



# Post-tuberculosis lung impairment: systematic review and meta-analysis of spirometry data from 14 621 people

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**These findings highlight a significant burden of functional lung impairment following tuberculosis. There is a need to implement effective strategies to diagnose post-tuberculosis lung impairment and to improve lung health in survivors of tuberculosis.** <https://bit.ly/3woP9oQ>

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## Abstract

**Background** A substantial proportion of tuberculosis patients remain with pulmonary symptoms and reduced physical capacity despite successful treatment. We performed a systematic review to analyse the burden of post-tuberculosis lung impairment measured by lung function testing.

**Methods** We searched the PubMed database for articles published between database inception and November 2020 and performed meta-analyses to estimate the prevalence, type and severity of lung impairment among drug-susceptible and multidrug-resistant tuberculosis survivors. Methodological quality of included studies was assessed using the Newcastle–Ottawa scale.

**Results** 54 articles were included in this review. For subjects with former drug-susceptible tuberculosis, the combined estimated mean was 76.6% (95% CI 71.6–81.6) of predicted for forced expiratory volume in 1 s (FEV<sub>1</sub>) and 81.8% (95% CI 77.4–86.2) for forced vital capacity (FVC). In former patients with multidrug-resistant tuberculosis, it was 65.9% (95% CI 57.1–74.7) for FEV<sub>1</sub> and 76.0% (95% CI 66.3–85.8) for FVC, respectively. The analysis of impairment types in former patients with drug-susceptible and multidrug-resistant tuberculosis showed that 22.0% *versus* 19.0% had obstructive, 23.0% *versus* 22.0% restrictive and 15.0% *versus* 43.0% had mixed impairment type, respectively. In the majority of studies, at least 10–15% of tuberculosis survivors had severe lung impairment.

**Conclusions** This systematic review showed long-term abnormal spirometry results in a significant proportion of tuberculosis survivors.

## Introduction

Tuberculosis (TB) remains one of the greatest public health challenges worldwide, with an estimated 9.9 million affected patients and associated 1.3 million deaths in 2020 [1]. TB survivors suffer from relevant residual morbidity [2, 3] and have a higher mortality risk compared to the standard population [4, 5]. In addition to evidence of an association between COPD and prior pulmonary TB from epidemiological studies [6, 7], it has been estimated that up to half of all former TB patients are left with post-TB lung disease (PTLD) at the end of TB treatment [8, 9].

While there is consensus among experts that spirometry can be a useful test to measure lung impairment after TB [3] and can also inform treatment decisions and treatment success evaluation in pulmonary rehabilitation in patients with PTLD [10], no evidence-based international guidelines are available to



provide recommendations for the evaluation and treatment of PTLT [11]. Spirometry is one of the basic diagnostic methods in pulmonary medicine and key for the diagnosis of common chronic lung diseases such as asthma and COPD. Several international guidelines on spirometry and reference values for spirometry values are available, guiding the investigation and analysis of results [12, 13]. Despite the unclear role of spirometry and its parameters in the diagnosis and monitoring of PTLT, it has already been used in many studies of PTLT [8, 9, 14], including host-directed therapy trials that are aiming for an improved outcome in pulmonary function in TB patients [15].

This systematic review aims to comprehensively describe the scientific evidence on the prevalence of pulmonary function impairment measured by spirometry in former patients with drug-susceptible and multidrug-resistant TB.

## Methods

The protocol for this review was registered with PROSPERO (CRD42018095000). The review methods and reporting of results follow PRISMA guidelines [16].

### Search strategy and selection criteria

Full reports of studies investigating pulmonary function in former TB patients at any time after active pulmonary TB were searched *via* PubMed (US National Library of Medicine National Institutes of Health Search database) from inception until November 2020, with keywords such as “pulmonary tuberculosis”, “lung impairment”, “lung function”, “spirometry” (a list including all search terms can be found in Supplement 1). Search terms including 6-min walk test and St. George’s Respiratory Questionnaire were also used as these assessments are often performed together with spirometry.

In addition to the systematic search, eligible articles on the topic known to the authors and articles identified by hand search, but not identified by the systematic search in PubMed, were also included. All articles were reviewed for relevance by title and abstract. Duplicates were removed. Inclusion criteria were original studies that reported spirometry measurements, full-text access and written in English. We excluded those studies that did not report spirometry outcomes in a format that could be further used for meta-analysis, *i.e.* figures only, editorials, commentaries, conference papers, abstracts only or brief communications, and studies targeting specific study populations such as patients with lobectomy or with previously known specific comorbidities, *e.g.* advanced COPD or exclusively elderly people.

### Data extraction

Relevant data, extracted from eligible articles by one reviewer (O.I., V.H. or A.R.) and cross checked by another reviewer (O.I., V.H. or A.R.), included author name, year of publication, study region, sample size, type of TB (drug-susceptible disease *versus* multidrug-resistant disease) and time point of lung function testing in relation to the last TB episode. The following spirometry data were also retrieved: absolute values and percentage (%) of predicted for expiratory volume in 1 s (FEV<sub>1</sub>), forced vital capacity (FVC) and FEV<sub>1</sub>/FVC ratio including means, medians and sds, interquartile range (IQR) as well as impairment type (*i.e.* normal, reduced FEV<sub>1</sub>, reduced FVC (restriction), reduced FEV<sub>1</sub>/FVC ratio (obstruction) or both reduced FVC plus reduced FEV<sub>1</sub>/FVC ratio present (mixed)) and severity of lung impairment (*i.e.* mild, moderate, moderately severe, severe or very severe). Discrepancies between the reviewers were resolved by discussion and re-examination of the corresponding publications.

