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Interstitial lung patterns in patients with Reumathoid Arthritis.

Revisión sistemática

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Interstitial lung patterns in patients with Reumathoid Arthritis.

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DEDICATORIA

Dedico este trabajo a mis padres y hermanos por ser mi fortaleza y apoyo, por impulsarme a alcanzar mis metas, a ser mejor persona, por ser ejemplo de rectitud, entrega y perseverancia.

A mi tíos Pepe y Paco por ser otros padres, un ejemplo para mí, por guiarme y apoyarme en este camino.

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RESUMEN

ANTECEDENTES: La artritis reumatoide es una enfermedad autoinmune crónica y degenerativa, que afecta principalmente a mujeres mayores. Las manifestaciones son principalmente osteoarticulares; sin embargo, se han informado manifestaciones extraarticulares, incluidas cardiovasculares, cutáneas y pulmonares. Las manifestaciones pulmonares constituyen un desenlace significativo, que puede comprometer la esperanza de vida del paciente. OBJETIVO: Resumir los patrones intersticiales en pacientes con Artritis Reumatoide. MÉTODOS: Se realizó una revisión sistemática de la literatura. RESULTADOS: Se identificaron 72 artículos con predominio de población femenina. Encontramos enfermedad pulmonar intersticial en pacientes con diagnóstico de AR. Los patrones intersticiales más comunes fueron la neumonía intersticial habitual y la neumonía intersticial no específica, mientras que las manifestaciones menos frecuentes incluyeron bronquiectasias y derrame pleural. El diagnóstico de enfermedad pulmonar intersticial asociada a artritis reumatoidea se desarrolló entre los 8 meses y los 21,2 años. Algunos estudios informaron datos relevantes que incluyen factores de riesgo que predisponen a la asociación entre artritis reumatoide con enfermedad pulmonar intersticial incluido el tabaquismo, edad avanzada, anticuerpos antiproteína citrulinada positivos y el péptido citrulinado anticíclico alto.

Palabras clave: Artritis reumatoide, enfermedad pulmonar intersticial, neumonía intersticial habitual, neumonía intersticial inespecífica, neumonía organizada.

ABSTRACT

BACKGROUND: Rheumatoid arthtritis (RA) is a chronic and degenerative autoinmune disease, which mainly affects older women. Manifestations are mainly osteoarticular; however, extraarticular manifestations have been reported, including cardiovascular, cutaneous, and pulmonary. Pulmonary manifestations constitute a significant outcome, which can compromise patient life expentancy. OBJECTIVE: Summarise interstitial patterns in Rheumatoid Arthtritis patients. METHODS: Systematic literature review. RESULTS: 72 articles with prevailing femenine population were identified. We found interstitial lung disease in patients with RA diagnosis. The most common interstitial patterns were usual interstital pneumonia and nonspecific interstitial pneumonia, while the least frequent manifestations included bronchiectasis and pleural effusion. RA-associated interstitial lung disease diagnosis developed between 8 months and 21.2 years. Some studies reported relevant data including RA-ILD predisposing risk factors including smoking, being older, reporting positive anti-citrullinated protein antibodies, high anti-cyclic citrullinated peptide.

Key-words: Reumathoid arthritis, interstitial lung disease, usual interstitial pneumonia, nonspecific interstitial pneumonia, organizing pneumonia.

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INTRODUCTION

Rheumatoid arthritis is a chronic and degenerative autoimmune disease which affects approximately 1% of the general population, especially older women (Messina et al. 2020). Most frequent manifestations are osteoarticular and can limit quality of life (Leonel et al. 2012). There are up to a 40% of extra-articular manifestations including pulmonary, cardiovascular, cutaneous, ocular and hematological. Among these, lung involvement constitutes up to an 80% of the cases with interstitial affliction (O'Dwyer et al. 2013).

Interstitial lung disease is a group of pathologies that affect the lung interstitium with specific patterns and outcomes. Some of the main types of interstitial lung disease are usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), desquamative interstitial pneumonia (DIP), lymphoid interstitial pneumonia (LIP), acute interstitial pneumonia (AIP), and respiratory bronchiolitis associated interstitial lung disease (RB-ILD) (see Table 1 for ILD types characteristics in CT). (Mueller-Mang et al. 2007).

Interstitial lung diseases can asymptomatically affect patient morbidity and mortality. Hence, early diagnosis and detection of specific patterns is fundamental to promote treatment and avoid poor outcomes, especially on RA that compromises the immune system. To inform state of the art knowledge on interstitial patterns in RA, this study presents a systematic literature review of interstitial patterns and risk factors associated specifically in RA-susceptible patients.

Table #1. ILD types characteristics in computed tomography

Caption: This table describes the main CT characteristics of different ILD types

	Main findings	Distribution
UIP	• Reticulation • Honeycombing • Traction bronchiectasis • Architecture distortion	• Apicobasal gradient • Subpleural • Spatial and temporal heterogeneity
NSIP	• Ground glass opacities (GGO) • Reticulation • Micronodules • Microcystic honeycombing	• Subpleural or patchy. • Subpleural respect • Spatial and temporal homogeneity
OP	• Consolidations • Ground glass opacities	• Subpleural • Peribronchovascular
DIP	• Ground glass opacities • Reticulation • Cysts • Air trapping	• Subpleural • Apicobasal. • Smoker
LIP	• GGO • Lung cysts	• Peribronchovascular • Diffuse
AIP	• Consolidation/ GGO • Architecture distortion	• Diffuse • Lower lobes
RB-ILD	• Centrilobulillary nodules • GGO • Bronchial wall thickening	• Upper lobes • Diffuse

(Palmucci et al. 2014; Mueller-Mang et al. 2007)

METHODS

PRISMA guidelines for systematic reviews (Yepes-Nuñez et al. 2021; Hutton, Catalá-López, and Moher 2016) and the PICOS (Population, Intervention, Comparator, Outcomes and Study type) framework were taken into consideration to formulate the research question (Table 2). Medline (Table 3) and Scopus (Table 4) databases were employed for article identification with no restrictions placed on geography or publication date.

Table #2. PICOS framework

Caption: This table describes the systematic review's research question according to the PICOS framework

Item	Definition
Population	Rheumatoid arthritis patients
Interventions	Not applicable
Comparators	Not applicable
Outcomes	Interstitial lung patterns
Study Type	Observational and experimental studies, prospective and retrospective studies with eligible baseline outcomes

Exclusion criteria were stablished for title and abstract reviews (Table 5). Articles were further selected based on a full-text review. Additionally, random screening verification was made by a secondary reviewer. Information extraction for each selected article was organized in an Excel spreadsheet, which included parameters such as title, publication year, journal, DOI, type of study, country, total number of subjects, employed statistical tests, and interstitial patterns. GRADE system was employed for quality analysis of the articles (Aguayo-Albasini, Flores-Pastor, and Soria-Aledo 2014).

Table #3. Search terms PUBMED

Caption: This table reports the search terms used for the identification of relevant citations on PUBMED platform

SEARCH DATE: 23/02/2022		**PUBMED**	
Items	*#*	*Search terms*	*Number of citations*
Population_rheumatoid arthritis	#1	"Arthritis, Rheumatoid"[Mesh]	
	#2	Rheuma* [TIAB] AND arthriti*[TIAB]	
	#3	#1 OR #2	166.714
Population_interstitial lung disease	#4	"Lung Diseases, Interstitial"[Mesh] ((Parenchy*[TIAB] OR Interstiti*[TIAB] OR disease [TIAB] OR diseases[TIAB]) AND (lung[TIAB] OR lungs[TIAB] OR	
	#5	pneumon*[TIAB]))	
	#6	#4 OR #5	348.202
Population_total	#7	#3 AND #6	5,039
Outcomes_Tomographic findings	#8	"Tomography, X-Ray Computed"[Mesh] OR "Tomography"[Mesh] OR "Multidetector Computed Tomography"[Mesh]	
	#9	Tomograph* [TIAB]	
	#10	#8 OR #9	1.206.618
Total	#11	#7 AND #10	788

Table #4. Search terms Scopus

Caption: This table reports the search terms used for the identification of relevant citations on SCOPUS platform

SEARCH DATE: 23/02/2022		**SCOPUS**	
Items	*#*	*Search terms*	*Number of citations*
Population_rheumatoid arthritis	#1	TITLE-ABS-KEY (Rheuma* AND arthriti*)	
Population_interstitial lung disease	#2	TITLE-ABS-KEY ((Parenchy* OR Interstiti* OR diseases OR disease) AND (lung OR lungs OR pneumon*))	
Outcomes_Tomographic findings	#3	TITLE-ABS-KEY (Tomograph*)	
Total	#4	#1 AND #2 AND #3	2275

Table #5. Eligibility criteria

Caption: This table reports the eligibility criteria for the selection of citations during the screening and full-text review, organized by order and category

Order	Category	Exclusion criteria	Notes
1	Duplicates, not in the language of interest.	1.1 Duplicates	
		1.2 Not in the language of interest	
2	Nature of study	Not study type of interest	Literature review, case reports, meta-analysis, systematic review
3	Population Rheumatoid arthritis	Not/not only rheumatoid arthritis patient	
4	Population Interstitial Lung Disease	Not interstitial lung disease	
5	Outcomes Tomographic findings	Not including analyzed thoracic tomography of patients	
		No results without intervention	
6	Potential	Potential (no applicable exclusion criteria)	

RESULTS

With a search conducted on February 23, 72 out of 2518 articles (Table 6) were identified and deemed appropriate for this study. Details are summarized in the PRISMA diagram including title and abstract review, as well as the followed full text revision of the citations (Figure 1). All selected studies were observational (Tables 7-14) and mainly retrospective (50%) as seen in Alamoudi et al o Ekici et al. (Alamoudi and Attar 2017; Ekici et al. 2021). Asia (37%) and Europe (31%) represented the majority of the studies conducted worldwide (Figure 2). Publications showed a rising tendency between 1994 (Mcdonagh et al. 1994) and 2021 (Lee et al. 2021; Mena-Vázquez et al. 2021; Paulin et al. 2021). Figure 3 describes the publication year range of all the articles identified in this systemic review.

Table #6. Studies included in the systematic review.

Caption: This table shows the studies included in the systematic review: author, studie title, publication year, journal

Author	**Year**	**Study title**	**Journal**
Akira et al.	1999	Thin-section CT findings in rheumatoid arthritis-associated lung disease: CT patterns and their courses.	Journal of Computer Assisted Tomography
Alamoudi et al.	2017	Pleuropulmonary manifestation in patients with rheumatoid arthritis in Saudi Arabia.	Ann Thorac Med
Assayag et al.	2014	Rheumatoid arthritis-associated interstitial lung disease: radiologic identification of usual interstitial pneumonia pattern.	Radiology
Avouac et al.	2020	Improving risk-stratification of rheumatoid arthritis patients for interstitial lung disease.	Plos One
Biederer et al.	2004	Correlation between HRCT findings, pulmonary function tests and bronchoalveolar lavage cytology in interstitial lung disease associated with rheumatoid arthritis.	European Radiology
Bilgici et al.	2005	Pulmonary involvement in rheumatoid arthritis.	Rheumatology International
Bonilla et al.	2021	Prevalence and clinical characteristics of symptomatic diffuse interstitial lung disease in rheumatoid arthritis in a Spanish population.	Revista Clinica Española (Barcelona)
Castellanos-Moreira et al.	2020	Anti-carbamylated proteins antibody repertoire in rheumatoid arthritis: evidence of a new autoantibody linked to interstitial lung disease.	Annals of Rheumathic Diseases
Chen el al.	2013	Asymptomatic preclinical rheumatoid arthritis-associated interstitial lung disease.	Clinical and Developmental Immunology
Chen et al.	2021	Distinctive Clinical Characteristics and Outcome of ILD-Onset Rheumatoid Arthritis and ACPA-Positive ILD: a Longitudinal Cohort of 282 Cases.	Clinical Reviews in Allergy and Immunology
Demir et al.	1999	High resolution computed tomography of the lungs in patients with rheumatoid arthritis.	Rheumatology International

