



Published in final edited form as:

Curr Opin Rheumatol. 2021 May 01; 33(3): 284–291. doi:10.1097/BOR.0000000000000787.

Interstitial lung disease throughout the rheumatoid arthritis disease course

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Abstract

Purpose of review: To summarize the current understanding of rheumatoid arthritis-associated interstitial lung disease (RA-ILD) throughout the rheumatoid arthritis (RA) disease course from preclinical to established disease.

Recent findings: ILD is a serious extra-articular manifestation of RA. Multiple studies have demonstrated a high prevalence of both subclinical and clinical ILD throughout the RA disease course. Investigations of patients without RA have demonstrated an association between RA-related autoantibodies like anti-citrullinated protein antibodies (ACPAs) and interstitial abnormalities on lung imaging. A significant proportion of RA-ILD patients develop ILD prior to articular manifestations, suggesting that the lung plays a central role RA development, perhaps through ACPA production. RA-ILD also occurs in early RA, when exuberant autoantibody production and systemic inflammation may propagate disease activity. In patients with established RA, a high burden of subclinical and clinical ILD results in significant morbidity, mortality, and healthcare expenditure. Multiple epidemiologic and genetic risk factors, as well as serum biomarkers, have been associated with RA-ILD.

Summary: Subclinical and clinical ILD occur frequently in preclinical, early, and established RA and may play a key role in RA-related autoantibody production and disease progression. Further studies to better understand the risk factors, prognosis, and potential therapies for RA-ILD are needed.

Keywords

Rheumatoid arthritis; interstitial lung disease; disease course; pathogenesis

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CONFLICTS OF INTEREST: All authors declare no conflicts of interest.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease that affects nearly 1% of adults.[1] Although the hallmark clinical manifestation of RA is a painful, destructive, inflammatory arthritis, extra-articular manifestations are common and contribute to excess morbidity and mortality.[2] RA-associated interstitial lung disease (RA-ILD) is a serious extra-articular complication of RA that involves several radiologic and pathologic subtypes. Previously considered a consequence of prolonged disease severity in longstanding RA, subclinical and clinical ILD are increasingly recognized throughout the entire RA disease course. In this review, we detail the pathogenesis of RA-ILD, summarize the current understanding of RA-ILD in preclinical, early, and established RA and describe the clinical importance of ILD among patients with RA.

LUNG INFLAMMATION AND RA PATHOGENESIS

Epidemiological, clinical, and molecular studies have demonstrated that the lung likely plays a central and complex role in the development of RA. According to the “mucosal origin” hypothesis, a combination of genetic factors and environmental exposures contribute to the development of RA-related autoantibodies at mucosal sites, including the lung, oropharynx, cervicovaginal site, gingiva, and gastrointestinal tract.[3] In the lung, injury to the alveoli, airway epithelium, and mucosa occurs through smoking, microbial dysbiosis, or other environmental/inhalant exposures.[4] In a genetically susceptible individual, this damage can lead to increased protein citrullination, production of neutrophil extracellular traps, generation of local RA-related autoantibodies, and, ultimately, the establishment of systemic autoimmunity.[5] Ongoing injury from repeat exposures and autoimmunity triggers chronic inflammation that can lead to airway and pulmonary interstitial remodeling.[6]

Multiple studies have suggested that the lung plays a key role in RA pathogenesis. Several investigations have identified respiratory risk factors for RA disease, including cigarette smoking and silica exposure.[7,8] The central role that the lung plays in the generation of RA-related autoantibodies such as anti-citrullinated protein antibodies (ACPA) is supported by evidence of elevated titers of ACPA antibodies in sputum samples of patients with RA, including the majority of early-RA patients.[9] Similarly, increased ACPA staining and lymphoid aggregates have been observed in transbronchial biopsies of RA patients and a recent study of ACPA-positive patients at risk of RA or having early untreated RA demonstrated evidence of citrulline-reactive B cells in bronchoalveolar lavage sampling, suggesting a direct link between lung inflammation and systemic RA disease progression. [10,11]

