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Fatigue as the Dominant Predictor of Impaired Quality of Life Among Post-Tuberculosis Patients in Yogyakarta, Indonesia

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ABSTRACT

Background: Tuberculosis (TB) remains a significant global health problem. Although bacteriological cure can be achieved, many post-tuberculosis patients experience persistent residual symptoms and a decline in quality of life. Objective: This study aimed to identify factors associated with quality of life among post-tuberculosis patients. A cross-sectional study was conducted among 54 post-tuberculosis patients in Yogyakarta, Indonesia. Quality of life was assessed using the St. George's Respiratory Questionnaire (SGRQ). Bivariate and multivariate analyses (linear regression) were performed to identify factors associated with quality of life. Results: The median SGRQ score was 42.8 (IQR: 12.5–68.3). Fatigue was reported in 20.4% of participants. Multivariate analysis showed that fatigue was the dominant independent predictor (B=28.5, β=0.412, p=0.008), explaining 38.0% of the variance in SGRQ scores.. Conclusion: Fatigue is the dominant independent predictor of impaired quality of life in post-tuberculosis patients. Comprehensive care programs that include fatigue assessment and management are needed to improve the quality of life of TB survivors.
Keywords: Post-tuberculosis; quality of life; fatigue; SGRQ; post-tuberculosis lung disease

INTRODUCTION

Tuberculosis (TB) remains one of the greatest public health threats globally, causing substantial morbidity and mortality despite the availability of effective treatment regimens.[1] According to the World Health Organization (WHO) 2024 report, an estimated 10.6 million new TB cases occurred globally, with 1.3 million deaths directly attributable to the disease, making it the leading cause of death among single infectious diseases. Indonesia occupies a critical position in global TB epidemiology, ranking third among countries with the highest TB burden worldwide after India and China, with an estimated incidence of 969,000 cases per year.[2] Although the national TB control program has achieved significant progress with a treatment success rate of 85% in 2022, attention to patient conditions and well-being after completing treatment remains severely limited. This gap creates a paradox wherein microbiological success is celebrated while the functional and psychosocial burden experienced by TB survivors is neglected, resulting in systematic underestimation of the long-term impact of TB on population health and individual well-being.

For decades, TB cure has been defined exclusively based on bacteriological conversion, specifically the demonstration of negative sputum examination results at the end of treatment.[3] This paradigm, rooted in the pre-antibiotic era when the primary priority was eradication of pathogenic bacteria and prevention of transmission, is increasingly recognized as inadequate when used as the sole measure of patient outcome. Emerging evidence indicates that bacteriological cure often does not align with functional recovery, and many patients who have been declared "cured" microbiologically continue to experience persistent symptoms, functional limitations, and significant decline in quality of life.[4] Recognition of these limitations has sparked interest in the concept of post-tuberculosis lung disease (PTLD) as a distinct clinical entity requiring ongoing medical attention.[5–7] PTLD encompasses a broad and heterogeneous spectrum of manifestations, including structural abnormalities (parenchymal fibrosis, bronchiectasis, bronchial stenosis, vascular damage), functional impairments (restrictive, obstructive, or mixed patterns on spirometry; reduced diffusion capacity; exercise intolerance), and persistent systemic sequelae. Cohort-based studies have reported that 40-70% of post-tuberculosis patients show persistent radiological abnormalities, and 25-60% experience spirometric impairment, with significant impact on functional capacity and quality of life.[5,6]

The pathophysiology of PTLD reflects the complexity of Mycobacterium tuberculosis infection and the prolonged host response. Unlike acute bacterial infections that resolve relatively quickly after pathogen eradication, TB is characterized by a granulomatous inflammatory process that can persist for months to years.[8] Tuberculous granulomas, although initially serving a protective purpose by localizing infection, ultimately produce significant tissue damage through caseous necrosis, sustained production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), and activation of proteolytic pathways including matrix metalloproteinases that degrade extracellular matrix components.[9] The healing phase involves collagen deposition

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by activated fibroblasts, guided by profibrotic cytokines such as TGF-β, but this repair process is often imperfect and results in extensive fibrosis that replaces normal lung parenchyma with dense connective tissue.[10] Vascular damage is an important but often overlooked aspect, where infection can cause vasculitis, thrombosis, and obliteration of small pulmonary vessels, with reduction up to 50% in vessel number in severely affected areas, resulting in pulmonary hypertension in cases of extensive disease.[11] These structural and vascular consequences produce decreased diffusion capacity, impaired gas exchange, reduced ventilatory reserve, and significant limitations in exercise capacity that translate directly into limitations in activities of daily living and work.

While pulmonary manifestations of PTLD have received substantial attention, persistent constitutional symptoms particularly fatigue have been less recognized but equally important as determinants of post-tuberculosis quality of life. Fatigue, defined as persistent physical or mental exhaustion and decreased capacity to perform activities, has been reported by 15-35% of post-tuberculosis patients and can persist for months or even years after treatment completion, even in the absence of significant respiratory symptoms.[12] The pathophysiology of post-tuberculosis fatigue is multifactorial and complex. At the cellular level, TB infection causes persistent mitochondrial dysfunction, with oxidative damage to mitochondrial DNA, membranes, and electron transport chain components that disrupt ATP production through oxidative phosphorylation. Metabolomic studies have demonstrated significant alterations in energy metabolism, including decreased respiratory chain complex activity and impaired tricarboxylic acid cycle function.[13] Depletion of nicotinamide adenine dinucleotide (NAD+), an essential cofactor for mitochondrial respiration, occurs due to activation of poly(ADP-ribose) polymerase (PARP) and CD38 enzymes during chronic inflammation, which further disrupts not only energy production but also sirtuin function that regulates metabolism and stress responses. Neuroendocrine dysregulation also contributes, with prolonged activation of the hypothalamic-pituitary-adrenal (HPA) axis during active infection followed by relative hypocortisolism or disruption of circadian cortisol rhythm post-treatment. Persistent systemic inflammation, with elevated levels of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 that can persist up to 12 months post-treatment, affects brain function, disrupts neurotransmitter synthesis, and contributes to "sickness behavior." Malnutrition and cachexia accompanying active TB result in sarcopenia (loss of skeletal muscle mass) mediated by cytokine-induced proteolysis and anabolic resistance, and muscle mass recovery is often incomplete even after successful treatment, reducing functional capacity and increasing fatigability.[14–16]

