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Correlation Serum Ferritin and Peroxidative Index with Pulmonary Function Pediatric Beta Thalassemia Major

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Abstract

Background: Beta thalassemia major is a genetic disorder that leads to abnormal hemoglobin production, requiring regular blood transfusions. A common complication is iron overload, which potentially damaging vital organs including the lungs. Oxidative stress due to iron overload is suspected to impair pulmonary function via lipid peroxidation. **Objective:** This study aims to analyze the correlation between serum ferritin levels and the peroxidative index with pulmonary function in pediatric patients with beta thalassemia major undergoing routine transfusions at RSUD Ulin Banjarmasin. **Methods:** This study was an analytical observational study with a cross-sectional approach involving children aged 6–18 years. Measured parameters included serum ferritin, peroxidative index (H_2O_2 to catalase ratio), and pulmonary function spirometry (FEV1/FVC ratio). **Result:** The Pulmonary dysfunction was identified in 68.85% of subjects, predominantly restrictive (65.57%). Mean ferritin level was 5,423.23±3,139.96 µg/L and mean peroxidative index was 46.42±66.38. There was no statistically significant correlation between serum ferritin (p = 0.239) or peroxidative index (p = 0.147) with pulmonary function. **Conclusion:** Although elevated ferritin and peroxidative index were observed, no significant association was found with pulmonary dysfunction. Monitoring these parameters may aid in early detection and management of pulmonary complications in thalassemia.

Keywords: Beta thalassemia major, Ferritin, Peroxidative index, Pulmonary function

Original Research Article

INTRODUCTION

Beta-thalassemia major is a form of hereditary hemolytic anemia caused by defect of production the beta-globin chain (Dewi et al., 2019). This condition is characterized by severe anemia that requires regular blood transfusions for survival (Vichinsky & Levine, 2012). In Indonesia, the prevalence of beta-thalassemia carriers remains high, ranging from 3% to 10%, contributing significantly to morbidity and mortality rates (Menteri Kesehatan Republik Indonesia, 2018). One of the primary factors associated with the increased morbidity and mortality is iron overload, resulting from ineffective erythropoiesis and repeated blood transfusions. This iron overload can lead to damage in several vital organs, including the lungs (Sposi, 2019).

A systematic review and meta-analysis found that 64.7% of patients with beta thalassemia major had some form of pulmonary dysfunction (Taksande et al. 2022). Study by Ahmed et al. (2021) reported that thalassemia patients may experience pulmonary dysfunction, predominantly restrictive pattern, which is associated with elevated serum ferritin levels. Chronic haemolysis in thalassemia can lead to oxidative stress and iron overload because it is a key driver of inflammation as erythrocyte destruction releases inflammatory mediators (Rabie et al., 2024).

Hemosiderosis (iron deposition in lung tissue) leads to oxidative stress, damaging alveolar structures. Reactive oxygen species (ROS) generated from labile iron cause lipid peroxidation, inflammation, and fibrosis (Eltagui et al., 2024; Basu et al., 2023). The underlying mechanism is presumed involving oxidative stress through the Fenton and Haber-Weiss reactions, which generate reactive oxygen species, particularly hydroxyl radicals, that leading to lipid peroxidation and cellular damage (Al-khyatt et al., 2024; Rabie et al., 2024).

Serum ferritin is commonly used as a practical and relatively inexpensive parameter for measuring iron overload (Wahidayat et al., 2018). Additionally, the peroxidative index—calculated based on hydrogen peroxide levels relative to catalase activity—can serve as an indicator of oxidative stress (Alfanie et al., 2019). Pulmonary function assessment can be measured with spirometry, the FEV_1/FVC ratio serving as a key indicator of pulmonary dysfunction patterns (Said et al., 2018). However, the mechanism of iron overload and oxidative stress contribute to pulmonary dysfunction due to long-term respiratory impairment in pediatric patients with beta-thalassemia major remains insufficiently understood. This study aims to analyze athe relationship between serum ferritin levels and the peroxidative index with pulmonary dysfunction and inform more monitoring and therapeutic strategies in children with beta-thalassemia major undergoing regular blood transfusions at Ulin General Hospital, Banjarmasin. Mention the urgency and importance of this study.

MATERIALS AND METHODS

This cross-sectional analytical study involved pediatric patients aged 6–18 years with confirmed beta thalassemia major from Hemoglobin (Hb) electrophoresis result which receiving regular blood transfusions and iron chelation therapy. Subjects were patients from RSUD Ulin Banjarmasin during the March–May 2024 period. The inclusion criteria were patients received iron chelation therapy and agreed to participate in the study by providing informed consent. Exclusion criteria included patients with known pulmonary or cardiac diseases. Ethical approval was granted by the Ethics Committee of RSUD.

