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Host Response Variability in Post-Tuberculosis Pulmonary Fibrosis and Related Structural and Functional Pulmonary Sequelae: A Scoping Review

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Systematic Review

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Host Response Variability in Post-Tuberculosis Pulmonary Fibrosis and Related Structural and Functional Pulmonary Sequelae: A Scoping Review

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Take-home message: Research on post-tuberculosis pulmonary fibrosis remains largely descriptive. IL-6, TNF-α and matrix metalloproteinases are the most consistent host signals and the leading targets for validation and host-directed prevention trials.

Word count: main text approximately 4,250 words (excluding abstract, references, tables and figure captions); abstract 249 words; 2 tables and 3 figures; 43 references. Supplementary material: Tables S1 to S9 and Figures S1 and S2.

Abstract

Background: Pulmonary fibrosis is among the most consequential forms of post-tuberculosis lung disease (PTLD), leaving permanent structural damage in people already cured of infection. Outcomes vary widely between individuals with comparable microbiological cure, and there is currently no way to predict who will develop fibrosis, prevent it, or treat its underlying biology. This scoping review mapped the evidence on host factors associated with variability in post-tuberculosis pulmonary fibrosis and related structural and functional sequelae.

Methods: Following PRISMA-ScR guidance, six databases were searched from inception to 31 August 2026. Studies of adults with treated pulmonary tuberculosis that examined host biological, molecular or clinical factors in relation to fibrotic, structural or functional outcomes were included. Two reviewers independently screened and appraised studies, and findings were charted against a predefined domain framework and an evidence gap map.

Results: Twenty studies were included, mostly observational and from high-burden settings. Evidence centred on clinical and radiological characterisation. Where biology was measured, persistent inflammation (IL-6, TNF-α) and matrix metalloproteinase activity were the most consistent signals associated with fibrotic and structural outcomes. Genetic, transcriptomic and metabolomic evidence was sparse, and no eligible study addressed epigenetic or microbiome factors.

Conclusions: Research on post-tuberculosis pulmonary fibrosis remains largely descriptive, and the critical gap is validated, targetable host biology. IL-6, TNF-α and matrix metalloproteinases are the strongest candidates and the priority for validation. Defining these pathways would open post-tuberculosis fibrosis to precision medicine, identifying survivors at risk early and treating them before irreversible damage is established.

Keywords: post-tuberculosis lung disease; pulmonary fibrosis; host response; biomarkers; scoping review

1. Introduction

Tuberculosis (TB) remains one of the leading causes of death from a single infectious agent, with an estimated 10.8 million incident cases and 1.25 million deaths reported globally in 2023 [1,2]. Although appropriate anti-tuberculosis chemotherapy achieves microbiological cure in the majority of patients, a substantial proportion of survivors are left with chronic respiratory impairment, now collectively recognised as post-tuberculosis lung disease (PTLD)[3–6]. Recent cohorts report that 50% to 74% of people successfully treated for pulmonary tuberculosis are left with PTLD, and that fibrosis is the most common radiological abnormality, present on CT in 57% of one cohort [6,24,25]. The damage is anatomical and permanent, so these survivors face persistent breathlessness, exercise limitation and increased mortality despite having been cured of the infection itself. PTLD encompasses a heterogeneous spectrum of structural and functional abnormalities, including airflow obstruction, restrictive impairment, bronchiectasis, cavitation and pulmonary fibrosis [7,8]. A recent systematic review and meta-analysis confirmed that abnormal lung function persists in a large proportion of pulmonary-TB survivors, establishing PTLD as one of the most common yet under-recognised chronic respiratory conditions worldwide [3,9]. Among these sequelae, pulmonary fibrosis is particularly consequential, being largely irreversible and associated with persistent respiratory symptoms, impaired lung function, reduced quality of life and increased long-term mortality [8,10].

A clinically important feature of TB is that respiratory outcomes vary widely: some individuals recover with minimal residual damage, whereas others develop extensive pulmonary fibrosis despite comparable microbiological cure and treatment [4,7]. This heterogeneity is increasingly attributed to variability in the host response, in which dysregulated immune and inflammatory pathways drive tissue destruction and aberrant repair [11,12]. In particular, matrix-metalloproteinase-mediated extracellular-matrix turnover and sustained cytokine signalling have been implicated in the transition from inflammation to established fibrosis [7,11]. Importantly, inflammatory and metabolic activity may persist within the lung beyond microbiological cure, suggesting a potentially modifiable window of ongoing injury [13]. Beyond immunopathology, host susceptibility is thought to be shaped by genetic, transcriptomic, proteomic, metabolomic and microbiome factors, together with clinical modifiers such as HIV co-infection, diabetes, smoking and disease severity [7].

Evidence concerning these host determinants, however, is dispersed across immunology, respiratory medicine, radiology, genetics and molecular biology, and has not been comprehensively mapped [14]. Recent consensus efforts have sought to standardise the field through an agreed research case definition and clinical standards for PTLD, reflecting growing recognition of the condition [8,15]. Existing reviews, however, have largely addressed the epidemiological burden, policy and clinical management of PTLD rather than the biological host-response factors that underlie fibrotic outcomes [4,16]. Consequently, the breadth, nature and integration of host-response evidence in post-tuberculosis pulmonary fibrosis have not been mapped, and it is currently unclear which host factors have been investigated, how they relate to defined fibrotic outcomes, and where the principal knowledge gaps lie [17]. A systematic mapping of this dispersed evidence is therefore needed to characterise host-response heterogeneity after pulmonary TB. The purpose is practical. Identifying which host pathways drive fibrotic damage is how candidate drug targets are found, and it is the route to treatments given during or soon after TB therapy that prevent fibrosis rather than managing its consequences once the lung is already scarred.

Therefore, this review aimed to systematically identify, map and synthesise the available evidence on host factors associated with variability in the development, severity and persistence of pulmonary fibrosis following treatment for pulmonary tuberculosis in adults. The review had three specific objectives. The first was to map the clinical and multi-omic landscape of host factors studied in post-TB lung disease. The second was to examine how these host factors relate to fibrotic, structural and functional pulmonary outcomes, and to identify candidate biomarkers and pathways. The third was to establish where the evidence gaps lie.

2. Methods

The review methodology follows Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) [18] standards. The protocol was registered with the Open Science Framework on 25 August 2026 (https://osf.io/4xnrz) [19] to provide a systematic and replicable process.

