Ref: Ro J Rheumatol. 2023;32(3)
DOI: 10.37897/RJR.2023.3.1

The diffusing capacity of the lungs for carbon monoxide - an independent predictor of interstitial lung disease in patients with rheumatoid arthritis - results of a prospective study

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ABSTRACT

Background. The diffusing capacity of the lungs for carbon monoxide (DLCO) represents the most sensitive independent factor for highlighting the interstitial lung disease associated with rheumatoid arthritis (RA-ILD). Many studies have analyzed this association between RA and lung modifications because it correlates with a decrease in the patients' quality of life and a higher mortality.

Objective. This study aimed to highlight the importance of DLCO as a predictor of ILD progression in RA, beside the pattern on high-resolution chest CT (HRCT) and the double seropositivity of the disease.

Patients and method. This prospective cohort study, carried out between August 2022 and May 2023, included 48 RA patients with ILD, fulfilling the 1987 ACR or 2010 ACR/EULAR classification criteria. Important attention was paid to respiratory functional tests, immunological changes, and specific lung pattern on HRCT. Patients with current malignancies, active infections or Overlap syndrome were excluded from the study.

Results. 48 RA patients, mostly women (81%) with a mean age of 65.54±10.58 years old and a median age of RA onset of 52.58±11.36 years, were included. The proportion of patients with a decreased DLCO was 64.6%. Using statistical tests, we found significant correlations between DLCO and age, double seropositivity and a specific pulmonary pattern on HRCT.

Conclusion. ILD, an underrecognized disease, may be considered one of the most serious of all extra-articular manifestations in RA, the risk for mortality being triple in these cases. Our results are in correlation with the published data and support the key role of DLCO in the diagnosis and follow-up of these patients.

Keywords: rheumatoid arthritis, HRCT, UIP, NSIP, DLCO, seropositivity, ILD

INTRODUCTION

The burden era of RA-ILD is an uncertain global situation in which it could not be exactly specified whether the disease onset belongs to the articular inflammatory process, or it is secondary to lung damage [1-4]. ILD is a well-known devastating extra-articular manifestation of RA, with a three-fold increased risk for mortality and morbidity. After diagnosis, median survival is only between 2.6-3 years [2].

Knowing that RA by itself is a risk factor for ILD, specialists must pay a rigorous attention to: smoker status, immunological investigations, seropositivity, male gender and therapy [5-8]. In accordance with recent studies, the general term "rheumatoid lung disease" illustrates the involvement of several parts of the lungs with different extension of inflammatory process or fibrosis [7-9].

The lung patterns on HRCT scan for RA-ILD include two idiopathic interstitial pneumonia aspects: nonspecific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP). UIP pattern is correlated with a decreased survival and a poor response to

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Article History:
Received: 11 September 2023
Accepted: 19 September 2023

treatment. HRCT scan nowadays is considered the "gold standard" in RA-ILD diagnosis, substituting lung biopsy [10-12].

DLCO under 45% or a decreased value with more than 10% is the most suitable and sensitive predictor for RA-ILD, leading to an earlier detection of lung involvement in RA disease, regardless abnormalities on HRCT images [13-15].

The therapeutic options for RA can possibly stop or prevent the onset of RA-ILD. The adverse effects of using Methotrexate (MTX) represents a controversial subject nowadays. Some specialists consider that it is not involved in the onset of RA-ILD; others, at the opposite side, support its role in the development of the disease. Glucocorticoids have been a first line treatment for a long time, but nowadays must be given with great attention and a careful monitoring due to their side effects [16-18]. There is evidence that supports the fact that MTX, Rituximab and Abatacept can be considered reliable options in the therapeutic strategy of RA-ILD [19].

PATIENTS AND METHODS

This prospective cohort study included 48 patients with RA, diagnosed using 1987 ACR or 2010 ACR/EULAR criteria. All the patients had ILD evidenced by HRCT. The study was carried out between August 2022 and May 2023. Patients were attending Rheumatology and Radiology departments in Clinical Rehabilitation Hospital, Iasi, Romania, where all clinical symptoms, immunological changes, imagistic aspects, abnormalities in respiratory functional tests were taken into consideration and laboriously noted.

Anti-cyclic citrullinated antibodies (ACPA) play a crucial role in RA-ILD, being more sensitive than rheumatoid factor (RF) [20, 21]. DLCO seems to be the most sensitive indicator (100%) of RA-ILD progression. It is considered an independent predictor due to the ability of an earlier detection of pulmonary dysfunctions with or without changes evidenced on HRCT [9-11].