Author	Year	Study title	Journal
Doyle et al.	2015	Detection of Rheumatoid Arthritis-Interstitial Lung Disease Is Enhanced by Serum Biomarkers.	American Journal of Respiratory and Critical Care Medicine
Duarte et al.	2019	The lung in a cohort of rheumatoid arthritis patients-an overview of different types of involvement and treatment.	Rheumatology (Oxford)
Ekici et al.	2021	Predictors of mortality in rheumatoid arthritis-associated lung disease: A retrospective study on ten years.	Joint Bone Spine
Medhat et al.	2021	Predictors of airway and parenchymal lung abnormalities in patients with rheumatoid arthritis.	Egyptian Rheumatologist
Eser et al.	2012	Extraarticular manifestations in Turkish patients with rheumatoid arthritis: Impact of EAMs on the health-related quality of life in terms of disease activity, functional status, severity of pain, and social and emotional functioning.	Rheumatology International
Fadda et al.	2018	Interstitial lung disease in Egyptian patients with rheumatoid arthritis: Frequency, pattern and correlation with clinical manifestations and anti-citrullinated peptide antibodies level	Egyptian Rheumatologist
Gabbay et al.	1997	Interstitial lung disease in recent onset rheumatoid arthritis.	American Journal of Respiratory and Critical Care Medicine
Gautam et al.	2020	Rheumatoid Arthritis Related Interstitial Lung Disease: Patterns of High-resolution Computed Tomography.	Cureus
Giles et al.	2014	Association of cross-reactive antibodies targeting peptidyl-arginine deiminase 3 and 4 with rheumatoid arthritis-associated interstitial lung disease	PLoS One
Gochuico et al.	2008	Progressive preclinical interstitial lung disease in rheumatoid arthritis.	Arch Intern Med
Habib et al.	2011	Pulmonary involvement in early rheumatoid arthritis patients.	Clinical Rheumatology

Author	Year	Study title	Journal
Hanaka et al.	2019	Radiological patterns of pulmonary involvement may predict treatment response in rheumatoid arthritis: A retrospective study.	Respir Investig
Hassan et al.	1995	High resolution computed tomography of the lung in lifelong non-smoking patients with rheumatoid arthritis.	Annals of Rheumathic Diseases
Huang et al.	2020	Rheumatoid arthritis-related lung disease detected on clinical chest computed tomography imaging: Prevalence, risk factors, and impact on mortality.	Seminars in Arthritis Rheumatism
Ito et al.	2019	Radiological fibrosis score is strongly associated with worse survival in rheumatoid arthritis-related interstitial lung disease	Modern Rheumatol
Kakutani et al.	2020	Related factors, increased mortality and causes of death in patients with rheumatoid arthritis-associated interstitial lung disease.	Modern Rheumatol
Kanat et al.	2007	Radiological and functional assessment of pulmonary involvement in the rheumatoid arthritis patients.	Rheumatology International
Kawano-Dourado et al.	2020	Baseline Characteristics and Progression of a Spectrum of Interstitial Lung Abnormalities and Disease in Rheumatoid Arthritis.	Chest
Kelly et al.	2014	Rheumatoid arthritis-related interstitial lung disease: associations, prognostic factors and physiological and radiological characteristics--a large multicentre UK study.	Rheumatology (Oxford)
Kim et al.	2017	Impact of interstitial lung disease on mortality of patients with rheumatoid arthritis.	Rheumatology International
Kim et al.	2010	Usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease.	European Respiratory Journal
Kim et al.	2020	Prognostic role of blood KL-6 in rheumatoid arthritis-associated interstitial lung disease.	PLoS One
Kim et al.	2020	Risk prediction model in rheumatoid arthritis-associated interstitial lung disease.	Respirology

Author	Year	Study title	Journal
Kinoshita et al.	2004	Role of KL-6 in evaluating the disease severity of rheumatoid lung disease: comparison with HRCT.	Respiratory Medicine
Lee et al.	2005	Histopathologic pattern and clinical features of rheumatoid arthritis-associated interstitial lung disease.	Chest
Lee et al.	2021	The Extent and Diverse Trajectories of Longitudinal Changes in Rheumatoid Arthritis Interstitial Lung Diseases Using Quantitative HRCT Scores.	Journal of Clinical medicine
Leone et al.	2020	Interstitial lung abnormalities a risk factor for rheumatoid arthritis interstitial lung disease progression: What's new.	Breathe
Leonel et al.	2012	Pulmonary function test: its correlation with pulmonary high-resolution computed tomography in patients with rheumatoid arthritis.	Rheumatology International
Li et al.	2019	A preliminary study of lung abnormalities on HRCT in patients of rheumatoid arthritis-associated interstitial lung disease with progressive fibrosis.	Clinical Rheumatology
Marten et al.	2009	Computer-assisted quantification of interstitial lung disease associated with rheumatoid arthritis: Preliminary technical validation.	European Journal of Radiology
McDonagh et al.	1994	High resolution computed tomography of the lungs in patients with rheumatoid arthritis and interstitial lung disease.	The British Journal of Rheumatology
McFarlane et a.	2019	Assessment of interstitial lung disease among black rheumatoid arthritis patients.	Clinical Rheumatology
Mena-Vázquez	2021	Predictors of Progression and Mortality in Patients with Prevalent Rheumatoid Arthritis and Interstitial Lung Disease: A Prospective Cohort Study.	Journal of Clinical medicine
Mohd Noor	2009	Clinical and high resolution computed tomography characteristics of patients with rheumatoid arthritis lung disease.	International Journal of Rheumathic Diseases

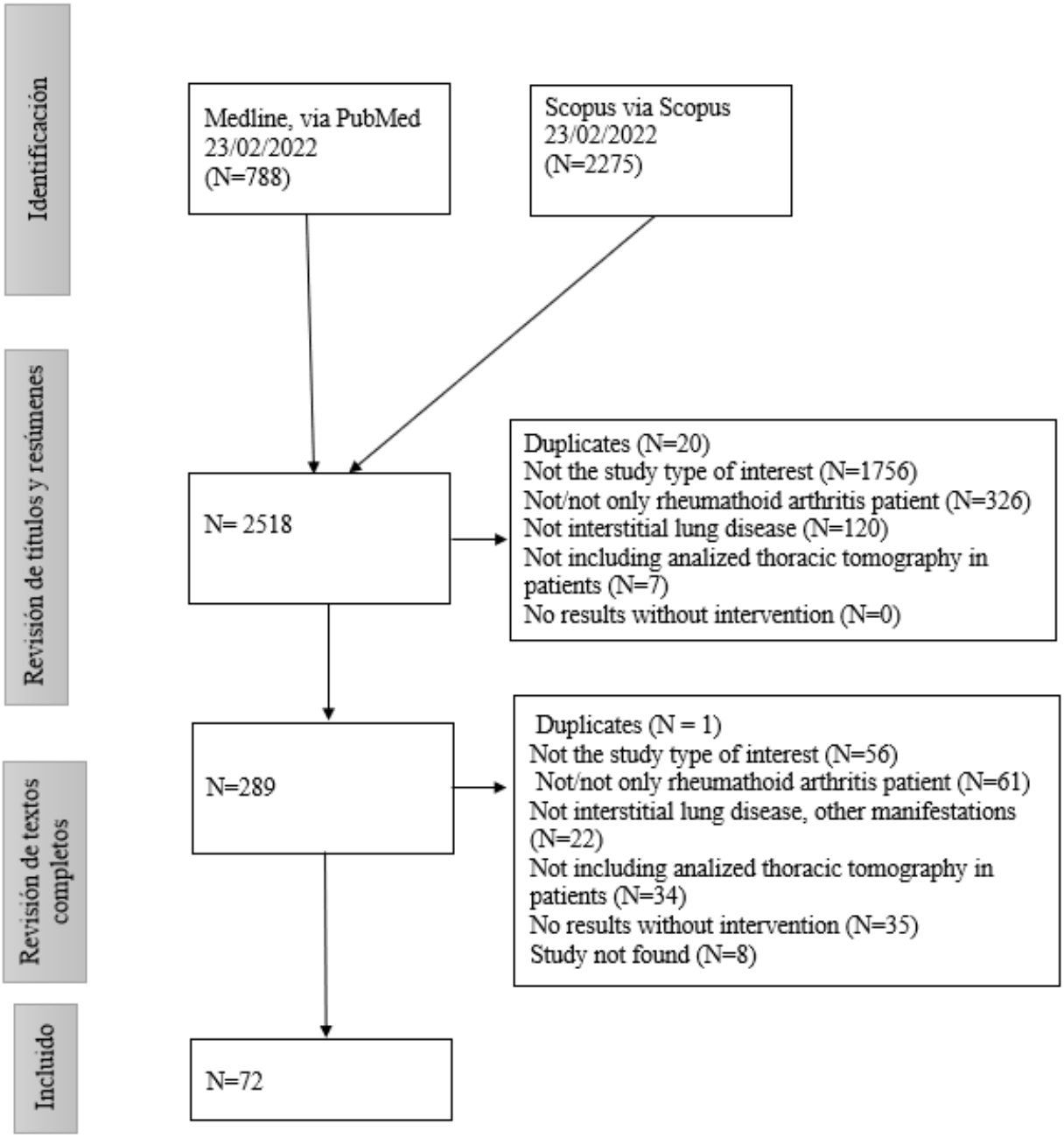
Author	Year	Study title	Journal
Mori et al.	2008	Comparison of pulmonary abnormalities on high-resolution computed tomography in patients with early versus longstanding rheumatoid arthritis.	Journal of Rheumatology
Morisset et al.	2017	The performance of the GAP model in patients with rheumatoid arthritis associated interstitial lung disease.	Respiratory Medicine
Nurmi et al.	2018	Several high-resolution computed tomography findings associate with survival and clinical features in rheumatoid arthritis-associated interstitial lung disease.	Respiratory Medicine
Nurmi et al.	2016	Variable course of disease of rheumatoid arthritis-associated usual interstitial pneumonia compared to other subtypes.	BMC Pulmonary Medicine
Okada et al.	2016	Clinical features of organizing pneumonia associated with rheumatoid arthritis.	Modern Rheumatology
Paulin et al.	2021	Development of a risk indicator score for the identification of interstitial lung disease in patients with rheumatoid arthritis.	Reumatologia Clinica
Paulin et al.	2018	Correlation between Lung and Joint Involvement in Patients with Rheumatoid Arthritis and Interstitial Lung Disease: A Cross-Sectional Study.	Revista de Investigación Clinica
Pérez-Dórame et al.	2015	Rheumatoid arthritis-associated interstitial lung disease: lung inflammation evaluated with high resolution computed tomography scan is correlated to rheumatoid arthritis disease activity.	Reumatologia Clinica
Remy-Jardin et al.	1994	Lung changes in rheumatoid arthritis: CT findings.	Radiology
A. Robles-Perez et al.	2016	Preclinical lung disease in early rheumatoid arthritis.	Chronic Respiratory Disease
Salaffi et al.	2019	High-resolution computed tomography of the lung in patients with rheumatoid arthritis: Prevalence of interstitial lung disease involvement and determinants of abnormalities.	Medicine (Baltimore)

Author	Year	Study title	Journal
Samy et al.	2021	Rheumatoid arthritis patients with interstitial lung disease: Clinical, radiological and laboratory characteristics.	Egyptian Rheumatologist
Saracoglu et al.	2005	Relationship between high-resolution computed tomography findings and the Stoke index in patients with rheumatoid arthritis.	Clinical Rheumatology
Solomon et al.	2016	Predictors of mortality in rheumatoid arthritis-associated interstitial lung disease.	European Respiratory Journal
Song et al.	2016	Association of Single Nucleotide Polymorphisms of PADI4 and HLA-DRB1 Alleles with Susceptibility to Rheumatoid Arthritis-Related Lung Diseases.	Lung
Sparks et al.	2019	Rheumatoid Arthritis Disease Activity Predicting Incident Clinically Apparent Rheumatoid Arthritis-Associated Interstitial Lung Disease: A Prospective Cohort Study.	Arthritis and Rheumatology
Tanaka et al.	2004	Rheumatoid arthritis-related lung diseases: CT findings.	Radiology
Wang et al.	2015	A retrospective study of clinical characteristics of interstitial lung disease associated with rheumatoid arthritis in Chinese patients.	Medical Science Monitor
Yamakawa et al.	2020	Impact of radiological honeycombing in rheumatoid arthritis-associated interstitial lung disease.	BMC Pulmonary Medicine
Yamakawa et al.	2019	Predictive factors of mortality in rheumatoid arthritis-associated interstitial lung disease analysed by modified HRCT classification of idiopathic pulmonary fibrosis according to the 2018 ATS/ERS/JRS/ALAT criteria.	Journal of Thoracic Disease
Yang et al.	2019	Clinical characteristics associated with occurrence and poor prognosis of interstitial lung disease in rheumatoid arthritis.	The Korean Journal of Internal Medicine
Yuksekkaya et al.	2013	Pulmonary involvement in rheumatoid arthritis: multidetector computed tomography findings.	Acta Radiologica
Yunt et al.	2017	High resolution computed tomography pattern of usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease: Relationship to survival.	Respiratory Medicine

Author	**Year**	**Study title**	**Journal**
Zamora-Legoff et al.	2017	Patterns of interstitial lung disease and mortality in rheumatoid arthritis.	Rheumatology (Oxford)
Zayeni et al.	2016	Pulmonary involvement in rheumatoid arthritis: A cross-sectional study in Iran.	Lung India
Zhang et al.	2017	Retrospective study of the clinical characteristics and risk factors of rheumatoid arthritis-associated interstitial lung disease.	Clinical Rheumatology
Zrour et al.	2005	Correlations between high-resolution computed tomography of the chest and clinical function in patients with rheumatoid arthritis. Prospective study in 75 patients.	Joint Bone Spine

*CT: Computed tomography, HRCT: High resolution computed tomography, ACPA: Anticitrullinated protein antibodies, ILD: interstitial lung disease, EAMs: extraarticular manifestations, UK: United Kingdom, KL-6: Krebs von den Lungen-6 glycoprotein, PADI4: Isoform 4 of the human peptylarginine deiminase. ATS: American Thoracic Society, ERS: European Respiratory Society,JRS: Japanese Respiratory Society, ALAT: Latin American Thoracic Society.

