The Relationship Between N-Terminal Pro-Brain Natriuretic Peptide Level and Left Ventricular Metabolic Index in Patients with Heart Failure with Mildly Reduced Ejection Fraction

Ⓘ **Mehmet Kış**[1], Ⓘ **Oktay Şenöz**[2], Ⓘ **Tuncay Güzel**[3]

[1]Dokuz Eylül University Faculty of Medicine, Department of Cardiology, İzmir, Turkey
[2]Bakırçay University, Çiğli Training and Research Hospital, Department of Cardiology, İzmir, Turkey
[3]Diyarbakır Gazi Yaşargil Training and Research Hospital, Clinic of Cardiology, Diyarbakır, Turkey

Abstract

Objectives: It has been determined that mortality and hospitalization rates due to cardiovascular diseases are higher in patients with left ventricular hypertrophy (LVH). In addition, LVH has been shown to be an independent risk factor for heart failure (HF). Previous studies in this area have focused more on preserved and low ejection fraction HF. Therefore, we aimed to contribute to the literature by investigating the relationship between N-terminal pro-brain natriuretic peptide level (NT-proBNP) and left ventricular metabolic index (LVMI) in heart failure with mildly reduced ejection fraction (HFmrEF).

Materials and Methods: Between January 2018 and October 2021, 213 patients diagnosed with heart failure with mildly reduced ejection fraction were included in the study. This study was designed as cross-sectional. The patients were divided into two groups according to their gender, as those with normal and abnormal LVMI. Pearson's correlations were used to assess the correlations between LVMI and NT-proBNP. A ROC curve was plotted to determine the diagnostic reliability of plasma concentration of NT-proBNP on LVMI.

Results: There were 90 patients in Group 1 (patients with normal LVMI) and 123 patients in Group 2 (patients with high LVMI). The mean LVMI value was 94.37 (±11.10) g/m² in Group 1 and 119.64 (±15.90) g/m² in Group 2. The mean NT-

Address for Correspondence: Mehmet Kış, Dokuz Eylül University Faculty of Medicine, Department of Cardiology, İzmir, Turkey
e-mail: drmehmet.kis@hotmail.com **ORCID:** orcid.org/0000-0003-0775-8992

Abstract

proBNP level was found to be 941.57 (±1190.81) pg/ml. NT-proBNP levels were statistically significantly higher in Group 2 than in Group 1 (1138.49±1330.7 vs. 672.46±907.52, p=0.005). The relationship between NT-proBNP (941.57±1190.81 pg/mL) levels and LVMI (108.96±18.81 g/m²) was tested by the Pearson correlation. A moderate, positive and significant relationship was found between these variables [r (211) = 0.368, p<0.001]. NT-proBNP >342 pg/mL had 57% sensitivity and 58% specificity [receiver operating characteristic (ROC) area under curve: 0.620, 95% CI: 0.544-0.695, p=0.003] for determining LVMI.

Conclusion: In patients with heart failure with mildly reduced ejection fraction, high NT-proBNP levels can predict LVMI elevation, which is an indicator of LVH. In this patient group, especially female gender and renal dysfunction may be risk factors for high LVMI.

Keywords: Mildly reduced ejection fraction, NT-proBNP, left ventricular metabolic index

Introduction

The plasma concentration of the cardiac natriuretic peptide, N-terminal pro-brain natriuretic peptide (NT-proBNP), is tightly correlated with cardiac function[1]. The increased release of NT-proBNP into the bloodstream by cardiac myocytes may be the result of left ventricular hypertrophy (LVH), high ventricular wall stress, or volume overload. Therefore, these peptides may have the potential to increase the efficacy of treatment strategies, as well as being diagnostic and prognostically significant biomarkers for patients with heart failure (HF)[2,3].

A diagnosis of heart failure with mildly reduced ejection fraction (HFmrEF) include the presence of symptoms and/or signs of HF, a high natriuretic peptide, and a slightly decreased EF (41%-49%)[4]. NT-pro-BNP measured at rest was recognized a diagnostic and prognostic biomarker of HF with reduced ejection fraction (HFrEF); however, its value in HFmrEF has not been fully determined[5]. The presence of high natriuretic peptides (BNP ≥35 pg/mL or NT proBNP ≥125 pg/mL) and evidence of structural heart disease make the diagnosis more likely, but it is stated that it is not mandatory if there is certainty regarding left ventricular ejection fraction (LVEF) measurement[4,5].

