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High prevalence of persistent tuberculosis-related symptoms 6 months after treatment in pulmonary tuberculosis

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ABSTRACT

Background The frequency and determinants of persistent symptoms after microbiological cure remain incompletely defined in pulmonary tuberculosis. We aimed to determine the prevalence of persistent tuberculosis-related symptoms 6 months after treatment initiation and identify associated predisposing factors.

Methods We analysed data from the prospective observational cohort study, enrolling adults treated for pulmonary tuberculosis at three tertiary hospitals in Korea between 2016 and 2018. Demographic, clinical and radiographic data, and symptoms were assessed using a standardised symptom checklist at baseline and at 2-month and 6-month follow-up visits. Symptom persistence was defined as the presence of any tuberculosis-related symptom at the 6-month visit. Multivariable logistic regression analysis was conducted to identify factors associated with persistent symptoms.

Results Among 354 participants (61% men, mean age of 58.5±19.4 years), symptom prevalence decreased from 80.2% at baseline to 25.1% at 6 months. Cough (14.4 %) and dyspnoea (7.6 %) were the most common persistent symptoms. Independent predictors of persistent symptoms included foreign nationality (adjusted OR (aOR) 5.586; 95% CI 1.618 to 19.28), chronic lung disease (aOR 5.034; 95% CI 1.995 to 13.26), presence of tuberculosis-related symptoms at 2 months (aOR 3.195; 95% CI 1.833 to 5.685) and bilateral infiltration on chest X-ray (aOR 1.933; 95% CI 1.018 to 3.650) in the multivariate analysis.

Conclusions A significant proportion of patients experience persistent tuberculosis-related symptoms even 6 months after treatment initiation. These findings highlight the need for ongoing clinical assessment and post-treatment care to address residual symptom burden following pulmonary tuberculosis.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Post-tuberculosis (TB) lung disease is increasingly recognised as a major cause of long-term morbidity among TB survivors, affecting up to 87% of patients. Functional impairment measured by spirometry is considered its hallmark, yet no standardised criteria exist for screening or diagnosis, and many patients remain symptomatic despite microbiological cure.

WHAT THIS STUDY ADDS

⇒ In this prospective cohort study, one-quarter of patients continued to experience TB-related symptoms 6 months after treatment initiation, with cough being the most common. Chronic lung disease, bilateral chest radiograph infiltration and presence of symptoms at 2 months were independently associated with persistent respiratory complaints, while low body mass index and rifampicin resistance predicted persistence of constitutional symptoms.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings underscore the importance of integrating systematic symptom assessment into TB follow-up care, especially at the 2-month milestone.

INTRODUCTION

Tuberculosis (TB) is a worldwide health concern with an estimated 10.8 million people being newly contracted in 2023.[1] Recent endeavours to deal with such burden have resulted in major improvements over the few years, with 88% of treatment success rate and 23% reduction in TB deaths in 2023 compared with 2015.[1] Although various preventive measures and anti-TB regimens have shown such great successes, persisting sequelae that continue after the treatment completion, or even after microbial cure, are now being recognised as a new, rising issue.[2]

Chronic respiratory abnormalities due to previous TB, or post-TB lung disease as a recently coined term, occur in a range of 18%–87% of the survivors.[2] The severity and prognosis of post-TB lung disease is quite heterogeneous among patients, including various patterns of lung damage involving the parenchyma, airways, pleura and even pulmonary vasculatures.[3] Post-TB lung disease also affects the psychological and socioeconomic well-being of the patient, often resulting in

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low quality of life and decreased social functioning.[4] Various secondary complications can occur as well, including secondary pulmonary infections, pulmonary hypertension, lung cancer and respiratory failure.[5–7] A recent study showed that the standardised mortality ratio among TB survivors was 2.91.[8]

Functional impairments measured by spirometry are known to be the hallmark of post-TB lung disease[9]; however, they are only in the stage of research investigation and no current definitive measures exist that can lead to practical screening or diagnosis guidelines.[10] There are also cases where patients have normal spirometry results while still suffering from ongoing symptoms.[11] Despite the clinical significance of the post-TB lung disease, not much research has been done on the symptomatology of such a phenomenon. In this study, we have explored the modality of TB-related symptoms regarding their persistence after treatment completion. We provide each of the TB-related symptoms of their prevalence, frequency and the related predisposing risk factors.

