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Correlation between Ferritin Level and NT-ProBNP in Thalassemia Patient at M. Djamil Hospital Padang

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ABSTRACT

Background: Thalassemia is a hereditary haemolytic anaemia caused by a genetic defect in the formation of globin chains. Routine blood transfusion is part of the management of thalassemia in Indonesia to maintain haemoglobin levels above the target haemoglobin. The consequence of this therapy is secondary excess of iron (ferritin), which adversely affects cardiac function. NT-pro BNP is one of the cheaper, more accessible, and non-invasive biomarkers that can be used to detect abnormalities in cardiac function. This study aims to analyse the correlation of ferritin levels with NT-proBNP in thalassemia patients.
Method: This is an observational analytic study with a cross sectional approach. The inclusion criteria in the study were thalassemia patients who were ≤18 years old and routinely received repeated transfusions. Patients with a history of congenital heart disease, heart failure, hyperthyroidism, overt valvular disease, sepsis, or chronic kidney disease were excluded from this study. Correlation analysis was carried out by analysing the relationship between ferritin levels and NT-proBNP levels in children with thalassemia at RSUP Dr. M Djamil Padang.
Result: A total of 27 children were included in this study. The median ferritin level of the samples was 3,465.00 (range 1,100-13,600) ng/ml. The median NT-Pro BNP level of the samples was 4.7767.00 (range 3.503-11.575). The results of the correlation analysis showed a significant positive correlation (p = 0.039) with a weak strength level (r = 0.399) between ferritin levels and NT-ProBNP levels.
Conclusion: There is a significant correlation between ferritin levels and NT-proBNP.

Keywords: Ferritin, NT-proBNP, Thalassaemia

INTRODUCTION

Thalassemia is a hereditary hemolytic anaemia caused by a genetic defect in the formation of globin chains due to a decrease or absence of synthesis of one or more globin chains that play a role in the formation of haemoglobin.[1,2] Thalassemia is classified into thalassemia α and β. Clinically, thalassemia is divided into thalassemia major (highly dependent on transfusion), thalassemia minor or career

(asymptomatic), and thalassemia intermedia.[3]

The diagnosis of thalassemia is established from clinical and laboratory examinations to identify the presence of impaired globin chain synthesis. The clinical picture of thalassemia patients is basically very varied, ranging from asymptomatic too dependent on blood transfusions. Regular blood transfusions and treatment with iron chelation have improved the survival of patients with thalassemia.. Patients with thalassemia β major are treated with continuous blood transfusions to keep hemoglobin levels close to normal and allow adequate tissue oxygenation. Repeated blood transfusions, coupled with extravascular hemolysis and increased intestinal iron absorption, will lead to significant hemosiderosis of all organs.[4]

The consequence of repeated transfusion therapy is secondary iron overload, which adversely affects the functioning of the heart, liver, and other organs, causes severe morbidity, and shortens life expectancy.[5] It also causes an increased risk of arthrosclerosis through an increase in free radical substances.[6] Excess iron produced due to repeated blood transfusions results in hemochromatosis in various organs, one of which is the heart. [7,8] Cardiac hemosiderosis (cardiomyopathy due to iron overload) can result in various other heart complications such as arrhythmias, pulmonary hypertension, high-output failure, pericarditis, myocarditis, and heart valve abnormalities such as mitral valve prolapse, mitral and aortic valve regurgitation, and aortic stenosis.[9] Hemochromatosis alone or in conjunction with immunogenetic factors is the main mechanism of heart failure and serious arrhythmia, which is the main cause of morbidity and mortality in thalassemia β major patients.[4] This complication results in the formation of thrombosis, which is the main cause of death in up to 63.6-71% of thalassemia patients.[10]

The gold standard for evaluating myocardial function, measuring myocardial volume, and detecting myocardial scars is cardiovascular magnetic resonance (CMR) using T2 MRI.[11] However, using CMR as a diagnostic tool is relatively expensive and rarely available, especially in developing countries, so other alternatives are needed to evaluate heart function.[12]

