

# Analysis of risk factors for the development of a post-bronchoscopy respiratory infection in lung cancer patients

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# Abstract

**Background:** The development of pneumonia following bronchoscopy is very important as a post-bronchoscopy complication. Most patients with post-bronchoscopy respiratory infections show typical pneumonia, and lung abscesses are rare. However, bronchoscopic techniques have advanced, and recently, we have observed patients with lung abscess after bronchoscopy. Therefore, the risk factors might vary from those in past reports. This study aims to identify the incidence of and risk factors for post-bronchoscopy respiratory infections. **Methods:** We retrospectively studied adult patients diagnosed with lung cancer by bronchoscopy at Fukujiji Hospital between January 2017 and June 2019. Patients in the infection and noninfection groups were compared. The incidence of lung abscess was compared between recent periods and 2013, when endobronchial ultrasonography with a guide sheath (EBUS-GS) was not yet used in our hospital. **Results:** We reviewed 327 patients, including 20 patients (6.1%) in the infection group. The risk factors for infection were necrosis and/or a cavity in the tumor ( $p < 0.001$ ), large tumor diameter ( $\geq 30$  mm) ( $p = 0.003$ ), and low serum albumin ( $< 4.0$  g/dL) ( $p = 0.012$ ). We developed a predictive score that included these risk factors, and the area under the curve of the score was 0.737 (95% CI: 0.610-0.864). Conversely, no significant differences in age, current smoking status, or abnormal bronchoscopic findings were observed, even though these factors were reported as risk factors in past reports. Other risk factors for infection were a high white blood cell count ( $p = 0.007$ ), high C-reactive protein level ( $p = 0.014$ ), and expression of programmed death-ligand 1 expression in the tumor cells ( $p = 0.033$ ). In total, 12 patients had lung abscesses (3.7%), which represents a higher incidence than that in 2013 (0.8%). Other types of infection were post-obstructive pneumonia in four patients (1.2%) and typical pneumonia in four patients (1.2%). **Conclusions:** The risk factors for developing post-bronchoscopy respiratory infection in our study varied from those in past reports, possibly because of the advancement of bronchoscopic techniques such as EBUS-GS.

## Introduction

A flexible fiberoptic bronchoscope can safely perform assessments, aid in diagnosis, and provide treatment to patients with respiratory diseases [1], and complications associated with bronchoscopy occur in 0.2-5.6% of patients with a mortality rate of 0.004-0.02% [2-5]. The development of pneumonia following bronchoscopy is very important in patients suffering from lung cancer since pneumonia causes a delay in treating the malignancy [6]. Most of the patients with post-bronchoscopy respiratory infections show a new infiltrate or consolidation on chest radiographic findings similar to the signs of typical pneumonia [3, 6, 7]. Additionally, lung abscesses rarely develop in post-bronchoscopy respiratory infections and occurred in 0.22-1.06% of patients in a past report [7, 8]. However, recently, we have observed patients with lung abscesses after bronchoscopy. Bronchoscopic techniques have been further developed to include methods such as endobronchial ultrasonography (EBUS), EBUS with a guide sheath (EBUS-GS) and EBUS-guided transbronchial needle aspiration (EBUS-TBNA); therefore, an updated review should be considered [8]. Some past reports have demonstrated the risk factors for post-bronchoscopy respiratory infection, such as an elderly age, current smoking status, and central location of the tumor [6,

9]. However, the risk factors for post-bronchoscopy respiratory infection might differ from those in past reports. This study aims to identify the incidence of and risk factors for post-bronchoscopy respiratory infections.

## Methods

### Study Design and Setting

We retrospectively studied patients who were diagnosed with lung cancer by bronchoscopic examination at the Respiratory Disease Center of Fukuji Hospital from January 2017 to June 2019. Patients with post-bronchoscopy respiratory infections were compared to patients who did not develop an infection after bronchoscopy. We selected adult patients (age  $\geq 18$  years) with lung cancer who were diagnosed by a bronchoscopic examination. The main outcome of our study was the diagnosis of post-bronchoscopy respiratory infection. Data were collected about the symptoms, laboratory data, radiological findings, bronchoscopic findings, histopathologic findings, and other relevant findings. Patients who were diagnosed by EBUS-TBNA without transbronchial lung biopsy (TBLB) and those who could not be diagnosed with lung cancer by bronchoscopic examination were excluded. The types of post-bronchoscopy respiratory infection in 2017-2019 were compared to those in 2013, when EBUS-GS was not yet used in our hospital. The study was approved by the Institutional Review Board of Fukuji Hospital. Patient consent was not required. The decisions made by this board are based on and in accordance with the Declaration of Helsinki.