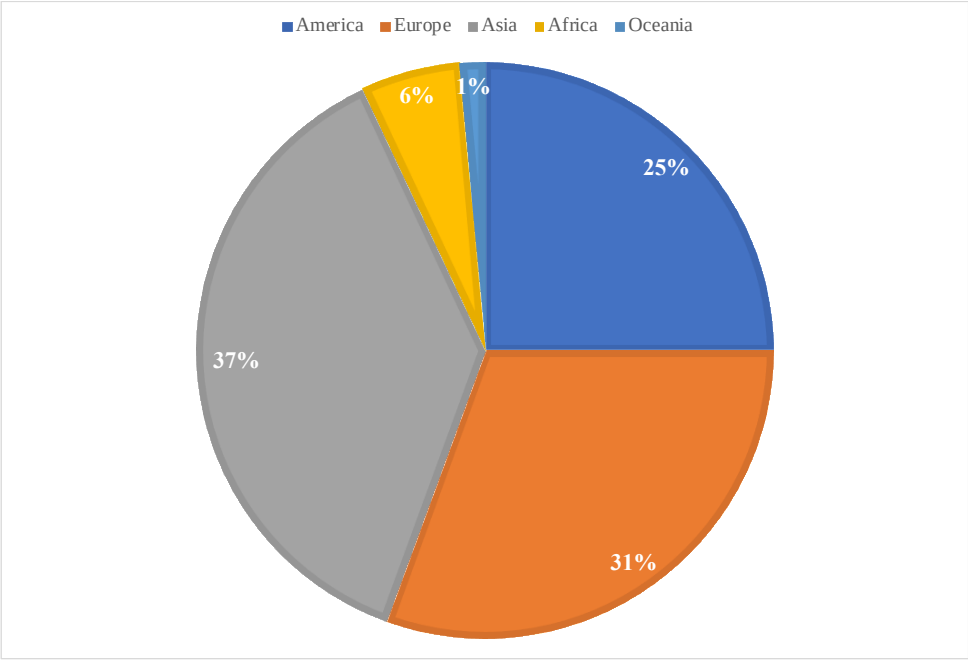
Figure #1. PRISMA Diagram



In 62 of the 72 identified articles in this review the majority of patients were women. Ages ranged between 21 (Gochuico et al., n.d.) and 72 (Ito et al. 2019). The most representative samples of RA patients included 3555 (Kim et al. 2017), 2729 (Bonilla Hernán et al. 2021) , 2702 (Kakutani et al. 2020), 1419 (2108) and 1129 patients (Duarte, Porter, and Leandro 2019). All reported data presented valid statistical tests with p values (p=<0.05). Average time of RA before interstitial disease associated diagnosis ranged between 8 months (patient average age: 48 $\pm$ 14 years) and 21.2 years (patient average age: 64.2 $\pm$ 11.8 years). In 12 studies less than 25% of patients presented ILD, in 18 studies percentages of ILD-diagnosis ranged between 25 and 75%, and in 13 studies RA-ILD patients exceeded 75%. The lowest ILD percentages were 3.8% (Okada et al. 2016), 5% (Hassan et al. 1995) and 6.3% (McFarlane et al. 2019). The most frequent interstitial patterns were UIP (41 articles), NSIP (29 articles), OP (14 articles). In addition, least frequent outcomes including bronchiectasis, pleural effusion, and RA-associated interstitial lung anomaly (ILA) were reported (Kawano-Dourado et al. 2020) (figure 4).

Figure #2. Percentage of continents according to the studies

Caption: This figure reports the percentage of continents that participate in the systematic review according to the studies included



Some studies reported relevant data including RA-ILD predisposing risk factors including smoking (Assayag et al. 2014; Bonilla Hernán et al. 2021; Duarte, Porter, and Leandro 2019; Gabbay et al. 1997; Gochuico et al., n.d.; Salaffi et al. 2019), being males (Huang et al. 2020; Kawano-Dourado et al. 2020; Kelly et al. 2014; Paulin et al. 2021), being older (Kim et al. 2017; Yang et al. 2019), reporting positive ACPAs (Avouac et al. 2020; Chen et al. 2021; Fadda et al. 2018), positive rheumatoid factor (RF) (Chen et al. 2021; Samy, Salah, and Hammoda 2021), reporting high anti-cyclic citrullinated peptide (anti-CCP) (Bonilla Hernán et al. 2021; Elemary et al. 2021),with the latter reported as the strongest predictor (Kelly et al. 2014), and erythrocyte sedimentation rate (ESR) > 80 mm/h (Yang et al. 2019).

Wang and Du (Wang and Du 2015) reported hepatitis B surface antigen (HbsAg) presence as a risk factor (OR=2.56, 95%). Additionally, Elemary et al. (Elemary et al. 2021) reported the presence of anomalies in pulmonary function tests as risk factors. 68% of patients with molecular factors such as Isoform 4 of the human peptylarginine deiminase (anti-PAD4) developed ILD in contrast with 29% without anti-PAD4. Smokers presented enhanced suceptibility (93%) versus non-smokers (71%) (Giles et al. 2014) due to elevated platelet derived growth factor AB (Gochuico et al., n.d.). In addition, RA-ILD sucetibility was associated to the 9th position of tryptophane in the HLA-DRB1 sequence (OR=22.89, CI 95%, p=0.037) (Song et al. 2016).

Figure #3. Studies according to years covered by data

Caption: This figure represents the data time frame reported in each study

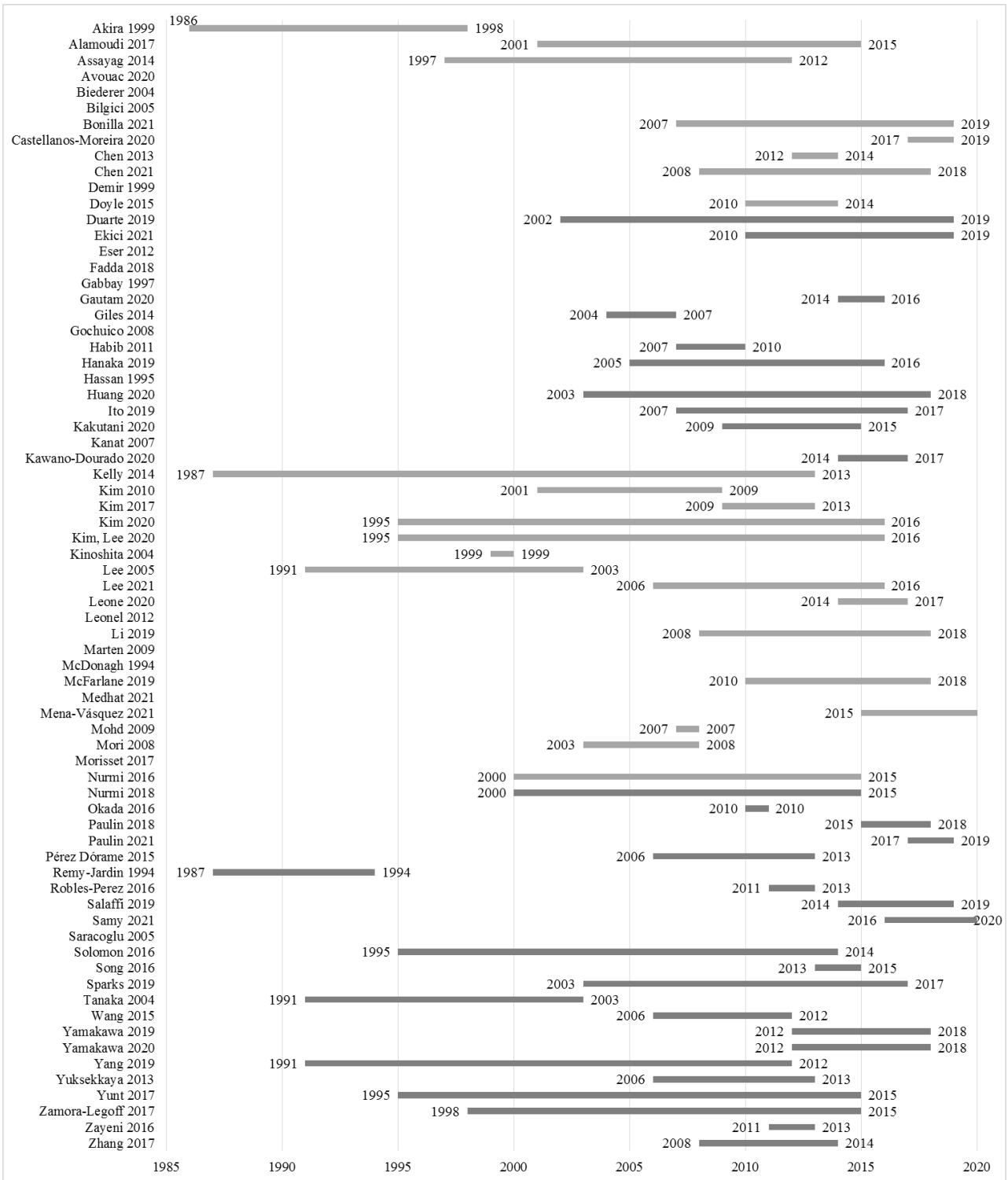
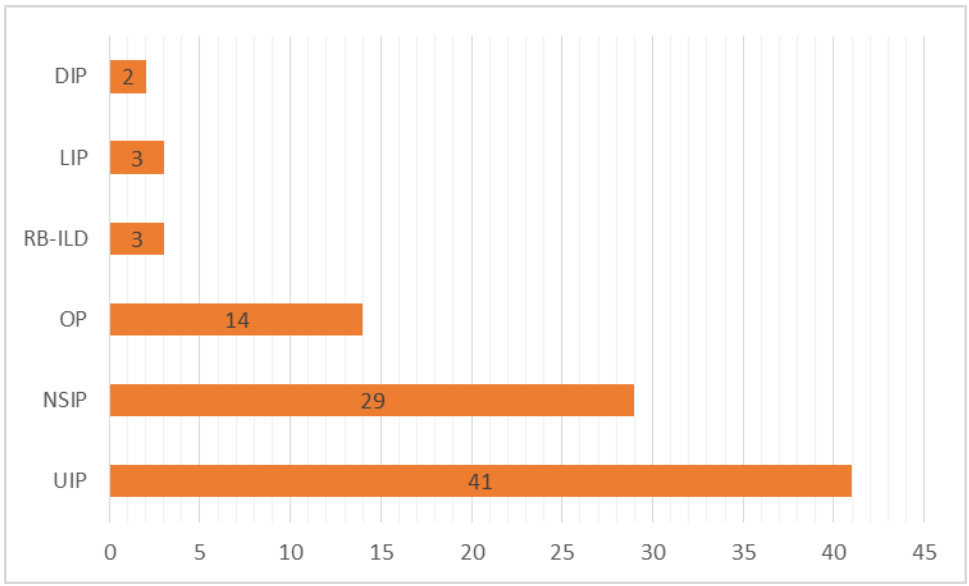


Figure #4. Types of ILD in RA patients
Caption: This figure reports the number of articles with different ILDs



Anti-carbamylated protein antibodies (anti-CarP) were more suceptible on RA-ILD patients than RA patients with no ILD (70%) (Castellanos-Moreira et al. 2020). ILD progression associated factors were: lung epithelial'derived surfactant protein D (SPD) rising levels, chemokine CCL18 and Krebs von den Lungen-6 glycoprotein (KL-6) (sensibility: 68-77%, specificity: 83-97%) (Avouac et al. 2020), use of metrotrexate (Gochuico et al., n.d.; Huang et al. 2020), sub-pleural distribution (Kawano-Dourado et al. 2020), UIP (Kelly et al. 2014), forced vital capacity (FVC) < 80%, anti-CCP, and tobacco (Mena-Vázquez et al. 2021). Some studies employed survival curves to associate mortality to ILD presence. (Ekici et al. 2021) They obtained an average survival of 5 years (78%), while Yamakawa et al. of 3.2 years (Yamakawa et al. 2019).

