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REVIEW ARTICLE

Clinical Course of Interstitial Lung Disease in Patients With Rheumatoid Arthritis

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Interstitial lung disease (ILD) is a frequent manifestation of rheumatoid arthritis (RA) that is associated with high mortality. RA-ILD may initially be asymptomatic, and lung function may be markedly impaired by the time it is diagnosed. The course of RA-ILD is highly variable, with some patients experiencing no discernable progression or a slow decline, whereas others experience more rapid deterioration. Some patients develop progressive pulmonary fibrosis, which is associated with high mortality. Although risk factors for the progression of RA-ILD have been identified, including older age, worse lung function, and a usual interstitial pneumonia pattern on high-resolution computed tomography, it is not possible to predict the course of RA-ILD in an individual patient. The association between RA disease activity and progression of RA-ILD remains unclear. Regular monitoring is important to enable the prompt identification of progression and early intervention to preserve lung function. The management of RA-ILD requires a multidisciplinary and individualized approach, taking account of the severity and progression of articular and lung disease, risk factors for the progression of RA-ILD, and the patient's preferences, and may include immunosuppression, antifibrotic therapy, and supportive care.

Introduction

Interstitial lung disease (ILD) is a frequent manifestation of rheumatoid arthritis (RA).[1–7] The reported prevalence of ILD in patients with RA varies widely depending on the population studied and the definition used, which may only require evidence of ILD on high-resolution computed tomography (HRCT) and not be restricted to clinically significant disease. For example, among 137 patients newly diagnosed with RA at a Danish rheumatology/pulmonology center, 6% had evidence of ILD on HRCT,[8] whereas among 151 patients with a mean RA duration of 7.5 years, 19% had evidence of ILD on HRCT.[4] RA-ILD has a variable clinical course but is associated with significant morbidity and mortality. In this narrative review, we discuss the clinical course of RA-ILD and its implications for monitoring and management.

Methods

We performed a PubMed search for English language papers published between January 1, 2000 and October 23, 2023 using the following search terms: (arthritis, rheumatoid) AND (interstitial lung disease OR pulmonary fibrosis) AND (natural history OR disease course OR disease progression OR clinical deterioration OR forced vital capacity OR respiratory function tests OR mortality OR survival OR survival rate). The papers identified were hand-searched for relevance. We identified 115 papers on retrospective observational studies and 22 papers on prospective observational studies that provided data on the clinical course of RA-ILD.

Key findings

Early onset of RA-ILD. ILD may be an early complication of RA or even the first presentation of the disease. Prospectively collected data from 679 patients with RA-ILD in a nationwide Danish registry showed that 15% of patients were diagnosed with ILD in the year before the RA diagnosis and 19% in the year after the RA diagnosis.[2] In a retrospective analysis of 137 patients with RA-ILD at a center in the United States, the ILD diagnosis

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predated the RA diagnosis in 10% of patients and was made at the same time as the RA diagnosis in 17% of patients.[9]

Although patients with RA-ILD often present with respiratory symptoms such as cough and dyspnea, RA-ILD may be asymptomatic. In a French cohort of 163 patients with RA (median duration of 14 years) who did not have a history of ILD or respiratory symptoms, 19% had evidence of ILD on HRCT.[10] Among 184 patients at a US center with RA (median duration of 8.5 years), 21% had evidence of ILD on HRCT, and there was no difference in shortness of breath scores between patients who did and did not have ILD.[11] Lung function may be markedly impaired by the time that RA-ILD is diagnosed. In a retrospective study on the medical records of 167 patients at a US tertiary care center, median forced vital capacity (FVC) at diagnosis of RA-ILD was 71% predicted, and median diffusing capacity for carbon monoxide (DLco) was 55% predicted.[12] Among 102 patients newly diagnosed with RA-ILD at a referral center in Denmark, FVC was relatively well-preserved (mean 90% predicted), but DLco was markedly impaired (mean 55% predicted).[13] These data illustrate the importance of screening high-risk patients with RA for ILD to enable RA-ILD to be detected promptly and treated before substantial lung function is lost.

RA-ILD may be associated with pulmonary fibrosis. Fibrotic features, such as reticulation, traction bronchiectasis, and honeycombing, which are radiographic features of the usual interstitial pneumonia (UIP) pattern, are commonly seen on HRCT scans from patients with RA-ILD (Figure 1).[12–16] Inflammatory features, such as ground glass opacities, are also commonly observed.[12–14,16] In contrast to other autoimmune disease-related ILDs, the most frequently observed pattern on CT in patients with RA-ILD is a UIP pattern. In a pooled analysis of data from 86 studies that included 4,897 patients with RA-ILD, 46% had a UIP pattern on CT,

