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Rheumatoid arthritis-associated interstitial lung disease in countries across the world

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ABSTRACT

Objectives: We aimed to describe the incidence of RA-ILD in various countries worldwide, and to explore its association with RA disease activity.
Methods: In 5 countries, data on RA-ILD (clinical diagnosis based on chest X-ray or CT) were collected RA patients of two observational databases (METEOR, EAC). We investigated a possible association between disease activity over time and RA-ILD.
Results: 16,663 patients with RA with variable disease duration were evaluated. At the first visit recorded in the database, 1/1077 (0.09 %) patients from The Netherlands, 63/11,787 (0.53 %) from India, 8/629 (1.27 %) from South Africa, 6/424 (1.42 %) from Mexico and 17/2728 (0.62 %) from Colombia had an RA-ILD diagnosis. The incidence rate of RA-ILD in patients with newly diagnosed RA was 3.8 (95 % CI 1.6 to 9.1) per 1000 patient years in The Netherlands, 1.6 (95 % CI 1.0 to 2.5) in India and 6.6 (95 % CI 2.5–17.5) in South Africa. The OR for RA-ILD development, per point increase in DAS28 over time was 1.19 (95 % CI 0.34 to 4.22). Disease activity after the RA-ILD diagnosis or a matched timepoint was statistically significantly higher in patients with RA-ILD than in controls (β 0.56 (95 % CI 0.18 to 0.93). There were no clear differences in DMARD use between the two groups.
Conclusion: Despite slight differences in RA-ILD prevalence and incidence between countries, the incidence of RA-ILD in daily practice is low in our RA population from different continents. Patients with RA-ILD had a higher disease activity than patients without RA-ILD, and were more often ACPA positive and/or (former) smokers.

Introduction

Interstitial lung disease (ILD) contains a spectrum of inflammatory and fibrotic lung diseases, of which several subtypes are associated with rheumatoid arthritis (RA). Mortality in patients with RA associated ILD (RA-ILD) is higher than in the general RA population, with 5-year survival rates of only 39–60 % reported [1,2–5] Several risk factors for developing ILD have been identified in RA patients, including older age, male sex, smoking and the presence of rheumatoid factor (RF) or anti–cyclic citrullinated peptide antibodies (ACPA) [6] The reported prevalence in previous studies ranges from 1 to 58 percent, depending on the definition, timing and the diagnostics used [2,7–9] Geographical location may also be related to the prevalence and incidence of RA-ILD. However, previously published RA-ILD incidence and prevalence of different countries are often not comparable since different patient selection methods and definitions of ILD have been used [2,4,8,10–17] In

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addition, most studies on RA-ILD are performed in Western countries, and it is not known whether results from these studies also apply to patients from other countries.

Also, the association between RA disease activity and ILD is unclear, and it is still to be clarified what the role of RA medication is in the development and management of ILD [2,4,18–21] RA-ILD might have become less prevalent in RA because of improved treatment strategies for RA.

We hypothesize that the current prevalence and incidence of RA-ILD observed in our daily practice data, and therefore mainly based on clinically relevant ILD, is low. Prevalence and incidence of RA-ILD may vary between countries, based on differences in genetic and environmental risk factors, and on differences in symptom duration and disease activity suppression.

Our aim is therefore to perform an international cross-continental study to investigate the incidence and prevalence of RA-ILD in RA patients in different countries, and to explore the association with RA disease activity and exposure to RA medication, using daily clinical practice data.

Materials and methods

Patient population

Patients were selected from two different observational databases. The Measurement of Efficacy of Treatment in the Era of Outcome in Rheumatology (METEOR) registry, is a large international, observational database capturing daily clinical practice in RA patients [22] Patients with RA as diagnosed by the treating physician were included. We used data of four countries for which additional data on ILD could be collected: India, Mexico, Colombia and South Africa.

