Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.62, No.6(2022). p.7-27; DOI: 10.14238/pi62.1.2022.7-26

Original Article

Prevalence of pulmonary dysfunction in patients with beta thalassemia major: a systematic review and meta-analysis

Taksande Amar, Yash Dalal, Himanshi Jindal, Taksande Bharati

Abstract

Background Many studies have been conducted on heart, liver, and endocrine abnormalities in thalassemia; however, studies on pulmonary dysfunction (PD) have been limited. Previous studies on the prevalence of restrictive lung disease (RLD) and obstructive lung disease (OLD) in β-thalassemia major patients have lacked agreement.

Objective To assess the prevalence of PD in β-thalassemia major patients by systematic review of the literature and meta-analysis.

Methods We searched *Cochrane Library, PubMed, Web of Science, MEDLINE, Scopus,* and *Embase* for relevant articles. Articles were selected according to the inclusion criteria and data were extracted. The primary outcome was prevalence of pulmonary dysfunction in β-thalassemia major with 95% confidence interval (95%CI). Subgroup analyses were applied to explore the prevalence in different age groups, regions, and serum ferritin levels. Sensitivity analysis and publication bias assessment were also conducted.

Results A total of 37 studies comprising 1,467 cases were included in this analysis. Pulmonary dysfunction was present in 64.7% (95%CI 57.6 to 71.1) of cases. The pooled prevalence of RLD (44.9%) was higher than that of OLD (7.6%) and diffusion impairment (DI) (35.6%). Subgroup analysis revealed that the region with the highest pooled prevalence of PD was the Americas (75.2%). The highest prevalence of RLD and DI was found in Asia (48.2% and 44.6%, respectively) and that of OLD in Europe (9.7%). Sensitivity analysis showed that the pooled results were robust.

Conclusion A high prevalence of pulmonary dysfunction, mainly RLD rather than OLD, was detected in β-thalassemia major patients. **[Paediatr Indones. 2021;62:7-26 ; DOI: 10.14238/pi62.1.2022.7-26**].

Keywords: *thalassemia; pulmonary dysfunction; restrictive; obstructive; iron overload; serum ferritin*

Beta-thalassemia is a heterogeneous, autosomal recessive hereditary anemia, characterized by reduced or absent β-globin chain synthesis.[1] Around 1.5% (80-90 million people) of the worldwide population are β-thalassemia carriers, with 50,000-60,000 new β-thalassemia cases born each year.[2] β-thalassemia is most prevalent in populations of Asia, the Indian subcontinent, Mediterranean countries, Africa, and the Middle East.[3-5] Patients with β-thalassemia are now surviving to older ages due to the increasing availability of blood transfusions and iron chelation. These patients are treated with monthly transfusions to minimize acute symptoms of the disease. However, receiving blood may cause complications, including infections, alloimmunization, and excess iron deposition in various organs that can lead to liver failure, heart failure, and endocrine disorders.

Iron overload is frequently observed in β-thalassemia major patients on transfusion therapy.[6] Excessive iron can cause organ damage when deposited

From the Department of Paediatrics, Jawaharlal Nehru Medical College, DattaMeghe Institute of Medical Sciences, SawangiMeghe, Wardha, Maharashtra State, India.

Corresponding author: Taksande Amar. Department of Paediatrics, Jawaharlal Nehru Medical College, DattaMeghe Institute of Medical Sciences, SawangiMeghe, Wardha, Maharashtra State, India 442004. Contact: +919822369233.Email: amar.taksande@gmail.com.

Submitted November 7, 2020. Accepted January 20, 2022.

in the liver, spleen, pancreas, heart, kidney, skin, pituitary, and other organs. Potential complications related to iron overload in transfused patients include cardiomyopathy, congestive heart failure, liver cirrhosis, arthritis, as well as endocrine disorders such as diabetes and other diseases.[7] Pulmonary function abnormality is a known complication of thalassemia, but the results of studies on pulmonary function have been inconsistent. Reported abnormalities vary and include restrictive lung disease, impaired diffusing capacity of lung for carbon monoxide (DLCO), small airway disease, and obstructive airway disease.[6,8,9-11] Of these, restrictive abnormalities are the most frequent, being reported in up to 80% of patients.[12-15]

The precise etiology of pulmonary dysfunction (PD) in thalassemia patients remains unknown. Previous post-mortem studies have shown the presence of iron in the lungs of thalassemia major (TM) patients.[16] Another study showed that TM patients with abnormal pulmonary function had higher serum ferritin levels compared to those with normal pulmonary function.[11] In a study, an inverse correlation between total lung capacity and lifetime estimates of transfusional iron load was established. Thus, iron overload was proposed to play an important part in causing pulmonary abnormalities.[13] However, such a claim was not supported by a subsequent study.[14] Since previous studies on the prevalence of restrictive lung disease (RLD) and obstructive lung disease (OLD) in β-thalassemia major patients have lacked agreement, we performed a meta-analysis of published studies to assess the pooled prevalence of pulmonary dysfunction in β-thalassemia major patients. In this report, we describe the first systematic review and meta-analysis which supplements our existing knowledge on the prevalence of pulmonary dysfunction in β-thalassemia major. Our objective was to establish the prevalence and the underlying etiology of PD in children with β-thalassemia major. This systematic review's aim is to provide sufficient evidence to guide policy-making, with the aim of prevention and effective management of PD in children with β-thalassemia major and to underpin further research.

Methods

The protocol for this systematic review and meta-analysis was registered at the *International Prospective Register of Systematic Reviews* (PROSPERO 2020 #CRD42020208769). This systematic review followed the recommendations of the meta-analyses in observational studies (MOOSE) guidance statement.[17] The search strategy was implemented in two stages, consisting of a bibliographic database search and a hand search of other sources.

Bibliographic database search

Electronic databases (*Cochrane library, PubMed, EMBASE, Scopus,* and *Web of Science*) were used as data sources. Searches were restricted to English language publications involving human subjects, but not restricted by date or publication type. Studies with insufficient data, abstracts only, conference abstracts, or duplicate publications were excluded. Studies with key data that were not accessible even after requests from authors were also excluded. Data extraction and quality control was independently done by two reviewers (YD and HJ). A third reviewer (AT) was involved if conflicting opinions occurred. We used the following terms for pulmonary dysfunction: 'pulmonary dysfunction' and 'pulmonary restrictive diseases' and 'pulmonary obstructive diseases' and 'impairment of pulmonary diffusion'. For thalassemia, we used the term 'beta thalassemia'. The last electronic search was carried out on September 10, 2020.

Hand search of other sources

We conducted manual searches for additional articles by scanning the reference lists of eligible papers, other relevant review articles, and specialist journals.

All studies were imported to the literature management software (*Endnote® X7*) to eliminate duplicates. Then, two authors (YD and HJ) independently conducted a preliminary screening of studies by reading titles and abstracts. After screening, the full texts of potentially relevant articles were downloaded. A second round of screening was conducted by reading full texts. Studies were selected if they met the inclusion criteria. Methods were adapted as per *Preferred Reporting Items for Systematic Reviews and Meta-analyses* (PRISMA) guidelines for meta-analyses.[18]

Eligibility criteria for considering studies to

include in the review

Studies considered in this meta-analysis were observational studies about the prevalence of PD in children with beta-thalassemia. Included studies had to provide the total number of patients with PD occurring in the cohort.

Inclusion criteria:

- Cross-sectional, cohort studies of children with β-thalassemia which report the prevalence of PD.
- All published and unpublished studies reported from 1 January 1980 to 10 September 2020.

Exclusion criteria:

- Studies not performed in human participants.
- Case series, reviews, letters, commentaries, and editorials.
- Studies with insufficient data, abstracts, conference abstracts, and duplicate publications.
- Studies with key data that were not accessible even after requests from authors.

Selection of studies for inclusion in the review

Two investigators (YD & HJ) independently identified articles and sequentially screened their titles and abstracts for eligibility. Full texts of articles deemed potentially eligible were acquired. These investigators independently further assessed the full text of each study for eligibility and consensually retained studies to be included. Disagreements were resolved by a third person- the first author of the study (TA). We used a screening guide to ensure that all review authors reliably applied the selection criteria. Agreement was measured using the kappa (κ) statistic.[19]

Data extraction and management

A standard data extraction form was used to retrieve relevant information and data from each study included in the analysis. Two review authors (YD & HJ) participated in data extraction independently. YD & HJ extracted data which included general information (authors, year and country), design of the study, and prevalence of PD. In studies where only primary data (sample size and number of outcomes) was provided, we calculated prevalence estimates from such data. Data were extracted using a preconceived and standardized data abstraction form. Studies with uninterpretable data were excluded from the analysis.

Appraisal of the quality of included studies

Two investigators (YD & HJ) evaluated included studies for methodological quality and risk of bias using an adapted version of the *Risk of Bias Tool for Prevalence Studies* developed by Hoy *et al*.[20] Furthermore, the reporting quality of each study was assessed using the *Strengthening the Reporting of Observational Studies* (STROBE) checklist.[21] The STROBE statement is a checklist of 22 items. These items relate to the article's title and abstract (item 1), the introduction (items 2 and 3), methods (items 4-12), results (items 13-17) and discussion sections (items 18-21), and other information (item 22 on funding). The STROBE assessments were performed by two authors, and scored from 0 to 22, with 22 reflecting the highest quality.

