

Peer review file

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Reviewer A

Comment 1: The introduction is too long and I suggest to shorten it somewhat to make it more precise and focused.

Reply 1: As you suggested we have tried to shorten the introduction.(p.6-p.7)

Comment 2: Inclusion criteria seem to be a measurement of the biomarkers 6 months before an AE-IPF. I do not understand the rationale behind limiting patients to those with biomarkers only 6 months before - why not 9 or 12 months before or simply at baseline? Please explain and also add the time from baseline measurements to AE-IPF.

Reply 2: We have added the intervals from the measurement of serum markers at stable state and the onset of AE in Table 1. Serum levels of KL-6 and SP-D tend to increase according to the disease progression. So, we suppose comparison of serum levels of KL-6 and SP-D at the onset of AE with those many months before AE is not good. We do not determine whether the changes of serum markers have been caused by AE or not. However, we could not measure timely before 2-3 months from AE. Hence, we selected the subjects of this study, whose serum markers were measured both within 6 months before AE onset and at the AE onset.

Changes in the text: We have added “The measurement interval between stable state and AE onset was 50 days (median) and less than 90 days in 62 cases (80.5%)” in p.12, L3-4.

Comment 3: The paragraph about “Diagnosis of underlying IIPs with chronic progression” is very long and could benefit from shortening by simply referring to ATS/ERS diagnostic guidelines and to table 1, as most of the data also can be seen there. Also, there are no data describing whether the patients have a progressive phenotype or not, as suggested by the heading “...with chronic progression”. Please adjust.

Reply 3: I have added chronic progression because all these cases did not show acute onset-disease at the diagnosis of ILD. Hence, you have misunderstood that subjects are progressive phenotype. we have deleted the “with chronic progression”. In addition, we

would like to shorten this part; however, other reviewers hope to know the subjects in details and we had added the information.

Comment 4: The authors state that they used the modified Japanese criteria for AE-IIP although recognizing that there are international guidelines from 2016. I suggest either to erase the last part or to argue/describe how the different criteria affect the study population.

Reply 4: As you suggested, we have deleted the international guideline in 2016 in p.11, L.1-3.

Comment 5: Treatment for AE-IIP – I suggest again to shorten and refer to table 1.

Reply 5: As you suggested, we have shortened the content about treatment and it was moved to “Diagnosis and treatment of AE-IIP” from p.10, L. 15 to p.11, L. 6.

Changes in the text: We have added “The AE-IIPs were generally treated with prednisolone following intravenous administration of methylprednisolone for three consecutive days with/without an immunosuppressant[9] and treatment in detail was shown in Table 1” in p.11, L. 3.

Comment 6: The main hypothesis seem to be that the authors can divide patients into two types of AE-IP – those with a DAD pattern and those with OP, based on combinations of HRCT pattern and the levels of Δ KL-6/ST-KL-6.

Reply 6: That is what we would like to say. To clarify this point, we have changed the conclusions.

Changes in the text: “Combining the HRCT pattern and the Δ KL-6/ST-KL-6 value can improve our ability to predict the survival of AE-IIP patients” in p.25, L.10-11.

Comment 7: P. 16, l. (2-7 and) 9-15. Shorten this paragraph as SLB in AE-IIP was not a part of this study (reading the methods section it seems as if all SLB were performed before AE-IIP). The argument that histology in AE-IPF is hard to collect in acute ill patients, samples might be non-representative and a significant overlap exist, all precluding histology as useful for prediction of survival can be argued in a much more abbreviated fashion.

Reply 7: I am sorry, but all IIP cases were not diagnosed by SLB. We have modified

the section of method.

Changes in the text: “The remaining 24 patients comprised the non-IPF-IIP group (n=24); one patient was diagnosed with nonspecific interstitial pneumonia by SLB[20], and the remaining 23 had unclassifiable IIP without SLB evaluation” in p.9, L.10-12.

We have shortened the paragraph as you suggested in p.19, L.13-15.

Comment 8: Similarly, p. 16-17, line 16 + 1-10 can be shortened to just say that discrepancies exist regarding radiology patterns and histology.

Reply 8: We have shortened the paragraph as you suggested from p.19, L.16 to p.20, L.3.

Comment 9: P. 21, line 7-9. Time from baseline measurement of biomarkers to A-IIP varied but was generally 3 months – these data seem not available anywhere but could be mentioned in the methods section.