The submission and approval of ethical approval by the ethics committee constitutes a critical step in this process, followed by the selection of an accessible population and the signed consent forms. Subsequently, patient characteristics are obtained, including age, gender, height, post-transfusion Hb levels, organomegaly, and type of iron chelation therapy and size of liver and spleen were obtained from medical records of participants. Subsequently, blood samples are collected for further analysis to determine ferritin levels, hydrogen peroxide levels, catalase activity, and peroxidative index. Lung function tests are performed using spirometry to obtain FEV1/FVC values for the classification of lung function. and data analysis.

Data collection included measurements of serum ferritin levels, H_2O_2 concentration, catalase activity, and pulmonary function assessed using spirometry (FEV_1/FVC ratio). Measurement of ferritin level using the automated immunoassay (CMIA) method. H_2O_2 levels were measured using a colorimetric assay, while catalase activity was assessed using the Aebi method. The peroxidative index was calculated based on the ratio of H_2O_2 level to catalase activity.

The sampling method applied was total population sampling. Descriptive data analysis was conducted using Microsoft Excel 2019. Normality and homogeneity tests were performed using the Kolmogorov–Smirnov test. Spearman correlation analysis was used to evaluate the relationship between the independent variables (serum ferritin level, H_2O_2 concentration, catalase activity, and peroxidative index) and the dependent variable (FEV_1/FVC ratio), as well as confounding variables (height and organomegaly). Data were analyzed using SPSS version 30.0.

RESULTS

A total of 61 pediatric patients with beta-thalassemia major were included in this study. The baseline characteristics of the participants are presented in Table 1.

Table 1. Baseline characteristics participants

Characteristics		Mean±SD	Total (%)
Gender	Male		30 (49.18)
	Female		31 (50.82)
Age		10.9±4.1	
	6 – 9 years		25 (40.98)
	10 – 12 years		14 (22.95)
	13 – 18 years		22 (36.07)
Height (cm)		130.61±18.20	
	Normal (≥P3)		28 (45.9)
	Short stature (<P3)		33 (54.1)
Iron chelating agent	Deferiprone	33	33 (54.09)
	Deferasiroks	28	28 (45.91)
Post transfusion Hb (g/dL)		14.68±1.04	
Hepatomegaly (cm)		1.67±0.49	
	Yes		35 (57.38)
	No		26 (42.62)
Splenomegaly (*Schuffner*)		1.87±0.5	
	Yes		53 (86.89)
	No		8 (13.11)
Pulmonary function	Normal		19 (31.15)
	Restrictive		40 (65.57)
	Obstructive		2 (3.28)

Pulmonary function, measured using the FEV_1/FVC ratio, showed that 65.57% of subjects had restrictive pattern of pulmonary dysfunction. Several factors may contribute to pulmonary impairment in patients with beta-thalassemia major, including serum ferritin levels, growth retardation, and hepatosplenomegaly. The mean serum ferritin level among participants was 5,423.23 ± 3,139.96 µg/mL, and the mean peroxidative index was 46.42 ± 66.38 (Table 2).

Table 2. Biochemical profile participants

Parameter	Mean±SD
Serum ferritin level (µg/l)	5,423.23±3,139.96
H_2O_2 level (µmol)	27.85±16.74
Catalase activity (U/L)	1.92±2.19
Peroxidative index	46.42±66.38

The patient population was divided into three categories based on their lung function: 19 patients had normal lung function, 40 had restrictive lung function, and 2 patients had obstructive lung function. The complete characteristics of the patients, as determined by the lung function test results (table 3).

Table 3. Comparison of clinical characteristics between participants with normal, restrictive, and obstructive pulmonary function

