Clinical profiles of subclinical disease among pulmonary tuberculosis patients: a prospective cohort study in South Korea

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Abstract

Background: Subclinical tuberculosis (TB) is a potential target for public health intervention because its early identification may reduce TB transmission. Here, we have described clinical and laboratory findings of subclinical disease among pulmonary TB patients.

Methods: In this prospective cohort study, we enrolled adult patients with pulmonary TB between 2016 and 2018. Subclinical TB was defined as the presence of radiographic or microbiologic test results consistent with TB without clinical symptoms. We implemented two-stage symptom assessment using a predefined TB symptom checklist. Demographic, clinical, and laboratory data were compared between subclinical and active disease using the multivariate binary logistic regression analysis. We evaluated treatment outcomes in the drug-susceptible cohort.

Results: Among 420 enrolled patients, 81 (19.3%) had subclinical TB. Multivariate analysis showed that age <65 years was the only significant variable associated with subclinical disease. Subclinical disease had a significantly lower proportion of acid-fast bacilli smear and culture positivity and multiple lobe involvement compared to active disease. Among 319 patients with treatment success in the drug-susceptible cohort, six (1.9%) recurrent cases were identified, and all were active disease. Patients with subclinical disease had a higher proportion of favorable outcomes; however, its odds ratio was insignificant.

Conclusions: Nearly one-fifth of tuberculosis cases were subclinical under the universal health coverage in South Korea. Despite its milder clinical presentation, the treatment outcomes of subclinical TB were not significantly different from that of active disease.

Background

The ‘End TB Strategy’ of the World Health Organization (WHO) seeks to reduce tuberculosis (TB) incidence by 90% and TB deaths by 95% by 2035.[1] The key approaches are optimum use of existing interventions, availability and wide use of new tools to improve efforts to find and treat people with active TB, and universal screening of individuals at high risk. Thus, the diagnosis of subclinical TB, which could allow the treatment of individuals before they become symptomatic and infectious, has been highlighted as essential to make significant progress for the WHO’s target.

Although our current understanding of *Mycobacterium tuberculosis* infection focuses on addressing one of two disease states, latent TB infection or active TB, recent research has demonstrated that human TB infection exists within a continuous spectrum of metabolic bacterial activity and antagonistic immunological responses.[2] Latent TB infection, which undergoes an imbalance of bacterial activities and host defenses, leads to disease progression through a subclinical phase of active infection.[3] Those patients with active and culture-positive disease who are asymptomatic are described having subclinical TB disease.[4]

TB screening using chest radiography is regularly performed for adults as part of health examinations for health insurance subscribers in South Korea.[5] It is mandatory for healthcare works, teachers, and workers at nursery and welfare facilities to undergo regular TB screening. The government of South Korea recently strengthened the strategies of TB elimination, which highlighted the early detection of TB infection in vulnerable populations such as older and homeless people. These health policies in South Korea have increased the detection of subclinical TB; however, its clinical characteristics and outcomes are not well understood. We hypothesized that subclinical TB would have milder disease activities with a lower bacterial burden and, thus, better clinical outcomes than active TB. Here, we have described the clinical and laboratory findings and treatment outcomes of subclinical disease among pulmonary TB patients.

Methods

Study design and subjects

We enrolled adult patients with pulmonary TB from the cohort study of pulmonary tuberculosis (COSMOTB) between November 2016 and September 2018 to compare the clinical characteristics of active and subclinical TB. Briefly, COSMOTB is a prospective observational cohort study to assess the prevalence of discordant results of phenotypic and molecular drug susceptibility tests.[6] COSMOTB was conducted at three university-affiliated tertiary hospitals in South Korea that participate in the public-private mix project for TB control in South Korea. TB specialist nurses under this project educate TB patients and monitor them for medication adherence and adverse drug reactions.

