Peer Review File
Article information: https://dx.doi.org/10.21037/jtd-22-809

Reviewer A

1. If the presence of pulmonary emphysema did not affect the diagnostic yield, why did you exclude lesions presenting with sole pulmonary emphysema as the background.

Reply 1: We apologize for not having explained our point adequately. Although the diagnostic yield varied depending on the severity of emphysema, the presence of emphysema itself has not been reported to reduce the yield. However, we considered that including patients with emphysema into patients without ILD (normal lung) might modify the diagnostic yield of EBUS-GS TBB. Therefore, for this study, we excluded patients with only pulmonary emphysema without ILD. To clarify this, we have added the following sentences.

Pages 5-6, lines 89-92 "In particular, regarding the presence of pulmonary emphysema influencing the diagnostic yield of EBUS-GS TBB, although the diagnostic yield varied depending on the severity of emphysema, the presence of emphysema itself has not been reported to reduce the yield."
Pages 6, lines 113-114 "We excluded patients with endobronchial lesions and only pulmonary emphysema without ILD."

2. Did you use only transbronchial forceps biopsy, or did you combine with others cytology tools such as the brush…?

Reply 2: We used only transbronchial forceps biopsy.
Pages 7, lines 128-129 "Samples for pathological evaluation were only collected by the guide sheath using forceps."

3. The main aim of the study is assessing the association of patients with ILD, not limited to IPF, but there is no information about the number and type of 44 cases of non-UIP patters (probable UIP, indeterminate for UIP, and alternative diagnosis). Sometimes the use of terms as IPF and UIP radiological pattern seems to be confused. Some cases of probable UIP and indeterminate for UIP radiological patters may finally correspond to IPF. It is important to

clarify this point.

Reply 3: As pointed out by the reviewer, we have added the detailed issue of non-UIP patterns (probable UIP, indeterminate for UIP, and alternative diagnosis) in table 5.

I also recommend reviewing these expressions:
1. Title: Impact of ILD in radial EBUS results for diagnosing PPLs or change "Impact"

Reply 1: We changed the title from "Impact" to "Diagnostic value and safety".
Pages 1, lines 3-5 "Diagnostic value and safety of endobronchial ultrasonography with a guide sheath transbronchial biopsy for diagnosing peripheral pulmonary lesions in patients with interstitial lung disease".

2. Running title: r-EBUS for lung lesions in with ILD

Reply 2: As pointed out by the reviewer, we have changed the running title.
Pages 1, line 18 "r-EBUS for lung lesions in ILD".

Abstract
Words:
3. Line 20 and in general: "radial endobronchial ultrasonography (r-EBUS)" or Radial Probe (RP-EBUS) instead of "endobronchial ultrasonography"

Reply 3: We agree with the suggestion. Accordingly, we have changed the expression of "endobronchial ultrasonography" to "radial endobronchial ultrasonography (r-EBUS)" in the section of the Abstract.

4. "with a guide sheath" and without a guide sheath. It is a useful method in general

Reply 4: As pointed out by the reviewer, we have changed the expression of "with a guide sheath" to "with and without a guide sheath" (Page 3, line 38-39).

5. Line 22: I suggest "diagnostic yield and complications of endobronchial ultrasonography transbronchial biopsy for peripheral pulmonary lesions…"

Reply 5: As pointed out by the reviewer, we have changed the expression of "diagnostic yield and complications of peripheral pulmonary lesions with endobronchial ultrasonography with a guide sheath transbronchial biopsy" to "diagnostic yield and complications of the procedure for peripheral pulmonary lesions" (Page 3, lines 45-46).

6. Line 26: Consider change "normal lung" by "without ILD". How do you define "normal lung"?

Reply 6: In our study, we excluded patients with the only finding of pulmonary emphysema. Therefore, normal lung was defined as no having ILD. We have corrected "normal lung" to "without interstitial lung disease"in the section of Abstract.

7. Line 31: It is not necessary to repeat "with endobronchial ultrasonography with a guide sheath transbronchial biopsy"

Reply 7: We agree with your idea. We have omitted it (Page 3, lines 47).

