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

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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...
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. 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. Of these, restrictive abnormalities are the most frequent, being reported in up to 80% of patients.

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. Another study showed that TM patients with abnormal pulmonary function had higher serum ferritin levels compared to those with normal pulmonary function. 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. However, such a claim was not supported by a subsequent study. 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. The search strategy was implemented in two stages, consisting of a bibliographic database search and a hand search of other sources.

**Bibilographic 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.
Studies considered in this meta-analysis were observational studies about the prevalence of PD in children with 
β-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.

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. Furthermore, the
reporting quality of each study was assessed using
the Strengthening the Reporting of Observational Studies
(STROBE) checklist. 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 ≤5 or
n(1-p) ≤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 I² index were used.
There are three categories for heterogeneity: I² index
less than 25% = low heterogeneity; I² index between
25%-75% = moderate heterogeneity, and I² 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. 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.

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 (κ=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).
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 (κ=0.88; P<0.001).

Prevalence of pulmonary dysfunction in β-thalassemia major

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 (I²=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 major.
| 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 TG25   | 1980 | Los Angeles    | NM           | 12             | NM        | NM        | 0       | 11             | NM         | NM         | 91.67     |
| 2  | Hoyt RW26    | 1986 | Philadelphia   | NM           | 14             | NM        | NM        | 14      | 30             | 68.57      | 5.71       | 85.71     |
| 3  | Grisaru D27  | 1990 | Israel         | NM           | 35             | 24        | 0         | 18      | 30             | 68.57      | 5.71       | 85.71     |
| 4  | Factor JM13  | 1994 | New York       | NM           | 29             | 21        | 0         | 7 (6 had RLD) | 22            | 72.41      | 0          | 75.86     |
| 5  | Tai DYH14    | 1996 | Singapore      | NM           | 14             | 4         | 1         | 12      | NM             | 28.57      | 7.14       | NM        |
| 6  | Cracowski C28| 1999 | France         | NM           | 15             | 8          | 0         | NM      | 8              | 53.33      | 0          | 53.33     |
| 7  | Kwity S29    | 1999 | Israel         | NM           | 21             | 15         | 2         | 5       | 18             | 71.43      | 9.52       | 85.71     |
| 8  | Dimopoulou J30| 2000 | Lebanon       | NM           | 36             | 11         | 2         | 13      | 13             | 30.55      | 5.55       | 36.11     |
| 9  | Kanji N72    | 2001 | Italy          | NM           | 48             | 16         | 0         | 14      | 16             | 33.33      | 0          | 33.33     |
| 10 | Filosa A31   | 2001 | Case-control   | 0            | 26             | 0         | 26        | 26      | 26             | 86.67      | 0          | 86.67     |
| 11 | Arora M32    | 2002 | China          | NM           | 29             | 4          | 4         | 10      | 13             | 13.79      | 13.79      | 44.83     |
| 12 | Li AMP       | 2003 | Hong Kong      | NM           | 41             | 11         | 4         | 13      | 37             | 26.83      | 9.76       | 90.24     |
| 13 | Khong PL33   | 2004 | Malaysia       | Cross-sectional | 37         | 13         | 0         | NM      | NM             | 35.14      | 0          | NM        |
| 14 | Jamal R34    | 2005 | Thailand       | Cross-sectional | 21         | 5          | 13        | NM      | 20             | 23.81      | 61.90      | 95.24     |
| 15 | Sritipayawan S35| 2006 | Italy        | Longitudinal | 18             | 7          | NM        | 5       | 9              | 38.89      | NM         | 50        |
| 16 | Said M36     | 2007 | India          | Observational | 31           | 5          | 1         | 13      | 15             | 16.12      | 3.22       | 48.39     |
| 17 | Piatti G37   | 2008 | Jordan         | Case control  | 40             | 14         | 6         | 10      | 30             | 35         | 15         | 75        |
| 18 | Parakh A38   | 2009 | Iran           | NM           | 60             | 25         | NM        | 28      | 46             | 41.67      | NM         | 46.67     |
| 19 | Abu-Ekteish FM39| 2010 | California    | Cohort       | 76             | 12         | 0         | 2       | 14             | 15.79      | 0          | 18.42     |
| 20 | Azarkeivan A10| 2011 | Iran          | NM           | 50             | 6          | 4         | 35      | 12             | 38.46      | 3.84       | 67.31     |
| 21 | Rahim F40    | 2012 | Iran          | NM           | 59             | 29         | 0         | 16      | 29             | 49.15      | 0          | 49.15     |
| 22 | Eidani E41   | 2013 | Iran          | NM           | 60             | 25         | NM        | 28      | 46             | 41.67      | NM         | 46.67     |
| 23 | Sohn EY42    | 2014 | Iran          | NM           | 76             | 12         | 0         | 2       | 14             | 15.79      | 0          | 18.42     |
| 24 | Alyasin S43  | 2015 | Iran          | NM           | 50             | 6          | 4         | 35      | 12             | 38.46      | 3.84       | 67.31     |
| 25 | Bouli E44    | 2016 | Pakistan      | Case-control  | 26             | 24         | 4         | NM      | 24             | 92.31      | 15.38      | 92.31     |
| 26 | Noori NM45    | 2017 | Egypt         | Case-control  | 30             | 8          | 6         | NM      | 14             | 26.67      | 20         | 46.67     |
| 27 | Hamed AES46   | 2018 | Turkey        | NM           | 26             | 2          | 12        | 2       | 15             | 7.69       | 46.15      | 57.69     |
| 28 | Gulhan B47   | 2019 | Turkey        | Cross-sectional | 49         | NM        | NM        | 31      | NM             | NM         | NM         | 63.27     |
| 29 | Ozyoruk D48   | 2020 | India         | NM           | 42             | 40         | 0         | NM      | 40             | 95.24      | 0          | 95.24     |
| 30 | Boddu A49    | 2021 | Italy         | Longitudinal | 73             | 26         | 0         | 25/63   | 44             | 35.62      | 0          | 60.27     |