Statistical analysis

In each study, the prevalence of pulmonary dysfunction was considered as the probability of binomial distribution. We estimated prevalence with 95% confidence intervals for each study via OpenEpi software online, which is available at http://www.openepi.com/OE2.3/Menu/OpenEpiMenu.htm. Results from the "Wald (Normal Approximation)" method was used if $np > 5$ or $n(1-p) > 5$, where n represents the total number and p is the prevalence in the group. Otherwise ($np \leq 5$ or $n(1-p) \leq 5$), the Mid-P of the exact estimation method was selected. Forest plots were drawn to visualize the combined prevalence and extent of heterogeneity between studies. To evaluate the heterogeneity of the studies, Cochran's Q test and I^2 index were used.[22] There are three categories for heterogeneity: I^2 index less than 25%=low heterogeneity; I^2 index between 25%-75%=moderate heterogeneity, and I^2 index more than 75%=high heterogeneity. Considering the heterogeneity of the studies, a random effects model was used instead of the fixed effects model because the former includes both within-study variance and between-study sampling error in the assessment of the uncertainty of the results of a meta-analysis. Sensitivity analysis was performed to check the stability and reliability of the main effect size for pulmonary dysfunction prevalence. Sensitivity analysis was undertaken by removal of three studies which

reported a high prevalence of PD in β-thalassemia major. In order to identify the cause of heterogeneity of pulmonary dysfunction prevalence, sub-group analysis of pulmonary dysfunction was carried out based on age, geographical region, study publication, study design, risk of bias, and serum ferritin, while the meta-regression model (method of moments) was carried out based on the year of publication.[23] Egger and Begg's tests were used to identify publication bias. Data analysis was performed using *Comprehensive Meta-Analysis Software version 2* and the significance level in the tests was considered to be <0.05. High-resolution forest plots, with random effects, were separately created.[24]

Results

Characteristics of included studies

Initially, a total of 841 articles were identified (**Figure 1**). After elimination of duplicates, screening titles and abstracts, 660 papers remained, of which 592 papers were completely irrelevant, and thus, excluded. Agreement between investigators on abstract selection was high ($\kappa=0.90$, $P<0.001$). Full texts of the remaining 68 studies were scrutinized for eligibility, among which 31 studies were excluded. There was no disagreement between investigators for full-text selection. Overall, 37 studies were found eligible, and hence, were included in the meta-analysis (**Figure 1**).

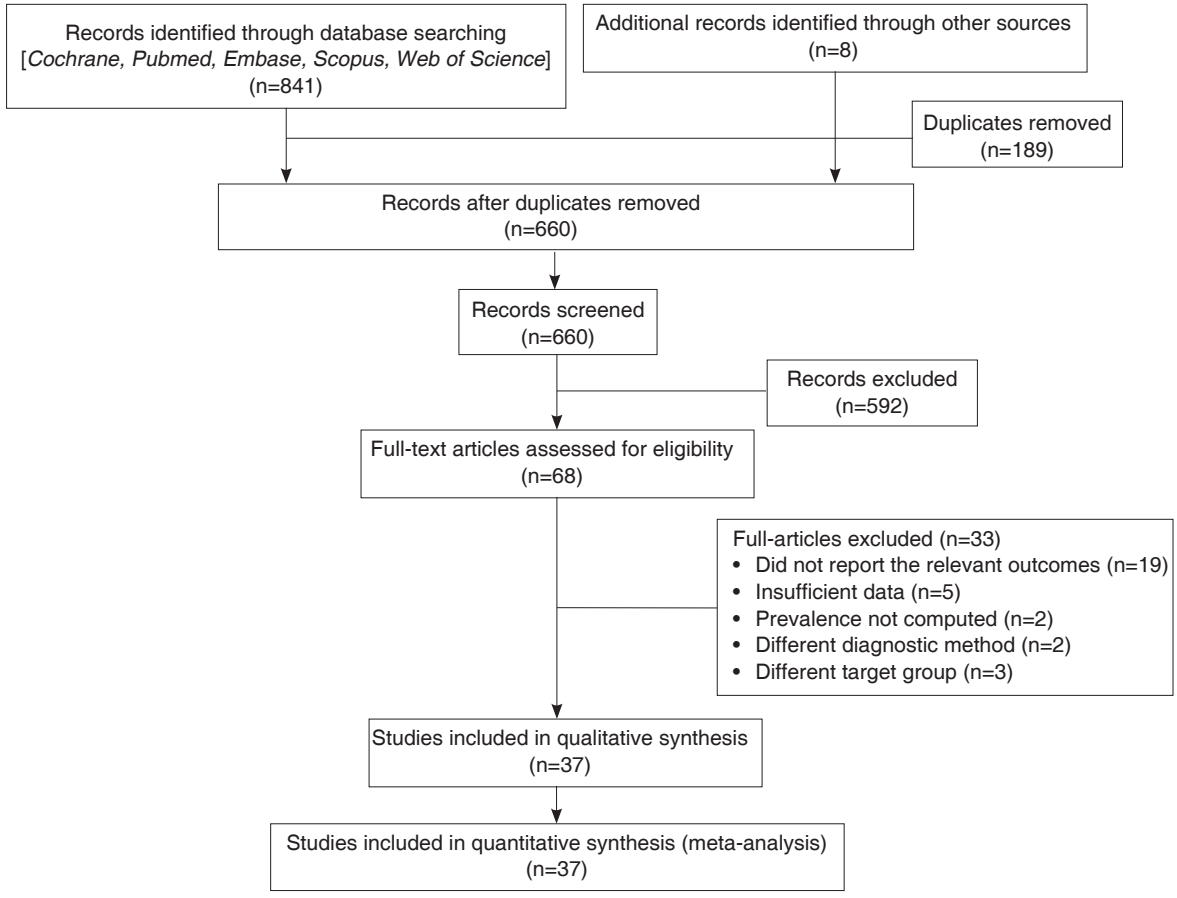


Figure 1. PRISMA flow chart diagram describing process of identification and selection of studies for inclusion

Studies were published from 1980 to 2020 with sample sizes ranging from 10 to 104 subjects, with an overall sample size of 1,467. Subjects' ages ranged from 6 to 48 years. Among the included articles, 21 were conducted in Asia, 9 in Europe, 4 in the Americas, and 3 in Africa. The prevalence of RLD, OLD, diffusion impairment (DI), and PD were reported in the 37 studies. Baseline characteristics of these studies are summarized in **Tables 1** and **2**.

Study quality

The results of the quality assessment are presented in **Table 3**. None of the studies met all the criteria of the quality assessment score. Based on the STROBE criteria, studies varied in their quality score from 11 to 20. A score of <14 was considered low quality and >14 was considered as good/fair quality. The quality of reporting was low for 15 studies, while it was good/fair for the remaining 22 studies. Of the 22 items from the STROBE assessment, the most common problems were a failure to estimate the required sample size and poor generalizability of the results.

Risk of bias and heterogeneity

Quality assessment was also conducted for ten different items in each study using the risk of bias assessment tool.[25] Of the 37 included studies, our summary assessment (**Table 4**) shows low risk of bias for 30 studies (81.08%) and moderate risk of bias for 7 studies (18.92%). Agreement between investigators on quality assessment of studies was high (β=0.88; P<0.001).

Prevalence of pulmonary dysfunction in β-thalassemia

The overall prevalence of pulmonary dysfunction in β-thalassemia major was 64.7% (95%CI 57.6 to 71.1) in the meta-analysis of 35 studies, according to the Der Simonian-Laird random-effects model. The forest plot is shown in **Figure 2**. The rate of heterogeneity in this study was high (I^2=82.44%; P<0.001). The lowest event rate of pulmonary dysfunction (18.4%) was reported by a study by Sohn *et al.*,[42] while the highest event rate (96.7%) was reported by Hoyt *et al.*[26] (**Figure 2**).

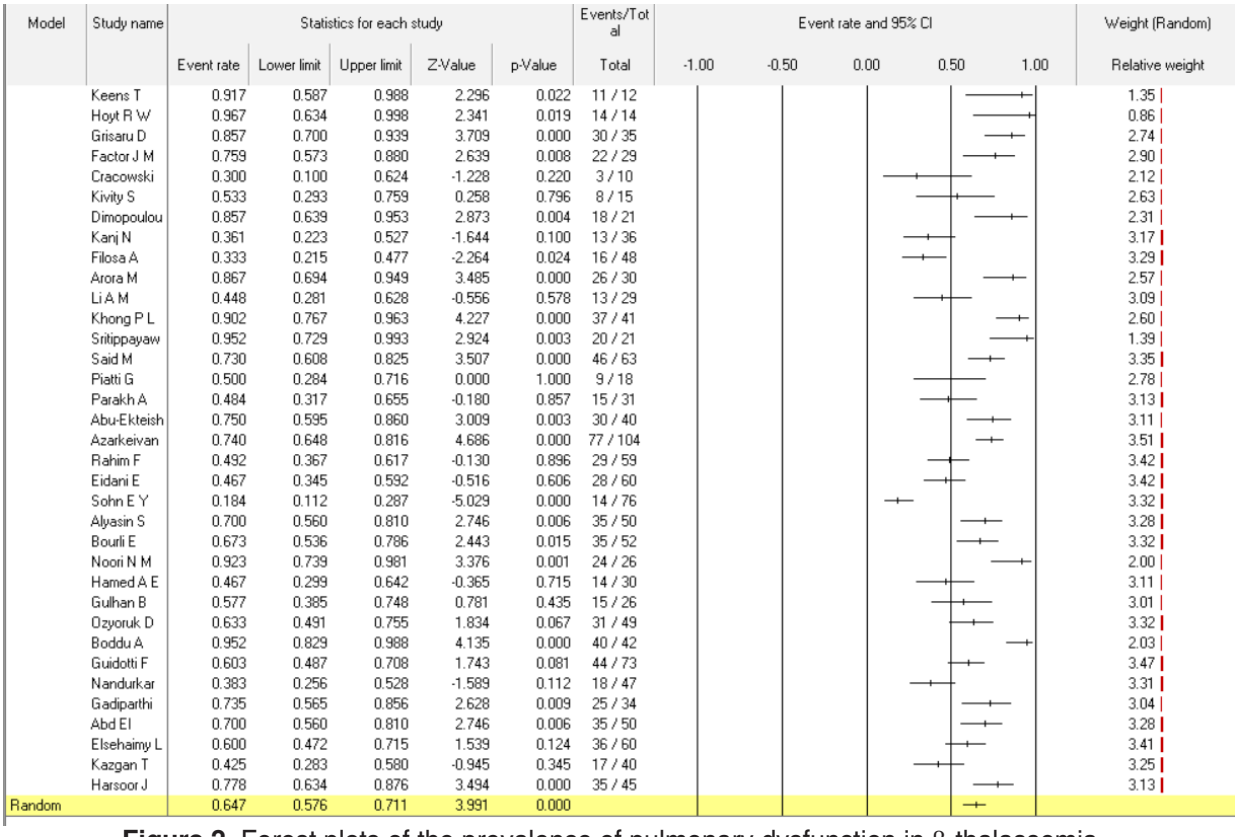


Figure 2. Forest plots of the prevalence of pulmonary dysfunction in β-thalassemia