2.1 Search Strategy

A comprehensive literature search was undertaken to identify published evidence examining host-response variability and factors associated with post-tuberculosis pulmonary fibrosis and related structural or functional sequelae. PubMed/MEDLINE, Web of Science Core Collection, Scopus, ScienceDirect, Cochrane Library, and CINAHL were searched from database inception to 31 August 2026. The search strategy combined controlled vocabulary, where available, with free-text terms addressing three core concepts: pulmonary tuberculosis; post-tuberculosis pulmonary fibrosis or related post-TB pulmonary sequelae; and host biological, molecular or clinical factors. Synonyms and spelling variants were incorporated using Boolean operators (AND/OR) and truncation where supported by individual databases. Scopus and ScienceDirect limit search strings to eight key terms, so truncated strings were used for these two databases. The search was intentionally broad to capture evidence relating to immune and inflammatory responses, cytokines, matrix-remodelling pathways, genetic and epigenetic susceptibility, transcriptomic, proteomic and metabolomic signatures, microbiome, tissue repair and relevant clinical predictors. Database-specific search strategies are presented in Table S6. Reference lists of included studies and relevant reviews were additionally examined to identify potentially eligible studies not retrieved through the electronic database searches.

2.2 Study Selection and Screening

Search results were exported in the available bibliographic formats (.bib, .csv and .txt) and imported into Zotero for duplicate removal. The deduplicated library was then screened. Two authors (VV and SC) screened titles and abstracts and then assessed potentially eligible full texts against the predefined eligibility criteria and the Population-Concept-Context (PCC) framework [20] as shown in Table S7. Disagreements were resolved through discussion and consensus, with third-reviewer (AV) adjudication planned where necessary. Eligibility was intentionally defined around post-tuberculosis pulmonary fibrosis and its related structural and functional pulmonary sequelae, rather than fibrosis as an isolated outcome. This broader approach was prespecified because pulmonary fibrosis may coexist with other PTLD phenotypes, including bronchiectasis, cavitation and persistent functional impairment. Studies were therefore eligible when they examined host biological, molecular or clinical

factors in relation to fibrosis, fibrotic remodelling, or relevant persistent post-treatment structural or functional lung abnormalities.

1.1 Data charting

Data were charted independently by two reviewers (VV and SC) using a structured charting form developed by the review team. Charted variables comprised study identifiers, country and setting, study design, population and diagnostic basis, sample size, interventions, host factors and their domain classification, outcome measures and the principal reported associations. Discrepancies were resolved by discussion, with third reviewer (AV) adjudication available where required.

2.3 Quality Appraisal of Included Studies

Although critical appraisal is not mandatory in scoping reviews, it was undertaken to provide a descriptive assessment of the methodological characteristics of the included evidence and to support transparent interpretation of the findings. This approach is consistent with PRISMA-ScR, which recommends reporting the rationale and methods for critical appraisal when it is performed. Two reviewers independently assessed the methodological quality of the included studies using the Joanna Briggs Institute (JBI) Critical Appraisal Checklists from the 2024 JBI Manual for Evidence Synthesis, selected according to study design: Checklist for Cohort Studies, Checklist for Case-Control Studies, Checklist for Analytical Cross-Sectional Studies, and Checklist for Quasi-Experimental Studies [21]. The non-randomised intervention study was additionally assessed using the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) framework [22]. Disagreements between reviewers were resolved through discussion and consensus, with third-reviewer adjudication planned where consensus could not be achieved. Appraisal findings were summarised descriptively and were not used as an exclusion criterion or to weight individual studies, consistent with the evidence-mapping purpose of a scoping review.

2.4 Data synthesis

Data extracted from the included studies were analysed using a predominantly descriptive and evidence-mapping approach, consistent with the objectives of a scoping review [20]. Study characteristics, geographical distribution, study designs, sample sizes, host-factor domains, biomarkers, outcome measures and reported associations were summarised using

frequencies, proportions, tables and graphical displays. Host factors were categorised into predefined domains, including immune/inflammatory, genetic, epigenetic, transcriptomic, proteomic, metabolomic, microbiome, tissue-repair/remodelling, clinical and radiological domains. The frequency and co-occurrence of these domains across studies were mapped to identify areas of concentration and under-investigation. Reported host-factor-outcome relationships were further charted according to fibrotic, structural, functional and inflammatory outcomes, allowing construction of an evidence-gap map. A descriptive narrative synthesis was undertaken to identify recurring biological pathways, patterns of association, differences between study populations and methodological or conceptual gaps. Where studies reported comparable biomarkers or outcomes, findings were described comparatively; however, effect estimates were not statistically pooled because of substantial heterogeneity in study designs, populations, host-factor measurements, definitions of fibrosis and outcome ascertainment. Mechanistic relationships were presented as reported or putative associations rather than causal effects, given the predominantly observational nature of the evidence.

3. Results

3.1 Study selection

The study selection process is presented in the PRISMA flow diagram (Figure 1). A total of 16,607 records were identified from six electronic databases: PubMed (n=236), CINAHL (n=411), Scopus (n=1,235), ScienceDirect (n=14,285), Cochrane Library (n=105), and Web of Science (n=335). Before screening, 4,835 duplicate records were removed, and 3,785 records were screened using an AI-assisted screening tool (Elicit, September 2026) and excluded according to a prespecified relevance rule based on the review eligibility criteria: records were considered ineligible when they did not address tuberculosis/post-tuberculosis disease, pulmonary fibrosis or relevant structural/functional sequelae, and host biological, molecular or clinical factors. The remaining 7,987 records underwent title and abstract screening. Of these, 3,425 were excluded and 4,562 reports were sought for retrieval. A total of 856 reports could not be retrieved despite repeated library/database searches, interlibrary-loan requests and attempts to contact authors where contact information was available, leaving 3,706 reports for full-text assessment. A total of 3,686 reports were excluded because they did not

report relevant host factors (n=1,543), did not address fibrotic remodelling (n=456), were reviews (n=584), or were opinion pieces (n=1,103). An additional 66 records were identified through other sources; 46 could not be retrieved and the remaining 20 were assessed but excluded for not meeting the inclusion criteria. Thus, 20 studies were included, all originating from the database-search arm.

