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ARTICLE

# Diagnostic Value of Endobronchial Ultrasound-Guided Intranodal Forceps Biopsies Combined with Rapid On-Site Evaluation for Mediastinal/Hilar Lymph Node Disease

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## Abstract

**Aims/Background** Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is the standard method for sampling mediastinal/hilar lymph node disease. However, the smaller samples obtained via needle aspiration have a lower diagnostic rate for benign compared to malignant diseases. The low diagnostic rates have been reported to be improved through using endobronchial ultrasound-guided intranodal forceps biopsy (EBUS-IFB), but the implementation of IFB presents technical challenges, as described with variable results in certain studies. The main objective of this study was to investigate the diagnostic value and safety of EBUS-IFB for mediastinal/hilar lymph node disease.

**Methods** A retrospective analysis was conducted on 150 patients with mediastinal/hilar lymph node disease at Tianjin Medical University General Hospital. EBUS-TBNA was performed using a rigid bronchoscope on the same lymph node of each patient under general anesthesia, with rapid on-site evaluation (ROSE) conducted to determine the presence of pathological tissue. Following this, a tunnel was established, and a 1.5 mm biopsy forceps was employed for EBUS-IFB. Subsequently, diagnostic rates and safety of the methods used were determined.

**Results** EBUS-IFB + EBUS-TBNA (the combined strategy) exhibited the highest diagnostic rates, with the addition of bronchial mucosa biopsy/transbronchial lung biopsy/neoplasm biopsy contributing to a successful diagnostic rate of 97.2% (139/143). The combined strategy (90.2%) and EBUS-IFB alone (88.1%) contributed to successful diagnosis for all diseases, with rates significantly higher than that of EBUS-TBNA (60.1%) ($p < 0.001$). The diagnostic rates for malignant disease detected with the combined strategy (97.4%) and EBUS-IFB alone (93.6%) were significantly higher than that with EBUS-TBNA alone (71.8%) ($p < 0.001$). Both the diagnostic rates for sarcoidosis detected with the combined strategy and EBUS-IFB alone were 87.8%, which was significantly higher than that with EBUS-TBNA alone (46.9%) ($p < 0.001$). The procedures implemented did not engender major complications.

**Conclusion** Routine EBUS-TBNA followed by ROSE to acquire pathological tissue, followed by tunnel formation and EBUS-IFB, can enhance the overall diagnostic rate for mediastinal/hilar lymph node lesions. This approach is particularly valuable for diagnosing malignant diseases and sarcoidosis. EBUS-IFB serves as a safe and feasible complement to EBUS-TBNA, despite the fact that the procedure was extended in duration.

**Key words: mediastinal and hilar lymphadenopathy; endobronchial ultrasound; transbronchial needle aspiration; intranodal forceps biopsies; rapid on-site evaluation**

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## Introduction

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is an important tool for diagnosing mediastinal/hilar lymph node lesions, yet its diagnostic rate for certain etiologies is clinically suboptimal. EBUS-TBNA is reported as a reliable technique for the diagnosis of thoracic malignancies (Schwalk et al, 2024) and non-small cell lung cancer (NSCLC), with the latter attaining an overall sensitivity of 95% (Yu Lee-Mateus et al, 2021). The amount of material obtained via TBNA is very limited, containing mainly cytologic specimens, which are not complete pathological structures (Wahidi et al, 2016), thus limiting its diagnostic capability for sarcoidosis and lymphomas (Madan et al, 2023). The diagnostic yield of EBUS-TBNA for sarcoidosis ranges from 54 to 93%, and for lymphoma, the diagnostic yield is approximately 66% (Agrawal et al, 2022), whereas the diagnostic rate of TBNA for lymphomas was as low as 38% (Steinfort et al, 2010). The continuous, rapid advancement of immunotherapy for lung cancer necessitates a more accurate diagnosis, thus requiring more tissue for the detection of molecular biomarkers, but in reality, cytological specimens from TBNA are not sufficient for successful molecular testing (Kuijvenhoven et al, 2021). Genetic studies and immunohistochemical determination of PD-L1 were only possible in 79% of samples obtained via EBUS-TBNA. Acquisition of more complete tissue samples is possible with mediastinoscopy, but this technique does not have unrestricted access to some mediastinal lymph node locations and is accompanied by a significantly higher complication rate (Bousema et al, 2019).

Recent studies have revealed that samples obtained from endobronchial ultrasound-guided intranodal forceps biopsies (EBUS-IFB), processed as histologic specimens, can complement EBUS-TBNA (Ray et al, 2020; Rüber et al, 2022), enhancing the diagnostic rates for sarcoidosis and lymphomas. Despite being recommended as the standard nomenclature by Cheng et al (2019), IFB has also been referred to in the literature as micro- or mini-forceps biopsy (MFB) and transbronchial forceps biopsy (TBFB). Franke et al (2012) conducted a retrospective analysis on 50 patients, showing that the diagnostic sensitivity increased from 50.0% to 82.0% when EBUS-TBNA was combined with EBUS-guided forceps biopsy. In a prospective study on 55 patients, Darwiche et al (2013) reported that endobronchial ultrasound-transbronchial forceps biopsy (EBUS-TBFB) increased the diagnostic rate for benign lesions from 64% to 93%. A meta-analysis also lends support to the benefit of adopting combined strategies, indicating that the overall diagnostic rate for EBUS-TBNA + EBUS-IFB at 92% was significantly higher than that of EBUS-TBNA alone at 67%, while EBUS-IFB increased the diagnostic rates for sarcoidosis and lymphomas (Agrawal et al, 2022). However, previous relevant studies included rather small samples, consisting of 2 to 136 patients (Harris et al, 2015; Ray et al, 2020), and most of them were single-center, retrospective studies, whose findings may not be generalizable to the populations at large.

IFB could enhance diagnostic rates, with variable results emanating from certain studies. Shiari et al (2021) found no statistically significant difference in the diagnostic rates for TBNA and TBFB. In addition, the implementation of IFB proce-

dures presents technical difficulties. For instance, Rüber et al (2022) reported problems with forceps penetrating the bronchial wall or lymph node capsule in 36% of cases, respectively. To address the difficulty penetrating bronchial wall, Bramley et al (2016) employed cautery-assisted transbronchial forceps biopsy (ca-TBFB) using 1.9 mm spiked forceps; however, the successful diagnostic rate of ca-TBFB was lower than that of TBNA. It should be mentioned that the results from previous studies present huge variations due to a range of factors, such as the variations in puncture needles, lymph node sizes and forceps, as well as patient heterogeneity, all of which are sources of selection bias (Cheng et al, 2019). Therefore, it is imperative to conduct more research to evaluate the diagnostic value of EBUS-IFB for mediastinal disease. In the present study, we employed EBUS-IFB following the establishment of a bronchial tunnel, and conducted a retrospective analysis on a large sample. The primary goal of this study was to assess the diagnostic value and safety of this technique for mediastinal/hilar lymph node disease.