Table 1.Characteristics of studies included in the meta-analysis

No	First author	Year	City or country	Study design	Population size	RLD cases	OLD cases	DI cases	Total PD cases	Pre RLD, %	Pre OLD, %	Pre PD, %
1	Keens TG[25]	1980	Los Angeles	NM	12	NM	NM	0	11	NM	NM	91.67
2	Hoyt RW[26]	1986	Philadelphia	NM	14	NM	NM	NM	14	NM	NM	100
3	Grisaru D[27]	1990	Israel	NM	35	24	2	18	30	68.57	5.71	85.71
4	Factor JM[13]	1994	New York	NM	29	21	0	7 (6 had RLD)	22	72.41	0	75.86
5	Tai DYH[14]	1996	Singapore	NM	14	4	1	12	NM	28.57	7.14	NM
6	Cracowski C[28]	1998	France	NM	10	0	2	2	3	0	20	30
7	Kivity S[29]	1999	Israel	NM	15	8	0	NM	8	53.33	0	53.33
8	Dimopoulou I[30]	1999	Greece	NM	21	15	2	5	18	71.43	9.52	85.71
9	Kanj N[12]	2000	Lebanon	NM	36	11	2	13	13	30.55	5.55	36.11
10	Filosa A[31]	2001	Italy	NM	48	16	0	14	16	33.33	0	33.33
11	Arora M[32]	2001	India	Case-control	30	26	0	26	26	86.67	0	86.67
12	Li AM[9]	2002	China	NM	29	4	4	10	13	13.79	13.79	44.83
13	Khong PL[33]	2003	Hong Kong	NM	41	11	4	13	37	26.83	9.76	90.24
14	Jamal R[34]	2005	Malaysia	Cross-sectional	37	13	0	NM	NM	35.14	0	NM
15	Sritippayawan S[35]	2005	Thailand	Cross-sectional	21	5	13	NM	20	23.81	61.90	95.24
16	Said M[36]	2005	Indonesia	Case-control	63	44	4	NM	46	69.84	6.34	73.02
17	Piatti G[37]	2006	Italy	Longitudinal	18	7	NM	5	9	38.89	NM	50
18	Parakh A[38]	2007	India	Observational	31	5	1	13	15	16.12	3.22	48.39
19	Abu-Ekteish FM[39]	2007	Jordan	Case control	40	14	6	10	30	35	15	75
20	Azarkeivan A[10]	2008	Iran	NM	104	77	3	NM	77	74.04	2.88	74.04
21	Rahim F[40]	2008	Iran	NM	59	29	0	16	29	49.15	0	49.15
22	Eidani E[41]	2010	Iran	NM	60	25	NM	NM	28	41.67	NM	46.67
23	Sohn EY[42]	2011	California	Cohort	76	12	0	2	14	15.79	0	18.42
24	Alyasin S[43]	2011	Iran	NM	50	6	4	NM	35	12	8	70
25	Bourli E[44]	2012	Greece	NM	52	20	2	32	35	38.46	3.84	67.31
26	Noori NM[45]	2012	Iran	Case-control	26	24	4	NM	24	92.31	15.38	92.31
27	Hamed AES[46]	2013	Egypt	Case-control	30	8	6	NM	14	26.67	20	46.67
28	Gulhan B[47]	2014	Turkey	NM	26	2	12	2	15	7.69	46.15	57.69
29	Ozyoruk D[48]	2015	Turkey	Cross-sectional	49	NM	NM	NM	31	NM	NM	63.27
30	Boddu A[49]	2015	India	NM	42	40	0	NM	40	95.24	0	95.24
31	Guidotti F[50]	2017	Italy	Longitudinal	73	26	0	25/63	44	35.62	0	60.27

Table 1.Characteristics of studies included in the meta-analysis (continued)

32	Nandurkar P[51]	2018	India	Case-control	47	NM	9	NM	18	NM	19.15	38.30
33	Gadiparthi M[52]	2019	India	NM	34	25	0	NM	25	73.53	0	73.53
34	Abd El Hakeem AA[53]	2019	Egypt	Case-control	50	17	0	35	35	34	0	70
35	Elsehaimy LA[54]	2019	Egypt	Case-control	60	35	1	NM	36	58.33	1.67	60
36	Kazgan T[55]	2019	Turkey	NM	40	17	11	NM	17	42.5	27.5	42.5
37	Harsoor J[56]	2020	India	Cross-sectional, descriptive	45	33	4	NM	35	73.33	8.89	77.78

NM=not mentioned; pre=prevalence

Table 2. Screening methodology of the included studies

No.	First author	Age range / mean (SD), years	Sex (M:F)	Lung function	Criteria used	Mean serm ferritin (SD), ng/mL
1	Keens TG[25]	6.3-30 / 18.4 (2.6)	4:8	RV,TLC,RV/TLC,MMEF	Polgar G *et al.*	NM
2	Hoyt RW[26]	10-39	11:8	FEV1,FEF 25-75%, DLCO,TLC,FRC, FVC,MEF 75%	ATS	Gp1 (F with TI): 216 (131) ug/L Gp2 (M with TM): 618 (362) ug/L Gp3 (F with TM): 2099 (1045) ug/L
3	Grisaru D[27]	8-33 / 19.8 (6.5)	17:18	FEV1,MMEF,FEF 50%,PEF,TLC, FRC,VC,F EV1/VC,DLCO,FRC	Cotes JE *et al.*	3674 (2199)
4	Factor JM[13]	6-40 / 19.8 (8.5)	14:15	FVC,FEV1,FEV1/FVC,FEF25-75%, DLCO,TLC	Polgar G *et al.*	1071 (571.02)
5	Tai DYH[14]	9-21 / (15)	7:7	FEV1,MMFER,TLC,RV,FRC, DLCO,PEFR	BTS	NM
6	Cracowski C[28]	6-18 / child (12); adult (33)	NM	FEV1,VC,FEV1/VC,TLC,DLCO	Cotes JE *et al.*	1633 (1340)
7	Kivity S[29]	8-21 / (12.73)	9:6	FVC,FEV1,FEV1/FVC	NM	1350 (250)
8	Dimopoulou I[30]	25 (5)	8:13	TLC,DLCO,PE max,RV,FVC, FEV1,FEV1/FVC	Cotes JE *et al.*	2669 (1237)
9	Kanj N[12]	10-58 / 18 (9)	17:19	FEV1/FVC,FEV3/FVC,FVC,FEFMAX,MMFR,RV/ TLC,DLCO	BTS	5698±4000
10	Filosa A[31]	8-23 / [GpA-10.8 (1.7); GpB-15.7 (1.1); GpC-19 (1.4)]	21:27	FVC,FEV1,FEF 50%, FEV1/FVC,PEF,DLCO,TLC	Cotes JE *et al.*	GpA (before pubertal sign): 2229 (866) GpB (at puberty): 2948 (1210) GpC (after puberty): 4327 (2442)
11	Arora M[32]	9-17 / 11.83 (1.91)	15:15	FRC,FVC,RV,TLC,FEV1,FEV1/FVC,PEF 25-75%,PEFR,DLCO	Pfaff JK *et al.*	3975 (870.7)
12	Li AM[9]	14.2 / 10.6-16.5	16:13	FEV1,FVC,MMFER,TLC,RV,FRC,DLCO,PEFR	BTS	5827.75 (3919.88 to 7939.5)
13	Khong PL[33]	9-40	18:23	FEV1/FVC,FEV1,FEF25%-75%, FEF50%,FEF75%FVC,TLC,RV/TLC,DLCO	ATS	NM
14	Jamal R[34]	10-24 / 15.8 (3.5)	NM	FVC,FEV1,FEV1/FVC,FEF 25-75%,TLC,VC,FRC,DLCO	ATS	NM
15	Sritippayawan S[35]	9-15 / 11.2 (2.6)	9:12	TLC,RV,RV/TLC,FVC,FEV1, FEV1/FVC, FEF 25-75%	ERS	2019.3 (1812.0)

Table 2. Screening methodology of the included studies (continued)

