with NT-proBNP ≥ 125 pg/ml (p < 0.001 for both). Of the 264 patients with NT-proBNP ≥ 125 pg/ml, 34% (89 patients) had DD and 11% (28) had an EF < 50%; while of the 171 patients with NT-proBNP < 125 pg/ml, only 10 patients (6%) had DD and only three patients (2%) had an EF < 50%. The flow-chart diagram of the study was shown in Figure 1.

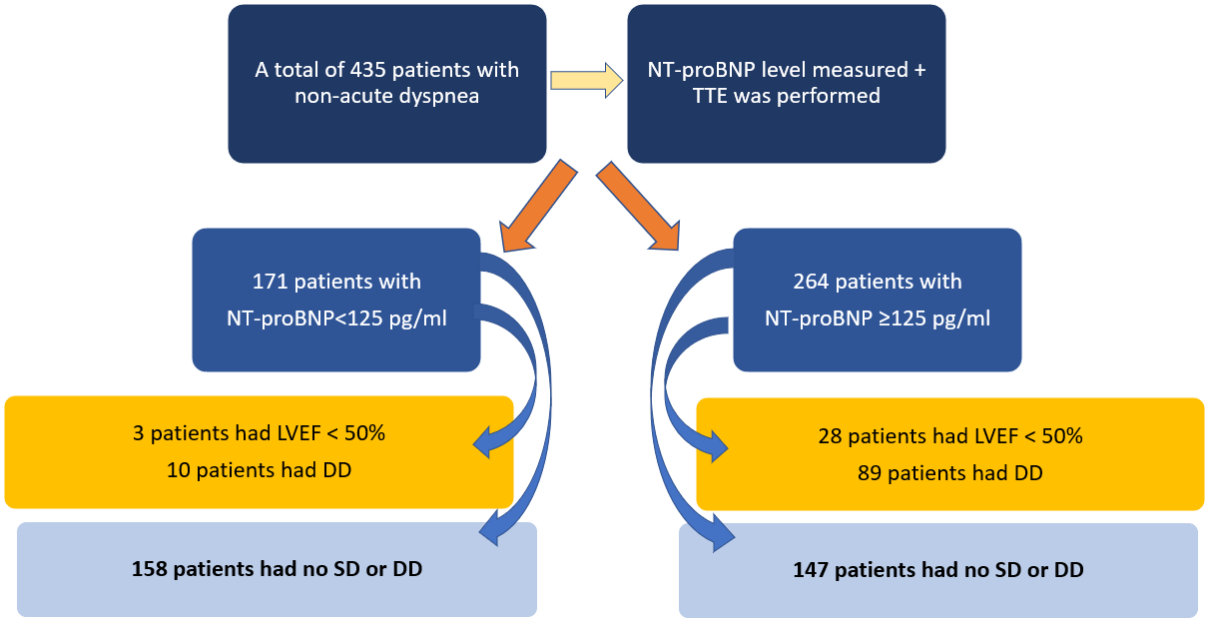

Figure 1. The flow-chart diagram of the study

Coronary artery disease (CAD), AF, recovery from coronavirus disease 2019 (COVID-19), and a need for hospitalization were more common in the patients with elevated NT-proBNP than in those without (36% vs. 18%, p = 0.002; 13% vs. 2%, p < 0.001; 26% vs. 6%, p < 0.001; and 31% vs. 11%, p < 0.001, respectively).

The demographic, clinical, and echocardiographic characteristics of the patients with NT-proBNP < 125 pg/ml and ≥ 125 pg/ml, as well as with SD and DD, are shown in Table 1.

There was no evidence of SD or DD with TTE in 158 (92%) of the patients with NT-proBNP < 125 pg/ml and in 147 (56%) of the patients with ≥ 125 pg/ml, for a total of 305 patients (70% of all the patients). The patients without SD or DD but with NT-proBNP ≥ 125 pg/ml had a significantly higher H2FPEF score ≥ 6, AF, malignancy, previous COVID-19 ailment, and need for hospitalization than those with NT-proBNP < 125 pg/ml (4% vs. 13%, p = 0.004; 1% vs. 5%, p = 0.013; 9% vs. 16%, p = 0.049; 5% vs. 29%, p < 0.001; and 11% vs. 25%, p = 0.002, respectively).

When the echocardiographic parameters were compared, in the patients without echocardiographic SD or DD but with NT-proBNP ≥ 125 pg/ml, the interventricular septal (IVS) thickness, LV mass index (LVMI), right ventricle (RV), right atrium (RA), LAVI, sPAP, and E/e' ratio were higher than in the patients with NT-proBNP < 125, and MAPSE was lower.

