Chapter 8
Rheumatoid Arthritis-Associated Interstitial Lung Disease

Julie Morisset and Joyce S. Lee

Introduction

Interstitial lung disease (ILD) is a frequent extra-articular manifestation of rheumatoid arthritis (RA) [1]. RA-ILD significantly impacts prognosis and is associated with increased morbidity and mortality [2–4]. The diagnostic process can be challenging as the initial symptoms can be minimal or go unrecognized. Moreover, the differential diagnosis of diffuse lung disease in RA encompasses a wide variety of diagnoses ranging from drug-induced lung toxicities to opportunistic infection and other types of RA lung disease (see Chap. 10). Due to its impact on prognosis and quality of life, RA-ILD requires prompt diagnosis to ensure optimal care.

Epidemiology of RA-ILD

In 1948, Ellman and Ball reported the first case series of patients with rheumatoid lung disease [5]. These three patients presented with diffuse lung disease on chest x-ray, and the two available autopsies revealed chronic fibrotic pneumonitis. Since then, the prevalence estimates of RA-ILD differ depending on the diagnostic definition, the population being studied, and the mode of detection being used. A wide range of prevalence estimates, varying between 1 and 58%, has been reported [1, 3, 6–16].

J. Morisset, MD
Département de Médecine, Centre Hospitalier de l'Université de Montréal, Montréal, QC, Canada
e-mail: julie.morisset@umontreal.ca

J.S. Lee, MD, MAS (✉)
Department of Medicine, University of Colorado Denver, Aurora, CO, USA
e-mail: joyce.lee@ucdenver.edu

A. Fischer, J.S. Lee (eds.), *Lung Disease in Rheumatoid Arthritis*, Respiratory Medicine, https://doi.org/10.1007/978-3-319-68888-6_8

High-resolution computed tomography (HRCT) is more sensitive than conventional chest x-ray to detect ILD [17]. In a cohort of patients with a recent diagnosis of RA, HRCT identified abnormalities compatible with ILD in 33% of patients, while chest x-ray detected abnormalities in only 6% of patients [14]. HRCT has also been shown to allow identification of subclinical ILD or interstitial lung abnormalities (ILA) in patients with RA without any respiratory symptoms. These radiographic abnormalities are seen in up to 44% of RA patients [7, 14, 18, 19]. Furthermore, in population-based studies, the 30-year incidence of clinically significant RA-ILD has been reported to vary between 6 and 8% of patients with RA [2, 20]. Although ILD is a common extra-articular manifestation of RA, it is believed to still remain under-recognized [21].

Risk Factors

Several risk factors have been linked to the development of RA-ILD (Table 8.1). Increased age has been identified as a significant predictor of RA-ILD [21, 22]. On multivariable regression analysis in a cohort of 356 RA patients, age greater than

Table 8.1 Risk factors for the development of rheumatoid arthritis-associated interstitial lung disease (RA-ILD)

Risk factor	Study/year	Details
Age	Doyle et al. [21]/2015	Older age associated with clinically evident RA-ILD (AUC = 0.8)
	Mori et al. [22]/2012	Age > 65; relative risk ratio for RA-ILD: 4.58 95%CI (1.67–12.53)
Male gender	Mori et al. [22]/2012	Male gender relative risk ratio for RA-ILD: 1.45 95%CI (0.36–5.84)
	Kelly et al. [23]/2014	Male gender associated with RA-ILD: OR 1.67 95% CI (1.2–2.2)
	Weyand et al. [24]/1998	RA-ILD more frequent in male patients ($p < 0.001$)
Smoking history	Doyle et al. [21]/2015	Ever-smoking history associated with clinically evident RA-ILD (AUC = 0.56)
	Kelly et al. [23]/2014	Ever-smoking history associated with RA-ILD: OR 1.91 95% CI (1.3–2.7)
Rheumatoid factor (RF)	Doyle et al. [21]/2015	Positive RF associated with clinically evident RA-ILD (AUC = 0.69)
	Mori et al. [22]/2012	Positive RF relative risk ratio for RA-ILD: 3.14 95% CI (1.17–8.42)
	Kelly et al. [23]/2014	Positive RF associated with RA-ILD: OR 2.81 95% CI (1.8–4.1)
Anti-cyclic citrullinated peptide (CCP) antibody	Doyle et al. [21]/2015	Positive CCP antibody associated with clinically evident RA-ILD (AUC = 0.76)
	Mori et al. [22]/2012	Positive CCP antibody relative risk ratio for RA-ILD: 2.73 95% CI (0.91–8.23)
	Kelly et al. [23]/2014	Positive CCP antibody associated with RA-ILD: OR 2.81 95% CI (1.8–4.1)
	Giles et al. [27]/2014	Higher titers of CCP antibodies associated with higher ILD score ($p = 0.001$)

