

**Examination of the diagnostic accuracy of pulmonary ultrasound in finding of interstitial lung disease in patients with rheumatoid arthritis**



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**Abstract**

**Introduction:** Rheumatoid arthritis is a common and systemic disease for unknown reasons. Pulmonary involvement is common in patients with rheumatoid arthritis. Lung ultrasound is a safe, easy, and accessible way to diagnose lung cancer. Therefore, the aim of this study was to investigate the diagnostic accuracy of pulmonary ultrasound (US) to find pulmonary parenchymal involvement in patients in patients with rheumatoid arthritis.

**Materials and Method:**

This study was performed cross-sectionally with a descriptive-analytical approach on 123 patients with rheumatoid arthritis. After obtaining written consent, all individuals were undergoing lung ultrasound. The results of ultrasound to determine the diagnostic accuracy of this modality in ILD diagnosis, were compared with the findings of HRCT. In the next step, a checklist also included personal information such as gender, age, smoking and drug history for each patient. The collected data were analyzed after coding and logging into SPSS-21 statistical software and analyzed using appropriate statistical tests.

**Results:**

Evidence of ILD in HRCT study was observed in 37 subjects (about 30%). Sensitivity and specificity in ILD diagnosis were 64.8% and 60.47%, respectively. The positive predictive value (PPV), negative predictive value (NPV), positive odds ratio and negative odds ratio were estimated at 41.38%, 80%, 1.64,

0.58, respectively and diagnostic accuracy was 61.79%. Ultrasound sensitivity in both mild and moderate B-Line was 48%, but US specificity in mild and moderate B-line was 61% and 98%, respectively, and ultrasound diagnostic accuracy was 58% and 82%, respectively. Our results showed that the sensitivity of ultrasound (64.86%) was significantly different from the expected analysis ( $P < 0.05$ ). In the HRCT study, a direct and significant relationship was observed between Bline count with the coefficient of 0.514.

### **Conclusion:**

According to the results of this study, the sensitivity of lung ultrasound for diagnosis lung parenchymal abnormalities in RA patients was significantly lower than expected. However, based on the evaluation of Warrick score and B Line correlation, lung ultrasound could be a novel diagnostic tool in ILD grading, especially in patients with lung involvement, as well as long-term control of this disease in RA patients.

**Keywords:** Ultrasonography, Rheumatoid arthritis, Lung involvement, Parenchymal abnormality.

### **Introduction:**

Rheumatoid arthritis is a systemic disease in which the destruction of cartilage and the formation of bone lesions occurs following a chronic inflammatory synovitis (1). The earliest pathological event is a non-specific inflammatory response, the trigger of which is unknown. Eventually, synovial hyperplasia and hypertrophy occur with the accumulation of macrophages and other mononuclear cells in the synovial layer. The activity of these cells is characterized by increased production of inflammatory cytokines, including  $TNF\alpha$  (Tumor necrosis factor alpha) and IL1B (Interleukin 1B), IL6 (Interleukin 6) (2). Rheumatoid arthritis is known to cause progressive and irreversible damage to the synovial joints following loss of joint space, bone, and their function, as well as deformity. Extra-articular involvement of this disease includes pulmonary, cardiovascular, and neural involvement and involvement of the reticuloendothelial system (3-5). Pulmonary involvement is relatively common in patients with rheumatoid arthritis. Clinical findings largely reflect pathological changes and include pleural effusion, obstructive bronchiolitis, interstitial fibrosis, pulmonary nodules, and pulmonary arthritis (6). The most common manifestation of lung involvement in RA is interstitial lung disease (7).

Diagnosis of rheumatoid arthritis is possible by clinical criteria of the American College of Rheumatology (ACR). In case, the clinical criteria are not sufficient, a positive rheumatoid factor (RF) and rheumatoid nodule and radiological changes (Erosion) can be used. ACR criteria include morning dryness of more than one hour for six weeks, arthritis in more than three of the 14 joints, arthritis of the hand (Pip, Mcp, Wrist), symmetrical involvement, rheumatoid nodules, positive rheumatoid factor, and radiological

evidence (erosion). (8,9). In 1998, it was revealed that specific rheumatoid arthritis antibodies targeted citrulline proteins, which led to the development of antibody tests against anti-CCPs by ELISA (10).

