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ORIGINAL RESEARCH

Patient-level factors predictive of interstitial lung disease in rheumatoid arthritis: a systematic review

Eric L. Matteson ,[1] Marco Matucci-Cerinic ,[2,3] Michael Kreuter,[4] Gerd R Burmester ,[5] Philippe Dieudé ,[6] Paul Emery ,[7,8] Yannick Allanore,[9] Janet Pope ,[10] Dinesh Khanna[11]

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For numbered affiliations see end of article.

Correspondence to
Dr Eric L. Matteson;
matteson.eric@mayo.edu

ABSTRACT

Objective Interstitial lung disease (ILD) is an important cause of mortality in some patients with rheumatoid arthritis (RA). Patient-level factors may predict which patients with RA are at the highest risk of developing ILD and are therefore candidates for screening for this complication of the underlying disease.

Methods A systematic literature review was performed using PubMed, Embase and Scopus over a 10-year period up to July 2021. Publications reporting patient-level factors in patients with RA with and without ILD that were assessed before development of ILD (or were unchanged over time and therefore could be extrapolated to before development of ILD) were retrieved for assessment of evidence. Genetic variation in *MUC5B* and treatment with methotrexate were not included in the assessment of evidence because these factors have already been widely investigated for association with ILD.

Results We found consistent associations of age, sex, smoking status and autoantibodies with development of ILD. For biomarkers such as Krebs von den Lungen 6, which have been shown to be diagnostic for ILD, there were no publications meeting criteria for this study.

Conclusions This analysis provides an initial step in the identification of patient-level factors for potential development of a risk algorithm to identify patients with RA who may be candidates for screening for ILD. The findings represent a useful basis for future research leading to an improved understanding of the disease course and improved care for patients with RA at risk of development and progression of ILD.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Interstitial lung disease (ILD) occurs in up to 10% of patients with rheumatoid arthritis and causes significant mortality. While some patient baseline factors such as age, male sex and the rs35705950 variant in the MUC5B promoter gene, are known to be associated with development of ILD, it is not currently possible to predict which patients will develop ILD.

WHAT THIS STUDY ADDS

⇒ We have conducted a systematic review of cohorts of patients with and without ILD, assessing the evidence for associations of a range of baseline factors with development of ILD.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Identification of patient-level factors may aid in the development of a risk algorithm to identify patients at the highest risk of ILD for screening, monitoring and possible early treatment.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic disease that results primarily in chronic joint inflammation. However, as treatments to alleviate joint pain have improved, the burden of extra-articular manifestations of RA on patients has increasingly come to the fore. Interstitial lung disease (ILD) is now one of the leading causes of death in patients with RA, with mean survival estimated to be 3–7 years from diagnosis of ILD.[1–3] In those patients who develop RA-ILD, their ILD also contributes significantly to decreased quality of life, progressive chronic disability and high usage of healthcare resources.[4 5]

The reported incidence of ILD among patients with RA varies considerably, and is dependent on the population, the method of detection or definition of ILD used. Approximately 2%–10% of patients with RA have been estimated to have clinically significant ILD,[2 6 7] but in addition, many patients may have asymptomatic ILD that is detected incidentally on imaging, and may progress to clinically significant ILD over time.[8 9] Acute exacerbations of ILD in patients with RA may also lead to worse outcomes in patients with RA-ILD.[10 11] However, data on the natural course and treatment patterns of RA-ILD are limited, with no currently established guidelines for screening, monitoring and

treatment. Treatment data come from small open-label studies or case studies, with almost no longitudinal studies to provide an evidence base.[12] Treatment for RA-ILD is therefore based on extrapolation from ILDs in other autoimmune diseases or from idiopathic pulmonary fibrosis (IPF).[12]

With more targeted immunomodulatory therapies and the availability of antifibrotic treatments for progressive fibrosing lung diseases, it is important that ILD is diagnosed early so that patients can be treated to slow or prevent irreversible loss of lung function, and ultimately prolong survival. Currently, only patients with RA who display pulmonary symptoms are likely to be evaluated for ILD.[12] Given the relatively low prevalence of ILD in patients with RA, screening all patients for the presence of ILD would impose a very high burden on healthcare systems. Ways to identify patients most at risk of ILD for screening in a more focused approach are therefore needed.

Patient characteristics known to be more common in RA-ILD include older age and male sex.[1 13 14] A promoter variant in the *MUC5B* gene (rs35705950) is also known to be associated with an increased risk of ILD in patients with RA.[15] This variant appears to be specific to the usual interstitial pneumonia pattern of ILD[15] and is associated with this pattern in other chronic fibrotic ILDs such as IPF[16] and chronic hypersensitivity pneumonitis.[17]

It is currently not possible to predict which patients with RA will develop clinically significant ILD, so an increased understanding of the patient-level baseline factors that increase the risk of ILD may help identify those patients who would benefit from early diagnosis by screening, potentially leading to monitoring and early treatment. We have therefore conducted a systematic literature review to assess which patient-level factors are associated with subsequent development of ILD when present in patients with RA and no reported ILD at baseline.