AUC area under the curve, *OR* odds ratio

65 years was associated with a 4.58-fold increased risk of ILD [22]. Male gender is also independently associated with RA-ILD [22–24]. In a multicenter cohort of 230 RA patients, male gender was found to be a significant predictor of RA-ILD (OR 1.67, 95% CI = 1.2–2.2) [23]. Smoking history is associated with an increased risk of RA [25, 26] and a greater risk of developing RA-ILD [21, 23]. The severity of RA may also be influenced by smoking exposure in a dose-dependent manner [26].

The presence of either rheumatoid factor (RF) or anti-cyclic citrullinated peptide (CCP) has also been found to be significant predictors for the development of ILD in RA [21–23]. There may be a relationship between the titer of CCP antibodies and the risk of ILD, as higher titers of CCP have been shown to correlate with more extensive RA-ILD on HRCT [27]. Finally, a model including a combination of these risk factors (older age, male sex, ever-smoking history, positive RF, and positive CCP) has an area under the curve between 0.82 and 0.86 to predict clinically evident RA-ILD and between 0.89 and 0.98 to predict subclinical ILD [21].

Clinical Presentation of RA-ILD

ILD can be diagnosed in the setting of long-standing RA, be identified at the time of RA diagnosis, or precede the onset of the articular symptoms [23, 28–33]. Patients with RA-ILD commonly report dyspnea (at rest and/or on exertion), exercise limitation, and dry cough [32, 34–37]. Shortness of breath can be minimal or difficult to recognize in the earlier stage of the lung disease given the physical limitation associated with their articular disease [38]. Less frequently, patients may present with chest pain, wheezing, and productive cough [39, 40].

Some patients with RA are identified to have subclinical ILD or ILA and don't report clinical symptoms, although their high-resolution computed tomography (HRCT) and/or pulmonary function tests are abnormal [14, 18, 21]. In a cohort of RA patients, Doyle et al. described the clinical characteristics of patients with ILA on HRCT [41]. Although patients with ILA had an array of disease severity and functional impairment, they were more likely to have lower forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) % predicted than patients without ILA [41]. The clinical significance of subclinical ILD in RA remains to be determined, although some data suggest that the radiological abnormalities will progress over time in a subset of patients [7, 42].

Diagnostic Evaluation of Patients with Suspected RA-ILD

Although RA-ILD frequently presents as respiratory symptoms in patients with a known diagnosis of RA, the onset of ILD has been reported to occur prior to the diagnosis of RA [23]. Accordingly, patients being investigated for a new diagnosis of an ILD should be questioned about symptoms that may suggest an underlying connective tissue disease (CTD). Moreover, physicians often perform serologic testing (including RF and CCP antibodies) in their initial work-up to

screen for the presence of an occult CTD [43]. Sometimes the work-up of ILD will lead to a clear diagnosis of RA, while another subset of patients with ILD will have a positive serologic profile without clinical evidence of RA [29]. A cohort of 74 patients with lung disease and positive CCP antibodies but no clinical evidence of RA has been described [29]. In this cohort, only 3 patients (9%) went on to develop articular manifestations of RA after a median follow time of 449 days [29]. This study supports the hypothesis that the lung may be an initial site in the pathogenesis of RA [33, 44, 45]. More studies are needed to better understand the natural history of these patients with ILD and positive serologies for RA but no clear RA diagnosis [46].