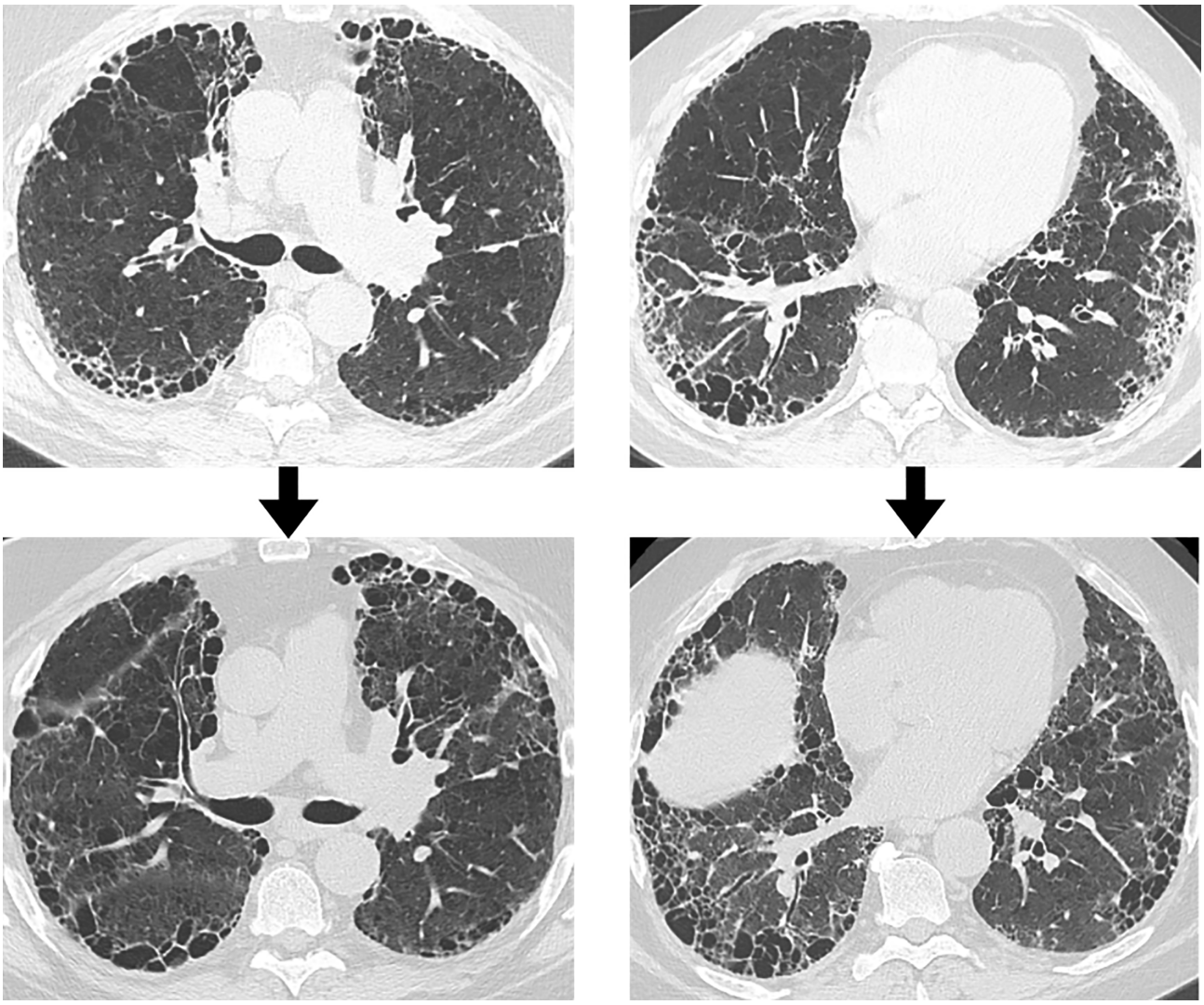


Figure 1. HRCT with axial images showing UIP-type fibrosis with reticulation, traction bronchiectasis, and honeycomb fibrosis (top row) and progression on scans taken 16 months later (bottom row). HRCT, high-resolution computed tomography; UIP, usual interstitial pneumonia. *Source*: Reproduced with permission from Mary E. Strek.

whereas 35% had a nonspecific interstitial pneumonia (NSIP) pattern.[17]

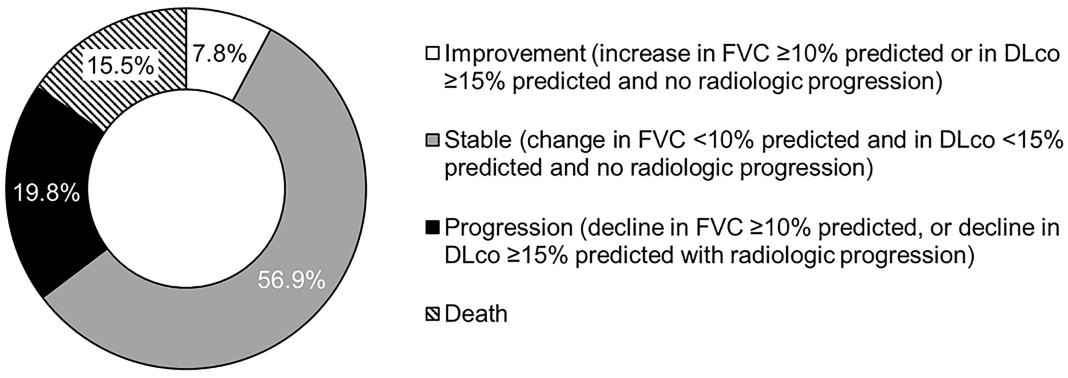
Progression of RA-ILD. The course of RA-ILD is highly variable, with some patients showing no discernable progression or a slow decline and others experiencing more rapid deterioration.[13,18–21] In a prospective multicenter study in Korea, group-based modeling of data from 140 patients with RA-ILD identified four distinctive trajectories of change in predicted FVC.[21] Over three years, 8% of patients were classified as "improving," 38% as "stable," 49% as "slowly declining," and 5% as "rapidly declining." The mean annual changes in FVC in these groups were +26.8 mL, −23.4 mL, −65.7 mL, and −139.6 mL.[21] Different courses of RA-ILD progression are also observed in terms of increases in the extent of ILD on HRCT. In a prospective cohort of 34 patients with RA-ILD, changes in automated quantitative ILD scores showed four types of trajectories over 24 months: improvement, worsening, improvement then worsening (convex-like), and worsening then improvement (concave-like).[19]

Although it is clear that RA-ILD may be progressive,[12,13,19–29] the criteria used to define progression vary across studies. In an analysis of medical records of 102 patients with RA-ILD at a referral center, progression defined as death from respiratory cause, relative decline in FVC ≥10%, relative decline in FVC ≥5% to <10% with worsening symptoms or worsening radiographic findings, relative decline in DLco ≥15%, or clinical characteristics of progression was observed in 52% of patients in the two years after RA-ILD diagnosis.[13] In an international retrospective analysis of data from 256 patients with RA-ILD, 13% had progression defined as an absolute or relative decline in predicted FVC ≥10% in the two years after RA-ILD diagnosis.[24] In a prospective multicenter study of 116 patients with RA-ILD receiving disease-modifying antirheumatic drugs (DMARDs), 20% had progression defined as a decline in predicted FVC ≥10%, or a decline in predicted DLCO ≥15% with radiologic progression, over a follow-up of 60 months (Figure 2).[20]

The INBUILD trial defined progressive pulmonary fibrosis (PPF) in patients with fibrosing ILDs other than idiopathic pulmonary fibrosis (IPF) as a relative decline in predicted FVC ≥10% or at least two of the following: a relative decline in predicted FVC ≥5% to <10%, worsened respiratory symptoms, and increased extent of fibrosis on HRCT within the previous two years despite management that was deemed appropriate in clinical practice.[30] In a retrospective review of the medical records of 168 patients at a single center in Korea, 34.5% fulfilled the INBUILD definition of PPF.[25] A retrospective analysis of data from 89 patients with RA-ILD at a Belgian center found that 53.9% had PPF according to the INBUILD trial definition.[28] Among 189 patients with fibrotic RA-ILD in the Canadian Registry for Pulmonary Fibrosis, 46% had PPF as defined by the INBUILD trial, had a lung transplant, or died.[31]

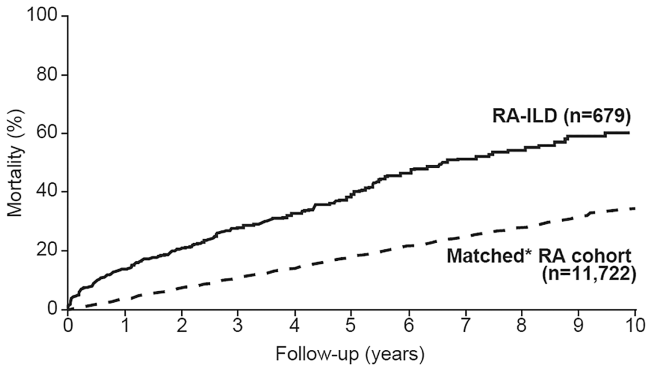
In May 2022, international respiratory societies proposed criteria to define PPF in patients with fibrosing ILDs other than IPF based on worsening of respiratory symptoms, decline in predicted FVC ≥5% or decline in predicted DLCO ≥10%, and/or radiologic evidence of progression in the past year.[32] To date, there are no published data on the proportion of patients with RA-ILD who meet these criteria.