### Definitions

Post-bronchoscopy respiratory infection was defined as a respiratory infection that developed a new or progressive infiltrate on chest radiographs or computed tomography (CT) scans with an elevated white blood cell count (WBC) and/or C-reactive protein (CRP) during the period from the bronchoscopic examination to starting treatment for lung cancer or within a month. The types of post-bronchoscopy infection are classified as lung abscesses in the tumor, post-obstructive pneumonia, and typical pneumonia (Fig. 1). Lung abscesses were defined as follows: (1) primary shadow developing enlargement, and (2) cavity formation, low-density area in a primary shadow appearing or enlargement in post-bronchoscopy respiratory infection. Post-obstructive pneumonia was defined as an infection of the lung parenchyma distal to a bronchial obstruction [10]. Typical pneumonia was defined as a new infiltrate or consolidation around the target lesion during bronchoscopic examination. Necrosis in the tumor was classified as a low-density area in the tumor with a maximum of 30 Hounsfield units nonenhanced CT scans [11, 12]. Lung cancer staging referred to the 8<sup>th</sup> edition of the TNM classification [13]. Abnormal bronchoscopic findings were identified with intrabronchial tumor observations via bronchoscopy.

### Statistical Methods

All data were analyzed and processed using EZR, version 1.35 [14]. Student's t test, Mann-Whitney U test, and Fisher's exact test were used to compare groups. Sensitivity, specificity, and odds ratios were

calculated. Receiver operating characteristic (ROC) curves and the area under the curve (AUC) were calculated for each predictor model. ROC curves determined the cutoff value, and the AUC accurately measured the prediction model. The level of statistical significance was set at  $p=0.05$  (2-tailed).

## Results

A total of 344 patients were diagnosed with lung cancer by bronchoscopic examinations at our hospital. Seventeen patients who were diagnosed with EBUS-TBNA without TBLB were excluded, so we reviewed 327 patients in our study. Among all patients, 20 patients (6.1%) developed post-bronchoscopy respiratory infections (the infection group), and 307 patients were in the noninfection group (Table 1). The median age was 68.5 years old (IQR: 64.5-78.5), and there were 16 males (80%) in the infection group. The infection group and the noninfection group were not significantly different in age (median (IQR): 68.5 years old (64.5-78.5) vs 73.0 years old (67.0-78.0),  $p=0.453$ ), sex (male:  $n=16$  (80.0%) vs  $n=181$  (59.0%),  $p=0.097$ ), underlying diseases ( $n=16$  (88.9%) vs  $n=262$  (87.6%),  $p=0.165$ ), current smoking status ( $n=7$  (36.8%) vs  $n=63$  (22.5%),  $p=0.165$ ), and symptoms ( $n=11$  (57.9%) vs  $n=124$  (40.8%),  $p=0.157$ ). The histological classification of lung cancer showed almost no significant difference, and other cancer subtypes, including non-small cell carcinoma, carcinoid tumor, combined with some histologic types, and pleomorphic adenoma, were more common in the infection group than in the noninfection group ( $n=5$  (25.0%) vs  $n=25$  (8.1%),  $p=0.027$ ). Programmed death-ligand 1 (PD-L1) expression in the tumor cells was more common in the infection group than in the noninfection group ( $n=10$  (50.0%) vs  $n=78$  (25.4%),  $p=0.033$ ). In terms of lung cancer stage, compared to those in the noninfection group, patients in the infection group had higher stage disease, especially since no patients in the infection group had stage I disease. The laboratory findings before the bronchoscopic examination showed higher inflammation (median WBC (IQR): 7525 cells/ $\mu$ L (6955-9155) vs 6660 cells/ $\mu$ L (5360-8190),  $p=0.007$ , median CRP (IQR): 0.59 mg/dL (0.16-2.71) vs 0.17 (0.05-0.86),  $p=0.014$ ) and lower serum albumin (median (IQR): 3.71 g/dL (3.22-4.08) vs 4.12 g/dL (3.80-4.33),  $p=0.012$ ) in the infection group than in the noninfection group. In radiographic findings, patients in the infection group had larger tumor diameters (median (IQR): 41.3 mm (32.7-57.9) vs. 29.6 mm (18.2-46.3),  $p=0.003$ ) and more necrosis and/or cavities in the tumors ( $n=8$  (40.0%) vs.  $n=29$  (9.4%),  $p<0.001$ ) than those in the noninfection group. The incidence of using a guide sheath ( $p=0.588$ ), abnormal bronchoscopic findings ( $p=0.175$ ), and antibiotic prophylaxis ( $p=0.429$ ) were not significantly different between the two groups.

