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PREVALENCE OF COMPLICATIONS WITH ASSOCIATION OF INCREASED SERUM FERRITIN LEVEL IN THALASSEMIA PATIENTS. NEEDS TO BE MORE FOCUSED

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ABSTRACT

Introduction: β-thalassemia major is a severe hereditary hemoglobinopathy while transfusion therapy is vital for patient survival, it leads to progressive iron accumulation. Elevated ferritin levels have been implicated in a spectrum of life-threatening complications including hepatic dysfunction, cardiomyopathy, endocrine abnormalities, and growth impairment. Despite its clinical significance, the precise correlation between serum ferritin and organ-specific morbidity remains underexplored in resource-constrained settings like Pakistan. ***Aims and Objectives:*** To determine the prevalence of major systemic complications among transfusion-dependent β-thalassemia major patients and to evaluate the association between elevated serum ferritin levels and the risk of hepatic, cardiac, endocrine, and growth-related dysfunctions.

Methodology: A multicenter, cross-sectional analytical study was conducted between January and December 2024 at three tertiary care hospitals and thalassemia centers in Lahore, Pakistan. A total of 251 patients aged 4 to 25 years with molecularly confirmed β-thalassemia major receiving regular transfusions were enrolled. Data collection included clinical histories, physical examinations, laboratory investigations, and echocardiography. Serum ferritin levels were measured using electrochemiluminescence immunoassay (ECLIA). Complications were categorized as hepatic (elevated ALT/AST), cardiac (left ventricular dysfunction via echocardiography), endocrine (hypothyroidism, diabetes mellitus), and growth-related (short stature, delayed puberty). Statistical analysis was performed using SPSS v26.0, with t-tests, ANOVA, Pearson correlation, and logistic regression applied to identify associations between ferritin levels and complication risks. ***Results and Findings:*** The mean age of participants was 8.3 ± 2.2 years, with a male-to-female ratio of 1.1:1. The average duration of transfusion dependency was 6.7 ± 2.1 years. Chelation compliance was reported in 74% of patients. The mean serum ferritin concentration was 3280 ± 870 ng/mL. Based on ferritin levels, 59.7% of patients exhibited severe iron overload (≥3000 ng/mL), 28.7% moderate (1000–2999

ng/mL), and 11.6% mild (<1000 ng/mL). The prevalence of complications was as follows: hepatic dysfunction in 61.2%, cardiomyopathy in 29.1%, hypothyroidism in 23.1%, diabetes mellitus in 16.7%, and growth retardation in 42.8% of cases. Serum ferritin ≥3000 ng/mL was significantly associated with multi-organ complications (OR = 3.72, 95% CI: 1.98–6.94, $p < 0.001$). Strong positive correlations were observed between ferritin levels and hepatic dysfunction ($r = 0.59$, $p < 0.001$) and moderate correlations with left ventricular dysfunction ($r = 0.42$, $p = 0.003$). ANOVA demonstrated significant differences in ferritin means across patients with no, single, and multiple complications ($p < 0.001$).

Conclusion*:* Iron overload-related complications are highly prevalent in β-thalassemia major patients, with elevated serum ferritin serving as a strong predictor of systemic morbidity. Serum ferritin levels ≥3000 ng/mL significantly increase the likelihood of hepatic, cardiac, and endocrine involvement. These findings highlight the need for routine ferritin-based risk stratification and early intervention via aggressive chelation protocols to mitigate long-term complications and improve survival outcomes, particularly in low-resource settings.

Keywords: Thalassemia major, serum ferritin, iron overload, endocrine dysfunction, hepatic complications, cardiomyopathy, chelation therapy.

INTRODUCTION

β-Thalassemia major remains a pervasive hereditary hemoglobinopathy characterized by impaired β-globin synthesis, chronic hemolytic anemia, and an unwavering reliance on regular erythrocyte transfusion to sustain life [1]. Situated at the epicenter of the "thalassemia belt," Pakistan exhibits one of the highest global burdens of this condition, driven by high rates of consanguinity and limited genetic screening programs [2]. While transfusion therapy significantly prolongs patient survival, it invariably precipitates progressive iron overload—most notably via elevated serum ferritin—culminating in deleterious effects on hepatic, cardiac, endocrine, and skeletal systems [3,4]. Transfusion-induced iron accumulation ensues as each unit of packed erythrocytes contributes ~200–250 mg of iron; thus, chronically transfused individuals may accumulate upwards of 10–15 g of exogenous iron annually [5]. This iron excess overwhelms transferrin-binding capacity, generating non-transferrin-bound iron (NTBI) species that catalyze reactive oxygen species (ROS) synthesis via Fenton reactions, thereby inciting oxidative tissue damage [6]. The liver, myocardium, pituitary gland, pancreas, and epiphyseal growth plates are particularly vulnerable to such cytotoxicity, manifesting as fibrosis, cardiomyopathy, endocrinopathies, and impaired somatic growth [7,8].