The development of respiratory symptoms in patients with RA or the presence of articular symptoms in a patient being evaluated for ILD should raise the suspicion of RA-ILD (Fig. 8.1). In patients with RA, other types of RA lung disease need to be considered [47], as well as the exclusion of drug toxicity and opportunistic infection [38]. ILD has been reported as a potential complication of many drugs used for the management of RA like methotrexate, TNF-alpha inhibitors, rituximab, tocilizumab, cyclophosphamide, and leflunomide [48–52]. Patients on immunosuppressive medications are at higher risk of opportunistic infections that can cause diffuse

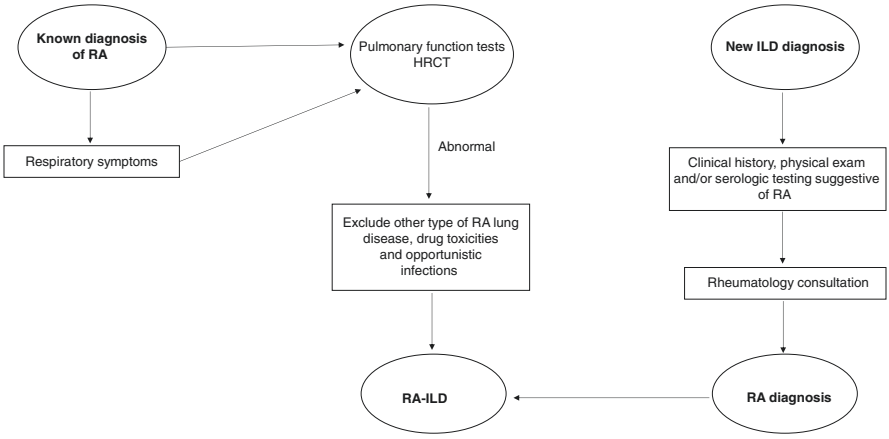

Fig. 8.1 Diagnostic approach to patients with rheumatoid arthritis-associated interstitial lung disease. When evaluating patients with a known diagnosis of rheumatoid arthritis (RA) presenting with respiratory symptoms, clinicians should perform appropriate investigations to exclude other types of RA lung disease, drug toxicities, and opportunistic infections. Pulmonary function tests and high-resolution computed tomography should be performed to better characterize the lung disease and its functional impairment. In patients being evaluated for a new ILD diagnosis, symptoms and signs, on either clinical history and physical exam or serologic testing suggestive of RA, should prompt a referral to rheumatology. In either clinical scenario, RA-ILD can be diagnosed when both a diagnosis of RA and ILD can be established. Abbreviations: *RA* rheumatoid arthritis, *HRCT* high-resolution computed tomography, *ILD* interstitial lung disease, *RF* rheumatoid factor, *CCP* anti-cyclic citrullinated peptide

lung disease and mimic ILD (e.g., *Pneumocystis jirovecii*, *Mycobacterium*, or fungal infections) [53].

A complete clinical history and physical exam are the first steps in the evaluation. Patients may report non-specific respiratory symptoms such as shortness of breath, cough, wheezing, or chest pain [32, 33, 37]. The physical exam may reveal crackles, but clubbing, wheezing, or signs of right heart failure can also be present [6, 7].