The odds ratios of a tumor diameter of 30 mm or more, necrosis and/or a cavity in the tumor, WBC of 6500 cells/ $\mu$ L or more, CRP of 0.55 mg/dL or more, and serum albumin less than 4.0 g/dL are shown in Table 2. Necrosis and/or a cavity in the tumor showed the highest odds ratio at 6.33 (95% confidence level (CI): 2.07-18.5,  $p<0.001$ ). We developed a predictive score for the development of post-bronchoscopy respiratory infections that included necrosis and/or cavities in the tumors, tumor diameter  $\geq 30$  mm, and serum albumin  $<4.0$  g/dL (Fig. 2). Each variable was assigned a value of 1 point, thus totaling 3 points. The ROC curve of the score demonstrated a high AUC of 0.737 (95% CI: 0.610-0.864). A score of 2 or more was regarded as the cutoff value, and the sensitivity, specificity, and odds ratio were 70.0%, 69.2%, and 5.21 (95% CI: 1.81-17.1), respectively.

Table 3 shows the characteristics of the infection group. Of all the patients, 12 patients had lung abscesses (3.7%), 4 patients had post-obstructive pneumonia (1.2%), and 4 patients had typical pneumonia (1.2%). The median duration from the bronchoscopic examination to treatments for post-bronchoscopy respiratory infection was 12.5 days (interquartile range (IQR): 7.0-18.3). Eight out of the 12 patients with lung abscesses showed necrosis and/or a cavity in the tumor; however, no patients with post-obstructive pneumonia and typical pneumonia showed those findings. All patients with post-obstructive pneumonia showed abnormal bronchoscopic findings and underwent biopsy without EBUS-GS. Conversely, many patients with lung abscesses and typical pneumonia underwent EBUS-GS and did not show abnormal bronchoscopic findings. One patient with a lung abscess required surgical treatment, and another patient died. In 2013, when EBUS-GS was not yet used in our hospital, 131 patients were diagnosed with lung cancer by bronchoscopic examination, and seven of these patients had post-bronchoscopy respiratory infection (5.3%), including only one patient with a lung abscess (0.8%) and six patients with other types of pneumonia (4.6%). The incidence of developing lung abscesses after bronchoscopy has increased in recent years (Fig. 3). In addition, the number of biopsies performed in 2019 was higher than that in 2017 ( $p=0.018$ ).

## Discussion

This study identified the characteristics and risk factors for developing a post-bronchoscopy respiratory infection. A total of 6.1% of all patients developed post-bronchoscopy respiratory infections, and the risk factors were high WBC counts or CRP levels, low serum albumin levels, necrosis and/or a cavity in the tumor, and large tumor diameter. However, these risk factors differ from those in past reports [6, 9]. We developed a predictive score that included necrosis and/or a cavity in the tumor, tumor diameter  $\geq 30$  mm, and serum albumin  $< 4.0$  g/dL. A score of a least 2 was a good predictor for developing a post-bronchoscopy respiratory infection. In total, 60% of the patients with post-bronchoscopy respiratory infections showed lung abscesses. The incidence of developing lung abscesses after bronchoscopy has increased in recent years. We believe that these different risk factors are caused by the advancement of bronchoscopic techniques.

A past report from 2012 to 2013 suggested risk factors for post-bronchoscopy respiratory infection, such as an elderly age, current smoking status, and central location of the tumor [6]. However, these factors did not differ significantly between the infection group and the noninfection group in our study. These differences might be caused by the increasing incidence of lung abscesses after bronchoscopy since the bronchoscopic techniques have been changed. Generally, lung abscesses are rare in post-bronchoscopy respiratory infections and occur in 0.22-1.06% of the patients [7, 8]. Similar to the percentage in past reports, 0.8% of the patients in our study had lung abscesses after bronchoscopy in 2013, when EBUS-GS was not yet used in our hospital. However, the incidence of lung abscesses after bronchoscopy increased to as high as 5.3% in 2019. Recently, the EBUS-GS technique has been used and has significantly increased the diagnosis rate of peripheral pulmonary lesions [15, 16]. Moreover, the number of TBLB procedures performed is higher because the specimens from EBUS-GS are smaller in size than those from routine TBLB [15]. The British Thoracic Society guidelines for bronchoscopy recommend taking at least

five biopsy samples [1], and an additional five bronchial forceps biopsies should be considered for phenotyping and genotyping exams [17]. In our hospital, the number of biopsy by bronchoscopy procedures performed increased from October 2018 because of phenotyping and genotyping, and the number of biopsies performed by bronchoscopy was significantly greater in 2019 than in 2017. Therefore, we thought that post-bronchoscopy lung abscesses can easily occur due to the type of approach, infection of the central tumor using EBUS-GS and increases in the number biopsies performed.

