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ORIGINAL RESEARCH

Additional Usefulness of Bronchoscopy in Patients with Initial Microbiologically Negative Pulmonary Tuberculosis: A Retrospective Analysis of a Korean Nationwide Prospective Cohort Study

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Purpose: Bronchoscopy is widely used for microbiological diagnosis of patients with minimal sputum production. However, the usefulness of bronchoscopy in patient groups who benefit from subsequent microbiological confirmation has not been established.

Patients and Methods: We retrospectively analyzed Korean tuberculosis (TB) cohort data from September 2018 to October 2019 to evaluate the usefulness of bronchoscopy in patients with microbiologically negative pulmonary TB (based on initial sputum polymerase chain reaction and culture results). The primary outcome was the proportion of microbiological diagnoses made after bronchoscopy. Secondary outcomes were the predictors of microbiological confirmation and the percentage of additional resistance detection after bronchoscopy.

Results: A total of 5194 patients were diagnosed with pulmonary TB, 937 of whom were microbiologically negative for pulmonary TB based on the initial sputum findings. Of these, 319 patients underwent bronchoscopy, and further microbiological confirmation was achieved in 157 (49.1%) patients. The predictors of microbiological confirmation after bronchoscopy were age >65 years, female sex, and low body mass index (BMI). The rate of additional resistance detection was 10.5% (multidrug resistant/rifampin-resistant 3.8%; isoniazid-resistant 5.7%).

Conclusion: Bronchoscopy can be used for the detection of resistant pathogens. Bronchoscopy should be considered for microbiologically negative pulmonary TB in women aged >65 years and with low BMI for subsequent microbiological confirmation.

Keywords: tuberculosis, pulmonary, bronchoscopy, cohort studies

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Introduction

Tuberculosis (TB) is one of the most common infectious diseases and remains a major global health problem.[1–3] According to the Global Tuberculosis Report 2020, an estimated 10 million individuals were diagnosed with TB, and 1.2 million TB-related deaths were reported in 2019.[1,4] The disease burden in South Korea is intermediate, with a TB incidence of 51.5 cases per 100,000 population in 2018.[5] Proper diagnosis is crucial for curing the disease and preventing TB transmission, and microbiological confirmation of TB from respiratory secretions is a key factor for diagnosis.[6]

However, this remains a challenge as up to 70% of patients with TB are smear negative and 40% are culture-negative in South Korea.[7] The diagnosis of TB is challenging for physicians when a patient shows multiple negative sputum results, even if there is a high suspicion of active disease.[8,9] Therefore, the choice remains whether to proceed with empiric treatment for pulmonary TB, wait for the TB culture with possible further delay, or perform an invasive test such as bronchoscopy to confirm the diagnosis.[10] This issue is on the rise because many patients with suspected TB visit clinics without any symptoms or screening chest images.[11,12]

Bronchoscopy has recently been widely used to aid microbiological diagnosis in patients with little sputum production.[13,14] The existing literature on the diagnostic yields of bronchoscopy in the diagnosis of TB varies from 30% to 80%.[15–20] However, the usefulness of bronchoscopy and the rate of subsequent microbiological confirmation have not yet been established. Moreover, it is unknown if the patient groups will benefit further from the diagnosis after bronchoscopy. To maximize the benefit of bronchoscopy while minimizing costs and complications, it is necessary to identify parameters to predict the yield of microbiological diagnosis for diagnosing sputum-negative pulmonary TB. Thus, we aimed to evaluate the effectiveness of microbiological diagnoses after bronchoscopy, predictors of microbiological confirmation, and percentage of additional resistance detection after bronchoscopy.

