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Assessment of Iron Overload and Its Association With Hepatic and Cardiac Function in Transfusion-Dependent Thalassemia

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ABSTRACT

ASSESSMENT OF IRON OVERLOAD AND ITS ASSOCIATION WITH HEPATIC AND CARDIAC FUNCTION IN TRANSFUSION-DEPENDENT THALASSEMIA OBJECTIVE: To assess iron overload and determine its association with hepatic and cardiac function in children with transfusion-dependent thalassemia (TDT) attending a tertiary care hospital in Pakistan. MATERIAL AND METHODS: This cross-sectional study was conducted over six months at the Department of Pediatrics and Hematology of multiple tertiary care hospitals in Pakistan. A total of 100 children aged 5–10 years with transfusion-dependent β-thalassemia receiving regular blood transfusions were enrolled through consecutive sampling. Clinical data including transfusion frequency and pre-transfusion hemoglobin levels were recorded. Serum ferritin was used to assess iron overload.

Keywords: Transfusion-dependent thalassemia, Iron overload, Serum ferritin, Liver function, Cardiac function, Echocardiography, Pediatric hematology, Pakistan

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INTRODUCTION

Transfusion-dependent thalassemia (TDT) is one of the most prevalent inherited hemoglobin disorders worldwide and remains a major public health challenge, particularly in low- and middle-income countries. The disease results from defective or absent synthesis of β-globin chains, leading to ineffective erythropoiesis, chronic hemolytic anemia, and severe anemia requiring lifelong regular blood transfusions. [(1)] Advances in transfusion therapy and iron chelation have significantly improved the survival of patients with TDT; however, repeated blood transfusions inevitably lead to progressive iron accumulation, which remains the leading cause of long-term morbidity and mortality. [(2)] Despite improvements in clinical management, iron overload continues to compromise the quality of life and survival of affected children, especially in countries where healthcare resources are limited. [(1)]

Pakistan bears a substantial burden of β-thalassemia, with an estimated carrier frequency of 5–7% and thousands of affected children born annually. [(3)] The majority of patients depend on regular transfusions provided through government hospitals and charitable thalassemia centers. Although iron chelation therapy has become more widely available, delayed initiation, poor compliance, financial constraints, and inconsistent follow-up contribute to inadequate control of iron burden in many patients.[(4)] Consequently, iron overload remains one of the most challenging complications in the management of transfusion-dependent thalassemia in Pakistan.[(5)]

Repeated blood transfusions result in progressive accumulation of iron because the human body lacks a physiological mechanism for excreting excess iron.[(6)] Each unit of transfused blood contains approximately 200–250 mg of iron, which is deposited in parenchymal tissues after transferrin-binding capacity is exceeded. [(2)] Excess intracellular iron promotes the generation of reactive oxygen species through oxidative reactions, leading to lipid peroxidation, mitochondrial dysfunction, inflammation, and cellular apoptosis.[(7)] Over time, these pathological processes result in irreversible structural and functional damage to multiple organs, particularly the liver, heart, and endocrine glands. [(1)]

The liver is the primary site of iron storage and is among the earliest organs affected by transfusional iron overload. Progressive hepatic iron deposition causes hepatocellular injury, fibrosis, and eventually cirrhosis if left untreated.[(6)] Elevated serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are commonly observed in children with significant iron overload and may serve as early biochemical indicators of hepatic dysfunction.[(8)] Monitoring liver enzymes is therefore an essential component of routine follow-up, particularly in resource-limited settings where direct quantification of hepatic iron concentration using magnetic resonance imaging (MRI) is often unavailable.[(9)]

Cardiac involvement is the most serious complication of iron overload and remains the leading cause of death among patients with transfusion-dependent thalassemia.[(10)] Iron deposition within the myocardium impairs myocardial contractility, disrupts electrical conduction, and predisposes patients to arrhythmias,

dilated cardiomyopathy, and congestive heart failure.[11] Although cardiac magnetic resonance imaging (MRI T2*) is considered the gold standard for detecting myocardial iron deposition, its high cost, limited availability, and need for specialized expertise restrict its routine use in many developing countries. [9] Consequently, echocardiography remains the most accessible and widely used non-invasive tool for evaluating cardiac function in children with transfusion-dependent thalassemia in Pakistan.[3]

