

Correlation of respiratory function tests with serum ferritin level in children with transfusion-dependent beta-thalassemia

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ABSTRACT

Objective: To determine the frequency of asymptomatic respiratory dysfunction and assess the correlation between respiratory function tests and serum ferritin levels in children with transfusion-dependent beta-thalassemia major.

Material and Methods: A cross-sectional study was conducted at the Pediatric Medicine Department, Allama Iqbal Teaching Hospital, DG Khan, Pakistan. We enrolled 136 children (5–15 years) with beta-thalassemia major confirmed by Hb electrophoresis and regular transfusion history. Exclusion criteria included congenital heart disease, pre-existing pulmonary disorders, active infections, or chest deformities. Serum ferritin levels were measured from venous blood samples analyzed at a centralized laboratory. Pulmonary function tests (FVC, FEV1, FEV1/FVC, PEFR, PEF 25–75%) were performed using standardized spirometry. Pearson correlation (r) assessed relationships between ferritin and respiratory parameters.

Results: The cohort (mean age 10.02 years (2.97); 56.6% male) exhibited a high prevalence of asymptomatic respiratory dysfunction (61.8%): restrictive pattern (56.6%), obstructive (5.1%), and normal function (38.2%). Mean serum ferritin was 3420.93 $\mu\text{g/L}$ (1354.90 $\mu\text{g/L}$). Inverse correlations were observed between serum ferritin and FVC ($r = -0.570$, $p < 0.001$) and FEV1 ($r = -0.321$, $p < 0.001$). No significant correlations existed with FEV1/FVC, PEFR, or PEF 25–75% ($p > 0.05$).

Conclusion: Asymptomatic restrictive respiratory dysfunction is prevalent in pediatric beta-thalassemia major. Elevated serum ferritin levels significantly correlate with reduced FVC and FEV1, indicating iron overload contributes to pulmonary impairment.

Keywords: Beta-thalassemia, Child, Cross-sectional studies, Ferritins, Iron Overload, Pakistan, Respiratory function tests.

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INTRODUCTION

Beta-thalassemia is a hereditary hemoglobinopathy characterized by deficient beta-globin chain synthesis, necessitating lifelong blood transfusions to maintain hemoglobin levels and prevent complications in affected children [1]. In Pakistan, beta-thalassemia represents a critical public health challenge. The carrier frequency is estimated at 5-7%, and there are over 100,000 transfusion-dependent patients nationwide [2,3]. Repeated transfusions inevitably cause iron

overload due to the body's limited excretory capacity, leading to multi-organ dysfunction [4]. While cardiac and hepatic complications are well-documented [5], respiratory implications remain understudied despite emerging evidence of pulmonary iron deposition [6].

Globally, 35–80% of transfusion-dependent thalassemia patients develop pulmonary dysfunction, predominantly restrictive patterns linked to iron-induced oxidative stress and fibrosis [7,8]. Regional studies from Egypt and India report significant inverse correlations between serum ferritin levels and forced vital capacity (FVC) in thalassemic children [9,10]. However, Pakistani data on this complication are scarce. Only one single-center study ($n=45$) has been conducted, reporting a 46.7% prevalence of pulmonary dysfunction [11]. Critically, that study did not analyze correlations with ferritin

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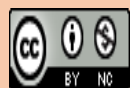
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levels. This knowledge gap is especially important given Pakistan's high thalassemia burden and unique environmental factors that may influence disease progression.

The present study addresses this void by investigating asymptomatic respiratory dysfunction frequency and serum ferritin-respiratory parameter correlations in Pakistani children with transfusion-dependent beta-thalassemia major.

MATERIAL AND METHODS

This cross-sectional study was conducted at the Pediatric Medicine Department of Allama Iqbal Teaching Hospital, DG Khan, Pakistan, from 15th January to 15th June 30, 2025. The minimum required sample size was calculated as 136 participants using the OpenEpi software tool, with a single proportion formula based on an expected respiratory dysfunction prevalence of 77.7% ($p=0.777$) [11], a 95% confidence level ($Z=1.96$), and a 7% margin of error ($d=0.07$):

$$n = Z^2 * p(1 - p) / d^2$$

Non-probability consecutive sampling was employed to enroll participants. Eligible children were aged 5 to 15 years with a confirmed diagnosis of transfusion-dependent beta-thalassemia major. The diagnosis was verified by hemoglobin electrophoresis. Additionally, all participants had a history of regular blood transfusions for at least two years. The upper age limit of 15 years is consistent with the World Health Organization's definition of childhood and ensures a homogenous pediatric cohort prior to the potential onset of adult-onset pulmonary complications. Exclusion criteria included several conditions to avoid confounders. These were: (1) congenital heart disease, (2) pre-existing pulmonary disorders (e.g., asthma or cystic fibrosis), (3) active respiratory infections, and (4) chest wall deformities. Ethical approval (008/01/MED/DGKMC dated 02 January 2025) was secured from the Institutional Review Committee of Allama Iqbal Teaching Hospital, DG Khan. Written informed consent was obtained from all parents or guardians prior to enrollment, adhering strictly to the Declaration of Helsinki principles.

