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ASSOCIATION OF LEVEL SERUM FERRITIN AND LUNG FUNCTION IN PEDIATRIC WITH TRANSFUSION – DEPENDENT THALASSEMIA

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ABSTRACT
Pulmonary dysfunction in children with thalassemia can be restrictive, obstructive, or diffusion impairment. Elevated serum ferritin levels are a cause of pulmonary dysfunction in transfusion-dependent thalassemia patients. The aim of this study was to assess relationship between serum ferritin levels and pulmonary dysfunction in transfusion-dependent thalassemia patients. This cross-sectional study was conducted on 44 transfusion-dependent thalassemia children between May and June 2025 at the Thalassemia Clinic of Adam Malik Hospital, Medan. Demographic characteristics were obtained from interviews and medical records. Lung function was assessed using a spirometer. Associations were analyzed using Shapiro Wilk, Kruskal-Wallis test, and multinomial logistic regression test. A total of 17 children (38.6%) had normal lung function, while 27 children (61.3%) had impaired lung function. Restrictive impairment was present in 24 children (54.5%), and obstructive impairment in 3 children (6.8%). Analysis showed significant differences in serum ferritin levels and splenomegaly in relation to impaired lung function, with p-values of <0.001 and 0.013, respectively. Each 1 ng/mL increase in ferritin levels increased the likelihood of developing restrictive and obstructive pulmonary dysfunction by 0.2% (OR = 1.002; 95% CI: 1.001–1.003). However, gender, hepatomegaly, and duration of transfusion did not show significant differences.

Keywords: pulmonary dysfunction; serum ferritin levels; transfusion-dependent thalassemia

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INTRODUCTION

Thalassemia is a group of blood disorders characterized by a decrease or absence of the formation of one or more globin chains.1 Transfusion-dependent thalassemia is a type of thalassemia that requires regular transfusions to maintain normal hemoglobin levels and reduce the risk of short-term and long-term complications.(Sheth, 2024). Indonesia is one of the countries in the global thalassemia belt, i.e., countries with a high frequency of thalassemia trait carriers. This is evidenced by epidemiological studies in Indonesia, which found that the frequency of the beta thalassemia gene ranges from 3-10%.(Indonesia, 2018) According to a 2008 report from the World Health Organization (WHO), more than 40,000 babies are born with β-thalassemia each year, and approximately 25,500 of them suffer from transfusion-dependent β-thalassemia.(Kattamis et al., 2020).

The pathophysiological mechanism in thalassemia includes chronic anemia, ineffective erythropoiesis, and iron overload.(Sheth, 2024),(Sadiq et al., 2024) The accumulation of iron can occur through two mechanisms: when iron levels increase due to long-term routine transfusions, or when iron absorption through the gastrointestinal tract increases. Iron accumulation can be toxic to many body tissues, leading to complications in various organs such as heart failure, hepatic cirrhosis, hepatocellular carcinoma, growth retardation, pulmonary abnormalities, infections, and

endocrine disorders.(Farmakis et al., 2022) Ferritin merupakan tempat penyimpanan terbesar zat besi dalam tubuh. Increased iron accumulation in the lungs can contribute to a number of lung diseases by increasing oxidative stress, which can lead to tissue damage, inflammation, and changes in lung structure and function.(Neves et al., 2019),(Taher & Saliba, 2017)

Several studies have revealed a high prevalence of restrictive lung disease, ranging from 35% to 73.53%, in children and adults with β-thalassemia major.(Gadiparthi et al., 2019) Research conducted by Chan et al. in 2022 and supported by research by Factor et al. showed that up to 80% of patients with thalassemia reported lung function impairment.(Ozyoruk & Misirlioglu, 2015),(Machado & Gladwin, 2024) This was also supported by research conducted by Gadiparthi et al., which showed that 38% of transfusion-dependent thalassemia patients had restrictive impairment, while 5% had obstructive impairment. 8 Similar results were also shown in a study conducted in 2019, where 70% of thalassemia patients experienced diffusion disorders, while 34% of them had restrictive abnormalities.(Gadiparthi et al., 2019)

Lung function testing can be performed using spirometry. Spirometry testing includes assessment of static lung function and dynamic lung function.(Bakhtiar A & Tantri E, 2017) Research conducted by Abd El Hakeem et al. showed that all children with thalassemia were clinically asymptomatic, but 35 patients (70%) of them had abnormal lung function.(Abd El Hakeem et al., 2019) The need for lung function evaluation in pediatric TDT patients is crucial to reduce the impact of complications from repeated transfusions. Therefore, this study aims to examine the association between elevated serum ferritin levels, as an indicator of iron overload, and pulmonary function impairment in patients with transfusion-dependent thalassemia.

