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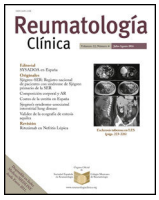

Special Article

SER-SEPAR recommendations for the management of rheumatoid arthritis-related interstitial lung disease. Part 1: Epidemiology, risk factors and prognosis☆

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ABSTRACT

Objective: To develop multidisciplinary recommendations to improve the management of rheumatoid arthritis-related interstitial lung disease (RA-ILD).
Methods: Clinical research questions relevant to the objective of the document were identified by a panel of rheumatologists and pneumologists selected based on their experience in the field. Systematic reviews of the available evidence were conducted, and evidence was graded according to the Scottish Intercollegiate Guidelines Network (SIGN) criteria. Specific recommendations were made.
Results: Six PICO questions were selected, three of which analysed the incidence and prevalence of RA-ILD, associated risk factors, and predictors of progression and mortality. A total of 6 specific recommendations on these topics, structured by question, were formulated based on the evidence found and/or expert consensus.
Conclusions: We present the first official SER-SEPAR document with specific recommendations for RA-ILD management developed to resolve some common clinical questions and facilitate decision-making for patients.

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Recomendaciones SER-SEPAR para el manejo de la enfermedad pulmonar intersticial difusa asociada a la artritis reumatoide. Parte 1: epidemiología, factores de riesgo y pronóstico

R E S U M E N

Objetivo: Elaborar unas recomendaciones multidisciplinares para mejorar el manejo de la enfermedad pulmonar intersticial difusa asociada a la artritis reumatoide (EPID-AR).
Métodos: Un panel de reumatólogos y neumólogos expertos identificó preguntas clínicas de investigación relevantes para el objetivo del documento. Se realizaron revisiones sistemáticas de la evidencia, que se graduó de acuerdo con los criterios del *Scottish Intercollegiate Guidelines Network* (SIGN). Tras ello, se formularon las recomendaciones.
Resultados: Se seleccionaron seis preguntas PICO, tres de las cuales específicamente evaluaron la incidencia y prevalencia de esta complicación, los factores de riesgo para su desarrollo, y los factores pronósticos de mortalidad y de progresión de la EPID-AR. Se formularon un total de 6 recomendaciones específicas sobre estos aspectos, estructuradas por pregunta, con base en la evidencia encontrada y/o consenso de expertos.
Conclusiones: Se presenta el primer documento oficial SER-SEPAR de recomendaciones específicas para el abordaje la EPID-AR, con el fin de ayudar en la toma de decisiones a los clínicos directamente implicados en su manejo y aproximar la práctica asistencial a la mejor evidencia posible.

Introduction

Rheumatoid arthritis (RA) is an immune-mediated systemic inflammatory disease that primarily affects the joints and causes joint destruction, impaired functional capacity, and quality of life, and may even reduce life expectancy. It is the most prevalent form of chronic polyarthritis in Spain with the greatest social and health impact. According to data from the EPISER study, RA has an estimated prevalence of .82% in the Spanish adult population.[1]

In addition to joint damage, in a variable percentage of cases the disease presents with different extra-articular manifestations, including pulmonary manifestations. The spectrum of respiratory complications caused by RA is very broad and includes pleural involvement, rheumatoid pulmonary nodules (including Caplan syndrome), interstitial lung disease (ILD) and follicular or obliterative bronchiolitis.[2,3] Bronchiectasis, primary pulmonary hypertension, secondary amyloidosis, thromboembolic disease, and cricoarytenoid arthritis have been reported more rarely.

ILD is one of the most frequent and severe pulmonary complications of RA.[4,5] The risk of RA patients developing this complication is almost 9 times higher than in the general population.[6] Furthermore, although there has been a significant improvement in prognosis in the last 25 years, [7] ILD is still the second leading cause of death from the disease, accounting for 10%–20% of deaths. This clinical fact warrants a common strategy between rheumatologists and pneumologists to improve the prognosis and quality of life of patients with this complication.

For this reason, the Spanish Societies of Rheumatology (SER) and Pneumology and Thoracic Surgery (SEPAR) promoted the drafting of a joint document of recommendations for the management of RA-ILD based on the best available evidence, with the aim of answering most of the common clinical questions, reducing the variability in medical care and facilitating decision-making for clinicians directly involved in the care of the condition.

Methods

A qualitative synthesis of the scientific evidence and consensus techniques was used in the drafting of these recommendations, which reflect the agreement of experts based on the available evidence and their clinical experience.[8]

The procedure for developing the project was as follows:

1 *Creation of the working group*. An interdisciplinary working group was formed by 5 rheumatologists from SER (JN, GB, IC, NMV, and AMO) and 5 pneumologists from SEPAR (MA, ECJ, MAN, CV, and JARP). The participants were endorsed by their society to participate in this document. The clinical and methodological aspects were coordinated, respectively, by one of the rheumatologists (JN) and a pneumologist (JARP), as principal investigators (PI), and two methodology specialists from the SER Research Unit.
2 *Identification of key areas*. The content and key aspects of the document were defined, and the clinical research questions with the greatest impact on clinical practice were formulated. The questions were reformulated in patient, intervention, comparison, and outcome (PICO) format.
3 *Literature search*. A search for published scientific evidence was conducted and progressively expanded until October 2020. The databases PubMed (MEDLINE), EMBASE, and Cochrane Library (Wiley Online) were used for this purpose. The process was completed with a manual search of the references of the studies identified, as well as posters and conference abstracts that the reviewers and experts considered to be of interest.
4 *Analysis and synthesis of the scientific evidence*. Rheumatologists from SER who are experts in evidence review conducted the systematic reviews and synthesis of the scientific evidence. The level of scientific evidence was assessed using Scottish Intercollegiate Guidelines Network (SIGN)[9] criteria (Appendix B Annex).
5 *Formulation of recommendations*. Once the critical reading had been completed, the PIs, together with the members of the expert group reviewing the evidence for each of the PICO questions, formulated the recommendations, based on formal evaluation or ïeasoned judgementöf the evidence for each of the questions. The quality, quantity, and consistency of the scientific evidence, the generalisability, applicability, and clinical impact of the results were considered. The strength of the recommendations was graded using the SIGN[7] system. For questions where the evidence was insufficient, recommendations were formulated based on consensus of the expert group.

The recommendations have been divided into five main areas: incidence and prevalence of ILD in RA, risk factors for the onset of ILD in RA, prognostic factors for mortality and pulmonary progression, as well as the safety of drug treatment in patients with RA-ILD, and its efficacy in managing this complication.

External review. The draft document was subjected to external review to ensure the validity and accuracy of the recommenda-

tions and, subsequently, to public exposure so that other SER and SEPAR members, as well as different groups and potentially interested entities, could evaluate the document, and offer criticism or suggestions.

General preliminary considerations

Identification of the type of RA-associated ILD

The most common histological types of RA-ILD are usual interstitial pneumonia (UIP) and non-specific interstitial pneumonia (NSIP).[2–7] The UIP pattern is as frequent or more frequent than NSIP. Other patterns described are organising pneumonia (OP), lymphoid interstitial pneumonia (LIP), diffuse alveolar damage (DAD), acute fibrinous and organising pneumonia (AFOP), desquamative interstitial pneumonia (DIP), respiratory bronchiolitis associated with interstitial lung disease and the combined pulmonary fibrosis + emphysema (CPFE) pattern.[2–7,10] These last three patterns are included in the spectrum of smoking-related lung lesions,[11] although they have also been described in patients with RA who are non-smokers.[12,13]

The ILD pattern must be correctly identified because of its therapeutic and prognostic implications, since the more inflammatory patterns (cellular NSIP, OP, LIP) will respond better to anti-inflammatory and immunosuppressive treatment than UIP.

