

Review

Post-Tuberculosis (TB) Treatment: The Role of Surgery and Rehabilitation

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Abstract: Even though the majority of tuberculosis (TB) programmes consider their work completed when a patient is ‘successfully’ cured, patients often continue to suffer with post-treatment or surgical sequelae. This review focuses on describing the available evidence with regard to the diagnosis and management of post-treatment and surgical sequelae (pulmonary rehabilitation). We carried out a non-systematic literature review based on a PubMed search using specific key-words, including various combinations of ‘TB’, ‘MDR-TB’, ‘XDR-TB’, ‘surgery’, ‘functional evaluation’, ‘sequelae’ and ‘pulmonary rehabilitation’. References of the most important papers were retrieved to improve the search accuracy. We identified the main areas of interest to describe the topic as follows: 1) ‘Surgery’, described through observational studies and reviews, systematic reviews and meta-analyses, IPD (individual data meta-analyses), and official guidelines (GRADE (Grading of Recommendations Assessment, Development and Evaluation) or not GRADE-based); 2) Post-TB treatment functional evaluation; and 3) Pulmonary rehabilitation interventions. We also highlighted the priority areas for research for the three main areas of interest. The collection of high-quality standardized variables would allow advances in the understanding of the need for, and effectiveness of, pulmonary rehabilitation at both the individual and the programmatic level. The initial evidence supports the importance of the adequate functional evaluation of these patients, which is necessary to identify those who will benefit from pulmonary rehabilitation.

Keywords: TB; post-treatment sequelae; surgery; pulmonary rehabilitation

1. Introduction

Pulmonary and pleural tuberculosis (TB) may be severe and challenging even with drug susceptible strains of *Mycobacterium tuberculosis* and may require a multidisciplinary approach for best management. Moreover, drug-resistant tuberculosis (TB) and, in particular, multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB frequently occur in patients who have had prior TB episodes and may worsen previously damaged lungs [1–3]. Managing these cases is difficult, requiring a multidisciplinary team approach [4] and expensive treatment (which is toxic and with treatment success still below expectations) [2,5].

The availability of new drugs (bedaquiline, delamanid, and pretomanid) after many years of neglect provides new perspectives, improved success rates and a reduced prevalence of adverse events [6–8]. The rapid detection of TB is also key in order to catch the disease process early and preserve lung function.

As new evidence is made available and more is known about drugs and regimens, more patients are surviving [9–12], and it is emerging that other aspects require attention: the importance of preventing transmission [13], ensuring adequate nutrition, considering adjuvant surgery, and post-treatment sequelae [2,3,14]. These were emphasised in a comprehensive review of the Global Tuberculosis Network (GTN) based on the consensus of about 100 global experts [2]. This review is focused on describing the available evidence on adjuvant surgery and diagnosis and management of post-treatment sequelae (pulmonary rehabilitation).

2. Materials and Methods

We carried out a non-systematic literature review based on a PubMed search using specific key-words, including various combinations of ‘TB’, ‘MDR-TB’, ‘XDR-TB’, ‘surgery’, ‘functional evaluation’, ‘sequelae’, and ‘pulmonary rehabilitation’. References of the existing reviews were retrieved to improve accuracy.

Manuscripts written in English, Spanish, and Russian were selected, including full articles and relevant abstracts.

The main areas of interest we identified to describe the topic are as follows:

- 1) ‘Surgery’, described through observational studies and reviews, systematic reviews, and meta-analyses, IPD (individual data meta-analyses) and official guidelines (GRADE or not GRADE-based). Due to the scant evidence on thoracoplasty and other less frequent surgical procedures, we concentrated on lung resection.
- 2) Post-TB treatment lung functional evaluations.
- 3) Pulmonary rehabilitation interventions.

The priorities for research have been identified for each main area of interest.

3. Surgery and TB

3.1. Observational Studies and Reviews

A limited number of observational studies and reviews are available on the topic; the majority suggests that adjuvant surgery in selected patients may be useful to improve treatment outcomes [2,15–27]. However, the strength of the conclusions from these studies is somewhat limited by the risk of bias related to the variability of the centres’ procedures, patients’ profiles, treatment regimens, timing and types of surgical procedures, and it is difficult, if not impossible, to identify homogenous patients to compare among studies.

3.2. Traditional Meta-analyses

A few meta-analyses are available on the topic [28–32]. A traditional meta-analysis of 15 reports of surgical resection found that treatment success was achieved in 84% (95% confidence interval (CI), 78%–89%) of patients, noting substantial heterogeneity among the studies [29].

Two other meta-analyses of MDR-TB patients who had either resection or non-resection surgery found that surgical patients had better outcomes than those who did not [28,30]; however, there was no distinction between the different forms of resection surgery.

