Clinical characteristics, subclinical features, and serum NT-proBNP levels in patients with heart failure according to the Vietnamese heart association in 2022

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Abstract

Background: Heart failure is the consequence of various underlying conditions such as valvular heart disease, myocardial disease, arrhythmias, coronary artery disease, etc. In 2022, the Vietnamese Heart Association issued new recommendations regarding heart failure. Particularly emphasized was the role of NT-proBNP in the diagnosis, prognosis, monitoring, and optimization of heart failure treatment. This study aims to investigate the clinical and subclinical characteristics of heart failure patients according to the VNHA 2022 guidelines and to assess the relationship and correlation of serum NT-proBNP levels with the severity of heart failure according to NYHA classification, degree of anemia, left ventricular ejection fraction, Sokolow index, and left ventricular mass index. **Subjects and methods:** A cross-sectional descriptive study was conducted on 108 hospitalized heart failure patients at the Department of Cardiology, Hue University of Medicine and Pharmacy from March 2023 to December 2023. **Results:** The average age in the study was 68.4 ± 13.5 years, with the HFrEF group having a higher average age compared to the HFmrEF or HFpEF groups. The male-to-female ratio was equal. More than half of the hospitalized heart failure patients (56.5%) had HFpEF. Hypertension was the most common comorbidity, accounting for 59.3%, followed by coronary artery disease (38.9%) and atrial fibrillation (29.6%). There were no differences in clinical symptoms among the three groups of heart failure patients. Left ventricular hypertrophy and anemia accounted for significant proportions, at 27.8% and 14.8%, respectively. Patients with HFpEF had higher BMI and atrial fibrillation rates compared to the HFmrEF and HFrEF groups. Among the HFrEF patients, those with Sokolow index ≥ 35 mm and higher LVMI were significantly more prevalent than in the other two heart failure groups. The three groups had no significant difference in left ventricular ejection fraction. There was a positive correlation between NT-proBNP levels and the Sokolow index (Rs = 0.309, $p < 0.05$) and between NT-proBNP levels and LVMI (Rs = 0.421). There was a strong negative correlation between NT-proBNP levels and ejection fraction (Rs = -0.637). NT-proBNP levels were significantly higher in the anemic heart failure group compared to the non-anemic heart failure group. **Conclusion:** HFpEF accounted for more than half of the hospitalized heart failure cases. The most common comorbidities remained hypertension, coronary artery disease, and atrial fibrillation.

Keywords: *heart failure, comorbidities, serum NT-proBNP, left ventricular mass index.*

1. INTRODUCTION

Heart failure is a major health issue for humanity, resulting from various conditions such as valvular heart disease, myocardial disease, arrhythmias, and coronary artery disease [1]. Currently, there are over 64 million people with heart failure worldwide, with a high rate of hospitalization and mortality [2]. In the United States, individuals aged 40 and above have about a 20% risk of developing heart failure, with over 650,000 cases diagnosed annually. By 2050, it is estimated that one-fifth of individuals over the age of 65 will have heart failure. The 5-year survival rates for heart failure stages A, B, C, and D are 97%, 96%, 75%, and 20%, respectively [3]. The European Society of Cardiology (2021) reported a heart failure prevalence of 1 - 2% in adults, with the mortality rate in heart failure patients still 3 - 5 times higher than in age-matched individuals without heart failure [4]. According to statistics from 2016 in 9 Asian countries, including Vietnam, the prevalence of heart failure is similar to the global average, around 1 - 3%. Hospitalization due to heart failure accounts for approximately 15%, with in-hospital mortality rates at 7% and mortality within 30 days at

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2-3% [68]. Over the past two decades, the prevalence of heart failure has increased due to the presence of preserved ejection fraction heart failure, accounting for approximately 54%, ranging from 40% to 71% [4].