The demographic, clinical, and echocardiographic characteristics of the patients with NT-proBNP < 125 and ≥ 125 without SD or DD are shown in Table 2.

NT-proBNP was positively correlated with age, hs-troponin-T, sPAP, the H2FPEF score, LAVI, LVMI, the E/e' ratio, and the IVS thickness, but was negatively correlated with MAPSE, LV EF, and the E/A ratio (Table 3).

In the multivariate logistic regression analysis, the presence of AF (OR 3.247, 95% CI 1.127–9.352, p = 0.029) and the NT-proBNP level (OR 1.000, 95% CI 1.000–1.000, p = 0.006) were independent predictors of the need for hospitalization (Table 4).

An NT-proBNP level ≥ 125 pg/ml had a negative predictive value (NPV) of 98% and a positive predictive value (PPV) of 11% for SD, and an NPV of 94% and a PPV of 33% for DD.

ROC curve analysis was performed to show the specificity and sensitivity of NT-proBNP in excluding SD and DD.

An NT-proBNP value below 752.1 pg/ml excluded SD with 72.5% sensitivity and 83.1% specificity (AUC = 0.862, 95% CI = 0.812–0.912, p < 0.001) (Figure 2). The cut-off of 752.1 pg/ml for the NT-pro-BNP had a negative predictive value of 95.8% (95% CI = 93.57%–97.27%) for SD.

An NT-proBNP value below 350.3 pg/ml excluded DD with 71.3% sensitivity and 75.5% specificity (AUC = 0.809, 95% CI = 0.763–0.855, p < 0.001) (Figure 3). The cut-off of 350.3 pg/ml for the NT-proBNP had a negative predictive value of 88.85% (95% CI = 85.47%–91.52%) for DD.

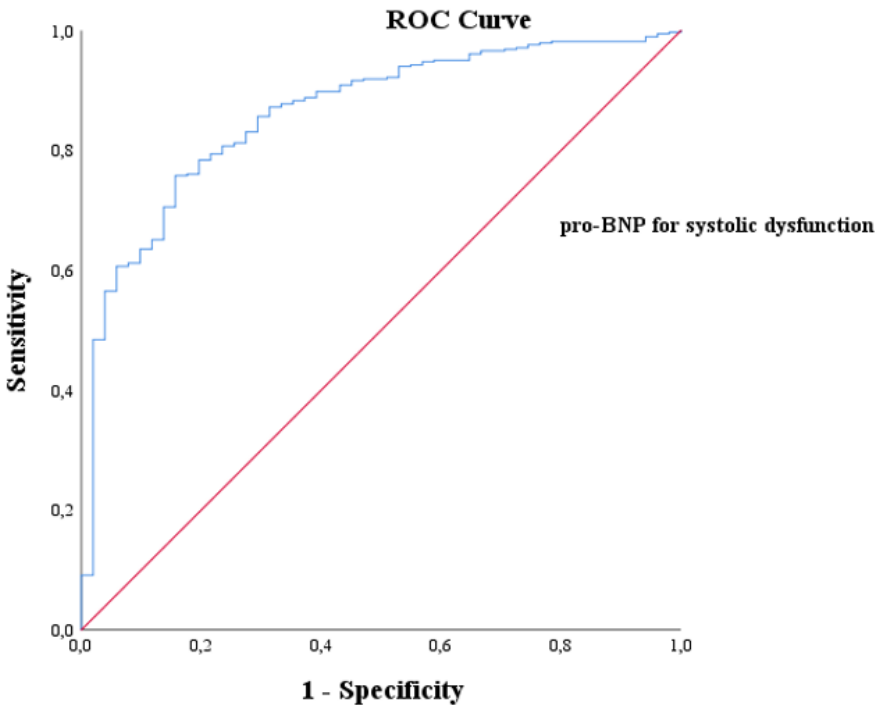

Figure 2. ROC curve analysis showing the specificity and sensitivity of the NT-proBNP in excluding systolic dysfunction