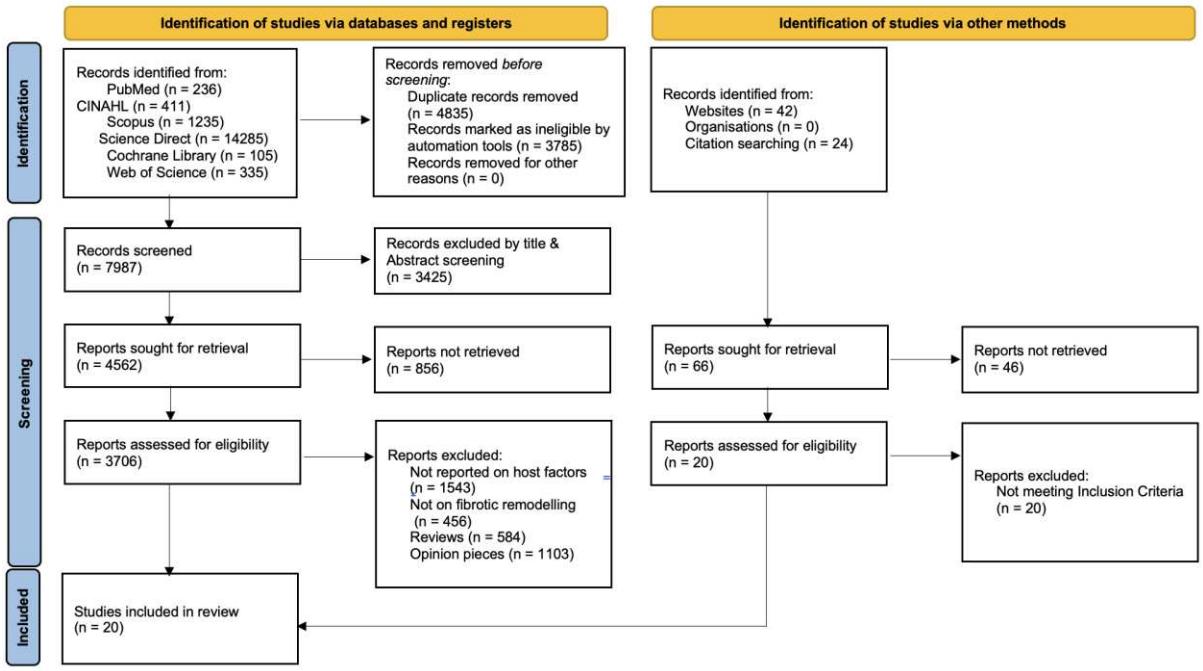


Figure 1: PRISMA Flow Diagram

3.2 Characteristics of the included studies

Twenty studies were included, representing diverse geographical settings across Asia, Africa, Europe, Australia, and the Americas. The evidence base comprised predominantly observational designs, including prospective and retrospective cohorts, cross-sectional and case-control studies, longitudinal investigations, and translational molecular studies. Study populations primarily included adults with treated or microbiologically cured pulmonary tuberculosis, with several studies focusing on multidrug-resistant TB, HIV-associated TB, or established post-TB structural lung disease. Sample sizes ranged from small tissue-based investigations (19 post-TB lung tissues and 13 controls) to a population-based COPD registry in which 267 participants had a TB history or post-TB lung changes [23]. The host-factor domains represented were immune and inflammatory mediators, genetic and proteomic markers, transcriptomic signatures, tissue-remodelling pathways, and clinical and radiological characteristics. Two groups of biomarkers dominated. The first comprised inflammatory cytokines, chiefly TNF-α and IL-6, with IL-17A and IL-1β reported less often. The second comprised matrix metalloproteinases, principally MMP-1, MMP-2, MMP-8 and MMP-9, alongside VEGF and other chemokines. Outcomes were assessed structurally (chest radiography, HRCT or CT, quantitative CT and FDG-PET/CT), functionally (spirometry, diffusion capacity and six-minute walk testing), and by quality-of-life measures and molecular assays. Pulmonary fibrosis, bronchiectasis, cavitation, airflow obstruction, restrictive impairment, persistent inflammation and other structural sequelae were reported. Notably, fibrosis was identified in 57% of participants in one cohort [6], while 74% had PTLD in another [24], and 50% developed PTLD following treatment in a further prospective cohort [25].

Table 1: Characteristics of included studies

Study Name	Country	Study design	Population included	Diagnosis	Sample size	Interventions used	Outcomes measured	Host factor(s) involved	Key findings
Messah et al. (2024) [26]	Indonesia	Comparative cross-sectional	Adult outpatients with MDR-TB vs drug-sensitive (DS) TB	Microbiologically confirmed pulmonary TB (MDR vs DS)	70 (34 MDR, 36 DS)	None (observational; ELISA, PCR-sequencing, HRCT)	Serum MMP-1 & MMP-9; MMP genotypes; cavity features & fibrosis location on HRCT	Genetic (MMP-1 −1607G, MMP-9 C1562T); proteomic (serum MMPs); tissue remodelling	Fibrosis distribution across lung segments differed by MDR vs DS; MMP-1 genotype linked to MDR and cavity-wall thickness; no genotype–serum-level correlation.
Sun et al. (2025)[27]	China	Case-control translational (single-cell	Human lung tissue from post-TB patients vs matched normal lung	Prior M. tuberculosis infection; post-TB lung tissue	19 post-TB lung tissues + 13 normal controls	None (scRNA-seq; siRNA/thrombin validation in vitro)	Single-cell gene-expression signatures (senescence, inflammation, fibrosis, apoptosis);	Transcriptomic; immune/inflammatory; tissue-repair (FOXO3, NF-κB)	Post-TB lung shows senescence/inflammation/fibrosis signatures; FOXO3↓ and NF-κB thromboinflammat

		transcriptomics)					vascular inflammation		ion drive senescence; candidate therapeutic targets.
Zifodya et al. (2026) [25]	Kenya	Prospective observational cohort	Adults with newly diagnosed pulmonary TB (Nairobi)	Microbiologically diagnosed pulmonary TB	205	Standard 6-month anti-TB therapy (all participants)	PTLD by spirometry at month 12 (restrictive/obstructive); whole-blood transcriptomic signatures	Transcriptomic (IL-6/JAK/STAT3, TNF-α, IFN); immune; clinical (MUAC, radiographic extent)	50% developed PTLD; radiographic extent predicted both phenotypes; restrictive PTLD marked by early IL-6/TNF-α profibrotic signature; obstructive by IFN signalling.
Kempker et al. (2026) [24]	Georgia	Prospective cohort	Adults (≥16 y) cured of DS- or MDR pulmonary TB (Tbilisi)	Microbiologically confirmed pulmonary TB,	123	None (post-treatment; plasma immunoa	PTLD (chest CT, spirometry, SGRQ); plasma cytokines &	Immune (IL-17A, IL-1β); proteomic (MMP-8, MMP-2);	74% had PTLD regardless of drug resistance; persistent cavitary disease associated

