



Dr Elisa Assis Palalane

PLLELI002

**INTERSTITIAL LUNG DISEASE (ILD) IN ADULTS PATIENTS WITH
AUTOIMMUNE CONNECTIVE TISSUE DISEASE (CTD) AT GROOTE SCHUUR
HOSPITAL**

University of Cape Town

Master of Philosophy in Rheumatology

2020

The copyright of this thesis vests in the author. No quotation from it or information derived from it is to be published without full acknowledgement of the source. The thesis is to be used for private study or non-commercial research purposes only.

Published by the University of Cape Town (UCT) in terms of the non-exclusive license granted to UCT by the author.

Table of contents

Declaration	2
Abstract	3
Acknowledgements	5
List of figures and tables	6
Abbreviations	7
CHAPTER 1: Introduction and Literature review	8
1.1 Context	8
1.2 Ethical considerations	13
CHAPTER 2: Publication-Ready Manuscript	14
APPENDIX	
1. Data capture form	
2. Ethical approval letter	
3. Hospital permission letter	
4. Instructions to the author from Clinical Rheumatology	
5. Palalane E, Alpizar-Rodriguez D, Botha S, et al SAT0595 INTERSTITIAL LUNG DISEASE IN SOUTH AFRICAN ADULTS PATIENTS WITH AUTOIMMUNE RHEUMATIC DISEASES Annals of the Rheumatic Diseases 2020;79:1252.	

Declaration

This research report is based on independent work performed by the candidate, Dr Elisa Palalane, and neither the whole work nor any part of it has been, is being, or is to be submitted for another degree to any other university. Part of this work was reported as a Poster presentation in EULAR E-Congress 2020 and the abstract published in the Annals of the Rheumatic Diseases (ARD) *prior to registration* for the abovementioned degree.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature:

Date: 22/10/20

Abstract

INTERSTITIAL LUNG DISEASE IN ADULT PATIENTS WITH AUTOIMMUNE CONNECTIVE TISSUE DISEASE AT GROOTE SCHUUR HOSPITAL

Elisa Palalane¹, Deshira Alpizar-Rodriguez^{2,3}, Stella Botha¹, Qonita Said-Hartley⁴, Gregory Calligaro⁵, Bridget Hodkinson¹

- 1 Division of Rheumatology, Groote Schuur Hospital, Cape Town, South Africa
- 2 Division of Rheumatology, University Hospital of Geneva, Geneva, Switzerland
- 3 Research Unit, Mexican College of Rheumatology, Mexico
- 4 Department of Radiology, Groote Schuur Hospital, Cape Town, South Africa
- 5 Division of Pulmonology, Groote Schuur Hospital, Cape Town, South Africa

Introduction. Interstitial lung disease (ILD) is prevalent in patients with autoimmune rheumatic diseases (ARD), leads to significant morbidity and mortality and is poorly characterized in South Africa (SA). We undertook this study to describe the clinical, serological and radiological features of ILD associated with ARD in a tertiary referral hospital.

Methods. A cross-sectional study of patients with ILD attending the rheumatology and respiratory outpatient clinics of Groote Schuur Hospital between October 2018 and September 2019. Clinical, serological and radiological features were documented. We compared features of 3 groups of patients: rheumatoid arthritis (RA), systemic sclerosis (SSc) and other autoimmune connective tissue diseases (OCTD) which included idiopathic inflammatory myopathies, mixed connective tissue disease, systemic lupus erythematosus, primary Sjogren's syndrome and overlap syndromes. Factors associated with usual interstitial pneumonia (UIP) subtype were assessed.

Results. Of 124 patients, 37 (29.8%) had RA, 32 (25.8%) SSc and 55 (44.4%) OCTD. Most patients were female (86.3%), of mixed racial ancestry (75.0%), and the median (IQR) age was 55 (46-66). Over one-third were smokers, emphysema was diagnosed in 22.6%, and one-third had previous pulmonary tuberculosis (PTB) infection. Smoking, emphysema, and previous PTB were higher in RA group but the difference was not statistically significant. All SSc patients and more than two-thirds of RA and OCTD patients had gastroesophageal reflux disease (GORD).

Nonspecific interstitial pneumonia (NSIP) was the commonest pattern of ILD (63.7%), followed by usual interstitial pneumonia (UIP) (26.6%) and other patterns (9.7%). RA patients had similar frequencies of NSIP and UIP. Patients with RA were significantly older (median (IQR)) at ILD onset (62 (55-68) years), compared to SSc (49 (38-56)) and OCTD (42 (33-56)) ($p < 0.001$). Pulmonary function tests (PFTs) were significantly worse in SSc and OCTD groups. Regarding MTX exposure, 37.1% patients has MTX prescribed before ILD diagnosis, 33.9% continued, started or restarted after ILD diagnosis. No case of acute pneumonitis was documented. Pulmonary function tests and high-resolution computer tomography severity correlated poorly, with PFTs underestimating the severity. In the analysis comparing patients with and without UIP, RA diagnosis (OR 3.8, 95% CI 1.5-9.5), older age (OR 1.1, 95% CI 1.0-1.1), COPD (OR 3.2, 95% CI 1.4-8.0), longer ARD-ILD interval, and higher FVC (OR 1.0, 95% CI 1.0-1.1) were significantly associated with UIP.

Conclusions: ILD was most commonly diagnosed in RA and SSc patients, with NSIP seen most frequently overall. Smoking, GORD, and PTB were frequent comorbidities. Amongst RA patients, we observed older age of onset and, interestingly, similar frequencies of NSIP and UIP patterns. The use of MTX was not associated with the development of acute pneumonitis in patients with ILD.

Acknowledgments

I'm grateful to God, the Almighty, for making me a curious person, to create all the condition for me to pursue my studies and to give me the opportunity and strength to achieve this level in my academic life beyond the borders of my country and far from my family.

From the bottom of my heart, I would like to thank the following people who have helped me undertake this research, without whom I would not have been able to complete this research:

I want to express my deepest appreciations to my supervisors especially Bridget Hodkinson for helping me choosing the topic, for her enthusiasm in the project, encouragement, patience and consistent support and guidance, during the course of this journey. Her meticulous reviews, thoughtful comments and recommendations on this dissertation were source of motivation and inspiration. Prof Hodkinson office was always open to me whenever I had an issue or had a question about my research or writing.

I would like to pay my special regard to my co-supervisor Deshire Alpizar-Rodriguez for her contribution and guidance with statistical analysis, continuous support and constructive feedback on the writing of the thesis. I am gratefully for her valuable comments on this thesis.

In addition, my acknowledge also goes to my co-supervisors, Stella Botha for her valuable input in protocol development and guidance through the research period, Greg Calligaro and Qonita Said-Hartley, for helping to better understand the disease in the lungs and to review the unclear image reports.

This research report is also a result of a teamwork and cooperation, thus, I would like to recognize the collaboration of the Division of Rheumatology team at Groote Schuur Hospital Bridget Hodkinson, Ayanda Gcelu, Stella Botha, Urisha Brijlal, Abdel Gaffar Mohamed, Mohamed Awad, and the medical registrars on rotation during the period of the study for the fellowship, help in recruiting the participants, and all sympathy and encouragement. A special *Khanimambo* goes to Ayanda and Urisha, for making the moments passed in GSH-UCT more pleasant. I am equally thankful to Amelia Lawrence for assisting me with the administrative issues.

I would like to express my sincere gratitude to the financial support received by Instituto de Bolsas De Moçambique (Mozambique Scholarship Institute) under the grant No 063/2017. Without their support and funding, I could not have reached this goal.

Special thanks my long-time friends, Anabela, Carol, Cecilia, Ceny, Crisina, Dirce, Eliane, Ernestina, Flávia, Leida, Lúcia, Márcia, Quimasse, Sheila, Virgínia, for the prayers, encouraging and the moral support before and during this journey.

My heartfelt gratitude to my parents, Assis and Maria, who set me off on the road to this MPhil a long time ago, for their unwavering support and constant prayers. My siblings, Jaime and Sergio, for their unconditional support and encouragement. To my sisters in law, Tacilta, Ercília and Selma, for continuous support, helping taking care of my children and being a real mum for them during my absence. To my cousins, Bruno e Tania, for helping to keep my children busy and having a fun during my absence and when I was busy writing.

Finally, my profound gratitude and recognition to my dear husband, Alberto, for his love and perseverance, for providing continuous guidance, for the permanent support before and throughout all this process. I am equally grateful to Noah and Maisha, for their patience, for being brave children and an inexhaustible source of joy.