From an echocardiographic point of view, mortality and hospitalization rates due to cardiovascular diseases were found to be higher in patients with left ventricular dysfunction and LVH[6]. In addition, LVH is an independent risk factor for HF[7]. Left ventricular mass (LVM) estimates have traditionally been indexed to body size and yielded the LVM index (LVMI) if corrected for body surface area[8].

In our study, we aimed to investigate the relationship between NT-proBNP level and LVMI in the heart failure patient population with mildly reduced ejection fraction.

Materials and Methods

Ethics committee approval of our study was obtained from İzmir Bakırçay University Non-Interventional Clinical Research Ethics Committee on 10.11.2021 with decision number 380.

Between January 2018 and October 2021, 213 consecutive patients diagnosed with HFmrEF were included in the study. After the study was explained in detail to the patients included in the study, signed voluntary consent forms were obtained. Patients younger than 18 years of age, patients with hypertrophic cardiomyopathy, severe renal and liver failure, active malignancies, acute coronary syndrome, cardiogenic shock, inability to perform optimal echocardiographic and ultrasonographic examination, and those who did not give informed voluntary consent were excluded from the study.

Patients older than 18 years of age, patients who were diagnosed with HFmrEF, and who gave informed voluntary consent were included in the study. The study was designed as a retrospective, cross sectional. Demographic data, biochemical parameters and imaging findings of the patients were recorded.

The patients were analyzed by dividing them into two groups as those with normal and abnormal LVMI. Group 1 consisted of patients with normal LVMI and Group 2 consisted of patients with abnormal LVMI. Abnormal LVMI cut-off value was accepted as >115 g/m² in males and >95 g/m² in females[9].

NT-proBNP Measurement

NT-proBNP level was measured quantitatively with the Elecsys proBNP device (Roche Diagnostics, Mannheim, Germany) using the electrochemiluminescence immunoassay method[10,11].

Echocardiography

Echocardiographic examination of the patients was performed using Vivid S6, GE Medical Systems, USA device. In accordance with the standard procedures of the American Society of Echocardiography; evaluation was made through parasternal short axis, long axis and apical four-chamber windows[12]. Left ventricular dimensions were measured using M-mode echocardiography from the parasternal long axis, including end-diastole ventricular internal diameter (LVIDd), end-diastole interventricular septal thickness (IVST), and posterior wall thickness (PWT), while other cardiac chambers were measured from the apical four-chambers. LVEF was evaluated from four chambers with the modified Simpson's method. LVM was calculated with the Devereux formula[13]. LVMI was calculated by dividing the LVM to body surface area. For the measurement of the IVS and PWT, the average of the measurements was taken from the parasternal long axis using two-dimensional and M-mode techniques.

Statistical Analysis

Statistical analyses were performed using SPSS (version 15.0, SPSS Inc., Chicago, Illinois). The normal distribution of data was evaluated with the Kolmogorov-Smirnov test. Continuous variables were shown as mean ± standard deviation (SD). Categorical variables were presented as frequency and percentage. Continuous variable groups were compared using the independent Student's t-test or the Mann-Whitney U test according to normality distribution. The chi-square test or Fisher's exact test was used to compare categorical variables. Receiver operating characteristics (ROC) curve analysis was applied to determine the optimal cut-off level for predicting LVH. The Pearson's correlations were used to assess the correlations between LVMI and NT-proBNP. The significance level for all hypotheses was accepted as <0.05.

Results

Two hundred and thirteen patients who met the inclusion criteria were included in the study. There were 90 patients in Group 1 (patients with normal LVMI) and 123 patients in Group 2 (patients with high LVMI). The mean age of the study population was 64.8 (±16.18) years, and there was no statistical difference in age between the two groups (p=0.507). However, the female sex ratio was significantly higher in Group 2 than in Group 1 (83.7% vs. 34.4%, p<0.001). Non-ischemic etiology comprised 36.2% of the entire population, and there was no significant difference between the groups in terms of ischemic and non-ischemic etiology.