Parameter	Pulmonary function		
	Normal (n=19)	Restrictive (n=40)	Obstructive (n=2)
Gender, n (%)			
Male	9 (47.4)	19 (47.5)	2 (100)
Female	10 (52.6)	21 (52.5)	0 (0)
Age (years)	9.7±4.2	11.4±4.0	10.5±0.7
Height (cm)	127.5±19.9	132.15±17.8	129±2.8
H/A, n (%)			
Normal (≥P3)	12 (63.2)	15 (37.5)	1 (50.0)
Short stature (<P3)	7 (36.8)	25 (62.5)	1 (50.0)
Iron chelating agents, n (%)			
Deferiprone	8 (42.1)	24 (60,0)	1 (50.0)
Deferasirox	11 (57.9)	16 (40,0)	1 (50.0)
Hemoglobin post-transfusion (g/dL)	12.96±0.75	15.57±0.9	13.15±1.48
Serum ferritin level (µg/L)	5,154.10±2,811.74	5,338.15±3.239.96	9,681.46±1.388
H_2O_2 level (µmol)	23.09±16.32	26.64±16.33	30.32±25.51
Catalase activity (U/L)	1.43±1.67	2.19±2.41	1.09±0.99
Peroxidative index	53.37±52.98	42.15±72.4	65.91±83.53

Correlation analysis revealed no statistically significant relationship between serum ferritin levels and the FEV_1/FVC ratio (p = 0.239), nor between the peroxidative index and the FEV_1/FVC ratio (p = 0.147) (Table 4).

Table 4. Correlation between pulmonary function and biochemical profile of participants

Characteristics	Pulmonary function		Nilai *p*
	Normal (n=19)	Abnormal (n=42)	
Serum ferritin level (µg/l)	5,154.10	5,544.98	0.239
H_2O_2 level (µmol)	30.13	26.82	0.935
Catalase activity (U/L)	1.43	2.14	0.284
Peroxidative index	53.37	43.28	0.147

*statistical analysis using Spearman Correlation

Subject characteristics based on variables influencing pulmonary function are presented in Table 5.

Tabel 5. Correlation between pulmonary function and confounding variables

Characteristics	Pulmonary function		Nilai *p*
	Normal (n=19)	Abnormal (n=42)	
H/A, n (%)			
Normal (≥P3)	12 (63.2)	16 (38)	0.71
Short stature (<P3)	7 (36.8)	26 (62)	
Hepatomegaly, n (%)			
Yes	9 (47.4)	26 (62)	0.296
No	10 (52.6)	16 (38)	
Splenomegaly, n (%)			
Yes	14 (73.7)	37 (88)	0.41
No	5 (26.3)	5 (12)	

*statistical analysis using Spearman Correlation

DISCUSSION

This study involved 61 pediatric beta thalassemia major patients, with the majority aged 6–9 years. Females constituted 50.82% of the sample. This result accordance with research from Lee et al. (2022) in South Korea, showing higher incidence in females, although global data (GBD) and national studies (Sani et al., 2016; Dewi et al., 2019) do not show sex-based differences in prevalence.

Pulmonary function abnormalities were found in 68.85% of participants, predominantly restrictive (65.57%) and obstructive (3.28%). This aligns with the 64.7% global prevalence reported in a meta-analysis by Taksande et al. (2022). Our prevalence is higher than reported in Indonesian studies (Sani et al., 2016; Dewi et al., 2019), which found restrictive abnormalities in 35.5% and 46.4%, respectively. Sharma et al. (2024) showed among 54 children diagnosed with thalassemia which conducted pulmonary function test, 38.89% had restrictive, 12.96% obstructive, and 29.63% mixed dysfunction.

The mean serum ferritin level in our study was 5.423.23 ± 3.139.96 µg/L, similar to Indonesian studies in Denpasar (3.196.5 µg/L) and Bandung (7.151.88 ± 2.136.79 µg/L for restrictive cases; 3.450.34 ± 1,487.65 µg/L for normal lung function). This is higher than the study in Istanbul (Ersoy et al., 2023) with result 2.750 ± 1.842 µg/L, possibly due to different iron chelation protocols.

No significant correlation was found between ferritin levels or peroxidative index and lung function. Ersoy et al. (2023) reported a significant effect of ferritin on MEF_{25-75} but not FVC, FEV1, or PEF because those parameters more sensitive to measure hyperactivity, inflammatory level, and severity than FEV_1. Chan et al. (2023) found no ferritin difference between normal and restrictive groups. Similarly, Bhagyalakshmi et al. (2022) and Alyasin et al. (2011) found no correlation using only FEV_1 and FVC. Iron overload in the lungs might to functional consequences, including increased lung rigidity and decreased blood oxygen saturation (hypoxemia). However, the functional changes did not accompany by abnormalities in histopathology (Sposi, 2019).