### Quality assessment

Methodological quality of the included studies was assessed by one reviewer (O.I., V.H. or A.R.) using the Newcastle–Ottawa scale (NOS). A “star system” was used to place publications in three categories – low, moderate and good [17]. The NOS is a valid tool to assess the internal and external quality of a study according to the Cochrane Collaboration [18].

### Data analysis

Accounting for possible heterogeneity between the studies, we fitted random effects models to derive pooled estimators of the means of spirometry using the restricted maximum-likelihood estimator for estimation of the between study variance  $\tau^2$  [19, 20]. If the standard deviations of the means were not reported in the manuscript, they were estimated from confidence intervals, IQRs, or by combining standard deviations of groups (as recommended in the Cochrane handbook [18]).

For meta-analysis of proportions of patients with obstructive, restricted and mixed impairment patterns on spirometry, logit-transformed and generalised linear mixed models (more specific, random intercept logistic regression models [21]) were fitted [22]. Confidence intervals for individual studies were calculated as

Wilson score intervals [23]. The maximum-likelihood method was used for estimation of the between study variance  $\tau^2$ .

To assess the extent of between-study heterogeneity,  $I^2$  was calculated [24]. Sources of heterogeneity were investigated using meta-regression analysis. The following pre-specified variables were analysed: year of publication, country, world region, patient selection, patient age, proportion of males, proportion of smokers and study quality. Pooled estimators of means and proportions were calculated for relevant subgroups. Publication bias was assessed by plotting study results against precision of the study [25] and the according regression tests [26].

All calculations were performed using the package “meta” in the statistical software package R (version 4.0.0, R Foundation for Statistical Computing, Vienna, Austria). p-values below 0.05 were considered significant and all confidence limits were calculated on the 95% level.

### *Role of the funding source*

The funders of the study played no role in study design, data collection, data analysis, data interpretation or writing of the report.

## **Results**

### *Study selection and general characteristics*

The database search yielded 1270 records. After title and content screening and eligibility assessment, a total of 54 [6, 8, 9, 27–77] studies were included in this review (figure 1).

The earliest study included was from 1971 and the latest from 2020. Included publications represented all World Health Organization regions [78] except for the Eastern Mediterranean region, with the smallest number of studies from Europe (n=3) and the largest from Africa (n=18).

In the majority of studies (patient series, clinical studies and cohort studies, n=46, 8725 people), participants were selected based on a clinical TB diagnosis and/or microbiologically based TB diagnosis or TB treatment in the past in order to assess the pulmonary TB outcome in these subjects. In this review, we named these studies “patient series”. The remaining studies (n=8, 5896 people) were population-based surveys, in which a TB history (either based on self-reporting or on chest X-ray analysis) was assessed as one of several risk factors for lung function impairment.

Almost all studies reported the distribution of sex (male/female) and age among participants. Less than half of the studies (n=18) clearly stated whether there was anti-TB drug resistance diagnosed in the included participants. Studies that did not specify the TB resistance status of participants were usually older and from settings known for having a low multidrug-resistant TB prevalence. Thus, studies that did not explicitly state the resistance profile of participants were merged into one group with the studies that explicitly included drug-susceptible TB patients only and analysed separately from studies that stated that they included exclusively multidrug-resistant TB patients. The total sample size out of 54 studies was 14 621 included people. Detailed study characteristics of all 54 studies are presented in Supplement 2.

### *Quality assessment*

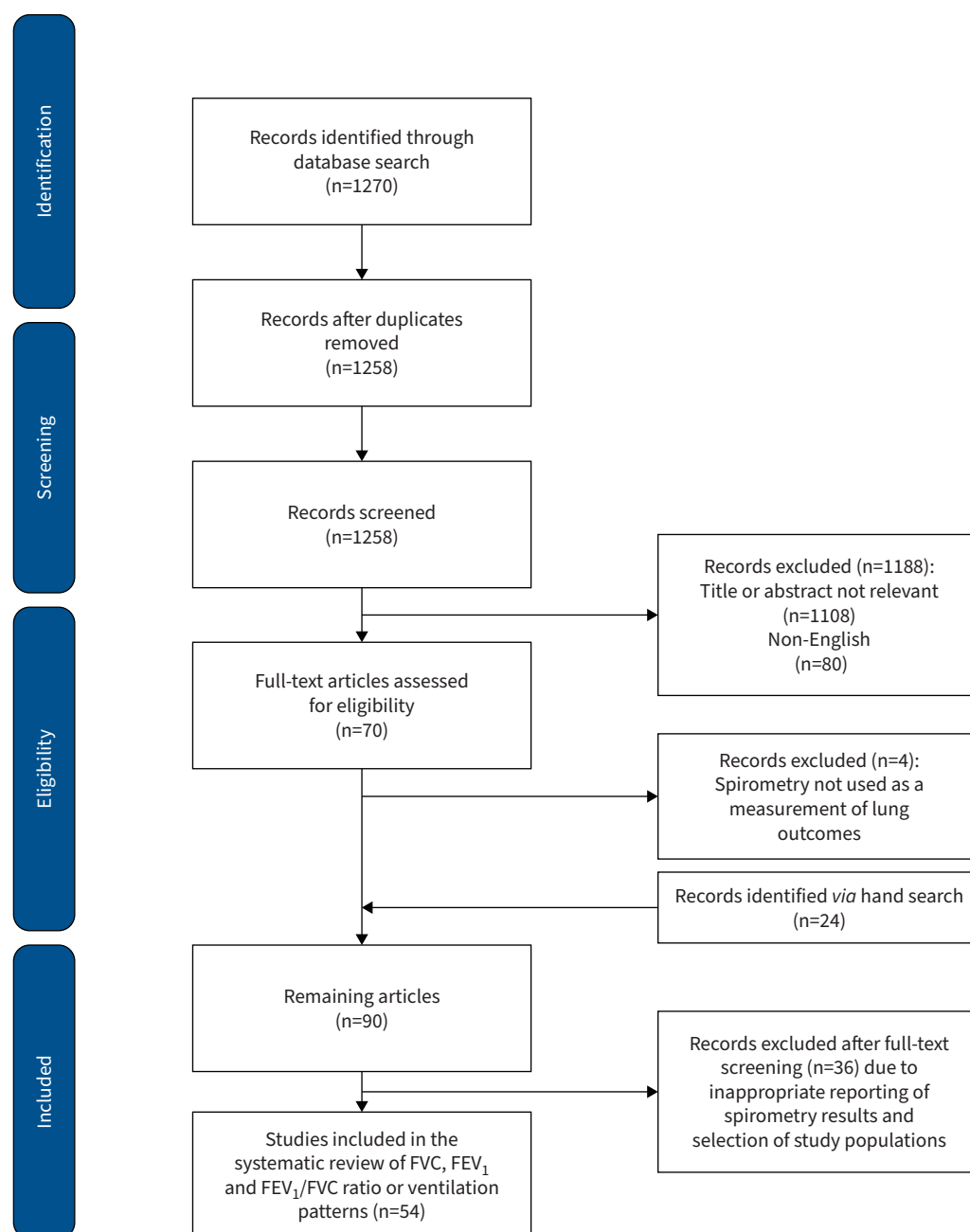
The quality assessment using the NOS showed that more than half of the studies (n=31) were of a good quality, 22 had moderate quality and one had low quality (Supplement 2).

