



Factors Associated with Diagnostic Yield of Transbronchial Biopsy for Suspected Lung Cancer

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Submitted: April 17th, 2026

Accepted: September 10th, 2026

Published: October 26th, 2026

Respir Sci. 2026; 7(1): 8-17

<https://doi.org/10.36497/respirsci.v7i1.238>



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Abstract

Background: Transbronchial biopsy (TBB) is an important diagnostic approach for identifying peripheral lung lesions in suspected lung cancer patients. As is known, the lesion characteristics and radiological findings may influence its diagnostic yield. Therefore, this study aimed to identify factors associated with TBB diagnostic yield to help optimize patient selection and improve diagnostic success.

Method: This cross-sectional study included 77 adults with suspected lung cancer who underwent TBB at Persahabatan Hospital between September and December 2024. Factors associated with TBB diagnostic yield, including tumor size, bronchus sign, and lesion location, were assessed. Receiver operating characteristic (ROC) analysis was performed to determine the optimal tumor-size cutoff. A parsimonious multivariable logistic regression model including tumor size and bronchus sign was used to identify independent factors associated with a positive TBB result.

Results: The overall diagnostic yield of TBB was 63.6%. In bivariate analysis, tumor size ≥ 2.95 cm and the presence of a bronchus sign were significantly associated with a positive TBB result. ROC analysis demonstrated modest discrimination for tumor size (AUC=0.693; 95% CI=0.562–0.824; $P=0.005$), with a cutoff of 2.95 cm yielding 87.8% sensitivity and 53.6% specificity. Lesions ≥ 2.95 cm had a higher diagnostic yield than lesions < 2.95 cm (76.8% vs. 28.6%; OR=8.27; 95% CI=2.67–25.65; $P<0.001$). In multivariable analysis, tumor size ≥ 2.95 cm remained independently associated with a positive TBB result (aOR=6.33; 95% CI=1.91–20.83; $P=0.002$), whereas bronchus sign was not independently associated (aOR=0.36; 95% CI=0.07–1.77; $P=0.206$).

Conclusion: Tumor size ≥ 2.95 cm was independently associated with a higher diagnostic yield of TBB in patients with suspected lung cancer. Tumor size may therefore be useful in identifying peripheral lung lesions more likely to yield a diagnostic transbronchial biopsy.

Keywords: bronchus sign, lung cancer, peripheral lung lesion, transbronchial biopsy, tumor size

INTRODUCTION

Lung cancer remains the leading cause of cancer-related mortality worldwide, with approximately 2.48 million new cases and 1.82 million deaths reported globally in 2022.¹ The increasing detection of pulmonary nodules and peripheral pulmonary lesions (PPLs) through advances in thoracic imaging has consequently increased the need for accurate and minimally invasive tissue diagnosis. Histopathological confirmation remains essential not only for establishing the diagnosis but also for obtaining adequate tissue for molecular and immunohistochemical characterization, including testing for alterations such as EGFR, ALK, ROS-1, and KRAS, as well as PD-L1 expression when clinically indicated.²

Peripheral pulmonary lesions can be challenging to diagnose because of their location beyond the reach of conventional bronchoscopy. Several techniques have therefore been developed to improve tissue acquisition, including fluoroscopy-guided transbronchial biopsy (TBB), radial endobronchial ultrasound (R-EBUS), navigation bronchoscopy, and robotic-assisted bronchoscopy.^{3–5}

Despite these advances, diagnostic yield remains heterogeneous. A large meta-analysis of guided bronchoscopy reported an overall diagnostic yield of approximately 69%, with larger lesions and the presence of a computed tomography (CT) bronchus sign associated with higher diagnostic yield. Recent meta-analyses of R-EBUS and robotic-assisted bronchoscopy

have similarly demonstrated that lesion size and bronchus sign remain important determinants of diagnostic success.^{6–8}

Transbronchial biopsy offers a minimally invasive approach for obtaining tissue from peripheral lesions and generally has a lower risk of pneumothorax than transthoracic biopsy. However, the availability of advanced bronchoscopic techniques does not eliminate the need to identify factors associated with procedural success. Lesion characteristics such as size and the CT bronchus sign may influence the ability to navigate to and adequately sample a lesion. Understanding these factors may be particularly useful in settings where advanced navigation of robotic technologies is not routinely available.^{3,6}

Although previous studies have identified several predictors of bronchoscopic diagnostic yield, substantial heterogeneity exists across patient populations, lesion characteristics and procedural techniques.^{5,6,8} Moreover, evidence regarding factors associated specifically with TBB diagnostic positivity in routine clinical practice remains limited in Indonesia. Therefore, identifying readily assessable pre-procedural factors that may predict biopsy success remains clinically relevant.

