

Peer Review File

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Reviewer A

Thank you for the opportunity to review this paper. The authors describe the results of cryobiopsy for ILD with emphasis on post-procedure exacerbations. The manuscript is interesting and describe an important issue. There several issues to address.

1. Abstract – you note in the abstract's results on the lower incidence of AE-ILD compared with surgical lung biopsy, while you did not include surgical lung biopsy and only base your assumptions on reported rates from prior research. Other research could have a different study population (maybe more severe ILD, given the almost normal FVC in your cohort) and obviously you could not imply from that comparison. Instead, add details on other outcomes as appear in you results section.

Reply 1: Changes made to abstract

Changes in text: Lines 60-62

2. Introduction – I would add on the well-balanced safety and diagnostic yield of cryobiopsy in ILD to highlight the reason for the rise in this technique. A recent multicenter study examined its yield in ILD and found it to have almost comparable safety with forceps TBB and with higher efficacy for almost all diagnoses (Freund at el. Respiration, PMID 37634496). I suggest using this study and others for this point and also for comparison of your complications rate with those from others.

Reply 2: Reference added

Changes in text: Reference 1

3. Methods –

a. Why did you chose 307 for the evaluation of AE-ILD? Is it a typo that should be 30 days? If not – I do not understand how an AE-ILD more than 6 months after the exam can be classified as post-procedural.

Reply 3: Thank you for bringing it to our attention. Typo has been fixed

Changes in text: Line 98

b. The methods are missing a statistical analysis section and a section on the procedure itself – how was it performed? Airway method? And so on.

Reply 3b: Done. Statistical analysis and procedural details have been added.

Changes to text: Lines 145-150

4. Results –

a. Did you find any association with continued anticoagulation or antiplatelet and procedural bleeding? Did you find any association between pneumothorax and lower PFTs?

Reply 4: Plavix was held in all patients and we did not do subgroup analysis based on PFT and anticoagulation due to small numbers.

Changes to text: Lines 70-72

b. Average should be reported with standard deviation. Medians should be reported with IQR (25th percentile-75th percentile). You should decide which to choose based on the normal/non-normal distribution of each variable (the results of the 4 patients with AE-ILD should be presented with medians).

Reply 4b: Changes made to results section

Changes to text: Line 79

c. The authors write – "Patients with AE-ILD had a higher...." – however, these are only 4 patients and you cannot really compare between the groups. If you do want to compare, you must use a relevant statistical study to show it is significant and not by chance. This should also be revised in the abstract.

Reply 4c: Statistical analysis done and reported.

Changes to text: Lines 207-220

d. Please reports on missing data. Did all patients have BAL results?

Reply 4d: Yes, all patients received BAL. Discussed in procedure section.

Changes to text: Line 137

Reviewer B

The authors reported on acute exacerbations of interstitial lung disease that occurred as a complication of transbronchial lung cryobiopsy in interstitial lung disease.

I believe that the discussion of complications in TBLC is important. However, I think there were several serious problems with this paper.

1. Many papers have already been published on cryo-biopsy; many reports of acute exacerbations of interstitial lung disease after TBLC have also been published and included in the ATS/ERS/JRS/ALAT guidelines. This retrospective observational study has a small sample size compared to previous reports. There is very limited information that can be obtained from this study.

Reply 1: We agree with small sampled size and acknowledge previous publications. Mentioned in limitations. We believe our multicenter, real world reporting and focus on exacerbation makes our study unique.

Changes to text: Lines 279-282

2. This article compares 4 patients who had an acute exacerbation of ILD after TBLC with 107 other patients without acute exacerbation of ILD. Despite this, the study did not perform the statistical analysis needed. I think this is very problematic. But, only 4 cases of acute exacerbation of ILD were included. Therefore, some might consider that the statistical analysis is not appropriate. If so, I believe that this paper should be reported as a case report.

Reply 2: Statistical analysis performed and section added to results.

Changes to text: Lines 208-220

3. The manuscript does not describe anything about the technique of the cryobiopsy. (e.g., bronchoscope model used, cryoprobe used, TBLC freezing time, method of hemostasis)

From the current manuscript, we cannot determine whether the TBLC was properly performed, and we doubt the veracity of this report.

Reply 3: Section on procedure with details of procedure has been added.

Changes to text: Lines 129-144

4. The manuscript also does not describe the treatment for acute exacerbations of ILD, and we cannot determine the mortality rate for acute exacerbations of ILD, nor whether deaths occurred after appropriate treatment was administered.

Reply 4: Sorry but treatment is mentioned in discussion section including steroids and one pt receiving ECMO. I have also included a statement in results section to mention the same.

Changes to text: Lines 216-219

5. In this study, 50% of patients with acute exacerbations of ILD were noted to have honeycombing on HRCT. Based on the ATS/ERS/JRS/ALAT IPF diagnostic guidelines, TBLC should not be performed in these patients. The authors need to answer the question of whether they performed a non-necessary examination.

Reply 5: Agree. All patients were discussed at multidisciplinary meetings prior to biopsy been pursued and a statement has been added.

Changes to text: Lines 130-134

6. Many indicators, such as ATS/ERS criteria, appear to be used in this manuscript, but the necessary citations to them are not provided. In addition, many of the references cited in the current manuscript are very old. These citations need to be properly made.

Reply 6: Reference added

Changes to text: Reference 3 and 7

7. It is stated that half of the cryobiopsies in the current study could not be diagnosed. The very low Diagnostic yield compared to previous reports must be discussed.

Reply 7: Made changes, yield after discussion at MDD was 74%

Changes to text: Lines 201-203