MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2015; 21: 708-715
DOI: 10.12659/MSM.890880

Received: 2014.04.18
Accepted: 2014.10.15
Published: 2015.03.07

A Retrospective Study of Clinical Characteristics of Interstitial Lung Disease Associated with Rheumatoid Arthritis in Chinese Patients

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Source of support: Departmental sources

Background: Interstitial lung disease (ILD) in rheumatoid arthritis (RA) is associated with a poor prognosis. The purpose of this study was to assess the characteristics of ILD that are associated with RA.

Material/Methods: This was a retrospective study of 544 Chinese patients with RA (427 women and 117 men). RA-ILD was diagnosed by high-resolution computed tomography (HRCT). Patients with RA-ILD or with RA alone were compared in terms of age, sex distribution, duration of disease, clinical and laboratory parameters, history of smoking, and medication.

Results: Based on HRCT imaging, 83 (15.26%) patients with RA were diagnosed with ILD. ILD was more frequent in older patients (59.60±9.66 *vs.* 50.54±13.76 years, $P<0.001$), in those with a longer duration of disease (7.46±7.40 *vs.* 5.27±6.32 years, $P=0.013$) and in male patients (34.9% *vs.* 19.1%, $P=0.001$). RA-ILD was found to be associated with hepatitis B surface antigen (HBsAg) positivity (odds ratio [OR]=2.56, 95% confidence interval [95% CI] 1.02–6.43) and smoking (OR=3.38, 95% CI 1.65–6.95). Higher levels of C-reactive protein (OR=3.59, 95% CI 1.58–8.15), anti-cyclic citrullinated peptide (CCP) (OR=2.24, 95% CI 2.09–4.13), and rheumatoid factor (OR=3.72, 95% CI 1.56–8.86) were detected in association with RA-ILD. RA-ILD was more frequently observed in patients treated with steroids (OR=1.91, 95% CI 1.18–3.09) or *Tripterygium wilfordii* (OR=2.56, 95% CI 1.21–5.40). Age (OR=2.20, 95% CI 1.04–4.65), age at RA onset (OR=2.55, 95% CI 1.11–5.90), anti-CCP (OR=2.47, 95% CI 1.19–5.17), and steroid use (OR=1.83, 95% CI 1.04–3.20) were independently associated with RA-ILD in multivariate analysis.

Conclusions: RA-ILD was associated with age, age at RA onset, anti-CCP, and steroid use. Anti-CCP antibodies might be important biomarkers of RA-ILD.

MeSH Keywords: Arthritis, Juvenile • C-Reactive Protein • Lung Diseases, Interstitial

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/890880

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Background

Rheumatoid arthritis (RA) is a common systemic disease that manifests as symmetric polyarthritis. This inflammatory autoimmune disease affects approximately 1% of the population and can cause functional disability. Nearly 50% of RA patients present extra-articular manifestations involving skin, eye, heart, and lungs [1], the most common being pulmonary involvement [2]. RA-associated interstitial lung disease (RA-ILD) is an important and early feature of RA, and can increase the mortality risk by 3-fold [3]. The effects of this complication of RA range from subclinical inflammation to end-stage pulmonary fibrosis [4]. Approximately half of RA-ILD cases present either at baseline or within 3 years of RA onset [5]. Accurate diagnosis of RA-ILD is complicated by the absence of overt symptoms in the early stages, and reported rates of ILD incidence vary from 3.7% to 80% [3,6–9]. The vast differences in these rates can be attributed to the populations being investigated, the criteria used for diagnosis, and the techniques used for detection. High-resolution computed tomography (HRCT) is considered to be a sensitive technique for the assessment of pulmonary abnormalities [10], particularly in cases of ILD.

Although ILD is a well-known complication of RA, details about the etiology and risk factors of this condition are limited. Environmental factors are involved in the development of RA-ILD [11–14]. Furthermore, some disease-modifying anti-rheumatic drugs (DMARDS), such as methotrexate (MTX) and leflunomide (LEF), are also associated with an increased risk of RA-ILD [15,16]. With the advent of biologic DMARDS, treatments such as anti-TNF have been associated with an increased risk of mortality attributable to RA-ILD [17]. However, the pathogenesis of RA-ILD is highly complex and biomarkers of disease development are critical for improved diagnosis and the identification of therapeutic strategies.

