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Original Article PEDIATRICS

Restrictive effects of thalassemia on respiratory functions: One center experience

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ABSTRACT

OBJECTIVE: Respiratory functions in thalassemia major (TM) patients concerning poor chelation are a frequently researched issue. Our study aims to evaluate the lung functions of our patients with TM in the chronic transfusion program and to correlate them with their age, ferritin levels, and pre-transfusion hemoglobin values.

METHODS: Height, weight, pulmonary function test (PFT) results, pre-transfusion hemoglobin levels, and ferritin levels of 97 patients (55 boys and 42 girls) without any underlying cardiac or chronic respiratory disease were recorded. PFT is consisted of forced vital capacity (FVC) and forced expiratory volume in one second (FEV1), the ratio of FEV1/FVC to peak expiratory flow (PEF), and forced mid-exhaled flow between 25% and 75% of mid-expiratory flow (MEF_{25-75}). Data were analyzed with IBM SPSS V25.

RESULTS: Low FVC was observed in 58 patients (60%), and low FEV1 was observed in 26 patients (27.6%). Low PEF was observed in 62 patients (64.5%), and low MEF_{25-75} was observed in 8 (8.3%). PFT was affected in 75 patients (78.1%). The pattern of involvement was restrictive. Age, height, and ferritin values significantly affected the MEF_{25-75} ($p<0.05$). Age and pre-transfusion hemoglobin values had a significant effect on the FVC test ($p<0.05$). There was a weak negative correlation between ferritin values and MEF_{25-75} ($r=-0.221$) and a weak positive correlation between pre-transfusion hemoglobin and FVC ($r=0.222$).

CONCLUSION: Age and height are the main risk factors affecting FEV1, MEF_{25-75}, and PEF. Serum ferritin has only an effect on MEF_{25-75} in our study. The respiratory functions of TM patients were affected in a restrictive pattern.

Keywords: Iron deposition; pulmonary functions; thalassemia major.

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Thalassemia major (TM) is one of the most common autosomal recessive hemoglobinopathies. The disease causes lifelong transfusion-dependent anemia. The basic pathophysiology of the disease depends on (1) severe anemia, (2) ineffective erythropoiesis and its consequences, and (3) iron accumulation in tissues due to chronic transfusion. There are three chelators in use today to prevent iron accumulation: Desferroxamine (DFO), deferiprone (DFP), and deferasirox (DFX). The curative treatment is stem cell transplantation [1].

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It is known that many target organs are damaged as a result of the mechanisms mentioned above in patients with TM. Excess iron in the body remains in the form of non-transferrin-bound iron. This unstable iron is the predominant form of iron that causes tissue damage [2]. The organs where tissue damage is most evident are the heart, liver, and endocrine organs. Cardiac complications are the primary cause of morbidity and mortality in TM [3]. Many studies have also shown that lung functions are affected in patients with TM [4–9]. The etiology of this condition could not be attributed to a single cause and is considered multifactorial. Like the involvement of other organ systems, pathology in the lung primarily results from tissue damage due to iron overload. However, chronic hypoxia is also responsible [10]. In the foreground, it has been shown that the lung is affected in a restrictive pattern. The fact that this effect is more common in patients with a higher ferritin value suggests that this may be due to iron accumulation in the lung tissue. Studies in adult TM patients suggest lung fibrosis and interstitial edema due to iron overload is the leading cause of pulmonary dysfunction [11]. Pulmonary functions in TM can manifest as restrictive patterns [6, 11]. Some studies have also reported that pulmonary dysfunction may be due to inadequate anatomical and functional lung development in early infancy in patients with TM. Decreased lung volumes in thalassemia patients were explained by the the enlarged liver and spleen's upward pressure exerted on the diaphragm. An increase in vital capacity and expiratory reserve volume is expected in TM patients after splenectomy [12].

Respiratory functions in TM patients concerning poor chelation are a frequently researched issue in societies where thalassemia is common. Our study aims to evaluate the lung functions of our patients with TM in the chronic transfusion program and to correlate them with their age, ferritin levels, and pre-transfusion hemoglobin values.

