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CORRELATION BETWEEN SHORT STATURE WITH SERUM FERRITIN LEVELS IN MAJOR BETA-THALASSEMIA PATIENTS AT KEDIRI DISTRICT GENERAL HOSPITAL

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KEYWORDS
beta thalassemia, ferritin levels, short stature.

ABSTRACT
In thalassemia, a lifelong sequence of blood transfusions leads to iron overload characterized by increased ferritin levels. Many factors, including iron overload may cause growth delay. High ferritin levels are believed to lead to short stature in children with thalassemia. This study aims to determine the correlation between short stature and ferritin levels in children with major beta thalassemia at Kediri District General Hospital. This research is an observational analytic with a cross-sectional design conducted on 17 subjects of beta thalassemia major patients at Pediatric Health Sciences (IKA) Kediri District General Hospital who met the inclusion and exclusion criteria in December 2022-January 2023. The measuring instrument used in this study was anthropometric status, explained through age stature, while the ferritin levels was obtained from the patient's medical record. Spearman's rank order correlation test was used in the analysis. There were 17 respondents, 82,36% children in short categories and 17,64% in normal categories. The Spearman correlation test has the p-value = 0.000 and r = -0,736. A strong negative correlation exists between short stature and ferritin levels in beta-thalassemia major patients at Kediri District General Hospital that means the higher ferritin levels, the higher incidence rate of short stature.

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INTRODUCTION

Thalassemia is a blood disorder that occurs in the synthesis of hemoglobin inherited in an autosomal recessive manner which causes red blood cells to be damaged and brittle easily. Thalassemia is divided into α thalassemia if there is an abnormality in the synthesis of the alpha-globin chain and thalassemia if there is an abnormal synthesis in the beta-globin chain. Beta thalassemia inherited from both thalassemia carrier parents and shows the most severe clinical symptoms is called thalassemia major. Thalassemia major is a chronic disease still a big problem because it can interfere with growth and development (Wahidiyat, 2016) (Permono & Ugrasena, 2006).

The prevalence of thalassemia carriers in Indonesia reaches 3-8%, which means that 3-8 out of 100 people are thalassemia carriers (Ministry of Health of the Republic of Indonesia, 2022). The number of cases of thalassemia major in Indonesia has increased from 2012 to 2018. In 2012 there were 4,896 cases of thalassemia, and in 2018 there were 8,761 cases (Indonesia, 2022).

β thalassemia major require regular blood transfusions throughout their lives to maintain hemoglobin levels above 9-10.5 g/dL to suppress ineffective erythropoiesis activity in the bone marrow and prevent growth disorders. However, repeated blood transfusions can result in iron overload due to the continuous accumulation of iron. In contrast, the body's ability to excrete iron is minimal. In

addition, the iron overload experienced by beta thalassemia primary patients is also caused by increased iron absorption in the gastrointestinal tract due to ineffective erythropoiesis. Excess iron accumulation is toxic to tissues and can cause heart failure, cirrhosis, growth disorders, and endocrine disorders. (Viprakasit et al., 2014) . Problems in the endocrine glands and anemia can interfere with children's growth, causing growth disorders such as short stature (Mariani, 2011).

Ferritin is the main iron storage protein (Torti & Torti, 2002). Serum ferritin examination is one of the tests that is often performed to measure the number of iron storage in thalassemia patients undergoing transfusion therapy. Ferritin levels in patients with β thalassemia major receiving repeated blood transfusion therapy and iron chelation therapy are expected to be less than 1500 ng/dl (Angulo et al., 2008).

In Indonesia, there have been few studies regarding the relationship between short stature with ferritin levels in patients with thalassemia beta major. Serum ferritin considered to be representative iron overload and hemosiderosis. Early detection of endocrine complications that in this study is short stature needed to improve their quality of life (Evi, 2021). In thalassemic patients a common finding is elevated ferritin levels and some studies have shown a relationship between survival and endocrine problems in thalassemic patients using serum ferritin as a prognostic marker. (Adil, 2012). This study aimed to determine the relationship between short stature with ferritin levels in patients with thalassemia beta major at Kediri District General Hospital.

