Editorial

The challenges in classifying rheumatoid arthritis-associated interstitial lung disease

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Interstitial lung diseases (ILD) constitute a large group of disorders with variable prognoses and treatment options (1). The current international guidelines on idiopathic interstitial pneumonias (IIP) and idiopathic pulmonary fibrosis (IPF), the most common type of IIP, have focused on the classification of subtypes based on high-resolution computed tomography (HRCT) patterns (2,3). At present, no similar classification guidelines to those for IPF and IIP have been issued for connective tissue disease (CTD)-related, such as rheumatoid arthritis-associated ILD (RA-ILD). Instead, these classification guidelines of IIP and IPF have often been adopted in clinical practice. Due to the risks associated with surgical lung biopsies, most patients are diagnosed and classified into the different subtypes based only on HRCT (4,5). A very recent review has nicely summarized studies reporting RA-ILD HRCT patterns and mortality (6).

Predicting the survival of the individual patient with ILD is extremely challenging, and only a few studies have explored this issue in RA-ILD (7). Thus, clinicians have very few tools to assist them when making a prognosis estimation in patients suffering from RA-ILD. Previously, factors reflecting the RA severity have been proposed to associate with worse survival, including increased erythrocyte sedimentation rate and high visual analogue pain scale, etc. (7). Male sex, age and both baseline lung function test results and the longitudinal change of their values have also associated with mortality (7-9).

In addition, some previous studies have investigated the prognostic role of HRCT and revealed that the extent of the radiologic ILD changes was related with mortality (10,11), and that the usual interstitial pneumonia pattern (UIP) in HRCT associated with worse survival than the other subtypes (12-14), although this has not been detected by all investigators (15). Some findings from our recent study revealed that the extents of reticulation, traction bronchiectasis and architectural distortion were associated with decreased survival, whereas the presence or extent of honeycombing was not beneficial in predicting survival, even though it correlated with hospitalizations due to respiratory reasons (16). Our finding contrasts with the study of Kim *et al.* in which the extents of honeycombing and traction bronchiectasis were independent predictors of worse outcome (12).

Overall, the studies regarding to the predictive value of HRCT in RA-ILD are sparse and partly controversial. Therefore, we read the article of Hideaki Yamakawa and co-authors with much interest and thank the authors for investigating this important topic (17).

They have analyzed the medical records of 96 patients

with RA-ILD using combined modified IPF (ATS/ERS 2018) and IIP (ATS/ERS 2013) guidelines for the classification of the cases, with the aim of identifying factors that would predict mortality by examining HRCT patterns. RA diagnoses were confirmed by a rheumatologist and a positive anticyclic citrullinated peptide (anti-CCP) value. In the study protocol, each subject's radiological findings were reviewed by two expert pulmonologists, but not by radiologists. Disagreements between the two pulmonologists were resolved by discussion and the interrater agreement between them was shown to be good (kappa value 0.75).

The cases were categorized based on HRCT into seven subgroups, namely definite UIP, probable UIP, indeterminate for UIP, non-specific interstitial pneumonia (NSIP), organizing pneumonia (OP), NSIP + OP and unclassifiable patterns. The authors concluded that indeterminate for UIP pattern (30%) was the most common type. One may speculate whether this conclusion was clinically meaningful, since if one combined the definite UIP (21%) and the probable UIP patterns (20%) then this accounted for more than 40% of the cases.

Different subtypes did not correlate positively with survival, which was in contrast to the results of some previous studies (8,12,14), whereas the existence of honeycombing did show a correlation. One may wonder, however, if the analyses had been performed differently, e.g., by comparing definite UIP cases with all other cases, or definite and probable UIP cases together with all others, then this might have produced somewhat different results. Indeed, in the rather recent longitudinal study of Yunt *et al.* the combined group of definite and possible UIP patterns had a significantly worse survival than the NSIP patients (18). Moreover, as the disease progressed, almost every second patient originally displaying a probable UIP pattern developed a definite UIP pattern (19). In addition, Yamakawa's group has recently published another study focusing on honeycombing in RA-ILD, revealing that honeycomb formation occurred in 40% of those RA-ILD patients in whom it was not present at baseline HRCT (20). Analyzing the longitudinal change or the extent of the radiological changes would have strengthened the present study even more. Furthermore, it remained unclear how the existence of honeycombing was detected—by reviewing the radiological reports or by re-analyzing HRCTs?

The question of distribution of the ILD changes is important but difficult to resolve. In idiopathic ILD forms, the distribution in the definite UIP pattern is typically subpleural and basal predominant, but often heterogeneous (2,3). In RA-ILD, the distribution of disease may not display a basal predominance but reticulation and honeycombing can be concentrated in the middle or upper zones of the lungs (21). In the recently published study of Jacob *et al.*, RA-ILD patients with a definite UIP pattern regardless of whether the distribution was IPF-like or not, demonstrated a similar outcome (22). In the study on which we are commenting here, the NSIP/UIP category was selected if the distribution was central/diffuse even when reticulation with traction bronchiectasis and honeycombing were present and ground-glass opacities were inconspicuous (17). Perhaps these patients could have been categorized as definite UIP? Honeycombing was present only in the definite UIP and in the NSIP/UIP subgroups. Some patients in the latter subgroup could just as correctly have been categorized as definite UIP, which might have changed the results.

We congratulate the authors for the clever study protocol and for compilation of the modified classification; however this would have been even more valuable if the HRCT scans had been re-analyzed by thoracic radiologists. This fact was also stated by the authors themselves who have mentioned in the discussion as the limitation of their study as follows: "*Expert thoracic radiologists should analyze HRCT findings, not pulmonologists*". Several previous studies have shown that the repeatability between radiologists on HRCT patterns analyses in IPF is low (23-25). Thus, one may assume that the repeatability between radiologists in a modification involving two distinct guidelines, as done in the present study and examining several IIP patterns would be even lower that simply analyzing IPF.

