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Peer review file

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Reviewer A

GENERAL COMMENTS:

The authors collected data from 250 patients with ILD who underwent transbronchial cryobiopsies to describe their complications and diagnostic yield and their prognostic factors. They concluded that using TBCB in the diagnostic setup for ILDs is safe with a limited risk of acute exacerbations and mortality. This report includes useful information to the readers of the Journal but has several concerns.

MAJOR COMMENTS:

1. Inconsistencies in histological and clinical diagnoses

The authors state cryobiopsy sampling contributed to a diagnosis in 180 (72%) of the 250 patients and that a consensus diagnosis was made in 204 (82%) patients after the multidisciplinary team discussion. According to the data presented in Table 2, however, the total number of histological diagnosis is 251 and that of clinical diagnosis, 254. Besides, the data in table 2 is much confusion because they failed to state the definition of "Clinical diagnosis."

The authors should clearly show the exact number of each histological diagnosis and how many patients of the diagnosis were finally classified into any clinical entities after MDD.

2. Presentation of what increases the diagnostic yield of ILD

The authors state that the gender, the total sum of biopsy sizes, the number of biopsies, and the presence of more than 50% alveolar tissue in biopsies increased the diagnostic yield. Although they found no combinations of factors to perform better than the individual elements alone, the results could be the most critical information in the paper, in my opinion.

To make the results more impressive, the authors might revise the rationale of the study; for example, "Although the recent COLDICE study comparing TBCB with SLB found excellent consistency concerning both histological and clinical diagnosis, what increases the diagnostic yield is still unclear." Besides, it would be better for them to emphasize the results with a revised discussion.

3. Redundancy in the discussion

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The authors repeat the results in the discussion, which makes the statement redundant. They should revise to make it much more concise.
MINOR COMMENTS:

4. FEV1 and DLCO should be FEV<sub>1<sub> and DL<sub>CO<sub> throughout the manuscript.
5. Page 9, line 194 and Table 5, FEV1%, FVC%, and DLCO% should be %FEV<sub>1<sub>, %FVC, and %DL<sub>CO<sub>.

Reviewer B

GENERAL COMMENTS
In a retrospective analysis of data prospectively collected from an uncontrolled consecutive case series, the authors add to the growing literature on the value of transbronchial cryobiopsy (TBCB) in evaluating patients with diffuse lung disease of unknown cause. There are some methodological issues and minor technical issues that might benefit from clarification and attention.

MAJOR COMMENTS
1. Methods (page 5, lines 101-103) – Were HRCT scans and biopsies classified based on previous interpretations as recorded in radiology and pathology reports or were they re- reviewed blinded to established clinical/final diagnosis following multidisciplinary team discussion (MDT)?
2. Methods (page 5, line 103) – This is an odd definition of "representative" given that it could mean that alveolated lung parenchyma comprised 50% of a very small or a very large biopsy. More traditionally the "adequacy" of TBCB is perhaps more reproducibly recorded as biopsy size +/- presence of alveolated parenchyma. Wonder if the authors might consider dispensing with this "representative" definition and instead including the data prospectively collected on biopsy size as maximum dimension and the number of biopsy pieces? Those might be more easily extrapolated to clinical practice elsewhere.
3. Methods (page 5, line 108) – How was the "contribution to a confident diagnosis of ILD" determined for TBCB specimens and how were patients selected for TBCB? Understanding the contributions of TBCB requires understanding of selection biases and comparison of clinical diagnoses made prior to knowing biopsy results with the "final" diagnosis following what is presumed to have been post-biopsy

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multidisciplinary team MDT. In methods MDT referenced only with regard to biopsy site selection – was an MDT diagnosis recorded then prior to biopsy? Armed with HRCT many diagnoses can be established with a high degree of confidence in the absence of any sort of biopsy, and is important to understand, 1) how patients were selected, 2) whether clinical diagnoses with confidence levels were recorded prior to biopsy, and 3) how the "final" diagnosis was established.

4. Results (page 7, line 142) – The size data for biopsies is useful but would be more useful if comparisons were made between those biopsies for which a specific diagnosis was made and those for which the outcome was "No specific pattern or non-contributing" (as summarized in Table 2). This gets to the very important issue that size and number of pieces is only one dimension of assessing adequacy of biopsy. Site selection plays a major role. Given that sites were selected prospectively in these patients it is important to understand what factors might account for those patients in whom a diagnosis was possible and those in whom it was not.

5. Results (page 7, Table 2) - Table 2 indicates that confidence levels (high versus low) were collected for pathological and clinical diagnoses of usual interstitial pneumonia (UIP) – at what point in this process were confidence levels recorded and for which conditions (only UIP)? And is the "Clinical diagnosis" the final diagnosis following MDD or the diagnosis prior to biopsy? This should be clarified if we are to understand the relationship between the two.

6. Results (page 10, line 228) – See previous comment #3. It is not possible to know what TBCB contributed before understanding what diagnoses were presumed based on pre-biopsy MDT.

7. Results (page 10, lines 230-233) – The results of re-biopsy in 24 patients (8 repeated TBCB; 16 SLB) accounting for just over half of those with unclassifiable ILD are interesting in that that 5 who continued to be unclassifiable after rebiopsy were disproportionately represented by those for whom TBCB was chosen (3 of 8 for TBCB compared to 2 of 16 for SLB).

8. Results (page 11, line 250, Table 5) – Was multiple biopy sites included in the model?

9. Results (Table 5) – See previous comments #3 and #6 regarding column labeled "TBCB contributed to diagnosis". Contributed how? Does this simply reflect whether a specific histopathological diagnosis was made?

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MINOR COMMENTS

1. Introduction (page 3, line 54) - Please provide reference for statement that TBCB has been shown to have a higher diagnostic yield than forceps biopsy.
2. Results (Table 2) – The header for the second column is labeled “No (%)” but no percentages are provided.
3. Results (page 8, line 169) – Table 5 is cited before Table 4.