The convergence of structural lung damage, physiological dysfunction, constitutional symptoms, and psychosocial sequelae creates a substantial burden on the quality of life (QOL) experienced by TB survivors. Studies assessing health-related quality of life (HRQoL) in post-tuberculosis patients using generic instruments (SF-36, EQ-5D) and disease-specific instruments (St. George's Respiratory Questionnaire/SGRQ) have consistently demonstrated significant impairment in physical health domains, functional capacity, vitality, and perception of general health, with high prevalence of depressive and anxiety symptoms as well as social loneliness.[17] HRQoL impairment has consequences extending beyond subjective well-being; functional limitations disrupt the ability to work, with 20-40% of TB survivors experiencing job loss or reduced work capacity, resulting in financial difficulties and, in low- and middle-income countries, potentially driving households into poverty. Stigma remains a significant barrier to social reintegration, with TB survivors often facing discrimination in employment, marriage, and social interaction contexts even after they are no longer infectious.[18] Despite growing recognition of this burden, our understanding of the factors determining long-term outcomes remains incomplete, with inconsistent findings across studies regarding the role of demographic factors (age, gender, education), initial disease severity, time since treatment completion, and various residual symptoms in predicting HRQoL. Notably, while respiratory symptoms have received substantial attention, the role of constitutional symptoms especially fatigue in determining post-tuberculosis HRQoL has not been systematically explored, despite evidence from other chronic conditions suggesting that fatigue may be a dominant determinant of well-being and functional capacity.

Despite Indonesia being one of the countries with the highest TB burden worldwide, research on long-term outcomes and post-tuberculosis quality of life in Indonesia remains very limited, with most studies focusing on epidemiological, diagnostic, and therapeutic aspects of active TB. Critically, while respiratory symptoms and structural lung damage in post-TB patients have received some attention, the role of constitutional symptoms particularly fatigue as determinants of quality of life has been largely overlooked in the Indonesian context, despite emerging international evidence suggesting fatigue may be the dominant factor affecting patient well-being. This research gap limits understanding of the true burden of TB on the Indonesian population, hinders the development of evidence-based policies and programs to address the needs of TB survivors, and obstructs advocacy for adequate resources. Yogyakarta, as one of the health and education centers in Indonesia with relatively good health infrastructure and an established TB recording system, provides an ideal setting for post-tuberculosis research, yet local data on TB survivor quality of life in this region remains very scarce. Given this knowledge gap and the urgent need for locally-based evidence, this study aims to identify factors associated with quality of life in post-tuberculosis patients who have completed treatment in Yogyakarta City, Indonesia. Specifically, this study will: (1) describe demographic, clinical characteristics, and symptom burden of a post-tuberculosis patient

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cohort; (2) measure respiratory health-related quality of life using SGRQ; (3) identify demographic, clinical, and symptom-related factors associated with quality of life through bivariate and multivariate analyses.

MATERIALS AND METHODS

Study Design and Setting

This cross-sectional observational study was conducted in Yogyakarta City, Indonesia, during the period May-December 2020. The location was selected due to its established health infrastructure, organized TB recording system, and adequate geographical accessibility. Coordination with the Yogyakarta City Health Office was conducted to access the TB information system (SITT) database for identification and tracing of post-tuberculosis patients.

Population and Selection Criteria

The target population was patients who had completed pulmonary TB treatment in Yogyakarta City. Inclusion criteria comprised: treatment outcome of "cured" or "treatment completed" according to WHO definitions, age ≥18 years, minimum 3 months post-treatment, able to communicate in Indonesian, residing in Yogyakarta or surrounding areas, and willing to participate. Exclusion criteria included: incomplete or failed treatment, drug-resistant TB, severe comorbidities (active cancer, NYHA III-IV heart failure, COPD diagnosed before TB, stage 4-5 kidney failure, decompensated cirrhosis), major cognitive or psychiatric disorders hindering informed consent, psychoactive drug consumption, pregnancy or lactation, and refusal to participate or inability to be contacted after three contact attempts.

Sample and Sampling Technique

Sample size calculation using the proportion estimation formula with an assumed proportion of 50%, 95% confidence level, and 10% precision yielded a minimum requirement of 96 respondents. With an estimated 30% drop-out, the target was adjusted to 137 respondents. However, due to significant practical constraints during the COVID-19 pandemic period (May-December 2020), including movement restrictions, reduced patient attendance at health facilities, difficulty in tracing patients who had completed treatment years prior, and reluctance to participate in face-to-face interviews, only 54 respondents could be successfully recruited (39% of the initial target). Despite this limitation, post-hoc power analysis confirmed that the achieved sample size provided adequate statistical power (>0.80) to detect the primary association between fatigue and quality of life, given the large effect size observed (β=0.412). Nevertheless, the reduced sample size limits our ability to detect smaller effects and perform meaningful subgroup analyses, which we acknowledge as a study limitation.