				favourable outcome		ssays, CT, spirometry)	MMPs; persistent cavitation	tissue remodelling	with higher MMP-8 and lower MMP-2, IL-17A and IL-1β.
Webber et al. (2025)[28]	South Africa	Prospective exploratory cohort	Adults ≤6 months after completing TB treatment	Completed treatment for pulmonary TB	48	None (FDG-PET/CT, PFT, blood + BAL immunoassays)	Radiologic extent (PET/CT); lung function; immune & metabolic markers	Immune (IFN-γ, TNFα, IL-12, IL-4, IL-33); proteomic (MMPs, VEGF); metabolic (PET); T-cells	Radiologic extent correlated with type-1/2 cytokines, MMPs, VEGF and activated T-cells; obstructive and restrictive pathology coexist (mixed pathology).
Motaung et al. (2026)[29]	South Africa	Case-control study	Mycobacteriologically cured DS pulmonary TB with minimal vs extensive persistent	Cured DS pulmonary TB (negative cultures at 4 months)	71 (37 minimal, 34 extensive inflammation)	None (18F-FDG PET/CT; 48-plex Luminex serum assay)	48 serum cytokine/chemokine biomarkers; total lung glycolysis (TLG) on PET; discriminatory markers	Immune/inflammatory (cytokines/chemokines); proteomic; metabolic (PET/TLG)	15 biomarkers elevated with extensive persistent inflammation; 14 discriminatory (AUC 0.71–0.81); 13 correlated with

			lung inflammation						TLG, so serum inflammatory mediators track persistent post-cure lung inflammation.
Jumaar et al. (2025)[30]	South Africa	Cross-sectional Observational (two populations)	Adults >1 year post-TB vs patients with active DS-TB (Cape Town)	Completed TB treatment (>1 y) / active DS-TB	22 people completed TB treatment and 21 people on active-TB treatment	None (circulating biomarker assays)	Circulating IL-6, IL-8, TNF-α, CRP, IL-1Ra vs lung function	Immune/inflammatory	Persistent pro-inflammatory state post-TB (IL-6 ~7×, TNF-α ~21×, CRP ~49× above normal); markers correlated with lung function.

Laila et al. (2025)[31]	India	Case-control study	Adults cured of drug-sensitive pulmonary TB within 1 year (Mysuru)	Cured drug-sensitive pulmonary TB	76 (38 with fibrosis, 38 without)	None (serum ELISA; chest X-ray fibrosis scoring 0–20)	Serum TNF-α; CXR fibrosis extent; ROC/AUC discriminative performance	Immune/inflammatory (TNF-α); proteomic; radiological	Fibrosis cases had far higher TNF-α (3242.7 vs 262.8 ng/L, p<0.001); AUC 0.79; elevated TNF-α associated with post-TB fibrosis and a candidate biomarker.
Auld et al. (2021)[32]	South Africa	Prospective cohort	Adults newly diagnosed with HIV and TB initiating ART	Newly diagnosed pulmonary TB with HIV	134 (112 with baseline spirometry)	ART + anti-TB treatment initiated (both)	Spirometry (restriction/obstruction/mixed) at baseline, 6 and 12 months	Clinical/immune (HIV, CD4); restrictive pattern	Restriction most common, symptomatic and persistent; baseline restriction predicted long-term impairment (aOR 5.44); obstruction did not.

Meghji et al. (2020) [33]	Malawi	Prospective cohort	Adults (≥15 y) first-episode pulmonary TB survivors; 60% HIV-positive	Pulmonary TB (77% microbiologically proven)	405	None (post-treatment follow-up to 1 year)	Spirometry, HRCT (bronchiectasis, destroyed lobe), SGRQ, 6-min walk; outcomes to 1 y	Clinical/radiological; HIV	At cure, 44% bronchiectasis, 9% destroyed lobe, 34% abnormal spirometry; PTLD common, disabling and linked to adverse outcomes.
Byrne et al. (2025) [6]	Australia	Retrospective cohort	Adults who completed TB treatment 2013–2022 (Sydney)	Confirmed TB	119	None (routine post-treatment PFT and CT)	PFT; chest CT (fibrosis, bronchiectasis, emphysema); suspected pulmonary hypertension	Clinical/radiological	PTLD in 68%; pulmonary fibrosis on CT in 57% (most common abnormality); pulmonary hypertension suspected in 68%.
Bajpai et al. (2023)[34]	India	Cross-sectional comparative	Adults with HRCT-confirmed bronchiectas	Post-tubercular bronchiectasis on HRCT	132 analysed (138	None (observational; HRCT,	Clinical, radiological (bronchiectasis type/site),	Clinical/radiological; smoking	Post-TB bronchiectasis had higher smoking, lower FEV1/FVC,

			is (post-TB vs non-TB)		enrolled)	spirometry, microbiology	spirometry, microbiology		cystic type; recurrent cough an independent risk factor; post-TB commonest cause.
Zubair et al. (2022)[35]	Pakistan	Retrospective cross-sectional (epidemiological prevalence)	Adults (≥18 y) treated for pulmonary or pleural TB (Karachi)	Clinical/microbiological pulmonary or pleural TB	321	None (post-treatment CXR review)	Chest X-ray sequelae: fibrosis, bronchiectasis, pleural thickening	Clinical (diabetes, drug resistance, smear); radiological	82.9% had radiological sequelae (fibrosis commonest); higher with diabetes, smear/culture positivity and drug-resistant TB (100%).
Dias et al. (2022)[36]	Brazil	Retrospective, Cross-sectional study	Patients (≥14 y) with post-TB bronchiectas	Post-TB bronchiectasis on CT with prior pulmonary TB	54	Symptomatic (bronchodilators, inhaled	CT bronchiectasis pattern, lobe involvement; spirometry; microbiology	Clinical/radiological	Mostly older, female, non-smokers; >⅔ had a ventilatory defect (mostly

			is (tertiary centre)			steroids, azithromycin) in subset			obstruction); >half upper-lobe involvement.
Allwood et al. (2020)[37]	South Africa	Prospective longitudinal cohort	Immunocompetent adults with a first episode of pulmonary TB	First-episode pulmonary TB (ambulatory)	49 enrolled (43 studied)	None (serial physiology + quantitative CT to 18 months)	Serial spirometry, plethysmography, DLco; quantitative CT fibrosis & gas-trapping scores	Clinical/functional; radiological	CT fibrosis scores fell but gas trapping emerged after treatment; at 1 y post-treatment 18.6% restriction, 16.3% obstruction, 78.6% reduced DLco.
Chakraborty et al. (2026)[38]	India	Prospective non-randomized cohort study	Adults within 1 year of completing anti-TB therapy (Pune)	Treated pulmonary TB	175	None (post-treatment spirometry +	Spirometry (restrictive/obstructive/PRISm); radiological structural damage	Clinical/functional; smear status	57% had spirometric abnormalities, predominantly restrictive (30%); smear positivity predicted severe

