Review Article


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A B S T R A C T

Currently, tuberculosis (TB) and COVID-19 account for substantial morbidity and mortality worldwide, not only during their acute phase, but also because of their sequelae. This scoping review aims to describe the specific aspects of post-TB and post-COVID (long-COVID-19) sequelae, and the implications for post-disease follow-up and rehabilitation.

In particular, evidence on how to identify patients affected by sequelae is presented and discussed. A section of the review is dedicated to identifying patients eligible for pulmonary rehabilitation (PR), as not all patients with sequelae are eligible for PR. Components of PR are presented and discussed, as well as their effectiveness.

Other essential components to implement comprehensive rehabilitation programmes such as counselling and health education of enrolled patients, evaluation of cost-effectiveness of PR and its impact on health systems as well as research priorities for the future are included in this scoping review.

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Introduction

Both, tuberculosis (TB) and COVID-19 currently account for substantial morbidity and mortality worldwide. Both can lead to cure, naturally or following treatment. However, what actually happens to people after the two diseases are considered cured is still not fully known, and is presently attracting major clinical and scientific interest. The aim of this scoping review is to describe these specific post-diseases aspects, and the implications for post-disease follow-up and rehabilitation.

Post TB lung disease (PTLD)

Over the last decades National TB Control Programmes concentrated their efforts on diagnosis and treatment of cases of sputum smear positive TB. The main target was to curb TB transmission by early diagnosis and successful treatment of infectious cases. This approach proved to be effective in reducing TB transmission and decreasing the burden of disease in many countries.
Post-COVID sequelae may affect several organs or body systems, but in this scoping review the focus will be on the lungs. Pulmonary fibrosis is a known sequela of severe lung damage secondary to many aetiologies including respiratory infections.35,36 Although the precise pathophysiological mechanisms underlying this complication remain unknown, the immune activation and alveolar epithelial injuries might lead to an aberrant reparative response with accumulation of fibroblasts and excessive deposition of collagen.35 Of note, persistent radiological signs of pulmonary fibrosis can be observed after 3 months since acute phase of disease in previously hospitalized patients.37,38

**Methodology**

PTLD has reached internationally acknowledged relevance during the last few years,1,8–10,12–15 thus we revised all international literature of the last 5 years searching on PubMed the following keywords: ‘tuberculosis’, ‘TB’, ‘post-TB’ and ‘sequelae’ or ‘rehabilitation’. Since COVID-19 has been recently identified, we revised all international literature searching on PubMed the following keywords: ‘tuberculosis’, ‘TB’, ‘post-TB’ and ‘sequelae’ or ‘rehabilitation’.

The selection of relevant articles among those identified for both conditions started with reading the abstract. The second phase consisted on reading the whole text of the relevant articles. Additional articles were identified through accurate evaluation of references of the selected papers.

**Identifying patients with sequelae**

**Post-TB sequelae**

PTLD includes structural and functional lung sequelae, with varying severity, such as fibrosis, pleural thickening, cavitation, bronchiectasis, lung function deficits (obstruction, restriction and mixed patterns), pulmonary hypertension, and colonization and infection with Aspergillus fumigatus, non-tuberculous mycobacteria and other bacteria.7,11,12,39,40 PTLD patients have a two-fold higher risk of spirometry abnormalities in comparison to the general population,10 and approximately 10% of them have lost more than half of lung function.41 As a consequence, persistent respiratory symptoms are common, and include residual cough, dyspnoea, wheeze, and reduced exercise capacity.42 In a cross-sectional study with 145 adults who completed TB treatment, 38% of patients had airflow obstruction, 58% low forced vital capacity (FVC), and the most frequent respiratory symptoms were wheeze (42%), dyspnoea (25%), and cough (19%).40 Functional impairment is even more prevalent in drug-resistant TB cases.41 In a prospective study with 405 patients in Malawi, 44% had bronchiectasis, and after 1 year, approximately 30% had respiratory symptoms and one in five had a decline of 100 mL in forced expiratory volume in one second (FEV1).44 In accordance with these findings, in a Brazilian cohort of PTLD patients followed-up for a mean time of 8.3 ± 4.9 years, a decline in FEV1, FVC, total lung capacity (TLC), Diffusing Capacity for carbon monoxide (DLCO), and six-minute walking test (6MWT) was demonstrated.45 The most important predictors of PTLD are generally a delay in diagnosis, multiple TB treatments, and drug-resistant TB.11