This accomplishment would not have been possible without them. Thank you. Elisa Palalane

List of tables

Table 1	Demographic, clinical and serological characteristics of 124 patients with ILD-ARD
Table 2	Details of interstitial lung disease in 124 patients with ILD-ARD
Table 3	Comparison of ILD-ARD patients features with and without usual interstitial pneumonia
Table 4	Multivariable analysis

Abbreviations

ANA	Anti-nuclear antibody
COPD	Chronic obstructive pulmonary disease
ARD	Autoimmune rheumatic disease
DAD	Diffuse alveolar damage
DIP	Desquamative interstitial pneumonia
DLCO	Diffusion capacity for carbon monoxide
FVC	Forced vital capacity
GORD	Gastroesophageal reflux disease
GSH	Groote Schuur Hospital
HIV	Human immunodeficiency virus
HRCT	High resolution computed tomography
IIM	Idiopathic inflammatory myopathy
ILD	Interstitial lung disease
LEF	Leflunomide
LIP	Lymphocytic interstitial pneumonia
MCTD	Mixed connective tissue disease
MTX	Methotrexate
NSIP	Nonspecific interstitial pneumonia
OCTD	Other connective tissue diseases
OP	Organizing pneumonia
pSS	Primary Sjögren syndrome
PFTs	Pulmonary function tests
PTB	Pulmonary tuberculosis
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SA	South Africa
Sc170	Anti-topoisomerase
SLE	Systemic lupus erythematosus
SSc	Systemic sclerosis
UCTD	Undifferentiated connective tissue disease
UIP	Usual interstitial pneumonia

CHAPTER 1: INTRODUCTION

1.1 Context

The lung is a common site for complications of systemic autoimmune rheumatic diseases (ARD). Lung involvement in ARD can involve parenchyma (interstitial lung diseases), airway, pleura (pleurisy and pleural effusions), and the pulmonary vessels (pulmonary hypertension (PH) and diffuse alveolar haemorrhage) [1]. Interstitial lung disease (ILD) and PH are the most common lung manifestations seen in the ARD [2]. This review focuses on ILD in the ARD.

Interstitial lung diseases are a heterogeneous group of inflammatory lung parenchyma disorders that have common radiological, pathological and clinical manifestations [3]. They are characterized by inflammation or fibrosis arising in the interstitium of the lung [4]. In patients with ARD, ILD is fairly common and leads to significant morbidity and mortality [1]. For example, SSc-ILD patients have estimated median survival of 5 to 8 years after ILD diagnosis [5]. Additionally, ILD is often challenging to treat due to its progressive nature, variable presentation, unpredictable response to therapy, and lack of guidelines to assist clinicians [6,7]. There is a need to evaluate ILD in ARD patients in order to clarify predictive factors, subtypes and outcomes and optimum therapies [5].

The ARD that are frequently complicated by ILD include (in order of descending frequency) systemic sclerosis (SSc), idiopathic inflammatory myopathies (IIM), rheumatoid arthritis (RA), mixed connective tissue disease (MCTD) and undifferentiated connective tissue disease (UCTD), systemic lupus erythematosus (SLE) and primary Sjögren's syndrome (pSS) [7].

Of concern, ARD treatment may lead to or exacerbate ILD. Patients with ILD prescribed methotrexate (MTX) and/or leflunomide (LEF) have been reported to have a higher risk of developing acute pneumonitis [2,5,8]. Nevertheless, there is a growing evidence that treatment with conventional disease modifying antirheumatic drugs (DMARDs) such as MTX and LEF can prevent or delay the onset of ILD, treat ILD and can be safely continued in patients with ILD diagnosis without increasing the risk of progression and/or exacerbation of ILD in patients with ARD [9-12].

ILD subtypes in ARD

According to its pathologic and radiologic features, ILD in ARD is classified into 6 subtypes: nonspecific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), organizing pneumonia (OP), lymphocytic interstitial pneumonia (LIP), diffuse alveolar damaged (DAD)/acute interstitial pneumonia (AIP), and rarely, desquamative interstitial pneumonia (DIP) (Table 1)[13,14]. Each subtype has different frequencies amongst the various ARDs, with varying prognosis and treatment choices. The most common subtypes in ARD are NSIP and UIP. Combined patterns are occasionally observed [2,7]. The combination of UIP and DAD in association with any ARD portends a poor prognosis. The estimated 5-year mortality of UIP in patients with ARD is 50% [13].

Prevalence of ILD in ARD

The published prevalence rate varies widely because of differences in study designs, populations and the way in which lung disease is defined [5]. The prevalence and characteristics of ILD in various rheumatic disorders are summarized in table 2.

Pathogenesis and risk factors for develop ILD in ARD

The pathogenesis of ARD-ILD is not clearly understood. Unknown triggers cause inflammatory cells to invade interstitial and alveolar spaces leading to epithelial damage that cause recruitment and activation of fibroblasts and myofibroblasts. This inflammation leads to increased extracellular matrix proteins and fibrogenic cell population, causing scarring within the lung [5].

Risk factors for the development and progression of ILD, have been identified based on demographic data, physiologic decline and radiography (Table 3). Older age at onset of ARD symptoms has been implicated as a risk factor in all diseases except in MCTD [1,2,4,5,15-18]. Disease duration at ILD onset differs depending on the ARD: ILD is associated with early disease in SSc, MCTD and IIM and with advanced disease in RA, SLE and pSS [1,2,4,5,15-20]. Smoking has been implicated in RA and pSS [1,2,4,5,15,16,19]. In RA, smoking-related increased citrullination of proteins within the lungs leads to ILD [21]. Male gender is a risk factor in all ARD [1,16,15,2,3,22,4,13,6,19,23]. Specific disease features such as gastro-oesophageal reflux disease (GORD) in SSc and MCTD have also been identified [4,6,3,22,24]. It has been consistently reported that oesophageal dilatation and the presence of a high degree of GORD is associated with more severe lung impairment and more rapid decline of pulmonary function values in SSc patients. However, until now, is not clear whether antacid treatment helps pulmonary functions preservation in ILD [1]. Specific auto-antibodies related to the different ARD (for example, anti-topoisomerase 1 (Scl70), rheumatoid factor (RF), anti-citrullinated antibody (anti-CCP) and anti-tRNA synthetase antibodies (ARS) including anti-Jo1 antibody) are associated with ILD development [13,21,25-29,22,30,31,15,4,32,33,24]. Silica exposure in gold miners is associated with the development of diffuse SSc, and with higher frequency of ILD [32].

Clinical presentation and diagnosis of ILD in ARD

Commonly, ILD presents with symptoms of progressive exertional dyspnoea, a persistent non-productive cough, bi-basal crackles on chest examination, diffuse bilateral infiltrates on chest radiographs (CXR) and restrictive lung patterns on pulmonary function tests (PFT) characterised by reduced total lung capacity and forced vital capacity (FVC) and impaired diffusion capacity for carbon monoxide (DLCO) [3,7,34].

Plain CXR are not very sensitive for identifying ILD, and are normal in up to 10% of ILD patients [5]. Isolated use of PFT is also insensitive with a high rate of tests not showing any abnormalities even in severe disease and can be affected by co-morbidities including PH that causes a disproportionate decrease in DLCO, and COPD that causes pseudo-normalization of lung volumes.

The 6-minute walk test (6MWT) is useful for determining functional capacity and degree of oxygen desaturation. However, it is confounded by non-pulmonary factors such as joint pain, weakness and anaemia and correlates weakly with FVC. It is a useful adjuvant to tracking overall functional status but cannot replace HRCT or PFT for ILD diagnosis or determination of severity [7,4]. Dyspnoea is also a symptom of PH (World Health Organisation group 1, 3 and 4 frequently seen in ARDs) and another non-lung parenchyma causes of PH that are frequent in many ARD including SSc, SLE and MCTD. In these cases, echocardiogram is recommended, with right heart catheterism when there is high suspicion of this complication [33].

Although pathologic evaluation of a lung biopsy specimen is the most sensitive technique and the gold standard for confirming the ILD and subtype, it is rarely used, as the histopathologic pattern and distribution of radiographic abnormalities observed on chest high resolution computed tomography (HRCT) can accurately predict and correlate with the histopathologic findings [7,2]. Therefore, HRCT has become the standard for evaluation of patients with suspected ILD both to determine disease subtype and to assess disease severity. Chest HRCT may reveal any combination of abnormalities in the lung parenchyma, including: inflammation, fibrosis and granulomas [3].

Combined, chest HRCT and PFT can be reliably used to diagnose and monitor ILD-ARD. They assist in assessing severity, determining the prognosis, gauging disease progression and measuring response to therapy [3,7].

