Turk Thorac J 2022; 23(4): 261-267 DOI: 10.5152/TurkThoracJ.2022.21263

Original Article

Screening for Subclinical Interstitial Lung Disease in Rheumatoid Arthritis Patients: Functional and Radiological Methods

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Cite this article as: Wagih Abdelwahab H, Shalabi NM, Mohamed Rashad Ghoneim M, et al. Screening for subclinical interstitial lung disease in rheumatoid arthritis patients: Functional and radiological methods. *Turk Thorac J.* 2022;23(4):261-267.

Abstract

OBJECTIVE: Interstitial lung disease is the most frequent lung symptom of rheumatoid arthritis and is a significant contributor to morbidity. As a result, the target of this research was to measure the frequency of radiological and functional abnormalities in rheumatoid arthritis patients who did not have any respiratory symptoms.

MATERIAL AND METHODS: This study consists of 30 patients diagnosed with rheumatoid arthritis. All involved cases were exposed to entire history taking and clinical examination. All patients were examined by high-resolution computed tomography and pulmonary function tests.

RESULTS: According to the computed tomography visual score, 73.3% showed interstitial lung disease. The most common abnormalities were reticular patterns (46.7%) followed by nodular patterns (40%) and septal lines (23.3%). However, 36% of the patients had a normal pulmonary function, while 32% had a small airway affection, 20% had restrictive lung disease, and 12% had obstructive lung disease. A significant association was found between supine expiratory volume and computed tomography visual score. Results showed no association between interstitial lung disease and all lung function test parameters.

CONCLUSION: Subclinical interstitial lung disease is frequent among rheumatoid arthritis patents. A combination of pulmonary function tests with computed tomography is essential to enhance the recognition of subclinical interstitial lung disease as normal pulmonary function alone cannot exclude its presence.

KEYWORDS: Rheumatoid arthritis, subclinical interstitial lung disease, pulmonary function test
Received: *November 15, 2021* ***Accepted:*** *February 28, 2022* ***Available Online:*** *April 22, 2022*

INTRODUCTION

Rheumatoid arthritis (RA), a progressive systemic inflammatory disease, causes substantial impairment, particularly when delayed therapy.[1] Besides articular illness, numerous organs might be implicated, with extra-articular manifestations (EAM) in the lungs, skin, heart, and eyes contributing to increased morbidity and mortality.[2] The lungs are commonly implicated, accounting for 10-20% of total mortality.[2,3]

Pulmonary manifestations may be presented as an EAM of the illness or caused by RA medication. Interstitial lung disease (ILD) is the widespread lung affection of RA and is a substantial contributor to morbidity. In an autopsy examination of 81 individuals with chronic RA, 34% exhibited ILD.[4]

Subclinical illness is common, and it is uncertain how to treat a patient with abnormalities but no symptoms.[5,6] Male sex, old age at the onset of RA, severe RA, and methotrexate therapy had the most excellent chance of progression.[7]

subclinical interstitial lung disease refers to asymptomatic persons with specific radiological, physiological, and histopathological pulmonary abnormalities. They also may have symptoms not related to ILD.[8,9] The significance of subclinical ILD illness is that early disease can progress and worsening can be avoided. As a result, this research aimed to determine the frequency of radiological and functional abnormalities in RA patients who did not have any respiratory symptoms.

MATERIAL AND METHODS

This observational cross-sectional study consists of 30 cases diagnosed with RA in agreement with the 2010 American College of Rheumatology, the European League Against Rheumatism[10] categorization criteria. This study was conducted from November 2018 to November 2019 following Mansoura University institutional research board ethics committee

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(code number: MS/17.06.27). Informed written consent was given from all included patients.

Patients with: (a) any respiratory symptoms attributed to ILD; (b) cannot correctly perform the 6-minute walk test (6MWT), lung function test, and CT; (c) pulmonary or cardiovascular diseases; (d) those with active infection; and (e) cancer were excluded from the study.