Reply 9: We have shown measurement of serum markers were performed within 6 months in the section of “Measurement of serum markers and related parameters”. And the actual interval from the measurement at the stable state to at the AE is shown in the Table 1 and 2. In addition we have the sentence below.

Changes in the text: The measurement interval between stable state and AE onset was 50 days (median) and less than 90 days in 62 cases (80.5%) in p.12, L.3.

Comment 10: Agree with the authors regarding the fourth limitation of KL-6 analysis that are available in few countries precluding its usability.

Reply 10: We hope KL-6 can be measured in more countries.

Reviewer B

Comment 1: A major concern for this manuscript is the statistical analyses. There are a large number of analyses being performed for the whole cohort, as well as based on HRCT patterns (peripheral vs multifocal vs diffuse, non-diffuse vs diffuse) and combined HRCT/biomarkers. It is uncertain whether these analyses were pre-specified.

Reply 1: In our previous reports, we have examined prognostic significance of various clinical parameters, and the KL-6 and SP-D at the onset of AE. We know most of

clinical parameters were not significant prognostic factors. However, we cannot delete general parameters in the list of the parameters analyzed because many clinicians and reviewers ask us whether general parameters are useful to predict survival of AE-IIP. We have supposed the changes of serum markers at AE onset compared with those at stable state is important and our colleague have published three HRCT patterns of AE-IPF. In this study, we have planned to clarify association of the serum marker changes and HRCT pattern, and prognostic value of combination of these parameters using Δ KL-6/ST-KL-6, Δ SP-D/ST-SP-D, ST-KL-6, ST-SP-D. Hence, our analysis was partially pre-specified; however, this is a retrospective study.

Comment 2: The authors reported all “significant” p-values ($p < 0.05$). For instance: Results, page 13 on Differences in clinical features between multifocal patterns with higher/lower Δ KL-6/ST-KL-6, without providing data for other radiological patterns. There is a concern about selective reporting. More importantly, given that many statistical analyses have been performed, the risk of type 2 errors is high. It doesn't appear that multiplicity adjustments have been considered in the analyses. Were collinearity tests performed for multivariate analyses?

Reply 2: As for problem about “Differences in clinical features between multifocal patterns with higher/lower Δ KL-6/ST-KL-6” shown in the Table S2 of the original manuscript. All the parameters included in the Table S2 is the same as Table 2 and in the Table 2, clinical features of diffuse, multifocal and peripheral patterns were shown. In addition to the Table S2, we have shown difference in clinical features between diffuse pattern and multifocal pattern with lower Δ KL-6/ST-KL-6 in Table S3. Then we have supposed there is no problem about selective reporting. However, we have not shown the difference in clinical features between peripheral pattern and multifocal pattern with higher Δ KL-6/ST-KL-6. Hence, we have added the supplementary Table S6 in revised manuscript to solve the selective reporting problem. The names of Table S2, and Table S3 were changed to Table S4 and Table S5 in the revised manuscript.

Next problem is multiplicity and multi-collinearity. We supposed that multi-collinearity test is performed for linear regression and we can exclude the parameters from multivariate analysis according to the VF. However, we performed multivariate Cox proportional hazard regression analysis and another approach is needed. We have consulted the institutional statistician and the additional analysis was performed.

Then correlation coefficient (CC) of two parameters was calculated by multivariate Cox analysis and one of the two parameters with absolute value of CC more than 0.7 was excluded according to p-value. Using this approach, we have excluded multicollinearity as possible. From this approach, number of parameters for multivariate Cox analysis can be reduced. Next, we performed the Spearman's rank correlation test and apparent correlated parameters with rho more than 0.7 were excluded.

Using these approaches, we can reduce number of parameters from 22 to 10. After these evaluation, multivariate Cox analysis with stepwise selection procedure was performed using the 10 parameters to predict survival of AE-IIP. The results of statistical analysis in revised manuscript were almost similar to those in previous version of the manuscript. Changes in the text: We have changed the section of the statistical analysis from p.12, L.15 to p.13, L.4.

Comment 3: The authors performed multivariate analyses without including HRCT patterns as one of the predictors. The authors have pre-determined to include HRCT patterns into the final analyses for the combined use of HRCT patterns and biomarkers.