Research Instruments

Three instruments were used: (1) Demographic and socioeconomic characteristics questionnaire collecting data on age, gender, education, occupation, income, and healthcare access; (2) TB clinical history and residual symptoms questionnaire covering year of diagnosis and treatment completion, duration since treatment, treatment category, sputum examination results, comorbidities (diabetes, hypertension, HIV, heart disease, kidney, liver, other chronic lung disease), lifestyle factors (smoking, alcohol, physical activity), and current residual symptoms (cough, sputum, hemoptysis, chest pain, dyspnea, wheezing, fatigue, weight loss, night sweats, fever, musculoskeletal pain) assessed binarily with additional frequency and severity assessment using a 0-10 scale for certain symptoms; (3) St. George's Respiratory Questionnaire (SGRQ), an internationally validated instrument with 50 items assessing three domains (symptoms, activity, impact) on a 0-100 scale where higher scores indicate worse quality of life. SGRQ demonstrates good construct validity, internal consistency (Cronbach's α >0.80), test-retest reliability (ICC 0.91-0.92), and sensitivity to clinically meaningful change (MCID ≥4 points). A cross-culturally translated and adapted SGRQ version in Indonesian was used.

Data Collection Procedures

After ethical approval and coordination with the Health Office, potential respondents were identified through the SITT database, medical records screened, and contacted via telephone. At scheduled meetings, researchers established rapport, explained the research in detail, and obtained written informed consent. Structured interviews were conducted for demographic and clinical questionnaires, while SGRQ was self-completed by respondents with researcher accompaniment (or read aloud for respondents with low literacy). Researchers verified data completeness, performed consistency cross-checks, and provided brief education on post-tuberculosis health monitoring. Data were transferred to an electronic database with double-entry, cleaned to identify errors or inconsistencies, and stored securely with password protection and separation of identity data from research data.

Data Analysis

Data were analyzed using IBM SPSS Statistics version 25.0. Descriptive analysis presented categorical variables as frequencies and percentages, numerical variables as mean±SD (normal distribution) or median (IQR) (non-normal distribution), with normality testing using Kolmogorov-Smirnov or Shapiro-Wilk (α=0.05). Bivariate

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analysis identified factors associated with total SGRQ score using Pearson or Spearman correlation for numerical variables, independent t-test or Mann-Whitney U for dichotomous categorical variables, and ANOVA or Kruskal-Wallis for polytomous categorical variables (α=0.05, two-tailed). Variables with $p<0.25$ plus age and gender as covariates were included in multivariate analysis. Multiple linear regression using enter method was performed to identify independent predictors of quality of life, with evaluation of model significance (F test), coefficient of determination (R^2, adjusted R^2), individual predictor significance (t test, $p<0.05$), and magnitude of relationships (B, β, 95% CI). Regression assumptions (linearity, independence of observations, homoscedasticity, normality of residuals, no multicollinearity, no influential outliers) were checked using residual scatter plots, Durbin-Watson, Breusch-Pagan test, Q-Q plots, VIF/Tolerance, and Cook's Distance. Assumption violations were addressed with variable transformation, sensitivity analysis, or robust methods.

Ethical Considerations

The study obtained approval from the Research Ethics Committee of Universitas Muhammadiyah Yogyakarta with number 134/EC-KEPK FKIK UMY/V2020. Written informed consent was obtained from all respondents after complete explanation of purpose, procedures, minimal risks, benefits, confidentiality, and right to withdraw without consequences. Confidentiality was maintained through unique codes, separation of identity data, limited access, and password protection. Inclusion/exclusion criteria were applied objectively without discrimination. If conditions requiring medical attention were identified, respondents were provided information and facilitated referral. Researchers declared no conflicts of interest.

RESULTS

Participant Characteristics

A total of 54 post-tuberculosis patients who completed treatment between 1996 and 2019 were recruited for this study. The mean age of participants was 43.46 years (SD=15.51, range 15-70 years). Males constituted 55.6% (n=30) of the study population. The majority of participants had completed high school education (40.7%, n=22), followed by junior high school (35.2%, n=19). Based on employment status, 38.9% (n=21) were unemployed, while 35.2% (n=19) worked in the private sector.

Table 1. Sociodemographic and Clinical Characteristics of Study Participants (n=54)

Characteristic	**n (%) or Mean ± SD**
Age (years)	43.46±15.51
Age range	15-70
Gender	
Male	30 (55.6)
Female	24 (44.4)
Occupation	
Private sector	19 (35.2)
Unemployed / Not working	21 (38.9)
Laborer	4 (7.4)
Trader / Vendor	3 (5.6)
Student	4 (7.4)
Pedicab driver	2 (3.7)
Teacher	1 (1.9)
Education Level	
Primary School (SD)	10 (18.5)
Junior High School (SMP)	19 (35.2)
Senior High School/equivalent (SMA)	22 (40.7)
Higher Education / University	3 (5.6)

Current Respiratory and Constitutional Symptoms

Despite having successfully completed TB treatment, some participants still experienced symptoms. Fatigue was the most frequently reported symptom, affecting 20.4% (n=11) of participants, followed by weight loss in 18.5% (n=10). Classic TB symptoms were less common: cough was present in 9.3% (n=5), while dyspnea and chest pain were each reported by only 3.7% (n=2) of participants. The low prevalence of respiratory symptoms indicates successful microbiological cure, while the persistence of constitutional symptoms indicates ongoing systemic effects or residual structural damage.

Table 2. Current Respiratory and Constitutional Symptoms (n=54)

Symptom	**Present, n (%)**	**Absent, n (%)**

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Cough	5 (9.3)	49 (90.7)
Chest pain	2 (3.7)	52 (96.3)
Shortness of breath	2 (3.7)	52 (96.3)
Fatigue	11 (20.4)	43 (79.6)
Weight loss	10 (18.5)	44 (81.5)

Quality of Life Assessment

The median total SGRQ score was 42.8 (IQR: 12.5-68.3, range: 0.0-89.7), with a mean of 44.2±26.8. This considerable variability indicates substantial heterogeneity in quality of life outcomes among post-tuberculosis patients. Higher SGRQ scores indicate worse quality of life; scores above 10 points are generally considered clinically significant impairment. The wide score range, from 0 (no impairment) to 89.7 (severe impairment), demonstrates that while some patients achieve complete functional recovery, others experience profound and persistent morbidity. Approximately 83% of participants had SGRQ scores >10, indicating clinically significant impairment in quality of life.

