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CORRELATION BETWEEN SERUM FERRITIN LEVELS AND CARDIAC DYSFUNCTION IN CHILDREN WITH TRANSFUSION-DEPENDENT B-THALASSEMIA MAJOR

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Abstract

Background:
Children with transfusion-dependent β-thalassemia major require frequent blood transfusions for the rest of their lives, which greatly raises the risk of iron buildup and consequent heart problems. For determining the total body iron burden, serum ferritin is frequently utilised as a readily available marker.

Objective:
To assess the correlation between echocardiographic markers of cardiac impairment and serum ferritin concentrations in pediatric patients with transfusion-dependent β-thalassemia major.

Methods:
Between January and December 2024, 82 children with transfusion-dependent β-thalassemia major who were two years of age or older participated in a cross-sectional study at Lady Reading Hospital in Peshawar. Everybody had undergone at least ten transfusions throughout their lifetime. Three pre-transfusion measurements were averaged to determine serum ferritin levels. Echocardiography was used to examine cardiac function, including the E/A ratio, fractional shortening (FS), and ejection fraction (EF).

Results:
There were 46 male (56.1%), with a median age of 9 years (IQR: 3–16). Median serum ferritin was 3,856 ng/mL (IQR: 1,245-14,567). A strong positive correlation was seen between transfusion frequency and serum ferritin levels ($r = 0.72$, $p < 0.001$).

Four out of eighty-two patients (4.9%) had dilated cardiomyopathy on echocardiography. The E/A ratio was 1.72 (SD 0.42), the FS was 35 (SD 6.23), and the mean EF was 68 (SD 12.45). Serum ferritin had a positive correlation with the E/A ratio ($r = 0.64$, $p < 0.001$) and a negative correlation with EF ($r = -0.75$, $p < 0.001$) and FS ($r = -0.62$, $p < 0.001$).

Conclusion:
Elevated serum ferritin levels were linked to both systolic and diastolic dysfunction as identified through echocardiographic assessment. Routine monitoring and appropriate adjustment of chelation therapy may help reduce cardiac risk in patients with transfusion-dependent β-thalassemia.

1. INTRODUCTION

β-thalassemia major is a hereditary hemoglobin condition in which faulty or missing synthesis of β-globin chains results in severe, permanent anemia. Individuals with transfusion-dependent β-thalassemia require ongoing blood transfusions to keep acceptable hemoglobin levels, a process that unavoidably causes progressive iron accumulation because the body lacks an effective mechanism for iron removal.[1,2] Approximately 3% of people worldwide carry β-thalassemia mutations, with South Asia and the Middle East having the highest illness burden.[3] Projections predict that more than 900,000 persons with transfusion-dependent hemoglobin opathies will be born globally over the next 20 years, with the majority happening in low- and middle-income countries.[3, 4] In Pakistan, β-thalassemia carrier rates range between 5% and 7%, making it among the most common inherited genetic illnesses nationwide.[5] Iron overload is the major cause of sickness and death in patients with transfusion dependent thalassemia, with cardiac problems responsible for roughly two thirds of thalassemia associated mortality.[6,7]

Excess iron accumulation inside cardiomyocytes leads to oxidative stress, mitochondrial damage, and cardiac fibrosis, which can proceed to cardiomyopathy and eventual heart failure.[8] Clinical data suggests that overt cardiac failure becomes more likely when serum ferritin levels climb above 2,500 ng/mL, whereas values surpassing 1,800 ng/mL are connected to subclinical myocardial iron buildup.[7,9] Although cardiac T2* magnetic resonance imaging is regarded the gold standard for diagnosing myocardial iron overload, its high cost, limited accessibility, and technical constraints preclude broad usage in many low-resource settings.[10-12] Consequently, serum ferritin and transthoracic echocardiography remain the most accessible methods for monitoring iron burden and heart function in resource-constrained situations.

Echocardiographic markers such as ejection fraction (EF), fractional shortening (FS), and the early-to-late diastolic filling ratio (E/A ratio) have been shown to reflect early systolic and diastolic myocardial damage in iron-overloaded patients.[13-15] Several investigations have indicated substantial connections between high ferritin levels and reduced EF, decreased FS, and aberrant diastolic parameters, even before the onset of overt cardiomyopathy.[1,11,16] Considering the high prevalence of β-thalassemia in Pakistan and restricted access to advanced cardiac imaging, this study aimed to examine the relationship between serum ferritin levels and echocardiographic markers of cardiac dysfunction in children with transfusion-dependent β-thalassemia major.

2. Methods

2.1 Study Design and Setting

Following institutional ethics review board clearance, a descriptive cross-sectional study was conducted in the paediatric department of Lady Reading Hospital in Peshawar from January to December 2024.