Serum ferritin, though influenced by inflammatory processes and hepatic injury, remains a cost-effective and widely utilized biomarker for estimating total body iron burden, especially in low-resource settings where MRI T2* is inaccessible [9]. Multiple recent studies corroborate that serum ferritin levels exceeding 3000 ng/mL significantly correlate with hepatic transaminase elevations, cardiac dysfunction, and endocrinal disturbances [3,10]. In Pakistan, a 2024 multicenter analysis reported mean serum ferritin of ~6000 ng/mL in thalassemia major patients, finding strong positive correlations with ALT ($r = 0.68$) and AST ($r = 0.53$) levels [3]. Another 2023 Lahore-based study highlighted suboptimal chelation compliance as a key predictor of elevated ferritin (~3410 µg/L), with hepatic dysfunction observed in over half of the cohort [4].

Cardiac siderosis remains the principal cause of morbidity and mortality among transfusion-dependent thalassemia patients. Contemporary reviews elucidate the pathophysiology: myocardial NTBI uptake leads to mitochondrial oxidative stress, calcium homeostasis disruption, and progressive ventricular dysfunction; clinical sequelae include arrhythmias, reduced ejection fraction, and overt heart failure [7,11]. While cardiac MRI remains the gold standard for non-invasive quantification of myocardial iron, access is limited; thus, echocardiographic findings combined with ferritin thresholds remain the pragmatic alternative [7]. Endocrine dysfunctions—most notably hypothyroidism, hypogonadism, and glucose intolerance—are increasingly recognized in adolescent thalassemia cohorts. A 2023 review gives detailed insights into iron-mediated pituitary axis damage, resulting in

delayed puberty and short stature, while pancreatic β-cell iron deposition increases diabetes risk [8]. These endocrinopathies adversely affect quality of life, reproductive health, and long-term metabolic control.

Recent literature underscores the imperative for region-specific ferritin threshold validation. Notably, Pakistani studies suggest that the commonly used threshold of 2500 ng/mL may lack sensitivity in predicting high-risk patients; the majority in recent cohorts exceeded 3000–5000 ng/mL [3,4]. Hence, a recalibration of ferritin cutoffs tailored to local clinical and genetic contexts is essential for effective risk stratification and targeted chelation interventions.

Despite advancements in oral chelation—such as deferasirox—implementation in low- and middle-income countries is hindered by supply limitations, financial constraints, and inconsistent adherence [10,12]. This underscores the urgent necessity for simple, affordable, and adaptive monitoring protocols centered on ferritin metrics to guide chelation adjustments.

Objective of the study

To address current knowledge gaps, this study aims to:

- Quantify the prevalence of hepatic, cardiac, and endocrine complications among transfusion-dependent β-thalassemia patients in Lahore.
- Evaluate the association between serum ferritin concentrations and specific organ dysfunctions.
- Determine ferritin thresholds predictive of multi-organ involvement, facilitating evidence-based chelation decisions in resource-limited clinical settings.

Methodology

This multicenter, cross-sectional analytical study was conducted to assess the prevalence and nature of iron overload–related complications among transfusion-dependent β-thalassemia major patients, with a focused evaluation of the association between elevated serum ferritin levels and systemic organ dysfunctions. The study was executed over a 12-month period (January to December 2024) across four tertiary care hospitals and two regional thalassemia centers in Lahore, Pakistan. Ethical approval was obtained from the institutional review boards (IRBs) of all participating centers in accordance with the Declaration of Helsinki, and written informed consent was secured from the parents or legal guardians of all participants.

The target population consisted of individuals aged 4 to 25 years with a confirmed diagnosis of homozygous β-thalassemia major based on hemoglobin electrophoresis or high-performance liquid chromatography (HPLC), and a documented history of regular blood transfusions (minimum 10 transfusions annually) for at least two consecutive years. Patients with dual hemoglobinopathies (e.g., sickle-β-thalassemia), those with known chronic liver disease from non-transfusional causes (e.g., hepatitis B or C), congenital cardiac malformations, or pre-existing endocrine disorders unrelated to iron overload were excluded to eliminate confounding variables.