METHODS

Study design and setting

The Cohort Study of Pulmonary Tuberculosis is a prospective observational cohort study, in which adults aged 19 years or older with pulmonary TB were enrolled between November 2016 and September 2018 and followed them to evaluate treatment outcomes.[12] Patients were diagnosed with pulmonary TB when *Mycobacterium tuberculosis* was identified by microbiological testing or when clinicians made a clinical diagnosis based on compatible radiographic findings together with clinical features and response to anti-TB treatment. Patients were treated according to the Korean TB guidelines. The standard 6 months regimen for drug-susceptible TB consisted of isoniazid, rifampicin, ethambutol and pyrazinamide. In patients considered to be at increased risk of hepatotoxicity, pyrazinamide was omitted at the discretion of the attending physician, and a prolonged three-drug regimen consisting of isoniazid, rifampicin and ethambutol for 9 months was used as an alternative. Non-standard regimens included modified first-line regimens in which one or more drugs were substituted due to prior drug intolerance, or drug-resistance, and individualised regimens predominantly composed of second-line agents for patients with identified drug-resistance TB.

This study was conducted at three university-affiliated tertiary hospitals, which participated in the Public-Private Mix TB control project in the Republic of Korea. TB specialist nurses in this project provided education and support for the patients and monitored them for adherence to treatment.[13] Patients who were subsequently diagnosed as having inactive TB or pulmonary diseases other than TB were excluded, as were those who withdrew consent. For this study, those who missed 2-month and 6-month hospital visits were further excluded.

Data collection

All patient data regarding their demographic, socioeconomic and clinical information were collected at each hospital. Low body mass index (BMI) was defined as less than 18.5 kg/m^2. Comorbid conditions known to be associated with TB outcomes or respiratory symptoms were assessed at study enrollment. Diabetes mellitus was defined based on a current use of antidiabetic medication.[14] Chronic lung disease was defined as chronic airway disease, including chronic obstructive pulmonary disease, asthma or bronchiectasis, identified based on a prior physician diagnosis or a current use of inhaled respiratory medication.

Microbiological tests were performed at the time of TB diagnosis. Acid-fast bacilli smear and culture tests and nucleic acid amplification tests were performed for every patient. *Mycobacterium* culture was conducted using both solid (3% Ogawa media) and liquid (BACTEC MGIT 960 system). Rifampicin resistance was determined by both phenotypic and molecular drug susceptibility tests, including Xpert MTB/RIF and line probe assay. A chest X-ray was performed at the time of TB diagnosis. Radiographic lesion location was recorded for each of four lung fields: right upper lung field, right lower lung field, left upper lung field and left lower lung field. Bilateral

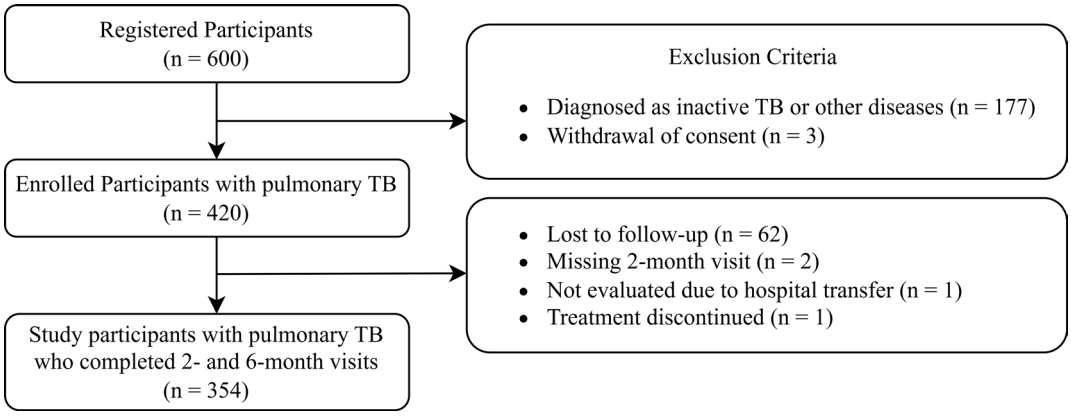


Figure 1 Flowchart of the study population. TB, tuberculosis.