NT-proBNP is a hormone produced by the heart when atrial or ventricular dilatation or excess volume occurs. Brain natriuretic peptides (BNPs) are secreted from cardiomyocytes.[13] NT-proBNP is a cheaper, easier-to-reach, and non-invasive alternative method compared to CMR for detecting heart function. In addition, NT-proBNP can be easily used for monthly control. Research by Kurtoğlu et al., showed that the detection value of high NT-proBNP levels above the cut-off value in patients with normal T2 MRI values makes this a more sensitive marker in the early detection of heart failure.[12]

Patients with diastolic dysfunction were found to have high levels of NT-proBNP.[14,15] Study by Salem E. Deraz et al., on the heart function of thalassemia patients with echocardiography concluded that the initial phase of cardiac hemosiderosis is characterised by an increase in the final systolic volume and borderline ejection fraction, while dilative cardiomyopathy is found at an advanced stage.[16] In the initial phase, there is an increase in NT-proBNP before an increase in diastolic pressure, and there is a strong relationship between plasma levels of NT-proBNP and excess iron.[8] N-terminal pro B-type natriuretic peptide (NT-proBNP) is secreted by the ventricles of the heart in response to excessive strain of cardiomyocytes, increased ventricular or ischemic wall stress, and decreased blood pressure, which will decrease systemic vascular resistance.[17,18]

In thalassemia patients, NT-proBNP has a positive relationship with age, iron deposition expressed as iron and ferritin levels, left ventricular dimensions, ferritin, left ventricular diameter at the systolic end, and left ventricular diameter at the diastolic end.[7] Study by Deraz et al.,, showed that

there was an increase in serum NT-proBNP in patients with beta thalassemia major ($p < 0.001$). It was also found that there was a significant relationship between NT-proBNP and ferritin levels ($r = 0.545$, $p < 0.001$).[16] Given the possibility that heart damage may be caused by excess iron from the results of repeated blood transfusions, researchers aim to find the correlation of ferritin levels with NT-proBNP in thalassemia patients who experience heart damage at Dr. M. Djamil Padang Hospital.

MATERIALS & METHODS

This is a cross-sectional study that took place at Dr. M Djamil Hospital Padang. The population was thalassemia patients from October to December 2022. The inclusion criteria for this study were age ≤ 18 years old and routinely received repeated transfusions. Patients with a history of congenital heart disease, heart failure, hyperthyroidism, overt valvular disease, sepsis, or chronic kidney disease were excluded from this study. Blood samples were collected by laboratory staff from eligible patients who met the predetermined inclusion criteria and did not have any of the exclusion criteria. The NT-proBNP examination was conducted using the Enzyme-Linked Imunosorbent Assay (ELISA) method. Ferritin level and other data, including age, sex, transfusion frequency, age of receiving the first transfusion, and echocardiography findings, were extracted from the patient's medical records. Descriptive statistics were used to present the data, and the Shapiro-Wilk test was applied to assess normality. Correlation analysis was performed using the Spearman correlation test. All analysis was performed on Statistical Package for Social Sciences (SPSS) version 25.0 (SPSS Inc. Chicago, IL, USA). A p-value < 0.05 was considered statistically significant.

RESULT

Twenty-seven subjects were included in this study. This study showed that most subjects were >10 years old (18 subjects) and male (17 subjects). The ferritin level is mostly in the range of 2501-4000 (9 subjects). Most subjects received blood transfusions once every four weeks and have already received transfusions since <4 years old. Only 16 patients were having echocardiography examinations, and all of them had normal heart function. (Table 1)

Table 1. Characteristic Subject

Characteristic	(n=27)
Age (years)	
2-10	9
> 10	18
Sex	
Female	10
Male	17
Ka Feritin level (ng/ml)	
1000-2500	8
2501-4000	9
4001-5500	1
5501-7000	4
>7000	5
Frequency of transfusions	
Once every 2 weeks	9
Once every 3 weeks	7
Once every 4 weeks	10
Once every 5 weeks	1
Echocardiography Examination	
Yes	16
Normal heart functions	16
Abnormal heart functions	0
No.	11
Age of first transfusion	
< 4 years old	18
≥ 4 years old	9

The median ferritin level in this study was 3,465.00 ng/ml, with the lowest ferritin level at 1,100 ng/ml and the highest at 13,600 ng/ml, while the median NT-Pro_BNP levels in all paediatric patients with thalassemia were 4,767 pg/ml, with the lowest level being 3,503 pg/ml and the highest being 11,575 pg/ml.

