PEDIATRIC SCIENCES JOURNAL
The Official Journal of the Pediatric Department, Faculty of Medicine, Cairo University, Egypt

Original Article

Silent Restrictive Lung Disease is Common Among Children with ß-thalassemia: A Single Center Study

Mona Hassan Eltagui*, Christine William S. Basanti, Magd Ahmed Kotb, Toka Emad Eldin Saad, Mai Mohamed Abd El Salam
Department of Pediatrics, Faculty of Medicine, Cairo University, Cairo, Egypt
* Correspondence: mai_abdelsalam84@yahoo.com
Received: 15/4/2024; Accepted: 15/6/2024; Published online: 30/6/2024

Abstract:
Background: ß-thalassemia syndromes are a group of hereditary blood diseases characterized by reduced or absent ß-globin chain synthesis, resulting in reduced hemoglobin in red blood cells. Pulmonary dysfunction ranging from restrictive to obstructive was reported among those with ß-thalassemia.
Aim of the work: to evaluate the pulmonary functions in patients with ß-thalassemia.
Patients and Methods: We conducted a cross-sectional study that included 60 ß-thalassemia patients following up at the Hematology Outpatient Clinic of Cairo University Children's Hospital. They all underwent assessment of forced vital capacity (FVC), forced expiratory volume in one second (FEV1), maximal expiratory flow (MEF) and peak expiratory flow (PEF) using spirometry and assessment of resistance (R) and reactance (Z) to different frequencies by impulse oscillometry (IOS).
Results: The mean ± SD age of the studied group was 10.63 ± 3.53 years. Of them, 32 (53.3%) were females and 28 (46.7%) were males. 39 (65%) were transfusion dependent, 23 (38.3%) were compliant to chelation therapy and only 8 (13.3%) did not need chelation therapy. 30 (50%) patients showed restrictive pattern in spirometry (FVC<80%, FEV1<80% and FEV1/FVC >80%") and 15 (50%) of them also showed abnormal high impulse IOS to 5 and 20HZ (readings above 150%). The non-compliant patients had airway obstructive pattern by spirometry MEF50 (p=0.075), and higher IOS resistance pattern to R5Hz (p= 0.007), R20Hz (p=0.007) and X5Hz (p= 0.003). Higher airway resistance on IOS (0.0001) was associated with transfusion dependency, and need for chelation therapy (p=0.039). Poor compliance to chelation therapy correlated with spirometry restrictive pattern (p=0.0006).
Conclusion: Restrictive lung disease is a common pulmonary dysfunction among children with ß-thalassemia. Compliance to adequate chelation therapy decreases the incidence of pulmonary dysfunction.

Level of Evidence of Study: IV (*1*).
Keywords: Pediatric; ß-thalassemia; Spirometry, Impulse Oscillometry; pulmonary functions; chelation therapy
Abbreviations: FEV1: Forced expiratory volume in one second; FVC: Forced vital capacity; IOS: Impulse oscillometry; MEF 25-75%: maximum expiratory flow 25-75% of FVC; NTDT: Non-transfusion dependent thalassemia; PEF: Peak expiratory flow; R5HZ: Resistance at 5 Hz; R20HZ: Resistance at 20 Hz; TDT: Transfusion dependent thalassemia

Introduction

ß-thalassemia syndromes are a group of hereditary blood diseases characterized by reduced or absent ß-globin chain synthesis, that result in decreased hemoglobin in red blood cells (RBC), decreased RBC production and anemia. Most thalassemia syndromes are inherited as recessive traits (*2*). The use of regular transfusion regimens in patients with ß-thalassemia has improved patients' life span and quality of life but can result in chronic iron overload (*3*). Many of the complications of ß-thalassemia result from iron deposition in the lungs, heart, and endocrine glands. Although pulmonary dysfunction is not the most significant clinical manifestation of thalassemia, a certain reduction of pulmonary functions has been reported to occur in most subjects with ß -thalassemia (*4*). Lung fibrosis and/or interstitial edema that result from iron overload are causes of pulmonary dysfunction in patients with thalassemia. Iron deposition can lead to airway narrowing and hence explains the airway obstruction seen in some patients. Hemosiderosis and subsequent oxidative tissue injury could lead to lung damage and fibrosis.