Definition of subclinical and active diseases

Patients were categorized as having active TB or subclinical TB. Active TB was defined as the presence of clinical TB-related symptoms with radiographic abnormalities or microbiologic evidence of *M. tuberculosis*. Subclinical TB was defined as the presence of radiographic or microbiologic test results consistent with TB without clinical symptoms. We implemented two-stage symptom assessment using a predefined checklist, which listed TB-related symptoms, such as cough, sputum, fever, general weakness, dyspnea, chest pain, body weight loss, and hemoptysis. First, TB patients met a TB specialist nurse at the hospital, who interviewed and identified patients' TB-related symptoms. Subsequently, patients met with a physician at the clinic, who reconfirmed their symptoms and their duration. As patients were identified as asymptomatic after two-stage assessment, they were categorized as subclinical TB disease.

Data collection

Participants were evaluated at each hospital on study entry. Demographic, clinical, and laboratory data were prospectively collected from enrolled patients using a case report form upon study entry. Acid-fast bacilli (AFB) smears using light and fluorescent microscopy and nucleic acid amplification test (NAAT) were conducted at each hospital. *Mycobacterium* culture testing using both solid (3% Ogawa media) and liquid (BACTEC MGIT 960 system, BD, NJ, USA) cultures were performed at the reference laboratory.

Culture-based phenotypic drug susceptibility tests were performed using the absolute concentration method on Löwenstein-Jensen medium.

Statistical analyses

Continuous variables are presented as means and standard deviations or medians and interquartile ranges, whereas discrete variables are presented as frequencies or percentages. To compare the baseline characteristics of patients with active or subclinical TB, univariate analysis was performed using the chi-squared test. Subsequently, we selected age, sex, and other clinical variables with p-values < 0.20 based on the univariate analysis and further performed multivariate binary logistic regression to evaluate the possible association between variables and subclinical TB.

For regression, unknown data were regarded as missing values. A p-value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS software (Statistical Product and Service Solutions, Chicago, IL, USA).

Sample size

We selected nine variables a priori for inclusion into our model, such as age at diagnosis, sex, body mass index, chronic respiratory disease, prior TB history, results of AFB smear and culture and NAAT. Assuming 20% of subclinical disease, we required a sample size of 400 to ensure a minimum of 10 events per variable, which are needed to minimize bias in logistic regression models[7].

Treatment outcomes

Participants were evaluated at 2 weeks, 4 weeks, 2 months, 4 months, 6 months, 9 months, 12 months, and 24 months after initiating anti-TB treatment in order to collect their treatment outcome. Those with successful outcomes were also followed for at least 1 year to identify recurrence. Treatment outcomes were defined in accordance with the Korean TB guidelines that were adopted from the WHO's definition. Treatment success was the sum of cured and treatment-completed patients within 1 year of anti-TB treatment. Favorable outcome was defined as patients who had achieved treatment success without recurrence within the post-treatment 1-year follow-up period. We evaluated association between subclinical disease and treatment outcome in the drug-susceptible cohort comprising patients with positive culture results susceptible to both isoniazid and rifampin and patients clinically diagnosed with TB without microbiological evidence using binary logistic regression and adjusting for age and sex.

Results

After screening 600 patients with presumptive pulmonary TB, 339 patients with active disease and 81 patients with subclinical disease were finally enrolled in this study (Fig. 1). Table 1 summarizes the baseline characteristics of the 420 enrolled patients. The mean patient age was 59.2 ± 19.6 years, with 258 men (61.4%). Patients with subclinical TB were younger than those with active TB (51.9 ± 19.2 vs. 61.0 ± 19.3 years, p = 0.000). The positivity of AFB smear and culture tests and NAAT among patients

with active disease were significantly higher than that among patients with subclinical disease. The prevalence of chronic pulmonary disease and prior TB history were similar between patients with subclinical and active disease. Multivariate analysis showed that age < 65 years was the only significant variable associated with subclinical disease, and positivity of initial NAAT was significantly associated with active disease (Table 2).