The aim of the present study was to use HRCT to identify the frequency of ILD in a population of Chinese patients with RA. Clinical characteristics were evaluated to further elucidate the characteristics associated with RA-ILD. This information will be beneficial in identifying patients at risk as well as providing the rationale for identification and development of therapeutic strategies.

Material and Methods

Patients

This was a retrospective analysis performed in 544 patients who were diagnosed with RA at the Third Hospital of Hebei Medical University (Shijiazhuang, China) between July 2006 and June 2011. Diagnosis criteria for RA were those from the American College of Rheumatology revised criteria [18]. The sole inclusion criterion was RA diagnosis. Exclusion criteria were: 1) pregnant women; 2) history of any autoimmune disease other than RA; 3) history of any lung disease other than ILD (such as pulmonary infection and chronic pulmonary diseases); or 4) any drug known to cause pulmonary changes (such as amiodarone). ILD was diagnosed using HRCT in these patients [19,20].

Data collection

Clinical, laboratory and socioeconomic characteristics were carefully recorded, including duration of disease, age, sex, erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), C-reactive protein (CRP), anti-cyclic citrullinated peptide (anti-CCP), hepatitis B surface antigen (HBsAg), anti-nuclear antibodies (ANA), immunoglobulin (Ig) G, IgA, IgM, complement (C) 3, C4, medication, and history of smoking. All biochemical assays were performed using automated clinical methods. Smokers were defined as individuals who had smoked more than 5 cigarettes a day during the previous 6 months, while non-smokers were defined as individuals who had smoked less than 20 packets of cigarettes during their lifetime [21].

HRCT scanning

The pulmonary appearance of all patients was evaluated by HRCT scans obtained with a Siemens 16-spiral CT scanner (technical scan parameters: 140 mA and 120 kV). The images were displayed at window and level settings optimized for the visualization of lung parenchyma (level, –600 HU; width, 1200 HU). The images were read blindly by 2 radiologists, and a consensus was reached. Images were returned to the attending physicians, who discussed the case between themselves and with the radiologists.

ILD refers to lesions of the interstitium, including edema, lymphangitis, pneumoconiosis, and fibrosis. These lesions are manifested by ground glass-like changes, grid-like changes, capsule, and intralobular interstitial thickening [6]. These changes are similar to those of idiopathic pulmonary fibrosis (IPF). ILD was diagnosed according to the HRCT images and the patients were classified into the following 2 groups: RA with ILD or RA without ILD.

Statistical analysis

Statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). CRP, ESR, RF, and anti-CCP values were categorized as: within the reference range (normal); 1×ULR (the upper limit of the reference range) to 3×ULR (moderate high); and more than 3×ULR (high). Age at RA onset was categorized as: ≤40 years old and >40 years old. Disease duration was categorized as: ≤2 years and >2 years.

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Table 1. Comparison of clinical data in RA patients with and without ILD.

	RA with ILD	RA without ILD	P value
Total number	83	461	
Sex (M/F)	29/54	88/373	0.001
Smoking status	13/70	24/437	<0.001
Smoking status (male)	13/16	23/65	0.059
Mean age (years)	59.60±9.66	50.54±13.76	<0.001
Age at RA onset (years)	52.13±11.87	45.26±14.22	<0.001
Mean disease duration (years)	7.46±7.40	5.27±6.32	0.013

RA – rheumatoid arthritis; ILD – interstitial lung disease.

Continuous data are expressed as the mean ±SD. The *t* test and rank-sum tests were used to compare normally and non-normally distributed quantitative data, respectively. The chi-square test with Yates correction was used to compare frequencies. Associations of variables with ILD were explored using odds ratios (ORs) and 95% confidence intervals in univariate and multivariate analysis. Variables that were significantly associated with ILD using univariate analyses (P<0.05) were included in a multivariate logistic analysis.