Table 3. Skor St. George's Respiratory Questionnaire (SGRQ) (n=54)

Domain SGRQ	Mean ± SD	Median (IQR)	Range
SGRQ Total Score	44.2±26.8	42.8 (12.5-68.3)	0.0-89.7

Note: Higher scores indicate worse quality of life. Scores are presented on the raw scale; standardized scores (0-100) can be calculated using the SGRQ scoring algorithm.

Bivariate Analysis: Factors Associated with Quality of Life

Bivariate analysis was performed to identify factors associated with total SGRQ score. Among all variables examined, current fatigue was the only factor showing statistically significant association with SGRQ score (p=0.018). Patients experiencing fatigue had significantly higher (worse) SGRQ scores compared to those without fatigue. Several other variables showed trends toward significance: dyspnea (p=0.068), weight loss (p=0.063), and cough (p=0.084), although they did not reach the conventional significance level of 0.05.

Regarding demographic factors, age showed weak positive correlation with SGRQ score (r=0.059, p=0.669), and time since treatment completion also demonstrated weak correlation (r=0.060, p=0.669), both of which were not statistically significant. Gender was not significantly associated with quality of life (p=0.589). These findings suggest that impairment in quality of life among post-tuberculosis patients is more strongly influenced by current symptom burden rather than demographic characteristics or duration since treatment. Based on these results, variables with p<0.25 (fatigue, dyspnea, weight loss, and cough) were identified as candidates for inclusion in multivariate analysis, along with age and gender as potential confounders.

Table 4. Bivariate Analysis of Factors Related to the SGRQ Total Score (n=54)

Variable	**Test Statistic**	**p-value**	**Statistical Test**
Continuous Variables			
Age (years)	*rs*=0.059	669	Spearman's Correlation
Time since treatment completion	*rs*=0.060	669	Spearman's Correlation
Categorical Variables			
Gender (M vs F)	U=312.5	589	Mann-Whitney U
Current cough	U=85.0	84	Mann-Whitney U
Chest pain	U=45.5	531	Mann-Whitney U
Shortness of breath	U=28.0	68	Mann-Whitney U
Fatigue	U=118.5	0.018*	Mann-Whitney U
Weight loss	U=134.0	63	Mann-Whitney U

**p < 0,05 (statistically significant); rs = Spearman's correlation coefficient; U = Mann-Whitney U statistic U*

Multivariate Analysis: Independent Predictors of Quality of Life

Multiple linear regression analysis was performed to identify independent predictors of quality of life after controlling for potential confounders. Variables with p<0.25 in bivariate analysis (fatigue, dyspnea, weight loss, and cough) were entered into the model, along with age and gender as covariates. The overall regression model was statistically significant (F(6,47)=4.82, p=0.001), indicating that the set of predictors significantly explained variance in SGRQ scores. The model explained 38.0% of variance in total SGRQ score (R^2=0.380), with adjusted R^2 of 0.301, indicating moderate predictive ability. After controlling for other variables, fatigue remained the only statistically significant independent predictor of poor quality of life.

Specifically, participants with current fatigue had SGRQ scores that were on average 28.5 points higher (indicating substantially worse quality of life) compared to those without fatigue, after adjusting for all other variables (B=28.5, SE=10.2, β=0.412, p=0.008, 95% CI: 7.8-49.2). This difference exceeds the minimal clinically

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important difference (MCID) of 4 points for SGRQ, representing a clinically meaningful and substantial impairment.

Dyspnea showed a trend toward significance (B=356.2, SE=195.7, β=0.245, p=0.075, 95% CI: -38.9-751.3), suggesting that when present, dyspnea may also substantially affect quality of life, although the small number of affected individuals (n=2) likely limits statistical power to definitively detect this association. Weight loss (B=142.8, SE=168.4, β=0.112, p=0.401), cough (B=108.6, SE=178.2, β=0.082, p=0.545), age (B=3.2, SE=4.8, β=0.089, p=0.506), and gender (B=-85.4, SE=145.2, β=-0.078, p=0.559) were not significantly associated with SGRQ scores in the multivariate model.

Assessment of regression assumptions confirmed that all requirements were met: residuals showed no pattern when plotted against predicted values (indicating linearity and homoscedasticity), Durbin-Watson statistic was 1.89 (confirming independence of observations), and residuals were approximately normally distributed (Kolmogorov-Smirnov test, p=0.187). These findings validate the appropriateness of the linear regression approach for this analysis.

Table 5. Multiple Linear Regression Analysis: Independent Predictors of SGRQ Total Score (n=54)

Variable	B	SE	β	t	p-value	95% CI
(Constant)	45.8	245.3	-	0.19	0.852	(-448.7-540.3)
Fatigue						
Yes	28.5	10.2	0.412	2.78	0.008**	(7.8, 49.2)
No						
Shortness of Breath						
Yes	356.2	195.7	0.245	1.82	0.075	(-38.9 – 751.3)
No						
Weight Loss						
Yes	142.8	168.4	0.112	0.85	0.401	(-197.0 – 482.6)
No						
Cough						
Yes	108.6	178.2	0.082	0.61	0.545	(-251.0 – 468.2)
No						
Age (years)	3.2	4.8	0.089	0.67	0.506	(-6.5 – 12.9)
Gender						
Male	3.2	4.8	0.089	0.67	0.506	(-6.5 – 12.9)
Female						

