Peer Review File

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Reviewer A

Comment 1: The title should report that the SLB is performed via VATS.
Reply 1: Thank you for your comment we have modified the title of our manuscript accordingly.
Changes in the text: See Page 1, line 1.

Comment 2: The authors should better detail the exclusion of the patients from the study and present a flow diagram of the selection process.
Reply 2: We have modified and added to our text accordingly to further clarify both the inclusion and exclusion process.
Changes in the text: See Page 7, lines 123-131 and Figure 1 on Page 28.

Comment 3: How did the authors determine that the sample size was adequate for their purpose?
Reply 3: Thank you for your comment. The study is a population-based retrospective study that included every patient in the entire nation from January 1, 2008 to December 3, 2020 that underwent a surgical lung biopsy for suspected ILD. It describes a single center experience. Power calculations were not made specifically, and all patients were included from this well-defined cohort of patients.
Changes in the text: None made

Comment 4: KM curves should report censored events.
Reply 4: We thank the reviewer for his comment. The Kaplan-Meier curves does take censored events into consideration (i.e., patients that had a follow-up of less than 5 years without mortality). Overall, 3 patients with NSIP, 3 patients with UIP, and 15 patients with other histological diagnosis than UIP and NSIP had a censored event during a 5-year survival analysis. Given this relatively high number, we did not specifically mark when censored events occurred on the graph itself. It is important to note that all of the censored events were due to patients not having a full 5-year follow-up as they entered the study within 5 years of the study end. In
other words, no patient was lost to follow-up.
Changes in the text: None made

Comment 5: In the discussion section, the authors should compare their results with other surgical techniques, like Awake or Non-intubated or Spontaneous ventilation SLB, and non-surgical procedure, criobiopsy.
Reply 5: We would like to thank for the comment. We are aware of these techniques and have mentioned them in our Discussion. It is an interesting approach for those highly selective patients that have been evaluated preoperatively with high safety

margins to tolerate awake non-intubated approach. We, however, do not believe that awake or non-intubated ventilation for SLB is common, or that it has much potential for other patient groups.
Changes in the text: These techniques are mentioned more thoroughly in the Discussion chapter but otherwise no major changes were made.

Reviewer B

Comment 1: You state the "median" ± standard deviation and range and mix it with mean, e.g. page 2 length of hospital stay, chest tube duration or in table 2 the DLCO is presented in mean and standard deviation but in table 6 DLCO is presented in median and standard deviation. See also your abstract line 32+33 (follow-up), line 176 operative time
Please go through the script and either present your data in median with range or mean with standard deviation.
Reply 1: We have decided to report both means and medians with range in tablets. In the text most commonly means are used to, as the values are normally distributed, but if not, as for length of stay, median is used.
Changes: Both means and medians are reported in tables.

Comment 2: You have excellent postoperative outcomes. However, on page 2 you display 30-days mortality and hospital mortality but in your abstract, it is 90-days mortality as it is in your "Results" and "Discussion" section. Your definition of 30-days mortality is incorrect (line 107 + 108). It is "death occurring within 30 days after surgery". Same applies to 90 days mortality. You should report 30- and 90-days mortality and be consistent throughout your manuscript.
Reply 2: Thank you for your comment we have modified our text as suggested, and 90 days mortality has been added to table 6.
Changes in the text: See page 8, lines 161-163. See page 12, lines 276-277. See page 16, line 398. See Table 6 on page 25.

Comment 3: Line 29 + 30: "A population-based retrospective study on 68 consecutive patients (mean age 58 yrs, 58.8% males) that underwent SLB in Iceland 2008-2020" needs a verb and "between".
Reply 3: We have modified our text as advised.
Changes in the text: See page 3, line 42.

Comment 4: Please write out the words CT, FVC, FEV1, VATS in your abstract, when using it for the first time. Same goes for HRCT and SLB in your main manuscript. Please check your text for this.
Reply 4: We have modified and checked our text as advised.
Changes in the text: See page 3, line 43, 49-52 and page 5, line 82 and 101.

Comment 5: Please arrange alphabetically your "Abbreviation" section and add

“TREND” and “COPD” to the list, as you are using them in your manuscript.
Reply 5: We have arranged our abbreviation section in alphabetical order and added TREND and COPD to the list as advised. TREND has also been spelled out in the text.
Changes in the text: See page 4 and page 6, line 109.

Comment 6: Line 60 – 62 pirfenidone/nintedanib are not mentioned in your cited reference 1 (Kayatta et al.). Please add correct reference or delete the passage or mark as your own thoughts.
Reply 6: Thank you for your comment we have revised the text as advised and added references accordingly.
Changes in the text: See page 5, line 80.

Comment 7: Line 67: “... in approximately 64%...”. Please add reference.
Reply 7: Thank you for your comment we have revised, modified and updated the text.
Changes in the text: See page 5, lines 86-89

Comment 8: Line 69 – 71: “... gold standard...” To my knowledge Raghu et al. revised their opinion on SLB and favor TBLC in their update on IPF (your reference No. 21). Jee et al. do not recommend SLB in CTD-ILD in their guidelines. Please rewrite that passage or delete.
Reply 8: We agree that the word gold standard is perhaps not the best phrasing and have changed the text accordingly. This study covers 13 years and cryobiopsy appeared only recently. Onto that our center is relatively small and we have chosen to use SLB as the main diagnostic method for ILD. We have also updated our discussion chapter with that statement.
Changes in the text: See page 5, lines 101-102 and page 13, lines 340-342.