METHODS

Publication database search criteria

Searches were conducted by Whitney Townsend (Librarian, University of Michigan) in three databases (PubMed, Embase and Scopus) between 1 January 2011 and 12 July 2021 on the following review question: what patient-level factors are more likely to be present in patients with RA who go on to develop ILD than those who do not? The search terms are provided in online supplemental online supplemental appendix.

Selection of relevant publications for inclusion

Reports (full papers and presentations from scientific meetings) of retrospective, prospective and/or epidemiological studies in patients with RA with and without ILD were included, provided that they reported baseline patient-level factors that were assessed before the development of ILD. Cross-sectional studies in patients with and without ILD were included if they reported factors such as age or sex that could be considered as unchanged over time—that is, they were present before the occurrence of ILD. When present, anticitrullinated protein antibodies (ACPA) and/or rheumatoid factor (RF) are known to occur early in the disease course, often before RA is apparent[18 19]; therefore, these were also considered as factors that could be extrapolated in cross-sectional studies.

Studies in patients with RA reporting patient-level factors assessed after the development of ILD or that could not be extrapolated, such as serum biomarkers other than ACPA, were excluded, as were studies reporting factors only predictive of RA-ILD outcome (eg, progression or mortality) without a comparator group without ILD, or any other studies that did not have a control/comparator group of patients without ILD.

MUC5B promoter variation has previously been shown to be predictive of ILD development in RA,[15 20] and the use of methotrexate or other disease-modifying antirheumatic drugs has also been widely investigated and found not to be associated with RA-ILD.[21–23] Studies in which these were the only potential predictive factors investigated were therefore also excluded.

Single case reports, case series, reviews and editorial articles were excluded. Studies in which the reported incidence of ILD was already adjusted for all baseline factors reported (so that it was not possible to identify any predictive factors) were also excluded.

The search results were first assessed to exclude clearly non-relevant articles by inspection of the titles, with abstracts also assessed in cases of uncertainty. Subsequently, the abstracts were assessed against inclusion and exclusion criteria. The criteria for screening were agreed by all authors and the articles were initially provisionally screened by a medical writer based on these criteria. Lists of both included and excluded abstracts were circulated to all authors for evaluation and confirmation. Authors could then suggest excluding further papers or including any that were initially excluded. All authors agreed on the final list of included papers. The final list of publications was checked for serial publication of the same data.

Data extraction and quality assessment

Data from the publications that met entry criteria were extracted and entered into spreadsheets circulated to each author. A separate sheet was prepared for each potential prognostic factor. In some studies, factors such as age and sex could not be assessed for prognostic value because patient populations were matched or analyses were already adjusted for these factors. The authors assessed against the Oxford grading criteria for prognostic studies.[24] For grading of evidence, the Oxford system incorporates seven questions:

1. Was the defined representative sample of patients assembled at a common (usually early) point in the course of their disease?
2. Was patient follow-up sufficiently long and complete?

3. Were outcome criteria either objective or applied in a 'blind' fashion?
4. Did adjustment for important prognostic factors take place?
5. How likely are the outcomes over time?
6. How precise are the prognostic estimates?
7. Can I apply this valid, important evidence about prognosis to my patient?

Of these, questions 2, 3 and 5 were not applied, as almost all studies were cross-sectional (question 2), outcome criteria were assessed by high-resolution CT in almost all cases (question 3) and the outcome was always ILD (question 5). Question 7 was also not applied at this stage as we wished to consider all possible factors. This left three criteria for the assessment of quality of evidence: question 1 (definition of the population), question 4 (adjustment for other factors) and question 6 (precision of the prognostic estimates). Authors were asked to assign a score between 0 and 2 for each question to grade the quality of evidence, with a maximum possible score of 6.

The process of grading was as follows: the publications meeting entry criteria were incorporated into a spreadsheet by a medical writer, with provisional scores based on the three applicable questions from the Oxford grading system highlighted above. The sheet was circulated to all authors for their comments and adjustments to the provisional grades. The final grades were agreed at a virtual meeting in December 2021 for all authors to discuss the findings and reach agreement on the quality of evidence available for each prognostic factor. Following the meeting, additional searches were conducted using the same criteria, with a cut-off date of 1 April 2022; the findings were again circulated to all authors for grading of evidence.

RESULTS

After excluding duplicates, the initial searches retrieved 5290 records. Of these, 5175 were excluded based on inspection of the title and/or abstract. The remaining 143 reports were retrieved and the full report assessed, resulting in exclusion of a further 86 reports that failed to meet entry criteria. The remaining 31 reports included eight instances of serial publication of the same study, giving a total of 23 studies, consisting of 17 full papers, 1 letter and 5 studies published as conference abstracts (figure 1).

The prognostic factors identified as predictors of RA-ILD included RA autoantibodies (RF or ACPA) (n=15), age (either overall or at RA onset) (n=5), sex (n=6), smoking status (however defined) (n=6), disease duration (n=8), body mass index (BMI) (n=2), and one report each of matrix metalloproteinase 7 (MMP7), education, extra-articular manifestations and RA disease activity (assessed in this case by the Disease Activity Score (DAS) 28). The studies and potential risk factors described are listed in table 1.