Highlight key points

- Pulmonary functions are affected in a restrictive pattern in patients with TM.
- Although iron accumulation is blamed in the pathophysiology, only a weak negative correlation was found between MEF_{25-75} and ferritin.
- Age and pre-transfusion hemoglobin value were found to be risk factors affecting FVC.
- It is important that patients with TM are regularly evaluated in terms of respiratory functions.

MATERIALS AND METHODS

The data of 239 patients with TM who were in the regular transfusion and chelation program at a local thalassemia center were reviewed retrospectively. Height, weight, pulmonary function test (PFT) results, pre-transfusion hemoglobin levels, and ferritin levels of 97 patients (55 boys and 42 girls) without any underlying cardiac or chronic respiratory disease were recorded. All patients were receiving transfusions regularly every three weeks. Patients with serum ferritin levels >500 ng/mL were using chelation. Patients diagnosed with chronic lung disease and asthma, receiving bronchodilator therapy, acute respiratory tract infection, or inadequate spirometry compliance were excluded from the study.

The device used for spirometry was the "Spirolab III" MIR spirometer. Before the test, the patients were given training. Spirometry was performed while patients were in the upright position. During the test, the patient was accompanied by competent health personnel. PFTs were performed on the day the patient was supposed to receive a transfusion but before the transfusion. The saturation of each patient was measured before PFT. Forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1), the ratio of FEV1/FVCs to peak expiratory flow (PEF), and forced mid-exhaled flow between 25% and 75% of expiratory flow (MEF_{25-75}) was recorded. PFT values were compared with predicted values (age, sex, and height) and expressed as a percentage of predicted average values. Reference standards for Turkish children [13, 14] were used to interpret the estimated values for spirometry indices. PFT was reported as usual, restrictive, and obstructive. The restrictive disease was defined as total lung capacity (TLC) below 80%, and the obstructive pattern was defined as FEV1/FVC ratio below 80% [15]. Informed consent was obtained from all parents and adolescent patients. Ethical approval was obtained from the Harran University Ethical Committee on January 18th, 2019 (number: HRU/19.01.27)

Statistical Analysis

Data were analyzed with IBM SPSS V25 (IBM Corp., Armonk, NY). Conformity to normal distribution was evaluated by Shapiro–Wilk and Kolmogorov–Smirnov tests. Yates correction, Pearson Chi-square, and Fisher's exact tests compared categorical variables according to groups. An independent two-sample t-test was used to compare normally distributed data according to paired

Table 1. Descriptive statistics of the patients

	Mean±SD	Median (min–max)
Age (years)	12.19±3.38	12 (6.58–19.07)
Height (cm)	139.07±16.14	140 (105–176)
Weight (kg)	34.17±10.17	33 (18–61)
BMI	17.3±2.32	17.28 (13.23–31.9)
Pre-transfusional hemoglobin (mg/dL)	8.65±1.03	8.7 (5.5 –11.09)
Ferritin (ng/dL)	2805.44±1892.69	2537.5 (115–7965)
FVC	76.88±13.98	75 (47–121)
FEV1	87.89±14.52	88 (55–126)
FEV1/FVC	113.26±4.51	115 (93–118)
PEF	72.72±19.22	71 (36–139)
MEF_{2575}	97.51±23.82	97 (51–190)

SD: Standard deviation; Min: Minimum; Max: Maximum; BMI: Body mass index; FVC: Forced vital capacity; FEV1: Forced expiratory volüme in one second; FEV1/FVC: Forced expiratory volüme in one second to forced vital capacity; PEF: Peak expiratory flow; MEF_{25-75}: Mid-expiratory flow.