Comment 9: Line 80 – 90: I do not understand your patient selection. Did you generate two lists: One from your Operation Registry and another one from your Pathology Registry, and then did a crosscheck/cross-referenced of both lists? How many patients did you retrieve with your search algorithm in total at the beginning of patient selection? You should present your patient selection clearer to the reader, maybe in a flow-chart/figure.
Reply 9: Thank you for your comment we have further clarified our patient selection and exclusion under the materials and methods section. We have also made a flow-chart to aid in that clarification. One list was generated from the operation registry which was then cross-referenced with operation referral and pathology registry. Patients that did no meet the criteria for “suspected ILD” were excluded from the study and not evaluated further.
Changes in the text: See Page 7, lines 123-131 and Figure 1 on Page 28

Comment 10: Line 88: I do not know the symbol “... authors (L.?, G.G., T.G.)”.
Reply 10: The authors letter “Þ” has been changed to its international spelling format of “Th” we have modified our text accordingly “(L.Th, G.G, T.G)”.

Changes in the text: see page 7, line 123

Comment 11: Line 101: Please describe your surgical technique more detailed: Uni-, bi-, triportal VATS? What stapler and magazines did you use? Did you use reinforced magazines?
Reply 11: This is a valuable comment. We have modified and described in more details our surgical technique in our text as advised under the section materials and methods.
Changes in the text: see page 8, lines 145-155.

Comment 12: Line 106: You define "excessive air leakage" more than 94 hours. Why? Most authors use either "air leakage longer than 5 or 7 days". The literature is inconsistent on that matter, but you should use either 5 or 7 days or explain 94 hours. Better use "prolonged air leakage" than "excessive air leakage".
Reply 12: Thanks for this comment. It is correct that the definition of prolonged air leakage differ between studies, such as following VATS lobectomies for NSCLC. We have previously used 96 hrs. as a definition, which also has been used in other studies. For comparison with these studies, we have decided to keep the same definition.
Changes in the text: We have added (4 days) following 96 hrs. in Materials and methods and updated Tables 6 and 7.

Comment 13: Line 111 – 115: I do not understand this passage. This needs to be rewritten.
Reply 13: Thanks for this comment. The passage has been modified and rewritten as advised.
Changes in the text: See page 8, lines 1168-180.

Comment 14: Line 118: "... and later reviewed by one senior..." – remove "a"
Reply 14: Thanks. We have modified our text accordingly as advised
Changes in the text: see page 9, line 185

Comment 15: Please add your used standardized sheets for radiological and pathological evaluation to your supplemental materials.
Reply 15: This is a good point raised by the reviewer. Our standardized sheets for radiological and pathological evaluation have been translated to English and added to our supplemental material. We have also modified our text under materials and methods accordingly.
Changes in the text: See page 8, line 170 and 187 and supplementary material.

Comment 16: Line 123: "... most common histology groups (IPF and NSIP)...". Later you use UIP and NSIP. Please correct.
Reply 16: Thanks. The text has been modified and changes made accordingly as advised.
Changes in the text: See page 9, line 191.
Comment 17: Line 165: You change the display of your data in this passage (n=51,

75%) and 45 (66,2%). Please be consistent within your manuscript.
Reply 17: Thanks. The text has been modified accordingly as advised.
Changes in the text: See page 11, lines 248-251.

Comment 18: Line 172: You use "NSIP (27,9%)" in your text but in table 4 NSIP is 29,4%. Please correct.
Reply 18: This is correct. The text has been modified accordingly as advised.
Changes in the text: See **page 11, line 259**

Comment 19: Line 179: 10 patients suffered minor postoperative complications. In your abstract you state seven suffered minor complications. In your discussion (line 238) it is two patients. Correct the numbers.
Reply 19: This is a good comment. We have reviewed and rechecked our patient data again and decided to remove arrythmias from tables 6 and 7 (formerly 5 and 6) as those were registered as atrial fibrillation and deemed not to be related to the surgery itself, bringing the number down to 8 patients. Only one patient suffered a major postoperative complication due to excessive bleeding, requiring a reoperation with subsequent mechanical ventilation and ICU stay the other patient received a major intraoperative complication. Seven patients (10.3%) suffered minor postoperative complications with most commonly being pneumonia. Therefore we registered a total of 10 (14.8%) postoperative complications in 8 patients (11.8%). The text has been modified as advised. Two patients in line 238 **(now 365)** represent severe intra-postoperative complications, the text has been modified accordingly.
Changes in the text: See page 11, lines 262-275, page 12, page 15, line 365. Tables 6 and 7 on pages 25-27.