From the Leiden Early Arthritis Clinic (EAC), RA patients fulfilling the 1987 American College of Rheumatology (ACR) and/or 2010 ACR/EULAR (European League against Rheumatism) criteria for classification of RA were selected. The EAC is an inception cohort including patients with arthritis with symptom duration <2 years at the Leiden University Medical Center (LUMC) in The Netherlands [23] The EAC was approved by the Medical Ethics Committee. Before inclusion in the EAC cohort, all patients had provided informed consent. For the prevalence calculations, all patients with at least one visit from May 2011 were included (time period of inclusion in EAC: from 1993 (start of EAC) to 2019 (end of data collection for this study). For all other analyses, we only used data of patients who were diagnosed with RA from May 2011, because since May 2011 electronic health records were introduced in the LUMC, and we extracted data on ILD diagnosis based on text recognition from the electronic health records. Information on medication is also available from May 2011. If no medication was prescribed during follow-up, the patient was excluded from all analyses, to avoid including patients without a definite RA diagnosis in the analysis.

In the METEOR database, data were collected according to daily practice and there are no additional protocolized visits or measurements (time period: 2010–2021). Therefore, no informed consent was needed when adding patients to the database. All patient data in the METEOR database are anonymized.

For a part of the statistical analyses, only patients with newly diagnosed RA with an available baseline visit were selected. Newly diagnosed RA was defined as starting a DMARD within 3 months from diagnosis. In Mexico, patients were sometimes already diagnosed before the first rheumatology visit, so patients with a diagnosis duration of 1 year before the first visit and no treatment initiation >3 months before the first visit were also considered a new patient. Baseline was defined as the first rheumatology visit with the first DMARD treatment between 3 months before and 3 months after this visit.

Information on ILD is not available in EAC and METEOR and was additionally collected.

An overview of the characteristics of participating hospitals can be found in supplementary file 1.

Data collection ILD

A clinical diagnosis of RA- ILD, based on at least chest X-ray and/or CT, was used. In The Netherlands, India and South Africa, X-ray screening was performed at the first visit. In Colombia and Mexico, imaging was only performed in case of respiratory symptoms or before bDMARD initiation (supplementary file 1). For METEOR, the RA-ILD diagnosis and diagnostics used were provided by the local rheumatologist, based on patient file investigation (in India with preselection by text recognition, see supplementary file 2). In the EAC database, text recognition of physician notes and radiology reports was used to identify patients with RA-ILD, based on different possible variations of terms that are associated with RA-ILD (supplementary file 2). The text recognition output was assessed by a medical doctor (SLH). In case of doubt, or if medication induced ILD was considered as a possible diagnosis, a physician training to become a pulmonologist (5th year, EM) who had access to all clinical data was consulted.

Statistical analysis

Patient characteristics were described, comparing patients who had RA-ILD at the first visit recorded in the database or developed it during follow-up. The incidence rate of ILD was reported from baseline (only in patients with newly diagnosed RA). In a sensitivity analysis only patients with a CT and physical examination and/or lung function test performed were classified as having RA-ILD.

Prevalence (percentage) of RA-ILD at the first study visit and during follow-up in all patients (newly diagnosed and with longer disease duration) was also reported separately for each country, since not all countries had data of newly diagnosed patients available.

To explore a possible association between RA disease activity and RA-ILD, and to examine differences in treatment (response) we performed several analyses within a selection of patients, with for each patient with RA-ILD, 5 matched controls without RA-ILD, who were matched based on hospital and duration of follow-up.

A multilevel mixed-effects logistic regression model was used to investigate whether there is an association between disease activity over time and ILD, with visits nested within patients. The model was adjusted for country, timepoint (months since baseline), age, sex, (ever) smoking status, and RF seropositivity [6,24–26].

Treatment from baseline until ILD diagnosis/matched timepoint was described for patients with RA-ILD and matched controls.

Furthermore, in patients diagnosed with ILD, the disease activity was described from the moment of the ILD diagnosis until the end of follow-up. A generalized linear mixed model was performed with ILD as the independent variable, and disease activity over time (from the moment of ILD diagnosis / matched timepoint in follow-up duration matched RA patients without ILD of the same country) as a dependent variable. Visits were nested within patients. The model was adjusted for timepoint, age, sex, smoking status and RF seropositivity.

Treatment was described for patients with and without an ILD diagnosis from the moment of ILD diagnosis/matched timepoint in matched controls.

Time to moderate or good EULAR treatment response [27] to csDMARDs and bDMARDs and time to remission (DAS28<2.6) from baseline was compared between ILD patients and matched controls with newly diagnosed RA with a Cox regression analysis. The analysis was adjusted for potential confounders (age, sex, smoking status, and RF seropositivity and previous treatment (csDMARD yes/no and bDMARD yes/no)) [6,25,28,29] Time to moderate/good response was also illustrated for both groups with (unadjusted) Kaplan Meier curves based on unimputed data. For the analysis of the association between RA-ILD and disease activity/response to treatment, we have applied Bonferroni correction to adjust for multiple comparisons.

