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Research Article

# Assessing Pulmonary Function Tests in Patients with Thalassemia Major: A Descriptive Cross-Sectional Study

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## ABSTRACT

**Background and objectives:** Major β-thalassemia refers to a severe form of β-thalassemia in which, patients need blood transfusions from an early age. Iron overload is an important and long-term complication of repeated blood transfusions. The lungs are one of the sites of iron deposition; therefore, it is essential to investigate lung dysfunction due to iron deposition. This study evaluates pulmonary function tests in β-thalassemia major patients receiving regular blood transfusions and chelation therapy.

**Methods:** In this cross-sectional descriptive study, 120 patients (68 males and 52 females) with β-thalassemia major aged 6 to 41 years who underwent blood transfusion at Bahrami Children's Hospital (Tehran, Iran) in 2021 were enrolled. The patients underwent hematological and pulmonary function tests on the day of transfusion. Association between pulmonary function tests and demographic and laboratory data was investigated.

**Results:** Spirometry indices including forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), and forced expiratory volume to forced vital capacity ratio (FEV1/FVC) were 86.14%±9.9, 87.86%±11.19, and 98.78%±10.97, respectively. In this study, the percentages of FEV1 and FEV1/FVC of patients older than 23 years were significantly lower compared to patients younger than 23 years. Moreover, a significantly lower FEV1/FVC ratio was seen in patients with higher body mass index and a serum ferritin level above 3,325 ng/dl. The most common impairment (19%) was a restrictive pattern.

**Conclusion:** Age is inversely associated with FEV1 and FEV1/FVC ratio. Moreover, higher body mass index and serum ferritin levels are significantly associated with reduced FEV1/FVC ratio.

**Keywords:** Thalassemia; Respiratory Function Tests; Blood Transfusion; Iron Overload

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## INTRODUCTION

Thalassemia syndromes are hemoglobinopathies in which globin chain biosynthesis is affected, and the affected globin chain may be categorized into α, β, or δβ thalassemia syndromes (1). Thalassemia syndromes are the most common single-gene disorders, affecting more than 200 million people worldwide (2, 3).

Beta-thalassemia's presentation varies from asymptomatic anemia diagnosed during annual health evaluations to severe chronic anemia, which could be fatal if not approached correctly (4). The impairment of globin chain biosynthesis is classified as β-thalassemia minor, intermedia, and major. Cooley's anemia or β-thalassemia major (BTM) is the most severe form with ineffective erythropoiesis, hemolytic anemia, and reduced tissue oxygenation capability (5). Patients with BTM require repeated and regular blood transfusions from an early age, which dispose them to short- and long-term complications.

Iron overload results in iron deposition in different organs' parenchyma, thereby leading to inflammatory changes and dysfunction (6). The heart, liver, and endocrine glands are among vital affected organs with various manifestations (7). The lungs are also among organs affected during iron overload, but since most of asymptomatic patients are not extensively investigated, signs of iron deposition were found in autopsy studies (8, 9). This study aims to evaluate pulmonary function test (PFT) in BTM patients receiving regular blood transfusions and chelation therapy at a hospital in Tehran, Iran.

## MATERIALS AND METHODS

### Subjects and study design

This analytical cross-sectional study included 120 BTM patients aged more than 6 years old who received medical care at the Bahrami Children's Hospital in Tehran (Iran) between March 2021 and June 2021.

Patients with a history of uncontrolled respiratory disease, respiratory failure, congestive heart failure, transfusion injury, diabetes, hypertension, and thoracic surgery were excluded. According to the national blood transfusion protocols, participants had blood transfusion (10 ml/kg) every 3 to 4 weeks to maintain hemoglobin level above 9 mg/dl. Data including personal information, age, medical history, physical examination results, laboratory test results, PFT results, and outcomes were collected from patients' medical records at the hospital. The study was approved by the ethics committee of Tehran University of Medical Sciences (ethics approval reference number: IR.TUMS.CHMC.REC.1399.129).