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Table 1 Baseline characteristics of study participants according to presence of persistent tuberculosis-related symptoms at 6 months after initiating treatment

Characteristics	Total (n=354)	Persistent symptoms		P value
		No (n=265)	Yes (n=89)	
Male	216 (61.0%)	156 (58.9%)	60 (67.4%)	0.153
Age, years				0.588
Mean±SD	58.5±19.4	58.2±19.5	59.5±19.1	
Median (IQR)	60 (45–75)	60 (44–75)	60 (47–76)	
BMI <18.5 kg/m^{2*}	50 (14.3%)	31 (11.9%)	19 (21.3%)	**0.027**
Foreigner	15 (4.2%)	8 (3.0%)	7 (7.9%)	0.066
Tobacco use				**0.007**
Never smoked†	167 (47.2%)	136 (51.3%)	31 (34.8%)	
Has smoked	187 (52.8%)	129 (48.7%)	58 (65.2%)	
Comorbidities				
Diabetes	58 (16.4%)	44 (16.6%)	14 (15.7%)	0.847
Chronic lung disease	25 (7.1%)	10 (3.8%)	15 (16.9%)	**<0.001**
TB symptoms (initial)	284 (80.2%)	204 (77.0%)	80 (89.9%)	**0.008**
TB symptoms (2 months)	156 (44.1%)	96 (36.2%)	60 (67.4%)	**<0.001**
Past TB history	73 (20.6%)	53 (20.0%)	20 (22.5%)	0.618
Positive AFB culture	243 (68.64%)	181 (68.30%)	62 (69.66%)	0.811
Positive AFB smear	93 (26.3%)	66 (24.9%)	27 (30.3%)	0.314
Bilateral infiltration on CXR	75 (21.2%)	49 (18.5%)	26 (29.2%)	**0.032**
Rifampicin resistance	37 (10.5%)	24 (9.1%)	13 (14.6%)	0.139
Treatment regimen				0.054
Standard‡	333 (94.1%)	253 (95.5%)	80 (89.9%)	
Others	21 (5.9%)	12 (4.5%)	9 (10.1%)	

*Four participants missing (n=350).
†Smoked less than 100 pack-years.
‡Standard treatment regimen consisted of isoniazid, rifampicin and ethambutol with or without pyrazinamide.
.AFB, acid-fast bacilli; BMI, body mass index; CXR, chest X-ray; TB, tuberculosis.

involvement on chest X-ray was defined as the presence of any radiographic lesions in at least one lung field on both the right and left sides. Chest CT was performed at the discretion of the attending physician, and detailed radiologic findings, including cavitation, consolidation, nodules, bronchiectasis, fibrotic scarring and atelectasis, were recorded.

Definition of TB-related symptoms

The primary outcome of our study was the persistence of TB-related symptoms at 6-month hospital visit. TB-related symptoms were assessed as patient-reported outcome measures using a structured symptom checklist (online supplemental table 1) administered at each study visit.[15] The checklist included respiratory and constitutional symptoms commonly associated with pulmonary TB (cough, sputum, dyspnoea, chest pain, blood-tinged sputum, weight loss, fever, night sweats, general weakness and anorexia). Presence of any one of those symptoms at the 6-month visit was considered as symptom persistence.

To improve objectivity and reduce misclassification, symptom assessment was performed using a two-step process. First, trained TB specialist nurses conducted standardised interviews to document patient-reported symptoms. Second, attending physicians reviewed and confirmed the presence of symptoms based on clinical evaluation, including medical history, physical examination and available clinical and radiographic information at the time of the visit. Symptoms considered to be clearly attributable to alternative acute conditions were not classified as TB-related symptoms. Although a formally validated symptom instrument was not used, the structured checklist and physician confirmation process were implemented to enhance consistency and clinical reliability across study sites, reflecting routine clinical assessment in real-world TB care. To improve the objectivity of symptom evaluation, standardised clinical measures were collected at each visit, including body weight, body temperature, Eastern Cooperative Oncology Group performance status and the modified Medical Research Council dyspnoea

