Author’s response to reviews

Title: Emphysematous change with scleroderma-associated interstitial lung disease: The potential contribution of vasculopathy?

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Reviewer reports:

Andrea Gramegna (Reviewer 1): To the authors:

This paper is a retrospective observational study on a small population of SSc-ILD coming from a single center. The study aimed to define this population according to three different dominions: clinical, radiological and pathological.
Major comments

1) The surgical lung biopsies were collected between 1997 and 2016. What about CT? This should be acknowledged as a limitation of the study and focus each aspect that may have changed since then in order to demonstrate the results not obsolete.

⇒ Reply: Thank you for your incisive comments. As you pointed out, not enough information was available. We added this point in the limitations paragraph as follows:

「Fifth, we used several types of HRCT scanning with the times. Therefore, imaging protocol may lead to a little different interpretation of radiological finding.」

2) Were all diagnosis re-defined at the light of the latest criteria?

⇒ Reply: Diagnosis of SSc was made by rheumatologists at other institution. As mentioned in the Methods paragraph, patients with SSc fulfilled the revised criteria for SSc of the ACR/EULAR classification. Additionally, as pathological classification of interstitial pneumonia, two pathologists review by the current classification of idiopathic interstitial pneumonia. In other words, we re-reviewed both SSc and interstitial pneumonia diagnosis. We would greatly appreciate your kind understanding of this matter.

3) Page 6, lines 56-59. I cannot understand the meaning.

⇒ Reply: Thank you very much for your comments. Therefore, we revised this sentence as follows

「The HRCT scans were analyzed for the following characteristics: honeycombing, ground-glass opacity, consolidation, reticulation, emphysema, cyst, traction bronchiectasis, bronchial wall thickening, mosaic attenuation, pulmonary artery dilation, enlarged mediastinal lymph nodes, micro-nodules, pleural thickening or effusion, and volume loss. These features were selected on the basis of previous studies.」

4) Page 9, line 1: it may be worth to say that there is no statistical difference between the two groups in term of smoking status

⇒ As you pointed out, this issue was very important to the readers. Therefore, we added the following sentences: 「Smoking history for patients with each type were not significantly different.」
5) Page 9, line 20: reticulation? Try to use the same terms you gave definitions in methods

⇒ Reply : Sorry. As you pointed, we revised the manuscript.

6) I cannot understand the meaning of the 'case descriptions' paragraph. Is this a sort of synopsis of results? I suggest not to repeat results in this paragraph and to include not-duplicated informations in the standard Result section.

⇒ Reply : This is just as you indicated. Therefore, we avoided a repetition and then simplified the results paragraph on this matter.

7) I would appreciate a synthesis of the major findings at the very beginning of the Discussion section. It is useful for the reader to better understand the following discussion.

⇒ Reply : Thank you for your important comment. Therefore, we added the following sentence in the beginning of Discussion paragraph.

「This study presented that pulmonary emphysematous changes (LAA within interstitial abnormalities on HRCT and destruction of fibrously thickened alveolar walls) are specific and novel radio-pathological features of SSc-ILD.」

8) Page 12, line 10-20: if you have excluded cicatricial emphysema (as per methods), please remove that sentence

⇒ Reply : As you pointed out, because of repeating this sentence (i.e. cicatrical emphysema), our mention might be importunate. However, this matter is very important in our manuscript and we thought that readers may take pains to understand. In order to avoid misunderstanding, we considered this sentence in Discussion as important. We would be very grateful for your consideration in regard to this matter.

9) Your second major findings sounds a bit strong in comparison to your data. I would re-formulate this paragraph (page 12) in a more dubitative / hypothetical tone.

⇒ Reply : We completely agree with you. Therefore, we re-formulated this paragraph and softened our hypotheses.
10) Page 13, from line 1 to line 33. Consider to shorten it to a couple of sentences.

⇒ Reply : As you pointed out, We simplified the paragraph on the mechanism of pulmonary emphysema formation. We would be grateful for your consideration in regard to this matter.

Minor comments

11) Page 8, 2nd line in Results: a parenthesis is missing.

⇒ Reply : I'm terribly sorry. We revised this point.

12) Page 8, line 56: please specify the absolute number of pPE patients.

⇒ Reply : As you pointed out, we specified the absolute number (16 patients).

13) Page 9, line 17: almost all (?), please specify the numbers.

