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# A Cross-Sectional Study of Cardiopulmonary Functions in Transfusion Dependent Thalassemia Patient

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## Abstract

**Introduction:** A Cross-Sectional Study of Cardiopulmonary Functions in Transfusion Dependent Thalassemia Patient and describe the correlation between the biochemical, hematological, echocardiographic, and Spirometry profiles of the patient with the severity and prevalence of Cardiopulmonary dysfunction in Transfusion Dependent Thalassemia patients.

**Methods:** A Cross-Sectional Study, a total of 100 patients diagnosed with Transfusion Dependent Thalassemia visiting the hospital for their regular packed cell transfusion were recruited in the study. Detailed history regarding Chelation Therapy and symptoms were obtained. Pulmonary Function Tests, as assessed by Spirometry and Echocardiographic changes, were compared with corresponding Serum Ferritin and MRI values to assess Iron overload status.

**Results**: 10% of patients in our study had symptoms of heart disease, while 14% had symptoms of underlying pulmonary affection. 12 % of the study population had abnormal 2D Echo characterized by z score >2.0 or Ejection fraction <60%. Among patients with Serum Ferritin Levels more than 5000ng/ml, 36% had a severe cardiac iron load on T2*Cardiac MRI. 65% of patients had Restrictive patterns on Spirometry, 2% had mixed patterns, and none had pure obstructive patterns. 57.% of patients with Serum Ferritin above 5000ng/ml had a restrictive pattern on Spirometry.

**Conclusion:** Most subjects did not have symptoms of Overt Cardiac Failure. PFT parameters were decreased with advancing age and Serum Ferritin values. Therefore, regular uninterrupted chelation therapy must be initiated with meticulous monitoring of Serum Ferritin levels. Annual Echocardiographic screening and Cardiac MRI to assess Left ventricular dimensions and functionality must be undertaken.

**Keywords:** Cardiac**,** Magnetic Resonance Imaging, Echocardiographic, Serum Ferritin

**Introduction**

Cardiac failure due to iron overload remains the most common cause of death in Transfusion Dependent Thalassemia. Cardiac complications are due to left ventricular diastolic dysfunction, leading to dilated cardiomyopathy and gradual cardiac failure. Cardiac iron overload increases the relative risk of further dilation, arrhythmias, and decreased systolic function. However, many patients are asymptomatic despite heavy cardiac burdens. We explore possible mechanisms behind cardiac iron-function relationships and relate these mechanisms to clinical observations.

**Materials and Methods**

This cross-sectional, observational study was conducted in 100 consecutive patients with TDT between the age group of 10-20 years undergoing regular packed red cell (PRC) transfusion and on iron chelation for a minimum period of two years, attending the Thalassemia Day Care Centre in a tertiary care hospital from January 2022 to December 2022 (12 months). Children with underlying pulmonary disease and those unable to perform Spirometry were excluded from the study. History and clinical examination were noted in a predesigned case record form. Details of packed red cell transfusion and chelation history were obtained.

Complaints regarding pre-existent pulmonary or cardiac impairment were asked for. Examination for liver and spleen enlargement was checked for and graded as described in the Hutchinson clinical manual. Weight was determined using a digital scale, and height was measured using a stadiometer. Iron overload was assessed based on Serum Ferritin, T2* weighted Magnetic Resonance Imaging (MRI) of the liver and heart, and 2D echocardiography of the heart was also done to look for ventricular dimensions and Ejection Fraction.

Conventional echocardiographic measurements were done according to the American Society of Echocardiography guidelines. Echocardiographic images were obtained with four standard transducer positions: parasternal, apical, suprasternal, and subcostal. The dimensions of the measured left ventricle were graded according to the corresponding Z score obtained for the child's Body Surface Area (BSA).

Spirometry was done using windows based digital Spirometer. All patients were advised to do the process three times, and the best of these three scores was taken. American Thoracic Society (ATS) criteria for the acceptability and repeatability of Spirometry were strictly followed.

**Statistical Analysis**

Data was analyzed using SPSS V15.0 (Statistical Package for Social Sciences, Version 15.0). Chi-square statistical tests were applied to compare percentages among more than two groups. Pearson Correlation Coefficient (r) was calculated between important variables and was tested for significance. All statistical tests were two-tailed. Alpha (α) Level of Significance was taken as $P<0.05$.