No.	First author	Age range / mean (SD), years	Sex (M:F)	Lung function	Criteria used	Mean serm ferritin (SD), ng/mL
16	Said M[36]	6-12 / 9.8 (1.91)	32:31	FEV1,FVC,FEV1/FVC,PEF	ATS/BTS	M: 4178.18 (2299.33) F: 4779.26 (3696.47)
17	Piatti G[37]	29.44 (2.89)	NM	FEV1,TLC,DLCO,FVC	Cotes JE *et al.*	1116.39 (590.83)
18	Parakh A[38]	8-22 / 13.56 (4.30)	25:6	FVC,TLC,DLCO,FEF 25%,FEF 50%, FEF 75%,FEV1	NM	GpA (normal PFT): 2686.13 (1416.25) GpB (abnormal PFT): 4173.13 (1612.90)
19	Abu-Ekteish FM[39]	7.5-18 / 12.5 (3.5)	23:17	TLC,DLCO,RV,FVC,TLC, FEV1/FVC,PEF	Bucci G *et al.*	3115 (224)
20	Azarkeivan A[10]	21.1 (7)	65:39	FVC,VC,FEV1,FEV1/VC	ATS	1856.4 (1490)
21	Rahim F[40]	10-45	27:22	TLC,FEV1,FEV1/FVC,RV,FRF 25-75%	Polgar G *et al.*	1594 (1800)
22	Eidani E[41]	10-45 / [M:19.75 (6); F: 20.03 (9.23)]	31:29	FEV1,FEV1/FVC,FEF 25-75%,DLCO,TLC	ATS	M: 2.53 (0.17); F: 2.63 (0.15)
23	Sohn EY[42]	11.8-48.4 / 25.6 (8.8)	37:39	FVC,FEV1,TLC,DLCO,FEF 25-75%,	Cotes JE *et al.*	3127
24	Alyasin S[43]	9-17 / 12.48 (2.2)	33:17	FEV1,FEV1/FVC,FEF 25-75%,FVC,PEF,	ATS	3346 (1667)
25	Bourli E[44]	9-34 / 21.33 (6.24)	25:27	FVC,FEV1,FEV1/FVC, MMFR,FEF 25-75% RV,TLC,DLCO,FRC	Device manufacture	M:1530 (1542); F:1820 (1277)
26	Noori NM[45]	10-20 / 14.8 (2.92)	NM	FEV1,FVC,FEV1/FVC	NM	3614.80 (2012.54)
27	Hamed AES[46]	7-17 / 12.4 (3.2)	12:18	FEV1,FVC,FEV1/FVC l	Miller MR *et al.*	NM
28	Gulhan B[47]	15.7 (5.2)	12:14	FEV1,FEV1/FVC,FEF 25-75%,DLCO,TLC	Cotes JE *et al.*	M: 2376; F: 2454
29	Ozyoruk D[48]	5-17 / 10.8 (3)	30:19	FEV1/FVC,FEV1, FVC,PEF, MEF25%-75%	Miller MR *et al.*	NM
30	Boddu A[49]	>7	26:16	FEV1,FVC,FEV1/FVC	NM	4152.57 (1822.77)
31	Guidotti F[50]	37 (7)	24:49	FVC,FEV1,FEV1/FVC,TLC,RV,DLCO	Cotes JE *et al.*	RLD: 1526 (1437); NRLD: 975 (779)
32	Nandurkar P[51]	6-14 / 9.44 (2.03)	35:12	FVC,FEV1,FEV1/FVC, FEF25-75%,	ATS	3217 (1351.853)
33	Gadiparthi M[52]	8-18 / 14.18 (4.95)	21:13	FVC,FEV1,FEV1/FVCATS	ATS	3610.82 (2679.15)
34	Abd El Hakeem AA[53]	13.2 (2.7)	31:19	FVC,FEV1,FEV1/FVC,PEFR, FEF 25-75%,TLC,DLCO	ATS	DI: 3543 (2292); CDRI: 4660 (2100); normal PFT: 2941 (2612)
35	Elsehaimy LA[54]	11.65 (2.57)	20:40	FVC,FEV1,FEV1/FVC,FEF 25-75%	Fabrii *et al.*	NM
36	Kazgan T[55]	6-20 / 13.27 (4.26)	21:19	FEV1,FVC,FEF 25-75%,PEFR	Miller MR *et al.*	3268.25 (2991.44)
37	Harsoor J[56]	5-15 / 7.78 (2.4)	1.6:1	FEV1,FVC,FEV1/FVC,PEFR,PEF 25-75%	BTS	>2500 <2500

RV=residual volume; ,TLC=total lung capacity; MEF=maximal expiratory flow; FEV1=forced expiratory volume in 1 second; DLCO= diffusing capacity for carbon monoxide; MMFR=maximal midexpiratory flow rate; FRC= functional residual capacity; FVC=forced vital capacity; MMEF= Maximal mid-expiratory flow; PEF= peak expiratory flow; PFT= pulmonary function test; VC=vital capacity; TLC=total lung capacity; FEF= Forced Expiratory Flow; PEFR= peak expiratory flow rate

Table 3. Quality assessment of the included studies

		STROBE quality of reporting					
No.	First author	Title & abstract (Item1)	Introduction (Items 2 and 3)	Methods (Items 4-12)	Results (Items 13-17)	Discussion and other information (Items 18-22)	Quality score (0-22)
1	Keens TG[25]	0	1	4	3	3	11
2	Hoyt RW[26]	0	2	4	3	3	12
3	Grisaru D[27]	0	2	4	3	3	12
4	Factor JM[13]	0	2	4	3	3	12
5	Tai DYH[14]	0	2	5	3	3	13
6	Cracowski C[28]	0	2	4	3	3	12
7	Kivity S[29]	0	2	4	3	3	12
8	Dimopoulou I[30]	0	2	5	4	4	15
9	Kanj N[12]	0	2	3	3	4	12
10	Filosa A[31]	0	2	5	3	3	13
11	Arora M[32]	1	1	5	3	3	13
12	Li AM[9]	0	2	5	4	4	15
13	Khong PL[33]	0	2	4	4	3	13
14	Jamal R[34]	1	2	5	4	3	15
15	Sritippayawan S[35]	1	2	5	4	4	16
16	Said M[36]	1	2	7	5	2	17
17	Piatti G[37]	1	2	6	4	3	16
18	Parakh A[38]	1	2	5	4	3	15
19	Abu-Ekteish FM[39]	0	1	4	5	2	12
20	Azarkeivan A[10]	0	2	3	5	2	12
21	Rahim F[40]	0	2	6	5	3	16
22	Eidani E[41]	0	2	3	5	3	13
23	Sohn EY[42]	0	2	8	4	3	17
24	Alyasin S[43]	1	2	8	5	4	20
25	Bourli E[44]	0	2	6	5	3	16
26	Noori NM[45]	1	2	4	5	3	15
27	Hamed AES[46]	0	2	7	5	3	17
28	Gulhan B[47]	0	2	7	5	5	19
29	Ozyoruk D[48]	0	2	5	5	2	14
30	Boddu A[49]	1	2	6	5	3	17
31	Guidotti F[50]	0	2	5	5	3	15
32	Nandurkar P[51]	1	2	5	4	2	14
33	Gadiparthi M[52]	0	2	7	5	3	17
34	Abd El Hakeem AA[53]	1	2	7	5	2	17
35	Elsehaimy LA[54]	1	2	3	4	3	13
36	Kazgan T[55]	0	2	5	4	4	15
37	Harsoor J[56]	1	2	7	4	5	19

Sensitivity analysis was performed to evaluate the effects of the methodological quality of each trial on the pooled results. It was based on removing one study at a time for prevalence of PD data, and showed that the overall result was reliable.

To reduce the heterogeneity, subgroup analysis

Table 4. Risk of bias assessment of included studies using the Hoy *et al.*[20] tool

Sr. No.	First author	Representation	Sampling	Random selection	Non response bias	Data collection	Case definition	Reliability and validity of study tool	Method of data collection	Prevalence period	Numerator and denominator	Summary assessment
1	Keens TG[25]	HR	LR	LR	HR	LR	LR	LR	LR	HR	HR	MR
2	Hoyt RW[26]	HR	LR	LR	LR	LR	HR	LR	LR	HR	HR	MR
3	Grisaru D[27]	HR	LR	LR	LR	LR	HR	HR	LR	HR	LR	MR
4	Factor JM[13]	HR	LR	LR	LR	LR	LR	HR	LR	LR	LR	LR
5	Tai DYH[14]	HR	LR	LR	LR	LR	LR	LR	LR	HR	LR	LR
6	Cracowski C[28]	HR	LR	LR	LR	LR	HR	HR	LR	LR	LR	LR
7	Kivity S[29]	HR	LR	LR	LR	LR	LR	HR	LR	HR	LR	LR
8	Dimopoulou I[30]	LR	LR	LR	LR	LR	LR	HR	LR	LR	LR	LR
9	Kanj N[12]	HR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR
10	Filosa A[31]	HR	LR	LR	HR	LR	LR	LR	LR	HR	LR	LR
11	Arora M[32]	HR	LR	LR	LR	LR	HR	HR	LR	LR	HR	MR
12	Li AM[9]	HR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR
13	Khong PL[33]	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR
14	Jamal R[34]	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR
15	Sritippayawan S[35]	LR	LR	LR	HR	LR	LR	LR	LR	LR	LR	LR
16	Said M[36]	HR	HR	LR	LR	LR	LR	LR	LR	LR	LR	LR
17	Piatti G[37]	HR	LR	LR	LR	LR	LR	LR	LR	HR	LR	LR
18	Parakh A[38]	HR	LR	LR	LR	LR	LR	HR	LR	LR	LR	LR
19	Abu-Ekteish FM[39]	HR	LR	LR	LR	LR	HR	HR	LR	LR	HR	MR
20	Azarkeivan A[10]	HR	LR	HR	LR	LR	HR	LR	LR	LR	LR	LR
21	Rahim F[40]	LR	LR	LR	LR	LR	LR	HR	LR	HR	LR	LR
22	Eidani E[41]	HR	LR	LR	LR	LR	HR	LR	LR	LR	LR	LR
23	Sohn EY[42]	HR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR
24	Alyasin S[43]	HR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR
25	Bourli E[44]	HR	LR	LR	LR	LR	LR	HR	LR	LR	LR	LR
26	Noori NM[45]	HR	LR	LR	HR	LR	LR	HR	LR	LR	HR	MR
27	Hamed AES[46]	HR	LR	LR	LR	LR	LR	HR	LR	LR	LR	LR
28	Gulhan B[47]	HR	LR	LR	LR	LR	LR	HR	LR	LR	LR	LR
29	Ozyoruk D[48]	HR	LR	LR	LR	LR	LR	HR	LR	LR	LR	LR
30	Boddu A[49]	HR	LR	LR	LR	LR	LR	HR	LR	LR	HR	LR
31	Guidotti F[50]	HR	LR	LR	LR	LR	LR	HR	LR	LR	LR	LR
32	Nandurkar P[51]	HR	LR	LR	LR	LR	HR	LR	LR	LR	LR	LR
33	Gadiparthi M[52]	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR
34	Abd El Hakeem AA[53]	HR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR
35	Elsehaimy LA[54]	HR	LR	LR	LR	LR	HR	HR	LR	LR	HR	MR
36	Kazgan T[55]	LR	LR	LR	HR	LR	LR	LR	LR	LR	LR	LR
37	Harsoor J[56]	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR

HR=high risk; LR=low risk; MR=moderate risk (LR: 0-3; MR: 4-6; HR: 7-9)

was performed. The pooled estimates of the prevalence of PD in different subgroups are shown in **Table 5**. There were no significant differences for subgroups of age group, region, study publication year, serum ferritin level, or study design. However, risk of bias was the exception (P<0.003).