The normality test of the two variables showed data on ferritin levels and NT-proBNP levels were not normally distributed (p-value<0.05), so correlation analysis was carried out using the Spearman test. The results of the Spearman test showed a significant positive correlation with the level of weak strength (r = 0.399) between ferritin levels and NT-ProBNP levels (p-value<0.05). (Figure. 1)

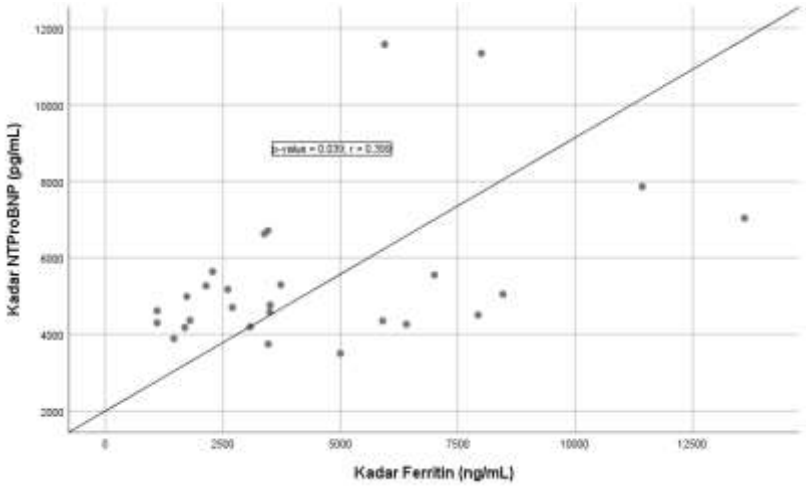

Figure 1. Correlation between Ferritin Level and NT-pro BNP in Thalassemia Patients

DISCUSSION

The number of male patients in this study was 17 (63%). The findings of this study are consistent with Deraz et al., as many as 58% of thalassemia children are male.[16] The study by Jamaluddin Kamil et al., also revealed that thalassemia was mostly found in men (59%). This study, however, contradicts several other studies in which women account for the majority of thalassemia patients. Thalassemia is an autosomal recessively inherited genetic disease from a single allele factor called chromosome 11p15.5. This disease can be suffered by anyone, regardless of gender, both male and female. The difference in results is likely due to differences in patient distribution. Thalassemia is not a genetic disease that is inherited through allele factors related to sex or sex chromosomes so there is no direct relationship between sex and the incidence of thalassemia.[19]

Patients with thalassemia will experience impaired synthesis characterized by the ineffectiveness of erythropoiesis formation, causing the need for lifelong transfusions that cause increased intestinal iron absorption, giving rise to the accumulation of ferritin levels. In this study, most patients had ferritin levels in the range of 2501-4000 ng/mL (33.3%). Normal median ferritin in children and adolescents (<18 years) ranges from 18.6 to 26.1 ng/mL, varying by age group.[20] This study showed that ferritin levels had been elevated in all patients. The results of this study are in line with the research of Permadi et al.,, which showed that there was a very significant increase in serum ferritin in beta thalassemia major patients of 2,818 ng / mL (2,505 – 3,977).[21] Similar results were also found in the study of Tubagus et al.,, which showed that the average ferritin level in beta thalassemia major patients in Surabaya was 5130 ng / ml.[22]

Ferritin began to increase significantly in the age group of 1-5 years who routinely received transfusions.[23] This increase is due

to the fact that the human body lacks the physiological mechanisms to remove excess iron produced from blood transfusions. In thalassemia patients, iron is transfused at 0.3 to 0.6 mg/kg per day, with an assumed monthly transfusion rate of 2 to 4 PRC units. Red blood cells that were previously transfused, when old, will be phagocytosed by reticuloendothelial macrophages. As a result, labile cellular iron will be released into the plasma to bind transferrin. After saturated transferrin binding, iron that is not transferrin bound will be transported through calcium channels to the liver (hepatocytes), heart (cardiac myocytes), and endocrine glands, resulting in iron accumulation. Thalassemia patients who have had transfusions for a long time will have more iron accumulation.[24]