RA-ILD is associated with high mortality,[1,2,5,6,28,33–37] with several studies suggesting a two- to three-fold greater risk of death in patients with RA-ILD compared with patients with RA without ILD.[1,2,6,28,35] Prospectively collected data from a nationwide Danish registry found that five-year mortality was 39% in patients with RA-ILD compared with 18% in a cohort of patients with RA without ILD matched by birth year, sex, and age at RA diagnosis (Figure 3).[2] Acute worsenings of RA-ILD, known as acute exacerbations, are associated with very high mortality.[38–42]



Among 116 patients with RA-ILD receiving disease-modifying anti-rheumatic drugs (DMARDs) over a 60-month follow-up. Radiologic progression: ≥20% increase in extent of ground-glass opacities, reticulation, honeycombing, diminished attenuation, centrilobular nodules, other nodules, emphysema, or consolidation.

Figure 2. Course of RA-ILD based on lung function, HRCT, and death.[20] HRCT, high-resolution computed tomography; RA-ILD, rheumatoid arthritis–interstitial lung disease.



*Matched by birth year, sex, age at RA diagnosis.

Figure 3. Survival in patients with RA-ILD and in a matched cohort of patients with RA without ILD.[2] RA, rheumatoid arthritis; ILD, interstitial lung disease. *Source*: Adapted with permission from BMJ Publishing Group Limited. Ann Rheum Dis, Hyldgaard C, et al, Vol. 76, Pages No. 1700–1706, Copyright 2017.

42 A retrospective study of 149 patients with RA-ILD who visited a Japanese hospital found that 18% had an acute exacerbation and that this was the most frequent cause of death.[40] An analysis of medical records from 310 patients with RA-ILD from a center in Korea suggested that the one-, three-, and five-year cumulative incidences of acute exacerbation were 9.2%, 19.8%, and 29.4%, respectively.[42] In this study, the 30- and 90-day mortality rates after an acute exacerbation were 12.6% and 29.9%, respectively.[42]

Predicting progression of RA-ILD. Several studies have shown that older age, lower FVC or DLco, a greater extent of ILD on HRCT, and a UIP pattern on HRCT are associated with a greater risk of death in patients with RA-ILD (Table 1). In a prospective cohort of 227 patients, compared with patients with predicted DLCO ≥80% at baseline, hazard ratios (HRs) for death over a mean follow-up of 4.7 years were 2.1 (95% confidence interval [CI] 0.9–4.8) in patients with predicted DLCO 50% to 80% and 3.8 (95% CI 1.5–9.5) in patients with predicted DLCO 30% to 50%. For patients with predicted FVC ≥80% at baseline, HRs for death were 1.8 (95% CI 1.1–3.0) in patients with predicted FVC50% to 80% and 1.8 (95% CI 0.6–4.9) in patients with predicted FVC 30% to 50% (Figure 4).[36] In a retrospective analysis of 266 patients, the HR for death over a median follow-up of 51 months in patients with >30% compared with ≤30% lung involvement was 2.2 (95% CI 1.2–3.9).[45] A retrospective analysis of data from patients with RA-ILD at a single US center showed that patients with a definite or possible UIP patten on HRCT (n = 123) had worse survival than those with NSIP on HRCT (n = 35) over a median follow-up of three years (Figure 5).[54] In a prospective study of 116 patients with RA-ILD receiving DMARDs, the mean survival after inclusion in the study was 56 months in patients with a UIP pattern on HRCT compared with 70 months in patients with an NSIP pattern.[20] As established in other ILDs,[58] decline in FVC is a predictor of death in patients with RA-ILD.[18,50] Modeling of data from 137 patients with RA-ILD suggested that the mortality rate was 2.5-fold greater in patients who had a decline in FVC ≥10% during follow-up than in patients who did not.[50] Smoking has been identified as a risk factor for progression of RA-ILD.[20,23] Recent data suggest that high exposure to small particulate matter (air pollution) may also increase the risk of hospitalizations and death in patients with RA-ILD.[59,60]

Fewer studies have investigated risk factors for deterioration in lung function, but the risk factors associated with a faster decline in FVC or DLco appear to be the same as those associated with death.[12,18,21,53,57,60] Male sex has been shown to be associated with a faster lung function decline or death in some studies,[51,57,61] but other studies have found no association between sex and progression of RA-ILD.[13,44,46] Few studies have investigated risk factors for acute exacerbation of RA-ILD, but there is some evidence that the risk of acute exacerbation is higher in patients with a UIP pattern on HRCT.[38,62,63]

There is some evidence of an association between RA disease activity and progression of RA-ILD. Higher RA disease activity based on the Disease Activity Score using 28 joints with erythrocyte sedimentation rate (DAS28-ESR) was associated with a greater risk of death in a prospective multicenter study of 227 patients[36] and in two retrospective single-center studies.[23,57] Higher disease activity based on the clinical disease activity index score was associated with a greater risk of death in a retrospective single-center study of 37 patients.[56] However, in a prospective study of 140 patients, no significant association was found between the trajectory of the DAS28 score and the trajectory of lung function.[21] Higher levels of circulating rheumatoid factor have been associated with higher mortality in patients with RA-ILD.[27,64,65] High anticyclic citrullinated peptide antibody titers have been associated with increased risk of RA-ILD progression.[20,45] Higher levels of circulating Krebs von den Lungen 6 and increases in C-X-X motif cemokine ligand 11/ITAC (interferon inducible T-cell alpha chemoattractant) and matrix metalloproteinase–13 over time have been associated with progressive versus stable RA-ILD.[27,66] Unlike IPF, the *MUC5B rs35705950 T* risk allele is not associated with progression of RA-ILD.[24]

Monitoring and management of RA-ILD. Although risk factors for the progression of RA-ILD have been identified, for an individual patient, the course of disease remains unpredictable. All patients with RA-ILD should be monitored, but patients with established risk factors for progression (such as a UIP pattern on HRCT) may warrant more frequent monitoring. In the absence of evidence-based guidelines, experts have recommended that pulmonary function tests be performed every three to six months, with repeat HRCT where clinically indicated.[67–69] Prompt detection of PPF in patients with RA-ILD provides the opportunity for early intervention. However, decisions about when to start