In the Marrone's meta-analysis [28], 24 studies identified a significant association between surgery and successful treatment compared to non-surgical interventions (OR 2.24, 95%CI 1.68–2.97). The meta-analysis from 23 single-arm studies demonstrated that, respectively, 92% (95%CI 88.1–95) and 87% (95% CI 83–91) of surgical patients achieved successful short and long-term outcomes. In the sub-group analysis (studies reporting both surgical and non-surgical treatment outcomes) favourable surgical outcomes (treatment success) were associated with increased drug-resistance, i.e., better results for XDR-TB patients than for MDR-TB ones.

Confounding by indication (a form of bias that occurs when the patients most likely to benefit are selected for therapy) was a major limitation in each meta-analysis.

Furthermore, antibiotic regimens were not standardized across studies, meaning that the studies could not account for factors such as the individual drug regimens or the timing of surgery in relation to culture conversion.

3.3. Evaluating the Role of Surgery Through IPD

A recent IPD based on the large MDR-TB cohort coordinated by McGill University [33–35] utilized a sophisticated analysis (propensity score matching) to evaluate the benefits offered by surgery. Individual patient data from 26 cohort studies were analysed, including clinical features and information on both medical and surgical therapy. Primary analyses compared treatment success (cure and completion) to a combined outcome of failure, relapse, or death. The effects of all forms of resection surgery, pneumonectomy, and partial lung resection were evaluated [35].

The final analysis was conducted on 4,238 patients from 18 surgical studies and 2,193 from 8 non-surgical ones. Pulmonary resection surgery (478 patients) was associated with improved treatment success (adjusted odds ratio (aOR), 3.0; 95% confidence interval (CI), 1.5–5.9), but pneumonectomy was not (aOR, 1.1; 95% CI, 0.6–2.3). Treatment success was achieved in 95.2% of patients undergoing surgery after culture conversion compared with 91.2% of those who had surgery before it (aOR, 2.6; 95% CI, 0.9–7.1).

Patients undergoing partial lung resection achieved better treatment success and lower failure/death rates than patients who had either pneumonectomy or no surgery. The median duration of medical therapy was 20 months (interquartile range [IQR], 13.7–24.0 months) for those who had surgery after culture conversion versus 29 months (IQR, 22–45 months) for those undergoing surgery before conversion. The loss to follow-up was lower among patients who had surgery (11%; 95% CI, 4–17%) than among those who had not (22%; 95% CI, 14–31%).

The authors concluded that, among MDR-TB patients, partial lung resection (but not pneumonectomy) was associated with improved treatment success, although selection bias cannot be excluded [35]. This finding can be explained with the lower rate of mortality among surgical versus non-surgical TB patients. Furthermore, patients undergoing surgery had, overall, more severe drug-resistance profiles and more extensive diseases [35]. Importantly, both surgical and non-surgical patients were rather young with a low probability of confounding co-morbidities [35].

A summary of the available evidence is reported in Table 1

Table 1. Main reports on the indications, type, and outcomes of surgery performed in patients affected by pulmonary tuberculosis complications.

First Author, Year, Country	Reference	Type of Paper; Patients Number and MDR/XDR-TB Proportion (%)	Indications for Surgery; Type of Surgery Assessed	Timing of Surgery	Favorable Outcome (Treatment Success)	Post-operative Complications/ Mortality (within 30 Days from Surgery)	Favouring Surgery
Sayir, 2019, Turkey	[24]	Case series; 9 pts, unspecified MDR/XDR %	Emergency: hemorrhage Elective: empyema Unspecified type of surgery	- After sputum smear negativity was achieved - After negative culture for empyema	Unspecified	Complications: unspecified Mortality: 11.1%	N/A
Yablonskii, 2019, Russia	[25]	Review; N/A pts and MDR/XDR %	Emergency: hemorrhage, spontaneous pneumothorax Urgent: recurrent haemoptysis Elective: localized cavitory disease with persistent sputum positivity Complications of TB diseases Assessment of all types of surgery Localised disease allowing for resection, failed bacteriological conversion, disease worsening	Unspecified	Treatment success: 67%–100%	Complications: 9%–30.8% Mortality: 0–5.5%	N/A
Borisov, 2019, Several Countries	[20]	Case series; 55 pts, 43.6% at least MDR; 56.4% XDR	Mostly lobectomy, segmentectomy, pneumonectomy Haemoptysis (100%), continuously positive smear (28.1%), pulmonary aspergillosis (40.6%)	After 8 months of therapy (median); range: 5–13)	Treatment success 69.1%	Complications: 23.7% (out of 38 evaluable patients) Mortality: 0	N/A
Chen, 2018, China	[26]	Case series; 32 pts, 12.5% MDR	Regional arterial embolization followed by pulmonary resection Fibro-cavitory and cavitory pulmonary TB (58.5%), tuberculoma with destruction (18.8%), tuberculous pleural empyema (18.8%), caseous pneumonia (3.4%), intrathoracic lymph nodes (0.5%) Unspecified type of surgery	After at least 6 months of standard therapy	Unspecified	Complications 18.75% Mortality: unspecified	N/A
Giller, 2018, Russia	[27]	Case series; 5,599 pts, unspecified MDR/XDR %	Unspecified type of surgery	After 1-3 years of treatment (for 84% of patients)	Treatment success: 92.1%–98%	Complications 1.9% Mortality: 0.1%	N/A
Fox, 2016, N/A	[35]	Meta-analysis; 478 pts (18 studies) 100% MDR (of whom 8.6% XDR)	Unknown indication for surgery Pneumonectomy (118 pts), partial lung resection (227 pts), unspecified (132 pts)	Unknown	Treatment success* 81% (pneumonectomy 69%; partial lung resection 90%)	Complications: unspecified Mortality: 8.4% (70% of deaths > 30 days from surgery)	Yes

