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Robotic-Assisted Bronchoscopic Lung Cryobiopsy Is Associated With Higher Diagnostic Yield in Diffuse Parenchymal Lung Disease: A Multicenter Retrospective Cohort Study

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Abstract

Background

Transbronchial lung cryobiopsy (TBLC) is increasingly used to obtain tissue for the diagnosis of diffuse parenchymal lung disease (DPLD). However, diagnostic performance and complication rates vary with procedural technique and institutional experience. Robotic-assisted bronchoscopy (RAB) with cone-beam computed tomography (CBCT) may improve target localization and parenchymal sampling.

Methods

We conducted a multicenter retrospective cohort study of 65 adults who underwent TBLC for suspected DPLD at three Mayo Clinic sites between January 2025 and June 2026. Patients underwent FB-TBLC with a 1.1-mm cryoprobe (*n* = 26), FB-TBLC with a 1.7-mm cryoprobe (*n* = 19), or RAB-TBLC with a 1.1-mm cryoprobe (*n* = 20). We compared specific histopathologic diagnostic yield and procedure-related complications among biopsy approaches.

Results

Specific histopathologic diagnostic yield was 61.5% with FB-TBLC using a 1.1-mm cryoprobe, 73.7% with FB-TBLC using a 1.7-mm cryoprobe, and 95.0% with RAB-TBLC (*P* = 0.032). After adjustment for radiographic fibrosis and maximum biopsy dimension, RAB-TBLC remained associated with higher diagnostic yield than FB-TBLC using a 1.1-mm cryoprobe (adjusted OR, 11.15; 95% CI, 1.76–219.95). Diagnostic yield did not differ between the two FB-TBLC groups. Complication rates were 34.6%, 42.1%, and 10.0%, respectively (*P* = 0.065).

Conclusion

RAB-TBLC using a 1.1-mm cryoprobe was associated with a higher specific histopathologic diagnostic yield than FB-TBLC, without a detectable increase in procedure-related complications. Prospective studies are needed to validate these findings and determine which components of the RAB sampling strategy contribute to diagnostic performance.

Background

Diffuse parenchymal lung disease (DPLD) comprises heterogeneous disorders with overlapping clinical and radiographic features but distinct treatments and prognoses. Diagnosis integrates clinical, serologic, and radiologic data, with tissue sampling when uncertainty persists. Surgical lung biopsy provides large, architecturally preserved specimens but carries substantial morbidity and may be contraindicated in patients with limited physiologic reserve[1–4].

Transbronchial lung cryobiopsy (TBLC) is a less invasive alternative for selected patients requiring histopathologic diagnosis. Prospective and randomized studies show that TBLC can yield diagnostically useful tissue and improve multidisciplinary diagnostic confidence. COLDICE showed high concordance between diagnoses based on TBLC and surgical lung biopsy when the TBLC-based diagnosis was made with high confidence, whereas the COLD trial supported a TBLC-first strategy, with surgical biopsy reserved for inconclusive FB-TBLC findings[3,4]. Nevertheless, outcomes remain technique- and center-dependent, and pneumothorax and clinically significant bleeding remain important complications[3–5].

Advances in cryobiopsy and bronchoscopic navigation may improve parenchymal sampling. The 1.1-mm cryoprobe has shown diagnostic performance comparable to larger cryoprobes in patients with suspected DPLD[6]. In FROSTBITE-2, it achieved a higher overall diagnostic yield than forceps biopsy, although the difference was not statistically significant in the smaller DPLD subgroup[7]. RAB-TBLC may enable precise target localization and sampling while avoiding the pleura, fissures, and major blood vessels. Distal airway wedging may provide catheter stability and local tamponade, potentially limiting bleeding and promoting clot formation, although evidence does not establish wedging as an independent protective factor against pneumothorax[8,9]. Together, robotic navigation, CBCT confirmation, distal wedging, and a 1.1-mm cryoprobe provide a rationale for targeted tissue acquisition in DPLD.

We hypothesized that RAB-TBLC using a 1.1-mm cryoprobe would achieve a higher specific histopathologic diagnostic yield than FB-TBLC without increasing complication rates. We therefore compared RAB-TBLC using a 1.1-mm cryoprobe with FB-TBLC using 1.1-mm and 1.7-mm cryoprobes and evaluated procedure-related complications.

METHODS:

Study Design and Population

This multicenter retrospective cohort included patients undergoing TBLC for suspected DPLD from January 2025 through June 2026. The Mayo Clinic Institutional Review Board approved the study (No. 26-002375).

The robotic cohort included 23 consecutive adults with suspected nonfibrotic DPLD and no history of lung transplantation who underwent RAB-TBLC with a 1.1-mm cryoprobe and standardized CBCT confirmation. Three cases without CBCT confirmation were excluded, leaving 20 patients; all three excluded cases yielded specific histopathologic diagnoses (two cases of sarcoidosis and one of organizing pneumonia).

The comparison cohort included 318 FB-TBLC procedures performed across three Mayo Clinic sites from January 2018 through June 2026. Restricting the cohort to the January 2025–June 2026 study period and to patients with suspected nonfibrotic DPLD identified 135 patients; 90 patients with prior lung transplantation were excluded. The final FB-TBLC cohort included 45 patients (26 who underwent

biopsy with a 1.1-mm cryoprobe and 19 with a 1.7-mm cryoprobe). Together with the 20 RAB-TBLC patients, the final cohort comprised 65 patients (Fig. 1).

Patients aged 18 years or older who underwent clinically indicated TBLC for suspected nonfibrotic DPLD from January 2025 through June 2026 were eligible if they had no history of lung transplantation. The RAB cohort underwent RAB-TBLC with a 1.1-mm cryoprobe, whereas the FB cohort underwent FB-TBLC with either a 1.1-mm or a 1.7-mm cryoprobe. Lung transplant recipients and RAB procedures without CBCT confirmation of tool position were excluded. Because the RAB cohort was restricted to patients with clinically nonfibrotic disease, the FB cohorts were screened for nonfibrotic DPLD to maintain cohort homogeneity. Subsequent multidisciplinary review identified a small number of patients with early radiographic or histopathologic fibrosis. These patients were retained because they were represented in similar proportions across all three groups, preserving cohort comparability and allowing assessment of the potential utility of the 1.1-mm cryoprobe in selected patients with fibrotic DPLD.

AI DISCLOSURE STATEMENT:

Generative artificial intelligence tools were used solely to assist with language editing, grammar, and clarity during manuscript preparation. The authors reviewed and verified the final manuscript and take full responsibility for its content. No generative artificial intelligence tools were used to generate, alter, or analyze the original research data or results.