Table 1. Risk factors for death in patients with RA-ILD*

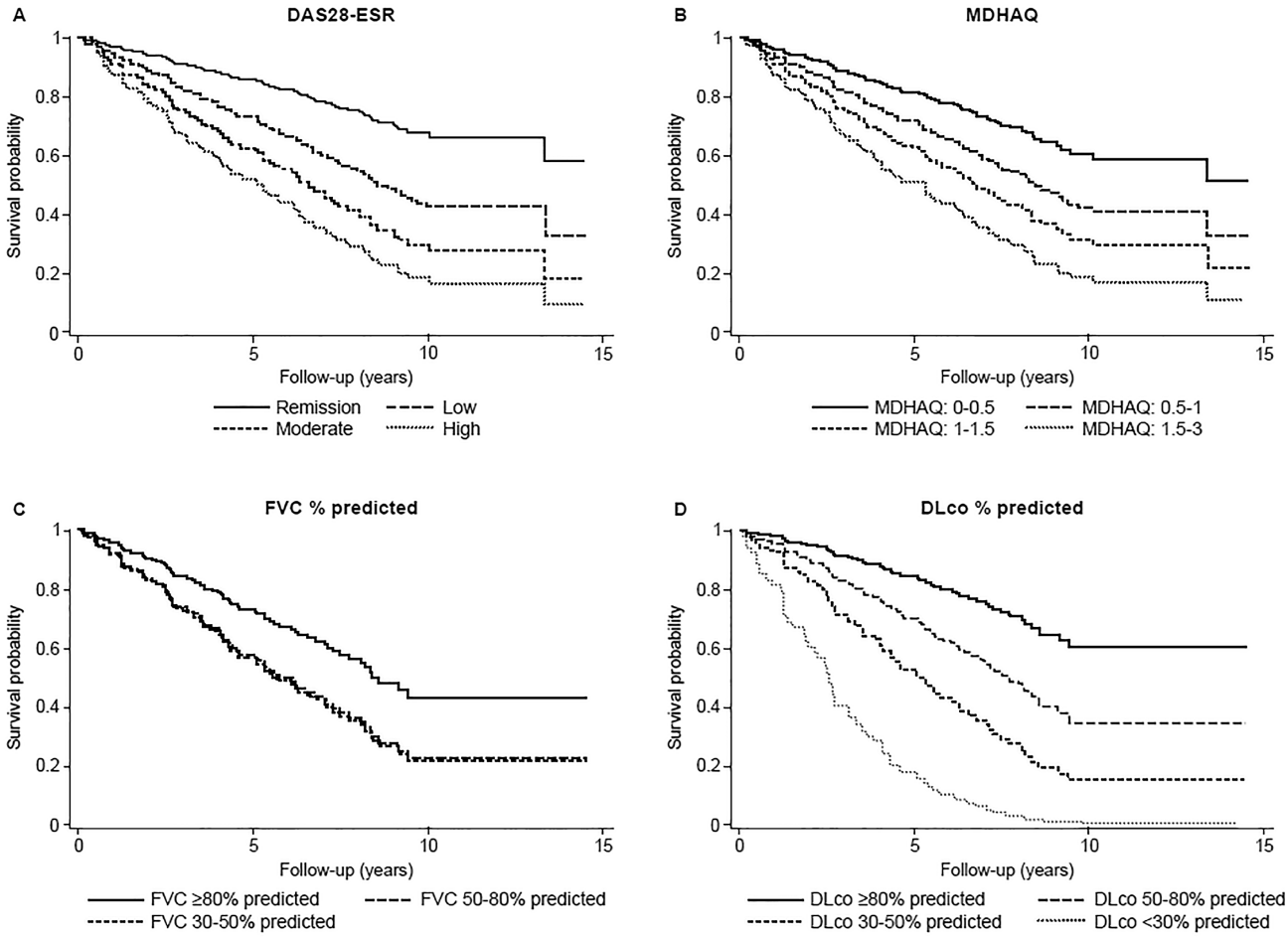
Risk factor	Key studies			
	Reference	Single or multicenter	Design	Number of patients with RA-ILD
Older age	Song et al[18] (2013)	Two centers	Retrospective	84 (UIP)
	Nurmi et al[43] (2017)	Single center	Retrospective	59
	Zamora-Legoff et al[44] (2017)	Single center	Retrospective	181
	Fu et al[45] (2019)	Single center	Retrospective	266
	Yamakawa et al[46] (2019)	Single center	Retrospective	96
	Li et al[47] (2020)	Single center	Retrospective	278
	Kim et al[48] (2020)	Single center	Retrospective	170
	Oh et al[49] (2022)	Single center	Retrospective	144
Lower FVC	Brooks et al[36] (2022)	Multicenter	Prospective	227
	Juge et al[24] (2021)	Multicenter	Retrospective	261
	Solomon et al[50] (2016)	Single center	Retrospective	137
	Song et al[18] (2013)	Two centers	Retrospective	84 (UIP)
Lower DLco	Brooks et al[36] (2022)	Multicenter	Prospective	227
	Juge et al[24] (2021)	Multicenter	Retrospective	261
	Zamora-Legoff et al[44] (2017)	Single center	Retrospective	181
	Hyldgaard et al[13] (2019)	Single center	Retrospective	102
	Nurmi et al[86] (2017)	Single center	Retrospective	59
Greater extent of ILD on HRCT	Fu et al[45] (2019)	Single center	Retrospective	266
	Ito et al[51] (2019)	Single center	Retrospective	97
	Li et al[47] (2020)	Single center	Retrospective	278
	Kim et al[48] (2020)	Single center	Retrospective	170
	Oh et al[49] (2022)	Single center	Retrospective	144
	Chai et al[33] (2023)	Single center	Retrospective	120
UIP pattern on HRCT	Nieto et al[52] (2021)	Two centers	Retrospective	47
	Nurmi et al[53] (2016)	Single center	Retrospective	59
	Solomon et al[50] (2016)	Single center	Retrospective	137
	Yunt et al[54] (2017)	Single center	Retrospective	15
	Kim et al[48] (2020)	Single center	Retrospective	170
	Ekici et al[55] (2021)	Single center	Retrospective	156
High RA disease activity (based on DAS28-ESR or CDAI)	Brooks et al[36] (2022)	Multicenter	Prospective	227
	Rojas-Serrano et al[56] (2022)	Single center	Retrospective	37
	Liu et al[57] (2022)	Single center	Retrospective	201
	Chai et al[23] (2023)	Single center	Retrospective	120

*CDAI, clinical disease activity index; DAS28-ESR, Disease Activity Score using 28 joints with erythrocyte sedimentation rate; DLco, diffusing capacity for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; RA, rheumatoid arthritis; UIP, usual interstitial pneumonia.

therapy and which therapies to use remain challenging. Therapeutic decision-making requires a multidisciplinary approach, involving, at minimum, input from a rheumatologist and pulmonologist, and should take account of the severity and progression of both articular and lung disease, risk factors for progression of ILD, and the patient's preferences.