Several research findings have demonstrated the importance of an underlying genetic predisposition to both RA and RA-ILD. One study identified that the human leukocyte antigen (HLA) shared epitope (*HLA-DRB1*) was associated with RA-ILD in the presence of smoking.[12] The *MUC5B* promoter variant, a known genetic risk factor for idiopathic pulmonary fibrosis (IPF), has also been identified as a risk factor for RA-ILD, specific to the usual interstitial pneumonia (UIP) subtype that is analogous to IPF.[13]

RA-ILD THROUGHOUT THE RA DISEASE COURSE

Ellmann and Ball initially noted the association between RA and ILD in 1948 when they described pulmonary lesions as part of the “rheumatoid state” in three patients.[14] Since this initial observation, multiple investigations have estimated the prevalence of RA-ILD from 2–60%. [12,15,16] This wide range is due to significant variability in study design, diagnostic methods, and disease definition, but symptomatic RA-ILD likely occurs in 5–17% of patients, whereas radiologic interstitial lung abnormalities on chest high resolution computed tomography (HRCT) may be seen in up to 60%. [6,17] Despite the heterogeneity in study designs, it is increasingly apparent that this full spectrum of lung disease – ranging from subclinical interstitial lung abnormalities to clinical ILD – can be seen throughout the entire RA disease course.

ILD in preclinical RA

Investigations of lung disease in patients prior to clinical RA diagnosis (pre-RA) have typically focused on patients at risk of developing RA based on autoantibody profile. Patients with elevations in serum RA-related autoantibodies – rheumatoid factor (RF) and ACPA – have a 50% risk of progressing to clinical RA within 3 years, making them an attractive population for investigations into RA pathogenesis. [18–20] Furthermore, multiple studies have identified an association between RA-related autoantibodies and lung abnormalities on imaging, even in patients without apparent inflammatory arthritis. A large cross-sectional study of the general population showed correlations between RF and ACPA levels with ILD features detected on cardiac CT chest scans. [21] Another cohort study of patients with IPF found an increased prevalence of ACPA. [22*] Other studies investigating patients with RA-related autoantibodies who lack clinical evidence of inflammatory arthritis have demonstrated a significant prevalence of radiologic pulmonary abnormalities. In one study of ACPA-positive patients with respiratory symptoms who lacked clinical evidence of RA, 39% had radiologically-detected ILD. [23] Similarly, 77% of patients with RF or ACPA positivity but without inflammatory arthritis had radiologic abnormalities on HRCT in a different investigation of 45 patients. [24] Finally, a study performed on patients at our center with elevated ACPA without RA demonstrated that known/suspected lung disease was the second most common reason for testing after arthralgias. [18]

Patients who develop ILD preceding or concurrent with RA diagnosis provide further evidence of the importance of ILD in the pre-RA period prior to clinical articular involvement (Table 1). Recent cohort studies of RA-ILD patients from Denmark, the United States, and China noted that 10–17% of patients were diagnosed with ILD prior to articular diagnosis of RA. [25**,26–28,29*] An additional 7–34% of patients were diagnosed with RA and ILD concurrently. [25**,26–28,29*] The largest of these cohorts, a nationwide study in Denmark, noted that 14% of RA-ILD cases were diagnosed with lung disease 1–5 years prior to RA diagnosis and, overall, RA-ILD was seen in 2.2% of incident RA patients. [27] These studies show that significant lung abnormalities on a spectrum of ILD may develop prior to articular disease manifestations and provide further evidence of the importance of lung inflammation in RA disease pathogenesis.

