Peer Review File

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Reviewer A

I have only few comments:

1) In the method part: maybe this sentence " In Malaysia, the estimated incidence rate of tuberculosis is 138 97 per 100,000 population, with a mortality rate of 6 per 100,000 population" could be reported in the introduction or the discussion part

- *Reply*: We have expanded on this in the Discussion section. Globally, tuberculosis has affected 10.6 million people, with 45% of cases originating in the South-East Asia region, as reported by the World Health Organization (WHO). Following this discussion, we have examined the implications of lung nodule biopsy in our high-tuberculosis-incidence region.
- *Changes in the text*: page 16, line 24 to page 17, line 3.

2) In the method part: precise if a ROSE was used?

- *Reply*: In our institution, rapid on-site examination services were unavailable, and we have included this information in the Methods section.
- *Changes in the text*: page 9, line 10-11.

3) In the result part: the length of the procedure should be more precise (length of the plannification + bronchoscopy procedure or bronchoscopy procedure only?)

- *Reply*: Thank you for your important question. In this study, we specifically report the total procedural time, which encompasses the period from the commencement of anesthetic sedation to the completion of the procedure. Unfortunately, we do not possess procedural data for the detailed steps such as planning and navigation, and we acknowledge this as a limitation of our study. Nevertheless, we fully concur with the reviewer's suggestion that the duration of manual airway mapping planning could be of interest. Based on the literature, this planning time typically ranges from 2 to 5 minutes. To support this information, we have included two additional references: Miyake *et al*. reported a planning time of 4.85 minutes, while Zhong *et al*. reported 1.32 minutes.
    - Miyake K, Morimura O, Inoue T, *et al*. The direct oblique method: a new gold standard for bronchoscopic navigation that is superior to automatic methods. J Bronchology Interv Pulmonol. 2018; 25(4):305-314.
    - Zhang L, Tong R, Wang J, Li M, He S, Cheng S, Wang G. Improvements to bronchoscopic brushing with a manual mapping method: A three-year experience of 1143 cases. *Thorac Cancer* 2016; 7(1):72-9.
- *Changes in the text*: We have provided clarification regarding this in the Results section on page 11, lines 12-13. Additionally, we have included a discussion of this limitation on page 19, lines 1-5.

4) In the discussion part: the long length of the procedure should be discussed... and also the use of fluoroscopy

- *Reply*: We acknowledge that our reported procedural time is longer compared to what has been reported in the literature. As mentioned earlier, our study reports the median total procedural time over a six-year period. To provide a more representative picture, we have included the procedural time for each batch, which has shown a significant reduction in time (p=0.015). This improvement is likely attributed to the enhancement and maturation of our technique over the years. We have incorporated this information into both the Results and Discussion sections.
- *Changes in the text*: We've included the procedural time data in the Results section on page 13, lines 10-12, and further discussed it in the Discussion section on page 19, lines 1-5.
- *Reply*: Thank you for your comment regarding fluoroscopy. We have expanded upon the role of fluoroscopy in the rEBUS procedure, incorporating your feedback and discussing findings from recent meta-analyses and randomized studies. Notably, a recent meta-analysis found no significant association between fluoroscopy usage and overall diagnostic yield, aligning with our study results. Additionally, Zheng *et al*. demonstrated the non-inferiority of rEBUS without fluoroscopy when combined with VBN and guide sheath in target PPLs with a direct bronchus sign. We have included these studies in the discussion section and added two new references to support these points.
    - Sainz Zuñiga PV, Vakil E, Molina S, *et al*. Sensitivity of radial endobronchial ultrasound-guided bronchoscopy for lung cancer in patients with peripheral pulmonary lesions: an updated meta-analysis. *Chest* 2020;157(4):994-1011.
    - Zheng X, Zhong C, Xie F, *et al*. Virtual bronchoscopic navigation and endobronchial ultrasound with a guide sheath without fluoroscopy for diagnosing peripheral pulmonary lesions with a bronchus leading to or adjacent to the lesion: a randomized non-inferiority trial. Respirology. 2023; 28(4):389-398.
- *Changes in the text*: The fluoroscopy discussion have been added to page 13, line 5-12.

5) In the discussion part : in the sentence "Although VBN is commonly used in pre-procedural planning to create a virtual pathway to the target, the automation algorithm of VBN pathway creation can fail due to poor quality of pre-procedural CT scans, such as due to mucous impaction, as well as the innate inefficiency of automated algorithms in small airway identification in the extreme peripheral regions of the lung." but with your methods, there is also the same issue: if there is no good quality CT scan, your manual reconstruction will fail also?

- *Reply*: We apologize for any confusion in our previous statement. When utilizing VBN, the creation of a navigational map from the central airway to the target PPL is typically the goal. However, this is often hindered by the detection limit of VBN reconstruction in the peripheral airway, resulting in a blind distance between the end of virtual pathway and the target. In contrast, manual navigation relies on the human eye, which can detect more airway details than a CT scan, especially at the peripheral region of the lung. However, as the reviewer correctly pointed out, the quality of the CT scan is crucial for both methods.