Coronary artery disease (64.8%) and hypertension (HT) (62.9%) were the most common comorbid diseases, and there was no statistically significant difference between the two groups (67.8% vs. 62.2%, p=0.435, 56.7% vs. 67.5%, p=0.107 respectively). Diabetes mellitus and hyperlipidemia were the following diseases with a rate of 26.3% and 22.1%, respectively. Demographic and clinical data of the patients included in the study are summarized in Table 1.

From biochemical parameters, mean urea value [31.66 (±18.86) vs. 24.79 (±15.19)], creatinine value [1.08 (±0.64) vs. 0.92 (±0.37)], and ferritin value [199.92 (±255.54) vs. 110.45 (±123.87)] were found to be higher in Group 2 than in Group 1 (p=0.004, 0.03, and 0.0123, respectively).

The mean of Nt-proBNP was found to be 941.57 (±1190.8) pg/mL. It was statistically significantly higher in Group 2 [1138.49 (±1330.7)] than in Group 1 [672.46 (±907.52)] (p=0.005). Laboratory data are presented in Table 2.

In the echocardiography, LVEF value of the patients was 45.28 (±2.96)%. Moderate-severe mitral regurgitation (MR) was seen in 41.8%, moderate-severe mitral stenosis (MS) in 6.6%, and moderate-severe aortic regurgitation (AR) in 10.8%. There was no significant difference between the groups in terms of moderate-severe valve disease and LVEF. The echocardiographic features of the patients are presented in Table 3.

Group 1 consisted of patients with a normal LVMI and no LVH, and the mean LVMI value was 94.37 (±11.10) g/m^2. Group 2 consisted of patients with a higher LVMI and found to have LVH. The mean LVMI value of Group 2 was determined as 119.64 (±15.90) g/m^2, and it was statistically significantly higher than that of Group 1 (p<0.001).

The most commonly used drugs by the patients are beta-blockers with the rate of 68.5%, antiaggregants with the rate of 55.9% and loop diuretics with the rate of 42.3%. The rate of using anticoagulants is 25.4% and the rate of using aldosterone antagonist is 27.7%. There was no statistically significant difference between the groups in terms of drugs used. This situation increases the strength of our study. Treatments of the study population are summarized in Table 4.

The relationship between NT-proBNP (941.57±1190.81 pg/mL) levels and LVMI (108.96±18.81 g/m^2) was tested with Pearson's correlation. A moderate, positive and significant relationship was found between these variables [r (211) = 0.368, p<0.001] (Figure 1).

NT-proBNP >342 pg/mL had 57% sensitivity and 58% specificity (ROC area under curve: 0.620, 95% CI: 0.544-0.695, p=0.003) for determining the LVMI (Figure 2).

Table 1. Baseline demographic and clinical characteristics of the study population

Variables	Group 1 (n=90)	Group 2 (n=123)	Total (n=213)	p-value
Age (years), mean ± SD	64.2 (±12.7)	65.3 (±13.4)	64.8 (±13.1)	0.507
Female sex, n (%)	31 (34.4)	103 (83.7)	134 (62.9)	**<0.001**
Hypertension, n (%)	51 (56.7)	83 (67.5)	134 (62.9)	0.107
Diabetes mellitus, n (%)	25 (27.8)	31 (25.2)	56 (26.3)	0.673
CAD, n (%)	61 (67.8)	77 (62.6)	138 (64.8)	0.435
Hyperlipidemia, n (%)	19 (20.1)	28 (22.8)	47 (22.1)	0.774
COPD, n (%)	6 (6.7)	16 (13.0)	22 (10.3)	0.133
CRF, n (%)	7 (7.8)	20 (16.3)	27 (12.7)	0.066
Peripheral artery disease, n (%)	7 (7.8)	4 (3.3)	11 (5.2)	0.140
CVD, n (%)	13 (14.4)	9 (7.3)	22 (10.3)	0.091
Anemia, n (%)	14 (15.6)	23 (18.7)	37 (17.4)	0.550
Smoking, n (%)	30 (33.3)	16 (13.0)	46 (21.6)	**<0.001**
Alcohol use, n (%)	2 (2.2)	1 (0.8)	3 (1.4)	0.389
NYHA Class 1, n (%)	45 (50)	57 (46.3)	147 (47.9)	0.811
Non-ischemic etiology, n (%)	30 (33.3)	47 (38.2)	77 (36.2)	0.464

Group 1: Normal LVMI, Group 2: High LVMI.
CAD: Coronary artery disease, COPD: Chronic obstructive lung diseases, CRF: Chronic renal failure, CRT: Cardiac resynchronization therapy, CVD: Cerebrovascular disease, ICD: Implantable cardioverter defibrillator, NYHA: New York Heart Association, SD: Standard deviation, n: Number
Significant p-values are shown in bold.