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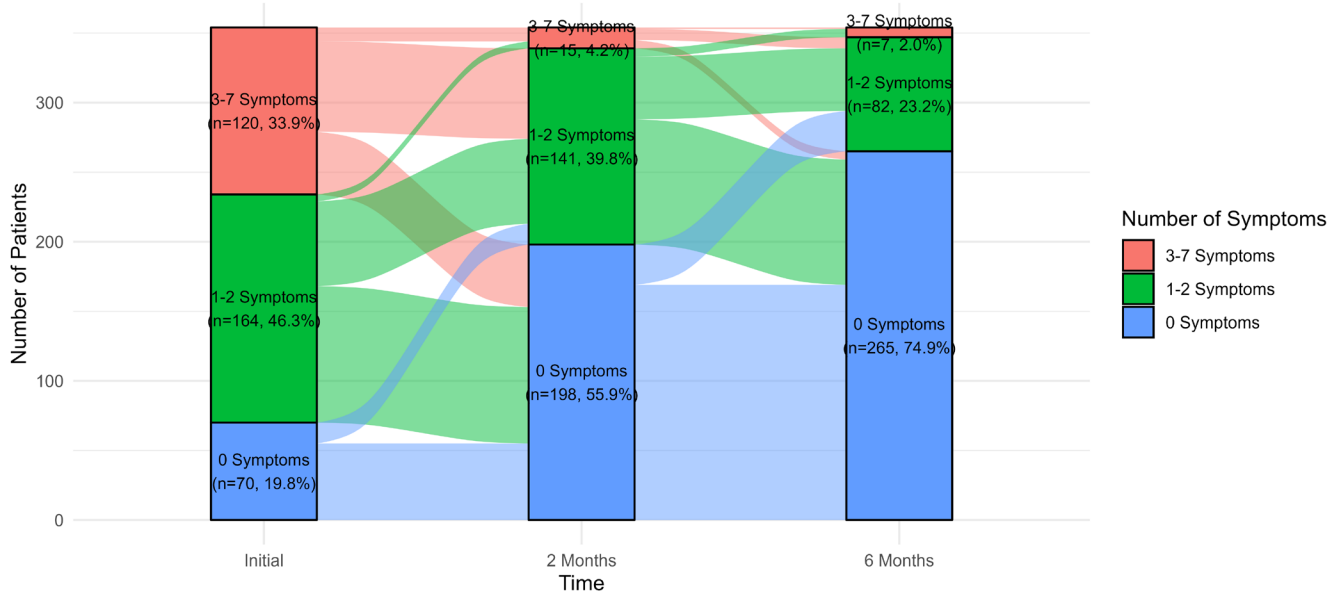


Figure 2 Changes in trend of the number of symptoms across treatment follow-up.

scale.[16] These objective and semi-objective assessments were used alongside patient-reported outcomes to provide a more comprehensive evaluation of symptom status. In addition, symptom assessment focused on symptoms present within the preceding 4 weeks, and for patients with pre-existing chronic symptoms, worsening compared with baseline was specifically evaluated to reduce misclassification.

Statistical analyses

For comparing the means or frequencies between two groups, Mann-Whitney U test was used for continuous variables and Fisher's exact test was used for categorical variables. After the univariate logistic regression analysis, variables that had p value <0.20 were included subsequently in the multivariate logistic regression analysis to identify factors associated with persistent TB-related symptoms. Age and sex were included as mandatory covariates in every multivariate logistic regression analysis for adjustments. Two-sided p value under 0.05 was considered statistically significant. All statistical tests were performed using the R V.4.5.0 (R Core Team 2025). An R package 'alluvial' was used to create the alluvial plot.[12]

We further conducted sub-group analysis to identify factors associated with each class of persistent TB-related symptoms, such as cough or sputum, respiratory symptoms and constitutional symptoms. We have classified TB-related symptoms into three subgroups: (1) cough or sputum, representing the cardinal symptoms of pulmonary TB;[17] (2) respiratory symptoms, a broader category encompassing cough, sputum, dyspnoea, chest pain and blood-tinged sputum and (3) constitutional symptoms, such as weight loss, fever, night sweats, general weakness and anorexia. Subgroup 1 is nested within Subgroup 2 by design, as we aimed to examine whether risk factors for symptom persistence differed when focusing on the hallmark TB symptoms vs the full spectrum of respiratory complaints, which may reflect distinct post-TB structural sequelae such as bronchiectasis and fibrosis.[3 18]

Patient involvement

Patients were not directly involved in setting the research question or developing the study design, as this study was conducted within the framework of the national Public-Private Mix tuberculosis control programme in Korea. However, patients' experiences and perspectives were indirectly incorporated through structured symptom assessments carried out by attending physicians and TB specialist nurses, which ensured that patient-reported outcomes were central to the study. Patients contributed to the study through detailed reporting of their TB-related symptoms at baseline, 2 months and 6 months, which shaped both the choice of outcome measures and the conduct of the research. Recruitment and follow-up procedures were facilitated by TB specialist nurses, who provided education, adherence support and systematic monitoring, thereby minimising participant burden.

Although patients and the public were not involved in governance or oversight of the study, the results will be shared with participants and local TB care teams. Plans for dissemination include providing accessible summaries to patients through hospital TB education programmes and integrating findings into community-level TB management strategies to support post-treatment care.