The inclusion criteria were: definite diagnosis of RA according to 1987 ACR or 2010 ACR/EULAR criteria, smoker status, double seropositivity for RA, a decreased value of DLCO (<45%), specific lung pattern illustrated on HRCT, age between 50-70 years old.

The exclusion criteria included: Overlap syndrome, active infections and current tumoral pathology.

We took into consideration some risk factors which we considered the most important, such as: male gender, age over 50 years, ACPA positivity, disease duration over 5 years, use of disease-modifying antirheumatic drugs (DMARDs)/biological therapy and smoking status.

Statistical analysis was made using a SPSS software. The correlations between DLCO (<45%), the presence of RF and ACPA and the presence of UIP or NSIP on HRCT was highlighted by applying Fisher's Exact Test, Mann-Whitney and Chi-Square Test. Written informed consent was explained and signed by all subjects included in this study.

RESULTS

The study included 48 RA patients, mostly females (39 cases-81.25%), non-smokers, with a mean age of 65.54 ± 10.58 years. The mean age of disease onset was 52.58 ± 11.36. The proportion of patients having a decreased DLCO (40 ± 20%) was 64.6%. RA double seropositivity was found in 58.1% cases and a specific lung pattern on HRCT in 77.4% cases. 81.25% patients received MTX as part of their initial therapy strategy.

Under therapy, many of the patients had a good evolution both in terms of disease activity and interstitial lung involvement. The pulmonary symptoms were reduced, most of the subjects having dyspnea and dry cough. Table 1 presents the immunological and pulmonary characteristics of the included patients.

TABLE 1. Immunological and pulmonary characteristics of the patients

Characteristics	N=48	%
DLCO<45%	31	64.6
Double seropositivity	18	58.1
CCP+	3	9.7
RF+	6	19.4
HRCT definite aspect	24	77.4
UIP pattern	4	8.33
NSIP pattern	34	70.83
HRCT non-specific aspect	7	22.6

In our study, a decreased DLCO (40±20%) was highlighted in 64.6% cases, 83.9% female and 16.2% male patients (Table 2, Table 3).

TABLE 2. Percentage of the patients with a decreased DLCO

DLCO %		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	normal	17	35.4	35.4	35.4
	decreased	31	***64.6%***	64.6	100.0
	Total	48	100.0	100.0	

There were no significant differences between a decreased DLCO and the gender of the patients (p = 0.396). There was an important association between a decreased DLCO and the age of the patients (p = 0.056) (Table 4).

TABLE 3. Correlations between DLCO and the gender of the patients

DLCO in association with patient's gender					
			Gender		Total
			Male	**Female**	
DLCO	normal	Count	4	13	17
		% within DLCO_ dummy	23.5%	76.5%	100.0%
	decreased	Count	***5***	26	31
		% within DLCO_ dummy	***16.1%***	***83.9%***	100.0%
Total		Count	9	39	48
		% within DLCO_ dummy	18.8%	81.3%	100.0%

TABLE 4. Correlations between DLCO and patient's age

DLCO in association with patient's age					
			DLCO %		Total
			NORMAL	**DECREASED**	
DLCO	51-60 years	Count	2	4	6
		% within DLCO_ final	11.8%	***12.9%***	12.5%
	61-70 years	Count	9	14	23
		% within DLCO_ final	52.9%	***45.2%***	47.9%

In our study, 58.1% cases had double seropositivity (RF and ACPA). A decreased DLCO was observed in 19.4% cases with an elevated level of RF and in 9.7% cases with high titer of ACPA. Significant correlations between a decreased DLCO and double seropositivity of RA were highlighted (p=0.054).

A decreased DLCO was evidenced in 77.4% of the cases having a specific pulmonary pattern on HRCT. 22.6% of RA patients without a definite pattern on HRCT for ILD had a decreased level of DLCO. RA-UIP unique tomographic pattern ("honeycombing" aspect, basal predominance, traction bronchiectasis) on HRCT was highlighted in 8.33% cases, whereas NSIP pattern ("ground glass" opacification, basal predominance, architectural distortion) was the most prevalent in 70.83% cases (Table 5).

Regarding the treatment history, 81.25% cases were treated with MTX, 79.16% used Leflunomide and 29.16% used TNF alpha inhibitors. During the study, 64.58% cases followed monotherapy with DMARDs, 8.33% cases used biologics in monotherapy and 27.08% cases used a combined therapy of biologics and DMARDcs. No significant data were highlighted regarding the analyzed correlations between the DLCO value and the followed therapy, especially MTX.