### PFTs

Pulmonary function tests were performed on patients using the MIR Spirolab III (version 4.6) spirometer prior to blood transfusion. A trained operator performed the PFTs, and the best results of three given examinations were reported. First, the patients were educated to test accurately. All children were tested in standing position. Forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), and forced expiratory volume to forced vital capacity ratio (FEV1/FVC) were reported. In this study, an impairment threshold of <80% was considered. The respiratory patterns were defined as obstructive pattern (both FEV1 and FEV1/FVC are <80%) or restrictive pattern (FVC <80% and FEV1/FVC ≥80%).

### Paraclinical assessments

A standing posterior anterior chest X-ray and blood samples were collected from all patients just before the blood transfusion. Hematological parameters including complete blood count and serum ferritin were evaluated. Serum ferritin was measured using an enzyme-linked immunosorbent assay kit (Pishtaz Teb Zaman Diagnostic, Tehran, Iran) according to the manufacturer's instructions.

### Statistical analysis

All statistical analyses were performed using the SPSS software (version 22). Continuous and categorical variables were presented by the mean (±standard deviation) and frequencies, respectively. For comparison analysis, the patients were categorized into two groups above and below the variables' means. The independent-samples t-test was used for comparison of the means. The variables were investigated using visual histograms and probability plots. A p-value of less than 0.05 was considered statistically significant.

## RESULTS

The study included 120 BTM patients (68 males and 52 females) with an average age of 23.1 years (age range: 4-41 years). Table 1 shows the baseline anthropometric and clinical characteristics of the participants by gender. Body mass index (BMI) of females was significantly higher than that of males (p=0.001). The patients were clinically stable, with SPO2 level of ≥96%, and no fever. Moreover, chest X-rays were normal.

Figure 1 shows the PFT distribution histograms. According to the PFT ratios, the patients' PFT patterns were evaluated. Overall, 65.8% of the patients had a normal PFT pattern. The restrictive pattern was the most common abnormality (19%) in BTM patients, while only 5% of the patients had obstructive patterns.

The average level of baseline characteristics was considered as the threshold for dividing the patients into two independent groups. The PFT's ratios below and above the thresholds were compared among the categorized groups. The results of final comparison analysis between the groups are summarized in table 2.

Patients with a mean age of ≤23 years had significantly higher FEV1 than those with a mean age of >23 years (p=0.035). Correspondingly, the FEV1/FVC index was significantly higher among younger subjects (p=0.007). There was no significant difference in pulmonary function parameters between males and females. Subjects with a higher BMI had lower FEV1/FVC, but there was no significant difference in cases of FEV1 and FVC alone (p=0.019). Moreover, patients with higher ferritin levels had a significantly lower FEV1/FVC ratio (p=0.001). Subjects with higher serum hemoglobin levels had higher FEV1 (p=0.043). Furthermore, longer intervals between transfusions were significantly associated with a higher FEV1 value (p=0.044).

**Table 1. Baseline characteristics of the patients**

| Variables | Total (n=120) | Male (n=68) | Female (n=52) | *p*-value |
|---|---|---|---|---|
| Age (years) | 23.1 ± 9.3 | 22.3 ± 9.1 | 24.2 ± 9.5 | 0.264 |
| Body mass index (kg/m$^2$) | 20.9 ± 3.6 | 20.1 ± 3.3 | 22.1 ± 3.8 | 0.001* |
| Ferritin (mg/dl) | 3325.4 ± 30.57.6 | 3193.4 ± 3162.6 | 3498 ± 2935.9 | 0.590 |
| Hemoglobin (mg/dl) | 9.8 ± 1.2 | 10 ± 1.3 | 9.6 ± 1 | 0.062 |
| FEV1 (%) | 86.1 ± 9.9 | 84.7 ± 7.9 | 88 ± 11.8 | 0.085 |
| FVC (%) | 87.9 ± 11.2 | 87 ± 9.4 | 88.9 ± 13.2 | 0.381 |
| FEV1/FVC (%) | 98.8 ± 10.1 | 98.1 ± 10.8 | 99.7 ± 11.2 | 0.411 |