Patients and Methods

Retrospective Analysis of the Prospective Cohort Data

We constructed a nationwide multicenter prospective observational cohort database called the "Korean TB cohort database." This cohort study was conducted in September 2018 to evaluate the characteristics of Korean patients with TB and to improve their management. Data were systematically collected from patients with TB who visited hospitals under the national public-private mix (PPM) TB control project and were notified of the national TB surveillance system. All notified patients with TB were followed up at regular intervals during anti-TB treatment, as recommended by the Korean TB guidelines. For this database, every patient with TB notified from the first to the tenth day each month was consecutively enrolled across the country. Data of participants during this period were collected by TB specialist nurses using the prespecified questionnaire and case report form, and were entered into Microsoft Access (Redmond, WA, USA). The regional data manager then organized the data gathered from local hospitals every month and sent them to the central data manager every quarter. To improve and maintain data quality, regional and central data managers conducted audits and identified missing and erroneous data. We retrieved and retrospectively analyzed data from the Korea TB cohort database from September 2018 to October 2019.

Study Setting and Participants

Every hospital under the PPM project in Korea participated in this study. The Republic of Korea, a country with an intermediate TB burden, has a high incidence of TB among other high-income countries. The national PPM TB control project was initiated in 2009 and expanded nationwide in 2011.[7] There are more than 210 TB specialist nurses at 127 PPM hospitals and 236 public health officials at 254 public health centers across the country. Approximately 70.7% of the newly notified patients with TB in Korea were treated at PPM hospitals in 2018. The main inclusion criterion for this study was the presence of pulmonary TB. TB patients were diagnosed based on clinical, radiological, microbiological, and pathological data, as judged by physicians based on the Korean TB guidelines, as follows: 1) if a patient has positive polymerase chain reaction (PCR) results, TB is considered, and 2) if a patient has negative PCR results, and pulmonary TB is clinically and radiologically suspected but the patient does not respond to antibiotics, smear-negative pulmonary TB is considered. After clinical treatment of pulmonary TB and confirmation of culture positivity, we can diagnose the patient with culture-positive pulmonary TB. After a trial of TB medication and clinical and radiological improvement but negative TB culture results, we can make a final diagnosis of culture-negative pulmonary TB. We can additionally perform chest computed tomography, bronchoscopy, and biopsy, and if the results of these tests show active TB, smear-negative pulmonary TB can be diagnosed. Drug-resistant TB was defined as pulmonary TB with resistance to anti-TB medications. Multidrug-resistant TB is caused by an organism that is resistant to at least isoniazid and rifampin, the two most potent TB drugs. Isoniazid-resistant TB refers to resistance to isoniazid and susceptibility to rifampin. Rifampin-resistant TB refers to resistance to rifampin and susceptibility to isoniazid.

Patients with TB and extrapulmonary involvement were excluded from the study. We also excluded patients without initial sputum, those with positive initial sputum PCR or TB culture, and those who did not undergo bronchoscopy for outcome analysis.

Independent Variables

Demographic and clinical data were collected based on in-depth interviews with TB specialist nurses at PPM-participating hospitals. Baseline characteristics such as age, sex, smoking history and amount, body mass index (BMI), comorbidities, initial presenting symptoms, prior TB history, sites of TB involvement, and laboratory findings were collected. The sputum study date and results, bronchoscopic washing date, results of bronchoaspiration, initial symptoms, and chest imaging were also collected. For the sputum study, expectorated sputum was collected, and bronchoscopic washing was performed on the bronchoscopic specimens. Data were coded as bivariate variables, except for microbiological test results, which were coded as categorical variables.

Primary and Secondary Outcomes

We aimed to evaluate the usefulness of bronchoscopy in patients with microbiologically negative pulmonary TB (based on initial sputum PCR and culture results). The primary outcome was the proportion of microbiological diagnoses made after bronchoscopy. Secondary outcomes were the predictors of microbiological confirmation and the percentage of additional resistance detection after bronchoscopy.

