

Journal club

Interstitial lung abnormalities a risk factor for rheumatoid arthritis interstitial lung disease progression: what's new

Commentary on:

Kawano-Dourado L, *et al.* Baseline characteristics and progression of a spectrum of interstitial lung abnormalities and disease in rheumatoid arthritis. *Chest* 2020; 158: 1546-1554.

to previous studies, seem to be present in the 20–60% of RA patients [4, 7, 8].

KAWANO *et al.* [9] focused their attention not only on the clinically evident RA-ILD, but also on RA-ILA trying to measure its prevalence and determine the risk factors for its progression.

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Methods

KAWANO *et al.* [9] undertook a monocentric, retrospective, observational cohort study. All the adult subjects with a diagnosis of RA, made according to international consensus, seen at the rheumatology clinic from 2014 to 2016 who underwent a chest computed tomography (CT) scan as part of their clinical evaluation entered the study. The clinical indication for chest CT scans, laboratory information and pulmonary function tests were extracted from medical records. Three observers reviewed the high-resolution CT scans (HRCTs) in order to assess the presence of ILA or ILD, and assign the subjects to the ILD arm or to the ILA arm. Then two independent readers, blinded to clinical data, evaluated the baseline HRCT and a follow-up one, when available, in order to identify progressors and non-progressors. In a subsequent step, ILAs were quantified by a semiquantitative visual inspection method derived from Goh *et al.* [10] in both the HRCTs, taking into account just five CT slices. The two readers also measured the fibrotic burden in those slices. Consensus was used to solve all the major discrepancies.

Context

The attention given to interstitial lung abnormalities (ILAs) by the scientific community is constantly growing. ILA may or may not progress to a clinically significant interstitial lung disease (ILD). However, ILA radiological progression has been proved to be connected to worse clinical outcomes (increased pulmonary function decline and risk of death) [1, 2]. Recently a Fleischner Society position paper proposed a strategy to both monitor and manage ILAs [3].

Rheumatoid arthritis (RA) is a connective tissue disease in which pulmonary involvement is common [4]. Individuals with RA-ILD show a poor prognosis [5], worse than RA patients without ILD. An important prognostic factor in RA-ILD is the radiological pattern, with a usual interstitial pneumonia pattern identified as independent predictor of mortality [6]. However, we are dealing with the tip of an iceberg, since there are still several undiagnosed cases of pulmonary involvement, due to their pauci-symptomatic nature. ILAs, according

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ILA/ILD extension and subpleural ILA localisation are risk factors for disease progression in RA subjects. A semiquantitative method to assess ILA/ILD extent and to measure the fibrotic burden is feasible to accurately determine ILA progression. <https://bit.ly/3mmMjk2>



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The aim of the study was the identification of the risk factors associated with RA-ILD progression.

even if they both showed a lung function decline over time.

Main results

Just 293 (27%) subjects seen at the RA clinic along the period under analysis had an interpretable HRCT, which was scored, out of a total of 1076 RA patients. ILA/ILD were identified in just 64 (22%) of those scans, while 25 (9%) results were indeterminate. Among those 64 subjects, 26 (41%) had ILA and 35 (55%) had ILD. In both ILA and ILD the most frequent distribution pattern was subpleural (46% and 69%, respectively). 16% of the individuals presented with extensive disease.

ILA was detected in nine out of 115 (8%) CT scans performed for non-pulmonary indications, while two out of 115 (2%) showed ILD. By contrast, the majority of ILA cases (57%) were identified in subjects who underwent a chest CT scan for pulmonary indications (altered physical examination and/or respiratory complaints).

Subjects with no ILA, when compared with those with ILA/ILD, were younger (59.5 ± 10.9 years, $p=0.001$), female (86% versus 72%, $p=0.023$), had no smoking history (70% versus 55%, $p=0.034$) and had a higher use of small molecule or biological disease modifying antirheumatic drugs (60% versus 36%, $p<0.001$).

A follow-up HRCT was available in the 87% of cases and the mean follow-up time was 4.4 ± 2.3 years. The readers identified 21 out of 56 progressors (38%), six of whom were in the ILA arm. Non-progressors seemed to have a lower ILA/ILD involvement at the baseline HRCT compared with progressors (4% (interquartile range (IQR) 2.5–7.5%) versus 11% (IQR 6–24%), $p=0.001$), this is the only significant difference in the baseline characteristics of these two populations. Non-progressors' baseline and follow-up HRCTs showed a lower increase in ILA/ILD extent (4–6%, $p=0.16$) when compared to progressors (11–21%, $p=0.001$), as would be expected. Although ILA progression seemed to be associated with the subpleural pattern on baseline scans no statistical significance was reached ($p=0.06$). However, non-progressors showed no difference in ILA extent between baseline and follow-up CT scans, while ILA progressors showed a significant one (5–15%; $p=0.0009$).