Data Collection

Clinical variables included age, sex, race, and body mass index (BMI). Procedural variables included biopsy location, number of biopsy targets, number of cryobiopsies obtained, cryoprobe size, cryoprobe activation time, procedure duration, use of adjunctive biopsy instruments, and maximum biopsy specimen dimension. For RAB procedures, the number of CBCT acquisitions, fluoroscopy time, and cumulative radiation dose were also recorded. Procedure duration was obtained from available procedural documentation.

Procedure-related adverse events were collected from the medical record and included pneumothorax, bleeding severity graded according to the Nashville Working Group scale, postprocedural respiratory deterioration requiring escalation of respiratory support or level of care, anesthetic complications, unplanned hospital admission, and 30-day mortality.

Radiographic Assessment

Eligibility for the nonfibrotic DPLD cohort was based on preprocedural CT interpretation by a cardiothoracic radiologist. The CT examinations were subsequently reviewed according to prespecified criteria by J.A. and G.K.; two thoracic radiologists (M.B.G. and M.N.) independently verified the findings

while blinded to biopsy platform and histopathologic findings. Discrepancies were adjudicated by consensus. The final radiographic classification was based on the consensus assessment. Therefore, the fibrosis variable reported in the analysis reflects the structured study review rather than the initial clinical classification used for eligibility.

Procedural Technique

All procedures were performed under general anesthesia without rigid bronchoscopy. Preprocedural high-resolution CT was used to identify representative parenchymal targets.

RAB-TBLC was performed using a shape-sensing robotic platform (Intuitive Surgical, Sunnyvale, CA) with CT-based three-dimensional target and pathway planning. CBCT confirmed the positions of the catheter and biopsy tool relative to the target in all cases. Radial endobronchial ultrasound and rapid on-site cytologic evaluation were not used. A transbronchial needle was used solely to puncture the airway wall and create a tract to facilitate passage of the 1.1-mm cryoprobe. Cryobiopsy activation times were 4 to 6 seconds. Endobronchial blockers were not used.

FB-TBLC was performed under fluoroscopic guidance using either a 1.1-mm or a 1.7-mm cryoprobe. A 7F Arndt blocker was prophylactically positioned in the ipsilateral mainstem or target lobar bronchus and inflated after each biopsy for airway isolation and bleeding control. Pleural proximity was assessed fluoroscopically before activation. Cryoprobe activation times were 4 to 8 seconds; CBCT was not used.

Histopathologic Classification

Final histopathologic findings and gross specimen dimensions were obtained from clinical pathology reports. Three ILD physicians independently classified the findings as specific or nondiagnostic, and a thoracic pathologist (H.D.T.) reviewed the slides and verified the classifications. Samples yielding a specific diagnosis on histologic examination were classified as diagnostic; nonspecific interstitial changes, normal lung parenchyma, and inadequate tissue were classified as nondiagnostic. This classification defined histopathologic diagnostic yield and was distinct from the final clinical diagnosis.

The primary outcome was specific histopathologic diagnostic yield, defined as the proportion of procedures in which TBLC yielded a specific histopathologic diagnosis. Safety outcomes included pneumothorax, bleeding severity graded according to the Nashville Working Group scale, postprocedural respiratory deterioration requiring escalation of respiratory support or level of care, anesthetic complications, unplanned hospital admission, and 30-day mortality.

Procedure-related characteristics included the number of biopsies, maximum biopsy specimen dimension, and procedure duration. Fluoroscopy time and cumulative radiation dose were described within the RAB cohort only and were not compared directly with the FB groups.

Statistical Analysis

Continuous variables are presented as median (interquartile range [IQR]) and categorical variables as number (percentage). Associations between biopsy approach and outcomes were evaluated with logistic regression. Univariable models estimated crude odds ratios (ORs) and 95% confidence intervals (CIs). Multivariable models included prespecified clinically relevant covariates (biopsy approach, BMI, procedure duration, biopsy specimen size, and fibrosis), as appropriate for each outcome, followed by backward stepwise selection. Because biopsy number was right-skewed, it was log10-transformed; its OR is therefore reported per 10-fold increase.

All analyses were performed using R, version 4.6.1 (R Foundation for Statistical Computing, Vienna, Austria). Two-sided P values < 0.05 were considered statistically significant.

RESULTS

Patient and Procedural Characteristics

A total of 65 patients underwent TBLC: 26 underwent FB-TBLC with a 1.1-mm cryoprobe, 19 underwent FB-TBLC with a 1.7-mm cryoprobe, and 20 underwent RAB-TBLC with a 1.1-mm cryoprobe (Table 1). The median age of the cohort was 62 years (IQR, 53–70 years), and 32 patients (49.2%) were male. Age, BMI, radiographic fibrosis, pleural effusions, and the number of biopsy targets did not differ significantly among groups (Table 1). The proportion of male patients differed among groups ($P = 0.045$), ranging from 26.3% in the FB-TBLC 1.7-mm group to 65.0% in the RAB-TBLC group. Although racial distribution also differed ($P = 0.041$), the cohort was predominantly White (92.3%).

Table 1
Patient, procedural, safety, and histopathologic characteristics by biopsy approach

Characteristic	Overall (N = 65)	FB-TBLC 1.1-mm (N = 26)	FB-TBLC 1.7-mm (N = 19)	RAB-TBLC 1.1-mm (N = 20)	*P* value
Patient characteristics					
Age, yr	62.0 (53.0–70.0)	61.5 (53.0–70.5)	65.0 (55.0–71.5)	62.0 (52.8–69.3)	0.986
Male sex	32 (49.2)	14 (53.8)	5 (26.3)	13 (65.0)	0.045
White race	60 (92.3)	25 (96.2)	19 (100.0)	16 (80.0)	0.041
Body mass index, kg/m²	27.0 (24.0–32.0)	26.5 (24.0–32.8)	29.0 (26.0–34.0)	26.2 (22.8–28.7)	0.273
Fibrosis on imaging	9 (13.8)	4 (15.4)	3 (15.8)	2 (10.0)	0.835
Pleural effusion					0.326
Unilateral	3 (4.6)	2 (7.7)	0 (0.0)	1 (5.0)	
Bilateral	6 (9.2)	3 (11.5)	0 (0.0)	3 (15.0)	
Safety outcomes					
Any complication	19 (29.2)	9 (34.6)	8 (42.1)	2 (10.0)	0.065
Pneumothorax	4 (6.2)	3 (11.5)	1 (5.3)	0 (0.0)	0.267
Bleeding	12 (18.5)	7 (26.9)	4 (21.1)	1 (5.0)	0.242
Nashville Bleeding Scale					0.470
Grade I	4 (6.2)	2 (7.7)	1 (5.3)	1 (5.0)	
Grade II	6 (9.2)	4 (15.4)	2 (10.5)	0 (0.0)	
Grade III	2 (3.1)	1 (3.8)	1 (5.3)	0 (0.0)	
Respiratory deterioration	8 (12.3)	1 (3.8)	5 (26.3)	2 (10.0)	0.071
Hospital disposition					0.109
Intensive care unit	5 (7.7)	3 (11.5)	2 (10.5)	0 (0.0)	
Hospital floor	2 (3.1)	0 (0.0)	2 (10.5)	0 (0.0)	
Procedural characteristics					
Initial biopsy location					0.015

Data are median (interquartile range) or No. (%). FB = flexible bronchoscopy; RAB = robotic-assisted bronchoscopy; TBLC = transbronchial lung cryobiopsy.