Statistical Analysis

Clinical data are presented as the mean and standard deviation and were compared using the *t*-test for continuous variables. For categorical variables, data are presented as percentages and numbers and were compared using Pearson's χ^2 test or Fisher's exact test. For the predictors, multivariate logistic regression analysis was performed by adjusting for significant factors ($P < 0.05$) in the univariate model. Statistical significance was defined as $p < 0.05$. All statistical analyses were performed using SPSS Statistics for Windows (version 20.0; IBM Corp., Armonk, NY, USA).

Results

Proportion of Microbiological Diagnoses After Bronchoscopy in Patients with Microbiologically Negative Pulmonary TB

A total of 5194 patients were diagnosed with pulmonary TB. Among them, we excluded patients without initial sputum acid-fast bacilli, TB PCR, and TB culture (n=1054), and those with missing sputum or bronchoscopic washing results (n=68). A total of 3135 (77.0%) patients were microbiologically positive and 937 (23.0%) were microbiologically negative based on the initial sputum findings. Of the microbiologically negative patients, 319 (34.0%) underwent bronchoscopy, and further microbiological confirmation was achieved in 157 (49.1%) patients (Figure 1). A total of 105 patients had additional TB culture-positive results, with the results of 52 of them confirmed only by PCR.

Characteristics of Microbiologically Negative Pulmonary TB According to Microbiological Confirmation After Bronchoscopy

When we compared the baseline characteristics of patients with or without additional microbiological confirmation after bronchoscopy (Table 1), those with additional microbiological confirmation (n=157) were older, leaner, and had a lower

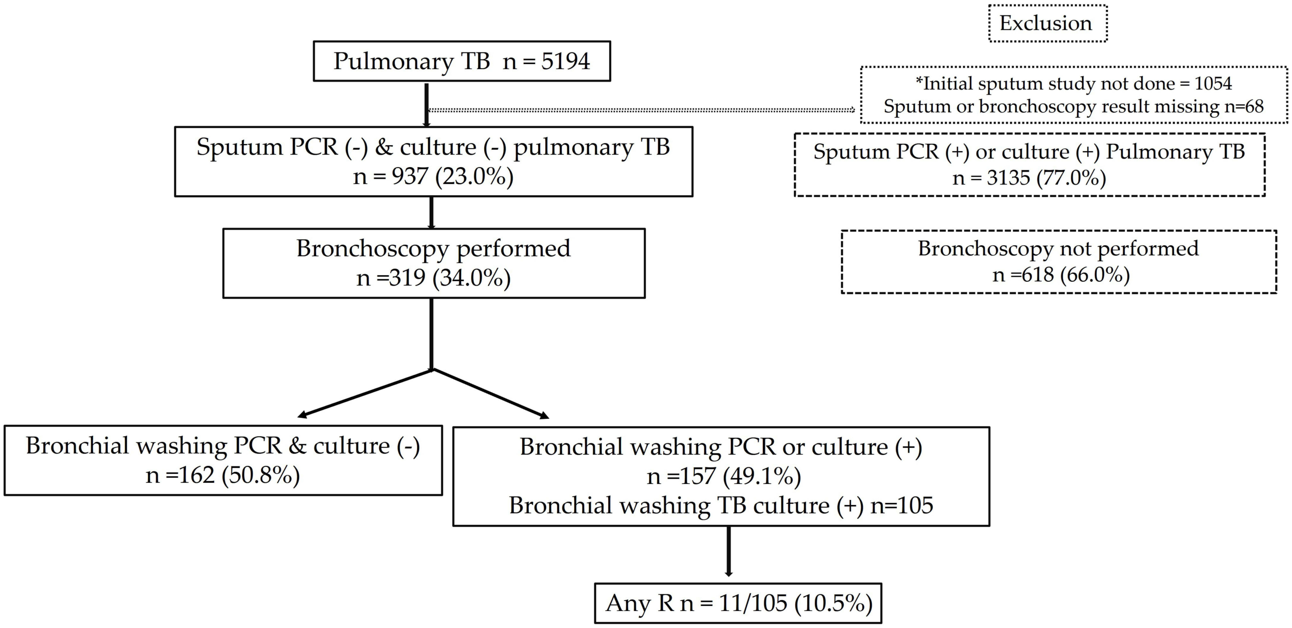

Figure 1 Flowchart of the analysis. *Initial sputum study: smear, PCR, and culture were performed.
Abbreviations: PCR, polymerase chain reaction; TB, tuberculosis.