In this study, most patients had transfusions at the age of <4 years (n = 18, 66.7%). This is in line with previous studies, where most subjects generally received their first transfusion before the age of 4 years (68.2%).[25] In this study, the age grouping of first transfusions was divided into <4 years and >4 years, which based on the average age of patients with thalassemia blood transfusions, which was 3.7 years. The age of the first transfusion is determined by the type of thalassemia suffered. The timing of the first-time transfusion can accurately reflect variations in the severity of thalassemia-β phenotypes. The results showed that HbF production variants and α-globulin gene defects had a major effect on the severity of thalassemia patients.[426] Patients with β-thalassemia intermediate may require only sporadic or no blood transfusions at all during the first two decades of life, although repeat transfusions may increase with age. Most first-time ages at diagnosis for intermediate-group patients and getting transfusions range from 2 to 8 years.

However, it is difficult to use "age at first transfusion" as a parameter in determining the severity of patients, as there is no uniformity in the provision of blood transfusions in Indonesia and it depends heavily on the clinical judgement and decision of individual medical professionals.[25]

Increased ferritin levels are strongly influenced by the frequency of blood transfusions. The grouping of transfusion frequency is based on research conducted by Amelia et al., which concluded that the frequency of transfusion will affect the high serum ferritin. Most of the patients in the study (37%) received transfusions once every four weeks. This result is supported by research by Madhu et al., which showed 55% of children with thalassemia receive transfusions once a month.[27] Another study by Irdawati also showed that the vast majority (16.53%) of children with thalassemia received transfusions once every four weeks.[28] Different research results were found by Shah et al., where the number of transfusions once every four weeks was most common in children aged 0–5 years, and with increasing age, the number of transfusions increased to once every two weeks.[29] In the era of transfusion therapy, iron overload in the myocardium was considered the leading cause of thalassemia cardiomyopathy. Although iron overload in patients with thalassemia also results from ineffective erythropoiesis, peripheral hemolysis, and increased intestinal iron absorption, the main cause is repeated blood transfusions. Iron toxicity has been linked to the production of free oxygen radicals, as a result of the Fenton and Haber-Weiss reactions, resulting in the emergence of free iron, which is the most toxic form of iron.[6]

In circulation, iron is usually transported by transferrin, so its toxicity is still limited. However, under conditions of iron overload, transferrin becomes fully saturated, and there is a certain amount of free iron, also called labile plasma iron, present in circulation and entering cardiomyocytes mainly through L-type Ca2+ channels in the form of Fe2+ (*ferrous iron*). Labile cellular iron is the form of iron most readily accessible to iron chelators in cardiomyocytes but is also the most toxic

form, inducing the formation of reactive oxygen, whereby labile cellular iron becomes a fenton-type reaction, causing the change of Fe2+ to Fe3+, resulting in free radicals, including highly reactive hydroxyl radicals. As a result, there is damage to lipids, proteins, and nucleic acids, which triggers cell damage and the depletion of antioxidants, resulting in cardiomyocyte apoptosis and myocardial fibrosis, which leads to heart dysfunction.[6] Therefore, it is important to monitor the function of the heart organ, either by examination of heart enzymes, an electrocardiogram, echocardiography, a 24-hour Holter monitor, or the standard modality used today, namely MRI T2*, in detecting iron overload accumulation in the preclinical heart.[26]

Based on the Indonesian Association of Haematology and Blood Transfusion (PHTDI), monitoring of heart organ function due to *iron overload* can be monitored every year, starting in children aged ≥ 10 years. However, study conducted by Rachmilewitz EA et al., stated that monitoring of heart function began at an earlier age, namely 7 or 8 years.[26] Monitoring of heart function in younger patients usually goes undetected, but earlier diagnosis of cardiomyopathy is essential because early intervention can slow disease progression. [30] One of the main modalities for monitoring cardiac function is echocardiography. As discussed earlier, in this study, most patients were in the age range of > 10 years, as many as 18 patients, but 2 patients refused to be examined for echocardiography, so only 16 patients (40.7%) had been examined for echocardiography in this study.

