Peer Review File

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Reviewer A

First, I would like to extend my appreciation for the positive feedback and constructive remarks that you have shared, which have bolstered my confidence in the potential impact of this proposal.

Regarding the areas for improvement our response is as follows:

Comment 1: Language and Typographical Errors: Some typographical and grammatical errors (e.g., "Oki and colleges" might be "Oki and colleagues") are present, which may need correction to improve readability. Also, et al to “et al.” etc

Reply: Changes were made as requested.

Changes in text: Line 56 (Oki et al.). line 58 (Shiari et al.). Line 92 (Positron emission tomography) added. Line 201 (Vachani et al).

Comment 2: Citation Formatting: The inline citation style seems inconsistent. Some citations are numbered, while others are not. A consistent citation style following a particular format (e.g., APA, MLA) would improve professionalism.

Reply: Changes were made as requested. References were rechecked using APA format.

Changes in text: Refer to lines 268 - 326

Comment 3: Explanation of Significance: The discussion section could benefit from further elaboration on the clinical implications and significance of the findings. Why do these findings matter, and what impact might they have on current practice or future research?

Reply: Discussion section is updated.

Changes in text: Refer to discussion and conclusion section starting at line 156.

Comment 4: Additional limitations to be added:

Potential Operator Bias: With only two interventional pulmonary physicians performing all the procedures, there could be operator bias influencing the results. An analysis or acknowledgment of this potential bias and how it was accounted for (if at all) would strengthen the discussion.

Non-standardized Number of Samples: The mention of non-standardized numbers of TBNA + MFB samples across patients is an important limitation, but it's discussed briefly. Exploring how this variability might have affected the results and providing statistical insights (e.g., range, variance) on this variability would make this limitation more tangible.

Introduction of ROSE (Rapid Onsite Evaluation) Halfway Through the Study: While the paper alludes to the potential effects of ROSE, there is no detailed exploration of how this change midway through the study might have introduced variability in the results. A more thorough analysis of this change, perhaps including a stratified analysis comparing periods before and after the introduction of ROSE, could provide better insights into its impact.

Reply: Explanation added to the manuscript in discussion section.

Changes in text: Check line 200 till 223.

Reviewer B

Comment 1: Different sampling methods should be correlated to clinical diagnoses, if any difference or significance. -compare with similar study by Vuorisalo et al in Acta Cytologica 2022

Reply: A new table 5 is added that correlates final diagnosis with MFB vs TBNA. We also did split the results into benign vs malignant for comparison in addition to concentration on sarcoidosis.

Changes in text: Table 5 is changed.

Comment 2: -no pathologist is as a co-author despite diagnoses are part of the study

Reply: We regret that we cannot include a pathologist as a co-author at this stage as our analysis is completed, but we acknowledge the importance of their involvement in future studies. Our main reliance in this study was on the report mentioned in the patient’s chart since IRB approval is mainly to access only electronic charts.

Changes in text: None.

Reviewer C

Comment 1:

I am not sure how much additional information this study adds to the medical literature. A prior study by Chrissian et al in Annals of Thoracic Surgery 2011, compared miniforceps to TBNA and they showed a higher diagnostic yield when the two techniques were combined. Can the authors explain what their study adds compared to older literature?

Reply: The authors updated the discussion section of the study to answer this question.

Changes in text: See discussion section starting at line 156. See also conclusion starting at line 235.

Comment 2:

I am confused as to why the authors chose to record and present data on cryobiopsy of lymph nodes. By reading the title and the introduction, I was under the impression that this was focusing on TBNA versus miniforceps and TBNA + miniforceps. The presentation of results on cryobiopsy takes away from the focus of the paper and makes for a disjointed reading. If the authors wish to include cryobiopsy, then I would suggest taking an approach whereby the report on the diagnostic yield of different biopsy tools and not specifically for miniforceps.

Reply: to clarify, we only included EBUS procedures in which Miniforceps Biopsy (MFB) was employed alongside TBNA for lymph node evaluation. In some cases, a **transbronchial lung** cryobiopsy was performed concurrently due to the presence of a nodule or mass in conjunction with interstitial changes. In other cases, the rationale for cryobiopsy was the ambiguity of the diagnosis, as exemplified in scenarios where distinguishing between hypersensitivity pneumonitis (HP) and sarcoidosis was challenging on prior imaging. We thought that including the data about cryobiopsy data in these cases will be beneficial for clearer understanding of the data.

Changes in text: No changes in text were done regarding cryobiopsy. The updated discussion section concentrated on MFB vs TBNA only. Table 4 retained.

Comment 3:

A major limitation is selection bias, and this should be discussed by the authors. Difficult lymph nodes were likely selected to perform miniforceps, and eliminating bias retrospectively is not possible. Cost has to be a consideration when considering the author's approach. They use 3 tools – a 21G and 18G needle and a miniforceps. Is that really cost-effective?

Reply: In our revised manuscript, we included a statement regarding selection bias, acknowledging its potential impact on the study's results. We also added a paragraph to the discussion section that talks about cost considerations.

Changes in text: Refer to paragraphs 218 to 233.

Comment 4 (Table 5):

Table 5 is confusing. I am not sure why diagnoses that cannot be made by EBUS TBNA (UIP, COP, pneumonia, hypersensitivity pneumonitis) were included in this table. Only the diagnoses that were made specifically by EBUS should be listed.