**Observations and Results**

Among the study subjects, 60 (58%) patients were male, and 42(41%) were female, with a male: female ratio of 1.4:1. Maximum patients were 10-15 years old. 91% of the patients belonged to the lower socioeconomic strata.

9(8.8%) patients included in the study were severely thin. 6% of the study subjects had an annual PRC requirement >220ml/kg/year, while the Mean PRC requirement was 175.56 +/- 37.77 ml/kg/year. All

patients were either on one or two combination-based iron chelating agents. 78(76.4%) of study subjects were on single-agent Deferasirox, of which the majority (32.4%) had received chelation for 2-5 years. Only 10(9.8%) patients were symptomatic for any underlying cardiac dysfunction, while 15(14.7%) had symptoms of pulmonary affection. 96(94.2%) patients had hepatomegaly and 94(91.2%) patients had splenomegaly.

Table 1: Clinico-epidemiological profile

| Parameters | Mean (SD) | Range |
|---|---|---|
| Age (years) | 13.0 (3.35) | 6-18 |
| BMI ($kg/m^2$) | 15.88 (2.51) | 10.7-25.9 |
| Annual PRC requirement (ml/Kg/Year) | 172.92 (35.57) | 90-300 |

Table 2: Biochemical and hematological profile of study subjects

| Parameters | Mean (SD) | Range |
|---|---|---|
| Hemoglobin (gm/dL) | 7.78 (0.55) | 6.3-9.5 |
| Total Bilirubin ((g/dl) | 1.51 (0.508) | 0.3-3.1 |
| AST (IU/dl) | 47.07 (19.78) | 0.1-124 |
| ALT (IU/dl) | 38.86 (22.37) | 10-117 |
| Total Protein (g/dl) | 6.7 (0.73) | 1.6-8.4 |
| Albumin (g/dl) | 3.85 (0.40) | 2-5.2 |
| Serum Ferritin (microgram/l) | 2968.13 (2214.02) | 524-9924 |

46(45%) patients had Serum Ferritin in the range of 1000-3000ng/ml while 19(18.6%) patients had Ferritin levels in excess of 5000ng/ml. 53(51.9%) patients had severe Hepatic Iron load. 11(9.8%) patients had severe Cardiac Iron load as detected by T2* MRI findings. 13(12.8%) patients had an Echocardiographic abnormal finding. (Z score >2.0 or EF<60%), Echocardiographic analysis comparing expected z scores revealed a significant increase in markers of ventricular dimensions (LVDd, LVDs, IVS, PWD) with age. Ejection Fraction (EF) did not show correlation with age. Among patients with Serum Ferritin Levels more than 5000ng/ml, 36% had a severe cardiac iron load on T2*Cardiac MRI. Our study suggests a strong correlation between T2* Cardiac MRI, LV dysfunction, and Serum Ferritin levels. 44.5% of patients with a severe cardiac iron load on MRI had abnormal echocardiographic findings. 67(65.6%) patients had a restrictive pattern on Spirometry, 2(1.9%) patients had a mixed pattern, and none had a pure obstructive pattern. 57.1% of patients with Serum Ferritin above 5000ng/ml had restrictive patterns on Spirometry. A significant association was found between Serum Ferritin levels and Pulmonary functions.60% of patients with a severe cardiac iron load on T2* Cardiac MRI had restrictive spirometry patterns. Our study revealed a significant association between T2* Cardiac MRI and Spirometry values.

Table 3: Co-relation between Serum Ferritin, Spirometry and Echocardiographic findings

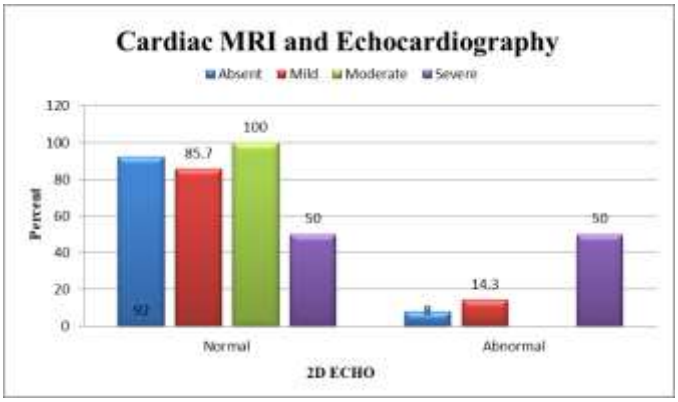
| Ferritin(ng/ml) | Spirometry | | | | 2D echo | |
|---|---|---|---|---|---|---|
| | Normal | Obstructive | Restrictive | Mixed | Normal | Abnormal |
| 0-200 | | | | | | |
| 200-1000 | 2 (12.5) | | 14 (87.5) | | 14 (87.5) | 2 (12.5) |
| 1000-3000 | 22 (47.8) | | 24 (52.2) | | 42 (91.3) | 4 (8.7) |
| 3000-5000 | 3 (14.3) | | 18 (85.7) | | 19 (90.5) | 2 (9.5) |
| 5000-10000 | 6 (31.6) | | 11 (57.9) | 2 (10.5) | 14 (73.7) | 5 (26.3) |
| P Value | 0.003* | | | | 0.346 | |