In 2022, the Vietnamese Heart Association (VNHA) issued new recommendations regarding heart failure, providing updates on diagnostic criteria as well as treatment approaches. Particularly emphasized was the role of B-type natriuretic peptide in the diagnosis, prognosis, monitoring, and optimization of heart failure treatment [1]. Building upon this, we conducted the research project titled: "Investigating the clinical and subclinical characteristics and serum NT-proBNP levels in heart failure patients according to the guidelines of the Vietnamese Heart Association in 2022" With two objectives: *1. To survey the clinical and subclinical characteristics in heart failure patients according to the guidelines of the Vietnamese Heart Association in 2022. 2. To assess the correlation and association between serum NT-proBNP levels and left ventricular ejection fraction, Sokolow index, left ventricular mass index, and anemia.*

2. MATERIALS AND METHODS

2.1. Inclusion criteria

All patients aged ≥ 18 years, diagnosed with heart failure according to the VNHA 2022 criteria, meeting the inclusion and exclusion criteria [1].

2.2. Exclusion criteria

- Patients with stroke or brain injury.
- Patients with acute coronary syndrome within < 10 days.
- Patients with liver cirrhosis. Chronic kidney disease, with blood creatinine > 250 µmol/l. Septicemia.
- Chronic obstructive pulmonary disease or bronchial asthma.
- End-stage heart failure.
- Cancer chemotherapy. Critically ill patients.
- Patients unwilling to participate in the study.

2.3. Study Time and Location

- Time: from March 2023 to December 2023.
- Location: Department of Cardiology, Hue University of Medicine and Pharmacy Hospital.

2.4. Research Methodology

- Study Design: cross-sectional descriptive study.
- Sampling Method: convenient sampling.
- Study variables.
- General characteristics: age, gender. Clinical parameters: clinical symptoms assessed according to Framingham criteria, comorbidities including hypertension, coronary artery disease, diabetes mellitus, anemia, smoking history, and BMI.
- Hematological parameters: complete blood count performed using an automated cell counter XT 1800 i, anemia defined as hemoglobin < 12 g/dL in females and < 13 g/dL in males [5].
- Serum NT-proBNP assay: Normal values < 20 pg/ml, exclusion of heart failure when NT-proBNP concentration < 100 pg/ml. Diagnosis of heart failure according to the recommendation is ≥ 125 pg/ml, thus we used a cut-off point of ≥ 125 pg/ml [1], [6].
- Other biochemical tests: serum creatinine, fasting blood glucose.
- 12-lead electrocardiogram: Evaluation of left ventricular Sokolow index, defined as the sum of S wave in lead V1 plus R wave in lead V5 or V6 ≥ 35 mm.
- Echocardiography: performed according to the recommendations of the American Society of Echocardiography [7]. Assessment of left ventricular diastolic dysfunction: measured on 2D echocardiography using the Simpson's method, categorizing EF into 3 levels [1]:

+ Heart failure with preserved ejection fraction (HFpEF): EF ≥ 50%.

+ Heart failure with mildly reduced ejection fraction (HFmrEF): EF: 41 - 49%.

+ Heart failure with reduced ejection fraction (HFrEF): EF ≤ 40%.

- Transthoracic echocardiography: performed according to the recommendations of the American Society of Echocardiography to evaluate left atrial diameter (LAd), left ventricular mass index (LVMI) (g/m^2), Left ventricular hypertrophy defined as increased LVMI in males when > 115 g/m^2, in females when > 95 g/m^2 [7].

2.5. Data Analysis Method: Statistical analysis was conducted using SPSS 20.0 software with a significance level set at $p < 0.05$.

3. RESULT S

3.1. Clinical and subclinical characteristics of the study sample

The results of our study indicate that 56.5% of hospitalized heart failure patients were classified as HFpEF, 24.1% belonged to the HFmrEF group, and the lowest proportion was HFrEF with 19.4%.