### *Spirometry methodology and time point*

Around 87.0% of the studies clearly stated the guidelines according to which spirometry measurement and quality control were performed, of which the vast majority followed American Thoracic Society/European Respiratory Society standards. Only 36/54 (66.7%) studies stated the reference standard used to analyse spirometry results. The time point for spirometry assessment in relation to end of TB treatment varied significantly between studies, with the median time of 6 months (IQR 0–26.5).

### *Differences in reporting of spirometry results*

Supplement 2 shows the different spirometric parameters and spirometric impairment types reported by each study. The quality, scope and comprehensiveness of spirometry data analysis and reporting differed greatly between the articles. 21 out of 54 (38.9%) studies reported absolute values for FVC and/or FEV<sub>1</sub> in litres, 41/54 (76.0%) studies reported values for FEV<sub>1</sub> and FVC as a percentage of predicted and in 11/54 (20.4%) studies none of these measurements for FVC, FEV<sub>1</sub> or FEV<sub>1</sub>/FVC ratio were included in the article or only presented graphically without measures of precision (*i.e.* SD and IQR). A total of 47/54

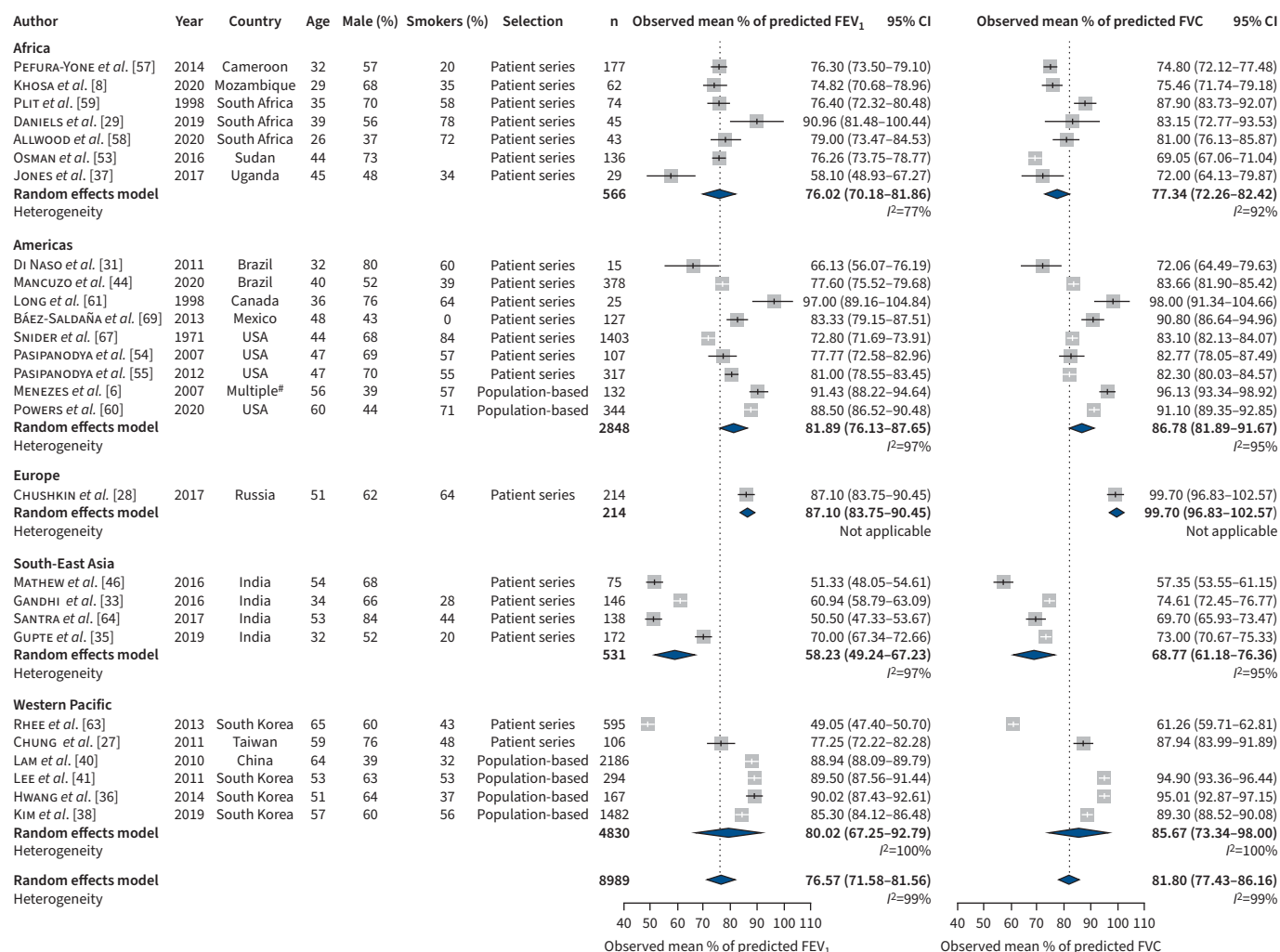


**FIGURE 1** Flow chart diagram of studies for the systematic review (PRISMA). FVC: forced vital capacity; FEV<sub>1</sub>: forced expiratory volume in 1 s.

(87.0%) articles reported on the type of ventilation impairment seen in spirometry (obstruction, restriction or mixed pattern), with some of them (n=21; 44.4%) also analysing the severity grade of lung impairment. Based on the type of data reported by each study, they were included in one or both of the following meta-analyses.