METHOD

The study was conducted using analytical observation with a cross-sectional design. Sampling was carried out in May–June 2025 using consecutive sampling until the required number of subjects was reached. The study subjects were children with major thalassemia aged 8–17 years who underwent routine transfusions at the Thalassemia Day Care Clinic of Adam Malik Hospital, Medan, and met the inclusion and exclusion criteria. Thalassemia patients with concomitant infectious and inflammatory diseases and a history of chronic lung disease were excluded from the study. This study was approved by the Ethics Committee of the University of North Sumatra with number 1372/KEPK/USU/2024 and the Ethics and Research Committee of Adam Malik Hospital with number DP.04.03/D.XXVIII.2.2.3/388/2025. Lung function tests [forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and FEV1/FVC ratio] by spirometer. Spirometry was repeated thrice and the best among three values was taken as final. The independent variable was serum ferritin levels, while the dependent variable was the results of pulmonary function tests, which included normal, restrictive, and obstructive.

The characteristics of the research subjects included age, gender, weight, height, organ enlargement, and iron chelators used. All subjects underwent a medical history review, physical examination, anthropometric measurements, serum ferritin level testing, and spirometry. Spirometry was performed using the Vitalongraph Alpha. All statistical procedures were conducted using the Statistical Package for Social Sciences (SPSS) Windows Version 30.0 (SPSS Inc., Chicago, IL, USA). Data were summarized as mean ± SD or numbers (percentages). The relationship between serum ferritin levels and pulmonary function impairment was assessed using the Kruskal-Wallis test. The relationship between gender, height based on age, splenomegaly, and hepatomegaly was assessed using the Mann-Whitney test. Multivariate analysis using multinomial logistic regression was performed to evaluate the effect of splenomegaly size and ferritin levels over the past 3 months on spirometry results, categorized as normal, restrictive, and obstructive. Significance was determined based on $p<0.05$.

RESULT

A total of 44 children with transfusion-dependent thalassemia were enrolled in this study, consisting of 22 males and 22 females. The subjects' ages ranged from 8 to 17 years, with an average age of 12 years. The results of the pulmonary function test showed that 17 children were classified as normal, while 27 exhibited pulmonary dysfunction. The general characteristics of the subjects based on the pulmonary function test results, including gender, age, body weight, height, hemoglobin levels, serum ferritin levels, hemoglobin levels, duration of transfusion, and type of pulmonary dysfunction, are presented in Table 1.

Tabel 1.
Characteristics of Children With Thalassemia Enrolled in the Study

Characteristics	(n=44)	%	Mean ± SD	Min-Max
Gender				
Male	22	50,0		
Female	22	50,0		
Age (years)			12,27 ± 2,57	8,00 - 17,00
Height (cm)			135,74 ± 13,71	107,00 - 161,00
Weight (cm)			32,59 ± 7,92	17,00 - 50,00
Height/Age				
Normal	23	52,3		
Short	21	47,7		
Hepatosplenomegaly	22	50%		
Splenomegaly				
Yes	40	90,9		
No	4	9,1		
Hepatomegaly				
Yes	22	50,0		
No	22	50,0		
Serum Ferritin Levels (ng/mL)			4.796,32 ± 3.016,70	1.362,00 - 16.425,00
Hemoglobin Levels (g/dL)			7,38 ± 0,95	3,50 - 8,80
Oxygen Saturation (%)			96,95 ± 1,26	95,00 - 99,00
Duration of Transfusion (month)			123,27 ± 4,70	60 – 180,00
Pulmonary Function Disorders				
Normal	17	38,6		
Restrictive	24	54,5		
Obstructive	3	6,8		

Tabel 2.
Correlation between pulmonary function test results and clinical data and laboratory results.