Demographic variables including age, gender, height, and weight were recorded for all participants. Transfusion history variables included duration of transfusions in years and frequency of transfusions per month. Under aseptic conditions, 3 mL venous blood samples were collected for serum ferritin analysis. All samples were processed at the hospital's central laboratory using a chemiluminescent immunoassay. The reference range for serum ferritin was 15–150 µg/L. Pulmonary function tests were performed using a calibrated spiroUSB PC-based spirometer. All testing adhered to the latest American Thoracic Society (ATS) guidelines to ensure standardization. The key spirometry parameters measured were: forced vital capacity (FVC), forced expiratory volume in one second (FEV₁), peak expiratory flow rate (PEFR), and forced expiratory flow at 25–75% of vital capacity (FEF_{25–75%}). Respiratory dysfunction was classified as restrictive if forced vital capacity was below 80 percent of predicted values and obstructive if the ratio of forced expiratory volume in one second to forced vital capacity was less than 0.70. We implemented several measures to ensure methodological rigor. The spirometer was calibrated daily. All ferritin testing was centralized to minimize inter-assay variability. Furthermore, a blinded analysis protocol was used; laboratory technicians and statisticians were masked to all clinical data during testing and analysis.

Statistical analysis employed IBM SPSS version 26.0. Continuous variables were expressed as mean plus or minus standard deviation, while categorical variables were reported as frequencies and percentages. Pearson correlation coefficients determined relationships between serum ferritin levels and respiratory parameters. Stratification analyses by age, gender, transfusion duration, and frequency utilized chi-square tests for categorical outcomes. A p-value less than 0.05 defined statistical significance.

RESULTS

The study cohort comprised 136 children with transfusion-dependent beta-thalassemia major,

with a mean age of 10.02 years (2.97 years) (range: 5–15 years). Males constituted of 77 (56.6%) participants. Anthropometric measurements revealed a mean height of 125.24 cm (14.59 cm) and mean weight of 27.21 kg (10.70 kg). Transfusion frequency averaged 2.33 (0.60) sessions monthly, with 103 participants (75.7%) receiving transfusions for over 5 years.

Respiratory dysfunction was prevalent in 84 participants (61.8%), with restrictive patterns predominating in 77 (56.6%), followed by obstructive patterns in 7 (5.1%). Normal pulmonary function was observed in 52 participants (38.2%). Descriptive statistics for respiratory parameters are presented in Table I, showing mean forced vital capacity of 1.11 L (0.67 L) and forced expiratory volume in 1 second of 0.96 L (0.53 L).

Stratification analyses demonstrated no statistically significant associations between

respiratory dysfunction and age ($p=0.640$), gender ($p=0.688$), transfusion frequency ($p=0.171$), or transfusion duration ($p=0.264$). The mean serum ferritin level was markedly elevated at 3420.93 $\mu\text{g/L}$ (1354.90 $\mu\text{g/L}$) (reference: 15–150 $\mu\text{g/L}$).

Correlation analyses revealed significant inverse relationships between serum ferritin and both forced vital capacity ($r = -0.570$, $p < 0.001$) and forced expiratory volume in 1 second ($r = -0.321$, $p < 0.001$). No significant correlations were observed with FEV₁/FVC ratio ($r=0.169$, $p=0.500$), peak expiratory flow rate ($r=-0.072$, $p=0.404$), or PEF 25–75% ($r=0.024$, $p=0.780$), as quantified in Table-II.

Figure-I illustrates the predominance of restrictive dysfunction (56.6%) over obstructive patterns (5.1%). Figure-II confirms a linear decline in FVC with rising ferritin ($r = -0.570$). Figure-III similarly shows reduced FEV₁ at higher ferritin levels ($r = -0.321$).