HRCT is essential in the evaluation of patients with suspected RA-ILD. It allows for the characterization of the radiological pattern and assessment of the disease severity [11, 39, 54]. Ground-glass opacities and reticulations are the most common HRCT findings [54]. The most frequently encountered HRCT patterns are usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP), and organizing pneumonia (OP) [54]. Similar to IPF, HRCT has been shown to be an effective tool to identify the UIP pattern in RA-ILD. The presence of UIP pattern on HRCT is highly specific for the presence of UIP pattern on surgical lung biopsy [55].

Pulmonary function tests (PFTs) are also fundamental to assess the physiologic severity of RA-ILD and are a useful test to monitor disease activity over time. Among patients with RA, up to 30% of patients will have abnormal PFTs [40]. Common findings on PFTs include evidence of restriction and a reduced diffusion capacity (DLCO) [36, 37, 41].

Bronchoscopy and bronchoalveolar lavage (BAL) are often not required in the work-up of patients with RA-ILD because it adds little value to the diagnostic process, unless there is a high suspicion for infection [56]. Cellularity may be increased in the BAL of these patients [57], although this does not correlate with extent of disease on HRCT [56]. BAL can be useful to exclude an opportunistic infection when clinically suspected [38, 56].

Similar to other forms of CTD (e.g., scleroderma), a surgical lung biopsy is rarely required in the diagnosis of RA-ILD [38]. At this time, the identification of the underlying histopathologic pattern is not part of the diagnostic and treatment algorithm of patients with RA-ILD. Surgical lung biopsy may be indicated in cases where the etiology of the lung disease is not clear in an RA patient. In patients with RA-ILD who undergo a surgical lung biopsy, the most frequently reported histopathologic patterns are UIP, NSIP, OP, lymphocytic interstitial pneumonia, and diffuse alveolar damage [58, 59].

Currently, there are no biomarkers that are diagnostic for RA-ILD or have utility in predicting disease progression. Doyle et al. recently demonstrated that the addition of a biomarker signature to a model of clinical and serologic variables (age, gender, smoking history, RF, and CCP antibodies) can increase the model's ability to predict the presence of RA-ILD and potentially facilitate an earlier diagnosis of RA-ILD [21]. The biomarker signature they proposed consists of matrix metalloproteinase-7 (MMP-7), pulmonary and activation-regulated chemokine (PARC), and surfactant protein D (SP-D). The role of these biomarkers in disease progression is unknown.

Phenotypes of RA-ILD

As previously mentioned, many different radiologic and histopathologic patterns have been described in patients with RA-ILD. Often, patients are categorized as having either a UIP or a non-UIP pattern of disease. There are accumulating data suggesting that RA patients with a UIP pattern exhibit a different phenotype, clinical evolution, and prognosis compared to RA patients without a UIP pattern of disease [4, 11, 32, 56, 58, 59]. In RA-ILD, the UIP pattern has been more frequently described in older, male patients with a history of smoking [4, 11, 58–60]. Notably, this is the clinical phenotype often associated with the idiopathic form of UIP (i.e., idiopathic pulmonary fibrosis) [43]. Moreover, RA-ILD patients with a UIP pattern appear to have a worse overall prognosis than RA-ILD patients with a non-UIP pattern, and a survival pattern appearing similar to patients with IPF [4, 61], though the data are conflicting [62]. RA-ILD patients with a UIP pattern are also reported to have more respiratory-related hospitalizations [32].

Natural History and Prognosis

ILD is one of the leading causes of death in patients with RA [63, 64]. A population-based study demonstrated that the mortality rate in RA-ILD is increasing despite the overall decline in RA mortality [3]. Patients with RA-ILD tend to die younger and are more likely to die from their lung disease or have an RA-related death compared to RA patients without ILD [3].