In the randomized double-masked Treatment for Rheumatoid Arthritis and Interstitial Lung Disease 1 (TRAIL-1) trial in patients with RA-ILD and >10% extent of fibrosis on HRCT, treatment with pirfenidone (n = 63) reduced the rate of decline in FVC over 52 weeks by 55% compared with placebo (n = 60) (–66 vs –146 mL), but the trial was underpowered to detect a difference in the primary endpoint (decline in predicted FVC ≥10% or death over 52 weeks).[70] An effect of pirfenidone was observed only among patients with a UIP-like pattern on HRCT, in whom the change in FVC over 52 weeks was –43 mL in the pirfenidone group versus –169 mL in the placebo group.[70] Pirfenidone is not licensed to treat ILDs other than IPF. In the randomized double-blind INBUILD trial in patients with PPF, treatment with nintedanib (n = 332) reduced the rate of decline in FVC over 52 weeks by 57% compared with placebo (n = 331) (–80.8 vs –187.8 mL/year).[30] Results from the subgroup of patients with RA-ILD (n = 89) (–82.6 vs –199.3 mL/year) were consistent with observations in the overall trial population.[71] The effect of nintedanib on reducing the rate of decline in FVC was similar in patients who were taking DMARDs and/or glucocorticoids to the patients who were taking the same with RA-ILD.[71] Nintedanib has been licensed by the Food and Drug Administration, European Medicines Agency, and other regulatory bodies for the treatment of chronic fibrosing ILDs with a progressive phenotype irrespective of etiology.

Although no data from randomized controlled trials are available, there is some low-quality evidence from retrospective analyses that suggest that immunosuppression may slow the progression of RA-ILD. A retrospective analysis of data from 92 patients with RA-ILD who received azathioprine, mycophenolate mofetil, or rituximab found that FVC and DLco improved slightly in the 12 months after starting treatment compared with



Models were adjusted for age, sex, smoking history, ILD duration, Rheumatic Disease Comorbidity Index score, and DMARDs.
DAS28-ESR, disease activity score in 28 joints-erythrocyte sedimentation rate; DLco, diffusing capacity for carbon monoxide; DMARD, disease-modifying antirheumatic drug; FVC, forced vital capacity; ILD, interstitial lung disease; MDHAQ, multidimensional health assessment questionnaire.

Figure 4. Survival in patients with RA-ILD (n = 227) in subgroups by (A) disease activity (A), functional status (B), predicted FVC (C), and predicted DLCO at baseline (D).[36] DLco, diffusing capacity for carbon monoxide; FVC, forced vital capacity; RA-ILD, rheumatoid arthritis–interstitial lung disease. *Source*: Published by Oxford University Press on behalf of the British Society for Rheumatology 2022.

declines in FVC and DLco in the previous 12 months.[72] However, in another retrospective study, an increased risk of respiratory mortality was observed in patients with RA-ILD taking azathioprine (n = 54) or cyclophosphamide (n = 21) compared with mycophenolate (n = 42).[73] A retrospective study of 31 patients with progressive RA-ILD who received rituximab after glucocorticoids and conventional DMARDs showed cessation of lung function decline after rituximab was initiated.[74] A prospective study of 57 patients with RA-ILD who received abatacept found that 72% showed stability or improvement in lung function over a median follow-up of 27 months.[75] Similarly, in a retrospective study of 190 patients with RA-ILD, about 80% of patients started on abatacept showed stability or improvement in FVC after a median follow-up of 12 months.[76]

Results of studies on the effects of anti–tumor necrosis factor (anti-TNF) DMARDs in patients with RA-ILD are conflicting and should be interpreted with caution because these studies did not compare randomized groups. In a prospective analysis of 42 patients with RA-ILD assigned to anti-TNF treatment for one year, no changes in FVC or in the extent of ILD on HRCT were observed, but there were some improvements in small airways disease.[77] In a retrospective single-center study, 30% of patients with RA-ILD taking anti-TNF agents (n = 46) experienced progression of ILD on HRCT over one year compared with no patients taking abatacept (n = 16).[78] In a prospective study of 70 patients, no association was found between the use of anti-TNF DMARDs and the progression of RA-ILD over two years, whereas the use of non–anti-TNF DMARDs was associated with a reduced risk of progression.[79] Prospective data from a registry suggested that patients with RA-ILD taking anti-TNF agents (n = 309) had a two-fold greater risk of five-year mortality than those taking rituximab (n = 43).[80]

Based on historical data, concerns were raised about a potential link between the use of methotrexate and the development or worsening of RA-ILD. However, recent studies indicate

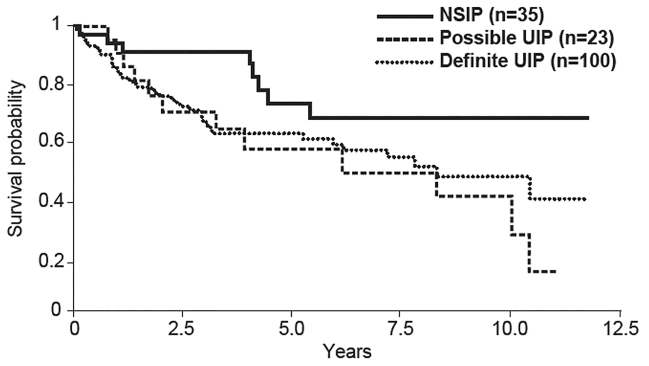


Figure 5. Survival in patients with newly diagnosed RA-ILD with a definite or possible UIP pattern or a NSIP pattern on HRCT.[44] HRCT, high-resolution computed tomography; NSIP, nonspecific interstitial pneumonia; RA-ILD, rheumatoid arthritis–interstitial lung disease; UIP, usual interstitial pneumonia. *Source*: Adapted from Respir Med, Vol 126, Yunt ZX et al, High resolution computed tomography pattern of usual interstitial pneumonia in rheumatoid arthritis-associated ILD: relationship to survival, Pages No. 100–104, Copyright 2017, with permission from Elsevier.

that methotrexate does not increase the risk of developing RA-ILD.[81–83] Further, recent studies do not suggest an increased risk of RA-ILD progression in patients treated with methotrexate. In a prospective multicenter study of 143 patients, the time to RA-ILD progression (defined as a decline in predicted FVC ≥10%, decline in predicted DLCO ≥15%, or death due to ILD or pneumonia) was similar between patients taking and not taking methotrexate.[84] Other studies have suggested that the use of methotrexate may slow the progression of RA-ILD.[85,86] A retrospective study of 170 patients with RA-ILD suggested that the use of methotrexate was associated with a lower risk of decline in predicted FVC ≥10% (odds ratio 0.27 [95% CI 0.09–0.77]) over a mean follow-up of 4.3 years.[86] In a prospective study of patients with RA-ILD in Korea, the risk of rapidly declining predicted FVC or death over one year (observed in 15 patients) was greater in patients who had never used methotrexate than in ever-users (relative risk 8.07 [95% CI 1.82–35.77]).[21]

