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ORIGINAL ARTICLE

Association between choroidal thickness and interstitial lung disease in patients with rheumatoid arthritis: A cross-sectional study

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ABSTRACT

Objectives: This study aimed to evaluate choroidal thickness (CT) in patients with rheumatoid arthritis (RA) and healthy controls and to determine its relationship with RA-associated interstitial lung disease (RA-ILD).

Patients and methods: A total of 63 patients with RA and 36 age- and sex-matched healthy controls were recruited in the cross-sectional study. Serological findings, Disease Activity Score-28, disease duration, and medical treatment of patients were recorded. Patients with RA were subdivided into two groups: patients with RA-ILD (Group 1) and patients with RA but without ILD (RA-noILD; Group 2). CTs were measured using enhanced depth imaging optical coherence tomography. CT was measured at five points: the subfoveal region, 750 µm nasal and temporal to the fovea, 1500 µm nasal and temporal to the fovea. Patients with RA-ILD were evaluated with delta high-resolution computed tomography (ΔHRCT) and pulmonary function test to determine the severity of interstitial lung disease.

Results: Four of 63 RA patients were excluded due to comorbidities. Thus, 59 RA patients, 20 in the RA-ILD group and 39 in the RA-noILD group, were included in the analyses. The RA groups were similar in terms of clinical characteristics and laboratory findings. There were statistically significant differences between Group 1, Group 2 and healthy controls (Group 3) compared to all CT values ($p<0.05$). The mean CT measured at 750 µm and 1500 µm nasal to the fovea was lowest in the RA-ILD group, followed by the RA-noILD and healthy groups ($p<0.05$). CT measurements did not correlate with the pulmonary function test and ΔHRCT.

Conclusion: RA-ILD patients had a thinner CT measured at nasal points. However, there was no association between CT measurements and the severity of ILD.

Keywords: Choroidal thickness, rheumatoid arthritis, ΔHRCT.

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by synovial tissue inflammation resulting in symmetric polyarthritis and synovial membrane hypertrophy with progressive bone destruction and eventually joint deformity when untreated. Although the most frequent manifestation of RA is arthritis, patients with RA may present with extra-articular manifestations (EAMs) of the disease.[1-3] Interstitial lung disease (ILD) may be a common type that causes a poor prognosis in cases of multiple EAMs.[4] Therefore, it is recommended to evaluate all patients with RA for ILD since there may have already been irreversible lung damage secondary

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to ILD, and ILD contributes to morbidity and mortality to a large extent. Several genetic, environmental, clinical, and serologic factors that contribute to the development of ILD were defined.[5-7] A published study stated that tumor necrosis factor alpha (TNF-α), TNF-beta (TNF-β), PDGF (platelet-derived growth factor), VEGF (vascular endothelial growth factor), interleukin (IL)-1, IL-4, IL-5, and IL-13 had a critical role in the pathogenesis of ILD.[7] Another well-recognized EAM of RA is ocular involvement, including keratoconjunctivitis sicca, episcleritis, and scleritis.[8,9] Along with these ocular complications, choroidal and retinal vessels have been reported to be affected in RA patients. Angiography using indocyanine green revealed obstruction of both choriocapillaris and choroidal arteries in RA patients.[9] Furthermore, inflammation in RA can trigger the acute phase response resulting in a rise in C-reactive protein, which is associated with an increase in ET-1 (endothelin 1). RA patients exhibit significantly elevated levels of ET-1, which may have a vasoconstrictor effect on the eye's choroid, which is the most vascular tissue.[10,11]

There is a limited number of studies in the literature evaluating choroidal thickness (CT) in RA patients. Two published studies reported that RA patients had a thinner CT than healthy controls.[12,13] The reason for this may be related to matrix-metalloproteinase (MMP)-2 and MMP-9, which are found to be higher in RA-associated ILD (RA-ILD) patients compared to RA without ILD (RA-noILD) patients and are effective on vascular structures as well.[14,15] Moreover, TNF-α, VEGF, and PDGF play a crucial function in the pathogenesis and pathophysiology of ocular involvement and ILD.[7,15,16] However, to the best of our knowledge, there is no study investigating the association of ILD with CT in patients with RA. The present study aimed to analyze CT in RA patients and healthy controls and to determine whether they are associated with ILD and the severity of lung involvement.