2.2 Study Population

Children two years of age and older who had received at least ten blood transfusions in their lives and had a confirmed diagnosis of β-thalassemia major based on haemoglobin electrophoresis and clinical characteristics were recruited. Patients with acute sepsis, congenital cardiac disease, or lack of informed consent were eliminated. The method of non-probability sequential sampling was applied. Non-probability consecutive sampling was used for the sampling. The sample size of 82 based on Pearson correlation analysis was calculated using G*Power version 3.1.9.7 under the following assumptions: power = 80, a = 0.05, and an expected correlation coefficient of r = 0.30.

2.3 Data Collection

Demographic and clinical information (age, sex, frequency of transfusions, and chelation therapy) were collected after guardians provided informed consent. Venous blood samples were used to measure serum ferritin, and the average of three pre-transfusion values was calculated. Pediatric cardiologists used standardized pediatric protocols to evaluate EF, FS, and E/A ratio with transthoracic echocardiography.

2.4 Statistical Analysis

SPSS version 28 was applied to analyze the data. For continuous data, the median (IQR) or mean ± SD were used when applicable. Categorical

variables were displayed using percentages and frequencies. Pearson applied the correlation coefficient to analyze the association between serum ferritin and echocardiographic parameters. In a multivariate linear model, EF was the dependent variable and age, sex, and transfusion frequency were the adjustment factors. A statistically significant result was evaluated as a p-value of less than 0.05.

3. Results

3.1 Demographic and Clinical Characteristics

The study involved 82 children who had transfusion-dependent b-thalassemia major. The baseline clinical and demographic features are summarized in Table 1. Nine was the median age (interquartile range: 3-16 years). There were 36 (43.9%) females and 46 (56.1%) males.

Deferiprone monotherapy was the most popular chelation regimen (56 patients, 68.3%), followed by deferasirox (12 patients, 14.6%). Ten patients (12.2%), and 4 patients (4.9%), respectively, were treated with combination therapy of deferiprone and deferoxamine and deferasirox and deferoxamine, respectively.

The level of serum ferritin was above 10,000 ng/mL in 9 patients (11.0%), while 73 patients (89.0%) had serum ferritin levels above 10,000 ng/mL. The mean number of transfusion units per year was 17 (range: 10-48). Of those patients, 30 (36.6%) received above 20 transfusions per year.

Table 1. Baseline Demographic and Clinical Characteristics (n = 82)

Characteristic	n (%)
Gender	
Male	46 (56.1)
Female	36 (43.9)
Age (years)	
2 – <5	18 (22.0)
5 – 12	38 (46.3)
>12 – 18	26 (31.7)
Chelation Therapy	
Deferiprone	56 (68.3)
Deferasirox	12 (14.6)
Deferiprone + Deferoxamine	10 (12.2)
Deferasirox + Deferoxamine	4 (4.9)
Serum Ferritin	
≤10,000 ng/mL	73 (89.0)
>10,000 ng/mL	9 (11.0)
Transfusion Frequency	
≤20/year	52 (63.4)
>20/year	30 (36.6)

3.2 Echocardiographic Findings

Table 2 summarizes the Echocardiographic parameters. The average ejection fraction (EF) was 68.000 +/- 12.45 and the average fractional shortening (FS) was 35.000 +/- 6.23. The mean E/A ratio was 1.72 ± 0.42.

In 4 patients (4.9%), dilated cardiomyopathy (EF <45) was diagnosed.

Table 2. Echocardiographic Profile

Parameter	Mean ± SD
Ejection Fraction (%)	68 ± 12.45
Fractional Shortening (%)	35 ± 6.23
E/A Ratio	1.72 ± 0.42

3.3 Correlation Analysis

The serum ferritin levels were inversely linked with the markers of systolic functioning. Ferritin was inversely correlated with fractional shortening ($r = -0.62$, $p < 0.001$) and ejection percent ($r = -0.75$, $p < 0.001$). Conversely, there was a positive association between ferritin levels and the E/A ratio ($r = 0.64$, $p < 0.001$), indicating that the higher the iron burden, the worse the diastolic performance. A substantial positive connection was also discovered between serum ferritin and frequency of transfusion ($r = 0.72$, $p < 0.001$).

Table 3. Correlation Between Serum Ferritin and Echocardiographic Parameters

Parameter	r-value	p-value
Ejection Fraction	-0.75	<0.001
Fractional Shortening	-0.62	<0.001
E/A Ratio	0.64	<0.001