# Methods

## Study Participants

In this retrospective study, patients with mediastinal/hilar lymph node disease who sought medical treatments at the Tianjin Medical University General Hospital from September 2018 to June 2022 were selected. Only patients who had undergone EBUS-TBNA, followed by EBUS-IFB performed using the formed residual needle path, were included (Fig. 1). All patients underwent preoperative chest computed tomography (CT) or positron emission tomography (PET) scans, and the size of the mediastinal/hilar lesions was measured. All patients were followed up for six months. The primary focus of this study was to compare the diagnostic rates of the EBUS-IFB, EBUS-IFB + EBUS-TBNA (the combined strategy), and EBUS-TBNA, as well as evaluate the safety of the procedures implemented. This study was conducted in accordance with the Declaration of Helsinki.

## Routine Examination

Following general anesthesia, all patients were administered muscle relaxants, i.e., intravenous rocuronium bromide injection (5E240702, Guangdong Jiabo Pharmaceutical Co., Ltd., Qingyuan, China). A rigid bronchoscope (size 12, 10318F, Karl Storz, Tuttlingen, Germany) was then inserted orally and connected to a jet ventilation open ventilation respirator (TKR-300B, Jiangxi Teli Anesthesia Respiratory Equipment Co., Ltd., Nanchang, China). Two experienced surgeons first performed a routine bronchoscopic examination using a bronchoscope (BF-260, Olympus, Tokyo, Japan) via the rigid bronchoscope. Based on the radiological findings and the bronchoscopist's judgment, patients were subjected to one or more sessions of bronchoalveolar lavage (BAL), endobronchial biopsy (EBB), transbronchial lung biopsy (TBLB), neoplasm biopsy, or microbiological investigations for further examinations.

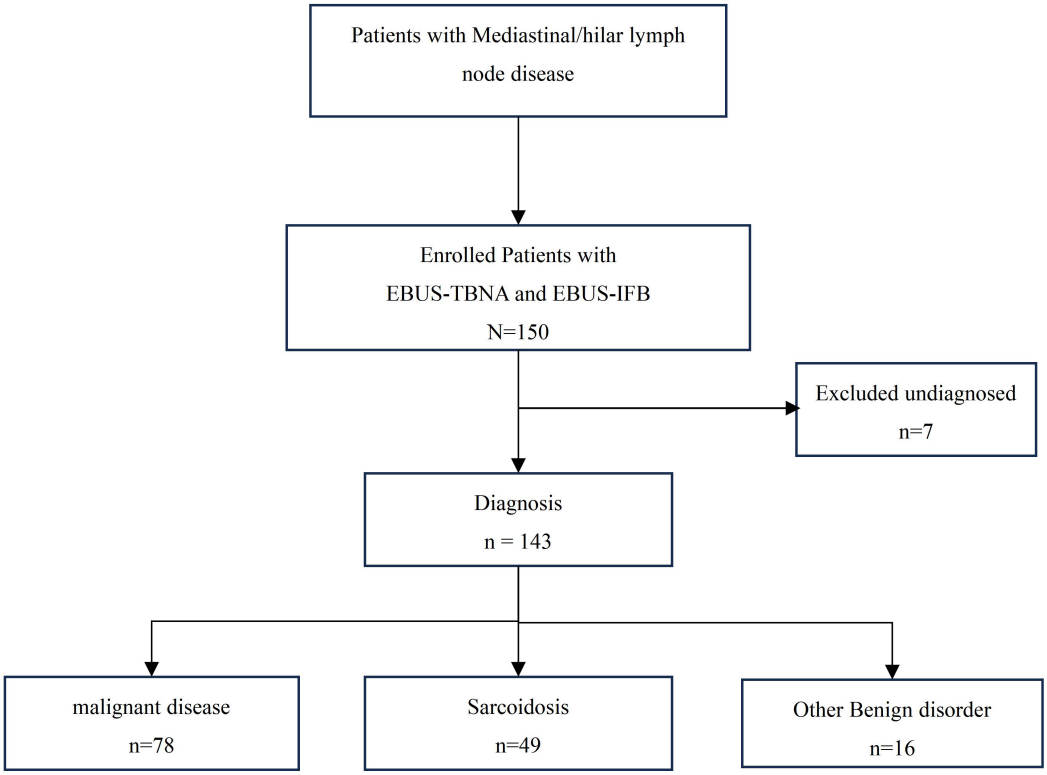


**Fig. 1. Schematic diagram depicting the selection and inclusion of patients.** Out of the 150 patients undergoing EBUS-IFB, 7 patients who were not definitively diagnosed were excluded, resulting in 143 patients with confirmed diagnoses being included in the study. Abbreviations: EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; EBUS-IFB, endobronchial ultrasound-guided intranodal forceps biopsy.

## EBUS-TBNA

An EBUS bronchoscope (BF-UC180F, Olympus) was used to identify the location, size, and vascular supply of suspicious lymph nodes. 22G puncture needles (NA-201SX-4022, Olympus) were utilized by the surgeons. For each target, the lymph node was sampled three times, with a minimum of 10 punctures per site. Each TBNA was accompanied by rapid on-site evaluation (ROSE), with adjustments to the puncture position based on the ROSE findings. The tissue obtained was placed in cell preservation solution (20140098, Tianjin Bailixin Biotechnology, Tianjin, China).

## Cold Tunneling Method

Under the EBUS guidance, an 18G needle (BC 1418, Hangzhou Kunbo Biotechnology, Hangzhou, China) was introduced at the TBNA puncture site. Multiple punctures were performed along the needle path for tissue sampling, and specimens were kept in cell preservation solution. This method established a tunnel that allowed the passage of biopsy forceps.

## Hot Tunneling Method

A pre-loaded Olympus-standard high-frequency cautery snare (SD-221L-25, Olympus) was then applied through the EBUS bronchoscope, advancing the sheath

slightly through the puncture tunnel. The metal tip of the snare was projected about 2 mm beyond the sheath, under the EBUS guidance. The snare was introduced at the site of the previous TBNA puncture mark to establish a tunnel (Fig. 2A,B).