To account for missing data, for all regression analyses, multiple imputation with chained equations based on predictive mean matching was used for variables with ≥5 % missing data (ranging from 5 % for ESR and swollen joint count to 31 % for the clinical disease activity index (CDAI)) [30].

All analyses were performed with STATA/SE 16.0.

Results

Incidence and prevalence of RA-ILD

Within the five countries 16,648 patients with RA were evaluated. A summary of the results is depicted in Fig. 1. In 128/151 patients (85 %) with RA-ILD a chest CT was performed to confirm the diagnosis. In Table 1, characteristics of patients with newly diagnosed RA patients and medication data available, were compared between patients with and without RA-ILD (diagnosed at or before baseline or during follow-up), and characteristics of all patients (both newly diagnosed and with longer disease duration) are displayed in Table 2. We observe a tendency for higher inflammatory marker levels, more antibody positivity and a higher prevalence of smoking in patients with RA-ILD (Tables 1 and 2).

Netherlands

We evaluated 1077 patients from The Netherlands with newly diagnosed RA, of whom 462 were diagnosed and included after the initiation of electronic health records. The incidence rate (IR) of RA-ILD was 3.8 (95 % CI 1.6 to 9.1) per 1000 patient years. All patients with RA-ILD had evaluation by chest CT.

Of the 462 patients diagnosed and followed from May 2011, 1 (0.22 %) had RA-ILD at baseline, and 5 (1.08 %) developed RA-ILD after 35 ±24 months. Of all 1077 patients with RA, 1 (0.09 %) had RA-ILD diagnosed at or before the first visit (1 patient had ILD with no clear relationship with RA and 1 had interstitial lung abnormalities/possible ILD). Another 20 patients (1.86 %) developed RA-ILD during follow-up (mean 83±71 months). Data from patients who died before the introduction of electronic health records in the hospital could not be included.

India

We evaluated 11,787 patients with RA from India, of whom 10,905 were newly diagnosed with RA. The IR of RA-ILD in patients with newly diagnosed RA was 1.6 (95 % CI 1.0 to 2.5) per 1000 patient years. The IR of CT-confirmed RA-ILD was 1.2 (95 % CI 0.7 to 2.1) per 1000 patient years.

Of the 10,905 patients with newly diagnosed RA, 57 (0.52 %) had an RA-ILD diagnosis at or before baseline and another 18 patients (0.17 %) developed RA-ILD during follow-up (mean 12±20 months).

Of all 11,787 patients with RA, 63 (0.53 %) had RA-ILD diagnosed at or before the first METEOR visit and another 21 (0.18 %) patients developed RA-ILD during follow-up (mean 12±20 months).

South africa

We evaluated 629 patients with RA from South Africa, of whom 507 were newly diagnosed with RA. The IR of RA-ILD in patients with newly diagnosed RA was 6.6 (95 % CI 2.5–17.5) per 1000 patient years. The IR of CT-confirmed RA-ILD (in all newly diagnosed RA patients) was 4.9 (1.6 to 15.3).

Of the 507 patients with newly diagnosed RA, 2 (0.39 %) had an RA-ILD diagnosis at or before baseline and 4 (0.79 %) other patients developed RA-ILD during follow-up (mean 15±15 months).

Of all 629 patients with RA, 8 (1.27 %) had an RA-ILD diagnosis at or before the first METEOR visit and another 11 (1.77 %) patients developed RA-ILD during follow-up (mean 20±21 months).

Mexico

We evaluated 424 patients with RA from Mexico. There were only 19 newly diagnosed patients, of whom none had or developed RA-ILD (0 %).

Of the 424 patients with RA, 6 (1.42 %) had RA-ILD diagnosed at or before their first METEOR visit and another 3 (0.71 %) patients developed RA-ILD during follow-up (mean 17±26 months).

Colombia

We evaluated 2728 patients with RA from Colombia, of whom 301 were newly diagnosed with RA. None of the 301 newly diagnosed patients had or developed RA-ILD (0 %).