	Pulmonary Function Test			p value
	Normal	Restrictive	Obstructive	
Ferritin Levels (ng/mL)	1.362 – 4.351	2.654 – 16.425	4.506-9313	< 0,001
Gender (n = 44)				
Male	10 (45,5%)	12 (54,5%)	0 (0,0%)	0,971
Female	7 (31,8%)	12 (54,5%)	3 (13,6%)	
Height/Age (n = 44)				
Normal	8 (34,8%)	14 (60,9%)	1 (4,3%)	0,780
Short Stature	17 (36,6%)	24 (54,5%)	3 (6,8%)	
Splenomegal7 (n = 44)				
Yes	13 (32,5%	24 (60,0%)	3 (7,5%)	0,013
No	4 (100,0%)	0 (0 %)	0 (0 %)	
Hepatomegali (n = 44)				
Yes	6 (27,3%)	14 (63,6)	2 (9,1%)	0,123
No	11 (50,0%)	10 (45,5%)	1 (4,5 %)	
Duration of Transfusion (month)	84 -180	60-180	96 - 180	0, 503

Table 2, bivariate analysis was performed on several variables. The relationship between serum ferritin levels and duration of transfusion with pulmonary fungal infection was assessed using the Kruskal-Wallis test. The relationship between gender, height based on age, splenomegaly, and

hepatomegaly was assessed using the Mann-Whitney test because the Chi-square test requirements were not met. Clinical and laboratory variables of the study subjects based on variables influencing lung function are presented in Table 2. Statistical analysis indicated a significant association between serum ferritin levels ($p < 0.001$) and splenomegaly ($p = 0.013$) with pulmonary dysfunction.

Table 3, post- hoc testing using Mann-Whitney showed that there was a significant difference in ferritin levels between normal and restrictive lung function ($p < 0.001$) and between normal and obstructive lung function ($p = 0.007$). However, no significant difference was found between the restrictive and obstructive groups ($p = 0.938$). These results indicate that patients with impaired lung function, whether restrictive or obstructive, tend to have higher ferritin levels compared to patients with normal lung function (Table 3).

Tabel 3.
Relationship between serum ferritin levels and Pulmonary Dysfunction

		n	Serum Ferritin Levels (ng/mL)	p-value*
Pulmonary Function Test	Normal	17	2.671 (1.362 – 4.351)	<0,001
	Restrictive	24	5.467 (2.564 – 16.425)	
	Obstructive	3	4.524 (4.506 – 9.313)	

Kruskal Wallis test. Mann-Whitney post hoc test: Normal vs Restrictive p<0.001; Normal vs Obstructive p=0.007; Restrictive vs Obstructive p=0.938.

Multinomial logistic regression analysis was performed to assess the effect of serum ferritin levels and the presence of splenomegaly on lung function status in patients categorized into three groups: normal, restrictive, and obstructive. The results of the analysis showed that serum ferritin levels significantly influenced the risk of developing lung function impairment, both restrictive ($p = 0.003$) and obstructive ($p = 0.004$) types (Table 4).

Tabel 4.
Results of Multinomial Regression Analysis of Serum Ferritin Levels and Splenomegaly

Result of Spirometri		B	Std. Error	Wald	Df	Sig.	Exp(B)	Lower Bound	Upper Bound
Restrictive	Intercept	-22, 093	2903.543	.000	1	.994			
	Kadar Ferritin (ng/mL)	.002	.001	8.950	1	.003	1.002	1.001	1.003
	Splenomegaly (1)	15.296	2903.543	.000	1	.996	43950.649	.000	
	Splenomegaly (2)	0			0				
Obstructive	Intercept	-24.127	2.746	77.194	1	<.001			
	Kadar Ferritin (ng/mL)	.002	.001	8.082	1	.004	1.002	1.001	1.003
	Splenomegaly (1)	15.358	.000		1		4676293.916	4676293.916	
	Splenomegaly (2)	0			0				

An increase in ferritin levels of 1 ng/mL increases the likelihood of developing restrictive and obstructive lung function disorders by 0.2% (OR = 1.002; 95% CI: 1.001–1.003). For the splenomegaly variable, the odds ratio (OR) values were extremely high, at 4,392,950.649 for restrictive type and 4,672,693.916 for obstructive type.