Prevalence of restrictive lung disease in β-thalassemia

The overall prevalence of RLD in β-thalassemia major was 44.9% (95%CI 36.5-53.6) in the meta-analysis of 33 studies, according to the Der Simonian-Laird random-effects model. The forest plot is shown in **Figure 3**. The rate of heterogeneity in this study was high (I^2=86.69%; P<0.001).

Sensitivity analysis was performed to evaluate the effects of the methodological quality of each trial on the pooled results and to assess the stability of the meta-analysis. The results remained largely unchanged.

To assess the heterogeneity, subgroup analyses were performed. The pooled estimates of the prevalence of RLD in different subgroups are shown in **Table 6**. There were significant differences among subgroups of age group (P=0.030), region (P<0.001), study publication year(P=0.017) and risk of bias (P=0.010). However, serum ferritin level (P=0.299) and study design (P=0.116) were the exceptions.

Prevalence of obstructive lung disease in β-thalassemia

The pooled prevalence of OLD in β-thalassemia major was 7.6% (95%CI 4.8 to 11.7), according to the Der Simonian-Laird random-effects model, in the meta-analysis of 32 studies. The forest plot is shown in **Figure 4**. The heterogeneity was high (I^2 =74.14%; P<0.001) in this study.

Sensitivity analysis was performed to evaluate the effects of the methodological quality of each trial on the pooled results and to assess the stability of the meta-analysis. The overall results were reliable. The statistically similar results indicated the stability of this meta-analysis. However, sensitivity analysis did not identify any factors that substantially influenced the heterogeneity of the results.

To assess heterogeneity, subgroup analysis was performed. The pooled estimates of the prevalence of OLD in different subgroups are shown in **Table 7**.

Table 5. Prevalence of PD in different subgroups

Stratification group	Number of studies	Total number of subjects	Total number of events	I^2	Prevalence of PD	95%CI	P value
Age							
Children <15 years	20	720	469	77.000	65.2	56.3 to 73.1	0.000
Children >15 years	17	681	400	85.933	61.5	49.3 to 72.4	0.000
Region							
Asia	19	808	549	82.735	70.1	60.9 to 77.9	0.000
Europe	9	337	188	68.411	55.1	44.6 to 65.2	0.001
America	4	131	61	92.544	75.2	26.4 to 96.2	0.000
Africa	3	140	85	52.463	59.9	47.3 to 71.3	0.122
Study published							
Before 2009	19	656	437	81.266	68.0	57.7 to 76.8	0.000
2009 - 2020	16	760	446	83.941	61.3	51.4 to 70.4	0.000
Serum ferritin							
<2500 ng/dL	12	421	262	65.566	60.1	49.8 to 69.5	0.001
>2500 ng/dL	18	708	428	88.300	64.8	57.3 to 76.3	0.000
Risk of bias							
LR	28	1199	712	82.710	60.1	52.4 to 67.4	0.000
MR	7	217	171	67.785	82.9	70.5 to 90.8	0.005
Study design							
Others	27	1070	654	83.511	62.6	54.2 to 70.3	0.000
Case control	8	346	229	68.631	71.5	60.7 to 80.3	0.004

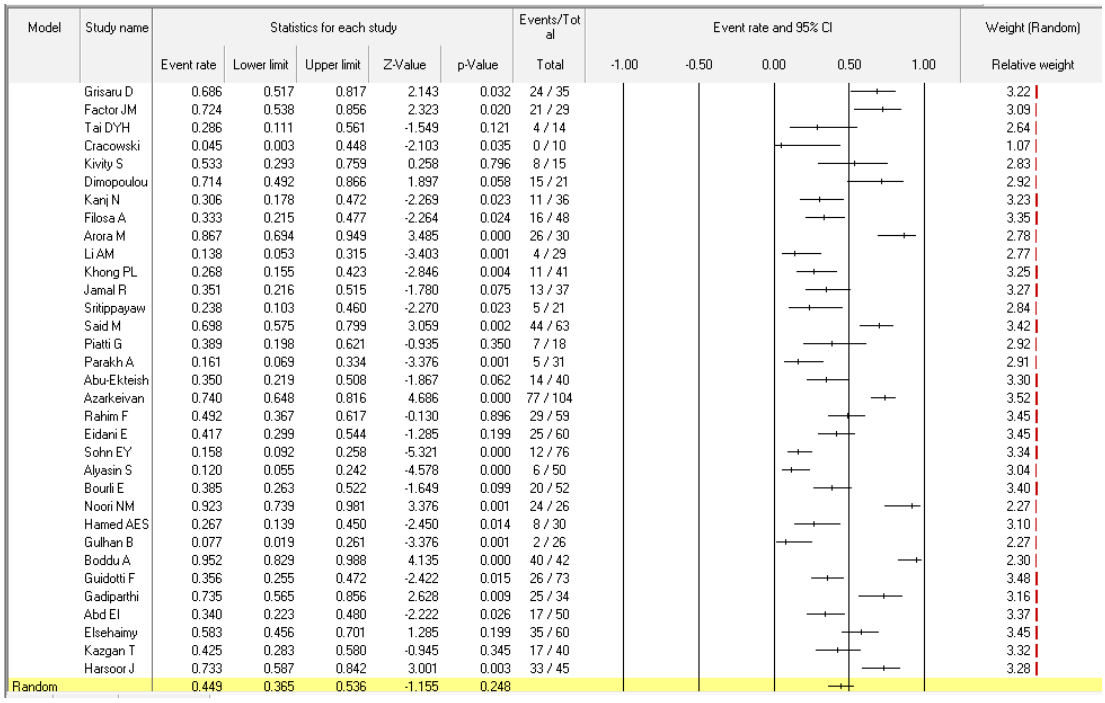


Figure 3. Forest plots of the prevalence of restrictive lung disease in β-thalassemia

Table 6. Prevalence of RLD in different subgroups

Stratification group	Number of studies	Total number of subjects	Total number of events	I^2	Prevalence of RLD	95%CI	P value
Age							
<15 years	17	665	340	87.880	50.6	37.7 to 63.5	0.000
15-18 years	16	680	284	85.535	39.3	28.9 to 50.8	0.001
Region							
Asia	22	878	447	88.193	47.8	36.5 to 59.4	0.000
Europe	6	222	84	58.945	39.8	28.9 to 51.9	0.001
America	2	105	33	96.101	40.9	5.0 to 90.2	0.010
Africa	3	140	60	80.631	39.9	22.7 to 60.1	0.000
Study published							
Before 2009	19	681	334	84.739	44.7	34.0 to 55.9	0.000
2009 - 2020	14	664	290	88.871	45.4	32.3 to 59.1	0.000
Serum ferritin							
<2500 ng/dL	10	407	195	84.440	41.7	28.3 to 56.6	0.000
>2500 ng/dL	18	725	334	89.635	50.2	37.0 to 63.3	0.000
Risk of bias							
LR	28	1154	501	86.434	40.4	31.9 to 49.6	0.002
MR	5	156	99	84.652	69.6	48.4 to 84.8	0.000
Study design							
Others	27	710	324	86.409	52.7	34.6 to 70.1	0.000
Case control	6	269	142	87.079	43.0	33.6 to 52.9	0.000

There were significant differences for subgroups of age (P=0.044), region (P=0.004), study publication year (P=0.040) and serum ferritin level (P=0.005). However, study design (P=0.834) and risk of bias (P=0.240) were the exceptions.

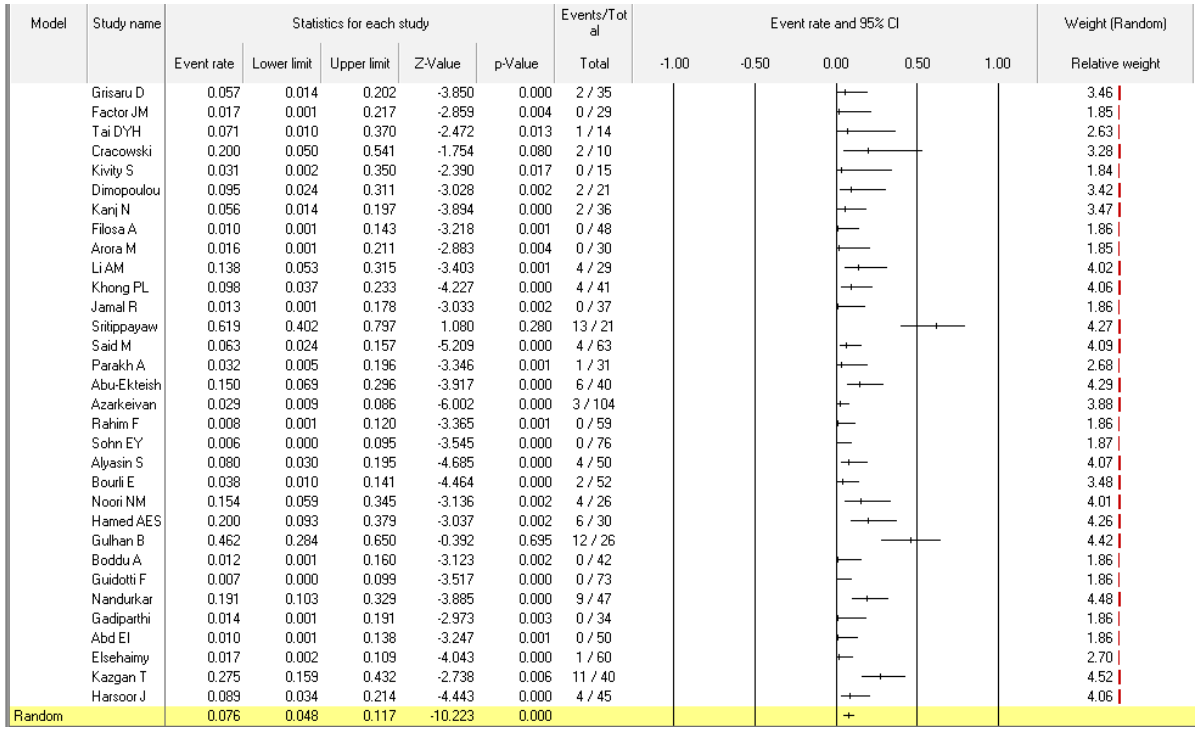


Figure 4. Forest plots of the prevalence of obstructive lung disease in β-thalassemia

Prevalence of lung diffusion impairment in β-thalassemia

The meta-analysis of 20 studies, according to the Der Simonian-Laird random-effects model, revealed that the pooled prevalence of lung diffusion impairment in β-thalassemia major was 35.6% (95%CI 26.5 to 45.8). The forest plot is shown in **Figure 5**. The heterogeneity was high in this study (I^2=81.91%; P<0.001).