Table 1. Cont.

First Author, Year, Country	Reference	Type of Paper; Patients Number and MDR/XDR-TB Proportion (%)	Indications for Surgery; Type of Surgery Assessed	Timing of Surgery	Favorable Outcome (Treatment Success)	Post-operative Complications/ Mortality (within 30 Days from Surgery)	Favouring Surgery
Subotic, 2016, N/A	[23]	Review; N/A pts and MDR/XDR %	Persistently positive sputum smear and/or culture despite appropriate chemotherapy, relapse, high risk of relapse based on drug resistance profile; Lobectomy, pneumonectomy, resection of tuberculoma	For infectious TB patients after at least 6–8 months of appropriate anti-TB therapy	Treatment success after surgery between 75% and 98%	Complications: 9%–26% Mortality: <5% after lung resection for TB	N/A
Marrone, 2013, N/A	[28]	Systematic review and meta-analysis; 706 pts, 100% MDR/XDR	Standardized or non-standardized indication for surgery Unspecified type of surgery	Unspecified	Treatment success: 87% at twelve months post-surgery; more favorable outcome for XDR than for MDR	Complications: 3% short-term; 8% long-term Mortality: unspecified	Yes
Xu, 2011, N/A	[29]	Systematic review and meta-analysis; 949 pts, 100% MDR	Unspecified indication for surgery Mainly pneumonectomy, lobectomy, segmentectomy	Unspecified	Treatment success: 84%	Complications: unspecified; Mortality: 3%	Unspecified

Legend: MDR: multidrug –resistant; XDR: extensively drug-resistant; * excluding lost to follow up; TB: tuberculosis; N/A: not applicable, Pts: patients.

3.4. World Health Organization (WHO), International Union Against Tuberculosis and Lung Disease (The UNION), and ATS/CDC/ERS/IDSA (American Thoracic Society/Centers for Disease Control and prevention/European Respiratory Society/Infectious Diseases Society of America) guidelines

In the consolidated WHO 2019 MDR-TB guidelines (and in the preceding 2016 and 2011 ones) the following recommendation were given (based on GRADE): in patients with rifampicin-resistant (RR)-TB or MDR-TB, elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended MDR-TB regimen [36].

In a regional WHO European guidance the indications and contra-indications for surgery were clearly defined [19,37]. Surgical interventions may have emergency (life threatening conditions), urgent (irreversible TB and haemoptysis), and elective natures.

Elective surgery indications include localised unilateral forms of bacteriologically-confirmed cavitary disease, MDR-/XDR-TB failing medical treatment, and complications/sequelae (spontaneous pneumothorax /pyopneumothorax; pleural empyema with or without bronchopleural fistula; aspergilloma; nodular-bronchial fistula; broncholith; and pachypleuritis/pericarditis with respiratory and blood circulation insufficiency; trachea/large bronchi stenosis; and post-TB bronchiectasis).

The following contra-indications have been identified [19,37]:

- Bilateral, extensive cavities;
- Impaired pulmonary function (forced expiratory volume in one second FEV1 (forced expiratory volume in 1 s) <1.5 L for lobectomy and < 2.0 L for pneumonectomy);
- Pulmonary-heart failure III–IV (New York Heart Association functional classification);
- Body mass index (BMI) up to 40%–50% of normality;
- Severe co-morbid conditions (uncontrolled diabetes, ulcer exacerbation, and liver/renal insufficiency);
- Active bronchial TB.