Moreover, the hypercoagulable state of thalassemic patients results in micro-embolization of the pulmonary arteries that may interfere with alveolar growth (*5*). Although pulmonary dysfunction in thalassemic patients was already reported in the early eighties, it represents one of the most underestimated complications. In fact, contradictory results were reported in different studies, ranging from a restrictive spirometry pattern to an obstructive one. It is noteworthy that none of the patients examined in these studies showed any clinical symptoms due to lung dysfunction, except for some reduced exercise tolerance (*6*). The aim of this study was to evaluate the pulmonary functions in patients with ß-thalassemia.

Subjects and Methods

This cross-sectional analytic study included 60 patients with ß-thalassemia aged between 6 and 18 years who were attending the Hematology Outpatient Clinic of the Pediatric Department of Cairo University Hospitals. This study was conducted in the laboratory of pulmonary functions of Children Hospital of Cairo University. The study was approved by the Ethics Committee of Cairo University (approval number: MS-177-2019). Written informed consent was obtained from the care givers.

Participants

The 60 children with ß-thalassemia were divided according to regularity of blood transfusion into regularly transfused (transfusion dependent thalassemia) and non- regularly transfused (non-transfusion dependent thalassemia). They were also divided according to compliance to chelation therapy into compliant and non-compliant groups. Patients suffering from bronchial asthma, any acute or chronic lung illness, patients with skeletal deformities or any neuromuscular disorders were not included in the study.

Methods

All the patients who fulfilled the inclusion criteria were subjected to full history taking with special emphasis on age, age of onset and frequency of blood transfusion and history of chelation therapy (type, route of administration and compliance). Transfusion-dependent thalassemia (TDT) requires lifelong regular transfusions for survival. Non-transfusion-dependent thalassemia (NTDT) was used to label patients who did not require lifelong regular monthly transfusions for survival, although they may require occasional or even frequent transfusions in certain clinical settings and usually for defined periods of time. We relied on Likert Scale scoring system to define compliance to chelation therapy. It is based on the number of missed doses of the medication; where1 represented “never missed a dose”, 2 represented “some of the time” (missed <25% of total doses), 3 represented “most of the time” (missed 25-50% of total doses) and 4 represented “all of the time” (missed >50% of total doses). Patients taking >75 % of the prescribed doses (score of 1 and 2) were considered to be adherent, whereas those with <75% (score 3 and 4) were considered non-adherent (*7*).

All patients were subjected to thorough physical examination and laboratory investigations including complete blood count, liver and kidney function tests, serum ferritin and pulmonary function tests. All underwent spirometry and impulse oscillometry (IOS).

1-Spirometry: Jaeger Master Screen spirometry (Jager Co, Wurzburg, Germany) was used. This system was calibrated for room temperature and pressure of saturated gas and volumes. Spirometry measurements included forced vital capacity (FVC), forced expiratory volume in one second (FEV1), the ratio between them FVC/FEV1, and maximum expiratory flow 25-75% (MEF 25-75%) of FVC. Calibration was performed on site before each testing session and according to the manufacturer’s instructions. To achieve good results, the procedure was carefully explained to the subjects and urged them to breath in fully, seal the lips around mouthpiece**,** seated position with no leaning forward, nose clip, and very vigorous effort right from the start to blast air out until absolutely no more air can be exhaled. At least 3 acceptable tests that meet these criteria were obtained and average was calculated.