## EBUS-IFB

Under EBUS guidance, a 1.5 mm biopsy forceps (RXQY-W1216-PA, Tianjin Guangyuan Foton Medical Technology Co., Ltd., Tianjin, China) was passed through the tunnel to perform biopsies in concert with ROSE (Fig. 2B–D), with the biopsy repeated at least three times until a satisfactory sample was obtained.

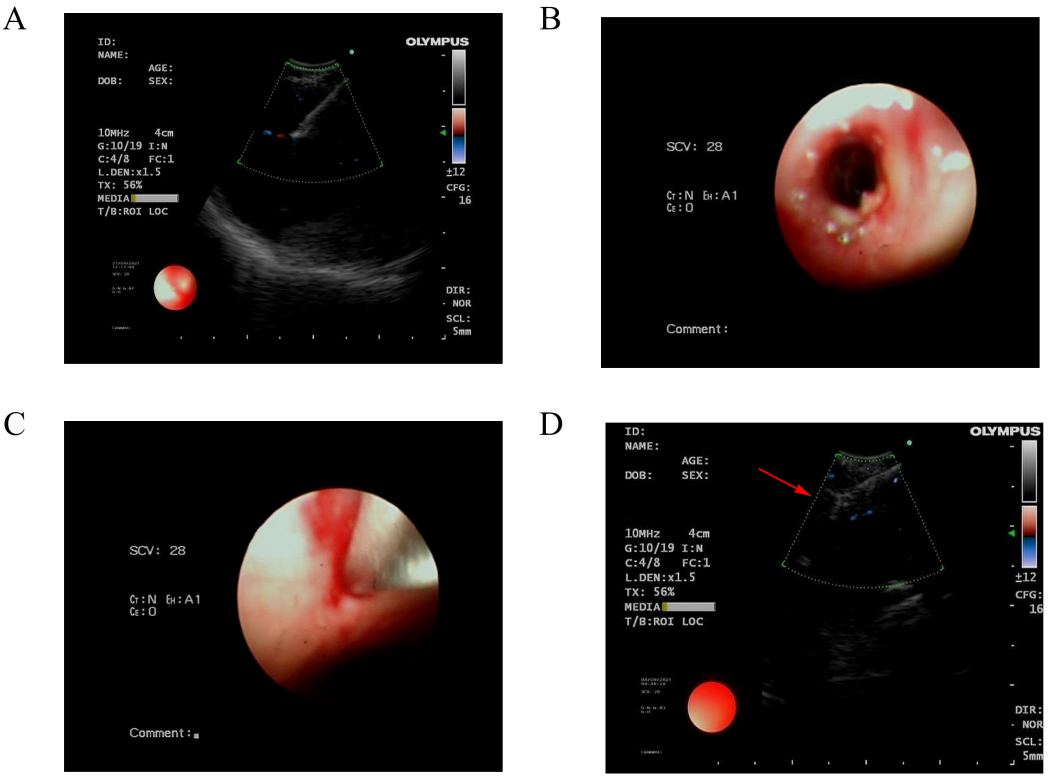


**Fig. 2. EBUS-TBNA and EBUS-IFB process.** (A) Performance of EBUS-TBNA at the 4R lymph node. (B) Tunnel formed by hot tunneling method at the 4R lymph node. (C) Biopsy forceps passing through the established tunnel. (D) Biopsy forceps open under EBUS guidance. Red arrows indicate open biopsy forceps. Abbreviations: EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; EBUS-IFB, endobronchial ultrasound-guided intranodal forceps biopsy.

## ROSE

After obtaining the sample smear, it was immediately placed into Diff-Quick staining solution (418091, Zhuhai Beso Biotechnology Co., Ltd., Zhuhai, China), specifically in solutions A and B for 35 seconds each, for staining. All cytological smears were rapidly interpreted by two cytology technicians using a specialized microscope.

### Specimen Processing

TBNA samples were immediately subjected to ROSE after smearing. The adequacy of the specimen in capturing the pathologic lesion was assessed. The remaining tissues from samples that were considered to have diagnostic potential were kept in cell preservation solution for use in cytological wax blocks, labeled as TBNA samples. IFB samples were preserved in formalin for histopathologic examination.

### Assessment of Safety and Postoperative Adverse Events

Bleeding during the procedure was evaluated against standardized definitions of bronchoscope-related hemorrhage. There are four levels of intraoperative bleeding (Folch et al, 2020):

• Grade 1: Suctioning of blood for less than 1 minute.

• Grade 2: Suctioning of blood for more than 1 minute, or need for rewedging of the bronchoscope or instillation of cold saline, vasoactive substances, or thrombogenic agents.

• Grade 3: Selective intubation with endotracheal tube (ETT) or balloon/bronchial blocker for less than 20 minutes, or premature interruption of the procedure.

• Grade 4: Persistent selective intubation for more than 20 minutes, or readmission to the intensive care unit (ICU), or need for packed red blood cell (PRBC) transfusion, or need for bronchial artery embolization or resuscitation.

Patients were closely monitored for 24 hours post-procedure, with chest CT or radiography performed routinely if symptoms arose. Body temperature was measured daily for a consecutive seven days post-procedure to screen for pneumonia or mediastinitis.

### Diagnostic Methods

Diagnostic rate is defined as the percentage of patients who are definitively diagnosed. A pathologic diagnosis approach was employed in this study, with pathologic results from TBNA or IFB samples that matched the final diagnosis regarded as definitive diagnostic outcomes. A diagnostic result from either method was qualified as a result of the combined strategy. In pathologic interpretation, atypical cells, suspicious cancer cells, and dysplastic cells were not considered malignant diseases. Separately, explicit characterization of granulomas was required for pathologically defining granulomatous lesions; the mere presence of a few epithelioid cells, clusters of epithelioid cells, or suspected granulomas did not qualify for a diagnosis of granulomatosis. The diagnostic criteria for sarcoidosis were adapted from the Diagnosis and Detection of Sarcoidosis (2020) guidelines by the American Thoracic Society (ATS) (Crouser et al, 2020), with a slight modification: the exclusion of infectious disease. The final diagnosis of all benign diseases was made based on findings from pathologic examination, imaging examination, microbiological tests, and other auxiliary tests, along with a follow-up evaluation over a six-month period to confirm the final diagnosis.