Grading ILD severity

The severity of ILD is based on clinical assessment, degree of PFT restriction and impaired gas exchange together with histologic and radiographic features[7]. Scoring systems for HRCT have been shown to provide prognostic information and thresholds therapeutic intervention, especially in SSc [35,26]. Goh *et al.* proposed a simple staging system based on disease extension on HRCT and degree of FVC impairment (table 4). This approach classifies the disease severity as “limited” or “extensive” which provides a more accurate prognostic score than can be achieved with any single index in isolation [35,13,7,33,20,16]. These simple criteria may be useful for other ILD-ARD.

Disease progression

Criteria for disease progression are % FVC decline $\geq 10\%$ or % FVC decline $<10\%$ and a decline of % DLCO $\geq 15\%$ [4].

Table 1: Histologic and radiographic features of main ILD subtypes adapted from Wallace et al [7], Hochberg [6] and Hellemon [36]

ILD subtype	Pathologic features	HRCT findings
NSIP	Uniform, homogeneous pattern with variable degrees of inflammation	<ul style="list-style-type: none"> • Bilateral, symmetric, basilar, peripheral ground-glass opacities • Traction bronchiectasis • Intra and interlobular septal thickening and consolidations can be seen • Subpleural sparing characteristic if seen
UIP	Fibrotic areas interposed with normal or near-normal lung; fibroblastic foci	<ul style="list-style-type: none"> • Bilateral, basilar, subpleural fibrosis with volume loss and architectural distortion • Subpleural cysts (“honeycombing”) • Traction bronchiectasis and bronchiolectasis common
LIP	Extensive lymphocytic infiltration associated with peribronchial lymphoid follicles	<ul style="list-style-type: none"> • Lower lobe predominant • Perivascular thin-walled cysts • Can have surrounding ground-glass or centrilobular nodules • Associated septal/bronchovascular thickening (interstitial thickening) common
OP	Inflammation in distal airways	<ul style="list-style-type: none"> • Central ground-glass opacity surrounded by denser consolidation • Airspace consolidation, often bilateral, usually patchy but can be lobar • Alternatively, can be nodular • Subpleural and/or peribronchovascular distribution • Area of involvement can change over time
DAD	Hyaline membrane	<ul style="list-style-type: none"> • Bilateral patchy ground-glass opacities with airspace consolidation
DIP	<p>Excess number of pigmented macrophages diffusely filling the alveoli, with associated thickening of the septa secondary to the presence of inflammatory cells</p> <p>Reactive pneumocytic epithelial cells and sporadic eosinophils can also be seen over the course of alveolar septa</p>	<ul style="list-style-type: none"> • Bilateral diffuse ground-glass appearance, reticular opacities interposed with relatively normal lung zones, forming a mosaic attenuation • Usually symmetrical and frequently involving the basal parts of the lungs. • Most common in subpleural area • Often associated with irregular lines and traction bronchiectasis • Peripheral microcysts implying dilated bronchioles and alveolar ducts may be seen • Honeycomb appearance is not common.
<p>NSIP, nonspecific interstitial pneumonia; UIP, usual interstitial pneumonia; OP, organizing pneumonia; LIP, lymphocytic interstitial pneumonia; DAD, diffuse alveolar damage; DIP, desquamative interstitial pneumonia.</p>		

Table 2: Estimated worldwide prevalence and characteristics of ILD [7,5,2,4,8,25,3,1,30,6,16,17,14,18]

ARD type	ILD prevalence	Characteristics
SSc	Clinically up to 90% Clinically significant in 8-27%	NSIP >> UIP >> COP > LIP, DAD and granulomatous lung disease
IIM	Up to 70 – 90% >70% when associated with anti-synthetase antibodies	NSIP >> UIP > DAD and OP
RA	4 – 68% Clinically evident in approximately 10%	UIP > NSIP > OP, DAD, LIP, DIP
MCTD	20 – 90%	NSIP >> UIP
pSS	2 – 30% Clinically evident in 9 – 24%	NSIP >> LIP, UIP > OP
UCTD	Limited data 47 – 78%	NSIP >> UIP
SLE	1 – 15% Clinically uncommon	NSIP >> LIP and OP >>> UIP

ARD, autoimmune rheumatic disease; ILD, interstitial lung disease; HRCT, high resolution computer tomography; SSc, systemic sclerosis; IIM, idiopathic inflammatory myopathy; ASS, anti-synthetase syndrome; RA, rheumatoid arthritis; MCTD, mixed connective tissue disease; pSS, primary Sjogren’s syndrome; UCTD, undifferentiated connective tissue disease; SLE, systemic lupus erythematosus; UIP, usual interstitial pneumonia

Table 3: Risk factors and predictors of disease progression in ILD-ARD
 [13,4,6,7,2,3,1,21,15,31,29,22,26,18,17,19]

ARD type	Risk factors	Poor prognostic factors or predictors of disease progression
SSc	Older age Male gender African American Silica exposure in gold mines Shorter disease duration Diffuse SSc GORD Abnormal NFC Nucleolar ANA (anti-Scl70, anti-PM/Scl, anti-Th/To and anti-U3RNP antibodies High CRP Presence of proteinuria	Increased age Male gender African American ethnicity Shorter duration of scleroderma Concomitant PAH/ cardiac involvement Early decline or low baseline FVC (<70%) and DLCO (< 40%) Higher extent of disease on CT (>20%) Presence of honeycombing/ UIP pattern High titres of anti-Scl70 Elevated serum KL-6 levels Increased alveolar epithelial permeability
IIM	Older age (> 45) Amyopathic disease Joint involvement Concomitant PAH Anti-MDA5 antibody, anti-PM-Scl, and anti-Ro-52 antibodies Anti-synthetase antibodies	Older age Amyopathic disease Acute and subacute presentation Concomitant PAH and MDA5 Anti-Ro52 Low initial FVC
RA	Older age (> 60) Male gender at middle age Smoking Longer disease duration Active joint disease Radiographic joint damage HLA-DRB1*502 High RF and anti-CCP antibody	Older age Male Smoking Digital clubbing Rapid decline of PFT during follow-up Decline in FVC > 10% anytime UIP pattern Extensive disease on images Low DLCO % predictor at presentation
MCTD	Advanced age Male gender Early disease Oesophageal dilatation, oesophageal Motor dysfunction Fulfilment of all MCTD criteria sets Presence of SSc clinical features Worse baseline functional status High anti-RNP antibody, anti-Ro52 antibody and no prior arthritis	Male gender Absence of arthritis Presence of anti-Ro52 Elevated anti-RNP titer
SLE	Older age at onset of SLE (> 50) Greater disease duration (>10y) Postpartum Scleroderma-like features (sclerodactyly, RP, and abnormal NFC), anti-(U1) RNP, and anti-Ro antibodies High levels of hsCRP Hypocomplementemia Presence of serum cryoglobulins LE cells in peripheral blood	No information was found in the literature

ARD type	Risk factors	Poor prognostic factors or predictors of disease progression
pSS	Older age Male gender Smoking Longer disease duration RP Oesophageal involvement Positive for ANA, RF, anti-La, anti-Ro Hypergammaglobulinemia Lymphopenia	Older age Oesophageal involvement
RA, rheumatoid arthritis; SSc, systemic sclerosis; IIM, idiopathic inflammatory myopathy; MCTD, mixed connective tissue disease; SLE, systemic lupus erythematosus; pSS, Sjogren's syndrome; ASS: anti-synthetase syndrome; HLA: human leukocyte antigen; CRP: C-reactive protein; hsCRP: high sensitive C-reactive protein; PAH: Pulmonary arterial hypertension; NFC: Nailfold capillaroscopy; RP: Raynaud's phenomenon		

Table 4: ILD simple staging system for systemic sclerosis (SSc) as proposed by Goh et al [35]

Limited disease	Minimal disease on HRCT (< 20%) Or Indeterminate disease on HRCT (10-30%) + FVC ≥ 70%
Extensive disease	Severe disease on HRCT (> 20%) Or Indeterminate disease on HRCT (10-30%) + FVC < 70%
HRCT: High resolution computed tomography; FVC: forced vital capacity	