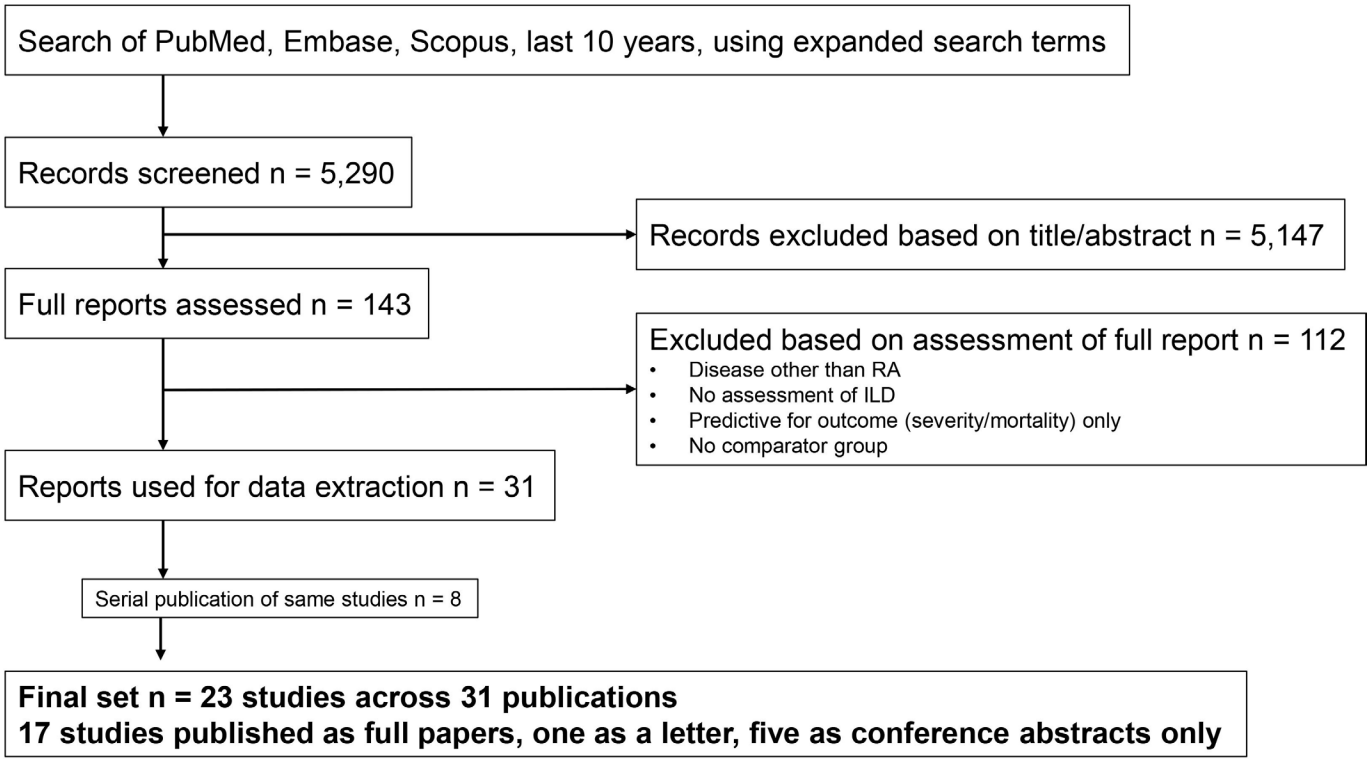

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of search results. ILD, interstitial lung disease; RA, rheumatoid arthritis.

Table 1 Reports included in the analysis

Reference	Potential predictive factors reported
Castellanos-Moreira *et al*[31]	Autoantibodies
Doyle *et al*[32]	Autoantibodies, age, sex, smoking status, MMP7
Furukawa *et al*[33]	Autoantibodies, age, sex, smoking status, RA disease duration
Giles *et al*[34]	Autoantibodies, age, sex, RA disease duration, BMI
Juge *et al*[35]	Autoantibodies, age, sex
Juge *et al*[15]	Autoantibodies, age, sex, smoking status, RA disease duration
Klester *et al*[28]	Autoantibodies, sex
Kronzer *et al*[38]	Age, sex, BMI, education, smoking status
Li *et al*[25]	Autoantibodies, age, sex, smoking status, RA disease duration
Natalini *et al*[26]	Autoantibodies
Paulin *et al*[36]	Autoantibodies, age, sex, smoking status, RA disease duration, extra-articular manifestations
Salaffi *et al*[30]	Autoantibodies, age, smoking status, RA disease duration
Sparks *et al*[39]	Age, RA disease activity
Tian *et al*[50]	Autoantibodies
Wang and Du[27]	Autoantibodies, age, sex, smoking status, RA disease duration
Wickrematilake[51]	Sex, smoking status
Yang *et al*[29]	Autoantibodies, age, sex
Yin *et al*[37]	Autoantibodies, age, sex, smoking status, RA disease duration

BMI, body mass index; MMP7, matrix metalloproteinase 7; RA, rheumatoid arthritis.

Autoantibodies

A total of 15 studies were retrieved in which autoantibodies were reported in groups of patients with and without ILD. These are summarised in table 2. Two of these, Li *et al*[25] and Natalini *et al*,[26] were considered to have high-quality evidence (score 5). The longitudinal study by Li *et al*[25] showed a significant association between RF positivity and ILD in multivariate analysis in 923 patients (OR 1.728; 95% CI 1.042 to 2.867). Patients with a high titre of ACPA had a greater incidence of ILD in this study (OR 1.359) but this was not significant.

