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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