						radiology)			structural damage; impairment largely irreversible.
Rodriguez-Saldaña et al. (2026)[39]	Peru	Prospective analytical cross-sectional	Adults (≥18 y) previously treated for pulmonary TB, ≥6 months post-treatment (northern Peru)	Previously treated pulmonary TB	106	None (HRCT + spirometry + questionnaires)	Structural sequelae (fibrosis, bronchiectasis, cavitary) on HRCT; spirometry; mMRC dyspnoea; quality of life	Clinical/radiological	Structural sequelae in 40.6%; multidimensional respiratory burden 59.4%; older age associated; sequelae linked to greater dyspnoea (OR 7.68).
Mehta & Dixit (2026)[40]	India	Prospective observational (interventional PR)	Adults with post-TB sequelae across radiological subtypes (fibrosis, fibrocavitary	Post-TB sequelae (radiologically classified)	60	24-week pulmonary rehabilitation (hospital- or home-based)	Spirometry (FEV1, FVC), 6-min walk, BMI, SGRQ, mMRC, DASS-21; radiological subtype response	Clinical/functional; radiological phenotype	PR improved BMI, 6MWT, DASS-21 and FEV1% across subtypes; greatest FEV1 gain in fibrosis & bronchiectasis, least in

			, bronchiectasis, combined)						fibrocavitary+bronchiectasis; PR beneficial across all phenotypes.
Oskin & Kotlyarov (2026)[23]	Russia	Population-based retrospective cohort	Adults (≥18 y) with COPD; subgroup with TB history/sequelae (Ryazan)	COPD (ICD-10 J44) with TB history (A15–A19, B90)	16,714 COPD (267 with TB/sequelae)	None (registry-based cohort)	COPD exacerbations, mortality; associations with fibrosis & bronchiectasis	Clinical/radiological (post-TB structural change)	Post-TB lung change associated with pulmonary fibrosis (OR 5.67) and bronchiectasis (OR 6.07); mediated TB→COPD exacerbations; higher mortality.
Sheng et al. (2026)[41]	China	Prospective cohort (5-year)	Adults treated for active pulmonary TB (Beijing)	Active pulmonary TB	53	None (serial PFT + chest CT over 5 years)	Longitudinal lung function; airflow obstruction; CT air trapping	Clinical/functional; radiological	Airflow obstruction rose from 13.2% to 17.0% over 5 years; TB-COPD phenotype with small-airway air

									trapping, including young non-smokers.

3.3 Study quality appraisal

Critical appraisal of the 20 included studies was undertaken using design-specific Joanna Briggs Institute (JBI) critical-appraisal tools, with the non-randomised intervention study additionally assessed using ROBINS-I. Overall, 10 studies (50.0%) were judged to have low methodological concern, while 10 studies (50.0%) were considered to have some concerns; no study was classified as having a high risk of bias. Among cohort studies, four were judged to have low concern and six to have some concerns, primarily reflecting limitations in confounding control, completeness of follow-up and reporting of analytical procedures. Two of three case-control studies were assessed as low concern, while one had some concerns. Among analytical cross-sectional studies, three were judged to have low concern and two to have some concerns, whereas the single prevalence study was assessed as low concern. The Mehta and Dixit study, assessed using the JBI quasi-experimental checklist, was judged to have some concerns, principally because of its single-arm design and absence of a concurrent control group. ROBINS-I classified this study as at moderate risk of bias overall, driven by confounding and selection of participants, with low risk in the remaining domains. Detailed item-level JBI assessments are presented in Supplementary Tables S1–5, with the ROBINS-I assessment provided in Supplementary Figure S1.

3.4 Breadth and co-occurrence of host-factor domains

Across the 20 included studies, host-factor assessment was predominantly centred on clinical and radiological domains, which were represented in 16 and 17 studies, respectively, and co-occurred in 14 studies (Figure S2). This pattern indicates that post-TB pulmonary fibrosis and related sequelae have most commonly been characterised through clinically measurable impairment and structural lung abnormalities. The immune/inflammatory domain was examined in eight studies and frequently occurred alongside clinical (5 studies) and radiological (5 studies) measures, as well as proteomic (4 studies) and tissue-repair/remodelling (3 studies) domains. Proteomic approaches were reported in five studies and were commonly integrated with immune/inflammatory, radiological and tissue-remodelling assessments, whereas transcriptomic approaches were limited to two studies. Genetic and metabolomic domains were each represented in only one and two studies, respectively, while no study investigated the microbiome and no study incorporated an epigenetic domain in the mapped evidence. Notably, the most multidimensional investigation

incorporated six domains, combining immune/inflammatory, proteomic, metabolomic, tissue-repair/remodelling, clinical and radiological measures.

3.5 Mechanistic evidence mapping of host factors and fibrotic outcomes

The mechanistic evidence map demonstrated a putative, interconnected pathway linking treated pulmonary TB with persistent immune activation, tissue remodelling and clinically evident fibrotic sequelae (Figure 2). The most consistently represented pathway originated from persistent immune/inflammatory responses, which were linked to cytokine signalling involving IL-6/JAK/STAT3, TNF-α, IFN and IL-17A, and subsequently to tissue-remodelling processes involving matrix metalloproteinases and extracellular-matrix pathways. These biological signals were reported in association with radiological fibrosis, persistent cavitary disease, bronchiectasis, restrictive impairment and reduced diffusing capacity. Genetic susceptibility, particularly the MMP-1 genotype, provided an additional potential link to tissue remodelling, while transcriptomic signatures were used to characterise inflammatory responses and fibrotic phenotypes. At the tissue level, FOXO3 downregulation and NF-κB-associated senescence were linked to fibrosis/senescence histology, whereas VEGF-related vascular remodelling was associated with pulmonary hypertension. Metabolic activity measured by FDG-PET was related to the extent of radiological disease and persistent lung inflammation, linking active inflammatory burden with structural sequelae. Clinical modifiers, including HIV, diabetes, smoking, drug resistance/smear positivity, older age and greater radiographic disease extent, were additionally linked to adverse structural or functional outcomes. Overall, the evidence map suggests that post-TB fibrosis may represent the clinical consequence of interacting inflammatory, remodelling and patient-level pathways, although the predominantly observational evidence does not establish causal direction.