In another large longitudinal study by Natalini *et al*.,[26] RF positivity at titres >15 U/mL at baseline was associated with ILD in a multivariate analysis, with greater risk at higher titres. ACPA positivity at titres >15 U/mL, as well as combined RF and ACPA positivity regardless of titre, were also associated with ILD. In cross-sectional studies reporting analyses adjusted for other baseline factors, Wang and Du[27] demonstrated an association of ACPA positivity with ILD and Klester *et al*[28] an association of RF positivity with ILD, while Yang *et al*[29] and Salaffi *et al*[30] found ACPA titre, but not positivity, to be associated with ILD. Juge *et al*[15] showed no association between RF and ACPA with ILD.

The remaining studies mostly reported varying degrees of association between RF and/or ACPA positivity and RA-ILD.[30–37] Most of these analyses were not adjusted for baseline factors and had low patient numbers, so the quality of evidence was considered to be low for the purposes of the current study.

Age

While all studies reported the age of participants, those in which the incidence of ILD was already adjusted for age were excluded from the analysis of age as a prognostic factor. A total of 12 studies were retrieved that reported age at inclusion or age at RA onset in groups with and without ILD, and these are summarised in table 3. Six of these studies were graded 3, with none scoring higher. Among the studies with evidence graded 3, the longitudinal study by Li *et al*[25] identified age >60 years as a predictive factor for development of ILD in a multivariate analysis adjusted for other baseline factors (HR 1.485; 95% CI 1.011 to 2.181; p=0.044). Age at RA onset was not significant in this analysis.

In a cross-sectional study with ORs adjusted for baseline factors, Wang and Du[27] reported association of age (>50 vs ≤50 years; HR 2.20; 95% CI 1.04 to 4.65) and age at RA onset (>40 vs ≤40 years; HR 2.55; 95% CI 1.11 to 5.90) with presence of ILD. Juge *et al*[15] also reported a significant association of age with ILD.

In unadjusted analyses, Doyle *et al*[32] reported an association of age with ILD (p<0.05), whereas Kronzer *et al*[38] found no association (p=0.41), and the remaining studies[29 30 33–37] provided low-quality evidence for our purposes (graded ≤2), with unadjusted analyses and low patient numbers.

Sex

While all studies reported the sex of participants, those in which the incidence of ILD was already adjusted for

Table 2 Studies reporting RA-specific autoantibodies as risk factors

	Study type	N	Association of RF with ILD	Association of ACPA with ILD	Adjusted for one or more baseline variables?	Grading
Natalini *et al*[26]	Prospective, longitudinal, multicentre registry	2228	Associations with ILD at baseline (none during follow-up) RF low (15–45 IU/mL) OR 2.69 (95% CI 1.11 to 6.51) RF high (>45 U/mL) OR 3.40 (95% CI 1.61 to 7.18) Combined RF/ACPA+ OR 2.90 (1.24 to 6.78)	High+ (>15 U/mL) OR 1.91 (95% CI 1.04 to 3.49) Combined RF/ACPA+ OR 2.90 (1.24 to 6.78)	Age, sex, race, smoking, articular disease severity	5
Li *et al*[25]	Retrospective, longitudinal, single-centre cohort	923	RF+, p=0.034, OR 1.728 (1.042 to 2.867)	High titre p=0.178, OR 1.359 (0.870 to 2.122)	Age, sex, smoking, RA duration and severity	5
Juge *et al*[15]	Retrospective, multicentre cohort	1234	ACPA or RF+, p=0.72	ACPA or RF+, p=0.72	Age, sex, country of origin	5
Wang and Du[27]	Retrospective, single-centre cohort	544	RF high titre: OR 2.47 (95% CI 2.09 to 4.13) p=0.016	ACPA high titre: OR 2.38 (95% CI 0.97 to 5.84), p=0.059	Age, age at RA onset, sex, steroid use, smoking, disease duration, HBsAg, *Triglypterum wilfordii*	4
Klester *et al*[28]	Prospective, single centre cohort	167	RF high titre: HR 1.09 (95% CI 1.001 to 1.11)		Age, sex, smoking	4
Yang *et al*[29]	Retrospective, single-centre cohort	308	RF high titre p=0.001 RF+ p=0.335		No	3
Castellanos-Moreira *et al*[31]	Prospective single-centre cohort			Associations of specific types of ACPA with ILD: anti-FCS (OR 3.42; 95% CI 1.13 to 10.40) and anti-CFFHP (OR 3.11; 95% CI 1.06 to 9.14)	Age, sex, smoking, disease duration	4
Yin *et al*[37]	Retrospective single-centrecohort	285		ACPA+, p<0.001	Age, disease duration	3
Juge *et al*[35]	Retrospective multicentre cohort	253		ACPA+, p=0.012	No	3
Doyle *et al*[32]	Prospective cohort, from two centres	189	RF+, p<0.05		No	3
Furukawa *et al*[33]	Prospective, single-centre cohort	450	RF+, 0.0027	ACPA+, p=0.3349	No	3
Paulin *et al*[36]	Prospective, single-centre cohort	118	RF+, p=0.88	ACPA+, p=0.98	No	3
Salaffi *et al*[30]	Retrospective, single-centre cohort	151	RF+/titre: NS	ACPA+, p=0.01 ACPA titre: p<0.001	No	3
Giles *et al*[34]	Prospective, single-centre cohort	177	RF+, p=0.035	ACPA+, p=0.003	No	3
Tian *et al*[50]	Retrospective, single-centre cohort	73		ACPA+, p=0.304	No	3

Grading was performed using Oxford criteria as detailed in the methods.
ACPA, anticitrullinated peptide antibodies; CFFHP, chimeric fibrin/filaggrin homocitrullinated peptide; FCS, fetal calf serum; HBsAg, hepatitis B surface antigen; ILD, interstitial lung disease; RA, rheumatoid arthritis; RF, rheumatoid factor.