Reply 3: We have planned to describe the Table 5 showing prognostic values of conventional HRCT pattern of AE and our new system using HRCT patterns and serum marker levels. Hence, we performed the multivariate analysis using parameters except for HRCT pattern in Table 3.

Comments 4: Discussion section (Page 20, Line 7): It appears that there have been more statistical analyses being performed with results not being presented.

Reply 4: We have added the content of Two Tables in the section of results.

Changes in the text: "Difference in clinical features between the diffuse pattern and multifocal pattern with lower Δ KL-6/ST-KL-6" was added in p.17, L.5-10.

"Difference in clinical features between peripheral pattern and multifocal patterns with higher Δ KL-6/ST-KL-6" was added in p.17, L.12-p.18, L.1.

Comment 5: Lung function has not been provided for the study population and included in the analyses.

Reply 5: Not all the subjects did not undergo lung function test within 6 months before the onset of AE diagnosis. In the place of lung function test, we have included the long-

term oxygen therapy at stable state before AE in the analysis. In addition, lung function at the diagnosis of AE was provided on Table 2 and 3.

[Comment 6: The readability of this manuscript can be improved. Consider the use of a professional editing service.](#)

Reply 6: We are sorry for our poor English expression. Original manuscript was edited using professional service. However, revised manuscript was edited again using the similar service.

-Should be “significant” poor prognostic factor instead of “significantly”

-I have modified the expression in the abstract. (p.5, L.5)

- Rephrase AE-non-IPF in the IIPs to non-IPF AE in IIPs.

- I have modified to “AE of non-IPF-IIP” according to the expression in the other parts.

- Methods, Page 7: Restructure the sentence from Line 11-14.

- For readers to understand well, we have added Figure S1 showing the patient flow (p.8. L.8).

- Methods, Page 8: Restructure the sentence from Line 3-5 – it is unclear whether patients with interstitial pneumonia with autoimmune features were included?

- Serological domain was evaluated; however, we suppose clinical domain was positive in only one cases. Hence, one case satisfied criteria of IPAF and the others did not satisfy.

Changes in the text: We added the next sentence; Of 16 patients with positive autoantibodies, one showed Reynaud’s phenomenon and satisfied the IPAF criteria(p.10, L.2-3).

- Methods, Page 9, HRCT findings at diagnosis of AE-IIPs: “The HRCT pattern was then classified as diffuse or non-diffuse.” This part is unclear until reading the result section of the manuscript. Consider changing to “The HRCT pattern was then grouped into diffuse or non-diffuse (peripheral or multifocal).

- We have modified as you suggested.

Changes in the text: The HRCT pattern was then classified as diffuse or non-diffuse (peripheral or multifocal). (p.11, L.10-11)

- Methods, Page 10: “ Δ KL-6/ST-KL-6 and Δ SP-D/ST-SP-D were divided by the respective median values for each parameter; i.e., 0.211 and 0.410.” Need to improve the clarity of this sentence.

- We have modified the sentence.

Changes in the text: Median values of Δ KL-6/ST-KL-6 and Δ SP-D/ST-SP-D were 0.211 and 0.410, respectively, and the two parameters were categorized into a higher and a lower group by their median values.(p.12, L.6-8)

- Background, Page 4, Line 8: Remove this phrase “... identified some prognostic factors”, given the results are provided in the subsequent paragraph on Page 5.

- As you suggested, we have removed the phrase.

- Background, Page 5, Line 1: Replace “IPF vs non-IPF” with “A diagnosis of IPF”

- As you suggested, we have changed the phrase. (p.6, L.13)

- Background, Page 5, Line 6: Does this sentence refer to patients with AE-IPF – please clarify

- As you suggested we have clarified the meaning of the sentence.

Changes in the text: We have changed the sentence; “AE-IPF patients with a diffuse pattern than in those with a peripheral or multifocal pattern” in p.7, L.4.

- Table 1: What is OMI? Is it a typo for “AMI”?

- OMI means old myocardial infarction.

Changes in the text: We have added “OMI, old myocardial infarction” in the abbreviation of Table 1(p.36, L.4).

Reviewer C

[Comment 1: Page 3: Rephrase line 6-8. Message is not clear.](#)

Response 1: I have changed the sentence.

Changes in the text: The sentence Reviewer C pointed was changed. “This study aimed to clarify whether changes in serum marker levels could improve the prognostic significance of HRCT patterns in patients with AE-IIPs.” (p.2, L.6)

Comment 2: Study flow diagram if added can give a clear picture of patients enrolled in the study and their grouping into various HRCT patterns.