Diagnosis of RA-ILD

If ILD is suspected (presence of cough and/or dyspnoea of more than 3 months duration or velcro-like crackles on respiratory auscultation), a chest X-ray and lung function test (LFT) including spirometry and diffusing capacity of the lungs for carbon monoxide (DLCO) are usually performed for initial screening. In general, chest X-ray is a very insensitive technique in the early stages. In ILD, spirometry shows restrictive ventilatory impairment together with decreased DLCO. However, in early stages, it is not uncommon for decreased DLCO to be the only abnormality present.

High-resolution computed tomography (HRCT) of the chest to confirm ILD is the gold standard for the diagnosis of this complication. The radiological pattern on HRCT correlates well with the histological pattern in most cases, and therefore a lung biopsy is usually not necessary. HRCT is also useful to quantify the extent of parenchymal involvement (alveolitis/fibrosis), to determine the potential reversibility of the lesions (alveolitis/fibrosis), to establish a prognosis (UIP vs. non-UIP) and to assess response to treatment.

Disease activity and response to treatment is monitored with LFTs (spirometry and plethysmography to assess forced vital capacity [FVC], DLCO and total lung capacity), the 6-minute walk test and assessment of dyspnoea with one of the different clinical scales. Chest HRCT is usually only repeated in cases where it is necessary to assess functional deterioration, treatment readjustments or if exacerbation, infection, or other respiratory complications, such as lung cancer, are suspected.

In advanced stages, Doppler echocardiography is also useful to detect onset of secondary pulmonary arterial hypertension.

Bronchoalveolar lavage is not routinely performed. It is only indicated if it helps in the differential diagnosis, primarily with infections. Lung biopsy is only performed if there is suspicion of non-RA-ILD, doubts about the presence of other entities such as neoplasms or infection, or to establish a histo-specific diagnosis in atypical cases.

The differential diagnosis of ILD is mainly infection, pulmonary drug toxicity, thromboembolic disease, heart failure, or lung cancer (fundamentally in smokers).

Definition of progressive fibrosing ILD

A variable percentage of patients with RA-ILD (around 40% at 5 years after ILD diagnosis)[14–16] develop progressive pulmonary fibrosis with severe deterioration of lung function, rapid progression to chronic respiratory failure, and high mortality. There is no standard or agreed definition of what is considered progressive fibrosing ILD. The randomised clinical trial INBUILD[17] used the following four criteria to define progression in patients with fibrosing ILD: 1) a decrease in baseline FVC > 10% of the percentage of the estimated theoretical value; 2) a decrease in FVC of between 5%–10% with evidence of progressive fibrosing on chest HRCT; 3) a decrease in FVC of between 5%–10% with worsening respiratory symptoms (dyspnoea and dry cough), or 4) a worsening of dyspnoea with progressive fibrosing on HRCT in the previous 24 months despite treatment.

Some experts also define progression as a decrease in FVC between 5%–10% with a worsening of DLCO greater than 15%.[18]

According to the INBUILD study,[17] fibrosing ILD is defined as fibrosis changes affecting more than 10% of the lung parenchyma.

However, and according to the classic definitions of the American Society of Pulmonology, worsening of any type of ILD (fibrosing or non-fibrosing) is defined as a decrease in FVC (expressed as a percentage of the predicted value) greater than 10% or a decrease in DLCO greater than 15% during follow-up.[19,20]

Results

A total of 18 recommendations have been formulated. This article contextualises the six recommendations made following the systematic literature review (SLR) of the epidemiology, risk factors, and prognosis of RA-ILD (Table1).

For further information on any of the sections summarised in this article, the full content of the document can be accessed on the SER website (www.ser.es).

Epidemiology of RA-ILD

— What is the incidence and prevalence of RA-IDP in patients with RA?

□ *Recommendation.* Based on its incidence and prevalence, it is recommended that the possibility of ILD should always be considered in the initial assessment and follow-up of patients with RA (recommendation grade √).

It is vital to establish the prevalence and incidence of ILD in RA. Knowing the magnitude of this complication is essential to define strategies for early diagnosis and treatment, and good health planning.

The scientific evidence for this recommendation was based on an SLR in which the population was adult subjects, the intervention was a diagnosis of RA according to ACR 1987 or ACR/EULAR 2010 criteria, and the outcome was the incidence or prevalence of ILD diagnosed by chest HRCT scan and/or lung biopsy.

Incidence of RA-associated ILD

The incidence of RA-associated ILD is 1.056 cases per 1000 patients (1.452 in males and .677 in females) according to a study conducted in a Japanese population (IORRA cohort) between 2004 and 2007.[21]

Outside the body of evidence, two other studies have been identified that evaluate the incidence in the Caucasian population, although the condition was not diagnosed with HRCT in all cases. In the study by Koduri et al.,[22] conducted in an English

Table 1
SER-SEPAR recommendations for the management of rheumatoid arthritis-associated interstitial lung disease: epidemiology, epidemiology, risk factors and prognosis of RA-ILD.

Recommendations	Recommendation grade
Based on its incidence and prevalence, it is recommended that the possibility of interstitial lung disease should always be considered in the initial assessment and follow-up of patients with rheumatoid arthritis	√
Patients with rheumatoid arthritis should be systematically screened for interstitial lung disease in cases with respiratory symptoms or if velcro-like crackles are heard	√
In cases without respiratory symptoms and with normal auscultation, the need for screening should be assessed individually according to the number of risk factors[a] for onset of this complication, regardless of the time since onset of rheumatoid arthritis	√
The presence of interstitial lung disease should always be considered when deciding on treatment, given the potential risk of pneumonitis described with some of the drugs commonly used in rheumatoid arthritis	√
In patients with rheumatoid arthritis, none of the investigational serum biomarkers tested so far has been shown to have better predictive value for the onset of interstitial lung disease than anti-citrullinated protein/peptide antibodies. Based on the current evidence, the drafting group does not recommend the use of other serum biomarkers in routine clinical practice	D
In patients with rheumatoid arthritis and interstitial lung disease it is recommended that the presence of prognostic factors associated with progression[b] and mortality[c] be considered when planning follow-up (frequency of check-ups) and treatment strategy	B

DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution computed tomography.

[a] The main risk factors for the development of interstitial lung disease, easily identifiable in the clinic, are male sex, older age, late disease onset, duration of rheumatoid arthritis, history of smoking, sustained moderate, or high disease activity, and rheumatoid factor and anti-citrullinated protein/peptide antibody positivity.

[b] The main predictors of progression of interstitial lung disease are the radiological pattern of usual interstitial pneumonia, elevated anti-citrullinated protein/peptide antibody titres, degree of baseline DLCO impairment, a ≥10% decrease (percentage of estimated theoretical value) in FVC during follow-up, extensive lung involvement on chest HRCT, and elevated serum levels of interleukin-6 and Krebs von den Lungen-6 glycoprotein.