ILD in Early RA

Multiple studies have also demonstrated a high prevalence of both subclinical and clinical ILD in patients with early RA, most often defined as the 2-year period after clinical RA diagnosis (Table 2). Two investigations examined patients with early RA using relatively comprehensive measures including radiologic imaging, functional testing, and nuclear lung scanning, showed that 44–53% of patients had lung abnormalities in at least one testing modality.[30,31] More recent studies relying on the use of HRCT imaging found evidence of clinical RA-ILD in 10–14% of RA patients with 1–2 years of disease duration.[32,33] Subclinical ILD was detected in 35–39% of early RA patients in studies from the United States and Saudi Arabia.[32,34*] The presence of ACPA in early RA seems to be especially associated with lung imaging abnormalities as one investigation found that 63% of patients with newly diagnosed, untreated, ACPA-positive RA had abnormalities on HRCT.[11]

Further evidence of the importance of the early RA period in RA-ILD comes from longitudinal studies that noted high incidence of RA-ILD shortly after clinical (articular) RA diagnosis. A large longitudinal study of RA patients in Denmark found that 34% of RA-ILD cases received their ILD diagnosis within the first year after RA diagnosis.[27] Similarly, a retrospective, single-center study noted that 17% of patients with RA-ILD were diagnosed with ILD and RA within the same year.[25**] Recently presented data from the Discus JointMan database of incident RA found that 47% of RA-ILD cases developed within two years of the onset of articular RA.[35]

One plausible explanation for the pivotal role that early RA plays in RA-ILD pathogenesis is that this period is characterized by exuberant systemic inflammation and autoantibody production. This may lead to progressive airway inflammation and lung damage. Support for this theory comes from data suggesting that higher levels of ACPA, inflammatory markers, and disease activity are all significant risk factors for RA-ILD.[29*,36*] It is also possible that increased healthcare utilization due to newly diagnosed RA may result in earlier detection of occult or subclinical pulmonary abnormalities related to RA and/or directly related to smoking.[37]

ILD in established RA

Multiple cohort studies have recognized the association between ILD and established RA (Table 3a). In Olmstead County, Minnesota, 7.7% of patients with incident RA subsequently developed RA-ILD over a lengthy follow-up of 40 years (compared to <2% of matched controls) using a stringent case definition that relied on radiologic, pathologic, and clinical diagnosis.[38] In an incident cohort of RA patients in the United Kingdom, 4% developed clinically apparent RA-ILD on HR-CT imaging during 15 years of follow up.[39*] Larger studies using billing codes found RA-ILD prevalence of 2.2% in Denmark and 4.6% in a United States Medicare database.[27,40*] These numbers may be underestimates, as an investigation using death records suggested that up to 10% of the RA population may be affected by RA-ILD.[41] In addition to clinical RA-ILD, a high prevalence of interstitial lung abnormalities on HRCT imaging, ranging from 30–67%, has been described in multiple cohort studies of RA patients (Table 3b).[17,42*,43*,44]

The importance of established RA disease in the development of RA-ILD has also been noted in multiple cohort studies of RA-ILD patients. In one longitudinal study, 51% of patients received their diagnosis of RA-ILD more than five years after RA diagnosis.[25**] In a smaller study of patients with RA-ILD in China, ILD was diagnosed subsequent to RA in 69% of cases with a median of 60 months between RA and RA-ILD diagnosis.[29*] Finally, a recent prospective registry study noted that RF and ACPA were each associated with prevalent, but not incident, RA-ILD, suggesting that significant lung inflammation may be associated with higher ACPA concentrations both locally and systemically.[45] Alternatively, elevations in autoantibodies may be more important for RA-ILD risk soon after diagnosis while other mechanisms such as prolonged disease activity and medication exposure may be more important for RA-ILD development in established RA.