Reply 2: We have added the study flow diagram as Figure S1 Supplementary file 1.

Pictures of HRCT was shown in Figure S2 Supplementary file 3.

Comment 3: 58/77 patients were smokers. Was spirometric evaluation done for these patients? Were they having only restrictive pattern or CPFE (combined pulmonary fibrosis and emphysema)? Smoking pack years could have influenced SP-D and KL-6 values?

Reply 3: We have added the spirometric data and smoking pack year in Table 1 and Table 2. Pulmonary function test was not performed in some cases; however, almost all the cases showed only restrictive pattern. We examined the correlation between smoking pack year and serum markers, and Δ SP-D, Δ SP-D/ST-SP-D was weakly correlated with smoking pack year by Spearman’s rank correlation test; rho was about 0.3. Serum AE-KL-6 of Non-CPFE cases was significantly higher than that of CPFE cases. However, distribution of CPFE between HRCT patterns, including diffuse, multifocal and peripheral patterns, was not significantly different.

These results are interesting; however, we suppose they are not directly associated with our aim and one reviewer told us to shorten our manuscript. Hence, I am sorry, but, we cannot include the results in this manuscript.

Comment 4: Number of exacerbations of IPF/non IPF-IIP in past were not noted? Does these serum markers and radiological findings have an impact on higher future risk of exacerbations too?

Reply 4: Thank you for your important comment. I am sorry, but we have no data about recurrence of AE. All the subjects included in this study were enrolled at the initial AE. As you say, we suppose the IIP with AE occurrence were poor prognostic even if the cases survived after AE. Such cases experience second AE. I am sorry, but we do not know whether another AE have happened or not because such cases have not been

checked.

Reviewer D

Comment 1: The non-IPF cohort consists, except for one case, of unclassifiable IIP, thus the term non-IPF IIP could be misleading as it supposes a mix of different pathologies. In this regard, one may not exclude that a significant proportion of those “unclassifiable IIP” are in fact IPF. This concern is also based on the fact that the diagnosis of unclassifiable fibrosis seems to be mainly based on clinical/radiological data but not histological observations.

Reply 1: I have mentioned in the manuscript, “All patients with a possible UIP pattern had traction bronchiectasis. Eight patients with unclassifiable IIPs and a possible UIP HRCT pattern might have had IPF.” This expression might be misleading. Hence, we have deleted the sentences, Non-IPF IIP (n=24) in this study were diagnosed clinically except one case, diagnosed as NSIP by SLB. Non-IPF IIP cases except for one NSIP was diagnosed as unclassifiable IIP. Hence, we have modified “remaining 23 were unclassifiable IIP without SLB evaluation” in the section of Diagnosis of underlying IIPs.

Comment 2: Some of the classifications seem unclear as (a) one of the patients in this group is classified as having a UIP pattern on HRCT and (b) 8 patients in the non-IPF IIP group have a possible UIP pattern but only 1 biopsy was performed?

Reply 2: I have added the footnote of Table S1; “**”: This case is SLB-proven nonspecific interstitial pneumonia; however, HRCT pattern at stable state evaluated by final HRCT before AE was UIP pattern with honeycombing.”

In all cases, HRCT at stable state was evaluated by final HRCT before AE. Hence, this kind of discrepancy can happen.

I am sorry, but we cannot perform SLB for all IIP patients. As for the 8 patients, SLB was not performed due to complication of old myocardial infarction in one, old age in 4 cases. The rest of 3 cases refused to undergo SLB.

Comment 3: The authors should restructure some of their results as the final message and the added value of KL-6 compared to HRCT pattern alone could be brought

forward more clearly.

Reply 3: We have drastically changed the order and the content of results section. Some information used in the discussion was moved in the results of revised manuscript. (p.16, L.4-p.18.L1)

Comment 4: The authors should try to validate their findings on an additional cohort, preferentially with patients included after 2011.

Reply 4: I am sorry, but this study included AE-IIP cases until 2016, hence, we could not collect similar number of cases from 2017 until now; however, we have another analysis using the subjects between 2011 and 2016, a part of the cohort of this study. Our classification of AE-IIP using HRCT pattern and KL-6 is also proved to be useful for the AE-IIP subjects between 2011 and 2016.