Lung abscesses are a type of liquefaction of the lung tissue and a formation of cavities containing necrotic debris or fluid caused by microbial infection [18]. Ishida M et al. reported that a risk factor for post-bronchoscopy lung abscess was a tumor diameter of 30 mm or more [8], which is similar to our report. We demonstrated risk factors such as necrosis and/or a cavity in the tumor and large tumor diameter. Conversely, all patients with post-obstructive pneumonia showed abnormal bronchoscopic findings and did not show necrosis and/or cavities in the tumors. Patients with typical pneumonia after bronchoscopy did not show necrosis, a cavity in the tumor or abnormal bronchoscopic findings. Therefore, the risk factors for post-bronchoscopy respiratory infection might differ among types of infection.

Other risk factors for post-bronchoscopy respiratory infection were low serum albumin before the bronchoscopic examination and PD-L1 expression in tumor cells. Low serum albumin might indicate that the immune systems of the patients in the infection group were worse than those of the patients in the noninfection group. Generally, the nutritional status as assessed by the serum albumin level relates to the immune response, and malnutrition is a common cause of immunodeficiency [19, 20]. In addition, PD-L1 expression in tumor cells is related to the immune system. The combination of programmed cell death 1 (PD-1) and PD-L1 leads to tumor immune evasion through the suppression of T cells [21], and the role of PD-1 is to regulate infections due to the limited function of macrophages as well as the T cell-independent B cell response [22]. A case report of a patient with a lung abscess after bronchoscopy showing high levels of PD-L1 was previously published [23]. Thus, immune disorder is an important risk factor for the development of post-bronchoscopy respiratory infections.

The British Thoracic Society guidelines for bronchoscopy do not recommend antibiotic prophylaxis before bronchoscopy for endocarditis, fever, or pneumonia [1]. In our study, antibiotic prophylaxis did not effectively prevent post-bronchoscopy respiratory infections. However, very few patients received antibiotic prophylaxis, so whether antibiotic prophylaxis was useful cannot be determined. Kanazawa H et al. reported that azithromycin was effective as prophylactic antibiotherapy in preventing infections post bronchoscopy compared to the no-treatment group (3.0% vs 14.8%,  $p=0.02$ ) [7]. Generally, the common causative organisms of lung infections after bronchoscopy are oro- or nasopharyngeal microbes, such as *Streptococcus*, *Staphylococcus*, *Moraxella*, *Neisseria*, and anaerobic bacterial species [5]. Therefore, prophylactic antibiotherapy might be better adapted to anaerobic bacteria. Many patients with post-bronchoscopy respiratory infections canceled their planned oncologic treatments [6], and some post-bronchoscopy respiratory infections could not improve with antibiotics and required surgical

invention [8]. Therefore, prophylactic antibiotherapy might be necessary for high-risk patients. A prospective study of effective antibiotic prophylaxis is required.

This investigation had several limitations. The study was conducted retrospectively in a single center. The target disease was lung cancer; therefore, the incidence in this study does not represent the overall incidence of bronchoscopy. Some medical data were not recorded. Some patients received prophylaxis antibiotherapy. We reviewed all types of infections together. Some patients did not have PD-L1 tumor cell expression data because the analysis was not requested or sample size from TBLB was too small.

## Conclusion

The study demonstrated the characteristics of post-bronchoscopy respiratory infections, which was mainly lung abscesses. The risk factors were high inflammation, low serum albumin, necrosis and/or a cavity in the tumor, and large tumor diameter. In addition, we developed a good predictive score, which included necrosis and/or a cavity in the tumor, tumor diameter  $\geq 30$  mm, and serum albumin  $< 4.0$  g/dL. We believe that these risk factors vary from those in past reports because of the advancement of bronchoscopic techniques.