Table 2. Summary of pulmonary functions of the patients

	Frequency (n)	Percentage
FVC		
Normal	38	40.0
Low	57	60.0
FEV1		
Normal	68	71.6
Low	26	27.4
FEV1/FVC		
>80	94	98.9
<80	0	0.0
PEF		
Normal	34	35.8
Low	61	64.2
MEF_{25-75}		
Normal	87	91.6
Low	8	8.4
PFT		
Normal	21	22.1
Pathological	74	77.9

FVC: Forced vital capacity; FEV1: Forced expiratory volüme in 1 s; FEV1/FVC: Forced expiratory volüme in one second to forced vital capacity; PEF: Peak expiratory flow; MEF_{25-75}: Mid-expiratory flow; PFT: Pulmonary function test.

groups, and the Mann–Whitney U-test was used to compare non-normally distributed data. Results are mean±standard deviation and median (minimum–maximum) for quantitative data. One-way ANOVA and the Kruskal–Wallis H test were used for multigroup comparisons. Linear and binary logistic regression tests were used to examine the risk factors affecting PFTs. A correlation test was used to examine the correlation between PFT and ferritin and pre-transfusion hemoglobin value. The significance level was taken as $p<0.050$.

RESULTS

The mean age of the patients was 12.1±3.3 years (Min=6.5, Max=19). The mean ferritin of the patients was 2750±1842 ng/dL (Min=226, Max=7490). All patients used DFX at 10-40 mg/kg/day as the main chelator. Twenty-three patients with a ferritin level >3000 ng/dL were using a combination of DFP (n=12) or DFO (n=11) according to the patient's clinical condition. Spirometric measurements of all patients were made before transfusion. The mean hemoglobin before transfusion was 8.6±1 g/dL (min=5.5; max=11). Since 25 of our patients were Syrian refugee guests, the ages of diagnosis and transfusion times were not clear. The age of diagnosis of our other patients ranged from 6 months to 6 years. Genetic mutation of 74 patients was evident. Fifteen types of TM mutations were detected in our cohort. Twenty-two patients were compound heterozygous. The most common mutation was IVSI-110 c.93-21 (G>A) homozygous; the second was IVSI-1c.92+1 (G>A) homozygous. The descriptive characteristics of our patients and results of the PFTs are summarized in Tables 1 and 2.

Three patients were excluded from the study when the test results were examined because the test compliance was insufficient. The mean FVC of the patients was 76.4±14.4 (min=39; max=121); the mean FEV1 was found to be 87.8±14.5 (min=55; max=126). Low FVC was observed in 58 patients (60%), and low FEV1 was observed in 26 patients (27.6%). The FEV1/FVC ratio of all patients was over 80%. PEF in 62 patients (64.5%) and MEF_{25-75} in 8 patients (8.3%) were below the required value. When all criteria were evaluated, it was observed that PFT was affected in 75 patients (78.1%).

When the patients were grouped according to age (<12 years and >12 years) and ferritin quartile values, no statistically significant difference was found between FVC, FEV1, FEV1/FVC, PEF, MEF_{25-75} values (Tables 3 and 4).

Table 3. Analysis of pulmonary functions and laboratory tests according to age

	<12 years		>12 years		Test stat.	p
	Mean±SD	Median (min–max)	Mean±SD	Median (min–max)		
Pre-transfusional hemoglobin	8.59±1.06	8.8 (5.5–10.78)	8.73±1.01	8.6 (6.5–11.09)	-0.397	0.691*
Ferritin	2530.33±1497.8	2636 (115–5284)	3093.98±2216.07	2474 (226–7965)	-1.372	0.174**
FVC	77.1±14.04	75.5 (47–116)	76.66±14.08	75 (52–121)	0.154	0.878**
FEV1	88.32±15.1	88 (55–126)	87.47±14.06	87 (63–126)	0.283	0.778**
FEV1/FVC	113.91±3.64	115 (103–118)	112.6±5.19	115 (93–117)	-1.154	0.248*
PEF	71.88±21.06	71.5 (36–139)	73.57±17.32	69 (44–106)	-0.629	0.529*
ME_{2575}	98.5±26.99	97.5 (51–190)	96.49±20.33	97 (51–141)	-0.320	0.749*

SD: Standard deviation; *: Mann-Whitney U-test; **: Independent two samples t-test; FVC: Forced vital capacity; FEV1: Forced expiratory volüme in 1 s; FEV1/FVC: Forced expiratory volume in 1 s to forced vital capacity; PEF: Peak expiratory flow; MEF_{25-75}: Mid-expiratory flow.