**Table 1. Clinical characteristics of patients.**

| Variable | Malignant diseases (*n* = 78) | Sarcoidosis (*n* = 49) | Other benign diseases (*n* = 16) | *p*-value |
|---|---|---|---|---|
| Age, years | 67.0 (61.0, 71.0) | 51.0 (47.0, 59.5) | 56.5 (41.5, 58.8) | <0.001 |
| Female, n (%) | 23 (29.5) | 35 (71.4) | 8 (50.0) | <0.001 |
| Smoking history, n (%) | 47 (60.3) | 8 (16.3) | 3 (18.8) | <0.001 |
| Concurrent malignant disease, n (%) | 7 (9.0) | 3 (6.1) | 0 (0.0) | 0.179 |
| Long axis of lymph node, mm | 25 (20, 35) | 30 (24, 37) | 21 (20, 22) | <0.001 |
| Short axis of lymph node grouping, mm | | | | <0.001 |
| ≥10–20 mm | 48 (61.5) | 30 (61.2) | 16 (100.0) | |
| 21–30 mm | 20 (25.6) | 19 (38.2) | 0 (0.0) | |
| ≥31 mm | 10 (12.8) | 0 (0.0) | 0 (0.0) | |
| Biopsy site, n (%) | | | | 0.038 |
| 2R | 2 (2.6) | 0 (0.0) | 0 (0.0) | |
| 4R | 15 (19.2) | 3 (6.1) | 3 (18.8) | |
| 4R+7 | 9 (11.5) | 1 (2.0) | 0 (0.0) | |
| 4L | 1 (1.3) | 0 (0.0) | 0 (0.0) | |
| 7 | 44 (56.4) | 42 (85.7) | 11 (68.8) | |
| 10R | 2 (2.6) | 2 (4.1) | 0 (0.0) | |
| 10L | 5 (6.4) | 1 (2.0) | 2 (12.5) | |
| TBNA needle, n (%) | | | | 0.789 |
| EBUS-22G | 25 (32.1) | 14 (28.6) | 6 (37.5) | |
| EBUS-22G + BC1418 | 53 (67.9) | 35 (71.4) | 10 (62.5) | |
| EBB/TBLB/neoplasm biopsy, n (%) | 47 (60.3) | 22 (44.9) | 9 (56.3) | 0.236 |

Data are presented as median (interquartile range) or n (%). Abbreviations: EBUS, endobronchial ultrasound; EBB, endobronchial biopsy; TBLB, transbronchial lung biopsy; TBNA, transbronchial needle aspiration.

**Table 2. Diagnostic yields of the methods used.**

| | Total (n) | EBUS-TBNA (%) | EBUS-IFB (%) | Combined strategy (%) | *p*-value IFB vs. TBNA | *p*-value Combined vs. TBNA | *p*-value Combined vs. IFB |
|---|---|---|---|---|---|---|---|
| Total cases | 143 | 86 (60.1) | 126 (88.1) | 129 (90.2) | <0.001 | <0.001 | 0.25 |
| Malignant cases | 78 | 56 (71.8) | 73 (93.6) | 76 (97.4) | <0.001 | <0.001 | 0.25 |
| Malignant lung cancer | 74 | 53 (71.6) | 69 (93.2) | 72 (97.3) | 0.001 | <0.001 | 0.25 |
| Small cell cancer | 34 | 27 (79.4) | 33 (97.1) | 34 (100.0) | 0.070 | 0.023 | 1.000 |
| Adenocarcinoma | 24 | 16 (66.7) | 23 (95.8) | 24 (100.0) | 0.039 | 0.034 | 1.000 |
| Squamous cell cancer | 7 | 6 (85.7) | 5 (71.4) | 6 (85.7) | | | |
| Sarcoma | 3 | 1 (33.3) | 2 (66.7) | 2 (66.7) | | | |
| Neuroendocrine carcinoma | 3 | 2 (66.7) | 3 (100.0) | 3 (100.0) | | | |
| Poorly differentiated carcinoma | 2 | 1 (50.0) | 2 (100.0) | 2 (100.0) | | | |
| NSCLC | 1 | 0 (0.0) | 1 (100.0) | 1 (100.0) | | | |
| Metastatic carcinoma | 4 | 3 (75.0) | 4 (100.0) | 4 (100.0) | | | |
| Renal cell carcinoma | 2 | 2 (100.0) | 2 (100.0) | 2 (100.0) | | | |
| Pancreatic carcinoma | 1 | 0 (0.0) | 1 (100.0) | 1 (100.0) | | | |
| Rectal carcinoma | 1 | 1 (100.0) | 1 (100.0) | 1 (100.0) | | | |
| Sarcoidosis | 49 | 23 (46.9) | 43 (87.8) | 43 (87.8) | <0.001 | <0.001 | 1.000 |
| Other benign diseases | 16 | 7 (43.8) | 10 (62.5) | 10 (62.5) | 0.25 | 0.25 | 1.000 |

Data are presented as n (%). Abbreviations: NSCLC, non-small cell lung cancer; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; EBUS-IFB, endobronchial ultrasound-guided intranodal forceps biopsy.

### Statistical Analysis

Data of categorical variables are presented as counts and percentages. Data that did not follow a normal distribution are expressed as median (interquartile range). Comparisons between the combined strategy, EBUS-IFB, and EBUS-TBNA were conducted using McNemar's test. Chi-square tests or Fisher's exact test were used for comparing the rates. While continuous variables were analyzed using the Mann–Whitney *U* test. Factors influencing the diagnostic rate of TBNA and IFB were analyzed using logistic regression. Multivariate regression analysis of significant univariate variables ($p < 0.1$) affecting TBNA diagnosis was conducted. All reported *p*-values were two-tailed, with $p < 0.05$ considered statistically significant. Statistical analyses were performed using Statistical Product and Service Solutions (SPSS) version 25 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 9 (Dotmatics, Boston, MA, USA).

## Results

### Clinical Information

A review was conducted on the 150 patients who underwent EBUS-IFB, excluding 7 cases who were not definitively diagnosed due to loss to follow-up or refusal of misalignment of pathologic results with clinical assessments in further investigation. Ultimately, 143 patients with definitive diagnoses were included in the statistical analysis. Among these patients, 66 patients (46.2%) were female, and 58 patients (40.6%) had a history of smoking (Table 1). The lymph node biopsy sites included 2R, 4R, 4L, 4R+7, 7, 10R, and 10L, with site 7 being the most frequently punctured location, accounting for 67.8% (97/143). Dual site biopsies were performed at sites 4R and 7 in 7.0% of cases (10/143). Regarding the biopsy needles, 31.5% of cases (45/143) used EBUS-22G, while 68.5% (98/143) used EBUS-22G combined with BC1418. Additionally, 54.5% of the cases (78/143) underwent EBB/TBLB/neoplasm biopsy (Table 1).