8. Line 33: "The diagnostic yield of endobronchial ultrasonography" instead of "The diagnostic yield of peripheral pulmonary lesions"
It is not necessary to repeat "with a guide sheath"

Reply 8: We have changed the expression to "the diagnostic yield of radial endobronchial ultrasonography in patients with interstitial lung disease was significantly lower than in those without ILD" (Page 3, lines 48-49).

Introduction
9. Line 52: Consider "it is gradually being" instead of "it has gradually been".

Reply 9: We have corrected the expression of "it has gradually been" to "it is gradually being" (Page 5, lines 68-69).

10. Line 57: Reference?

Reply 10: In addition to disease progression, the clinical course of IPF can be complicated by a variety of events, including infection and lung cancer. Therefore, we have added the appropriate reference text.
Page 5, lines 72-73 “All peripheral pulmonary lesions (PPLs) encountered in patients with ILD were not always malignant lesions (5)”.

11. Line 60: Better explain the risk of radiation or chemotherapy in patients with pulmonary fibrosis

Reply 11: We thank you for the appropriate comments. Anti-cancer therapies including radiotherapy, chemotherapy and surgical therapy have the possibility of causing acute exacerbation and/or fatal complications. Thus, careful selection of a suitable treatment strategy is required.
Page 5, lines 75-77 “anti-cancer therapies including radiotherapy, chemotherapy and surgical therapy have the possibility of causing acute exacerbation of ILD and/or fatal complications”.

12. Line 67: radial endobronchial ultrasonography

Reply 12: Thank you for your advice. We have changed the expression of “endobronchial ultrasonography” to “radial endobronchial ultrasonography” (Page 5, line 82).

Methods
13. Line 91: patients or lesions?

Reply 13: We thank you for the appropriate comments. The term “patients” was correct. We have changed “patients (lesions)” to “patients” (Page 6, line 110).

14. Line 93: Review the concept of PPLs and add the bibliography reference; Do you mean lesions within the outer third ellipse?

Reply 14: Thank you for your insightful comments. We have added the bibliography reference in the main text (Page 6, line 113).

15. Line 95: Pneumonologist or pneumologist?

Reply 15: Thank you for your advice. Pneumonologist is correct (Page 6, line 114).

16. Line 102: Avoid imprecise terms such as “for the majority of cases”

Reply 16: Thank you for your advice. Spirometry was performed in 64.0% cases.
Page 7, line 121 “Spirometry was performed a day prior to the bronchoscopy in 64.0% cases.”

Results
17. Line 153: What does “ILAs” mean?

Reply 17: We apologize for the error. We have corrected ILAs to ILD.
Page 9, lines 174-176 “A total of 431 lesions in 431 patients were included in the analyses after excluding 87 endobronchial lesions, 27 lesions that had an uncertain final diagnosis, and 146 lesions presenting solely with pulmonary emphysema without ILD”.

18. Line 155: Substantial differences or significative differences?

Reply 18: Thank you for your advice. The term “significant differences” is correct.
Page 9, lines 178-180 “In addition to lesion lobe, there were significant differences in proportion of males, outer lesions, and solid nodules between patients with ILD and those without ILD.”

19. Line 160 and in general: “The diagnostic yield of r-EBUS” instead “The diagnostic yield of PPLs”

Reply 19: Thank you for your advice. We have corrected “The diagnostic yield of PPLs” to “The diagnostic yield of EBUS-GS TBB” in general.

Discussion
20. Line 217: “not limited to IPF” or “not limited to UIP pattern”?

Reply 20: We have corrected “not limited to IPF” to “not limited to UIP pattern in patients with IPF”.

Page 11, lines 234-235 “Our study indicated that the presence of ILD not limited to UIP pattern in patients with IPF had a significant influence on the lower diagnostic yield based on EBUS-GS TBB”.

21. Line 256: “the rate of pneumothorax was 4.3%”

Reply 21: We appreciate your insightful comments. We have corrected it.
Page 13, lines 275-276 “In our patients with ILD, the rate of pneumothorax was 4.3%, which was significantly higher than that in patients without ILD.”

22. Figure 2. The nodule seems to be visible on his chest X-ray (image c)

Reply 22: Thank you for your advice. We have corrected the expression as follows:
Page 20, lines 409-412 “b) The nodule was invisible on the posterior-anterior position of his chest X-ray. c) The nodule was visible at a 45° angle on the right side. Additionally, on fluoroscopy, the probe position was consistent with the lesion”.