8

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Discussion

In this study, we found a positive correlation between NT-proBNP level and LVMI, which is an indicator of LVH, in HFmrEF patients.

Additional supportive methods are still needed in the diagnosis and follow-up of HFmrEF. Evaluation of plasma NT-proBNP levels is one of the recently investigated methods. There are studies showing the high
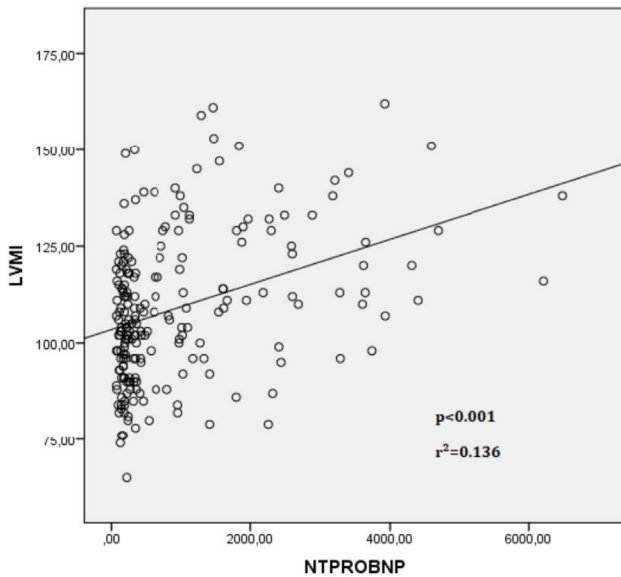

Figure 1. Correlation between NT-proBNP and LVMI in heart failure with mildly reduced ejection fraction

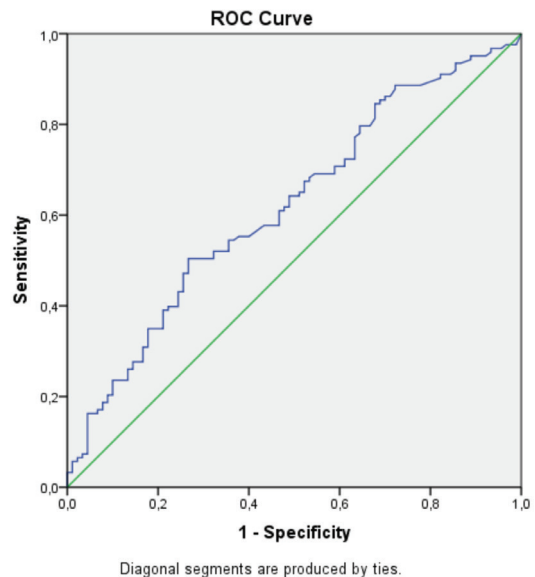*NT-proBNP: N-terminal pro-brain natriuretic peptide level, LVMI: Left ventricular metabolic index*

Figure 2. Receiver–operating characteristics curve of NT-proBNP for predicting the LVMI

ROC: Receiver operating characteristic curve, NT-proBNP: N-terminal pro-brain natriuretic peptide level, LVMI: Left ventricular metabolic index

Table 2. Baseline laboratory parameters of the patients

Variables (Mean ± SD)	Group 1 (n=90)	Group 2 (n=123)	Total (n=213)	p-value
Urea, mg/dL	24.79±15.19	31.66±18.86	27.68±17.13	**0.004**
Creatinine, mg/dL	0.92±0.37	1.08±0.64	1.01±0.55	**0.03**
Uric acid, mg/dL	5.36±2.16	5.21±1.52	5.3±1.92	0.627
Nt-ProBNP, pg/mL	672.46±907.52	1138.49±1330.7	941.57±1190.8	**0.005**
WBC, 10^9/L	8.27±3.15	8.38±7.70	8.33±2.89	0.438
Hemoglobin, g/dL	13.03±1.83	12.74±1.83	12.86±1.83	0.261
Ferritin, ng/mL	110.45±123.87	199.92±255.54	158.12±209.08	**0.013**
Fasting glucose, mg/dL	115.42±40.12	118.31±42.37	117.08±41.35	0.307
TSH, mU/L	1.69±1.56	1.41±1.20	1.53±1.38	0.067
Ca, mg/dL	9.28±0.54	9.16±0.65	9.21±0.61	0.159
Sodium, mEq/L	139.58±2.96	138.63±3.22	139.02±3.13	0.698
Potassium, mg/dL	4.50±0.48	4.32±0.60	4.39±0.55	0.179
CRP, mg/dL	1.44±3.18	1.29±2.11	1.35±2.61	0.207