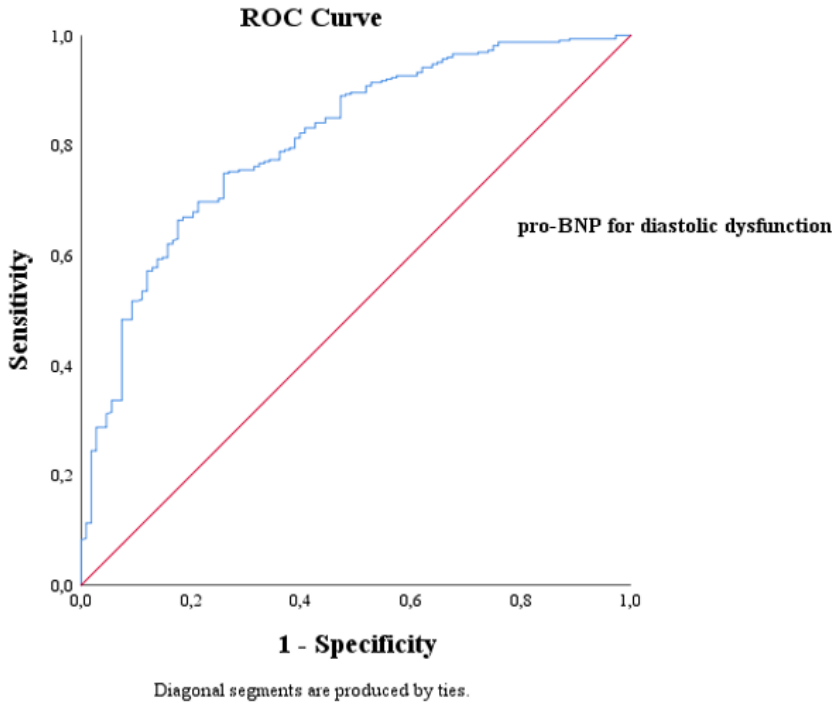

Figure 3. ROC curve analysis showing the specificity and sensitivity of the NT-proBNP in excluding diastolic dysfunction

Table 1. Demographic, clinical and echocardiographic characteristics of patients with NT-proBNP <125 and ≥125 pg/ml

	Total Patients (n=435)	**NT-proBNP<125 (n=171, 39%)**	**NT-proBNP≥125 (n=264, 61%)**	**p-value**
Age (year)	58.02 ± 9.7	54.18 ± 12.3	59.13 ± 7.8	0.083
Gender, Male, n(%) Female, n(%)	220 (50.6 %) 215 (49.4 %)	83 (48.5 %) 88 (51.5 %)	137 (51.9 %) 127 (48.1 %)	0.494
HR (bpm)	76.24 ± 13.9	76.33 ± 14.4	76.31 ± 14.4	0.722
BMI (kg/m^2)	28 ± 4.8	27.32 ± 4.3	28.63 ± 4.7	0.463
LV EF <50%	51 (12%)	3 (2%)	28 (11%)	<0.001*
LV diastolic dys + (n,%) diastolic dys – (n,%)	108 (25%) 327 (75%)	10 (6%) 161 (94%)	89 (33%) 166 (67%)	<0.001*
H_2FPEF Score ≥ 6, n(%)	64 (16.7 %)	8 (4.7 %)	56 (21.2 %)	<0.001*
H_2FPEF Score	2 (0-9)	1 (0-5)	3 (0-9)	<0.001*
HT, n(%)	135 (31%)	43 (25%)	92 (35%)	0.077
DM, n(%)	91 (21%)	30 (18%)	61 (23%)	0.178
CAD, n(%)	126 (29%)	30 (18%)	96 (36%)	0.002*
COPD, n(%)	78 (18%)	27 (16%)	51 (19%)	0.236
AF, n(%)	36 (8%)	3 (2%)	33 (13%)	<0.001*
Malignancy, n(%)	50 (12%)	14 (8%)	36 (14%)	0.082
Previous COVID-19, n(%)	80 (18%)	11 (6%)	69 (26%)	<0.001*
Hospitalization, n(%)	100 (23%)	19 (11%)	81 (31%)	<0.001*
Laboratory Findings				
Hgb (gr/dl)	12.67 ± 2.1	13.29 ± 1.6	12.19 ± 2.2	<0.001*