RESULTS

A total of 354 participants with pulmonary TB who completed 2-month and 6-month hospital visits were included in the analysis (figure 1). Persistent symptoms

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Table 2 Logistic regression analysis for persistent tuberculosis-related symptoms at 6 months after the initiation of anti-tuberculosis treatment

	Univariate		Multivariate	
Characteristics	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Male	0.692 (0.413 to 1.140)	0.154	1.418 (0.606 to 3.429)	0.428
Age, years	1.004 (0.991 to 1.016)	0.577	1.001 (0.986 to 1.017)	0.891
BMI <18.5 kg/m^2*	2.014 (1.058 to 3.759)	**0.030**	1.861 (0.911 to 3.745)	0.084
Foreigner	2.742 (0.935 to 7.867)	0.058	5.586 (1.618 to 19.28)	0.006
Tobacco use				
Never smoked†	Reference		Reference	
Has smoked	1.972 (1.206 to 3.275)	**0.008**	2.169 (0.959 to 5.186)	0.071
Comorbidities				
Diabetes	1.067 (0.565 to 2.118)	0.847		
Chronic lung disease	5.169 (2.254 to 12.35)	**<0.001**	5.034 (1.995 to 13.26)	**<0.001**
TB symptoms (initial)	2.658 (1.319 to 5.963)	**0.010**	1.837 (0.819 to 4.516)	0.159
TB symptoms (2 months)	3.642 (2.207 to 6.126)	**<0.001**	3.195 (1.833 to 5.685)	**<0.001**
Past TB history	0.863 (0.488 to 1.569)	0.618		
Positive AFB culture	1.066 (0.638 to 1.813)	0.811		
Positive AFB smear	1.313 (0.765 to 2.218)	0.315		
Bilateral infiltration on CXR	1.819 (1.038 to 3.144)	**0.034**	1.933 (1.018 to 3.650)	**0.042**
Rifampicin resistance	1.718 (0.813 to 3.490)	0.142	1.477 (0.617 to 3.395)	0.367
Treatment regimen				
Standard‡	Reference		Reference	
Others	2.372 (0.937 to 5.810)	0.060	1.662 (0.581 to 4.585)	0.330

Bold indicates two-sided p-values <0.05.
*Four patients missing (n=350).
†Smoked less than 100 pack-years.
‡Standard treatment regimen consisted of isoniazid, rifampicin and ethambutol with or without pyrazinamide.
CXR, chest X-ray.AFB, acid-fast bacilli; BMI, body mass index; TB, tuberculosis.

at 6 months were observed in 89 (25.1%) participants. There were 216 men (61.0%) among all participants with the average age of 58.5±19.4 years (table 1). Low BMI was more prevalent in patients with TB-related symptoms at 6 months after treatment initiation (p=0.027). Compared with participants who did not have TB-related symptoms at 6 months, those with persistent symptoms were more likely to have smoking history (p=0.007) and chronic lung disease (p<0.001) than the other group. Subgroup analysis regarding chronic lung disease showed no specific disease having significant differences between the two groups (online supplemental table 2). Bilateral infiltration on chest radiographs was seen more frequently in those with persistent symptoms (p=0.032). Chest CT findings were broadly comparable between participants with and without persistent symptoms, and no individual radiographic feature showed a statistically significant association with symptom persistence (online supplemental table 3).

The proportion of participants with TB-related symptoms decreased from 80.2% (284 participants) at baseline to 44.1% (156) at 2 months and 25.1% (89) at 6 months (figure 2). The presence of TB symptoms at the initial visit (p=0.004) and 2 months (p<0.001) after treatment was significantly associated with persistent symptoms at 6 months. At baseline, the most common symptoms were cough (219 patients, 61.9%), sputum production (163, 46.1%) and dyspnoea (76, 21.8%) (online supplemental table 4). Constitutional symptoms such as weight loss (17.2%) and fever (15.8%) were also frequent. By 6 months, the proportion of patients with any TB-related symptoms decreased to 25.1%, with cough (14.4%) and dyspnoea (7.6%) being the most persistent. The total number of symptoms in each patient at baseline was mostly 1 or 2 (46.3%), which decreased to 23.2% in the final visit at 6 months. Those with 3–7 symptoms declined from 33.9% initially to 2.0% at 6 months.