Table 1
Baseline characteristics of enrolled patients with active and subclinical TB disease

Variables	All patients (n = 420)	Active TB disease (n = 339)	Subclinical TB disease (n = 81)	P-value[2]
Sex				
Male	258 (61.4%)	208 (61.4%)	50 (61.7%)	0.951
Female	162 (38.6%)	131 (38.6%)	31 (38.3%)	
Age (years)				
< 65	237 (56.4%)	178 (52.5%)	59 (72.8%)	0.001
≥ 65	183 (43.6%)	161 (47.5%)	22 (27.2%)	
Body mass index (kg/m^2)[1]				
< 18.5	65 (15.7%)	58 (17.1%)	7 (8.6%)	0.062
≥ 18.5	348 (84.3%)	276 (81.4%)	72 (88.9%)	
Comorbidities				
Chronic respiratory disease	30 (7.1%)	28 (8.3%)	2 (2.5%)	0.069
Diabetes mellitus	75 (17.9%)	60 (17.7%)	15 (18.5%)	0.863
Prior TB history	83 (19.8%)	70 (20.6%)	13 (16.0%)	0.350
Initial AFB smear test result				
Positive	116 (27.6%)	105 (31.0%)	11 (13.6%)	0.002
Negative	304 (72.4%)	234 (69.0%)	70 (86.4%)	
Initial AFB culture test result				

TB, tuberculosis; AFB, acid-fast bacilli; NAAT, nucleic acid amplification test; CXR, chest x-ray; INH, isoniazid; RIF, rifampicin

[1] Unknown data are regarded as missing.

[2] chi-square test

Variables	All patients (n = 420)	Active TB disease (n = 339)	Subclinical TB disease (n = 81)	P-value[2]
Positive	289 (68.8%)	245 (72.3%)	44 (54.3%)	0.002
Negative	131 (31.2%)	94 (27.7%)	37 (45.7%)	
Initial NAAT result[1]				
Positive	264 (65.5%)	228 (67.3%)	36 (46.2%)	0.000
Negative	139 (34.5%)	97 (28.6%)	42 (53.8%)	
Drug susceptible test[1]				
Susceptible to both INH and RIF	249 (87.1%)	212 (87.2%)	37 (86.0%)	0.829
Resistant to either INH or RIF	37(12.9%)	31 (12.8%)	6 (14.0%)	

TB, tuberculosis; AFB, acid-fast bacilli; NAAT, nucleic acid amplification test; CXR, chest x-ray; INH, isoniazid; RIF, rifampicin

[1] Unknown data are regarded as missing.

[2] chi-square test

Table 2
Multivariate analysis for factors associated with subclinical tuberculosis diseases compared to active tuberculosis disease

Variables	Adjusted OR (95% CI)	p-value
Male	1.6 (0.62–1.83)	0.826
Age < 65 years	2.24 (1.26–4.01)	0.006
BMI < 18.5 kg/m^2	0.65 (0.27–1.54)	0.324
Chronic respiratory diseases	0.35 (0.08–1.55)	0.167
Initial AFB smear test (+)	0.57 (0.26–1.26)	0.166
Initial AFB culture test (+)	0.48 (0.44–1.48)	0.481
Initial NAAT (+)	0.53 (0.29–0.97)	0.040

OR, odds ratio; CI, confidence interval; BMI, body mass index; AFB, acid-fast bacillus; NAAT, nucleic acid amplification test

We also compared the radiographic findings of chest computed tomography (CT) between subclinical and active disease (Table 3). Among 420 enrolled patients, 412 (98.1%) had undergone chest CT. Subclinical disease had a significantly higher proportion of single lobe involvement compared to active disease (70.4% vs. 57.7%, p = 0.023). Active disease was associated with radiographic findings such as consolidation and fibrotic scar. Among 412 patients with chest CT, 248 (60.1%) had undergone bronchoscopy for microbiological tests (Fig. 2). Among 168 patients with multiple lobe involvement on chest CT, patients with subclinical disease underwent significantly more bronchoscopy than did patients with active disease (20 [83.3%] vs. 84 [58.3%], p = 0.020). However, the positivity of AFB culture tests between bronchoscopic and sputum specimens was similar among all patients, regardless of symptoms and extent of lobe involvement on chest CT.