Table 3 Studies reporting age (or age at RA onset) as a risk factor

	Study type	N	Association with ILD	Adjusted for one or more baseline variables?	Grading
Li *et al*[25]	Retrospective, longitudinal, single-centre cohort	923	OR 1.485 (95% CI 1.011 to 2.181); p=0.044	Sex, smoking, RA duration and severity, ACPA, RF	3
Wang and Du[27]	Retrospective, single-centre cohort	544	Age at RA onset OR 2.55 (95% CI 1.11 to 5.90); p=0.028	Sex, steroid use, ACPA, RF, smoking, disease duration, HBsAg, *Tripterygium wilfordii* use	3
Juge *et al*[15]	Retrospective, multicentre cohort	1234	Higher age, p<0.0001	Sex, country of origin	3
Salaffi *et al*[30]	Retrospective, single-centre cohort	151	Higher age, p<0.0001 Higher age at RA onset p=0.0253	Sex, disease duration, smoking, RF, ACPA, Disease severity, HAQ-DI	3
Doyle *et al*[32]	Prospective cohort from two centres	189	Higher age, p<0.05	No	3
Kronzer *et al*[38]	Prospective, single centre cohort	317	p=0.41	No	3
Furukawa *et al*[33]	Prospective, single-centre cohort	450	Higher age, p<0.0001	No	2
Juge *et al*[35]	Retrospective, multicentre cohort	253	Higher age at RA onset p<0.0001	Disease duration	2
Giles *et al*[34]	Prospective, single-centre cohort	177	Higher age, p=0.065	No	2
Yin *et al*[37]	Retrospective, single-centre cohort	285	Higher age, p<0.001	No	2
Paulin *et al*[36]	Prospective, single-centre cohort	118	Higher age, p=0.001	No	1
Yang *et al*[29]	Retrospective, single-centre cohort	308	p=0.731	No	1

Grading was performed using Oxford criteria as detailed in the methods.
ACPA, anticitrullinated peptide antibodies; HBsAg, hepatitis B surface antigen; ILD, interstitial lung disease; RA, rheumatoid arthritis; RF, rheumatoid factor.

sex were excluded from the analysis of sex as a prognostic factor. Eleven studies reported sex in groups of patients with and without ILD, and these are summarised in table 4. Four reported a strong association of male sex with ILD in adjusted analyses,[15 25 28 35] while Doyle *et al*[32] reported an association of male sex with ILD in an unadjusted analysis in a large longitudinal study. The remaining reports[27 29 33 34 36 37] had only low-quality evidence for our purposes, with unadjusted analyses and low patient numbers.

Smoking

Smoking could be assessed in a variety of ways, such as current/past/never smoking, never/ever smoking, and number of pack-years, all reliant on patient reporting. For the purposes of evidence grading, any method of assessing smoking status was permitted. Nine studies reported potential associations between smoking and ILD, and these are summarised in table 5. Of the four adjusted analyses, three of which examined ever smoking vs never smoking, three reported no association with ILD[15 25 27] whereas the other reported a strong association.[36]

RA disease duration

Eight studies reported RA disease duration and its potential association with ILD and are summarised in table 6. Three of these reported adjusted analyses. All were graded ≥3. The longitudinal study by Li *et al*[25] reported an association of disease duration with subsequent development of ILD in adjusted analyses, with short disease duration (<5 years vs >10 years) showing an association with subsequent development of ILD (OR 2.099; 95% CI 1.369 to 3.217; p=0.001). However, there was no difference in risk of ILD between patients with disease duration of 5–10 years and >10 years. One other study, by Wang and Du,[27] reported an association of disease duration with ILD after adjustment for baseline factors (duration >2 years vs ≤2 years: OR 1.66; 95% CI 1.02 to 2.69, p=0.040). Juge *et al*[15] found no difference in RA disease duration in patients with and without ILD. In unadjusted analyses, two studies reported significant differences in disease duration between ILD and non-ILD groups,[33 37] and three reported no significant differences.[30 34 36]

Body mass index

Two cross-sectional studies reported BMI in groups with and without ILD (table 7). In a multivariate analysis, Kronzer *et al*[38] assessed BMI according to different categories and found a significantly higher risk of ILD in patients with a BMI ≥30 versus those with a BMI 20–<25 (OR 2.42; 95% CI 1.11 to 5.24; p<0.05), with a non-significant increased risk in those with BMI 25–30. Giles