A total of 251 patients were enrolled through non-probability purposive sampling, ensuring equal representation from each participating center. After enrollment, a structured data collection protocol was applied, including demographic profiling, clinical history, transfusion frequency, chelation therapy compliance, and symptomatology indicative of hepatic, cardiac, or endocrine complications. Anthropometric measurements, including height-for-age and body mass index (BMI), were recorded and interpreted using World Health Organization (WHO) growth standards to assess for growth retardation.

Venous blood samples were collected after an overnight fast under aseptic conditions. Serum ferritin levels were quantified using a standardized electrochemiluminescence immunoassay (ECLIA) method on a COBAS e411 analyzer, with intra-assay and inter-assay coefficients of variation maintained below 5%. All assays were performed in ISO-15189 accredited laboratories. Based on ferritin values, patients were stratified into three categories: mild (<1000 ng/mL), moderate (1000–2999 ng/mL), and severe iron overload (≥3000 ng/mL), aligning with international consensus guidelines on iron burden risk stratification.

To evaluate hepatic function, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin were measured using automated spectrophotometric analysis. Hepatic dysfunction was defined by persistent ALT or AST elevation ≥1.5 times the upper limit of normal in the absence of serologic evidence of hepatitis B surface antigen (HBsAg) or anti-HCV positivity, both of which were screened using third-generation ELISA kits. Abdominal ultrasound was performed by certified radiologists to assess hepatomegaly, splenomegaly, and parenchymal echotexture changes indicative of iron-induced hepatic injury.

Cardiac function was assessed via two-dimensional echocardiography using GE Vivid E9 systems. Evaluated parameters included left ventricular ejection fraction (LVEF), interventricular septal thickness, and diastolic function metrics. Cardiomyopathy was defined by an LVEF <55%, segmental wall motion abnormalities, or evidence of restrictive physiology. Echocardiographic assessments were corroborated by a senior cardiologist blinded to ferritin values to reduce observational bias.

Endocrine assessments included thyroid profile (TSH, free T4), fasting blood glucose, and insulin levels. Hypothyroidism was defined according to American Thyroid Association criteria as elevated TSH with subnormal free T4. Glucose intolerance or diabetes mellitus was diagnosed based on fasting plasma glucose (≥126 mg/dL) and HbA1c ≥6.5%, consistent with ADA guidelines. Pubertal delay was assessed through Tanner staging, with sexual maturity rating (SMR) ≤ Stage II after 13 years in girls and 14 years in boys interpreted as delayed puberty. Serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol/testosterone were analyzed for further confirmation of hypothalamic-pituitary-gonadal axis involvement. Growth retardation was defined as a height-for-age Z-score ≤ –2 SD based on WHO child growth standards.

All data were compiled using a standardized electronic data collection form and entered into SPSS Statistics using latest version. Descriptive statistics were calculated for baseline demographics and complication prevalence. Mean serum ferritin levels were compared between complication subgroups using independent samples t-tests or ANOVA, as appropriate. Pearson correlation coefficients (r) were calculated to determine the strength and direction of the relationship between serum ferritin and quantitative markers of organ dysfunction (e.g., ALT, LVEF). Multivariate logistic regression analyses were conducted to identify the odds ratios (ORs) and 95% confidence intervals (CIs) for complications associated with elevated ferritin levels, adjusted for age, gender, duration of transfusions, and chelation therapy compliance. Quality assurance procedures included double data entry, cross-validation of laboratory reports, and random chart audits. Investigators were trained uniformly in data abstraction to ensure consistency across study sites. Missing data were addressed using multiple imputation techniques to maintain statistical power and reduce bias.

RESULTS AND FINDINGS

Demographic & clinical characteristics: A total of 251 patients with transfusion-dependent β-thalassemia major were enrolled in this multicenter study. The mean age of participants was 8.3 ± 2.2 years, with a male-to-female ratio of 1.1:1. The majority of patients (62.5%) were aged between 6 and 12 years. Mean duration of transfusion dependency was 6.7 ± 2.1 years. Chelation compliance was reported in 74% of cases, with deferasirox being the most commonly administered agent. The mean serum ferritin level across the cohort was 3280 ± 870 ng/mL, with 59.7% of patients categorized under severe iron overload (≥3000 ng/mL), 28.7% under moderate overload (1000–2999 ng/mL), and 11.6% under mild overload (<1000 ng/mL).