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

| No. | First author | Year | Country | Study Design | N | Age range / mean (SD), years | Sex (M:F) | Lung function | Criteria used | Mean serum ferritin (SD), ng/mL |
|-----|--------------|------|---------|--------------|---|-----------------------------|-----------|---------------|---------------|-------------------------------|
| 32  | Nandurkar P51 | 2018 | India   | Case-control | 47 | 31-30 / 18.4 (2.6) | 4:8       | RV,TLC,RV/TLC,MMEF | Polgar G et al. | NM                           |
| 33  | Gadiparthi M52 | 2019 | India   | NM           | 34 | 25 / 0                    | 35:35     | NM            | Polgar G et al. | 73.53                         |
| 34  | Abd El Hakeem AA53 | 2019 | Egypt    | Case-control | 50 | 17 / 0                   | 35:35     | NM            | Polgar G et al. | 70                           |
| 35  | Elsehaimy LA54  | 2019 | Egypt    | Case-control | 60 | 35 / 1                   | 35:35     | NM            | Polgar G et al. | 60                           |
| 36  | Kazgan T55     | 2019 | Turkey   | NM           | 40 | 17 / 11                  | 35:35     | NM            | Polgar G et al. | 42.5                          |
| 37  | Harsoor J56    | 2020 | India    | Cross-sectional, descriptive | 45 | 33 / 4                    | 35:35     | NM            | Polgar G et al. | 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 serum ferritin (SD), ng/mL |
|-----|--------------|-----------------------------|-----------|---------------|---------------|-------------------------------|
| 1   | Keens TG25   | 6.3-30 / 18.4 (2.6)         | 4:8       | RV,TLC,RV/TLC,MMEF | Polgar G et al. | NM                           |
| 2   | Hoyt RW26    | 10-39                       | 11:8      | FEV1,FEF 25-75%, DLCO,TLC,FRC, FVC,MMEF 75% | Polgar G et al. | 3674 (2199)               |
| 3   | Grisaru D27  | 8-33 / 19.8 (6.5)           | 17:18     | FEV1,MMEF,FEF 50%,PEF,TLC, FRC,VC,F EV1/VC,DLC,DC | Cotes JE et al. | 1071 (571.02)             |
| 4   | Factor JM13  | 6-40 / 19.8 (8.5)           | 14:15     | FVC,FEV1,FEV1/FVC,FEF25-75%, DLCO,TLC | Polgar G et al. | 3810 (250)                 |
| 5   | Tai DYH14    | 9-21 / 15                  | 7:7       | FEV1,MMFER,TLC,RV,FRC, DLCO,PEFR | BTS          | 1633 (1340)               |
| 6   | Cracowski C28 | 6-18 / child (12); adult (33) | NM       | FEV1,VC,FEV1/VC,TLC,DLCO | Cotes JE et al. | 2669 (1237)             |
| 7   | Kivity S29   | 8-21 / (12.73)             | 9:6       | FVC,FEV1,FEV1/FVC | NM          | 5698±4000                  |
| 8   | Dimopoulou I30 | 25 (5)                  | 8:13      | TLC,DLC,PE max,RV,FVC, FEV1,FEV1/FVC | Cotes JE et al. | 1530 (250)                 |
| 9   | Kanj N12     | 10-58 / 18 (9)             | 17:19     | FEV1/FVC,FEV3/FVC,VC,F,FEF MAX,MMFR,RV/ TLC,DLCO | BTS          | 3975 (870.7)             |
| 10  | Filosa A31   | 8-23 / [GpA-10.8 (1.7); GpB-15.7 (1.1); GpC-19 (1.4)] | 21:27     | FVC,FEV1,FEV1/VC,F,FEF50%,PEF,DLCO,TLC | Cotes JE et al. | 3975 (866)                |
| 11  | Arora M32    | 9-17 / 11.83 (1.91)        | 15:15     | FRC,FVC,RV,TLC,FEV1/FVC,FEF 25-75%,PEF,DLCO | Pfaff JK et al. | 5827.75 (3919.88 to 7939.5) |
| 12  | Li AM8       | 14.2 / 10.6-16.5          | 16:13     | FEV1,FVC,MMFER,TLC,RV,FRC,DLCO,PEFR | BTS          | 4327 (2442)               |
| 13  | Khong PL33   | 9.40                       | 18:23     | FEV1/FVC,FEV1/VC,F,FEF 25-75%,PEF,FEF50%,FEF75%,DLCO,TLC, RV/TLC,DLCO | ATS          | 3975 (866)                |
| 14  | Jamal R34    | 10-24 / 15.8 (3.5)        | NM        | FVC,FEV1,FEV1/FVC,FEF 25-75%,TLC,VC,F,RC,DLCO | ATS          | 2948 (1210)               |
| 15  | Sritippayawan S35 | 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 semi ferritin (SD), ng/mL |
|-----|--------------|-------------------------------|-----------|---------------|---------------|-------------------------------|
| 16  | Said M       | 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     | 29.44 (2.89)                  | NM        | FEV1, TLC, DLCO, FVC   | Cotes JE et al. | 1116.39 (590.83) |
| 18  | Parakh A     | 8-22 / 13.56 (4.30)           | 25:6      | FVC, TLC, DLCO, FEF 25%, PEF 50%, PEF 75%, FEV1 | NM | GpA (normal PFT): 2866.13 (1416.25) GpB (abnormal PFT): 4173.13 (1612.90) |
| 19  | Abu-Ekteish F | 7.5-18 / 12.5 (3.5)           | 23:17     | TLC, DLCO, FVC, TLC, FEV1/FVC, PEF | Bucci G et al. | 3115 (224) |
| 20  | Azarkeivan A  | 21.1 (7)                      | 65:39     | FVC, VC, FEV1/FVC, VC  | ATS           | 1856.4 (1490) |
| 21  | Rahim F      | 10-45                         | 27:22     | TLC, FEV1, FVC, DLCO, TLC | Polgar G et al. | 1594 (1800) |