#### **Meta-analysis of spirometric parameters: FVC and FEV<sub>1</sub>**

Those 27/54 (50.0%) studies that reported values for FVC and/or FEV<sub>1</sub> as a percentage of predicted, as well as an indicator of variance, were included in this meta-analysis. For studies reporting on drug-susceptible TB, the combined estimated mean of percentage of predicted was 76.6% (95% CI 71.6–81.6) for FEV<sub>1</sub> and 81.8% (95% CI 77.4–86.2) for FVC (figure 2). Heterogeneity in this analysis was substantial for both estimates ( $I^2=99\%$ ). Main sources of heterogeneity were world region and study type (tests for subgroup differences  $p<0.0001$ ). Patient series tend to give significant lower estimates and more



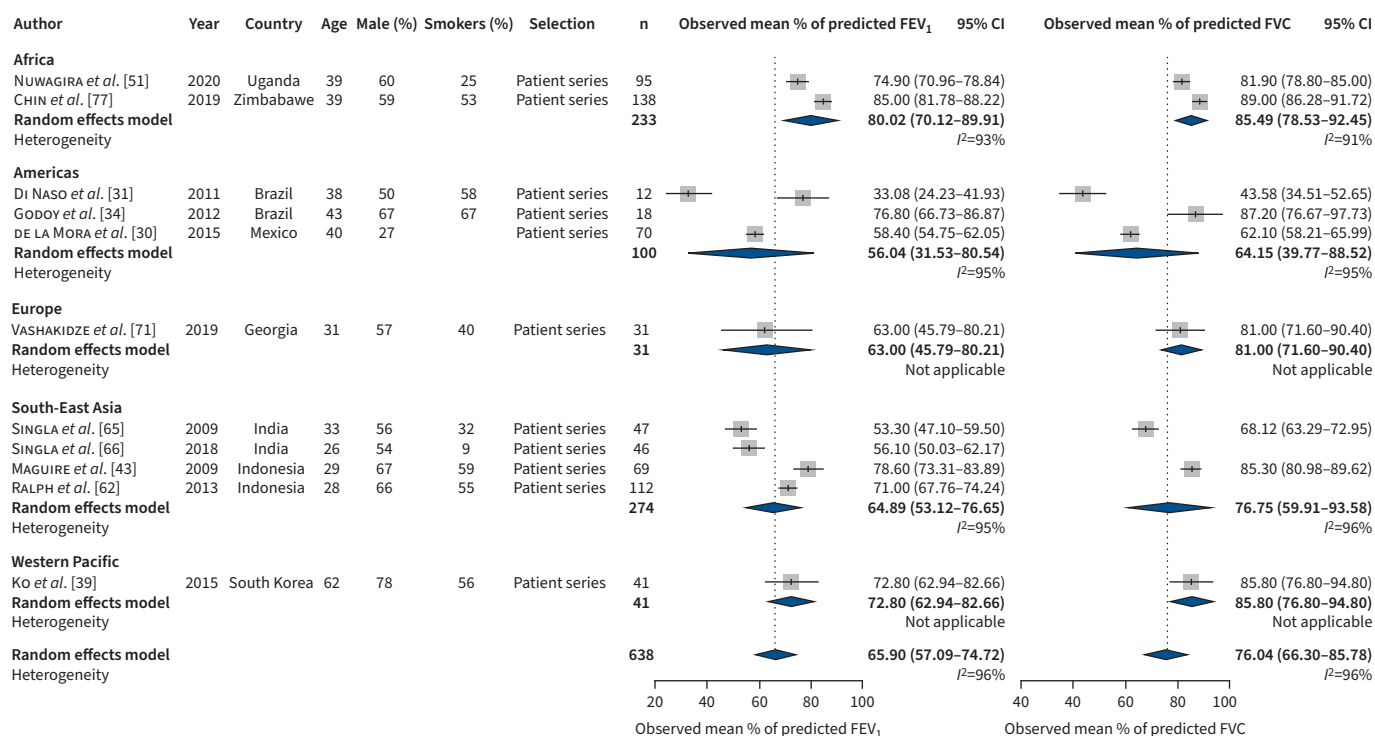
**FIGURE 2** Forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV<sub>1</sub>) for drug-susceptible tuberculosis studies. #: Countries: Brazil, Uruguay, Mexico, Chile and Venezuela.

heterogeneous results than population-based studies, with a combined estimate of 72.9 (95% CI 67.4–78.4,  $I^2=99\%$ ) for FEV<sub>1</sub> and 79.0 (95% CI 74.3–83.6,  $I^2=98\%$ ) for FVC compared to population-based studies with estimates of 88.7 (95% CI 87.0–90.4,  $I^2=85\%$ ) for FEV<sub>1</sub> and 93.2 (95% CI 90.5–95.8,  $I^2=94\%$ ) for FVC (Supplement 3, figures A and B). Meta-regression and subgroup analysis for age, percentage of males, percentage of smokers and the NOS did not yield significant results.