Reviewer B

1. Before comparing ILD group with normal lungs group, the authors did not used propensity score matching, there is a bias in conclusion.

Reply 1: Thank you for your insightful comments. We have added the issue as a bias in the discussion section.
Page 13, lines 281-284 “Finally, before comparing the diagnostic outcomes and complications between ILD and without ILD patients, there was a bias in baseline characteristics between the two groups. A larger sample and a prospective randomized design will be needed to overcome these limitations”.

2. ILA was first presented in results without interpretation of definition. Furthermore, the concept between ILA and ILD was not the same. That means not all patients with ILA can be diagnosed as ILD. The authors should examine it.

Reply 2: Thank you for your advice. We have changed the expression of “ILA” to “ILD”

correctly.

3. For the fluoroscopically invisible lesions, how did the authors judge the position between the probe and lesions? Furthermore, it is hard to discriminate GGN with ILD in biopsy procedure. GGN may be excluded in this study.

Reply 3: Thank you for your precious comments. We judged the position between the probe and lesions according to the previous reports. Concretely, if an EBUS image could not be visualized, as in the case of a solid lesion, the probe was manipulated under X-ray fluoroscopic guidance until a whitish acoustic shadow (e.g., a blizzard sign or mixed blizzard sign) could be visualized.
Page 7, lines 132-134 "Furthermore, if an EBUS image could not be visualized, as in the case of a solid lesion, the probe was manipulated under X-ray fluoroscopic guidance until a whitish acoustic shadow (e.g., a blizzard sign or mixed blizzard sign) could be visualized (21-23)."

Reviewer C

1. There is insufficient background evidence for the purpose of the study. Is there any evidence that biopsies are difficult for ILD patients (except IPF)?

Reply 1: Thank you for insightful comments. A previous report showed that reticular shadows around the PPLs in patients with ILD would make their detection challenging, resulting in a lower diagnostic yield without radial endobronchial ultrasonography. However, the diagnostic yield of EBUS-GS TBB for PPLs in patients with ILD was reported to be lower, about 60%, compared with the diagnostic yield of about 70% as described on the previous meta-analysis report, which might be related to the small sample size. Therefore, we have clarified the background evidence for the purpose of our study by adding the previous reports.
Page 6, lines 94-97 "Additionally, a previous study reported that the diagnostic yield of EBUS-GS TBB for PPLs in patients with ILD was reported to be lower, about 60%, as compared with the diagnostic yield of about 70% as described on the previous meta-analysis report, which might be related to the small sample size (15,18)."

2. The distinction between ILD (title, manuscript), ILA (figure 1), and IPF (table) is not clear. It is not clear whether what you are describing is ILD or IPF. The difficulty of the radial EBUS approach depends on the pattern of ILD. An explanation of the patterns of ILDs included in this study is needed.

Reply 2: We are sorry for the confusion. We have deleted ILA. In our study, we classified the patterns of ILD on high-resolution computed tomography according to the official ATS/ERS/JRS/ALAT Clinical Practice Guidelines for diagnosis of IPF.
Page 8, lines 146-150 "Based on the background lung, patients were classified into having ILD (ILD group) and not having ILD (without ILD). ILD was identified based on radiological findings according to the official ATS/ERS/JRS/ALAT Clinical Practice Guidelines for diagnosis of IPF and classified into the two groups of UIP and non-UIP patterns (probable UIP, indeterminate for UIP, and alternative diagnosis) (26)."

Reviewer D

1. Abstract-page 2 line 22-24: please check the syntax

Reply 1: We have revised the sentence clearly.
Page 3, lines 39-41 "However, the diagnostic yield and complications of radial endobronchial ultrasonography transbronchial biopsy for peripheral pulmonary lesions remains elusive in patients with interstitial lung disease."

2. Keywords (page 3 line 47): please consider adding "transbronchial lung biopsy", in order to differentiate from EBUS for mediastinum nodal biopsy?