The UNION guidelines (which are not designed with the GRADE approach) suggest that ‘surgery should be considered for treating drug-resistant (DR)-TB only in patients meeting the three following conditions: 1) a fairly localised lesion, 2) an adequate respiratory reserve, and 3) a lack of sufficient available drugs to design a regimen potent enough to ensure a cure. Ideally, surgery needs to be performed at the moment chemotherapy has achieved the lowest possible bacillary load (sputum smear and culture converted to negative) within a complete cycle of chemotherapy [38].

In the recently published ATS/CDC/ERS/IDSA guidelines [39] the PICO (population, intervention, comparator, outcomes) question 19 was on ‘Surgery for MDR-TB’ as follows: ‘Should elective lung resection surgery (i.e., a lobectomy or pneumonectomy) be used as an adjunctive therapeutic option in combination with antimicrobial therapy, versus medical therapy alone for adults with MDR-TB?’

The following recommendations were issued:

‘Recommendation 19A: We suggest elective partial lung resection (e.g., a lobectomy or wedge resection), rather than medical therapy alone, for adults with MDR-TB receiving antimicrobial-based therapy (conditional recommendation, very low certainty in the evidence). The writing committee believes this option would be beneficial for patients for whom clinical judgement, supported by bacteriological and radiographic data, suggest a strong risk of treatment failure or relapse with medical therapy alone.

Recommendation 19B: We suggest medical therapy alone, rather than including elective total lung resection (pneumonectomy), for adults with MDR-TB receiving antimicrobial therapy (conditional recommendation, very low certainty of evidence)’ [39].

In summary, all major guidelines are consistent in recommending surgery in selected cases, following chemotherapy and favouring elective partial lung resection when possible, based on specific indications: failure of drug therapy, relapse, localized (e.g., cavity) or extensive pulmonary TB, clinical complications (e.g., haemoptysis or empyema) [39]. However, recent evidence suggests that bilateral surgery can also be safe and effective [40].

The patients undergoing surgery are candidates for pulmonary rehabilitation [20,39].

3.5. Priorities for Research

The ATS/CDC/ERS/IDSA guidelines proposed the following priorities for TB research on TB and surgery [39]: ideal timing for surgery; optimal drug regimens and duration before and after surgery; the role of surgery in special populations and patients with co-morbidities (e.g., HIV co-infection), optimal surgical approaches, optimal infection control measures to be implemented peri-operatively, and the role of pulmonary rehabilitation.

4. Post-TB Treatment Sequelae and Rehabilitation

There is evidence that patients with pulmonary TB have up to a five to six times higher probability of abnormal pulmonary function when compared with LTBI (latent TB infection) individuals [41]. TB sequelae are likely to follow delayed diagnosis, extensive disease, and long and/or repeated treatments [42]. TB sequelae are risk factors for bronchiectasis and COPD (chronic obstructive pulmonary disease), both conditions are more common in smokers and in the presence of in-door or out-door drug pollution [43]. The most common alterations are represented by obstructions with or without restriction. Airflow obstruction is usually without response to the bronchodilator, and often coupled with bronchiectasis and/or tracheobronchial stenosis, alterations of the lung parenchyma (cavities and pulmonary fibrosis) or of the pleura (empyema, fibrothorax, bronchopleural fistula, and pneumothorax). Restriction can affect gas exchange, as well as other vascular complications including pulmonary or bronchial arteritis, thrombosis, artery dilatation, Rasmussen aneurysm, or 'cor pulmonale' [43]. Both mechanical and gas exchange alterations can limit daily activities, exercise capacity, and impair quality of life (QoL) [43].

4.1. Post-TB Treatment Functional Evaluation

A baseline examination with functional evaluation can be performed safely when the patient is smear and culture negative (on at least two samples two weeks apart) and is undergoing effective treatment; otherwise, infection control measures are necessary [13]. As the patient might need a different approach when resting and when making exercise (e.g., walking), a careful evaluation should be ideally performed both at rest and under exercise conditions [43,44].

At rest, spirometry with response to the bronchodilator, diffusing capacity of the lung for carbon monoxide (DLCO), arterial blood gases analysis are recommended to study lung mechanics, complemented by plethysmography at the initial evaluation (if feasible) (Figure 1) [43].

Spirometry is the most widely accepted test to assess lung function impairment. It can be conducted with a simple spirometer, which costs a minimum of 150\$ and can be used at point-of-care or with a sophisticated apparatus which includes plethysmography (which is able to diagnose lung restriction and 'air trapping' by measuring the Residual Volume (RV)). The core parameters evaluated by spirometry are forced expiratory volume (FEV)₁ (low FEV₁ indicates airflow obstruction), FVC (Forced Vital Capacity) and their ratio (FEV₁/FVC) [43]. DLCO describes the status of gas exchanges at the pulmonary level, which can be hampered even in the presence of normal spirometry and plethysmography.