Table 4 Studies reporting male sex as a risk factor

	Study type	N	Association with ILD	Adjusted for one or more baseline variables?	Grading
Juge *et al*[15]	Retrospective, multicentre cohort	1234	Male, p<0.0001	Age, country of origin	4
Klester *et al*[28]	Prospective, single-centre cohort	167	Female, HR 0.17 (95% CI 0.04 to 0.53)	Age, smoking	4
Juge *et al*[35]	Retrospective, multicentre cohort	253	Male, p=0.0006	Disease duration	3
Li *et al*[25]	Retrospective, longitudinal, single-centre cohort	923	Male, OR 1.882 (95% CI 1.177 to 3.009) p=0.008	Age, smoking, RA duration and severity, ACPA, RF	2
Doyle *et al*[32]	Prospective cohort, from two centres	189	Male, p<0.1	No	3
Furukawa *et al*[33]	Prospective, single-centre cohort	450	Male, p<0.0001	No	2
Yin *et a*[37]	Retrospective, single-centre cohort	285	p=0.44	No	2
Paulin *et al*[36]	Prospective, single-centre cohort	118	Male, OR 3.94 (95% CI 1.2 to 12.91); p=0.023	Age, smoking, extra-articular manifestations, disease activity	2
Wang and Du[27]	Retrospective, single-centre cohort	544	Male, OR=1.62 (95% CI 0.83 to 3.15); p=0.159	Age, steroid use, ACPA, RF, smoking, disease duration, HBsAg, *Tripterygium wilfordii* use	2
Yang *et al*[29]	Retrospective, single-centre cohort	308	p=1.000	No	2
Giles *et al*[34]	Retrospective, single-centre cohort	177	Male, p=0.092	No	1

Grading was performed using Oxford criteria as detailed in the methods.
ACPA, anticitrullinated protein antibodies; HBsAg, hepatitis B surface antigen; ILD, interstitial lung disease; RA, rheumatoid arthritis; RF, rheumatoid factor.

et al[34] reported no difference in mean BMI (assessed as a continuous parameter) between ILD and non-ILD groups in an unadjusted analysis (p=0.31).

RA disease activity

A study by Sparks *et al*[39] reported an association of baseline RA disease activity with subsequent development of ILD (table 7). This longitudinal study primarily assessed the association between disease activity (DAS28 score) and ILD over time, but also included an analysis of the association between DAS28 at baseline and subsequent development of ILD. Patients with moderate-high disease activity (based on DAS28 at baseline) had a higher risk of developing ILD than those with low disease activity/remission at baseline in a multivariable analysis (HR 2.55; 95% CI 1.45 to 4.49).

Extra-articular manifestations

One cross-sectional study[36] reported an association of extra-articular manifestations, defined as dry eye, dry mouth and/or rheumatoid nodules, with ILD in patients with RA after adjusting for other baseline factors (OR 3.96; 95% CI 1.47 to 10.68) (table 7).

Educational status

One cross-sectional study[38] found that, after adjusting for other baseline factors, patients with an education level lower than a college degree had a decreased likelihood of ILD (OR 0.53; 95% CI 0.30 to 0.95) (table 7).

Matrix metalloproteinase 7

MMP7 was the only non-genetic biomarker (other than autoantibodies) for which an association with the development of ILD was investigated.[32] An adjusted analysis reported a significant association with the development of ILD (table 7).

DISCUSSION

ILD is one of the leading causes of mortality in patients with RA. The ability to better identify patients with RA who are most at risk of developing ILD could enable more efficient screening for ILD using a risk factor-guided approach and potentially leading to early intervention to slow lung function decline and reduce the burden of ILD in this group. To date, there are few prospective data describing patient-level baseline factors that may predict its occurrence. A recent post hoc analysis of 21 clinical trials (phase 2, 3, 4 and extended follow-up) of patients with RA treated with tofacitinib, with measures of joint

Table 5 Studies reporting smoking as a risk factor

	Study type	n	Comparison	Association with ILD	Adjusted for one or more baseline variables?	Grading
Juge *et al*[15]	Retrospective, multicentre cohort	1234	Ever smoker vs never smoker	p=0.53	Age, sex, country of origin	4
Li *et al*[25]	Retrospective, longitudinal, single-centre cohort	923	Ever smoker vs never smoker	OR 1.070 (95% CI 0.663 to 1.726); p=0.783	Age, sex, smoking, RA duration and severity, ACPA, RF	4
Paulin *et al*[36]	Prospective, single-centre cohort	118	Ever smoker vs never smoker	OR 5.85 (95% CI 2.12 to 16.09); p=0.001	Extra-articular manifestations, disease activity	3
Wang and Du[27]	Retrospective, single-centre cohort	544	Current smokers vs ex/never smokers	OR=1.71 (95% CI 0.67 to 4.38); p=0.263	Age, sex, steroid use, ACPA, RF, disease duration, HBsAg, *Tripterygium wilfordii* use	3
Doyle *et al*[32]	Prospective cohort, from two centres	189	Pack-years	p<0.1	No	3
Wickrematilake[51]	Retrospective, single-centre cohort	384	Ever smoker vs never smoker	p<0.0001	No	3
Salaffi *et al*[30]	Retrospective, single-centre cohort	151	Current smoker vs ex/never smoker	p=0.03	No	3
Furukawa *et al*[33]	Prospective, single-centre cohort	450	Ever smoker vs never smoker	p=0.2673	No	2
Yin *et al*[37]	Retrospective, single-centre cohort	285	Not stated	p=0.3	No	2

Grading was performed using Oxford criteria as detailed in the methods.
The remaining studies all reported unadjusted analyses with varying degrees of association (or no association) of smoking with ILD.[27 30 32 33 37 51]
ACPA, anticitrullinated protein antibodies; HBsAg, hepatitis B surface antigen; ILD, interstitial lung disease; RA, rheumatoid arthritis; RF, rheumatoid factor.