For former patients with multidrug-resistant TB, the combined estimated mean of percentage of predicted was 65.9% (95% CI 57.1–74.7,  $I^2=96\%$ ) for FEV<sub>1</sub> and 76.0% (95% CI 66.3–85.8,  $I^2=96\%$ ) for FVC (figure 3). Similar to studies reporting on drug-susceptible TB, the estimated percentage of predicted for FEV<sub>1</sub> was lower compared to that for FVC. Visual inspection and tests for funnel plot asymmetry did not indicate publication bias.

### Meta-analysis of abnormal ventilation patterns on spirometry

A total of 47/54 (87.1%) studies reported the impairment type identified by spirometry. Among them, all studies assessed pulmonary obstruction, many also assessed restriction ( $n=37$ ) and some less mixed patterns ( $n=31$ ). The combined estimated proportions of people with obstruction and restriction were almost equal in studies reporting on drug-susceptible TB (figure 4) and multidrug-resistant TB (figure 5), with 0.2 (95% CI 0.2–0.3,  $I^2=98\%$ ) and 0.2 (95% CI 0.2–0.3,  $I^2=98\%$ ), respectively, in studies on drug-susceptible TB (figure 4) versus 0.2 (95% CI 0.1–0.3,  $I^2=56\%$ ) and 0.2 (95% CI 0.2–0.3,  $I^2=45\%$ ), respectively, in studies on multidrug-resistant TB (figure 5). However, a mixed impairment pattern was more prevalent among studies on multidrug-resistant TB with 0.4 (95% CI 0.2–0.7,  $I^2=89\%$ ) compared to



**FIGURE 3** Forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV<sub>1</sub>) for multidrug-resistant tuberculosis studies.

studies on drug-susceptible TB with 0.2 (95% CI 0.1–0.2,  $I^2=96\%$ ). Notably, while the combined estimates for obstruction (Supplement 3, figure C) and mixed impairment (Supplement 3, figure D) were almost similar in patients' series *versus* population-based surveys in survivors of drug-susceptible TB, the proportion of survivors of drug-susceptible TB with restriction was significantly higher in patient series compared to population surveys (Supplement 3, figure E). In this analysis too, the amount of heterogeneity was high. Again, world region and study type (only for pulmonary restriction) were significant sources of heterogeneity, while age, percentage of males, percentage of smokers and NOS score were not. In addition, in this analysis visual inspection and tests for funnel plot asymmetry did not indicate publication bias.