Under exercise conditions it is useful to have the patient undergo the 6-min walking test (6MWT) or the cardiopulmonary exercise test (CPET) which provides additional information on the physiological reserve (and, indirectly on QoL) [43,44]. The 6MWT measures the distance covered (in metres) in 6 min. It can be done in any setting, is cheap and easy to interpret: it correlates with QoL and improves after rehabilitation [43–45]. CPET is a more sophisticated, expensive, and technology-dependent tool which cannot be performed in all centres. It provides information on the exercise capacity-limiting determinants (respiratory: mechanical or as exchange-related; muscular; and cardio-vascular).

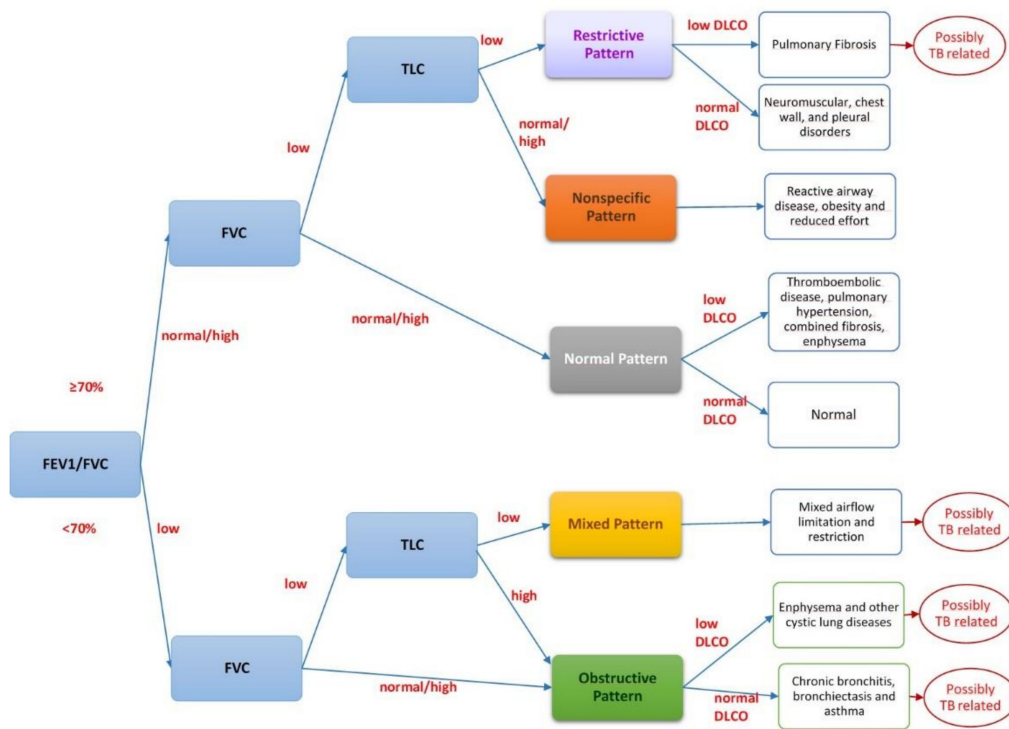


Figure 1. Interpreting spirometry. **Legend:** FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; FEV1/FVC ratio: the percentage of the FVC expired in one second; DLCO: diffusing capacity of the lung for carbon monoxide; TLC: total lung capacity.

Different tools exist to evaluate QoL, including generic questionnaires (e.g., 36-item Short Form (SF) health survey or SF-36 and its shortened version with 12 questions, the SF-12) or specific tools as the SGRQ (St. Georges’s Respiratory Questionnaire) specifically investigating QoL in chronic respiratory diseases (Table 2).

Table 2. Available tests to evaluate health-related quality of life (HRQoL).

NON-DISEASE SPECIFIC			
Questionnaire and Items	Domains	Mode and Time of Administration	Score
The Short Form (36) Health Survey SF-36v2 36 items	<ol style="list-style-type: none"> 1. Vitality 2. Physical functioning 3. Bodily pain 4. General health perceptions 5. Physical role functioning 6. Emotional role functioning 7. Social role functioning 8. Mental health 	Self-administered 10 ± 8 min	Higher scores indicate better HRQoL The correct calculation of SF-36 requires the use of special algorithms, which are strictly controlled by a private company *
Euroqol 5 dimensions EQ-5D//	<ol style="list-style-type: none"> 1. Mobility 2. Self-care 3. Usual activities 4. Pain/discomfort 5. Anxiety/depression and additional perceived health status measured through a visual-analogue scale (VAS)	Self-administered 5/10 min.	Two scores, one for the 5 domains and another for the VAS. 5 domains score: 1– scores indicate worse HRQoL VAS score: 0–100 Higher scores indicate better HRQoL
World Health Organization Quality of Life questionnaire WHOQOL-100 100 items	<ol style="list-style-type: none"> 1. Physical Health 2. Psychological 3. Level of Independence 4. Social Relations 5. Environment 6. Spirituality/Religion/Personal beliefs 	Self-administered if respondents have sufficient ability; otherwise, interviewer assisted/administered 30 min.	Produces scores relating to particular facets of QoL, scores relating to larger domains and a score relating to overall QoL and general health. Higher scores indicate better HRQoL *
World Health Organization Quality of Life questionnaire WHOQOL-BREF 26 items	<ol style="list-style-type: none"> 1. Physical health 2. Psychological 3. Social relationships 4. Environment 	Self-administered if respondents have sufficient ability; otherwise, interviewer assisted/administered 10/15 min.	Produces a quality of life profile. It is possible to derive four domain scores. Higher scores indicate better HRQoL #