Progression of ILD

The progression of subclinical lung abnormalities to clinical ILD and clinical ILD to more severe stages has been an area of intense investigation. Multiple studies have demonstrated that ILD progresses in about 30% of patients using serial imaging. In one cohort study of 923 RA patients in China who did not have RA-ILD at the time of diagnosis, over 30% subsequently had evidence of RA-ILD on HRCT imaging over 9 years of follow up and 30% of patients with serial scans showed evidence of progressive imaging abnormalities.[46**] Similar findings were noted in a prospective cohort of RA patients in the United Kingdom and a retrospective study of RA patients in Brazil, where 34–38% of RA patients with HRCT abnormalities had radiologic progression over 2–4.4 years of follow up.[43*,47] In another study of 193 RA patients who underwent cardiac CT as part of a prospective trial on cardiovascular risk, 36% had evidence of ILD on imaging and those abnormalities progressed in 39% of the patients who had repeat scans.[48] When subclinical RA-ILD was studied specifically, 57% of patients with HRCT abnormalities had progression on repeat imaging.[49] Patients who are ACPA-positive may be at particularly high risk of progression, as one study found that in ACPA-positive RA patients with baseline lung abnormalities on HRCT, 86% progressed over one year.[34*] This finding suggests that RA-related autoantibody profiling may have utility in stratifying risk of disease progression. However, most studies investigating ILD progression have been retrospective and imaging may have been performed among patients with clinical suspicion for progression.

RA-ILD OUTCOMES AND RISK FACTORS

Studies indicate that 5–17% of patients with RA will develop clinical ILD and, despite significant advances in therapy for articular RA, the prevalence may be increasing over time. [41,50**] RA-ILD is associated with increased mortality compared to both the general population and RA patients without ILD.[16,40*,41,42*] Median survival after diagnosis is only 2.6–8 years with a five year mortality around 40% noted in several studies. [27,38,47,51–53] Furthermore, one nationwide study of mortality in the United States noted that 6.6% of RA-related deaths met criteria for RA-ILD, suggesting an under-ascertainment of RA-ILD in clinical practice and a high lifetime risk and mortality burden from this serious disease.[41] Among patients with RA-ILD, the radiologic usual interstitial pneumonia pattern, also seen in IPF, may be associated with increased mortality and worse

prognosis based on results from several studies.[26,51,53–55] Other investigations, including a recent meta-analysis of 1,256 patients that compared UIP to other patterns of RA-ILD, have highlighted the importance of pulmonary physiologic parameters in predicting outcomes in RA-ILD.[54,56,57]

In addition to excess mortality, patients with RA-ILD have evidence of more severe RA, functional impairment, worse quality of life, and substantial healthcare costs.[58] In one study, 72% of patients had an inpatient admission and 76% had an emergency ward visit within 5 years of RA-ILD diagnosis.[50**] The overall mean healthcare cost per RA-ILD patient was estimated to be \$173,405.[50**] A discussion of management of RA-ILD is outside the scope of this review, but has been covered previously in this journal.[59]

Although the importance of clinical ILD has long been understood, several studies have examined the relevance of subclinical RA-ILD detected by imaging. One recent investigation found that the prevalence of subclinical RA-ILD was 7.7% in several research cohorts and that these abnormalities were associated with increased all-cause mortality.[60] Among patients with RA, the presence of lung abnormalities on CT imaging has been associated with more severe RA disease,[58] as well as increased mortality compared to patients with normal imaging.[42*]

Identifying risk factors and prognostication tools for development and progression of ILD are areas of active ongoing research.[61] Previously identified epidemiologic and clinical risk factors for the development of ILD include older age, male sex, elevated ACPA antibodies, high RA disease activity, and longer RA duration.[26,28,36,38,52,62–66] In addition, several potentially modifiable risk factors including cigarette smoking and obesity have been recognized.[26,67] Genetic risk factors associated with RA-ILD include the *MUC5B* promoter variant[13] and, in a Japanese population, the *HLA-DR2* allele.[6,68] Novel auto-antibodies including anti-carbamylated proteins antibody and anti-malondialdehyde-acetaldehyde antibody as well as serum biomarkers including matrix metalloproteinase 7, pulmonary and activation-regulated chemokine, surfactant D, and interferon- γ -inducible protein 10 have also been associated with RA-ILD.[69–72]