Creatinine (mg/dl)	0.8 ± 0.2	0.77 ± 0.2	0.82 ± 0.2	0.174
Hs-troponin-T (pg/ml)	4.47 (3-588)	3 (3-104)	7.13 (3-588)	<0.001*
NT-proBNP (pg/ml)	133.5 (6.95-14364)	65.63 (6.95-123.8)	383 (127.5-14364)	<0.001*
Treatment				
Beta-blocker, n(%)	147 (34%)	31 (18%)	116 (44%)	<0.001*
CCB, n(%)	95 (22%)	29 (17%)	66 (25%)	0.102
ACE inh/ ARB, n(%)	144 (32%)	32 (19%)	112 (42%)	<0.001*
Diuretic, n(%)	107 (25%)	15 (8%)	92 (35%)	<0.001*
Statin, n(%)	125 (28%)	39 (22%)	86 (33%)	0.028*
Chemotherapy, n(%)	50 (12%)	14 (8%)	36 (14%)	0.082
Echocardiography				
LVEDV (ml)	97.54 ± 21.9	97.1 ± 19.7	97.91 ± 23.9	<0.001*
LVESV (ml)	35.82 ± 16.7	33.69 ± 12	37.65 ± 19.7	<0.001*
EF (%)	62.56 ± 9	64.67 ± 6.1	60.75 ± 10.7	<0.001*
LVEDD (mm)	45.8 ± 4.2	45.75 ± 3.9	45.84 ± 4.6	<0.001*
IVS (mm)	11.3 ± 2.1	10.9 ± 1.6	11.7 ± 2	<0.001*
LV mass index (gr/m^2)	124.76 ± 39.5	111.96 ± 28.23	135.73 ± 44.5	<0.001*
LA (mm)	36.9 ± 4.9	35.5 ± 4.4	38.2 ± 5.1	<0.001*
RV (mm)	26.8 ± 2.6	26.6 ± 2.7	26.9 ± 2.5	<0.001*
RA (mm)	32.5 ± 3.7	31.6 ± 3	33.3 ± 0.4	<0.001*
E/A ratio	0.94 ± 0.4	1.04 ± 0.4	0.86 ± 0.4	0.008*
E/e' ratio	9.62 ± 3.2	8.59 ± 2.3	10.51 ± 3.5	<0.001*
LAVI (ml/m^2)	24.54 ± 10.6	21.75 ± 9	26.93 ± 11.3	<0.001*
CO (L/min)	5.02 ± 1.5	5.17 ± 1.4	4.15 ± 1.6	0.202
sPAP (mmHg)	28.46 ± 7.7	26.5 ± 6.7	30.14 ± 8.1	<0.001*
TAPSE (mm)	21.83 ± 5	21.6 ± 5.4	22.02 ± 4.6	0.006*
MAPSE (mm)	14.12 ± 1.8	15.27 ± 1.9	13.98 ± 1.8	<0.001*