⇒ Reply : As you pointed out, we revised this sentence as follows : 「The major HRCT pattern was NSIP in 19 patients (90.5%).」

Nobuhiro Akuzawa, M.D., Ph.D. (Reviewer 2): Authors present novel findings including radiographical and pathological characteristics regarding SSc-ILD. Basically, this manuscript is well-written. Some points should be revised.

Major points:

1. Authors refer to lung vasculopathies associated with SSc-ILD. If possible, please show data concerning pulmonary hypertension (e.g. estimated right ventricular pressure based on echocardiography), because pulmonary artery hypertension (PAH) is a fatal complication of SSc with a poor prognosis.

⇒ Reply : Thank you for pointing out this very important issue. Therefore, we added this point in the methods paragraph and Table 1 as far as we could get available data (RVSP on
echocardiography). Additionally, we added this limitation as follows: 「Additionally, only two patients received PAH-specific drug therapy during the follow-up period, and most patients could not be evaluated for PAH by right heart catheterization.」

2. Certainly as authors say, microcirculation impairment and related vasculopathy is a hallmark of systemic sclerosis and thus may cause digital ulcers or renal crisis. Basically, SSc is a systemic disease. However, this manuscript lacks data of clinical findings (e.g. whether such findings as digital ulcers, hypertension, renal dysfunction and so on exist or not.) Please add and analyze data that may be important to evaluate general conditions of SSc patients. Moreover, please clarify medication history profile including vasodilators (endothelin receptor antagonists, PDE-5 inhibitors and prostacyclin and so on.) If possible, medication history regarding ACE-inhibitors and Ca-antagonists should be also added.

⇒ Reply: Thank you for the very precise identification. We added these points (i.e. digital ulcers, renal dysfunction, hypertension, PAH-specific drug, ACE-inhibitor, and Ca-antagonists) in Table 1 (and Table 1 legend as follows): 「†PAH-specific drugs include only beraprost sodium (N = 2).」

Minor Points:

1. In the Methods section: authors should be careful of usage of abbreviation(s). "Suggestive of UIP [unusual interstitial pneumonia]" is inappropriate. "Suggestive of unusual interstitial pneumonia (UIP)" is appropriate.

⇒ Reply: As you pointed out, we revised this sentence.

2. In the Method section: "The HRCT scans were analyzed for t positive findings discriminated on the basis of previous studies." Please add a brief explanation regarding "t positive findings."

⇒ Reply: Thank you very much for your comments. Therefore, we revised this sentence as follows

「The HRCT scans were analyzed for the following characteristics: honeycombing, ground-glass opacity, consolidation, reticulation, emphysema, cyst, traction bronchiectasis, bronchial wall thickening, mosaic attenuation, pulmonary artery dilation, enlarged mediastinal lymph
nodes, micro-nodules, pleural thickening or effusion, and volume loss. These features were selected on the basis of previous studies.

3. In the Results section: "The proportion of patients who smoked was 38.1%" In my opinion, "the proportion of patients who had smoke" may be appropriate. Please clarify this point. In addition, authors probably forget to type a close bracket "3 patinets (14.3%)."

⇒ Reply: Thank you for your important comment. Therefore, we revised these matter as you pointed out.

4. In the Table 1: Mistyping ("mediation") should be revised.

⇒ Reply: I'm terribly sorry. We revised this point.

5. EULAR/EUSTAR recommends that CYC should be considered for the treatment of SSc-ILD, but the proportion of patients treated with CYC is no more than 25% in p-PE with SSc-ILD patients. Authors had better consider and refer to recommended therapeutic strategies to p-PE with SSc-ILD.

⇒ Reply: As you pointed out, CYC should be considered for SSc-ILD treatment. However, because SSc-ILD is refractory to pharmacological therapies including steroids and/or immune-suppressants, the selection of an appropriate treatment is difficult. In randomized controlled trials, treatment with CYC and AZP has been reported to improve the pulmonary function of patients with SSc-ILD. The effects of treatment with Cyclosporine for IIPs and CTD-ILD have also been reported. In contrast, meta-analyses have shown that the treatment of SSc-ILD patients with CYC did not significantly improve their pulmonary function. The patients in our study might be mild grade with SSc-ILD as mentioned above, and therefore, the proportion of patients treated with CYC is no more than 25%. That is just as you pointed out, our study focused on not therapeutic strategy but radio-pathological finding. Because of getting off track and become to be longer sentence, we apologize beforehand if our revision would not fully respond in the length.