All involved cases were subjected to (a) the whole history taking, clinical examination in rheumatology and immunology clinic; (b) high-resolution computed tomography (HRCT) in diagnostic radiologically & intervention department; (c) pulmonary function testing and 6MWT in Chest Medicine Department.

Evaluation of RA activity was made utilizing the Disease Activity Score-28 (DAS28).[11,12] Also, The quantities of rheumatoid factor (RF) and Anti-cyclic citrullinated peptide (CCP) were detected by ELISA and expressed in units per milliliter.

All patients were examined by a 128-multidetector CT machine (Philips Medical System, Best, the Netherlands) in both supine and prone positions. Non-contrast HRCT scan was performed during the inspiratory and expiratory breath-holding phases. Both visual and automated methods made the following imaging interpretations:

1- Visual assessment: The presence of septal lines, reticular lesions, peripheral fibrosis, traction bronchiectasis, ground-glass opacities, and/or honeycombing. Visual abnormalities were graded by a modified quantitative scale[13] into 0; normal, 1; minimal disease, 2; mild, 3; moderate disease, or 4; severe.

3- Automated method to measure lung attenuation: It was done using a quantitative CT densitometry lung analysis model that was inherited from the A picture archiving and communication system (PACS). Lung extraction was done to isolate the lungs from other tissues and structures. Followed by obtaining the lung density histogram of each CT according to the classified model self-created according to the following parameters[14]: total lung volume and mean lung density of lung parenchyma ranged from −250 Hounsfield units (HU) to −910 HU. High attenuation areas percentage (specified by attenuation values between −600 HU and −250 HU). Low attenuation areas percentage (emphysema) (LAAs; specified attenuation values below −910 HU).[15]

MAIN POINTS

- Interstitial lung disease is the most frequent lung symptom of rheumatoid arthritis (RA) and is a considerable contributor to morbidity.
- Because early diagnosis may hinder the progress to end-stage lung disease, this study planned to detect the frequency of radiological and functional chest abnormalities in RA patients.
- Normal pulmonary function tests cannot exclude interstitial lung disease in patients with RA, and high-resolution computed tomography is still required.

The lung function test was conducted in line with the requirements of the American Thoracic Society (ATS).[16] The percentages of patients with diminished total lung capacity (TLC) or diminished forced vital capacity (FVC) <80% of expected with a normal forced expiratory volume in first second (FEV1)/FVC, along with diffusion lung capacity of carbon monoxide (DLCO) less than 75% of predicted, were recorded as restrictive lung disease.

Small airway disease is also identified by decreased forced expiratory flow (FEF) at 25-75% of lung capacity (FEF25-75) and normal FEV1, FVC, and FEV1/FVC ratio. A decreased FEF (25-75) was determined arbitrarily as 80% of the anticipated.[17,18]

The 6MWT was applied using the ATS guidelines recommendations.[19] Each patient was advised to walk for 6 minutes, through which peripheral oxygen saturation (SpO_2) and 6-minute walk distance were recorded. Alternations in SpO_2 (ΔSpO_2) throughout the 6MWT were analyzed by subtracting the measurements at the starting point from those instantly following walking 6 minutes.[20]

STATISTICAL ANALYSIS

Data were analyzed using statistical Package for Social Sciences 26.0 (IBM SPSS Corp.; Armonk, NY, USA) package program. Discrete variables were denoted as frequency and percentage, while continuous parametric variables were represented by mean (standard deviation). Non-parametric data were presented as median (min-max). Significance testing was done using Fisher's exact test for discrete variables, Welch's *t*-test for parametric data, Mann–Whitney *U* test for non-parametric variables. The 5% was set as a significance level.

RESULTS

The study included 30 patients, 26 (86.7%) were females, and 66.7% of them were smokers. Most smokers were passive smokers (85%) and cigarette smoking (73.7%). The most common comorbidity was hypertension (20%), and 36.3% of the patients have no comorbidity (Table 1).