Changes in the text: We added the next sentence; “The classification can also predict survival AE-IIP patients who were diagnosed between 2011 and 2016 (n=31) (see Table S7, Supplementary file 10).” (p.18, L.13-15)

Comment 5: The authors state that KL-6 and SP-D are “recognized” serum biomarkers in IPF and IIP. I would be careful with such a statement as (a) their use is not validated and (b) in IIP the data is scarce.

Response 5: I am sorry, I have modified the manuscript according to your suggestions. Changes in the text: We have modified the expression of background to the next sentence: “Krebs von den Lungen (KL)-6 and surfactant protein (SP)-D are serum biomarkers of ILDs and prognostic significance was suggested in IPF and the other IIPs”.(p.7, L.9-10)

Comment 6: The SLB were probably performed at diagnosis but this is not clear in the text, the authors should correct this.

Reply 6: According to your comment, we have added one sentence in the section of “Diagnosis and treatment of AE-IIPs”

Changes in the text: SLB was not performed for the diagnosis of AE-IIPs.(p.11, L.3)

Comment 7: The authors should define “clinical IPF” as compared to “IPF”, do they mean “working diagnosis of IPF?”

Reply 7: Clinical IPF cases means IPF cases with UIP HRCT pattern before the onset of acute exacerbation without SLB evaluation, and they were not “working diagnosis of IPF”.

Changes in the text: We have changed “clinical IPF cases” to “clinically diagnosed IPF cases with UIP HRCT pattern” (p.9, L.9-10)

Comment 8: The authors state that they ruled out hypersensitivity pneumonitis based on bronchoscopic finding, they should mention they correlated this with clinical/radiological data if they did so.

Reply 8: We ruled out HP not only based on only bronchoscopic findings, but also radiological and other clinical findings. We have described as below.

We have already mentioned in the limitation section, we suppose “the possibility that we included AE patients with a disease other than an IIP cannot be excluded.”

Changes in the text: Chronic hypersensitivity pneumonia was ruled out based on clinical and bronchoscopic findings. Percentages of lymphocytes in BAL were less than 40%, except in two cases[22]. Granulomatous lesions were not detected on TBLB specimens. HRCT did not show prominent mosaic attenuation[22]. (p.10, L3-6)

Comment 9: The authors should be cautious with the statement: “Eight patients with unclassifiable IIPs and a possible UIP HRCT 12 pattern might have had IPF”. Do they have histological data for these patients?

Reply 9: We have included this expression because non-IPF case might include IPF, if SLB had been performed; however, we have no histological data. We have deleted this expression to avoid misleading.

Changes in the text: We have deleted this expression to avoid misleading. (p.10, L.11)

Comment 10: The authors state that serum markers were measured at the onset of the AE. Could they precise how many days after hospitalization/high dose immunosuppressive treatment as biomarker levels may vary with time during an AE (and compare between their groups, especially in the multifocal pattern)?

Reply 10: For almost all cases, if the cases were diagnosed as AE-IIP, Steroid therapy was started. Serum markers were measured within two days before the start of therapy. Median intervals for each the HRCT pattern (peripheral, multifocal, and diffuse pattern)

were 0 day (Table 2). Kruskal-Wallis analysis showed there was significant difference in the intervals. Treatment was started at the diagnosis of AE for all diffuse AE-IIP cases, interval was 0 days in other words.

Changes in the text: We have added in the footnote of Table 2; “The interval was ≤ 2 days for all cases. There was significant difference in the intervals. Treatment was started on the same day as the diagnosis of AE for all diffuse AE-IIP cases. The intervals for multifocal pattern and peripheral pattern were > 0 day in 11, 4 cases, respectively”. (p.39, L.11-13)

Comment 11: Some patients were treated with PMX-DHP, where incidental data exists concerning the lowering of SP-D. Could the authors comment on this?

Reply 11: You suggested important points; however, we do not have that kind of data. We would like to check it in the future cases.

Comment 12: The authors should dissociate current from former smokers in their demographic data.

Reply 12: We have dissociated current and former smokers in Table 1 and 2 as you suggested.

Comment 13: The authors should provide FVC and DLCO at diagnosis for each group.

Reply 13: I am sorry, FVC and DLCO could not be performed at the diagnosis of AE; however, we have added the results of pulmonary function test at the diagnosis underlying IIP in Table 1 and Table 2.