DISCUSSION

The subjects included 44 children with a balanced gender distribution between males and females (50.0% each). The average age of the subjects was 12.27 ± 2.57 years, with an age range of 8 to 17 years. Median height was 135.74 ± 13.71 cm, and median weight was 32.59 ± 7.92 kg. Based on the height-to-age ratio, 52.3% of the subjects were classified as having normal height, while 47.7% experienced stunted growth (short). Other studies also showed the same comparison between boys and girls. Another study also showed that 52 out of 100 samples showed the highest number of males.(Chan et al., 2023a) There is no significant relationship between gender and height-for-age (H/A) and pulmonary dysfunction.(Bhalodiya et al., 2023). Bivariate statistical analysis of TB/U on

pulmonary function impairment showed insignificant results (p = 0.780). Males (n = 12) were more likely to have short stature than females (n = 10). The same findings were reported in a study by Dama, which showed that males had more growth disorders than females.(Dama & Dama, 2015) This study found that 21 subjects (47%) had growth disorders. These results are consistent with a previous study that performed logistic regression analysis on factors suspected to cause growth disorders, which also showed no association between TB/U and restrictive lung function disorders.(Bourli et al., 2012) The etiological factors causing growth disorders in transfusion-dependent thalassemia vary and may include endocrinopathies caused by iron overload, chronic anemia, and folate and zinc deficiencies involved in these complications. Close monitoring of growth can lead to early identification and treatment of these complications to ensure that patients achieve adult height that is close to normal.(Chandra, 2011)

Most subjects (90.9%, n=40) had splenomegaly, and 50% (n=22) had hepatosplenomegaly. Splenomegaly was also significantly associated with lung function patterns (p = 0.013), with most cases showing a restrictive pattern, while all patients without splenomegaly had normal lung function. Sheila et al., Abu Ekteish et al., and Carnelli et al. demonstrated that hepatosplenomegaly affects the diaphragm and reduces lung volume in thalassemia patients, thereby impairing lung functio.(S et al., 2022)·(Abu-Ekteish et al., 2007) Hepatosplenomegaly found in thalassemia patients can elevate the diaphragm and reduce lung volume. Hepatosplenomegaly can cause a restrictive lung pattern by reducing chest wall expansion, while increased vital capacity and expiratory reserve volume are observed in patients after splenectomy. Other studies indicate that hepatosplenomegaly has no effect on impaired lung function in transfusion-dependent thalassemia patients.(S et al., 2022)·(Liang et al., 2024) In chronic hematologic disorders, splenomegaly may reflect greater disease burden—due to extramedullary hematopoiesis, hemolysis, or iron accumulation—which could predispose patients to pulmonary complications (Chan et al., 2023). However, the extremely high odds ratios for splenomegaly, coupled with wide confidence intervals in multinomial regression, indicate possible quasi-complete separation. This statistical phenomenon, common in small samples when a predictor nearly perfectly classifies the outcome, warrants cautious interpretation.(Chan et al., 2023b)

Pulmonary function evaluation showed that the majority of study subjects had impaired pulmonary function. Of the 44 subjects, only 17 subjects (38.6%) had normal pulmonary function, while 27 subjects (61.3%) had impaired pulmonary function. Restrictive impairment was the most prevalent type, found in 24 subjects (54.5%), followed by obstructive impairment in 3 subjects (6.8%). The study results also revealed a significant difference in serum ferritin levels between the group with normal lung function and the group with impaired lung function. The restrictive impairment group had the highest ferritin levels (6,383.91 ± 3,061.43 ng/mL), followed by the obstructive group (6,114.33 ± 2,770.14 ng/mL), and the lowest in the normal group (3,245.67 ± 1,875.23 ng/mL). These differences were statistically significant with a p-value <0.001. Other studies have also shown that serum ferritin levels of 2500 ng/mL are a risk factor for the development of pulmonary dysfunction in transfusion-dependent thalassemia patients. While the pathophysiological mechanisms underlying these pulmonary abnormalities remain unclear, there is emerging evidence linking them to iron overload.(Liang et al., 2024)

Mechanistically, ferritin functions not only as an iron-storage protein but also as an acute-phase reactant, with elevated levels reflecting both increased body iron stores and systemic inflammation. In pulmonary diseases, excess iron can catalyze the formation of reactive oxygen species, promoting oxidative stress, inflammation, and tissue remodeling, all of which can contribute to lung function decline.(Cloonan et al., 2017). Genetic evidence also supports the potential causal role of iron status in lung function. A Mendelian randomization study by Yu et al. demonstrated that higher genetically predicted ferritin levels were associated with improved FVC and FEV_1, although no significant effect was observed on the FEV_1/FVC ratio. This apparent discrepancy between genetic

and observational studies may be explained by the confounding effects of inflammation in the latter, wherein elevated ferritin reflects an inflammatory response rather than purely iron status.(Yu et al., 2022).