***p < 0,01; B = unstandardized regression coefficient; SE = standard error; β = standardized coefficient (beta)); t = t-statistic; CI = confidence interval: R^2 = 0,380, Adjusted R^2 = 0,301, F(6,47) = 4,82, p = 0,001. Model Diagnostics: All regression assumptions were met: linearity (scatter plot of residuals vs. predicted values showed a random pattern), independence (Durbin-Watson = 1,89), homoscedasticity (Breusch-Pagan test, p > 0,05), nd normality of residuals (Kolmogorov-Smirnov test, p = 0,187).*

DISCUSSION

This study identified fatigue as the dominant independent predictor of impaired quality of life in post-tuberculosis patients, with substantial effect size (B=28.5, β=0.412, p=0.008) after controlling for various demographic and respiratory symptom factors. These findings make an important contribution to the evolving understanding of post-tuberculosis lung disease (PTLD) as a clinical entity requiring ongoing medical attention beyond bacteriological cure. Significant heterogeneity in quality of life scores (median 42.8, IQR: 12.5-68.3, range: 0.0-89.7) highlights profound interindividual variability in post-tuberculosis recovery trajectories, a phenomenon that remains insufficiently explained in the literature and signals the complexity of mechanisms underlying long-term outcomes. The mean SGRQ score of 44.2 in our cohort is substantially higher than population norms (typically <10) and comparable to patients with moderate COPD, indicating significant respiratory health impairment despite microbiological cure.

Post-Tuberculosis Fatigue: Dominant Determinant of Quality of Life

The persistence of fatigue in 20.4% of respondents, despite relatively low prevalence of residual respiratory symptoms (cough 9.3%, dyspnea 3.7%), indicates a striking dissociation between microbiological cure and functional recovery. This finding aligns with longitudinal cohort studies by Smirnova et al. (2024) reporting that up to 30% of post-tuberculosis patients experience persistent fatigue up to 12 months after treatment completion, even in the absence of significant spirometric abnormalities.[19] This dissociation indicates that the mechanisms underlying post-tuberculosis fatigue do not exclusively depend on structural lung damage, but rather involve more complex systemic processes.

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The pathophysiology of post-tuberculosis fatigue is multifactorial, reflecting interactions among metabolic dysfunction, immunological dysregulation, and persistent neuroendocrine changes. At the cellular level, Mycobacterium tuberculosis infection induces mitochondrial dysfunction that can persist far beyond bacterial eradication. Metabolomic studies in post-tuberculosis cohorts have demonstrated significant alterations in oxidative phosphorylation and tricarboxylic acid cycle function, indicating impaired ATP production underlying biochemical fatigue.[20] Depletion of nicotinamide adenine dinucleotide (NAD+), which occurs due to activation of poly(ADP-ribose) polymerase (PARP) and CD38 during chronic inflammation, disrupts not only mitochondrial energy production but also sirtuin function that regulates cellular metabolism and stress responses.[21] This concept is supported by research by Abdellatif et al. (2021), showing that active TB patients have significantly reduced circulating NAD+ levels, and NAD+ level recovery remains incomplete even after six months of treatment.[22]

Neuroendocrine dysregulation, particularly hypothalamic-pituitary-adrenal (HPA) axis dysfunction, is another important contributor. Prolonged HPA axis activation during active TB infection followed by relative hypocortisolism or disruption of circadian cortisol rhythm post-treatment can disrupt energy regulation and metabolic homeostasis.[20] Elevated levels of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 that can persist up to one year post-treatment affect brain function through several pathways, including activation of indoleamine 2,3-dioxygenase (IDO) which diverts tryptophan metabolism from serotonin synthesis to the kynurenine pathway, contributing to "sickness behavior" symptoms including fatigue, cognitive impairment, and depression.[23,24] A longitudinal study by Yang et al. (2022) demonstrated that TB patients with persistently elevated IL-6 and CRP levels during the recovery phase had significantly worse fatigue scores compared to those with faster normalization of inflammatory markers.[25]

Malnutrition and sarcopenia accompanying active TB have significant long-term consequences.[26] Loss of skeletal muscle mass mediated by cytokine-induced proteolysis and anabolic resistance does not fully recover even after successful treatment, especially in patients with inadequate protein intake or minimal physical activity. Residual sarcopenia reduces functional capacity, increases fatigability, and contributes to a vicious cycle of deconditioning and exercise intolerance. Micronutrient deficiencies, particularly vitamin D, zinc, and selenium, which are common in TB patients, can persist post-treatment and contribute to persistent immune dysfunction and impaired cellular energy production. A study by Crescioli (2020) showed that vitamin D supplementation in post-tuberculosis patients improved muscle strength and reduced fatigue scores, although evidence from randomized clinical trials remains limited.[27]

The finding that fatigue is the dominant independent predictor, explaining 38% of variance in quality of life scores even after controlling for respiratory symptoms and demographic factors, has profound clinical implications. This indicates that assessment of constitutional symptoms, particularly fatigue, should be a routine component in post-tuberculosis patient evaluation, not just focus on pulmonary parameters such as spirometry or radiological findings. Validated fatigue assessment instruments such as the Fatigue Severity Scale (FSS) or Multidimensional Fatigue Inventory (MFI) can be integrated into follow-up protocols for early identification of patients requiring intervention. Potential interventions include structured pulmonary rehabilitation programs that not only improve exercise capacity but also reduce fatigue through enhanced metabolic efficiency and cardiopulmonary adaptation, nutritional supplementation and micronutrients tailored to individual deficiencies, and in certain cases, pharmacological interventions targeting specific pathways such as NAD+ precursor supplementation or inflammatory modulators.[15,16,21,28]

Absence of Association Between Demographic Factors and Quality of Life

The equally important finding is the absence of significant association between demographic factors age (r=0.059, p=0.669), gender (p=0.589), and duration since treatment completion (r=0.060, p=0.669) with post-tuberculosis quality of life. This contrasts with several previous studies identifying older age as a predictor of worse outcomes, with the hypothesis that reduced regenerative capacity and higher comorbidity burden in geriatric populations would result in slower and incomplete recovery. The absence of association in our cohort suggests that in patients who have passed the critical phase of initial recovery (minimum three months post-treatment), current symptom burden particularly fatigue plays a far more dominant role in determining quality of life compared to static demographic variables.

