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Correlation Between Pulmonary Functions and Iron Overload in Transfusion Dependent Thalassemia Patients Registered in Chughtai Thalassemia Center: A Cross-Sectional Study

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Abstract

Objective: To find correlation between pulmonary function abnormalities with raised serum ferritin levels and Pattern of pulmonary dysfunction in patients with Transfusion Dependent Thalassemia.

Methodology: A Cross-sectional study was Conducted at Thalassemia Centre, Chughtai Institute of pathology, Lahore, Pakistan from March 2025 to September 2025. Fifty patients aged between 7–38 years with transfusion-dependent β-thalassemia who had received ≥20 blood transfusions or had serum ferritin levels greater 1000 ng/mL were enrolled. Patients with known pulmonary disease, acute infection, or inflammatory conditions were excluded. Serum ferritin levels were measured to assess iron overload, and C-reactive protein was used to exclude inflammation. Pulmonary function was evaluated using spirometry, measuring forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and FEV1/FVC ratio. Patterns and severity of pulmonary dysfunction were correlated with serum ferritin levels.

Results: Out of 50 patients, 52% exhibited a restrictive pattern of pulmonary dysfunction, 8% had an obstructive pattern, and 40% had normal pulmonary function. Mean serum ferritin levels increased progressively with the severity of restrictive lung disease (normal: 1888 ng/mL; mild: 3685 ng/mL; moderate: 5289 ng/mL; severe: 9206 ng/mL; p = 0.003). Patients with obstructive patterns also demonstrated significantly elevated ferritin levels. A significant correlation was observed between higher serum ferritin levels and impaired pulmonary function.

Conclusion: Restrictive pulmonary dysfunction is the most common respiratory abnormality in patients with transfusion-dependent thalassemia and is significantly associated with iron overload. Regular pulmonary function monitoring and strict adherence to iron chelation therapy are recommended to reduce iron-related pulmonary complications.

Keywords: Iron Overload, Thalassemia, Pulmonary Disease.

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Introduction

Thalassemia is one of the most prevalent inherited single-gene disorders transmitted through an autosomal recessive pattern. In this condition, both parents carry a genetic mutation that can be passed to their offspring. The disease results from reduced or absent synthesis of globin chains, leading to ineffective erythropoiesis and chronic hemolytic anemia.[1] In Pakistan, the prevalence of the β-thalassemia trait is estimated to range from 5–7%.[2] Approximately 5000 children are newly diagnosed with β-thalassemia major every year. Clinically, individuals with thalassemia commonly present with symptoms related to progressive anemia that necessitates regular blood transfusions. In many developing countries, periodic blood transfusion remains the primary treatment strategy. However, repeated transfusions together with increased gastrointestinal absorption of iron eventually lead to iron overload in patients with transfusion-dependent thalassemia.[3]

Infants with β-thalassemia major usually appear healthy at birth but typically become transfusion dependent around six months of age due to worsening anemia and poor growth. These patients generally require transfusions once or twice every month, and the frequency of transfusions often increases as they grow older. Each transfusion contributes additional iron to the body, which is reflected by elevated serum ferritin levels. Excessive iron accumulation disrupts normal iron homeostasis and results in increased levels of extracellular non-transferrin-bound iron.[4] Over time, this excess iron tends to deposit in various organs including

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the liver parenchyma, myocardium, and endocrine glands.[5] Although the involvement of these organs is well documented, comparatively less attention has been given to pulmonary complications. Some studies have suggested that iron overload may also impair lung function, but the exact relationship remains uncertain.[6]

In the absence of infection or inflammatory processes, serum ferritin concentration is widely used to evaluate body iron stores. Elevated ferritin levels generally correlate with iron overload in patients with transfusion-dependent thalassemia.[7] Iron accumulation can exert toxic effects on multiple organs such as the liver, lungs, myocardium, and endocrine glands. These harmful effects can be reduced through appropriate iron chelation therapy. Chelation treatment is usually initiated after a patient has received at least 20 units of packed red cells or when serum ferritin levels rise above 1000 microgram/dl.[8] Iron chelators bind excess iron and facilitate its removal from the body, after which the iron-chelator complexes are excreted through urine or feces.