Table #7. Data extraction table- Country and objectives

Caption: This table shows the data extraction about country made and objectives from all the studies included in the systematic review

Author	Year	Country	Objective
Akira et al.	1999	Japan	Describe long term follow up CT evaluation in RA-ILD.
Alamoudi et al.	2017	Saudi Arabia	Determine the prevalence of pleuropulmonary manifestations and to identify the associated risk factors.
Assayag et al.	2014	USA	To determine the accuracy of CT in identifying the histopathologic UIP pattern in RA-ILD
Avouac et al.	2020	France, Japan, Switzerland	To determine the performance of 3 circulating markers for the diagnosis and progression of RA-ILD.
Biederer et al.	2004	Germany	NR
Bilgici et al.	2005	Turkey	To assess the relationships between clinical characteristics, lung involvement, frecuency of pulmonary involvement in RA.
Bonilla et al.	2021	Spain	Prevalence of symptomatic ILD in RA and its characterstics in our area.
Castellanos-Moreira et al.	2020	Spain	Analize association between Anti-CarP and ILD in RA patients
Chen el al.	2013	China	Define HRCT and pulmonary function test abnormalities capable of identifying asymptomatic, preclinical forms of RA-ILD that may represent precursors to more severe fibrotic lung disease.
Chen et al.	2021	China	To invetsigate the clinical features and outcome of RA-ILD and ACPA positive ILD only patients.
Demir et al.	1999	Turkey	To assess pulmonary involvement with HRCT in lifelong non-smoking patients with RA.
Doyle et al.	2015	USA	To identify clinical risk factors, autoantibodies, and biomarkers associated with the presence of RA-ILD.

Author	Year	Country	Objective
Duarte et al.	2019	UK	To characterize the different types of lung disease and response to treatment in a UK cohort of RA patients.
Ekici et al.	2021	Turkey	To evaluate mortality rate and mortality-associated factors in RA patients with HRCT proven lung involvement
Medhat et al.	2021	Egypt	To investigate the frecuency and types of pulmonary involvement using HRCT and pulmonary function tests and to identify different disease parameters as predictors of lung involvement.
Eser et al.	2012	Turkey	To investigate extraarticular manifestations in Turkish patients with RA.
Fadda et al.	2018	Egypt	To determine the frecuency and pattern of ILD among RA patients, correlate it with clinical manifestations and ACPA.
Gabbay et al.	1997	Australia	To determine the prevalence of RA-ILD using a number of sensitive techniques in patients with joint disease of less than 2 years duration.
Gautam et al.	2020	Pakistan	To evaluate HRCT findings in patients of RA related ILD and categorize the radiological findings according to clinical findings.
Giles et al.	2014	USA	NR
Gochuico et al.	2008	USA	To identify asymptomatic lung disease and potential therapeutic targets in patients having RA and preclinical ILD.
Habib et al.	2011	Saudi Arabia	To disclose the pulmonary involvement in early RA patients not more than 2 years disease duration using the computed tomography (CT) as well as the pulmonary function tests as ways of pulmonary involvement assessment.
Hanaka et al.	2019	Japan	relationship between lung radiological patterns and rheumatoid arthritis (RA) disease activity or RA treatment response in patients with RA-associated lung disease (RA-LD).
Hassan et al.	1995	UK	To define pulmonary involvement on HRCT. In life-long non smoking RA, and to relate the results to pulmonary function, bronchial reactivity and serological factors.
Huang et al.	2020	USA	to determine the real-world prevalence and investigate risk factors for rheumatoid arthritis (RA)-related lung disease on chest computed tomography (CT) imaging.
Ito et al.	2019	Japan	Identify CT patterns and patient characteristics that can predict poor prognosis in RA-ILD.
Kakutani et al.	2020	Japan	To clarify the relationship between chronic ILD with a pattern of UIP or non-UIP and mortality in RA patients

Author	Year	Country	Objective
Kanat et al.	2007	Turkey	Evaluate findings of HRCT and PFT in RA and their role in prediction of respiratory system involvement.
Kawano-Dourado et al.	2020	Brazil	What are baseline characteristics associated with RA-ILD progression?
Kelly et al.	2014	UK	to examine predictive and prognostic factors for the development of RA-ILD and to report on the physiological and radiological characteristics of the condition from a large multicentre UK network
Kim et al.	2017	Korea	To identify the prevalence of interstitial lung disease (ILD) in Korean patients with rheumatoid arthritis (RA) and assess its effect on mortality
Kim et al.	2010	USA	To determine whether or not the usual interstitial pneumonia pattern found on high-resolution computed tomography (HRCT) is of prognostic significance in rheumatoid arthritis-associated interstitial lung disease (RA-ILD).
Kim et al.	2020	Korea	to investigate the prognostic value of Krebs von den Lungen-6 (KL-6) levels in RA-ILD patients.
Kim et al.	2020	Korea	Prognosis
Kinoshita et al.	2004	Japan	To determine the role of KL-6 (Krebs von den Lungen-6) in evaluating the disease severity of pulmonary lesions in rheumatoid arthritis (RA) compared with high resolution computed tomography (HRCT) findings.
Lee et al.	2005	Korea	To investigate the histopathologic pattern and clinical features of patients with rheumatoid arthritis (RA)-associated interstitial lung disease (ILD) according to the American Thoracic Society/European Respiratory Society consensus classification of idiopathic interstitial pneumonia.
Lee et al.	2021	South Korea	to validate quantitative high-resolution computed tomography (HRCT) imaging analyses of interstitial lung disease (ILD) in rheumatoid arthritis (RA) patients, and to delineate a broad spectrum of annual longitudinal changes of ILD severity in the RA-ILD cohorts.
Leone et al.	2020	NR	RA-ILA trying to measure its prevalence and determine the risk factors for its progression.
Leonel et al.	2012	Mexico	Try to evaluate lung aVection and to correlate an easier and cheaper method with the high-resolution computed tomography (HRCT) Wndings in patients with RA.

Author	Year	Country	Objective
Li et al.	2019	China	Evaluates lung abnormalities on high-resolution CT (HRCT) and clarifies which abnormality can predict the progressive fibrosis of rheumatoid arthritis (RA)–associated interstitial lung disease
Marten et al.	2009	Germany	To validate a threshold-based prototype software application (MeVis PULMO 3D) for quantification of chronic interstitial lung disease (ILD) in patients with rheumatoid arthritis (RA) using variable threshold settings for segmentation of diseased lung areas.
McDonagh et al.	1994	UK	NR
McFarlane et a.	2019	USA	RA-ILD among Blacks is predominantly a disease of elderly females with higher rates of GERD and CVD risk factors.
Mena-Vázquez	2021	Spain	Eighteen patients (15.5%) died, with a mean survival of 71.8 (1.9) months after diagnosis of ILD.
Mohd Noor	2009	Malaysia	to determine the characteristics of RA patients with lung disease in relation to clinical characteristics, pulmonary function test (PFT) and high-resolution computed tomography (HRCT) thorax.
Mori et al.	2008	Japan	To identify the predominant radiological abnormalities in the lungs of patients with early rheumatoid arthritis (RA) and in those with longstanding RA.
Morisset et al.	2017	USA, Korea, Italy	NR

Author	Year	Country	Objective
Nurmi et al.	2018	Finland	To compare the presence and extent of several high-resolution computed tomography (HRCT) ob- servations in different subtypes of rheumatoid arthritis-related interstitial lung disease (RA-ILD) and to examine associations between radiological findings, hospitalization, age, RA duration, pulmonary function tests (PFT) and survival.
Nurmi et al.	2016	Finland	to compare the disease course of patients with RA-ILD categorized into either UIP or other types of ILDs.
Okada et al.	2016	Japan	To clarify the clinical features of organizing pneumonia (OP) associated with rheumatoid arthritis (RA) and to determine whether development of OP is related to RA activity.
Paulin et al.	2021	Argentina	o discern which factors are associated with the presence of ILD in RA patients and to develop a score that could help to stratify the risk of having ILD in RA patients
Paulin et al.	2018	USA	To evaluate the relationship between lung and joint involvement in RA ILD.
Pérez-Dórame et al.	2015	Mexico	To describe the association between rheumatoid arthritis disease activity (RA) and interstitial lung damage (inflammation and fibrosis), in a group of patients with rheumatoid arthritis-associated interstitial lung disease (RA-ILD).
Remy-Jardin et al.	1994	France	To evaluate lung changes in RA
A. Robles-Perez et al.	2016	Spain	To investigate the frequency of asymptomatic lung abnormalities in early RA patients and the potential association of positive RA blood reactive biomolecules with lung involvement.

Author	Year	Country	Objective
Salaffi et al.	2019	Italy	to evaluate: the prevalence of ILD involvement in RA over high-resolution computed tomography (HRCT); the relationships between pulmonary function tests (PFTs), patient-centered measurements, and ILD; and the potential risk factors contributing to RA-ILD patients.
Samy et al.	2021	Egypt	To analyze clinical, radiological and laboratory characteristics of RA-ILD in an Egyptian cohort.
Saracoglu et al.	2005	Turkey	to evaluate the relationship between high-resolution computed tomog- raphy (HRCT) findings and the Stoke index (SI) in pa- tients with rheumatoid arthritis (RA).
Solomon et al.	2016	USA	NR
Song et al.	2016	South Korea	to investigate whether the single nucleotide polymorphisms (SNPs) of PADI4 and HLA-DRB1 alleles were associated with RA-LD.
Sparks et al.	2019	USA	To evaluate rheumatoid arthritis (RA) disease activity and risk for RA-associated
Tanaka et al.	2004	USA	To evaluate computed tomographic (CT) findings of rheumatoid arthritis–related lung disease and categorize findings according to pathologic features
Wang et al.	2015	China	to assess the characteristics of ILD that are associated with RA
Yamakawa et al.	2020	Japan	NR
Yamakawa et al.	2019	Japan	To elucidate prognosis by using our modified HRCT pattern classification according to the latest guideline on idiopathic pulmonary fibrosis (IPF).

Author	Year	Country	Objective
Yang et al.	2019	South Korea	To analyze clinical characteristics of interstitial lung disease (ILD) associated with rheumatoid arthritis (RA), especially in patients with poor prognosis.
Yuksekkaya et al.	2013	Turkey	To evaluate the MDCT pulmonary findings of patients with RA and to compare these findings with the clinical status.
Yunt et al.	2017	USA	We sought to examine the prognostic value of the high-resolution computed tomography (HRCT) patterns in patients with RA-ILD.
Zamora-Legoff et al.	2017	USA	To characterize a cohort of patients with RA who have interstitial lung disease (ILD) and to assess the utility of previously developed mortality staging systems [gender, age, lung physiology (GAP) and ILD-GAP].
Zayeni et al.	2016	Iran	NR
Zhang et al.	2017	China	to explore the clinical characteris- tics and risk factors of rheumatoid arthritis (RA)-associated interstitial lung disease (ILD).
Zrour et al.	2005	Tunisia	To define the usefulness of high-resolution CT (HRCT) in evaluating lung abnormalities in unselected patients with rheu- matoid arthritis (RA) and to determine whether HRCT findings were correlated with clinical and lung function test (LFT) abnormalities.

* CT: Computed tomography, HRCT: High resolution computed tomography, ACPA: Anticitrullinated protein antibodies, ILD: interstitial lung disease, UK: United Kingdom, RA: reumathoid arthritis, ILD: Interstitial lung disease, RA-ILD: Reumathoid arthritis associated interstitial lung disease, USA: United States of America, Anti-CarP: CarP antibody, OP: organizing pneumonia, UIP: Usual interstitial pneumonia, IPF: idiopathic pulmonary fibrosis, PADI4: Isoform 4 of the human peptylarginine deiminase, SI: Stoke index, SNPs: single nucleotide polymorphisms, PFT: Pulmonary function test, GERD: gastroesophageal reflux disease, CVD: cardiovascular disease, GAP: gender, age, lung physiology. NR: not reported, LFT: lung function test.