PATIENTS AND METHODS

This cross-sectional study was performed at the department of rheumatology of the Pamukkale University Faculty of Medicine between August 2021 and December 2022. The study assessed 63 RA patients who fulfilled the American College of Rheumatology (ACR) diagnostic criteria and followed up by the rheumatology clinic and 36 age-, body mass index (BMI)-, and sex-matched healthy individuals without any sign or symptom suggestive of medical comorbidity who presented to the ophthalmology clinic of the same hospital for a routine ophthalmological examination.[17,18]

The age, sex, BMI, weight, and height of each participant, as well as disease duration, serological findings, Disease Activity Score in 28 joints (DAS28), and medical treatment of patients were recorded. All patients underwent a thorough physical examination. Moreover, hematological parameters, including C-reactive protein, anti-citrullinated protein autoantibodies, erythrocyte sedimentation rate, and rheumatoid factor, were studied. Following detailed evaluations, patients were subdivided into two groups, patients with RA-ILD (Group 1) and patients with RA-noILD (Group 2), according to the clinical features, high-resolution computed tomography (HRCT), and pulmonary function tests (PFTs),[19-25] whereas the healthy individuals were assigned to Group 3. Moreover, the delta (Δ) HRCT scoring system was used to ascertain the extent and severity of ILD. Using a Likert-type scale (0=absent; 1=1-25%; 2=26-50%; 3=51-75%; 4=76-100%) modified by Kazerooni et al.,[26] each lung lobe, including the right upper lobe, right middle lobe, right lower lobe, left upper lobe, and left lower lobe, was evaluated to determine the extent of pulmonary parenchymal abnormality. All HRCT scans were evaluated and scored by a board-certified radiologist and a second radiologist with seven and three years of experience in thoracic imaging, respectively, who were blinded to the characteristics of patients with an interobserver agreement. The scoring system of patients with RA-ILD is presented in Table 1.

Meeting the 2010 ACR/European Alliance of Associations for Rheumatology (EULAR) RA classification criteria and a diagnosis of RA-ILD were considered the inclusion criteria for the study.[18,25] As part of the inclusion criteria, an expert pneumologist performed a systematic diagnostic workup in accordance with current best practices after confirming the diagnosis of RA-ILD.[25] The patient data for this study were obtained during routine clinical practice.

Table 1. ΔHRCT scoring system of patients with RA-ILD

	RUL	RML	RLL	LUL	LLL
Components	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Ground glass opacity	0.8±0.7	0.85±0.87	1.2±1.05	0.75±0.71	1.3±0.9
Fibrosis	1.05±0.7	1.05±1.05	1.3±1.05	0.85±0.74	1.55±1.2
Bronchiectasis	0.65±0.67	0.95±1.05	1.3±1.08	0.1±0.3	1.2±1.2
Honeycombing	0.05±0.22	0	0.1±0.4	0.05±0.22	0.1±0.4
Total HRCT score	17.5±11.4				

ΔHRCT: Delta High-Resolution Computed Tomography; RA-ILD: Rheumatoid Arthritis-Associated Interstitial Lung Disease; RUL: Right upper lobe; RML: Right medial lobe; RLL: Right lower lobe; LUL: Left upper lobe; LLL: Left lower lobe; SD: Standard deviation.

We included patients whose spherical refractive error was between +2 and -2 diopters to avoid refractive error magnitude influencing the main outcome measures of CT. All participants were reported on the aim of the study before participation.