Group 1: Normal LVMI, Group 2: High LVMI.
Ca: Calcium, CRP: C-reactive protein, Nt-ProBNP: N-terminal pro-brain natriuretic peptide, TSH: Thyroid stimulating hormone, WBC: White blood cell, SD: Standard deviation, n: Number
Significant p-values are shown in bold.

sensitivity and specificity of NT-proBNP in the diagnosis of HFrEF[14]. There are also studies on the relationship between NT-proBNP and LVH in the population without HF. However, it has not been adequately studied in patients with HFmrEF.

Lubien et al.[15] found that high peptide levels were an accurate indicator of diastolic abnormalities detected by echocardiography, regardless of the patient's history or the signs and symptoms of congestive HF. In a study that included 313 asymptomatic patients (51% female, mean age: 61 years) with HT and diastolic dysfunction, higher NT-proBNP was associated with a greater LVMI (p=0.003). In conclusion, elevation in natriuretic peptide levels was found to be predominantly associated with subclinical

Table 3. Echocardiographic features of the patients

Variables	Group 1 (n=90)	Group 2 (n=123)	Total (n=213)	p-value
LVEF (%), mean ± SD	45.49±3.08	45.14±2.89	45.28±2.96	0.396
LVEDD (cm), mean ± SD	47.42±4.20	47.20±4.33	47.29±4.26	0.712
LVEDS (cm), mean ± SD	30.50±4.43	30.49±4.55	30.49±4.49	0.995
LVDD, n (%)	70 (77.8)	107 (87.0)	177 (83.1)	0.076
LVMI (g/m^2), mean ± SD	94.37±11.10	119.64±15.90	108.96±18.80	**<0.001**
SPAP (mmHg), mean ± SD	27.90 (±12.67)	29.02±10.06	28.55±11.20	0.474
Moderate-Severe MR, n (%)	28 (31.1)	61 (49.6)	89 (41.8)	0.053
Moderate-Severe MS, n (%)	6 (6.7)	8 (6.5)	14 (6.6)	0.121
Moderate-Severe AR, n (%)	10 (11.1)	13 (10.6)	23 (10.8)	0.496
Moderate-Severe AS, n (%)	0 (0)	8 (6.5)	8 (3.8)	0.107

Group 1: Normal LVMI, Group 2: High LVMI.
AR: Aortic regurgitation, AS: Aortic stenosis, LVDD: Left ventricular diastolic dysfunction, LVEDD: Left ventricular end diastolic diameter, LVESD: Left ventricular end systolic diameter, LVEF: Left ventricular ejection fraction, LVMI: Left ventricular metabolic index, MR: Mitral regurgitation, MS: Mitral stenosis, SPAP: Pulmonary arterial pressure, SD: Standard deviation, n: Number
Significant p-values are shown in bold.