percentage of male patients than those without additional microbiological confirmation (n=162). Mean age was 56.9 ±20.8 years and 56.1±17.3 years in patients with and without microbiological confirmation, respectively. Smoking status, past TB history, comorbidities, initial symptoms, and chest radiographic results did not differ significantly between the two groups.

Predictors of Microbiological Confirmation After Bronchoscopy

The predictors of microbiological confirmation after bronchoscopy were age >65 years (odds ratio [OR] 1.94, 95% confidence interval [CI], 1.232–3.077; p=0.004), female sex (male sex OR, 0.614, 95% CI, 0.387–0.974; p=0.038), and low BMI (BMI <18.5; OR, 3.237; 95% CI, 1.720–6.292; p<0.001). Smoking history, past TB history, comorbidities, initial symptoms, and chest radiographic results did not affect the results of bronchoscopic washing. On multivariate analysis after adjusting for age, sex, BMI, symptoms, and the presence of cavitation on chest radiographs, age (age ≥65 years, OR 1.751, 95% CI 1.093–2.816; p=0.020), sex (male OR 0.609, 95% CI, 0.378–0.982), and BMI (BMI <18.5, OR 3.007, 95% CI 1.534–5.894) were still significant predictors of microbiological positivity after bronchoscopy (Table 2).

Percentage of Additional Resistance Detection After Bronchoscopy

The rate of additional resistance detection among additional culture-positive patients after bronchoscopy (n=105) was 10.5% (multidrug-resistant/rifampin-resistant 3.8%; isoniazid-resistant 5.7%) (Table 3).

Discussion

In our study, bronchoscopy proved to be an effective tool for the diagnosis of sputum-negative pulmonary TB, achieving microbiological confirmation in 49.1% of the patients, with 10.5% of patients being found to have resistance to anti-TB medication. We also found that the benefit was maximized, particularly for those aged >65 years, female patients, and those with low BMI.

There is a need to identify the optimal methods for diagnosing pulmonary TB in bacteriologically negative patients.[21] Kwak et al reported that in more than half of the patients with smear-negative pulmonary TB, the diagnosis was delayed, which led to a poor prognosis.[22] Further mycobacterial culture could provide additional information on drug sensitivity for a more accurate treatment of drug-resistant TB.[23]

Table 1 Baseline Characteristics of Patients with Microbiologically Negative (Based on Initial Sputum PCR and Culture Results) Pulmonary TB Who Underwent Bronchoscopy According to Microbiological Confirmation After Bronchoscopy

Variables	Bronchial Washing PCR (+) or Culture (+) n=157	Bronchial Washing PCR (-) and Culture (-) n=162	p
Age	56.9±20.8	56.1±17.3	0.72
≥65 years	73 (46.5)	50 (30.9)	0.004
Sex			
Male	65 (41.4)	92 (58.6)	0.047
BMI	21.3±3.2	22.6±3.5	0.001
<18.5	37 (23.6)	14 (8.7)	<0.001
Occupation	45 (28.7)	55 (34.4)	0.274
Smoking			
Never	99 (63.1)	89 (54.9)	0.285
Past	30 (19.4)	34 (21.0)	
Current	28 (17.8)	39 (24.1)	
Past TB			
New	122 (77.7)	130 (80.2)	0.529
Recurrent	29 (18.5)	29 (17.9)	
Comorbidity	79 (50.3)	92 (56.8)	0.247
DM	32 (20.4)	31 (19.1)	0.78
Chronic lung disease	11 (6.8)	6 (3.8)	0.238
Chronic heart disease	3 (1.9)	6 (3.7)	0.334
Chronic liver disease	1 (0.6)	5 (3.1)	0.107
Chronic kidney disease	5 (3.2)	9 (5.6)	0.301
Neuropsychiatric disease	9 (5.7)	8 (4.9)	0.752
Malignancy	16 (10.2)	18 (11.1)	0.79
Symptoms	95 (60.5)	88 (54.3)	0.264
Cough, sputum	48 (30.6)	51 (31.5)	0.861
Dyspnea	20 (12.7)	29 (17.9)	0.201
Hemoptysis	10 (6.4)	7 (4.3)	0.415
Fever	14 (8.9)	20 (12.3)	0.321
Radiographic result			
Presence of cavity	18 (11.5)	16 (9.9)	0.645
Bilateral	39 (24.8)	34 (21.0)	0.092