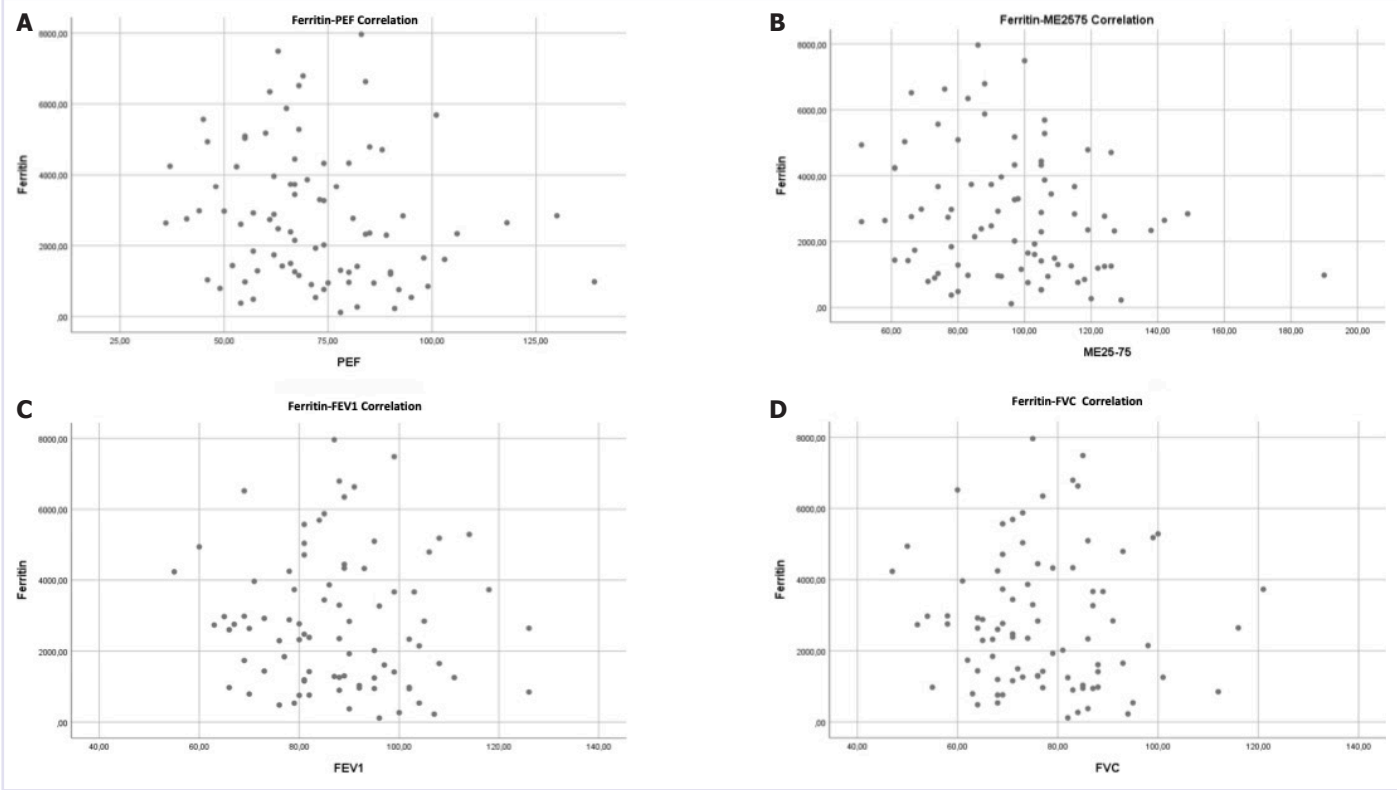

Figure 1. Correlation of ferritin and pulmonary function tests **(A)** Ferritin-peak expiratory flow correlation **(B)** Ferritin-mid-expiratory flow correlation **(C)** Ferritin-forced expiratory volume in 1 s correlation **(D)** Ferritin-forced vital capacity correlation.