Characteristic	Overall (N = 65)	FB-TBLC 1.1-mm (N = 26)	FB-TBLC 1.7-mm (N = 19)	RAB-TBLC 1.1-mm (N = 20)	*P* value
Patient characteristics					
Left lower lobe	15 (23.1)	6 (23.1)	5 (26.3)	4 (20.0)	
Left upper lobe	9 (13.8)	6 (23.1)	1 (5.3)	2 (10.0)	
Right lower lobe	16 (24.6)	6 (23.1)	9 (47.4)	1 (5.0)	
Right upper lobe	25 (38.5)	8 (30.8)	4 (21.1)	13 (65.0)	
Number of biopsy targets	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.857
Number of biopsies	6.0 (4.0–10.0)	6.0 (5.0–8.0)	4.0 (3.0–5.5)	15.5 (11.0–21.3)	< 0.001
Procedure duration, min	31.0 (17.5–46.0)	19.0 (16.0–26.5)	43.0 (30.8–60.0)	38.5 (19.8–55.5)	0.002
Maximum biopsy dimension, cm	0.70 (0.40–1.00)	0.50 (0.40–0.88)	1.00 (0.70–1.20)	0.70 (0.40–1.30)	0.011
Histopathologic outcomes					
Specific histopathologic diagnosis	49 (75.4)	16 (61.5)	14 (73.7)	19 (95.0)	0.032
Nondiagnostic	16 (24.6)	10 (38.5)	5 (26.3)	1 (5.0)	

Data are median (interquartile range) or No. (%). FB = flexible bronchoscopy; RAB = robotic-assisted bronchoscopy; TBLC = transbronchial lung cryobiopsy.

Although clinical eligibility required a preprocedural assessment of nonfibrotic DPLD, the final structured imaging review identified fibrotic features in 9 patients (13.8%): 4 of 26 (15.4%) in the FB-TBLC 1.1-mm group, 3 of 19 (15.8%) in the FB-TBLC 1.7-mm group, and 2 of 20 (10.0%) in the RAB-TBLC group (*P* = 0.835).

Biopsy location differed across groups (*P* = 0.015), with RAB-TBLC more frequently targeting the right upper lobe and FB-TBLC with a 1.7-mm cryoprobe more frequently targeting the right lower lobe. RAB-TBLC involved more biopsies per procedure (median, 15.5 [IQR, 11.0–21.3]) than FB-TBLC with a 1.1-mm cryoprobe (6.0 [5.0–8.0]) or a 1.7-mm cryoprobe (4.0 [3.0–5.5]; *P* < 0.001). Procedure duration also differed among groups (median, 19.0 minutes for FB-TBLC with a 1.1-mm cryoprobe, 43.0 minutes for FB-TBLC with a 1.7-mm cryoprobe, and 38.5 minutes for RAB-TBLC; *P* = 0.002; Table 1), although RAB-TBLC and FB-TBLC with a 1.7-mm cryoprobe did not differ significantly (*P* = 0.688; Fig. 2). CBCT guidance and transbronchial needles were used exclusively during RAB procedures. Median maximum biopsy dimension differed among groups (0.50 cm [IQR, 0.40–0.88] for FB-TBLC with a 1.1-mm

cryoprobe, 1.00 cm [0.70–1.20] for FB-TBLC with a 1.7-mm cryoprobe, and 0.70 cm [0.40–1.30] for RAB-TBLC; *P* = 0.011). FB-TBLC with a 1.7-mm cryoprobe yielded larger specimens than FB-TBLC with a 1.1-mm cryoprobe (*P* = 0.004; Fig. 2). Among RAB-TBLC procedures, median fluoroscopy time was 4.90 minutes (IQR, 2.85–8.12), and median cumulative radiation dose was 23.55 mGy (IQR, 14.81–56.04) (e-Figure 1).

Overall complication rates were 10.0% with RAB-TBLC, 34.6% with FB-TBLC using a 1.1-mm cryoprobe, and 42.1% with FB-TBLC using a 1.7-mm cryoprobe (*P* = 0.065; Table 1). No anesthetic complications or deaths within 30 days occurred.

A specific histopathologic diagnosis was established in 49 patients (75.4%). Diagnostic yield differed by biopsy approach (*P* = 0.032): it was 95.0% with RAB-TBLC, 73.7% with FB-TBLC using a 1.7-mm cryoprobe, and 61.5% with FB-TBLC using a 1.1-mm cryoprobe (Fig. 3). Histopathologic diagnoses varied across biopsy approaches (Fig. 4). RAB-TBLC yielded specific diagnoses in 10 distinct histopathologic categories and had fewer nondiagnostic results (5.0%) than FB-TBLC using a 1.1-mm (38.5%) or a 1.7-mm (26.3%) cryoprobe (Fig. 4).

Adjusted Diagnostic Yield

In univariable logistic regression, biopsy approach was significantly associated with histopathologic diagnostic yield (*P* = 0.018). Compared with FB-TBLC using a 1.1-mm cryoprobe, RAB-TBLC was associated with greater odds of a specific histopathologic diagnosis (OR, 11.88; 95% CI, 1.96–230.10), whereas FB-TBLC using a 1.7-mm cryoprobe was not (OR, 1.75; 95% CI, 0.49–6.78). The number of biopsies was not associated with diagnostic yield (OR per 10-fold increase, 5.76; 95% CI, 0.76–58.24) (Fig. 5).