Abbreviations: HR: heart rate, BMI: body mass index, HT: hypertension, DM: diabetes mellitus, CAD: coronary artery disease, COPD: chronic obstructive pulmonary disease, AF: atrial fibrillation, NT-proBNP: N-termina prohormone brain natriuretic peptid, Hs-troponin-T: high sensitive troponin-T, Hgb: haemoglobin, CCB: calcium channel blockers, ACE: angiotensin converting enzyme, ARB: angiotensin receptor blocker, LV: left ventricular, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, LVEF: left ventricular ejection fraction, LVMI: left ventricular mass index, LVEDD: left ventricular end-diastolic diameter, IVS: interventricular septum, LAVI: left atrial volume index, E: early diastolic transmitral flow, A: late diastolic transmitral flow, e': early diastolic tissue velocity, CO: cardiac output, RV: right ventricular, RA: right atrial, TAPSE: tricuspid annular plane systolic excursion, MAPSE: mitral annular plane systolic excursion. sPAP: pulmonary artery systolic pressure.

Table 2. Demographic, clinical, and echocardiographic characteristics of patients with NT-proBNP <125 and ≥125 pg/ml without systolic or diastolic dysfunction

	Total Patients (n=305)	**NT-proBNP<125 (n=158)**	**NT-proBNP≥125 (n=147)**	**p-value**
Age (year)	56.21 ± 9.1	55.77 ± 12	56.69 ± 4.4	0.990
Gender, Male, n(%)	145 (48%)	77 (49%)	68 (46%)	0.662
Female, n(%)	164 (52%)	83 (51%)	81 (54%)	
HR (bpm)	76.09 ± 14.1	75.33 ± 13.7	77.14 ± 14.8	0.963
BMI (kg/m^2)	26.92 ± 4.8	26.26 ± 4	27.74 ± 4.9	0.202
H_2FPEF Score ≥ 6, n(%)	25 (8%)	6 (4%)	19 (13%)	0.004*
H_2FPEF Score	1 (0-8)	1 (0-7)	2 (0-8)	<0.001*
HT, n(%)	65 (21%)	32 (20%)	33 (22%)	0.896
DM, n(%)	40 (13%)	18 (12%)	22 (15%)	0.530
CAD, n(%)	52 (17%)	23 (14%)	29 (20%)	0.145
COPD, n(%)	49 (16%)	23 (14%)	26 (18%)	0.192
AF, n(%)	9 (3%)	1 (1%)	8 (5%)	0.013*
Malignancy, n(%)	38 (12%)	14 (9%)	24 (16%)	0.049*
Previous COVID-19, n(%)	51 (17%)	8 (5%)	43 (29%)	<0.001*
Hospitalization, n(%)	55 (18%)	18 (11%)	37 (25%)	0.002*
Laboratory Findings				
Hgb (gr/dl)	12.72 ± 2	13.18 ± 1.8	12.17 ± 2.1	<0.001*
Creatinine (mg/dl)	0.79 ± 0.2	0.78 ± 0.2	0.80 ± 0.2	0.373
Hs-troponin-T (pg/ml)	3.62 (3-588)	3 (3-406)	5.64 (3-588)	<0.001*
NT-proBNP (pg/ml)	118.45 (6.95-4178.6)	71.53 (6.95-124.70)	271.3 (127.5-4178.6)	<0.001*
Treatment				
Beta-blocker, n(%)	66 (21%)	20 (13%)	46 (31%)	<0.001*
CCB, n(%)	48 (16%)	23 (14%)	25 (17%)	0.309
ACE inh/ ARB, n(%)	59 (19%)	24 (15%)	35 (23%)	0.025*
Diuretic, n(%)	43 (14%)	12 (8%)	31 (21%)	0.001*
Statin, n(%)	55 (18%)	21 (13%)	34 (23%)	0.027*
Chemotherapy, n(%)	38 (12.3 %)	14 (9%)	24 (16%)	0.049*
Echocardiography				
LVEDV (ml)	94.31 ± 17.7	92.62 ± 17.5	95.74 ± 17.9	0.324
LVESV (ml)	32.47 ± 8.8	32.28 ± 10	32.83 ± 7.7	0.091
EF (%)	64.75 ± 4.8	65.09 ± 4.6	64.85 ± 5.0	0.098
LVEDD (mm)	45.21 ± 3.6	45.5 ± 3.6	44.86 ± 3.6	0.324
IVS (mm)	11.1 ± 2	10.8 ± 2	11.3 ± 2	<0.001*
LV mass index (gr/m^2)	116 ± 30	110.42 ± 27.9	122.65 ± 31.5	<0.001*
LA (mm)	36.1 ± 0.5	35.5 ± 0.5	36.8 ± 0.5	<0.001*
RV (mm)	26.6 ± 0.2	26.4 ± 0.3	26.8 ± 0.2	0.023*
RA (mm)	32.1 ± 0.3	31.5 ± 0.3	32.8 ± 0.3	0.023*
E/A ratio	0.98 ± 0.4	1.06 ± 0.4	0.89 ± 0.4	<0.001*
E/e' ratio	8.79 ± 2.2	8.31 ± 2	9.36 ± 2.2	0.017*
LAVI (ml/m^2)	23.29 ± 10.2	21.89 ± 9.1	24.96 ± 11.2	0.003*
CO (L/min)	5.1 ± 1.5	5.3 ± 1.5	4.94 ± 1.5	0.707
sPAP (mmHg)	26.67 ± 6	25.84 ± 5.8	27.65 ± 6.2	<0.001*
TAPSE (mm)	22.11 ± 4.8	21.93 ± 4.6	22.32 ± 5.2	0.302
MAPSE (mm)	14.95 ± 1.7	15.86 ± 1.6	14.68 ± 1.9	<0.001*

Abbreviations: HR: heart rate, BMI: body mass index, HT: hypertension, DM: diabetes mellitus, CAD: coronary artery disease, COPD: chronic obstructive pulmonary disease, AF: atrial fibrillation, NT-proBNP: N-termina prohormone brain natriuretic peptid, Hs-troponin-T: high sensitive troponin-T, Hgb: haemoglobin, CCB: calcium channel blockers, ACE: angiotensin converting enzyme, ARB: angiotensin receptor blocker, LV: left ventricular, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, LVEF: left ventricular ejection fraction, LVMI: left ventricular mass index, LVEDD: left ventricular end-diastolic diameter, IVS: interventricular septum, LAVI: left atrial volume index, E: early diastolic transmitral flow, A: late diastolic transmitral flow, e': early diastolic tissue velocity, CO: cardiac output, RV: right ventricular, RA: right atrial, TAPSE: tricuspid annular plane systolic excursion, MAPSE: mitral annular plane systolic excursion. sPAP: pulmonary artery systolic pressure

Table 3. Correlation analysis of NT-proBNP with clinical, laboratory and echocardiographic parameters