The management of RA-ILD should not be limited to pharmacological therapies. Targeting phenotypic traits that are clinically relevant and treatable, including both pulmonary and extrapulmonary manifestations of disease as well as comorbidities, has been proposed as an approach for delivering holistic and patient-centered care to patients with ILDs.[87] Patients should be given advice on smoking cessation and reminded of the importance of vaccinations against respiratory infections such as influenza, pneumococcal pneumonia, and COVID-19. Pulmonary rehabilitation is recommended for patients with ILD to improve exercise capacity, symptoms, and quality of life.[88] Ambulatory oxygen is recommended for patients with severe exertional hypoxemia.[89] Patients with severe and progressive RA-ILD that has not responded to treatment who do not have extrapulmonary contraindications should be considered for lung transplantation.[90] Education and psychological support should be offered to all patients.[91]

Conclusions

ILD is a frequent manifestation of RA that can have a significant impact on morbidity and mortality. The clinical course of RA-ILD is highly variable. Some patients develop PPF, which is associated with poor outcomes. Although risk factors for the progression of RA-ILD have been identified, it is not possible to predict the course of RA-ILD in an individual patient, so regular monitoring, including pulmonary function tests, is important. Prompt identification of PPF in patients with RA-ILD presents the opportunity for intervention to preserve lung function and improve outcomes. Management of RA-ILD requires a multidisciplinary and individualized approach that considers risk factors for progression.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. As corresponding author, Dr Matteson confirms that all authors have provided the final approval of the version to be published, and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Helsinki Declaration requirements.

REFERENCES

1. Bongartz T, Nannini C, Medina-Velasquez YF, et al. Incidence and mortality of interstitial lung disease in rheumatoid arthritis: a population-based study. Arthritis Rheum 2010;62(6):1583–1591.
2. Hyldgaard C, Hilberg O, Pedersen AB, et al. A population-based cohort study of rheumatoid arthritis-associated interstitial lung disease: comorbidity and mortality. Ann Rheum Dis 2017;76(10):1700–1706.
3. Raimundo K, Solomon JJ, Olson AL, et al. Rheumatoid arthritis-interstitial lung disease in the United States: prevalence, incidence, and healthcare costs and mortality. J Rheumatol 2019;46(4):360–369.
4. Salaffi F, Carotti M, Di Carlo M, et al. 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(38):e17088.
5. Huang S, Doyle TJ, Hammer MM, 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(6):1216–1225.
6. Samhouri BF, Vassallo R, Achenbach SJ, et al. The incidence, risk factors, and mortality of clinical and subclinical rheumatoid arthritis–associated interstitial lung disease: a population-based cohort. Arthritis Care Res (Hoboken) 2022;74(12):2042–2049.
7. Albrecht K, Strangfeld A, Marschall U, et al. Interstitial lung disease in rheumatoid arthritis: incidence, prevalence and related drug prescriptions between 2007 and 2020. RMD Open 2023;9(1):e002777.

8. Hyldgaard C, Harders S, Blegvad J, et al. Clinical and preclinical pulmonary disease in newly diagnosed rheumatoid arthritis: a two-year follow-up study. Scand J Rheumatol 2023;52(6):601–608.
9. Mohning MP, Amigues I, Demoruelle MK, et al. Duration of rheumatoid arthritis and the risk of developing interstitial lung disease. ERJ Open Res 2021;7(1):00633–02020.
10. Juge PA, Granger B, Debray MP, et al. A risk score to detect subclinical rheumatoid arthritis-associated interstitial lung disease. Arthritis Rheumatol 2022;74(11):1755–1765.
11. Matson SM, Deane KD, Peljto AL, et al. Prospective identification of subclinical interstitial lung disease in a rheumatoid arthritis cohort is associated with the MUC5B promoter variant. Am J Respir Crit Care Med 2022;205(4):473–476.
12. Zamora-Legoff JA, Krause ML, Crowson CS, et al. Progressive decline of lung function in rheumatoid arthritis-associated interstitial lung disease. Arthritis Rheumatol 2017;69(3):542–549.
13. Hyldgaard C, Ellingsen T, Hilberg O, et al. Rheumatoid arthritis-associated interstitial lung disease: clinical characteristics and predictors of mortality. Respiration 2019;98(5):455–460.
14. Tanaka N, Kim JS, Newell JD, et al. Rheumatoid arthritis-related lung diseases: CT findings. Radiology 2004;232(1):81–91.
15. Juge PA, Lee JS, Ebstein E, et al. MUC5B promoter variant and rheumatoid arthritis with interstitial lung disease. N Engl J Med 2018; 379(23):2209–2219.
16. Nurmi HM, Kettunen HP, Suoranta SK, et al. Several high-resolution computed tomography findings associate with survival and clinical features in rheumatoid arthritis-associated interstitial lung disease. Respir Med 2018;134:24–30.
17. Joy GM, Arbiv OA, Wong CK, et al. Prevalence, imaging patterns and risk factors of interstitial lung disease in connective tissue disease: a systematic review and meta-analysis. Eur Respir Rev 2023;32(167): 220210.
18. Song JW, Lee HK, Lee CK, et al. Clinical course and outcome of rheumatoid arthritis-related usual interstitial pneumonia. Sarcoidosis Vasc Diffuse Lung Dis 2013;30(2):103–112.
19. Lee JS, Kim GJ, Ha YJ, et al. The extent and diverse trajectories of longitudinal changes in rheumatoid arthritis interstitial lung diseases using quantitative HRCT scores. J Clin Med 2021;10(17):3812.
20. Mena-Vázquez N, Rojas-Gimenez M, Romero-Barco CM, et al. Predictors of progression and mortality in patients with prevalent rheumatoid arthritis and interstitial lung disease: a prospective cohort study. J Clin Med 2021;10(4):874.
21. Chang SH, Lee JS, Ha YJ, et al. Lung function trajectory of rheumatoid arthritis-associated interstitial lung disease. Rheumatology (Oxford) 2023;62(9):3014–3024.
22. Jacob J, Hirani N, van Moorsel CHM, et al. Predicting outcomes in rheumatoid arthritis related interstitial lung disease. Eur Respir J 2019;53(1):1800869.
23. Chai D, Sun D, Wang Y, et al. Progression of radiographic fibrosis in rheumatoid arthritis-associated interstitial lung disease. Front Med (Lausanne) 2023;10:1265355.
24. Juge PA, Solomon JJ, van Moorsel CHM, et al. MUC5B promoter variant rs35705950 and rheumatoid arthritis associated interstitial lung disease survival and progression. Semin Arthritis Rheum 2021;51(5): 996–1004.
25. Kwon BS, Choe J, Chae EJ, et al. Progressive fibrosing interstitial lung disease: prevalence and clinical outcome. Respir Res 2021; 22(1):282.
26. Mena-Vázquez N, Rojas-Gimenez M, Romero-Barco CM, et al. Characteristics and predictors of progression interstitial lung disease in rheumatoid arthritis compared with other autoimmune disease: a retrospective cohort study. Diagnostics (Basel) 2021;11(10):1794.
27. Chen J, Chen Y, Liu D, et al. Predictors of long-term prognosis in rheumatoid arthritis-related interstitial lung disease. Sci Rep 2022; 12(1):9469.
28. Denis A, Henket M, Ernst M, et al. Progressive fibrosing interstitial lung disease in rheumatoid arthritis: a retrospective study. Front Med (Lausanne) 2022;9:1024298.
29. Hilberg O, Hoffmann-Vold AM, Smith V, et al. Epidemiology of interstitial lung diseases and their progressive-fibrosing behaviour in six European countries. ERJ Open Res 2022;8(1):00597–02021.
30. Flaherty KR, Wells AU, Cottin V, et al; INBUILD Trial Investigators. Nintedanib in progressive fibrosing interstitial lung diseases. N Engl J Med 2019;381(18):1718–1727.
31. Hambly N, Farooqi MM, Dvorkin-Gheva A, et al. Prevalence and characteristics of progressive fibrosing interstitial lung disease in a prospective registry. Eur Respir J 2022;60(4):2102571.
32. Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: an official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med 2022;205(9):e18–e47.
33. Koduri G, Norton S, Young A, et al; ERAS (Early Rheumatoid Arthritis Study). Interstitial lung disease has a poor prognosis in rheumatoid arthritis: results from an inception cohort. Rheumatology (Oxford) 2010;49(8):1483–1489.
34. Jeganathan N, Nguyen E, Sathananthan M. Rheumatoid arthritis and associated interstitial lung disease: mortality rates and trends. Ann Am Thorac Soc 2021;18(12):1970–1977.
35. Sparks JA, Jin Y, Cho SK, et al. Prevalence, incidence and cause-specific mortality of rheumatoid arthritis-associated interstitial lung disease among older rheumatoid arthritis patients. Rheumatology (Oxford) 2021;60(8):3689–3698.
36. Brooks R, Baker JF, Yang Y, et al. The impact of disease severity measures on survival in U.S. veterans with rheumatoid arthritis-associated interstitial lung disease. Rheumatology (Oxford) 2022; 61(12):4667–4677.
37. Farquhar HJ, Beckert N, Beckert L, et al. Survival of adults with rheumatoid arthritis associated interstitial lung disease - a systematic review and meta-analysis. Semin Arthritis Rheum 2023;60:152187.
38. Izuka S, Yamashita H, Iba A, et al. Acute exacerbation of rheumatoid arthritis-associated interstitial lung disease: clinical features and prognosis. Rheumatology (Oxford) 2021;60(5):2348–2354.
39. Tanaka N, Nishimura K, Waki D, et al. Annual variation rate of KL-6 for predicting acute exacerbation in patients with rheumatoid arthritis-associated interstitial lung disease. Mod Rheumatol 2021;31(6): 1100–1106.
40. Otsuka J, Yoshizawa S, Kudo K, et al. Clinical features of acute exacerbation in rheumatoid arthritis-associated interstitial lung disease: comparison with idiopathic pulmonary fibrosis. Respir Med 2022; 200:106898.
41. Hozumi H, Kono M, Hasegawa H, et al. Acute exacerbation of rheumatoid arthritis-associated interstitial lung disease: mortality and its prediction model. Respir Res 2022;23(1):57.
42. Kwon BS, Lee HY, Choe J, et al. Acute respiratory deterioration in rheumatoid arthritis-associated interstitial lung disease: a single-center study. Chest 2022;162(1):136–144.
43. Nurmi HM, Purokivi MK, Kärkkäinen MS, et al. Are risk predicting models useful for estimating survival of patients with rheumatoid arthritis-associated interstitial lung disease? BMC Pulm Med 2017; 17(1):16.
44. Zamora-Legoff JA, Krause ML, Crowson CS, et al. Patterns of interstitial lung disease and mortality in rheumatoid arthritis. Rheumatology (Oxford) 2017;56(3):344–350.
45. Fu Q, Wang L, Li L, et al. 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(4):1109–1116.