This study has a prevalence of restrictive lung function disorders similar to several published studies. Guidotti et al. summarized literature data on lung function in patients with transfusion-dependent thalassemia. The study results were heterogeneous in terms of the observed patterns of lung abnormalities. However, restrictive lung function patterns have been generally reported in many studies with a prevalence ranging from 13.8 to 79%. A study conducted by Redha et al. also showed that 62.1% of TDT patients exhibited abnormal lung function results, with 35.1% having restrictive disorders and 27% having obstructive disorders.(Al Lawati et al., 2023) The exact pathophysiological mechanism is unknown, but iron accumulation in the lungs and chronic hypoxia associated with chronic anemia are believed to be important contributing factors to the development of pulmonary dysfunction in patients with transfusion-dependent thalassemia. Iron accumulation was detected in alveolar macrophages in thalassemia patients, supporting the hypothesis that increased systemic iron levels elevate pulmonary iron content.(Guidotti et al., 2017) ,(Neves et al., 2019).

This Iron overload, as indicated by increased ferritin levels, appears to be the cause of some thalassemia complications. In patients who receive blood transfusions well, poor compliance with chelation therapy and subsequent iron overload remain the main causes of poor growth.(Najafipour et al., 2008)It is well known that increased iron load can enhance oxidative tissue damage through the production of free radicals via at least two mechanisms. First, iron can act as a cofactor for superoxide dismutase, an enzyme required for the formation of hydrogen peroxide (H_2O_2) from superoxide radicals. Second, iron is known to increase the production of hydroxyl radicals (OH) from H_2O_2.(Cycle et al., 2004) ,(Kanj et al., 2000) Increased iron accumulation in the lungs can lead to a number of lung diseases by increasing oxidative stress, which can result in tissue damage, inflammation, and changes in lung structure and function and/or mitochondrial dysfunction.(Ali et al., 2017). This study has strengths and limitations. The strength of this study is that it is the first study in North Sumatra, specifically at Adam Malik Hospital in Medan, to link serum ferritin levels with pulmonary dysfunction in a group of pediatric thalassemia patients. Further prospective cohort studies are needed to assess pulmonary dysfunction in children with repeated transfusions. A multicenter study is also needed to assess risk factors and confounders associated with impaired lung function in transfusion-dependent thalassemia patients.

CONCLUSION

In this cohort of transfusion-dependent thalassemia children, impaired lung function was strikingly prevalent, with restrictive patterns predominating. Elevated serum ferritin levels and splenomegaly emerged as significant predictors of both restrictive and obstructive ventilatory impairments. Multinomial regression revealed that each 1 ng/mL rise in serum ferritin increased the odds of restrictive or obstructive dysfunction by 0.2% (OR = 1.002; 95% CI: 1.001–1.003). Splenomegaly was strongly associated with impaired pulmonary function, potentially via mechanical limitation of diaphragmatic excursion and lung volume. However, interpretation warrants caution given the limited sample size and possible quasi-complete separation in the data. Other clinical parameters including sex, height-for-age, hepatomegaly, and transfusion duration showed no significant association with lung function status. These findings underscore the multifactorial etiology of respiratory impairment in this population, driven by iron-mediated oxidative injury, chronic inflammation, and structural chest wall constraints. Early and routine respiratory assessment, rigorous iron chelation, and proactive management of splenomegaly are imperative to safeguard pulmonary function in transfusion-dependent patients. Longitudinal and mechanistic investigations are essential to clarify the causal pathways linking iron overload and splenomegaly to specific

patterns of lung decline, and to determine whether targeted interventions can attenuate long-term respiratory morbidity in this high-risk group

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