METHODS

This type of research is observational analytic with a cross-sectional design. The research was conducted at the SMF Pediatrics (IKA) Kediri District General Hospital in December 2022-January 2023. 17 patients with major beta thalassemia admitted. The sample was taken using a purposive sampling method based on inclusion criteria, namely pediatric patients aged 1- 18 years old that diagnosed with β-thalassemia major, had blood transfusions ≥ 10 times at SMF IKA RSUD Kediri Regency, and their parents gave their consent to participate in the study. The exclusion criteria were patients with fever characterized by an increase in temperature ≥ 380 C, acute infection, inflammation chronic disease, splenectomy, and malignancy based on medical records and physical examination.

The instrument for collecting data in this study was measuring the height using a tape measure and the patient's age. Meanwhile, the patient's serum ferritin level data were taken from secondary data from medical records. Data analysis to determine the correlation between the two variables using the Spearman correlation test with a significance value of $p < 0.05$. 1 The software used is the statistical processing computer program Statistical Package for Social Science (SPSS) 26.0.

RESULTS AND DISCUSSION

There were 17 samples of beta thalassemia primary patients met the inclusion and exclusion criteria. The general characteristics of β thalassemia significant patients at Kediri District Hospital are shown in Table 1.

Table 1. General Characteristics of Beta Primary Thalassemia Patients at Kediri District Hospital

Sample Characteristics	Amount (n)	Percentage (%)
Gender		
Man	7	41.18%
Woman	10	58.82%
Age		
<5 years	2	11.77%

Sample Characteristics	Amount (n)	Percentage (%)
5 - <10 years	4	23.54%
10 - < 15 years	3	17.64%
15 - < 18 years	8	47.05%
Abdomen Examination		
Splenomegaly	5	41.18%
Hepatosplenomegaly	12	58.82%
Classification Therapy		
Deferiprone	10	58.82%
Deferasirox	7	41.18%

Based on the study's results measuring height for age using the z score and serum ferritin levels as shown in Table 2. The results of the Spearman correlation test between the level of adherence to iron chelation treatment and ferritin levels are shown in Table 3.

Table 2. Height-for-Age Values with Ferritin Levels

Characteristics Sample	Amount(n)	Percentage(%)
Stature For Age		
Normal	3	17.64%
Stunted	14	82.36%
Ferritin Levels		
<1000ng/mL	2	11.76%
1000-2000ng/mL	2	11.76%
>2000ng/mL	13	76.48%

The relationship between short stature and serum ferritin levels has a p-value of 0.000 < α 0.05 and an r-value of -0.736, so it can be concluded that short stature growth and serum ferritin levels have a significant and strong correlation.

Table 3. Spearman Correlation Test Results Between Short Stature and Ferritin Levels

	Serum Ferritin Levels
Short stature	R-0.736
	0.000
	N 17

Characteristics of the sample based on the data obtained showed that the number of female samples was more than males. Namely, ten samples (66.7%) were female, and seven (33.3%) were male. According to Mendel's law, thalassemia is passed from parent to child in an autosomal recessive manner. The pattern of autosomal recessive inheritance is a horizontal line so that there are many sufferers in one generation, but not for every generation. Patients with β thalassemia major have a 25% chance that both parents are carriers (Hoffbrand & PAH, 2013). The characteristics of the sample based on age obtained the highest number of samples aged 15-<18 years with eight samples (47.05%). Patients with β thalassemia major usually appear normal at birth; symptoms will be found in children aged 2 to 6 years (Cappellini et al., 2014).