FUTURE DIRECTIONS

There are many remaining unanswered questions about RA-ILD and its involvement throughout the RA disease course. Investigations in this area have been limited by significant heterogeneity in study methods, diagnostic approaches, and disease definitions. Consensus agreement on a research definition for both clinical RA-ILD as well as subclinical RA-ILD would be a significant advance in standardizing research in this area. Additional investigation into differences between groups, including differences between RA patients with and without RA-ILD and patients with RA-onset vs. ILD-onset RA-ILD may provide significant pathogenic and prognostic insights. Since RA-ILD is composed of several heterogenous subtypes, additional dedicated and adequately powered studies are needed to understand possible differences in etiology, natural history, and contribution to clinical outcomes. Prospective studies of patients with subclinical and clinical ILD are needed to understand the natural history and optimal treatment and monitoring for these

patients. Ultimately, additional studies to better evaluate screening strategies, target populations, risk factors, and potential therapies that can reduce the incidence and disease burden of RA-ILD are major unmet needs.

CONCLUSION

Since Ellmann and Ball's initial recognition of RA-ILD nearly 70 years ago, there have been significant advances in the understanding of RA-ILD and its involvement throughout the RA disease course. Multiple studies have demonstrated the presence of both subclinical and clinical ILD in patients with preclinical RA, early RA, and established RA. RA-ILD is associated with significantly increased mortality and morbidity compared to both the general population and RA patients without RA-ILD. Further studies to better understand the risk factors, prognosis, and potential therapies for RA-ILD are needed.

Acknowledgments

FINANCIAL SUPPORT AND SPONSORSHIP: T.J.D. is supported by NIH/NHLBI grants (grant numbers K23 HL119558, R03 HL148484), reports research funding from Bristol-Myers Squibb and involvement in a clinical trial funded by Genentech and Bristol-Myers Squibb, and has received consulting fees from B.I. J.A.S. is supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (grant numbers K23 AR069688, R03 AR075886, L30 AR066953, P30 AR070253, and P30 AR072577), the Rheumatology Research Foundation (R Bridge Award), and the R. Bruce and Joan M. Mickey Research Scholar Fund. J.A.S. has received research support from Bristol-Myers Squibb and performed consultancy for Bristol-Myers Squibb, Gilead, Inova Diagnostics, Optum, and Pfizer unrelated to this work. The funders had no role in the decision to publish or preparation of this manuscript. The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard University, its affiliated academic health care centers, or the National Institutes of Health.

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KEY POINTS

- ILD is a serious extra-articular manifestation of RA and a significant driver of morbidity, mortality, and healthcare costs in RA patients.
- Subclinical and clinical RA-ILD can be seen throughout the entire RA disease course from preclinical to established disease.
- The presence of high titers of ACPA in pulmonary samples, including in patients prior to RA diagnosis, suggests that the lung plays a central role in RA pathogenesis.
- Risk factors for RA-ILD include older age, smoking, male sex, longer RA disease duration, and elevated ACPA as well as the *MUC5B* promoter variant.
- Further efforts to study risk factors, prognosis, and management of RA-ILD are necessary and would be aided by standardized diagnostic criteria for subclinical and clinical RA-ILD.

Table 1: Selected studies reporting ILD in preclinical RA or concurrent with articular diagnosis.

| Study | Country | Study Period | Total patients with RA-ILD | ILD diagnosis occurred before articular RA diagnosis | Concurrent articular RA and ILD diagnoses |
|------------------------|---------|--------------|----------------------------|--|---|
| Hyldegaard, et al.[27] | Denmark | 2004–2016 | 679 | 14%* | 34% (within one year) |
| Mohning, et al.[25] | USA | 2000–2014 | 137 | 10% | 17% (within one year) |
| Kelly, et al.[26] | UK | 1987–2012 | 230 | 10% | 7% |
| Zhang, et al.[28] | China | 2008–2013 | 237 | 13.5% | Not reported |
| Chen, et al.[29] | China | 2008–2017 | 241 | 17.4% | 13.7% |

* = ILD diagnosis 1–5 years prior to RA diagnosis

ILD = interstitial lung disease; RA = rheumatoid arthritis.