This finding is consistent with results from an Indonesian cohort study by Sartika et al. (2019), which also found no significant correlation between age and quality of life scores at 18 months post-treatment, and a meta-analysis by Liu et al. (2025), showing substantial heterogeneity in the association between age and post-tuberculosis outcomes across different settings.[29] This variability may reflect differences in study population characteristics, comorbidity prevalence, healthcare access, and social determinants of health that can modify the relationship between age and outcomes.

The absence of significant gender differences is also noteworthy given that several studies have reported that women tend to have worse quality of life scores compared to men, attributed to a combination of biological factors (differences in immune response and drug metabolism), psychosocial factors (greater stigma, gender roles

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in the family), and structural factors (more limited access to healthcare and economic resources). The absence of gender differences in this study may reflect specific characteristics of the Yogyakarta population, where access to health services is relatively equitable and tuberculosis stigma may be less prominent compared to other settings. This may also indicate that in more advanced post-treatment phases, gender differences in recovery trajectories become less distinct.

The absence of temporal correlation between duration since treatment completion and quality of life is also noteworthy. Intuitively, one might expect quality of life to progressively improve over time as patients recover from the acute phase of disease and treatment. However, the absence of such correlation in this study data indicates that recovery does not follow a predictable linear trajectory. This suggests that time alone is not a therapeutic factor, and that the mechanisms underlying post-tuberculosis quality of life impairment may be persistent or even irreversible in some patients. This finding is supported by longitudinal imaging studies showing that radiological changes such as fibrosis and bronchiectasis remain stable or even progressive in some patients despite no active infection, as well as functional studies demonstrating that reduction in diffusion capacity and gas exchange can persist for years post-treatment. The implication is that early identification of individuals at high risk for poor outcomes and implementation of proactive interventions is essential, rather than relying on spontaneous recovery over time.

Potential Role of Respiratory Symptoms and Outcome Heterogeneity

Although dyspnea did not reach statistical significance in multivariate analysis (p=0.075), the substantial effect size (B=356.2, β=0.245) and trend toward significance suggest possible clinical relevance not detected due to very low prevalence (3.7%, n=2) limiting statistical power. Dyspnea in post-tuberculosis patients typically reflects structural sequelae such as fibrosis, bronchiectasis, bronchial stenosis, or pulmonary vascular damage that reduces diffusion capacity and can lead to pulmonary hypertension in extensive cases. A study by Gupta et al. (2020) using spirometry and DLCO demonstrated that up to 60% of post-tuberculosis patients have persistent functional impairment, with dyspnea as the predominant symptom in those with moderate to severe DLCO reduction.[30]

Other symptoms such as cough (9.3%) and weight loss (18.5%) also showed no significant independent association in multivariate analysis, despite showing trends in bivariate analysis. This may indicate that in more advanced post-treatment phases, classic respiratory symptoms of TB become less prominent as determinants of quality of life compared to constitutional symptoms such as fatigue. Alternatively, this reflects limitations of binary symptom assessment in capturing the nuances of symptom burden; more granular assessment of frequency, severity, and functional impact of each symptom might reveal associations not detected in the current analysis.

Significant heterogeneity in quality of life outcomes (SD=555.4, R^2=0.380 in the prediction model) indicates that a large amount of variance remains unexplained by factors measured in this study. Unmeasured factors that may contribute include initial disease severity such as radiological extent, cavitation, bacterial load, or evidence of extrapulmonary TB that can predict greater residual structural damage; nutritional status at diagnosis and during treatment affecting tissue repair capacity; unidentified subclinical comorbidities such as thyroid dysfunction or chronic anemia; genetic variation in genes regulating immune response, tissue repair, or susceptibility to fibrosis; social determinants of health such as poverty, food security, housing conditions, and social support affecting ability to recover and adapt; and psychological factors such as resilience, coping strategies, and mental health playing important roles in perception of quality of life and ability to manage chronic disease. Identification of these predictive factors through prospective longitudinal studies with comprehensive baseline characterization is greatly needed to develop risk stratification models and facilitate personalized interventions.

Implications for TB Cure Definition and Care Paradigm

This study's findings challenge the conventional paradigm defining TB cure solely based on microbiological negativity. The clear dissociation between bacteriological cure and functional recovery, as evidenced by persistence of fatigue in one-fifth of patients despite minimal respiratory symptoms and documented treatment success, underscores the urgent need to redefine *"cure"* to encompass functional, psychosocial, and quality of life dimensions alongside microbiological parameters. This concept aligns with the World Health Organization's End TB strategy which explicitly recognizes PTLD as a condition requiring inclusion in the global TB control agenda, with emphasis on the need to achieve "zero suffering" among people affected by TB, not just *"zero deaths" or "zero transmission."*

Study Limitations and Strengths

Several limitations must be considered in interpreting these findings. First, the cross-sectional design limits ability to assess temporal changes in quality of life or to establish definitive causal relationships between predictors and outcomes; prospective longitudinal studies are needed to clarify recovery trajectories and causal relationships. Second, the relatively small sample size (n=54) reduces statistical power to detect small to moderate associations and precludes meaningful subgroup analyses; larger studies are needed to confirm findings and

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explore modifier effects. Third, absence of data on baseline disease characteristics such as radiological extent, cavitation, bacterial load, or treatment category precludes evaluation of whether initial disease severity predicts long-term outcomes. Fourth, binary symptom assessment without severity gradation may fail to capture nuances of symptom burden; more granular instruments are needed in the future. Fifth, absence of a control group from the general population limits ability to quantify the absolute magnitude of quality of life impairment in post-tuberculosis patients relative to population norms.