Table 3
Comparison of chest computed tomography findings of active and subclinical tuberculosis diseases

Radiographic findings	All patients (n = 412)	Active TB disease (n = 331)	Subclinical TB disease (n = 81)	p-value
Extent of lobe involvement				
Single lobe	244 (60.2%)	187 (57.7%)	57 (70.4%)	0.023
Multiple lobes	168 (41.7%)	144 (44.7%)	24 (29.6%)	
Tree-in-bud sign	247 (60.0%)	191 (57.7%)	56 (69.1%)	0.060
Cavitation	165 (40.0%)	129 (39.0%)	36 (44.4%)	0.368
Consolidation	242 (58.7%)	204 (61.6%)	38 (46.9%)	0.016
Fibrotic scar	73 (17.7%)	65 (19.6%)	8 (9.9%)	0.039
Atelectasis	71 (17.2%)	62 (18.7%)	9 (11.1%)	0.104
Emphysema	58 (14.1%)	45 (13.6%)	13 (16.0%)	0.569
Bronchiectasis	82 (19.9%)	67 (20.2%)	15 (18.5%)	0.728
TB, tuberculosis				

Among all patients, 75 with subclinical disease and 308 with active disease were included in the drug-susceptible cohort. Overall, there were 27 (7.0%) mortality and 319 (83.3%) treatment-success cases. Among 319 patients with treatment success, six (1.9%) recurrent cases were identified, and all were patients with active disease. Patients with active disease had a higher proportion of mortality during or before anti-TB treatment, and patients with subclinical disease had a higher proportion of treatment success and favorable outcome; however, the odds ratio of each treatment outcome was insignificant (Table 4).

Table 4
Comparison of treatment outcome of active and subclinical tuberculosis diseases among the drug-susceptible cohort

	Active TB disease (n = 308)	Subclinical TB disease (n = 75)	p-value
Mortality[1]			
Number (%)	26 (8.4%)	1 (1.3%)	0.031[5]
OR (95% CI)	Reference	0.15 (0.02–1.10)	0.054
Adjusted OR[4] (95% CI)	Reference	0.21 (0.03–1.61)	0.123
Treatment success[2]			
Number (%)	252 (81.8%)	67 (89.3%)	0.118[5]
OR (95% CI)	Reference	1.86 (0.85–4.01)	0.122
Adjusted OR[4] (95% CI)	Reference	1.59 (0.71–3.54)	0.259
Favorable outcome[3]			
Number (%)	246 (79.9%)	67 (89.3%)	0.057[5]
OR (95% CI)	Reference	2.11 (0.96–4.62)	0.062
Adjusted OR[4] (95% CI)	Reference	1.88 (0.85–4.15)	0.122

TB, tuberculosis; OR, odds ratio; CI, confidence interval

[1] Incidence of mortality during or before anti-TB treatment

[2] Sum of cured and treatment completed cases within 1 year of anti-TB treatment

[3] Sum of treatment success and no recurrence

[4] adjusted by age and gender

[5] chi-square test

Discussion

This was one of the first and largest studies to evaluate the clinical characteristics of subclinical TB among human immunodeficiency viruses-uninfected patients. The prevalence of subclinical TB in our cohort was 19.2%. Demographic and past medical profiles of patients with subclinical and active TB were similar. We initially hypothesized that subclinical TB would have better treatment outcomes than active

TB because of its mild nature. Patients with subclinical disease in our study had a significantly lower proportion of acid-fast bacilli smear and culture positivity and multiple lobe involvement on chest CT compared to patients with active disease. In addition, the proportions of treatment success and favorable outcomes among the drug-susceptible cohort were higher among patients with subclinical disease; however, the difference was not statistically significant. Thus, our results revealed that although subclinical TB had a milder clinical presentation, treatment outcome was not significantly different from active TB.