The median duration of RA in studied patients (min-max) was 7 months (0.5-25). Most patients were classified as moderate activity (73.3%), and 20 patients (66.7%) were ACCP negative. The median level of RF was 24.5 U/mL (min-max: 0-64). The most common medications used for treatment were methotrexate (96.7%), followed by leflunomide (93.3%), hydroxychloroquine (60%), steroid (40%), and glucosamine (13.3%).

According to the CT visual score results, 73.3% (22 patients) showed ILD (26.7% had minimal disease). The most common abnormalities were reticular patterns (46.7%) followed by nodular patterns (40%) and septal lines (23.3%) (Table 2). However, 36% of the patients had normal pulmonary function (Figure 1), while 32% had a small airway affection, 20% had restrictive, and 12% had obstructive lung disease (Figure 2). Also, 36.7% had exercise-induced desaturation during 6MWT.

Table 1. Characteristics of Studied Patients

		N	%
Age	Mean (SD)	45.7 (8.9)	
Smoking	Smoker	20	66.7
	Non-smoker	10	33.3
Smoking pattern, n = 20	Passive	17	85.0
	Active	3	15.0
Sex	Male	4	13.3
	Female	26	86.7
Occupation	Housewife	20	66.7
	Farmer	7	23.3
	Worker/painter/ architecture	3	10.0
Comorbidity*	No	19	36.3
	diabetes milletus (DM)	5	16.6
	hypertension (HTN)	6	20
	Others	4	13.3

*Groups are not mutually exclusive.
SD, standard deviation.

Table 2. Visual CT Parameters in Studied Patients

		N	%
CT score	Normal = 0	8	26.7
	ILD ≥1	22	73.3
	1 = minimal disease	8	26.7
	2 = mild disease	7	23.3
	3 = moderate disease	7	23.3
Nodules	No	18	60.0
	Yes	12	40.0
Septal line	No	23	76.7
	Yes	7	23.3
Reticulation	No	16	53.3
	Yes	14	46.7
Mosaic attenuation	No	24	80.0
	Yes	6	20.0
Bronchial wall thickening	No	28	93.3
	Yes	2	6.7
GGO	No	25	83.3
	Yes	5	16.7

CT, computed tomography; GGO, ground-glass opacities.

In regard with the association between the presence of ILD in CT and patients' parameters, there was no significant association between ILD on 1 side and age (P = .6), smoking (P = .682), sex (P = 1), occupation [farmer P = 1, workers P = .209]. Results also showed no association between ILD on 1 side and RF (P = 534), duration of RA (P = .629), DAS28 score (P = 1), ACCP (P = 1) Table 3.

Results showed that there is no association between ILD and all lung function test parameters including Fev25.75 (P = 1), DLCO (P = 1), fev1 (P = .298), FVC (P = .562), TLC (P = 1), delta SpO_2 (P = .417), residual volume (RV) (P = .968), RV/TLC ration (P = 905).The median of 6min walk distance was lower in the normal group (362.5) than ILD (406.5) group with no significant difference (P = .184). Also, exercise-induced desaturation during 6MWT and exhaled CO was not significantly associated with the ILD (Table 4).

The RA medications were not significantly associated with ILD, for example, methotrexate (P = .267), leflunomide (P = .469), hydroxychloroquine (P = .678), and glucosamine (P = .284).

Regarding the association between the presence of ILD by visual CT score and automated quantitative values for ILDs, a significant association was found between supine expiratory volume and CT visual score (2951.1 in ILD vs. 1987.9 in ILD patients without ILD, P = .032). Also, the Supine expiratory LAA mean was higher in patients with ILD (P = .013), as shown in Table 5.