**Table 2. Comparison analysis of PFT results based on demographic and laboratory indicators**

| Variables | FEV1 (%) | FVC (%) | FEV1/FVC (%) |
|---|---|---|---|
| **Age** | | | |
| Total (n=120) | 86.14 ± 9.90 | 86.86 ± 11.19 | 98.78 ± 10.97 |
| Age ≤ **23 y (n=60)** | 88.03 ± 10.80 | 87.48 ± 12.55 | 101.42 ± 10.77 |
| Age > 23 y (n=60) | 84.25 ± 8.59 | 88.25 ± 9.73 | 96.13 ± 10.61 |
| *p*-value | 0.035* | 0.709 | 0.007* |
| **Sex** | | | |
| Total (n=120) | 86.14 ± 9.90 | 87.86 ± 11.19 | 98.78 ± 10.97 |
| Men (n=68) | 84.70 ± 7.91 | 87.04 ± 9.36 | 98.05 ± 10.84 |
| Women (n=52) | 88..01 ± 11.85 | 88.94 ± 13.23 | 99.72 ± 11.18 |
| *p*-value | 0.085 | 0.381 | 0.411 |
| **BMI** | | | |
| Total (n=120) | 86.14 ± 9.90 | 87.86 ± 11.19 | 98.78 ± 10.97 |
| BMI ≤ 21 kg/m2 (n=61) | 86.55 ± 7.96 | 86.26 ± 8.92 | 101.06 ± 10.90 |
| BMI > 21 kg/m2 (n=59) | 85.71 ± 11.63 | 89.52 ± 13.00 | 85.71 ± 10.62 |
| *p*-value | 0.644 | 0.113 | 0.019* |
| **Ferritin** | | | |
| Total (n=120) | 86.14 ± 9.90 | 87.86 ± 11.19 | 98.78 ± 10.97 |
| Ferritin ≤ 3325 mg/dl (n=80) | 87.01 ± 10.36 | 86.87 ± 11.92 | 100.95 ± 10.96 |
| Ferritin > 3325 mg/dl (n=40) | 84.4 ± 8.77 | 89.85 ± 8.77 | 94.44 ± 9.75 |
| *p*-value | 0.174 | 0.171 | 0.001* |
| **Hemoglobin** | | | |
| Total (n=120) | 86.14 ± 9.90 | 87.86 ± 11.19 | 98.78 ± 10.97 |
| Hemoglobin ≤ 9.8 mg/dl (n=72) | 84.76 ± 11.12 | 87.34 ± 11.93 | 97.63 ± 10.27 |
| Hemoglobin > 9.8 mg/dl (n=48) | 88.20 ± 7.37 | 88.64 ± 10.05 | 100.50 ± 11.85 |
| *p*-value | 0. 043* | 0.535 | 0.175 |
| **Transfusion periods** | | | |
| Total (n=120) | 86.14 ± 9.90 | 87.86 ± 11.19 | 98.78 ± 10.97 |
| Injection periods ≤ 25 days (n = 61) | 85.52 ± 7.60 | 86.39 ± 9.37 | 99.78 ± 11.04 |
| Injection periods > 25 days (n = 59) | 87.10 ± 12.72 | 90.14 ± 12.72 | 97.22 ± 10.79 |
| *p*-value | 0.0443 | 0.097 | 0.210 |

Data are presented as mean ± standard deviation. BMI: body mass index.