Serum ferritin is the most commonly used surrogate marker for assessing body iron stores because it is inexpensive, minimally invasive, and readily available[2] Although ferritin levels may be influenced by inflammatory conditions, infections, and liver disease, serial serum ferritin estimation remains the cornerstone of monitoring iron overload in many low-resource healthcare systems. Similarly, routine assessment of hemoglobin levels and transfusion frequency provides valuable information regarding disease severity, adequacy of transfusion therapy, and the risk of progressive iron accumulation. [12] Collectively, these readily available clinical and biochemical parameters offer a practical approach for evaluating iron burden where advanced diagnostic facilities are lacking.

Several studies have demonstrated an association between elevated serum ferritin levels and hepatic dysfunction, while evidence regarding its relationship with cardiac function has been inconsistent. [13] Most published studies have been conducted in high-income countries where comprehensive iron monitoring, MRI T2* assessment, and standardized chelation protocols are routinely available. In contrast, data from Pakistan remain limited, and the existing literature is largely restricted by small sample sizes, single-organ assessment, or lack of comprehensive evaluation of both hepatic and cardiac function.[14] Furthermore, few studies have specifically focused on young children with transfusion-dependent thalassemia, a population in whom early detection of iron-related organ damage is critical for preventing irreversible complications. [15]

Therefore, this study was designed to assess iron overload using serum ferritin and to determine its association with hepatic and cardiac function in children aged 5–10 years with transfusion-dependent thalassemia attending a tertiary care hospital in Pakistan. Hepatic function was evaluated using serum ALT and AST levels, while cardiac function was assessed by echocardiography. In addition, the study examined the relationship of iron overload with pre-transfusion hemoglobin levels and transfusion frequency. By generating evidence from a resource-limited setting where MRI-based assessment is not routinely feasible, this study aims to address the existing research gap regarding affordable and clinically applicable indicators of iron overload and their relationship with early organ dysfunction, thereby providing data to support evidence-based monitoring strategies for children with transfusion-dependent thalassemia in Pakistan.

MATERIALS AND METHODS

This analytical cross-sectional study was conducted in the Department of Pediatrics in collaboration with the Department of Hematology at multiple tertiary care teaching hospitals in Pakistan, over a period of six months, from January 2026 to June 2026. The study was approved by the Institutional Review Board prior to commencement, and written informed consent was obtained from the parents or legal guardians of all participants before enrollment. All study procedures were performed in accordance with the ethical principles of the Declaration of Helsinki.

Children aged 5–10 years with a confirmed diagnosis of transfusion-dependent β-thalassemia (TDT) were recruited consecutively from the hospital's thalassemia clinic during the study period. The diagnosis of β-thalassemia was established based on hemoglobin electrophoresis or high-performance liquid chromatography (HPLC), together with clinical findings consistent with transfusion dependency. Eligible participants were those receiving regular packed red blood cell transfusions at intervals of two to five weeks for at least one year prior to enrollment. Children with acute febrile illness, active bacterial or viral infection, chronic liver disease unrelated to iron overload (including hepatitis B or C infection), congenital or acquired structural heart disease, chronic kidney disease, malignancy, autoimmune disorders, or any other chronic systemic illness that could independently affect hepatic or cardiac function were excluded. Patients who had undergone hematopoietic stem cell transplantation or had incomplete clinical or laboratory records were also excluded.

The required sample size was calculated using the formula for estimating proportions in cross-sectional studies, assuming a 95% confidence level, 80% study power, an anticipated prevalence of clinically significant iron overload among children with transfusion-dependent thalassemia based on previously published literature, and a margin of error of 5%. After accounting for possible incomplete data, a total sample of 100 participants was considered adequate for statistical analysis.