### Diagnostic Outcomes

The diagnostic results are summarized in Table 2. Both the combined strategy (90.2%) and the EBUS-IFB (88.1%) showed significantly higher overall diagnostic rates compared to the EBUS-TBNA (60.1%) ($p < 0.001$) (Fig. 3). There was no significant difference in the diagnostic rates between the combined strategy and the EBUS-IFB (Table 2). The combined group + EBB/TBLB/neoplasm biopsy resulted in a successful diagnostic rate of 97.2% (139/143), with the remaining 2.8% (4/143) being definitively diagnosed using additional lung biopsies or thoracoscopy. The final diagnoses were malignant diseases in 78 cases, sarcoidosis in 49 cases, and other benign disease in 16 cases, which included 6 cases of tuberculosis and 10 cases of inflammatory or reactive lymphadenopathy. All patients were followed up for over 6 months to confirm their final diagnosis. The concordance rate between ROSE and the final diagnosis was 91.6% (131/143).

For malignant diseases, the combined strategy (76/78, 97.4%) and the EBUS-IFB (73/78, 93.6%) exhibited significantly higher diagnostic rates compared to the

EBUS-TBNA (56/78, 71.8%) ($p < 0.001$). The diagnostic rate for adenocarcinoma was 95.8% if detected with the EBUS-IFB vs. 66.7% with the EBUS-TBNA ($p = 0.039$) (Table 2). The diagnostic rate for sarcoidosis was 87.8% in both the combined strategy and EBUS-IFB alone categories vs. 46.9% in the EBUS-TBNA category ($p < 0.001$). For other benign disease, the rates were 62.5% in both the combined strategy and EBUS-IFB categories vs. 43.8% in the EBUS-TBNA category ($p = 0.25$) (Table 2).

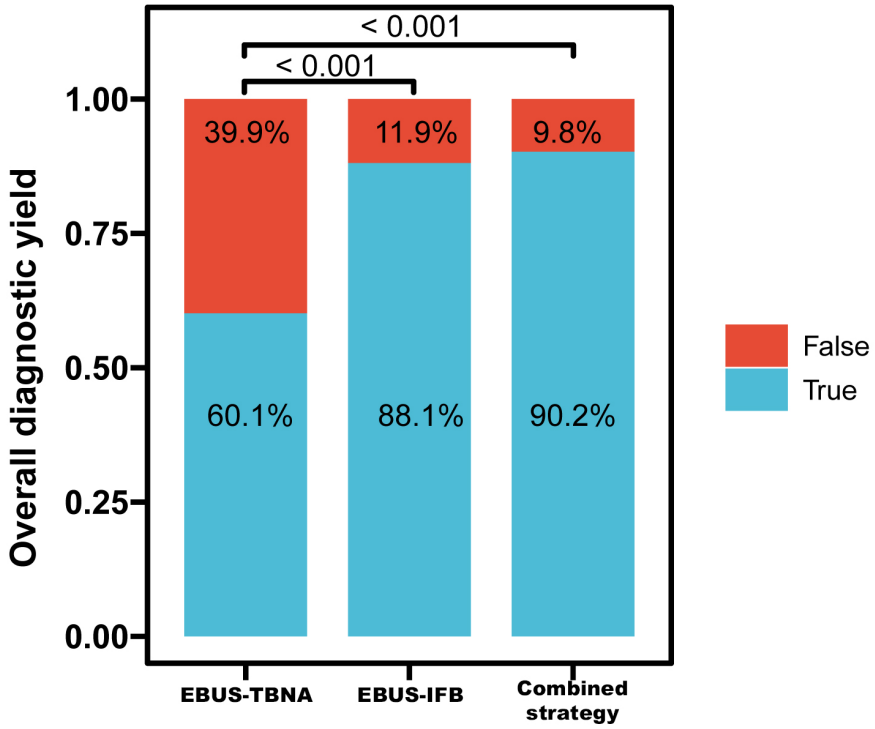


**Fig. 3. The comparison of diagnostic yield of the three diagnostic methods used to classify the diseases under study.** The differences in diagnostic yield between EBUS-TBNA and EBUS-IFB, as well as between EBUS-TBNA and the combined strategy, are significant ($p < 0.001$).

In the EBUS-TBNA category, there was no significant difference in the diagnostic rates with regard to the different needles used, with EBUS-22G and EBUS-22G + BC1418 contributing to diagnostic rates at 55.6% (25/45) and 62.2% (61/98), respectively ($p = 0.448$). The method of tunnel establishment showed no significant difference in diagnostic rates for the EBUS-IFB category, with cold tunneling and hot tunneling contributing to diagnostic rates at 87.8% (86/98) and 88.9% (40/45) ($p = 0.846$) (Table 3). Univariate regression analysis showed that all variables in Table 4 had no significant effect on the diagnosis rate of EBUS-IFB.

## Diagnostic Failures

Of the malignant diseases in which EBUS-TBNA failed to diagnose, 90.9% of the cases (20/22) were successfully diagnosed through EBUS-IFB. Only 2 out of 78 malignant disease patients were not able to be diagnosed by the combined strategy; additional lung biopsy was required to reach definitive diagnoses for a

**Table 3. Comparison of diagnostic rates of using cold and hot tunneling methods for EBUS-IFB category.**

| Final diagnosis | Total cases | Cold tunneling | | Hot tunneling | | *p*-value |
|---|---|---|---|---|---|---|
| | | n | Diagnostic rate, n (%) | n | Diagnostic rate, n (%) | |
| Malignant diseases | 78 | 53 | 51 (96.2) | 25 | 22 (88) | 0.374 |
| Sarcoidosis | 49 | 35 | 31 (88.6) | 14 | 12 (85.7) | 1.000 |
| Other benign disease | 16 | 10 | 4 (40.0) | 6 | 6 (100.0) | 0.034 |
| Total disease | 143 | 98 | 86 (87.8) | 45 | 40 (88.9) | 0.846 |

case of squamous cell carcinoma and a case of sarcoma. Notably, there were 2 cases (1 case of adenocarcinoma, and 1 case of squamous cell carcinoma) diagnosed by EBUS-TBNA where EBUS-IFB failed. Of the sarcoidosis patients who were not successfully diagnosed by EBUS-TBNA, 76.9% of the cases (20/26) were successfully diagnosed by EBUS-IFB, while 12.4% of the cases (6/49) failed to be diagnosed with EBUS-IFB were successfully diagnosed by EBB. Six out of the 16 patients with other benign diseases remaining undiagnosed in the combined strategy category were subsequently diagnosed: 1 case of tuberculosis confirmed by EBB, 2 cases of tuberculosis diagnosed via thoracoscopy, and 3 cases of reactive lymphadenopathy confirmed by repeated bronchoscopy and follow-up.