Various predictors of mortality in patients with RA-ILD have been described [4, 59, 65–69]. Patient-specific variables (e.g., age, male sex, and low socioeconomic status), ILD-specific variables (e.g., DLCO, FVC, extent of fibrosis on HRCT, and UIP pattern either on HRCT or surgical lung biopsy), and RA-specific variables (e.g., baseline pain, disease activity score, and disability score) have been shown to be associated with mortality in RA-ILD [69]. Of these variables, only a few have been identified to be independent predictors of mortality in multivariable models (Table 8.2) [69]. Age is the only variable that has been identified as a significant predictor on multivariable analysis in multiple studies. A recent systematic review highlighted the variable methodological quality of studies evaluating predictors of mortality in RA-ILD as many of them lacked multivariable analysis [69].

In general, patients with RA-ILD tend to experience disease progression over time [7, 42, 62]. Acute exacerbations (AE) have been described in some patients with RA-ILD [62, 70]. Risk factors for AE in RA-ILD include older age at ILD diagnosis, UIP pattern on HRCT, and use of methotrexate [70]. AE of RA-ILD is associated with increased mortality [70]. Finally, patients with RA-ILD are at risk of serious infections requiring antibiotic therapy and hospitalization [53]. Pneumonia is the most frequent infection (3.9 cases per 100 person-year), and a prednisone dose greater than 10 mg daily is associated with an increased risk of serious infection [53].

Table 8.2 Independent predictors of mortality on multivariate analysis in rheumatoid-associated interstitial lung disease

Study/year	Sample size	Predictor	Hazard ratio (95% CI)
Dixon et al. [66]/2010	367	Age (per decade)	2.28 (1.64–3.15)
		Disease activity score (DAS28 score [71])	1.43 (1.11–1.85)
Kim et al. [4]/2010	82	Female sex	0.30 (no CI provided) (*p*-value, 0.008)
		Baseline DLCO% predicted	0.96 (no CI provided) (*p*-value, 0.003)
		Definite UIP pattern on HRCT	2.34 (no CI provided) (*p*-value, 0.05)
Koduri et al. [67]/2010	52	Age at onset	1.04 (1.00–1.09)
Solomon et al. [59]/2013	48	Age (per year)	1.04 (no CI provided) (*p*-value, 0.01)
		Presence of fibrosis on surgical lung biopsy	2.1 (no CI provided) (*p*-value, 0.02)
Solomon et al. [68]/2015	137	Age (year increase over 64.7)	1.06 (1.03–1.10)
		Ever-smoking history	2.05 (1.03–4.08)
		FVC % predicted (10% lower than mean baseline FVC % predicted)	1.36 (1.16–1.60)

CI confidence interval, *DLCO* diffusing capacity of the lung for carbon monoxide, *UIP* usual interstitial pneumonia, *HRCT* high-resolution computed tomography, *FVC* forced vital capacity

Conclusion

RA-ILD is a prevalent pulmonary manifestation of RA. It is associated with reduced survival and substantial morbidity. Early diagnosis remains a challenge in RA-ILD due to the non-specific symptoms at initial presentation. There may be important disease phenotypes within RA-ILD, but the current paradigm does not support identification of radiologic or histopathologic forms of RA-ILD to guide management. Further research is needed to better characterize and identify these phenotypes in order to provide personalized and comprehensive care to RA-ILD patients.

References

1. Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL. Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years. Ann Rheum Dis. 2003;62(8):722–7.
2. 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):1583–91.