2-Impulse Oscillometry: Jaeger Master Screen Impulse Oscillometry system (Jaeger Co, Wurzburg, Germany) was used. The system was calibrated through a single volume of air (2L) at different rates (flow) and with a reference resistance device (0.2KPa L-1 S-1) (*8*). The machine was also calibrated for ambient temperature and pressure of saturated gas and humidity. In this

noninvasive method, we assessed resistance (R) to 5 and 20 hertz (Hz) sound waves and reactance (X) at 5Hz sound waves.

Restrictive pattern in spirometry was defined as FVC<80%, FEV1<80% and FEV1/FVC >80% Small air way obstruction was defined as MEF25-75 reading "below 60%". Abnormal IOS was any reading above 150%. In central airway obstruction, the resistance at all frequency increases (R5Hz and 20RHz), while, in small airway obstruction, the resistance at R5Hz lower frequencies increases but is unchanged at 20RHz higher frequencies (*9*).

The child was tested when relaxed, wearing loose fitting clothes with no belts or girdles that make it harder for him/her to breathe. Nose clip was used as the parent or guardian gently held the sides of the face of the child to decrease the shunt compliance of the cheeks.

Statistical Analysis

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences, IBM, USA) version 25. Data were summarized using mean, standard deviation, range and median in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non- parametric Mann-Whitney test. For comparing categorical data, Chi square (x^2) test was performed. Correlations between quantitative variables were done using Spearman correlation coefficient. P-values less than 0.05 were considered as statistically significant.

Results

Our study included 60 ß-thalassemia patients following up at the Hematology Outpatient Clinic of Cairo University Children's Hospital. Of them 32 (53.3%) were females and 28 (46.7%) were males. The age of our study group ranged between 6 and 18 years with mean 10.63 ± 3.53 years. 15 (25%) were below 3rd percentile for weight for age, 7 (11.7%) were below 5th percentile, 32 (53.3%) were between 25th and 50th percentile, 3(5%) were between 50th and 75th percentile and 3(5%) were between 75th and 90th percentile of age and sex norms. As for height, 17 (28.3%) were below 3rd percentile for age, 11 (18.3%) were below 5th percentile, 25 (41.7%) were between 25th and 50th percentile, 3(5%) were between 50th and 75th percentile and 4 (6.7%) were between 75th and 90th percentile.

Table 1. Spirometry and impulse oscillometry among the studied patients with ß-thalassemia

		Total N= 60	NTDT N=21	TDT N = 39	P value
FVC	Mean ± SD	82.38 ± 13.85	82.3± 11.63	82.38 ±14.86	0.998
	Range	46.1 – 136.4	46.1-136.4	64-105.3	
FEV1	Mean ± SD	85.17 ± 12.5	86.6±9.44	84.1±13.6	0.42
	Range	51.8 – 118.4	73.2-108	51.8- 118.4	
FEV1/FVC	Mean ± SD	103.54 ± 9.89	103.9±11.04	103.07±9.08	0.778
	Range	79.5 – 116.1	79.5-116.1	87.1-115.6	
MEF75	Mean ± SD	72.98 ± 16.72	77.59±15.16	70.52±16.9	0.118
	Range	32.8 – 102.5	46.4-102.5	32.8- 98.2	
MEF50	Mean ± SD	80.29 ± 19.04	88.59±18.54	75.81±17.75	0.017
	Range	44.6 – 121.2	54.4-121.2	44.6-116.2	
MEF25	Mean ± SD	80.74 ± 27.92	89.3±32.63	75.9±23.76	0.123
	Range	35.2 – 154.8	37.2-154.8	35.2-124.7	
PEF	Mean ± SD	66.13 ± 15.68	71.59±14.95	63.23±15.5	0.051
	Range	29.4 – 93	42.3-93	29.4- 88.9	
R5HZ	Mean ± SD	151.27 ± 61.87	122.9±15.87	156.6±58.3	0.002
	Range	85.1 – 390	85.2-147	85.1-390	
R20HZ	Mean ± SD	126.51 ± 39.79	109.2±25.07	143.6±61.9	0.004
	Range	65.3 – 245.2	65.3-171.4	77.9-344.2	
X5HZ	Mean ± SD	159.3 ± 124.2	107.8±32.24	185.7±144.1	0.002
	Range	26.8 – 733.9	57.3-164.1	26.8-733.9	