46. Yamakawa H, Sato S, Tsumiyama E, et al. Predictive factors of mortality in rheumatoid arthritis-associated interstitial lung disease analysed by modified HRCT classification of idiopathic pulmonary fibrosis according to the 2018 ATS/ERS/JRS/ALAT criteria. J Thorac Dis 2019;11(12):5247–5257.
47. Li L, Liu R, Zhang 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(5):1457–1470.
48. Kim HC, Lee JS, Lee EY, et al. Risk prediction model in rheumatoid arthritis-associated interstitial lung disease. Respirology 2020;25(12): 1257–1264.
49. Oh JH, Kim GHJ, Cross G, et al. Automated quantification system predicts survival in rheumatoid arthritis-associated interstitial lung disease. Rheumatology (Oxford) 2022;61(12):4702–4710.
50. Solomon JJ, Chung JH, Cosgrove GP, et al. Predictors of mortality in rheumatoid arthritis-associated interstitial lung disease. Eur Respir J 2016;47(2):588–596.
51. Ito Y, Arita M, Kumagai S, et al. Radiological fibrosis score is strongly associated with worse survival in rheumatoid arthritis-related interstitial lung disease. Mod Rheumatol 2019;29(1):98–104.
52. Nieto MA, Rodriguez-Nieto MJ, Sanchez-Pernaute O, et al. Mortality rate in rheumatoid arthritis-related interstitial lung disease: the role of radiographic patterns. BMC Pulm Med 2021;21(1):205.
53. Nurmi HM, Purokivi MK, Kärkkäinen MS, et al. Variable course of disease of rheumatoid arthritis-associated usual interstitial pneumonia compared to other subtypes. BMC Pulm Med 2016;16(1):107.
54. Yunt ZX, Chung JH, Hobbs S, et al. High resolution computed tomography pattern of usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease: relationship to survival. Respir Med 2017;126:100–104.
55. Ekici M, Baytar Y, Kardas RC, et al. Predictors of mortality in rheumatoid arthritis-associated lung disease: a retrospective study on ten years. Joint Bone Spine 2021;88(3):105133.
56. Rojas-Serrano J, Mejía M, Rivera-Matias PA, et al. Rheumatoid arthritis-related interstitial lung disease (RA-ILD): a possible association between disease activity and prognosis. Clin Rheumatol 2022; 41(6):1741–1747.
57. Liu L, Fang C, Sun B, et al. Predictors of progression in rheumatoid arthritis-associated interstitial lung disease: a single-center retrospective study from China. Int J Rheum Dis 2022;25(7):795–802.
58. Karimi-Shah BA, Chowdhury BA. Forced vital capacity in idiopathic pulmonary fibrosis–FDA review of pirfenidone and nintedanib. N Engl J Med 2015;372(13):1189–1191.
59. Liu B, Sun G, Liu Y, et al. Observational studies: ambient air pollution and hospitalization for RA-ILD in a heavily polluted city in China. Medicine (Baltimore) 2022;101(19):e29309.
60. Kim SH, Kim SY, Yoon HY, et al. PM_{10} increases mortality risk in rheumatoid arthritis-associated interstitial lung disease. RMD Open 2024; 10(1):e003680.
61. Kim EJ, Elicker BM, Maldonado F, et al. Usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease. Eur Respir J 2010;35(6):1322–1328.
62. Hozumi H, Nakamura Y, Johkoh T, et al. Acute exacerbation in rheumatoid arthritis-associated interstitial lung disease: a retrospective case control study. BMJ Open 2013;3(9):e003132.
63. Xie M, Zhu C, Ye Y. Incidence, risk factors, and prognosis of acute exacerbation of rheumatoid arthritis-associated interstitial lung disease: a systematic review and meta-analysis. BMC Pulm Med 2023; 23(1):255.
64. Tyker A, Ventura IB, Lee CT, et al. High-titer rheumatoid factor seropositivity predicts mediastinal lymphadenopathy and mortality in rheumatoid arthritis-related interstitial lung disease. Sci Rep 2021;11(1): 22821.
65. Chen N, Diao CY, Gao J, et al. Risk factors for the progression of rheumatoid arthritis-related interstitial lung disease: clinical features, biomarkers, and treatment options. Semin Arthritis Rheum 2022;55: 152004.
66. Avouac J, Cauvet A, Steelandt A, et al. Improving risk-stratification of rheumatoid arthritis patients for interstitial lung disease. PLoS One 2020;15(5):e0232978.
67. Nambiar AM, Walker CM, Sparks JA. Monitoring and management of fibrosing interstitial lung diseases: a narrative review for practicing clinicians. Ther Adv Respir Dis 2021;15:17534666211039771.
68. Bendstrup E, Kronborg-White S, Møller J, et al. Current best clinical practices for monitoring of interstitial lung disease. Expert Rev Respir Med 2022;16(11–12):1153–1166.
69. Koduri G, Solomon JJ. Identification, monitoring and management of rheumatoid arthritis–associated interstitial lung disease. Arthritis Rheumatol 2023;75(12):2067–2077.
70. Solomon JJ, Danoff SK, Woodhead FA, et al. Safety, tolerability, and efficacy of pirfenidone in patients with rheumatoid arthritis-associated interstitial lung disease: a randomised, double-blind, placebo-controlled, phase 2 study. Lancet Respir Med 2023;11(1):87–96.
71. Matteson EL, Aringer M, Burmester GR, et al. Effect of nintedanib in patients with progressive pulmonary fibrosis associated with rheumatoid arthritis: data from the INBUILD trial. Clin Rheumatol 2023;42(9): 2311–2319.
72. Matson SM, Baqir M, Moua T, et al. Treatment outcomes for rheumatoid arthritis-associated interstitial lung disease: a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. Chest 2023;163(4):861–869.
73. Kelly CA, Nisar M, Arthanari S, et al. Rheumatoid arthritis related interstitial lung disease - improving outcomes over 25 years: a large multicentre UK study. Rheumatology (Oxford) 2021;60(4):1882–1890.
74. Narváez J, Robles-Pérez A, Molina-Molina M, et al. Real-world clinical effectiveness of rituximab rescue therapy in patients with progressive rheumatoid arthritis-related interstitial lung disease. Semin Arthritis Rheum 2020;50(5):902–910.
75. Mena-Vázquez N, Rojas-Gimenez M, Fuego-Varela C, et al. Safety and effectiveness of abatacept in a prospective cohort of patients with rheumatoid arthritis-associated interstitial lung disease. Biomedicines 2022;10(7):1480.
76. Atienza-Mateo B, Fernández-Díaz C, Vicente-Rabaneda EF, et al. Abatacept in usual and in non-specific interstitial pneumonia associated with rheumatoid arthritis. Eur J Intern Med 2024;119:118–124.
77. Detorakis EE, Magkanas E, Lasithiotaki I, et al. Evolution of imaging findings, laboratory and functional parameters in rheumatoid arthritis patients after one year of treatment with anti-TNF-α agents. Clin Exp Rheumatol 2017;35(1):43–52.
78. Nakashita T, Ando K, Takahashi K, et al. Possible effect of abatacept on the progression of interstitial lung disease in rheumatoid arthritis patients. Respir Investig 2016;54(5):376–379.
79. Mena-Vázquez N, Godoy-Navarrete FJ, Manrique-Arija S, et al. Non-anti-TNF biologic agents are associated with slower worsening of interstitial lung disease secondary to rheumatoid arthritis. Clin Rheumatol 2021;40(1):133–142.
80. Druce KL, Iqbal K, Watson KD, et al. Mortality in patients with interstitial lung disease treated with rituximab or TNFi as a first biologic. RMD Open 2017;3(1):e000473.
81. Kiely P, Busby AD, Nikiphorou E, 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(5):e028466.