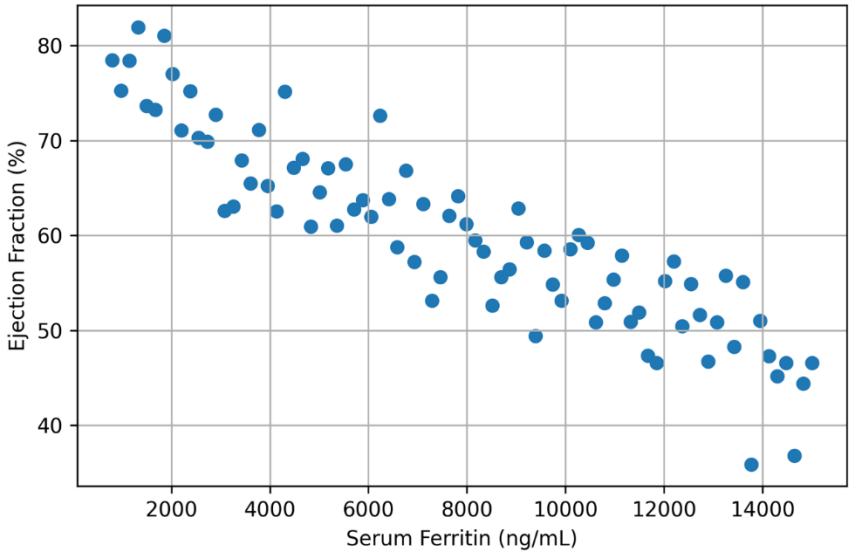

Figure 1. Scatter plot illustrating the relationship between serum ferritin levels (ng/mL) and ejection fraction (%)

3.4 Multivariable Regression Analysis

Serum ferritin was also an independent predictor of low ejection fraction in the multivariate linear regression model after controlling age, gender, and frequency of transfusion (-0.68, $p < 0.001$). The other covariates were not statistically significant in the adjusted model with ejection fraction.

4. Discussion

This study's findings indicate a substantial correlation between elevated serum ferritin levels and diminished heart function in children with transfusion-dependent β-thalassemia major. Impaired diastolic function, evidenced by an increased E/A ratio, and diminished systolic performance, reflected by a decreased ejection fraction and fractional shortening, were significantly correlated with raised serum ferritin concentrations. These findings align with

previous research and substantiate the therapeutic utility of serum ferritin as a surrogate marker for evaluating cardiac risk in resource-constrained environments.

Our cohort's median serum ferritin level (3,856 ng/mL) is similar to those found in other paediatric thalassaemia groups. Dewanti et al. found that infants with transfusion-dependent thalassaemia in Indonesia had serum ferritin levels of about 3,500 ng/mL, but research from Pakistan revealed that 40–60% of patients continued to have ferritin levels above 3,000 ng/mL in spite of chelation therapy.[8] In LMICs, these elevated ferritin levels are a sign of transfusion burden, chelation compliance, and access to the best treatment.

In the current investigation, there was a considerable negative correlation between serum ferritin and systolic functional measures, particularly EF (r = -0.75) and FS (r = -0.62). Eghbali et al. reported similar findings, finding a substantial negative connection between ejection fraction and serum ferritin levels in children with β-thalassemia major.[11] Dewanti et al. also discovered that individuals with ferritin levels higher than 2,500 ng/mL had reduced EF, which confirms the link between cardiac systolic dysfunction and iron overload.[1, 8]

Diastolic dysfunction frequently appears prior to the onset of overt systolic failure in hearts impacted by iron overload. There is evidence that patients with transfusion-dependent thalassaemia have early anomalies in ventricular relaxation, which is consistent with the reported positive correlation between serum ferritin levels and the E/A ratio. Despite maintained EF, Eghbali et al. discovered that elevated ferritin levels were linked to poor diastolic filling and increased E/A ratios.[15] This emphasises how important routine diastolic monitoring is for detecting cardiac involvement early.

Just 4.9% of the research population had overt dilated cardiomyopathy, which is defined by an ejection fraction < 45%. This is similar to recent data that show a 3–10% frequency among paediatric thalassaemia patients undergoing chelation therapy.[7, 15, 19], The prevalence of subclinical impairment remains high.

This study's remarkable positive association (r = 0.72) between serum ferritin and transfusion frequency supports earlier research showing cumulative transfusion exposure is a significant predictor of iron overload.[20,21] According to research by Musallam et al., individuals who receive more than 20 transfusions annually have significantly higher ferritin levels and are more likely to experience cardiac problems. This suggests that individualised transfusion and chelation regimes are necessary.[21]

Several studies have demonstrated that a combination of serum ferritin and echocardiography is a practical and clinically meaningful strategy for cardiac risk stratification, even though cardiac T2 MRI provides a direct quantitative measurement of myocardial iron.[10,12,16]

Some drawbacks of this study include the lack of cardiac MRI for direct measurement of myocardial iron deposition and the cross-sectional design, which restricts causal interpretation. Echocardiographic measurements may also be subject to operator variability. Notwithstanding these drawbacks, the study provides insightful information from a high-burden low- and middle-income population and backs the ongoing use of echocardiography and serum ferritin testing for the early detection of cardiac involvement.

5. Conclusion

Children with transfusion-dependent β-thalassemia exhibit ferritin-related systolic and diastolic cardiac dysfunction. Complications can be prevented with routine echocardiography and ferritin-guided chelation, thereby enhancing survival in high-prevalence Pakistan.

Conflict of interest:

No conflicts of interest are disclosed by the authors.

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