3. Olson AL, Swigris JJ, Sprunger DB, et al. Rheumatoid arthritis-interstitial lung disease-associated mortality. Am J Respir Crit Care Med. 2011;183(3):372–8.
4. Kim EJ, Elicker BM, Maldonado F, et al. Usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease. Eur Respir J. 2010;35(6):1322–8.
5. Ellman P, Ball RE. Rheumatoid disease with joint and pulmonary manifestations. Br Med J. 1948;2(4583):816–20.
6. 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(8):622–7.
7. Gochuico BR, Avila NA, Chow CK, et al. Progressive preclinical interstitial lung disease in rheumatoid arthritis. Arch Intern Med. 2008;168(2):159–66.
8. Richman NC, Yazdany J, Graf J, Chernitskiy V, Imboden JB. Extraarticular manifestations of rheumatoid arthritis in a multiethnic cohort of predominantly Hispanic and Asian patients. Medicine. 2013;92(2):92–7.
9. Zrour SH, Touzi M, Bejia I, 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(1):41–7.
10. Norton S, Koduri G, Nikiphorou E, Dixey J, Williams P, Young A. A study of baseline prevalence and cumulative incidence of comorbidity and extra-articular manifestations in RA and their impact on outcome. Rheumatology (Oxford). 2013;52(1):99–110.
11. Zou YQ, Li YS, Ding XN, Ying ZH. The clinical significance of HRCT in evaluation of patients with rheumatoid arthritis-associated interstitial lung disease: a report from China. Rheumatol Int. 2012;32(3):669–73.
12. Carmona L, Gonzalez-Alvaro I, Balsa A, Angel Belmonte M, Tena X, Sanmarti R. Rheumatoid arthritis in Spain: occurrence of extra-articular manifestations and estimates of disease severity. Ann Rheum Dis. 2003;62(9):897–900.
13. 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(8):1513–21.
14. Gabbay E, Tarala R, Will R, et al. Interstitial lung disease in recent onset rheumatoid arthritis. Am J Respir Crit Care Med. 1997;156(2 Pt 1):528–35.
15. Gordon DA, Stein JL, Broder I. The extra-articular features of rheumatoid arthritis. A systematic analysis of 127 cases. Am J Med. 1973;54(4):445–52.
16. Stack BH, Grant IW. Rheumatoid interstitial lung disease. Br J Dis Chest. 1965;59(4): 202–11.
17. Padley SP, Hansell DM, Flower CD, Jennings P. Comparative accuracy of high resolution computed tomography and chest radiography in the diagnosis of chronic diffuse infiltrative lung disease. Clin Radiol. 1991;44(4):222–6.
18. Chen J, Shi Y, Wang X, Huang H, Ascherman D. Asymptomatic preclinical rheumatoid arthritis-associated interstitial lung disease. Clin Dev Immunol. 2013;2013:406927.
19. Carotti M, Salaffi F, Manganelli P, Salvolini L, Bichi Secchi E, De Berardinis S. The subclinical involvement of the lung in rheumatoid arthritis: evaluation by high-resolution computed tomography. Reumatismo. 2001;53(4):280–8.
20. Turesson C, Eberhardt K, Jacobsson LT, Lindqvist E. Incidence and predictors of severe extra-articular disease manifestations in an early rheumatoid arthritis inception cohort. Ann Rheum Dis. 2007;66(11):1543–4.
21. Doyle TJ, Patel AS, Hatabu H, et al. Detection of rheumatoid arthritis-interstitial lung disease is enhanced by serum biomarkers. Am J Respir Crit Care Med. 2015;191(12):1403–12.
22. Mori S, Koga Y, Sugimoto M. Different risk factors between interstitial lung disease and airway disease in rheumatoid arthritis. Respir Med. 2012;106(11):1591–9.
23. Kelly CA, Saravanan V, Nisar M, 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(9):1676–82.

