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**Reviewer A**

**General comments:** In this paper, the authors compared the clinical and CT presentations of patients with IIM-ILDs with those of patients with non-IIM CTD-ILDs in a real-world setting. The authors concluded that IIM-ILDs were more likely than non-IIM CTD-ILDs to present acutely and simultaneously with the onset of the IIM, and that IIM-ILDs were associated with higher odds of NSIP/OP and younger age of onset.
IIM-ILDs are notorious for their frequently fulminant course and dismal prognosis. The authors are commended for their work focusing on this topic, and for their painstaking effort and thorough review and collection of important data in carrying out this clinical study. However, there are concerns regarding a number of aspects of this paper that must be addressed before further recommendation for its publishment

**Reply:** We thank the Reviewer for a careful review and valuable comments. Our replies can be found below each comment. In the manuscript, the revisions are marked by red color.

**Comment 1:** IIM-ILDs are known for their acute and often rapidly progressive course and their presentation even before the onset of musculo-cutaneous manifestations. Lone ILD is possible. The prognostic roles of certain myositis-specific/-associated Abs have also been repeatedly described. It is not a novel rationale for rheumatologists, pulmonologists, and intensivists to include IIM-ILD in the differential diagnosis for unexplained pneumonitis / ARDS. A review by Jablonski et al in 2020 have already provided detailed discussion about these issues (CHEST 2020; 158(1):252-263). This present work supports for the existing rationales, but seems not to add much novel knowledge to this topic in its present form.

**Reply 1:** As the Reviewer stated, IIM-ILDs have a dismal reputation of rapid or fulminant course. This reputation is, however, based on uncontrolled cohorts consisting of only patients with IIM or IIM-ILD. We were unable to find any comparative studies in which the control group consists of other CTDs.

Depending on populations and definitions, high percentages of acute onset ILD have been detected in both IIM-ILD and non-IIM-ILD cohorts as well. For example, in a series of 107 patients with DM/PM related ILD, 18.7% presented with acute onset ILD, 51.4% with progressive lung manifestations, and 29.9% were asymptomatic (1). On the other hand, Roca and colleagues have showed that 23.8% of the patients with SjS-ILD patients had an acute onset disease (2). Also, in SLE an acute lupus pneumonitis is observed in 1-14% of patients (3,4) while in a series of 55 patients with SLE-ILD an acute form of ILD was seen in 12.7% of the patients (5). In RA-ILD, the radiological OP pattern which typically clinically presents an acute disease, has been detected in up to 11% of the patients (6).

Therefore, we think that it is justifiable to state, that the acute onset of ILD is not a phenomenon that solely applies to IIM. Without controlled studies one cannot state that some feature is more common in one disease compared to other diseases. Thus, we think that the present comparative study was necessary.

Jablonski et al. have indeed described how clinicians should manage ARDS patients keeping IIM-ILD in mind. However, in that review they also state that in real-life, this does not often actualize and that the appropriate antibody tests are often not conducted. Therefore, Jablonski et al. have suggested more clinical studies to be performed to increase the understanding and recognition of IIM-ILD (7).

**Changes in the text:** We have tried to explain the rationale of this study in the third paragraph of the Introduction. We have not added further information in it to keep the introduction short.

**Comment 2:** The cohort of non-IIM CTD-ILDs was consisted of patients with various CTDs. Although grouped together in this present study, the ILDs associating with different CTDs may have very different clinical/CT manifestations and trajectories (ex. the course of scleroderma-ILD may be quite different from that of RA-ILD; different patients with Sjogren synd.-ILD may have different speed of progression). In other words, the comparison made in this study may be confounded by the heterogeneity among patients with different CTD-ILDs. One suggestion regarding this issue - maybe the author may consider to narrow the focus a bit and compare, for example, IIM-NSIP with Sjogren synd / MCTD / RA-related NSIP.

**Reply 2:** The Reviewer is correct about the fact, that CTD-ILDs are a very heterogenous group, not only regarding to the disease course or CT presentations but other aspects as well. This is also true within a single CTD-ILD; any CTD-ILD consists of a spectrum of different clinical and radiological presentations.

However, the basis of the present study was the existing scientific literature and clinical experience, which both strongly suggest that the clinical course of IIM-ILD differs from that of other CTD-ILDs. In the present study we wanted to perform a direct comparison to explore whether this actually is the case. We collected a cohort large enough to have sufficient statistical power to compare these populations. Any constrictions in the control population would presumably deteriorate the statistical power.

In our study, the radiological patterns were quite variable in each CTD-ILD, although RA-ILD expectedly was an exception with a high percentage of UIP / probable UIP patterns. Consequently, narrowing the cohort based on radiological pattern, for example only to NSIP as suggested, would shrink the cohort from 154 patients to only 19 patients. Reaching sufficient statistical power is not possible with such a small patient population.