Table-I: Descriptive Statistics of Respiratory Function Tests

Test	Mean (SD)	Minimum	Maximum
FVC (L)	1.11 (0.67)	0.8	3.81
FEV ₁ (L)	0.96 (0.53)	0.02	2.45
FEV ₁ /FVC (%)	93.60 (10.89)	48	126
PEFR (L/min)	123.51 (44.94)	35.0	250
PEF 25–75%	1.47 (0.68)	0.19	3.74

Table-II: Correlation Analysis Between Serum Ferritin and Respiratory Parameters

Parameter	Pearson Correlation (r)	P-value
FVC	-0.570	<0.001
FEV ₁	-0.321	<0.001
FEV ₁ /FVC	0.169	0.500
PEFR	-0.072	0.404
PEF 25–75%	0.024	0.780

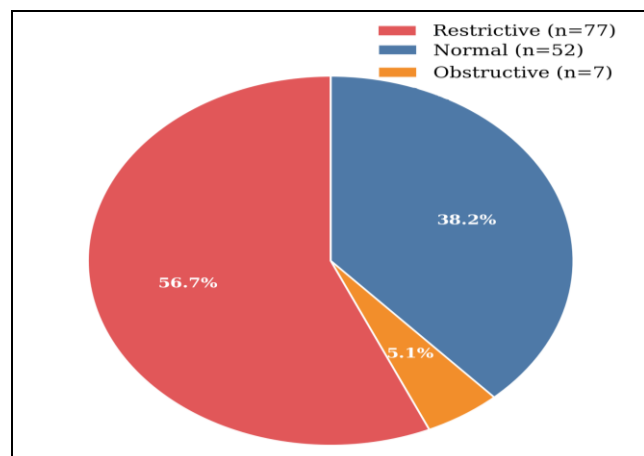


Figure-I: Distribution of respiratory dysfunction patterns: A Pie chart showing 38.2% normal, 5.1% obstructive, 56.6% restrictive.

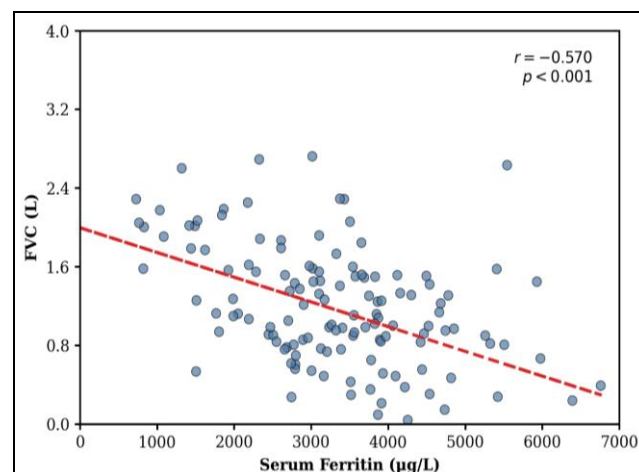


Figure-II: Scatter Plot of Serum Ferritin vs. FVC: Inverse linear relationship with regression line; FVC decreases as ferritin increases.

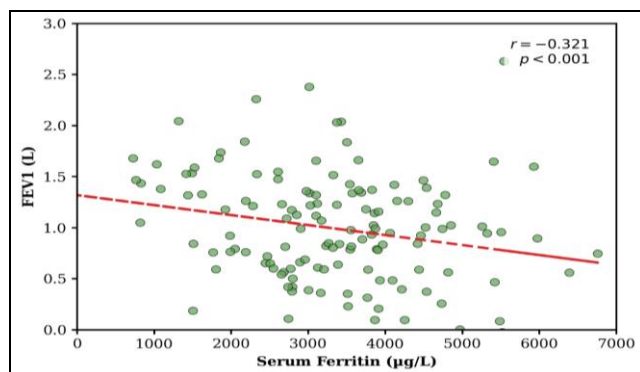


Figure-III: Scatter plot of serum ferritin vs. FEV₁: Inverse linear relationship with regression line; FEV₁ decreases with rising ferritin.

DISCUSSION

This study demonstrates a high prevalence of asymptomatic respiratory dysfunction (61.8%) among Pakistani children with transfusion-dependent beta-thalassemia major, predominantly manifesting as restrictive patterns (56.6%). Critically, we identified significant inverse correlations between serum ferritin levels and both forced vital capacity ($r = -0.570$, $p < 0.001$) and forced expiratory volume in 1 second ($r = -0.321$, $p < 0.001$), suggesting iron overload directly contributes to pulmonary impairment. These findings align with Egyptian and Indian studies reporting similar restrictive dysfunction prevalence (35-73.5%) and ferritin-FVC correlations, but extend evidence to Pakistan's unique population where thalassemia affects 5-7% of carriers.