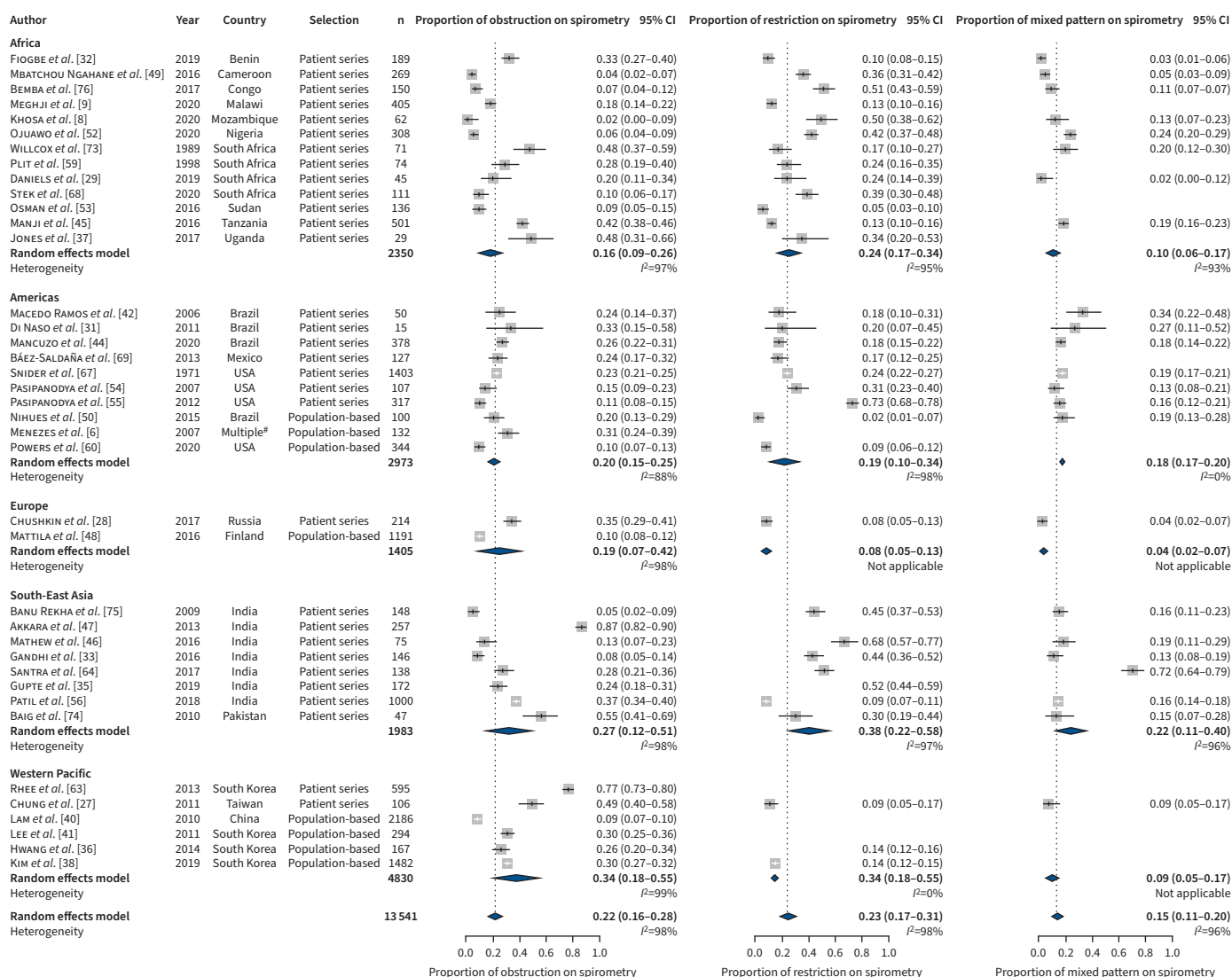
### Severity of lung impairment

A total of 21/54 (38.9%) studies provided a grading of severity of lung impairment. The majority of studies graded the severity of lung impairment for obstruction only (11 studies, table 1). Nine of them followed the Global Initiative for Chronic Obstructive Lung Disease classification for obstruction severity, table 1. The proportion of patients with moderate or severe lung impairment was extremely heterogenous across the 21 studies, which can partially be explained by the different denominators (*e.g.* all participants *versus* participants with lung impairment) used by the respective authors. The data indicate that, in the majority of studies, about 10–15% of participants had severe lung impairment, which is less than 50% of predicted.

### Discussion

This systematic review and meta-analyses included the spirometry results from 54 studies with highly heterogeneous study populations, study designs and geographical origins published from 1971 to 2020, leading to a substantial heterogeneity in the data. In summary, our analyses showed a globally significant burden of abnormal lung function in spirometry of TB survivors. Although FEV<sub>1</sub> and FVC were on average reduced by 24.0% and 20.0%, respectively, which is just below the limit of normality, a relevant proportion of previous TB patients were affected by obstructive (low FEV<sub>1</sub>/FVC ratio), restrictive (low FVC) or combined obstructive/restrictive pulmonary disease, with about 10–15% having severe impairment. FEV<sub>1</sub> and FVC were on average significantly lower in patient series compared to population-based studies. This could be due to two main reasons. First, previous data showed that lung function continues to recover significantly for up to 12–18 months after the end of TB treatment [9, 79]. Therefore, in patient series that included former TB patients at around 6 months after TB treatment, lung

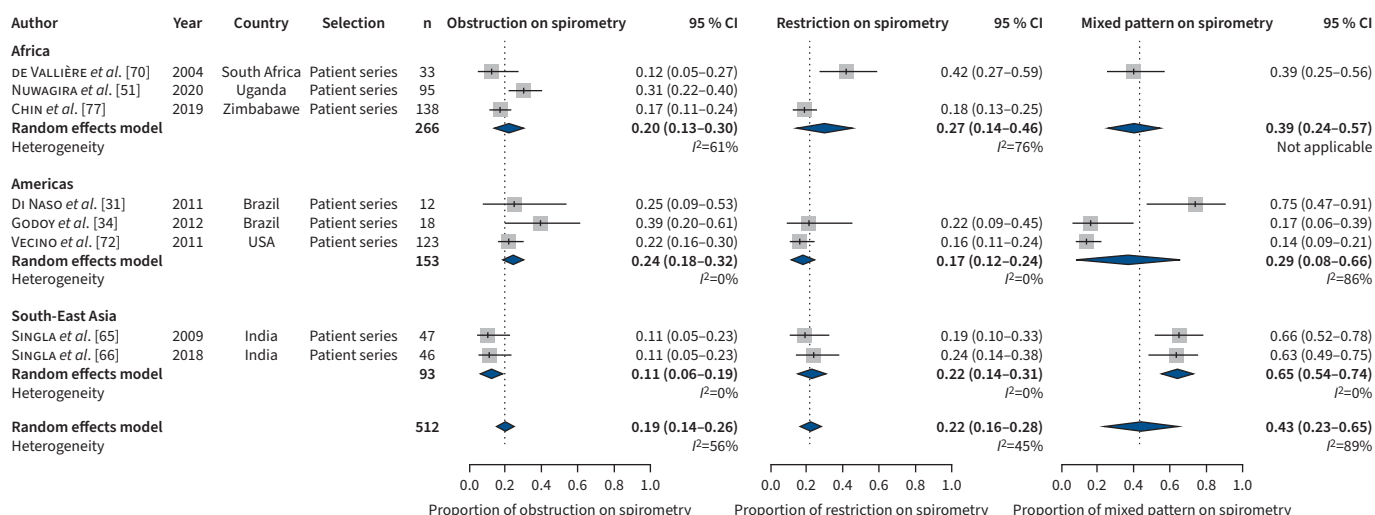




**FIGURE 4** Type of ventilation disorder for drug-susceptible tuberculosis studies. <sup>#</sup>: Countries: Brazil, Uruguay, Mexico, Chile and Venezuela.

function was measured at a time when improvement is possible in many patients. Second, there is a possibility of selection bias due to lower secondary mortality [5] and morbidity [9] in patients with less pulmonary sequelae, leading to increased recruitment of former TB patients with less severe PTLD compared to those with more severe PTLD in population-based surveys.