Table 6 Studies reporting RA disease duration as a risk factor

	Study type	N	Association with ILD	Adjusted for one or more baseline variables?	Grading
Li *et al*[25]	Retrospective, longitudinal, single-centre cohort	923	0–5 vs >10 y, OR 2.099 (95% CI 1.369 to 3.217); p=0.001 5–10 vs >10 y, OR 0.922 (95% CI 0.559 to 1.522); p=0.751	Age, sex, smoking, RA severity, ACPA, RF	5
Wang and Du[27]	Retrospective, single-centre cohort	544	>2 vs ≤2 y, OR 1.32 (95% CI 0.74 to 2.35); p=0.353	Age, sex, steroid use, ACPA, RF, smoking, HBsAg, *Tripterygium wilfordii* use	4
Juge *et al*[15]	Retrospective, multicentre cohort	1234	p=0.38	Age, sex, country of origin	4
Furukawa *et al*[33]	Prospective, single-centre cohort	450	Longer duration, p=0.0041	No	3
Paulin *et al*[36]	Prospective, single-centre cohort	138	p=0.29	No	3
Salaffi *et al*[30]	Retrospective, single-centre cohort	151	NS	No	3
Giles *et al*[34]	Retrospective, single centre cohort	177	p=0.17	No	3
Yin *et al*[37]	Retrospective, single-centre cohort	285	Longer duration, p=0.003	No	3

Grading was performed using Oxford criteria as detailed in the methods.
ACPA, anticitrullinated protein antibodies; HBsAg, hepatitis B surface antigen; ILD, interstitial lung disease; NS, not significant; RA, rheumatoid arthritis; RF, rheumatoid factor; y, year.

Table 7 Studies reporting other risk factors

	Study type	n		Association with ILD	Adjusted for one or more baseline variables?	Grading
Kronzer *et al*[38]	Prospective, single-centre cohort	317	BMI	BMI ≥30 OR 2.42 (95% CI 1.11 to 5.24)	Age, sex, race, ACPA, education, smoking	5
Giles *et al*[34]	Retrospective, single-centre cohort	177	BMI	p=0.31	No	3
Sparks *et al*[39]	Prospective, single-centre cohort	1419	Disease activity	Moderate-high DAS28 HR 2.22 (95% CI 1.28 to 3.82)	Age, sex, smoking, ACPA/RF	4
Paulin *et al*[36]	Prospective, single-centre cohort	138	More extra-articular manifestations	OR 3.96 (95% CI 1.47 to 10.68); p=0.006	Age, smoking, disease activity	4
Doyle *et al*[32]	Prospective cohort, from two centres	189	MMP7	OR 1.82 (95% CI 1.15 to 2.90); p=0.004 (BRASS cohort) OR 1.50 (95% CI 1.14 to 1.98) (ACR cohort)	Age, gender, smoking, RF, ACPA	5
Kronzer *et al*[38]	Prospective, single-centre cohort	314	Education level lower than college	OR 0.53 (95% CI 0.30 to 0.95)	Age, sex, race, ACPA, BMI, smoking	3

Grading was performed using Oxford criteria as detailed in the methods.
ACPA, anticitrullinated peptide antibodies; BMI, body mass index; DAS, Disease Activity Score; ILD, interstitial lung disease; MMP7, matrix metalloproteinase 7; RA, rheumatoid arthritis; RF, rheumatoid factor.

disease activity as the primary outcome, suggested older age, current smoking and high disease activity (DAS28 score and erythrocyte sedimentation rate) as predictive of ILD in the clinical trial setting,[40] though it is not clear how applicable these findings may be to the general RA population.

We have conducted a comprehensive literature search to identify a series of patient-level factors in patients with RA that may be associated with subsequent development of ILD. Age, sex and smoking status were confirmed as predictive of ILD development. There is consistent evidence of an association between both RF and ACPA and subsequent development of ILD across these studies, although in the case of ACPA, >75% of patients were ACPA positive in most cases and correlations, where shown, were with higher titres of ACPA rather than seropositivity or negativity. The interpretation of these data is complicated by the possible role of serology in initial diagnosis of RA, where some seronegative patients with other symptoms may not be diagnosed, but the data do suggest the relevance of serology as a predictor and that B cell activation may play a significant role in the development of ILD in RA.

The age and sex of patients have been widely reported to be associated with risk of ILD. In the studies reported here, older age and male sex were confirmed as risk factors for the development of ILD. Both age at inclusion into the study and age at RA onset were reported to be associated with risk of ILD. It is well recognised that ILD is more common in older patients with RA,[7] although age at RA onset may be a more useful parameter when considering risk of ILD at baseline. While some studies used a single cut-off for age (eg, 60 years), there is no clear rationale for any specific cut-off point and therefore, consideration of different age categories may be more useful.