Table #8. Data extraction table- Study types

Caption: This table shows the data extraction about study types from all the studies included in the systematic review

Author	Year	Study types		
		1. Observational 2. Experimental	**1. Prospective. 2.Retrospective. 3. Does not apply 4.Does not specify**	**1. Cross sectional 2. Cohort 3. Case-controls 4. Pilot study - Observational 5. Other Observational study. 6. Does not apply 7.Does not specify**
Akira et al.	1999	1. Observational	2. Retrospective	7. Does not specify
Alamoudi et al.	2017	1. Observational	2. Retrospective	7. Does not specify
Assayag et al.	2014	1. Observational	1. Prospective	2. Cohort
Avouac et al.	2020	1. Observational	2. Retrospective	7. Does not specify
Biederer et al.	2004	1. Observational	1. Prospective	7. Does not specify
Bilgici et al.	2005	1. Observational	4. Does not specify	5. Other observational study
Bonilla et al.	2021	1. Observational	1. Prospective	7. Does not specify
Castellanos-Moreira et al.	2020	1. Observational	4. Does not specify	1. Cross sectional
Chen el al.	2013	1. Observational	2. Retrospective	7. Does not specify
Chen et al.	2021	1. Observational	1. Prospective	7. Does not specify
Demir et al.	1999	1. Observational	1. Prospective	7. Does not specify
Doyle et al.	2015	1. Observational	1. Prospective	2. Cohort
Duarte et al.	2019	1. Observational	2. Retrospective	7. Does not specify
Ekici et al.	2021	1. Observational	2. Retrospective	7. Does not specify
Medhat et al.	2021	1. Observational	4. Does not specify	1. Cross sectional
Eser et al.	2012	1. Observational	4. Does not specify	7. Does not specify
Fadda et al.	2018	1. Observational	4. Does not specify	1. Cross sectional
Gabbay et al.	1997	1. Observational	4. Does not specify	7. Does not specify
Gautam et al.	2020	1. Observational	1. Prospective	7. Does not specify
Giles et al.	2014	1. Observational	1. Prospective	2. Cohort
Gochuico et al.	2008	1. Observational	1. Prospective	7. Does not specify
Habib et al.	2011	1. Observational	2. Retrospective	7. Does not specify
Hanaka et al.	2019	1. Observational	2. Retrospective	7. Does not specify
Hassan et al.	1995	1. Observational	4. Does not specify	7. Does not specify
Huang et al.	2020	1. Observational	1. Prospective	2. Cohort
Ito et al.	2019	1. Observational	2. Retrospective	7. Does not specify
Kakutani et al.	2020	1. Observational	2. Retrospective	7. Does not specify
Kanat et al.	2007	1. Observational	1. Prospective	7. Does not specify
Kawano-Dourado et al.	2020	1. Observational	2. Retrospective	7. Does not specify
Kelly et al.	2014	1. Observational	4. Does not specify	7. Does not specify
Kim et al.	2017	1. Observational	1. Prospective	2. Cohort
Kim et al.	2010	1. Observational	2. Retrospective	2. Cohort
Kim et al.	2020	1. Observational	2. Retrospective	7. Does not specify
Kim et al.	2020	1. Observational	2. Retrospective	2. Cohort

Author	Year	Study types		
		1. Observational **2. Experimental**	**1. Prospective.** **2.Retrospective.** **3. Does not apply** **4.Does not specify**	**1. Cross sectional** **2. Cohort** **3. Case-controls** **4. Pilot study - Observational** **5. Other Observational study.** **6. Does not apply** **7.Does not specify**
Kinoshita et al.	2004	1. Observational	1. Prospective	7. Does not specify
Lee et al.	2005	1. Observational	2. Retrospective	7. Does not specify
Lee et al.	2021	1. Observational	2. Retrospective	2. Cohort
Leone et al.	2020	1. Observational	2. Retrospective	2. Cohort
Leonel et al.	2012	1. Observational	4. Does not specify	7. Does not specify
Li et al.	2019	1. Observational	2. Retrospective	7. Does not specify
Marten et al.	2009	1. Observational	2. Retrospective	7. Does not specify
McDonagh et al.	1994	1. Observational	4. Does not specify	3. Case-control
McFarlane et a.	2019	1. Observational	2. Retrospective	1. Cross sectional
Mena-Vázquez	2021	1. Observational	1. Prospective	2. Cohort
Mohd Noor	2009	1. Observational	4. Does not specify	1. Cross sectional
Mori et al.	2008	1. Observational	1. Prospective	7. Does not specify
Morisset et al.	2017	1. Observational	2. Retrospective	7. Does not specify
Nurmi et al.	2018	1. Observational	2. Retrospective	7. Does not specify
Nurmi et al.	2016	1. Observational	2. Retrospective	7. Does not specify
Okada et al.	2016	1. Observational	2. Retrospective	7. Does not specify
Paulin et al.	2021	1. Observational	4. Does not specify	3. Case-control
Paulin et al.	2018	1. Observational	4. Does not specify	1. Cross sectional
Pérez-Dórame et al.	2015	1. Observational	2. Retrospective	2. Cohort
Remy-Jardin et al.	1994	1. Observational	2. Retrospective	7. Does not specify
A. Robles-Perez et al.	2016	1. Observational	1. Prospective	7. Does not specify
Salaffi et al.	2019	1. Observational	2. Retrospective	7. Does not specify
Samy et al.	2021	1. Observational	4. Does not specify	1. Cross sectional
Saracoglu et al.	2005	1. Observational	2. Retrospective	7. Does not specify
Solomon et al.	2016	1. Observational	4. Does not specify	2. Cohort
Song et al.	2016	1. Observational	4. Does not specify	1. Cross sectional
Sparks et al.	2019	1. Observational	1. Prospective	2. Cohort
Tanaka et al.	2004	1. Observational	2. Retrospective	7. Does not specify
Wang et al.	2015	1. Observational	2. Retrospective	7. Does not specify
Yamakawa et al.	2020	1. Observational	2. Retrospective	7. Does not specify
Yamakawa et al.	2019	1. Observational	2. Retrospective	7. Does not specify
Yang et al.	2019	1. Observational	2. Retrospective	7. Does not specify
Yuksekkaya et al.	2013	1. Observational	2. Retrospective	7. Does not specify
Yunt et al.	2017	1. Observational	1. Prospective	2. Cohort
Zamora-Legoff et al.	2017	1. Observational	2. Retrospective	2. Cohort

Author	Year	Study types		
		1. Observational **2. Experimental**	**1. Prospective.** **2.Retrospective.** **3. Does not apply** **4.Does not specify**	**1. Cross sectional** **2. Cohort** **3. Case-controls** **4. Pilot study - Observational** **5. Other Observational study.** **6. Does not apply** **7.Does not specify**
Zayeni et al.	2016	1. Observational	4. Does not specify	1. Cross sectional
Zhang et al.	2017	1. Observational	2. Retrospective	7. Does not specify
Zrour et al.	2005	1. Observational	1. Prospective	2. Cohort

Table #9. Data extraction table: Demographic data

Caption: This table shows the data extraction about number of patients, mean age and gender from the participants of all the studies included in the systematic review

Author	Year	Number of patients		Mean age (years)	Gender
		Total	Included		
Akira et al.	1999	29	29	59 ± 11	Male: 13
Alamoudi et al.	2017	419	419	45.7 ± 15.9	Female: 364, male: 55
Assayag et al.	2014	83	69	58	Female: 65%
Avouac et al.	2020	147	147	66 ± 12	Female: 69%
Biederer et al.	2004	61	53	61	Male: 19, female:34
Bilgici et al.	2005	54	52	53.63 ± 11.19	Female: 46
Bonilla et al.	2021	2729	2729	57.3 ±13.3	Male: 706
Castellanos-Moreira et al.	2020	179	179	64.2 ± 9.7	Female: 141
Chen el al.	2013	103	103	49.1±14.7	Female: 76
Chen et al.	2021	241	241	59 + 12.7	Female:143
Demir et al.	1999	34	34	45.26±11.6	Female: 26, male:8
Doyle et al.	2015	1145	113	NR	NR
Duarte et al.	2019	1129	1129	68.3 ± 12	NR
Ekici et al.	2021	21309	156	55.5+ 12.1	Female: 108
Medhat et al.	2021	100	100	55.7+ 11.4	Female: 77, male: 23
Eser et al.	2012	150	150	53.2+ 12.1	Female: 126, male: 24
Fadda et al.	2018	88	88	50.15+ 9	Females: 75, male: 13.
Gabbay et al.	1997	36	36	51.8 ±16	Female: 25, male: 11
Gautam et al.	2020	54	54	44.17+ 11.3	Male:18, female: 36
Giles et al.	2014	176	176	59+ 9	Male: 71
Gochuico et al.	2008	74	74	21	Male:7, female:36
Habib et al.	2011	40	40	37.6+ 10.3	Male: 12, female: 28
Hanaka et al.	2019	200	77	61	NR
Hassan et al.	1995	100	20	59	Female: 18
Huang et al.	2020	1500	190	64.2 ± 11.8	Female: 80%
Ito et al.	2019	97	65	72	Male: 31
Kakutani et al.	2020	2702	2702	62.8 ± 12.5	Female: 82.2
Kanat et al.	2007	70	16	57.9 ± 1.5	Female: 46, male: 8
Kawano-Dourado et al.	2020	1076	1069	65.6 ± 9.9	NR
Kelly et al.	2014	230	230	64	Male: 110
Kim et al.	2017	5376	3555	NR	Male:560
Kim et al.	2010	99	84	69 ± 6 RA-UIP, 65 ± 10 RA-non-UIP, 72 ± 9 IPF	NR
Kim et al.	2020	158	84	61,4	Male: 45.2%

Author	Year	Number of patients		Mean age (years)	Gender
		Total	Included		
Kim et al.	2020	153	153	61	Female: 88
Kinoshita et al.	2004	47	47	63.5	Female: 33, male:14
Lee et al.	2005	42	42	Underwent SLBx:60.3 ± 7.3. Did not Undergo SLBx: 65.8 ± 9.3	Male: 20, female:22
Lee et al.	2021	60	60	Cohort 1: 62.7 + 8.3. Cohot 2: 67.1 ±8.7)	Female: cohort 1: 12 (46.2%), cohort 2: 24 (70.6%).
Leone et al.	2020	1076	293	59.5±10.9	Female: 86%
Leonel et al.	2012	112	36	Group 1: 48 ± 7.6, group 2: 46 ± 11.4	Female: 36
Li et al.	2019	1096	213	64.9 ± 11.4	Female: 119 (55.9%)
Marten et al.	2009	22	20	63±9	Male: 7, female: 13
McDonagh et al.	1994	40	40	66	Male: 14 in each group
McFarlane et a.	2019	1142	503	62.6 ± 2.2	Female: 88%.
Mena-Vázquez	2021	116	116	68.3 (9.9)	Female: 63 (54.3%)
Mohd Noor	2009	80	63	56.7 ±10	Male: 7 (11.1%), female: 56 (88.9%)
Mori et al.	2008	126	126	60	Predominantly female
Morisset et al.	2017	309	309	65	Female: 54%
Nurmi et al.	2018	60	60	66.5±11.2	Male: 56%
Nurmi et al.	2016	1047	59	66 ± 11.1	Male: 59.5%
Okada et al.	2016	499	499	59.7	Males: 133, female:366.
Paulin et al.	2021	118	118	56.6 ±15.6	Male: 26 (22%)
Paulin et al.	2018	60	46	59.9	Male: 14 (30.4%)
Pérez-Dórame et al.	2015	69	34	60.5 ±10.5	Female: 30 (88%)
Remy-Jardin et al.	1994	84	84	57 ± 9	Male: 29, Female: 55
A. Robles-Perez et al.	2016	40	40	47 ± 12	Male: 10 (25%), female: 30 (75%)
Salaffi et al.	2019	151	151	53.4 ±7.6	Male: 45 (29.8%), female: 106 (70.3%)
Samy et al.	2021	160	160	37.8 ± 11.3	Female:136 (85%), male: 24 (15%).
Saracoglu et al.	2005	40	40	49.2 ±12	Female: 31 (77.5%), male: 9 (22.5%).
Solomon et al.	2016	300	137	64.7 ± 10.6	Female: 68 (50%)
Song et al.	2016	116	116	53.8 ± 9.3	Female: 105 (90.5%)
Sparks et al.	2019	1419	1419	55.8 ±82.3	Female: 82.3%

Author	Year	Number of patients		Mean age (years)	Gender
		Total	Included		
Tanaka et al.	2004	63	63	61.7±11.2	Male: 27, Female: 36
Wang et al.	2015	544	544	51.9 ± 13.6	Female: 427, male: 117
Yamakawa et al.	2020	78	40	65.3 ±11.6	Male: 16
Yamakawa et al.	2019	96	96	69	Female: 61%
Yang et al.	2019	308	308	59 ± 13.3	Female:232
Yuksekkaya et al.	2013	85	84	56 ± 12.1	Male: 20, female: 64
Yunt et al.	2017	385	158	67.3	Male: 79 (50%)
Zamora-Legoff et al.	2017	181	181	67.4	Female: 48%
Zayeni et al.	2016	44	44	49 ± 13	Male: 9 (20.45%), female: 35 (79.55%).
Zhang et al.	2017	550	550	61 ± 13	Male: 165 (30%), female: 385 (70%)
Zrour et al.	2005	75	75	48 ± 14	Female: 63 (84%), male: 12

*NR: not reported, IPF: idiopathic pulmonary fibrosis, RA-UIP: Reumathoid arthritis-usual interstitial pneumonia associated, SLBx: surgical lung biopsy.