Sensitivity analysis done by removing one study at a time for prevalence of DI data showed that the overall result was reliable. To assess heterogeneity, subgroup analysis was performed. The pooled estimates of the prevalence of DI in different subgroups are shown in **Table 8**. There were no significant differences for subgroups of age group, study publication year, serum ferritin level, or study design. However, region was the exception (P<0.001).

Publication bias

We used funnel plots to assess for publication bias. In **Figure 6**, the vertical line represents the summary of the prevalence of pulmonary dysfunction. The diagonal lines represent the 95% confidence limits around the summary prevalence estimate. These show the expected distribution of studies in the absence of heterogeneity or selection biases. The funnel plot asymmetry was assessed using Egger's linear regression test and Begg and Mazumdar rank correlation statistics. Evidence of publication bias in the prevalence of PD and OLD in β-thalassemia was indicated by the Egger weighted regression statistics (P=0.01 and P<0.01, respectively) and Begg and Mazumdar rank correlation statistics (P=0.01 and P<0.01, respectively) (**Figures 6A** and **C**). We did not find evidence of publication bias in the prevalence of RLD and DI in β-thalassemia, as indicated by the Egger weighted regression statistics (P=0.327 and P=0.187, respectively) and Begg and Mazumdar rank correlation statistics (P=0.285 and P=0.205, respectively), as shown by the lack of asymmetry in the corresponding funnel plots (**Figures 6B** and **D**).

Table 7. Prevalence of OLD in different subgroups

Stratification group	Number of studies	Total number of subjects	Total number of events	I^2	Prevalence of OLD	95%CI	P value
Age							
<15 years	18	712	67	73.657	9.5	5.6 to 15.9	0.000
15-18 years	14	602	30	74.663	5.4	2.4 to 11.7	0.000
Region							
Asia	22	865	84	76.427	9.5	5.7 to 15.4	0.000
Europe	5	204	6	49.903	5.1	1.7 to 14.7	0.000
America	2	105	0	0.000	1.0	0.1 to 7.0	0.000
Africa	3	140	7	78.754	4.2	0.5 to 29.9	0.007
Study published							
Before 2009	18	663	44	71.501	7.0	3.7 to 12.7	0.000
2009 - 2020	14	651	53	76.800	8.3	4.3 to 15.5	0.000
Serum ferritin							
<2500 ng/dL	9	389	32	87.586	7.4	1.9 to 24.4	0.000
>2500 ng/dL	18	743	53	54.836	5.3	5.1 to 12.6	0.000
Risk of bias							
LR	27	1123	84	76.498	7.5	4.5 to 12.3	0.000
MR	5	191	13	56.611	7.9	3.4 to 17.1	0.000
Study design							
Others	24	968	67	77.823	6.7	3.7 to 11.7	0.000
Case control	8	346	30	56.611	10.3	5.7 to 17.9	0.000

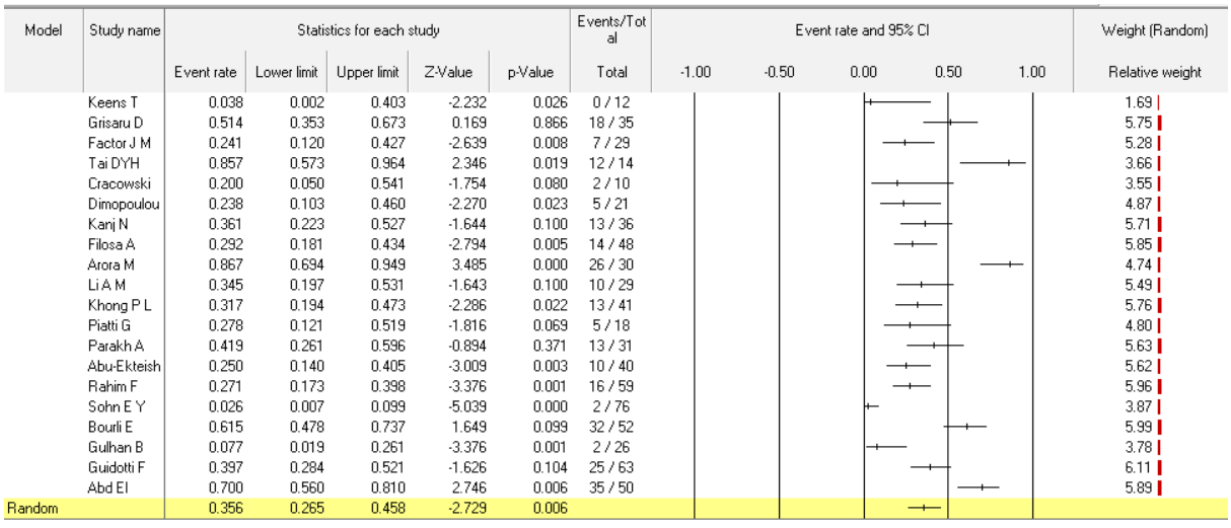
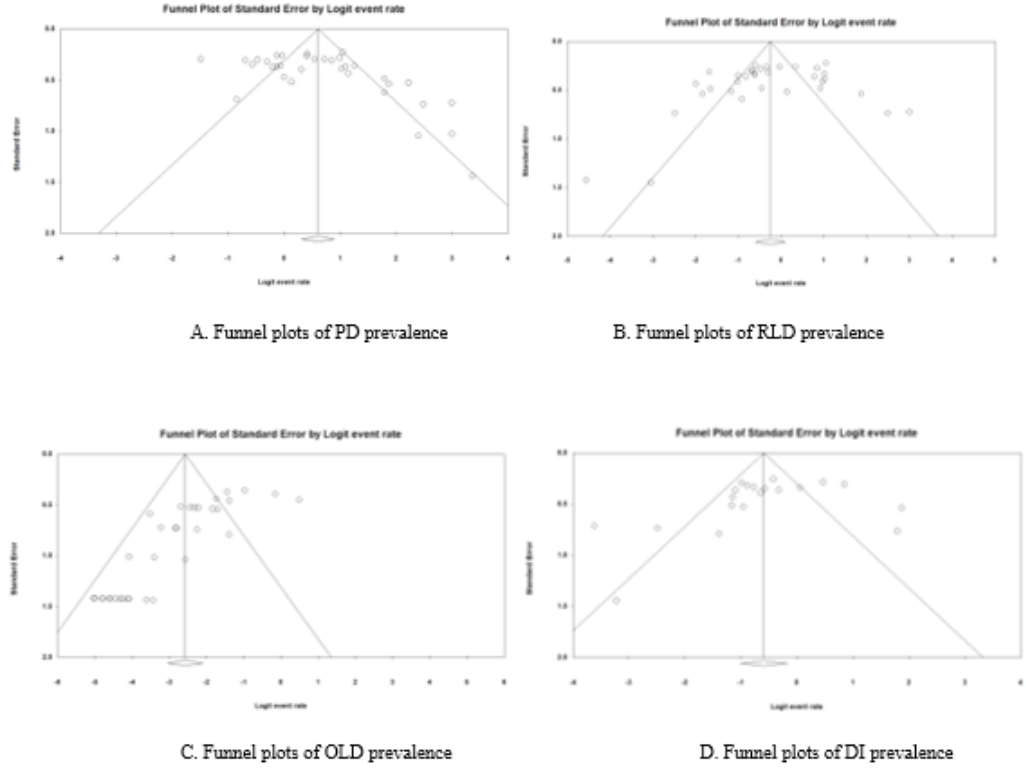


Figure 5. Forest plots of the prevalence of lung diffusion impairment in β-thalassemia

Table 8. Prevalence of DI in different subgroups

Stratification group	Number of studies	Total number of subjects	Total number of events	I^2	Prevalence of OLD	95%CI	P value
Age							
<15 years	6	239	110	87.819	47.6	28.3 to 67.6	0.000
15-18 years	14	481	150	78.633	30.4	20.9 to 42.0	0.001
Region							
Asia	9	315	131	78.636	44.6	31.8 to 58.1	0.000
Europe	7	238	85	75.127	30.9	19.3 to 45.5	0.000
America	3	117	9	79.085	7.5	1.2 to 35.5	0.008
Africa	1	50	35	0.000	7.0	5.6 to 81	1.000
Study published							
Before 2009	15	453	164	76.306	39.3	27.0-53.2	0.000
2009 - 2020	5	267	96	87.224	31.1	18.7-47.1	0.000
Serum ferritin							
<2500 ng/dL	9	271	89	81.071	32.7	20.2-48.3	0.000
>2500 ng/dL	9	301	96	86.296	34.5	17.9-56.0	0.000
Risk of bias							
LR	16	603	206	80.535	33.5	24.4 to 44.0	0.000
MR	4	117	54	88.381	43.5	15.2 to 76.7	0.000
Study design							
Others	17	600	189	74.732	31.6	23.7 to 40.8	0.000
Case control	3	120	71	92.412	62.5	25.0 to 89.3	0.000



A. Funnel plots of PD prevalence

B. Funnel plots of RLD prevalence

C. Funnel plots of OLD prevalence

D. Funnel plots of DI prevalence

Figure 6. Funnel plots for the assessment of publication bias in the prevalence of PD, RLD, OLD, and DI in β-thalassemia

Discussion

Thalassemia is an autosomal recessive hereditary disorder, in which long-term extravascular hemolysis increases iron absorption in the intestinal tract and decreases the bioavailability of iron. This phenomenon coupled with long-term multiple blood transfusions could lead to iron overload and increase the amount of iron ions. The consequence of hemolysis is the deposition of iron in different tissues, leading to damage of various organs including the lungs.[28] At present, bone marrow transplantation is the only available curative option for thalassemia major; but due to graft-versus-host disease and a lack of immunologically-matched donors, the main treatment remains to be traditional long-term blood transfusion and iron chelation therapy to maintain normal hemoglobin concentrations in the body.