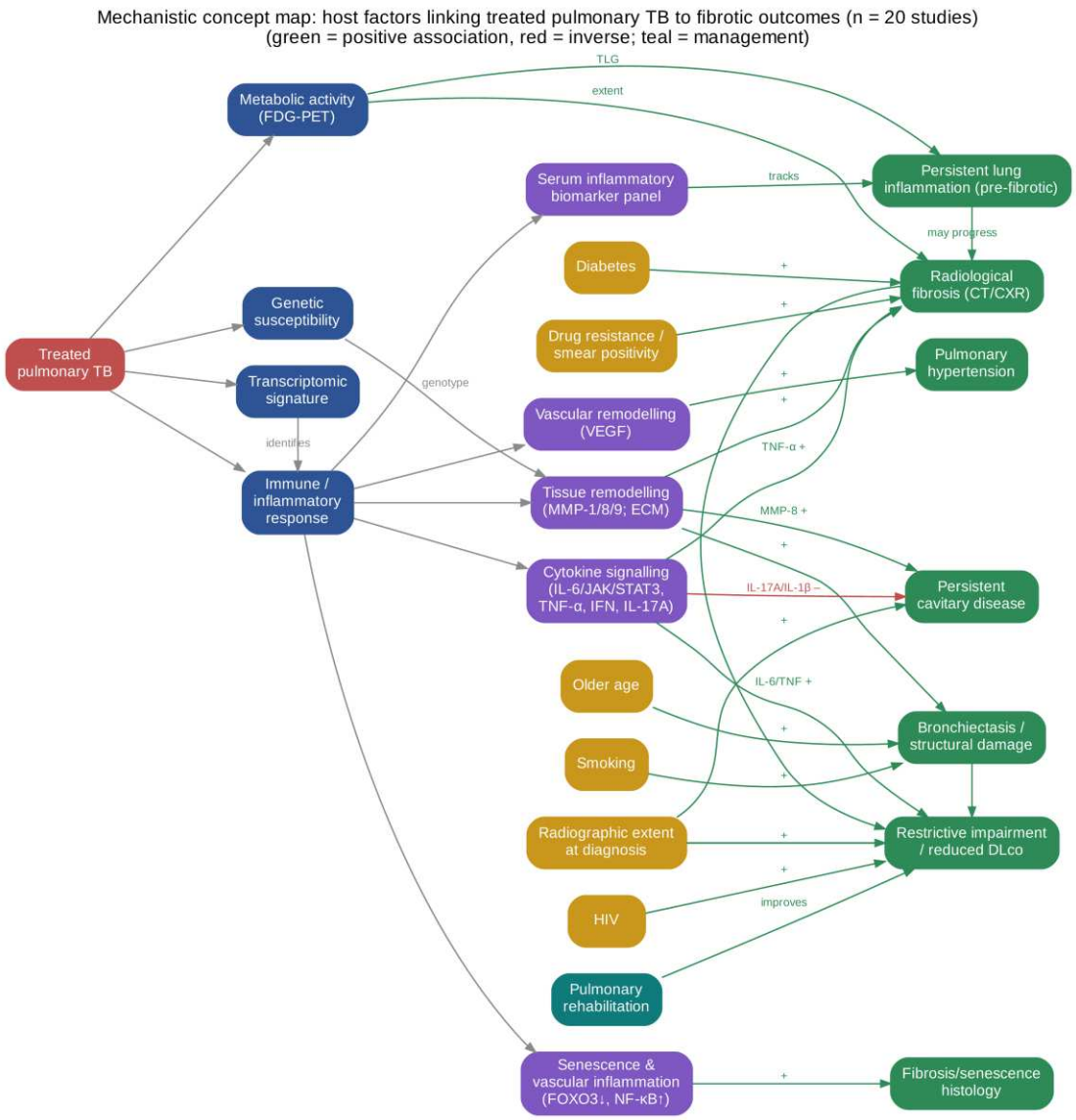


Figure 2: Mechanistic evidence map linking host factors to fibrotic and functional post-tuberculosis outcomes

3.6 Candidate blood-based biomarkers for risk stratification

Several studies measured circulating immune and matrix-remodelling mediators that could be repurposed as inexpensive, blood-based tools for identifying tuberculosis survivors at risk of fibrotic PTLD as shown in Table S8. Interleukin-6 (IL-6) and tumour-necrosis-factor-α (TNF-α) were the most consistently implicated: TNF-α discriminated radiographic fibrosis from non-fibrosis with good accuracy in cured drug-sensitive patients [31] (area under the curve 0.79), and both cytokines were markedly elevated and correlated with lung-function impairment in post-treatment cohorts [25,30] . Matrix metalloproteinases, particularly MMP-8 with

reciprocal changes in MMP-2, IL-17A and IL-1β, tracked persistent cavitary disease [24], while broader multiplex panels distinguished extensive from minimal residual inflammation [29].

3.7 **Imaging of persistent inflammation and structural fibrosis**

Imaging featured in most studies and provides the practical link between measurable inflammation and established structural fibrosis as depicted in Table 2. Chest radiography, though least sensitive, supported semiquantitative fibrosis scoring in high-burden settings and remains the most scalable screening tool . High-resolution computed tomography (HRCT) was the reference standard for phenotyping post-tuberculosis damage (fibrosis, bronchiectasis, cavitation and destroyed lobe) [6,33], and quantitative CT enabled longitudinal tracking of fibrosis and gas-trapping after treatment [37,41]. ^{18}F-fluorodeoxyglucose positron-emission tomography/CT (FDG-PET/CT) extended this by quantifying metabolically active inflammation (total lung glycolysis) and correlating it with both structural extent and circulating immune markers [28,29], raising the possibility of identifying metabolically active, potentially modifiable pre-fibrotic lesions. Pulmonary function testing provided the functional correlate.