In the multivariate logistic regression analysis for persistent TB-related symptoms at 6 months (table 2), being a foreigner (adjusted OR (aOR) 5.586; 95% CI 1.618 to 19.28), having chronic lung disease (aOR 5.034; 95% CI 1.995 to 13.26), presence of TB-related symptoms at 2 months (aOR 3.195; 95% CI 1.833 to 5.685) and bilateral infiltration on chest X-ray (aOR 1.933; 95% CI 1.018

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Table 3 Univariate and multivariate logistic regression analysis for persistent TB-related symptom subgroups (cough or sputum, respiratory symptoms, constitutional symptoms) at 6 months after the initiation of anti-tuberculosis treatment

	Cough or sputum		Respiratory symptoms		Constitutional symptoms	
	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
Characteristics	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)
Male	0.786 (0.440 to 1.373)	1.892 (0.733 to 5.152)	0.618 (0.362 to 1.031)	1.263 (0.532 to 3.089)	1.316 (0.373 to 4.452)	2.243 (0.535 to 9.753)
Age, years	**1.015 (1.001 to 1.031)**	1.012 (0.995 to 1.030)	1.004 (0.991 to 1.017)	1.000 (0.985 to 1.016)	1.006 (0.975 to 1.040)	1.007 (0.969 to 1.050)
BMI <18.5 kg/m^{2*}	**2.195 (1.091 to 4.266)**	2.124 (0.982 to 4.458)	**1.956 (1.018 to 3.672)**	1.804 (0.875 to 3.648)	**5.444 (1.514 to 18.81)**	**6.666 (1.520 to 30.06)**
Foreigner	1.139 (0.254 to 3.718)		2.194 (0.716 to 6.274)	**4.827 (1.384 to 16.28)**	2.350 (0.124 to 13.63)	
Tobacco use						
Never smoked†	–	–	–	–	–	
Has smoked	**1.909 (1.095 to 3.406)**	**2.661 (1.056 to 7.302)**	**2.177 (1.315 to 3.670)**	2.187 (0.958 to 5.290)	0.737 (0.209 to 2.492)	
Comorbidities						
Diabetes	0.932 (0.467 to 1.998)		0.992 (0.525 to 1.973)		1.993 (0.371 to 36.93)	
Chronic lung disease	**4.092 (1.729 to 9.490)**	**2.819 (1.106 to 7.061)**	**5.550 (2.416 to 13.28)**	**5.550 (2.191 to 14.69)**	3.092 (0.454 to 12.90)	2.252 (0.254 to 14.15)
TB symptoms (initial)	**3.409 (1.437 to 10.07)**	1.812 (0.707 to 5.597)	**2.476 (1.227 to 5.562)**	1.681 (0.750 to 4.120)	NA	NA
TB symptoms (2 months)	**3.819 (2.155 to 7.000)**	**3.117 (1.693 to 5.911)**	**3.748 (2.249 to 6.380)**	**3.282 (1.866 to 5.902)**	**6.000 (1.518 to 39.74)**	**6.196 (1.297 to 46.99)**
Past TB history	0.912 (0.483 to 1.815)		0.872 (0.489 to 1.605)		0.441 (0.129 to 1.722)	
Positive AFB culture	1.100 (0.618 to 2.023)		1.128 (0.668 to 1.945)		0.793 (0.234 to 3.082)	
Positive AFB smear	1.479 (0.812 to 2.633)	1.084 (0.555 to 2.060)	1.329 (0.768 to 2.259)		1.631 (0.419 to 5.532)	
Bilateral infiltration on CXR	1.051 (0.529 to 1.984)		**1.979 (1.126 to 3.433)**	**2.039 (1.075 to 3.843)**	0.822 (0.124 to 3.276)	
Rifampicin resistance	1.064 (0.413 to 2.418)		1.389 (0.632 to 2.880)		**12.08 (3.453 to 44.12)**	**12.59 (3.088 to 56.64)**
Treatment regimen						
Standard‡	–		–	–	–	–
Others	0.743 (0.170 to 2.283)		2.046 (0.784 to 5.039)	1.508 (0.518 to 4.143)	3.789 (0.553 to 16.04)	2.326 (0.265 to 13.93)

Bold indicates two-sided p-values <0.05.
*Four patients missing (n=350).
†Smoked less than 100 pack-years.
‡Standard treatment regimen consisted of isoniazid, rifampicin, and ethambutol with or without pyrazinamide.
CXR, chest X-ray.AFB, acid-fast bacilli; aOR, adjusted OR; BMI, body mass index; TB, tuberculosis.