[c] The main prognostic factors associated with increased mortality are advanced age at diagnosis of interstitial lung disease, male sex, duration of rheumatoid arthritis, moderate or high disease activity, the usual radiological pattern of interstitial pneumonia, low baseline FVC and/or DLCO, a decrease in FVC > 10% or DLCO > 15% during follow-up, extensive lung involvement on chest HRCT, GAP and CPI (composite physiologic index) indices, and elevated serum levels of Krebs von den Lungen-6 glycoprotein.

cohort of patients with RA onset, this complication was only investigated in the presence of respiratory symptoms or signs as part of routine clinical care practice. After a follow-up of 3 years, the incidence of ILD was 4.1 per 1000 patients. In another prospective population-based cohort study (Rochester, Minnesota) the cumulative incidence of ILD at 10, 20, and 30 years was 3.5, 6.3, and 7.7%, respectively.[6] In this study, the risk of RA patients developing this complication was much higher than that of the general population (HR: 8.96).

Prevalence/frequency of RA-ILD

Eleven articles have been identified in which all patients diagnosed with RA (consecutive unselected patients) were screened for ILD.[23–33] The main results of these studies are shown in Table 2. The frequency of this complication shows great variability, ranging from 11.9% to 55.7%. This variability can be explained by the differences between the populations studied (great heterogeneity in demographic characteristics, time since onset, and degree of disease activity, frequency of smoking and percentage of patients with respiratory symptoms) and by the lack of uniformity in the HRCT findings used to establish a diagnosis of ILD.

Of the eleven articles identified, three included patients with RA of less than two years' duration.[25–27]In these studies, the variability of the prevalence of ILD is lower and ranges from 27.5% to 41.8%, with higher figures in populations with a higher frequency of smoking.[25,26]

In the eight studies conducted in patients with established RA (more than two years since onset)[23,24,28–33] there is wide disparity in the frequency figures, even between the two studies that investigated this question prospectively.[23,24] Thus, Bilgici et al.,[23] in a cohort of 52 unselected RA patients from a single centre in Turkey, found chest CT changes consistent with ILD in 55.7%. Dawson et al.,[24] in a cohort of 150 consecutive RA patients in two hospitals in the North of England, describe findings of fibrosing alveolitis, a term comparable to UIP and fibrosing NSIP patterns, in 19% of cases. In general, and predictably, in these eight studies, the higher the percentage of patients included with respiratory symptoms, the higher the frequency of ILD.

Outside the body of evidence, in a prospective study conducted in Spain in patients with RA onset without respiratory symptoms in which only those with radiographic or LFT abnormalities underwent chest HRCT, the prevalence of confirmed ILD at disease diagnosis was 5%, increasing to 7.5% at 5 years since onset.[34] These figures are lower than those reported in a Chinese cohort in which the frequency of ILD at diagnosis was 9.76%, increasing to 30.9% at 5-year follow-up.[35]

However, if we only consider the frequency of symptomatic or clinically significant RA-ILD (which is not the issue raised in the research question), the prevalence by HRCT in several landmark studies is between 10% and 29%.[36–39] Finally, the prevalence of ILD in the only autopsy study to investigate this complication is 35%.[40]

Risk factors for onset of ILD in RA

— In patients with RA, what are the risk factors for onset of ILD?

☐ *Recommendation.* Patients with RA should be systematically screened for ILD in cases with respiratory symptoms or if velcro-like crackles are heard (recommendation grade √).

☐ *Recommendation.* In cases without respiratory symptoms and with normal auscultation, the need for screening should be assessed individually according to the number of risk factors for onset of this complication, regardless of the time since onset of RA (recommendation grade √).

☐ *Recommendation.* The presence of ILD should always be considered when deciding on treatment, given the potential risk of pneumonitis described with some of the drugs commonly used in RA (recommendation grade √).

☐ *Recommendation.* In patients with RA, none of the investigational serum biomarkers tested so far has been shown to have better predictive value for the onset of ILD than ACPA antibodies. Based on the current evidence, the drafting group does not recommend the use of other serum biomarkers in routine clinical practice (recommendation grade D).

Despite its frequency and severity, to date there are no recommendations on screening for this complication, in either the initial assessment or in the follow-up of RA patients. However, as mentioned above, when the entire RA population was screened for ILD by HRCT, a non-negligible percentage of subclinical dis-

Table 2
Main characteristics of the 11 studies that have analysed the prevalence of RA-ILD included in the systematic review of the literature.

Study	Country	N° of centres	N	Age (years)	Time since onset (years)	Smoking (%)	RF (+)/ACPA (+) (%)	Respiratory symptoms	Frequency of ILD
Bilgici et al.[23] (2005)	Turkey	1	52	53.6 ± 11.2	8.37 ± 8.17	25%	67.3%/NS	Asymptomatic 59.6% (31/52) Symptomatic 21% (11)	55.76%
Dawson et al.[24] (2001)	UK	1	150	58.9 ± 10.3	12.7 ± 8	70%	77%/NS	Asymptomatic; 15 had crackles on respiratory auscultation (10%)	18.6%
Mohd Noor et al.[28] (2009)	Malaysia	1	63	56.7 ± 10	14 ± 12	6%	66.7%/NS	Asymptomatic 67%	44.4%
Mori et al.[29] (2008)	Japan	1	126	60 ± 12.4	61 patients with established RA (Time since onset: 11.8 ± 9.7)	20%	83%/93.8%	Patients with established RA: Asymptomatic 68.8% (42/61) Symptomatic 31.2% (19)	Total: 11.9% (15/126)
					65 patients with time since onset: 2.6 ± 4.5			Asymptomatic patients 83.1% (54/65) Symptomatic 16.9% (11)	13.1% (8/61) 10.7% (7/65)
Skare et al.[30] (2011)	Brazil	1	71	58.7 ± 10.4	11.8 ± 6.9	35.8%	704%/38%	Asymptomatic 44.75% (30/71) Symptomatic 55.25%	54.92%
Wang y Du[31] (2015)	China	1	544	NS	5.6 ± 6.5	6.8%	NS/NS	NS Crackles on auscultation: 52 (9.5%)	15.26%
Zhang et al.[32] (2017)	China	1	550	61 ± 13	8 ± 9	20.4%	76.5%/NS	Asymptomatic 59% Symptomatic 41%	43.1%
Zrour et al.[33] (2005)	Tunisia	1	74	48 ± 14	96 ± 88 m (8 years)	14.6%	60.6%/NS	Asymptomatic 74.7% Symptomatic 25.3%	28%
Gabbay et al.[25] (1997)	Australia	1	36	51.8 ± 16	< 2	55.5%	64%/NS	Asymptomatic	33%
Gochuico et al.[26] (2008)	United States	1	74	NS	< 2	50%	NS/NS	Asymptomatic	41.89%
Habib et al.[27] (2011)	Saudi Arabia	3	40	37.6 ± 10.3	< 2	12.5%	35% /NS	Asymptomatic	27.5%

ACPA: Anti-citrullinated Protein/peptide Antibodies; ILD: Interstitial Lung Disease; NS: Not specified; RF: Rheumatoid Factor.

ease was detected (between 11.9% and 55.7%), confirming that it is underdiagnosed. In fact, in clinical practice, it is not uncommon for ILD to be diagnosed late, as it is often asymptomatic or pseudo-symptomatic in its early stages.

Therefore, knowing the main risk factors associated with the onset of RA-ILD will help us identify the subgroup of patients at greatest risk of developing this complication who may benefit from specific screening to diagnose them early (even if they do not have respiratory symptoms or signs).