82. Ibfelt EH, Jacobsen RK, Kopp TI, et al. Methotrexate and risk of interstitial lung disease and respiratory failure in rheumatoid arthritis: a nationwide population-based study. Rheumatology (Oxford) 2021; 60(1):346–352.
83. Juge PA, Lee JS, Lau J, et al. Methotrexate and rheumatoid arthritis associated interstitial lung disease. Eur Respir J 2021;57(2):2000337.
84. Kim JW, Chung SW, Pyo JY, et al. Methotrexate, leflunomide and tacrolimus use and the progression of rheumatoid arthritis-associated interstitial lung disease. Rheumatology (Oxford) 2023;62(7):2377–2385.
85. Rojas-Serrano J, Herrera-Bringas D, Pérez-Román DI, et al. Rheumatoid arthritis-related interstitial lung disease (RA-ILD): methotrexate and the severity of lung disease are associated to prognosis. Clin Rheumatol 2017;36(7):1493–1500.
86. Kim K, Woo A, Park Y, et al. Protective effect of methotrexate on lung function and mortality in rheumatoid arthritis-related interstitial lung disease: a retrospective cohort study. Ther Adv Respir Dis 2022;16:17534666221135314.
87. Khor YH, Cottin V, Holland AE, et al. Treatable traits: a comprehensive precision medicine approach in interstitial lung disease. Eur Respir J 2023;62(1):2300404.
88. Rochester CL, Alison JA, Carlin B, et al. Pulmonary rehabilitation for adults with chronic respiratory disease: an official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med 2023; 208(4):e7–e26.
89. Jacobs SS, Krishnan JA, Lederer DJ, et al. Home oxygen therapy for adults with chronic lung disease. An official American Thoracic Society clinical practice guideline. Am J Respir Crit Care Med 2020; 202(10):e121–e141.
90. Leard LE, Holm AM, Valapour M, et al. Consensus document for the selection of lung transplant candidates: an update from the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2021;40(11):1349–1379.
91. Wijsenbeek MS, Holland AE, Swigris JJ, et al. Comprehensive supportive care for patients with fibrosing interstitial lung disease. Am J Respir Crit Care Med 2019;200(2):152–159.