Every patient completing TB treatment should be clinically evaluated to identify PTLD, ideally as soon as possible at the end of treatment.1 Essential examinations/investigations recommended to identify post-TB sequelae include: clinical assessment (history, examination), chest imaging, in particular, chest X-ray and CT, where available and affordable, to detect fibrosis, cavities, pleural thickening, bronchiectasis, pulmonary hypertension,
secondary bacterial and fungal infections; arterial blood gas analysis and/or pulse oximetry, pulmonary function testing (PFT), including 6MWT, spirometry, plethysmography and DLCO to detect obstructive, restrictive and mixed patterns; and cardiopulmonary exercise testing to assess the integrative responses of the cardiovascular, respiratory and musculoskeletal systems to incremental exercise in patients with PTLD and subjective evaluation (symptoms score and QoL questionnaire). In situations where all the examinations listed above cannot be performed, the following examinations/investigations should be prioritized: clinical history; evaluation of QoL; evaluation of functional status; 6MWT; spirometry; pulse oximetry, and chest X-ray.

**Identifying patients eligible for pulmonary rehabilitation (PR)**

**Post-TB patients**

Clinical Standards on PTLD recommended that former TB patients with clinical and radiological signs and symptoms consistent with post-TB sequelae should be evaluated for PR. Patients with functional impairments such as reduced pulmonary function (airflow obstruction or restriction or mixed abnormalities, and/or impaired diffusing capacity for carbon monoxide), abnormal blood gas (PaO₂ < 80 mmHg and/or PaCO₂ > 45 mmHg and/or nocturnal and exercise-induced desaturation), and reduced exercise capacity should also benefit from PR. In addition, PR can be indicated in the presence of comorbidities, like chronic obstructive pulmonary disease, asthma, bronchiectasis, pulmonary fibrosis, and pulmonary hypertension. PR is also beneficial for patients with at least one hospitalization or two exacerbations in the last 12 months, and impairment in QoL.

**Post-COVID-19 patients**

Clinical Standards on post-COVID-19 sequelae recommend that every patient with previous history of COVID-19, lung function impairment (airflow obstruction or restriction or mixed and/or impaired DLCO), reduced exercise tolerance and related impairment in QoL and other relevant signs or symptoms (fatigue or exhaustion or asthma or weakness; respiratory symptoms, dyspnoea, cough, chest pain); PaO₂ < 80 mmHg and/or PaCO₂ > 45 mmHg and/or exercise-induced desaturation) should be evaluated for PR.

Debeaumont et al. evaluated COVID-19 patients, 6 months after their discharge from the hospital, and showed that persistent dyspnoea was associated with reduced physical fitness. Those patients should benefit from PR. In addition, patients who had severe acute illness, and those with abnormal chest X-ray or CT or reduced DLCO will probably need early and effective respiratory rehabilitation.

**Post-ICU patients with COVID-19** should be a target population for rehabilitation. Patients with severe lung impairment during COVID-19 acute illness are prone to pulmonary function tests and 6MWT alterations, and are a subgroup of patients that could also benefit from PR.

**Components of pulmonary rehabilitation**

Pulmonary rehabilitation programmes cannot be planned without considering local organisation of health services. They should also be organised according to feasibility, effectiveness and cost-effectiveness criteria.

Knowledge on PR is mostly derived from experiences in chronic respiratory diseases, especially chronic obstructive pulmonary disease (COPD). In this setting, PR showed to be relatively more cost-effective than pharmacotherapy. There are obviously notable differences between these conditions, PTLD and/or post-COVID.