| 22  | Eidani E     | 10-45 / [M:19.75 (6); F: 20.03 (9.23)] | 31:29     | FEV1, FVC, FEV1/FVC, 25-75% | ATS | M: 2.53 (0.17); F: 2.63 (0.15) |
| 23  | Sohn E       | 11.8-48.4 / 25.6 (8.8)        | 37:39     | FVC, FVC, TLC, DLCO, FEF 25-75% | Cotes JE et al. | 3127 |
| 24  | Alyasin S    | 9-17 / 12.48 (2.2)            | 33:17     | FEV1, FEV1/FVC, FEV1/FVC, FVC, PEF | ATS | 3346 (1667) |
| 25  | Bourli E     | 9-34 / 21.33 (6.24)           | 25:27     | FVC, FEV1/FVC, FVC, MMFR, FEF 25-75%, RV, TLC, DLCO | Device manufacture | M:1530 (1542); F:1820 (1277) |
| 26  | Noori NM     | 10-20 / 14.8 (2.92)           | NM        | FEV1, FVC, FEV1/FVC | NM | 3614.80 (2012.54) |
| 27  | Hamed AES    | 7-17 / 12.4 (3.2)             | 12:18     | FEV1, FVC, FEV1/FVC I | Miller MR et al. | NM |
| 28  | Gulhan B     | 15.7 (5.2)                    | 12:14     | FEV1, FEV1/FVC, FEV1/FVC, FEF 25-75%, DLCO, TLC | Cotes JE et al. | 2376; F: 2454 |
| 29  | Ozoryuk D    | 5-17 / 10.8 (3)               | 30:19     | FEV1, FVC, FEV1, FVC, PEF, MEF25%-75% | Miller MR et al. | NM |
| 30  | Boddu A      | >7                            | 26:16     | FEV1, FVC, FEV1/FVC | NM | 4152.57 (1822.77) |
| 31  | Guidotti F   | 37 (7)                        | 24:49     | FVC, FEV1, FEV1/FVC, TLC, RV, DLCO | Cotes JE et al. | RLD: 1526 (1437); NRLD: 975 (779) |
| 32  | Nandurkar P  | 6-14 / 9.44 (2.03)            | 35:12     | FEV1, FVC, FEV1/FVC, FEV1/FVC, 25-75% | ATS | 3217 (1351.853) |
| 33  | Gadipathi M  | 8-18 / 14.18 (4.95)           | 21:13     | FEV1, FEV1, FEV1/FVCATS | ATS | 3610.82 (2679.15) |
| 34  | Abd El Hakeem A | 13.2 (2.7)  | 31:19     | FEV1, FEV1/FVC, PEF, FEF 25-75%, DLCO | ATS | DI: 3543 (2292); CDRT: 4660 (2100); normal PFT: 2941 (2612) |
| 35  | Elsehaimy LA | 11.65 (2.57)                  | 20:40     | FEV1, FEV1, FEV1/FVC, FEF 25-75% | Fabrii et al. | NM |
| 36  | Kazgan T     | 6-20 / 13.27 (4.26)           | 21:19     | FEV1, FVC, FEV1, PEF | Miller MR et al. | 3268.25 (2991.44) |
| 37  | Harsoor J    | 5-15 / 7.78 (2.4)             | 1.6:1     | FEV1, FVC, FEV1/FVC, PEF, FEF 25-75% | BTS | >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 mid-expiratory 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.
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.\textsuperscript{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\textsuperscript{25} | HR             | LR       | LR               | HR                | LR              | LR             | LR                                | HR                       |               | LR                       | MR                  |
| 2       | Hoyt RW\textsuperscript{26} | HR             | LR       | LR               | LR                | HR              | LR             | LR                                | HR                       |               | LR                       | MR                  |
| 3       | Grisaru D\textsuperscript{27} | HR             | LR       | LR               | LR                | HR              | HR             | LR                                | LR                       | LR               | LR                       | MR                  |
| 4       | Factor JM\textsuperscript{13} | HR             | LR       | LR               | LR                | LR              | HR             | LR                                | LR                       | LR               | LR                       | MR                  |
| 5       | Tai DYG\textsuperscript{14} | HR             | LR       | LR               | LR                | LR              | LR             | LR                                | LR                       | LR               | LR                       | MR                  |
| 6       | Cracowski C\textsuperscript{28} | HR             | LR       | LR               | LR                | HR              | LR             | LR                                | LR                       | LR               | LR                       | MR                  |
| 7       | Kivity S\textsuperscript{30} | LR             | LR       | LR               | LR                | HR              | LR             | LR                                | LR                       | LR               | LR                       | MR                  |
| 8       | Dimopoulou P\textsuperscript{30} | LR             | LR       | LR               | LR                | LR              | HR             | LR                                | LR                       | LR               | LR                       | MR                  |