After adjustment for fibrosis and maximum biopsy specimen dimension, RAB-TBLC remained associated with higher diagnostic yield than FB-TBLC using a 1.1-mm cryoprobe (adjusted OR, 11.15; 95% CI, 1.76–219.95). Neither fibrosis (adjusted OR, 4.57; 95% CI, 0.67–93.09) nor maximum biopsy specimen dimension (adjusted OR, 3.76; 95% CI, 0.56–34.70) was independently associated with diagnostic yield (Fig. 5). Diagnostic yield did not differ significantly between the FB-TBLC 1.7-mm and 1.1-mm groups (adjusted OR, 1.10; 95% CI, 0.24–5.11).

Biopsy approach was not significantly associated with procedure-related complications. Compared with FB-TBLC using a 1.1-mm cryoprobe, RAB-TBLC was associated with lower odds of complications, although the difference was not statistically significant (OR, 0.21; 95% CI, 0.04–1.11). Complication odds also did not differ significantly between FB-TBLC using a 1.7-mm cryoprobe and FB-TBLC using a 1.1-mm cryoprobe (OR, 1.37; 95% CI, 0.40–4.71). In a separate univariable analysis, a 10-fold increase in the number of biopsy specimens was associated with lower odds of procedure-related complications (OR, 0.07; 95% CI, 0.01–0.53).

DISCUSSION

In this multicenter cohort, RAB-TBLC using a 1.1-mm cryoprobe achieved a 95.0% specific histopathologic diagnostic yield, the highest observed among the three groups. RAB-TBLC remained associated with a higher diagnostic yield than FB-TBLC using a 1.1-mm cryoprobe after adjustment for radiographic fibrosis and maximum specimen dimension. RAB-TBLC had the lowest observed complication rate despite greater sampling, although differences were not statistically significant. Biopsy number was not associated with diagnostic yield, suggesting that sampling quantity alone did not explain the difference. To our knowledge, this is the first multicenter cohort comparing RAB-TBLC and FB-TBLC for DPLD. These findings support prospective evaluation of robotic navigation, CBCT, and a 1.1-mm cryoprobe as an integrated strategy for targeted parenchymal sampling.

These findings extend evidence supporting FB-TBLC in DPLD. Observational and prospective studies demonstrate that TBLC provides specific histopathologic patterns and improves multidisciplinary diagnostic confidence[10–12]. COLDICE showed high concordance between diagnoses based on TBLC and surgical lung biopsy when the TBLC-based multidisciplinary diagnosis was made with high confidence[3], whereas COLD supported a TBLC-first strategy that reserved surgical biopsy for inconclusive findings[4]. By contrast, CAN-ICE reported more modest agreement, highlighting variability across patients and centers[13]. Systematic reviews and meta-analyses generally report yields below the 95% observed in our robotic cohort[5,14]. However, these comparisons are contextual because our endpoint was a specific histopathologic diagnosis rather than a multidisciplinary diagnosis or concordance with surgical biopsy.

Evidence supporting the 1.1-mm cryoprobe provides additional context. Bian and colleagues found comparable multidisciplinary diagnostic yield with 1.1-mm and 1.9-mm cryoprobes in patients with suspected ILD[6]. More recently, FROSTBITE-2 demonstrated a higher overall histopathologic diagnostic yield with the 1.1-mm cryoprobe than with conventional forceps biopsy. The DPLD subgroup was considerably smaller, however, and the difference within that subgroup was not statistically significant[7]. Our study compared RAB-TBLC and FB-TBLC using the same 1.1-mm cryoprobe, making probe caliber a less likely explanation for the observed difference and suggesting that the higher yield may be related to localization and sampling strategy. Differences in initial biopsy location may reflect procedural sequencing rather than differences in disease distribution: FB-TBLC typically begins with right lower-lobe sampling to preserve subsequent sampling options if bleeding occurs, whereas RAB-TBLC allowed site selection based primarily on radiographic targets, potentially explaining the greater frequency of upper-lobe sampling.

RAB-TBLC should be interpreted as a bundled strategy rather than an isolated robotic-platform effect. Robotic navigation may provide distal stability, whereas CBCT confirms tool position within the target. Zhou et al. demonstrated the feasibility of CBCT-guided FB-TBLC for ILD[9]. Studies of peripheral pulmonary lesions similarly support complementary roles for robotic navigation and CBCT in target access and tool confirmation[8,15–17]. Importantly, Shaller et al. reported similar diagnostic yields for FB and RAB when both approaches used CBCT[18]. Because FB-TBLC in our cohort relied on fluoroscopy alone, the higher diagnostic yield and lower observed complication rate with RAB-TBLC may reflect the

combined effects of CBCT confirmation, target selection, catheter stability, tract creation, and sampling strategy rather than robotic navigation alone. Precise targeting may facilitate sampling away from the pleura, fissures, and major vessels, potentially reducing pneumothorax and bleeding, respectively. Distal wedging may provide stability and local tamponade, potentially limiting bleeding, although its independent protective effect against pneumothorax has not been established.

The relationship between biopsy number and diagnostic yield warrants attention. Despite substantially greater sampling with RAB-TBLC, the number of biopsies was not associated with diagnostic yield. Prior studies have shown that obtaining multiple specimens and sampling multiple locations can improve yield[10,19]. Our findings do not contradict these observations; rather, they suggest that diagnostic yield may plateau once adequate tissue is obtained, with additional biopsies providing limited incremental benefit. Precise navigation to representative areas of pathology may therefore be more important than biopsy number alone.

Procedure duration and biopsy dimensions provide additional context. RAB-TBLC required more time than FB-TBLC using a 1.1-mm cryoprobe but was similar in duration to FB-TBLC using a 1.7-mm cryoprobe. Maximum biopsy dimension was similar between RAB-TBLC and FB-TBLC using a 1.1-mm cryoprobe and was larger with the 1.7-mm cryoprobe, yet it was not associated with diagnostic yield. Together with the lack of association between biopsy number and yield, these findings suggest that the higher RAB-TBLC yield may reflect precise localization and targeted sampling of radiographically abnormal parenchyma rather than biopsy size or quantity alone.

Safety findings were encouraging. No RAB-TBLC procedure was associated with pneumothorax or clinically significant bleeding; one Nashville grade I bleeding event required no intervention. Two patients required transient increases in supplemental oxygen but returned to their baseline oxygen requirements and did not require unplanned admission. Overall complication rates did not differ significantly among groups, and serious events were uncommon. Published complication rates after TBLC vary with patient selection, biopsy location, probe position, airway management, and bleeding-control technique[5,14]. Prospective protocols have used routine endobronchial balloon occlusion for bleeding control[20]. In our cohort, prophylactic endobronchial blockade was used in the FB-TBLC groups but not in the RAB-TBLC group, limiting attribution of safety differences to the platform. Standardized, intervention-based definitions of bleeding are needed in future comparative studies[21]. Radiation exposure data were available only for RAB-TBLC and therefore could not be compared directly.