Evaluation of ocular parameters

All participants underwent a thorough ophthalmological examination, including visual acuity testing, intraocular pressure measurement, fundus examination, refractive error evaluation, biomicroscopy, and CT measurement. The study excluded participants with active ocular inflammation, any systemic diseases (e.g., diabetes mellitus, rheumatological disease, and systemic hypertension), glaucoma, corneal or lenticular opacity, any active ocular surface disorder (e.g., dry eye), recent or current use of topical eye drops, ocular surgery or trauma, or failure to cooperate during any of the measurements. To rule out the potential of diurnal variations, participants underwent all measurements between 09:00 am and 11:00 am.

Measurement techniques

Choroidal thickness

The high-definition 5-line raster scan protocol, which offers the ability to capture the best possible images, comprising 6.0 mm parallel lines

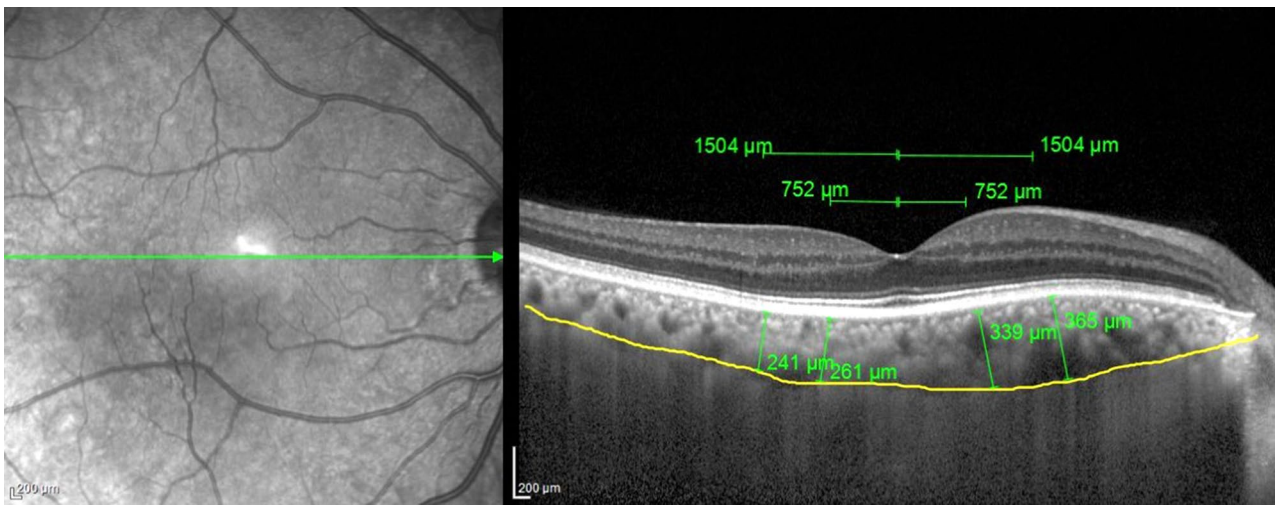

Figure 1. Enhanced-depth imaging optical coherence tomographic images of a healthy subject. Yellow lines show CT measurements taken perpendicularly from the outer edge of the hyperreflective retinal pigment epithelium. The CT was measured at four points: the 750 µm nasal and temporal to the fovea, 1500 µm nasal and temporal to the fovea.
CT: Choroidal thickness.

with 1024 A-scans/B-scans, with an average of four B-scans per image, was followed to acquire choroidal images. Cirrus software Version 6.16.2 (Cirrus Software Solutions, Marlow, UK) was used to bring the choroid closer to the zero-delay line due to the pixelation and low resolution of inverted images. The thinnest point of the macula was selected on the image as differences in positioning could affect the measured foveal thickness. The size of the image was doubled and centered on the fovea. The linear measurement tool of the Cirrus software was utilized for manual measurement of the subfoveal CT (sfCT) through the outer part of the hyperreflective line that corresponds to the retinal pigment epithelium attached to the inner surface of the sclera.[27] CT was also measured at distances of 750 µm (N750.0) and 1500 µm (N1500.0) nasal and 750 µm (T750.0) and 1500 µm (T1500.0) temporal to the fovea (Figure 1).