Comment 20: How did you treat your complications? Have you had any readmissions to ICU? Did you have to reoperate on the complications? How did you handle the liver laceration. Did you have acute exacerbations of ILD (AE-ILD) after surgery? Classify your complications in a third column according to Clavien-Dindo to make it clearer for the reader.
Reply 20: Thanks for the comments. One patient had a major bleeding from a trocar site that required an reoperation and subsequent mechanical ventilation and ICU stay. Liver laceration was observed and required no major surgical intervention or ICU stay. We reported no AE-ILD. No patients needed readmission to ICU or a reoperation due to the surgical lung biopsy itself. Results chapter has been revised and modified to make it clearer.
Changes in the text: See page 11, lines 262-275

Comment 21: Line 185 – 188: If you compare two types of histology please check for statistical significant differences between both. Maybe add a third column to your table 6.
Reply 21: We thank the Reviewer for this suggestion. We agree and have added a column to the abovementioned table (now labelled as table 7) with p-values for the

comparison of individual variables. We have also updated the statistical analysis chapter to describe the statistical tests used for these comparisons.
Changes in the text: See Table 7 page 26.

Comment 22: Line 191: "... as was the length of stay, or two days median in both groups." I do not understand this passage. Please rephrase.
Reply 22: Please see our answer previously above. We have further clarified the text by also reporting mean values with SD.
Changes in the text: See page 12, lines 285-287.

Comment 23: Line 192-198 and Figure 1: In figure 1 you show a p value of 0.00048. However, you neither explain it in your text nor beneath your figure. Which parameter did you test against which? UIP vs. NSIP? UIP vs. Other? Please explain.
Reply 23: This is an excellent comment by the reviewer and we agree that this needs to be clarified. We used a log-rank test to compare the three histological groups. For the statistical test mentioned above, we performed a test to evaluate if there was difference in survival between the three groups (i.e., the null hypothesis was that there was no difference in survival between the three groups).
However, we agree that this may be confusing to the reader. We have thus removed the p-
value from the figure. Additionally, we have performed a Cox regression to compare mortality between individual histological groups. Patients with UIP had higher long-term
mortality compared to patients with NSIP (HR 4.27, 95% CI 1.53-11.92, p=0.006) and patients
with other diagnosis than UIP or NSIP (HR 4.99, 95% CI 1.82-13.72, p=0.002). We have
updated our material and methods and results chapter in accordance with this.
Changes in the text: See Figure 2 page 29

Comment 24: The "Discussion" Section is excellent. Your results are very well discussed.
Reply 24: Thank you for that.
Changes in the text: None made

Comment 25: Line 211 – 215: I absolutely agree with you. Do you have a reference for that or is it your interpretation of the data? If so, please mark in text.
Reply 25: Thanks. This is an interpretation of the results. We have modified the manuscript accordingly to reflect that.
Changes in the text: See page 13, lines 318-321.

Comment 26: Line 267: I totally agree with you. Could you mention the Icelandic Death Registry also in your materials and methods section.
Reply 26: We have modified our materials and method section accordingly as advised

and added the Icelandic Death Registry to the text.
Changes in the text: see page 8, line 164-166

Comment 27: Line 269: "... reviewed by a radiologist..." – remove "an"
Reply 27: We have modified our text accordingly as advised
Changes in the text: see page 16, line 418

Comment 28: Table 1: The table description is confusing as it shows 81 total biopsies but beneath you write 97. Please be more precise.
Reply 28: Thanks for this comment. We have revised and modified Table 1 as well as our text and added a new table to further clarify.
Changes in the text: See Table 1 and 2 on page 20 and page 10, lines 213-218

Comment 29: Table 2: Classify smoking into "non-/ex-/active smokers" and add the pack years. It makes it easier to read.
Reply 29: Thanks for this comment. We have modified Table 3 accordingly and classified smoking into non-smoker/ex-smoker >12months/ex-smoker but within 12months/active smoker. Pack years was registered for 49 patients and has been added with mean and SD. Table 7. has also been updated accordingly.
Changes in the text: See page 10, lines 220-223, Table 3 on page 21 and Table 7 on page 26.

Comment 30: Table 2: "... with %(Pre/Pred) (83.8) and FEV1 85.3 and DLCO 45 (66.2): I do not understand these values. In your manuscript (lines 159 – 162) you performed spirometry in 83.8% of patients and 63.2% of patients received DLCO measurement. Please correct.
Reply 30: We have modified our Table 3 to better illustrate these numbers. These numbers represent the percentage from N=68. We have also noticed wrong numbers with the spirometry percentage and have now corrected it. The correct value is 85.3%. 58 or 85.3% of patients underwent spirometry of whom DLCO was performed in 45 patients or 66.2%. The manuscript has also been modified accordingly. We apologize for the wrong numbers.
Changes in the text: See Table 3 on page 21 and lines 241-245 on page 11.