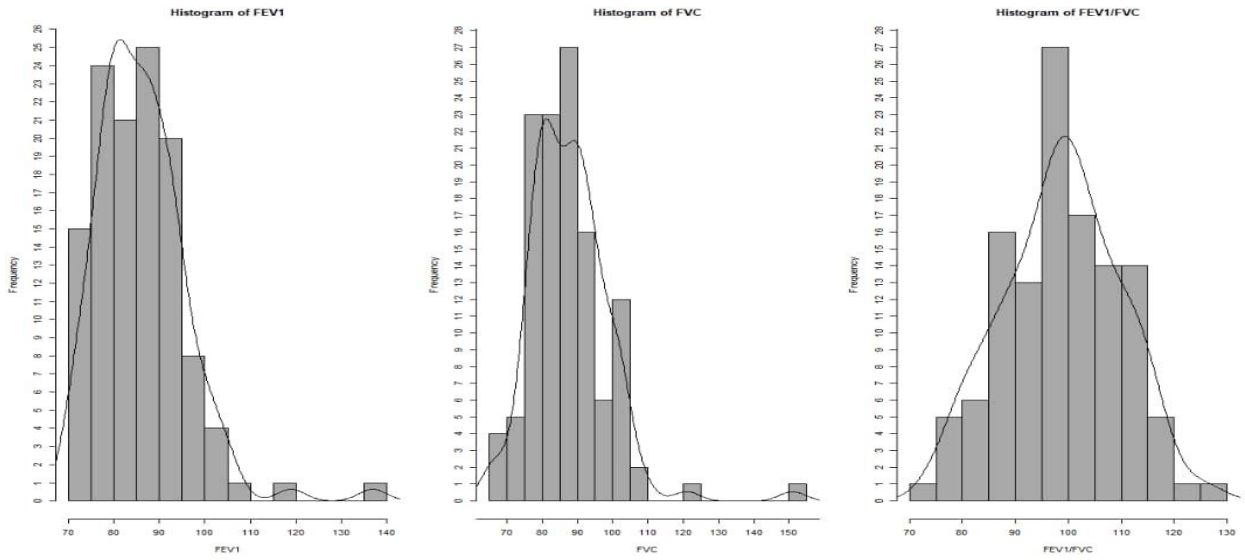


**Figure1. PFT distribution histograms in the study population**

## DISCUSSION

Transfusion-dependent β-thalassemia patients receive regular transfusions every 3 to 4 weeks to cope with the reduced oxygen capacity due to hemolytic anemia and ineffective erythropoiesis in course of the disease. Despite relieving symptoms and improving prognosis, transfusions have short- and long-term adverse effects that lead to various diseases, mainly iron deposition in different organs. This results in parenchymal defects, inflammation, and ultimately organ dysfunction. The heart, liver, and endocrine glands are among the most common iron deposition sites. Delayed puberty and growth retardation are also among complications of iron overload (7). Autopsy investigations in thalassemia patients receiving blood transfusions revealed iron deposition in the lungs; however, respiratory symptoms are not the common chief complaints among thalassemia patients (8).

Different PFTs and patterns have been reported by previous studies on thalassemia patients. The underlying mechanism of respiratory dysfunction is not clear yet, but various studies reported that iron deposition in different parts of the lung is responsible for diverse manifestations. For example, two studies explained that iron deposition in parenchyma leads to oxidants formation and ultimately fibrosis and restrictive pattern (10, 11), while another study revealed iron deposition in bronchial airways and obstructive pattern (8). Azarkeivan et al. (12) and Abu Ekteish et al. (13) reported a restrictive PFT pattern in 72.7% and 25% of thalassemia patients, respectively.

Jamal et al. (7) and Abd El Hakeem et al. (14) reported diffusion impairment by using diffusing capacity for carbon monoxide (DLCO) in 87.9% of subjects. Diffusional impairment, diagnosed by DLCO tests, suggests early pulmonary function abnormalities. This defect presents an alveolocapillary membrane disruption depending on the membrane integrity, the concentration of hemoglobin, and capillary blood volume (15, 16).