Statistical analysis

G*Power version 3.1.7 (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) was used to determine the sample size. According to the research results of a published study, it was determined that the total number of participants should be at least 72 for the distribution of the effect size between the groups to detect a large effect size (f=0.40), with a type 1 error rate (a) of 0.05 and a study power of 0.85.[17]

Data were analyzed using IBM SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean ± standard deviation and median (minimum and maximum values), while categorical variables were presented as numbers and percentages. Demographic characteristics were summarized using descriptive statistics. The normality assumption of the data was tested by the Kolmogorov-Smirnov test. Nonparametric tests were used for the statistical evaluation of nonnormally distributed data. The correlation between nonparametric variables was evaluated by Spearman's correlation analysis. A correlation coefficient (r) of 0.8 was considered excellent agreement. The post hoc Bonferroni correction (Mann-Whitney U test) and the Kruskal-Wallis variance analysis were used for intergroup comparisons. The level of statistical significance was set at $p<0.05$.

Interobserver variability was established with the evaluation of participants' HRCT by two different radiologists at the same-day appointments (A and B same day). The mean values evaluated by each observer were compared to assess interobserver variation. For each probe, the mean was calculated, and the intraclass correlation coefficient (ICC) was computed using a two-way random model. The corresponding

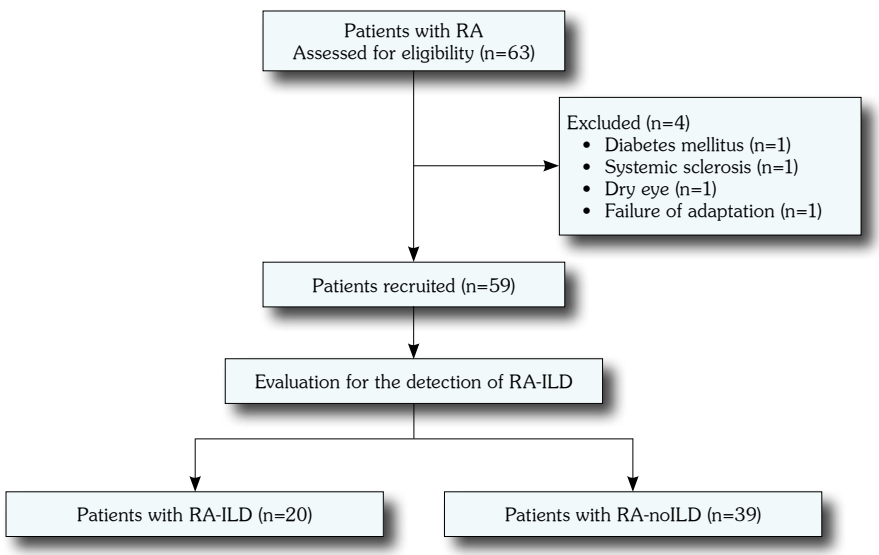

Figure 2. Flow chart of participants recruited in the study.

RA-ILD: Rheumatoid arthritis-associated interstitial lung disease; RA-noILD: Rheumatoid arthritis without interstitial lung disease.