The average age is 68 ± 13.5 years. Patients

with HFrEF had a higher average age (78.4 ± 15.9) compared to HFmrEF (66.9 ± 10.3) or HFpEF (65.6 ± 12.3). The ratio of females to males in the study was equivalent (50%). Hypertension was the most common comorbidity, accounting for 59.3%, followed by coronary artery disease at 38.9% and atrial fibrillation (29.6%). Patients with HFpEF had a higher prevalence of atrial fibrillation (39.3%) compared to the HFmrEF (19.2%) and HFrEF (14.3%) groups. 14.8% of the patients participating in the study had anemia. Patients with HFpEF had a higher BMI (21.4 ± 2.2) compared to HFmrEF (20.8 ± 2.6) and HFrEF (19.4 ± 2.3). (Table 1)

Table 1. The general characteristics of the study subjects

Parameter	Statistic	HFrEF (n = 21)	HFmrEF (n = 26)	HFpEF (n = 61)	p-value[a]	Total (n = 108)
Age (years)	Mean (SD)	78.4 (15.9)	66.9 (10.3)	65.6 (12.3)	**< 0.001**	68.38 (13.5)
Male sex	n(%)	11 (52.4)	14 (53.9)	29 (47.5)	0.844	54 (50.0)
Hypertension	n(%)	10 (47.6)	18 (69.2)	36 (59.0)	0.331	64 (59.3)
CAD	n(%)	10 (47.6)	11 (42.3)	21 (34.4)	0.183	42 (38.9)
AF	n(%)	3 (14.3)	5 (19.2)	24 (39.3)	**0.039**	32 (29.6)
Diabetes	n(%)	6 (28.6)	5 (19.2)	7 (11.5)	0.182	18 (16.7)
Anemia	n(%)	6 (28.6)	5 (19.2)	5 (8.2)	0.059	16 (14.8)
Smoking	n(%)	4 (19.0)	8 (30.8)	19 (31.1)	0.415	31 (28.7)
BMI (kg/m²)	Mean (SD)	19.4 (2.3)	20.8 (2.6)	21.4 (2.2)	**0.004**	20.9 (2.4)

HFpEF, heart failure with preserved ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFrEF, heart failure with reduced ejection fraction; CAD, Coronary artery disease; AF, Atrial fibrillation; BMI, Body mass index; SD, standard deviation.

[a]P-value from ANOVA (F-test) for continuous variables or from χ 2 test for categorical variables

NYHA II accounted for the highest proportion at 43.5%, while NYHA IV had the lowest proportion at 8.3%. Patients with HFrEF were more likely to be admitted with NYHA IV status compared to patients with HFmrEF and HFpEF ($p < 0.001$). There were no differences in clinical symptoms among the three groups of heart failure patients. 84.3% of patients experienced exertional dyspnea, which was the most common symptom of heart failure. The hepatojugular reflux (+) and pulmonary edema accounted for a very low proportion of 1.9%. (Table 2)

Table 2. Clinical symptoms characteristics of heart failure

Parameter	Statistic	HFrEF (n = 21)	HFmrEF (n = 26)	HFpEF (n = 61)	p-value[a]	Total (N = 108)
NYHA class						
NYHA I	n(%)	3 (14.3)	6 (23.1)	14 (23.0)	0.689	23 (21.3)
NYHA II	n(%)	7 (33.3)	12 (46.2)	28 (45.9)	0.584	47 (43.5)
NYHA III	n(%)	5 (23.8)	6 (23.1)	18 (29.5)	0.247	29 (26.9)
NYHA IV	n(%)	6 (28.6)	2 (7.7)	1 (1.6)	**< 0.001**	9 (8.3)
Paroxysysmal nocturnal dyspnea	n(%)	11 (52.4)	11 (42.3)	25 (41.0)	0.662	47 (43.5)
Neck vein distension	n(%)	3 (14.3))	3 (11.5)	6 (9.8)	0.856	12 (11.1)
Rales	n(%)	5 (23.8)	8 (30.8)	13 (21.3)	0.647	26 (24.1)
Radiographic cardiomegaly	n(%)	9 (42.9)	16 (61.5)	23 (37.7)	0.123	48 (44.4)
Third sound gallop	n(%)	2 (9.5)	2 (7.7)	6 (9.8)	0.208	10 (9.3)
Hepatojugular reflux	n(%)	0 (0.0)	0 (0.0)	2 (3.3)	0.464	2 (1.9)