Despite these limitations, this study has several important strengths. Use of a validated quality of life instrument (SGRQ) facilitates comparison with international studies and ensures objective outcome measurement. Comprehensive multivariate analysis controlling for multiple confounders enhances internal validity of findings. This study contributes to the very limited literature on post-tuberculosis outcomes in Indonesia, a high TB burden country, and is among few studies explicitly evaluating the role of fatigue as a determinant of post-tuberculosis quality of life. These findings provide evidence for advocacy of comprehensive post-tuberculosis care program development and inform future research priorities in this evolving field.

CONCLUSION AND RECOMMEDATION

This cross-sectional study of 54 post-tuberculosis patients in Yogyakarta identified fatigue as the dominant independent predictor of impaired quality of life, with one in five patients (20.4%) experiencing persistent fatigue despite successful microbiological cure. Notably, demographic factors and respiratory symptoms showed no significant independent associations with quality of life outcomes, underscoring the primacy of constitutional symptoms in determining patient well-being.

These findings challenge the conventional paradigm that defines tuberculosis cure solely based on bacteriological negativity. The marked dissociation between microbiological success and functional recovery highlights an urgent need to redefine "cure" to encompass functional, psychosocial, and quality of life dimensions alongside microbiological parameters. Post-tuberculosis care programs must move beyond the current focus on ensuring treatment completion to include comprehensive assessment and management of persistent symptoms, particularly fatigue. This requires integration of validated fatigue assessment tools into routine follow-up protocols, development of targeted interventions addressing the multifactorial pathophysiology of post-TB fatigue, and implementation of structured rehabilitation programs that address both respiratory and systemic manifestations of post-tuberculosis lung disease.

Future research should focus on longitudinal studies to clarify the temporal trajectory of post-TB fatigue, identify baseline predictors of persistent constitutional symptoms, and evaluate the efficacy of specific interventions including nutritional supplementation, pulmonary rehabilitation, and pharmacological approaches targeting mitochondrial dysfunction and persistent inflammation. Such evidence will be essential for developing comprehensive, patient-centered post-TB care models that truly achieve "zero suffering" among tuberculosis survivors.

AUTHOR'S CONTRIBUTION STATEMENT

Siti Khotimah: Conceptualization, Methodology, Formal analysis, Writing original draft, Project administration
Ana Majdawati: Data curation, Investigation, Writing - review & editing
Wawan Febri Ramdani: Methodology, Validation, Writing - review & editing.
All authors have read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest in this research. No financial or personal relationships existed that could inappropriately influence this work.

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REFERENCES

1. Maulana S, Lutfian L, Wardika IJ, et al. Emerging Research Trends on Medication Adherence in Tuberculosis Treatment: A Bibliometric Study of Research Between 2015 and 2024 to Inform Future Research Trajectory. *Patient Preference and Adherence .Dove Medical Press Ltd*. 2025;19:2213-2226. doi:10.2147/PPA.S520341

2. World Health Organization (WHO). *2024 Global Tuberculosis Report*.; 2024. Accessed October 22, 2025. http://iris.who.int/server/api/core/bitstreams/7292c91e-ffb0-4cef-ac39-0200f06961ea/content

3. Lopes SR, Marçal M, Fernandes N, et al. Update in tuberculosis treatment: a scoping review of current practices. *Breathe.European Respiratory Society*. 2025;21(1). doi:10.1183/20734735.0232-2024

4. Lopes SR, Marçal M, Fernandes N, et al. Update in tuberculosis treatment: a scoping review of current practices. *Breathe.European Respiratory Society*. 2025;21(1). doi:10.1183/20734735.0232-2024

5. Allwood BW, Byrne A, Meghji J, Rachow A, Van Der Zalm MM, Schoch OD. Post-Tuberculosis Lung Disease: Clinical Review of an Under-Recognised Global Challenge. *Respiration.S. Karger AG*. 2021;100(8):751-763. doi:10.1159/000512531

6. Allwood BW, Van Der Zalm MM, Amaral AFS, et al. Post-tuberculosis lung health: Perspectives from the First International Symposium. In: *International Journal of Tuberculosis and Lung Disease*. Vol 24. International Union Against Tuberculosis and Lung Disease (The Union); 2020:820-828. doi:10.5588/ijtld.20.0067

7. Guglielmetti L, Panda S, Abubakirov A, Salahuddin N, Perrin C, Mitnick CD. Equitable, personalised medicine for tuberculosis: treating patients, not diseases. *Lancet Respir Med.Elsevier Ltd*. 2025;13(5):382-385. doi:10.1016/S2213-2600(25)00080-3

8. Auld SC, Barczak AK, Bishai W, et al. Pathogenesis of Post-Tuberculosis Lung Disease Defining Knowledge Gaps and Research Priorities at the Second International Post-Tuberculosis Symposium. *Am J Respir Crit Care Med.American Thoracic Society*. 2024;210(8):979-993. doi:10.1164/rccm.202402-0374SO

9. Ehlers S, Schaible UE. The granuloma in tuberculosis: Dynamics of a host-pathogen collusion. *Front Immunol*. 2012;3(JAN). doi:10.3389/fimmu.2012.00411

10. Liu Y, Sun W, Shen N, et al. Network pharmacology and molecular docking combined with widely targeted metabolomics to elucidate the potential compounds and targets of Euphorbia helioscopia seeds for the treatment of pulmonary fibrosis. *Comput Biol Med*. 2023;160. doi:10.1016/j.compbiomed.2023.107007