Echocardiography is the main modality used in monitoring left and right ventricular diastolic and systolic functions and can detect pericardial and valvular involvement in thalassemia cardiomyopathy. Based on the Thalassemia Clinical Practice Guidelines issued by the Medical Staff of Children's Health Sciences at M. Djamil Hospital, heart function examinations are recommended to be carried out annually in thalassemia patients aged ≥ 10 years. This examination should be done more strictly in patients with moderate to severe heart function disorders so that supervision is more optimal. Examination of left ventricular function is performed by assessing *the ejection fraction* (EF). The results of the left ventricular function examination can be subjectively classified into: normal function (EF ≥ 55%), mild dysfunction (EF 41–55%), moderate dysfunction (EF 31–40%), and severe dysfunction (EF ≤ 30%). EF scores in children range from 56% to 78%. Meanwhile, the assessment of right ventricular function is carried out using TAPSE (*Tricuspid Annular Plane Systolic Excursion*). TAPSE values of <10 mm in children and <16 mm in adults indicate decreased right ventricular function. [31,32] All patients in this study showed EF values of more than 55% and TAPSE values of >10 mm, indicating normal heart function.

In thalassemia major patients, there are two types of cardiomyopathies, namely dilated cardiomyopathy and restrictive cardiomyopathy. The early stage of cardiomyopathy in most thalassemia major patients is characterized by restrictive cardiomyopathy with diastolic dysfunction that will progress to dilated cardiomyopathy in the late stages. History of disease, physical examination, and supporting examinations should be part of the patient's initial evaluation and are part of the follow-up and regular cardiac screening of patients with thalassemia cardiomyopathy. Symptoms of heart failure found in thalassemia patients are the same as symptoms of heart failure in general. Dyspnea or fatigue is often reported to be a major complaint by patients. Other complaints, such as orthopnea, paroxysmal nocturnal dyspnea, decreased tolerance for activities, and swelling of the ankle, can also be found.[6] A physical examination is performed to assess signs of left or right heart failure. Physical examination results that can be found include tachycardia,

tachypneaeu, pulmonary rhonchi, pleural effusion, increased jugular venous pressure, peripheral edema, hepatomegaly, cardiomegaly, a third heart sound, a heart murmur, and so on. [11,12] Anamnesis and physical examinations performed on patients in the study so far have not shown symptoms or signs of diastolic dysfunction as an early stage of thalassemia cardiomyopathy. This has also been supported by echocardiography, which results in patients finding no left or right ventricular diastolic dysfunction.

The median NT-proBNP in pediatric patients with thalassemia based on the results of this study was 4,767.00 (3,503-11,575). This figure is higher than the study of Kautsar et al., which showed a significant increase in NT-proBNP in beta thalassemia major patients with a median of 133.65 (5-613.10) pg/ml.[8] Another study by Singh et al., also showed elevated serum NT-proBNP levels in beta thalassemia major patients with a median of 1,703 pg/mL (range 310-9,000 pg/mL).[33]

Natriuretic peptides are secreted in response to an increase in heart volume and an excess of pressure that occurs. This release results in better myocardial relaxation in response to myocardial stretching through vasoconstriction as well as sodium and water retention. Daniel et al.,'s research on the relationship of NT-proBNP in thalassemia patients β has shown that NT-proBNP is a sensitive biomarker for detecting systolic and latent diastolic dysfunction, while NT-proBNP is slightly more sensitive than BNP due to its longer half-life.[8] Cardiac myocytes are the main source that produces the prohormone BNP (proBNP). ProBNP is divided into NT-proBNP and BNP by the protease furin. The main regulatory mechanism in cardiac BNP production (NT-pro) is heart wall pressure. When chronic heart failure develops, there is an increase in heart wall pressure, resulting in stretching of the heart muscle. This stretching triggers the production of BNP, which will affect the physiology of the body in ways such as diuresis, vasodilation, inhibition of renin and aldosterone production, and triggering cell growth and myocyte vascularization.[34,35]

In thalassemia patients, BNP and NT-pro-BNP levels are associated with the diagnosis of heart failure and left ventricular dysfunction.[13] Kremastinos et al., showed that BNP and NT-proBNP levels were elevated in patients with beta thalassemia major and left ventricular diastolic dysfunction, whereas NT-proBNP proved to be a more sensitive biomarker in detecting asymptomatic left ventricular diastolic dysfunction. In addition, elevated levels of NT-proBNP may be an indication of the need for more aggressive chelation therapy.[36]