Table 2. Comparison of clinical and demographic characteristics and measurements of CT

	Group 1 (n=20)			Group 2 (n=39)			Group 3 (n=36)				Mann-Whitney U test with Bonferroni correction	
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	*p*	Group	*p*
Age (year)			56.1±8.5			54.2±9.8			52.3±7.6	0.312		
Sex										0.752		
Male	5	25		8	20.9		6	16.6				
Female	15	75		31	79.1		30	83.4				
Body mass index (kg/m^2)			24.9±2.9			24.8±2.8			25.2±2.7	0.792		
Disease duration (year)			5.8±3.4			7.6±5.4			-	0.221		
DAS-28			2.7±0.4			2.9±0.4			-	0.714		
Serological findings												
RF (IU/mL)			67.2±74.9			73.8±66.3			-	0.136		
ACPA			150.9±216.1			106.9±103.8			-	0.294		
Laboratory findings												
CRP (mg/dL)			7.4±10.1			4.9±7			-	0.282		
ESR (mm/h)			24.2±22.8			26.0±18.6			-	0.410		
Medical treatment												
Glucocorticoid use	10	50		20	51.25		-			0.116		
cDMARDS use	8	40		24	61.5		-			0.247		
Biologic DMARD use choroidal thickness (µm)	12	60		15	39.5							
T750			178.2±52.1			206.4±44.4			424±78.8	<0.001*	1<2	0.132
											2<3	<0.001
											1<3	<0.001
T1500			183.9±43.9			204.1±44.8			445.7±84.4	<0.001*	1<2	=0.281
											2<3	<0.001
											1<3	<0.001
SFCT			179.0±49.4			208.8±52.1			393.0±56.2	<0.001*	1<2	=0.108
											2<3	<0.001
											1<3	<0.001
N750			168.9±52.1			212.1±42.5			409.0±68.6	<0.001*	1<2	=0.007
											2<3	<0.001
											1<3	<0.001
N1500			166±53.1			207.2±44.7			463.0±80.0	<0.001*	1<2	=0.016
											2<3	<0.001
											1<3	<0.001

CT: Choroidal thickness; SD: Standard deviation; DAS28: Disease Activity Score in 28 joint; RF: Rheumatoid factor; ACPA: Anti-citrullinated Protein Antibody; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; cDMARDS: Conventional Disease-Modifying Antirheumatic Drugs; T750 µm: 750 µmtemporal; T1500: 1500 µm temporal; SFCT: Subfoveal choroidal thickness; N750: 750 µm nasal; N1500: 1500 µm nasal; Kruskal-Wallis test was used; * $p<0.05$: statistically significant.

95% confidence intervals (CIs) were calculated. An ICC of 0.75-0.90 indicates good reliability, and values greater than 0.90 indicate excellent reliability.[28]

RESULTS

Characteristics of the RA group

Of the 63 RA patients assessed for eligibility, four were excluded from the study: one due to diabetes mellitus, one due to systemic sclerosis, one due to dry eye, and one due to failure of adaptation (Figure 2). Thus, 59 RA patients and 36 healthy controls (30 females, 6 males; mean age: 52.3±7.6; range, 44.7 to 59.9 years) were included in the study. Following detailed examinations, 20 RA-ILD patients (15 females, 5 males; mean age: 56.1±8.5 years; range, 47.6 to 64.6 years) were assigned to Group 1, and 39 RA-noILD patients (8 males, 31 females; mean age: 54.2±9.8 years; range, 44.4 to 60 years) were assigned to Group 2. Groups 1, 2, and 3 were similar in terms of age and sex distribution, and BMI (p=0.312, p=0.752, and p=0.792, respectively; Table 2).

A mean disease duration of 5.8±3.4 years and a DAS28 score of 2.7±0.4 were measured in Group 1, while a mean disease duration of 7.6±5.4 years and a DAS-28 score of 2.9±0.4 were measured in Group 2. There was no difference between patients with RA-ILD and RA-noILD in terms of disease duration, DAS28 scores, serum rheumatoid factor, anti-citrullinated protein autoantibodies levels, laboratory results, and medical treatment (p>0.05, Table 2).