The prevalence of subclinical TB varies widely across epidemiological settings, populations, and screening tools used. For example, its prevalence is generally high in studies performing active case finding among high-risk groups during which all participants are screened with high-sensitivity tests.[2] According to a review of 12 national prevalence surveys in Asia between 1990 and 2012, the proportion of cases that did not report TB symptoms and were only detected due to chest x-ray screening ranged from 40% in Pakistan to 79% in Myanmar.[8] Under the universal health coverage in South Korea, screening with chest x-ray is a simple, inexpensive, and important tool for national health examinations in various settings. It may improve active case finding of subclinical TB, which should be emphasized when planning public health interventions for TB control because early identification of subclinical disease may reduce its transmission.

Current microbiological tests to diagnose active TB, such as AFB smear and culture tests and NAAT, are also employed to detect subclinical TB. However, patients with subclinical disease who do not have a symptomatic productive cough cannot expectorate good quality sputum specimens, which limits effective diagnosis. Thus, the use of bronchoscopy may improve yields of microbiologic tests in patients with subclinical disease. One retrospective Korean study showed that the proportion of patients diagnosed using bronchoscopic specimens increased from 6.6% in 2005 to 26.7% in 2013.[9] In addition, chest CT, which is widely used in routine clinical settings in South Korea, is a useful and non-invasive tool to identify subtle nodular lesions and determine disease activity that can aid the detection of subclinical disease. In our study, 98% of enrolled TB patients underwent chest CT, and 83% of asymptomatic patients with multiple lobe involvement on chest CT underwent bronchoscopy. Unless other diagnostic tools are available, it is important to develop a cost-effective algorithm to diagnose subclinical disease using chest CT and bronchoscopy. The WHO has prioritized the development of novel tests using non-sputum-based specimens types, and urine-based tests were recently developed and introduced, which may be useful in clinical point-of-care settings to diagnose TB in people living with human immunodeficiency viruses.[10]

The degree of AFB smear positivity is considered an important marker for potential transmission. In our study, the rate of positivity of the initial AFB smear test in subclinical disease was only 13.6%, suggesting that these patients may pose a low risk for transmission; however, the overall contribution of subclinical disease to transmission is not yet well understood. A recent review suggested that subclinical disease might enter an unstable state with infection taking a waxing-waning course during which periods of progression may be triggered by precipitating factors.[3] Therefore, a transition from smear-negative to smear-positive disease may occur depending on the host’s immunity during heterogenous periods of

subclinical disease. In a previous large cohort study, patients with smear-negative, culture-positive TB were responsible for 13% of TB transmissions.[11] Thus, we cannot confirm that subclinical disease is less infectious than active disease. A prevention strategy concerning transmission from patients with subclinical disease should also be highlighted.

This study has a couple of limitations. First, adequate power to detect differences between treatment success and favorable outcomes in the drug-susceptible cohort was limited by the sample size. Second, the study was conducted in university-affiliated hospitals that actively participate in the public-private mix project, and more severe TB patients, who were referred from primary healthcare facilities, might have been enrolled in our study. Thus, our results cannot be inferred to other TB clinics, such as public health centers and other private hospitals.

Conclusions

Nearly one-fifth of tuberculosis cases in our adult cohort were subclinical, which might ascribe to frequent health examinations using chest x-ray and low-dose chest under the universal health coverage in South Korea. Our study revealed that although subclinical TB had a milder clinical presentation, its treatment outcomes were not significantly different from those of active TB. Early identification of subclinical disease, however, is an important target for TB control to prevent TB transmission. More research is necessary to develop diagnostic algorithms based on currently available tools and to customize treatment strategies based on disease extent for subclinical TB.

Abbreviations

WHO:World Health Organization; TB:Tuberculosis; COSMOTB; cohort study of pulmonary tuberculosis:AFB; Acid-fast bacilli:NAAT; nucleic acid amplification test:CT; computed tomography

Declarations

Ethic approval and consent to participate

The protocol and informed consent forms were approved for their scientific content and compliance with human subject research regulations by the institutional review boards of Chungbuk National University Hospital (No. 2016-10-003). All adult participants provided written informed consent to participate in this study. All methods were carried out in accordance with relevant guidelines and regulations.

Availability of data and materials

All relevant data are within the manuscript.

Competing interests

The authors have declared that no competing interests exist.