Table 2. Cont.

NON-DISEASE SPECIFIC			
Questionnaire and Items	Domains	Mode and Time of Administration	Score
DISEASE SPECIFIC			
TUBERCULOSIS			
Functional Assessment of Chronic Illness Therapy FACIT-TB 47 items	1. Physical Well-Being	Self-administered 16.3 ± 3.1 min.	0–180 Higher scores indicate better HRQoL
	2. Psychological Well-Being		
	3. Function Well-Being		
	4. Social Well-Being		
	5. Spiritual Well-Being		
	6. Environment		
	7. Perception		
Pulmonary Tuberculosis Scale of the System of Quality of Life Instruments for Chronic Diseases QLICD-PT 40 items	1. Physical domain	Self-administered Approximately 10 min.	0–100
	2. Psychological domain		
	3. Social domain		
	4. TB Specific domain		
OTHER PULMONARY DISEASES			
Saint George Respiratory Questionnaire SGRQ (Asthma and COPD) 76 items	1. Symptoms	Self-administered 15/20 min.	0–100 Higher scores indicate worse HRQoL
	2. Activity		
	3. Impacts		
Maugeri Respiratory Failure Questionnaire MRF-28 (Chronic respiratory failure) 28 items	1. Daily activities	Self-administered 15 ± 6 min	0–100 Higher scores indicate worse HRQoL
	2. Cognition		
	3. Invalidity, and additional items related to fatigue, depression and problems with treatment		

Table 2. Cont.

NON-DISEASE SPECIFIC			
Questionnaire and Items	Domains	Mode and Time of Administration	Score
Quality of Life-Bronchiectasis QOL-B (<i>Non CF-Bronchiectasis</i>) 37 items	1. Respiratory Symptoms	Self-administered 4–5 min.	0–100 Higher scores indicate better HRQoL
	2. Physical		
	3. Role		
	4. Emotional		
	5. Social Functioning		
	6. Vitality,		
	7. Health Perceptions		
	8. Treatment Burden		
Asthma Quality of Life Questionnaire AQLQ (<i>Asthma</i>) 32 items	1. Symptoms	Self-administered 4–5 min.	1–7 Higher scores indicate better HRQoL
	2. Activity Limitation		
	3. Emotional Function		
	4. Environmental Exposure		

HRQoL: Health-Related Quality of Life; QoL: Quality of Life, COPD: Chronic Obstructive Pulmonary Disease; TB: tuberculosis.* <https://www.optum.com/solutions/life-sciences/answer-research/patient-insights/sf-health-surveys.html>; # Details on scoring are included in manuals available from The WHOQOL Group: <https://www.who.int/healthinfo/survey/whoqol-qualityoflife/en/index2.html>.

4.2. Pulmonary Rehabilitation

Pulmonary rehabilitation is a non-pharmacological intervention aimed at improving the physical and psychological conditions of individuals affected by chronic lung diseases [46]. It includes different interventions including, among others, the integration of an optimised medical treatment (drugs, Long-Term Oxygen Therapy-LTOT, ventilation) with physiotherapy, exercise training, education, and behavioural changes [39,43,44].

4.2.1. LTOT and Ventilation

The importance of LTOT and mechanical ventilation in supporting the management of post-TB treatment sequelae is well known [44]. Intermittent positive pressure ventilation through a nasal mask (NIPPV) applied during exercise in patients with pulmonary TB sequelae improved arterial blood gas measurements, reduced breathlessness, and increased exercise tolerance [47]. The use of a poncho (wraparound) ventilator and mouth intermittent positive pressure ventilation (MIPPV) was studied, showing beneficial results [48].

4.2.2. Physiotherapy

The role of physiotherapy in expectorating secretions is well known and largely utilised [44]. Mechanical methods of vibration massage have been proposed to prevent early post-resectional complications (atelectasis, non-specific pneumonia, residual post-resection pleural cavity, and bronchial fistulas) after surgical interventions for TB and to improve the functional status [49].