REFERENCES

1. Ha Y-J, Lee YJ, Kang EH (2018) Lung involvements in rheumatic diseases: update on the epidemiology, pathogenesis, clinical features, and treatment. *BioMed Research International*. doi:10.1155/2018/6930297
2. Mathai SC, Danoff SK (2016) Management of interstitial lung disease associated with connective tissue disease. *BMJ (Online)* 352. doi:10.1136/bmj.h6819
3. Grippi MA, Elias JA, Fishman J, Kotloff RM, Pack AI, Senior RM, Siegel MD (2015) *Fishman's pulmonary diseases and disorders*. McGraw-Hill Education,
4. Dellaripa PF, Fischer A, Flaherty KR. (2014) *Pulmonary manifestations of rheumatic disease: a comprehensive guide*. Springer, New York. doi:10.1007/978-1-4939-0770-0
5. Atzeni F, Gerardi MC, Barilaro G, Masala IF, Benucci M, Sarzi-Puttini P (2018) Interstitial lung disease in systemic autoimmune rheumatic diseases: a comprehensive review. *Expert Review of Clinical Immunology* 14 (1):69-82. doi:10.1080/1744666X.2018.1411190
6. Hochberg MC, Gravallese EM, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH (2019) *Rheumatology*. Elsevier, Philadelphia, PA
7. Wallace B, Vummidi D, Khanna D (2016) Management of connective tissue diseases associated interstitial lung disease: a review of the published literature. *Current Opinion in Rheumatology* 28 (3):236-245. doi:10.1097/BOR.0000000000000270
8. Kelly C, Iqbal K, Iman-Gutierrez L, Evans P, Manchegowda K (2016) Lung involvement in inflammatory rheumatic diseases. *Best Practice & Research Clinical Rheumatology* 30 (5):870-888. doi:10.1016/j.berh.2016.10.004
9. Fragoulis G, Nikiphorou E, Larsen J, Korsten P, Conway R (2019) Methotrexate-associated pneumonitis and rheumatoid arthritis-interstitial lung disease: current concepts for the diagnosis and treatment. *Frontiers in Medicine* 6:238
10. Conway R, Low C, Coughlan RJ, O'Donnell MJ, Carey JJ (2015) Methotrexate use and risk of lung disease in psoriasis, psoriatic arthritis, and inflammatory bowel disease: systematic literature review and meta-analysis of randomised controlled trials. *BMJ* 350 (mar13 17). doi:10.1136/bmj.h1269
11. Kiely P, Busby AD, Nikiphorou E, Sullivan K, Walsh DA, Creamer P, Dixey J, Young A (2019) Is incident rheumatoid arthritis interstitial lung disease associated with methotrexate treatment? Results from a multivariate analysis in the ERAS and ERAN inception cohorts. *BMJ Open* 9 (5). doi:10.1136/bmjopen-2018-028466
12. Nokhatha SAA, Harrington R, Conway R (2020) Methotrexate and the lung in rheumatoid arthritis. *European Medical Journal Rheumatology* 7 (1):80-90
13. Dellaripa PF (2018) Interstitial lung disease in the connective tissue diseases; a paradigm shift in diagnosis and treatment. *Clinical Immunology* 186:71-73. doi:10.1016/j.clim.2017.09.015
14. Doyle TJ, Dellaripa PF (2017) Lung manifestations in the rheumatic diseases. *Chest* 152 (6):1283-1295. doi: 1210.1016/j.chest.2017.1205.1015. Epub 2017 May 1225.
15. Yazisiz V, Arslan G, Ozbudak İ, Turker S, Erbasan F, Avci A, Ozbudak O, Terzioglu E (2010) Lung involvement in patients with primary Sjögren's syndrome: what are the predictors? *Rheumatology International* 30 (10):1317-1324. doi:10.1007/s00296-009-1152-8
16. Farquhar H, Vassallo R, Edwards AL, Matteson EL (2019) Pulmonary complications of rheumatoid arthritis. *Seminars in Respiratory and Critical Care Medicine* 40 (02):194-207
17. Barba T, Mainbourg S, Nasser M, Lega J-C, Cottin V (2019) Lung diseases in inflammatory myopathies. *Seminars in Respiratory and Critical Care Medicine* 40 (02):255-270
18. Hannah J, D'Cruz DP (2019) Pulmonary complications of systemic lupus erythematosus. *Seminars in Respiratory and Critical Care Medicine* 40 (02):227-234
19. Chung A, Wilgus ML, Fishbein G, III JPL (2019) Pulmonary and bronchiolar Involvement in Sjögren's syndrome. *Seminars and Critical Care Medicine* 40 (02):235-254
20. Mackintosh JA, Stainer A, Barnett JL, Renzoni EA (2019) Systemic sclerosis associated interstitial lung disease: a comprehensive overview. *Seminars in Respiratory and Critical Care Medicine* 40 (02):208-226
21. Solomon J, Chung J, Cosgrove GP, Demoruelle M, Fernandez-Perez E, Fischer A, Frankel S, Hobbs SB, Huie T, Ketzer J, Mannina A, Olson AL, Russell G, Tsuchiya Y, Yunt Z, Zelarney P, Brown K, Swigris J (2016) Predictors of mortality in rheumatoid arthritis-associated interstitial lung disease. *European Respiratory Journal* 47 (2):588-596. doi:10.1183/13993003.00357-2015
22. Reiser S, Gunnarsson R, Aaløkken TM, Lund MB, Mynarek G, Corander J, Haydon J, Molberg Ø (2018) Progression and mortality of interstitial lung disease in mixed connective tissue disease: a long-term observational nationwide cohort study. *Rheumatology (Oxford, England)* 57 (2):255. doi:10.1093/rheumatology/kex077

23. Choi W-I, Dauti S, Kim HJ, Park SH, Park JS, Lee CW (2018) Risk factors for interstitial lung disease: a 9-year nationwide population-based study.(Report). *BMC Pulmonary Medicine* 18 (1). doi:10.1186/s12890-018-0660-2
24. Mackintosh JA, Anna Stainer, Joseph L. Barnett, and Elisabetta A. Renzoni (2019) Systemic sclerosis associated interstitial lung disease: a comprehensive overview. *Seminars in Respiratory and Critical Care Medicine*, 40 (02):208-226
25. Kelly CA, Saravanan V, Nisar M, Arthanari S, Woodhead FA, Price-Forbes AN, Dawson J, Sathi N, Ahmad Y, Koduri G, Young A (2014) Rheumatoid arthritis-related interstitial lung disease: associations, prognostic factors and physiological and radiological characteristics-a large multicentre UK study. *Rheumatology (Oxford, England)* 53 (9):1676. doi:10.1093/rheumatology/keu165
26. Winstone TA, Assayag D, Wilcox PG, Dunne JV, Hague CJ, Leipsic J, Collard HR, Ryerson CJ (2014) Predictors of mortality and progression in scleroderma-associated interstitial lung disease: a systematic review. *Chest* 146 (2):422-436. doi:10.1378/chest.13-2626
27. Khanna D, Nagaraja V, Tseng C-h, Abtin F, Suh R, Kim G, Wells A, Furst DE, Clements PJ, Roth MD, Tashkin DP, Goldin J (2015) Predictors of lung function decline in scleroderma-related interstitial lung disease based on high-resolution computed tomography: implications for cohort enrichment in systemic sclerosis-associated interstitial lung disease trials.(clinical report). *Arthritis Research & Therapy* 17 (372). doi:10.1186/s13075-015-0872-2
28. Mathai SC, Hummers LK, Champion HC, Wigley FM, Zaiman A, Hassoun PM, Girgis RE (2009) Survival in pulmonary hypertension associated with the scleroderma spectrum of diseases: impact of interstitial lung disease. *Arthritis & Rheumatism* 60 (2):569-577. doi:10.1002/art.24267
29. Fujisawa T, Hozumi H, Kono M, Enomoto N, Hashimoto D, Nakamura Y, Inui N, Yokomura K, Koshimizu N, Toyoshima M, Shirai T, Yasuda K, Hayakawa H, Suda T (2014) Prognostic factors for myositis-associated interstitial lung disease.(research article). *PLoS ONE* 9 (6). doi:10.1371/journal.pone.0098824
30. Kamen DL, Strange C (2010) Pulmonary manifestations of systemic lupus erythematosus. *Clinics in Chest Medicine* 31 (3):479-488. doi:10.1016/j.ccm.2010.05.001
31. Palm O, Garen T, Berge Enger T, Jensen JL, Lund M-B, Aaløkken TM, Gran JT (2013) Clinical pulmonary involvement in primary Sjogren's syndrome: prevalence, quality of life and mortality-a retrospective study based on registry data. *Rheumatology (Oxford, England)* 52 (1):173. doi:10.1093/rheumatology/kes311
32. Ashmore P, Tikly M, Wong M, Ickinger C (2018) Interstitial lung disease in South Africans with systemic sclerosis. *Rheumatology International* 38 (4):657-662. doi:10.1007/s00296-017-3893-0
33. Wells A, Devaraj A, Renzoni EA, Denton CP (2019) Multidisciplinary evaluation in patients with lung disease associated with connective tissue disease. *Seminars in Respiratory and Critical Care Medicine*. 40 (02): 184-193
34. King TE (2018) Approach to the adult with interstitial lung disease: clinical evaluation. *UpToDate*. www.uptodate. Accessed 26 May 2018.
35. Goh NSL, Desai SR, Veeraraghavan S, Hansell DM, Copley SJ, Maher TM, Corte TJ, Sander CR, Ratoff J, Devaraj A, Bozovic G, Denton CP, Black CM, Du Bois RM, Wells AU (2008) Interstitial lung disease in systemic sclerosis: a simple staging system. *American Journal of Respiratory and Critical Care Medicine* 177 (11):1248. doi:10.1164/rccm.200706-877OC
36. Hellemons ME, Moor CC, Thüsen JVD, Rossius M, Odink A, Thorgersen LH, Verschakelen J, Wuyts W, Wijsenbeek MS, Bendstrup E (2020) Desquamative interstitial pneumonia: a systematic review of its features and outcomes. *European Respiratory Review* 29 (156). doi:10.1183/16000617.0181-2019