Comment 14: The authors should rephrase the fact that they used the median of δ KL-6(or SP-D)/ST-KL-6(or SP-D) as a cut-off as this could be clarified.

Reply 14: We have shown median of δ KL-6(or SP-D)/ST-KL-6(or SP-D) as a cut-off in the method section. We have added the information in the footnote of Tables.

Changes in the text:

We have described the cut-off; “Median values of Δ KL-6/ST-KL-6 and Δ SP-D/ST-SP-D were 0.211 and 0.410, respectively, and the two parameters were categorized into a higher and a lower group by their median values. (p.12, L.6-8).

We have added the cut off in footnote of Table 2; “† Δ KL-6/ST-KL-6 was divided into

higher/lower by its median value, 0.211. ‡ Δ SP-D/ST-SP-D was divided into higher/lower by its median value, 0.410.” (p.39, L.4-5)

Comment 15: Do the authors have (even incidental) histological data from patients with a low/high rise in KL-6 and a multifocal pattern in order to see if this corresponds to DAD/COP respectively.

Reply 15: I am sorry, but we have no histological data of AE-IIP. This is stated in the paragraph of limitation in the discussion. (p.24, L.13-15)

Comment 16: Could the authors comment on the fact that KL-6 and SP-D levels are almost significantly more elevated in the δ KL-6/ST-KL-6<0.211 multifocal group compared to >0.211 and that they had more oxygen? Is the absence of a rise due to increased baseline alveolar injury?

Reply 16: As you suggested we have added the sentence; “ST-KL-6 and ST-SP-D in multifocal pattern with lower Δ KL-6/ST-KL-6 tended to be higher than that with higher Δ KL-6/ST-KL-6 (see Table S4, Supplementary file 7)”. LTOT was more frequently introduced in multifocal pattern with lower Δ KL-6/ST-KL-6. Then we suppose that increase in baseline KL-6 and SP-D (ST-KL-6 and ST-SP-D) is due to the baseline alveolar injury.

Changes in the text: We have added below:

ST-KL-6 and ST-SP-D in multifocal pattern with lower Δ KL-6/ST-KL-6 tended to be higher than that with higher Δ KL-6/ST-KL-6 (see Table S4, Supplementary file 7)(p.17, L.2-3)

ST-SP-D of multifocal pattern and lower Δ KL-6/ST-KL-6, suggesting histological DAD, tended to be higher than that of multifocal pattern and higher Δ KL-6/ST-KL-6. Hence, higher ST-SP-D might suggest presence of increased baseline alveolar injury and future occurrence of DAD-type AE. (p.24, L.2-5)

Comment 17: Could the authors provide similar data regarding the IPF cohort (ie is the effect preserved when isolating IPF patients?)

Reply 17: We have examined similar analysis for IPF cases. We re-analyzed prognostic factors for AE-IPF and adjusted the prognostic significance of proposed classification of AE-IIP using HRCT and KL-6 for AE-IPF. Then, similar usefulness of our

classification of AE-IIP was confirmed for AE-IPF. We have added Table 6 and Figure 2.

Changes in the text: We have added; Our proposed classification of AE-IIP patients can predict the survival of AE-IPF (n=53) (Table 6) after adjustment for other prognostic factors, although univariate analysis cannot show the significant survival difference (p=0.057, Wilcoxon test) (Fig.2).(p.18, L.11-13)

Comment 18: Figure 1 should be reworked with a clear legend as to which line is which group.

Reply 18: As you suggested, we have modified the figure 1a-1d.

Comment 19: The authors should clearly state if there is histologic material available at the time of exacerbation as this could provide some insights in the underlying histologic pattern.

Reply 19: I am sorry, but we have no histological material at the diagnosis of acute exacerbation. We have already described the problem of histology at AE in the discussion. This part was simplified according to the suggestion of reviewer A. Histology might be able to provide some insights as previously reported; however, there is some problem in general clinical settings. Please see the Changes in the text.

Changes in the text: SLB-proven OP in AE-IPF was associated with better survival in both these reports. However, radiologic findings might be more important than histologic findings in general clinical settings when diagnosing AE-IPF and predicting patient survival because morphological overlaps between organizing DAD and OP[29] and sampling errors due to the patchy nature of acute lesions in AE-IPF[27] were reported.