According to the results of the SLR, the main risk factors for the onset of RA-ILD are:

1 Male sex[35,41] (level of evidence 2+).
2 Advanced age and late onset of the disease (level of evidence 2++).[32,35,36,42,43] No cut-off point is established in most studies, except two: >60 years (OR: 1.48; 95% CI: 1.01–2.18)[35] and ≥65 years (RR: 4.58; 95% CI: 1.67–12.53).[42]
3 Duration of the disease, onset of ILD being more frequent during the first 5–10 years of RA progression[28,32,35] (level of evidence 2+).
4 Smoking[32,36,44,45] (level of evidence 2++). Smoking and smoking rate are strongly associated with onset of ILD, with an OR: 3.76 (95% CI: 1.59–8.88) in the case of having smoked ≥25 pack-years and 1.9 (95% CI: .68–5.24) if less than 25 pack/years.[44] Several studies indicate that smokers' increased risk of developing ILD is associated with the presence of the shared epitope, showing that there is an important gene-environment interaction between the shared epitope alleles and smoking.[1,42,44]
5 Moderate or high sustained RA activity[45] (level of evidence 2++). Patients with moderate/high maintained disease activity according to DAS28-CRP scores are at twice the risk of developing ILD than patients in remission or with low disease activity (results adjusted for sex, smoking, RA duration, and serostatus: HR: 2.22; 95% CI: 1.28–3.82).[45] The risk of ILD in the different disease activity statuses is as follows: low disease activity (DAS28 > 2.6–3.2) 1.41 (95% CI: .61–3.28), moderate disease activity (>3.2-5.1) 2.08 (95% CI: 1.06–4.05), and high disease activity (>5.1) 3.48 (95% CI: 1.64–7.38).[45]
6 RF positivity (level of evidence 2++) and, especially, ACPA positivity (level of evidence 1+), especially at high titres.[10,32,35,46–48] In a meta-analysis (which included 7 studies with 1685 patients; I^2: 0%), the risk of ILD and pulmonary fibrosis in the presence of ACPA was almost 5 times higher (OR: 4.68; 95% CI: 2.07–10.57).[46]

In addition to RF and ACPA, the usefulness of other potential biomarkers predictive of the onset of ILD is being investigated, most notably antibodies directed against carbamylated proteins (anti-CarP). A correlation has been demonstrated between levels of all anti-CarP specificities (foetal calf serum, fibrinogen, and chimeric fibrine/filagrine homocitrullinated peptide) and the presence of ILD, after adjustment for other known risk factors[49] (level of evidence 3). Promising preliminary results have also been obtained with serum levels of extracellular matrix metalloproteinase 7 (MMP-7), interferon gamma-inducible protein-10 [IP-10] or CXCL10, interleukin-18, and 90- and 70-KDa heat shock proteins (HSP90/70)[50–53] (level of evidence 2). None of these are yet available in clinical practice, nor have they as yet been shown to have greater predictive value for the development of this complication than ACPAs.

Likewise, some genetic biomarkers have been identified, including mutations in the MUC5B gene[54] (which encodes one of the proteins of the mucin family) (level of evidence 2+) and mutations in the telomerase genes that cause accelerated telomere shortening[55,56] (in cases with a family history of ILD) (level of evidence 2+).

Finally, onset of ILD has also been linked to some of the drugs commonly used in the treatment of this disease. This issue is reviewed in depth in the second part of the recommendations, also published in this journal.

To avoid late diagnosis of ILD in RA patients, the drafting group recommends regular questioning about the presence of respiratory symptoms and auscultation at least once a year for dry velcro-like crackles. The presence of velcro-like crackles correlates well with the presence of pulmonary fibrosis.[57] In addition, two studies have shown that conventional respiratory auscultation is acceptably diagnostically accurate to detect ILD compared to digital stethoscope.[58,59]

The group also considers that patients with respiratory symptoms (cough and/or dyspnoea of more than 3 months' duration in the absence of known underlying pulmonary disease or pre-existing heart disease) should be routinely screened, and all those with velcro-like crackles detected on auscultation, even if asymptomatic. In asymptomatic patients with normal auscultation, the need for ILD screening will be assessed on an individual basis according to the number of risk factors for onset of the complication, regardless of time since onset of RA.

Risk factors for onset of RA-ILD

— What are the prognostic factors for mortality and progression of Lund disease in patients with RA-ILD?

☐ *Recommendation:* In patients with RA and ILD, it is recommended that the presence of prognostic factors associated with progression and mortality be considered when planning follow-up (frequency of check-ups) and treatment strategy (recommendation grade B).

ILD remains the second leading cause of premature death in RA, after cardiovascular complications.[2–7] Approximately half of patients have stable or very slowly progressive ILD, whereas in the other half lung function deteriorates more or less rapidly.[60,61] This heterogeneity in the course of the disease makes it essential to identify prognostic factors for severe disease and mortality. The SLR identified factors associated with progression of ILD and factors associated with increased mortality in patients with RA-ILD.

Predictors of RA-ILD progression

☐ Radiological pattern of UIP: the risk of progression in patients with UIP is approximately three times higher than in patients with NINE[16,35] (level of evidence 2+).
☐ Elevated ACPA titres (3 times above the upper limit of normal) with an OR of 4.03 (95% CI: 1.04–15.6)[62] (level of evidence 2+).
☐ The degree of baseline DLCO deterioration,[35,62,63] having been demonstrated with two cut-off points: DLCO < 45% (percentage of predicted value) (OR: 3.02; 95% CI: 1.13–8.03)[35] and, only in patients with a progressive fibrosing phenotype, DLCO < 54%: (OR: .85; 95% CI: .74–.98)[63] (level of evidence 2+).
☐ In patients with UIP pattern, a drop ≥10% in FVC during follow-up (OR: .89; 95% CI: .82–.97) (level of evidence 2+).[64]
☐ Overall, the risk of progression of ILD increases the lower the baseline DLCO values, and the greater the worsening of FVC and/or DLCO during follow-up[16] (level of evidence 2+).
☐ Extensive distribution on fibrotic changes on HRCT, principally traction bronchiectasis (≥ 4 lung areas affected with > 50% of the subpleural total)[65] (level of evidence 2++).
☐ Elevated serum levels of IL-6 and KL-6 (level of evidence 2+).[64,66]

Prognostic factors for mortality in RA-ILD

Patients with RA-ILD have a 3- to 10-fold higher adjusted mortality risk than RA patients without the complication, regardless of

the follow-up period and the presence of comorbidities[6,67,68] (level of evidence 2+).

The main prognostic factors for mortality identified in the SLR are:

- Advanced age at diagnosis of ILD[22,35,60,62,64,67,69–72]: no cut-off point is established in most of the studies found, except three: >60 years (HR: 3.18; 95% CI: 1.27 to 7.94[35] and HR: 2.32; 95% CI: 1.27 to 4.25[62]) and ≥65 years (OR: 1.08; 95% CI: 1.02–1.15)[70] (level of evidence 2+).
- Male gender[67,73,74]: men have 3.6- to 14.5-fold higher mortality than women with this complication[67] (level of evidence 2+).
- Duration of RA[60,75]: the longer the duration of disease at diagnosis of ILD, the higher the mortality (HR per decade: 1.81; 95% CI: 1.16–2.83)[60] (level of evidence 2+).
- Moderate or high disease activity (DAS28-VSG >3.2) is also associated with increased mortality (OR: 1.6; 95% CI 1.0–2.5).[75]
- Radiological pattern of UIP[69,70,73,74,76,77]: according to the conclusions of a recent meta-analysis that included 10 retrospective studies with 1.256 patients with RA-ILD (I^2: 76%),[76] the UIP pattern has a mortality risk almost 2 times higher than non-UIP patterns (RR: 1.66; 95% CI: 1.07–2.76) (level of evidence 1++). In analysis by subgroups, when the UIP pattern was compared with the NSIP pattern the RR was 2.39 (95% CI: .86–6.68) and 1.45 (95% CI: .89 to 2.37) when the UIP was compared with other non-NSIP patterns. Increased mortality has also been described with a probable UIP pattern[77] (level of evidence 2+) and, in general, with all the forms of fibrosing RA-ILD (HR: 2.1; 95% CI: 1.11–4.26)[69] (level of evidence 2+).

