DOI: 10.38103/jcmhch.95.15

Original research

STUDY OF SERUM FERRITIN AND NT-proBNP LEVELS IN PATIENTS WITH HEART FAILURE

Doan Chi Thang[1], Hansana Phetchinda[2], Huỳnh Văn Minh[2]
[1]Hue Central Hospital
[2]Hue University of Medicine and Pharmacy

ABSTRACT

Objectives: *To investigate serum ferritin levels in patients with heart failure and to assess the correlation of ferritin, NT-proBNP levels with heart failure severity and between NT-proBNP and ferritin.*

Methods: *Cross - sectional description study on 101 patients diagnosed with heart failure and undergoing inpatient treatment at the Department of Internal Cardiology, Cardiovascular Center, Hue Central Hospital from 05/2022 to 08/2023.*

Results: *The average age of the study sample was 70.0 ± 16.4 years. Females constitute a higher proportion with a female/male ratio = 1.7. NYHA III heart failure accounted for the highest rate (47.5%). In terms of ejection fraction, EF ≥50% accounted for the highest rate of 54.5%. As many as 93 patients (92.1%) had anemia in the study. The incidence of ferritin reduction in the NYHA I/II heart failure group (57.4%) was higher than in NYHA III/IV (55.6%). Regarding ferritin and ejection fraction, ferritin decreased in the group with reduced EF at a rate of 56.1%, higher than in the group with non-reduced EF at a rate of 43.9%, however the difference was not statistically significant ($p > 0.05$). Anemia patients with reduced ferritin had significantly higher levels of NT-proBNP (14271.97 ± 12810.17 pg/ml) than the anemia group with normal ferritin (8255.60 ± 11121.41 pg/ml), $p < 0.05$. NT-proBNP has a moderate positive correlation with ferritin ($r = 0.422$; $p < 0.05$), a moderate negative correlation with RBC ($r = -0.465$; $p < 0.05$), Hb ($r = -0.352$; $p < 0.05$), HCT ($r = -0.408$; $p < 0.05$) in patients with heart failure according to NYHA III/IV.*

Conclusions: *Serum ferritin in patients with heart failure may be an indicator of iron deficiency. Our study shows that there is a positive correlation between NT-proBNP and ferritin in patients with severe heart failure.*

Keywords: *Ferritin, NT-proBNP, heart failure.*

I. INTRODUCTION

Heart failure is a clinically common syndrome and is a consequence of the majority of cardiovascular pathologies such as valvular heart disease, cardiomyopathy, coronary heart disease, congenital heart disease and some other pathologies that affect the heart. Heart failure is now one of the global health problems of non-communicable diseases that severely affect more than 64.3 million people worldwide [1].

Recently, it has been recognized that iron deficiency is an independent factor that increases the state of heart failure, reduces the quality of life, and increases mortality in chronic heart failure in general and in chronic heart failure with a reduced ejection fraction in particular [2]. Studies suggest that correction of iron deficiency with intravenous iron in patients with chronic heart failure may have clinical benefits. Iron serves as the key to oxygen absorption, transport and storage, and metabolism in skeletal muscle. It also makes an important contribution to erythropoiesis. Meanwhile, serum ferritin is considered the gold standard in diagnosing serum iron deficiency with stored iron levels in the body [3]. Serum ferritin is a marker of iron

Received: 11/3/2024. **Revised:** 29/4/2024. **Accepted:** 16/5/2024.
Corresponding author: Doan Chi Thang. Email: thangdoanchi1981@gmail.com. Phone: 0905469595

storage that is widely used in epidemiological studies, and accurately reflects differences in iron levels in the body by age and sex. The 2021 European Society of Cardiology recommendation for the diagnosis and treatment of iron deficiency states that intravenous iron supplementation should be given in patients with reduced EF or mild-reduced EF, iron deficiency, to improve symptoms and quality of life, as well as reduce the risk of hospitalization for heart failure in patients [4].

In recent years, the investigation of complete iron deficiency via serum ferritin testing has been of interest in heart failure patients worldwide due to its association with prognosis and also in new guidelines for the treatment of heart failure, especially when combined with other heart failure biomarkers such as NT-proBNP. Therefore, we carried out the present study to investigate the serum ferritin levels in patients with heart failure and evaluate the association of ferritin and NT-proBNP levels with the severity of heart failure and between NT-proBNP and ferritin.

II. MATERIALS AND METHODS

A cross-sectional descriptive study was conducted on 101 patients diagnosed with heart failure and undergoing inpatient treatment at the Department of Internal Cardiology, Cardiovascular Center, Hue Central Hospital from May 2022 to August 2023.