Comparison of parameters of the choroid

The mean CT measured at five points in Group 1, Group 2 and Group 3 are illustrated in Table 2. There were statistically significant differences between Group 1, Group 2 and Group 3 in terms of all CT measurements (p<0.05, for the relevant variables). The mean CT measured at N750.0 (168 µm, 221 µm, and 409 µm, respectively; p<0.001) and N1500.0 (166 µm, 207 µm, and 463 µm, respectively; p<0.001) points was lowest in Group 1, followed by Groups 2 and 3. However, Groups 2 and 3 were similar in terms of mean CT measured at temporal points and sfCT (p>0.05).

Relationship between ILD severity and ocular parameters

The clinical, radiological, and pulmonary function test (PFT) results of the RA-ILD group are presented in Table 3. The interobserver agreement was excellent for the evaluation of

Table 3. Description of incident RA-ILD cases

	n	%	Mean±SD
Clinical symptoms			
Dyspnea	9	45	
Dry cough	9	45	
Fatigue	7	35	
Weakness	50	10	
RA-ILD subtype			
Cellular NSIP	5	25	
Fibrotic NSIP	7	35	
UIP/AIP/DAD	8	40	
Pulmonary function test results			
Percent predicted FEV1			86.3±19.1
Percent predicted FVC			85.3±21.9
FEV1/FVC			82.1±4.9

RA-ILD: Rheumatoid Arthritis-Associated Interstitial Lung Disease; SD: Standard deviation; NSIP: Non-Specific Interstitial Pneumonia; UIP: Usual Interstitial Pneumonia; AIP: Acute Interstitial Pneumonia; DAD: Diffuse Alveolar Damage; FEV1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity.

Table 4. Spearman's rank correlation coefficients of ΔHRCT scores and clinical variables with CT

	HRCT score		FVC		FEV1/FVC		FEV1	
Ocular parameters	*p*	r	*p*	r	*p*	r	*p*	r
SFCT (µm)	0.910	0.27	0.883	0.35	0.111	-0.367	0.412	-0.015
T750 (µm)	0.850	0.045	0.765	0.71	0.067	-0.329	0.908	-0.122
T1500 (µm)	0.832	0.051	0.755	0.74	0.156	-0.417	0.608	-0.194
N750 (µm)	0.997	0.001	0.423	0.190	0.192	-0.304	0.948	-0.283
N1500 (µm)	0.842	0.48	0.365	0.214	0.145	-0.338	0.227	-0.373

ΔHRCT: Delta High-resolution computed tomography; CT: Choroidal thickness; FVC: Forced vital capacity; FEV1: Forced expiratory volume in 1 second; SFCT: Subfoveal choroidal thickness; T750: 750 temporal; T1500: 1500 temporal; N750: 750 nasal; N1500: 1500 nasal; * p<0.05, statistically significant.

the ΔHRCT scores (ICC=0.957; 95% CI: 0.969-0.995). There was no correlation between the mean CT measured at temporal or nasal points and ΔHRCT scores. Moreover, no significant correlation was found between CT measurements and PFT (p>0.05, Table 4).

DISCUSSION

Rheumatoid arthritis is an autoimmune and systemic inflammatory disorder, with the most frequent EAM being lung involvement, which can affect up to 60% of patients with RA.[28] Vascular inflammation is also common in RA. All types of blood vessels can be affected, particularly small vessels.[29] Ischemia manifests as infarction, gangrene, or atrophy based on the location and size of the affected vessels.[30] In our study, the RA-ILD group had a statistically thinner mean CT measured at the nasal points than the other groups. Moreover, there was no correlation between CT measurements and the HRCT score, which indicates the severity of lung involvement.