It is important to highlight that in two studies[60,78] the radiological pattern is no longer a predictor of mortality after adjustment for confounding variables in multivariate analysis, the main prognostic factors being the degree of baseline deterioration in respiratory function tests (FVC and DLCO) and the magnitude of their worsening during follow-up.

- A low baseline DLCO or a decrease in DLCO > 15% during follow-up (level of evidence 2++).[60,61,71–73,76,79] Only the study by Zamora-Legoff et al.[60] establishes a cut-off point for baseline DLCO, setting it at less than 40% (HR: 2.48; 95% CI: 1.55–3.95) (level of evidence 2+). The prognostic value of baseline DLCO is independent of the presence or absence of emphysema due to smoking[76] (level of evidence 1++).
- A low baseline FVC during follow-up (HR: 2.57; 95% CI: 1.79–3.70) (level of evidence 1++) or a decrease in FVC > 10%[61,71,76] (level of evidence 2+). These studies do not establish a cut-off point for baseline FVC.
- Extensive lung involvement on thoracic HRCT has been demonstrated when more than 20% of the lung parenchyma is involved[10,80,81] (level of evidence 2++), and when more than 30% is involved 30%[61,71] (level of evidence 2+).
- Elevated serum levels of KL-6, which are associated with higher mortality (3–4 times higher)[64,74] (level of evidence 2+).

Finally, the usefulness of the GAP index (calculated with gender, age, and FVC and DLCO values) to predict the risk of mortality at 1, 2 and 3 years in patients with RA-ILD has been demonstrated[60,82] (level of evidence 2+). The CPI score[83] (level of evidence 2+) also appears to be useful for this purpose.

Discussion

RA-ILD is a complex clinical situation, both because of its frequency and potential severity, and because of the difficulty in its therapeutic management. There is little published evidence on the subject, most is of low methodological quality, and with contradictory results in some aspects. There are also no recommendations yet agreed upon by scientific societies.

This why we present the first official document drawn up by the SER and SEPAR with specific recommendations for the management of RA-ILD, which aims to serve as a guide for professionals caring for these patients and to bring clinical practice in line with the best possible evidence. These recommendations have been reached through a strict and validated methodology of systemic reviews of the scientific literature and expert consensus techniques.

Epidemiological information is essential to measure the socio-health importance of diseases and to contribute to proper health planning. Therefore, one of the main objectives of the paper was to determine the prevalence and incidence of ILD in RA patients. However, the SLR revealed great variability in the studies that have investigated this issue, and therefore its actual frequency could not be reliably established. As a guideline, the prevalence of symptomatic ILD diagnosed by chest HRCT varies between 10% and 29%,[36–39] whereas its incidence varies between 1.05 and 4.1 cases per 1000 patients,[21,22] and the risk of developing this complication in RA patients is much higher than in the general population.[6,84]

In more than three-quarters of patients, ILD develops after RA has been diagnosed, usually in the first 5–10 years of disease progression.[2–7,21,22,28,32,35,85] In these cases, it is not uncommon for it to be diagnosed late, since it is often asymptomatic in its initial stages or presents with few symptoms, and goes unnoticed until advanced stages, when the extent of fibrotic changes limits therapeutic possibilities and survival (UIP is the most frequent histopathological pattern in RA). Less frequently, ILD occurs at onset of RA or precedes the joint manifestations by months or years.[2–7] This circumstance has been reported in up to 10%–14% of patients with RA and ILD and is not always present and is often confused with idiopathic forms, despite their different prognosis and treatment.[68,86,87]

Although a significant improvement in prognosis has been observed over the last 25 years,[7] RA-ILD is still the second leading cause of premature death in RA, after cardiovascular complications.[2–7] Patients with RA-ILD have an adjusted mortality risk 3–10 times higher than RA patients without this complication[6,67] and their median survival from diagnosis of ILS varies from 2.6 to 8.1 years.[88]

Although ILD is a frequent and under-diagnosed complication with high morbidity and mortality, there are as yet no recommendations for screening. In the absence of studies supporting the cost-effectiveness of universal screening, a reasonable strategy would be to design a selective screening proposal based on patients' clinical risk. This clinical risk would be defined by the presence of respiratory symptoms (cough and/or dyspnoea of an unrelated cause of more than 3 months' duration), by the presence of dry velcro-like crackles on respiratory auscultation, or by the number of risk factors for the patient developing this complication. This initiative towards a multidisciplinary approach to selective screening criteria to identify patients with RA and ILD early was launched as a joint collaboration between the SER and SEPAR as part of the RA-EPIDSER project.[89] A tool to enable early identification of these patients with good sensitivity will help improve their survival and quality of life.

Another important point is that RA-ILD behaves heterogeneously in terms of its clinical course and prognosis. ILD will be stable or progress very slowly in approximately half of patients, while in the other half lung function deteriorates rapidly, especially in patients with fibrosing ILD.[60,61] This heterogeneity in progression makes it essential to identify prognostic factors for pulmonary

progression and mortality to detect patients with a more severe profile early, who will be candidates for specific treatment as soon as the diagnosis of ILD is confirmed and for close clinical follow-up. The main prognostic factors include UIP pattern, extensive lung involvement on chest HRCT, the severity of deterioration of FVC and DLCO at diagnosis of RA-ILD, and the extent that these parameters have worsened during follow-up.[10,60,61,69–74,76,77,79–81] Apart from the clinical and functional variables already in use, it remains to be seen how useful some of the biomarkers under investigation are, mainly IL-6 and KL-6, will be as tools to help predict progression and mortality in the short and medium term. Although the prognostic predictive capacity of these biomarkers has been validated in some studies (most with a small sample size), their use in daily clinical practice is limited and international guidelines are reluctant to recommend their use[90] mainly due to the lack of efficiency studies demonstrating the cost-benefit compared to other currently used clinical and functional variables, the absence of consensus on the measurements that could be most useful, and the need for additional validation studies with a large number of patients.

Ethical responsibilities

Protection of humans and animals. The authors declare that no experiments on humans or animals have been conducted for this research.

Data confidentiality. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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Authorship

All the authors made substantial contributions to a) the conception and design of the study and the data analysis, b) drafting of the article or critical review of the intellectual content, and c) final approval of the version presented.

Conflict of interests

José Antonio Rodríguez Portal has received funding from Roche and Sanofi for attendance at courses/congresses; honoraria from Roche, Boehringer and Janssen for presentations; financial support from Bristol, Janssen, Roche, and Boehringer for consultancy for pharmaceutical companies and other technologies; and has participated in clinical trials funded by Gilead, Roche and Boehringer.

Noé Brito García has no conflict of interests to declare.