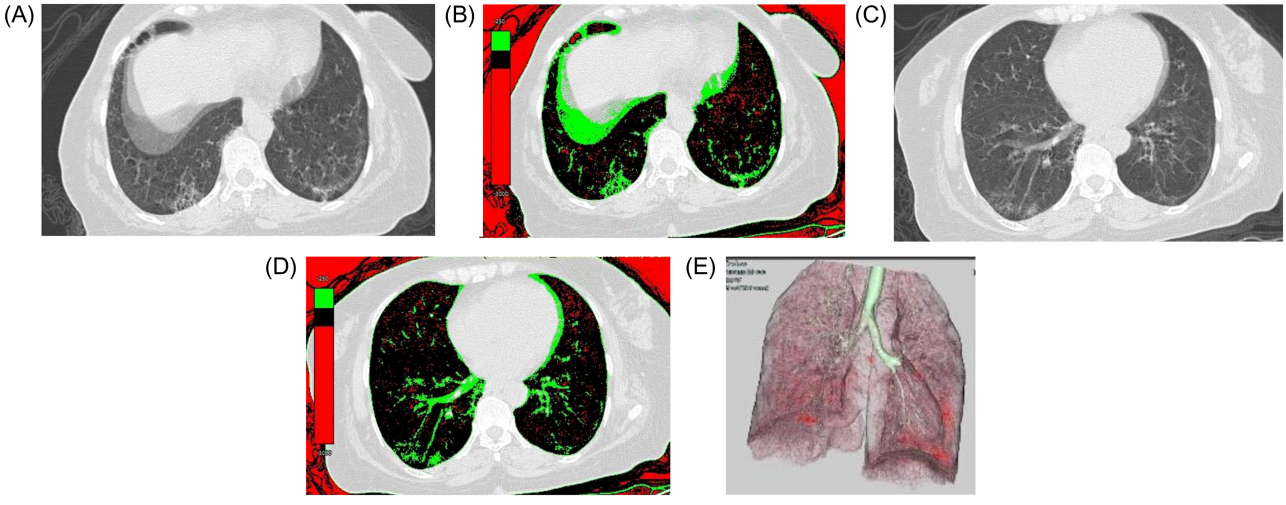

Figure 1. (A and C) Axial CT images showing the volume of HRCT supine in inspiratory phase; in a female patient with normal pulmonary functions test and color overlay maps for lung densitometry. (B and D) Posterior segments of both lower lung lobes showing subpleural reticulation, honeycombing (green colored). CT score was 3, HAA 13 %, and LAA 3.4 %. (E) 3D display of volume of the LAA of both lungs (red colored). CT, computed tomography; LAA, low attenuation areas.

Table 3. Association Between the Presence of ILD in CT with Different Parameters of Studied Patients

		CT score		
		Normal	ILD	Significance
Age	Mean (SD)	44.6 (8.8)	46.2 (9.1)	$t = -0.42$, $P = .680$*
Smoking	Smoker	6 (30)	14 (70)	$P = .682$
	Non-smoker	2 (20)	8 (89)	
Smoking pattern, n = 20	Passive	5 (29.4)	12 (70.6)	$P = 1$
	Active	1 (3.3)	2 (66.7)	
Sex	Male	1 (25)	3 (75)	$P = 1$
	Female	7 (26.9)	19 (73.1)	
Occupation	Housewife	5 (25)	15 (75)	r
	Farmer	1 (14.3)	6 (85.7)	$P = 1$
	Worker/painter/architecture	2 (66.7)	1 (33.3)	$P = .209$
Duration of RA (months)	Median (min-max)	7 (3-15)	7 0.5-25)	$Z = -0.519$, $P = 0.629$
DAS 28 score	Low/moderate	6 (26.1)	17 (73.9)	$P = 1$
	High	2 (28.6)	5(71.4)	
RF	Median (min-max)	22 (0-64)	26.5 (8-64)	$Z = 0.635$, $P = .534$
ACCP	Negative	5 (25)	15 (75)	$P = 1$
	Positive	3 (30)	7 (70)	

*Welch's *t*-test.
CT, computed tomography; r, reference; ILD, interstitial lung disease; SD, standard deviation; RF, rheumatoid factor; RA, rheumatoid arthritis.