Many mechanisms have been proposed for the aforementioned restrictive presentation of the disease. Hepatomegaly resulting from iron deposition in the liver may contribute to the restrictive pattern by pushing the diaphragm up, thus preventing the lungs from expanding adequately (7, 10). Moreover, due to the disease essence, thalassemia patients experience chronic anemia that may affect alveolar growth until 8 years of age and participate in restrictive pattern formation (12). Chelation drugs, which are used to prevent the undesired effects of blood transfusion, may cause toxicity as well as alveolar and parenchymal

inflammation, and ultimately fibrosis (10). In the present study, iron overload was assessed using serum ferritin; however, ferritin is not the best modality to investigate iron overload (17). Liver biopsy is the best approach for determining the extent of iron overload; however, it is not frequently performed due to its invasive nature. In addition, magnetic resonance imaging can be used to assess the body's iron storage (10, 14). In this study, the average serum ferritin level was 3,325 ng/ml (range: 153 to 12,000 ng/ml). A serum ferritin level of above 3,325 ng/ml was significantly associated with a decreased FEV1/FVC ratio. Similarly, Noori et al. reported decreased FEV1/FVC in patients with higher ferritin levels (18). Moreover, Abd El Hakeem et al. reported that PFT abnormalities may be significantly associated with ferritin levels above 2,500 ng/dl (14). However, some studies reported no significant association between serum ferritin levels and PFT abnormalities (13, 19).

In this study, older age and higher BMI were associated with PFT abnormalities. Patients older than 23 years had significantly lower FEV1 and FEV1/FVC than younger patients did, and a BMI above 21 was significantly associated with a decreased FEV1/FVC. However, some previous studies reported no significant association between age and PFT results (15, 20). Similar to our findings, some studies reported a significant positive association between BMI and FEV1 (8, 19). However, some studies suggested a positive correlation between age and the severity of restrictive impairment (12, 14). An association between a higher serum ferritin level and older age has also been reported (21). Older age could explain higher serum ferritin levels due to more transfusion episodes, thus more severe restrictive impairment. In our study, the lower FEV1 and FEV1/FVC in older subjects can be due to greater iron deposition in the lungs and more frequent blood transfusions.

In the present study, a hemoglobin level above 9.8 g/dl and a blood transfusion interval of more than 25 days were significantly associated with higher FEV1, which requires more extensive evaluation.

Radiologic investigations revealed no abnormality. However, Hamed et al. reported interstitial marking in chest X-rays of 23.3% of thalassemia patients (11).

This study is among the few to assess PFT abnormalities among Iranian thalassemia patients. However, given the cross-sectional nature of the study, evaluation of associations and causalities were limited. Iron overload assessment was based on serum ferritin levels before transfusion. Serum ferritin is not specific to iron overload and is affected by various factors. Also, assessing average serum ferritin level over a period provides a better assessment. Thus, it is recommended to perform longitudinal studies with a larger population and better iron overload evaluation techniques. Another limitation of this study was the lack of a control group. In general, lung problems are common in populated cities, especially Tehran, due to exposure to air pollution (22, 23). Therefore, a decrease in lung function over the years is expected and a reverse association of FEV1 and FEV1/FVC with older age in our study population may be due to the increased exposure to air pollution with age. Given the lack of studies on the general population of Tehran, comparison of PFT findings were limited. In this study, only PFT was used to evaluate respiratory function. Using methods such as body plethysmography and DLCO enables a more comprehensive investigation of V/Q mismatch.

## CONCLUSION

Based on the findings, the majority of BTM patients have a normal PFT with a restrictive pattern. Our findings indicated that FEV1 and FEV1/FVC are reversely associated with older age. Moreover, FEV1/FVC is significantly lower in patients with higher serum ferritin levels and BMI.

Moreover, FEV1 is associated with blood transfusion intervals.

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## DECLARATIONS

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### Ethics approvals and consent to participate

The study was approved by the ethics committee of Tehran University of Medical Sciences (Ethics approval reference number: IR.TUMS.CHMC.REC.1399.129).

### Conflict of interest

The authors declare that there is no conflict of interest regarding publication of this article

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