Table 4. Medications used by the patients

Medications	Group 1 (n=90)	Group 2 (n=123)	Total (n=213)	p-value
ACEi, n (%)	38 (42.2)	50 (40.6)	88 (41.3)	0.818
Betablockers, n (%)	62 (68.9)	84 (68.3)	146 (68.5)	0.926
Statine, n (%)	33 (36.7)	38 (30.9)	71 (33.4)	0.377
Antiaggregant, n (%)	54 (60.0)	65 (52.8)	119 (55.9)	0.299
Anticoagulant, n (%)	21 (23.3)	33 (26.8)	54 (25.4)	0.984
ARBs, n (%)	13 (14.4)	14 (11.4)	27 (12.7)	0.507
Loop diuretic, n (%)	42 (46.7)	48 (39.0)	90 (42.3)	0.265
Aldosterone antagonist, n (%)	23 (25.6)	36 (29.3)	59 (27.7)	0.550
Thiazide diuretic, n (%)	14 (15.6)	13 (10.6)	27 (12.7)	0.280
Non-dihidropiridine CCB, n (%)	5 (5.6)	6 (4.9)	11 (5.2)	0.825
Digoxin, n (%)	3 (3.3)	7 (5.7)	10 (4.7)	0.422
Amiodarone, n (%)	2 (2.2)	5 (4.1)	7 (3.3)	0.456
Oral antidiabetic, n (%)	20 (22.2)	20 (16.3)	40 (18.8)	0.271
Insulin, n (%)	7 (7.8)	9 (7.3)	16 (7.5)	0.900

Group 1: Normal LVMI, Group 2: High LVMI
ACEi: Angiotensin converting enzyme inhibitors, ARBs: Angiotensin receptor blockers, CCB: Calcium channel blockers, SD: Standard deviation, n: Number

diastolic dysfunction in asymptomatic hypertensive heart disease and preserved ejection fraction[16].

Talwar et al.[17] found that the presence of HT did not affect NT proBNP concentrations in patients with or without LVH. In this study, we wanted to show the relationship between LVMI and NT-proBNP levels in patients with HFmrEF. We found that NT-proBNP levels were significantly higher in patients with HFmEF and high LVMI.

A study including 662 patients, which was conducted to investigate the relationship between NT-proBNP quartiles and LVH risk in patients without HF and to evaluate the relationship between NT-proBNP and the hallmarks of LVH, showed a progressive increase in LVH formation with increasing NT proBNP quartiles in patients without HF. In addition, significant positive linear relationships of Lg(NT-proBNP) with LVM and LVMI were determined[18].

Likewise, NT-proBNP levels were compared in patients with LVH in a population study that included 215 patients with and without a diagnosis of HT, with findings supporting our study. It was shown that NTproBNP was increased in both groups. It has been demonstrated that the presence of HT in LV hypertrophy does not significantly affect peptide levels[19].

In another study investigating the diagnostic value of NT-proBNP level to detect LVH in hypertensive patients with HFpEF, 27 patients with a diagnosis of essential HT were included. A significant correlation was found between LVM determined by magnetic resonance imaging and plasma NT-proBNP concentration (r=0.598; p=0.001)[20]. The main limitation of this study is that the number of patients studied was small and only patients with sinus rhythm were included in the study. In our study, pre-study power analysis was performed, and the number of patients was larger and not only those with sinus rhythm but also all patients with HFmrEF were included, regardless of rhythm. This is another advantage of our work.

The use of antihypertensive drugs may alter BNP concentrations. Beta-blockers, ACE inhibitors, and diuretics may have variable effects on circulating BNP concentrations[21]. The fact that there was no statistically significant difference in terms of the drugs used in both groups in our study is one of the most important parameters that increases the power of the study.

When the sensitivity and specificity of NT-proBNP with HFmrEF in detecting LVH were tested with the ROC curve, we found that NT-proBNP level of 342 pg/mL and above had moderate sensitivity (57%) and specificity (58%) for detecting LVH. Although this result suggests that NT-proBNP cannot be used as an ideal screening test for LVH in HFmrEF in clinical use, it may show that it can be a very useful test for confirming the diagnosis when used together with other methods such as echocardiography.

Study Limitations

The present study has some limitations. The most important of these is the retrospective design of the study. NT-proBNP was found to be a predictor of LVH detection in HFmrEF patients, but the sensitivity and specificity were weak at the determined cut-off value.

Conclusion

Plasma Ntpro-BNP levels are useful in determining left ventricular metabolic index elevation, which is an indicator of left ventricular hypertrophy, in patients with heart failure with mildly reduced ejection fraction. It may be useful to rule out left ventricular hypertrophy in this patient population.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from İzmir Bakırçay University Non-Interventional Clinical Research Ethics Committee on 10.11.2021 with decision number 380.

Informed Consent: Signed voluntary consent forms were obtained from all patients who include in this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.K., Design: M.K., Data Collection and/or Processing: T.G., Analysis and Interpretation: O.Ş., Supervision: O.Ş. Writing: M.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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