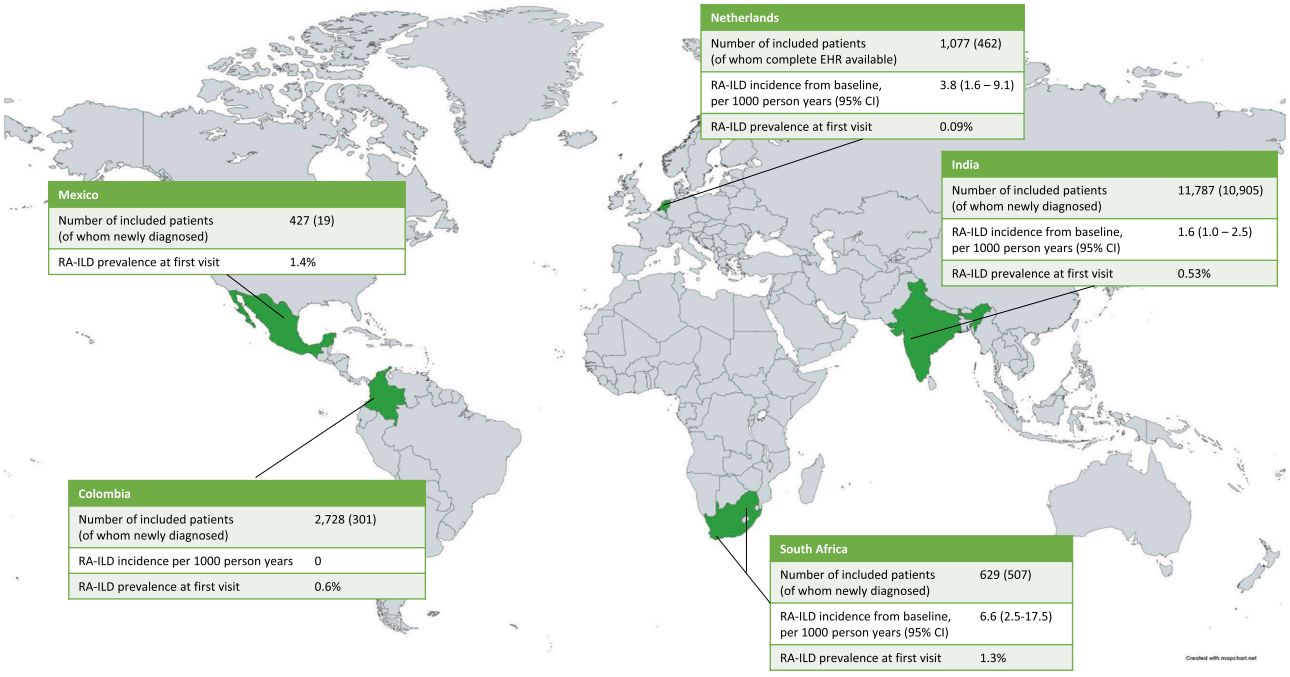


Fig. 1. Incidence and prevalence of RA-ILD per country.

Table 1
Baseline characteristics of patients with newly diagnosed RA with and without RA-ILD at baseline or during follow-up.