Comment 31: Table 4: Please arrange your table top down beginning with the most cases. HP and Sarcoidosis above COP and SOP with RA. Delete "Other" as it does not show any values. Remove COPD from your description as it is not shown in the table. Either write SOP with associated RA or SOP with RA. Please be consistent.
Reply 31: This is a good comment. Table 4 has been renamed (Table 5) and modified as advised.
Changes in the text: See Table 4 page 23

Comment 32: Table 5: Please add the rate of AE-ILD to your postoperative outcomes. Your description is confusing "... and length of stay from 2008 – 2020...". Please rewrite

or delete 2008-2020.
Reply 32: Thanks for this comment. No patients had AE-ILD. Table 5 has been renamed Table 6, AE-ILD has been added to Table 6 and 7. The footnote for the second part has been removed.
Changes in the text: See Table 6, page 25 and Table 7 on page 26.

Comment 33: Table 6: Please add a third column with p-values calculated for your comparison between UIP and NSIP. Change the smoking status (see point 28.)
Reply 33: We thank the Reviewer for this suggestion. We agree and have added a column to the abovementioned table (now labelled as table 7) with p-values for the comparison of individual variables. Smoking status has been updated in accordingly and now shows the same smoking variables as listed in Table 3.
Changes in the text: See Table 7 on page 26.

Reviewer C

MAJOR COMMENTS
Comment 1:. Materials and methods (p 6, line 89) - A large number of patients (86) were excluded because they "did not meet the criteria for suspected ILD". What criteria used for case selection/exclusion?
Reply 1: Thank you for your comment. We have modified and added to our text accordingly as well as adding a flow diagram to further clarify both the inclusion and exclusion process.
Changes in the text: See Page 7, lines 123-131, see also Figure 1 on Page 28.

Comment 2: Materials and methods (p 6, line 96) - Assuming that the PFT/DLCO numbers were taken from the most recent pre-operative testing? May be worth affirming that was the case and perhaps, if feasible, including mean (+/- STD) interval between testing and biopsy.
Reply 2: The reviewer is correct; spirometry and DLCO values were always taken from the newest spirometry, if available. The text and Table 3 has been modified accordingly. Unfortunately, we are unable to provide the mean interval between testing and biopsy since the exact date of testing was not always registered in hospital and private office records.
Changes in the text: See Table 3 on page 21, lines 138-139 on page 7 and lines 241-, page 11.

Comment 3: Materials and methods (p 6, line 123) - The text implies that the histological findings were used as the final diagnosis for statistical analysis/comparisons. The authors might consider including the results of multidisciplinary discussion (MDD) as a final step in diagnostic pathway given that it is considered by many, including current published diagnostic guidelines, as the preferred diagnostic reference standard.
Reply 3: This is a good comment. Unfortunately, we do not have MDD for all the

patients, and therefore we could not include it as it would have been missing for so many patients. We have provided a statement in material and methods to address the issue as well as registering it as an limitation in the discussion chapter.
Changes in the text: See page 7, lines 141-143 and page 16, lines 425-428.

Comment 4: Results (p 7, line 144) - The authors indicate that 75% of patients had a single biopsy which may explain the high percentage of NSIP diagnoses given preference for upper lobe biopsy. It might be worth clarifying in Materials and methods whether there was a preoperative biopsy site selection process (eg, upper lobe biopsies in patients with upper lobe predominant disease)? The impressive survival differences between NSIP and UIP patients, presumably defined purely on the basis of histology, was effective despite single site biopsies which might impact current recommendations that multiple sites be sampled. At a minimum reliance on single site biopsies is something the authors may wish to address in the Discussion if only to help the reader understand why single site biopsies were preferred and why they seemed to work in this patient population.
Reply 4: Thanks for this comment. There was no consensus about where to take the biopsy from, other than we tried to avoid the lingula. The most inflamed part of the lung was chosen, and if both sides were similar we usually chose the right side as there are two fissures, making the biopsy technically easier.
Changes in the text: See page 8, lines 145-155 and page 15, lines 390-397

Comment 5:. Results (p 8, Table 3) - 23 patients had radiological honeycombing while 16 patients had SLB diagnoses of UIP with another 5 who had HP (presumably fibrotic?). It might be interesting to understand what the relationship was, if any, between the CT findings and the SLB diagnoses. How well did honeycombing predict for a SLB diagnosis of UIP?
Reply 5: This is an interesting comment but due to few patients in each of these subgroups we are not able to elaborate on this or report further details. But this could be of interest for further studies in the future.
Changes in the text: No changes made

Comment 6: Results (p 8, line 167) - How was "fibrosis" defined on CT scans? 24 (35.3%) had traction bronchiectasis and 23 (33.8%) had honeycombing, the latter presumably a subset of the former. And yet 34 (50%) had "fibrosis". It might be helpful to clarify in Materials and methods criteria used to identify fibrosis on CT scan.
Reply 6: Thank you for your comment the text has been updated and modified accordingly as advised.
Changes in the text: See page 8, lines 174-180.

Comment 7: Results (p 8, Table 6) - Not sure it is feasible or statistically meaningful given relatively small numbers, but the authors might consider adding a column in Table 6 for p values in comparisons of NSIP vs UIP to help the reader understand where there might be meaningful differences.