CHAPTER 2: PUBLICATION-READY MANUSCRIPT

TITLE PAGE

TITLE: Interstitial lung disease subtypes and clinical features in patients with Autoimmune Rheumatic Diseases in South Africa

AUTHORS:

Elisa Palalane¹, Deshira Alpizar-Rodriguez², Stella Botha¹, Qonita Said-Hartley³, Gregory Calligaro⁴, Bridget Hodkinson¹

AFFILIATIONS:

1 Division of Rheumatology, Groote Schuur Hospital, Cape Town, South Africa

2 Research Unit, Mexican College of Rheumatology, Mexico

3 Department of Radiology, Groote Schuur Hospital, Cape Town, South Africa

4 Division of Pulmonology, Groote Schuur Hospital, Cape Town, South Africa

CORRESPONDENCE:

Elisa Palalane, J47 Division of Rheumatology, Groote Schuur Hospital, Observatory, Cape Town, 7925, South Africa. Email: elisa.palalane@gmail.com

ABSTRACT

Introduction. Interstitial lung disease (ILD) in patients with autoimmune rheumatic diseases (ARD) is poorly characterized in South Africa. We describe the clinical, serological and radiological features of ILD associated with ARD in a tertiary referral hospital.

Methods. A cross-sectional study of 124 patients attending rheumatology and respiratory outpatient clinics. We compared three groups of patients: rheumatoid arthritis (RA), systemic sclerosis (SSc) and other autoimmune connective tissue diseases (OCTD). Factors associated with usual interstitial pneumonia (UIP) were assessed.

Results. Of 124 patients, 37 (29.8%) had RA, 32 (25.8%) SSc and 55 (44.4%) OCTD. Most patients were female (86.3%), of mixed racial ancestry (75.0%), and the median (IQR) age was 55 (46-66 years). Over one-third were smokers, emphysema was diagnosed in 22.6%, one-third had previous pulmonary tuberculosis (PTB) infection, and the majority (75.6%) had gastroesophageal reflux disease. Nonspecific interstitial pneumonia (NSIP) was the commonest ILD pattern (63.7%), followed by UIP (26.6%) and other patterns (9.7%). Patients with RA were older, had similar frequencies of NSIP and UIP, and had significantly better pulmonary function tests than the SSc and OCTD groups. No case of acute pneumonitis was documented in ILD-ARD patients treated with methotrexate (MTX).

Conclusions: ILD was most commonly diagnosed in RA and SSc, with NSIP seen most frequently overall, with similar frequencies of NSIP and UIP patterns amongst RA patients. The use of MTX was not associated with the development of acute pneumonitis in patients with ILD.

KEY POINTS

- ILD was most commonly diagnosed in RA and SSc patients
- NSIP and UIP frequencies were not different amongst South African RA patients
- Use of MTX before and after ILD diagnosis was not associated with development of acute pneumonitis

KEY WORDS

- Interstitial lung disease
- Systemic rheumatic diseases
- Autoimmune rheumatic diseases
- Autoimmune connective tissue disease
- Epidemiology
- South Africa

Introduction.

Interstitial lung diseases (ILD) are a heterogeneous group of inflammatory lung parenchyma disorders that have common radiological, pathological and clinical manifestations [1]. In patients with autoimmune rheumatic diseases (ARD), ILD is highly prevalent, leads to significant morbidity and mortality [2] and is difficult to treat due to its variable presentation, progression and response to therapy, with a relative lack of guidelines to assist clinicians [3,4].

In ARD, ILD is classified according to pathologic and radiologic features into six subtypes: nonspecific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), organizing pneumonia (OP), lymphocytic interstitial pneumonia (LIP) and diffuse alveolar damaged (DAD)/acute interstitial pneumonia (AIP) and rarely desquamative interstitial pneumonia (DIP) [1,5,6]. Each subtype has different frequencies in the various ARDs, with distinct treatment and prognosis. The most common types are NSIP and UIP. The presence of UIP and DAD in association with any ARD type portends the worst prognosis, with a 5-year mortality of about 50% [5].

ILD prevalence differs between ARDs, in systemic sclerosis (SSc) 70-90% patients are diagnosed with ILD, in idiopathic inflammatory myopathies (IIM) 15-70%, in mixed connective tissue disease (MCTD) 20-85%, in rheumatoid arthritis (RA) 4-68%, in primary Sjogren's Syndrome (pSS) 10-30% and in systemic lupus erythematosus (SLE) 2-10% [4].

Risk factors for the development and progression of ILD in ARD include older age, male sex, smoking, disease duration (early in SSc, MCTD and IIM, advanced in RA, SLE and pSS), silica exposure in SSc, gastroesophageal reflux disease (GORD) and the presence of autoantibodies including anti-topoisomerase 1, rheumatoid factor (RF) and anti-tRNA synthetase antibodies such as anti-Jo1 antibodies [7,5,8-14]. It has been consistently reported that oesophageal dilatation and the presence of a high degree of GORD is associated with more severe lung impairment and more rapid decline of pulmonary function values in SSc patients. However, until now, is not clear whether antacid treatment helps pulmonary functions preservation in ILD [2].

To date there are no published studies from sub-Saharan Africa examining ILD in all ARDs. Most of the data related to ILD in ARD are based on studies done in patients with SSc. A recent retrospective study of SSc patients from South African (SA) showed an ILD prevalence of 40%, and the majority (63%) developed ILD within the first year of SSc diagnosis. Interstitial lung disease was the cause of death in 44%, and was associated with gold mining exposure [14]. This study will describe the clinical, serological and radiological features of ILD-ARD and their associations in patients attending a tertiary referral hospital.

Patients and Methods

This cross-sectional study included patients with ARD-ILD attending a South African tertiary level state hospital. The University of Cape Town Faculty of Health Sciences Human Research Ethics Committee approved the study. Patients from the Rheumatology and Respiratory outpatient clinics seen between October 2018 and September 2019 were included if they met the following criteria: age \geq 18 years, ARD diagnosed according to classification criteria for each disease, and ILD diagnosed on high resolution computerized tomography (HRCT) and pulmonary function tests (PFTs). Patients with non-parenchymal lung disease (including pleural disease, airway disease or tumors) were excluded.

Clinical details, autoantibody status, PFTs, current and previous medications, and smoking status (ever/current at the time of ILD diagnosis) were collated. Plain chest radiographs (CXR) and HRCT images were reviewed by a rheumatologist (EP), pulmonologist (GC) and radiologist (QSH), and ILD was classified into subtypes. We defined severe ILD as FVC $<$ 70%, adapted from the staging system proposed by Goh et al for SSc [15], and estimated the extent of involvement using qualitative assessment. Chronic obstructive pulmonary disease (COPD) was defined either by PFT or emphysema seen on HRCT images

[16]. COPD with ILD was differentiated for the purposes of this study by identifying concomitant areas of radiological emphysema (in a patient with a smoking history) as an alternative explanation for the finding of an obstructive and restrictive picture. Gastroesophageal reflux disease (GORD) was defined by reflux symptoms and/or barium swallow and/or a dilated esophagus on HRCT.

Patients were divided in three groups: RA, SSc and “other” autoimmune connective tissue diseases (OCTD) which included 14 patients with IIM, 10 with MCTD, 10 with SLE, three with pSS and 16 patients with overlap syndrome (majority with overlap SLE and SSc).

The ANOVA, Kruskal Wallis and Chi squared were used to test the associations depending on the distribution of data and type of variables. Cohen’s kappa coefficient for agreement was used to measure the assessment of extensive disease. Sporadically missing covariates data were managed using multiple imputation, only if the proportion of missing data was less than 50%. Factors associated with UIP were assessed by univariable and multivariate analyses. Analyses were performed with STATA 14.0 (Stata Corp LP, College Station, Tx, USA) and p-values ≤ 0.05 were considered significant.