Any programme, to qualify as PR, should have some minimum and unavoidable requirements. These include comprehensive baseline and post-PR outcome measurements, a structured and supervised exercise training programme, an education/behavioural
### Table 1
Proposed components of a pulmonary rehabilitation programme for PTLD or for COVID survivors.

<table>
<thead>
<tr>
<th>Components</th>
<th>Indication</th>
<th>Interventions</th>
<th>Adoptions to special settings and situations</th>
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<tbody>
<tr>
<td><strong>Aerobic exercise:</strong> Endurance Training (limited evidence on COVID)</td>
<td>Impaired exercise capacity, limited by dyspnoea, fatigue and or other symptoms. Restriction in daily life activities.</td>
<td>Treadmill and/or cycle-ergometer 30 min. 2–5 times/week for 4–8 weeks Continuous or interval training Low-Intensity (40–60%) or High-Intensity (60–80%) set according to maximal heart rate (220-age) or maximal oxygen consumption or the equation of Luxton or symptom limited (target Borg scale ≤4) In- or out-patients or tele-monitoring Suggest maintenance program</td>
<td>Free walks 30 min. 2–5 times/week for 4–8 weeks Intensity set according to perceived symptoms (target Borg scale ≤4) Out-patients or home setting Suggest maintenance program</td>
</tr>
<tr>
<td><strong>Strength training:</strong> Upper and lower extremities (limited evidence on TB and COVID)</td>
<td>Sarcopenia, reduced strength of peripheral muscles. Lower muscle weakness with risk for falls. Impaired activities of daily living involving the upper extremities (including dressing, bathing, and household tasks)</td>
<td>Free weights (dumbbells and ankle-brace) 20–30 min. 2–5 times/week for 4–8 weeks 2–3 set of 6–12 repetitions Intensity set to 80% of MVV or 1MR and/or adjusted on perceived muscles fatigue (target Borg scale ≤4) In or out-patients or tele-monitoring Suggest maintenance program</td>
<td>Free weights (dumbbells and ankle-brace) 20–30 min. 2–5 times/week for 4–8 weeks 2–3 set of 6–12 repetitions Intensity set according to perceived muscles fatigue (target Borg scale ≤4) Out-patients or home setting Suggest maintenance program</td>
</tr>
<tr>
<td><strong>Inspiratory muscle training:</strong> Calisthenics and stretching exercises (limited evidence on TB and COVID)</td>
<td>Impaired daily life activities Calisthenics exercises Stretching exercises Nordic walking or Aqua fitness or home exercise Intensity/load set at 30–60% of maximal inspiratory pressure Interval training, 3 sets with 10 breaths followed by 1-minute break between each set. 15–20 min. 2–5 times/week for 4–8 weeks</td>
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<tr>
<td><strong>Respiratory exercise:</strong> Dynamic hyperinflation Dyspnoea</td>
<td>2–5 times per week for 30 min Adaptive breathing strategies Yoga breathing Pursed-lips breathing Computer-aided Breathing feedback 2–4 times per week for 30 min each Structured and comprehensive educational programmes Age specific, gender-sensitive, delivered in the local language and extended to family and/or care-givers Individual or group sessions 15–60 min. Importance of physical activity and exercise to improve quality of life Maintaining results achieved with pulmonary rehabilitation (follow-up plan) Advantages/importance of smoking cessation and risk of comorbidities (e.g., diabetes, etc.) Importance of adhering to medical prescriptions in terms of management of comorbidities and vaccinations Achieving an optimal healthy life style</td>
<td>Adaptive breathing strategies Yoga breathing Pursed-lips breathing Computer-aided 2–4 times per week for 30 min each Structured and comprehensive educational programmes Age specific, gender-sensitive, delivered in the local language and extended to family and/or care-givers Individual or group sessions 15–60 min. Importance of physical activity and exercise to improve quality of life Maintaining results achieved with pulmonary rehabilitation (follow-up plan) Advantages/importance of smoking cessation and risk of comorbidities (e.g., diabetes, etc.) Importance of adhering to medical prescriptions in terms of management of comorbidities and vaccinations Achieving an optimal healthy life style</td>
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<tr>
<td><strong>Education:</strong> Impaired/reduced self-efficacy and collaborative Self-Management</td>
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<tr>
<td><strong>Psychological support:</strong> Depression, anxiety and cognitive dysfunction</td>
<td>Psychological assessment Psychological support Relaxation technique Consider self-help group Choose the technique suitable for the subject among those available, based on respiratory capacity, mucus rheology, collaboration and patient preferences 15–30 minutes one or more times/day Choose the duration of treatment based on chronic (long term) or acute problem (short term) Suggest maintenance program when needed</td>
<td>Psychological assessment Psychological support Relaxation technique</td>
<td></td>
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<tr>
<td><strong>Airway clearance techniques:</strong> Difficult to remove secretions or mucous plugs. Frequent bronchial exacerbations (≥2/year). Concomitant diagnosis of bronchiectasis.</td>
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programme intended to foster long-term health-enhancing behaviour, and provision of recommendations for home-based exercise and self or supervised physical activity programmes.\textsuperscript{1–73}