Of note (Table 2), IIM-ILD too can manifest in all possible radiological ILD patterns, UIP, NSIP, NSIP/OP overlap *etc*. Therefore, it is perhaps not rational to restrict the analysis to a specific radiological ILD pattern like NSIP or UIP. We have, anyhow, checked whether leaving all patients

with a radiological UIP out would change the results. It did not. This data (below in table) was not added to the revised manuscript.

| | **All CTD-ILD (n=100)** | **IIM-ILD (n=19)** | **other CTD-ILD (n=81)** | **p-value** |
|---|---|---|---|---|
| ILD before CTD or simultaneously | 62 (62.0) | 18 (94.7) | 44 (54.3) | 0.001 |
| **Onset** | | | | |
| Acute, ICU | 6 (6.0) | 5 (26.3) | 1 (1.2) | 0.001 |
| Acute, ICU or pulmonology ward | 35 (35.0) | 12 (63.2) | 23 (28.4) | 0.004 |
| NSIP/OP overlap in HRCT | 8 (8.0) | 6 (31.6) | 2 (2.5) | <0.001 |
| Age | 65.0 (26.3 – 84.0) | 59.5 (35.8 – 74.8) | 66.3 (26.3 – 84.0) | 0.020 |
| Fever* | 37 / 61 (60.7) | 12 / 14 (85.7) | 25 / 47 (53.2) | 0.029 |

*data not available from all patients

One possibility to narrow the focus could also be to leave the RA-patients out due to the predominating UIP pattern and a high proportion of them in the control group possibly causing bias, which was addressed by Reviewer 2 (please see Comment and Reply 2). We have now added a sensitivity analysis omitting the RA patients to the revised version of the manuscript.

| | **All CTD-ILD (n=76)** | **IIM-ILD (n=18)** | **Other CTD-ILDs (n=58)** | **p-value** |
|---|---|---|---|---|
| Age | 64.5 (26.3 – 84.0) | 61.2 (48.2 – 74.8) | 65.5 (26.3 – 84.0) | 0.169 |
| Fever* | 33 / 42 (78.6) | 13 / 14 (92.9) | 20 / 28 (71.4) | 0.111 |
| ILD before CTD or simultaneously | 63 (82.9) | 18 (100.0) | 45 (77.9) | 0.021 |
| **Onset** | | | | |
| Acute, ICU | 5 (6.6) | 5 (27.8) | 0 (0.0) | <0.001 |
| Acute, ICU or pulmonology ward | 26 (34.2) | 12 (66.7) | 14 (17.3) | 0.001 |
| **Radiological pattern** | | | | |
| UIP or probable UIP | 22 (28.9) | 3 (16.7) | 19 (32.8) | 0.188 |
| NSIP | 10 (13.2) | 3 (16.7) | 7 (12.1) | 0.614 |
| OP | 13 (17.1) | 5 (27.8) | 8 (13.8) | 0.169 |
| NSIP/OP overlap | 6 (7.9) | 6 (33.3) | 0 (0.0) | <0.001 |

*data missing form 4 IIM-ILD patients and 30 others

**Changes in the text:** This new table was added as Table 5. New sentence was added to the Results (page 8, paragraph 4): “In sensitivity analysis omitting the patients with RA, the IIM-ILD patients were still statistically significantly more likely to develop an acute onset of the ILD simultaneously or prior to CTD with more overlap NSIP/OP radiological appearance (Table 5)” and in the Methods (page7, paragraph 1): “A sensitivity analysis omitting the patients with RA was also performed.“ In the Discussion (page 12, paragraph 1) this issue was addressed as follows: “A high proportion of

RA-ILD patients could have caused a bias, but the sensitivity analysis omitting them did not change the main results."

**Comment 3:** Extending from point 2: For CTD-ILDs, NSIP and UIP may be regarded as two ends of a spectrum of pulmonary parenchymal pathological changes. End-stage ILD, regardless of what the initial pattern is, may all look like UIP. Therefore, the finding that IIM-ILD was more likely to manifest as NSIP/OP may actually be attributed to the timing of detection relative to other CTD-ILDs, rather than being an independent phenotypic finding.

**Reply 3:** Indeed, UIP is often regarded as an end-stage ILD pattern. However, to the best of our knowledge, there is scarcity of follow-up studies showing an evolution from NSIP/OP to UIP. Furthermore, in most articles (8,9), a certain type of typical ILD pattern seems to be consistent for a specific disorder regardless of the timing of the evaluation (UIP typical for rheumatoid arthritis, NSIP typical for scleroderma *etc*.). Finally, also patients with a radiological UIP pattern may present an acute onset of the ILD, which we have now expressed in the text.