Dyspnea on ordinary exertion	n(%)	16 (76.2)	21 (80.8)	54 (88.5)	0.356	91 (84.3)
Bilateral ankle edema	n(%)	9 (42.9)	7 (26.9)	13 (21.3)	0.161	29 (26.9)
Noctural cough	n(%)	8 (38.1)	10 (38.5)	22 (36.1)	0.972	40 (37.0)
Pleural effusion	n(%)	0 (0.0)	2 (7.7)	0 (0.0)	0.051	2 (1.9)
Hepatomegaly	n(%)	1 (4.8)	0 (0.0)	2 (3.3)	0.583	3 (2.8)
Tachycardia (≥ 120 beats per minute)	n(%)	4 (19)	2 (7.7)	4 (6.6)	0.228	10 (9.3)

HFpEF, heart failure with preserved ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association;

[a]P-value from ANOVA (F-test) for continuous variables or from χ 2 test for categorical variables

Patients with HFrEF had a higher proportion of left ventricular hypertrophy on ECG based on the Sokolow index (57.1%) compared to patients with HFmrEF (19.2%) and HFpEF (18.0%). Left ventricular mass index elevation was more prevalent in the HFrEF group (66.7%) compared to the HFmrEF (26.4%) and HFpEF (14.8%) groups. The average left atrial diameter was 41.6 ± 10.6 mm with no significant difference between the groups. (Table 3).

Table 3. Characteristics of imaging subclinical features in heart failure patients

Parameter	Statistic	HFrEF (n = 21)	HFmrEF (n = 26)	HFpEF (n = 61)	p-value[a]	Total (N = 108)
SKI 35 mm	n(%)	12 (57.1)	5 (19.2)	11 (18.0)	**0.001**	28 (25.9)
CTR > 0.5	n(%)	10 (45.4)	16 (61.5)	23 (37.7)	0.123	49 (45.4)
LVH	n(%)	14 (66.7)	7 (26.4)	9 (14.8)	**<0.001**	30 (27.8)
LAd (mm)	Mean (SD)	42.2 (8.5)	42.4 (10.5)	41.0 (11.3)	0.818	41.6 (10.6)

HFpEF, heart failure with preserved ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFrEF, heart failure with reduced ejection fraction; SKI, Sokolow index; CTR, Cardiothoracic Ratio; LVH, Left ventricular hypertrophy; LAd, Left atrial diameter; SD, standard deviation

[a]P-value from ANOVA (F-test) for continuous variables or from X^2 test for categorical variables

3.2. The correlation of NT-proBNP and left ventricular ejection fraction, Sokolow index, left ventricular mass index, and anemia.

There is a statistically significant difference in NT-proBNP concentration among the three heart failure groups classified by left ventricular ejection fraction. As the ejection fraction decreases, the NT-proBNP concentration increases, with a Spearman correlation coefficient of Rs = -0.637 and p < 0.001. (Table 4, Figure 1)

Table 4. The correlation between NT-proBNP concentration and LVEF

LVEF	Quantity (n = 108)	NT-proBNP concentration		
		Median	Quartile range	p-value
≥ 50%	61	1226	607 - 2196	**< 0.001**
41 - 49%	26	1939,5	966,5 - 4106,75	**Rs = -0,637**
≤ 40%	21	13734	4733 - 24180,5	**df = 2**

LVEF, Left ventricular ejection fraction; Rs, Spearman rank correlation coefficient.