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Appendix A. Supplementary data

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References

1. Silva-Fernández L, Macía-Villa C, Seoane-Mato D, Cortés-Verdú R, Romero-Pérez A, Quevedo-Vila V, et al. The prevalence of rheumatoid arthritis in Spain. Sci Rep. 2020;10:21551.
2. Farquhar H, Vassallo R, Edwards AL, Matteson EL. Pulmonary complications of rheumatoid arthritis. Semin Respir Crit Care Med. 2019;40:194–207.
3. Yunt ZX, Solomon JJ. Lung disease in rheumatoid arthritis. Rheum Dis Clin North Am. 2015;41:225–36.
4. Kadura S, Raghu G. Rheumatoid arthritis-interstitial lung disease: manifestations and current concepts in pathogenesis and management. Eur Respir Rev. 2021;30:210011.
5. Spagnolo P, Lee JS, Sverzellati N, Rossi G, Cottin V. The lung in rheumatoid arthritis: focus on interstitial lung disease. Arthritis Rheumatol. 2018;70:1544–54.
6. Bongartz T, Nannini C, Medina-Velasquez YF, Achenbach SJ, Crowson CS, Ryu JH, et al. Incidence and mortality of interstitial lung disease in rheumatoid arthritis: a population-based study. Arthritis Rheum. 2010;62:1583–9.
7. Kelly CA, Nisar M, Arthanari S, Carty S, Woodhead FA, Price-Forbes A, et al. Rheumatoid arthritis related interstitial lung disease — improving outcomes over 25 years: a large multicentre UK study. Rheumatology (Oxford). 2021;60:1882–90.
8. Grupo de trabajo sobre GPC. Elaboración de Guías de Práctica Clínica en el Sistema Nacional de Salud. Manual Metodológico. Madrid: Plan Nacional para el SNS del MSC. Instituto Aragonés de Ciencias de la Salud-I+CS; 2007. Guías de Práctica Clínica en el SNS: I+CS Nº 2006/0I.
9. NHS Scotland. 50: A guideline developers' handbook. SIGN; 2011.
10. Kelly CA, Saravanan V, Nisar M, Arthanari S, Woodhead FA, Price-Forbes AN, et al. Rheumatoid arthritis-related interstitial lung disease: associations, prognostic factors and physiological and radiological characteristics—a large multicentre UK study. Rheumatology (Oxford). 2014;53:1676–82.
11. Flaherty KR, Fell C, Aubry MC, Brown K, Colby T, Costabel U, et al. Smoking-related idiopathic interstitial pneumonia. Eur Respir J. 2014;44:594–602.
12. Cottin V, Cordier JF. Combined pulmonary fibrosis and emphysema in connective tissue disease. Curr Opin Pulm Med. 2012;18:418–27.
13. Jacob J, Song JW, Yoon HY, Cross G, Barnett J, Woo WL, et al. Prevalence and effects of emphysema in never-smokers with rheumatoid arthritis interstitial lung disease. EBioMedicine. 2018;28:303–10.
14. Spagnolo P, Distler O, Ryerson CJ, Tzouvelekis A, Lee JS, Bonella F, et al. Mechanisms of progressive fibrosis in connective tissue disease (CTD)-associated interstitial lung diseases (ILDs). Ann Rheum Dis. 2021;80:143–50.
15. Olson A, Hartmann N, Patnaik P, Wallace L, Schlenker-Herceg R, Nasser M, et al. Estimation of the prevalence of progressive fibrosing interstitial lung diseases: systematic literature review and data from a physician survey. Adv Ther. 2021;38:854–67.
16. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Progressive decline of lung function in rheumatoid arthritis-associated interstitial lung disease. Arthritis Rheumatol. 2017;69:542–9.
17. Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SLF, Inoue Y, et al. Nintedanib in progressive fibrosing interstitial lung diseases. N Engl J Med. 2019;381:1718–27.
18. George PM, Spagnolo P, Kreuter M, Altinisik G, Bonifazi M, Martinez FJ, et al. Progressive fibrosing interstitial lung disease: clinical uncertainties, consensus recommendations, and research priorities. Lancet Respir Med. 2020;8:925–34.
19. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183:788–824.
20. Raghu G, Rochwerg B, Zhang Y, Garcia CA, Azuma A, Behr J, et al. An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. An update of the 2011 clinical practice guideline. Am J Respir Crit Care Med. 2015;192:e3–19.
21. Shidara K, Hoshi D, Inoue E, Yamada T, Nakajima A, Taniguchi A, et al. Incidence of and risk factors for interstitial pneumonia in patients with rheumatoid arthritis in a large Japanese observational cohort, IORRA. Modern Rheumatology. 2010;20:280–6.
22. Koduri G, Norton S, Young A, Cox N, Davies P, Devlin J, et al. Interstitial lung disease has a poor prognosis in rheumatoid arthritis: results from an inception cohort. Rheumatology (Oxford). 2010;49:1483–9.
23. Bilgici A, Ulusoy H, Kuru O, Celenk C, Unsal M, Danaci M. Pulmonary involvement in rheumatoid arthritis. Rheumatol Int. 2005;25:429–35.
24. Dawson JK, Fewins HE, Desmond J, Lynch MP, Graham DR. Fibrosing alveolitis in patients with rheumatoid arthritis as assessed by high resolution computed tomography, chest radiography, and pulmonary function tests. Thorax. 2001;56:622–7.
25. Gabbay E, Tarala R, Will R, Carroll G, Adler B, Cameron D, et al. Interstitial lung disease in recent onset rheumatoid arthritis. Am J Respir Crit Care Med. 1997;156:528–35.
26. Gochuico BR, Avila NA, Chow CK, Novero LJ, Wu HP, Ren P, et al. Progressive preclinical interstitial lung disease in rheumatoid arthritis. Arch Intern Med. 2008;168:159–66.
27. Habib HM, Eisa AA, Arafat WR, Marie MA. Pulmonary involvement in early rheumatoid arthritis patients. Clin Rheumatol. 2011;30:217–21.
28. Mohd Noor N, Mohd Shahrir MS, Shahid MS, Abdul Manap R, Shahizon Azura AM, Azhar Shah S. Clinical and high resolution computed tomography characteristics of patients with rheumatoid arthritis lung disease. Int J Rheum Dis. 2009;12:136–44.