24. Weyand CM, Schmidt D, Wagner U, Goronzy JJ. The influence of sex on the phenotype of rheumatoid arthritis. Arthritis Rheum. 1998;41(5):817–22.
25. Oliver JE, Silman AJ. Risk factors for the development of rheumatoid arthritis. Scand J Rheumatol. 2006;35(3):169–74.
26. Saag KG, Cerhan JR, Kolluri S, Ohashi K, Hunninghake GW, Schwartz DA. Cigarette smoking and rheumatoid arthritis severity. Ann Rheum Dis. 1997;56(8):463–9.
27. Giles JT, Danoff SK, Sokolove J, 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(8):1487–94.
28. Mori S, Cho I, Koga Y, Sugimoto M. A simultaneous onset of organizing pneumonia and rheumatoid arthritis, along with a review of the literature. Mod Rheumatol. 2008;18(1):60–6.
29. Fischer A, Solomon JJ, du Bois RM, et al. Lung disease with anti-CCP antibodies but not rheumatoid arthritis or connective tissue disease. Respir Med. 2012;106(7):1040–7.
30. Brannan HM, Good CA, Divertie MB, Baggenstoss AH. Pulmonary disease associated with rheumatoid arthritis. JAMA. 1964;189:914–8.
31. Akira M, Sakatani M, Hara H. Thin-section CT findings in rheumatoid arthritis-associated lung disease: CT patterns and their courses. J Comput Assist Tomogr. 1999;23(6):941–8.
32. Nurmi HM, Purokivi MK, Karkkainen MS, Kettunen HP, Selander TA, Kaarteenaho RL. Variable course of disease of rheumatoid arthritis-associated usual interstitial pneumonia compared to other subtypes. BMC Pulm Med. 2016;16(1):107.
33. Gizinski AM, Mascolo M, Loucks JL, et al. Rheumatoid arthritis (RA)-specific autoantibodies in patients with interstitial lung disease and absence of clinically apparent articular RA. Clin Rheumatol. 2009;28(5):611–3.
34. Zayeni H, Haji-Abbasi A, Foumani SA, et al. Pulmonary involvement in rheumatoid arthritis: a cross-sectional study in Iran. Lung India. 2016;33(1):49–52.
35. 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.
36. 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(2):136–44.
37. Saag KG, Kolluri S, Koehnke RK, et al. Rheumatoid arthritis lung disease. Determinants of radiographic and physiologic abnormalities. Arthritis Rheum. 1996;39(10):1711–9.
38. Hamblin MJ, Horton MR. Rheumatoid arthritis-associated interstitial lung disease: diagnostic dilemma. Pulm Med. 2011;2011:872120.
39. Skare TL, Nakano I, Escuissiato DL, Batistetti R, Rodrigues Tde 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(4):325–30. 336–327.
40. Pappas DA, Giles JT, Connors G, Lechtzin N, Bathon JM, Danoff SK. Respiratory symptoms and disease characteristics as predictors of pulmonary function abnormalities in patients with rheumatoid arthritis: an observational cohort study. Arthritis Res Ther. 2010;12(3):R104.
41. Doyle TJ, Dellaripa PF, Batra K, et al. Functional impact of a spectrum of interstitial lung abnormalities in rheumatoid arthritis. Chest. 2014;146(1):41–50.
42. 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(6):517–21.
43. Raghu G, Collard HR, Egan JJ, 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(6):788–824.
44. Makrygiannakis D, Hermansson M, Ulfgren AK, et al. Smoking increases peptidylarginine deiminase 2 enzyme expression in human lungs and increases citrullination in BAL cells. Ann Rheum Dis. 2008;67(10):1488–92.