Table 2: Selected studies investigating RA-ILD or pulmonary abnormalities in early-RA (within 1–2 years of articular RA diagnosis).

| Study | Country | Study Period | Population | n | Methods of detection of ILD or other pulmonary abnormalities | Findings |
|--------------------------|--------------|--------------|--------------------------------|-----|--|---|
| Reynisdottir, et al.[11] | Sweden | n/a | New RA diagnosis, no treatment | 105 | HRCT | 63% of ACPA-positive with pulmonary abnormalities |
| Doyle, et al.[31] | USA | n/a | New RA diagnosis, no treatment | 18 | ABG, CXR, spirometry, plethysmography, eucapnic hyperventilation | 53% with at least 1 abnormality |
| Gabbay, et al.[30] | Australia | n/a | RA <2 years duration | 36 | CXR, HRCT, BAL, PFTs, nuclear scan | Clinical RA-ILD in 14% Subclinical RA-ILD in 44% |
| Habib, et al.[32] | Saudi Arabia | 2007–2009 | RA <2 years duration | 40 | HRCT, PFTs | Clinical RA-ILD in 10% Subclinical RA-ILD in 35% |
| Dong, et al.[34] | USA | 2011–2013 | RA <1 year duration | 18 | HRCT, PFTs | 39% with abnormalities |
| Mori, et al.[33] | Japan | 2003–2007 | RA <1 year duration | 65 | HRCT, PFTs | 13.8% with classic ILD pattern |

ABG = arterial blood gas; BAL = bronchoalveolar lavage; CXR = chest radiograph; ILD = interstitial lung disease; HRCT = high resolution computed tomography; n/a = not available; PFTs = pulmonary function tests; RA = rheumatoid arthritis.

Table 3: Selected studies investigating RA-ILD in patients with established RA (>2 years after articular diagnosis)

| Study | Country | Study Period | n with ILD / n with RA studied | Methods of detection of ILD or pulmonary abnormalities | Finding |
|--------------------------------------|---------|--------------|--------------------------------|--|--|
| a) Clinical RA-ILD Prevalence | | | | | |
| Duarte, et al.[39] | UK | 2002–2018 | 87 / 1,129 | HRCT | 4% RA-ILD prevalence |
| Bongartz, et al.[38] | USA | 1955–1995 | 45 / 582 | HRCT, clinical, pathologic | 7.7% RA-ILD prevalence |
| Hyldgaard, et al.[27] | Denmark | 2004–2016 | 679 / 31,333 | ICD codes | 2.2% RA-ILD prevalence |
| Sparks, et al.[40] | USA | 2008–2017 | 23,678 / 509,787 | ICD codes | 4.6% RA-ILD prevalence |
| Kim, et al.[16] | Korea | 2009–2012 | 64 / 3,555 | CXR, HRCT | 1.8% RA-ILD prevalence |
| Huang, et al.[42] | USA | 2003–2017 | 30 / 190 | CT | 15.8% RA-ILD prevalence |
| b) Radiologic Abnormalities | | | | | |
| Huang, et al.[42] | USA | 2003–2017 | 190 | CT (retrospective) | 30% with any clinical abnormalities |
| Esposito, et al.[44] | USA | n/a | 77 | HR-CT (prospective) | 35% with any subclinical abnormalities |
| Bilgici, et al.[17] | Turkey | n/a | 52 | HR-CT (prospective) | 67.3% abnormalities |
| Kawano-Dourado, et al.[43] | Brazil | 2014–2016 | 293 | CT (retrospective) | 44% abnormalities |

CT = computed tomography; CXR = chest radiograph; HR-CT = high resolution computed tomography; ICD = international classification of diseases; ILD = interstitial lung disease; n/a = not available; RA = rheumatoid arthritis.