Some evidence on effectiveness of PR programmes targeting PTLD patients exists only in selected settings with adequate resources, logistics, and expert healthcare providers.\textsuperscript{74–77} Recently, a few positive experiences of PR programmes targeting post-COVID patients have been reported.\textsuperscript{31,78–85} Depending on the residual individual deficits in post–COVID patients, PR should be offered with the objective to improve respiratory, physical and psychological impairments.\textsuperscript{31,78,86–88}

PR programmes should be adapted to the context and resources available to make them as accessible as possible for those benefiting from it (including children and adolescents) in different settings.\textsuperscript{9,89–95} The core components of a PR programme are summarised in Table 1.\textsuperscript{96–105}

The Global Tuberculosis Network (GTN) is monitoring PR pilot testing activities and it will share the results when available.

**Evaluation of effectiveness of pulmonary rehabilitation**

Implementation of a rehabilitation programme implies a plan to evaluate its effectiveness. The main recommendation is generally to compare the core variables before and after rehabilitation.\textsuperscript{1}

As previously discussed, on completion of TB treatment or at discharge from hospital post COVID, before starting a PR programme tailored to a patient’s needs, a comprehensive assessment is necessary. Therefore, having a baseline assessment, i.e., before programme, the simplest way to evaluate the effectiveness of PR is to compare the core variables at baseline vs. at the end of the programme.\textsuperscript{74–76,80} The minimal evaluation set includes the patient’s functional exercise capacity, dyspnoea and health status.\textsuperscript{8,9,17} If possible, a series of health outcomes including social, economic and psychological impact should be evaluated in clinical studies.\textsuperscript{8,17}

The most popular tool to measure exercise capacity is the 6MWT.\textsuperscript{73–75,90} Nevertheless, the cardiopulmonary exercise test or the incremental shuttle walk test and the 5 repetition ‘sit to stand’ test are recommended too.\textsuperscript{89,108} Regarding PTLD patients, PR has proven to significantly improve the distance covered during the 6MWT (by approximately 35–45 m), an improvement comparable to that observed in subjects with COPD.\textsuperscript{107} QoL evaluation is extremely important, but it is usually measured by questionnaires, with inter-studies variability. Nevertheless, the questionnaires whose use actually show significant improvement were the St George’s Respiratory Questionnaire, the Short Form Health Survey 36 and the Clinical COPD questionnaire.\textsuperscript{107–109} Similarly, the clinical evaluation based on symptoms (dyspnoea, chest pain, haemoptysis and cough) employed different scales. Unfortunately, no data are available on other strong outcomes such as mortality and morbidity.