Table #10. Data extraction table: statistical analysis

Caption: This table shows the data extraction about statistical analysis from all of the studies included in the systematic review

Author	Year	Statistical analysis		
		TEST: **1. Chi2** **2.Fisher** **3. T student** **4. Wilcoxon** **5. Man Whitney** **6. Anova** **7. Friedman** **8. Kruskall Wallis** **9. Pearson** **10. Ro Spearman** **11. Kaplan Meier** **12. Others.** **13. Does not specify**	**p < 0.05** **1. Yes.** **2. No** **3. Does not specify**	**Notes**
Akira et al.	1999	13	3. Does not specify	NA
Alamoudi et al.	2017	1,3	1. Yes	Multivariate regression analysis
Assayag et al.	2014	1, 3	1. Yes	NA
Avouac et al.	2020	1,3	3. Does not specify	ROC
Biederer et al.	2004	3,9,11	1. Yes	Mc Nemar
Bilgici et al.	2005	1,3,5,9,10	1. Yes	Yates correction
Bonilla et al.	2021	1,3,5	3. Does not specify	NA
Castellanos-Moreira et al.	2020	1,2,3,5	1. Yes	NA
Chen el al.	2013	1,3	1. Yes	NA
Chen et al.	2021	2,3,5,11	1. Yes	NA
Demir et al.	1999	2,5	1. Yes	NA
Doyle et al.	2015	2,3,4	1. Yes	Multivariate analysis
Duarte et al.	2019	1,5	1. Yes	Logistic regression model
Ekici et al.	2021	1,2,3,5,6,,8	1. Yes	NA
Medhat et al.	2021	1,2,3	1. Yes	Multiple Logistic regression model, ROC curve
Eser et al.	2012	3	1. Yes	NA
Fadda et al.	2018	1,3,5,8	1. Yes	Logistic regression model
Gabbay et al.	1997	3,4,	1. Yes	NA
Gautam et al.	2020	13	3. Does not specify	NA
Giles et al.	2014	1,2,3,8	1. Yes	Multivariable regression models
Gochuico et al.	2008	3,4	1. Yes	NA
Habib et al.	2011	1,3,4	1. Yes	Multivariate regression analysis
Hanaka et al.	2019	2,3,5,8,11	1. Yes	Multivariate regression analysis
Hassan et al.	1995	2,5	1. Yes	

Author	Year	Statistical analysis		
		TEST: **1. Chi2** **2.Fisher** **3. T student** **4. Wilcoxon** **5. Man Whitney** **6. Anova** **7. Friedman** **8. Kruskall Wallis** **9. Pearson** **10. Ro Spearman** **11. Kaplan Meier** **12. Others.** **13. Does not specify**	**p < 0.05** **1. Yes.** **2. No** **3. Does not specify**	**Notes**
Huang et al.	2020	1,2,3,4	1. Yes	Multivariate regression analysis
Ito et al.	2019	11	1. Yes	Cox
Kakutani et al.	2020	12	1. Yes	Multivariate regression analysis
Kanat et al.	2007	1,2,3, 10	1. Yes	NA
Kawano-Dourado et al.	2020	2,3,10	1. Yes	NA
Kelly et al.	2014	1,5	1. Yes	Logistic regression analysis
Kim et al.	2017	3,11	1. Yes	NA
Kim et al.	2010	1,2, 3,4,11	1. Yes	NA
Kim et al.	2020	2,3,5,11,12	1. Yes	ROC curve
Kim et al.	2020	12	1. Yes	ROC curve
Kinoshita et al.	2004	9	3. Does not specify	NA
Lee et al.	2005	5	1. Yes	NA
Lee et al.	2021	1,2,3,5,8,9,10	1. Yes	NA
Leone et al.	2020	10	1. Yes	NA
Leonel et al.	2012	5, 11	1. Yes	ROC curve
Li et al.	2019	1,2,3	1. Yes	NA
Marten et al.	2009	9	1. Yes	NA
McDonagh et al.	1994	3,4	1. Yes	NA
McFarlane et a.	2019	1	3. Does not specify	NA
Mena-Vázquez	2021	4,11	1. Yes	Cox
Mohd Noor	2009	1,3,5	1. Yes	NA
Mori et al.	2008	1,5	1. Yes	NA
Morisset et al.	2017	12	1. Yes	COX
Nurmi et al.	2018	1,2,3,11,10	1. Yes	Cox regression
Nurmi et al.	2016	1,2,3,5	1. Yes	Shapiro Wilk test
Okada et al.	2016	1,3,5	1. Yes	NA
Paulin et al.	2021	3, 5	1. Yes	NA
Paulin et al.	2018	9.10	1. Yes	NA
Pérez-Dórame et al.	2015	4. 10	1. Yes	NA
Remy-Jardin et al.	1994	1	1. Yes	Linear regression analysis

Author	Year	Statistical analysis		
		TEST: **1. Chi2** **2.Fisher** **3. T student** **4. Wilcoxon** **5. Man Whitney** **6. Anova** **7. Friedman** **8. Kruskall Wallis** **9. Pearson** **10. Ro Spearman** **11. Kaplan Meier** **12. Others.** **13. Does not specify**	**p < 0.05** **1. Yes.** **2. No** **3. Does not specify**	**Notes**
A. Robles-Perez et al.	2016	1,2,3,5	1. Yes	NA
Salaffi et al.	2019	1,3,9	1. Yes	ROC
Samy et al.	2021	1,3	1. Yes	NA
Saracoglu et al.	2005	5. 10	1. Yes	NA
Solomon et al.	2016	11	1. Yes	NA
Song et al.	2016	1,2,5	1. Yes	Logistic regression analysis
Sparks et al.	2019	12	1. Yes	NA
Tanaka et al.	2004	10	1. Yes	NA
Wang et al.	2015	3	1. Yes	Multivariate regression analysis, rank- sum test.
Yamakawa et al.	2020	2,3,5,11	1. Yes	NA
Yamakawa et al.	2019	2,11	1. Yes	Cox, ANOVA
Yang et al.	2019	2,3,11	1. Yes	NA
Yuksekkaya et al.	2013	1,3. 10	1. Yes	NA
Yunt et al.	2017	1	1. Yes	NA
Zamora-Legoff et al.	2017	1,11	1. Yes	Rank sum test, Cox model
Zayeni et al.	2016	1,2,3	1. Yes	NA
Zhang et al.	2017	1, 3	1. Yes	ANOVA, logistic regression
Zrour et al.	2005	1,2,3,8	1. Yes	NA

*NA: not applicable.

Table #11. Data extraction table – High resolution computed tomography (HRCT) findings

Caption: This table shows the data extraction about HRCT findings, abnormal HRCT or presence of interstitial lung disease (ILD) from the participants of all the studies included in the systematic review

Author	**Year**	**HRCT**		**ILD Patients**	
		HRCT Abnormal N°	HRCT Abnormal %	**N°**	**%**
Akira et al.	1999	29	NR	NR	NR
Alamoudi et al.	2017	NR	67.1	NR	23.1
Assayag et al.	2014	69	NR	69	NR
Avouac et al.	2020	40	27	40	27
Biederer et al.	2004	49	NR	49	NR
Bilgici et al.	2005	35	67.3	NR	NR
Bonilla et al.	2021	NR	NR	90	NR
Castellanos-Moreira et al.	2020	37	21	37	21
Chen el al.	2013	NR	NR	63	61
Chen et al.	2021	146	60	146	NR
Demir et al.	1999	23	68	23	68
Doyle et al.	2015	NR	NR	46	41
Duarte et al.	2019	87	7.7	45	51,7
Ekici et al.	2021	156	100	140	89.7
Medhat et al.	2021	68	68	NR	NR
Eser et al.	2012	43	28	NR	NR
Fadda et al.	2018	63	72	63	72
Gabbay et al.	1997	21	58	9	25
Gautam et al.	2020	25	46	20	37
Giles et al.	2014	NR	NR	58	33
Gochuico et al.	2008	31	42	31	42
Habib et al.	2011	11	27,5	11	27,5
Hanaka et al.	2019	77	100	77	100
Hassan et al.	1995	6	30	1	5
Huang et al.	2020	54	28,4	30	15.8
Ito et al.	2019	65	100	65	100
Kakutani et al.	2020	260	26,8	260	26,8
Kanat et al.	2007	34	63	34	100
Kawano-Dourado et al.	2020	89	30	64	22
Kelly et al.	2014	230	100	230	100
Kim et al.	2017	64	26.2	24	37,5
Kim et al.	2010	84	100	84	100
Kim et al.	2020	84	100	84	100
Kim et al.	2020	153	100	153	100
Kinoshita et al.	2004	22	46.8	NR	NR

Author	Year	HRCT		ILD Patients	
		HRCT Abnormal N°	HRCT Abnormal %	N°	%
Lee et al.	2005	NR	NR	NR	NR
Lee et al.	2021	60	100	60	100
Leone et al.	2020	64	22	64	22
Leonel et al.	2012	20	NR	13	36
Li et al.	2019	213	NR	213	100
Marten et al.	2009	20	NR	20	100
McDonagh et al.	1994	16	NR	16	NR
McFarlane et a.	2019	NR	NR	32	6.36%
Mena-Vázquez	2021	116	NR	116	100
Mohd Noor	2009	45	71.4	28	44.4
Mori et al.	2008	126	NR	15	12
Morisset et al.	2017	236	76	236	NR
Nurmi et al.	2018	60	NR	60	NR
Nurmi et al.	2016	59	NR	59	NR
Okada et al.	2016	188	37.7	19	3.8
Paulin et al.	2021	NR	NR	52	NR
Paulin et al.	2018	46	NR	46	100
Pérez-Dórame et al.	2015	NR	NR	NR	NR
Remy-Jardin et al.	1994	NR	NR	NR	NR
A. Robles-Perez et al.	2016	11	NR	2	NR
Salaffi et al.	2019	29	19.2	29	19.2
Samy et al.	2021	102	63.7	102	63.7%
Saracoglu et al.	2005	23	57.5	NR	NR
Solomon et al.	2016	137	NR	137	NR
Song et al.	2016	94	81	NR	NR
Sparks et al.	2019	85	NR	85	NR
Tanaka et al.	2004	NR	NR	NR	NR
Wang et al.	2015	83	15.2	83	15.2
Yamakawa et al.	2020	40	NR	40	NR
Yamakawa et al.	2019	96	NR	96	NR
Yang et al.	2019	77	NR	67	NR
Yuksekkaya et al.	2013	84	NR	5	NR
Yunt et al.	2017	158	NR	158	NR
Zamora-Legoff et al.	2017	181	NR	181	NR
Zayeni et al.	2016	43	NR	19	44
Zhang et al.	2017	237	43.1	237	43.1
Zrour et al.	2005	37	49.3	21	28

*NR: not reported, HRCT: High resolution computed tomography, N°: number, %: percentage, ILD: interstitial lung disease.

Table #12. Data extraction table: ILD types (number)

Caption: This table shows the data extraction about number of patients with the different ILD types from all of the studies included in the systematic review

Author	Year	ILD TYPES N°						
		UIP	NSIP	OP	DIP	LIP	AIP	RB-ILD
Akira et al.	1999	NR	NR	NR	NR	NR	NR	NR
Alamoudi et al.	2017	NR	NR	NR	NR	NR	NR	NR
Assayag et al.	2014	20	NR	NR	NR	NR	NR	NR
Avouac et al.	2020	21	17	NR	NR	NR	NR	NR
Biederer et al.	2004	NR	NR	NR	NR	NR	NR	NR
Bilgici et al.	2005	NR	NR	NR	NR	NR	NR	NR
Bonilla et al.	2021	28	20	6	NR	6	NR	NR
Castellanos-Moreira et al.	2020	NR	NR	NR	NR	NR	NR	NR
Chen el al.	2013	NR	59	NR	NR	NR	NR	NR
Chen et al.	2021	88	33	15	NR	7	NR	NR
Demir et al.	1999	NR	NR	NR	NR	NR	NR	NR
Doyle et al.	2015	NR	NR	NR	NR	NR	NR	NR
Duarte et al.	2019	18	18	4	NR	NR	NR	NR
Ekici et al.	2021	89	51	NR	NR	NR	NR	NR
Medhat et al.	2021	NR	NR	NR	NR	NR	NR	NR
Eser et al.	2012	NR	NR	NR	NR	NR	NR	NR
Fadda et al.	2018	39	17	NR	NR	NR	NR	NR
Gabbay et al.	1997	NR	NR	NR	NR	NR	NR	NR
Gautam et al.	2020	6	14	NR	NR	NR	NR	NR
Giles et al.	2014	NR	NR	NR	NR	NR	NR	NR
Gochuico et al.	2008	10	NR	NR	NR	NR	NR	NR
Habib et al.	2011	NR	NR	NR	NR	NR	NR	NR
Hanaka et al.	2019	21	23	NR	NR	NR	NR	33
Hassan et al.	1995	NR	NR	NR	NR	NR	NR	NR
Huang et al.	2020	24	NR	NR	NR	NR	NR	NR
Ito et al.	2019	65	NR	NR	NR	NR	NR	NR
Kakutani et al.	2020	120	NR	NR	NR	NR	NR	NR
Kanat et al.	2007	NR	NR	NR	NR	NR	NR	NR
Kawano-Dourado et al.	2020	NR	NR	NR	NR	NR	NR	NR
Kelly et al.	2014	150	55	11	NR	NR	NR	NR
Kim et al.	2017	NR	NR	NR	NR	NR	NR	NR
Kim et al.	2010	20	19	NR	NR	NR	NR	NR
Kim et al.	2020	30	NR	NR	NR	NR	NR	NR
Kim et al.	2020	95	NR	NR	NR	NR	NR	NR
Kinoshita et al.	2004	NR	NR	NR	NR	NR	NR	NR
Lee et al.	2005	10	6	NR	NR	NR	NR	NR

