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Research Article

Correlation between serum ferritin levels and follicle-stimulating hormone (FSH) in patients with beta-thalassemia major at Universitas Airlangga Hospital

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ABSTRACT

Patients with beta-thalassemia major require repeated blood transfusions. Repeated blood transfusions and increased gastrointestinal iron intake can lead to iron overload in various organs, including the pituitary gland. Iron accumulation in the pituitary gland can damage gonadotroph cells and interfere with follicle-stimulating hormone (FSH) secretion, leading to hypogonadism. This study analyzes the correlation between serum ferritin and FSH in patients with beta-thalassemia major. A cross-sectional study was conducted, enrolling adult patients (≥18 years) with beta-thalassemia major undergoing transfusions at Airlangga University Hospital's Medical Hematology-Oncology Clinic. The analysis was performed using Spearman's Rho correlation test. Out of 51 patients, 29 were female (56.9%) and 22 were male (43.1%), with a median age of 25 years. The mean serum ferritin level was 937.17 ± 210.61 µg/L, and the majority (64.7%) had serum ferritin levels <1000 µg/L. The median FSH level was 14.15 IU/L. 68.18% of male patients had FSH levels above the normal range, whereas 89.65% of female patients remained within the normal range. Spearman's Rho analysis demonstrated no correlation between serum ferritin and FSH ($r = 0.239$; $p = 0.092$; 95% CI). In conclusion, this study found no statistically significant correlation between serum ferritin and FSH in patients with beta-thalassemia major.

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INTRODUCTION

Thalassemia is still one of the global health burdens with about 1.31 million cases in 2021 (Tuo et al., 2024). Thalassemia is a genetic disorder of the globin chain that has a prevalence of 3-10% in Indonesia (Taher et al., 2018; Rujito, 2019). Patients diagnosed with beta thalassemia major require lifelong blood transfusions as a symptomatic therapeutic intervention (Kemenkes, 2018). However, repeated transfusions can lead to iron overload because the human body lacks a natural mechanism for excreting excess iron (Nienhuis et al., 2012; de Jongh et al., 2017; Porter et al., 2021).

Iron overload has been shown to cause damage to various organs, including the liver, heart, and endocrine glands (Shah et al., 2019; Rasel et al., 2024). Hypogonadism is one of the endocrine complications observed in patients with beta thalassemia major, with a global prevalence ranging from 20% to 77.5%, and secondary hypogonadism is the predominant form (Srisukh et al., 2016; Carsote et al., 2022; Venou et al., 2023). This condition arises from iron accumulation in the pituitary gland, particularly in gonadotroph cells, which are vulnerable to iron-induced cytotoxicity (Venou et al., 2023). Damage to these cells has been shown to disrupt the hypothalamic-pituitary-gonadal (HPG) axis, thereby inhibiting follicle-stimulating hormone (FSH) secretion. FSH is a hormone that plays a critical role in the human reproductive process (Sanctis et al., 2012; Jouda et al., 2018; Venou et al., 2023).

Serum ferritin level is a frequently used diagnostic parameter for monitoring body iron status due to its practicality (Plays et al., 2021). Despite extensive research on the relationship between iron overload and pituitary dysfunction, the correlation between serum ferritin and FSH levels has shown variability: some studies report a negative correlation, whereas others find no significant association. In Indonesia, research evaluating these hormonal parameters specifically in adult patients with thalassemia remains relatively limited. The objective of this study is to examine the relationship between serum ferritin levels and FSH levels in patients with beta thalassemia major at Airlangga University Hospital.

METHODS

This was an observational analytic study with a cross-sectional design, conducted at the Medical Hematology-Oncology Clinic of Airlangga University Hospital from January to December 2025. Samples were selected using consecutive and total sampling from the population of thalassemia patients at the research site that met the inclusion criteria (1) a diagnosis of beta thalassemia major; (2) age over 18 years; and (3) regular blood transfusions since diagnosis. Patients with inflammation were excluded from this study. The data was collected from medical records and laboratory test results. Blood samples were collected for laboratory testing from patients after written informed consent was obtained. Serum ferritin and FSH are measured using ELISA.

The analysis was conducted using IBM SPSS Statistics version 27 software. Demographic characteristics and clinical data were presented as means, standard deviations, medians, or percentages. Data normality was assessed using the Kolmogorov-Smirnov test. Spearman's Rho correlation test was used to assess the correlation between serum ferritin and FSH levels. The statistical significance level was set at $p < 0.05$. The research protocol has been approved by the Airlangga University Hospital Health Research Ethics Committee (certificate number 110/KEP/2023).