Criteria for disease selection: admitted patients diagnosed with heart failure according to the standards of the European Society of Cardiology 2021 [4]: typical symptoms/signs of heart failure and biochemical marker BNP ≥ 35 pg/ml or NT-proBNP ≥ 125 pg/ml and echocardiography to determine the cause and functional and anatomical abnormalities of the heart (including evaluation of the anatomical morphology of the heart, degree of dilation of the heart chambers, and thickness of heart walls. Evaluation of left ventricular systolic function through left ventricular ejection fraction (EF). Evaluation of left ventricular diastolic function and left heart chamber filling pressure. Evaluation of right ventricular function and pulmonary arterial pressure. Diagnosis of some causes of heart failure: Regional dyskinesia (myocardial infarction), dilated cardiomyopathy, hypertrophic cardiomyopathy, valvular heart disease, right ventricular dysplasia ... Evaluation of thrombosis in the chambers of the heart).

Exclusion criteria: causes of acute anemia (such as gastrointestinal bleeding, trauma...) or have received a blood transfusion within 120 days, treatment with oral or intravenous erythropoiesis or iron medication or heart failure due to cyanosis congenital heart disease or pregnancy or liver failure or did not consent to participate in the study.

Each patient is surveyed according to the study form with the following procedure: Conduct meticulous history, medical history, and physical examination to select research subjects meeting the standard criteria. Biochemical tests, blood are taken to ensure the correct procedures. Quantification of serum ferritin by turbidimetric immunoassay method was performed on a Cobas 8000 e602 machine from ROCHE.Normal values of ferritin depend on gender: men: from 30 - 300 ng/mL; women: from 10 - 200 ng/mL.In our study, ferritin decreased when ferritin concentration was < 100 ng/mL.

Biochemical analysis of NT-proBNP was performed by ELISA immunoassay. Normal values <20 pg/mL, when NT-proBNP concentration <100 pg/mL, rule out heart failure. NT-proBNP concentration > 500 pg/mL confirms that the patient has heart failure. Our study took the cutoff point as 125pg/mL.

In our study, we used a specialized echocardiography machine Affiniti 70 from Philips. Ejection fraction (EF%): the most accurate is to use the Simpson method with modifications to two cross-sections on 2D ultrasound.

LVEF (%) = (EDV-ESV)/EDV x 100%

In which: EDV: Left ventricular end-diastolic volume.

ESV: End-systolic left ventricular volume.

LVEF: Left ventricular ejection fraction.

Data processing with SPSS 26.0 and Excel 2021 software

III. RESULTS

Table 1: General characteristics of the objects

Variable	Classify	n	%
Median age (years) X ± SD	70.0 ± 16.4		
Age group	< 60	22	21.9
	≥ 60	79	78.2
Sex	Male	38	37.6
	Female	63	62.4
Heart failure according to the NYHA	Grade I	13	12.9
	Grade II	35	34.7
	Grade III	48	47.5
	Grade IV	5	5.0
Ejection fraction LVEF (%)	≤ 40	37	36.6
	41 - 49	9	8.9
	≥ 50	55	54.5
	Hb ≥ 12 g/dl in Female and ≥ 13 g/dl in male	8	7.9
	10 to <12 in female / <13 in male	25	24.8
	8 to < 10	46	45.5
	6 to < 8	20	19.8
	< 6	2	2.0
Median ferritin (IQR) (ng/ml)	270.8 (94.5 - 592.7)		
Ferritin group (ng/ml)	< 100	28	27.7
	100 - < 300	29	28.7
	≥ 300	44	43.6
Median NT-proBNP (IQR) (pg/ml)	4997.0 (1437.0 - 14143.0)		

The majority of patients in the study were in the elderly group accounting for 78.2%. Females constitute a higher proportion with female/male ratio = 1.7. NYHA III heart failure accounted for the highest rate (47.5%). In terms of ejection fraction, EF ≥ 50% accounted for the highest rate of 54.5%. There are 93 patients had anemia in the study. In particular, the highest level of anemia is moderate with Hb (g/dL) from 8 to < 10 g/dL, accounting for 45.5%.

Table 2: Association between ferritin and heart failure levels according to the NYHA

Indicators		Degree of heart failure according to NYHA			p
		III/IV n (%)	I/II n (%)	Total n (%)	
Reduced ferritin (ng/mL)	Yes	30 (55.6)	27 (57.4)	57 (56.4)	> 0.05
	Not	24 (44.4)	20 (42.6)	44 (43.6)	
Sum		54 (100.0)	47 (100.0)	101 (100.0)	

The proportion of reduced ferritin in the NYHA I/II heart failure group was higher than in NYHA III/IV group but the difference was not statistically significant (p > 0.05).