Baseline demographic and clinical characteristics, including age, sex, age at diagnosis, duration of transfusion therapy, frequency of blood transfusions, type and duration of iron chelation therapy, and pre-transfusion hemoglobin levels, were recorded using a structured data collection form. The average transfusion frequency was calculated as the number of transfusions received per month over the preceding six months. Anthropometric measurements, including height and weight, were obtained using standardized techniques, and body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m²).

Venous blood samples were collected immediately before the scheduled blood transfusion under aseptic conditions. Serum ferritin concentration was measured using a chemiluminescent immunoassay and was considered the primary biochemical indicator of body iron stores. Liver function was assessed by measuring serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) using an automated biochemistry analyzer. Hemoglobin concentration was determined using an automated hematology analyzer as part of the routine complete blood count. All laboratory investigations were performed in the hospital's central diagnostic laboratory following standardized quality control procedures.

Participants were categorized according to serum ferritin concentration into three groups to evaluate the relationship between iron burden and organ dysfunction. **Group I (mild iron overload)** included children with serum ferritin levels <1,000 ng/mL, **Group II (moderate iron overload)** included those with serum ferritin levels between 1,000 and 2,500 ng/mL, and **Group III (severe iron overload)** comprised children with serum ferritin levels >2,500 ng/mL.

Table I. Classification of study participants according to serum ferritin levels

Group	Serum Ferritin (ng/mL)	Interpretation
Group I	<1,000	Mild iron overload
Group II	1,000–2,500	Moderate iron overload
Group III	>2,500	Severe iron overload

Cardiac function was evaluated using two-dimensional transthoracic echocardiography performed by an experienced pediatric cardiologist who was blinded to the participants' laboratory findings. Echocardiographic assessment included

measurement of left ventricular ejection fraction (LVEF) using the modified Simpson's biplane method. An LVEF ≥55% was considered normal, whereas values below 55% were regarded as evidence of impaired left ventricular systolic function. Standard cardiac chamber dimensions and wall motion were also assessed to exclude structural abnormalities.

The primary outcome measures were hepatic dysfunction, assessed by serum ALT and AST concentrations, and cardiac function, assessed by left ventricular ejection fraction on echocardiography. The principal independent variable was serum ferritin concentration as a marker of iron overload. Additional variables, including pre-transfusion hemoglobin level, transfusion frequency, duration of transfusion therapy, age, sex, and iron chelation therapy, were evaluated for their potential association with hepatic and cardiac function.

Data were analyzed using SPSS version 26.0. Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as frequencies and percentages. Comparisons among serum ferritin groups were performed using one-way ANOVA with Tukey's post hoc test, while independent-samples *t*-test was used for two-group comparisons. Categorical variables were compared using the chi-square or Fisher's exact test. Pearson's correlation analysis assessed associations between serum ferritin levels and clinical parameters. Variables significant in univariate analysis were included in multiple linear regressions to identify independent predictors after adjustment for confounders. A two-tailed p value <0.05 was considered statistically significant.

RESULTS

A total of 100 children with transfusion-dependent β-thalassemia were enrolled in the study. The mean age of the participants was 7.4 ± 1.6 years, with males comprising 56.0% (n = 56) of the study population. Based on serum ferritin concentration, 12 (12.0%) children had mild iron overload (Group I), 33 (33.0%) had moderate iron overload (Group II), and 55 (55.0%) had severe iron overload (Group III).

The baseline demographic and clinical characteristics of the study population are presented in Table 1. There were no statistically significant differences among the three serum ferritin groups regarding age, sex distribution, or body mass index (p > 0.05). However, children with severe iron overload had significantly longer duration of transfusion therapy, higher transfusion frequency, and lower pre-transfusion hemoglobin levels compared with those in the mild and moderate iron overload groups.