| 9       | Kanj N\textsuperscript{12} | HR             | LR       | LR               | LR                | LR              | LR             | LR                                | LR                       | LR               | LR                       | MR                  |
| 10      | Filosa A\textsuperscript{31} | HR             | LR       | LR               | HR                | LR              | LR             | LR                                | LR                       | LR               | LR                       | MR                  |
| 11      | Arora M\textsuperscript{13} | HR             | LR       | LR               | LR                | LR              | LR             | LR                                | LR                       | LR               | LR                       | MR                  |
| 12      | Li AM\textsuperscript{9} | HR             | LR       | LR               | LR                | LR              | LR             | LR                                | LR                       | LR               | LR                       | MR                  |
| 13      | Khong PL\textsuperscript{33} | LR             | LR       | LR               | LR                | LR              | LR             | LR                                | LR                       | LR               | LR                       | MR                  |
| 14      | Jamal R\textsuperscript{34} | LR             | LR       | LR               | LR                | LR              | LR             | LR                                | LR                       | LR               | LR                       | MR                  |
| 15      | Sritippayawan S\textsuperscript{35} | LR             | LR       | LR               | LR                | LR              | LR             | LR                                | LR                       | LR               | LR                       | MR                  |
| 16      | Said M\textsuperscript{36} | HR             | LR       | LR               | LR                | LR              | LR             | LR                                | LR                       | LR               | LR                       | MR                  |
| 17      | Piatti G\textsuperscript{37} | HR             | LR       | LR               | LR                | LR              | LR             | LR                                | LR                       | LR               | LR                       | MR                  |
| 18      | Parakh A\textsuperscript{38} | HR             | LR       | LR               | LR                | LR              | LR             | LR                                | LR                       | LR               | LR                       | MR                  |
| 19      | Abu-Ekteish FM\textsuperscript{39} | HR             | LR       | LR               | LR                | LR              | LR             | LR                                | LR                       | LR               | LR                       | MR                  |
| 20      | Azarkeivan A\textsuperscript{19} | HR             | LR       | LR               | LR                | LR              | LR             | LR                                | LR                       | LR               | LR                       | MR                  |
| 21      | Rahim F\textsuperscript{40} | LR             | LR       | LR               | LR                | LR              | LR             | LR                                | LR                       | LR               | LR                       | MR                  |
| 22      | Eidani E\textsuperscript{41} | HR             | LR       | LR               | LR                | LR              | LR             | LR                                | LR                       | LR               | LR                       | MR                  |
| 23      | Sohn EY\textsuperscript{42} | HR             | LR       | LR               | LR                | LR              | LR             | LR                                | LR                       | LR               | LR                       | MR                  |
| 24      | Alyasin S\textsuperscript{43} | HR             | LR       | LR               | LR                | LR              | LR             | LR                                | LR                       | LR               | LR                       | MR                  |
| 25      | Bortol E\textsuperscript{44} | HR             | LR       | LR               | LR                | LR              | LR             | LR                                | LR                       | LR               | LR                       | MR                  |