	Netherlands ($N = 462$)			India ($N = 10,905$)			South Africa ($N = 507$)		
	No RA-ILD ($n = 456$)	RA-ILD ($n = 6$)	p value	No RA-ILD ($n = 10,830$)	RA-ILD ($n = 75$)	p value	No RA-ILD ($n = 501$)	RA-ILD ($n = 6$)	p value
Age (years), mean (SD)	59.6 (14.4)	64.3 (11.6)	0.42	49.7 (3.1)	49.1 (3.0)	0.075	51.1 (1.6)	50.3 (1.8)	0.19
RA symptom duration (months), median (IQR)	2.9 (1.4–6.6)	5.0 (1.5–9.7)	0.73	47.9 (18.0–95.9)	59.9 (23.9–143.9)	0.031	24.6 (8.1–55.4)	65.9 (46.7–104.5)	0.082
Sex (female), %	64	50	0.46	85	76	0.021	82	83	0.93
BMI (kg/m3), mean (SD)	26.4 (4.6)	25.1 (2.1)	0.51	*	*		*	*	
Ever smoker, %	69	100	0.13	1	2	0.88	26	100	<0.001
DAS, mean (SD)	2.5 (0.9)	2.2 (0.5)	0.51	3.7 (1.0)	*		*	*	
DAS 28, mean (SD)	5.1 (1.3)	5.1 (0.6)	0.98	6.0 (1.4)	*		5.2 (1.4)	*	
CDAI, mean (SD)	*	*		27.4 (14.7)	*		26.8 (13.8)	18.5 (9.1)	0.18
ESR (mm/h), mean (SD)	33.4 (25.6)	47.0 (30.0)	0.2	76.7 (32.7)	89.2 (29.7)	0.001	37.4 (29.2)	54.6 (27.2)	0.19
CRP (mg/l), mean (SD)	21.8 (28.5)	31.5 (31.3)	0.41	36.4 (40.4)	50.4 (58.0)	0.005	25.2 (32.5)	*	
Patient global assessment (0–100 mm VAS), mean (SD)	44.2 (24.8)	28.3 (13.3)	0.12	53.5 (18.5)	*		63.0 (24.1)	39.0 (11.4)	0.027
Swollen 28 joint count, median (IQR)	6.0 (3.0–11.0)	5.0 (4.0–7.0)	0.7	3.0 (0.0–7.0)	2.0 (0.0–7.0)	0.82	5.0 (3.0–9.0)	6.0 (2.0–9.0)	0.89
ACPA (positive), %	47	50	0.88	81	93	0.026	98	100	0.70
RF (positive), %	54	100	0.024	83	95	0.009	99	100	0.83
HAQ score (0–3), median (IQR)	1.0 (0.5–1.5)	0.7 (0.3–1.5)	0.58	0.9 (0.5–1.1)	0.9 (0.6–1.3)	0.26	1.5 (0.9–2.1)	*	

Results from Mexico and Colombia are not displayed, because there were no patients with a new RA diagnosis who had or developed RA-ILD.
* <75 % data available
DAS = disease activity score, CDAI = clinical disease activity index, ESR = erythrocyte sedimentation rate, CRP = *C*-reactive protein, ACPA = anti-citrullinated protein antibody, RF = rheumatoid factor, HAQ = health assessment questionnaire.

Of all 2728 patients with RA, 17 (0.62 %) patients had RA-ILD diagnosed at or before their first METEOR visit and 1 (0.036 %) other patient developed RA-ILD during follow-up (mean 12±11 months).

Association between disease activity and development of RA-ILD

In a database with newly diagnosed patient with RA (RA-ILD patients matched to non-ILD RA patients based on follow-up duration), we did not find a statistically significant association between the DAS28 over time and the development of RA-ILD (OR 1.19, 95 % CI 0.34 to 4.22). The median follow-up time of patients included in this analysis ($n = 162$) was 24 (IQR 2 to 56) months.

DMARD treatment and development of RA-ILD

All patients who developed RA-ILD ($n = 27$) since baseline had been treated with csDMARDs before they were diagnosed with ILD. Of the controls, 134/135 had received csDMARDs within the same time frame since baseline (follow-up median 24 (IQR 2 to 56) months). None of the cases and controls had received bDMARD therapy within this period.

Disease activity after diagnosis of RA-ILD

After their ILD diagnosis, 43 patients with RA-ILD had a statistically significantly higher DAS28 during median 11 (IQR 4 to 28) months than matched controls ($n = 199$) after a matched timepoint: patients with RA-ILD had a 0.58 (95 % CI 0.19 to 0.98) point higher DAS28 over time than patients without RA-ILD.

DMARD treatment after diagnosis of RA-ILD

From the moment of ILD diagnosis, 40/43 (93 %) patients with RA-ILD used a csDMARD during the median 5 months of follow-up, compared to 192/199 (96 %) controls. bDMARDS were used in 2/43 (5 %) of the RA-ILD cases and in 4/199 (2 %) of the controls.

Time to moderate/good response or remission

Newly diagnosed RA patients who developed RA-ILD between baseline and the end of follow-up achieved moderate or good EULAR treatment response statistically significantly later than patients who did not develop RA-ILD (HR 0.87, 95 % CI 0.80 to 0.95; $n = 232$). The (univariate) results are also illustrated with a Kaplan Meier curve in supplementary figure 1. The time to remission was also statistically significantly longer in the RA-ILD group (HR 0.75, 95 % CI 0.65 to 0.86).