Baseline demographic and clinical characteristics according to serum ferritin group

Variable	Mild (<1000 ng/mL) (n=12)	Moderate (1000–2500 ng/mL) (n=33)	Severe (>2500 ng/mL) (n=55)	p-value
Age (years), mean ± SD	6.9 ± 1.4	7.3 ± 1.5	7.6 ± 1.7	0.412
Male, n (%)	7 (58.3)	17 (51.5)	32 (58.2)	0.823
BMI (kg/m²), mean ± SD	15.8 ± 1.3	15.5 ± 1.4	15.3 ± 1.6	0.536
Duration of transfusion therapy (years)	3.1 ± 1.0	4.2 ± 1.3	5.5 ± 1.6	<0.001
Transfusion frequency (per month)	1.3 ± 0.3	1.8 ± 0.4	2.4 ± 0.5	<0.001
Hemoglobin (g/dL), mean ± SD	8.9 ± 0.7	8.2 ± 0.6	7.8 ± 0.7	<0.001

The biochemical profile of the participants is shown in Table 2. Mean serum ferritin concentration increased significantly across the three study groups. Similarly, serum ALT and AST levels were significantly higher in children with severe iron overload than in those with mild and moderate iron overload (p < 0.001 for both comparisons).

Biochemical profile according to serum ferritin group

Parameter	Mild	Moderate	Severe	p-value
Serum ferritin (ng/mL)	786 ± 142	1,842 ± 396	4,152 ± 1,032	<0.001
ALT (U/L)	28.6 ± 8.4	39.8 ± 11.2	58.7 ± 16.3	<0.001
AST (U/L)	31.2 ± 7.9	42.1 ± 12.4	61.4 ± 18.2	<0.001

Cardiac assessment by echocardiography demonstrated progressive deterioration in left ventricular systolic function with increasing iron overload. Children in the severe iron overload group had significantly lower mean left ventricular ejection fraction (LVEF) than those in the mild and moderate groups. Reduced systolic function (LVEF <55%) was observed predominantly among children with severe iron overload.

Echocardiographic findings according to serum ferritin group

Echocardiographic parameter	Mild	Moderate	Severe	p-value
LVEF (%), mean ± SD	67.1 ± 3.2	64.5 ± 3.8	61.8 ± 4.4	<0.001
LVEF <55%, n (%)	0 (0.0)	1 (3.0)	8 (14.5)	0.041

Comparison of hepatic dysfunction according to iron overload demonstrated a significantly greater proportion of abnormal liver enzymes among children with severe iron overload. Elevated ALT was observed in 72.7% of children in the severe group compared with 24.2% in the moderate group and 8.3% in the mild group. Similarly, elevated AST was significantly more frequent in children with severe iron overload (p < 0.001).

Hepatic dysfunction according to serum ferritin group

Variable	Mild (n=12)	Moderate (n=33)	Severe (n=55)	p-value
Elevated ALT, n (%)	1 (8.3)	8 (24.2)	40 (72.7)	<0.001
Elevated AST, n (%)	1 (8.3)	7 (21.2)	37 (67.3)	<0.001

Correlation analysis demonstrated significant positive relationships between serum ferritin concentration and hepatic enzyme levels. Higher serum ferritin levels were associated with increased ALT (r = 0.61, p < 0.001) and AST (r = 0.57, p < 0.001). Serum ferritin also demonstrated a moderate negative correlation with left ventricular ejection fraction (r = –0.38, p < 0.001) and pre-transfusion hemoglobin (r = –0.34, p = 0.001), whereas a positive correlation was observed with transfusion frequency (r = 0.54, p < 0.001).

Multiple linear regression analysis was performed after adjusting for age, sex, duration of transfusion therapy, and iron chelation therapy. Serum ferritin remained an independent predictor of

elevated ALT (β = 0.46, p < 0.001), elevated AST (β = 0.42, p < 0.001), and reduced left ventricular ejection fraction (β = –0.27, p = 0.006). Higher transfusion frequency was independently associated with increased serum ferritin concentration (β = 0.39, p < 0.001), while lower pre-transfusion hemoglobin independently predicted higher iron burden (β = –0.23, p = 0.018).