The authors have, however, presented a suitable combination of the two present classifications of IIP and IPF. Hopefully this will increase the interest of experts in this field in developing its own specific radiological classification for RA-ILD, which would be beneficial not only for research purposes but would also be of assistance in clinical practice.

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Footnote

Conflicts of Interest: Both authors have completed the

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References

1. American Thoracic Society, European Respiratory Society. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. Am J Respir Crit Care Med 2002;165:277-304.
2. Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2018;198:e44-68.
3. Travis WD, Costabel U, Hansell DM, et al. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 2013;188:733-48.
4. Kaarteenaho R. The current position of surgical lung biopsy in the diagnosis of idiopathic pulmonary fibrosis. Respir Res 2013;14:43.
5. Raghu G, Remy-Jardin M, Myers J, et al. The 2018 Diagnosis of Idiopathic Pulmonary Fibrosis Guidelines: Surgical Lung Biopsy for Radiological Pattern of Probable Usual Interstitial Pneumonia Is Not Mandatory. Am J Respir Crit Care Med 2019;200:1089-92.
6. Bendstrup E, Møller J, Kronborg-White S, et al. Interstitial Lung Disease in Rheumatoid Arthritis Remains a Challenge for Clinicians. J Clin Med 2019. doi: 10.3390/jcm8122038.
7. Assayag D, Lubin M, Lee JS, et al. Predictors of mortality in rheumatoid arthritis-related interstitial lung disease. Respirology 2014;19:493-500.
8. Solomon JJ, Chung JH, Cosgrove GP, et al. Predictors of mortality in rheumatoid arthritis-associated interstitial lung disease. Eur Respir J 2016;47:588-96.
9. Song JW, Lee HK, Lee E, et al. Clinical course and outcome of rheumatoid arthritis-related usual interstitial pneumonia. Sarcoidosis Vasc Diffuse Lung Dis 2013;30:103-12.
10. Lee H, Choe J, Kim S, et al. Important Prognostic Factor in Rheumatoid Arthritis Patients with Interstitial Lung Disease Is Not Usual Interstitial Pneumonia Pattern but Interstitial Lung Disease Extent On Chest High-Resolution Computed Tomography. Arthritis Rheum 2012;64:S528.
11. Sathi N, Urwin T, Desmond S, et al. Patients with limited rheumatoid arthritis-related interstitial lung disease have a better prognosis than those with extensive disease. Rheumatology 2011;50:620.
12. Kim EJ, Elicker BM, Maldonado F, et al. Usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease. Eur Respir J 2010;35:1322-8.
13. Akira M, Sakatani M, Hara H. Thin-section CT findings in rheumatoid arthritis-associated lung disease: CT patterns and their courses. J Comput Assist Tomogr 1999;23:941-8.
14. Tsuchiya Y, Takayanagi N, Sugiura H, et al. Lung diseases directly associated with rheumatoid arthritis and their relationship to outcome. Eur Respir J 2011;37:1411-7.
15. Nurmi HM, Purokivi MK, Kärkkäinen MS, et al. Variable

course of disease of rheumatoid arthritis-associated usual interstitial pneumonia compared to other subtypes. BMC Pulm Med 2016;16:107.
16. Nurmi HM, Kettunen H, Suoranta S, et al. Several high-resolution computed tomography findings associate with survival and clinical features in rheumatoid arthritis-associated interstitial lung disease. Respir Med 2018;134:24-30.
17. Yamakawa H, Sato S, Tsumiyama E, et al. Predictive factors of mortality in rheumatoid arthritis-associated interstitial lung disease analysed by modified HRCT classification of idiopathic pulmonary fibrosis according to the 2018 ATS/ERS/JRS/ALAT criteria. J Thorac Dis 2019;11:5247-57.
18. Yunt ZX, Chung JH, Hobbs S, et al. High resolution computed tomography pattern of usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease: Relationship to survival. Respir Med 2017;126:100-4.
19. Salvatore M, Singh A, Yip R, et al. Progression of probable UIP and UIP on HRCT. Clin Imaging 2019;58:140-4.
20. Yamakawa H, Sato S, Nishizawa T, et al. Impact of radiological honeycombing in rheumatoid arthritis-associated interstitial lung disease. BMC Pulm Med 2020;20:25.
21. Rajasekaran BA, Shovlin D, Lord P, et al. Interstitial lung disease in patients with rheumatoid arthritis: A comparison with cryptogenic fibrosing alveolitis. Rheumatology 2001;40:1022-5.
22. Jacob J, Hirani N, van Moorsel, et al. Predicting outcomes in rheumatoid arthritis related interstitial lung disease. Eur Respir J 2019. doi: 10.1183/13993003.00869-2018.
23. Lynch DA, Godwin JD, Safrin S, et al. High-resolution computed tomography in idiopathic pulmonary fibrosis: Diagnosis and prognosis. Am J Respir Crit Care Med 2005;172:488-93.
24. Gruden JF, Panse PM, Gotway MB, et al. Diagnosis of usual interstitial pneumonia in the absence of honeycombing: Evaluation of specific CT criteria with clinical follow-up in 38 patients. AJR Am J Roentgenol 2016;206:472-80.
25. Watadani T, Sakai F, Johkoh T, et al. Interobserver variability in the CT assessment of honeycombing in the lungs. Radiology 2013;266:936-44.

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