FVC: forced vital capacity; FEV1: forced expiratory volume in one second; MEF75, 50, 25: maximal expiratory flow at 75%, 50% and 25% of forced vital capacity; NTDT: Non transfusion dependent thalassemia; PEF: peak expiratory flow; R5HZ: resistance at 5HZ; R20HZ: resistance at 20 HZ; TDT: transfusion dependent thalassemia; X5HZ: reactance at 5HZ.

The age at start of blood transfusion in our study group ranged between 2 and 54 months with median 7.5 months and the frequency of blood transfusion ranged between every 3 to 12 weeks with mean 5.47 ± 2.55 weeks. 39 (65%) patients of our study group were TDT while 21 (35%) patients were NTDT. Clinically 30 (50%) patients had undergone splenectomy and 26 (43.3%) patients had splenomegaly reaching between 3 and 25 cm below left costal margin with a median of 5 cm. 8 (13.3%) patients were not in need of iron chelation therapy. Only 52 (86.7%) patients of the study population received chelation therapy, 29 (55.8%) were on deferasirox with dose ranging between 20 and 40 mg/kg/day and mean ± SD 26.6 ± 6 mg/kg/day while 23 (44.2%) patients were on deferiprone with a dose ranging between 55 and 90 mg/kg/day and a mean± SD of 77.17 ± 9.81 mg/kg/day. Only 23 (44.2%) were complaint to chelation therapy.

None of our patients had any pulmonary symptoms in the form of dyspnea or cough or clubbing. Hemoglobin level in the study group ranged from 4.8 to 9.9 g/dl with mean 6.94 ± 0.99 g/dl and serum ferritin ranges from 500 to 8352 ng/ml with median 2067.5 ng/ml. Compliant group had a mean ± SD Hb 6.72 ± 0.96 and ferritin 2111.5 ±1254.9, while the non-compliant group has a mean ± SD Hb 7.00 ± 1.06 and ferritin 3126.3±1750.8 (p = 0.340) and (p=0.018) respectively. Thirty (50%) patients showed restrictive pattern in spirometry as defined by FVC<80%, FEV1<80% and FEV1/FVC >80%, 9 (15%) patients showed small air way obstruction defined by MEF25-75 reading below 60% and 21(35%) patients showed normal pattern. Out of the 30 patients with restrictive lung disease, 15 had normal oscillometry and only 15 patients showed abnormal IOS readings. Out of the 9 patients with small air way obstruction; 2 patients showed abnormal IOS readings (Tables 1 and 2). Twenty-one (35%) patients showed abnormal findings in IOS "reading above 150%"; 17 of them showed air way obstruction and 4 showed decreased compliance. Only 4 (19.1) patients of those with abnormal IOS showed normal spirometry readings. (Tables 1, 2 and 3).

Table 2. Spirometry and impulse oscillometry according to blood transfusion rate and compliance to chelation therapy in the studied children with ß-thalassemia