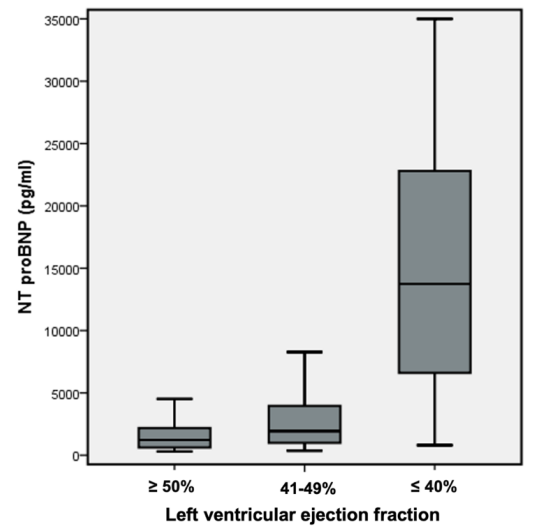

Figure 1. Distribution of NT-proBNP concentration according to LVEF

The NT-proBNP concentration in the Sokolow ≥ 35 mm group (4572 (1354.75 - 18678.75) pg/ml) was higher than in the Sokolow < 35 mm group (1564.5 (706.5 - 2940) pg/ml), with a correlation coefficient Rs = 0.309, p < 0.05.

Table 5. The correlation between NT-proBNP concentration and Sokolow index

Parameter		Quantity (n = 108)	NT-proBNP concentration		
			Median	Quartile range	p-value
SKI	≥ 35 mm	27	4572	1354.75 - 18678.75	**0.001**
	< 35 mm	81	1564.5	706.5 - 2940	**Rs = 0,309**

SKI, Sokolow index; Rs, Spearman rank correlation coefficient.

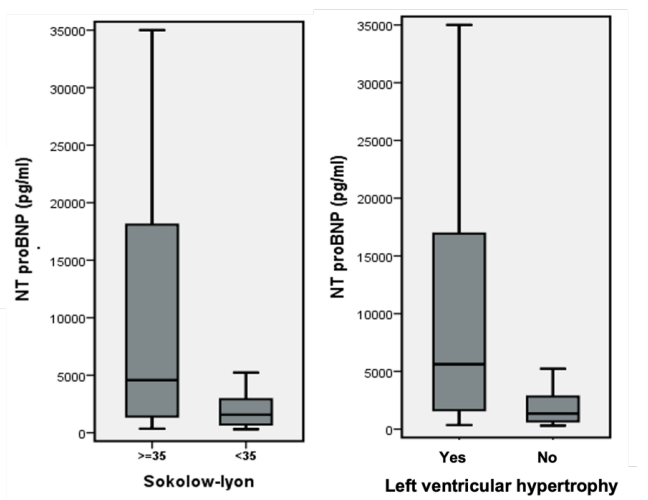

Figure 2. Distribution of NT-proBNP concentration according to the Sokolow index

The group of patients with anemia had higher NT-proBNP concentrations compared to the group without anemia (2820.5 (1130.75 - 22203) pg/ml versus 1657 (745.75 - 3663.75) pg/ml), and this difference was statistically significant (p < 0.05) (Table 6, Figure 3).

Table 6. The correlation between NT-proBNP concentration and anemia

Parameter		Quantity (n = 108)	NT-proBNP concentration		
			Median	Quartile range	p-value
Anemia	Yes	27	4572	1354.75 - 18678.75	0.019
	No	16	2820.5	1130.75 - 22203	