Risk factors affecting the FVC test were analyzed by linear regression analysis. Age and pre-transfusion hemoglobin values significantly affected the FVC test ($p<0.05$). There was a 2.271% increase in FVC value when there was a 1-unit change in age and a 3.075% decrease in FVC value when a 1-unit change in pre-transfusion hemoglobin value occurred. No significant correlation was found between ferritin value and FVC. Age, height, and ferritin values significantly affected the MEF_{25-75} test ($p<0.05$). When a 1-unit change occurred in the ferritin value, an increase of 0.003% was observed in the MEF_{25-75} value (Table 5).

TABLE 4. Analysis of pulmonary functions and laboratory tests according to ferritin quartiles

Ferritin quartiles (ng/dL)	<Q1: 1248		Q1–Q2 (1248–2537)		Q2–Q3 (2537–4163)		>Q3 (4163)		p
	Mean±SD	Median (min–max)	Mean±SD	Median (min-max)	Mean±SD	Median (min–max)	Mean±SD	Median (min–max)	
Age	12.19±0.85	11.26 (6.58–19.07)	12.44±0.64	12.56 (6.74–17.89)	11.17±0.59	11.63 (6.61–16.87)	12.58±0.72	12.96 (6.87–16.77)	0.503*
BMI	17.22±0.41	16.86 (14.96–22.49)	17.49±0.86	17.19 (13.69–31.9)	17.07±0.41	17.26 (14.11–21.1)	17.31±0.34	17.35 (14.04–21.03)	0.923*
Pre transfusional hemoglobin	8.31±0.20	8.3 (5.5–10.3)	8.66±0.24	8.8 (6.5–10.6)	9.05±0.22	8.9 (6.67–11.09)	8.63±0.22	8.6 (6.7–10.7)	0.135**
FVC	80.00±2.80	82 (55–112)	76.58±2.35	76 (62–98)	74.71±4.01	69 (52–121)	76.19±2.98	76 (47–100)	0.441*
FEV1	91.43±2.91	92 (66–126)	87.72±2.65	87.5 (69–108)	84.62±3.89	80 (63–126)	86.76±3.12	88 (55–114)	0.528**
FEV1/FVC	113.13±0.91	115 (103–118)	112.44±0.84	113 (106–117)	112.76±1.41	116 (93–118)	113.43±0.84	115 (105–118)	0.652*
PEF	77.83±4.20	78 (46–139)	75.05±3.64	72 (52–106)	68.14±5.07	66 (36–130)	67±3.49	67 (37–101)	0.100*
MEF_{25-75}	105.04±5.43	105 (71–190)	96.32±4.76	101 (61–138)	94.81±5.61	93 (51–149)	87.57±4.43	88 (51–126)	0.164*

SD: Standard deviation; *: Kruskal-Wallıs H; **: One-way Anova; BMI: Body mass index; FVC: forced vital capacity; FEV1: Forced expiratory volüme in one second; FEV1/FVC:forced expiratory volüme in one second to forced vital capacity; PEF: Peak expiratory flow; MEF_{25-75}: Mid-expiratory flow.