Table 4. Association Between the Presence of ILD in CT with Functional Assessment of Studied Patients

		CT score		
		Normal	ILD	Significance
Fev 25.75	Normal	3 (27.3)	8 (72.7)	$P = 1$
	Reduced	3 (21.4)	11 (78.6)	
DLCO	Normal	4 (22.2)	14 (77.8)	$P = 1$
	Reduced	1 (33.3)	2 (66.7)	
Fev1	Normal	3 (16.7)	15 (83.3)	$P = .298$
	Reduced	3 (42.9)	4 (57.1)	
FVC	Normal	4 (20)	16 (80)	$P = .562$
	Reduced	2 (40)	3 (60)	
TLC	Normal	4 (22.2)	14 (77.8)	$P = 1$
	Reduced	1 (33.3)	2 (66.7)	
TLC	Median (min-max)	98 (71-165)	101(67-254)	$Z = 0.165$, $P = .905$
pumonary function test (PFT) abnormalities, n = 25	Normal	3 (33.3)	6 (66.7)	r
	Obstructive	0 (0)	3 (100)	$P = 1$
	Restrictive	1 (20)	4 (80)	$P = 1$
	Small airway	2 (25)	6 (75)	$P = 1$
6MWD	Mean (SD)	362.5 (49.2)	406.5 (47.7)	$t = -1.5$, $P = .184$*
Delta SpO_2	No desaturation	4 (21.1)	15 (78.9)	$P = .417$
	Desaturation	4 (36.4)	7 (63.6)	
Exhale CO	Median (min-max)	3 (2-20)	5 (2-10)	$Z = -0.143$, $P = .945$

*Welch's *t*-test.
CT, computed tomography; r, reference; ILD, interstitial lung disease; 6MWD, 6-minute walk distance; SD, standard deviation.

Table 5. Association Between the Presence of ILD in Visual CT with Quantitative CT Parameters

		CT score group		
		Normal N (%)	ILD N (%)	Significance
		Volume (mL)		
Supine	Inspiratory	2686.8 (1550.5-30673)	4019.1 (1659.5-6089.5)	$Z = 1.2$, $P = .245$
	Expiratory	1987.9 (1470.4-2826.5)	2951.1 (1641.9-22083)	$Z = 2.1$, $P = .032$
Prone	Inspiratory	3623.5 (1828.5-32240)	4198.5 (2038.2- 55117)	$Z = 0$, $P = 1$
	Expiratory	2197.1 (558.1)	2798.1 (843.2)	$t = -1.7$, $P = .128$
		high attenuation area (HAA) (%)		
Supine	Inspiratory	13 (6.8-38.1)	8.5 (5.3-709)	$Z = -1.6$, $P = .121$
	Expiratory	19.3 (15.3-44.5)	13.4(9.1-86)	$Z = -1.5$, $P = .137$
Prone	Inspiratory	9.6 (7.2-33.5)	7.9 (4.8-27.7)	$Z = -0.797$, $P = .426$
	Expiratory	24.5 (20.4-29.4)	17.3 (9.1-33.3)	$Z = -1.4$, $P = .152$
		LAA (%)		
Supine	Inspiratory	16.5 (0-36.2)	15.2 (1.2-38.4)	$Z = -0.27$, $P = .78$
	Expiratory	18.4 (0-19.2)	9 (0-28.4)	$Z = -1.2$, $P = .200$
Prone	Inspiratory	22.9 (12.6)	16.4 (11.9)	$t = 0.54$, $P = .318^*$
	Expiratory	11.1 (10.4)	9.7 (7.99283)	$t = -0.95$, $P = .812^*$

*Welch's *t*-test.
CT, computed tomography; ILD, interstitial lung disease; LAA, low attenuation areas.