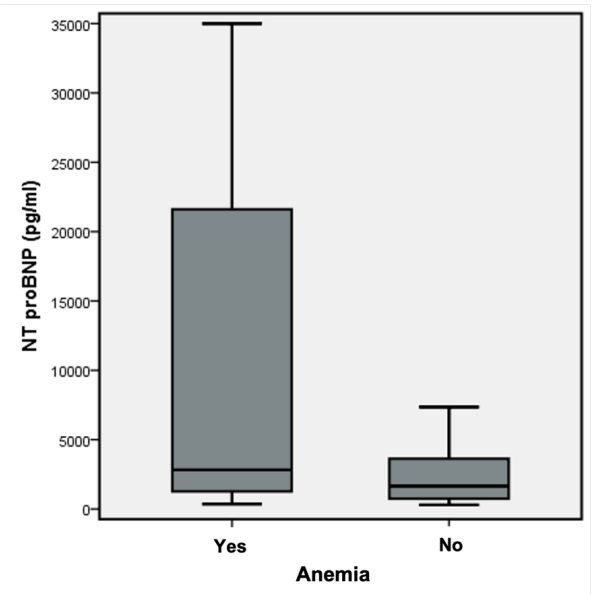

Figure 3. Distribution of NT-proBNP concentration according to anemia

4. DISCUSSION

In our study, the gender distribution was balanced, with an equal proportion of male and female participants. The mean age of the study sample was 68.4 ± 13.5 years, which is consistent with findings from other studies in Vietnam, such as Nguyen Thanh Xuan (2023) reporting an average age of 71.61 ± 13.03 years [8]. In Australia, a pooled analysis of clinical characteristics of heart failure patients also showed a similar mean age of 68.9 years, with females comprising 50.6% of the analyzed population [9]. The HFrEF group had a higher average age compared to the HFmrEF or HFpEF groups. Besides the potential for comorbidities in older patients, the aging process itself is also associated with significant changes in EF [10]. More than half of the hospitalized patients (56.5%) had preserved EF heart failure, while 24.1% belonged to the mildly reduced EF group. This aligns with the general trend of HFpEF cases accounting for approximately 50% of heart failure hospitalizations in the United States, increasing from 33% in 2005 to 39% in 2010 [11].

Among the clinical trials on heart failure synthesized up to 2020, the common comorbidities observed were hypertension (63%), coronary artery disease (44%), and diabetes mellitus (33%), with a lower prevalence of renal disease or atrial fibrillation [12]. However, more than half of the reports in this synthesis focused only on the HFrEF population (51%). In our study involving heart failure patients regardless of EF, hypertension remained the most common comorbidity, followed by CAD and atrial fibrillation. The prevalence of anemia was 14.8%. Our findings are consistent with the study by Mehmet Kis et al. (2022) reporting an anemia prevalence of 17.4% [13].

Patients with HFpEF exhibited significantly higher BMI and atrial fibrillation rates compared to those with HFmrEF and HFrEF. This is related to the pathophysiological mechanism of HFpEF, where obesity is a crucial factor leading to left ventricular hypertrophy, increased myocardial stiffness, altered substrate utilization, activation of neurohormonal pathways, and systemic inflammation [14]. Additionally, the prevalence of atrial fibrillation in HFpEF patients is common, often associated with

similar mechanisms of cardiac remodeling and diastolic dysfunction related to frequency, which may also present similar symptoms to HFpEF and alter echocardiographic findings and natriuretic peptide levels, thereby affecting the assessment of HFpEF [15].

The results of our study showed that 84.3% of patients experienced exertional dyspnea, which accounted for the highest proportion, while T3 murmurs accounted for 9.3%. Regarding the NYHA classification, NYHA II accounted for 43.5%, whereas NYHA IV had the lowest proportion at 8.3%. These findings are consistent with a study by Fabiana G. Marcondes-Braga et al. (2020), which reported exertional dyspnea in 86.2% of cases, ankle edema in 18.3%, nocturnal dyspnea in 21.6%, and T3 murmurs in 7.2%. Similarly, in terms of NYHA classification, class II accounted for 62.3%, while class IV accounted for only 0.7% [16]. Additionally, among patients with HFrEF, there were more cases of hospital admission classified as NYHA IV compared to the HFmrEF or HFpEF groups. Other clinical manifestations were similar among the groups.