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Authors' contribution

Conceptualization: JM, KML. Data curation: JM, CC, SSJ, HYP, SSL, KML. Formal analysis: JM. Funding acquisition: KML. Methodology: JM, CC, SSJ, HKP, SSL, KML. Writing – original draft: JM, KML. Writing – review & editing: JM, CC, SSJ, HYP, SSL, KML.

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Figures

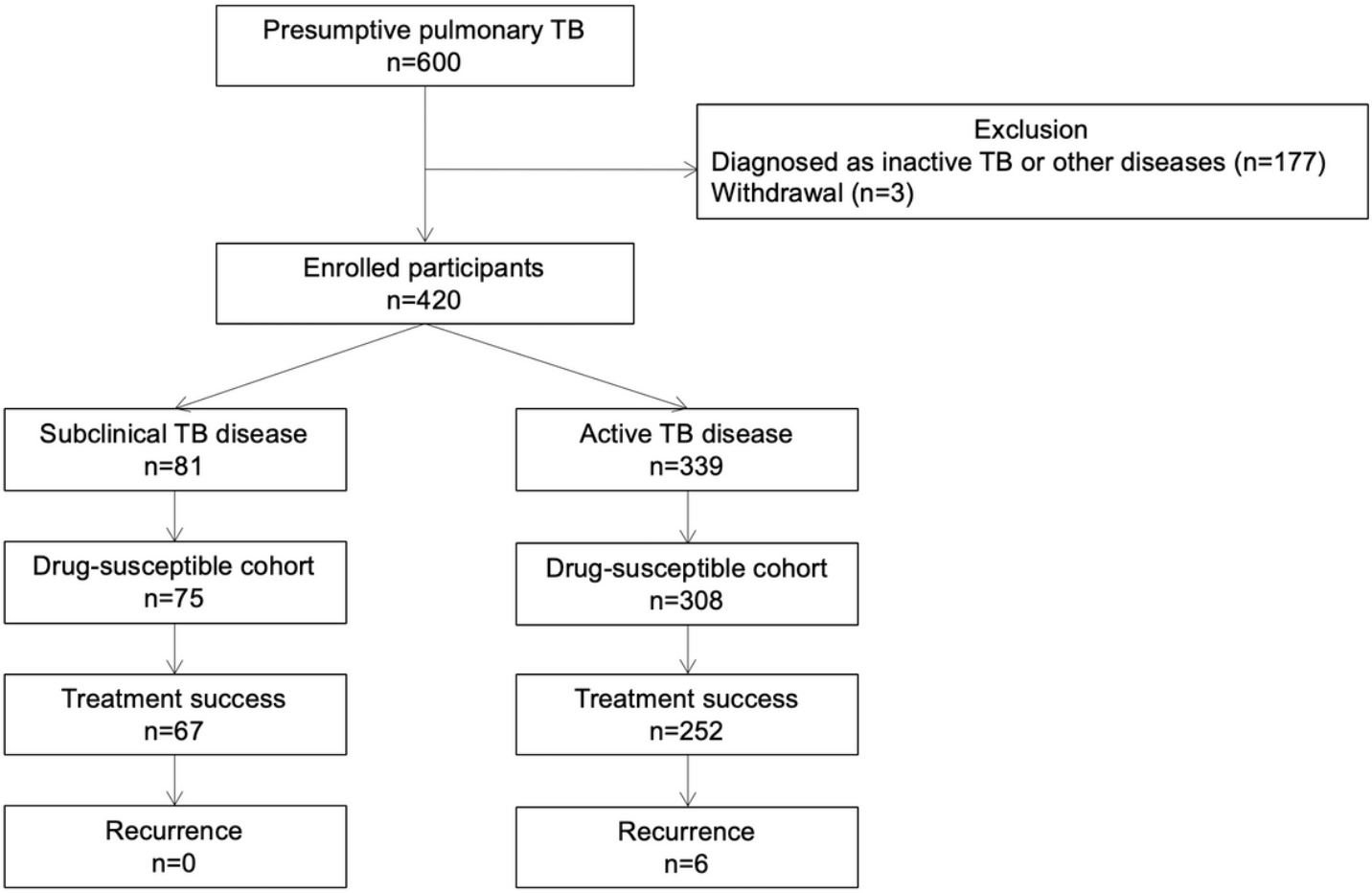

Figure 1

Flow char of patient enrollment and final outcomes of drug-susceptible cohort. TB, tuberculosis. Drug-susceptible cohort comprises patients who have positive culture results susceptible with both isoniazid and rifampin and who are clinically diagnosed with tuberculosis without microbiological evidence.