Currently, three major iron chelating agents are commonly used in clinical practice: Deferasirox, Deferiprone, and Deferoxamine. These drugs may be administered either as monotherapy or in combination depending on the clinical requirement.[9] In many cases, patients with transfusion-dependent thalassemia (TDT) require combination therapy with two iron chelators to achieve more effective reduction of iron burden.

Pulmonary function is commonly assessed using spirometry, a test that evaluates the mechanical performance of the lungs, chest wall, and respiratory muscles.[10] Spirometry is widely utilized in the diagnosis and monitoring of several pulmonary disorders. It measures different parameters including forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), and the ratio of FEV1 to FVC (FEV1/FVC). These parameters reflect the volume of air that can be inhaled and exhaled, as well as the rate of airflow during expiration.

FVC represents the total volume of air that can be forcefully expelled after maximal inspiration. FEV1 indicates the amount of air exhaled during the first second of forced expiration. Another important parameter, the FEV_1/FVC ratio, assists in distinguishing between different types of pulmonary dysfunction. A decreased FEV1/FVC ratio typically indicates an obstructive pattern of lung disease, whereas a normal FEV1/FVC ratio accompanied by reduced FVC is suggestive of a restrictive ventilatory defect.[11]

This center-based study was carried out at the thalassemia center of the Chughtai Institute of Pathology, Lahore. The primary objective of the study was to evaluate the correlation between iron overload and pulmonary dysfunction in patients with thalassemia who had received more than 20 blood transfusions. Additionally, the study aimed to determine the pattern of pulmonary impairment associated with iron overload in individuals with transfusion-dependent thalassemia. Spirometry was performed to assess lung function in patients who were receiving regular transfusions and had undergone more than 20 transfusion episodes. Serum ferritin levels were measured to evaluate the iron status of the body in the absence of infection or inflammation. C-reactive protein (CRP) testing was also performed to exclude the possibility of underlying infection or inflammatory conditions in these transfusion-dependent thalassemia patients.

Methodology

This institution based cross-sectional study was done at thalassemia center of Chughtai institute of pathology, Lahore Pakistan from March, 2025 to September, 2025. A formal ethical approval from institutional review board (IRB Number is 1235) was taken before conducting this study. Informed written consent was taken from the parents of thalassemia patients. 50 subjects aged between 7-38 years were included in this study. All the subjects were diagnosed cases of transfusion dependent B-Thalassemia (diagnosed by High performance liquid chromatography or HB-Electrophoresis). All of these thalassemia patients were on regular transfusions since the diagnosis of thalassemia.

The inclusion criteria for this study comprised thalassemia patients who had received at least 20 blood transfusions or had serum ferritin levels exceeding 1000 ng/mL. Patients with pre-existing pulmonary diseases, active chest infections, or other significant comorbid conditions such as hepatic or cardiac disorders were excluded from the study. In addition, children who were unable to perform spirometry were not included in the analysis.

In our institute, iron chelation with Deferasirox is started at the dose of 20-40 mg/Kg in patients whose serum ferritin level exceeds 1000 ng/ml. All the thalassemia patients included in the study were on iron chelation therapy. Many of these thalassemia patients were on dual therapy with iron chelators (deferasirox + deferoxamine/ deferiprone). Regular monitoring of granulocyte counts through complete blood counts (CBC), along with periodic liver and renal function tests, is carried out in these patients to assess for potential adverse effects of the iron chelators. Moreover, regular screening for any transfusion transmitted infection such as Hepatitis B, Hepatitis C, HIV, Syphilis and malaria is also carried out in our thalassemia center.