HRCT is the standard radiographic technique for diagnosing lung involvement in patients who suffer from pulmonary symptoms or have abnormal lung function tests (11). Unfortunately, due to the high cost and the amount of radiation received by the patient each time, this method cannot be performed repeatedly for patients (12). Recently, pulmonary ultrasound has been proposed as a safe, easy, and accessible diagnostic method for pulmonary fibrosis, bronchiolitis, and pneumothorax (13). The biggest advantage of lung ultrasound is that it is non-invasive and does not expose the patient to radiation. This method is much cheaper than HRCT and can be done frequently (14). Ultrasound symptoms, such as B-lines, irregular pleurisy, or lack of lung sliding, are good screening tools for lung involvement (15). There is a specific strategy for treating this disease that blocks various stages of the pathogenesis of the disease. In recent years, most of the world's leading rheumatology centers believe that the best time to treat rheumatoid arthritis is in the early stages of the disease (RA-Early), so when the diagnosis of rheumatoid arthritis is confirmed, serious treatment is needed. The most appropriate treatment in this case is combination therapy with several drugs (Combination Therapy) (64). Due to the high prevalence of rheumatoid arthritis and conventional treatments, clinical observations show that combination therapy moderates the symptoms of the disease in rheumatoid arthritis patients (16). Therefore, the aim of this study was to evaluate the accuracy of pulmonary ultrasound in finding ILD in patients with rheumatoid arthritis compared to the gold standard method, ie HRCT, so that perhaps due to the benefits of ultrasound, which include cheapness, availability and no need to irradiate ionized radiation, this method could be used to find the ILD in these patients and reduce the amount of HRCT in them in unnecessary cases.

### **Materials and method:**

This study is an analytical and cross-sectional study. The study population is included from all patients with rheumatoid arthritis referred to Razi Hospital Hospital in Rasht-Iran in 1398, which was known as ILD, or according to the recent RA diagnosis, ILD has not been diagnosed yet and has an include and exclude criteria.

#### *Inclusion Criteria*

RA disease

#### *Exclusion Criteria*

1- Age under 18

- 2- Previous history of lung disease (other than ILD in the case group), CHF, history of recent infection, history of previous lung surgery

*Sampling method and calculation of sample size*

The sample size was calculated to determine the diagnostic accuracy of ultrasound in finding parenchymal lung disease in patients with rheumatoid arthritis with 95% confidence and 80% test strength for significant hypothesis of Sensitivity = 80% based on the sampling formula below 117 people.

$$1-\alpha=0.95 \quad Z_{1-\alpha/2}= Z_{0.975}=1.96$$

$$1-\beta=0.90 \quad Z_{1-\beta}= Z_{0.9}=1.28$$

$$\text{Sensitivity}=92\% \quad P_0=80\%$$

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 P_0(1 - P_0)}{(P_1 - P_0)^2}$$

$$\frac{(1.96 + 1.28)^2 0.8(1 - 0.8)}{(0.92 - 0.8)^2} = 117$$

RA patients who had been diagnosed with ILD and had previously undergone HRCT, did not need to undergo re-HRCT. For new cases and for patients who were eligible to undergo HRCT, this modality was performed. The checklist included personal information such as gender, age, smoking and medication used for each patient. All of the subjects underwent lung ultrasound due to the safety of the ultrasound.

The device used to perform was the TOSHIBA ultrasound with the Linear probe (13-14 MHz). In order to perform ultrasound, 14 intercostal spaces were considered, so that in the second anterior intercostal space in the parasternal and the fourth intercostal space in the midclavicular, anterior axillary and midaxillary and in the posterior 8th intercostal space in the paravertebral, sub-scapular and posterior axillary. The numbers of B lines observed in all spaces, were added together and classified.