		Non- Compliant to Chelation Therapy N=29	Compliant to Chelation Therapy N = 23	P value
FVC	Mean ± SD	77.7± 15.8	87.42 ±9.37	0.01
	Range	46.1-136.4	72.5-108.1	
FEV1	Mean ± SD	78.5±12.4	92±9.36	0.0001
	Range	51.8-118	71.6- 108	
FEV1/FVC	Mean ± SD	101.1±9.14	105.6±9.18	0.09
	Range	84.5-115.2	87.1-116.4	
MEF75	Mean ± SD	68.99±18.8	77.03±13.9	0.087
	Range	32.8-101.4	53.5- 102.5	
MEF50	Mean ± SD	74.8±16.5	84.5±20.89	0.075
	Range	45.1-116.2	44.6-121.2	
MEF25	Mean ± SD	73.5±19.7	85.17± 33.5	0.147
	Range	49.4-114.3	35.2-154.8	
PEF	Mean ± SD	62.8±17.9	69.3±13.4	0.14
	Range	29.4-93	43.2- 88.3	
R5HZ	Mean ± SD	163.9±66.2	126.6±13.05	0.007
	Range	46.1-136.4	98.8-147.9	
R20HZ	Mean ± SD	156.23±66.9	107.1±17.9	0.0007
	Range	86.3-344.2	65.3-135.5	
X5HZ	Mean ± SD	211±157.5	112.6±36.7	0.003
	Range	54.8-733.9	26.8-212.1	

FVC: forced vital capacity; FEV1: forced expiratory volume in one second; MEF75, 50, 25: maximal expiratory flow at 75%, 50% and 25% of forced vital capacity; PEF: peak expiratory flow; R5HZ: resistance at 5HZ; R20HZ: resistance at 20 HZ; X5HZ: reactance at 5HZ.

The comparison between the findings of spirometry and IOS in both TDT and NTDT groups were shown in table (1). There were differences between both groups regarding MEF 50 (p=0.017), R5Hz (p=0.002), R20Hz (p=0.004) and X5Hz (p=0.002). The mean ±SD of MEF 50 was lower in TDT group (75.81 ±17.75) than in NTDT group (88.59 ±18.54) (p=0.017). While the mean of R5Hz, R20Hz and X5Hz were higher in TDT group (156.6±58.3, 143.6±61.9 and 185.7±144.1) than in

NTDT group (129.9±15.87, 109.2±25.07 and 107.8±32.24) (p= 0.002, p= 0.004 and p= 0.002 respectively). However, there were statistically insignificant differences between them regarding each of the following (FVC, FEV1, FEV1/FVC, MEF75, MEF25, PEF and R20Hz). Accordingly these parameters among children with TDT detect airway resistance to both the large, central airways as well as the resistive component of the small airway.

The comparison between compliant patients to chelation therapy and non-compliant patients regarding IOS and spirometry findings were shown in table (2). The FVC and FEV1 were lower in the non-compliant group (p=0.01) and (p=0.0001) respectively, while R5HZ, R20HZ and X5HZ were higher among the compliant group (p=0.007), (p=0.0007) and (p=0.003). All the IOS findings were abnormal in non-compliant patients. Non-adherence to chelation therapy significantly compromised pulmonary compliance and both central and peripheral airway resistance.

The relations between all spirometry and IOS findings and each of the age of patients at study inclusion and the age at start of blood transfusion were shown in Table 4. The degree of small and central airway obstruction was related to disease duration and frequency of blood transfusion (p=0.001, 0.005 respectively).

Table 3. Spirometry and Impulse oscillometry findings in the 60 patients with ß-thalassemia

		Number	%
Spirometry	Normal Pattern	21	35
	Restrictive Pattern	30	50
	Small Airway Obstruction	9	15
Impulse oscillometry (IOS)	Normal Pattern	39	65
	Airway Obstruction	21	35

Table 4. Correlations of Spirometry and Impulse oscillometry findings in 60 patients with ß-thalassemia

	Spirometry Restrictive pattern		Small air way obstruction		Central airway obstruction*	
	r	P value	r	P value	r	P value
Age at transfusion	0.189	0.317	-0.03	0.834	-0.247	0.057
Duration of disease	0.1515	0.249	-0.3926	0.001	-0.3527	0.005
Sex	0.262	0.161	0.2157	0.129	0.056	0.670
Ferritin	-0.149	0.255	-0.172	0.186	0.0334	0.800
Transfusion Dependency	-0.0145	0.919	- 0.269	0.1505	0.582	0.0001
Chelation therapy Compliance	- 0.494	0.0006	0.3203	0.1106	0.135	0.335
Need for Chelation therapy	0.129	0.366	0.256	0.172	0.266	0.039