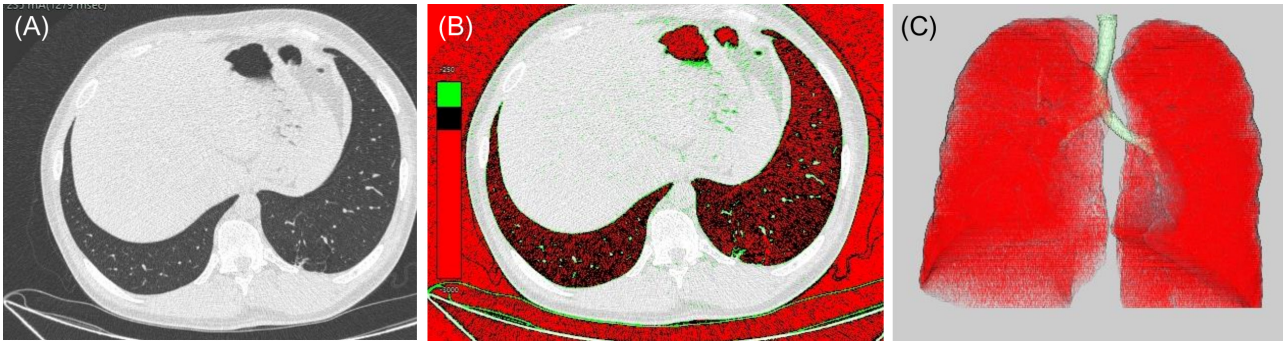

Figure 2. Axial CT images showing the volume of HRCT supine in inspiratory phase in a male patient with obstructive lung disease by spirometry. (B) Color overlay maps for lung densitometry; a posterior segment of left lower lung lobes showing fine subpleural reticulation (green colored), CT score was 1, HAA 4.7%, and LAA 35.5 %. (C) 3D display of volume of the LAA of both lungs. CT, computed tomography; LAA, low attenuation areas.

DISCUSSION

In this study, we evaluated the frequency of pulmonary radiological and functional abnormalities in RA patients who did not have any respiratory symptoms. We found that 73.3% of the studied patients had subclinical ILD identified by HRCT (26.7% of them had minimal disease). Nine of the 30 studied patients had normal pulmonary function tests, and most of them had subclinical ILD in HRCT. The drugs applied for the treatment of RA were not significantly associated with ILD in this study. There was no significant association between ILD on 1 side and age, smoking, sex, and occupation. The results also showed no association between ILD on 1 side and RF, duration of RA, DAS28 score, and ACCP.

This study showed that about 3/4 of the studied patients had subclinical ILD identified by HRCT (about 1/4 of them had minimal disease). However, in Nasr et al.[17] 38.3% (23/60) of all involved RA patients had subclinical ILD and only 16 patients (26.7%) had an abnormal pulmonary function. In addition, in Gochuico et al.[6,21] 33% having RA had subclinical ILD. Lung volumes (i.e, the percentages of predicted FEV1, FVC, and TLC) were normal in patients who had RA-ILD at baseline and were not statistically significantly different from those patients having RA without ILD. In this study, (9/30 patients) had normal pulmonary function tests, and most of them had subclinical ILD in HRCT. Following these results, normal pulmonary function tests cannot exclude ILD in patients with RA, and HRCT is still required.

In Gochuico et al.[6] DLCO percentage was statistically significantly lower between patients with RA–ILD than between patients without RA-ILD. In contrast to Gochuico et al.[6] subclinical ILD was detected in most patients who had a normal DLCO percentage in this study.

In Robles-Pérez et al.[22] subclinical ILD with maintained FVC was discovered in 2 of the RA patients (5%). Four out of 6 patients (18.8%) with a significant decline in DLCO values had airway or parenchymal abnormalities on the HRCT. In agreement with Robles-Pérez et al.[22] 2 of 3 patients with reduced DLCO in this study had ILD in HRCT.