TABLE 5. Risk factors that effect FVC, FEV1, MEF_{25-75}, PEF

	FVC		FEV1		MEF_{25-75}		PEF	
	B (%95 CI)	p	B (%95 CI)	p	B (%95 CI)	p	B (%95 CI)	p
(Constant)	155.821 (108.109–203.533)	<0.001	174.855 (124.872–224.838)	<0.001	223.938 (144.561–303.315)	<0.001	173.147 (107.88–238.415)	<0.001
Age	2.271 (0.647–3.895)	2.784	2.480 (0.818–4.141)	0.004	3.444 (0.743–6.146)	0.013	2.731 (0.51–4.952)	0.017
Height	-0.636 (-1.078–-0.194)	-2.862	-0.676 (-1.132–-0.221)	0.004	-1.094 (-1.83–-0.357)	0.004	-0.905 (-1.51–-0.3)	0.004
Weight	0.296 (-0.384–0.976)	0.866	0.254 (-0.439–0.947)	0.467	0.358 (-0.774–1.49)	0.531	0.602 (-0.328–1.533)	0.201
Pre-transfusional hemoglobin	-3.075 (-5.946–-0.205)	-2.133	-3.425 (-6.389–-0.46)	0.024	-2.474 (-7.25–2.302)	0.306	-2.693 (-6.62–1.234)	0.176
Ferritin	-0.001 (-0.002–0.001)	-0.700	-0.001 (-0.002–0.001)	0.346	-0.003 (-0.006–0)	0.023	-0.002 (-0.004–0)	0.064

B: Unstandardized coefficient; Adjusted R^2: 0,134, SE=22,26; FVC: Forced vital capacity; FEV1: Forced expiratory volüme in 1 s; PEF: Peak expiratory flow; MEF_{25-75}: Mid-expiratory flow.