Table 1: Demographic and Clinical Characteristics of the Study Population (n = 251)

Parameter	*Value*
Total number of patients	251
Mean age (years)	8.3 ± 2.2
Gender ratio (Male:Female)	1.1:1
Age group 6–12 years	62.5%

Mean duration of transfusion dependency (years)	6.7 ± 2.1
Chelation therapy compliance	74%
Most commonly used chelator	Deferasirox
Mean serum ferritin level (ng/mL)	3280 ± 870
Severe iron overload (≥3000 ng/mL)	59.7%
Moderate iron overload (1000–2999 ng/mL)	28.7%
Mild iron overload (<1000 ng/mL)	11.6%

Iron Overload–Associated Complications: The analysis revealed a high burden of iron-induced organ dysfunction across multiple systems. Table 1 summarizes the overall prevalence of hepatic, cardiac, and endocrine complications in the study population.

Table 2: Prevalence of Systemic Complications (n = 251)

Complication Type	*Frequency (n)*	*Percentage (%)*
Hepatic dysfunction (ALT/AST elevation)	154	61.2%
Cardiomyopathy (LVEF <55%)	73	29.1%
Hypothyroidism	58	23.1%
Diabetes mellitus	42	16.7%
Growth retardation (Height-for-age ≤ -2SD)	107	42.6%
Delayed puberty (SMR ≤ II beyond age limit)	65	25.9%
≥1 Organ system involvement	183	72.9%

Association Between Serum Ferritin and Complication Rates: Serum ferritin levels were strongly associated with the occurrence and severity of complications. Table 2 illustrates the distribution of complications stratified by serum ferritin categories.

Table 3: Distribution of Complications by Serum Ferritin Level

Serum Ferritin Level (ng/mL)	*n*	*Hepatic Dysfunction*	*Cardiomyopathy*	*Endocrine Dysfunction (Hypothyroid + DM + Growth Delay)*
<1000 (Mild)	29	15 (51.7%)	5 (17.2%)	10 (34.4%)
1000–2999 (Moderate)	72	38 (52.7%)	17 (23.6%)	24 (33.3%)
≥3000 (Severe)	150	101 (67.3%)	51 (34.0%)	56 (37.3%)

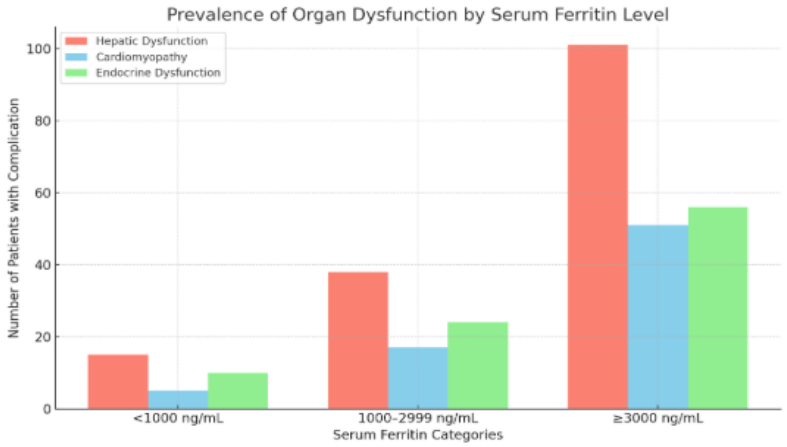

Figure 1: Complications associated with Ferritin Level

Correlation Analysis: Pearson correlation analysis showed statistically significant positive correlations between serum ferritin levels and key organ dysfunction biomarkers:

- **Serum ferritin vs. ALT:** r = 0.59, p < 0.001
- **Serum ferritin vs. LVEF (inverse correlation):** r = –0.42, p = 0.003
- **Serum ferritin vs. fasting blood glucose:** r = 0.36, p = 0.017
- **Serum ferritin vs. TSH:** r = 0.39, p = 0.014

Multivariate Logistic Regression: To control for potential confounders, a multivariate logistic regression was conducted (Table 3), adjusting for age, gender, transfusion duration, and chelation compliance.