45. Klareskog L, Stolt P, Lundberg K, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum. 2006;54(1):38–46.
46. Fischer A, Antoniou KM, Brown KK, et al. An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features. Eur Respir J. 2015;46(4):976–87.
47. Chansakul T, Dellaripa PF, Doyle TJ, Madan R. Intra-thoracic rheumatoid arthritis: imaging spectrum of typical findings and treatment related complications. Eur J Radiol. 2015;84(10):1981–91.
48. Curtis JR, Sarsour K, Napalkov P, Costa LA, Schulman KL. Incidence and complications of interstitial lung disease in users of tocilizumab, rituximab, abatacept and anti-tumor necrosis factor alpha agents, a retrospective cohort study. Arthritis Res Ther. 2015;17:319.
49. Roubille C, Haraoui B. Interstitial lung diseases induced or exacerbated by DMARDS and biologic agents in rheumatoid arthritis: a systematic literature review. Semin Arthritis Rheum. 2014;43(5):613–26.
50. Suissa S, Hudson M, Ernst P. Leflunomide use and the risk of interstitial lung disease in rheumatoid arthritis. Arthritis Rheum. 2006;54(5):1435–9.
51. Camus P, Kudoh S, Ebina M. Interstitial lung disease associated with drug therapy. Br J Cancer. 2004;91(Suppl 2):S18–23.
52. Camus P, Fanton A, Bonniaud P, Camus C, Foucher P. Interstitial lung disease induced by drugs and radiation. Respiration. 2004;71(4):301–26.
53. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Risk of serious infection in patients with rheumatoid arthritis-associated interstitial lung disease. Clin Rheumatol. 2016;35(10):2585–9.
54. Tanaka N, Kim JS, Newell JD, et al. Rheumatoid arthritis-related lung diseases: CT findings. Radiology. 2004;232(1):81–91.
55. Assayag D, Elicker BM, Urbania TH, et al. Rheumatoid arthritis-associated interstitial lung disease: radiologic identification of usual interstitial pneumonia pattern. Radiology. 2014;270(2):583–8.
56. Biederer J, Schnabel A, Muhle C, Gross WL, Heller M, Reuter M. Correlation between HRCT findings, pulmonary function tests and bronchoalveolar lavage cytology in interstitial lung disease associated with rheumatoid arthritis. Eur Radiol. 2004;14(2):272–80.
57. Perez T, Farre JM, Gosset P, et al. Subclinical alveolar inflammation in rheumatoid arthritis: superoxide anion, neutrophil chemotactic activity and fibronectin generation by alveolar macrophages. Eur Respir J. 1989;2(1):7–13.
58. Lee HK, Kim DS, Yoo B, et al. Histopathologic pattern and clinical features of rheumatoid arthritis-associated interstitial lung disease. Chest. 2005;127(6):2019–27.
59. Solomon JJ, Ryu JH, Tazelaar HD, et al. Fibrosing interstitial pneumonia predicts survival in patients with rheumatoid arthritis-associated interstitial lung disease (RA-ILD). Respir Med. 2013;107(8):1247–52.
60. Assayag D, Lee JS, King TE Jr. Rheumatoid arthritis associated interstitial lung disease: a review. Medicina. 2014;74(2):158–65.
61. Tsuchiya Y, Takayanagi N, Sugiura H, et al. Lung diseases directly associated with rheumatoid arthritis and their relationship to outcome. Eur Respir J. 2011;37(6):1411–7.
62. 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):103–12.
63. Young A, Koduri G, Batley M, et al. Mortality in rheumatoid arthritis. Increased in the early course of disease, in ischaemic heart disease and in pulmonary fibrosis. Rheumatology (Oxford). 2007;46(2):350–7.
64. Suzuki A, Ohosone Y, Obana M, et al. Cause of death in 81 autopsied patients with rheumatoid arthritis. J Rheumatol. 1994;21(1):33–6.
65. Wolfe F, Michaud K, Gefeller O, Choi HK. Predicting mortality in patients with rheumatoid arthritis. Arthritis Rheum. 2003;48(6):1530–42.

66. Dixon WG, Hyrich KL, Watson KD, Lunt M, Symmons DP. Influence of anti-TNF therapy on mortality in patients with rheumatoid arthritis-associated interstitial lung disease: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis. 2010;69(6):1086–91.
67. Koduri G, Norton S, Young A, et al. Interstitial lung disease has a poor prognosis in rheumatoid arthritis: results from an inception cohort. Rheumatology (Oxford). 2010;49(8):1483–9.
68. Solomon JJ, Chung JH, Cosgrove GP, et al. Predictors of mortality in rheumatoid arthritis-associated interstitial lung disease. Eur Respir J. 2016;47(2):588–96.
69. 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(4):493–500.
70. 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.
71. Prevoo ML, van't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995;38(1):44–8.