Possibly due to the variety of ways in which smoking status may be assessed, there was wide variation in the reported predictive ability of smoking status for development of ILD. In this analysis, we included a variety of measures of smoking (pack-years, never/ever smoking and current/past/never smoking). Pack-years may be the most useful parameter, providing the most information regarding exposure to tobacco smoke, but data may not always be available, and even then may not be reported accurately by the patient. Categories of never/past/current smoker may be more useful in considering risk of ILD.

Associations between RA disease activity or RA disease duration and development of ILD were reported in few studies meeting the criteria for this analysis, but a strong cross-sectional association between RA-ILD and disease activity measured by DAS28 has been reported,[39] and further investigations are certainly warranted. Patients with high disease activity are also likely to have high autoantibody titres, which could be a confounding factor.

With regards to the apparent association between high BMI and increased risk of ILD seen by Kronzer *et al*,[38] a study designed specifically to look at BMI and ILD with appropriate image weighting would be important to confirm any effect. High BMI has been shown to be associated with more severe disease activity in several

studies.[41–43] The only other study looking at BMI found no effect in an unadjusted analysis.[34] This could open stimulating perspectives with the dissemination of treat-to-target strategies and the availability of numerous drugs in RA. The impact of modern RA management on ILD prevalence and ILD progression merits investigation.

Genetic factors—specifically the *MUC5B* rs35705950 variant—have been widely investigated,[15 20 44] and it is accepted that patients with RA that carry the *MUC5B* rs35705950 risk allele are at significantly higher risk of RA-ILD. We did not include the *MUC5B* promoter variant in our systematic review because the data regarding its prognostic impact are already established. When assessing overall risk of ILD in patients with RA, any available information on *MUC5B* status would clearly have an impact, although such data may not be routinely available.

For three potential factors we found only one report for each—namely extra-articular manifestations, educational status and MMP7. Regarding the first two, there is clearly insufficient evidence to judge whether these may be useful predictors of RA-ILD. While there is no obvious rationale for educational status in itself being a predictive factor, there may be associations with lifestyle factors that could impact RA disease activity and thereby increase likelihood of ILD. In the case of MMP7, it may be considered in the context of a spectrum of biomarkers that could potentially be predictive. Several studies have examined soluble biomarkers such as Krebs von den Lungen 6 in RA-ILD, but almost all have compared markers in separate cohorts of patients with and without ILD[45–47] or have looked at the effect of biomarkers on outcome or severity of ILD[48 49] and do not provide information on markers in patients without ILD who subsequently develop ILD. Nevertheless, these robust data support associations of soluble biomarkers such as Krebs von den Lungen 6 and C reactive protein with ILD and represent a potentially important area for prediction of ILD.

The independent contribution of the different factors reported here remains to be identified, and as most studies were retrospective, there is a need for longitudinal studies designed to assess the impact of different factors on subsequent development of ILD. In addition, the differences in how baseline factors were adjusted for between studies may have impacted the results. Nevertheless, this analysis provides the first step in the identification of patient-level factors that may aid in the development of a risk algorithm to identify patients at highest risk of ILD for screening, followed by monitoring and possible early treatment. Identification of additional biomarkers and prospective, longitudinal clinical studies in patients with RA that assess development of ILD as a primary outcome are needed to address critical management needs important to reducing the burden of RA-ILD and improving outcomes in these patients.

Author affiliations
[1]Division of Rheumatology, Mayo Clinic College of Medicine and Science, Rochester, Minnesota, USA
[2]Department of Experimental and Clinical Medicine, Division of Rheumatology, University of Florence, Firenze, Italy
[3]Unit of Immunology, Rheumatology, Allergy and Rare Diseases (UnIRAR), IRCCS San Raffaele Hospital, Milan, Italy
[4]Center for Interstitial and Rare Lung Diseases, Pneumology, Thoraxklinik, University of Heidelberg, German Center for Lung Research, Heidelberg, Germany
[5]Department of Rheumatology and Clinical Immunology, Charité Universitätsmedizin Berlin, Berlin, Germany
[6]Rheumatology Department, Bichat Hospital APHP, Université Paris Cité, Paris, France
[7]Leeds NIHR BRC, Leeds Teaching Hospitals NHS Trust, Leeds, UK
[8]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK
[9]Department of Rheumatology, APHP, Université Paris Cité, Paris, France
[10]Division of Rheumatology, St Joseph's Hospital, Western University, London, Ontario, Canada
[11]DIvision of Rheumatology, University of Michigan, Ann Arbor, Michigan, USA

Contributors All authors contributed to analysing the data, writing, reviewing and amending the article and approved the final version for submission.The guarantor (ELM) accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish

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ORCID iDs
Eric L. Matteson http://orcid.org/0000-0002-9866-0124
Marco Matucci-Cerinic http://orcid.org/0000-0002-9324-3161
Gerd R Burmester http://orcid.org/0000-0001-7518-1131
Philippe Dieudé http://orcid.org/0000-0002-4814-0307
Paul Emery http://orcid.org/0000-0002-7429-8482
Janet Pope http://orcid.org/0000-0003-1479-5302

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