29. Mori S, Cho I, Koga Y, Sugimoto M. Comparison of pulmonary abnormalities on high-resolution computed tomography in patients with early versus longstanding rheumatoid arthritis. J Rheumatol. 2008;35:1513–21.
30. Skare TL, Nakano I, Escuissiato DL, Batistetti R, Rodrigues T de O, Silva MB. Pulmonary changes on high-resolution computed tomography of patients with rheumatoid arthritis and their association with clinical, demographic, serological and therapeutic variables. Rev Bras Reumatol. 2011;51:325–30.
31. Wang JX, Du CG. A retrospective study of clinical characteristics of interstitial lung disease associated with rheumatoid arthritis in Chinese patients. Med Sci Monit. 2015;21:708–15.
32. Zhang Y, Li H, Wu N, Dong X, Zheng Y. Retrospective study of the clínical characteristics and risk factors of rheumatoid arthritis-associated interstitial lung disease. Clin Rheumatol. 2017;36:817–23.
33. Zrour SH, Touzi M, Bejia I, Golli M, Rouatbi N, Sakly N, et al. Correlations between high-resolution computed tomography of the chest and clinical function in patients with rheumatoid arthritis. Prospective study in 75 patients. Joint Bone Spine. 2005;72:41–7.
34. Robles-Pérez A, Luburich P, Bolivar S, Dorca J, Nolla JM, Molina-Molina M, et al. A prospective study of lung disease in a cohort of early rheumatoid arthritis patients. Sci Rep. 2020;10:15640.
35. Li L, Liu R, Zhang Y, Zhou J, Li Y, Xu Y, et al. A retrospective study on the predictive implications of clinical characteristics and therapeutic management in patients with rheumatoid arthritis-associated interstitial lung disease. Clin Rheumatol. 2020;39:1457–70.
36. Salaffi F, Carotti M, Di Carlo M, Tardella M, Giovagnoni A. High-resolution computed tomography of the lung in patients with rheumatoid arthritis: prevalence of interstitial lung disease involvement and determinants of abnormalities. Medicine (Baltimore). 2019;98:e17088.
37. Huang S, Doyle TJ, Hammer MM, Byrne SC, Huang W, Marshall AA, Iannaccone CK, et al. Rheumatoid arthritis-related lung disease detected on clinical chest computed tomography imaging: prevalence, risk factors, and impact on mortality. Semin Arthritis Rheum. 2020;50:1216–25.
38. Olson AL, Swigris JJ, Sprunger DB, Fischer A, Fernandez-Perez ER, Solomon J, Murphy J, Cohen M, Raghu G, Brown KK. Rheumatoid arthritis-interstitial lung disease-associated mortality. Am J Respir Crit Care Med. 2011;183:372.
39. Doyle TJ, Dellaripa PF, Batra K, Frits ML, Iannaccone CK, Hatabu H, et al. Functional impact of a spectrum of interstitial lung abnormalities in rheumatoid arthritis. Chest. 2014;146:41–50.
40. Suzuki A, Ohosone Y, Obana M, Mita S, Matsuoka Y, Irimajiri S, et al. Cause of death in 81 autopsied patients with rheumatoid arthritis. J Rheumatol. 1994;21:33–6.
41. Song ST, Kim SS, Kim JY, Lee SY, Kim K, Kwon IS, et al. Association of single nucleotide polymorphisms of PADI4 and HLA-DRB1 alleles with susceptibility to rheumatoid arthritis-related lung diseases. Lung. 2016;194:745–53.
42. Mori S, Koga Y, Sugimoto M. Different risk factors between interstitial lung disease and airway disease in rheumatoid arthritis. Respir Med. 2012;106:1591–9.
43. Kiely P, Busby AD, Nikiphorou E, Sullivan K, Walsh DA, Creamer P, et al. Is incident rheumatoid arthritis interstitial lung disease associated with methotrexate treatment? Results from a multivariate analysis in the ERAS and ERAN inception cohorts. BMJ Open. 2019;9, e028466-e.
44. Saag KG, Kolluri S, Koehnke RK, Georgou TA, Rachow JW, Hunninghake GW, et al. Rheumatoid arthritis lung disease. Determinants of radiographic and physiologic abnormalities. Arthritis Rheum. 1996;39:1711–9.
45. Sparks JA, He X, Huang J, Fletcher EA, Zaccardelli A, Friedlander HM, et al. Rheumatoid arthritis disease activity predicting incident clinically apparent rheumatoid arthritis-associated interstitial lung disease: a prospective cohort study. Arthritis Rheumatol. 2019;71:1472–82.
46. Zhu J, Zhou Y, Chen X, Li J. A metaanalysis of the increased risk of rheumatoid arthritis-related pulmonary disease as a result of serum anticitrullinated protein antibody positivity. J Rheumatol. 2014;41:1282–9.
47. Giles JT, Danoff SK, Sokolove J, Wagner CA, Winchester R, Pappas DA, et al. Association of fine specificity and repertoire expansion of anticitrullinated peptide antibodies with rheumatoid arthritis associated interstitial lung disease. Ann Rheum Dis. 2014;73:1487–94.
48. Yin Y, Liang D, Zhao L, Li Y, Liu W, Ren Y, et al. Anti-cyclic citrullinated peptide antibody is associated with interstitial lung disease in patients with rheumatoid arthritis. PLoS One. 2014;9, e92449-e.
49. Castellanos-Moreira R, Rodriguez-Garcia SC, Gomara MJ, Ruiz-Esquide V, Cuervo A, Casafont-Sole I, et al. Anti-carbamylated proteins antibody repertoire in rheumatoid arthritis: evidence of a new autoantibody linked to interstitial lung disease. Ann Rheum Dis. 2020;79:587–94.
50. Chen J, Doyle TJ, Liu Y, Aggarwal R, Wang X, Shi Y, et al. Biomarkers of rheumatoid arthritis-associated interstitial lung disease. Arthritis Rheumatol. 2015;67:28–38.
51. Matsuo T, Hashimoto M, Ito I, Kubo T, Uozumi R, Furu M, et al. Interleukin-18 is associated with the presence of interstitial lung disease in rheumatoid arthritis: a cross-sectional study. Scand J Rheumatol. 2019;48:87–94.