There are some studies in the literature evaluating CT in patients with RA. However, CT changes in RA are contradictory. Tetikoglu et al.[31] reported that RA patients had a thicker CT than healthy controls due to systemic inflammation, neutrophilic infiltration, and immune complex deposition. Machado et al.[32] also showed a thicker choroid secondary to posterior scleritis. However, Duru et al.[33] stated that the immunological mechanisms of RA that cause vascular inflammation could also be a precursor of choroidal vascular damage. They also reported that RA patients in remission according to the DAS-28 score had statistically significantly lower CT values compared to healthy controls. The reason for this result was explained by the lack of an improvement in choroidal thinning even in remission since the degenerative changes of the vascular wall and fibrinoid necrosis persist. Another study showed statistically thinner CT in RA patients than in healthy controls. In addition, a negative correlation was found between disease activation and CT thickness.[34] In our study, RA patients had a statistically thinner CT measured at the nasal points compared to the healthy control group. Our study also showed that the CT measured at the temporal points was numerically thinner, though not significant. The possible reason for this was probably due to the degenerative and occlusive condition induced by the chronic inflammatory vascular wall of the choroid, leading to decreased CT as a result of ischemia and atrophy.

Recent studies in the literature have identified biomarkers such as MMP-7, IL-18, IL-13, and C-X-C motif chemokine ligand 10 (CXCL10) in patients with RA-ILD compared to RA-noILD patients.[35,36] The literature review revealed that these biomarkers were associated with vascular pathologies.[35,36] Chen et al.[35] reported that MMPs were effective in vascular remodeling and vascular smooth muscle cell proliferation. Xia et al.[36] reported that increased secretion of CXCL10 secondary to hypoxia was associated with vascular smooth muscle migration and angiogenesis after ischemia. Another study showed the critical role of IL-13 released from T helper 2 cells in vascular remodeling and smooth muscle proliferation.[37]

These may explain why a highly vascularized structure such as the choroid was affected more in RA-ILD patients than in other groups in our study.

In RA patients, anatomical structures, such as parenchyma, pleura, and upper or lower airways, and the vascular structure may be involved.[38] Therefore, these patients may present with very different HRCT findings. In our study, the severity of lung involvement was evaluated with the ΔHRCT scoring. Rheumatoid nodules, mosaic perfusion, and pleural effusion detected on HRCT of RA-ILD patients are not evaluated in this scoring system. This limitation may explain why there was no significant relationship or correlation between ΔHRCT score and CT in our study. Therefore, evaluating the severity of lung involvement with a scoring system that includes all HRCT findings could have provided us with more objective and healthy data.

Pulmonary function tests is most commonly used to detect lung changes. Asymptomatic patients with RA may have PFT alterations between 30 and 45% of the time.[39] However, no significant correlation was found between CT measurements and PFTs. This may be due to two reasons. First, nutrition, education levels, and environmental factors affect PFTs.[40] Second, PFTs lack sufficient sensitivity and negative predictive value for the detection of ILD.[41] Therefore, there is a need for studies to verify this result.

This study has two limitations. First, although testing diffusing capacity for carbon dioxide is more specific than other PFT components, its correlation with CT could not be evaluated. The reason for this was the unwillingness and noncompliance of patients to participate during the test. Second, the study's cross-sectional design limited its ability to show a correlation between the ΔHRCT scoring and CT. Thus, a prospective study is required to determine whether this correlation remained stable with the progression of lung severity or whether treatment affected it.

In conclusion, RA-ILD patients had thinner CT than RA-noILD patients and healthy controls. This may be related to occlusion or degeneration secondary to chronic inflammation of the vascular wall. Furthermore, patients with RA-ILD should be regularly followed up with optical coherence tomography for the evaluation of the choroid.

Ethics Committee Approval: The study protocol was approved by the Pamukkale University Faculty of Medicine Ethics Committee (date: 15.06.21, no: 60116787-020-110161). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept: K.S., S.N.; Design: K.S.; Control/supervision: K.S., U.F., K.H.; Data collection and/or processing: K.S., C.V., U.F.; Analysis and/or interpretation: K.S., S.N., Y.M.; Literature review: K.S.; Writing the article: K.S., U.F., S.N., U.R.A.; Critical review: K.S., K.H., C.V.; References and fundings: K.S., Y.M., U.R.A.; Materials: K.S., S.N., K.U., K.H., C.V.

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