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RESULTS

Table 1 shows the demographic characteristics of 51 patients with beta thalassemia major who enrolled in this study. Out of 51 patients, 29 were female (56.9%) and 22 were male (43.1%). The median age of the subjects was 25 years, with a range from 19 to 48 years. The majority of patients had a normal BMI.

Table 2 shows the blood test results of all patients. Blood test results showed that the patients had microcytic hypochromic anemia, with a mean Hb of 9.19 ± 1.98 g/dL, a mean MCV of 72.04 ± 6.86 fL, and a mean MCH of 23.91 ± 2.87 pg.

According to Table 3, all patients had serum ferritin levels above the normal range (70–200 µg/L). The mean serum ferritin level was 937.17 ± 210.61 µg/L. The majority of patients (64.7%) had serum ferritin levels < 1000 µg/L. The median FSH level for all patients was 14.15 IU/L with a range of 0.30–61.16 IU/L. The distribution of FSH levels exhibited disparities between genders. The majority of male patients (68.18%) had FSH levels above the normal range (>12.4 IU/L), whereas most female patients (89.65%) had FSH levels within the normal range (4.7–21.5 IU/L).

Table 1. Demographic Characteristics

Characteristics	N (%)	Value	
		Mean ± SD	Median (Min-Max)
Gender			
Male	22 (43.1%)		
Female	29 (56.9%)		
Age (years)			25 (19-48)
Age at time of initial diagnosis (years)			7 (1-37)
Time since diagnosis (years)		16.81 ± 7.16	
Body Mass Index (kg/m^2)		19.26 ± 2.24	
Underweight	20 (39.2%)		
Normal	28 (54.9%)		
Overweight	2 (3.9%)		
Obese	1 (2%)		

Table 2. Blood Test Result

Parameter	Value	
	Mean ± SD	Median (Min – Max)
RBC (10^6/µL)		3.59 (2.46 – 5.41)
HGB (g/dL)	9.19 ± 1.98	
HCT (%)	27.72 ± 5.58	
MCV (fL)	72.04 ± 6.86	
MCH (pg)	23.91 ± 2.870	
MCHC (g/dL)		33.3 (28.7 – 35.0)
WBC (10^3/µL)		6.62 (2.53 – 41.67)
Trombosit (10^3/µL)		170 (26 – 1351)

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Table 3. Serum Ferritin Level and FSH Level Result

Parameters	N (%)	Value	Min – Max
Serum Ferritin (µg/L) (mean ± SD)		937.17 ± 210.61	488.9 – 1374.2
<1000	33 (64.7%)		
≥1000	18 (35.3%)		
FSH (IU/L) (median)		14.15	0.30 – 61.16
Male			
<1.5 IU/L	0		
1.5–12.4 IU/L	7 (31.82%)		
>12.4 IU/L	15 (68.18%)		
Female			
<4.7 IU/L	1 (3.45%)		
4.7-21.5 IU/L	26 (89.65%)		
>21.5 IU/L	2 (6.9%)		

Based on the Spearman's Rho test results in Table 4, there is no statistically significant correlation between serum ferritin and FSH levels among patients with beta-thalassemia major in this study, according to the 95% CI.