Reply 7: We thank the Reviewer for this suggestion. We agree and have added a column to the abovementioned table (now labelled as table 7) with p-values for the comparison of individual variables.
Changes in the text: See Table 7 on page 26

Comment 8:. Discussion (p 9, line 207) - The authors might consider adding MDD as a step between SLB/histological diagnosis and "diagnostic yield". That may not be feasible given the considerable work already done but it would strengthen the manuscript and make it more comparable to other current publications exploring value of lung biopsy, whether TBLC or SLB, in evaluation of patients with ILD that is ambiguous after clinical and radiological evaluation.
Reply 8: Please see our previous reply above. We do not have this information in enough details to report it.
Changes in the text: No changes made.

MINOR COMMENTS
Comment 1: Discussion (p 9, line 219) - The authors may wish to add recent reference regarding diagnostic yield of TBLC compared to SLB (Fortin et al. Am J Respir Crit Care Med 2023; 207:1612).
Reply 1: Thanks for this suggestion. We have added this reference to our list.
Changes in the text: See page 13, lines 325-330

Reviewer D

Major concerns:
Comment 1:. Multidisciplinary discussion (MDD) after SLB among thoracic surgeons, pathologists, radiologists, and pulmonologists is crucial for definitive diagnosis of ILD and further treatment for the patients. For example, UIP pattern confirmed in biopsied specimen contains IPF (idiopathic IP), CVD-IP, CHP and other diseases. The final diagnosis after MDD is indispensable for treatment, but this manuscript never mentioned MDD. If there was no MDD after SLB, it would be a significant limitation of this manuscript, which should be discussed in the limitation part.
Reply 1: Please see our replies to two of the previous reviewers above. We have also revised and reviewed our material and methods as well as discussion chapter to address MDD.
Changes in the text: See materials and methods and discussions chapter.

Comment 2: I could not find any relationship or difference between CT findings and histopathological diagnosis. Is there any difference in terms of CT findings between NSIP and UIP? Radiologic evaluation in Table 3 should be connected to Table 6.
Reply 2: This is a valid point raised by the reviewer. Unfortunately, our number of patients and database does not make it possible for go into further details regarding this matter. But it is certainly of interest fur future studies.
Changes in the text: No changes made.

Minor concerns:

Comment 1: Line 40: I think the number of minor complications is wrong. Please correct it.

Reply 1: Thank you for your comment, the number is correct we have rechecked our data and modified our text and tables accordingly to have it more clear as was advised. Please see our reply to previous reviewer.

Changes in the text: See page 11, lines 271-275, page 12, lines 284-285, page 15, line 365. Tables 6 and 7 on pages 26-28.

Comment 2: Line 63-65: I could not understand this sentence. Please clarify it.

Reply 2: Thank you for your comment. We have revised this sentence, so that it is more to the point.

Changes in the text: See page 5, lines 81-84

Comment 3: Line 66-68: You mentioned the rate of successful diagnosis via bronchoscopy, but no papers have not been cited. Please add some articles to support this number.

Reply 3: We have revised, modified and added references so that the text is in line with the ATS/ERS/JRS/ALAT meeting in 2022.

Changes in the text: See page 5, lines 91-101

Comment 4: Line 69-70: I do not think that SLB for suspected ILD is "golden standard" because general anesthesia should be avoided for patients with severe respiratory failure. SLB should be applied to the patients who can endure one-lung ventilation and cannot have definitive diagnosis even after other modality including TBLB or cryo-biopsy.

Reply 4: We agree and have responded to one of the previous reviewers. Please see our reply there.

Changes in the text: See our previous reply.

Comment 5: Line 89: What is the criteria? Please mention it in the methods.

Reply 5: Thank you for your comment. We have modified and added to our text accordingly as well as adding a flow diagram to further clarify both the inclusion and exclusion process.

Changes in the text: See Page 7, line 123-131, see also Figure 1 on Page 28.

Comment 6: Line 127-133: The difference between NSIP and UIP should be evaluated statistically. You should add P-value in Table 6 and statistical method in that section.

Reply 6: We thank the Reviewer for this suggestion. We agree and have added a column to the abovementioned table (now labelled as table 7) with p-values for the comparison of individual variables. We have also updated the statistical analysis chapter to describe the statistical tests used for these comparisons.

Changes in the text: See page 9 lines 196-205 and Table 7 on page 26-27

Comment 7:. Line 154: not "it" but "It".

Reply 7: The text has been modified as advised
Changes in the text: See page 10, line 231

Comment 8: Line 156-157: What was the results in the other half of the TBB and BAL-samples?
Reply 8: We have revised and modified our text accordingly to further clarify the rest of the samples. TBB 5 (12.1%) cases, 5 (12.1%) had plausible COP changes while the rest of the samples either showed without any diagnosis chronic inflammatory changes with or without interstitial changes. BAL 27 (64.3%) had normal upper respiratory flora with the rest having either very few bacterial colonies or showing a negative culture.
Changes in the text: See page 10, lines 233-240

Comment 9: Line 169-170: the word of "unclassifiable" should be avoided. The five patients had no clear evidence of ILD from the resected samples. This is totally different from "unclassifiable interstitial pneumonia" and confusing.
Reply 9: We agree with the reviewer and suggest the work non-classifiable.
Changes in the text: We have added non-classifiable to the text and tables. See line 255

Comment 10: Line 180: the exact number of prolonged air leak should be added.
Reply 10: Thanks. We have replied to one of the previous reviewers regarding the air leakage. Air leakage has been revised and is now reported as 4 days (>96 hours). Please see our answer there.
Changes in the text: See previous answer.