The predominance of nonfibrotic DPLD is important when interpreting these findings. ATS/ERS/JRS/ALAT guidance supports TBLC as an alternative to surgical biopsy in experienced centers and emphasizes careful patient selection[22]. Although eligibility in our cohort was based on preprocedural CT interpretation, structured thoracic radiology and pathology review identified fibrotic features in nine patients (13.8%) initially classified as having nonfibrotic disease. Because fibrotic cases were similarly distributed across groups, they were retained to preserve comparability and explore a potential role for RAB-TBLC in selected patients with fibrotic DPLD. Recent Mayo Clinic data suggest that

radiographic phenotype may influence TBLC diagnostic yield, particularly in patients with honeycombing[23]. Although our findings provide a preliminary signal of potential utility in fibrotic DPLD, the small number of fibrotic cases limits definitive conclusions and generalizability to advanced fibrotic disease.

Several limitations warrant consideration. The retrospective, nonrandomized design introduces selection bias and residual confounding. Procedural approaches differed in imaging guidance, probe size, biopsy number and location, activation time, and bleeding-control technique, with RAB incorporating navigation, CBCT, a 1.1-mm cryoprobe, tract creation, and greater sampling. Center effects, operator experience, procedural era, and local practice may also have contributed. Thus, the study cannot determine which component of the RAB strategy drove the observed association.

The analytic cohort was small relative to the institutional FB-TBLC experience. The 318 FB-TBLC procedures identified at the outset spanned January 2018 through June 2026. Restricting this population to the January 2025 to June 2026 period in which RAB-TBLC was performed, and to patients with suspected nonfibrotic DPLD, excluded 183 procedures ([n] performed before January 2025 and [n] with fibrotic DPLD), leaving 135 patients. A further 90 were lung transplant recipients, in whom TBLC is performed primarily for allograft assessment and whose histopathologic findings are not comparable with those of native-lung DPLD. Their exclusion left 45 FB-TBLC patients. The same eligibility criteria defined the RAB cohort, from which three procedures without CBCT confirmation were also excluded. All three yielded specific diagnoses, so this exclusion did not favor RAB-TBLC. The reduction from 318 to 45 therefore reflects the study's eligibility criteria rather than discretionary case selection, and it limited confounding by procedural era and transplant status. It also reduced statistical power, and the findings may not extend to transplant recipients, fibrotic disease, or FB-TBLC practice before 2025.

Within this restricted cohort, the RAB group was particularly small, and only one RAB-TBLC procedure was nondiagnostic. Consequently, effect estimates were imprecise, as reflected by the wide confidence intervals, and the adjusted findings should be interpreted as supportive associations rather than evidence of a causal effect.

Data were independently verified by ILD physicians, thoracic radiologists, and a thoracic pathologist, reflecting a multidisciplinary approach. However, the primary endpoint was specific histopathologic yield rather than the final multidisciplinary diagnosis. A specific histopathologic pattern may not establish the final diagnosis, whereas nonspecific tissue may still inform multidisciplinary assessment. Nevertheless, the study lacked blinded central pathology rereview, a uniform surgical biopsy reference standard, and a formal multidisciplinary diagnostic endpoint [24].

Finally, retrospectively ascertained safety outcomes may be influenced by documentation and local management practices, and the limited event rate restricts definitive safety comparisons. Radiation exposure was measured only for RAB-TBLC. Procedures were performed at specialized tertiary centers, limiting generalizability to lower-volume settings. Learning curves, resource utilization, and cost-effectiveness were not assessed.

Conclusions:

RAB-TBLC using a 1.1-mm cryoprobe was associated with a higher specific histopathologic diagnostic yield than FB-TBLC without a statistically significant increase in complications. These findings support prospective evaluation of robotic navigation, CBCT confirmation, and small-caliber cryobiopsy as an integrated strategy for DPLD.

Abbreviation List

BMI, body mass index

CBCT, cone-beam computed tomography

CI, confidence interval

CT, computed tomography

DPLD, diffuse parenchymal lung disease

FB, flexible bronchoscopy

ILD, interstitial lung disease

IQR, interquartile range

OR, odds ratio

RAB, robotic-assisted bronchoscopy

TBLC, transbronchial lung cryobiopsy

Declarations

CONFLICT OF INTEREST

The authors declare that they have no competing interests

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Author Contribution

Author Contributions: J.A. and G.K. contributed equally to this work and share first authorship. J.A., G.K., and J.Z. contributed to the conception and design of the study, data acquisition, analysis, and interpretation of the data, and drafting of the manuscript. M.B.G. and M.N. performed the thoracic imaging review and contributed to interpretation of the radiographic data. H.D.T. performed the pathology review, contributed to specimen interpretation, confirmed the final results, and revised the manuscript. N.A., R.P.B., Y.M.B., S.F.-B., B.T.L., A.L., S.A., M.M.R., J.H.R., M.L.S., K.L.S., L.T.V., A.K., E.S.Y.,H.M., M.I., and K.K.S. contributed to data acquisition and/or interpretation, provided critical intellectual input, and critically revised the manuscript. All authors reviewed and approved the final version of the manuscript and agree to be accountable for the accuracy and integrity of the work. J.A. is the guarantor of the manuscript and takes responsibility for the integrity of the work as a whole.

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DATA AVAILABILITY STATEMENT

The data underlying this study contain potentially identifiable patient information and are not publicly available because of institutional and patient privacy restrictions. Deidentified data may be made available from the corresponding author upon reasonable request and subject to approval by Mayo Clinic and applicable institutional policies and data use agreements.