All types of lung impairment, obstruction, restriction and mixed, were found in former TB patients, indicating that several additional co-factors (genetic background of host and pathogen, comorbidities, risk-behaviour, environment, *etc.*) may be contributing to and modulating the development of PTLD. About 22% of former TB patients had pulmonary obstruction. This is a higher proportion than in general populations included in the Burden of Obstructive Lung Disease (BOLD) study [7]. TB was shown to be associated with COPD diagnosis in several studies [6, 7, 80, 81]. A major driver of both COPD and pulmonary TB is past or ongoing exposure to cigarette smoke [7]. Smoking was also shown to be associated with delayed time to culture conversion [82] and less favourable outcomes of TB treatments [7]. There was a high prevalence of smoking as a co-risk factor in the included studies. As nonsmoking populations are usually used as a reference, the individual and interactive effect of TB and smoking on the development of lung impairment in former TB patients could not be investigated in most studies. Unfortunately, the fact that smoking habits were inconsistently defined, queried and reported in the reviewed studies also prevented the analysis of the effect of smoking in this meta-analysis.



**FIGURE 5** Type of ventilation disorder for multidrug-resistant tuberculosis studies.

23% of people with a history of drug-susceptible TB had pulmonary restriction, meaning a low value for FVC. Worldwide, TB ranks among the leading causes of restrictive lung diseases [83]. In addition, in the BOLD study, an association between TB and restrictive spirometry pattern was shown [7]. The proportions of patients with restriction were highly variable and reached up to 68% in some studies. The timing of spirometry assessment could be one reason. While restriction seemed to be the prevailing spirometric abnormality early, during and after TB treatment, there is an indication for a decrease in restriction and increase in the proportion and severity of obstruction towards later time points when TB treatment had been completed [9, 58, 84, 85]. This observation could be explained by a relative improvement in vital capacity due to a decrease in parenchymal inflammation during and after treatment, but would need further investigations in future studies.

While in studies reporting on drug-susceptible TB only 15% of participants had mixed impairment, in patients with multidrug-resistant TB, mixed impairment was the prevailing abnormality in up to 70% of participants. Further, patients with multidrug-resistant TB suffered from substantially greater FEV<sub>1</sub> and FVC impairment in spirometry than patients with drug-susceptible TB. This is plausible given that, in many settings, appropriate diagnosis of multidrug-resistant TB and initiation of antimycobacterial treatment are often delayed and treatment efficacy less than optimal, both of which can lead to a higher degree of chronicity of TB with greater lung damage in affected patients. Thus, there is an indication in the data for an association between severity of lung damage, duration of illness and mixed impairment type, which needs confirmation by greater studies.

Apart from differences in study design, there could be other sources for the heterogeneity observed in our data. For instance, the use of inadequate reference standards or diagnostic thresholds, especially for study populations that are not represented by common standards like the Global Lung Function Initiative, could lead to over- or under-reporting of lung impairment [13, 86, 87]. In addition, there was an indication for a systematic under-reporting of restriction or mixed impairment types within the reviewed studies. We observed a much greater focus on COPD and airways disease in studies on post-TB lung diseases. This could possibly be explained by the tremendous disease burden caused by chronic airways diseases such as COPD and asthma globally and the importance of spirometry for the diagnosis of COPD.

Furthermore, differences in the quality of spirometry data, which are not captured by the NOS, can also contribute to heterogeneity in the data. Some studies contributing to heterogeneity can be identified as outliers: *e.g.* RHEE *et al.* [63] included only patients with more than one lung lobe destroyed by TB, SANTRA *et al.* [64] selected patients based on obstruction or mixed pattern spirometry results and MATHEW *et al.* [46] included 29% patients who defaulted from TB treatment. Some of the observed heterogeneity is an inherent effect of the many studies with large sample sizes, resulting in the very exact estimates with narrow confidence intervals that were included into the meta-analyses. Those very small confidence intervals lead to a large  $I^2$  that is induced by differences between studies, which may not be clinically relevant. Therefore, the summary estimates should not be interpreted as exact numbers but as indicators for