Table 4. Correlation Test Result

	FSH	
	Correlation Coefficient (r)	**p-value**
Serum Ferritin	0.239	0.092

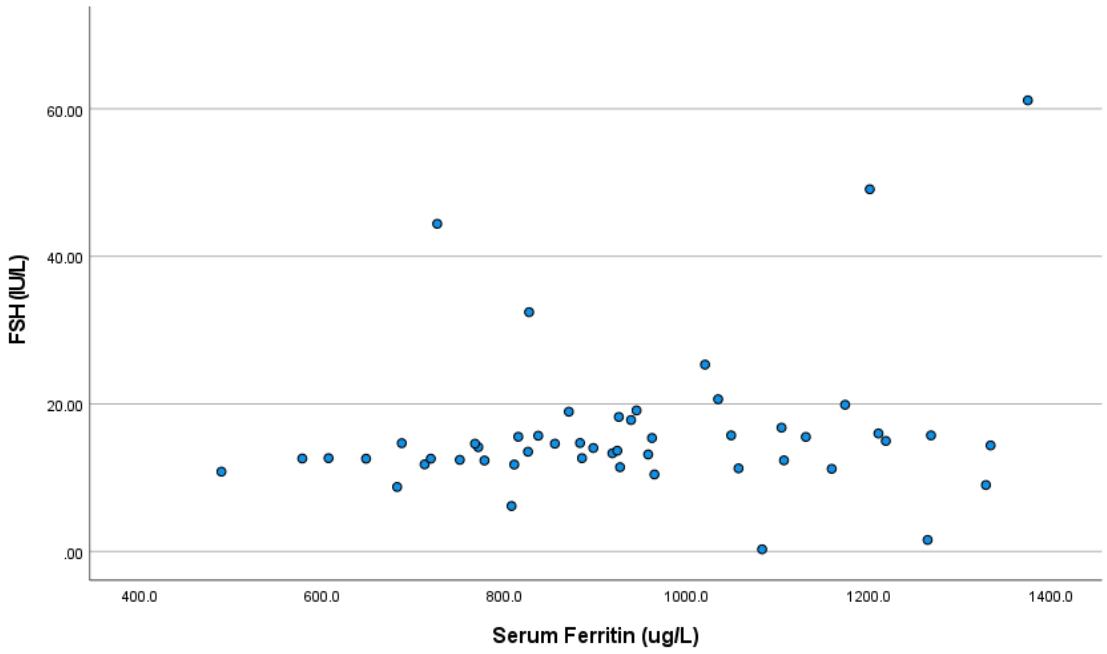

Figure 1. Scatter Plot Diagram

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Based on the Spearman's Rho test results in Table 4, there is no statistically significant correlation between serum ferritin and FSH levels among patients with beta-thalassemia major in this study, according to the 95% CI.

DISCUSSION

Thalassemia is an autosomal recessive genetic disorder, meaning that the probability of its occurrence is equal in males and females (Sadiq et al., 2024; Gulani & Weiler, 2023). The present study included a higher proportion of female patients; however, other studies have reported the opposite pattern, with a greater proportion of male subjects (Islam et al., 2025; Sari et al., 2023). The majority of patients in this study had a normal BMI (54.9%). Lidoriki et al. (2020) and Saefudin et al. (2024) reported similar results, while Shah et al. (2021) and Cahyanur et al. (2025) reported that the majority of their patients were underweight. The prevalence of malnutrition varies significantly across countries, ranging from 5.2% to 74.5%, and it occurs primarily among children and adolescents (Soliman et al., 2023). The factors contributing to low BMI in patients with thalassemia are numerous, including macro- and micronutrient deficiencies, chronic anemia and hypoxia, organ damage due to iron overload, inadequate iron chelation therapy, and endocrine system disorders (Soliman et al., 2023).

Mutations in the hemoglobin gene disrupt globin chain production, leading to ineffective erythropoiesis and increased hemolysis (Hoffman et al., 2017; Sadiq et al., 2024). This results in low hemoglobin levels in patients with beta thalassemia major, as observed in this and prior studies (Elsaikh & Elfatih, 2020; Sadiq et al., 2024). Furthermore, impaired globin synthesis results in microcytic and hypochromic erythrocytes, characterized by low MCV and MCH values (Hoffman et al., 2017; Brihi & Pathak, 2024).

Serum ferritin levels were elevated in all patients in this study. Repeated blood transfusions and increased iron absorption via the gastrointestinal system resulted in increasing body iron levels and elevated serum ferritin levels (Taher et al., 2017; Hussein et al., 2022). This finding is consistent with the other studies (Ibrahim et al., 2023; Ahmad et al., 2025). The majority of patients had serum ferritin levels below 1000 µg/L, consistent with findings reported by Spasiano et al. (2021). Bhatti et al. (2025) also reported mean serum ferritin levels similar to those in this study, with results relatively lower than in several other studies. This finding is likely associated with the compliance of iron chelation therapy. Several studies have demonstrated the benefit of iron chelation therapy in reducing serum ferritin levels (Meabed et al., 2022; Permatasari et al., 2023; Choudhury et al., 2025). In patients with thalassemia, this therapy helps reduce serum ferritin levels, minimize the risk of complications, and enhance quality of life (Lee et al., 2024). In this study, patients with serum ferritin levels greater than 1000 µg/L were identified, indicating hemosiderosis (de Jongh et al., 2017). In this condition, patients with beta-thalassemia major may experience organ damage, increasing the risk of heart and liver disorders and mortality (Shah et al., 2022; Tantiworawit et al., 2024). Serum ferritin levels are influenced by several factors, including age, the frequency and number of blood transfusions, and inflammatory conditions (Koperdanova & Cullis, 2015; Koreti et al., 2018; Bhalodiya et al., 2023).