Results

Of 124 patients with ILD-ARD, 37 (29.8%) had RA, 32 (25.8%) SSc (24 diffuse cutaneous and 8 limited cutaneous disease) and 55 (44.4%) OCTDs (Table 1). Most patients were female (86.3%), of mixed racial ancestry (75.0) and the median time to develop ILD after ARD diagnosis was 2 years. The median (IQR) age at ARD symptom onset and ILD diagnosis were 45 (35-55 years) and 55 (46-66 years) respectively. Within three years of ARD diagnosis, two thirds of the SSc and OCTD patients and almost half of RA patients had developed ILD. Compared to the SSc and OCTD groups, RA patients were older at ARD diagnosis ($p < 0.001$), had longer disease duration before onset of ILD ($p = 0.06$) and were older at ILD diagnosis ($p < 0.001$).

ILD features

Thirteen patients (10%) were asymptomatic and the ILD diagnosis was made based on images requested for other reasons (Table 2). The most frequent CXR abnormalities were reticular, reticulonodular or nodular infiltrates. Of note, five out of 124 (4.0%) had no parenchymal abnormalities on CXR, but HRCT revealed NSIP. The commonest pattern was NSIP, and in the RA group the frequency of NSIP and UIP was similar. Patients in the SSc and OCTD groups had worse PFTs with significantly lower forced vital capacity (FVC), and diffusion capacity for carbon monoxide (DLCO). The percentage of patients with severe disease (FVC $< 70\%$) was greater in SSc and OCTD groups (50.0% and 58.2%) in contrast with 32.4% of RA patients ($p = 0.05$).

Usual Interstitial Pneumonia

To demonstrate the predictors associated with the most serious ILD patterns, UIP, we compared patients with and without UIP (Table 3). As expected, RA was associated with UIP (OR 3.8, 95% CI 1.5-9.5). Other associated variables were age (OR 1.1, 95% CI 1.0-1.1), COPD (OR 3.2 (95% CI 1.4-8.0), age at ILD diagnosis, longer ARD-ILD intervals, and better FVC at ILD diagnosis (OR 1.0 (95% CI 1.0-1.1). Interestingly, the PFTs in the UIP group were better overall than the non-UIP group, particularly median (IQR) of percentage of FVC at UIP diagnosis was 79 vs 71 in non-UIP patients, with OR 1.6, (95% CI 0.8 – 3.0) and p -value = 0.128. In the multivariate analysis (table 4), adjusting for ARD type, concomitant COPD, tobacco smoking and exposure time to MTX, COPD and MTX mean time exposure before ILD diagnosis remained significantly associated with UIP (OR 2.8, (95% CI 1.0 – 8.0) and 1.0 (95% CI 1.0 – 1.0) respectively).

Co-morbidities

A high prevalence of smoking (over 60%) and previous PTB (33.1%) was observed. A significant number of patients (22.6%) had COPD in addition to their ILD. There was no difference in the prevalence of smoking amongst all groups of ILD. No patient was HIV positive. All SSc patients and more than two thirds of other patients had GORD. In the SSc group, eight (72.7%) patients had significant environmental/occupational exposure, including gold-mining related silica exposure (two patients), organophosphates (one patient), biomass fuels (one patient), sand (two patients), cotton (one patient) and one patient with multiple exposures (printing fumes, spray paint and metal dust).

Autoantibodies

The majority (74.2%) of patients were antinuclear antibody positive, including 86.4% of RA patients. C including 80% of RA patients (Table 2). Regarding SSc, nine patients had positive anti-topoisomerase antibodies, and one patient had anticentromere antibodies. Eight of 14 IIM patients had anti Jo-1 antibodies.

Methotrexate and leflunomide exposure

Regarding methotrexate (MTX) exposure, 37.1% of patients were prescribed MTX before ILD diagnosis, and 33.9% continued, started or restarted after ILD diagnosis (59.5% of RA, 25.0% of SSc and 21.8% of patients with OCTD). No case of acute pneumonitis was documented, despite a mean (SD) follow-up of 14.8 (29.1) months after ILD diagnosis. Regarding leflunomide, 2% of the patients were exposed before ILD diagnosis, and 6% after diagnosis.

Discussion

In this study of ILD in ARD, we described the clinical, serological and radiological features of ILD in ARDs. We have shown that ILD is most commonly diagnosed in RA and SSc, and overall, NSIP was seen most frequently. This is similar to reports elsewhere [4,7,5] where were described the ILD phenotypes and management in different ARDs.

In the RA group, patients developed ARD at an median age 54 years compared to other groups, and also developed ILD later. This is described elsewhere [8,7,17-19], where were is reported that one of the risk factors to develop ILD in RA is age > 60 years. We found similar distribution of NSIP and UIP in RA, in contrast to other studies that reported higher frequency of UIP [5,4,7,17]. The UIP patients had better PFTs compared to other ILD subtypes, yet UIP is described as one of the most severe ILD patterns with poor response to treatment and poor outcomes [17,5,4,7,3,8]. This finding can be related to the higher mortality among patients with UIP pattern, implying that patients with worse PFTs may have already died at the time the study was conducted. The SSc and OCTD patients tended to have early onset of ILD, with the majority presenting with ILD within the first year of ARD symptoms onset. Pulmonary function tests in these groups tended to be more severe than the RA group, with lower DLCO scores in reflecting either worse lung disease or concomitant pulmonary hypertension.

Smoking was highly prevalent in this cohort, particularly amongst RA patients. This is an area for intervention, given the evidence that smoking is a risk for ILD in ARD patients [2,7,8,17]. GORD was a frequent comorbidity in our ILD patients, particularly, as expected, in the SSc group, highlighting the importance of aggressive therapy of this problem since GORD in these patients is associated with more severe and quicker decline of pulmonary functions although is not clear whether antacid treatment helps pulmonary functions preservation in ILD [20,21,9]. Almost a third of patients in all groups had a prior history of PTB, reflecting the high prevalence in TB in the general population of SA. This needs to be taken into account when offering immunosuppressant therapy for the ARD and ILD. Elsewhere, a history of TB and COPD has been identified as a risk factor for ILD, particularly amongst male smokers [22]. The role of isoniazid prophylaxis in ILD-ARD patients in a TB endemic area needs to be explored.

Around one third of the patients in this cohort were treated with MTX (more than half in RA group), either before or after ILD onset. This proportion was much higher amongst RA patients where 65.9% of the patients were exposed before ILD onset and 59.5% after ILD onset. No case of acute pneumonitis was observed in any patients of our ILD patients exposed to MTX - in total 7605 patient-years of exposure overall. One RA patient with ILD experienced exacerbation of ILD symptoms eight months after initiating leflunomide in combination with MTX and died of respiratory failure a few months later. Elsewhere, MTX or LEF have been associated with acute pneumonitis if prescribed to patients with ILD [7,17,18]. Nevertheless, there is a growing evidence that treatment with conventional disease modifying antirheumatic drugs such as MTX and LEF can be used to prevent or delay the onset of ILD, treat ILD and can be safely continued in patients with ILD diagnosis without increasing the risk of progression and/or exacerbation of ILD [23-26].

Plain chest radiographs are not very sensitive for identifying ILD, and were normal in 4% of our cohort and up to 10% of ILD patients elsewhere [17]. Some patients with HRCT-ILD had normal PFTs. and, PFT and HRCT severity correlated poorly, with PFTs underestimating the severity.

We suggest routine ILD screening with HRCT, in all newly diagnosed ARD patients, especially patients with SSc and OCTD, where around 2/3 of the patients had developed ILD in the first 3 years of their ARD and bearing in mind that 10% of our cohort were asymptomatic. This screening should be repeated during the first three years after ARD symptoms onset as the majority of patients in this cohort developed ILD within this period.

Limitations of this study include missing data (serology, environmental and/or occupational exposure history), but we did attempt to correct this through statistical imputation. In addition, we could not calculate the prevalence or risk factors for ILD in this population because this cross-sectional review focused only on patients with ILD. The extent of lung involvement on chest HRCT was made by qualitative assessment rather than by the recommended quantitative CT analysis. We did not have echocardiogram, right heart catheterisation or 6-minute walk test data for the majority of patients. All subjects were seen at a tertiary referral centre, thus potentially introducing referral bias may decrease our ability to generalise these results to the larger ILD-ARD community. We have not yet collated the therapy and outcomes of our patients. These limitations will be addressed in a prospective case-controlled study.