The failure rate of EBUS-TBNA for sarcoidosis was 53.1% (26/49), which was significantly higher than that for malignant disease (28.2%, 22/78) ($p = 0.032$) (Fig. 4A). Significant differences in age, sex, and smoking status were observed between patients with sarcoidosis and those with malignant diseases (Fig. 4B–D). Univariate regression analysis showed that all variables in Table 5, except for sex, had no significant effect on the diagnosis rate of EBUS-TBNA. Multivariate regression analysis of significant variables ($p < 0.1$), including sex, smoking, and combination with EBB/TBLB/neoplasm biopsy, showed no significant differences (Table 6).

### Safety

During the procedure, only 7.0% of the patients (10/143) experienced grade 2 bleeding, which did not require intervention. There were no serious complications, such as pneumothorax, mediastinal emphysema, infections, respiratory failure, or deaths. Also, no bronchoscopic injuries were observed in these patients.

### Procedure Time

The duration for conducting EBUS-TBNA was 15 (14, 15) minutes versus 10 (9, 11) minutes, as the duration needed to conduct EBUS-IFB ($p < 0.001$). The total procedure time was 62 (60, 64) minutes.

## Discussion

The main objective of this study was to investigate the diagnostic value and safety of EBUS-IFB for mediastinal/hilar lymph node disease, by retrospectively evaluating the accuracy of EBUS-IFB, followed by the establishment of a bronchial

**Table 4. Univariate logistic regression analysis of factors affecting diagnostic rate of EBUS-IFB.**

| Variable | Number of cases | $\beta$ | SE | OR (95% CI) | $p$-value |
|---|---|---|---|---|---|
| Age, years | 143 | 0.02 | 0.02 | 1.02 (0.97–1.06) | 0.462 |
| Sex | | | | | |
| Male | 77 | | | | |
| Female | 66 | –0.58 | 0.52 | 0.56 (0.20–1.57) | 0.269 |
| Smoking status | | | | | |
| Non-smoker | 85 | | | | |
| Smoker | 58 | 1.29 | 0.66 | 3.62 (0.99–13.21) | 0.052 |
| Lymph node grouping based on short axis | | | | | |
| 10–20 mm | 94 | | | | |
| 21–30 mm | 39 | 0.25 | 0.61 | 1.28 (0.39–4.25) | 0.686 |
| ≥31 mm | 10 | 0.28 | 1.10 | 1.32 (0.15–11.34) | 0.802 |
| Long axis of lymph node, mm | 143 | 0.05 | 0.03 | 1.05 (0.99–1.11) | 0.128 |
| Lymph node puncture site | | | | | |
| Hilar | 12 | | | | |
| Mediastinal | 131 | 0.44 | 0.82 | 1.55 (0.31–7.74) | 0.596 |
| Combined EBB/TBLB/neoplasm biopsy | | | | | |
| No | 65 | | | | |
| Yes | 78 | –0.48 | 0.54 | 0.62 (0.22–1.78) | 0.373 |
| Tunneling method | | | | | |
| Cold tunneling | 98 | | | | |
| Hot tunneling | 45 | 0.11 | 0.57 | 1.12 (0.37–3.83) | 0.846 |
| EBUS-IFB procedure time | 143 | 0.09 | 0.18 | 1.09 (0.76–1.56) | 0.636 |
| Total procedure time | 143 | 0.01 | 0.09 | 1.01 (0.84–1.22) | 0.889 |

Abbreviations: SE, Standard Error; OR, odds ratio; CI, confidence interval.

tunnel, in diagnosing the diseases. We applied two methods of tunnel construction. To the best of our knowledge, this is the first study attempting to compare the effects of these tunnel construction methods on IFB diagnosis rate, and the only study that utilized ROSE to guide both EBUS-TBNA and EBUS-IFB procedures. All procedures were performed using a rigid bronchoscope on the patients under general anesthesia, in order to maximize the safety of patients. The present study demonstrated that EBUS-IFB increased the diagnostic rates for malignant diseases and sarcoidosis. The combined strategy had the highest overall diagnostic rate, with significantly higher rates of diagnosing malignant tumors and sarcoidosis compared to using EBUS-TBNA alone. The techniques applied in this study proved to be safe for patients, as no significant complications were reported, and notably, the use of bronchoscopic techniques allowed for a successful diagnosis in 97.2% of the patients, thereby avoiding additional surgical procedures.

Our findings showed that the EBUS-IFB can significantly improve diagnostic rates, with 90.9% of cases of malignant disease failed to be detected by EBUS-TBNA successfully diagnosed by EBUS-IFB; the diagnostic rate of the combined strategy even reached an astounding 97.4%. Rüber et al (2022) reported that the