Therefore, this study aimed to evaluate factors associated with the diagnostic yield of TBB in patients with suspected lung cancer and peripheral lung lesions. Specifically, we evaluated the associations of tumor size, CT bronchus sign and lesion location with TBB diagnostic yield and determined the optimal tumor-size cutoff for predicting a positive biopsy result.

METHOD

This cross-sectional study was conducted at Persahabatan Hospital, Jakarta, Indonesia, between September and December 2024. The study was approved by the Health Research Ethics Committee of Persahabatan Hospital with number 0228/KEPK-RSUPP/10/2024 (approval date: 16 October 2024). The study was conducted in accordance with the principles of the Declaration of Helsinki and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

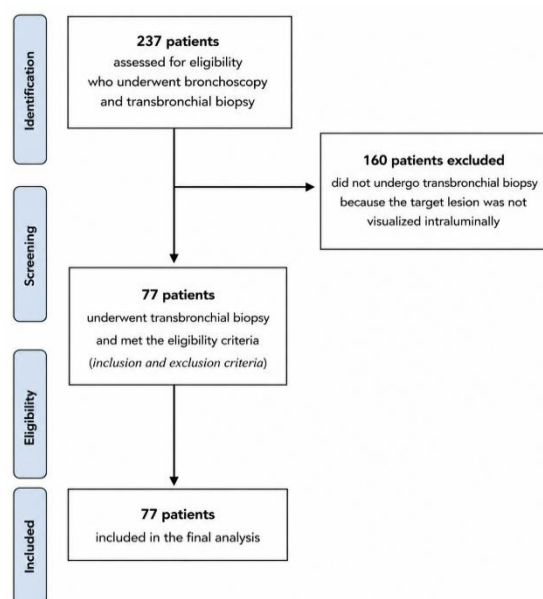


Figure 1. Flow diagram of patient selection

A total of 77 patients were included using consecutive sampling. The inclusion criteria for this study were patients aged ≥ 18 years with suspected lung cancer who underwent TBB at Persahabatan Hospital as part of routine clinical care. Patients were excluded if they refused the TBB procedure or declined participation in the study.

The study used routinely collected clinical, radiological, bronchoscopy and histopathological data. No additional invasive procedure was performed. Written informed consent for bronchoscopy and TBB was obtained as part of routine clinical care.

Pre-procedural CT images were reviewed to assess lesion size, lesion location and the presence of a bronchus sign. CT assessment was performed by two pulmonologists who were involved in the bronchoscopic procedure. The readers were aware of the histopathological results because the CT assessment was performed as part of routine clinical care. Interobserver agreement was not formally assessed.

The maximum axial diameter of the largest lesion was measured using the lung window. CT-slice thickness varied among patients because some CT examinations had been performed at referring hospitals before the patients were referred to Persahabatan Hospital. Both digital CT images and printed film were included. Lesion size was recorded based on the longest axial diameter available on the pre-procedural CT examination. Meanwhile, a bronchus sign was defined as the presence of a bronchus directly leading to or extending into the target peripheral lung lesion on CT.

All procedures were performed under general anesthesia. The bronchoscopy procedures were performed by a consultant pulmonologist. Flexible bronchoscopes (Fujinon with a 2.8-mm or 2.2-mm working channel, or Olympus with

a 2.2-mm working channel) were advanced to the target bronchial segment on pre-procedural CT findings.

Forceps biopsies were obtained using conventional biopsy forceps, with a mean of five biopsy passes per lesion. Fluoroscopic guidance was used in 68 patients (88.3%), radial endobronchial ultrasound (R-EBUS) alone in seven patients (9.1%), and a combination of fluoroscopy and R-EBUS in two patients (2.6%).

Biopsy specimens were immediately imprinted onto glass slides and fixed in 10% neutral-buffered formalin. Tissue specimens were processed into paraffin blocks, sectioned at 3-10 μ m thickness, stained with hematoxylin and eosin, and examined by pathologists at Persahabatan Hospital. Histopathological findings were categorized as positive or negative for malignancy and were used as the study outcome.