In conclusion, ILD was most commonly diagnosed in RA and SSc, with NSIP seen most frequently overall, with similar frequencies of NSIP and UIP patterns amongst RA patients. The use of MTX was not associated with the development of acute pneumonitis in patients with ILD. We believe that, when necessary, we can continue prescribing MTX to ILD patients. In addition, our findings call for aggressive treatment of GORD. Smoking cessation may be a valuable intervention in these patients. Prospective longitudinal studies that allow us to investigate risk factors for ILD, the response to and safety of immunosuppressive therapy, as well as the role of TB prophylaxis will inform future practical guidelines for ILD-related to ARD.

Acknowledgements

Nil

Conflict of interest

None of the authors have any conflict of interest to declare

References

1. Grippi MA, Elias JA, Fishman J, Kotloff RM, Pack AI, Senior RM, Siegel MD (2015) Fishman's pulmonary diseases and disorders. McGraw-Hill Education
2. Ha Y-J, Lee YJ, Kang EH (2018) Lung involvements in rheumatic diseases: update on the epidemiology, pathogenesis, clinical features, and treatment. *BioMed Research International*. doi:10.1155/2018/6930297
3. Hochberg MC, Gravallese EM, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH (2019) *Rheumatology*. Elsevier, Philadelphia, PA
4. Wallace B, Vummidi D, Khanna D (2016) Management of connective tissue diseases associated interstitial lung disease: a review of the published literature. *Current Opinion in Rheumatology* 28 (3):236-245. doi:10.1097/BOR.0000000000000270
5. Dellaripa PF (2018) Interstitial lung disease in the connective tissue diseases; a paradigm shift in diagnosis and treatment. *Clinical Immunology* 186:71-73. doi:10.1016/j.clim.2017.09.015
6. Doyle TJ, Dellaripa PF (2017) Lung manifestations in the rheumatic diseases. *Chest* 152 (6):1283-1295. doi: 1210.1016/j.chest.2017.1205.1015. Epub 2017 May 1225.
7. Mathai SC, Danoff SK (2016) Management of interstitial lung disease associated with connective tissue disease. *BMJ (Online)* 352. doi:10.1136/bmj.h6819
8. Dellaripa PF, Fischer A, Flaherty KR. (2014) Pulmonary manifestations of rheumatic disease: a comprehensive guide. Springer, New York. doi:10.1007/978-1-4939-0770-0
9. Yazisiz V, Arslan G, Ozbudak İ, Turker S, Erbasan F, Avci A, Ozbudak O, Terzioğlu E (2010) Lung involvement in patients with primary Sjögren's syndrome: what are the predictors? *Rheumatology International* 30 (10):1317-1324. doi:10.1007/s00296-009-1152-8
10. Reiseter S, Gunnarsson R, Mogens AT, Lund MB, Mynarek G, Corander J, Haydon J, Molberg Ø (2018) Progression and mortality of interstitial lung disease in mixed connective tissue disease: a long-term observational nationwide cohort study. *Rheumatology (Oxford, England)* 57 (2):255. doi:10.1093/rheumatology/kex077
11. Winstone TA, Assayag D, Wilcox PG, Dunne JV, Hague CJ, Leipsic J, Collard HR, Ryerson CJ (2014) Predictors of mortality and progression in scleroderma-associated interstitial lung disease: a systematic review. *Chest* 146 (2):422-436. doi:10.1378/chest.13-2626
12. Fujisawa T, Hozumi H, Kono M, Enomoto N, Hashimoto D, Nakamura Y, Inui N, Yokomura K, Koshimizu N, Toyoshima M, Shirai T, Yasuda K, Hayakawa H, Suda T (2014) Prognostic factors for myositis-associated interstitial lung disease.(research article). *PLoS ONE* 9 (6). doi:10.1371/journal.pone.0098824
13. Kamen DL, Strange C (2010) Pulmonary manifestations of systemic lupus erythematosus. *Clinics in Chest Medicine* 31 (3):479-488. doi:10.1016/j.ccm.2010.05.001
14. Ashmore P, Tikly M, Wong M, Ickinger C (2018) Interstitial lung disease in South Africans with systemic sclerosis. *Rheumatology International* 38 (4):657-662. doi:10.1007/s00296-017-3893-0
15. Goh NSL, Desai SR, Veeraraghavan S, Hansell DM, Copley SJ, Maher TM, Corte TJ, Sander CR, Ratoff J, Devaraj A, Bozovic G, Denton CP, Black CM, Du Bois RM, Wells AU (2008) Interstitial lung disease in systemic sclerosis: a simple staging system. *American Journal of Respiratory and Critical Care Medicine* 177 (11):1248. doi:10.1164/rccm.200706-877OC
16. Singh D, Agusti A, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, Criner GJ, Frith P, Halpin DMG, Han M, López Varela MV, Martínez F, Montes de Oca M, Papi A, Pavord ID, Roche N, Sin DD, Stockley R, Vestbo J, Wedzicha JA, Vogelmeier C (2019) Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease: the GOLD science committee report 2019. *The European Respiratory Journal* 53 (5). doi:10.1183/13993003.00164-2019
17. Atzeni F, Gerardi MC, Barilaro G, Masala IF, Benucci M, Sarzi-Puttini P (2018) Interstitial lung disease in systemic autoimmune rheumatic diseases: a comprehensive review. *Expert Review of Clinical Immunology* 14 (1):69-82. doi:10.1080/1744666X.2018.1411190
18. Kelly C, Iqbal K, Iman-Gutierrez L, Evans P, Manchegowda K (2016) Lung involvement in inflammatory rheumatic diseases. *Best Practice & Research Clinical Rheumatology* 30 (5):870-888. doi:10.1016/j.berh.2016.10.004
19. Farquhar H, Vassalo R, Edwards AL, Matteson EL (2019) Pulmonary complications of rheumatoid arthritis. *Seminars in Respiratory and Critical Care Medicine* 40 (02):194-207
20. Mackintosh JA, Stainer A, Barnett JL, Renzoni EA (2019) Systemic sclerosis associated interstitial lung disease: a comprehensive overview. *Seminars in Respiratory and Critical Care Medicine*, 40 (02):208-226

21. Roofeh D, Jaafar S, Vummidi D, Khanna D (2019) Management of systemic sclerosis-associated interstitial lung disease. *Current Opinion in Rheumatology* 31 (3):241-249. doi:10.1097/BOR.0000000000000592
22. Choi W-I, Dauti S, Kim HJ, Park SH, Park JS, Lee CW (2018) Risk factors for interstitial lung disease: a 9-year nationwide population-based study.(Report). *BMC Pulmonary Medicine* 18 (1). doi:10.1186/s12890-018-0660-2
23. Fragoulis G, Nikiphorou E, Larsen J, Korsten P, Conway R (2019) Methotrexate-associated pneumonitis and rheumatoid arthritis-interstitial lung disease: current concepts for the diagnosis and treatment. *Frontiers in Medicine* 6:238
24. Kiely P, Busby AD, Nikiphorou E, Sullivan K, Walsh DA, Creamer P, Dixey J, Young A (2019) Is incident rheumatoid arthritis interstitial lung disease associated with methotrexate treatment? Results from a multivariate analysis in the ERAS and ERAN inception cohorts. *BMJ Open* 9 (5). doi:10.1136/bmjopen-2018-028466
25. Conway R, Low C, Coughlan RJ, O'Donnell MJ, Carey JJ (2015) Methotrexate use and risk of lung disease in psoriasis, psoriatic arthritis, and inflammatory bowel disease: systematic literature review and meta-analysis of randomised controlled trials. *BMJ* 350 (mar13 17). doi:10.1136/bmj.h1269
26. Nokhatha SAA, Harrington R, Conway R (2020) Methotrexate and the lung in rheumatoid arthritis. *European Medical Journal Rheumatology* 7 (1):80-90

Table 1. Demographic, clinical and serological characteristics of 124 patients with ILD-ARD