## List Of Abbreviations

EBUS: endobronchial ultrasonography

EBUS-GS: endobronchial ultrasonography with a guide sheath

EBUS-TBNA: endobronchial ultrasonography-guided transbronchial needle aspiration

TBLB: transbronchial lung biopsy

CT: computed tomography

WBC: white blood cell count

CRP: C-reactive protein

ROC: receiver operating characteristic

AUC: area under the curve

IQR: interquartile range

PD-L1: programmed death-ligand 1

CI: confidence interval

PD-1: programmed cell death 1

EGFR: epidermal growth factor receptor

LDH: lactate dehydrogenase

## Declarations

Ethics Approval and Consent to Participate:

The study was approved by the Institutional Review Board of Fukujuji Hospital. It was determined that patient consent was not required. The decisions made by this board are based on and in accordance with the Declaration of Helsinki.

Consent for Publication: Not applicable

Availability of Data and Materials:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests: All authors state that they have no conflicts of interest.

Funding: Not applicable

Authors' Contributions:

KY conceived and designed the work with the corresponding author. RY, MS, KF, KF, TO, FU, KA, KM, YT, HK, MO, TU, KO, and KY collected patient data. All authors read and approved the final manuscript.

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## Tables

Table 1. Baseline characteristics of the patients in the study

	Infection (n=20)	No infection (n=307)	<i>p</i> -value
Age, median (IQR), years	68.5 (64.5-78.5)	73.0 (67.0-78.0)	0.453
Sex (male/female)	16/4	181/126	0.097
Underlying disease, n (%) <sup>a</sup>	16 (88.9)	262 (87.6)	1.000
Current smoker, n (%) <sup>b</sup>	7 (36.8)	63 (22.5)	0.165
Experiencing symptoms, n (%) <sup>c</sup>	11 (57.9)	124 (40.8)	0.157
Histological classification of lung cancer			
Adenocarcinoma, n (%)	9 (45.0)	202 (65.8)	0.089
Squamous cell carcinoma, n (%)	6 (30.0)	59 (19.2)	0.250
Neuroendocrine tumor, n (%)	0 (0)	21 (6.8)	0.628
Other, n (%)	5 (25.0)	25 (8.1)	0.027
EGFR mutation, n (%)	3 (15.0)	68 (22.1)	0.583
PD-L1 expression, n (%)	10 (50.0)	78 (25.4)	0.033
Stage			
I, n (%)	0 (0)	123 (40.1)	<0.001
II, n (%)	6 (30.0)	45 (14.7)	0.102
III, n (%)	8 (20.0)	61 (19.9)	0.045
IV, n (%)	6 (30.0)	78 (25.4)	0.607
Laboratory findings			
WBC, median (IQR), cells/ $\mu$ L <sup>d</sup>	7525 (6955-9155)	6660 (5360-8190)	0.007
CRP, median (IQR), mg/dL <sup>e</sup>	0.59 (0.16-2.71)	0.17 (0.05-0.86)	0.014
	183 (157-216)	197 (170-226)	0.389

LDH, median (IQR), U/L <sup>f</sup>			
Albumin, median (IQR), g/dL <sup>g</sup>	3.71 (3.22-4.08)	4.12 (3.80-4.33)	0.012
Radiographic findings			
Right lobe/left lobe	9/11	178/128	0.255
Upper lobe, n (%)	10 (50.0)	142 (46.3)	0.821
Middle lobe/lingula, n (%)	1 (5.0)	39 (12.7)	0.487
Lower lobe, n (%)	9 (45.0)	122 (39.7)	0.815
Tumor diameter, median (IQR), cm	41.3 (32.7-57.9)	29.6 (18.2-46.3)	0.003
Necrosis and/or a cavity in the tumor, n (%)	8 (40.0)	29 (9.4)	<0.001
Bronchoscopic technique			
The number of biopsies performed, median (IQR)	6.0 (6.0-7.3)	6.0 (6.0-7.0)	0.902
Used a guide sheath, n (%)	14 (70.0)	235 (76.5)	0.588
Diagnosis by TBLB, n (%)	19 (95.0)	267 (87.0)	0.488
Abnormal bronchoscopic findings	7 (35.0)	56 (21.8)	0.175
Fever ( $\geq 38$ degree C) within 24 hr after bronchoscopy, n (%)	3 (15.0)	23 (7.5)	0.205
Antibiotic prophylaxis, n (%)	3 (15.0)	29 (9.4)	0.429

a: infection group n=18, noninfection group n=299, b: infection group n=19, noninfection group n=280, c: infection group n=19, noninfection group n=304, d: infection group n=20, noninfection group n=305, e: infection group n=20, noninfection group n=294, f: infection group n=20, noninfection group n=297, g: infection group n=20, noninfection group n=298.