- *Reply*: Interestingly, the Osaka group demonstrated that with the same high-quality CT scans, VBN was unable to generate a complete and accurate navigational pathway in nearly half the time, while a manual method successfully identified a complete airway in approximately 9 out of 10 cases. We have expanded on this discussion in our manuscript and included a new reference by Miyake *et al*.
    - Miyake K, Morimura O, Inoue T, *et al*. The direct oblique method: a new gold standard for bronchoscopic navigation that is superior to automatic eethods. J Bronchology Interv Pulmonol. 2018; 25(4):305-314.
- *Changes in the text*: The discussion was elaborated in page 16, line 6-15.

Reviewer B

The authors studied guided bronchoscopy using radial EBUS in conjunction with basic tools without other navigational or robotic tools. This is very interesting and very much needed as advanced bronchoscopy tools are not available in many centers around the globe. This study can add to the body of the literature that basic bronchoscopy tools can have comparable diagnostic yield to advanced bronchoscopy techniques.

- *Reply*: We appreciate your kind words and concur that non-automated rEBUS techniques remain relevant and valuable in today's practice.

Please address the following questions and comments for a better understanding and stronger report:
In line 237: 49 patients had incomplete follow up data for final diagnosis conclusion. Therefore, it is recommended to recalculate the sensitivity by counting those lost subjects. It will make a stronger study if you intend to keep all the subjects in the study. You may report sensitivity in two ways if you wish, one to be stricter and include all the lost cases for follow up and the other one more lenient as is reported currently.

- *Reply*: We appreciate your valuable suggestion and the effort you've invested in enhancing our paper, which we genuinely value. In response to the reviewer's advice, we have revised the methodology for assessing diagnostic accuracy using the AQuIRE registry. We have incorporated three sensitivity levels into our analysis:
    - *Lenient*: This level excludes 49 patients without follow-up data.
    - *Minimum*: It is based on the assumption that all 49 patients without follow-up data actually had the disease (malignancy or tuberculosis), i.e., they were considered false negatives.
    - *Maximum*: It is based on the assumption that all 49 patients without follow-up data actually did not have the disease (malignancy and tuberculosis), i.e., they were considered true negatives.

  We have presented the results for the minimum sensitivity level in the Results section and updated the supplementary material (Table 4 and 6) to reflect these changes. Additionally, we have included a new reference to the AQuIRE registry to provide readers with a better understanding of the statistical

methods and assumptions elaborated upon in the statistical section. These revisions aim to enhance the transparency and comprehensibility of our analysis.

  - Ost DE, Ernst A, Lei X, *et al*. Diagnostic yield and complications of Bronchoscopy for peripheral lung lesions. results of the AQuIRE registry. *Am J Respir Crit Care Med* 2016; 193(1):68-77.

- *Changes in the text*: We have elaborated the statistical analysis in page 10, line 8-21. The results section had been amended at page 12 line 15-23. Supplementary Table 4 and 6 have been edited.

In similar studies of diagnostic yield in peripheral lung lesions, the subjects with inconclusive results at index bronchoscopy are followed up to at least 12 months. Authors in this study used 6 months follow up which is not the common way of reporting

- *Reply*: We fully acknowledge this limitation. Regrettably, we were only able to collect six months of follow-up data for the purposes of this study. This limitation arises, in part, because our institution serves as a tertiary reference center, and after six months, many cases are referred back to their respective centers for subsequent follow-up. However, we recognize and have discussed this limitation in the manuscript. We also acknowledge that a 12-month follow-up period, as recommended by the AQuIRE registry, would have been more appropriate.
- *Changes in the text*: We have added this as limitation in discussion section at page 18, line 23-25.

In line 250: define type A bronchus sign

- *Reply*: We have clarified the methodology section by categorizing bronchus sign into three types: Type A, when the airway leads directly into the target; Type B, when the airway is located adjacent to the target; and Type C, for target lesions devoid of a leading airway. Additionally, we have included a new reference to support these categorizations.

  - Minezawa T, Okamura T, Yatsuya H, *et al*. Bronchus sign on thin-section computed tomography is a powerful predictive factor for successful transbronchial biopsy using endobronchial ultrasound with a guide sheath for small peripheral lung lesions: a retrospective observational study. *BMC Med Imaging* 2015; 15:21.

- *Changes in the text*: We have amended methods section, page 7, line 17-19.

In line 264: define target to pleural distance. Is it parietal pleura or both visceral and parietal, including the lung fissures? Airways start branching at the lung hilum and the lesions close to lung fissures or mediastinal pleura are counted as peripheral lesions. Please clarify if you measure the distance of the target to the mediastinal pleura and fissure as well.

- *Reply*: In the methodology section, we have provided clarification regarding the assessment of target lesion characteristics and measurements. Specifically, we recorded the target lesion size by assessing the largest diameter of the target PPLs on axial CT scan in lung window reconstruction. Additionally, we determined the target-to-pleural distance by measuring the distance from the center of the target to

the closest point on the parietal or visceral pleura in the direction of the biopsy. To support these methods, we have included a new reference.

- Matsumoto Y, Izumo T, Sasada S, *et al*. Diagnostic utility of endobronchial ultrasound with a guide sheath under the computed tomography workstation (ziostation) for small peripheral pulmonary lesions. *Clin Respir J* 2017;11(2):185-192.

- *Changes in the text*: We have amended methods section, page 8, line 1-4.