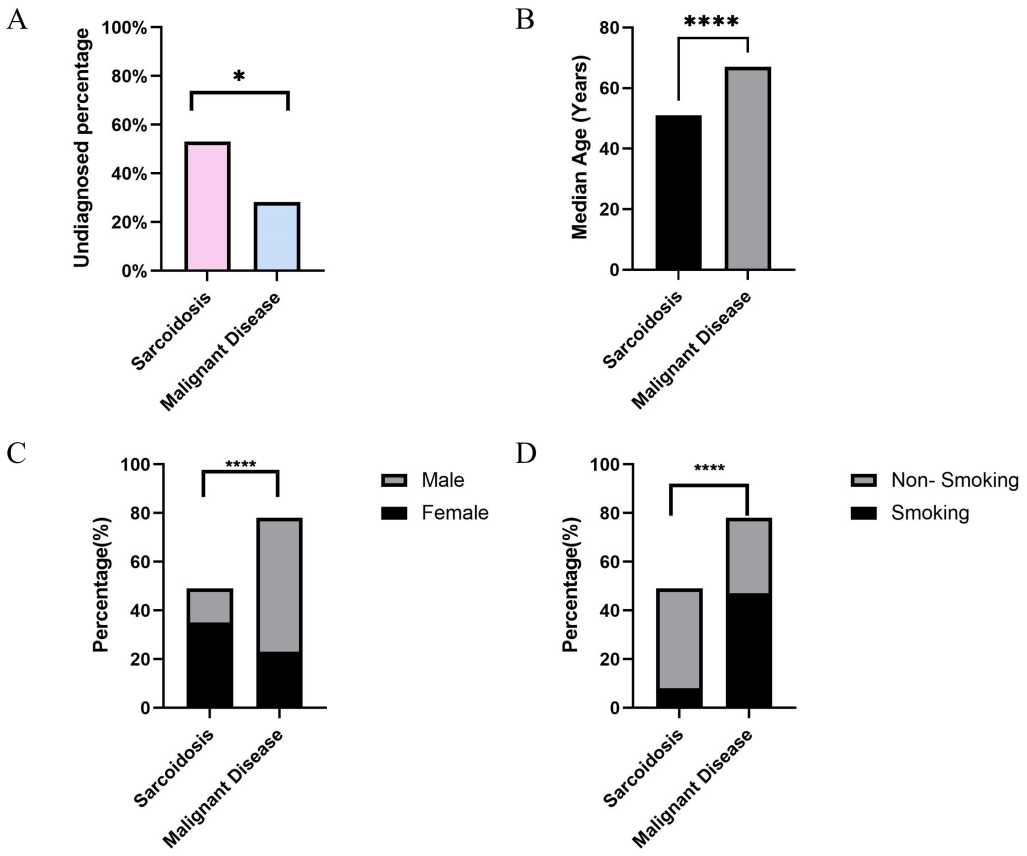


**Fig. 4. Comparison of diagnostic outcomes between sarcoidosis and malignant disease patient groups.** (A) Comparison of TBNA failure rate. (B) Comparison of median age. (C) Comparison of sex percentage. (D) Comparison of smoking status. *$p < 0.05$, ****$p < 0.0001$.

EEBUS-TBNA combined with EBUS-TBFB significantly improved the lung cancer diagnostic rate, as compared to EBUS-TBNA alone (97.1% vs. 76.5%, $p = 0.016$), a finding which is similar to our results. However, some studies did not show a clear advantage of IFB in diagnosing malignant disease. Bramley et al (2016) found that the sensitivity of TBNA was higher than that of ca-TBFB. Radchenko et al (2019) also reported that the diagnostic rate of EBUS-TBNA was higher than that of EBUS-MFB, whereas Ray et al (2020) found no significant difference in diagnostic rates between ca-TBFB and EBUS-TBNA, although the specimen quality obtained by ca-TBFB was higher. It must be noted that in our study, two tumor patients were diagnosed only by TBNA and not by IFB. Therefore, this observation supports that IFB is a complement to, rather than a replacement for, TBNA. Since the diagnostic outcomes for malignant disease detected with EBUS-IFB are largely inconsistent, obtaining more tissues via IFB molecular testing may be advantageous for diagnosing malignant disease.

In this study, we found that EBUS-IFB significantly improved the diagnostic rate for sarcoidosis, which is consistent with previous studies. Agrawal et al (2022) included six studies in a meta-analysis showing that the diagnostic rate for sarcoidosis with EBUS-TBNA combined with EBUS-IFB was 93%, significantly higher than the 58% with EBUS-TBNA alone ($p < 0.0001$). The number of cases

**Table 5. Univariate logistic regression analysis of factors affecting EBUS-TBNA diagnosis for sarcoidosis and malignant diseases.**

| Variable | Number of cases | $\beta$ | SE | OR (95% CI) | *p*-value |
|---|---|---|---|---|---|
| Age, years | 127 | 0.03 | 0.02 | 1.03 (1.00–1.06) | 0.104 |
| Sex | | | | | |
| Male | 69 | | | | |
| Female | 58 | –0.83 | 0.37 | 0.44 (0.21–0.91) | 0.027 |
| Smoking status | | | | | |
| Non-smoker | 72 | | | | |
| Smoker | 55 | 0.67 | 0.38 | 1.95 (0.93–4.11) | 0.079 |
| Lymph node grouping based on short axis | | | | | |
| 10–20 mm | 78 | | | | |
| 21–30 mm | 39 | 0.05 | 0.40 | 1.06 (0.48–2.32) | 0.894 |
| ≥31 mm | 10 | 0.97 | 0.82 | 2.6 (0.53–13.26) | 0.239 |
| Long axis of lymph node, mm | 127 | 0.01 | 0.02 | 1.01 (0.98–1.05) | 0.394 |
| Lymph node puncture site | | | | | |
| Hilar | 10 | | | | |
| Mediastinal | 117 | 0.54 | 0.67 | 1.72 (0.47–6.29) | 0.411 |
| Combined EBB/TBLB/neoplasm biopsy | | | | | |
| No | 58 | | | | |
| Yes | 69 | –0.68 | 0.38 | 0.51 (0.24–1.06) | 0.072 |
| TBNA needle | | | | | |
| EBUS-22G | 39 | | | | |
| EBUS-22G + BC1418 | 88 | 0.35 | 0.39 | 1.42 (0.66–43.07) | 0.37 |

in individual studies was generally low, ranging from 8 to 59, with only one study having a sample larger than ours. The EBUS-TBNA diagnostic rate for sarcoidosis was only 46.9% in this study, but it is higher than that reported in Radchenko et al (2019) (at 33.3%). Several potential reasons for the low diagnostic rate of TBNA are as follows: (1) TBNA is more compatible with testing of cytological samples; therefore, pathologists may find it challenging to detect granulomas via TBNA. (2) Laboratory technologists may have the misconception that IFB could yield better results, especially with the aid of ROSE, leading to selection bias. We successfully diagnosed 76.9% of sarcoidosis patients using IFB, who failed to be diagnosed by TBNA, and those undiagnosed by IFB were successfully diagnosed via EBB. Notably, the use of bronchoscopy and related techniques in the present study contributed to a 100% diagnostic rate for sarcoidosis. The ATS's Diagnosis and Detection of Sarcoidosis (2020) guideline suggested an 87% diagnostic rate of EBUS, with approximately 13% of patients potentially requiring mediastinoscopy (Crouser et al, 2020). Our study highlights the value of IFB in diagnosing sarcoidosis, a method that could potentially spare patients from mediastinoscopy.