* Detected by abnormal pattern on Impulse oscillometry (IOS)

Discussion

Although lung impairment in patients with ß-thalassemia was reported since the early eighties, it represents one of the most underestimated complications. In fact, contradictory results were reported in different studies, ranging from a restrictive spirometry pattern to an obstructive one (*6*). This study aimed to evaluate the pulmonary functions in patients with ß-thalassemia.

It is alarming that 50% of our studied cohort had silent restrictive pattern in spirometry tests. Restrictive patterns are associated with underlying lung disease as idiopathic pulmonary, interstitial pneumonia, cryptogenic organizing pneumonia and other fibrosing lung disease (*10*). We did not study the pulmonary pressure or investigate any of these underlying conditions, as it was beyond the scope of the study, yet more studies are needed to verify the underlying pathology among these children with silent restrictive pattern. It is not clear if this restriction is part of the clinical spectrum of ß-thalassemia or a complication (*11*). More studies are needed to fill the gap of knowledge.

The restrictive abnormality predominant in our study may be attributed to factors including iron accumulation in lung parenchyma from repeated transfusions, upward pressure on the diaphragm by the enlarged liver and spleen when present and insufficient anatomic and functional development of the lung during early infancy due to chronic hypoxia (*8*).

Children who were non-compliant to chelation therapy had more restrictive pulmonary affection and had more evident central and small air way obstruction. That is why difficulties

facing chelation drugs should be addressed firmly to allow these patients to get their full benefit and avoid the risk of progressive lung injury with long standing anemia and its complications. It is well documented that deferoxamine is a major cause of lung induced interstitial lung disease (*12*). The restrictive pulmonary affection was not related to age at onset of transfusion, hence it seems that this restricted pattern maybe an idiosyncratic toxicity. In any case more studies are needed to evaluate other potentiating factors as the anemia, other drugs, etc. It is important to note that our study was a cross-sectional one, thus we are not aware if steroids, or change of dose or timing schedule as day after day, or giving other medications would influence the outcome, halt the progression or even reverse the lung injury. The silent nature of this progressive lung disease in children with ß-thalassemia is another challenging aspect. It is not clear, but the spirometry testing seems to be an important integral part of follow up of children with ß-thalassemia. Prospective trials are needed to verify the optimum timing of the spirometry testing. The difficulties facing chelation therapy should be addressed to maintain normal pulmonary functions, such as the availability of chelation drugs, their tolerability, transfusion iron burden and the patient's compliance. All these factors must be regularly reviewed, and the chelation modified accordingly (*13*).

While chelation therapy is lifesaving, quality of life is a major determinant of choice of type management. Hence, prevention of ß-thalassemia by stringent pre-marital testing should be enforced seriously in Egypt, prenatal diagnosis (*14*) and prompt early bone marrow transplantation should be offered to those indicated. Egypt has successfully terminated bilharziasis (*15*) and on its way to terminate hepatitis C virus infection (*16*). We strongly recommend that ß-thalassemia be the next disease to be terminated.

The quality of life of children with ß-thalassemia is poor and challenging (*17*). The restrictive pattern was not the only detected abnormality in our study. Silent central and peripheral airway obstruction was also noted in our studied cohort as detected by the MEF50 and IOS R5HZ, R20HZ and X5HZ. Again it is very intriguing that it is silent. We did not test for exercise tolerance, which seems necessary at this point. It corelated with transfusion dependency (p=0.0001), but not ferritin (p=0.800). We did not perform MRI heart or liver to detect tissue hemochromatosis (*18*), so we are not sure why they developed this silent airway obstruction, and whether it is dynamic or progressive to culminate into chronic airway obstruction disease.