Lung abnormalities in children with β-thalassemia have not been well studied. To the best of our knowledge, ours is the first comprehensive systematic review to explore the pooled prevalence of pulmonary dysfunction in TM. All the included studies were observational, i.e., cross-sectional, case-control, or cohort studies. In addition, the majority of included studies were carried out in Asian countries, while the rest were from European, African, and American regions. Pulmonary dysfunction in TM patients has not gained much attention and published data often pertain to small pediatric populations. Although pulmonary function abnormalities in TM were described in 1980, the pathogenetic mechanism is still unclear and data are contradictory, probably because of study heterogeneity and the multifactorial nature of the pathogenesis. Conflicting results reported in the literature have ranged from restrictive spirometric patterns to an obstructive ones.[2] Most studies report iron overload as the principal hypothetical factor responsible for pulmonary abnormalities,[12,14] as it damages the liver, heart, and endocrine glands. In a similar way, iron accumulation in the lungs has been proposed as the cause of PFT abnormalities observed in TM patients. In a study necropsy findings showed that iron was predominantly found in bronchial glands and epithelial cells rather than in the parenchyma.57 Several studies have revealed high prevalences of RLD, ranging from 35% to 73.53%, among children and adults with β-thalassemia major.[13,39,44,52]

Iron deposition in the airway lining, recurrent pulmonary infections, asthma, disproportionate growth of the alveoli relative to the airways and chest cage, as well as bronchial hyperreactivity after transfusion, have been proposed as triggers for the pathogenesis of OLD in β-thalassaemia major patients.[32,33] Previous studies have reported prevalences of OLD ranging from 13.79% to 61.60% among β-thalassaemia major patients.[9,35,47] Among the included studies, the proportions of study populations with an obstructive pattern ranged from 1.67% to 61.90%, while the those with a restrictive pattern ranged from 7.69% to 95.24%. This variation has brought to light the importance of pulmonary function testing in the TM population. The pooled prevalence of RLD in β-thalassemia major (43.7%) is higher than that of OLD (7.1%) and DI (35.6%). The diffusional capacity of the lungs is determined by the pulmonary capillary blood volume, hemoglobin concentration, and the integrity of the alveolo-capillary membrane; thus, a reduction of DLCO usually reflects a defect in the alveolo-capillary membrane leading to a ventilation-perfusion mismatch. Tai *et al.*[14] proposed that DI due to defects in the alveolo-capillary membrane could account for altered lung function as studied in thalassemia patients. A previous study reported that diffusion impairment was the most common impairment of lung function in children with thalassemia, affecting 34%.[9] Our results confirmed that the pooled prevalence of DI in β-thalassemia major was 35.6%. Several studies reported that restrictive pulmonary impairment increases with age;[8,11,13,39] however, other studies did not show such an association.[9,37] On subgroup analysis in our study, no significant difference in PD prevalence was observed between TM patients below and above 15 years of age.

Further analyses showed that the region with the highest pooled prevalence of PD was the Americas (75.2%). However, the region with the highest prevalence of RLD and DI was Asia (48.2% and 44.6%, respectively) and the region with the highest prevalence of OLD was Europe (9.7%). The difference in the prevalence of PD between countries could be due to genetic susceptibility to the toxic effects of iron overload in endocrine glands and serum ferritin. It may also indicate differences in quality of care, follow-up, and treatment, including the quality of

blood transfusions and the type and frequency (regular or irregular) of chelation therapy. Numerous studies have tried to correlate serum ferritin levels with pulmonary function abnormalities, but the results are conflicting.[12,28,38-41] Although serum ferritin measurement is not the best quantitative estimate of body iron stores, thalassemic patients with a serum ferritin concentration of ≥3,000 ng/dL have been reported to have a high risk of lung injury.[8] Ferritin levels of >2,500 ng/dL have been reported to be associated with a 4-fold higher risk of death.[40] A study showed that TM patients with abnormal pulmonary function had higher serum ferritin levels compared to those with normal pulmonary function.11 Another study showed an inverse correlation between total lung capacity and lifetime estimates of transfusional iron load was established.[13] The pooled prevalence of PD was higher in patiens with serum ferritin levels of ≥2,500 ng/dL (64.8%) than in those with levels ≤2,500ng/dL (60.1%), but the difference was not statistically significant (P=0.568). Iron overload has been thought to play an important part in causing pulmonary abnormalities in β-thalassemia major patients.[58]

To our knowledge, this is the first systematic review and meta-analysis to compile current data on the prevalence of PD among β-thalassemia major patients. The main strengths of this study were the use of a comprehensive and a predefined literature search strategy and the involvement of two independent reviewers throughout the review process as well as in data extraction. Furthermore, the methodological quality of most included articles had a low risk of bias.

However, there were limitations in our analysis. First, significant heterogeneity was detected in the pooled analyses of prevalence. Although subgroup analyses with the addition of different regions were performed, the heterogeneity was not significantly reduced. This heterogeneity may have been due to differences in the number of cases or basic characteristics. Second, there was insufficient data to conduct a complete evaluation of all regions around the world. Third, due to the deficiency of the original data, we could not perform further subgroup analyses by gender or length of blood transfusion. In addition, there was a lack of authentic definitions in studies for the diagnoses of PD, RLD, OLD, and diffusion impairment. Even though we followed a comprehensive search strategy, there was a possibility of non-inclusion of some studies.

In conclusion, the pooled prevalence of PD was 64.7% in β-thalassemia major patients, with RLD (43.7%) as the more common type of PD than OLD (7.1%). Also, the prevalence of RLD (43.7%) is more common than the OLD (7.1%) in the same patients. Corresponding treatment and prevention measurements may be necessary to prevent PD problems. The overall prevalence of PD in β-thalassemia patients varied from country to country.

Conflict of interest

None declared.

References

1. Survival and Complications in Thalassemia - BORGNA-PIGNATTI - 2005 - Annals of the New York Academy of Sciences - Wiley Online Library [Internet]. [cited 2020 Sep 12]. Available from: https://nyaspubs.onlinelibrary.wiley.com/doi/abs/10.1196/annals.1345.006.
2. Galanello R, Origa R. Beta-thalassemia. Orphanet J Rare Dis. 2010;5:11. DOI: 10.1186/1750-1172-5-11.
3. Kountouris P, Lederer CW, Fanis P, Feleki X, Old J, Kleanthous M. IthaGenes: an interactive database for haemoglobin variations and epidemiology. PloS One. 2014;9:e103020. DOI: 10.1371/journal.pone.0103020.
4. Ladis V, Karagiorga-Lagana M, Tsatra I, Chouliaras G. Thirty-year experience in preventing haemoglobinopathies in Greece: achievements and potentials for optimisation. Eur J Haematol. 2013;90:313-22. DOI: 10.1111/ejh.12076.
5. Shah FT, Sayani F, Trompeter S, Drasar E, Piga A. Challenges of blood transfusions in β-thalassemia. Blood Rev. 2019;37:100588. DOI: 10.1016/j.blre.2019.100588.
6. Fung EB, Harmatz PR, Lee PDK, Milet M, Bellevue R, Jeng MR, *et al.* Increased prevalence of iron-overload associated endocrinopathy in thalassaemia versus sickle-cell disease. Br J Haematol. 2006;135:574-82. DOI: 10.1111/j.1365-2141.2006.06332.x.
7. Lobo C, Angulo IL, Aparicio LR, Drelichman GI, Zanichelli MA, Cancado R, *et al.* Retrospective epidemiological study of Latin American patients with transfusional hemosiderosis: the first Latin American epidemiological study in iron overload – the RELATH study. Hematology. 2011;16:265-73.

DOI: 10.1179/102453311X13085644680302.