Statistical analyses were performed using IBM SPSS Statistics version 26. Continuous variables were summarized as mean $\pm$ standard deviation (SD) or median (min-max), whereas categorical variables were presented as frequencies and percentages. Associations between categorical variables and biopsy positivity were analyzed using the chi-square test or Fisher's exact test, as appropriate.

Given the limited number of positive biopsy events, a parsimonious multivariable logistic regression model including tumor size and bronchus sign was constructed using the enter method to identify factors independently associated

with positive biopsy results. The presence of the bronchus sign was used as the reference category.

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the ability of lesion size to predict positive biopsy results. The optimal cutoff value was selected using the Youden index, and the area under the curve (AUC), sensitivity, specificity, 95% confidence interval, and value of P were reported. Statistical significance was defined as a two-sided value of $P < 0.05$.

RESULT

The mean age of the 77 patients with suspected lung cancer who underwent bronchoscopy and TBB was 58 ± 12.73 years, and the majority were male (61%).

Table 1. Baseline characteristics (n=77)

Variables	n	%
Age, years (mean $\pm$ SD)	58.18 $\pm$ 12.73	
Gender		
Female	47	61.0
Male	30	39.0
Lung lesion location		
Right upper lobe	25	32.5
Medial lobe	9	11.7
Right lower lobe	17	22.1
Left upper lobe	19	24.7
Left lower lobe	7	9.1
Lung lesion diameter, cm [Median (min-max)]	5.2 (0.7-13.2)	
Bronchus sign		
Presence	66	85.7
Absence	11	14.3
Histopathology results		
Lung adenocarcinoma	31	40.3
Squamous cell carcinoma	4	5.2
NSCLC	1	1.3
Granuloma	13	16.8
Negative	28	36.3

The median lesion diameter was 5.20 (0.7-13.2) cm, with the most frequent lesion location being the right upper lobe (39.0%). In addition, 66 patients (85.7%) had a bronchus sign. Overall, 49 patients (63.6%) had positive TBB results, with adenocarcinoma as the most common histopathological diagnosis (40.3%).

Table 2. Association between lesion location and biopsy results

Lesion Location	Biopsy Result		P ^a
	Positive	Negative	
Right upper lobe	17 (68.0%)	8 (32.0%)	0.100
Medial lobe	5 (55.6%)	4 (44.4%)	
Right lower lobe	7 (41.2%)	10 (58.8%)	
Left upper lobe	16 (84.2%)	3 (15.8%)	
Left lower lobe	4 (57.1%)	3 (42.9%)	

Note: ^aPearson chi-square test; P<0.05 was considered statistically significant

The proportion of positive TBB results varied across lesion locations, ranging from 41.2% in the right lower lobe to 84.2% in the left upper lobe. However, lesion location was not significantly associated with TBB diagnostic yield (P=0.100).

ROC curve analysis demonstrated that tumor size had modest discriminatory ability for predicting a positive TBB result, with a cut-off of 2.95 cm, AUC of 0.693 (95% CI=0.562-0.824; P=0.005), sensitivity of 87.8% and specificity of 53.6%.

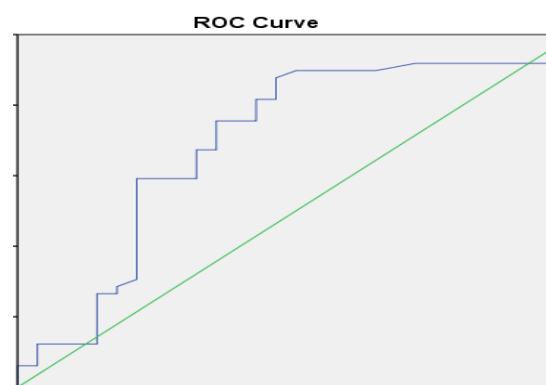


Figure 2. ROC analysis for tumor size

Table 3 shows that, using the 2.95-cm cutoff, lesions measuring ≥ 2.95 cm had a substantially higher diagnostic yield than lesions measuring < 2.95 cm. A positive biopsy result was obtained in 43 of 56 lesions (76.8%) measuring ≥ 2.95 cm, compared with 6 of 21 lesions (28.6%) measuring < 2.95 cm. The analysis found that tumor size ≥ 2.95 cm was significantly associated with a positive TBB result, with an unadjusted OR of 8.27 (95% CI=2.67-25.65; P<0.001).