	Variable	r	P
NT-proBNP	Age	0.200	<0.001*
	Hs-troponin-T	0.649	<0.001*
	Hgb	-0.357	0.385
	MAPSE	-0.317	<0.001*
	sPAP	0.475	<0.001*
	PA diameter	0.265	0.085
	H_2FPEF Score	0.405	<0.001*
	LVEF	-0.320	<0.001*
	LAVI	0.440	<0.001*
	LVMI	0.360	<0.001*
	E/A	-0.122	0.018*
	E/e'	0.414	<0.001*
	IVS thickness	0.306	<0.001*

Abbreviations: Hs-troponin-T: high sensitive troponin-T, Hgb: haemoglobin, LV: left ventricular, LVEF: left ventricular ejection fraction, LVMI: left ventricular mass index, IVS: interventricular septum, LAVI: left atrial volume index, E: early diastolic transmitral flow, A: late diastolic transmitral flow, e': early diastolic tissue velocity, MAPSE: mitral annular plane systolic excursion. sPAP: pulmonary artery systolic pressure, PA: pulmonary artery

Table 4. Multivariate logistic regression analysis of clinical and echocardiographic parameters predicting hospitalization

Variable	OR	95 % Confidence Interval	p-value
AF	3.247	1.127-9.352	0.029*
NT-proBNP	1.000	1.000-1.000	0.006*
LVEF	1.015	0.981-1.051	0.392
sPAP	0.987	0.953-1.022	0.453
CAD	0.958	0.914-1.004	0.070

Abbreviations: CAD: coronary artery disease, AF: atrial fibrillation, NT-proBNP: N-termina prohormone brain natriuretic peptid, LVEF: left ventricular ejection fraction, sPAP: pulmonary artery systolic pressure

Discussion

Of the 435 patients who were included in our study, most (61%, 264) has an NT-proBNP value higher than the cut-off, and 56% (147) of them had increased NT-proBNP levels but no evidence of SD or DD.

The patients without SD or DD but with NT-proBNP ≥ 125 pg/ml had a significantly higher H2FPEF score ≥ 6, AF, malignancy, previous COVID-19 ailment, and need for hospitalization than those with NT-pro-BNP < 125 pg/ml. Even though the EF was preserved and did not meet the criteria for DD according to the guidelines, we found that the IVS thickness, LVMI, RV, RA, LAVI, sPAP, and E/e' ratio were higher, and the MAPSE was lower, in the patients with a high NT-proBNP. These results show that a normal LVEF and the no DD may not necessarily mean complete echocardiographic normality.

Measurement of NPs and echocardiography are recommended in all patients with suspected chronic HF.[5,6] The upper limits of normality in the non-acute setting are 35 pg/mL for BNP and 125 pg/mL for NT-proBNP. In previous studies, the NPVs of the NP concentrations below the said thresholds ranged from 0.94 to 0.98.[9-12] In this study, the NPVs of < 125 pg/ml NT-proBNP were 98% for SD and 94% for DD. Apart from supporting the diagnosis of HF, high BNP concentrations also have prognostic significance.[13,14] In this study, the need for hospitalization for all causes increased significantly in patients with high BNP. It should be kept in mind that BNP may be elevated for cardiac reasons other than HF, or it can also be elevated for non-cardiovascular causes. These causes include AF, increasing age, and acute or chronic kidney disease. Conversely, NP concentrations may be disproportionately low in obese patients.[5,6,15] We therefore excluded patients with acute-chronic renal failure and BMI > 35 kg/m^2. In this study, the frequency of AF increased in the group without SD or DD but with high NT-proBNP. Since an H2FPEF score of ≥ 6 would most likely confirm the diagnosis of HF with preserved LVEF, a higher score in the group with high BNP but no DD in TTE is reasonable.

In addition, according to our data, the rate of diagnosis of malignancy and of chemotherapy treatment was significantly higher in the group without SD or DD but with high BNP. This makes sense given the cardiotoxic effects of chemotherapeutic agents.[16] In the absence of echocardiographic evidence of HF, elevated BNP appears to reflect subclinical myocardial involvement in this patient group, as shown in previous studies.