4.2.3. Exercise Training

Post TB sequelae may cause obstructive or restrictive damage and decrease the effort tolerance [50]. Patients undergoing long and/or multiple rounds of treatment may suffer from cachexia, asthenia, and muscle fatigue [44]. Before initiating a specific rehabilitation programme, patients should undergo a complete lung functional assessment, including spirometry and exercise capacity testing to enable an appropriate exercise training regime. Exercise capacity is usually based on cardiopulmonary exercise testing or walking tests (6MWT, incremental shuttle walking test (ISWT)) in order to set physical training sessions that exceed the physical loads of daily life activities [45,51–58]. Some studies documented the positive role of aerobic training on symptoms, anxiety, depression, and QoL [45,51–58].

4.2.4. Education and Psychological Counselling

Education about lung disease and its management is an important aspect of pulmonary rehabilitation [43–45]. It implies that specialists teach patients about respiratory diseases and support them through self-management training. Knowledge about the disease helps patients to understand, recognize, and treat their symptoms in order to achieve a better control of the disease in daily life. It may consist of one or more interventions, including smoking cessation, oxygen therapy, nutrition, physical activity, and the proper use of medications [43–45].

Psychological support is extremely important because depression and anxiety are often associated with TB and may contribute to fatigue and reduce physical activity. Psychological counselling should be offered either individually or in small groups as discussion will enable patients to feel more comfortable with their disease and favour their participation in social activities [43–45].

4.3. Effectiveness of Pulmonary Rehabilitation in TB

The available information on the effectiveness of rehabilitation is summarised in Table 3.

Table 3. Summary of studies reporting pre/post pulmonary rehabilitation (PR) interventions and their effects on outcome measures in post-TB sequelae patients.

Author, Year; [Ref] Country	Reference	Study Population Design Lung Function and Exercise Tests PR Duration and Setting	Outcome Measures Significantly Improved		Outcome Measures Not Significantly Improved		Gain in 6MWT or ISWT (meters/m)
			LFT	Exercise Capacity and QoL	LFT	Exercise Capacity and QoL	
Visca, 2019, Italy	[45]	43 patients; Retrospective study Spirometry, BGA, 6MWT Spontaneous walking SpO ₂ 3 weeks, inpatient	FEV1 LFEV1% FVC% PaO ₂ SaO ₂	6MWD m 6MWD % HR average SpO ₂ average (6MWT) SpO ₂ min (6MWT) Modified Borg dyspnoea final Modified Borg fatigue final SpO ₂ baseline (SW) SpO ₂ min (SW)	FVC L * FEV1/FVC * RV ^ PaCO ₂ * pH ^ FiO ₂ ^ (BGA)	HR baseline ^ HR max * SpO ₂ baseline (6MWT) ^ Modified Borg dyspnoea baseline Modified Borg fatigue baseline ^ SpO ₂ baseline (SW) * FiO ₂ ^ (6MWT, SW)	+35 m
Tada, 2002, Japan	[51]	37 patients Study design # Spirometry, BGA, 6MWT, Pimax, QoL 3.9 weeks, inpatient	VC L FEV1 L PaO ₂ Pimax	6MWD m Dyspnoea # QoL #	_#	_#	+36 m
Jones, 2017, Uganda	[52]	29 patients Prospective study Spirometry (baseline only), ISWT Sit-to-Stand, BMI, Mid upper arm circumference, QoL 6 weeks, outpatient and homebased	BMI (kg/m ²) Mid upper arm circumference (cm)	ISWT (m) Borg score after ISWT Sit-to-stand time (seconds) CCQ total score CCQ symptom score CCQ mental state score CCQ functional state scoreP HQ-9 total score Karnofsky score	Not specified	Not specified	+90 m
Ando, 2003, Japan	[53]	32 patients Prospective non randomized open trial Spirometry, BGA, 6MWT, HRQL 9 weeks, outpatient	VC L	6MWD m TDI MRC ADL	FEV1 L * PaO ₂ * PaCO ₂ *	Not specified	+42 m
Singh, 2018, India	[54]	29 patients Prospective cohort study Spirometry, 6MWT, HRQL 8 weeks, inpatient	Not specified	6MWD m CRQ	FEV1 L * FVC L * FEV1/FVC ^	MMRC *	+38 m

Table 3. Cont.