Reply: We appreciate your feedback regarding Table 5. Part of the answer is in comment 2 reply. In our revised manuscript, we included a different table for the EBUS only diagnoses relating them to MFB and TBNA D vs ND numbers.

Changes in text: new table 5 is included. Old table is removed.

Comment 5:

The 2020 ATS guidelines for sarcoid cite a diagnostic yield of 87% with EBUS TBNA. How do you reconcile this with the comments about lower diagnostic yield in the introduction?

Reply: Thank you for pointing out the discrepancy in the introduction. In our revised manuscript, we updated the data to reflect a clearer understanding of the diagnosis yield in sarcoidosis.

Changes in text: Line 53 changed. See discussion starting at line 183.

Comment 6:

The references to older studies describing tools used before miniforceps are unnecessary and I would delete. The miniforceps has been on the market for over a decade. There are several studies that have been performed with miniforceps that could be highlighted (Chrissian, Radchenko, etc).

Reply: In our revised manuscript we highlighted some of the older studies regarding Miniforceps to understand the development over the decade. The historical aspect could be of interest to some readers, so no changes are done to this part.

Changes in text: lines 157 to 172

Comment 7:

List state and country for Philadelphia.

Reply: Change is done as requested.

Changes in text: Line 65 and 66.

Comment 8:

Why was ROSE not used in all cases? Was this due to technical factors like not having ROSE available? Please be more specific.

Reply: In the methods and discussion sections, we provided detailed information regarding why ROSE was not used in all cases.

Changes in text: Refer to lines 82 to 85, also 207 to 219.

Comment 9:

What was the rationale for alternating 21G and 19G needles?

Reply: Our study is retrospective in nature and the authors did not choose what instruments to be used in each case. In general, this is what is available at our bronchoscopy suite. We are not the only center that uses alternating needles. For example, refer to study done by Herth in 2008.

Herth FJF, Morgan RK, Eberhardt R, Ernst A. Endobronchial ultrasound-guided miniforceps biopsy in the biopsy of subcarinal masses in patients with low likelihood of non-small cell lung can-cer. Ann Thoracic Surgery. 2008 2008/06;85(6):1874-1878.

In this 2008 prospective study sequential 22/19 gauge needles were used then 1.15 mm MFB in 75 patients. A specific diagnosis was made in 36% of patients with the 22-gauge needle, 49% with the 19-gauge needle, and in 88% with the miniforceps. The increase in diagnostic yield with miniforceps was most significant in patients with sarcoidosis (88% vs 36% for TBNA, $p = 0.001$) or lymphoma (81% vs 35%, $p = 0.038$).

Changes in text: None.

Comment 10:

What was the discretionary criteria used by the bronchoscopist to perform a mini forceps biopsy, and was this determined beforehand or during the procedure?

Reply: Your question about discretionary criteria is important. In general, bronchoscopists decided **during** the procedure whether MFB is to be implemented in addition to TBNA. If a malignant condition is suspected, then MFB is done to acquire more tissue for molecular analysis and in suspected benign disease to obtain higher diagnostic yield especially in sarcoidosis where nearly all the patients received MFB.

Changes in text: Refer to lines 75 and 76.

Comment 11:

Please provide a definition of "unequivocal diagnosis."

Reply: It means that the diagnosis was definitive without the need for further procedures.

Changes in text: lines 97 and 98.

Comment 12:

Was the diagnosis calculated per lymph node?

Reply: Diagnosis is calculated on a case basis.

Changes in text: Clarification added lines 100 to 103.

Comment 13:

I do not understand dependent samples equating to using a McNemar test. Do you mean paired data?

Reply: We revised the wording to clarify that paired data were analyzed using the McNemar test to enhance the clarity of the manuscript.

Changes in text: Lines 108 and 109.

Comment 14:

You do not need to give percentages of both men and women – one will suffice;

Reply: Wording changed.

Changes in text: lines 113 to 114.

Comment 15:

Which paratracheal node? Which hilar stations?

Reply: Our study is not the first study to use this designation for lymph node stations. For example, the aforementioned 2011 Chrissian et al. study used similar classification. Paratracheal stations (2 and 4) subcarinal is station (7) and hilar are (10, 11,12).

Changes in text: none.

Comment 16:

You do not need to state what test you used to show the difference.

Reply: We appreciate your feedback. We will remove the mention of the test used to show the difference from line 146 in the revised manuscript.

Changes in text: Statistical test name is removed from line 146.

Comment 17:

Too much data given the discussion section – the data presentation should stay in the result section, and then the discussion section should present what you found, its relevance, how it compares to prior studies, and limitations of the study.

Reply: Discussion section revised per request.

Changes in text: Refer to discussion section starting at line 156.

Comment 18:

The Vachani study looked at diagnostic yield for peripheral nodules, not lymph node biopsies. I would delete this reference.

Reply: Although the Vachani study focused on peripheral nodules rather than lymph node biopsies, we believe it retains relevance to our study's methodology, primarily from a mathematical perspective with potential clinical implications.

Changes in text: None.

Comment 19 (Table 1.3):

I am not sure about the relevance of Table 1.3 for the manuscript: It is somewhat interesting but does not add much.

Reply: Table 1.3 is removed.

Changes in text: Table 1.3 is removed. Text discussing the findings in it retained with removal of line 122.