Table 3: Association between ferritin and ejection fraction (EF)

Indicators		Reduced - EF			p
		Yes n (%)	No n (%)	Total n (%)	
Reduced ferritin (ng/mL)	Yes	32 (56.1)	25 (43.9)	57 (100.0)	> 0.05
	No	23 (52.3)	21 (47.7)	44 (100.0)	

Reduced ferritin at a rate of 56.1% higher in the EF group without a decrease of 43.9%, a difference not statistically significant (p >0.05).

Table 4: Comparison of NT-proBNP levels between the anemia group with reduced ferritin and anemia with normal ferritin

Index	Anemia with reduced ferritin	Anemia with normal ferritin	p
NT-proBNP (pg/mL)	14271.97 ± 12810.17	8255.60 ± 11121.41	< 0.05

Anemia patients with reduced ferritin had significantly higher NT-proBNP levels than the anemia group with normal ferritin p < 0.05.

Table 5: Correlation between NT-proBNP, hematological markers, and serum ferritin in patients with severe heart failure (NYHA III/IV)

	Ferritin (ng/mL)	RBC (T/L)	Hb (g/dL)	HCT (%)	MCV (fL)	MCHC (g/dL)
r	0.422	-0.465	-0.352	-0.408	0.167	0.242
p	< 0.05	< 0.05	< 0.05	< 0.05	> 0.05	> 0.05

NT-proBNP (pg/mL) was moderate positively correlated with ferritin, negatively correlated with RBC (T/L), HB (g/dl), HCT (%) in patients with NYHA severe heart failure with p < 0.05. There is no correlation between MCV (fL) and MCHC (g/dL) and NT-proBNP (pg/mL) in patients with severe heart failure, according to the NYHA.

IV. DISCUSSION

Iron deficiency is characterized by a decrease in the tissue's ability to store iron to supply erythropoiesis, which is a common problem in chronic heart failure. Through the study, we noted that up to 43.64% of heart failure patients had ferritin < 300 ng/mL, the median was 270.8 ng/mL (Quartile: 94.5 - 592.7 ng/mL) higher than normal. This result is similar to the results of Nguyen Van Long (2018) at the Department of Internal Cardiology of Hue Central Hospital and the Department of Internal Cardiology of Hue University of Medicine and

Pharmacy, which showed that ferritin levels in the blood had a median of 271.7 ng/mL (quartile: 140.8 - 422.7 ng/mL) [7]. Another study by Dam Hai Son (2021) also showed high ferritin results, with an average ferritin concentration of 204.3 ± 567.0 ng/mL [2]. The rate of ferritin reduction in our study in the NYHA I/II heart failure group was higher than that of NYHA III/IV, however the difference was not statistically significant $p > 0.05$. This result is different from Dam Hai Son's study on 240 chronic heart failure patients treated at the Vietnam Heart Institute, the group of NYHA III and IV patients had an iron deficiency rate of 46.3%, higher than this rate in patients NYHA I, II (35.4%) [46]. Von Haehling noted that iron deficiency is very common in heart failure patients and that the rate increases to NYHA [5]. With the association between ferritin and ejection fraction, our study showed that ferritin reduction increased the risk of heart failure with reduced EF, which increased by 1.2 times compared to the group without ferritin reduction but was not statistically significant ($p > 0.05$). Research by Klip [6] in 1506 heart failure patients, 753 heart failure patients with iron deficiency were found, although LVEF levels were higher in the heart failure group with iron deficiency (34 ± 14%) than in the heart failure group without iron deficiency (32 ± 13%), but this difference was statistically significant with $P < 0.05$. Research by Kok Leng Tan et al [7] then shows a positive correlation between LVEF levels and serum ferritin levels ($r = 0.624$, $p < 0.001$). This difference may be due to the small size of our sample, which cannot yet correlate between ferritin index and ejection fraction. Therefore, a large sample size analysis study is needed to find an association between iron deficiency and LVEF levels and anemia are among the most commonly seen comorbidities in patients with heart failure, and both are independently associated with clinical exacerbations in patients [8]. Iron deficiency can manifest itself in two distinct forms with intertwined pathophysiology, namely relative iron deficiency and absolute deficiency. Absolute iron deficiency reflects depleted iron stores, while relative iron deficiency is characterized by reduced iron availability although iron stores remain sufficient or remain abundant due to hepcidin inhibiting iron absorption from the small intestine or liver breast and macrophages releasing iron stores. In heart failure, understanding of what causes iron deficiency anemia is limited. However, several factors have been shown to be independently associated with iron deficiency in heart failure patients, including advanced age, renal failure, female sex, malnutrition, chronic inflammation, decreased iron absorption, increased iron loss, and severity of heart failure [9].