Comment 11: Line 228: IPF is wrong. UIP is correct.
Reply 11: Thank you for your comment, the text has been modified accordingly as advised.
Changes in the text: See page 14, line 352

Comment 12: Line 230-231: the diagnosis of IPF would be important for treatment, but this definitive conclusion should be done via MDD. As I mentioned major concern #1, please discuss it.
Reply 12: Please see our previous answers regarding this matter. Unfortunately we do not have this information completely enough registered to report it in our study.
Changes in the text: Please see our revised material and methods and discussion chapters.

Comment 13: Line 238: Intra- and postoperative "severe" complications were rare.
Reply 13: The text has been modified accordingly as advised.
Changes in the text: See page 15, line 365

Comment 14: Table 4: please change the word "unclassifiable".
Reply 14: See our previous answer to the same comment. Table 5 has been updated as

advised with the word non-classifiable instead of unclassifiable.
Changes in the text: We have added the word non-classifiable to our manuscript.

Comment 15: Table 6: the number of patients should be placed at the top of the table.
Reply 15: Table 6 has been renamed to Table 7 and modified accordingly.
Changes in the text: See Table 7, page 26

Reviewer E

Comment 1: As much of the outcomes and discussion focus on safety of the VATS biopsy in this cohort, I would recommend including information on the patient's baseline O2 requirements (rest and exertional if available), presence of pulmonary hypertension, and BMI. Could the authors also comment on what cardiac testing (if any) the patients underwent prior to surgery as part of their pre-operative evaluation?
Reply 1: Thank you for your comment. Due to the retrospective nature of the study, the 13 year time period and the fact that we surveyed both private office and in hospital records. Most common limitation that we faced when surveying older and sometimes newer records was the fact that not every parameter was registered. We are therefore unable to provide you a complete and reliable data to the aforementioned questions.
Every patient is evaluated individually before surgery, however no specific cardiac testing was routinely performed on all patients prior to surgery as part of pre-operative evaluation.
Changes in the text: None made.

Comment 2: The authors note that 75% of patients underwent a single biopsy only, with only 17% of patients have multiple biopsies from different lobes. This differs from the standard procedure at many ILD centers in which biopsies are taken from all 3 lobes in the majority of cases. Could the authors comment on this difference and whether increased complications were identified in the patients undergoing multiple vs single biopsies?
Reply 2: Thank you for your comment. We did not see an increased complication rate if multiple biopsies were taken or not. Only one patients which had the right upper and lower lobe was biopsied had prolonged air-leakage. Every imaging study was reviewed prior to surgery by the surgeon and the best suitable site selected for biopsy if not indicated by a multidisciplinary meeting. Usually, the most inflamed part of the lung was chosen rather than the most fibrotic part, and if both sides were similar we usually chose the right side as it had two fissures, making the biopsy technically easier. We also tried to avoid the lingula if possible. Intraoperative assessment of the selected lung and lobe was then made which guided the final biopsy site. We believe, although not scientifically proven, that taking multiple samples from different lobes would increase the rate for intra- and postoperative complications, most importantly air leakage.
Changes in the text: See our results chapter as well as page 15, lines 390-397.

Comment 3: Were any cases of acute exacerbation of the underlying ILD noted

following VATS biopsy or were all reported respiratory complications (pneumonia, mechanical ventilation) thought to be from other etiologies?
Reply 3: Thanks for this comment. There were no such exacerbation registered in our database or hospital charts.
Changes in the text: No changes made.

Comment 4: In the discussion the authors note cryobiopsy as an alternative to VATS biopsy, noting its lower diagnostic yield and significant complication rate. One other main limitation to cryobiopsy is availability of experienced physicians to perform this, and it remains unavailable in many locations. Could the authors include a statement on whether or not this was being performed in their country in the time period of the included cases?
Reply 4: We have replied to a similar comment from one of the previous reviewers. Please see our answer above. Please also see our revised discussion chapter.
Changes in the text: See above and see also page 14 lines 340-343