Table 3 also shows that a positive bronchus sign was observed in 66 patients, with 46 patients (69.7%) having a positive biopsy result. Meanwhile, 3 of 11 patients (27.3%) did not have a bronchus sign. The presence of a bronchus sign was also significantly associated with a positive TBB result in bivariate analysis (OR=6.13; 95% CI=1.47-25.55; P=0.014).

Table 3. Proportion of positive histopathological results based on tumor size and bronchus sign

Variables	Histopathological Results		P	OR (95% CI)
	Positive	Negative		
Tumor Size (cm)				
≥ 2.95	43 (76.8%)	13 (23.2%)	0.001 ^a	8.27 (2.67 – 25.65)
< 2.95	6 (28.6%)	15 (71.4%)		
Bronchus Sign				
Presence	46 (69.7%)	20 (30.3%)	0.014 ^{b*}	6.13 (1.47 – 25.55)
Absent	3 (27.3%)	8 (72.7%)		

Note: ^aChi-square test; ^bFisher's exact test; *P<0.05 was considered statistically significant; OR=odds ratio

Multivariable logistic regression was performed using tumor size and bronchus sign as predictors of a positive TBB result. The model was significant ($P < 0.001$) and demonstrated a Nagelkerke R^2 of 0.268. The Hosmer-Lemeshow test indicated no evidence of poor model fit ($P = 0.545$).

After adjustment for bronchus sign, tumor size ≥ 2.95 cm remained independently associated with a positive TBB result, with an adjusted OR of 6.33 (95% CI=1.91-20.83; $P = 0.002$). In contrast, the presence of a bronchus sign was not independently associated with biopsy positivity after adjustment for tumor size (aOR=0.36; 95% CI=0.07-1.77; $P = 0.206$). The model correctly classified 75.3% of cases, with a sensitivity of 87.8% and a specificity of 53.6% at the default probability threshold of 0.50.

Table 4. Multivariate logistic regression analysis of factors associated with positive transbronchial biopsy

Variables	aOR (95% CI)	P
Tumor Size (cm)		
≥2.95	6.33 (1.91-20.83)	0.002*
<2.95	Ref	
Bronchus Sign		
Presence	0.36 (0.07-1.77)	0.206
Absent	Ref	

Note: * $P < 0.05$ was considered statistically significant; aOR=adjusted odds ratio

DISCUSSION

This study evaluated factors associated with diagnostic positivity of transbronchial biopsy (TBB) in patients with suspected lung cancer and peripheral lung lesions. As is known, the overall diagnostic positivity was 63.6%, with the principal finding being that lesion size ≥ 2.95 cm was associated with a positive

biopsy result (aOR=6.33; 95% CI=1.91-20.83; $P = 0.002$). In addition, the CT bronchus sign was also significantly associated with biopsy positivity in bivariate analysis but did not significantly associate with biopsy positivity in multivariate analysis.

The overall diagnostic positivity observed in this study is comparable with previous studies of guided bronchoscopy for peripheral pulmonary lesions. An updated meta-analysis including 16,389 lesions from 126 studies reported an overall diagnostic yield of approximately 69%, although substantial heterogeneity was observed across studies. Importantly, lesion size > 2 cm and the presence of a bronchus sign were associated with higher diagnostic yield.^{3,6}

Lesion size was the strongest independent factor associated with diagnostic positivity in this study. ROC analysis identified 2.95 cm as the optimal cutoff, with an AUC of 0.693 (95% CI=0.562-0.842; $P = 0.005$), sensitivity of 87.8%, and specificity of 53.6%. Lesions ≥ 2.95 cm had a diagnostic positivity of 76.8%, compared with 28.6% among lesions < 2.95 cm. In the bivariate analysis, lesions ≥ 2.95 cm were associated with an OR of 8.27 (95% CI=2.67-25.65; $P < 0.001$). After adjustment for bronchus sign and lesion location, the association remained significant, with an aOR of 6.33 (95% CI=1.91-20.83; $P = 0.002$).