TABLE 1 Severity of lung impairment

Author	Year	Type of TB	Mild (%)	Moderate (%)		Severe (%)		Any impairment (%)	Severity classification used by authors
				Moderate	Moderately severe	Severe	Very severe		
AKKARA <i>et al.</i> [47] <sup>#</sup>	2013	TB	21.5		37.2		41.3	86.8	ATS
BÁEZ-SALDAÑA <i>et al.</i> [69] <sup>#</sup>	2013	TB	13	3	5	1.5	1.5	41	ATS/ERS
BAIG <i>et al.</i> [74] <sup>#</sup>	2010	TB	5.9		23		69.2	100	GOLD
BEMBA <i>et al.</i> [76] (obstruction)	2017	TB	4.9		0		4.9	68.7	ATS/ERS
BEMBA <i>et al.</i> [76] (restriction)	2017	TB	34.9		25.2		14.6	68.7	ATS/ERS
BEMBA <i>et al.</i> [76] (mixed)	2017	TB	0		6.8		8.7	68.7	ATS/ERS
CHIN <i>et al.</i> [77] <sup>#</sup>	2019	TB (MDR)	–		64		14	35	GLI 2012
CHUSHKIN <i>et al.</i> [28] <sup>#</sup>	2017	TB	2.8		15.9		9.3	47.6	ATS/ERS
DANIELS <i>et al.</i> [29] <sup>#</sup>	2019	TB	20		10	50	10	48	GOLD
DI NASO <i>et al.</i> [31] (DS TB)	2011	TB (DS)	53.3		13.3		13.3	80	NA
DI NASO <i>et al.</i> [31] (MDR TB)	2011	TB (MDR)	8.3		16.7		75	100	NA
FIOGBE <i>et al.</i> [32] (obstruction)	2019	TB (DS)	23		10		0	45	ATS/ERS
FIOGBE <i>et al.</i> [32] (restriction)	2019	TB (DS)	3.2		6		1	45	ATS/ERS
FIOGBE <i>et al.</i> [32] (mixed)	2019	TB (DS)	0		0		2.1	45	GOLD
HWANG <i>et al.</i> [36] <sup>#</sup>	2014	TB	45		43.7		11.3	NA	GOLD
KHOSA <i>et al.</i> [8] (obstruction)	2020	TB (DS)	1.6		–		–	64.5	Criée <i>et al.</i> [91]
KHOSA <i>et al.</i> [8] (restriction)	2020	TB (DS)	27.4		22.6		–	64.5	Criée <i>et al.</i> [91]
KHOSA <i>et al.</i> [8] (mixed)	2020	TB (DS)	–		1.6		11.3	64.5	Criée <i>et al.</i> [91]
MANCUZO <i>et al.</i> [44] (obstruction)	2020	TB	21.4		4.5		0.5	63	Pereira [92]
MANCUZO <i>et al.</i> [44] (restriction)	2020	TB	16.7		0.3		1.3	63	Pereira [92]
MANCUZO <i>et al.</i> [44] (mixed)	2020	TB	3.2		7.7		7.4	63	Pereira [92]
MANJI <i>et al.</i> [45] (obstruction)	2016	TB	56		23		21	74	ATS/ERS/NLHEP
MANJI <i>et al.</i> [45] (restriction)	2016	TB	43		30		27	74	ATS/ERS/NLHEP
MATTILA <i>et al.</i> [48] <sup>#</sup>	2017	TB	10		57		38	NA	GOLD
NUWAGIRA <i>et al.</i> [51] <sup>#</sup>	2020	TB (MDR)	0		55		45	NA	GOLD
OJUAWO <i>et al.</i> [52] (obstruction)	2020	TB	1.9	3.9	0	0	0	72	ATS/ERS
OJUAWO <i>et al.</i> [52] (restriction)	2020	TB	5.2	22.1	0	8.4	6.5	72	ATS/ERS
OJUAWO <i>et al.</i> [52] (mixed)	2020	TB	0	0	4.5	13.6	5.8	72	ATS/ERS
OSMAN <i>et al.</i> [53] <sup>#</sup>	2016	TB	8.3		58.3		16.7	16.7	NA
RALPH <i>et al.</i> [62]	2013	TB (DS and MDR)	–		27			NA	Pellegrino <i>et al.</i> [93]
MACEDO RAMOS <i>et al.</i> [42]	2006	TB	29.4		22.6		23.6	76	Brazilian Society of Pulmonology and Phthysiology 2000
SANTRA <i>et al.</i> [64] <sup>#</sup>	2017	TB	12		52	44	30	100	GOLD
VECINO <i>et al.</i> [72]	2011	TB (DS and MDR)	–		11		9	52	ATS and Cocchiarella <i>et al.</i> [94]

The denominator used to calculate the proportion of subjects with a specific severity grade of impairment types varied among the studies, e.g. denominator=total study population with both normal and impaired lung function combined *versus* denominator=only participants with lung impairment. #: Only the severity of pulmonary obstruction was presented in the respective manuscript. ATS: American Thoracic Society; DS: drug susceptible; ERS: European Respiratory Society; GLI: Global Lung Function Initiative; GOLD: Global Initiative for Chronic Obstructive Lung Disease; MDR: multidrug resistant; NA: not applicable; NLHEP: National Lung Health Education Program; TB: tuberculosis.

the relevance of the overall problem of TB sequelae resulting in spirometric impairment. Results of this systematic review document a clearly heterogeneous study situation.

Although this study presents robust evidence for impaired lung function by spirometry in people with a history of TB, the clinical relevance of this finding is not clear. Only few studies systematically assessed different health outcomes such as physiological capacity tests (e.g. 6-min walk test), health-related quality of life (HRQoL) or frequency of exacerbations and hospitalisation together with spirometry results in a

relevant number of post-TB patients. Publications on systematically performed prospective long-term evaluations of lung function and the prognosis of TB are not available to date. However, there is convincing evidence for the association of impaired FEV<sub>1</sub> with a greater risk of death in normal populations and in COPD patients [88, 89]. FEV is also a predictor for hospitalisation risk and associated with HRQoL in COPD patients [89, 90]. There is supporting evidence for a similar relationship between morbidity and mortality and spirometry parameters in former TB patients. A population-based study from Brazil showed that respiratory diseases were among the main causes of death among previous TB patients [5]. Also, MEGHJI *et al.* [9] showed in a Malawian cohort that post-TB lung impairment in spirometry was associated with adverse clinical outcomes during the first 12 months after end of treatment.

This systematic review has some limitations leading to the fact that not all available research data from other databases (*i.e.* Embase or Cochrane) could be included in the review and meta-analysis and the effect of co-morbidities and cigarette smoking could not be addressed. Additionally, the search terms used were broad but probably not exhaustive as no consistent terminology has been used in this field for decades. Further, a significant number of studies were excluded because of language barriers. Also, studies that presented outcome measures that were either not comparable to other studies (*e.g.* absolute values for FEV<sub>1</sub> and FVC in litres or graphical data) or that did not include estimates for precision could not be included in this meta-analysis. Strengths of this work include the diversity of study settings and the use of objective outcome measures produced by spirometry.

To conclude, this is the first systematic review and meta-analysis of spirometry outcomes in TB survivors. The findings highlight a significant burden of lung impairment after TB, especially in survivors of multidrug-resistant TB. Our results underpin the need to improve TB control to prevent chronic lung impairment in affected populations. Effective strategies to follow up TB survivors with sequelae are needed to improve health and wellbeing for these individuals. For future clinical and programmatic interventions, to be effective to reduce the burden of post-TB sequelae, a better understanding of the pathomechanisms and risk factors leading to different pulmonary impairment types and long-term adverse clinical outcomes will be important.

#### Points for future research

- Explore the relevance of these findings for clinical practice.
- Understand the pathomechanisms and risk factors leading to different pulmonary impairment types and long-term adverse clinical outcomes after TB.

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Data sharing: The data are available on request from the corresponding author.

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