Small air way obstruction was present among the third of our studied cohort, it could be related to direct narrowing secondary to iron deposition or indirectly through reduction in the elastic recoil as well as a disproportionate growth of alveolar mass relative to the airway and chest cage secondary to chronic hypoxia. Some attribute that chronic immunological factors, minor incompatibilities in the transfused red cells, and toxicities secondary to Deferoxamine treatment represent the main causes of intrinsic airway obstruction (*9*). The number of studied patients was small, thus a larger size future study would delineate the role of chelating agents in the development of restrictive lung injury.

Our study demonstrated that airway involvement was more in TDT which may be due to direct narrowing secondary to iron deposition resulting from frequent and early blood transfusion. This was in contrast to the studies (*9*, *10*) which showed no correlation between frequency of blood transfusion per year and pulmonary dysfunction. More work up beyond the scope of this study is needed to verify the underlying cause of the lung injury among our studied cohort. The mere longer duration of disease was associated with small peripheral and central airway obstruction. It is not clear why it was masked. We did not study exercise tolerance, yet maybe the associated anemia limited their exercise and did not allow the airway disease to present itself.

Although the chronic effect of iron overload represents the most reasonable explanation for restrictive impairment of lung function, there was no correlation between serum ferritin and any parameter of pulmonary functions in this study. This may be explained by the fact that serum ferritin is not the best quantitative estimate of body iron stores and measurement of hepatic iron content by liver biopsy or magnetic resonance imaging (MRI) must be done. However, serum ferritin is routinely used to assess iron overload in Egyptian thalassemia patients as it is less invasive than the liver biopsy, cheaper and more available than MRI.

Conclusion

Pulmonary dysfunction can be a silent complication of ß-thalassemia. The frequency of pulmonary dysfunction among our studied patients was 65%. The most frequent pulmonary dysfunction in patients with ß-thalassemia is restrictive lung disease. The degree of pulmonary dysfunction is related to age but not related to duration or frequency of blood transfusion. It is recommended to test patients with ß-thalassemia by spirometry and impulse oscillometry as a

part of their routine follow up. Good compliance to chelation therapy decreases pulmonary dysfunction, so, adherence to chelation therapy with adequate doses is highly recommended. Drug induced lung injury maybe incriminated in the restrictive lung disease in children with ß-thalassemia. Early initiation of chelation regimens can protect lung parenchyma from the ongoing process of damage but once occurred, is usually irreversible. Further studies with larger number of patients should be done to validate the sensitivity of impulse oscillometry in detecting early pulmonary changes in ß- thalassemic patients.

Author Contributions:

All shared in design, data curation analysis and drafting of the work. All approved the final manuscript.

FUNDING

Authors declare there was no extramural funding provided for this study.

CONFLICT OF INTEREST

The authors declare no conflict of interest in connection with the reported study. Authors declare veracity of information.