8. Carnelli V, D'Angelo E, Pecchiari M, Ligorio M, D'Angelo E. Pulmonary dysfunction in transfusion-dependent patients with thalassemia major. Am J Respir Crit Care Med. 2003;168:180-4. DOI: 10.1164/rccm.200211-1292OC.
9. Li AM, Chan D, Li CK, Wong E, Chan YL, Fok TF. Respiratory function in patients with thalassaemia major: relation with iron overload. Arch Dis Child. 2002;87:328-30. DOI: 10.1136/adc.87.4.328.
10. Azarkeivan A, Mehrvar A, SohrabPour H, Mehrvar N, Vosough P. Pulmonary function test in transfusion-dependent β-thalassemia patients. Pediatr Hematol Oncol. 2008;25:598-606. DOI: 10.1080/08880010802237294.
11. Filosa A, Esposito V, Meoli I, Baron I, Romano L. Evidence of lymphocyte alveolitis by bronchoalveolar lavage in thalassemic patients with pulmonary dysfunction. Acta Haematol. 2000;103:90-5. DOI: 10.1159/000041026.
12. Kanj N, Shamseddine A, Gharzeddine W, Kanj M, Nasr TA, Koussa S, *et al*. Relation of ferritin levels to pulmonary function in patients with thalassemia major and the acute effects of transfusion. Eur J Haematol. 2000;64:396-400. DOI: 10.1034/j.1600-0609.2000.90106.x.
13. Factor JM, Pottipati SR, Rappoport I, Rosner IK, Lesser ML, Giardina PJ. Pulmonary function abnormalities in thalassemia major and the role of iron overload. Am J Respir Crit Care Med. 1994;149:1570-4. DOI: 10.1164/ajrccm.149.6.8004315.
14. Tai DY, Wang YT, Lou J, Wang WY, Mak KH, Cheng HK. Lungs in thalassaemia major patients receiving regular transfusion. Eur Respir J. 1996;9:1389-94. DOI: 10.1183/09031936.96.09071389.
15. Fung KP, Chow OK, So SY, Yuen PM. Pulmonary function in thalassemia major. J Pediatr. 1987;111:534-7. DOI: 10.1016/s0022-3476(87)80113-0.
16. Cooper DM, Mansell AL, Weiner MA, Berdon WE, Chetty-Baktaviziam A, Reid L, *et al.* Low lung capacity and hypoxemia in children with thalassemia major. Am Rev Respir Dis. 1980;121:639-46. DOI: 10.1164/arrd.1980.121.4.639.
17. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283:2008-12. DOI: 10.1001/jama.283.15.2008.
18. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535. DOI: 10.1136/bmj.b2535.
19. Viera A, Garrett J. Understanding interobserver agreement: the kappa statistic. Fam Med. 2005;37:360-3. PMID: 15883903.
20. Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C, *et al*. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol. 2012;65:934-9. DOI: 10.1016/j.jclinepi.2011.11.014.
21. Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, *et al*. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Int J Surg. 2014;12:1500-24. DOI: 10.1016/j.ijsu.2014.07.014.
22. Higgins J, Green S. Cochrane handbook for systematic reviews of interventions. Version 5.1.0 [updated March 2011] [cited YEAR MONTH DATE]. The Cochrane Collaboration, 2011. Available from: www.handbook.cochrane.org.
23. Borenstein M, Hedges L, Higgins J, Rothstein H. Meta-regression. In: Introduction to meta-analysis. Chichester: John Wiley and Sons; 2009. p. 187-203.
24. Borenstein M, Rothstein H. Comprehensive meta-analysis: a computer program for research synthesis computer program. Englewood Cliffs: Biostat, Inc; 1999.
25. Keens TG, O'Neal MH, Ortega JA, Hyman CB, Platzker AC. Pulmonary function abnormalities in thalassemia patients on a hypertransfusion program. Pediatrics. 1980;65:1013-7. PMID: 7367114.
26. Hoyt RW, Scarpa N, Wilmott RW, Cohen A, Schwartz E. Pulmonary function abnormalities in homozygous beta-thalassemia. J Pediatr. 1986;109:452-5. DOI: 10.1016/s0022-3476(86)80116-0.
27. Grisaru D, Rachmilewitz EA, Mosseri M, Gotsman M, Lafair JS, Okon E, *et al.* Cardiopulmonary assessment in beta-thalassemia major. Chest. 1990;98:1138-42. DOI: 10.1378/chest.98.5.1138.
28. Cracowski C, Wuyam B, Klein V, Lévy P. Lung function and exercise capacity in thalassaemia major. Eur Respir J. 1998;12:1130-6. DOI: 10.1183/09031936.98.12051130.
29. Kivity S, Gazy C, Heno N, Greif Z, Topilsky M. Effect of the Leukostop filter on pulmonary function following blood transfusion in patients with thalassemia major. Pediatr Pulmonol. 1999;28:277-81. DOI: 10.1002/(sici)1099-0496(199910)28:4<277::aid-ppul7>3.0.co;2-3.
30. Dimopoulou I, Kremastinos DT, Maris TG, Mavrogeni S, Tzelepis GE. Respiratory function in patients with thalassaemia and iron overload. Eur Respir J. 1999;13:602-5. DOI: 10.1183/09031936.99.13360299.
31. Filosa A, Esposito V, Meoli I, Stefanelli F, Cassandro R. Evidence of a restrictive spirometric pattern in older

thalassemic patients. Respiration. 2001;68:273–8. DOI: 10.1159/000050510.

32. Arora M, Chandra J, Suri JC, Narayan S, Dutta AK. Pulmonary function tests in beta thalassemia. Indian J Pediatr. 2001;68:239-42. DOI: 10.1007/BF02723198.
33. Khong PL, Chan GC, Lee SL, Au WY, Fong DY, Tsang KW, *et al.* β-Thalassemia major: thin-section CT features and correlation with pulmonary function and iron overload. Radiology. 2003;229:507-12. DOI: 10.1148/radiol.2292021805.
34. Jamal R, Baizura J, Hamidah A, Idris N, Jeffrey AH, Roslan H. Abnormalities in lung function among multiply-transfused thalassemia patients: results from a thalassemia center in Malaysia. Southeast Asian J Trop Med Public Health. 2005;36:265-9. PMID: 15906681.
35. Sritippayawan S, Lekhanont P, Harnruthakorn C, Samransamruajkit R, Deerojanawong J, Seksarn P, *et al.* Restrictive lung disease and serum TGF-[beta] 1 in thalassemia major children. Asian Pac J Allergy Immunol. 2005;23:121. PMID: 16252842.
36. Said M, Sastroasmoro S, Gatot D, Supriyatno B, Ananta Y. Comparison of pulmonary functions of thalassemic and of healthy children. Paediatr Indones. 2016;45:1-6. DOI: 10.14238/pi45.1.2005.1-6.
37. Piatti G, Allegra L, Fasano V, Gambardella C, Bisaccia M, Cappellini MD. Lung function in β-thalassemia patients: a longitudinal study. Acta Haematol. 2006;116:25-9. DOI: 10.1159/000092344.
38. Parakh A, Dubey AP, Chowdhury V, Sethi GR, Jain S, Hira HS. Study of pulmonary function tests in thalassemic children. J Pediatr Hematol Oncol. 2007;29:151-5. DOI: 10.1097/MPH.0b013e318033a73d.
39. Abu-Ekteish FM, Al-Rimawi HS, Al-Ali MK, Shehabi IM. Pulmonary function tests in children with beta-thalassemia major. Chron Respir Dis. 2007;4:19–22. DOI: 10.1177/1479972306070376.
40. Rahim F, Keikhaei B, Ebadi A. Clinical manifestation of pulmonary dysfunction in β-thalassemia major. J Med Sci. 2008;8:484-90. DOI: 10.3923/jms.2008.484.490.
41. Eidani I, Keikhaei B, Rahim F, Bagheri A. Evaluation of pulmonary function in beta-thalassemia major patients. Pak J Med Sci. 2009;25:749-54.
42. Sohn EY, Noetzli LJ, Gera A, Kato R, Coates TD, Harmatz P, *et al.* Pulmonary function in thalassaemia major and its correlation with body iron stores. Br J Haematol. 2011;155:102–5. DOI: 10.1111/j.1365-2141.2011.08808.x.
43. Alyasin S, Moghtaderi M, Amin R, Kashef S, Karimi M. Pulmonary function test in transfusion-dependent β-thalassemia major patients: a pilot study. Pediatr Hematol Oncol. 2011;28:329-33. DOI: 10.3109/08880018.2010.543449.
44. Bourli E, Dimitriadou M, Economou M, Vlachaki E, Christoforidis A, Maratou E, et al. Restrictive pulmonary dysfunction and its predictors in young patients with β-thalassaemia major. Pediatr Pulmonol. 2012;47:801-7. DOI: 10.1002/ppul.22506.
45. Noori NM, Keshavarz K, Shahriar M. Cardiac and pulmonary dysfunction in asymptomatic beta-thalassanemia major. Asian Cardiovasc Thorac Ann. 2012;20:555-9. DOI: 10.1177/0218492312439706.
46. Hamed AelS, Ragab IA, Kamel TB, Abd-El-Gawad AO. Effect of using bedside leukocyte filter on pulmonary functions in patients with thalassemia major. Pediatr Hematol Oncol. 2013;30:761-7. DOI: 10.3109/08880018.2013.838724.
47. Gülhan B, Yalçın E, Ünal Ş, Oğuz B, Özçelik U, Ersöz DD, *et al*. Effects of blood transfusion on cytokine profile and pulmonary function in patients with thalassemia major. Clin Respir J. 2016;10:153–62. DOI: 10.1111/crj.12193.
48. Ozyoruk D, Misirlioglu ED. Pulmonary functions in children with thalassemia major. J Pediatr Hematol Oncol. 2015;37:605-10. DOI: 10.1097/MPH.0000000000000425.
49. Boddu A, Kumble A, Mahalingam S, Baliga BS, Achappa B. Pulmonary dysfunction in children with beta thalassemia major in relation with iron overload-a cross sectional hospital based study. Asian J Med Sci. 2015;6:47-50. DOI: 10.3126/AJMS.V615.11782.
50. Guidotti F, Piatti G, Marcon A, Cassinerio E, Giuditta M, Roghi A, et al. Pulmonary dysfunction in thalassaemia major: is there any relationship with body iron stores? Br J Haematol. 2017;176:309-14. DOI: 10.1111/bjh.14396.
51. Nandurkar P, Goel M, Sharma S. A study on cardiopulmonary function tests in thalassemia major patients (6-14 years) and its correlation to serum ferritin. J Pulm Respir Med. 2018;8:450. DOI:10.4172/2161-105X.1000450.
52. Gadiparthi M, Bhaskaranand N, Kini PG, Hebbar SA, Mundkur SC. Pulmonary function tests in β-thalassemia major and its correlation with serum ferritin levels. Int J Contemp Pediatr. 2019;6:306-9. DOI: 10.18203/2349-3291.ijcp20190450.
53. Abd El Hakeem AA, Mousa SMO, AbdelFattah MT, AbdelAziz AO, Abd El Azeim SS. Pulmonary functions in Egyptian children with transfusion-dependent β-thalassemia. Transfus Med. 2019;29:55-60. DOI: 10.1111/tme.12539.
54. Elsehaimy LA, Zineldin MF, Khalil WA. Evaluation of pulmonary functions in pediatric patients with beta-thalassemia major. Al-Azhar Assiut Med J. 2019;17:264-7

DOI: 10.4103/AZMJ.AZMJ_46_19.

55. Kazgan T, Yagci-Küpeli B, Özhan AK. Asymptomatic respiratory dysfunction in patients with thalassemia major. Cukurova Med J. 2019;44:1317-22. DOI: 10.17826/cumj.525791.
56. Harsoor J, Ratageri VH, Shilpa C, Illalu S, Wari P. Pulmonary function tests in children with beta-thalassemia major. Karnataka Pediatr J. 2020;35:52-6. DOI:10.25259/KPJ_2_2020.
57. Witzleben CL, Wyatt JP. The effect of long survival on the pathology of thalassæmia major. J Pathol Bacteriol. 1961;82:1-12. PMID: 13786138
58. Santamaria F, Villa MP, Werner B, Cutrera R, Barreto M, Ronchetti R. The effect of transfusion on pulmonary function in patients with thalassemia major. Pediatr Pulmonol. 1994;18:139-43. DOI: 10.1002/ppul.1950180304.