	All n=124	RA n=37 (29.8%)	SSc n=32 (25.8%)	OCTD n=55 (44.4%)	p value
Female, n (%)	107 (86.3)	31 (83.8)	27 (84.4)	49 (89.1)	0.719
Age at ARD symptoms onset, years (median (IQR))	45 (35-55)	54 (45-62)	42 (34-52)	40 (29-49)	<0.001
Ethnic background (self-reported), n (%)	93 (75.0)	29 (78.4)	26 (81.3)	38 (69.1)	0.768
• Mixed ancestry	26 (21.0)	6 (16.2)	5 (15.2)	15 (27.3)	
• Black	3 (2.4)	1 (2.7)	1 (3.1)	1(1.8)	
• White					
• Other	2 (1.6)	1 (2.7)	0 (0.0)	1(1.8)	
Ever Smoker, n (%)	75 (60.5)	28 (75.7)	17 (53.1)	30 (54.5)	0.078
Current Smoker, n (%)	28 (22.6)	13 (35.1)	6 (18.8)	9(16.4)	0.090
Past smoker, n (%)	47 (37.9)	15 (40.5)	11 (34.4)	21 (38.2)	0.869
Previous pulmonary tuberculosis, n (%)	41(33.1)	13 (35.1)	12 (37.5)	16 (26.1)	0.688
Environmental or occupational exposure, n (%)	21/35(60.0)	4/5 (80.0)	8/11 (72.7)	9/19 (47.4)	0.242
GORD, n (%)	94 (75.8)	25 (67.6)	32 (100.0)	37 (67.3)	0.001
COPD, n (%)	28 (22.6)	13 (35.1)	6 (18.7)	9 (16.4)	0.090
HIV, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	-
RF, n (%)	79 (63.7)*	36 (97.3)	12 (37.5)	31 (56.4)	<0.001
ACPA, n (%)	22/46 (47.8)	16/20 (80)	1/5 (20)	5/21 (23.8)	0.001
ANA, n (%)	92 (74.2)*	32 (86.4)	20 (62.5)	40 (72.3)	0.072
ATA, n (%)	12/45 (27.0)	-	9/27 (33.3)	3/18 (16.7)	0.215
ACA, n (%)	3/37 (8.0)	-	1/22 (4.5)	2/15 (13.3)	0.336
Anti-Jo1, n (%)	8/17 (47.1)	0(0)	0/1 (0)	8/16 (50.0)	<0.001

* Multiple imputation was performed. Abbreviations: OCTD: Other Connective Tissue Diseases; RA: rheumatoid arthritis; SSc: systemic sclerosis; IQR: Interquartile range; GORD: gastroesophageal reflux, COPD: chronic obstructive pulmonary disease, HIV: human immunodeficiency virus, RF: rheumatoid factor; ANA: anti-nuclear antibody; ATA: anti-topoisomerase antibody; anti-Jo1, anti-histidyl transfer RNA synthetase antibody; ACA: anti-centromere antibody; ever smoker, having positive smoking history either current or past; current smoker, patients who still smoking at the time of review.

Table 2. Details of interstitial lung disease in 124 patients with ILD-ARD

	All=124	RA n=37	SSc n=32	OCTD n=55	p value
Symptomatic at ILD Dx, n (%)	111 (89.5%)*	34 (91.9)	29 (90.6)	48 (87.3)	0.756
Age at ILD symptoms onset, years (median (IQR))	49 (40-61)	62 (55-68)	49 (38-56)	42 (33-56)	<0.001
ARD-ILD interval years (median (IQR))	2 (0-7)	5 (1-13)	2 (0-7.5)	1 (0-4)	0.058
ARD-ILD interval < 1y, n (%)	56 (45.2)	12 (32.4)	15 (46.9)	29 (52.7)	0.155
ARD-ILD interval < 3y, n (%)	76 (61.3)	17 (45.9)	20 (62.5)	39 (70.9)	0.054
Disease subtype, n (%)					
NSIP	79 (63.7)	19 (51.3)	26 (81.2)	34 (61.8)	<0.001
UIP	33 (26.6)	18 (48.6)	4 (12.5)	11 (20.0)	
Other ^a	12 (9.7)	0 (0.0)	2(6.3)	10 (18.2)	
FVC at ILD Dx, absolute (liters), median (IQR)	2.1 (1.8-2.4)*	2.1 (1.8-2.6)	2.1 (1.9-2.5)	2.1 (1.6-2.3)	0.217
FVC at ILD Dx, (% expected), median (IQR)	74 (60-85)*	83 (70-100)	71 (64-82)	68 (56-82)	<0.001
FVC ≤70%, n (%)	60 (48.4)*	12 (32.4)	16 (50.0)	32 (58.2)	0.052
DLCO at ILD Dx, median (IQR)	48 (38-54)*	51 (42-58)	50 (41-59)	44 (35-50)	0.020
MTX before ILD onset, n (%)	46 (37.1)*	24 (65.9)	8 (25.0)	14 (25.5)	<0.001
MTX after ILD onset, n (%)	42 (33.9)*	22 (59.5)	8 (25.0)	12 (21.8)	<0.001
MTX exposure before ILD diagnosis (months, mean (SD))	21.7 (46.2)*	46.9 (63.1)	12.0 (35.3)	9.9 (29.2)	<0.001
MTX exposure after ILD diagnosis (months, mean (SD))	14.8 (29.1)*	19.7 (33.2)	15.1 (34.4)	11.4 (22.3)	0.049
LEF before, n (%)	2 (1.6)*	2 (5.4)	0 (0.0)	0 (0.0)	0.092
LEF after, n (%)	7 (6)*	5 (13.5)	1 (3.1)	1 (1.8)	0.045
LEF exposure after ILD diagnosis (months, mean (SD))	0.4 (2.4)*	1.1 (4.2)	0 (0)	0.02 (0.1)	0.545
^a LIP, OP and acute pneumonitis. *Multiple imputation was performed. Abbreviations: OCTD: Other Connective Tissue Diseases RA: rheumatoid arthritis; SSc: systemic sclerosis; ILD: interstitial lung disease; ACTD: autoimmune connective tissue disease; IQR: Interquartile range; FVC: Forced vital capacity; DLCO: Diffusion capacity for carbon monoxide; MTX: Methotrexate; LEF: leflunomide					

Table 3. Comparison of ILD-ARD patients features with and without usual interstitial pneumonia

	UIP n=33 (26.6)	Non- UIP 91 (73.4)	OR (95% CI) ^a
Diagnosis			
RA, n (%)	18 (54.5)	19 (20.8)	3.8 (1.5-9.5)
SSc, n (%)	4 (12.1)	28 (30.8)	0.5 (0.1-1.9)
OCTD, n (%) ^b	11 (33.3)	44 (48.4)	1
Female, n (%)	26 (78.8)	81 (89.0)	0.4 (0.2-1.3)
Age, median (IQR)	67 (56-72)	50 (41-61)	1.1 (1.0-1.1)
Age at ARD symptoms onset, years (median (IQR))	50 (38-56)	42 (34-52)	1.0 (0.9-1.1)
Black ethnicity, n (%)	5 (15.1)	21 (23.1)	0.6 (0.2-1.7)
Ever Smoker n (%)	25 (75.8)	50 (54.9)	1.6 (0.7-3.8)
Concomitant COPD, n (%)	13 (39.4)	15 (16.5)	3.2 (1.4-8.0)
Age at ILD symptoms onset, median (IQR)	61 (53-67)	47 (38-57)	1.1 (1.0-1.1)
Symptomatic at ILD Dx, n (%)	30 (90.9)	81 (89.0)	1.2 (0.3-4.8)
ARD-ILD interval (years), median (IQR)	7 (2-14)	1 (0-4)	1.0 (1.0-1.2)
ARD-ILD interval < 1y (%), n (%)	7 (21.2)	49 (53.8)	0.2 (0.1-0.6)
ARD-ILD interval < 3y (%), n (%)	12 (36.4)	64 (70.3)	0.2 (0.1-0.6)
FVC at ILD Dx, percentage (%), median (IQR)	79 (66-100)	71 (59-82)	1.6 (0.8-3.0)
FVC < 70% (%), n (%)	13 (39.4)	47 (51.6)	0.6 (0.3-1.4)

^a Odds ratio were calculated by univariable logistic regression analysis. ^b IIM, Idiopathic Inflammatory Myopathy; MCTD, Mixed Connective Tissue Disease; SLE, Systemic Lupus Erythematosus; pSS, primary Sjogren syndrome; and overlap syndromes. RA, Rheumatoid Arthritis; SSc, Systemic Sclerosis; OCTD, other connective tissue diseases; ACTD, autoimmune connective tissue disease; ILD, interstitial lung disease; COPD, chronic obstructive lung disease; FVC, forced vital capacity.

Table 4. Multivariable analysis

```
logistic UIP ib3.groups COPDemphysema ever smoker MTXexposurebeforeILD onset
Logistic regression                               Number of obs   =       123
                                                    LR chi2(5)      =       24.60
                                                    Prob > chi2     =       0.0002
Log likelihood = -59.230934                       Pseudo R2      =       0.1720
```

	UIP	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
groups							
1		2.084064	1.098725	1.39	0.164	.7415745	5.856893
2		.5335737	.3503677	-0.96	0.339	.1473189	1.932548
COPDemphysema		2.835487	1.50458	1.96	0.050	1.00221	8.022254
ever smoker		1.265954	.6821332	0.44	0.662	.4403169	3.63974
MTXexposurebe		1.012554	.0052492	2.41	0.016	1.002318	1.022894
_cons		.1494756	.0704932	-4.03	0.000	.0593117	.3767036