Author	Year	ILD TYPES N°						
		UIP	NSIP	OP	DIP	LIP	AIP	RB-ILD
Lee et al.	2021	C1: 17, C2: 14	C1: 7, C2: 11	NR	NR	NR	NR	NR
Leone et al.	2020	NR	NR	NR	NR	NR	NR	NR
Leonel et al.	2012	NR	NR	NR	NR	NR	NR	NR
Li et al.	2019	NR	NR	NR	NR	NR	NR	NR
Marten et al.	2009	NR	NR	NR	NR	NR	NR	NR
McDonagh et al.	1994	NR	NR	NR	NR	NR	NR	NR
McFarlane et a.	2019	22	8	NR	NR	NR	NR	NR
Mena-Vázquez	2021	71	41	NR	NR	NR	NR	NR
Mohd Noor	2009	NR	NR	NR	NR	NR	NR	NR
Mori et al.	2008	2	11	2	NR	NR	NR	NR
Morisset et al.	2017	236	NR	NR	NR	NR	NR	NR
Nurmi et al.	2018	36	8	7	NR	NR	NR	NR
Nurmi et al.	2016	35	8	7	NR	NR	NR	NR
Okada et al.	2016	NR	NR	19	NR	NR	NR	NR
Paulin et al.	2021	32	NR	NR	NR	NR	NR	NR
Paulin et al.	2018	28	NR	NR	NR	NR	NR	NR
Pérez-Dórame et al.	2015	NR	NR	NR	NR	NR	NR	NR
Remy-Jardin et al.	1994	8	NR	NR	NR	NR	NR	NR
A. Robles-Perez et al.	2016	NR	1	1	NR	NR	NR	NR
Salaffi et al.	2019	18	7	1	NR	NR	NR	NR
Samy et al.	2021	NR	NR	NR	NR	NR	NR	NR
Saracoglu et al.	2005	NR	NR	NR	NR	NR	NR	NR
Solomon et al.	2016	108	29	NR	NR	NR	NR	NR
Song et al.	2016	NR	NR	NR	NR	NR	NR	NR
Sparks et al.	2019	NR	69	NR	NR	NR	NR	NR
Tanaka et al.	2004	26	19	5	NR	NR	NR	11
Wang et al.	2015	NR	NR	NR	NR	NR	NR	NR
Yamakawa et al.	2020	14	8	NR	NR	NR	NR	NR
Yamakawa et al.	2019	20	13	6	NR	NR	NR	NR
Yang et al.	2019	32	17	13	1	2	NR	2
Yuksekkaya et al.	2013	5	NR	NR	NR	NR	NR	NR
Yunt et al.	2017	100	35	NR	NR	NR	NR	NR
Zamora-Legoff et al.	2017	NR	NR	NR	NR	NR	NR	NR
Zayeni et al.	2016	19	NR	NR	NR	NR	NR	NR
Zhang et al.	2017	44	138	NR	NR	NR	NR	NR
Zrour et al.	2005	NR	NR	NR	NR	NR	NR	NR

*ILD: interstitial lung disease, N°: number, UIP: Usual interstitial pneumonia, NSIP: nonspecific interstitial pneumonia, OP: organizing pneumonia, DIP: desquamative interstitial

pneumonia, LIP: lymphoid interstitial pneumonia, AIP: acute interstitial pneumonia, RB-ILD: respiratory bronchiolitis associated interstitial lung diseas, C1: cohort 1, C: cohort 2.

Table #13. Data extraction table – ILD types (percentage)

Caption: This table shows the data extraction about the percentage of patients with the different ILD types from all of the studies included in the systematic review

Author	Year	ILD TYPES %						
		UIP	NSIP	OP	DIP	LIP	AIP	RB-ILD
Akira et al.	1999	NR	NR	NR	NR	NR	NR	NR
Alamoudi et al.	2017	NR	NR	NR	NR	NR	NR	NR
Assayag et al.	2014	29	NR	NR	NR	NR	NR	NR
Avouac et al.	2020	NR	NR	NR	NR	NR	NR	NR
Biederer et al.	2004	NR	NR	NR	NR	NR	NR	NR
Bilgici et al.	2005	NR	NR	NR	NR	NR	NR	NR
Bonilla et al.	2021	31.1	22.2	6.7	NR	6.7	NR	NR
Castellanos-Moreira et al.	2020	38	38	8	5	NR	NR	11
Chen el al.	2013	NR	57.3	NR	NR	NR	NR	NR
Chen et al.	2021	53,4	22	10	NR	4,7	NR	NR
Demir et al.	1999	NR	NR	NR	NR	NR	NR	NR
Doyle et al.	2015	NR	NR	NR	NR	NR	NR	NR
Duarte et al.	2019	40	40	8,9	0	0	0	0
Ekici et al.	2021	57	32.7	NR	NR	NR	NR	NR
Medhat et al.	2021	NR	NR	NR	NR	NR	NR	NR
Eser et al.	2012	NR	NR	NR	NR	NR	NR	NR
Fadda et al.	2018	62	27	NR	NR	NR	NR	NR
Gabbay et al.	1997	NR	NR	NR	NR	NR	NR	NR
Gautam et al.	2020	11	25	NR	NR	NR	NR	NR
Giles et al.	2014	NR	NR	NR	NR	NR	NR	NR
Gochuico et al.	2008	14	NR	NR	NR	NR	NR	NR
Habib et al.	2011	NR	NR	NR	NR	NR	NR	NR
Hanaka et al.	2019	27	30	NR	NR	NR	NR	43
Hassan et al.	1995	NR	NR	NR	NR	NR	NR	NR
Huang et al.	2020	12,6	NR	NR	NR	NR	NR	NR
Ito et al.	2019	100	NR	NR	NR	NR	NR	NR
Kakutani et al.	2020	46	NR	NR	NR	NR	NR	NR
Kanat et al.	2007	NR	NR	NR	NR	NR	NR	NR
Kawano-Dourado et al.	2020	NR	NR	NR	NR	NR	NR	NR
Kelly et al.	2014	65	24	5	NR	NR	NR	NR
Kim et al.	2017	NR	NR	NR	NR	NR	NR	NR
Kim et al.	2010	23.8	22,6	NR	NR	NR	NR	NR
Kim et al.	2020	35,7	NR	NR	NR	NR	NR	NR
Kim et al.	2020	62	NR	NR	NR	NR	NR	NR
Kinoshita et al.	2004	NR	NR	NR	NR	NR	NR	NR
Lee et al.	2005	NR	NR	NR	NR	NR	NR	NR

Author	Year	ILD TYPES %						
		UIP	NSIP	OP	DIP	LIP	AIP	RB-ILD
Lee et al.	2021	C1: 65.4%, C2: 41.2%	C1: 26.9%, C2: 32.4%	NR	NNR	NR	NR	NR
Leone et al.	2020	NR	NR	NR	NR	NR	NR	NR
Leonel et al.	2012	NR	NR	NR	NR	NR	NR	NR
Li et al.	2019	NR	NR	NR	NR	NR	NR	NR
Marten et al.	2009	NR	NR	NR	NR	NR	NR	NR
McDonagh et al.	1994	NR	NR	NR	NR	NR	NR	NR
McFarlane et a.	2019	NR	NR	NR	NR	NR	NR	NR
Mena-Vázquez	2021	61.2	35.3	NR	NR	NR	NR	NR
Mohd Noor	2009	NR	NR	NR	NR	NR	NR	NR
Mori et al.	2008	1.6	8.7	1.6	NR	NR	NR	NR
Morisset et al.	2017	NR	NR	NR	NR	NR	NR	NR
Nurmi et al.	2018	60	13.3	11.6	NR	NR	NR	NR
Nurmi et al.	2016	59	13.5	12	NR	NR	NR	NR
Okada et al.	2016	NR	NR	3.8	NR	NR	NR	NR
Paulin et al.	2021	26.92	NR	NR	NR	NR	NR	NR
Paulin et al.	2018	NR	NR	NR	NR	NR	NR	NR
Pérez-Dórame et al.	2015	13	29	NR	NR	NR	NR	NR
Remy-Jardin et al.	1994	10	NR	NR	NR	NR	NR	NR
A. Robles-Perez et al.	2016	NR	NR	NR	NR	NR	NR	NR
Salaffi et al.	2019	62	24.1	3.5	NR	NR	NR	NR
Samy et al.	2021	NR	NR	NR	NR	NR	NR	NR
Saracoglu et al.	2005	NR	NR	NR	NR	NR	NR	NR
Solomon et al.	2016	NR	NR	NR	NR	NR	NR	NR
Song et al.	2016	6	1	NR	NR	NR	NR	NR
Sparks et al.	2019	NR	NR	NR	NR	NR	NR	NR
Tanaka et al.	2004	NR	NR	NR	NR	NR	NR	NR
Wang et al.	2015	NR	NR	NR	NR	NR	NR	NR
Yamakawa et al.	2020	NR	NR	NR	NR	NR	NR	NR
Yamakawa et al.	2019	21	14	6	NR	NR	NR	NR
Yang et al.	2019	47.8	25.4	19.4	1.5	3	NR	3
Yuksekkaya et al.	2013	NR	NR	NR	NR	NR	NR	NR
Yunt et al.	2017	63	22	NR	NR	NR	NR	NR
Zamora-Legoff et al.	2017	NR	NR	NR	NR	NR	NR	NR
Zayeni et al.	2016	44.1	NR	NR	NR	NR	NR	NR
Zhang et al.	2017	18.6	57.8	NR	NR	NR	NR	NR

*ILD: interstitial lung disease, %: percentage, UIP: Usual interstitial pneumonia, NSIP: nonspecific interstitial pneumonia, OP: organizing pneumonia, DIP: desquamative interstitial pneumonia, LIP: lymphoid interstitial pneumonia, AIP: acute interstitial pneumonia, RB-ILD: respiratory bronchiolitis associated interstitial lung diseas, C1: cohort 1, C: cohort 2.

Table #14. Data extraction table

Caption: This table shows the data extraction about other HRCT findings and RA mean duration notes from all of the studies included in the systematic review

Author	Year	Other HRCT Findings	RA mean duration notes
Akira et al.	1999	Group 1: reticulation with or without honeycombing (n=19). Group 2: Centrilobular branching lines with or without bronchiectasis. (n=5). Group 3: Consolidation (n=5).	NR
Alamoudi et al.	2017	Ground glass opacity 31/100, honeycombing 31/100, bronchiectasis 31/100, air space consolidation 28/100, lymphadenopathy 25/100, pleural effusion 19/100, atelectasis/collapse 16/100, septal thickening 14/100, rheumathoid nodule 13/100, bronchial dilatation 11/100, emphysema 1/100.	3.5 ± 4.6 years
Assayag et al.	2014	UIP: 20/69, possible UIP pattern: 18/69, inconsistent UIP pattern: 31/69	NR
Avouac et al.	2020	NSIP + COPD: 2	11±10 years
Biederer et al.	2004	GGO 19/71, reticular lesion pattern 56/71, nodules 26/71, consolidations 7/71, bronchiectasis 12/71, emphysema 28/71, pleural irregularities 21/71, pleural effussion 4/71, enlarged mediastinal lymph nodes 42/73	NR
Bilgici et al.	2005	Reticulonodular patterns: 22, GGO: 7. Bronchiectasis: 6. Bronchiectasis + reticulonodular pattern: 3.	8.37 ± 8.17 years
Bonilla et al.	2021	Probable UIP: 5 (5.6%), UIP + probable UIP: 33 (36.3%), Fibrosis emphysema Syndrome: 12 (13.3%), others: 13 (14.4%)	NR
Castellanos-Moreira et al.	2020	NR	8.5 ± 7.4 years
Chen el al.	2013	RA-no ILD: GGO (7/40), airspace abnormalities (1/40), architectural distortion (2/40)	4.3±5.7 years
Chen et al.	2021	Definitive UIP: 66 (45.2%), probable UIP: 12 (8.2%)	NR
Demir et al.	1999	Bronchiectasis: 9 patients	5.38 years
Doyle et al.	2015	38 patients (34%) indeterminate RA-ILD, 46 (41%) RA-ILD	NR
Duarte et al.	2019	Lung fibrosis 5 (11.1%) patients. Bronchiectasis: 31 (35.6% patients). Panbronchiolitis and obliterative bronchiolitis: 2(2.3%). Reumathoid nodules: 4 (4.6%). Pleural effussion: 3 (3.4%).	14 years
Ekici et al.	2021	Airway disease (AD): 16 (10.3%)	4.5 years