Reply 2: We agree with your idea. We have added the term of "transbronchial lung biopsy" as a keyword.
Page 4, lines 63-64 "bronchoscopy, endobronchial ultrasound (EBUS), interstitial lung disease (ILD), lung cancer, transbronchial lung biopsy"

3. Introduction- page 4 from line 56 to line 69. This paragraph could be written as:
"Accurate pathological diagnosis is crucial to determine treatment plan in patients with ILD. In particular, surgery could exacerbate IPF, while radiation or chemotherapy are also risk

factors for the development of pulmonary fibrosis (5-6). PPLs biopsy, including peripheral lung cancer, can be performed using guided bronchoscopy, US or CT-guided trasthoracic needle biopsy (TTNB) or surgical lung biopsy (SLB) (7-8). According to previous reports on the diagnostic yield and complications, guided bronchoscopy can be an initial option for diagnosing PPLs (7-8). For the diagnosis of PPLs via guided bronchoscopy, endobronchial ultrasonography with a guide sheath transbronchial biopsy (EBUS-GS TBB) has improved the diagnostic yield for PPLs, including small PPLs (7-12).”

Reply 3: As pointed out by the reviewer’s comments, we have corrected the sentence as follows.

Page 5, lines 72-84 “All peripheral pulmonary lesions (PPLs) encountered in patients with ILD were not always malignant lesions (5). Therefore, these lesions required pathological diagnosis to establish if the lesions were malignant or not. Furthermore, in determining the treatment policy in patients with lung cancer with co-existing idiopathic pulmonary fibrosis (IPF), anti-cancer therapies including radiotherapy, chemotherapy and surgical therapy have the possibility of causing acute exacerbation of ILD and/or fatal complications (6-7). Therefore, accurate diagnosis is crucial to present the treatment plan to patients with ILD. PPLs, including peripheral lung cancer, can be diagnosed based on bronchoscopy, transthoracic needle biopsy (TTNB) and surgical lung biopsy (SLB). According to previous reports on the diagnostic yield and complications, bronchoscopy can be an initial option for diagnosing PPLs (7-8). For the diagnosis of PPLs via bronchoscopy, radial endobronchial ultrasonography with a guide sheath transbronchial biopsy (EBUS-GS TBB) has improved the diagnostic yield of PPLs, including small PPLs (8-13).”

4.Introduction (from page 4 line 73 to page 5 line 75): please correct “the lesion size and its segment. Few reports have assessed the diagnostic yield of EBUS-GS TBB in pathological background lung. In particular, the presence of...”

Reply 4: As pointed out by the reviewer’s comments, we have corrected the sentences as follows.

Page 5-6, lines 85-92 “Several studies have reported that the factors affecting the diagnostic yield of EBUS-GS TBB were the probe position relative to the lesion, the bronchus sign (represents a bronchus directly leading to the lesion) on computed tomography (CT), the lesion size, and its segment (14, 15). Few reports have assessed the diagnostic yield of

EBUS-GS TBB in lungs with a background pathology. In particular, regarding the presence of pulmonary emphysema influencing the diagnostic yield of EBUS-GS TBB, although the diagnostic yield varied depending on the severity of emphysema, the presence of emphysema itself has not been reported to reduce the yield."

5. Page 5 line 78: "...considerably affected the EBUS-GS TBB results" (15,16). Furthermore, there has been limited [...]of patients with ILD, not limited to IPF, with the diagnostic yield and complications of EBUS-GS TBB for PPLs.

Reply 5: As pointed out by the reviewer's comments, we have corrected the sentences.
Page 6, lines 92-98 "Furthermore, the presence of usual interstitial pneumonia (UIP) pattern on CT in patients with IPF considerably affected the EBUS-GS TBB results (16,17). Additionally, a previous study reported that the diagnostic yield of EBUS-GS TBB for PPLs in patients with ILD was reported to be lower, about 60%, as compared with the diagnostic yield of about 70% as described on the previous meta-analysis report, which might be related to the small sample size (15,18). Thus, there has been limited data assessing the association of patients with ILD regarding the diagnostic yield and complications of EBUS-GS TBB."

6. Page 5 line 83 and 86: please cancel "as the background lung". Please also cancel from line 83 "because of" to line 85 "EBUS image.". This sentence should be included in the Discussion section.