We found that NT-proBNP was moderately correlated with ferritin in patients with severe heart failure, according to the NYHA, with $p < 0.01$. The study of Can Balkan (2011) showed a positive correlation between ferritin and NT-proBNP [10]. Similarly, research by Diyas Anugrah et al. published in 2023 also found a positive correlation between NT-proBNP and ferritin with $r = 0.399$ and $p < 0.05$ [11]. The increase in NT-proBNP and ferritin is probably related to the inflammatory process during heart failure. Currently, inflammation has been recognized as the main pathophysiological agent of heart failure [12]. The observation that heart failure with reduced ejection fraction is associated with high circulating levels of pro-inflammatory cytokines has opened up a new area of research suggesting an important potential role of the immune system in the pathogenesis of heart failure. Serum ferritin is also a well - known marker of inflammation, but it remains unclear whether serum ferritin reflects or causes inflammation, or whether it is involved in the inflammatory cycle. Some authors argue that serum ferritin arises from damaged cells and is therefore a marker of cell damage. The protein in serum ferritin is considered benign, but it has lost (i.e. removed) most of the normal supplemental iron which when not combined is highly toxic. Therefore, the fact that serum ferritin levels can be correlated with both disease and iron stores in the body is expected on the basis of simple chemical kinetics. Serum ferritin levels are also correlated with other phenotypic indicators such as erythrocyte morphology. Overall, this systematic approach aims to explain some of the apparent paradoxes of serum ferritin, including (i) why it correlates with biomarkers of cell damage, (ii) why it correlates with biomarkers of hydroxyl radical formation (and oxidative stress), and (iii) why it is correlated with the presence the

type and/or severity of many diseases. This has led to suggestions about how one might exploit the inevitable corollary of recognizing that serum ferritin levels are primarily a consequence of stress and cell damage [13]. Ferritin is elevated in inflammation and NT-proBNP is elevated in heart failure (inflammation is considered a motivating factor). This connection needs to be clarified by larger, better-designed studies.

V. CONCLUSION

The observation of variability of serum ferritin in patients with heart failure may be an indicator of iron deficiency. Our study shows that there is a positive correlation between NT-proBNP and ferritin in patients with severe heart failure.

REFERENCES

1. Groenewegen A, Rutten FH, Mosterd A. Epidemiology of heart failure. European Journal of Heart Failure,. 2020;22(8):1342-1356.
2. Son DH, Hieu TB, Tuan PM, Huong NT. Serum iron deficiency in patients with chronic heart failure with reduced ejection fraction. Vietnam Journal of Cardiology. 2021;94 + 95:33-40.
3. Jelani QU, Katz SD. Treatment of anemia in heart failure: potential risks and benefits of intravenous iron therapy in cardiovascular disease. Cardiol Rev. 2010;18(5):240-50.
4. McDonagh TA, Metra M, Adamo M, Böhm M BH, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, . 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2021;42(36):3599-3726.
5. Ebner N, von Haehling S. Why is Iron Deficiency Recognised as an Important Comorbidity in Heart Failure? Card Fail Rev. 2019;5(3):173-175.
6. Klip IT. Iron deficiency in chronic heart failure: an international pooled analysis. Am Heart J. 2013;165(4):575-582.
7. Tan KL, Ng SL, Chong SE, Isa W Y H W H, Tan J J, et al. (2020), “”, , pp. Iron Deficiency in Heart Failure Patients with Reduced Ejection Fraction and the Correlation with Left Ventricular Ejection Fraction. Malaysian Journal of Medicine and Health Sciences. 2020;16(1):126-130.
8. Anand IS, Gupta P. Anemia and Iron Deficiency in Heart Failure: Current Concepts and Emerging Therapies. Circulation. 2018;138(1):80-98.
9. van der Wal HH, Grote BN, Dickstein K, Anker SD LC, Ng LL, van Veldhuisen DJ, Voors AA, van der Meer P,. Iron deficiency in worsening heart failure is associated with reduced estimated protein intake, fluid retention, inflammation, and antiplatelet use. Eur Heart J. 2019;40(44):3616-3625.
10. Balkan C, Yakar TS, Basol G, Tuluce K, Ay Y. Relation between NT-ProBNP Levels, Iron Overload, and Early Stage of Myocardial Dysfunction in β-Thalassemia Major Patients. Echocardiography. 2011;29(3):318-325.
11. Anugrah D. Correlation between Ferritin Level and NT-ProBNP in Thalassemia Patient at M. Djamil Hospital Padang. International Journal of Research and Review. 2023;10(9):138-147.
12. Reina-Couto M, Pereira-Terra P, Quelhas-Santos J, Silva-Pereira C. Inflammation in Human Heart Failure: Major Mediators and Therapeutic Target. Front Physiol. 2021;12:746494.
13. Kell DB, Pretorius E. Serum ferritin is an important inflammatory disease marker, as it is mainly a leakage product from damaged cells. Metallomics. 2014;6(4):748-73.