Study Liang et al. (2024) showed children with impaired pulmonary function had higher serum ferritin levels but their study included diffusion impairment by result from diffusing capacity of the lung (DLCO) that not applied in the present study. A cross-sectional study in Indonesia by Dewi et al. (2019) with 28 children also found no correlation, possibly due to inadequate sample size. Liang et al. (2024) found that diffusion abnormalities contributed to 26.43% of cases. In thalassemia patients, pulmonary dysfunction more commonly associated with iron overload and the impact on lung tissue and other organs, may not directly by oxidative stress parameters that measured in the blood (Guidotti et al., 2017).

Ahmed et al. (2023) found no significant difference between FVC, FEV1, and FEV1/FVC among thalassemia and non-thalassemia group while forced expiratory (FEF) 25-75% and peak expiratory flor rate (PEFR) had significant difference in both groups. They conclude that the lung may be considered a site for organ damage. Study by Abd El Hakeem et al. (2018) showed severity of diffusion impairment in children with thalassemia was having serum ferritin level > 2,500 µg/L. Predicting factors for restrictive impairment such as age, longer duration of regular blood transfusion, shorter duration of chelation and serum ferritin level above the dangerous threshold (Abd Al Hakeem et al., 2018). But this study did not evaluate duration of blood transfusion and chelation agent use.

Until now, no studies have specifically assessed the relationship between H_2O_2, catalase activity, or peroxidative index and pulmonary function in thalassemia. These markers may not fully reflect pulmonary oxidative burden. Study by Tolba et al. (2015) found reduced catalase and glutathione reductase levels in thalassemia. A study on beta-thalassemia mice by Yatmark et al. (2015) showed lower catalase in iron-overloaded animals. Decrease of catalase activity may result from chronic level of oxidative stress itself, while an increase its activity could reflect a protective response by the body to eliminate reactive oxygen species (ROS) (Bou-Fakhredin et al., 2022).

In our study, H_2O_2 and catalase levels did not differ significantly between those with and without pulmonary dysfunction. The potential etiology may be multifactorial, Multifactorial lung damage: Pulmonary dysfunction may result from chronic anemia, thoracic deformities, splenomegaly, or repeated infections, not just iron overload. Ferritin is an indirect marker. It reflects total body iron, but it does not necessarily indicate tissue-specific iron deposition, especially in the lungs. Timing and

variability: Ferritin levels fluctuate with transfusions and inflammation; therefore, a single measurement may not capture chronic exposure. (Harsoor et al., 2020). External factors such as genetics, nutrition, pollution, and antioxidant intake may influence oxidative stress levels (Fibach & Dana, 2019). Das et al. (2004) showed vitamin E reduced lipid peroxidation in erythrocyte membranes. In this study did not including vitamin E or other antioxidant as variables that may influence oxidative stress level.

Growth retardation and organomegaly were also analyzed. About 54.1% of patients were short stature and 75.7% had restrictive lung dysfunction. The endocrine system seems particularly sensitive to iron deposition. Growth failure and hypogonadism are regarded among commonest endocrinopathies in thalassemia due to hemosiderosis (Almahmoud et al., 2024). Study by Almahmoud et al. (2024) showed 37.1% had reduced height velocity in one year and 40.3% had reduced height velocity in two consecutive years. However, no significant relationship was found between short stature and lung dysfunction ($p = 0.149$). Ersoy et al. (2023) found height affected MEF_{25-75}. Predicted lung volumes based on height may not always reflect true pulmonary capacity (Harsoor et al., 2020). Sani et al. (2014) found stunting protective (OR 0.13, CI 95% 0.03–0.51, $p = 0.004$), possibly due to growth deficits in bones other than the thoracic cage. Some studies analyzed sitting height to standing height ratio had associate with pulmonary function (Barroso et al., 2018).

Organomegaly may theoretically restrict diaphragm movement and reducing functional residual capacity. However, our study found no significant association between organomegaly and lung function. Sani et al. (2014) also found no such association. The novelty of our study was its comprehensive evaluation of oxidative stress, ferritin, and anthropometric factors in relation to lung function in thalassemia. Limitations include the absence of data on duration using iron chelation therapy, and lack of assessment of environmental and nutritional factors such as pollution, recurrent infections, antioxidant use, nutritional status, and transfusion-related allergies that maybe affect ferritin level and pulmonary function. Please add the health implication of this study.

CONCLUSION

There was no significant correlation between serum ferritin levels and peroxidative index with pulmonary function in pediatric beta thalassemia major patients. Despite this, elevated ferritin and oxidative stress levels were common, and spirometry abnormalities were prevalent. Monitoring these parameters may still have clinical utility for early risk identification and intervention.

CONFLICT OF INTEREST

The authors report there are no competing interest to declare.

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