A detailed personal and family history was taken from the patients. Clinical examination was done and findings were recorded on a structured proforma. Patients were instructed to avoid medications other than iron chelators before transfusion. Venous samples for serum ferritin levels and CRP were taken before transfusion. Patients were subjected to spirometry after giving a detailed demonstration about spirometry. They were advised to take normal breaths followed by deep inspiration and holding the breath for a few seconds, after that they were advised for forceful expiration into spirometer through a mouthpiece. The procedure was repeated thrice and the best attempt among these three attempts was considered for result interpretation. Results of Pulmonary function test were interpreted by an experienced pulmonologist.

Serum ferritin was measured using Alinity Ci to assess body iron status while spirometry was performed using MIR spiro 1.1. Lung function test included FEV1 (Forced expiratory volume in first second), FVC (Forced vital capacity) and FEV1/FVC ratio. Spirometry results were consulted with a pulmonologist for better interpretation. The pattern of pulmonary dysfunction (obstructive or restrictive) based on spirometry results in these TDT patients was identified. The pulmonary dysfunction was then correlated with serum ferritin levels and degree of severity of pulmonary dysfunction was evaluated. CRP was done to exclude any underlying infection or inflammation.

According to American thoracic society, mild restrictive pattern corresponds to FVC less than 80% of the predicted value, moderate severity corresponds to FVC less than 60%, and severe severity to less than 50% of the predicted value, in the absence of total lung capacity (TLC) data.[12]

Data was entered in MS Excel sheet and analyzed using SPSS 23. Mean, median and standard deviation were used for quantitative data while frequency and percentage was used for qualitative data. Pearson correlation coefficient was used wherever applicable. P Value < 0.05 was taken significant.

Results

Out of a total of 80 patients registered in chughtai thalassemia center, 50 subjects were included in the study on the basis of inclusion and exclusion criteria mentioned above. Out of these 50 patients, 56% were females and 44% were males aged between 7-38 years [Table I]. All of these patients were a diagnosed case of thalassemia major since the age of 6 months. These patients were transfusion dependent and majority of them required more than 20 transfusions/ year. Moreover, all of these patients were on iron chelation therapy. Most of them were taking deferasirox, which is an oral iron chelator but some of them were also on combination therapy with deferoxamine or deferiprone along with deferasirox. Anthropometry findings suggested that most of these patients were underweight and had stunted growth.

Out of 50 patients included in the study, 26 subjects (52%) had restrictive pattern of pulmonary disease. 4 subjects (08%) were having obstructive pattern of pulmonary disease while 20 (40%) subjects had normal pulmonary functions. Patients with obstructive pattern of lung disease had low FEV1/FVC ratio while those with restrictive pattern of pulmonary disease had normal or high FEV1/FVC ratio with low FVC.

Severity of Pulmonary dysfunction was categorized according to American thoracic society into Mild, Moderate and Severe. Patients having mild, moderate and severe restrictive pattern of pulmonary dysfunction were 57.69%, 34.6% and 7.6% respectively. (Table2). Majority of thalassemia major patients had decreased FVC [mean 72.3% with SD 5.5%]. The FEV1/FVC ratio in most of these patient was found to be normal or high [Mean 82% with SD 4.2%].

Mean ferritin levels in mild restrictive pattern were found to be 3685ng/ml while in moderate and severe restriction it was found to be 5289 ng/ml and 9206 ng/ml respectively (table). Serum ferritin levels were significantly high in case of severe restrictive pattern of pulmonary dysfunction i.e. > 9000 ng/ml. Mean Serum ferritin levels in patients with normal lung functions were found to be less than 2000 ng/ml. Whereas, Mean ferritin levels in patients with obstructive pattern of lung disease was 5403ng/ml which is also significantly high. Therefore, a significant correlation (r= -0.423) between high serum ferritin levels and pulmonary dysfunction was found in patients with transfusion dependent Thalassemia.