Reviewer F

Comment 1: At one time surgical lung biopsy was considered to be the "gold standard" for the management of patients with suspected interstitial lung disease. However, concerns regarding post-operative flares of the underlying disease, in many cases severe. dissuaded clinicians from proceeding with a surgical biopsy. In their series, an acute post-operative flare does seem to have occurred in their patients, even with patient enrollment between 2008 and 2020. Can the authors please comment on why they do not think this occurred in their patients and if this possibility dissuaded some clinicians from proceeding with a surgical lung biopsy during the included time of the retrospective study thereby decreasing the number of included patients.
Reply 1: We would like to thank for this valuable comment. Before 2008 most surgical lung biopsies in Iceland were performed in majority of cases via open thoracotomy as reported by Sigurdsson et al (1), with a 30- and 90 day operative mortality of 2.7% and 4.1% and a major complication rate of 4% and 12% for minor complications. There was a consensus between the pulmonologists to refrain from referring patients to surgery with end stage interstitial lung disease, severe respiratory failure and substantially reduced spirometry or DLCO as it was deemed so that the patient was unlikely to tolerate surgery and would most likely not benefit from the surgery. Therefore, the most severely affected patients were never referred to our center, we are therefore unable to provide further comments regarding those patients.
We did not see an increase in patient referrals for surgical lung biopsy between the two studies and number of patients in the two studies remained roughly the same (68 vs 73 pts.). One proposed explanation to why we did not see an increase in patients referrals between the studies was that as the diagnostic confidence of the radiologist became greater the need for SLBs was reduced.
Our study is the first study that compares the safety of VATS technique after the overnight shift from thoracotomy to VATS for patients with suspected interstitial

disease in Iceland. Since these patients can be troublesome to place under general anesthesia and surgery while at the same increasing the risk for catastrophic postoperative complications with the most lethal one being AE-ILD. We felt that it was important to report our findings from a small center in Iceland performing VATS SLBs. It is our understanding by reporting that VATS technique, is indeed a safe option for patients with suspected interstitial lung disease could persuade clinicians to refer patients more often for a surgical biopsy.
Changes in the text: None made

Reviewer G

I am grateful for your submission of an excellent manuscript.
In this study, conducted over a span of 13 years in Iceland, wherein 68 consecutive patients were retrospectively observed, the authors assert that surgical lung biopsy for the diagnosis of Interstitial Lung Disease (ILD) is a secure procedure with a notable diagnostic efficacy. I, as a reviewer, indeed concur with this conclusion.

The issue lies in the fact that as the authors themselves mentioned in the discussion section, there are numerous similar studies reporting comparable results, thus rendering this paper not contributive to new knowledge. Although the authors asserted that early diagnosis of ILD during the initial stages of the disease could result in early treatment and potentially enhance survival, it is challenging to view this assertion as corroborated by the findings of the current study. And, survival is intricately tied to the progression of the underlying disease; therefore, within the context of this study focused on assessing the reliability of diagnostic methods, the comparison of survival rates does not seem logically justified.

While I hold the researchers in high regard for undertaking a commendable and challenging study that gathers nationwide data from the sparsely populated country of Iceland, I am of the opinion that unless this paper presents novel information, it may not be suitable for publication in the Journal of Thoracic Disease (JTD)

Reply 1: We do not agree that our study lacks novelty, and we think it is important to report outcome of SLB from a whole population, even though the center is relatively small.
Changes in the text: No changes made

Reviewer H

Comment 1: What has been revealed by this study? There are already many publications on the efficacy and safety of surgical lung biopsy in interstitial lung disease. Some systematic reviews have also been conducted. One of the most reliable reports is in the ATS/ERS/JRS/ALAT guidelines, which you also cited. See Supplemental Table E8 in citation #2. I could not understand what was the new finding in this study in this

paper when there are other large scale studies.
Reply 1: We do not agree that this study should not be published. We feel that it is important for a small single center nation to report its findings in order to compare itself with other larger nations. It is also important to report that although we are a small center our complication rate remains low and comparable to other larger centers. Please also see our reply to the previous reviewer.
Changes in the text: We have stressed the strength of our study in the Discussion part.

Comment 2: The information provided in this manuscript regarding HRCT is inadequate. CT findings are described, but there is no description based on IPF diagnostic guidelines (citation #2, #21) or HRCT pattern classification based on the Classification of Idiopathic Interstitial Pneumonia (Travis, AJRCCM, 2013). I find this to be a serious omission in the information provided in the manuscript.
Reply 2: Thanks for this comment. The variables for lung abnormalities on HRCT in this study were chosen based on known findings and patterns in interstitial lung diseases (2). We have also updated our material and methods section as advised.
Changes in the text: see page 9, lines 179-180.

Comment 3: The pathological diagnosis in Table 4 is also seriously deficient: NSIP and UIP are the classification of pathology patterns based on the classification of idiopathic interstitial pneumonia, while HP and Sarcoidosis are the disease names. I find it strange that these are listed in the same category.
Reply 3: Thank you for your comment we have revised Table 5 to further clarify the presentation of our data.
Changes in the text: See Table 5 on page 24.

Comment 4: International guidelines state that MDD is required for diagnosis, but is MDD being performed? If so, it should be stated. If not, it means that the diagnosis is not based on the guidelines and should be stated in the limitation.
Reply 4: We have answered the same comment raised by two previous reviewers. Please see our replies there.
Changes in the text: See above.

Comment 5: It is unreasonable that there is no description about acute exacerbation of ILD, which is the most serious postoperative complication of SLB. Even if there were 0 cases, I think it needs to be mentioned.
Reply 5: This is a good point. We had no such cases and we stress this in the Results section. We have also updated our Table 6 and included AE-ILD.
Changes in the text: See our results section and Table 6 on page 25.