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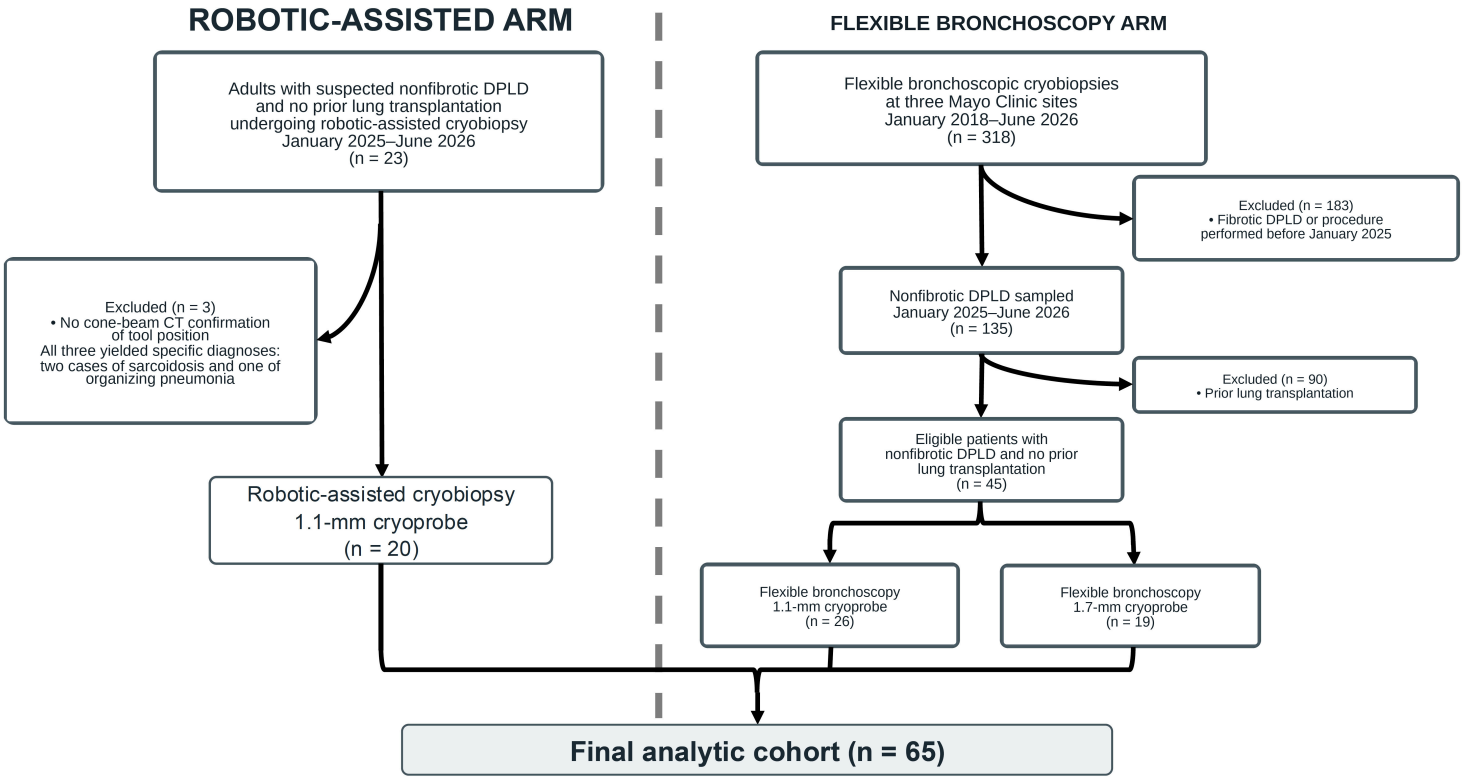
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Figures



DPLD = diffuse parenchymal lung disease. Flexible and robotic cases were drawn from the same January 2025–June 2026 sampling window.

Figure 1

Study cohort selection. The robotic-assisted and flexible bronchoscopy cohorts were retrospectively identified from the same January 2025 through June 2026 analytic period. The robotic cohort included consecutive patients who underwent robotic-assisted TBLC. Three robotic cases were excluded because CBCT confirmation of tool position was not performed; all three yielded specific histopathologic diagnoses. CBCT = cone-beam computed tomography; DPLD = diffuse parenchymal lung disease; TBLC = transbronchial lung cryobiopsy.

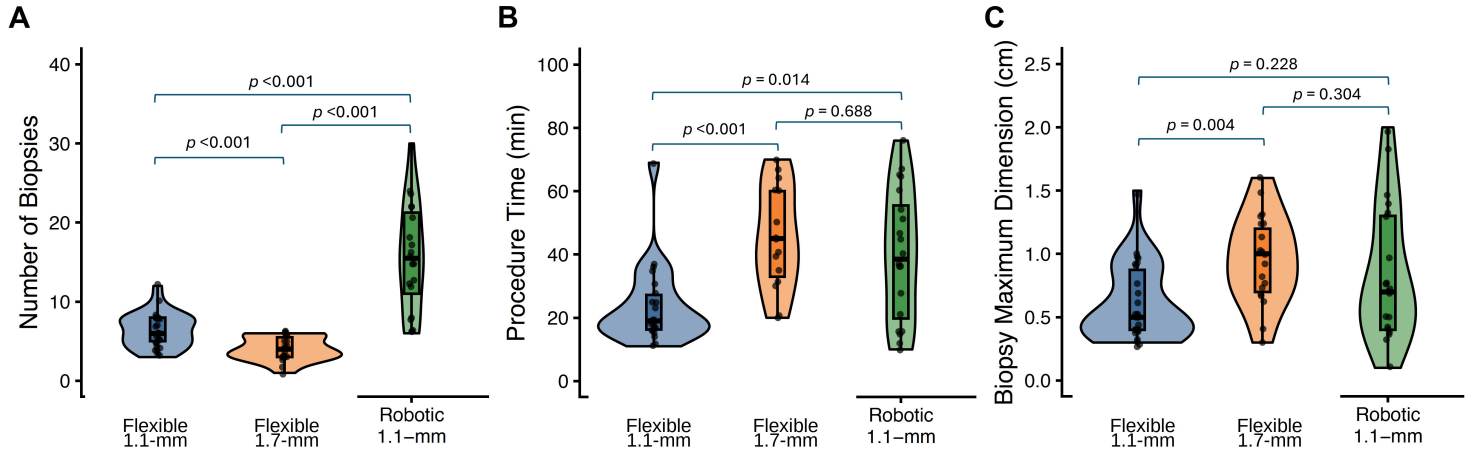


Figure 2

Comparison of biopsy characteristics among flexible and robotic transbronchial cryobiopsy techniques. Violin plots with overlaid boxplots and individual observations compare (A) the number of biopsies obtained, (B) procedure duration, and (C) maximum biopsy dimension among flexible bronchoscopy with a 1.1-mm cryoprobe, flexible bronchoscopy with a 1.7-mm cryoprobe, and robotic bronchoscopy with a 1.1-mm cryoprobe. Center lines indicate medians, boxes indicate interquartile ranges, and whiskers extend to 1.5 × the interquartile range. Pairwise comparisons were performed using Wilcoxon rank-sum tests with Benjamini–Hochberg adjustment for multiple comparisons. Adjusted P values are shown above the corresponding group comparisons.