Discussion

Patients with Beta Thalassemia major become transfusion dependent as soon as they reach the age of 6 months. Normally by the age of 6 months the switch from HbF (Fetal hemoglobin) to HbA (Adult hemoglobin) has taken place, the process termed as fetal-to-adult hemoglobin switch.[13] But in the patients with thalassemia major HbF persists (>90%) as there is failure of normal fetal-adult hemoglobin shift and that leads to severe hemolytic anemia and ineffective erythropoiesis Thus, to combat severe anemia, patients become transfusion dependent from the age of 6 months.[14]

Table I: Correlation of Anthropometry with ferritin levels and spirometry findings.

	median	SD	mean
Age (yrs)	12	9.3	15.86
Weight (Kgs)	40	14.53	44.34
Height (Cm)	137	15.44	140
ferritin	3183.00	2541.11	3613.66
FEV1	74	14.19	78.26
FVC	78	13.28	82.87
FEV1/FVC	85	6.9	84.8

Table II: Severity of pulmonary dysfunction.

Severity type	Restrictive	Percentage
Mild	15	57.69%
Moderate	09	34.6
Severe	02	7.6
Total	26	52% of total subjects

Patients with Beta thalassemia Major are at high risk of iron overload due to multiple blood transfusions. One Red cell concentrate contains 200-250mg of iron.[15] While the excretion of iron through body is around 1-2mg per day.[16] In absence of adequate chelation this excess iron has tendency to get deposited in multiple organs such as liver, myocardium, endocrinal organs and pulmonary interstitium resulting in organ dysfunction. Deposition of excess iron in lung parenchyma leads to pulmonary hemosiderosis which causes pulmonary functions abnormalities as seen in our study.

Almost all of our registered thalassemia patients were on iron chelation therapy. Combination therapy with Deferoxamine and deferasirox or deferiprone is given to most of these patients for effective removal of excess iron from the body. Deferoxamine eliminates excess iron through fecal route while other iron chelators remove iron through urine as well.[17]

Serum ferritin was used to assess iron status of TDT patients. As ferritin is an acute phase reactant, it increases during infection and inflammation. Thus, C-Reactive protein (CRP) was also used in these patients to rule out any possibility of infection or inflammatory body condition. A detailed history and examination was done prior to spirometry. None of the patients included in this study had any cardiac or hepatic dysfunction. Pulmonary functions were assessed by Spirometry.

According to our study, restrictive pattern of lung disease was found to be the most common pulmonary dysfunction in transfusion dependent thalassemia

Table III: Correlation between degrees of pulmonary dysfunction with serum ferritin levels.

Severity of pulmonary dysfunction	N	Mean ferritin	Std. Deviation	Pearson correlation coefficient	P-Value
Normal	20	1888.60	1418.996	Sig. (2 tailed): 0.002 r = -0.423	0.002
Mild	15	3685.13	1934.283		
Moderate	09	5289.89	2077.340		
Severe	02	9206.00	3826.862		
Total	50	3613.66	2541.110		

patients. This pulmonary dysfunction resulted from increased iron accumulation in pulmonary interstitium. A total of 50 TDT patients were included in this study, 26 were found to have restrictive pattern of disease. Varying degree of restrictive pattern of lung disease was observed in these patients. (Table III). Severity of pulmonary dysfunction increased with increase in serum ferritin levels. The results were similar to many studies conducted previously on TDT patients.

A similar study conducted on 42 children with beta thalassemia major at the pediatric department of Kasturba Medical College, 95% subjects were found to have restrictive pattern of lung dysfunction on assessment of their lung functions. The results of this study were quite comparable to the one conducted at out center. Severity of pulmonary dysfunction had a significant correlation with high serum ferritin levels.[18]

Another cross sectional study conducted at a teaching hospital in Rahim Yar Khan demonstrated similar results. In this study a total of 115 patients with TDT were assessed for pulmonary dysfunction and iron overload. 31.30% TDT patients were found to have restrictive pattern while 10% had obstructive pattern of lung dysfunction.[19] According to this study obstructive pattern of lung disease was also common in certain population with transfusion dependent thalassemia. Comparing the results with our study, 08% of our registered thalassemia patients had obstructive lung disease with Serum ferritin levels more than 5000ng/dl.