| 26      | Noori NM\textsuperscript{45} | HR             | LR       | LR               | LR                | LR              | LR             | LR                                | LR                       | LR               | LR                       | MR                  |
| 27      | Hamed AES\textsuperscript{46} | HR             | LR       | LR               | LR                | LR              | LR             | LR                                | LR                       | LR               | LR                       | MR                  |
| 28      | Gulhan B\textsuperscript{47} | HR             | LR       | LR               | LR                | LR              | LR             | LR                                | LR                       | LR               | LR                       | MR                  |
| 29      | Ozyoruk D\textsuperscript{48} | HR             | LR       | LR               | LR                | LR              | LR             | LR                                | LR                       | LR               | LR                       | MR                  |
| 30      | Boddu A\textsuperscript{49} | HR             | LR       | LR               | LR                | LR              | LR             | LR                                | LR                       | LR               | LR                       | MR                  |
| 31      | Guidotti F\textsuperscript{50} | HR             | LR       | LR               | LR                | LR              | LR             | LR                                | LR                       | LR               | LR                       | MR                  |
| 32      | Nandurkar P\textsuperscript{51} | HR             | LR       | LR               | LR                | LR              | LR             | LR                                | LR                       | LR               | LR                       | MR                  |
| 33      | Gadiparthi M\textsuperscript{52} | LR             | LR       | LR               | LR                | LR              | LR             | LR                                | LR                       | LR               | LR                       | MR                  |
| 34      | Abd El Hakeem AA\textsuperscript{53} | HR             | LR       | LR               | LR                | LR              | LR             | LR                                | LR                       | LR               | LR                       | MR                  |
| 35      | Elsehaimy LA\textsuperscript{54} | HR             | LR       | LR               | LR                | LR              | LR             | LR                                | LR                       | LR               | LR                       | MR                  |
| 36      | Kazgan T\textsuperscript{55} | LR             | LR       | LR               | LR                | LR              | LR             | LR                                | LR                       | LR               | LR                       | MR                  |
| 37      | Harsoor J\textsuperscript{56} | LR             | LR       | LR               | LR                | LR              | LR             | LR                                | LR                       | LR               | LR                       | MR                  |

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 (I²=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 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 (I²=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.

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**Table 5. Prevalence of PD in different subgroups**

| Stratification group | Number of studies | Total number of subjects | Total number of events | I² | 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 |
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.
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 | I² | 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 | I² | 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                    | 76.633 | 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   |

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-thalassaemia 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 $\geq 3,000$ 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 patients with serum ferritin levels of $\geq 2,500$ ng/dL (64.8%) than in those with levels $\leq 2,500$ng/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 $\beta$-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 $\beta$-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 $\beta$-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 $\beta$-thalassemia patients varied from country to country.

**Conflict of interest**

None declared.

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