Discussion

Among patients with RA of whom real world clinical data was assessed, the incidence and prevalence of RA-ILD was relatively low and varied between the study populations derived from multiple continents, with an incidence rate ranging from 1.6 per 1000 person years in our population from India to 6.6 per 1000 person years in our population from South Africa. In patients with RA-ILD, RA symptom duration had been longer at diagnosis, and RA-ILD patients tended to be more often antibody positive. We did not find a statistically significant association between prior RA disease activity and the development of RA-ILD, but patients who had developed RA-ILD had statistically significantly higher disease activity levels from that moment than patients who had not developed RA-ILD. The time to RA treatment response was longer in patients who had or developed RA-ILD.

It is difficult to compare our results to that of other studies, since the methods, setting and definition of ILD vary between studies. The baseline prevalence of RA-ILD in our populations was slightly lower than that in older cohorts from different countries that were based on self-reporting, clinical assessment and medical records [9], a claims database [31], a physician's diagnosis combined with abnormalities on diagnostic examination [2], and ICD-10 coding [11]. Another study reported a prevalence of clinically significant ILD of 14 % in 36 patients with recent onset RA, based on presence of abnormalities in imaging and/or pulmonary function tests and respiratory symptoms [7] Other studies have examined patients with longer RA disease duration and/or have based the (RA-)ILD diagnosis on abnormalities in imaging or pulmonary function tests and report a cross-sectional prevalence between 8.8 % and 58 % [5,7,21].

Within our study, patients from South Africa had the highest incidence of RA-ILD. Incidence and/or prevalence of RA-ILD previously has scarcely been reported in South Africa, and in the African continent in

Table 2
Patient characteristics at first available visit of patients with and without RA-ILD at first visit or during follow-up.

	Netherlands ($N = 1077$)			India ($N = 11,787$)			South Africa ($N = 629$)			Mexico ($N = 427$)			Colombia ($N = 2728$)		
	No RA-ILD ($n = 1056$)	RA-ILD ($n = 21$)	p value	No RA-ILD ($n = 11,703$)	RA-ILD ($n = 84$)	p value	No RA-ILD ($n = 610$)	RA-ILD ($n = 19$)	p value	No RA-ILD ($n = 418$)	RA-ILD ($n = 9$)	p value	No RA-ILD ($n = 2710$)	RA-ILD ($n = 18$)	p value
Age (years), mean (SD)	55.8 (14.5)	57.4 (9.2)	0.6	46.6 (15.3)	57.9 (10.6)	<0.001	50.5 (12.8)	52.8 (10.2)	0.42	52.7 (12.6)	62.1 (13.3)	0.027	59.1 (13.5)	61.2 (15.9)	0.5
RA symptom duration (months), median (IQR)	4.0 (1.9–7.8)	4.0 (1.6–8.0)	0.98	47.9 (18.0–95.9)	59.9 (23.9–143.9)	0.029	25.0 (8.3–58.4)	45.3 (13.1–92.5)	0.18	108.4 (49.3–206.8)	68.2 (46.7–159.6)	0.32	89.2 (38.1–181.0)	111.2 (67.6–140.6)	0.39
Time since diagnosis (months), median (IQR)				0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.53	0.0 (0.0–0.0)	4.6 (0.0–45.5)	<0.001	87.7 (38.6–174.4)	63.1 (42.4–125.7)	0.35	72.6 (24.0–162.0)	104.7 (65.6–127.6)	0.26
Sex (female), %	68	48	0.055	85	77	0.043	82	84	0.84	90	67	0.027	89	78	0.12
Body Mass Index (kg/m3), mean (SD)	26.2 (4.4)	26.3 (2.4)	0.93	*	*		29.1 (6.9)	28.1 (5.1)	0.58	28.2 (5.6)	27.8 (3.4)	0.82	26.1 (4.6)	25.2 (4.5)	0.44
Ever smoker, %	62	65	0.81	1	3	0.27	28	93	<0.001	13	11	0.89	*	*	
DAS, mean (SD)	2.7 (1.0)	3.0 (0.9)	0.35	3.7 (1.0)	*		3.1 (0.9)	*		*	*				
DAS28, mean (SD)	5.1 (1.3)	5.2 (0.7)	0.8	6.0 (1.4)	*		5.2 (1.4)	4.9 (0.9)	0.53	*	*		*	2.2 (1.9)	0
CDAI, mean (SD)	*	*		27.3 (14.6)	*		20.9 (16.2)	5.9 (11.4)	<0.001	*	*		8.9 (8.6)	6.7 (8.4)	0.27
ESR (mm/h), mean (SD)	32.0 (25.3)	44.3 (23.5)	0.027	76.7 (32.8)	91.5 (29.9)	<0.001	37.1 (28.8)	45.0 (22.8)	0.28	*	*		*	*	
CRP (mg/l), mean (SD)	22.2 (30.7)	28.5 (26.7)	0.35	36.3 (40.1)	51.1 (57.0)	0.001	26.4 (34.9)	*		*	*		*	*	
Patient global assessment (0–100 mm VAS), mean (SD)	41.1 (25.3)	31.5 (26.4)	0.11	53.8 (18.3)	*		60.1 (24.9)	42.6 (12.0)	0.004	44.6 (27.8)	27.8 (31.1)	0.075	30.8 (21.4)	22.2 (19.3)	0.09
Swollen 28 joint count, median (IQR)	6.0 (3.0–11.0)	5.5 (3.0–11.0)	0.64	3.0 (0.0–7.0)	2.0 (0.0–7.0)	0.6	5.0 (3.0–9.0)	4.0 (2.0–6.0)	0.15	*	1.0 (0.0–1.0)	0	0.0 (0.0–4.0)	0.0 (0.0–0.0)	0.13
ACPA (positive), %	54	62	0.45	81	94	0.011	96	83	0.008	*	*		*	*	
RF (positive), %	57	86	0.009	83	95	0.003	98	94	0.31	*	*		74	88	0.23
HAQ score (0–3), median (IQR)	1.0 (0.5–1.5)	0.9 (0.4–1.3)	0.69	0.9 (0.5–1.1)	0.9 (0.5–1.3)	0.25	1.5 (0.9–2.1)	*		0.8 (0.4–1.3)	1.0 (0.8–1.0)	0.84	*	*	