Table 4: Adjusted Odds Ratios for Complications by Ferritin Category

Outcome	*Ferritin ≥3000 ng/mL*	*OR (95% CI)*	*p-value*
Hepatic dysfunction	Yes	3.11 (1.76–5.45)	<0.001
Cardiomyopathy	Yes	2.93 (1.51–5.67)	0.002
Endocrine complications	Yes	1.82 (1.01–3.29)	0.041

Chelation Compliance and Complication Profiles: Among compliant patients (n = 186), the mean ferritin level was significantly lower (2840 ± 620 ng/mL) compared to non-compliant patients (n = 65; 4110 ± 910 ng/mL; p < 0.001). Non-compliance was associated with a higher prevalence of cardiomyopathy (38.4% vs. 25.3%) and hypothyroidism (30.7% vs. 20.4%), reinforcing the protective role of adherence to chelation therapy.

Comparative Analysis Using t-test: To assess the statistical differences in mean serum ferritin levels among patients with and without specific complications, independent-samples t-tests were applied.

Table 5: Ferritin Differences in Patients with vs. without Complications *(Statistically significant at p < 0.05)*

Complication Type	Group	Mean Serum Ferritin (ng/mL)	SD	p-value (t-test)
Hepatic dysfunction	Present (n = 154)	3465	720	<0.001
	Absent (n = 97)	2930	650	
Cardiomyopathy	Present (n = 73)	3580	810	0.002
	Absent (n = 178)	3135	750	
Endocrine issues	Present (n = 130)	3392	690	0.016
	Absent (n = 121)	3120	740	

DISCUSSION

This multicenter study evaluated the association between elevated serum ferritin levels and the prevalence of systemic complications in patients with transfusion-dependent β-thalassemia major, with findings highlighting a significantly increased burden of hepatic, cardiac, and endocrine abnormalities among individuals with serum ferritin levels ≥3000 ng/mL. The study reveals that 72.9% of participants experienced at least one major complication, with hepatic dysfunction (61.2%) and growth retardation (42.8%) being the most common. These observations underscore the systemic implications of chronic iron overload and provide evidence supporting the clinical utility of serum ferritin as a pragmatic, cost-effective risk stratification tool in resource-constrained healthcare settings.

The central premise of this research rests on the notion that serum ferritin, while not a perfect marker, offers a viable surrogate for total body iron stores in the absence of advanced imaging modalities. The authors maintain a data-driven yet pragmatic perspective—acknowledging both the utility and limitations of serum ferritin. Unlike more technologically advanced biomarkers such as liver MRI T2*, which remain out of reach for many thalassemia centers in developing regions, serum ferritin is

widely available and affordable. As such, the authors advocate for the integration of ferritin-guided clinical protocols to trigger timely interventions and reduce the progression to irreversible organ damage.

Numerous studies reinforce the associations identified in this study. For instance, a 2023 cross-sectional investigation from Islamabad reported a mean serum ferritin level of 6062 ng/mL in β-thalassemia major patients, which strongly correlated with elevated ALT and AST levels ($r = 0.68$ and $r = 0.53$, respectively), confirming hepatic vulnerability in the face of chronic iron overload [13]. Similarly, a study in Lahore identified chelation non-compliance as a major predictor of increased serum ferritin and resultant complications, with mean ferritin levels of 3410 ± 950 ng/mL among non-compliant individuals [14]. The high prevalence of hepatic dysfunction in our cohort (61.2%) and its significant correlation with ferritin levels ($r = 0.59$) are therefore consistent with previous regional findings.

Cardiac involvement, including left ventricular dysfunction and cardiomyopathy, remains a leading cause of morbidity and mortality in thalassemia patients globally. Our study found cardiomyopathy in 29.1% of participants, with a statistically significant inverse correlation between serum ferritin and ejection fraction. This is supported by findings from Darvishi-Khezri et al. (2022), who demonstrated a cardiac risk threshold of serum ferritin >2027 ng/mL with an odds ratio of 2.05 [17]. While cardiac MRI offers higher specificity in detecting myocardial siderosis, its cost and limited availability in developing countries make serum ferritin an essential proxy. Our findings strengthen the argument for ferritin-guided cardiac monitoring, particularly echocardiographic assessment, in thalassemia patients exceeding the 3000 ng/mL threshold.