The drugs applied for the treatment of RA were not significantly associated with ILD in this study. Methotrexate in Robles-Pérez et al[22] also was not associated with ILD development or progression.

Despite no statistically significant association detected between the presence of subclinical ILD and RF levels in this study, a higher level of RF was noticed in patients with subclinical ILD contrasted with those without ILD. In agreement with our results, individuals with RA-ILD in Wang et al[23] are more expected to have elevated values of RF; however, this association did not achieve statistical significance. Similarly, no significant difference was noticed in Wang et al[23] regarding Anti-CCP between RA individuals with ILD and those without ILD. Also, this study detected no significant association between subclinical ILD and ACCP levels.

Moreover, Wilsher et al[24] found that anti-CCP antibodies and RF correlated poorly with radiologic abnormalities in RA patients.

No significant association was detected in this study between the presence of subclinical ILD on 1 side and age, smoking, sex, occupation, duration of RA, and DAS28 score. However, Sparks et al[25] stated a higher risk for RA-ILD in patients with elevated values of DAS28 score in a prospective group of RA patients. These results indicate that reducing systemic inflammation may modify the natural history of RA-ILD development. In contrast to Sparks et al[25] and in line with our results, data from Robles-Pérez et al[22] showed that some RA patients show lung diseases across time despite improving joint symptoms or inflammatory markers. So, other factors related to RA might promote lung affection.

In Gochuico et al.[6] there was no statistically significant difference in the mean duration of articular disease among patients with RA with versus without subclinical ILD. Consequently, ILD may arise at any moment of the rheumatologic disease.

There were no significant differences between smokers and non-smokers regarding the prevalence of HRCT patterns or lung function parameters in RA patients.[24] In contrast, Gochuico et al[6] decided that cigarette smoking is linked with the presence of subclinical ILD in patients with RA, but is not related to disease progression.

This study found a significant association between supine expiratory volume and CT visual score. Also, the mean supine expiratory low attenuation area was higher in patients with ILD. However, total inspiratory lung volumes, mean expiratory lung density, and expiratory high attenuation area showed a significant correlation with the HRCT score in Hasan et al.[14]

Other non-invasive diagnostic tests, such as nailfold capillaroscopy (NFC), are available and helpful for the early diagnosis of collagen tissue diseases (CTDs). In Çakmakçı Karadoğan et al.[26] mean capillary density measured by NFC was significantly reduced only in the CTDs-ILD group as compared to the control group. Also, NFC findings discriminate the usual interstitial pneumonia from non-specific interstitial pneumonia patterns.

The main limiting factor of this study is the number of patients included. Despite this, the present study helps to explain that subclinical lung affection in RA is not uncommon. However, in the future, larger multicenter studies are needed to confirm and expand the results of this study.

Certain people are at risk for ILD such as connective tissue disorders. Early diagnosis may hinder the progress to end-stage lung disease. Diagnosis of ILD in RA can be challenging since patients cannot notice dyspnea due to reduced physical activity with advanced arthritic symptoms.[27] So, combining pulmonary function tests with CT is essential to enhance the recognition of subclinical interstitial lung disease as normal pulmonary function alone cannot exclude its presence.

Ethics Committee Approval: This study was approved by Ethics committee of Mansoura University, (Approval No: MS/17.06.27).

Informed Consent: Written and verbal informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – H.W.A., R.E.; Design – N.S.F.; Supervision – N.M.S., H.W.A., R.E.; Data Collection and/or Processing – F.E., F.H.; Analysis and/or Interpretation – N.S.F., M.M.R.G.; Literature Review – H.W.A., M.M.R.G.; Writing – H.W.A.; Critical Review – H.W.A., N.M.S., M.M.R.G., N.S.F., F.H., F.E., R.E.A.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: The authors declared that this study has received no financial support.

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