**Discussion**

Cardiac failure due to iron overload remains the most common cause of death in patients with transfusion-dependent thalassemia. Complications are related to left ventricular dysfunction, pulmonary dysfunction, and right ventricular abnormalities, even in the absence of overt heart failure. Iron overload leading to pulmonary damage is seen in many studies. Restrictive lung disease has been found in Thalassemia patients, but the pathophysiology is unclear.

Only 14.7 % of patients had any symptoms of pulmonary affection, and similarly, only 9.8% of patients had cardiac symptoms, most belonging to the 14–18-year age group. Most patients tend to remain asymptomatic until the late stages.

Measuring tissue iron, total body iron and adjusting chelation therapy appropriately is crucial to patient management. Liver Biopsy, initially considered the gold standard to detect Iron load, is invasive and associated with complications. It can also be erroneous due to the heterogeneous distribution of Iron throughout the liver and is unsuitable for related long-term follow-up. Recently, Biopsy has been replaced by magnetic resonance imaging. T2*MRI can measure the concentration of iron in the liver and the heart and is non-invasive. Severe Liver Iron overloading in patients can be explained as Iron accumulation starts earlier in the liver with each transfusion, with ineffective erythropoiesis, Hepatotropic viral infections, and improper compliance to chelation therapy. In contrast, Iron loading on the heart starts only after ten years of age among those undergoing adequate transfusion.




Graph 1: Correlation between Cardiac MRI and Echocardiographic Findings.

Echocardiographic analysis of ventricular dimensions revealed increased chamber size with age advancement. However, the ejection fraction was preserved. Since Cardiomyopathy is the leading cause of mortality and morbidity in thalassemia patients, early diagnosis may be helpful for the control of disease progression, transfusion planning, time to start, and dosage of chelation. Conventional 2D echo parameters were utilized in our study, which have been observed to remain normal till late stages. 36% of the patients with

Serum Ferritin more than 5000ng/ml had severe iron loading on T2*Cardiac MRI, while none of the patients with serum ferritin <1000ng/ml had any cardiac iron load. With increasing number of transfusions, Serum Ferritin levels increases, and corresponding cardiac iron load also increases. (4) As stated previously, iron loading on the heart starts only after 10 years of age if the patient is on adequate chelation. It is not possible to predict myocardial iron concentration from myocardial T2* MRI value definitively because no validation has been performed with cardiac tissue. However, a strong correlation exists between Cardiac MRI, LV dysfunction, and Serum Ferritin levels.

Individual Spirometric values used to assess pulmonary affection showed a decrease in values across FeV1, FVC, and Fev1/FVC, indicating a restrictive pattern. Increasing Iron deposition in the lung parenchyma with a load of transfusions and reduction in lung volumes by the rising pressure on the diaphragm by the enlarged liver and spleen contributed to the pulmonary affection. (11) Among the patients with Ferritin levels >5000ng/ml, 57.1% had abnormal spirometry values (P value 0.003). Although multifactorial, the degree and duration of Iron overload decides the restrictive ventilatory deficit. A defective alveolocapillary membrane may have accounted for diffusional impairment in many patients.

8.9 % of patients had both pulmonary and cardiac dysfunctions. Although there was no statistical significance, right ventricular dysfunction and pulmonary hypertension are more common among those who did not have signs of overt heart failure. (13) One of the limitations of our study is the cross-sectional assessment of lung function at one point. It would be more informative to follow these patients and assess longitudinal changes in their lung function. Like the heart, the lung is prone to infiltration and damage by hemosiderosis and a high output state of chronic anemia. The prevalence of pulmonary hypertension further complicates this.

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