In this study, we found that the failure rate of TBNA in sarcoidosis was significantly higher than that in malignant diseases, with age, sex, and smoking status between the two patient groups presenting significant differences. The difference in failure rate is likely related to the disease characteristics themselves, as the in-

**Table 6. Multivariable logistic regression analysis of factors affecting EBUS-TBNA diagnosis for sarcoidosis and malignant diseases.**

| Variable | Number of cases | $\beta$ | SE | OR (95% CI) | $p$-value |
|---|---|---|---|---|---|
| Sex | | | | | |
| Male | 69 | | | | |
| Female | 58 | –0.72 | 0.53 | 0.49 (0.17–1.37) | 0.172 |
| Smoking status | | | | | |
| Non-smoker | 72 | | | | |
| Smoker | 55 | 0.20 | 0.54 | 1.23 (0.42–3.56) | 0.709 |
| Combined EBB/TBLB/neoplasm biopsy | | | | | |
| No | 58 | | | | |
| Yes | 69 | –0.73 | 0.39 | 0.48 (0.23–1.03) | 0.06 |

cidence of malignant diseases is higher in older males with a history of smoking, while sarcoidosis more frequently affects women aged 30–60 (Grunewald et al, 2019). Regression analysis of factors affecting the TBNA diagnostic rate for both patient groups showed that lymph node size, biopsy site, and biopsy needle had no significant impact. As previously mentioned, the high failure rate in sarcoidosis is likely related to the fact that TBNA is more compatible with testing of cytological samples rather than histological specimens.

Establishing a bronchial tunnel facilitates the smooth entry of forceps into the lesion. A previous study has used different sizes of forceps, ranging from 0.8 mm to 1.9 mm (Agrawal et al, 2022). Difficulty in passing forceps through the airway can lead to IFB failure. Based on our experiences, for thicker bronchial walls, the hot tunneling approach was more likely to form a tunnel. Our center used to utilize the cold tunneling method, but with the progress of technologies, and we began to adopt the hot tunneling technique, particularly after encountering difficulties in tunnel formation. Although there was no statistically significant difference, the diagnostic rate was higher with hot tunneling, suggesting potential advantages. There has been limited research on the impact of forceps size on IFB diagnostic rates; smaller forceps may pass through the airway wall more easily but likely collect smaller samples. Nakai et al (2024) reported that specimens obtained with 1.9 mm biopsy forceps were three times larger than those obtained with 0.96 mm forceps, yet these specimens yielded comparable diagnostic rates for advanced lung cancer. However, 1.9 mm biopsy forceps are challenging to pass through the working channel of a bronchoscope (Cheng et al, 2024). The higher diagnostic rate for IFB achieved in our center was associated with the established tunnels that allow easier access to more tissues. Further prospective studies are needed to assess the impact of biopsy forceps on diagnostic rates.

To our knowledge, this study is the first to fully utilize ROSE to guide both EBUS-TBNA and EBUS-IFB procedures. Our ROSE concordance rate with the final diagnosis was 91.6%. A study by Iliaz et al (2022) on 328 cases revealed that the ROSE and the ultimate cytologic approach had a concordance rate of 91.6% in identifying lymph nodes. It has been found that the ROSE accuracy may vary

depending on the clinical expectation, pulmonary pathology, and professional experience of the pathologist (Silav et al, 2023). Previous studies on EBUS-IFB have rarely or infrequently used ROSE, and no reports have yet indicated that ROSE enhances IFB diagnostic rates. Mehta et al (2020) conducted IFB on mediastinal lymph nodes with negative EBUS-TBNA ROSE results, which increased the diagnostic rate by 27%. Being concordant with our perspectives, ROSE plays a crucial role in selecting candidates for EBUS-IFB, potentially sparing patients from additional examinations.

In terms of complications or adverse events, only minor bleeding that did not require intervention was encountered in this study, and no severe adverse events occurred. All procedures at our center were performed using a rigid bronchoscope on patients under general anesthesia, allowing for high-volume aspiration in the case of significant bleeding and simultaneous use of various tools to control bleeding, thus ensuring patient safety (Diaz-Mendoza et al, 2019). However, some centers have reported a higher incidence of complications: Franke et al (2012) reported a bleeding rate requiring intervention as high as 6%, along with cases of mediastinal emphysema and arrhythmias, whereas Rüber et al (2022) reported two cases of respiratory failure, with one of which requiring non-invasive mechanical ventilation. A meta-analysis by Agrawal et al (2022) suggested that complications associated with EBUS-IFB are higher than those with EBUS-TBNA but lower than those with mediastinoscopy. Cheng et al (2019) found that the EBUS-IFB procedure is associated with an overall complication rate of 1.5%, which is comparable to the rate associated with EBUS-TBNA, after analyzing approximately 300 published cases.

Several limitations of this study should be highlighted. First of all, this is a single-center, retrospective study. Secondly, the patients in the sample might be prone to selection bias since the discretion to perform IFB lies with the bronchoscopist. Thirdly, tissue specimens obtained were not subjected to genetic testing. Next, there were no patients with lymphoma in this study and thus, the diagnostic value of the tested methods for lymphoma was not assessed. The procedures conducted in the present study were performed with a rigid bronchoscope on the patients under general anesthesia, representing stringent protocols requiring a coordinated team and highly skilled bronchoscopists; however, such conditions and equipment may not be available in some endoscopic centers.

## Conclusion

Routine EBUS-TBNA with ROSE to confirm the acquisition of pathological tissue, followed by tunnel formation and EBUS-IFB, can enhance the overall diagnostic rate for mediastinal/hilar lymph node lesions. This combined approach is particularly valuable for diagnosing malignant diseases and sarcoidosis. However, it is crucial to highlight that EBUS-IFB is a valuable complement to, rather than a substitute for, EBUS-TBNA, offering a safe and feasible diagnostic procedure that may spare patients from the unnecessary invasive surgical interventions, although this procedure might take a longer period to complete.

## Key Points

- Endobronchial ultrasound-guided intranodal forceps biopsy (EBUS-IFB) can enhance the diagnostic rate for malignant diseases and sarcoidosis, whereas the combined strategy achieves the highest diagnosis rate.
- Hot tunneling contributes to a higher diagnostic rate, and is more capable of forming a tunnel in the case of thicker bronchial walls.
- This is the only study that fully utilized rapid on-site evaluation (ROSE) to guide both endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and EBUS-IFB procedures. ROSE pre-selects candidates for EBUS-IFB procedure, which potentially spares the patients from additional examinations.
- EBUS-IFB is a safe and feasible complement to EBUS-TBNA. All procedures at our center were performed using a rigid bronchoscope on patients under general anesthesia, to maximize patient safety.

## Availability of Data and Materials

The data used to support the findings of this study are available from the corresponding authors upon request.

## Author Contributions

JF designed the research study. ZW and NW performed the research. ZW and PX analysed the data. ZW drafted the manuscript. All authors contributed to the important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

This study was approved by the Tianjin Medical University General Hospital (Ethics number: IRB2023-YX-265-01). The entire experimental procedure adhered to the principles of informed consent, with patients or their family members being provided with information about the study. And informed consent was obtained from all study participants.

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## Conflict of Interest

The authors declare no conflict of interest.

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