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to 3.650) were significantly associated with symptom persistence. Low BMI, history of smoking and presence of initial TB-related symptom were statistically significant in the univariable logistic regression analysis but did not reach statistical significance in the adjusted model.

In all the subgroup analysis, presence of TB-related symptoms at 2 months was significantly associated with persistent cough or sputum, respiratory symptoms and constitutional symptoms at 6 months (table 3). In addition, ever smoker and chronic lung disease were significantly associated with persistent cough or sputum at 6 months. For overall respiratory symptoms, being a foreigner, chronic lung disease and bilateral infiltration on chest X-ray were independently associated with persistence. Regarding constitutional symptoms, low BMI and rifampicin resistance remained statistically significant in the adjusted model.

DISCUSSION

In this prospective cohort study of people treated for pulmonary TB, we found that a substantial proportion of patients continued to report TB-related symptoms even 6 months after treatment initiation. At baseline, 80.2% of patients reported at least one respiratory symptom, and although this proportion declined over time, 25.1% still had persistent symptoms at 6 months. Cough was the most frequent symptom throughout the study period. Logistic regression analyses identified chronic lung disease, presence of symptoms at 2 months and bilateral chest X-ray infiltration as consistent risk factors for persistent respiratory symptoms. In addition, low BMI and rifampicin resistance were associated with the persistence of constitutional symptoms. These findings highlight the heterogeneous and enduring nature of post-TB morbidity, even among those who completed standard anti-TB therapy.

The persistence of TB-related symptoms at 6 months has important clinical implications. While microbiological cure remains a critical goal of TB treatment, from a patient-centred care perspective, achieving a life free from ongoing discomfort or limitations after treatment is equally important.[4] In this context, assessing the presence of residual symptoms at the 6-month mark is a meaningful indicator of treatment success and long-term health outcomes, guiding the need for further clinical evaluation or supportive care.

In some patients, these persistent symptoms may reflect ongoing physiological consequences of severe pulmonary damage, which can develop during active TB and persist despite microbiological cure. Identifying such structural abnormalities through follow-up imaging or pulmonary function testing is crucial, as appropriate interventions, including bronchodilators, pulmonary rehabilitation or long-term respiratory care, may be necessary.[19] Even after completing treatment, the lingering presence of symptoms can lead to ongoing distress, as patients feel that the burden of TB has not fully left them, resulting in anxiety, fear and mental strain that ultimately impair their quality of life.[20 21] Therefore, symptom persistence should not be dismissed as benign and tailored symptomatic treatment and psychosocial support should be considered as part of comprehensive post-TB care.

The strong association between chronic lung disease and persistent respiratory symptoms highlights the importance of assessing baseline lung function and identifying pre-existing comorbidities when predicting long-term outcomes. In our cohort, chronic lung disease was defined as having at least one of chronic obstructive pulmonary disease, asthma or bronchiectasis and was present in less than one-tenth of participants in our study. Although the composite variable was strongly associated with symptom persistence, a post hoc subgroup analysis revealed no statistically significant differences for any individual disease subtype. Unsurprisingly, however, this is most likely attributable to the limited statistical power resulting from the small number of patients within each subcategory. Additionally, a form of Simpson's paradox may contribute, in such a way that heterogeneous conditions aggregated together reveal a strong overall signal that is diluted when examined separately within each small stratum.[22] We weigh our interpretation more heavily on the former, believing that small sample size is the primary reason behind this discordance. A severe form of pulmonary TB, as indicated by bilateral infiltration on chest radiography, may exacerbate structural lung damage and lead to lasting functional impairments that persist even after microbiological cure, contributing to ongoing respiratory symptoms. The observation that ever-smokers were more likely to report persistent cough or sputum suggests the possible presence of undiagnosed chronic bronchitis or other smoking-related airway diseases. These findings underscore the need for comprehensive respiratory evaluation, including smoking history,[23] in the management of TB patients with prolonged symptoms.

Previous studies have emphasised the importance of structured follow-up during TB treatment, because it is closely linked with better treatment outcomes.[24 25] Current TB guidelines recommend regular follow-up visits to monitor microbiological response, laboratory findings and medication adherence.[26–30] Our findings support these recommendations, emphasising that clinicians should carefully evaluate symptom changes at each follow-up visit. Based on our findings, assessing symptoms at the 2-month visit and identifying any modifiable factors to cause lung damage might help improve patient-centred outcome.