FSH levels vary by gender, age, and puberty status (Zhao et al., 2025). Furthermore, FSH levels in women who are still menstruating fluctuate throughout the menstrual cycle (Padmanabhan & Cardoso, 2020). The median FSH level of all patients was 14.15 IU/L, which falls within the normal ranges for both

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genders. Most male patients had FSH levels above the normal range, whereas most female patients had levels within the normal range. Chowdhury et al. (2023) reported that both female and male patients had FSH levels within the normal range. FSH levels of patients in this study were relatively higher than those reported in other studies (Mahmud et al., 2018; Yenzeel, 2017; Baloch et al., 2019). Studies show that patients with beta thalassemia major typically have lower FSH levels than healthy individuals (Majeed, 2017; Uysal et al., 2017; Al-Mahdawi et al., 2020). In patients with beta thalassemia major, iron overload results in the formation of NTBI, which, upon entering pituitary gland cells, triggers increased production of reactive oxygen species (ROS) (de Jongh et al., 2017; Knutson, 2019; Gatterman et al., 2021). FSH-producing gonadotroph cells are sensitive to iron toxicity (Knutson, 2019; Venou et al., 2023). Oxidative stress, driven by increased ROS levels, can induce cellular damage and death (de Jongh et al., 2017). Consequently, this disrupts FSH secretion and the HPG axis (De Sanctis et al., 2012; Jouda et al., 2018). Although less prevalent, excess iron can also be deposited in the gonads, causing damage, particularly in patients with severe iron overload (Srisukh et al., 2016; De Sanctis, 2018; Harrer et al., 2025). In such cases, the testes and ovaries will exhibit impaired responsiveness to hormonal signals; consequently, negative feedback on FSH secretion is absent, leading to elevated FSH levels (Santi et al., 2020; Padmanabhan & Cardoso, 2020; Tsilionis et al., 2024; Negri et al., 2025). Although most patients have FSH levels within the normal range, clinical evaluation and other hormonal tests, including LH, testosterone, estrogen, anti-Müllerian hormone (AMH), and semen analysis, remain necessary to assess the patient's overall condition (Taher et al., 2025).

This study found no correlation between serum ferritin and FSH levels in patients with beta-thalassemia major. This finding aligns with the results of other cross-sectional studies conducted by Lubis et al. (2020) and Shakkour et al. (2021). A previous prospective study also reported no correlation between serum ferritin levels and FSH, both before and after GnRH analog therapy (Abo-Elwafa et al., 2017). Khan et al. (2021) reported divergent results between male and female subjects, finding a negative correlation between serum ferritin levels and FSH in male subjects, while no correlation was observed in female subjects. In contrast to this study's findings, Takhviji et al. (2020) observed a negative correlation between serum ferritin and FSH. Hagag et al. (2016) and Ansaf et al. (2021) also reported a negative correlation between the two parameters, where higher serum ferritin levels were associated with lower FSH levels. As previously stated, the serum ferritin levels in this study were comparatively lower than those observed in other studies. In thalassemia patients with serum ferritin levels greater than 1800 µg/L, hypogonadism develops more rapidly (Chirico, 2014). Furthermore, according to Roidos (2024), patients with serum ferritin levels > 2500 µg/L are 2.75 times more likely to develop hypogonadism than those with levels < 1000 µg/L. Genetic variability must be considered when examining differences in results (Abo-Elwafa, 2017).

This study has several limitations, including its relatively small sample size. The cross-sectional design limits the ability to assess changes in the patients' condition over time. The variables evaluated are limited to serum ferritin and FSH, hindering a comprehensive assessment of HPG-axis function.

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CONCLUSION

The present study found no statistically significant correlation between serum ferritin levels and FSH. Future studies should consider a cohort design with a larger sample size and evaluate other hormones, including LH, estrogen, and testosterone. Additionally, assessing patient compliance with iron chelation therapy is recommended.

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