IQR: interquartile range, EGFR: epidermal growth factor receptor, PD-L1: programmed death-ligand 1, TBLB: transbronchial lung biopsy, WBC: white blood cell count, CRP: C-

Table 2. The odds ratios of several variables for diagnosing post-bronchoscopy respiratory infection

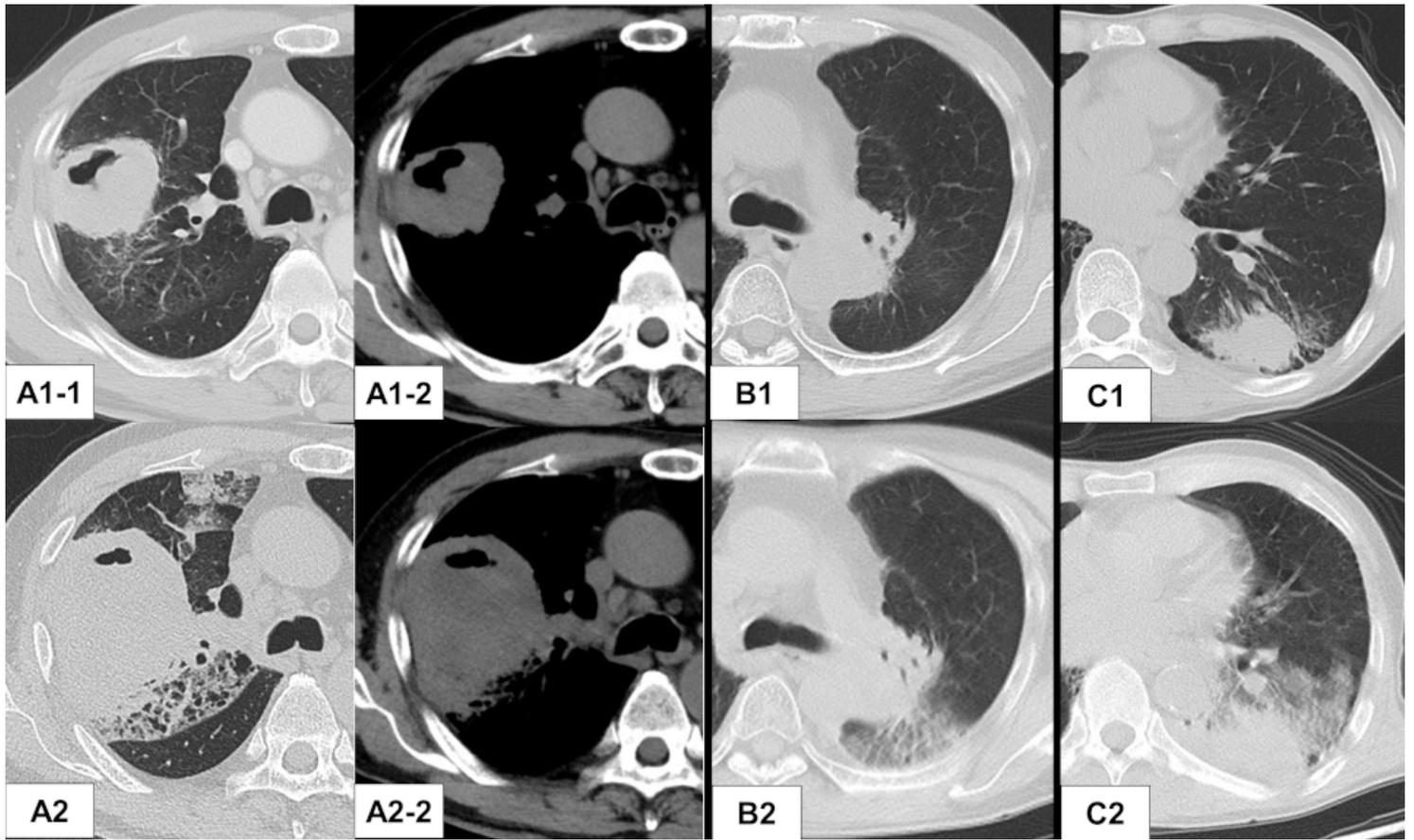
	Odds ratio	95% CI		Sensitivity	Specificity	<i>p</i> -value
		Lower limit	Upper limit			
Tumor diameter $\geq 30$ mm	4.01	1.25	16.9	80.0	50.2	0.010
Necrosis and/or a cavity in the tumor	6.33	2.07	18.5	40.0	91.6	<0.001
WBC $\geq 6500$	4.79	1.35	26.0	85.0	45.9	0.009
CRP $\geq 0.55$	2.94	1.07	8.35	55.0	70.7	0.023
Albumin <4.0 g/dL	3.50	1.22	11.4	70.0	60.1	0.010