Study by Kremastinos et al., showed that the increase in NT pro-BNP in thalassemia patients was influenced by age, but this increase became significant for heart damage only when patients entered the third decade of age. This is because NT-proBNP is secreted in the early stages before cardiac diastolic disorders occur. The insignificant increase in younger age is likely also due to good chelation strategies by clinicians.[37] NT-proBNP was found to be elevated after the fourth year of receiving a blood transfusion. [26] Other factors that can affect BNP or NT-proBNP levels in patients with heart failure include body mass index (BMI), sex, or certain disease conditions such as anaemia, pulmonary embolism, pulmonary hypertension, kidney failure, and sepsis. Several different studies mention other factors that can cause differences in NT-proBNP levels, including recurrent acute respiratory tract infections (ARI), thyroid function, liver function, and electrolyte imbalance disorders. The frequent frequency of ARI is a risk factor for increased NT-proBNP levels. Infection in the body is a factor that affects NT-proBNP levels. A 1 g/dL decrease in haemoglobin levels can also increase NT-proBNP levels by 20%.[38]

The results of this study showed a significant correlation with the level of weak strength between ferritin levels and

NT-ProBNP levels in thalassemia patients at Dr. M. Djamil Padang Hospital (r = 0.399, p = 0.039). These results are in line with the research of Singh et al., which showed a significant correlation between serum NT-proBNP and ferritin levels in thalassemia patients (r = 0.306, p = 0.006).[17] Similar results were also found by Delaporta et al., which showed a significant low correlation between NT-proBNP levels and serum ferritin levels (r = 0.387, p <0.001).[4] Kostopoulou et al., also showed a correlation between elevated NT-proBNP levels and excess iron and ferritin in patients with beta thalassemia major.[13] Research by Deraz et al., found an increase in serum NT-proBNP in patients with beta thalassemia major with moderate correlation strength (r = 0.545, p < 0.001).[16]

One of the important organs affected by iron overload is the heart, especially in thalassemia patients. The main causes of cardiomyopathy in thalassemia patients are increased iron absorption in the intestine, hemolysis, and lifelong blood transfusions resulting in iron overload in the myocardium.[15] Serum ferritin has been shown to have a positive relationship with the number of blood transfusions in beta-thalassemia patients. In addition, it has been shown that serum ferritin levels of >1800 µg/L are associated with increased cardiac iron concentrations, and serum ferritin > 2500 µg/L is associated with an increased prevalence of cardiomyopathy events. Serum ferritin levels are widely used in the evaluation of the iron status of thalassemia patients but are not a reliable indicator for determining cardiac iron levels.[8] This is due to the fact that serum ferritin levels can also be elevated in other conditions such as inflammation, collagen disease, liver disease, and malignancy. In addition, low serum ferritin levels do not necessarily mean a low risk of iron-induced cardiomyopathy. Several studies in the last decade suggest that serum ferritin cannot be used as a predictive indicator of myocardial iron deposition due to a lack of association with iron overload in the heart.

Cardiomyopathy due to iron overload is characterised by early diastolic dysfunction that precedes systolic dysfunction. *Brain natriuretic peptide* (BNP) and amino-terminal pro-BNP (NT-proBNP) are released after increased heart pressure and volume overload. Elevated NT-proBNP is detected early in the course of the disease and appears to be a reliable indicator for early detection of cardiac hemosiderosis in beta thalassemia patients.[15] Study by Zoair et al., found that NT-proBNP can be used as a diagnostic biomarker for cardiomyopathy in children with with *a* cut-off value of 1500 pq/ml, sensitivity of 85% and specificity of 100% Research by Delaporta et al., showed a significant increase in NT-proBNP levels in cardiac hemosiderosis without signs of heart failure. Elevated serum ferritin levels may be the cause of chronic heart problems leading to diastolic dysfunction in beta thalassemia and NT-proBNP release.[17]

CONCLUSION

There was a significant positive correlation with weak strength levels between ferritin levels and NT-proBNP.

Declaration by Authors

Ethical Approval: Approved by Health Research Ethics Committee Dr. M Djamil Hospital (LB.02.02/5.7/381/2022)

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