Table 2: Imaging of persistent inflammation and structural fibrosis

Modality	**What it measures**	**Fibrosis-relevant finding**	**Supporting studies**	**Clinical application / availability**
Chest X-ray	Gross structural sequelae; semiquantitative fibrosis score	Fibrosis the commonest sequela; CXR fibrosis score correlates with TNF-α	[31,35]	Cheapest and most scalable; suited to population screening
High-resolution CT	Fibrosis, bronchiectasis, cavitation, destroyed lobe	Fibrosis in 57%; bronchiectasis 29–44%	[6,24,25]	Reference standard for structural phenotyping

Quantitative CT	Fibrosis & gas-trapping scores over time	Fibrosis scores fall while gas trapping emerges after treatment	[37,41]	Longitudinal monitoring / research
FDG-PET/CT	Metabolically active inflammation (TLG, SUV)	Inflammation correlates with structural extent and serum immune markers	[28,29]	Identifies active pre-fibrotic disease; HDT trial endpoint
Spirometry + DLco	Restrictive pattern; reduced diffusing capacity	Baseline restriction predicts long-term impairment; reduced DLco common	[25,32,37,38]	Functional correlate; cheap and routine

3.8 Population representation and generalisability

The evidence base was concentrated in high-tuberculosis-burden, low- and middle-income settings, strengthening its relevance to the populations that carry most of the global PTLD burden as shown in Table S9. Sub-Saharan Africa (South Africa, Malawi, Kenya; seven studies) and South/Southeast and East Asia (India, Pakistan, China, Indonesia; eight studies) predominated, with only one high-income cohort (Australia). HIV co-infection, an important effect modifier of post-tuberculosis lung injury, was explicitly enrolled or characterised in two sub-Saharan cohorts (one enrolling only people with HIV [32], the other with 60% HIV-positive participants [33]), and diabetes, smoking and drug resistance were captured across several Asian studies. This distribution enhances applicability to endemic settings but limits generalisability in three respects: HIV, though clinically pivotal, was formally analysed in few studies; paediatric and older adults were under-represented; and molecular/omics work clustered in better-resourced centres. Findings should therefore be read as broadly representative of adult, high-burden settings, while recognising sparse data on key subgroups.

3.9 Evidence Gaps Across Host-Factor Domains and Fibrotic Outcomes

The evidence gap map demonstrated an uneven distribution of research across host-factor domains and post-TB fibrotic outcomes (Figure 3). The evidence base was predominantly concentrated on clinical and radiological factors, particularly in relation to radiological fibrosis, bronchiectasis or structural lung damage, and restrictive or other functional impairment. Immune/inflammatory factors were comparatively well represented and were investigated across multiple outcomes, including radiological fibrosis, restrictive impairment, persistent cavitary disease and persistent post-treatment inflammation. Proteomic and tissue-repair/remodelling domains provided additional molecular evidence but remained concentrated within relatively few host-factor-outcome combinations. In contrast, genetic, transcriptomic and metabolomic evidence was limited, with relatively few studies linking these domains directly to defined fibrotic outcomes. Notably, no eligible studies were identified addressing epigenetic or microbiome-related host factors across the mapped outcomes. Evidence was also sparse for histological or molecularly defined fibrosis and pulmonary hypertension. The map indicates that the current literature remains weighted toward clinical, inflammatory and radiological phenotyping, with limited integration of molecular host-response domains with longitudinal measures of fibrosis. These gaps highlight the need for future studies combining molecular, cellular, structural and functional measures to better characterise host-response heterogeneity after pulmonary TB.

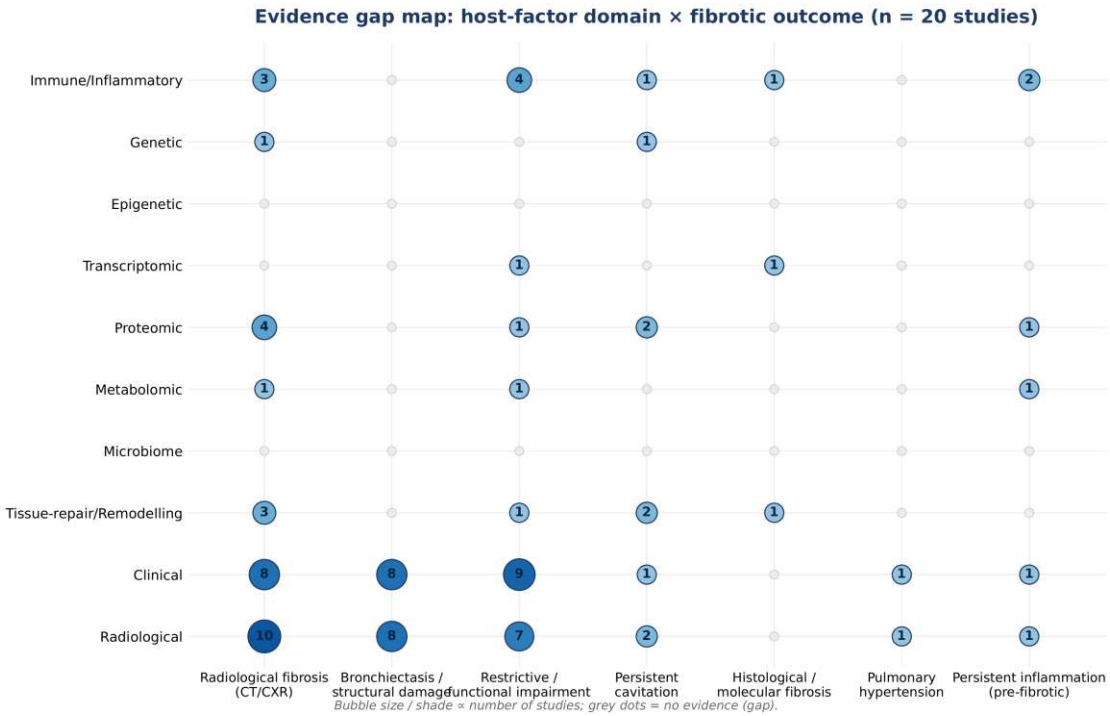


Figure 3: Evidence gap map of host-factor domains against post-tuberculosis fibrotic and functional outcomes

4. Discussion

Three findings matter most. First, research on post-tuberculosis pulmonary fibrosis remains largely descriptive: most included studies characterised patients clinically and radiologically, and far fewer measured the biology thought to drive fibrosis. Second, where biology was measured, the same signals recurred across settings and study designs. Persistent inflammation, most consistently reflected in IL-6 and TNF-α, and matrix metalloproteinase activity emerged as the strongest candidates for biomarker validation and host-directed therapy research. Third, the domains most likely to explain why outcomes differ between individuals, including genetics, epigenetics, the microbiome and integrated multi-omics, were almost absent. Set against the high proportion of survivors left with residual lung disease, this imbalance between disease burden and mechanistic understanding is the main gap the field needs to close.