**Follow-up**

Monitoring of patients undergoing PR is important during PR and at its end, this should occur with a formal evaluation. The
impact of PR needs to be assessed also in the longer term since the early (end of programme) evaluation could miss clinical problems arising later and miss if the benefits achieved after PR are maintained and for how long. Any follow-up has to be arranged based on local feasibility and organisation of health services. In fact, for TB, individuals completing an episode of TB treatment, especially those with residual pulmonary sequelae (e.g., residual cavitations), and/or affected by other infections (e.g., aspergilloma and/or non-tubercular mycobacteria) remain at elevated risk of recurrent TB. Recurrence may occur due to endogenous reactivation or following exogenous reinfection.

Special considerations

Patients with sequelae, but without apparent need (or with contra-indications) for PR have a lower priority. However, if feasible, their follow-up can also be considered. In consideration of the risk of recurrence PTLD patients have, infection control and prevention measures (and reassessment of the patient’s potential contagiousness) are recommended during all steps of the process.

Counselling & health education

Every patient who participates in a PR programme should undergo counselling/health education. Patients should be counselled about their disease, available treatments, benefit of healthy lifestyle, and smoking avoidance. Booklets, videos, and telehealth can be used for patient education, and the patient’s family should be encouraged to participate. Counselling/health education should include a follow-up plan to maintain the results achieved with PR (Table 2).

Table 2

Recommended topics for counselling/health education.

- Basic principles of disease: epidemiology, clinical aspects, transmission, diagnosis, and treatment
- Simple concepts of infection control (e.g. how long will they be considered contagious)
- Common symptoms they might experience after acute disease (post-COVID-19 or post-TB)
- How to monitor and manage their symptoms at home, and when they should go to a health facility/call a doctor
- Support for lifestyle interventions, such as physical activity, adequate nutrition, and smoking cessation
- Management of comorbid physical and mental health conditions
- Risks of reinfection and how they can manage this risk
- Address stigmatization of their COVID-19/TB infection and ongoing symptoms
- Maintaining results achieved with pulmonary rehabilitation (follow-up plan)

Evaluate cost-effectiveness and impact on health systems

PR is one of the most cost-effective interventions in patients with COPD, resulting in substantial cost savings through the prevention of readmission. Although PR is associated with significant improvements in pulmonary function in post-TB patients, and could accelerate the recovery of lung disease in post-COVID-19 patients, there is a need for randomized-controlled trials to identify effective and cost-effective strategies to deliver PR in different settings and populations.

In addition to cost-effectiveness, we have to consider the feasibility of PR programmes in low and high burden countries. In fact, the idea inspiring the recently published reference document was to generate universal standards, offering to countries/settings an

Table 3

Research priorities.