Results

Characteristics of patients

The study included 544 patients with RA (427 women and 117 men). Mean age was 51.9±13.6 years (range 14–81 years), and the mean disease duration was 5.6±6.5 years. Thirty-seven patients were smokers.

Abnormal HRCT findings suggestive of ILD were detected in 83 (15.26%) patients. The main abnormalities of RA-ILD were ground glass-like attenuation, interlobular septum thickening, honeycombing, reticular patterns, and consolidated appearance. Non-productive cough and exertional dyspnea are the 2 main respiratory symptoms of ILD, both of which are aggravated after exercise. Rales were identified in 52 patients following lung auscultation. Patients with combined ILD/IPF were treated with LEF, non-steroidal anti-inflammatory drugs (NSAID) or corticosteroids, hydroxychloroquine, and acetylcysteine. Patients with ILD alone were treated with LEF or MTX, NSAID or corticosteroids, and hydroxychloroquine.

Characteristics associated with RA-ILD

Patients were divided into 2 groups (RA with ILD and RA without ILD). According to the lung HRCT analysis, 83 (15.26%) patients with RA were diagnosed with ILD, with significantly more males than females being affected (male sex in RA with ILD and RA without ILD groups: 34.9% *vs.* 19.1%, *P*=0.001). The mean age of RA patients with ILD was significantly greater than those without ILD (59.60±9.66 *vs.* 50.54±13.76 years, *P*<0.001) and this difference was reflected by the age at RA onset in the 2 groups (52.13±11.87 *vs.* 45.26±14.22 years, *P*<0.001). The mean disease duration was significantly longer in RA patients with ILD compared with those without ILD (7.46±7.40 *vs.* 5.27±6.32 years, *P*=0.013). Of the 37 smokers (36 men and 1 woman), 13 were diagnosed with ILD, and there were more smokers with RA in the ILD group than in the group without ILD (15.7% *vs.* 5.2%, *P*<0.001) (Table 1).

The levels of CRP (57.70±55.81 *vs.* 40.01±44.70 mg/L, *P*<0.001), anti-CCP (924.14±1163.66 *vs.* 754.97±1073.50 RU/ml, *P*=0.012), and RF (657.81±895.06 *vs.* 352.66±589.22 IU/ml, *P*=0.001), as well as ESR (75.99±31.46 *vs.* 65.32±31.63 mm/h, *P*=0.005) were significantly higher in RA patients with ILD compared with those without ILD. Furthermore, there was a statistically significant increase in the frequency of HBsAg positivity among the RA-ILD patients (8.4% *vs.* 3.5%, *P*=0.039). However, no significant differences were detected in the other laboratory parameters (ANA, IgG, IgA, IgM, C3, and C4) between the 2 groups (*P*>0.05) (Table 2).

In terms of treatment history, there was no association between ILD and medication such as MTX, sulfasalazine (SAZ) and LEF or combined administration of MTX+SAZ, or MTX+LEF. However, ILD was more commonly diagnosed in RA patients treated with steroids (41.0% *vs.* 26.7%, *P*=0.008) or *Tripterygium wilfordii* (13.3% *vs.* 5.6%, *P*=0.011) (Table 3).

Associated factors for ILD in RA patients

In univariate analysis, age was associated with RA-ILD (OR=3.69, 95% CI 2.05–6.65), as well as increased age at the time of RA onset (OR=3.72, 95% CI 1.92–7.21) and male sex (OR=2.28, 95% CI 1.37–3.78). Other characteristics exhibiting a statistically

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Table 2. Comparison of laboratory parameters in RA patients with and without ILD.