Microbiological cure of tuberculosis should not be regarded as synonymous with restoration of pulmonary health. A 2025 systematic review and meta-analysis demonstrated substantial residual lung-function impairment among pulmonary-TB survivors, while recent clinical

reviews have emphasised the need for assessment and continued care beyond completion of anti-TB therapy [4,9]. Importantly, recent consensus work has sought to harmonise PTLD research by defining disease using abnormalities across clinical, functional and imaging domains attributable to previous TB [15]. Our synthesis further suggests that persistent inflammation and tissue remodelling may represent biological processes linking treated TB with subsequent fibrosis and structural lung damage. Experimental clinical evidence that doxycycline can modulate TB-associated matrix metalloproteinase activity provides proof-of-concept for host-directed approaches, although this evidence derives from treatment during active TB and should not be interpreted as evidence of established therapy for post-TB fibrosis [42]. Similarly, recent transcriptomic studies demonstrate persistent inflammatory and altered tissue-repair signatures within human TB lesions, providing a mechanistic rationale for further investigation of host-response pathways [43]. The practical significance of these signals is that the process has measurable handles. Inflammatory [24,25] and tissue-remodelling markers [24] can be measured in blood, which makes them usable both for identifying survivors at risk and as pharmacodynamic endpoints in host-directed-therapy trials. Three things would have to be established before they could be used clinically: that they predict fibrotic outcomes prospectively, that validated thresholds can be defined, and that they respond to intervention. None of this has yet been done, so these remain research tools rather than clinical tests. Rather than proposing an established biomarker-guided treatment algorithm, our findings point toward longitudinal, multimodal phenotyping and evaluation of host-directed, antifibrotic and rehabilitation strategies.

Two implications follow for the care of tuberculosis survivors. The first applies now. Because a large minority, and in some cohorts a majority, of treated patients are left with structural or functional lung damage, completion of anti-tuberculosis therapy should be treated as a point of assessment rather than discharge, with symptom review and lung function testing, and targeted imaging and pulmonary rehabilitation where indicated, in line with current PTLD clinical standards [8]. Clinical features recurring across this evidence base, including HIV, diabetes, smoking, drug resistance, bacillary burden and radiographic extent of disease, indicate who warrants closer follow-up, although none is yet a validated risk-stratification tool. The second implication is conditional. If the inflammatory and matrix-remodelling pathways mapped here are confirmed prospectively, they would allow survivors at highest risk to be identified while damage is still potentially modifiable, and would provide the targets

against which preventive host-directed treatment could be developed and tested. That is the clinical prize, and it is why the mechanistic gaps identified in this review matter.

This review has several strengths and limitations. To our knowledge, it represents the first systematic map of host-response evidence in post-tuberculosis pulmonary fibrosis and related post-TB pulmonary sequelae. The review incorporated dual independent screening, a prespecified domain framework spanning biological, molecular and clinical host factors, and a structured evidence-mapping approach. Although critical appraisal is not mandatory for scoping reviews, methodological quality was assessed using design-specific appraisal tools, strengthening the transparency and interpretation of the mapped evidence. In addition, the development of an evidence gap map enabled identification of areas of evidence concentration and under-investigation across host-factor domains and fibrotic, structural and functional outcomes. The intentionally broad eligibility framework also allowed the review to capture the interconnected spectrum of post-TB pulmonary injury rather than considering fibrosis in isolation. As a scoping review, we mapped the breadth of evidence without meta-analysis, and critical appraisal, although undertaken with JBI and ROBINS-I tools, was provisional and based on available reports; half of the studies carried some methodological concern, and most associations derived from observational designs that preclude causal inference. Host-factor and outcome coding required interpretive judgement, and heterogeneous, non-standardised definitions of “fibrosis” (chest radiography, HRCT, spirometric restriction, histology and molecular signatures) limited comparability. The evidence was geographically concentrated, with sparse data on HIV-stratified, paediatric and older populations, and molecular work clustered in well-resourced centres. In addition, 902 reports (856 from the database searches and 46 from other sources) could not be retrieved despite interlibrary loan requests and attempts to contact authors, which may have excluded relevant evidence.

Future work should concentrate on three priorities. The first is prospective longitudinal cohorts that combine molecular host-response measures, the lung microbiome and epigenetic profiling with serial quantitative imaging and lung function. The second is a standardised, validated definition of post-tuberculosis fibrosis and an agreed core outcome set, without which studies cannot be compared. The third is rigorous validation of candidate biomarkers such as IL-6, TNF-α and MMP-8 for risk stratification. The reason for pursuing this biology is therapeutic. Systematically defining the pathways that drive post-tuberculosis

fibrosis is how new drug targets will be found, and host-directed treatment given during or shortly after TB therapy is the most realistic prospect of preventing fibrosis rather than managing established scarring. Interventional trials of host-directed and rehabilitative strategies are the step that converts mechanistic insight into prevention.

5. Conclusion

Half to three-quarters of people cured of pulmonary tuberculosis are left with chronic lung disease, and fibrosis, the least reversible form, affected more than half of one cohort. Cure of the infection is not restoration of the lung. This review shows that the host biology behind that outcome remains incompletely characterised, so affected survivors can neither be identified in advance nor offered treatment that alters the course. Recurrent associations involving IL-6, TNF-α, matrix metalloproteinases and other inflammatory mediators suggest that persistent immune activation and dysregulated extracellular-matrix remodelling may be important components of fibrotic and related post-TB phenotypes. The observed relationships between host factors, radiological abnormalities, cavitation, bronchiectasis and functional impairment further indicate that post-TB fibrosis should be considered within a broader continuum of persistent structural and functional lung injury rather than as an isolated radiological outcome. Candidate biomarkers such as IL-6, TNF-α and matrix metalloproteinases are promising but remain insufficiently validated for routine risk prediction or treatment selection. Ultimately, a more integrated understanding of host-response variability could enable earlier identification of individuals at risk of persistent pulmonary damage and provide a rational foundation for targeted host-directed, antifibrotic and rehabilitation strategies. The priority now is to link biological heterogeneity to clinically meaningful post-TB pulmonary outcomes, so that post-TB fibrosis can be identified earlier and, where possible, prevented.

6. Declarations

Author contributions: VV and SC: conceptualisation, protocol development and registration, searches, screening, data charting, critical appraisal, analysis and synthesis, and writing of the original draft. AV: review methodology, critical review and revision of the manuscript, and supervision. LW: critical review of the manuscript and supervision. All authors approved the final version and agreed to be accountable for the work.

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Data availability: All data analyzed in this review derive from published studies. The data charting template and extracted data are available from the corresponding authors on reasonable request.

Ethics: Not applicable; this review used published data only.

Protocol registration: Open Science Framework, registered 25 August 2026, https://osf.io/4xnrz [19].

Declaration of artificial intelligence use: An AI-assisted screening tool (Elicit, September 2026) was used for the pre-screening step described in the Methods, applying a prespecified relevance rule. Generative AI tools were used for language editing only; no content, data or interpretation was generated by AI. The authors reviewed and edited all text and take full responsibility for the content.

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