Abbreviations: BMI, body mass index; DM, diabetes mellitus; PCR, polymerase chain reaction.

Table 2 Predictors of Further Microbiological Confirmation After Bronchoscopy in Patients with Microbiologically Negative (Based on Initial Sputum PCR & Culture Results) Pulmonary TB Who Underwent Bronchoscopy

Variables	Univariate		Multivariate	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**
Age				
≥65 years	1.947 (1.232–3.077)	0.004	1.754 (1.093–2.816)	0.02
Sex				
Male	0.614 (0.387–0.974)	0.038	0.609 (0.378–0.982)	0.042
BMI				
<18.5	3.237 (1.72–6.267)	<0.001	3.007 (1.534–5.894)	0.001
Smoking		0.287		
Never	Ref			
Past	0.793 (0.449–1.400)		–	
Current	0.645 (0.367–1.134)		–	
Past TB				
New	Ref			
Recurrent	1.066 (0.602–1.886)	0.827	–	
Comorbidity				
DM	1.082 (0.623–1.878)	0.78	–	
Chronic lung disease	0.545 (0.197–1.513)	0.244	–	
Malignancy	0.908 (0.445–1.851)	0.79	–	
Symptoms				
Cough, sputum	1.043 (0.649–1.677)	0.861	–	
Dyspnea	1.494 (0.805–2.770)	0.203	–	
Hemoptysis	1.439 (0.699–2.960)	0.323	–	
Fever	1.431 (0.704–2.906)	0.322	–	
Radiographic result				
Presence of cavity	1.182 (0.580–2.411)	0.645	–	
Bilateral	1.451 (0.843–2.496)	0.179	–	

Abbreviations: BMI, body mass index; DM, diabetes mellitus; OR, odds ratio; CI, confidence interval.

Previous studies have shown that bronchial aspirates increase the culture rate of patients with suspected TB with negative sputum smear results.[20,24,25] However, the yields of bronchoscopic washing samples varied as reported previously.[16] Park et al reported that 68% of paucibacillary pulmonary TB showed positive results on mycobacterial culture after bronchoscopy.[19] Schoch et al reported that bronchoscopy, performed in 87 of 92 sputum smear-negative cases, yielded four additional smear-positive and six culture-positive cases.[20] Ahmad et al reported that bronchoalveolar lavage detected 61/190 (32.1%) pulmonary TB cases in a subset of patients with negative sputum results, and suspected pulmonary TB.[21] The difference in the additive yields of bronchoscopy might depend on the characteristics of the patients and/or TB.

Table 3 Additional Resistance Detection After Bronchoscopy

No.	Sex	Age	Drug Susceptibility Test Result (Resistance Pattern)
1	F	31	Isoniazid, rifampin, streptomycin
2	M	32	Isoniazid, streptomycin
3	F	68	Isoniazid, rifampin, ethambutol, protionamide
4	F	41	Isoniazid, pyrazinamide
5	M	79	Isoniazid, streptomycin
6	M	70	Isoniazid
7	F	31	Isoniazid
8	M	36	Rifampin
9	M	24	Isoniazid, rifampin, ethambutol, quinolone
10	F	78	Isoniazid
11	F	68	Streptomycin

Abbreviations: F, female; M, male.