Our findings align with Patel *et al.* (2024), who reported serum ferritin $>2500 \mu\text{g/L}$ correlated with restrictive patterns ($\text{OR}=4.1$, $p<0.01$) in thalassemia patients. Similarly, Rahman *et al.* (2022) identified FVC reduction proportional to ferritin elevation ($r=-0.48$, $p<0.001$), reinforcing iron overload as a key driver of pulmonary decline. Contrastingly, Gadiparthi *et al.* (2019) found no correlation, highlighting regional variability in chelation access.

The predominance of restrictive dysfunction supports the hypothesis of iron-mediated parenchymal damage, where hemosiderin deposition induces oxidative stress and subclinical fibrosis [11]. This mechanism differs from cardiac iron toxicity pathways, explaining why pulmonary dysfunction often precedes

cardiac complications [12]. The absence of correlations with FEV₁/FVC or PEFR indicates small airways remain initially spared [13], consistent with histological studies showing preferential iron accumulation in alveolar macrophages rather than bronchial epithelium [14].

Notably, our correlation strengths exceed those reported by Abd El Hakeem *et al.* ($r = -0.28$ for FVC) and Ahmed *et al.* ($r = -0.31$ for FEV₁), potentially reflecting Pakistan's limited access to chelation therapy [15], where majority of thalassemia patients experience suboptimal iron control [16, 17]. The lack of association with transfusion frequency/duration suggests cumulative iron deposition rather than transfusion intensity drives pulmonary toxicity [18].

This study has several limitations that warrant acknowledgment. First, the single-center design at a tertiary care facility in Pakistan may limit the generalizability of findings to non-tertiary settings or other geographic populations. Second, while serum ferritin is a practical and widely used marker, it is an indirect measure of systemic iron overload; future studies would benefit from direct quantification of pulmonary iron deposition via thoracic MRI, which is considered the gold standard. Third, although our sample size met the calculated minimum, a formal power analysis for correlation strength was not performed a priori. Fourth, we did not account for chelation therapy adherence variations, which may influence iron accumulation rates. Finally, the lack of healthy controls prevented comparative analysis of respiratory parameters against age-matched peers without thalassemia.

RECOMMENDATIONS

1. Longitudinal studies correlating serial ferritin measurements with spirometry decline
2. Trials assessing whether intensive chelation (e.g., deferasirox-deferiprone combination) reverses pulmonary dysfunction

3. Exploration of genetic modifiers influencing pulmonary iron susceptibility.

In Pakistani children with transfusion-dependent beta-thalassemia, asymptomatic restrictive pulmonary dysfunction is highly prevalent and significantly correlated with serum ferritin elevation. These findings underscore the need for routine pulmonary function monitoring alongside cardiac and hepatic iron surveillance, particularly in resource-limited settings where suboptimal chelation exacerbates iron toxicity. Early intervention through optimized chelation may mitigate pulmonary decline in this vulnerable population.

CONCLUSION

This study demonstrates that asymptomatic restrictive dysfunction affects 56.6% of pediatric transfusion-dependent beta-thalassemia patients in Pakistan. Strong inverse correlations between serum ferritin and FVC ($r=-0.570$) and FEV₁ ($r=-0.321$) confirm iron overload contributes substantively to pulmonary impairment. Routine spirometry and aggressive iron chelation are recommended to mitigate progression.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

GRANT SUPPORT & FINANCIAL DISCLOSURE

Declared none

AUTHORS CONTRIBUTION

Nusrat Hussain: Substantial contributions to study design, acquisition of data, manuscript drafting or reviewing it critical for important intellectual content, final approval, accountable for all aspects of publication.

Ayaz Ali Qureshi: Substantial contributions to acquisition of data, manuscript drafting or reviewing it critical for important intellectual content, final approval, accountable for all aspects of publication.

Irfan Karim: Manuscript drafting or reviewing it critical for important intellectual content, has

given, final approval of the version to be published.

Ashifa Sahar Khan: Substantial contributions to concept, study design, critical review, final approval of the version to be published.

Sobia Rubab: Substantial contributions to acquisition of data, manuscript drafting or reviewing it critical for important intellectual content, final approval of the version to be published.

Shakil Ahmed Leghari: Critical review, proofreading, final approval of the version to be published.

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