	RA with ILD N=83	RA without ILD N=461	P value
RF (IU/ml)	657.81±895.06	352.66±589.22	0.001
Anti-CCP (RU/ml)	924.14±1163.66	754.97±1073.50	0.012
CRP (mg/L)	57.70±55.81	40.01±44.70	<0.001
ESR (mm/h)	75.99±31.46	65.32±31.63	0.005
HBsAg (positive/negative)	7/76	16/445	0.039
ANA (positive/negative)	38/45	193/268	0.506
IgG (g/L)	13.85±3.82	13.47±3.80	0.405
IgA (g/L)	2.99±1.26	2.90±1.24	0.520
IgM (g/L)	1.09±0.59	1.05±0.57	0.594
C3 (g/L)	1.28±0.38	1.25±0.39	0.524
C4 (g/L)	0.28±0.10	0.29±0.10	0.932
LDH(U/L)	154.07±29.25	157.96±30.26	0.389

RA – rheumatoid arthritis; ILD – interstitial lung disease; RF – rheumatoid factor; CCP – cyclic citrullinated peptide; CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; HBsAg – hepatitis B antigen; ANA – anti-nuclear antibodies; Ig – immunoglobulin; C3 – complement component 3; C4 – complement component 4.

Table 3. Comparison of treatment history in RA patients with and without ILD.

	RA with ILD N=83	RA without ILD N=461	P value
MTX (with/without)	14/69	87/374	0.665
SAZ (with/without)	3/80	29/432	0.484
LEF (with/without)	14/69	69/392	0.658
MTX+SAZ (with/without)	2/81	21/440	0.550
MTX+LEF (with/without)	7/76	29/432	0.470
Traditional Chinese medicine (with/without)	62/21	299/162	0.081
Steroids (with/without)	34/49	123/338	0.008
Tripterygium wilfordii (with/without)	11/72	26/435	0.011

RA – rheumatoid arthritis; ILD – interstitial lung disease; MTX – methotrexate; SAZ – sulfasalazine; LEF – leflunomide.

significant association with ILD were high levels of RF, anti-CCP, CRP, and ESR, and HBsAg positivity. Treatment with steroids (OR=1.91, 95% CI 1.18–3.09) or *Tripterygium wilfordii* (OR=2.56, 95% CI 1.21–5.40) was also associated with ILD (Table 4).

Variables that were significantly associated with ILD in univariate analysis were included in a multivariate analysis. Results showed that age (OR=2.20, 95% CI 1.04–4.65, *P*=0.04), age at RA onset (OR=2.55, 95% CI 1.11–5.90, P=0.028), anti-CCP levels (OR=2.47, 95% CI 1.19–5.17, *P*=0.016), and steroid use (OR=1.83, 95% CI 1.04–3.20, *P*=0.035) were independently associated with RA-ILD (Table 5).

Discussion

Pulmonary complications in RA are common, the most serious being RA-ILD. The reported prevalence of this disease varies

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Table 4. Characteristics associated with ILD in patients with RA.

Variables		OR	95% CI	P value
Sex	Male *vs.* Female	2.28	1.37~3.78	0.001
Age (years)	>50 *vs.* <50	3.69	2.05~6.65	<0.001
Age at RA onset (years)	>40 *vs.* <40	3.72	1.92~7.21	<0.001
Disease duration(years)	>2 *vs.* <2	1.66	1.02~2.69	0.040
RF	High *vs.* moderate high	2.08	1.03~4.22	0.036
	High *vs.* normal	3.72	1.56~8.86	0.002
	Moderate high *vs.* normal	1.74	0.61~4.99	0.385
Anti-CCP	High *vs.* moderate high	0.92	0.40~2.09	0.546
	High *vs.* normal	2.24	2.09~4.13	0.017
	Moderate high *vs.* normal	2.44	0.94~6.34	0.023
ESR	High *vs.* moderate high	1.61	0.96~2.70	0.086
	High *vs.* normal	2.20	0.65~7.45	0.201
	Moderate high *vs.* normal	1.36	0.37~4.81	0.635
CRP	High *vs.* moderate high	1.18	0.69~2.02	0.386
	High *vs.* normal	3.59	1.58~8.15	0.002
	Moderate high *vs.* normal	3.04	1.25~7.36	0.013
Smoking		3.38	1.65~6.95	0.001
Smoking (male)		2.30	0.96~5.50	0.059
HBsAg	Positive *vs.* negative	2.56	1.02~6.43	0.039
ANA	Positive *vs.* negative	1.17	0.73~1.88	0.506
MTX		0.85	0.46~1.58	0.665
SAZ		0.56	0.17~1.88	0.484
LEF		1.15	0.62~2.16	0.658
MTX+SAZ		0.52	0.12~2.25	0.550
MTX+LEF		1.37	0.58~3.24	0.470
Steroid use		1.91	1.18~3.09	0.008
Traditional Chinese medicine		1.60	0.94~2.72	0.081
Tripterygium wilfordii		2.56	1.21~5.40	0.011