<table>
<thead>
<tr>
<th>Research priority</th>
<th>Proposed type of study</th>
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<tr>
<td><strong>TB</strong></td>
<td><strong>COVID</strong></td>
</tr>
<tr>
<td>1. To describe the frequency and severity of PTLD in different populations and subgroups of TB patients over time since the completion of TB treatment, including in children and adolescents</td>
<td>To describe the frequency and severity of post-COVID-19 disease in different populations and subgroups of COVID survivors over time since hospital discharge or viral clearance, including in children and adolescents</td>
</tr>
<tr>
<td>2. To identify risk factors for severe PTLD and associated poor health outcomes, including increased mortality</td>
<td>To identify risk factors for severe post-COVID-19 and associated poor health outcomes, including increased mortality</td>
</tr>
<tr>
<td>3. To quantify the health and economic impact of PTLD at the individual and population level, including the impact of managing PTLD on health systems</td>
<td>To quantify the health and economic impact of post-COVID-19 at the individual and population level, including the impact of managing post-COVID on health systems</td>
</tr>
<tr>
<td>4. To identify feasible, accurate and cost-effective tools to evaluate patients at the end of TB treatment for their risk of PTLD and subsequent poor health outcomes</td>
<td>To identify feasible, accurate and cost-effective tools to evaluate patients at the end of hospitalization and/or at viral clearance for their risk of post-COVID and subsequent poor health outcomes</td>
</tr>
<tr>
<td>5. To develop optimal approaches and algorithms to diagnose and manage PTLD, and to discriminate between PTLD and recurrent TB</td>
<td>To develop optimal approaches and algorithms to diagnose and manage post-COVID</td>
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<tr>
<td>6. To identify effective and cost-effective strategies to prevent PTLD during anti-TB treatment, including, for example, adjuvant therapies and interventions to reduce concomitant risk factors for poor lung health outcomes (e.g., smoking cessation programmes)</td>
<td>To identify effective and cost-effective strategies to prevent post-COVID during hospitalization or home treatment, care, including, for example, adjuvant therapies and interventions to reduce concomitant risk factors for poor lung health outcomes (e.g., smoking cessation programmes)</td>
</tr>
<tr>
<td>7. To identify effective and cost-effective strategies to deliver pulmonary rehabilitation in specific sub-groups (using standard measures of minimum clinically important difference), including individual patient follow-up in different settings and populations</td>
<td>To identify effective and cost-effective strategies to deliver pulmonary rehabilitation in specific sub-groups (using standard measures of minimum clinically important difference), including individual patient follow-up in different settings and populations</td>
</tr>
<tr>
<td>8. To investigate the role of patient education programmes in improving long-term health outcomes post-TB</td>
<td>To investigate the role of patient education programmes in improving long-term health outcomes post-COVID</td>
</tr>
<tr>
<td>9. To investigate the role of social protection and support programmes in improving health outcomes and quality of life among former TB patients</td>
<td>To investigate the role of social protection and support programmes in improving health outcomes and quality of life among COVID survivors</td>
</tr>
<tr>
<td>10. To identify a set of standard indicators for the surveillance of PTLD that are feasible to implement within national TB programmes</td>
<td>To identify a set of standard indicators for the surveillance of post-COVID that are feasible to implement within national health programmes</td>
</tr>
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</table>

ideal guide where to go, although not all countries or settings are immediately able to meet them. COVID-19 has impacted healthcare systems globally, with many services reduced or temporarily cancelled. In this sense, several PR programmes had to be adapted to ensure their continuity. Due to social distancing, and movement restrictions preventing attendance to in- or outpatient PR programmes, traditional face-to-face rehabilitation needs to be adapted through the use of tele-rehabilitation. It has been shown that tele-rehabilitation is as effective as traditional PR, and could alleviate burden on health systems. However, PR programmes should have a plan to work with a limited rehabilitation team. In a Northern Italian rehabilitation hospital, organizational changes were required to overcome work overload during COVID-19 pandemic. Remodelled tasks, development of algorithms on patient management, and use of online communications systems helped to relieve the workload.

**Research priorities for the future**

There is obviously a strong need for extensive research on the epidemiology, assessment and management of both PTLD and post-COVID in adults and children to gain a better understanding on the two diseases and to guide the development of future standards and guidelines. Political commitment and appropriate funding mechanisms will be essential to enable research in these fields in the forthcoming years. Key research priorities are highlighted in Table 3.

Among others, the priority studies needed to respond the main research questions include cohort, case–control, cross-sectional, diagnostic accuracy and operational research studies, as well as randomized controlled trials.

**Conclusions**

Several patients continue to require care after completing TB treatment or after recovering from acute COVID. There is increasing evidence on the PR interventions useful for PTLD; however, full implementation of these programmes is still lagging behind. Beyond implementing what is already acknowledged as effective, there is currently a strong need to investigate additional PR interventions in PTLD and to accumulate the increasing evidence on approaches to PR in post-COVID disease. Research priorities set to improve our understanding of the measures that will prove to be most effective (and cost-effective) to prevent, detect and treat PTLD and post-COVID are listed in this scoping review. Since the evidence currently available is modest, periodical evaluation on PR in these two conditions is mandatory to guide clinicians, TB programme managers and public health officers towards evidence-based planning and implementation of adequate measures to assess and manage them.

**Conflict of interest**

The authors declare that they have no conflict of interest.

**References**