TABLE 5. Correlations between DLCO and HRCT aspect

DLCO in association with HRCT aspect					
			DLCO final		Total
			Normal	**Decreased**	
HRCT	**with specific pattern (UIP/ NSIP)**	Count	13	24	37
		% within DLCO_ final	76.5%	***77.4%***	77.1%
	without specific pattern	Count	4	7	11
		% within DLCO_ final	23.5%	***22.6%***	22.9%
Total		Count	17	31	48
		% within DLCO_ final	100.0%	100.0%	100.0%

DISCUSSION

DLCO value and HRCT aspect have the most important role in the "ILD era" for patients with RA disease. Taking into consideration that RA is by itself a major risk factor for developing ILD, it is recommended to pay attention to every clinical sign. Recent studies focus on discovering possible correlations between clinical signs, genetic and immunological changes, treatment's strategies, and imagistic abnormalities in RA-ILD [2,5,11]. A value of DLCO under 45% indicates a high probability of progression to RA-ILD [1,14]. Most of the studies draw attention to the fact that an earlier diagnosis, using pulmonary functional tests, especially DLCO, plays a major role in RA-ILD prognostic [15-17].

The aim of our study was to distinguish the high sensibility of DLCO as an independent predictor of lung involvement in RA. The main risk factors for pulmonary involvement in RA are: male gender, smoking status, elevated levels of RF and ACPA, age between 50-70 years, treatment with tsDMARDs/ bDMARDs and a disease duration more than 5 years [3,8].

DLCO decrease may be considered the first "red flag" due to its ability to identify RA-ILD cases on early stages, even when the HRCT aspect is normal [9].

Regarding female gender, non-smoker status and age at the onset of the disease, our results were comparable to those reported by Albrecht [22] and McFarlane [23]. Sparks et al. [24] highlighted a positive correlation with a younger age of RA onset.

A decreased DLCO (40±20%) was found in 64.6% of the cases, similar with the literature results [3,4,6,25]. Because of the female frequency (39/48), a reduced DLCO was more frequent in women (83.9%).

We significantly found correlations between low levels of DLCO, HRCT lung patterns, and double seropositivity (RF, ACPA antibodies). In our study, 77.4%

cases have a definite pattern of RA-ILD, 70.83% cases having NSIP (usually "ground glass" aspect, with a basal distribution) and 8.33% cases having UIP (usually "honeycombing" aspect). Close results, where NSIP pattern had a more elevated frequency than UIP, were revealed by Spraks et al. (NSIP 81.2% cases) [23] and by Denis et al. [26]. On the other side, in a retrospective study a higher frequency of UIP pattern (33.09% cases) in RA-ILD subjects [25]. McFarlane et al. also found in Black RA population a more frequent UIP pattern (75% cases) [24]. Of note, Duarte highlighted equal percentages (40%) for each pattern of ILD (NSIP or UIP) [27].

A systematic review and meta-analysis showed that elderly patients, especially males, smokers, with a seropositive disease, a decreased DLCO along with typical changes on HRCT, were highly prone to an increased risk of mortality and morbidity in RA-ILD, especially those having a "honeycombing" aspect [28].

Regarding RA seropositivity, our study highlighted a percentage of 58.1% cases with high levels of RF and ACPA. 19.4% cases had a positive RF and 9.7% cases only ACPA positivity.

With reference to the therapy history, a percentage of 81.25% cases were treated with MTX and 79.16% cases took Leflunomide. Few patients were using biological treatment (8.33%). In different studies it was highlighted that MTX exposure is not considered an enhancer of developing RA-ILD, not even of exacerbation of the already existing disease [25,27,29].

Our study has limitations due to the reduced number of the included patients. However, we found significant correlations between DLCO, HRCT aspect and the specific antibodies in RA. We consider our study a small contribution in the field, supporting the fact that lung damage can be a real serious problem for these patients.

CONCLUSION

RA by itself is known as an important risk factor for ILD development. An early diagnosis of pulmonary manifestations plays a major role in disease prognosis. Lung function tests, along with imaging investigations, are of real use in the management of these cases. The detection of a low value of DLCO should raise an alarm signal for further investigations. Good control of RA and ILD must be a priority for the physician. Therapy in these cases must be individualized, using drugs that show both articular and pulmonary efficacy.

Conflict of interest: none declared
Financial support: none declared

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