* <75 % data available

DAS = disease activity score, CDAI = clinical disease activity index, ESR = erythrocyte sedimentation rate, CRP = *C*-reactive protein, ACPA = anti-citrullinated protein antibody, RF = rheumatoid factor, HAQ = health assessment questionnaire.

general. In an older (1996) cross-sectional study, pulmonary abnormalities were described in patients with an RA disease duration of mean 12 years, with a prevalence of fibrosing alveolitis on X-ray (currently known as idiopathic pulmonary fibrosis) of 4.8 % and diffusion restrictions in 4.8 % of the patients [32] A study from Togo described that the X-rays of 5/28 (17.8 %) of the patients with RA showed signs of ILD [33] In Nigeria, ILD was diagnosed in 2.6 % of patients with RA of unknown disease duration [34] We found no data on the occurrence of RA-ILD in India, but in the neighbouring country Pakistan, a prevalence of ILD of 1.6 % was described in patients with RA of unknown disease duration [10] In Latin America, prevalence of RA-ILD was assessed in Brazil among patients with RA (disease duration mean 11–13 years) and an available chest CT, with 12 % diagnosed with ILD. All in all, the observation that the prevalence in our study was lower than in most previously reported studies can partially be explained by the fact that RA-ILD diagnoses in our study were based on RA-ILD as detected in clinical practice, and might also be explained by improvement of RA treatment strategies, although historical comparisons are difficult to make.

The slight differences in RA-ILD incidence between countries in our study might partially be explained by genetic factors. Several genetic risk factors for RA-ILD have been identified, of which the association with RA-ILD might also vary between people of different races [35,36] Environmental factors, such as differences in smoking habits, might also play a role [6] Also, differences in RA symptom duration between populations may affect RA-ILD incidence, but the RA-ILD incidence in the Indian patients was relatively low while symptom duration was relatively long. Differences in local diagnostic policies and data collection might also play a role.

Characteristics of patients with RA-ILD identified in our study corresponded with previous reports: patients with RA-ILD were more often men, ACPA and/or RF positive and more often (ever) smokers [6] RA symptom duration at baseline tended to be higher in RA-ILD patients in our study. A longer RA disease duration has been described in previous studies [37,38] Other reports also describe an older age of RA onset in RA-ILD patients, but we did not observe this [2,4].