RA – rheumatoid arthritis; ILD – interstitial lung disease; RF – rheumatoid factor; CCP – cyclic citrullinated peptide; CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; HBsAg – hepatitis B surface antigen; ANA – anti-nuclear antibodies; MTX – methotrexate; SAZ – sulfasalazine; LEF – leflunomide.

greatly depending on the disease definitions and techniques used for diagnosis, as well as the investigated populations [22]. Advances in biomarker technologies and diagnostic techniques are required to improve the diagnosis and management of RA-ILD. The present study aimed to investigate the clinical characteristics of RA-ILD in a population of 544 Chinese patients with RA diagnosed by HRCT. Furthermore, we analyzed the associations between patient clinical and laboratory parameters as well as patient demographics and treatments to evaluate the factors associated with ILD in this population of RA patients.

In the present study, pulmonary abnormalities were detected by HRCT in 15.26% of patients with RA. This was higher than that reported by Habibet et al. (10%) [23] but lower than that reported by Zou et al. (43%) [24] and by Giles et al. (33%) [25]. Variation in the reported frequency of pulmonary involvement

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Table 5. Multivariate analysis of factors associated with ILD in patients with RA.

	OR	95% CI	P value
Age	2.20	1.04~4.65	0.040
Age at RA onset	2.55	1.11~5.90	0.028
Anti-CCP	2.47	1.19~5.17	0.016
Steroid use	1.83	1.04~3.20	0.035
RF	2.38	0.97~5.84	0.059
CRP	2.14	0.93~4.93	0.075
Smoking	1.71	0.67~4.38	0.263
Sex	1.62	0.83~3.15	0.159
Disease duration (years)	1.32	0.74~2.35	0.353
HBsAg	2.47	0.79~7.60	0.122
Tripterygium wilfordii	1.96	0.80~4.79	0.139

RA – rheumatoid arthritis; ILD – interstitial lung disease; RF – rheumatoid factor; CCP – cyclic citrullinated peptide; CRP – C-reactive protein.

in patients with RA depends on several factors, including disease definitions and investigated population, as well as the techniques used for diagnosis. Detection of ILD has been reported as being less than 5% using plain radiography [26], but detection was increased to 20–30% using HRCT [27]. In the present study, some patients underwent plain radiography before HRCT, and in some of them, some non-specific changes were observed. Subsequently, HRCT showed normal images in some of these patients, while pulmonary fibrosis was present in the others. Therefore, HRCT should be performed instead of plain radiography for the diagnosis of RA-ILD.

There are no evident respiratory symptoms in early-stage RA-ILD. Therefore, HRCT provides a sensitive approach to the identification of pulmonary abnormalities during the early stages when lesions, such as ground glass attenuation, which was the most common abnormality detected in our study. In fact, Bilgici et al. [21] reported abnormal HRCT findings in 67.3% of RA patients, and McDonagh et al. [6] reported lung abnormalities on HRCT in patients initially thought to be normal and included as controls; they also reported the ground glass-like sign as being most common in RA-ILD patients [6].While there are no convincing data on the sensitivity of HRCT scanning for RA-ILD, it is likely that early disease may occasionally be missed [27]. RA-ILD has a poor prognosis; therefore, HRCT scans should be obtained in all patients with suspected ILD. Lung biopsy remains the criterion standard for the diagnosis of ILD. However, it is an invasive method, and should not be used in asymptomatic patients. Indeed, a previous study showed that some degree of abnormality could be observed using HRCT in patients without symptoms [6].