It is remarkable that the interobserver agreement among the readers was strong both when scoring the baseline CT scan and the changes $>10\%$ (the Spearman rank correlation coefficient was 0.91 and 0.80, respectively).

Less than half of the patients had baseline and/or follow-up pulmonary function tests available for analysis, nevertheless spirometry in both the ILA arm and the ILD arm did not differ significantly,

Commentary

The data of KAWANO *et al.* [9] are consistent with those previously reported in literature regarding the prevalence of ILA/ILD in RA [11–14], such as the baseline demographic characteristics (male sex, older age and smoking history) associated with ILA/ILD [8, 12, 15, 16].

This study is the first to quantify ILA progression in a RA cohort and to identify subpleural ILA distribution as radiological risk factor for RA-ILD progression. The adoption of a modified semiquantitative visual inspection method to assess the extent of ILA/ILD and to measure the fibrotic burden is supported by a good agreement between the readers.

The Fleischner Society position paper [3] recently redefined the concept of ILA: when interstitial abnormalities are found during a screening programme in high-risk populations, such as patients with connective tissue diseases (*e.g.* RA), they could not be labelled as ILA, since they are not incidental findings, and should be considered pre-clinical ILDs. Clinician should actively and promptly investigate this condition through accurate clinical examination, lung function and exercise tests, as well as chest CT.

Figure 2b in KAWANO *et al.* [9] shows that the ILA extent (%) evaluation from five slices of the CT scan can differentiate progressors versus non-progressors. Given the high prevalence of interstitial abnormalities in RA subjects, low-dose CT or limited slices CT might be used for screening and, more importantly, for follow-up of pre-clinical ILDs in this population.

The most important limitation to this study and the generalisability of its results is due to the retrospective and monocentric design of the study itself. The number of cases in the final analysis is pretty small and there are several missing data. In a study whose aim is identifying the risk factors for RA-ILD progression a complete analysis of lung function tests should have been included; however, the retrospective design did not allow it. A reduction over time of more than 10% in predicted forced vital capacity is, worldwide, considered a marker of ILD progression and it is used as the primary end-point in the majority of ILD trials. Nevertheless, the interval between the baseline and follow-up CT scans was numerically higher in the progressors group (4.9 ± 2 versus 4.1 ± 2.4 years). Although this difference did not reach statistical significance (possibly due to the limited study population), it could be considered as a potential confounding factor, since progression is more likely to be identified in cases with longer between-scan intervals.

There are a couple of other potential limitations inherent to the study design and pointed out by

the authors themselves. Patients were enrolled just among those seen at the RA clinic, with the risk of losing those cases seen only at the ILD clinic, probably limiting the inclusion of more severe subjects. Finally, the prevalence of ILA in the population under analysis could have been overestimated by a selection bias, since just chest CT scans performed upon clinical indication have been analysed.

Implications for practice

On a daily basis, this study will be helpful to arouse physicians' attention on those RA patients presenting to their clinics with altered physical examination (*e.g.* crackles at lung auscultation) and/or chronic respiratory symptomatology. RA patients with respiratory symptoms and/or positive physical examination have a higher risk of having a finding of ILD at the chest HRCT and, consequently, of disease progression. For this reason, we would expect a change in physicians' habits, resulting in a wider use of chest CT scans (the standard for radiological evaluation for ILA/ILD), which should be promptly performed in this category of patients. These patients should also undergo a watchful

follow-up with comprehensive lung function tests every 3–6 months as is used in many centres for other ILDs.

Considering the incidence of ILD in RA patients, a screening low-dose CT or limited slices CT should be performed in this high-risk population, even if asymptomatic. The difference in the baseline ILA/ILD involvement is an important baseline difference, that could potentially be used to guide the need or the interval for chest CT repetition in clinical practice.

A multidisciplinary approach is pivotal in RA-ILD management, considering also the uncertainty about the pharmacological treatment's efficacy in preventing disease progression in those subjects with subclinical disease.

In the future, we expect this study to open the doors for the design of more extensive and much needed multicentric prospective studies to screen the RA population looking for the real prevalence of ILA in this cohort and to identify risk factors and biomarkers associated with disease progression. This would be helpful to stratify the risk for adverse clinical outcomes and perhaps to identify an earlier therapeutic window for those patients.

Nevertheless, this study highlights the importance of the semi-quantitative methodology for both research studies and clinical practice.

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Conflict of interest

P.M. Leone has nothing to disclose. L. Richeldi reports personal fees from Boehringer Ingelheim, personal fees from Roche, personal fees from Sanofi-Aventis, personal fees from Promedior, personal fees from Chiesi, personal fees from GlaxoSmithKline, outside the submitted work.

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