Considering the different yields of bronchoscopic washing results according to patient characteristics and the potential adverse effects of bronchoscopy,[26] there should be evidence of patient groups who would benefit from bronchoscopy. Our study has several strengths that differ from those of previous studies that dealt with the indicators for the prediction of TB positivity detected using bronchoscopy. First, our study included patients within the prevalent age range of TB patients compared with previous studies that included younger patients. A previous study showed that bronchoscopy was useful in obtaining culture confirmation of pulmonary TB in approximately 10% of patients with negative results.[27] However, these patients were predominantly young men (median age, 37 years). In another previous single-center study investigating factors associated with microbiological positivity after bronchoscopy, patients were also too young (mean age, 37.4 years) to represent the common diagnosis of pulmonary TB.[28]

Second, this was a multicenter prospective study, and various variables, including BMI, other epidemiologic factors, and drug sensitivity results, were collected from a nationwide quality-controlled database. A previous study conducted in this regard was a single-center study and did not evaluate other factors such as BMI or further drug sensitivity results.[29] However, we observed additional roles of BMI, age, and sex as predictive factors. Patient factors other than TB (symptoms or imaging findings) were more affected in our study. Chest imaging findings with cavity or bilateral infiltration did not affect the results. This might be because such severe cases with a subsequent high bacterial burden could be ruled out in the current study because patients with this condition tested positive for mycobacteria in sputum specimens. Older lean female patients benefit after bronchoscopy because they are more fragile and may not be able to expectorate well.[29] Furthermore, the drug sensitivity test (with approximately 10% of patients with additional microbiological confirmation observed to have resistance) enabled suitable treatment and prevention of treatment failure in these patients.

Our study had some limitations. Although the cohort design was prospective, we retrospectively analyzed yearly data. Therefore, a selection bias could not be ruled out. This national cohort included only patients with TB; therefore, those who were excluded from the diagnosis of TB by bronchoscopy were excluded from this cohort. One benefit of performing bronchoscopy is the differential diagnosis of pulmonary TB from non-TB mycobacterial diseases or lung malignancies. As patients classified as having other diseases were excluded, the important role of bronchoscopy in ruling out other important pulmonary diseases might have been underestimated. Nevertheless, we found 50% more microbiological confirmation of TB diagnosis in our study. Another limitation is that the decision to perform bronchoscopy was not randomly distributed. Patients who underwent bronchoscopy might have been the ones who physicians judged to have an additive yield on bronchoscopy. However, we overcame this limitation by multivariate adjustment, including age, sex, BMI, symptoms, and presence of cavitation on chest radiographs, which are the main characteristics that physicians focus on for the yield of sputum studies. Moreover, bronchoscopy yields differ depending on the technical expertise of the operators performing the procedures. However, this is the same in the real world, and more than 200 different pulmonary specialists from 127 PPM hospitals performed bronchoscopy; therefore, some physician technical errors might not have influenced the results in comparison with the study performed at a single-center hospital.[28]

Although this is the first retrospective analysis of a prospective multicenter cohort database that dealt with the predictors of microbiological yield after bronchoscopy for TB diagnosis, further prospective randomized studies including those across countries are needed to confirm our findings.

Conclusion

Bronchoscopy can be used for the detection of resistant pathogens. Bronchoscopy should be considered for microbiologically negative pulmonary TB in women aged >65 years and with low BMI for subsequent microbiological confirmation in countries with intermediate TB burden.

Abbreviations

BMI, body mass index; PCR, polymerase chain reaction; PPM, public-private mix; TB, tuberculosis.

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Disclosure

The authors declare no conflicts of interest in this work.

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