Author, Year, [Ref] Country	Reference	Study Population Design Lung Function and Exercise Tests PR Duration and Setting	Outcome Measures Significantly Improved		Outcome Measures Not Significantly Improved		Gain in 6MWT or ISWT (meters/m)
			LFT	Exercise Capacity and QoL	LFT	Exercise Capacity and QoL	
Yoshida, 2006, Japan	[55]	10 patients Observational study Spirometry, BGA, treadmill test 6MWT 3 weeks, inpatient	Not specified	VO ₂ peak (Treadmill) 6MWD m	VC L ^ VC % ^ FEV1 L ^ FEV1/FVC% * MVV L * PaO ₂ * PaCO ₂ ^ pH ^	Treadmill: VEmax L/min ^ VEmax/MVV * HRmax ^ Modified Borg dyspnoea final * Modified Borg fatigue final * 6MWT: SpO ₂ % ^ Pulse rate ^ Modified Borg dyspnoea final * Modified Borg fatigue final *	+68 m
Wilches, 2009, Colombia (Case report)	[56]	1 patient § Case report Spirometry, BGA, 6MWT, HRQL 32 weeks, inpatient	Not specified	Not specified	Not specified	6MWD * HADS * SF36 * MRC * Borg dyspnoea final *	+110 m
Betancourt-Peña, 2015, Colombia	[57]	11 patients Quasi-experimental study Spirometry (baseline only) 6MWT BMI, HRQL 8 weeks, outpatient	Not specified	6MWD VO ₂ peak (Treadmill) SGRQ HADS	BMI (kg/m ²) *	SpO ₂ baseline ^ SpO ₂ final ^ 6MWT desaturation ^ MRC *	+110.2 m
Rivera Motta, 2016, Colombia (conference abstract)	[58]	8 patients Spirometry, 6MWT, Treadmill test QoL 8 weeks, inpatient	Not specified	VO ₂ peak (Treadmill) 6MWD m SF36 SGRQ	Not specified	Not specified	+63.6

* with positive trend; ^ stable or worsened; # article in Japanese, details not reported in abstract; § post MDR-TB patient; ADL: activities of daily living score; BGA: blood gas analysis; BMI: body mass index; CCQ: clinical chronic obstructive pulmonary disease (COPD) questionnaire; CRQ: chronic respiratory disease questionnaire; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; FEV1/FVC ratio: the percentage of the FVC expired in one second; FiO₂: fraction of inspired oxygen; HADS: Hospital Anxiety and Depression Scale; HR: heart rate; HRQL: health-related quality of life; 6MWD: 6-min walk distance; 6MWT: 6-min walk test; ISWT: incremental shuttle walking test; LFT: lung function tests; mMRC: Modified Medical Research Council dyspnoea scale; MRC: Medical Research Council dyspnoea scale; MVV: maximum voluntary ventilation; PaCO₂: partial pressure of arterial carbon dioxide; PaO₂: partial pressure of arterial oxygen; pH: potential of hydrogen; PHQ-9: patient health questionnaire-9; Pimax: maximal inspiratory pressure; PR: pulmonary rehabilitation; QoL: quality of life; RV: residual volume; SaO₂: oxygen saturation in arterial blood; SF36: 36-Item Short Form Health Survey; SGRQ: St. George Respiratory Questionnaire; SpO₂: peripheral capillary oxygen saturation; SW: spontaneous walking; TB: tuberculosis; TDI: transition dyspnoea index; VC: vital capacity; VEmax: maximum minute expired ventilation; VO₂: oxygen consumption.

In the vast majority of the studies, the spirometry parameters, oxygen saturation, and exercise capacity tests (6MWT or ISWT, range 35–110 m) improved significantly. When QoL tests were performed, they also improved significantly [45,51–58]. Unfortunately the different studies reported different parameters, making a meta-analytic evaluation difficult.

4.4. Priorities for Research

A comprehensive review on TB and rehabilitation [44] recommended that future studies investigating pulmonary rehabilitation include the following information to ensure comparative analyses:

- a) Patients' characteristics (age, sex, ethnicity, etc);
- b) A description of the TB disease, (history of previous treatment, bacteriological status, drug-resistance profile, treatment history -drugs and regimens; and adverse events observed) [7,8];
- c) The physiopathological status, spirometry with response to bronchodilator, assessment of lung volumes through plethysmography, DLCO, arterial blood gas analysis, 6MWT, radiological evaluation—ideally a computerized tomography (CT) scan, a QoL evaluation with both general and a specific tools (St. George's questionnaire);
- d) Rationale and design of the pulmonary rehabilitation plan, with a pre-/post-test comparison;
- e) Cost-assessment and evaluation of programmatic feasibility [59].

5. Conclusions

This review describes the evidence available on adjuvant surgery (as described in the most important recent guidelines), as well as on the diagnosis and management of patients with post-treatment sequelae. The initial evidence supports the importance of adequate functional evaluations of these patients, which is necessary to identify those who will benefit from pulmonary rehabilitation.

A collection of high-quality standardised variables would allow the research to advance in the understanding of the need for, and the effectiveness of, pulmonary rehabilitation both at the individual and at the programmatic level.

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