52. Doyle TJ, Patel AS, Hatabu H, Nishino M, Wu G, Osorio JC, et al. Detection of rheumatoid arthritis-interstitial lung disease is enhanced by serum biomarkers. Am J Respir Crit Care Med. 2015;191:1403–12.
53. Harlow L, Rosas IO, Gochuico BR, Mikuls TR, Dellaripa PF, Oddis CV, et al. Identification of citrullinated HSP90 isoforms as novel autoantigens in rheumatoid arthritis-associated interstitial lung disease. Arthritis Rheum. 2013;65:869–79.
54. Juge P-A, Lee JS, Ebstein E, Furukawa H, Dobrinskikh E, Gazal S, et al. MUC5B promoter variant and rheumatoid arthritis with interstitial lung disease. N Engl J Med. 2018;379:2209–19.
55. Juge PA, Borie R, Kannengiesser C, Gazal S, Revy P, Wemeau-Stervinou L, et al. Shared genetic predisposition in rheumatoid arthritis-interstitial lung disease and familial pulmonary fibrosis. Eur Respir J. 2017;49:1602314.
56. Antoniou KM, Margaritopoulos GA, Proklou A, Karagiannis K, Lasithiotaki I, Soufla G, et al. Investigation of telomerase/telomeres system in bone marrow mesenchymal stem cells derived from IPF and RA-UIP. J Inflamm (Lond). 2012;9:27.
57. Sgalla G, Walsh SLF, Sverzellati N, Fletcher S, Cerri S, Dimitrov B, et al. Velcro-typecrackles predict specific radiologic features of fibrotic interstitial lung disease. BMC Pulm Med. 2018;18:103.
58. Manfredi A, Cassone G, Cerri S, Venerito V, Fedele AL, Trevisani M, et al. Diagnostic accuracy of a velcro sound detector (VECTOR) for interstitial lung disease inrheumatoid arthritis patients: the InSPIRAtE validation study (INterStitial pneumonia in rheumatoid ArThritis with an electronic device). BMC Pulm Med. 2019;19:111.
59. Pancaldi F, Sebastiani M, Cassone G, Luppi F, Cerri S, Della Casa G, et al. Analysis of pulmonary sounds for the diagnosis of interstitial lung diseases secondary to rheumatoid arthritis. Comput Biol Med. 2018;96:91–7.
60. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Patterns of interstitial lung disease and mortality in rheumatoid arthritis. Rheumatology (Oxford). 2017;56:344–50.
61. Hyldgaard C, Ellingsen T, Hilberg O, Bendstrup E. Rheumatoid arthritis-associated interstitial lung disease: clinical characteristics and predictors of mortality. Respiration. 2019;98:455–60.
62. Fu Q, Wang L, Li L, Li Y, Liu R, Zheng Y. Risk factors for progression and prognosis of rheumatoid arthritis-associated interstitial lung disease: single center study with a large sample of Chinese population. Clin Rheumatol. 2019;38:1109–16.
63. Dawson JK, Fewins HE, Desmond J, Lynch MP, Graham DR. Predictors of progression of HRCT diagnosed fibrosing alveolitis in patients with rheumatoid arthritis. Ann Rheum Dis. 2002;61:517–21.
64. Lee YS, Kim HC, Lee BY, Lee CK, Kim M-Y, Jang SJ, et al. The value of biomarkers as predictors of outcome in patients with rheumatoid arthritis-associated usual interstitial pneumonia. Sarcoidosis Vasc Diffuse Lung Dis. 2016;33:216–23.
65. Li L, Gao S, Fu Q, Liu R, Zhang Y, Dong X, et al. A preliminary study of lung abnormalities on HRCT in patients of rheumatoid arthritis-associated interstitial lung disease with progressive fibrosis. Clin Rheumatol. 2019;38:3169–78.
66. Avouac J, Cauvet A, Steelandt A, Shirai Y, Elhai M, Kuwana M, et al. Improving risk-stratification of rheumatoid arthritis patients for interstitial lung disease. PLoS One. 2020;15:e0232978.
67. Kim D, Cho SK, Choi CB, Choe JY, Chung WT, Hong SJ, et al. Impact of interstitial lung disease on mortality of patients with rheumatoid arthritis. Rheumatol Int. 2017;37:1735–45.
68. Hyldgaard C, Hilberg O, Pedersen AB, Ulrichsen SP, Løkke A, Bendstrup E, et al. A population-based cohort study of rheumatoid arthritis-associated interstitial lung disease: comorbidity and mortality. Ann Rheum Dis. 2017;76:1700–6.
69. Solomon JJ, Ryu JH, Tazelaar HD, Myers JL, Tuder R, Cool CD, et al. Fibrosing interstitial pneumonia predicts survival in patients with rheumatoid arthritis-associated interstitial lung disease (RA-ILD). Respir Med. 2013;107:1247–52.
70. Yang JA, Lee JS, Park JK, Lee EB, Song YW, Lee EY. Clinical characteristics associated with occurrence and poor prognosis of interstitial lung disease in rheumatoid arthritis. Korean J Int Med. 2019;34:434–41.
71. Song JW, Lee HK, Lee CK, Chae EJ, Jang SJ, Colby TV, et al. Clinical course and outcome of rheumatoid arthritis-related usual interstitial pneumonia. Sarcoidosis Vasc Diffuse Lung Dis. 2013;30:103–12.
72. Rojas-Serrano J, Herrera-Bringas D, Pérez-Román DI, Pérez-Dorame R, Mateos-Toledo H, Mejía M. Rheumatoid arthritis-related interstitial lung disease (RA-ILD): methotrexate and the severity of lung disease are associated to prognosis. Clin Rheumatol. 2017;36:1493–500.
73. Kim EJ, Elicker BM, Maldonado F, Webb WR, Ryu JH, Collard HR, et al. Usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease. Eur Respir J. 2010;35:1322–8.
74. Kim HC, Choi KH, Jacob J, Song JW. Prognostic role of blood KL-6 in rheumatoid arthritis-associated interstitial lung disease. PLoS One. 2020;15:e0229997.
75. Kakutani T, Hashimoto A, Tominaga A, Kodama K, Nogi S, Tsuno H, et al. Related factors, increased mortality and causes of death in patients with rheumatoid arthritis-associated interstitial lung disease. Mod Rheumatol. 2019:1–7.
76. Singh N, Varghese J, England BR, Solomon JJ, Michaud K, Mikuls TR, et al. Impact of the pattern of interstitial lung disease on mortality in rheumatoid arthritis: a systematic literature review and meta-analysis. Semin Arthritis Rheum. 2019;49:358–65.
77. Yunt ZX, Chung JH, Hobbs S, Fernandez-Perez ER, Olson AL, Huie TJ, 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.
78. Solomon JJ, Chung JH, Cosgrove GP, Demoruelle MK, Fernandez-Perez ER, Fischer A, et al. Predictors of mortality in rheumatoid arthritis-associated interstitial lung disease. Eur Respir J. 2016;47:588–96.
79. Nurmi HM, Kettunen H-P, Suoranta S-K, Purokivi MK, Kärkkäinen MS, Selander TA, et al. Several high-resolution computed tomography findings associate with survival and clinical features in rheumatoid arthritis-associated interstitial lung disease. Respiratory medicine. 2018;134:24–30.
80. Ito Y, Arita M, Kumagai S, Takei R, Noyama M, Tokioka F, et al. Radiological fibrosis score is strongly associated with worse survival in rheumatoid arthritis-related interstitial lung disease. Mod Rheumatol. 2019;29:98–104.
81. Jacob J, Hirani N, van Moorsel CHM, Rajagopalan S, Murchison JT, van Es HW, et al. Predicting outcomes in rheumatoid arthritis related interstitial lung disease. Eur Respir J. 2019;53:1800869.
82. Morisset J, Vittinghoff E, Lee BY, Tonelli R, Hu X, Elicker BM, et al. The performance of the GAP model in patients with rheumatoid arthritis associated interstitial lung disease. Respir Med. 2017;127:51–6.
83. Nurmi HM, Purokivi MK, Kärkkäinen MS, Kettunen HP, Selander TA, Kaarteenaho RL. Are risk predicting models useful for estimating survival of patients with rheumatoid arthritis-associated interstitial lung disease? BMC Pulm Med. 2017;17:16.
84. Ng KH, Chen DY, Lin CH, Chao WC, Chen YM, Chen YH, et al. Risk of interstitial lung disease in patients with newly diagnosed systemic autoimmune rheumatic disease: a nationwide, population-based cohort study. Semin Arthritis Rheum. 2020;50:840–5.
85. Duarte AC, Porter JC, Leandro MJ. The lung in a cohort of rheumatoid arthritis patients-an overview of different types of involvement and treatment. Rheumatology (Oxford). 2019;58:2031–8.
86. Gizinski AM, Mascolo M, Loucks JL, Kervitsky A, Meehan RT, Brown KK, et al. Rheumatoid arthritis (RA)-specific autoantibodies in patients with interstitial lung disease and absence of clinically apparent articular RA. Clin Rheumatol. 2009;28:611–3.
87. Singh K, Al-Sadawi M, Rodriguez Ortega R, Akter K, Zrodlowski T, Zmijewski C, et al. Interstitial lung disease as the initial manifestation of rheumatoid arthritis: a case report and review of the literature. Am J Med Case Rep. 2019;7:342–7.
88. Assayag D, Lubin M, Lee JS, King TE, Collard HR, Ryerson CJ. Predictors of mortality in rheumatoid arthritis-related interstitial lung disease. Respirology. 2014;19:493–500.
89. Narváez J, Aburto M, Seoane-Mato D, Bonilla G, Acosta O, Candelas G, et al. Criterios de cribado de la enfermedad pulmonar intersticial difusa asociada a la artritis reumatoide: propuesta de expertos basada en metodología Delphi. Reumatol Clin. 2022, http://dx.doi.org/10.1016/j.reuma.2021.12.006.90.
90. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of idiopathic pulmonary fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Eur Respir J. 2017;50:1700936.