Multiple linear regression analysis for predictors of serum ferritin and organ dysfunction

Variable	Standardized β	95% CI	p-value
Transfusion frequency	0.39	0.24–0.55	<0.001
Hemoglobin	–0.23	–0.41 to –0.04	0.018
Serum ferritin → ALT	0.46	0.32–0.60	<0.001
Serum ferritin → AST	0.42	0.27–0.57	<0.001
Serum ferritin → LVEF	–0.27	–0.46 to –0.08	0.006

Overall, children with severe transfusional iron overload demonstrated significantly higher hepatic enzyme levels, lower pre-transfusion hemoglobin concentrations, and reduced left ventricular systolic function compared with children having mild or moderate iron overload. After adjustment for relevant clinical variables, serum ferritin remained an independent predictor of hepatic dysfunction and early cardiac impairment, highlighting its value as an accessible marker for monitoring iron-related complications in children with transfusion-dependent thalassemia in resource-limited settings.

DISCUSSION

The present study evaluated iron overload and its association with hepatic and cardiac function among children with transfusion-dependent β-thalassemia (TDT) in a resource-limited healthcare setting in Pakistan. The findings demonstrated that more than half of the study population had severe iron overload, with progressively worsening hepatic and cardiac parameters as serum ferritin levels increased. Higher serum ferritin concentrations were significantly associated with elevated ALT and AST levels, reduced left ventricular ejection fraction (LVEF), lower pre-transfusion hemoglobin levels, and increased transfusion frequency. Furthermore, serum ferritin remained an independent predictor of hepatic dysfunction and early cardiac impairment after adjustment for potential confounding factors. These findings emphasize the clinical importance of routine monitoring of iron burden in children receiving long-term transfusion therapy.

Taher and Saliba stated that iron overload remains the most important long-term complication of chronic transfusion therapy in patients with TDT. [16] In the present study, the mean serum ferritin concentration was markedly elevated, and 55% of participants had ferritin levels exceeding 2,500 ng/mL, indicating severe iron overload. This finding reflects the continuing challenge of maintaining adequate iron balance in developing countries despite the availability of iron chelation therapy. Similar observations have been reported from Pakistan, India, Bangladesh, and other low- and middle-income countries, where delayed initiation of chelation therapy, poor treatment adherence, irregular drug availability, and financial constraints frequently result in persistently elevated ferritin levels.([17] Although serum ferritin is influenced by inflammatory conditions and hepatic disease, it remains the most practical and affordable indicator of iron burden in healthcare systems where MRI T2* is not routinely available.[18]

The present study demonstrated a significant positive association between serum ferritin concentration and liver enzyme levels. Children with severe iron overload had substantially higher ALT and AST values than those with mild or moderate iron overload, suggesting progressive hepatocellular injury with increasing iron accumulation[19] These findings are biologically plausible because excess iron is initially deposited within hepatocytes and Kupffer cells, where it catalyzes the production of reactive oxygen species, resulting in oxidative stress, lipid peroxidation, inflammation, and fibrosis. [20] Rabadiya et al have similarly reported elevated transaminase levels among transfusion-dependent thalassemia patients with high ferritin concentrations, supporting the role of serum ferritin as an indirect marker of hepatic iron toxicity. [19]. Although liver biopsy and MRI-based liver iron concentration provide more accurate estimates of hepatic iron stores, these investigations are expensive, invasive, or unavailable in many public-sector hospitals in Pakistan. Therefore, the combined use of serum ferritin and routine liver function tests remains a practical strategy for identifying children at increased risk of hepatic complications.