CI: confidence interval, WBC: white blood cell count, CRP: C-reactive protein

Table 3. The characteristics of the types of post-bronchoscopy respiratory infections

	Lung abscess (n=12)	Post-obstructive pneumonia (n=4)	Typical pneumonia (n=4)
Necrosis and/or a cavity in the tumor, n (%)	8 (40.0)	0 (0.0)	0 (0.0)
Using a guide sheath, n (%)	10 (70.0)	0 (0.0)	4 (100)
Abnormal bronchoscopic findings	3 (35.0)	4 (100)	0 (100)

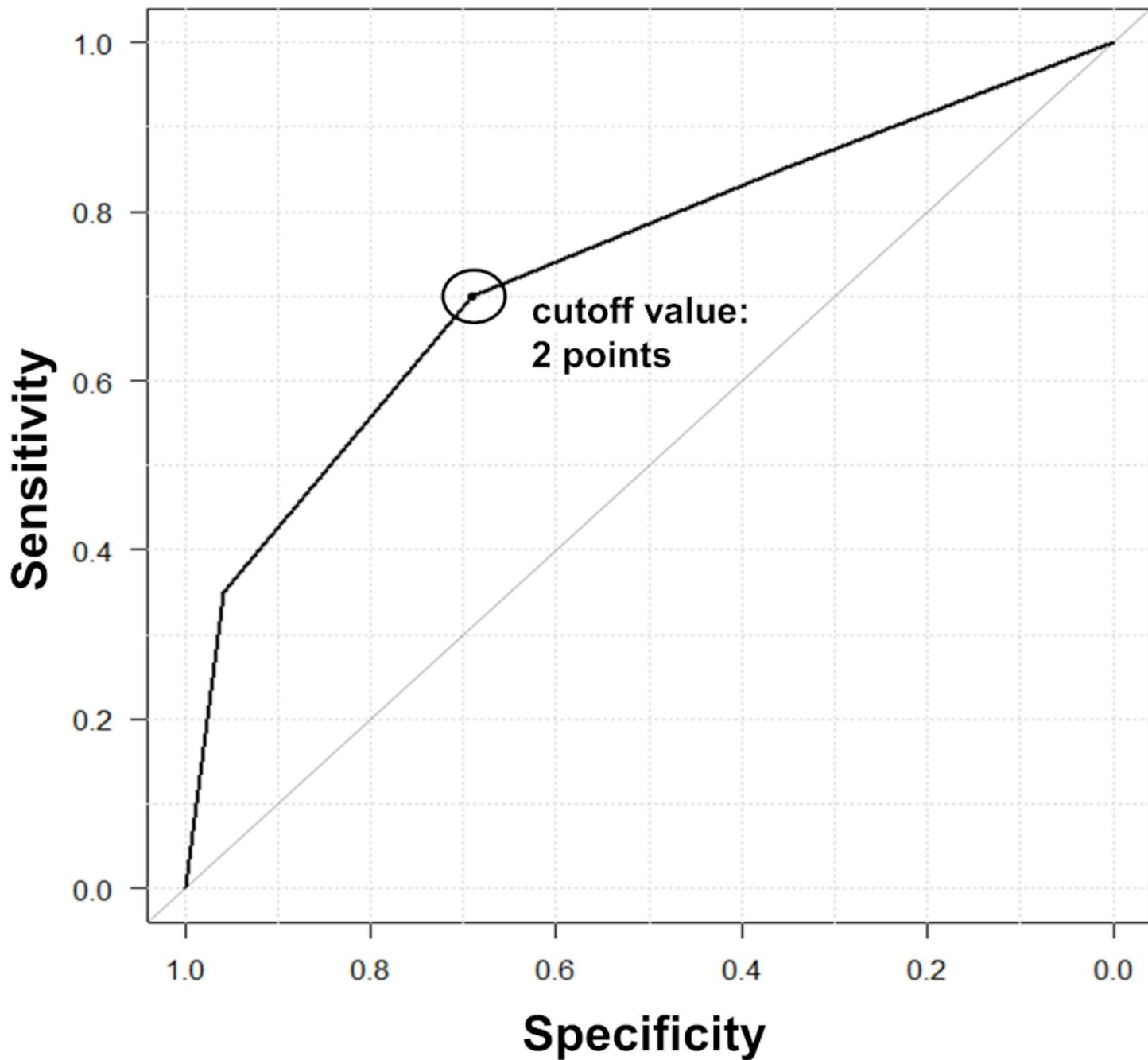
## Figures



**Figure 1**

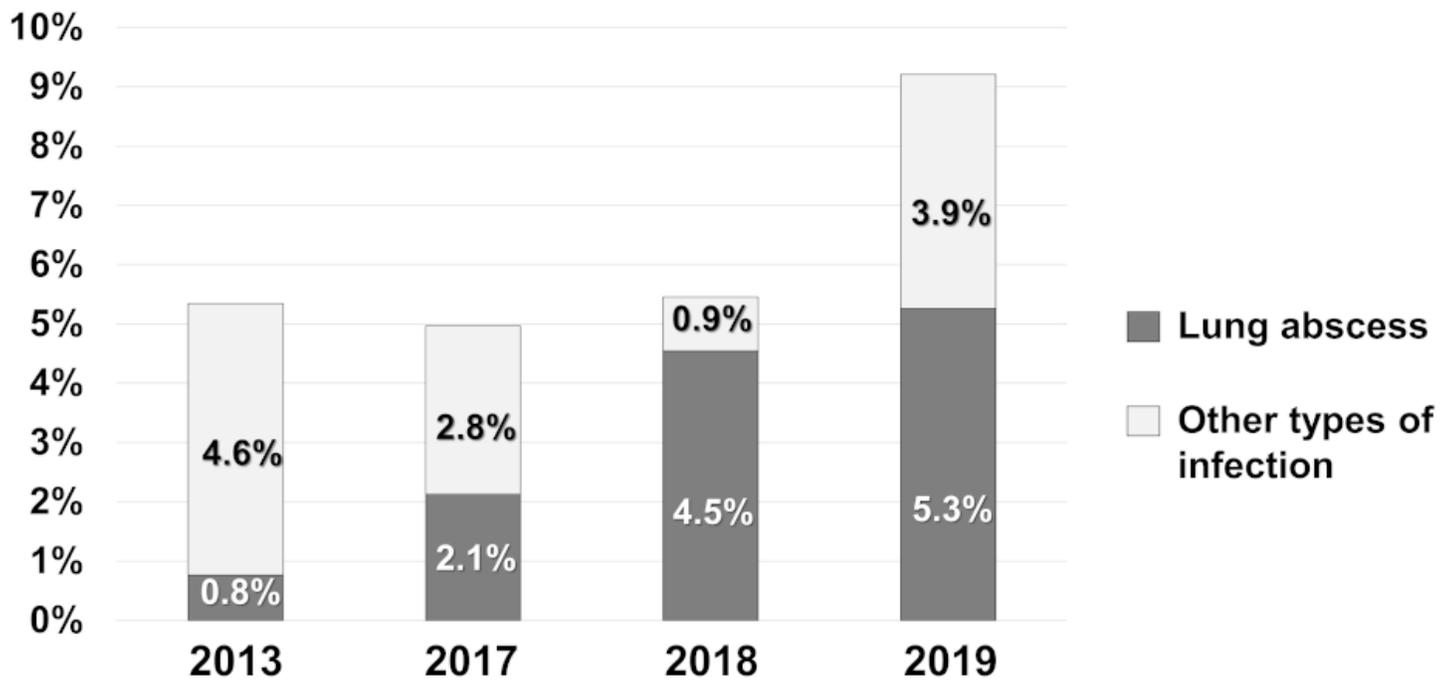
The types of post-bronchoscopy infections were classified as lung abscesses, post-obstructive pneumonia, and typical pneumonia

A1-1: A tumor with central necrosis and a cavity  
A1-2: Mediastinal window setting of A1-1  
A2-1: Lung abscess in a tumor after bronchoscopy  
A2-2: Mediastinal window setting of A2-1  
B1: A tumor in the central area and obstructive bronchi  
B2: Post-obstructive pneumonia distal to a bronchial obstruction after bronchoscopy  
C1: A tumor in the lung field  
C2: A new infiltrate around the target lesion that appeared as pneumonia after bronchoscopy



**Figure 2**

The receiver operating characteristic curve of the score for predicting post-bronchoscopy respiratory infections. The area under the curve was 0.737 (95% CI: 0.610-0.864). The predictive accuracy for post-bronchoscopy respiratory infection at a cutoff value of 2 points or more included a sensitivity of 70%, specificity of 69.2%, and odds ratio of 5.21 (95% CI: 1.81-17.1). CI: confidence interval



**Figure 3**

The incidence of developing post-bronchoscopy respiratory infections in 2013, 2017, 2018, and 2019  
 Data in 2019 were from January to June.