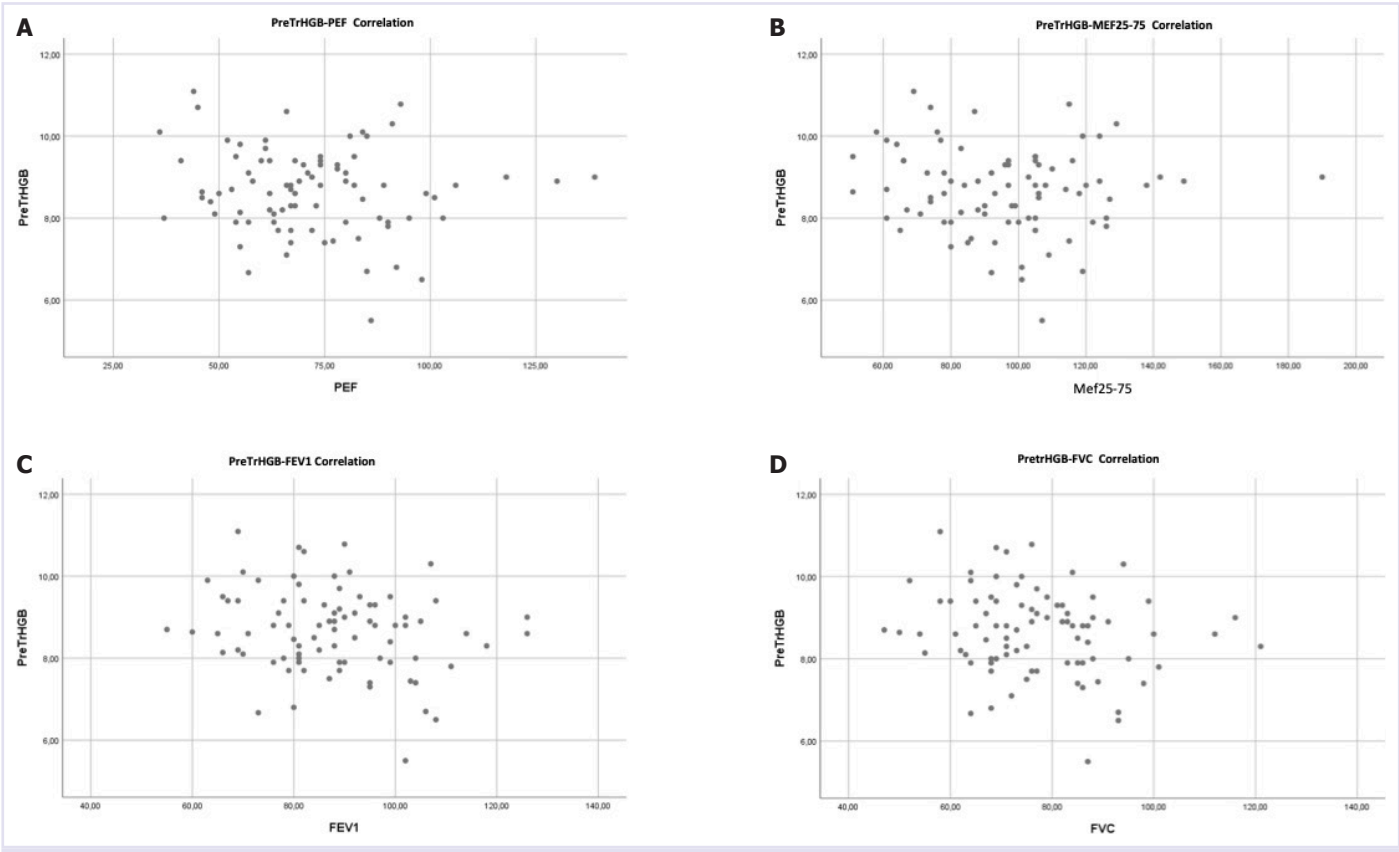

FIGURE 2. Correlation of pretransfusional hemoglobin value and pulmonary function tests **(A)** Pre-transfusional hemoglobin-peak expiratory flow correlation **(B)** Pre-transfusional hemoglobin-mid-expiratory flow correlation **(C)** Pre-transfusional hemoglobin-forced expiratory volume in 1 s correlation **(D)** Pre-transfusional hemoglobin-forced vital capacity correlation.

There was a weak negative correlation between ferritin values and MEF_{25-75} (r=-0.221) and a weak positive correlation between pre-transfusion hemoglobin and FVC (normal-low) (r=0.222) (Fig. 1, 2).

DISCUSSION

Many factors have been implicated in the etiology of respiratory dysfunction in TM patients. The possible mechanism causing pulmonary defect is iron accumulation resulting from repeated transfusions; some researchers have supported that the degree and duration of iron overload may be substantial in the pathogenesis of pulmonary function abnormalities [16–18]. The association between somatic iron stores and pulmonary function cannot be approved by some studies [18]. Our study aimed to evaluate PFT findings in asymptomatic TM patients and describe the relationship between patients' ferritin levels.

Low FVC was observed in 58 patients (60%), and low FEV1 was observed in 26 patients (27.6%). Low PEF was observed in 62 patients (64.5%), and low MEF_{25-75} was observed in 8 (8.3%). When all criteria were evaluated, it was observed that PFT was affected in 75 patients (78.1%). The pattern of involvement was restrictive. In a study conducted in Turkiye, Ozyoruk and Misirlioglu found 67% decreased FVC, 30% decreased FEV1, 46.9% decreased PEF, and 10% decreased MEF_{25-75} [7]. In the present study, the pulmonary involvement has a similar pattern, with better PFT results. This result may be attributed to the ferritin levels between the two cohorts. The lower ferritin mean in our group suggests that the chelation of the study group was sufficient. Similarly, in Panwar et al.'s [19] study, the median SF value of the patients was closer to our cohort at 2735 ng/dL. Pulmonary dysfunction was observed in most of the patients. The authors demonstrated the reversibility of pulmonary dysfunction by administering intensive chelation with intravenous DFO for four weeks to 17 patients with pulmonary dysfunction [1, 19]. The reversibility of toxicity findings with chelation applies to cardiac and endocrine dysfunctions [1]. Likewise, Parakh et al. [8] also stated that early and sufficient chelation in TM patients could prevent pulmonary complications.