In fact, the most striking thing was that a high rate of 29% of the patients in the group with no evidence of HF but with high BNP had recovered from COVID-19. Among the frequent cases at our cardiology outpatient clinic are those of patients who complain of dyspnea and who had recovered from COVID-19 or are referred to us because of high BNP levels, or who request cardiac evaluation even if they are asymptomatic. In previous studies, COVID-19 was associated with subclinical myocardial involvement both during the active disease and after the patient's recovery. In one study, the NT-proBNP level was shown to be independently associated with in-hospital death rates in people with COVID-19 pneumonia and without HF, emphasizing its prognostic importance.[17] In a study that evaluated patients discharged from COVID-19, subclinical myocardial involvement with global longitudinal strain (GLS) was shown in both the left and right ventricles, but the BNP value was not mentioned.[18] Another study showed that the pro-BNP level was higher in patients with myocardial injury during hospitalization than in patients without myocardial injury, and that the patients with myocardial injury had impaired LV-GLS after recovery.[19] It is true that in our daily medical practice, there are many patients who had recovered from COVID-19 and are referred to us because of high pro-BNP, but we could not see any evidence of HF in the echocardiography. From this, it can be concluded that

COVID-19 may have a subclinical effect on the myocardium.

In the Breathing Not Properly trial, a cutoff of 100 pg/mL BNP was shown to have a sensitivity and specificity of 90% and 76%, respectively, for ruling out HF.[20] Similarly, the N-terminal Pro-BNP Investigation of Dyspnea in the Emergency department (PRIDE) study[21] and the International Collaborative of NT-pro-BNP (ICON) study demonstrated that the diagnostic performance of the measurement of NT-proBNP with a cut-off point of 300 pg/mL is similar to that with a BNP value of 100 pg/mL.[22] It should be noted that in this study, the cut-off values were found to be higher, especially for SD.

In this study, an NT-proBNP value below 752.1 pg/ml excluded SD with 72.5% sensitivity and 83.1% specificity, and a 752.1 pg/ml cut-off for pro-BNP had an NPV of 96% for SD. On the other hand, an NT-proBNP value below 350.3 pg/ml excluded DD with 71.3% sensitivity and 75.5% specificity, and a 350.3 pg/ml cut-off for pro-BNP had an NPV of 89% for DD.

This study showed that low pro-BNP values most likely exclude LV SD or DD in non-obese patients with non-acute dyspnea, but high values are not specific, so high cut-off values seem appropriate to use especially for SD. In addition, inthis study, the NT-proBNP cut-off value was higher than the NT-proBNP cut-off values in previous studies.

Morever, NT-proBNP was found to have prognostic significance and to be an important predictor of all-cause hospitalization. Patients who were undergoing chemotherapy and recovering from COVID-19 were frequently seen in the group with high BNP without echocardiographic HF. Although ongoing chemotherapy and recovery from COVID-19 are not considered among the causes of high BNP values in the guidelines, it should be emphasized that they characterize many cases at our cardiology outpatient clinic and are involved in many echocardiography indications in daily medical practice.

This study had limitations. First, it was retrospective, and the patients were not followed up. Also, strain measurement was not performed as an indicator of subclinical myocardial involvement, except when there was evidence of overt HF.

In conclusion, different diagnostic cut-off values of NT-proBNP for HF remain unclear. NP measurement may support the identification of patients with subclinical LV dysfunction, which will allow preventive measures to be taken to slow the progression of the condition to clinical HF. BNP concentrations should be interpreted in light of many clinical factors. Above all, this study clearly showed that NT-proBNP has prognostic value in presentations of non-acute dyspnea.

Compliance with Ethical Standards

The study was approved by the local Ethics Committee (approval number: 2067; 12/2021).

Conflict of Interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author Contribution

PKO: Study Conception; PKO, EAG: Study Design; PKO: Supervision; PKO, EAG: Materials; PKO, EAG: Data Collection and/or Processing; EAG: Statistical Analysis and/or Data Interpretation; PKO: Literature Review; PKO: Manuscript Preparation: PKO; and PKO, EAG: Critical Review

Financial Disclosure

None.