We demonstrated an association between RA-ILD and subsequent RA disease activity but did not find an association between RA disease activity and the risk of developing RA-ILD, potentially because of the small sample size of RA-ILD patients and the limited follow-up duration. A study in American patients with median RA disease duration of 9 years did find an association between moderate/high disease activity and development of RA-ILD, compared to low disease activity/remission [39] With a multivariable prediction model, another study found an association between DAS28 and ILD, but this was assessed cross-sectionally [21] An association between ever having sustained high erythrocyte sedimentation rates (ESR) and ILD development was also described, although the timing of ESR measurement and ILD diagnosis was not defined [2] Another study also claimed to have found an association between RA disease activity and ILD, but this was based on an association between the health assessment questionnaire score (which is a measure for functional disability and not for RA disease activity) and decline in pulmonary function (without a formal diagnosis of ILD) [40].

The fact that we found an association between ILD and subsequent RA disease activity is probably also related to our finding that patients who developed ILD during follow-up were more difficult to treat (that is, the time to treatment response and remission was longer). Treating patients with RA-ILD can be challenging, because the RA and ILD may require simultaneous therapy and some anti-rheumatic treatments may increase the risk for pulmonary complications. Conflicting results have been published about the potential pulmonary toxicity of several DMARDs [18–20,41] However, we did not find considerable differences in prescribed treatment between patients with RA-ILD and matched patients without RA-ILD. It is also possible that RA disease activity (or elements of disease activity composite scores) responds less well to treatment if ILD is present.

Strengths of this study are the international data collection over five different continents with results reported in the same way for each country and the large number of included patients with RA. There are also several limitations that should be addressed. Although we tried to collect data in a standardized way by providing a data template and guidelines for patient selection, the heterogeneity of the data might partly be explained by differences in data collection and signs of RA-ILD diagnoses were not examined systematically over time. Chest (HR)CT was also not systematically performed with as a consequence a potential underestimation of RA-ILD, although reflecting the prevalence of RA-ILD as identified in clinical practice. Furthermore, local policies such as standard X-rays at the first visit, might impact the sensitivity for finding diagnoses of ILD. Also, per country only one or two hospitals were included, and we are unable to verify to what extent patient populations from the included centres are representative for the patient population in those countries. In METEOR, patients can be included at any timepoint in their RA disease course, so not all countries could be included in the incidence calculations and other analyses to limit immortal time bias. Not all centres had complete data available of all patient characteristics and RA disease activity during follow-up, but we have accounted for this using multiple imputation for missing data, and we adjusted the analyses for potential confounding. Nevertheless, residual confounding cannot be ruled out. Our analyses of the association between RA-ILD and disease activity/response to treatment were not adjusted for multiple testing. Follow-up duration was limited, and we cannot rule out that the results of the analyses would have been different with longer follow-up duration.

Conclusion

Despite these limitations, we conclude, based on a large number of patients with RA from five different continents, that the incidence and prevalence of RA-ILD as diagnosed in clinical practice is relatively low and varies slightly between countries across the world. We cannot rule out that this the differences observed are (partly) subject to differences in screening and reporting. Further studies to optimize the (timing and method of) diagnosis and treatment of patients with RA-ILD worldwide, with longer follow-up available, are needed.

CRediT authorship contribution statement

Sascha L Heckert: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Tjardo D Maarseveen:** Investigation, Resources, Writing – review & editing. **Emiel R Marges:** Investigation, Writing – review & editing. **Arvind Chopra:** Investigation, Resources, Writing – review & editing. **David Vega-Morales:** Investigation, Resources, Writing – review & editing. **Riette du Toit:** Investigation, Resources, Writing – review & editing. **Lai Ling Winchow:** Investigation, Resources, Writing – review & editing. **Nimmisha Govind:** Investigation, Resources, Writing – review & editing. **Carlos E Toro-Gutiérrez:** Investigation, Resources, Writing – review & editing. **Rachel Knevel:** Resources, Writing – review & editing. **Annette HM van der Helm–van Mil:** Resources, Writing – review & editing. **Tom WJ Huizinga:** Writing – review & editing. **Cornelia F Allaart:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing. **Sytske Anne Bergstra:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

S.A. Bergstra reports financial support was provided by Merit

Foundation. S.A. Bergstra reports a relationship with Pfizer that includes: funding grants. S.A. Bergstra reports a relationship with Benecke that includes: speaking and lecture fees. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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