The association between larger lesion size and higher diagnostic yield is biologically plausible. Larger lesions provide a greater target volume for

bronchoscopic sampling, may offer a larger bronchial interface, and may be easier to localize and access using bronchoscopic instruments. A larger target may also reduce sampling error because small deviations in forceps position are less likely to result in complete sampling failure.^{3,5,7}

These findings are consistent with the meta-analysis by Nadig et al, which demonstrated that lesions >2 cm were associated with significantly higher diagnostic yield during guided bronchoscopy.³ Similarly, a systematic review and meta-analysis in 2024 of R-EBUS-guided bronchoscopy involving 7,252 peripheral pulmonary lesions found that lesions >2 cm were associated with higher diagnostic yield.^{6,7} The consistency of this association across different bronchoscopic techniques supports lesion size as an important pre-procedural characteristic when estimating the probability of successful tissue acquisition.

However, the AUC of 0.693 indicates modest discriminatory ability. Therefore, the 2.95-cm threshold identified in this study should not be interpreted as an absolute cutoff for selecting bronchoscopy. Rather, lesion size should be considered together with other radiological and procedural characteristics. Furthermore, because the cutoff was derived and tested within the same dataset, optimism bias cannot be excluded, and external validation is required before the threshold can be generalized.

The CT bronchus sign was significantly associated with biopsy positivity in the bivariate analysis. Patients

with a bronchus sign had a positive biopsy rate of 69.7%, compared with 27.3% among patients without a bronchus sign, corresponding to an OR of 6.13 (95% CI=1.47-25.55; P=0.014). A systematic review and meta-analysis by Ali et al demonstrated that the presence of a CT bronchus sign was associated with a higher diagnostic yield during guided bronchoscopy.⁶ A meta-analysis by Nadig et al similarly identified the bronchus sign as a factor associated with higher diagnostic yield.³ The bronchus sign may facilitate access to peripheral lesions by indicating a bronchial pathway leading toward the target lesion.^{3,6,9}

However, the bronchus sign did not remain independently associated with biopsy positivity after multivariable analysis (aOR=0.36; 95% CI=0.07-1.77; P=0.206). This may be explained by the small number of bronchus-sign-negative lesions, the high prevalence of the bronchus sign (85.7%), and possible misclassification due to heterogeneous CT protocols. Adjustment for lesion size may also have attenuated its association with biopsy positivity. Thus, in this study, lesion size showed a stronger association with biopsy positivity than the bronchus sign.

Lesion location was not significantly associated with diagnostic positivity. Although positivity was numerically higher in upper-lobe lesions, the differences were not statistically significant. This may reflect the small number of patients in each location category and the limited ability of lobar location alone to represent bronchoscopic accessibility. Other

anatomical factors, such as lesion-to-hilum distance, lesion-to-pleura distance, and bronchial anatomy, may be more relevant.^{8–10}

Most patients underwent fluoroscopy-guided TBB, while only seven underwent R-EBUS alone and two underwent combined guidance. The small number of patients receiving R-EBUS precluded meaningful comparison between guidance modalities. Recent meta-analyses have demonstrated promising diagnostic yields for R-EBUS and robotic bronchoscopy, particularly for larger lesions and those with a bronchus sign.^{5,10–12} Advanced techniques such as cone-beam CT-assisted bronchoscopy may further improve localization and diagnostic yield in challenging peripheral lesions.^{13,14}

This study has several limitations, including its single-center design and relatively small sample size; the 2.95-cm cutoff was derived and tested in the same study and therefore requires external validation. In addition, CT examinations originated from different institutions with varying acquisition protocols and slice thicknesses, potentially introducing measurement variability. A CT assessment was also performed by two pulmonologists who were aware of the histopathological results, and interobserver agreement was not assessed. Procedural techniques were also not standardized, and the R-EBUS probe position was not consistently documented; and this study did not assess complication rates, molecular tissue adequacy, or the final diagnosis following a negative biopsy.

CONCLUSION

The diagnostic positivity of transbronchial biopsy in this study was 63.6%, assessed by histopathological positivity rather than tissue adequacy for molecular testing. Lesion size ≥ 2.95 cm was the only independent factor associated with a positive biopsy result. The CT bronchus sign was significantly associated with biopsy positivity in bivariate analysis but was not independently associated after adjustment. Lesion location was not significantly associated with biopsy positivity. The 2.95-cm cutoff demonstrated modest discriminatory ability and requires external validation prior to clinical application.

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