**Changes in the text:** A new sentence was added to the Results (page 8, paragraph 4): "Among all subjects with acute onset ILD the most common radiological patterns were OP (41.5%), UIP/probable UIP (19.5%), NSIP (12.2%), and NSIP/OP overlap (12.2%)."

**Comment 4:** The exclusion of infectious process, particularly opportunistic infections, was not addressed in the main text as well as the supplemental tables. This is important especially for those patients presenting with fever and an acute and severe disease (for example, opportunistic infections by CMV or Pneumocystis carinii may masquerade as NSIP / OP).

**Reply 4**: We thank the Reviewer for this very relevant comment. Since this is a retrospective study, there was no systematic list of microbiological samples taken from all participants. Each patients´ medical records were carefully read. In all cases with a possibility of an acute respiratory infection, appropriate microbiological samples were collected according to the clinician´s consideration. For example, BAL was performed in 63.4% of the patients with an acute onset disease.

**Changes in the text:** The following sentence was added to the "Methods" (page 6, paragraph 3): "In all cases with a possibility of an acute respiratory infection, appropriate microbiological samples were collected according to the clinician's consideration. Bronchoalveolar lavage was performed in 63.4% of the patients with an acute onset disease to exclude infections."

**Comment 5:** The tables contain abundant information, but the layout was a bit difficult to follow. This may be improved by the adjustment in subtitles and indentation.

**Reply 5:** We agree that particularly Table 1 is a bit complex and tried to improve the readability.

**Changes in the text**: Indentations were added and spacing was slightly increased in Table 1. In Table 2, the line "fever" was transferred above "lung functions". In Tables 2-3, the subtitles were marked using bold text.

**Comment 6:** Table 5 and 6 were mentioned only briefly in one sentence - may consider shifting them to the supplemental material.

**Reply 6:** This is also true, thank you for the suggestion.

**Changes in the text:** As suggested, we moved tables 5 and 6 to the supplement. The last paragraph of the results (page 8) was therefore altered as follows: "Detailed data of each IIM-ILD patients diagnostics, treatment, outcome and given medications is described in supplementary Tables S2-S4."

**Comment 7:** Some grammar errors.

**Reply 7:** We apologize for the errors. The manuscript was checked several times, but still errors are possible, especially for non-native English writers. We tried our best to find as many as possible and fix them but unfortunately some may still remain.

**Changes in the text:** In the Introduction, the article "an" was added before the words "acute respiratory failure" (page 3, paragraph 3). In the "Methods", the abbreviation "SjS" was corrected (page 4, paragraph 2.1). Similar error was corrected in Table 1. In page 5, paragraph 2.3 the article "a" was added before the word "disagreement". In the last paragraph of the "Discussion" (page 12), the word "re-analyzed" was corrected. In "Conclusion" the order of the words and the word "dyspnoea" were corrected.

**Reviewer B**

**General Comments:** The authors gathered clinical and radiological data from 22 IIM-ILD and 132 other CTD-ILD patients. They compared the data using multivariate analysis and found that the patients with IIM-ILD were younger, more often non-smokers, and displayed radiological NSIP/OP overlap patterns more frequently. In multivariate analysis, NSIP/OP overlap pattern, acute onset disease treated in the intensive care unit, and ILD preceding or being diagnosed simultaneously with CTD were significantly associated with IIM-ILD. The authors conclude that, unlike other CTD-ILDS, IIM-ILD often develops acutely, simultaneously with the systemic disease. This report includes valuable information but has several concerns.

**Reply:** We thank the Reviewer for a careful review and comprehensive comments. Our replies can be found below each comment. In the manuscript, the revisions are marked using red color.

**Major Comments**

**Comment 1:** Rationale of the study

The authors state that the clinical presentation of any CTD-ILD can vary from an indolent disease course to acute respiratory failure and that, in particular, those with CADM and/or MDA5 positivity and ASyS presented an acute onset of disease. They rationalize their study because a rapid disease onset has also been described in other CTD-ILDs.

Although the exact clinical presentation of RA-associated ILD depends on the underlying lung pathology, symptoms often develop insidiously. They include dyspnea on exertion and a nonproductive cough (UpToDate, Interstitial lung disease in rheumatoid arthritis, last updated: Aug 05, 2022). In addition, SSc-associated ILD typically presents with the subacute onset of dyspnea on exertion and sometimes nonproductive cough (UpToDate, Overview of pulmonary complications of systemic sclerosis (scleroderma), last updated: Oct 22, 2021).

Since a rapid disease onset is unlikely in other CTDs, is it rational to compare clinical and radiological data between IIM-ILD and other CTD-ILD?

**Reply 1:** We thank the reviewer for the important issue, which was also raised by reviewer 1. However, we would like to highlight that there are no previous direct comparative studies to explore the differences in clinical courses of IIM-ILD and other CTDs.