References

1. S. Tenny, M. Varacallo, *Evidence Based Medicine.* (StatPearls Publishing; Treasure Island (FL), 2020; https://www.ncbi.nlm.nih.gov/books/NBK470182/).
2. Langer AL, "Beta-Thalassemia. In: Adam MP, Feldman J, Mirzaa GM, et al., editors." in *GeneReviews® [Internet]* (Seattle (WA): University of Washington, Seattle; 1993-2024.; https://www.ncbi.nlm.nih.gov/books/NBK1426/)*Gene Reviews*.
3. A. Lal, T. Wong, S. Keel, M. Pagano, J. Chung, A. Kamdar, L. Rao, A. Ikeda, G. Puthenveetil, S. Shah, J. Yu, E. Vichinsky, The transfusion management of beta thalassemia in the United States. *Transfusion (Paris)* **61**, 3027–3039 (2021).
4. K. C. Chan, C. T. Au, A. W. K. Leung, A. M. Li, C. Li, M. M. T. Wong, C. S. T. Li, H. L. Cheung, P. Fan, S. C. Ling, R. C. H. Li, S. Y. Ha, Pulmonary function in patients with transfusion-dependent thalassemia and its associations with iron overload. *Sci. Rep.* **13**, 3674 (2023).
5. A. Eldor, E. A. Rachmilewitz, The hypercoagulable state in thalassemia. *Blood* **99**, 36–43 (2002).
6. F. M. Abu-Ekteish, H. S. Al-Rimawi, M. K. Al-Ali, I. M. Shehabi, Pulmonary function tests in children with beta-thalassemia major. *Chron. Respir. Dis.* **4**, 19–22 (2007).
7. A. T. Jebb, V. Ng, L. Tay, A Review of Key Likert Scale Development Advances: 1995–2019. *Front. Psychol.* **12**, 637547 (2021).
8. Jane Kirkby, "Application and Interpretation of Paediatric Lung Function Tests in Health and Disease," thesis, Portex Unit of Paediatric Anaesthesia, Pain Research, Critical Care, Respiratory Medicine, Physiology and Physiotherapy. UCL, Institute of Child Health, UK (2012).
9. K. Desiraju, A. Agrawal, Impulse oscillometry: The state-of-art for lung function testing. *Lung India* **33**, 410 (2016).
10. P. J. Martinez-Pitre, B. R. Sabbula, M. Cascella, "Restrictive Lung Disease" in *StatPearls* (StatPearls Publishing, Treasure Island (FL), 2024; http://www.ncbi.nlm.nih.gov/books/NBK560880/).
11. G. Zengin Ersoy, Restrictive effects of thalassemia on respiratory functions: One center experience. *North. Clin. Istanb.*, 589–596 (2023).
12. M. Schwaiblmair, Drug Induced Interstitial Lung Disease. *Open Respir. Med. J.* **6**, 63–74 (2012).
13. A. Adramerina, M. Economou, Challenges of Iron Chelation in Thalassemic Children. *Thalass. Rep.* **14**, 1–9 (2024).
14. N. Suwannakhon, J. Hemvuthiphan, T. Pangeson, K. Mahingsa, A. Pingyod, W. Bumrungpakdee, T. Sanguansermsri, Non-invasive prenatal screening & diagnosis of ß-thalassaemia in an affected foetus. *Indian J. Med. Res.* **157**, 447 (2023).
15. M. El-Kassas, R. E. Sheemy, M. Elbadry, Strategies and achievements in controlling and eliminating schistosomiasis from Egypt. *Egypt. Liver J.* **14**, 31 (2024).
16. A. M. Metwally, D. M. Elmosalami, H. Elhariri, L. A. El Etreby, A. Aboulghate, M. M. El-Sonbaty, A. Mohsen, R. M. Saleh, G. A. Abdel-Latif, S. Samy, S. E. El Deeb, A. M. Fathy, M. M. Salah, M. A. Abdel Mawla, H. M. Imam, N. A. Ibrahim, F. A. Shaaban, R. Y. Elamir,

M. Abdelrahman, M. H. El-Sayed, Accelerating Hepatitis C virus elimination in Egypt by 2030: A national survey of communication for behavioral development as a modelling study. *PLOS ONE* **16**, e0242257 (2021).
17. I. Youssry, H. Fawzy, N. Asem, D. Abd Elaziz, COVID-19 Lockdown aggravated the Health-Related Quality of Life in Children with Transfusion-Dependent-Thalassemia. *Pediatr. Sci. J.* **4**, 1–9 (2023).
18. M. S. Soltanpour, K. Davari, The Correlation of Cardiac and Hepatic Hemosiderosis as Measured by T2*MRI Technique with Ferritin Levels and Hemochromatosis Gene Mutations in Iranian Patients with Beta Thalassemia Major. *Oman Med. J.* **33**, 48–54 (2018).