Comment 6: I thought it was a problem that in the introduction, cryobiopsy was described as if it were a procedure whose efficacy has not been studied. Many studies have already been conducted on cryobiopsy, and furthermore, its position is described in the IPF diagnosis guidelines (citation #21). I suggest that the description be changed

to be based on this guideline.
Reply 6: Thanks for this comment. We have both modified and revised our text accordingly by updating our introduction so that it is more in accordance with the ATS/ERS/JRS/ALAT clinical guidelines from 2022.
Changes in the text: See page 5, lines 91-101

Reviewer I

ABSTRACT
Comment 1:
- I recommend removing the numbers in the conclusion, since they should appear in the results section
Reply 1: Thanks. We have modified the text accordingly as advised
Changes in the text: See page 3, line 64.

INTRODUCTION
Comment 2:
- Page 5, line 64. I suggest modying the sentence "blood biomarkers are not yet available for the diagnosis of ILD", since it is imprecise. We have useful biomarkers (autoimmunity, ACE), although they are not diagnostic by themselves.
Reply 2: Thank you for your comment. The manuscript has been modified accordingly as advised.
Changes in the text: See page 5, lines 83-84

METHODS
Comment 3:
- Page 6, line 123. I suggest not talking about "IPF" as histology group, since the histological diagnosis would be "UIP"
Reply 3: Thanks. The text has been modified and changes made accordingly as advised.
Changes in the text: See page 9, line 191

RESULTS
Comment 4:
- I recommend putting all the numerical data with the same decimal places (add a decimal to the age or the DLCO). The same recommendation is valid for the data in the tables
Reply 1: We agree. We revised all tables accordingly as advised
Changes in the text: See Tables

Comment 5: - I suggest putting first the number of patients who have DLCO, and clarify if the 63% of those who have it decreased correspond to the total or to those who have it performed
Reply 1: We agree and have changed the manuscript accordingly. DLCO was lowered in 43 (63%) of patients while being normal in 2 (2.9%). Percentage is calculated from

the total number of patients (n=68).
Changes in the text: See Table 3 and results chapter.

Comment 6: Some of the CT radiological findings described require clarification, such as "fibrosis"
Reply 1: Thank you for your comment the text has been updated and modified accordingly as advised.
Changes in the text: See page 8, lines 174-180

Comment 7: The results provided in table 4 mix clinical histological diagnoses. For example, SOP is not a pathological diagnosis, probably is COP, and the clinical diagnosis is SOP. IPAF or nitrofurantoin induced interstitial lung disease are not histological diagnoses either. I consider that this mixture of results makes it difficult to understand the purpose of the study. Please provide only histological diagnoses, or add a second column or extra table with the correlation between histological and clinical or definitive diagnoses
Reply 1: Thank you for your comment. We have revised table 5 to further clarify the presentation of our data.
Changes in the text: See Table 5 on page 24.

DISCUSSION
Comment 8:
- Page 9, line 209. I suggest not talking about “IPF” as histology group, since the histological diagnosis would be “UIP”. In the following line, IPF and UIP are repeated as synonyms, when they are not.
Reply 1: Thank you for your comment the text has been modified accordingly.
Changes in the text: See the discussion chapter

Comment 9:- In the discussion, concepts are mixed between series of UIP, IPF or patients with surgical biopsy. I recommend carrying out the discussion clearly differentiating whether one is talking about series with SLB or patients with iPF, since the very performance of the SLB is a bias that modifies the characteristics of the population.
Reply 1: We thank for the comment and have changed sentences in the Discussion so that surgical series on SLB, rather than IPF are referred to.
Changes in the text: See our discussion chapter

Comment 10: The reading of the tests (images or biopsy) by a single observer should be added as a limitation, in addition to the unicentric nature of the study.
Reply 1: Thank you for your comment we have addressed the comment in our discussion chapter.
Changes in the text: Please see our discussion chapter, page 16, lines 419-422.
Comment 11: I recommend removing the numbers in the conclusion, since they should

appear in the results section
Reply 11: The text has been modified accordingly as advised. A separate conclusion section has also been added at the end.
Changes in the text: See page 17, lines 430-440.

TABLES AND FIGURES
Comment 12:
- Table foot, table 1. I suggest removing this sentence “In total 97 biopsies were taken that include multiple biopsies from a single lobe” from here and adding it to the body of the manuscript.
Reply 1: Thanks. We have modified the text accordingly.
Changes in the text: See page 10, line 218

Comment 13: Table 2. It is difficult to read some of the results in Table 2. I recommend highlighting the different sections in bold (such as spirometry or comorbidities).
Reply 1: We thank for this advice. Table 2 has been renamed Table 3 and has been modified and different sections highlighted in bold as advised.
Changes in the text: See Table 3. page 21.

Comment 14: - Table 4. Delete category “Other” if there were 0 (0%).
Reply 14: Table 4. has been renamed as Table 5 and modified accordingly as advised.
Changes in the text: See Table 5, page 24

Comment 15: - In table 5, I recommend leaving only one decimal in the results of the days, as in other tables, since the second decimal of a day does not contribute anything.
Reply 1: We have revised Table 5 which has been renamed to Table 6 accordingly as advised
Changes in the text: See Table 6 on page 25