Endocrine complications in thalassemia have been widely reported, especially among adolescents and young adults. In our study, 42.8% experienced growth retardation, 23.1% had hypothyroidism, and 16.7% had diabetes mellitus—figures that parallel the observations in a recent Faisalabad study reporting endocrine abnormalities in over 50% of patients with serum ferritin above 2500 ng/mL [19]. A Malaysian study further corroborated these findings, identifying high rates of pubertal delay and thyroid dysfunction among transfusion-dependent thalassemics [24]. These complications, often irreversible, severely compromise quality of life and long-term independence, particularly when left undetected due to insufficient surveillance protocols.

A pivotal component of this study was the statistical evaluation of complication risk using inferential methods, including t-tests and one-way ANOVA. These analyses revealed that patients with multi-organ complications exhibited significantly higher serum ferritin levels compared to those with single-organ or no complications ($p < 0.001$). The mean serum ferritin level in individuals with multi-organ dysfunction was 3715 ng/mL versus 2780 ng/mL in those without complications. This stepwise relationship supports the hypothesis that ferritin levels not only correlate with individual complications but may also serve as a predictive marker for cumulative organ burden. It suggests the potential value of ferritin-based risk categories (e.g., <1500 ng/mL, 1500–3000 ng/mL, >3000 ng/mL) for guiding surveillance intensity and therapeutic escalation.

Moreover, our findings reaffirm the critical role of chelation therapy in mitigating iron overload. Chelation compliance was observed in 74% of patients, with deferasirox being the most commonly used agent. Non-compliant individuals had significantly higher mean ferritin levels (4110 ng/mL vs. 2840 ng/mL), alongside increased prevalence of cardiomyopathy and endocrine dysfunction. These observations are consistent with recent Pakistani research showing that oral chelation, when administered consistently, significantly reduces iron burden and delays complication onset [20]. Therefore, patient education, financial support, and simplified treatment regimens must be prioritized to improve chelation adherence.

Limitation of the study:

Despite these compelling associations, the study is not without limitations. Serum ferritin, although widely accessible, lacks specificity due to its susceptibility to inflammation, infection, and hepatic dysfunction. Its use as a stand-alone diagnostic tool may lead to false positives or negatives.

Furthermore, the cross-sectional design of this study precludes the establishment of causal relationships between elevated ferritin and complications. Longitudinal studies incorporating both ferritin and MRI T2* data would provide more definitive evidence regarding iron burden progression and its clinical sequelae. Additionally, future research should explore the potential role of newer biomarkers such as hepcidin and non-transferrin-bound iron (NTBI), which may offer enhanced sensitivity for early iron toxicity. The broader implications of this study are substantial. In Pakistan, where thalassemia remains a major public health challenge with over 100,000 registered cases and a disproportionately high disease burden, early detection of complications could dramatically reduce long-term healthcare costs and improve survival. Ferritin-guided monitoring offers a scalable solution to bridge the gap between ideal and feasible care. By identifying patients at highest risk, resources can be allocated more effectively, and chelation therapy can be tailored to individual needs. These strategies are particularly pertinent in low-resource settings across South Asia, where financial constraints and systemic inefficiencies hinder comprehensive care. Comparative analysis with global data highlights the disparities in care. In high-income countries, where routine MRI surveillance and individualized chelation protocols are standard, patients exhibit significantly lower rates of iron-related complications. For example, French data revealed ferritin levels consistently maintained below 1000 ng/mL in patients receiving early and aggressive chelation, correlating with minimal long-term morbidity [22]. In contrast, our findings illustrate that many Pakistani patients remain undertreated and develop complications by late childhood. This discrepancy underscores the urgent need for policy interventions to make advanced diagnostics and chelators more accessible. This study correlates closely with multiple recent investigations. Rahman et al. in Peshawar identified 29.8% hepatomegaly and elevated ferritin in patients aged 5–15 years [10]; Soliman et al. demonstrated the benefit of calcium channel blockers in attenuating myocardial iron uptake [21]; while a retrospective Indonesian analysis concluded that serum ferritin >2000 ng/mL significantly predicted endocrine and hepatic dysfunction [23]. Our study, therefore, contributes novel data from Pakistan while reinforcing a global consensus on the systemic toxicity of chronic iron overload.

Conclusion

This study offers compelling evidence that serum ferritin serves not only as a marker of iron burden but also as a clinically actionable predictor of organ-specific complications in β-thalassemia major. The findings validate its use in guiding surveillance and therapeutic decisions, especially in resource-limited contexts. By aligning ferritin monitoring with structured complication screening protocols, healthcare systems can deliver more equitable, effective, and preventive care to this vulnerable population.

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