Depending on populations and definitions, high percentages of acute onset ILD have been detected in both IIM-ILD and non-IIM-ILD cohorts as well. For example, in a series of 107 patients with DM/PM related ILD, 18.7% presented with acute onset ILD, 51.4% with progressive lung manifestations, and 29.9% were asymptomatic. (1). On the other hand, Roca and colleagues have showed that 23.8% of the patients with SjS-ILD patients had an acute onset disease (2). Also, in SLE an acute lupus pneumonitis is observed in 1-14% of patients (3,4) while in a series of 55 patients with SLE-ILD an acute form of ILD was seen in 12.7% of the patients (5). In RA-ILD, the radiological OP pattern which typically clinically presents an acute disease, has been detected in up to 11% of the patients (6).

Therefore, we think that it is justifiable to state, that the acute onset of ILD is not a phenomenon that solely applies to IIM. Without controlled studies one cannot state that some feature is more common in one disease compared to other diseases. Thus, we think that the present comparative study was necessary.

**Changes in the text:** We have tried to explain the rationale of this study in the Introduction, third paragraph. We have not added further information in it to keep the introduction short.

**Comment 2:** Composition of CTD-ILD

The authors show CTD diagnoses in the cohort of 154 patients. According to them, the most common CTDs were RA (78/50.6%), followed by UCTD (23/15.0%), IIM (22/14.3%), and SSc (18/11.7%). The results mean more than half of the CTD-ILDs are associated with RA. Does that cause significant bias when comparing IIM-ILD and other CTD-ILD?

**Reply 2:** The reviewer is correct that a bias is possible due to the high proportion of patients with RA. Without them, the total cohort would have comprised of 76 patients and the IIM-ILD subgroup would have been diminished to 18 patients, since four patients had concomitant RA and IIM-ILD.

The basis of the present study was the existing scientific literature and clinical experience, which both strongly suggest that the clinical course of IIM-ILD differs from that of other CTD-ILDs. In the present study we wanted to perform a direct comparison to explore whether this actually is the case. We collected a cohort large enough to have sufficient statistical power to compare these populations. Any constrictions in the control population could have made the statistical power insufficient.

We have, however, now added a sensitivity analysis omitting the RA patients. The main results remained the same and are shown below. Age and fever, however, lost their statistical significance in this comparison.

| | **All CTD-ILD (n=76)** | **IIM-ILD (n=18)** | **Other CTD-ILDs (n=58)** | **p-value** |
|---|---|---|---|---|
| Age | 64.5 (26.3 – 84.0) | 61.2 (48.2 – 74.8) | 65.5 (26.3 – 84.0) | 0.169 |
| Fever* | 33 / 42 (78.6) | 13 / 14 (92.9) | 20 / 28 (71.4) | 0.111 |
| ILD before CTD or simultaneously | 63 (82.9) | 18 (100.0) | 45 (77.9) | 0.021 |
| **Onset** | | | | |
| Acute, ICU | 5 (6.6) | 5 (27.8) | 0 (0.0) | <0.001 |
| Acute, ICU or pulmonology ward | 26 (34.2) | 12 (66.7) | 14 (17.3) | 0.001 |
| **Radiological pattern** | | | | |
| UIP or probable UIP | 22 (28.9) | 3 (16.7) | 19 (32.8) | 0.188 |
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**Comment 3:** Underlying diseases of IIM-ILD

The authors state that it is unclear whether IIM-ILD has a distinct clinical presentation among CTD-ILDs. IIM is, however, a heterogeneous group of disorders characterized by muscle inflammation

and weakness, including DM/CADM, PM, and inclusion body myositis, as well as ASyS. In particular, MDA-5 antibodies can be associated with a rapidly progressive course of ILD and vasculopathy affecting the skin. Thus, it seems unreasonable to consider IIM-ILD as a single entity for comparison.

**Reply 3:** Again, the reviewer makes a good point. However, as the results show, despite of the heterogeneity of these disorders we have been able to point a clinically distinguishable group of patients with an acute and potentially fatal lung manifestation. Narrowing the analysis based on a specific antibody may be problematic in many ways: 1) Given the rarity of IIM-ILD, gathering a statistically powered cohort of patients with a specific IIM and a specific antibody may be difficult. 2) As we saw in this study, the acute onset was not limited to MDA-5 positive individuals, which was mentioned in the results (page 8, paragraph 2). 3) In a real-life situation, the IIM-ILD patients must be recognized early on clinical grounds, before the antibody assay results confirming IIM have arrived.

**Changes in the text:** -

**Minor Comments**

**Comment 1:** Typo

DLCO should be DLco throughout the manuscript.

**Reply 1:** Thank you for your exactness.

**Changes in the text:** This word is now corrected throughout the manuscript and tables.

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