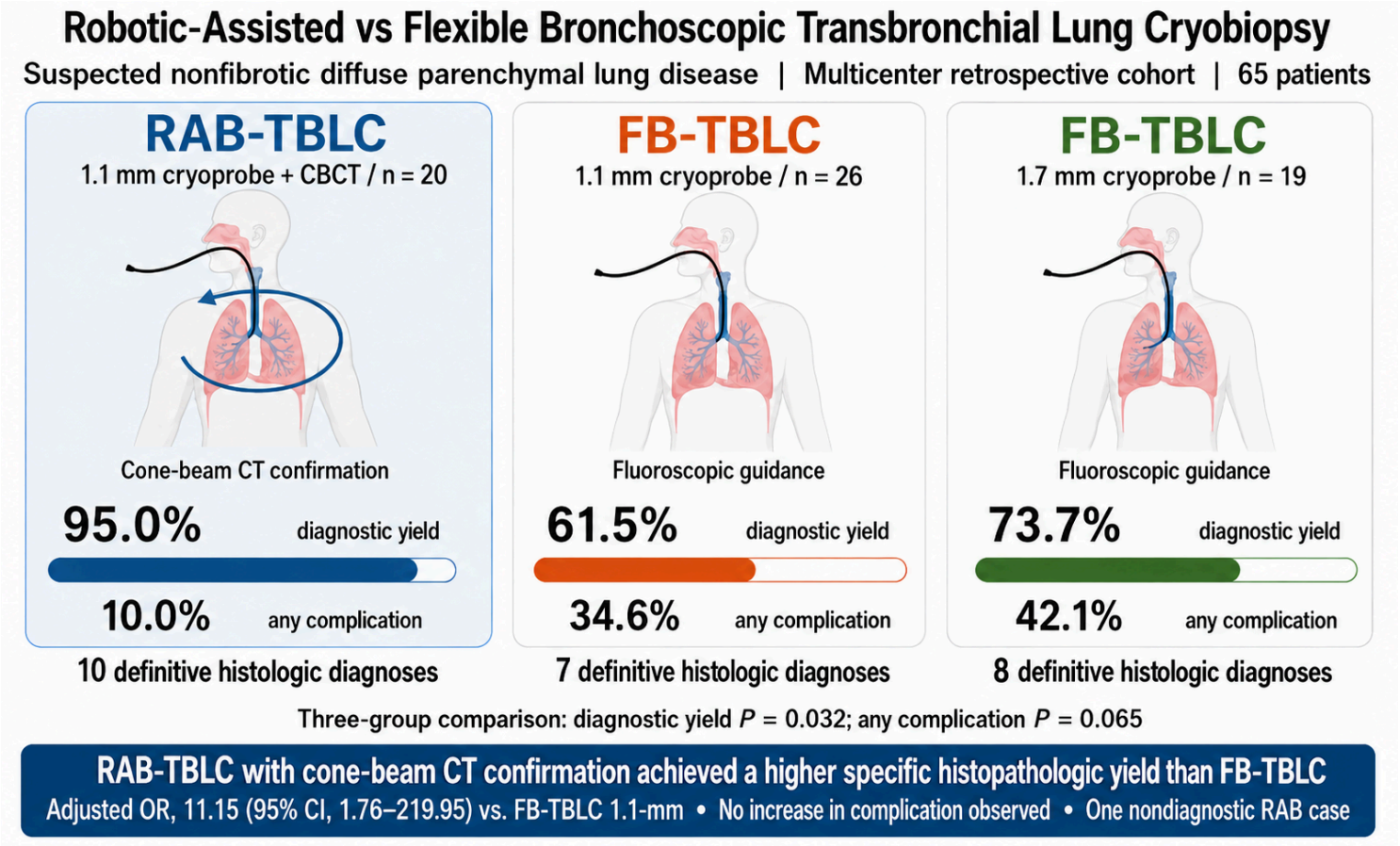


Figure 3

Central illustration: study design and principal findings. Diagnostic yield, complication rates, and the number of distinct histopathologic diagnostic categories are shown for robotic-assisted transbronchial lung cryobiopsy (RAB-TBLC) with a 1.1-mm cryoprobe and cone-beam computed tomography (CBCT) confirmation and for flexible bronchoscopy-guided TBLC (FB-TBLC) with 1.1-mm and 1.7-mm cryoprobes under fluoroscopic guidance. P values are from the three-group comparisons. The adjusted odds ratio is for RAB-TBLC versus FB-TBLC with a 1.1-mm cryoprobe.