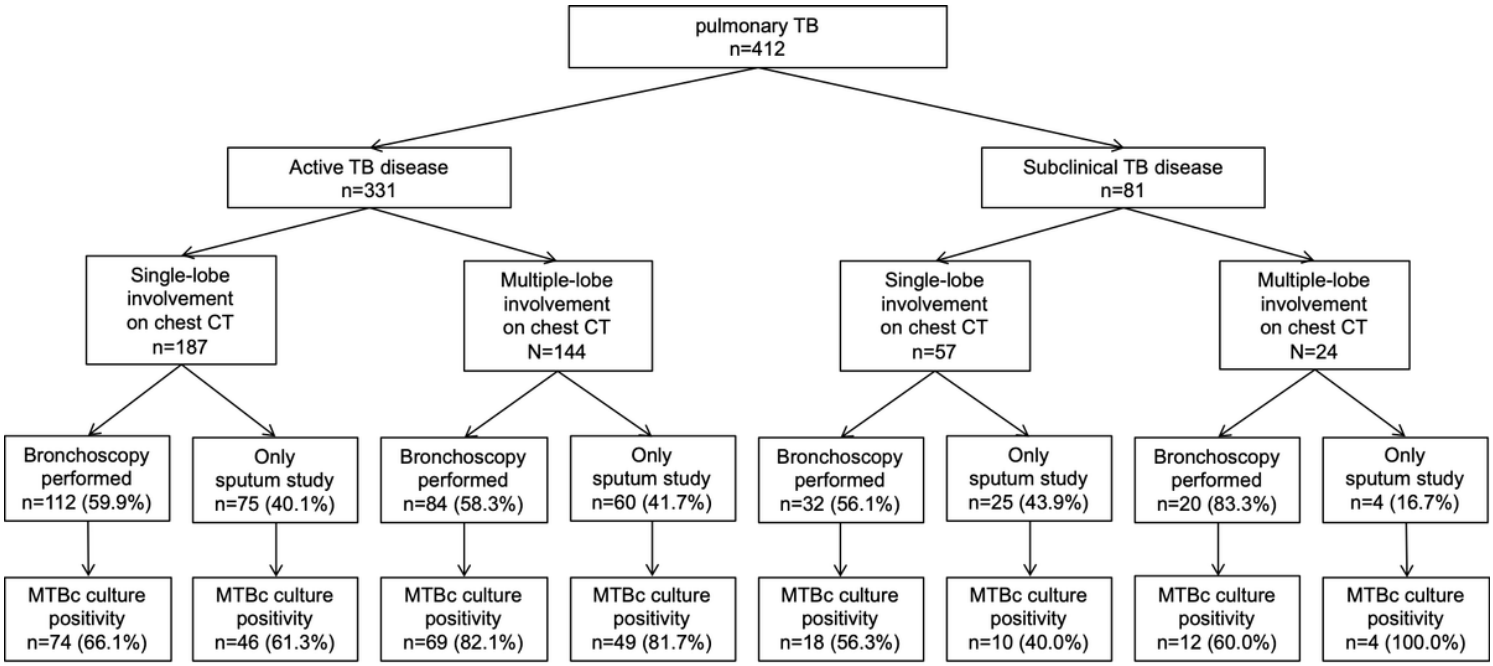

Figure 2

Mycobacterium tuberculosis culture results stratified by number of lobe involvement on chest computed tomography and additional performance of bronchoscopy. TB, tuberculosis; CT, computed tomography; MTBc, Mycobacterium tuberculosis.