When comparing the parameters in clinical assessment, patients with HFrEF seemed to have a higher prevalence of left ventricular hypertrophy on ECG (based on the Sokolow index) compared to the HFmrEF and HFpEF groups. Moreover, on echocardiography, patients with HFrEF had a higher prevalence of increased left ventricular mass index (LVMI) compared to the HFmrEF and HFpEF groups. Previous studies also reported similar results, demonstrating significantly higher LVMI in patients with HFrEF compared to HFpEF [17], [18]. However, the proportion of patients with left ventricular hypertrophy index > 0.5 did not significantly differ among the three groups of heart failure patients. Recently, a meta-analysis in 2023 by Sadi Elasan et al. on 13 studies evaluating the correlation between left ventricular hypertrophy index and ejection fraction showed a weak correlation with r = -0.12 [19]. Additionally, some patients in the study were positioned lying down due to advanced age and dyspnea, leading to non-standard imaging and measurement errors.

The NT-proBNP levels differed among the different heart failure groups classified according to ejection fraction (EF). There was a strong correlation between EF and NT-proBNP, with NT-proBNP levels increasing as EF decreased, with a strong correlation coefficient of Rs = -0.637, $p < 0.001$. This result is consistent with a study by Hanan Radwan et al. (2014), which found significantly higher NT-proBNP levels in the EF < 40% group compared to other subgroups with EF ranging from 40% to 50% and above 50% [20]. It is related to increased pressure in the left ventricular wall due to changes in hemodynamics and reflects the inadequate response of the ventricle to increased preload, often seen in cases of reduced ejection fraction.

The specific correlation between NT-proBNP and the Sokolow index has not been extensively studied. In our study, NT-proBNP levels were higher in the Sokolow ≥ 35 mm group compared to the < 35 mm group (4572 (1354.75 - 18678.75) vs. 1564.5 (706.5 - 2940) pg/ml), and this difference was statistically significant with $p < 0.001$. NT-proBNP showed a moderate correlation with this index with Rs = 0.309. Meanwhile, NT-proBNP levels were higher in patients with increased left ventricular mass index, with a statistically significant difference compared to patients without this condition, indicating a positive correlation between NT-proBNP and LVMI with r = 0.421 ($p < 0.0001$). This finding was also observed in the study by Helder Andrade et al. (2011), which found that NT-proBNP levels were higher in patients with left ventricular hypertrophy compared to those without left ventricular hypertrophy with $p < 0.0001$ (2957 ± 4116 vs. 929 ± 1267 pg/ml), as well as in the ARIRANG study by Min-Soo Ahn et al. (2015) [21], [22]. This suggests that NT-proBNP has a moderate correlation with clinical features of left ventricular hypertrophy, such as ECG or echocardiography.

In our study, patients with anemia had higher NT-proBNP levels compared to those without anemia (2820.5 (1130.75 - 22203) pg/ml vs. 1657 (745.75 - 3663.75) pg/ml), and this difference was statistically significant ($p < 0.05$). Similarly, a study by Morten Schou et al. (2007) showed that NT-proBNP levels were higher in the anemia group compared to the normal group (2,889 (27 - 35000) pg/ml vs. 1022 (21 - 31737) pg/ml) with $p < 0.001$ [23]. A study by Innac Karrakoyun et al. (2017) demonstrated a statistically significant inverse correlation between hemoglobin levels and NT-proBNP with r = -0.179. These results indicate that NT-proBNP is associated with anemia in heart failure patients. Therefore, it should be noted that anemia may lead to increased NT-proBNP levels in heart failure patients, considering that anemia

is a common comorbidity that is increasing and receiving attention in current guidelines on heart failure.

5. CONCLUSION

HFpEF accounted for more than half of the hospitalized heart failure cases. The most common comorbidities remained hypertension, coronary artery disease, and atrial fibrillation. HFpEF patients had higher BMI and atrial fibrillation rates compared to HFmrEF and HFrEF groups, whereas HFrEF patients had higher Sokolow index (≥ 35 mm) and increased LVMI compared to the other two heart failure groups. Anemia in hospitalized heart failure patients was prevalent and significantly associated with increased NT-proBNP levels. Serum NT-proBNP levels were strongly correlated with ejection fraction and moderately correlated positively with Sokolow index and LVMI.

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