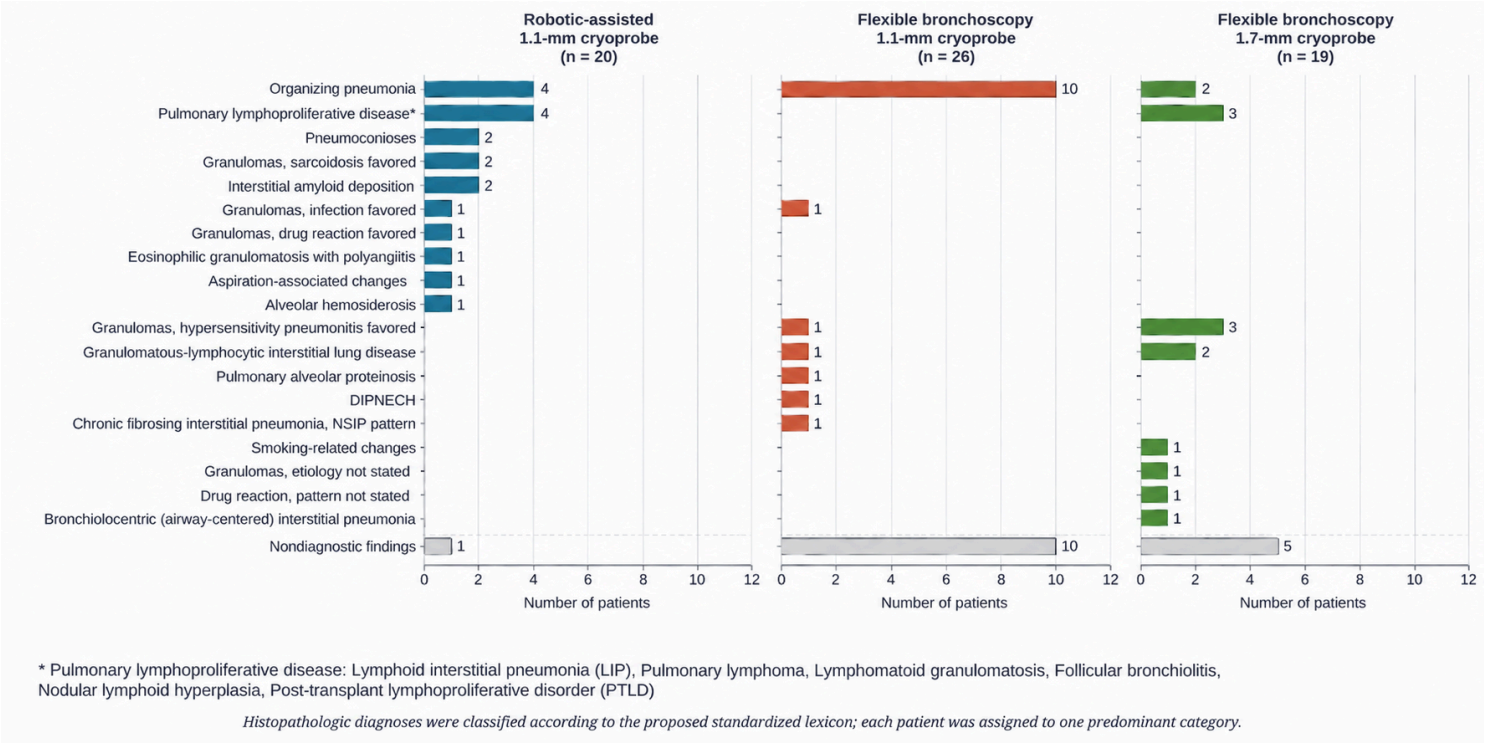


Figure 4

Distribution of histopathologic diagnoses by biopsy approach. Bars show the number of patients assigned to each predominant histopathologic diagnostic category among RAB-TBLC using a 1.1-mm cryoprobe, FB-TBLC using a 1.1-mm cryoprobe, and FB-TBLC using a 1.7-mm cryoprobe. Each patient was assigned to one predominant histopathologic diagnostic category. AL = amyloid light-chain; DIPNECH = diffuse idiopathic pulmonary neuroendocrine cell hyperplasia; EGPA = eosinophilic granulomatosis with polyangiitis; FB = flexible bronchoscopy; ILD = interstitial lung disease; MALT = mucosa-associated lymphoid tissue; NSIP = nonspecific interstitial pneumonia; RAB = robotic-assisted bronchoscopy; TBLC = transbronchial lung cryobiopsy.

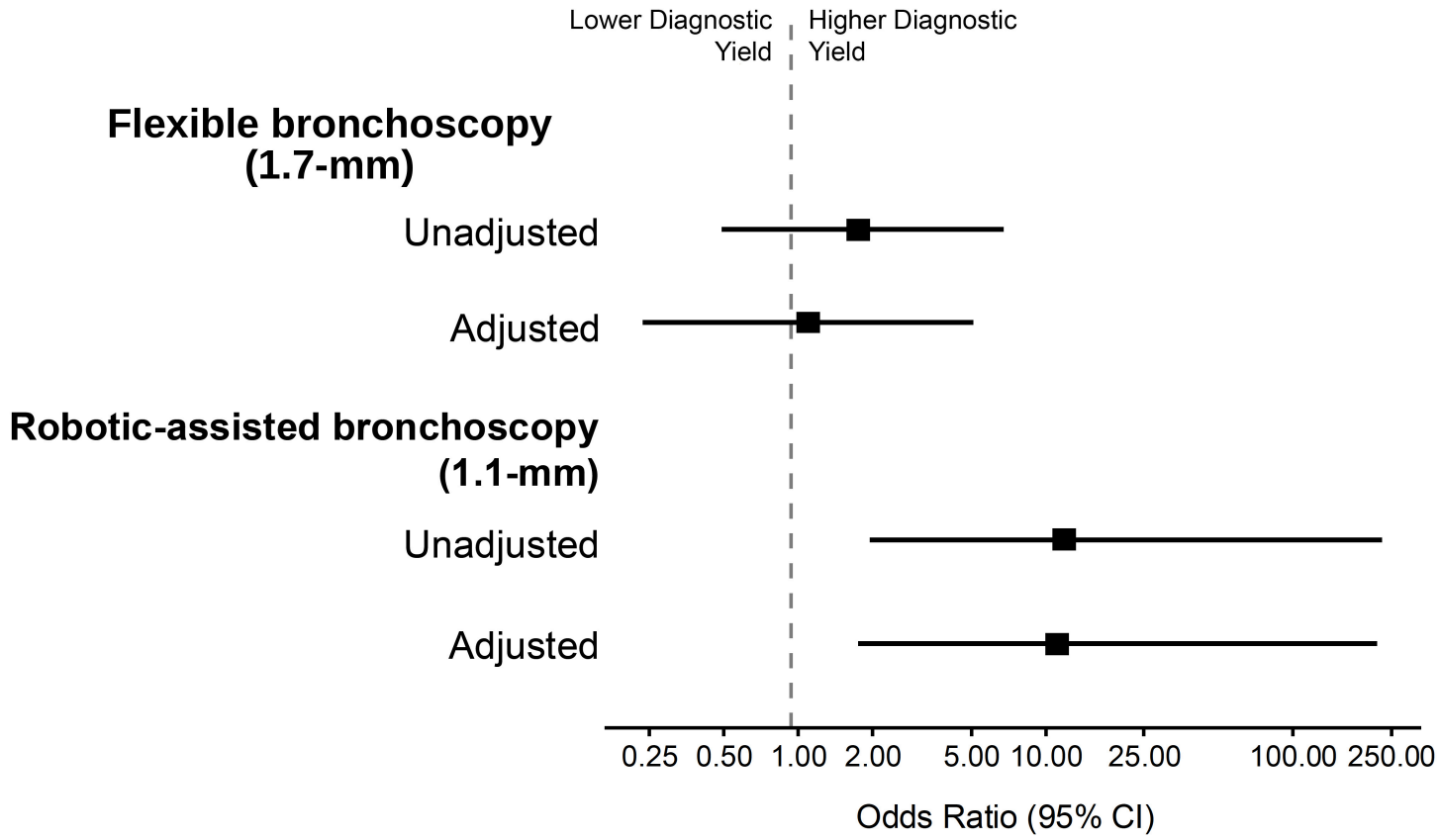


Figure 5

Association between biopsy approach and diagnostic yield. Forest plot showing unadjusted and adjusted odds ratios for obtaining a specific histopathologic diagnosis according to biopsy approach. FB-TBLC using a 1.1-mm cryoprobe was the reference group. Adjusted estimates account for radiographic fibrosis and maximum biopsy specimen dimension. Error bars represent 95% confidence intervals. CI = confidence interval; FB = flexible bronchoscopy; TBLC = transbronchial lung cryobiopsy.

Supplementary Files

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