The mechanism of RA-ILD and associated risk factors remain to be fully elucidated. Nevertheless, a recent study suggests that lung inflammation observed using HRCT was associated with RA disease activity [28]. Several studies [8,17,27,29–32] have reported that smoking, older age, male sex, disease severity, high RF, subcutaneous nodules, and long-standing RA might be risk factors for the development of ILD. The present study indicated that older age, smoking, male sex, being older at the time of RA onset, and having a high "inflammatory burden" were all associated with a diagnosis of ILD in RA patients in univariate analysis. In multivariate analyses, age, age at RA onset, anti-CCP, and steroid use were independently associated with RA-ILD. In addition, RF and anti-CCP were the only autologous antibodies associated with RA-ILD in univariate analyses in the present study, and anti-CCP remained significant in the multivariate analysis. A recent meta-analysis showed that anti-CCP levels were highly associated with the risk of ILD in RA patients [33]. We also found that HBsAg was related to RA-ILD, but this may be because detection of RF had interfered with the result [34]. Previous studies showed a relation between HBsAg and RF [35,36]. However, more research is needed to determine whether there is a real relationship between HBsAg and RA-ILD risk. Additional markers of disease activity, such as anti-PAD3/4XR [25], could also be explored.

Besides RA itself, many drugs may be associated with the development of pulmonary damage: NSAIDS, intravenous immunoglobulin, synthetic DMARDs, gold, penicillamine, MTX, steroids, LEF, and anti-TNF-α have all been shown to induce varying patterns of ILD [23,37–39]. Although gold and penicillamine are

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not used as first-line drugs in RA treatment, MTX and LEF are used worldwide. Zou et al. [24] reported an increased prevalence of honeycombing and subpleural nodules in patients treated with MTX and/or LEF. However, a more recent study found no association between MTX therapy and progression of chronic pulmonary fibrosis [23,40,41]. No correlations have been observed between pulmonary conditions in RA and MTX dosage [42]. Most subsequent studies have not demonstrated a definite association between MTX and RA-ILD.

In the present study, most patients relied on Chinese traditional medicine. However, there is a wide variety and composition of these medicines, preventing us from analyzing all of them. *Tripterygium wilfordii* is a Chinese traditional herb that is used in RA and that have been shown to have beneficial effects [43–45]. In the present study, steroids and *Tripterygium wilfordii* therapies were associated with RA-ILD. It is unlikely that ILD was due to treatment with MTX, LEF, or SAZ. However, since several surrogate parameters of high RA disease activity were associated with a diagnosis of ILD and since glucocorticoid or *Tripterygium wilfordii* are commonly used to treat patients with more severe disease in China, the observed association may be due to increased disease activity as a confounding variable rather than to the treatment itself. However, a recent review pointed out that even if many small studies and case reports claimed associations between drugs and the development of ILD, more studies are necessary to correctly evaluate any causative relationship [46], making the comparison of the results of the present study difficult.

The present study suffers from some limitations. Indeed, even if the sample size was large, a larger sample could allow reaching stronger conclusions, and a multicenter study with central imaging review could be planned. Secondly, we did not screen a complete panel of auto-antibodies; therefore, we might have missed auto-antibodies that could be stronger predictors of ILD presence in RA patients. In addition, the conclusions of the present study are limited by its retrospective design. Indeed, the simultaneous assessment of the outcome and exposure prevents the investigation of any temporal relationship. Finally, we limited our analysis of the possible causative factors to routine biochemistry for RA patients and to their medical history. Exploratory studies should be performed to discover new potential markers of the presence of ILD in RA patients.

Conclusions

Further studies are required to fully elucidate the risk factors associated with the development of ILD in RA patients, as well as identification of prognostic and diagnostic biomarkers of the disease. This aim will be achieved by more comprehensive analysis of clinical samples and may be facilitated by the development of a novel mouse model of RA-ILD [47]. This information will improve the diagnosis and management of RA-ILD.

In conclusion, we observed an ILD frequency of 15% in RA patients and identified several associated factors of ILD in RA patients, including age, age at RA onset, high anti-CCP, and steroid use. However, the pathophysiological links between these factors and pulmonary parenchymal changes remain to be elucidated. We recommend that HRCT should be carried out to confirm abnormalities to better inform clinical decisions regarding the treatment of RA.

Competing interests

The authors declare no conflicts of interest.

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