Reply 6: As pointed out by the reviewer's comments, we have corrected the sentences as follows.
Page 6, lines 103-104 "We hypothesised that the diagnostic yield of EBUS-GS TBB for PPLs in patients with ILD might be lower than that in patients without ILD."
Page 12, lines 262-265 "We considered that the diagnostic yield of EBUS-GS TBB in patients with ILD was lower than in those without ILD, because of the difficulty in correctly reaching the lesions around reticular shadows and distinguishing lesions as background lung on EBUS image".

7. Page 5 between line 81 and 82: In this section the Authors could include studies on US artifacts affecting images.

Reply 7: We have added the issue of studies on US artifacts affecting images according to the previous reports.

Page 6, lines 98-102 “In patients with IPF, honeycomb structures have been reported to show a patchy combination of hyper- and hypoechoic patterns on radial endobronchial ultrasonography in autopsied lungs. Therefore, these changes might prevent the recognition of lesions by radial endobronchial ultrasonography (19)”.

8. Methods-page 5 line 94: “lung area and were not visible on bronchoscopy. Patients with endobronchial lesions and with sole pulmonary emphysema were excluded.”

The Authors stated that pulmonary emphysema does not affect the EBUS-TBB diagnostic yield. Why these patients are excluded from the study? Please explain

Reply 8: Thank you for precious advice. Although the diagnostic yield varied depending on the severity of emphysema, the presence of emphysema itself has not been reported to reduce the yield. However, we considered that including patients with emphysema into patients without ILD (normal lung) might modify the diagnostic yield of EBUS-GS TBB. Therefore, for our study, we excluded patients with only pulmonary emphysema without ILD. To clarify this issue, we have added the following sentences.

Pages 5-6, lines 89-92 “In particular, regarding the presence of pulmonary emphysema influencing the diagnostic yield of EBUS-GS TBB, although the diagnostic yield varied depending on the severity of emphysema, the presence of emphysema itself has not been reported to reduce the yield.”

9. Bronchoscopy procedure-page 6 from line 112 to line 114: the Authors should either publish the data about VBN or exclude this method from the analysis and the paper. In particular, the use of this technique can modify the diagnostic yield of the biopsy. It is not enough to express the use of this method with “the majority of cases” (line 114)

Reply 9: Thank you for precious advice. We have added the information about VBN in the section of Methods.

Page 7, lines 134-137 “The virtual bronchoscopic navigation (VBN) was created on the workstation (Ziostation2, Ziosoft Ltd, Tokyo, Japan, or SYNAPSE VINCENT version 4.0, Fuji Medical Systems, Tokyo, Japan) by an experienced chest radiologist (S.I.) in 81.3% of total cases.”

10. Results-Patients' characteristics section-page 8 line 153 and 154: please explain the acronym ILAs at least once (i.e. line 153)-the acronym was not used before in the text

Reply 10: We are sorry for the confusion. We have corrected ILAs to ILD.
Page 9, lines 174-177 "A total of 431 lesions in 431 patients were included in the analyses after excluding 87 endobronchial lesions, 27 lesions that had an uncertain final diagnosis, and 146 lesions presenting solely with pulmonary emphysema without ILD. Finally, we identified 69 lesions associated with ILD and 362 lesions in normal lungs (Figure 1).

11. Results-Patients' characteristics section-page 8 from line 155-157: please briefly explain the differences also in the text (not only in Table 1)

Reply 11: Thank you for your precious advice. As pointed out by the reviewer's comments, we have briefly added the differences between the two groups.
Page 9, lines 178-180 "In addition to lesion lobe, there were significant differences in proportion of males, outer lesions, and solid nodules between patients with ILD and those without ILD."

12. Results-page 8 from line 160 to line 161: please rewrite this sentence, for example "The EBUS-GS TBB in patients with ILD has a significantly lower diagnostic yield than in patients with normal lungs"

Reply 12: As pointed out by the reviewer's comments, we have corrected the sentence.
Page 9, lines 184-185 "The EBUS-GS TBB in patients with ILD had a significantly lower diagnostic yield than in patients without ILD".

13. Results: page 8 from line 169 to 171: This section could be included in the Patients' characteristics one.

Reply 13: As pointed out by the reviewer's comments, we have moved these sentences to 'Patient characteristics' subsection.

Page 9, lines 180-181 “Furthermore, the histological findings between the two groups are shown in Table 2. The most frequent histological finding was adenocarcinoma in both groups”.