References

1. Ibrahim NE, Gaggin HK, Konstam MA, Januzzi JL. Established and emerging roles of biomarkers in heart failure clinical trials. *Circ Heart Fail*. 2016;9(9):e002528. doi:10.1161/CIRCHEARTFAILURE.115.002528
2. Kramer F, Sabbah HN, Januzzi JJ, et al. Redefining the role of biomarkers in heart failure trials: expert consensus document. *Heart Fail Rev*. 2017;22(3):263-277. doi:10.1007/s10741-017-9608-5
3. Ibrahim NE, Januzzi JL. Beyond natriuretic peptides for diagnosis and management of heart failure. *Clin Chem.* 2017;63(1):211-222. doi:10.1373/clinchem.2016.259564
4. Smith SA, Mentz RJ, Roessig L, et al. Using natriuretic peptides for selection of patients in acute heart failure clinical trials. *Am J Cardiol*. 2015;116(8):1304-1310. doi:10.1016/j.amjcard.2015.07.049
5. McDonagh TA, Metra M, Adamo M, et al. ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599-3726. doi:10.1093/eurheartj/ehab368
6. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the management of heart failure: Executive summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145(18):e876-e894. doi:10.1161/CIR.0000000000001062
7. Mitchell C, Rahko PS, Blauwet LA, et al. Guidelines for performing a comprehensive transthoracic echocardiographic examination in adults: recommendations from the American Society of Echocardiography. *J Am Soc Echocardiogr.* 2019;32(1):1-64. doi:10.1016/j.echo.2018.06.004
8. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016;29(4):277-314. doi:10.1016/j.echo.2016.01.011
9. Paulus WJ. H_2FPEF Score: At last, a properly validated diagnostic algorithm for heart failure with preserved ejection fraction. *Circulation*. 2018;138(9):871-873. doi:10.1161/CIRCULATIONAHA.118.035711
10. Cowie MR, Struthers AD, Wood DA, et al. Value of natriuretic peptides in assessment of patients with

possible new heart failure in primary care. *Lancet.* 1997;350(9088):1349-1353. doi:10.1016/S0140-6736(97)06031-5

11. Zaphiriou A, Robb S, Murray-Thomas T, et al. The diagnostic accuracy of plasma BNP and NTproBNP in patients referred from primary care with suspected heart failure: results of the UK natriuretic peptide study. *Eur J Heart Fail.* 2005;7(4):537-541. doi:10.1016/j.ejheart.2005.01.022
12. Kelder JC, Cramer MJ, Verweij WM, Grobbee DE, Hoes AW. Clinical utility of three B-type natriuretic peptide assays for the initial diagnostic assessment of new slow-onset heart failure. *J Card Fail.* 2011;17(9):729-734. doi:10.1016/j.cardfail.2011.04.013
13. Gardner RS, Ozalp F, Murday AJ, Robb SD, McDonagh TA. N-terminal pro-brain natriuretic peptide. A new gold standard in predicting mortality in patients with advanced heart failure. *Eur Heart J*. 2003;24(19):1735-1743. doi:10.1016/j.ehj.2003.07.005
14. Januzzi JL Jr. Natriuretic peptide testing: a window into the diagnosis and prognosis of heart failure. *Cleve Clin J Med*. 2006;73(2):149-155. doi:10.3949/ccjm.73.2.149
15. Castiglione V, Aimo A, Vergaro G, Saccaro L, Passino C, Emdin M. Biomarkers for the diagnosis and management of heart failure. *Heart Fail Rev*. 2022;27(2):625-643. doi:10.1007/s10741-021-10105-w
16. Thavendiranathan P, Poulin F, Lim KD, Plana JC, Woo A, Marwick TH. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: a systematic review. *J Am Coll Cardiol*. 2014;63(25 Pt A):2751-2768. doi:10.1016/j.jacc.2014.01.073
17. Selçuk M, Keskin M, Çınar T, et al. Prognostic significance of N-Terminal Pro-BNP in patients with COVID-19 pneumonia without previous history of heart failure. *J Cardiovasc Thorac Res.* 2021;13(2):141-145. doi:10.34172/jcvtr.2021.26
18. Mahajan S, Kunal S, Shah B, et al. Left ventricular global longitudinal strain in COVID-19 recovered patients. *Echocardiography.* 2021;38(10):1722-1730. doi:10.1111/echo.15199. Epub 2021 Sep 23
19. Italia L, Ingallina G, Napolano A, et al. Subclinical myocardial dysfunction in patients recovered from COVID-19. *Echocardiography.* 2021;38(10):1778-1786. doi:10.1111/echo.15215
20. McCullough PA, Nowak RM, McCord J, et al. B-type natriuretic peptide and clinical judgment in emergency diagnosis of heart failure: analysis from Breathing Not Properly (BNP) Multinational Study. *Circulation.* 2002;106(4):416-422. doi:10.1161/01.cir.0000025242.79963.4c
21. Januzzi JL Jr., Camargo CA, Anwaruddin S, et al. The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. *Am J Cardiol.* 2005;95(8):948-54. doi:10.1016/j.amjcard.2004.12.032
22. Januzzi JL Jr., Chen-Tournoux AA, Christenson RH, et al. N-Terminal Pro-B-Type natriuretic peptide in the emergency department: The ICON-RELOADED Study. *J Am Coll Cardiol*. 2018;71(11):1191-1200. doi:10.1016/j.jacc.2018.01.021