β thalassemia significant patients with splenomegaly without hepatomegaly in 5 samples (29.41%) and hepatosplenomegaly in 12 samples (70.59%). Splenomegaly occurs due to extramedullary erythropoiesis (Andriastuti et al., 2016). Severe anemia in patients with β thalassemia major causes the kidneys to release erythropoietin, a hormone that stimulates the bone marrow to produce more red blood cells resulting in ineffective erythropoiesis—increased erythropoiesis results in bone marrow hyperplasia and expansion, resulting in bone deformities. Erythropoietin also stimulates

the extramedullary hematopoiesis tissue in the liver and spleen resulting in hepatosplenomegaly (Potts & Mandleco, 2012). Based on the data obtained, ten samples (58.82%) received Deferiprone iron chelation therapy. And seven samples (41.18%) received Deferasirox therapy. Deferiprone is effective in chelating iron in the heart compared to the parenteral injection of deferoxamine (Pepe et al., 2011). Deferasirox effectively chelates iron in the liver compared to the parenteral use of Deferoxamine (Neufeld, 2006). Iron chelation therapy is urgently needed in patients with β thalassemia major with repeated blood transfusions (Permono & Ugrasena, 2006). Iron chelation should be started when ferritin levels rise above 1000 ng/mL or the patient has received 10–20 units of PRC (Pepe et al., 2011).

From this study, the results of research subjects with stunted were 14 samples (82.36%), and the normal height was three (17.64%). Most of the major beta thalassemia patients in this study had short stature. This is following research at dr. Moewardi Surakarta, out of 30 samples of thalassemia patients, 22 samples (73.33%) were stunted according to the stature for age. Eight samples (26.67%) were normal (Alifprilia, 2018). As a result of impaired synthesis and secretion of these hormones will cause disturbances in the growth and metabolism of patients with β thalassemia major. The growth of people with thalassemia will be relatively normal until 9 to 10 years. Iron buildup can interfere with osteoid maturation and precipitate into hydroxyapatite crystals, disrupting normal bone metabolism (Moiz et al., 2018). In addition, malnutrition in thalassemia patients is caused by ineffective erythropoiesis; the rapid turnover of erythrocytes also increases the need (Ayukarningsih et al., 2022). The growth of patients with major beta-thalassemia for 4-5 years when receiving regular transfusions will experience normal growth in both body weight and height. Growth disturbances in patients with beta-thalassemia, prominent in children under ten, are associated with hyperactivity of the bone marrow, a few or no transfusions, and patients experiencing hypersplenism (Bulan, 2009).

This study found that he lowest ferritin level was 725.2 ng/mL, and the highest was 2986.7 ng/mL. Research subjects who had ferritin levels <1000 ng/mL in 2 samples (11.76%), 1000-1000 ng/ml in 2 samples (11.76%), and > 2000 ng/mL in 13 samples (76.48%). Average ferritin values range from 20-200 ng/ml (Nuari et al., 2016). The ferritin levels of the study subjects were far above the normal range. Iron overload occurs if the ferritin level exceeds the average value (Organization, 2017). High levels ferritin have been strongly correlated with growth disorders, endocrine disorders or other complications (Monaliza, 2018). So the research subject have excess iron. Iron overload in patients with β thalassemia major is caused by repeated blood transfusions, ineffective erythropoiesis, and increased iron absorption through digestion. In contrast, the body's ability to excrete iron is minimal (Cappellini et al., 2014).

The results of data analysis using the Spearman correlation test between short stature and ferritin levels in patients with thalassemia beta major at Kediri District General Hospital obtained a p-value of 0.000 and an r-value of -0.736. This shows that there is a significant result between short stature and serum ferritin levels in patients with major beta thalassemia and has a strong correlation. This follows previous research, which stated a significant correlation between ferritin levels and the incidence of short stature in India (Rathaur et al., 2020). Other studies have also shown similar results. Multivariate analysis to test variables showed that serum ferritin levels affected the incidence of short stature in thalassemia children. This study also showed that age affected the incidence of short stature apart from ferritin levels. (Fadlyana et al., 2017). Some studies show that short stature will occur when serum ferritin levels are > 3000 ng/L. High serum ferritin levels will cause growth disorders (Shalitin et al., 2005). Our study found a relationship between serum ferritin levels and the incidence of short stature caused by excess iron in the endocrine glands, which interferes with growth hormones. (Fadlyana et al., 2017).

CONCLUSION

Based on the results of the research that has been done, it can be concluded that there is a significant relationship between short stature and serum ferritin levels with a p-value of 0.000 and a strong correlation (r=-0.736) in Major beta-thalassemia patients at Kediri District Hospital.

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