A study conducted in the Department of Pediatrics at Assam Medical College and Hospital on patients who were compound heterozygous for HbE/β-thalassemia reported similar findings. Hemoglobin E/β-thalassemia (HbE/β-thalassemia) is a compound heterozygous condition involving HbE variant and β-thalassemia, and it often results in a severe clinical phenotype. Affected patients typically develop significant anemia requiring regular blood transfusions, similar to those with β-thalassemia major. Consistent with our observations, these transfusion-dependent thalassemia (TDT) patients demonstrated an increased prevalence of restrictive pulmonary dysfunction, likely attributable to iron overload.[20]

The present findings of deranged pulmonary function tests in patients with beta thalassemia major are consistent with observations reported by Harsoor J., in a study held in university of health sciences India, who demonstrated a high prevalence of pulmonary function abnormalities in transfusion-dependent children. The restrictive pattern noted in most patients may be attributed to chronic anemia, repeated blood transfusions, iron overload, and resultant oxidative damage to lung parenchyma, leading to reduced lung compliance. Additionally, iron deposition in pulmonary tissues and recurrent respiratory infections may contribute to impaired ventilatory mechanics. The progressive nature of pulmonary dysfunction with increasing age and transfusion duration, as highlighted in Harsoor's study, underscores the cumulative impact of disease burden and treatment-related complications.[21]

Ece and colleagues evaluated respiratory function in patients with β-thalassemia major and investigated the acute effects of blood transfusion on pulmonary parameters. Their study, conducted in a pediatric population, demonstrated that a significant proportion of patients exhibited impaired pulmonary function, predominantly showing a restrictive pattern of pulmonary dysfunction. The authors observed measurable improvements in certain spirometric indices following transfusion, suggesting that correction of anemia may temporarily enhance respiratory mechanics by improving oxygen delivery and reducing the work of breathing. However, persistent abnormalities in lung function despite transfusion indicated underlying structural or functional lung involvement, possibly related to chronic iron overload, repeated transfusions, or long-standing disease effects.[22]

In a cross-sectional study conducted in Pakistan, Faruqi and colleagues evaluated patients with beta thalassemia major to assess the relationship between iron overload and liver function abnormalities. The study enrolled transfusion-dependent individuals and demonstrated that excessive iron accumulation was significantly associated with deranged liver enzymes, indicating hepatic involvement as a common complication of chronic transfusion therapy. Elevated serum ferritin levels correlated with impaired liver function parameters, reflecting the systemic impact of iron overload. Although the study primarily focused on hepatic outcomes, these findings are relevant to the present study, as iron-mediated tissue damage is a

multisystem process that may also contribute to pulmonary dysfunction.[23]

Our findings indicate a significant association between elevated serum ferritin levels and pulmonary dysfunction in patients with transfusion-dependent thalassemia. Among the various patterns observed, restrictive lung dysfunction was the most prevalent. Adequate iron chelation therapy, along with strict treatment compliance, is essential to minimize pulmonary hemosiderosis in these patients. In addition, routine pulmonary function testing is advisable for TDT patients with serum ferritin levels above 2500 ng/mL to enable early identification and appropriate management of respiratory impairment.

Limitations: A single center based study, smaller sample size and gold standard for iron overload assessment is hepatic biopsy which was not feasible. All the patients were on iron chelation therapy.

Conclusion

Concluding the study, Restrictive pattern of lung disease of varying severity was observed to be the most common form of pulmonary dysfunction in transfusion dependent thalassemia patients. Although obstructive pattern of pulmonary dysfunction was also observed in some patients. The severity of pulmonary dysfunction has a significant correlation with high serum iron levels. Thus as it is evident from our study, all transfusion dependent thalassemia patients should undergo pulmonary functions assessment on regular basis for early detection and appropriate management of respiratory impairment.

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