Constitutional symptoms reflect the activity of *Mycobacterium tuberculosis* and are often associated with a high bacillary burden. These symptoms are also driven by elevated systemic inflammatory mediators, such as interleukin-1 and tumour necrosis factor-alpha,[31] indicating that they may serve as surrogate markers of the host immune response. In this study, underweight and rifampin resistance were significantly associated with the persistence of constitutional symptoms at 6 months. In underweight individuals, impaired nutritional status may weaken host immunity, leading to

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dysregulated inflammatory responses and sustained production of pro-inflammatory cytokines, which in turn contribute to prolonged constitutional symptoms.[26] Rifampicin-resistant TB may result in delayed bacterial clearance and prolonged antigenic stimulation, thereby causing low-grade chronic inflammation and persistent systemic symptoms even after completion of standard therapy.[32]

Being a foreigner was independently associated with persistent respiratory symptoms at 6 months. However, this finding should be interpreted with caution given the small number of foreign participants and the correspondingly wide CI. Although data on countries of origin were collected, these are not reported to protect participant anonymity and to avoid potential stigmatisation of specific nationalities in the context of TB. Nevertheless, several plausible mechanisms may explain this association. Foreign-born TB patients might face barriers to healthcare access and treatment adherence, including language barriers, unfamiliarity with the healthcare system, TB-related stigma and limited social support networks.[33] A systematic review of qualitative studies in low-incidence countries found that migrants frequently encountered challenges in accessing diagnostic and treatment services, with stigma and communication difficulties identified as the most prominent barriers.[34] In the Korean context, immigrants with TB have been shown to have lower treatment success rates compared with Korean nationals, although this gap has narrowed following the implementation of pre-entry screening policies.[35] Furthermore, socioeconomic disparities and immigrant status have been identified as strong independent predictors of multidrug-resistant TB in Korea, suggesting that structural disadvantages may compound the clinical course of TB in this population.[36 37] These factors, particularly language barriers that may hinder accurate symptom communication and follow-up adherence, combined with potential socioeconomic vulnerabilities, could plausibly contribute to prolonged symptom burden.

This study has several limitations. First, a formally validated patient-reported outcome instrument was not used in our study; however, no validated tool currently exists that is specifically designed to assess TB-related symptom persistence during or after treatment, a gap identified as a key research priority by recent international consensus efforts on post-TB lung disease. Second, we also recognise that symptoms could not be definitively attributed to TB sequelae rather than alternative causes. Third, spirometry and radiologic findings were not uniformly collected across participants, limiting the ability to correlate symptoms with objective lung impairment. To partially address these limitations, chronic lung disease and smoking history were included as covariates in multivariable models to account for major non-TB contributors to persistent respiratory symptoms. Nevertheless, some degree of misclassification and potential overestimation of TB-attributable symptom persistence cannot be excluded. Fourth, patients with a prior history of TB treatment were included in the cohort, and we could not determine whether their persistent symptoms represented a continuation from previous episodes or a relapse following a period of symptom remission. These patients may have had pre-existing structural lung damage from prior TB, potentially predisposing them to bilateral chest X-ray infiltration and rifampicin resistance, which could confound the observed associations with symptom persistence. Baseline pulmonary function testing was not routinely performed at the time of TB diagnosis, precluding comparison of pre-treatment and post-treatment functional status. Although prior TB history was not a significant predictor in our multivariable models, the possibility of residual confounding from unmeasured sequelae of previous TB episodes cannot be excluded. Fifth, the study was conducted in tertiary university-affiliated hospitals in Korea within a public-private mix TB control model, which may limit generalisability to primary care settings, community-based programmes, or other countries with different TB epidemiology and healthcare systems.

In conclusion, persistent symptoms remain common 6 months after treatment initiation in participants with pulmonary TB, with respiratory complaints affecting one quarter of participants. Early symptom burden, pre-existing lung disease and host vulnerability factors such as low BMI were associated with prolonged morbidity. These findings support the need for integrated post-treatment care strategies that address ongoing symptoms and functional recovery in TB survivors.

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Patient consent for publication Consent obtained directly from patient(s)

Ethics approval This study involves human participants and was approved. The study protocol was approved for its scientific content and compliance with human subject research regulations by the institutional review boards of Chungbuk National University Hospital (No. 2016-10-003). Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available upon reasonable request. The ownership of the primary datasets lies with the Korea Disease Control and Prevention Agency. The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request with permission of the Korea Disease Control and Prevention Agency. The corresponding author should initially be contacted for the request to access the raw data.

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