The diffusion capacity of the lungs has been studied with diffusion capacity of the lungs for carbon monoxide and shown to decrease in TM patients. Since our study was a retrospective study and the primary purpose was to screen the respiratory functions of the patients, spirometry was used as the only method. Li et al. [18] reported that diffusion disorder was the most common pulmonary dysfunction in children with thalassemia, affecting 34% of patients. Abu-Ekteish et al. [20] reported that 25% of the cases were affected in their study. Panwar et al. [19] detected lung dysfunction in 50 patients; they stated that 39 of them had diffusion disorders, and 11 patients had restrictive defects. Similar to our study, no obstructive defects were observed in patients. Baruah and Bhattacharjee also used spirometry alone to assess pulmonary function; they observed a restrictive pattern in 71.2% of PFTs [21]. They stated that the mean SF was significantly higher in the group with impaired pulmonary functions and drew attention to the importance of good chelation. The low SF mean of patients with normal PFT compared to the higher SF mean of patients with impaired PFT in our study supports the importance of good chelation.

Priftis et al. [22] found a strong positive correlation between the total number of units of transfused blood and the siderophages in mean SF and bronchoalveolar lavage (BAL) in patients who received multiple transfusions. This result supports the theory of iron accumulation in the lung tissue after repeated transfusions and, thus, the formation of pulmonary hemosiderosis. This study compares the BAL of patients with idiopathic pulmonary hemosiderosis (IPH) and those receiving chronic transfusion; similar amounts of hemosiderin-loaded macrophages and lymphocytic infiltrates suggestive of alveolitis in IPH were found [22]. In a study on post-mortem TM patients, the iron was concentrated in the bronchial epithelial and mucous glands in the autopsy of the patients [23].

Factor et al.'s study [16], in 29 patients, found an inverse relationship between TLC and transfusional iron load and suggested that the degree and duration of iron overload may be essential in the pathogenesis of the restrictive-type respiratory disorder. Tai et al. [17] calculated the iron load that the patients were exposed to with the transfusions they received. They showed that the calculated lifetime iron load was not correlated with restrictive disease, the major pulmonary disorder in 14 patients. This result, different from many studies that associate chronic transfusion exposure with pulmonary disorder, may be related to the small number of patients in the study. Similarly, in the study of Li et al. [18], no relationship was found between pulmonary function abnormalities and body iron content in TM patients, and it was argued that other factors play a role in respiratory dysfunction. It is well known that an increased iron load can increase oxidant tissue damage by producing free radicals [24]. It has also been suggested that some iron-dependent microorganisms facilitate tissue damage. Toxicity is secondary to DFO treatment and has been suggested to play a role in tissue damage [25]. When FEV1, FVC, PEF, and MEF_{25-75} were examined separately, it was seen that patient age significantly affected the results. The main reason for this is the increase in test compliance with age. Assuming that increasing age will increase tissue damage in the patient, significant deterioration of PFT can be expected at later ages. Since our study was conducted only in a narrow age group, no significant result existed between age and PFT.

Our study included a large number of patients. It is a retrospective observational study. Therefore, some patient data could not be fully reached. In addition, only ferritin was used to show body iron load and liver and cardiac iron loads were not included in the study because they were not monitored regularly and standardly in every patient. Since ferritin is also an acute phase reactant, it may not fully reflect the iron load.

Conclusion

Consistent with the literature, restrictive-type pulmonary involvement was observed in our cohort. Age and height are found to be the main risk factors affecting FEV1, MEF_{25-75}, and PEF. SF could only affect MEF_{25-75} in our study. The respiratory functions of TM patients were affected in a restrictive pattern compared to the average population. Controlled prospective studies are needed to define lung functions in the TM patient group and to determine the factors that affect them.

Ethics Committee Approval: The Harran University Clinical Research Ethics Committee granted approval for this study (date: 18.01.2019, number: HRU/19.01.27).

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Authorship Contributions: Concept – GZE, EN, ME; Design – GZE, EN; Supervision – ME, ASS, GD; Fundings – OT, ASS, GD; Materials – EN, OT, ASS; Data collection and/or processing – GZE, EN, ME, OT, ASS, GD; Analysis and/or interpretation – GZE, EN; Literature review – GZE, EN, ME; Writing – GZE; Critical review – EN, ME.

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