14. Results-page 8 from line 173: Please consider “Multivariate logistic analysis” as a title.

Reply 14: Thank you for your advice. We have changed the sub section heading of “Multivariate logistic analysis of factors associated with the successful diagnosis based on EBUS-GS TBB” to “Factors possibly affecting the successful diagnosis based on EBUS-GS TBB”.
Page 10, line 193 “Factors possibility affecting the successful diagnosis based on EBUS-GS TBB”.

15. Results-page 9 from line 181 to 183: This title could be omitted

Reply 15: Thank you for your precious advice. We have omitted the title of “***The diagnostic yield between UIP pattern and non-UIP patterns and multivariate logistic analysis of factors associated with the successful diagnosis based on EBUS-GS TBB in patients with ILD”.***

Page 10, line 200-201 “The diagnostic yield according to the pattern of ILD and factors associated with the diagnostic yield of EBUS-GS TBB in patients with ILD”.

16. Results-page 9 from line 191 to 192: please consider rewriting the sentence, i.e. “the complications rate in patients with ILD was significantly higher (8.7% vs 1.1%, P=0.002).

Reply 16: Thank you for your precious advice. We have rewritten the sentence.
Page 10, line 208-209 “The complications rate in patients with ILD were significantly higher than in those without ILD (8.7% vs 1.1%, $P = 0.002$).

17. Results-page 9 from line194 to 196: please insert the sentence from “There was” to “normal lungs” before the word “Pneumothorax” at line 192

Reply 17: As pointed out by the reviewer’s comments, we have rewritten the sentence as follows.
Page 10, line 209-213 “There was a significant difference in the prevalence of pneumothorax among the patients with ILD and those with normal lungs (4.3% vs 0.6%, $P = 0.031$) (Table 7). Pneumothorax occurred in three patients with ILD (4.3%). Of these, two required thoracic drainage. Conversely, two patients with normal lungs did not require thoracic drainage (0.6%)”.

18. Discussion-page 11 line 223-224: please rewrite the sentence as “In patients with ILD there might be technical...” The sentence from line 227 to 229 (from “In addition” to “diagnostic yield” should be cancelled.

Reply 18: We rewritten the sentence and deleted the other as you have suggested.
Page 12, lines 240-243 “In patients with ILD, there might be technical problems related to the difficulty of detecting the lesions because reticular shadows around PPLs preclude their detection and make it difficult to perform biopsies from the lesions appropriately during EBUS-GS TBB”.

19. Discussion-page 11 line 230: please consider rewriting the sentence as “Moreover, in patients with ILD...”

Reply 19: Thank you for your advice. We have corrected the sentence.
Page 12, lines 244-246 “Moreover, in patients with ILD, the insertion of the device to target bronchus was reported to be difficult because of bronchial narrowing and torsion associated with traction bronchiectasis as anatomical changes (17)”.

20. Discussion-page 11 from line 241 to 243: please rewrite the sentence as “A previous report[...] increased in the PPL lung compared to the other one”. The sentence from line 246 (“We consider...” to page 12 line 248 should be cancelled.

Reply 20: Thank you for the advice. We have rewritten the sentence and deleted the other as

you have suggested.

Page 12, lines 255-260 “A previous report demonstrated that in patients with ILD, inflammatory cell infiltration and fibrotic changes increased in the PPL lung compared to the other one (29)”.

Page 12, lines 294-298 “Furthermore, in patients with ILD, the diagnostic yield of EBUS-GS TBB within or near fibrotic lesions was reported to be lower than that of PPLs distant from fibrotic lesions because small biopsy forceps may be associated with sampling only inflammatory cells or fibrotic changes around lung cancer co-existing with ILD (30)”.

21. Conclusions section: please rewrite the sentences in this section more clearly.

Reply 21: Thank you for the precious advice. We have rewritten the sentences in the conclusion section clearly.

Page 13-14, lines 287-291 “In conclusion, the presence of ILD significantly affected the diagnostic yield of EBUS-GS TBB for PPLs. Moreover, in patients with ILD, the probe position relative to the lesion was a significant predictor of the diagnostic yield of EBUS-GS TBB. Regarding complications, the rate of pneumothorax during EBUS-GS TBB in patients with ILD was significantly higher than in those without ILD.”