Cardiac dysfunction secondary to iron deposition is the leading cause of mortality among patients with transfusion-dependent thalassemia. In the present study, left ventricular ejection fraction decreased significantly with increasing serum ferritin levels, and serum ferritin demonstrated a modest but significant inverse correlation with LVEF. [21] Although only a small proportion of children exhibited overt systolic dysfunction, the observed decline in cardiac performance suggests that myocardial involvement begins early, even during childhood. Similar findings have been reported in previous studies demonstrating that persistent iron overload is associated with progressive impairment of ventricular function before the onset of clinical heart failure.([22] Since myocardial iron deposition may remain clinically silent for several years, routine echocardiographic surveillance provides an important opportunity for early detection of cardiac dysfunction, particularly in settings where cardiac MRI T2* cannot be performed.

An important finding of this study was the significant relationship between transfusion frequency and serum ferritin concentration. Children requiring more frequent transfusions exhibited significantly higher ferritin levels, reflecting the cumulative iron burden associated with chronic transfusion therapy. [23] Each unit of packed red blood cells introduces approximately 200–250 mg of elemental iron into the body, and because there is no physiological mechanism for iron excretion, repeated transfusions inevitably result in progressive iron accumulation. Similar associations have been reported in previous studies, highlighting transfusion burden as one of the strongest determinants of iron overload. [16] These findings further emphasize the importance of individualized chelation therapy based on transfusion requirements and serial assessment of iron burden.

The inverse association observed between pre-transfusion hemoglobin concentration and serum ferritin may reflect more severe disease requiring frequent transfusions. Children with persistently low hemoglobin levels often receive transfusions at shorter intervals, thereby increasing cumulative iron exposure so maintaining recommended pre-transfusion hemoglobin levels through optimized transfusion protocols may reduce ineffective erythropoiesis and improve growth; however, it also necessitates careful adjustment of iron chelation therapy to prevent excessive iron accumulation. [24]

Multiple linear regression analysis identified serum ferritin as an independent predictor of elevated ALT, AST, and reduced left ventricular ejection fraction after adjustment for demographic and clinical variables. These findings strengthen the evidence that iron overload
contributes directly to hepatic injury and early cardiac dysfunction rather than merely reflecting disease severity. [25] Although MRI T2* remains the international reference standard for assessing tissue iron concentration, its routine use is limited in Pakistan because of high cost and restricted availability. Under these

circumstances, serum ferritin, together with liver function tests and echocardiography, provides a feasible and clinically useful approach for longitudinal monitoring of children with transfusion-dependent thalassemia .[25]

The findings of the present study highlight the importance of routine monitoring of serum ferritin, liver enzymes, and cardiac function for early detection of iron-related organ damage in children with transfusion-dependent thalassemia, while emphasizing that improved adherence to iron chelation, standardized monitoring protocols, better access to essential medications, and strengthened specialized thalassemia services are critical to reducing complications and improving long-term outcomes, particularly in resource-limited settings such as Pakistan.[26]

Future multicenter prospective studies incorporating serial ferritin measurements, MRI T2* assessment, and long-term clinical follow-up are warranted to validate these findings and better characterize the progression of iron-related organ damage in children with transfusion-dependent thalassemia.

Overall, the present study demonstrates that iron overload remains highly prevalent among Pakistani children with transfusion-dependent β-thalassemia and is significantly associated with hepatic dysfunction and early deterioration of cardiac function. The findings support the continued use of serum ferritin as a practical and cost-effective marker of iron burden in resource-constrained healthcare settings and underscore the importance of regular biochemical and echocardiographic monitoring to facilitate early intervention and improve long-term clinical outcomes. [27]

CONCLUSION

Iron overload was significantly associated with hepatic dysfunction and early cardiac impairment in children with transfusion-dependent β-thalassemia. Higher serum ferritin levels were associated with elevated liver enzymes, reduced left ventricular ejection fraction, lower hemoglobin levels, and increased transfusion frequency, highlighting the importance of serum
ferritin as a practical and cost-effective marker for monitoring iron burden in resource-limited settings. Regular assessment of serum ferritin, liver function tests, and echocardiography may facilitate early detection of organ damage and timely optimization of iron chelation therapy. Future multicenter prospective studies incorporating MRI T2* and long-term follow-up are recommended to validate these findings and improve monitoring strategies for children with transfusion-dependent thalassemia.

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