Author	Year	Other HRCT Findings	RA mean duration notes
Medhat et al.	2021	Ground glass opacity (GGO) in 36 (52.9%), air trapping in 26 (38.2%), thickened septal/non-septal lines in 21 (30.9%), nodules in 17 (25%), Caplan's syndrome in 8 (11.8%) and bronchial wall thickening in 8 (11.8%) while 3 (4.4%) showed honeycombing and bronchiectasis. Only 32 (32%) of the 68 patients with HRCT abnormalities had PFT abnormalities, and 6 (6%) of the 32 patients without HRCT abnormalities had PFT abnormalities.	14.9 + 6.8 years
Eser et al.	2012	Most frequent HRCT findings were pleuritis, pulmonary nodules, interstitial disease, ground glass attenuation, and honeycombing.	147.3± 99.4 months
Fadda et al.	2018	Other ILD: 7 patients	10.2 + 6.2 years
Gabbay et al.	1997	Emphysema 3 (8%) patients, ILD and emphysema 2 (6%) patients.	NR
Gautam et al.	2020	GGO, honeycombing, interlobular septal thickening, bronchiectasis, traction bronchiectasis.	NR
Giles et al.	2014	GGO: 22 (13%), reticulation/traction bronchiectasis/honeycombing: 36 (22%).	NR
Gochuico et al.	2008	NR	RA without lung disease: 11.3, RA preclinical ILD: 13.7, with pulmonary fibrosis: 2.7 years
Habib et al.	2011	NR	18 ± 3.2 months
Hanaka et al.	2019	The bronchiolitis pattern group comprised 15 patients with a follicular bronchiolitis pattern, 10 patients with a diffuse panbronchiolitis pattern, and 8 patients with a bronchiolitis obliterans pattern	NR
Hassan et al.	1995	Bronchiectasis 5 patients 25%, GGO 1 patient (ILD).	9 years
Huang et al.	2020	Bronchiectasis (14.2%), pleural disease (9.5%).	21.2 years
Ito et al.	2019	Definitive UIP: 11 (16.9%), possible UIP: 29 (44.6%), inconsistent with UIP:25 (38.5%),	NR
Kakutani et al.	2020	NR	10 years
Kanat et al.	2007	Emphysema: 4(7%), air-space consolidation: 2 (4%), lymph node involvement: 1(2%).	9.8+ 7.1 years
Kawano-Dourado et al.	2020	ILA 25 patients (8%)	6.5 years

Author	Year	Other HRCT Findings	RA mean duration notes
Kelly et al.	2014	NR	9 years
Kim et al.	2017	NR	NR
Kim et al.	2010	Other: 2 (2.38%) patients	NR
Kim et al.	2020	Non-UIP: 54 (64.2%) patients	NR
Kim et al.	2020	Alternative diagnosis: 58 (37.9%). UIP: definitive: 59 (38.6%), probable UIP: 33 (21.6%), indeterminate for UIP: 3 (2%). Emphysema: 74 (48.4%).	5 years
Kinoshita et al.	2004	HRCT revealed four main abnormal patterns: narrow spread honeycombing with subpleural linear shadows (Fig. 4); subtle fibrosis consists of a nonseptal line, septal thickening, intralobular reticular opacities, and localized GGO (Fig. 5); airway disease such as bulla, emphysema, and bronchial dilatation and wal, thickening; and patchy air-space consolida- tion associated with GGO within a small area.	NR
Lee et al.	2005	IAD with OP= 2 patients.	NR
Lee et al.	2021	Other ILD: C1: 2, C2: 9.	4.6 - 9.8 years
Leone et al.	2020	25 (9%) results were indeterminate. Among those 64 subjects, 26 (41%) had ILA and 35 (55%) had ILD. In both ILA and ILD the most frequent distribution pattern was subpleural (46% and 69%, respectively). 16% of the individuals presented with extensive disease.	NR
Leonel et al.	2012	Pleural thickness: 12/36 (30%), bronchiectasis: 9/36 (4%), honeycomb pattern: 5/36 (7.2%), ground-glass opacity:4/36 (9%), bullas: 4/36 (9%), cystic lesions: 3/36 (8%).	NR
Li et al.	2019	Lung abnormalities of 213 RA-ILD patients demonstrated bilateral infiltration (93.4%), with lower predominance (93.4%) and subpleural predominance (77.9%). The abnormalities of the two separate groups appeared the similar distribution. The upper predominance, peribronchovascular predominance, and unilateral infiltration were all uncommon in both groups.	24 months
Marten et al.	2009	NR	10.75 $\pm$ 9.8 years
McDonagh et al.	1994	Honeycomning, GGO, emphysema, bullae, bronchiectasis, pleural disease, parenchymal nodules	9 years
McFarlane et a.	2019	Probable UIP: 6 cases.	NR

Author	Year	Other HRCT Findings	RA mean duration notes
Mena-Vázquez	2021	4/116 other types of ILD.	4 years
Mohd Noor	2009	Consisted of 28 (44.4%) patients the in interstitial lung disease group, five (7.9%) in the obstructive group, six (9.5%) in mixed group and another six (9.5%) were grouped into miscellaneous. The miscellaneous group consisted of one patient with nodules, one with non-specific cysts and three with focal ground glass at middle lobe or apical, respectively reported as focal infection. The most frequent abnormalities were reticulation in 29 (46%) patients, ground glass opacities in 24 (38.1%) and bronchiectasis in 18 (28.6%).	14 $\pm$ 12 years
Mori et al.	2008	Bronchiolitis pattern:10 patients (7.9%). The most frequent finding was bronchial dilatation, which was observed in 52 of 126 patients with RA (41.3%). Ground-glass attenuation was the second most common abnormality (27.0%), followed by parenchymal micronodules (15.1%), subpleural micro-nodules (15.1%), linear attenuation (reticulation, 11.9%), bronchial wall thickening (11.9%), nodules (10.3%), honeycombing (8.7%), and airspace consolidation (4%).	NR
Morisset et al.	2017	Definitive UIP: 56/236 (24%), possible UIP: 38/236 (16), inconsistent with UIP: 142/236 (16%).	NR
Nurmi et al.	2018	9 others. Reticulation (93.1%) and GGO (72.4%) were the most common findings in the whole group. Traction bronchiectasis (59.6%), honeycombing (53.4%) and architectural distortion (41.4%) were also rather frequent, whereas emphysema (29.3%), bronchiectasis (24.6%) and pleural plaques (32.6%).	15.5 years
Nurmi et al.	2016	8 others. A diffuse alveolar damage (DAD) pattern was detected in one patient without an underlying ILD, thus likely representing RA-DAD.	NR
Okada et al.	2016	ILD other than OP, bronchial diseases (bronchiolitis, bronchiectasis), chronic obstructive pulmonary disease (COPD), and pleuritic diseases, were found in 13.0%, 4.8%, 3.5%, and 2.2%, respectively.	13.2 years
Paulin et al.	2021	20 (38.46%) Pattern inconsistent with UIP.	6 years
Paulin et al.	2018	UIP: 10 (21.7%), possible UIP: 18 (39.1%), inconsistent with UIP: 18 (39.1%).	40 months

Author	Year	Other HRCT Findings	RA mean duration notes
Pérez-Dórame et al.	2015	20%: Small airway disease.	12 months
Remy-Jardin et al.	1994	Most frequent finding: bronchiectasis and/or bronchiolectasis: 23 patients (30%).	12 years
A. Robles-Perez et al.	2016	Emphysema, nonspecific pulmonary nodules, nonspecific air trapping or cylindric bronch- iectasis.	12 months
Salaffi et al.	2019	3 patients with OP and NSIP.	7.5 ± 3.8 years
Samy et al.	2021	NR.	4.98 ± 5.53 years
Saracoglu et al.	2005	Abnormalities observed on HRCT were reticulation in 5 (12.5%), in- terlobular septal thickening in 4 (10%), bronchiectasis in 4 (10%), pleural disease in 5 (12.5%), ground-glass opacity in 1 (2.5%) and subpleural nodules in 4 (10%) of the patients.	9.5 ± 7.6 years
Solomon et al.	2016	NR	NR
Song et al.	2016	Bronchiolitis obliterans: 0.9%. Airway abnormalities including bronchiectasis and bronchial wall thickening were found in 92 (79.3 %) patients. Bronchiectasis and bronchial wall thickening were present in 64 (55.2 %) and 47 (40.5 %) RA patients, respectively.	9.9 +7.5 years
Sparks et al.	2019	UIP/AIP/DAD: 16 (18.8), Cellular NSIP (42:49.4%), fibrotic NSIP (27:31.8%).	11 years
Tanaka et al.	2004	GGO (91%) and reticulation (98%) were the most frequent findings in patients. Honeycombing (60%), traction bronchiectasis (75%), and architectural distortion (62%) were also frequently seen. Nodules were observed in 31 (49%) patients; these were centrilobular in 23 (37%) patients and indeterminate in eight (13%).	7.6 ±9.2 years
Wang et al.	2015	NR	5.6 ± 6.5 years
Yamakawa et al.	2020	18 UIP + NSIP patients.	4.7 years
Yamakawa et al.	2019	Probable UIP: 19, early UIP: 3, 26 NSIP/ UIP, 5 NSIP/OP, 4 unclassificable.	3.9 years
Yang et al.	2019	NR	8.7 years

Author	Year	Other HRCT Findings	RA mean duration notes
Yuksekkaya et al.	2013	Nodules (78.6%) and pleural thickening (48.8%). The most common CT patterns were follicular bronchiolitis (FB) in 28 (33.3%) patients and nodular disease (ND) in 12 (14.3%) others.	NR
Yunt et al.	2017	Possible UIP: 23 (15%)	NR
Zamora-Legoff et al.	2017	Pulmonary nodules: 30%, emphysema: 14%	4.9 years
Zayeni et al.	2016	Nodule: 7, cyst: 2, bronchiectasis:15, bronchiolectasia: 2, air trapping: 12.	3.8 years
Zhang et al.	2017	NR	8 + 9 years
Zrour et al.	2005	Reticular densities, micronodular or nodular densities, septal thickening, GGO.	8± 88 months

*HRCT: High resolution computed tomography, RA: reumathoid arthritis, ILD: Interstitial lung disease, NR: not reported, n: number, UIP: Usual interstitial pneumonia, NSIP: Nonspecific interstitial pneumonia, OP: organizing pneumonia, AIP: Acute interstitial pneumonia, DAD: diffuse alveolar damage, COPD: chronic obstructive pulmonary disease, IAD: ILA: Interstitial lung abnormality, GGO: ground glass opacity, IAD: inflammatory airway disease.

DISCUSSION AND CONCLUSION

This systematic review compiles observational studies of the presence of interstitial lung disease in RA-diagnosed patients, where from 21390 RA-patients, 4941 presented associated ILD. The majority of the RA-diagnosed patients were female; however, Kelly and Paulin considered the male sex as a risk factor for RA-ILD development (Kelly et al. 2014; Paulin et al. 2021). UIP and NSIP were the most frequent interstitial patterns.

RA-ILD predisposing risk factors were smoking, being male, being older and reporting high anti-CCP. Other factors included reporting SPD rising levels, CCL18, KL-6, and the presence of UIP.

The most frequently reported interstitial pattern on RA-patients is UIP (Avouac et al. 2020; Biederer et al. 2004; Castellanos-Moreira et al. 2020; Elemary et al. 2021; Gabbay et al. 1997), followed by NSIP and OP (Chatzidionisyou and Catrina 2016; Iqbal and Kelly 2015). RA affects mainly females (Kadura and Raghu 2021; Messina et al. 2020); however, men are more susceptible to interstital lung condition (Kelly et al. 2014; Paulin et al. 2021). ILD is the third most common cause of death in RA patients (Marigliano et al. 2013).

In this review it was observed that the development of interstital lung disease since the diagnosis of RA ranges between 3.5 (Alamoudi and Attar 2017) and 21 years (Huang et al. 2020). Early diagnosis categorization of RA-ILD is fundamental considering its effect on morbidity and mortility. The further identification of potential risk factors associated to ILD could contribute to the detection of early pulmonary involvement and therefore prevent or reduce the impact of the disease. Consecuently, it is key to continue the investigation on the morbidity and mortality of RA patients

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