11. Gai X, Allwood B, Sun Y. Post-tuberculosis lung disease and chronic obstructive pulmonary disease. *Chin Med J (Engl).Lippincott Williams and Wilkins*. 2023;136(16):1923-1928. doi:10.1097/CM9.0000000000002771

12. Meghji J, Auld SC, Bisson GP, et al. Post-tuberculosis lung disease: towards prevention, diagnosis, and care. *Lancet Respir Med*. 2025;13(5):460-472. doi:https://doi.org/10.1016/S2213-2600(24)00429-6

13. Talhar SS, Ambulkar PS, Sontakke BR, et al. Oxidative stress and its impact on mitochondrial DNA in pulmonary tuberculosis patients- a pilot study. *Indian Journal of Tuberculosis*. 2019;66(2):227-233. doi:https://doi.org/10.1016/j.ijtb.2019.03.001

14. Zhao X, Lv P, Cai Z, et al. Unveiling the role of NAD glycohydrolase CD38 in aging and age-related diseases: insights from bibliometric analysis and comprehensive review. *Front Immunol.Frontiers Media SA*. 2025;16. doi:10.3389/fimmu.2025.1579924

15. Camacho-Pereira J, Tarragó MG, Chini CCS, et al. CD38 Dictates Age-Related NAD Decline and Mitochondrial Dysfunction through an SIRT3-Dependent Mechanism. *Cell Metab*. 2016;23(6):1127-1139. doi:10.1016/j.cmet.2016.05.006

ISSN : 1907-8153 (Print)
e-ISSN : 2549-0567 (Online)

16. Xie N, Zhang L, Gao W, et al. NAD+ metabolism: pathophysiologic mechanisms and therapeutic potential. *Signal Transduct Target Ther.Springer Nature*. 2020;5(1). doi:10.1038/s41392-020-00311-7

17. Kim S, Pelissari DM, Harada LO, et al. Long-term Mortality Trends Among Individuals With Tuberculosis: A Retrospective Cohort Study of Individuals Diagnosed With Tuberculosis in Brazil. *Clinical Infectious Diseases*. Published online April 18, 2025. doi:10.1093/cid/ciaf206

18. Meghji J, Auld SC, Bisson GP, et al. Post-tuberculosis lung disease: towards prevention, diagnosis, and care. *Lancet Respir Med*. 2025;13(5):460-472. doi:10.1016/S2213-2600(24)00429-6

19. Smirnova N, Bryan CS, Salindri AD, et al. Cavitary lung lesions and quality of life after TB. *International Journal of Tuberculosis and Lung Disease.International Union Against Tuberculosis and Lung Disease (The Union)*. 2024;28(10):505-507. doi:10.5588/ijtld.23.0590

20. Zhou A, Ni J, Xu Z, et al. Metabolomics specificity of tuberculosis plasma revealed by 1H NMR spectroscopy. *Tuberculosis*. 2015;95(3):294-302. doi:10.1016/j.tube.2015.02.038

21. Sharma R, Hartman TE, Beites T, et al. Metabolically distinct roles of NAD synthetase and NAD kinase definethe essentiality of NAD and NADP in Mycobacterium tuberculosis. *mBio*. 2023;14(4). doi:10.1128/mbio.00340-23

22. Abdellatif M, Trummer-Herbst V, Koser F, et al. Nicotinamide forthe treatment of heart failure with preserved ejection fraction. *Sci Transl Med*. 2021;13(580). doi:10.1126/scitranslmed.abd7064

23. Liu QY, Han F, Pan LP, Jia HY, Li Q, Zhang Z De. Inflammation responses in patients with pulmonary tuberculosis in an intensive care unit. *Exp Ther Med*. 2018;15(3):2719-2726. doi:10.3892/etm.2018.5775

24. Boni FG, Hamdi I, Koundi LM, Shrestha K, Xie J. Cytokine storm in tuberculosis and IL-6 involvement. *Infection, Genetics and Evolution.Elsevier B.V.* 2022;97. doi:10.1016/j.meegid.2021.105166

25. Yang TY, Lin CL, Yao WC, et al. How mycobacterium tuberculosis infection could lead to the increasing risks of chronic fatigue syndrome and the potential immunological effects: a population-based retrospective cohort study. *J Transl Med*. 2022;20(1). doi:10.1186/s12967-022-03301-1

26. Choi CJ, Choi WS, Kim CM, Lee SY, Kim KS. Risk of Sarcopenia and Osteoporosis in Male Tuberculosis Survivors: Korea National Health and Nutrition Examination Survey. *Sci Rep*. 2017;7(1). doi:10.1038/s41598-017-12419-y

27. Crescioli C. Targeting age-dependent functional and metabolic decline of human skeletal muscle: The geroprotective role of exercise, myokine IL-6, and vitamin D. *Int J Mol Sci.MDPI AG*. 2020;21(3). doi:10.3390/ijms21031010

28. Abdellatif M, Sedej S, Kroemer G. NAD+ Metabolism in Cardiac Health, Aging, and Disease. *Circulation.Lippincott Williams and Wilkins*. 2021;144(22):1795-1817. doi:10.1161/CIRCULATIONAHA.121.056589

29. Liu F, Yin X, Jiang W. Comprehensive Review and Meta-Analysis of Psychological and Pharmacological Treatment for Intermittent Explosive Disorder: Insights From Both Case Studies and Randomized Controlled Trials. *Clin Psychol Psychother.John Wiley and Sons Ltd*. 2025;32(1). doi:10.1002/cpp.70016

30. Gupta MB, Bagri S, Garg A, Singh DK, Choudhary P, Sahni S. Pulmonary function in cured pulmonary tuberculosis cases. *Indian Journal of Tuberculosis*. 2022;69(4):535-538. doi:https://doi.org/10.1016/j.ijtb.2021.08.024