Number of B Line	SCORE
<5	0 (normal)
6-15	1 (mild)
16-30	2 (moderate)
>30	3 (severe)

HRCT was performed using a standard GE device with 2 mm thick cut-outs in the supine position at the deep inspiratory from the base of the neck to the base of the lungs, and no contrast material was used. The parenchymal findings of HRCT were interpreted separately by two radiologists, Blinded, and scored according to Warrick's criteria. In this criterion, each of the HRCT findings has a different value, which includes the following:

Findings	SCORE
GGO appearance	1
Irregular pleural margin	2
Septal/subpleural line	3
Honeycombing	4
Subpleural cyst	5

Also, the extent of the disease in HRCT was obtained by counting the number of pulmonary segments involved for the above abnormalities, which were defined as follows:

Segment	SCORE
1-3	1
4-9	2
>9	3

The severity and extent of the involvement in HRCT was finally calculated by summing up the scores obtained, which ranged from 0-30. Scoring for both ultrasound and HRCT was performed by a radiologist in a Blinded manner in relation to clinical information and other imaging modalities. A score of 7 or higher was considered an ILD in HRCT.

#### *Data Analysis*

After collecting data, the data study entered to SPSS software version 21. Sensitivity, Specialty, Positive predictive value (PPV), Negative predictive value (NPV), Accuracy, LR + and LR- were used to determine the accuracy of ultrasound diagnosis based on HRCT results. The 95% confidence interval for all diagnostic indicators was estimated. Z test was used to compare with the expected indicators (Sensitivity = 80% and PPV = 70%). The significance level of the tests in this study was less than 0.05.

### *Ethical Considerations*

The permission to start and conduct research was obtained from the university's ethics committee. All of the patients studied had previously undergone routine CT scans under the supervision of a physician, or newly diagnosed patients underwent HRCT for the ILD with a specialist physician's opinion and no additional radiation to patients were given. Pulmonary ultrasound, which is a completely safe modality, was also performed after patient satisfaction. All participants in the study could leave the study at any time if they did not wish. The information of all the people studied was kept confidential.

### **Results**

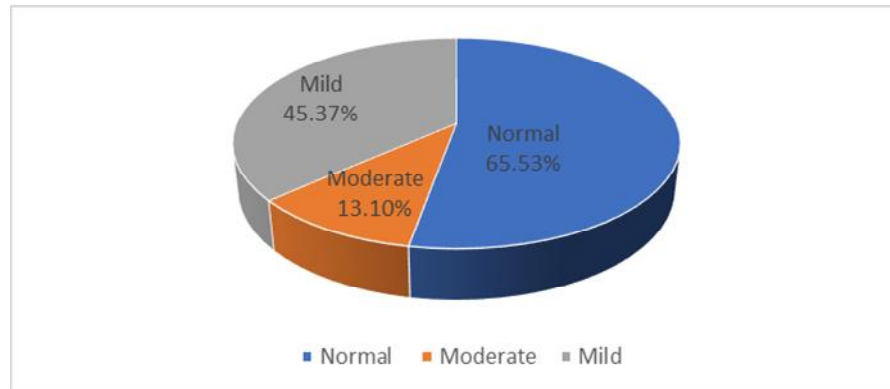
A total of 123 people entered the study and 120 (97.6%) were female and 3 (2.4%) were male. The mean age of the patients studied was  $40 \pm 8.82$  years with a minimum age of 27 years and a maximum age 67 years. The mean duration of rheumatoid arthritis with a minimum of one month and a maximum of 30 months was  $6.78 \pm 5.5$  months. Of the subjects studied, only one male was a male smoker, and the other subjects had no history of smoking.

In the study of the drug history in patients, the highest frequency of medication use observed in 59 patients (49.2%) and was related to the concomitant use of three drugs, hydroxychloroquine, methotrexate and folic acid. You can see the frequency of other medications in Table 1.

**Table 1:** Frequency and percentage of drug history in patients

Type of medication	Frequency	Percentage
Prednisolone + methotrexate + folic acid + hydroxychloroquine	19	15.4
methotrexate + folic acid	24	19.5
methotrexate + folic acid + hydroxychloroquine	59	48
Methotrexate + hydroxychloroquine + prednisolone and other drugs	18	14.6
Total	120	100

In the lung ultrasound examination of the subjects, in terms of the number of Bline and the classification of patients, as you can see in Figure 1, no disease was in the severe class (B Line<30) and most patients (53%) were categorized in the normal class (B Line<5). The frequency of mild and moderate (6<B Line<15) and moderate (16<B Line<30) was 45 (37%) and 13 (10%), respectively.



**Figure 1:** Frequency and percentage of ultrasound classification of patients based on B Lines

In the study of the frequency of HRCT findings based on Warrick's criteria in the study subjects, the median score of patients with the lowest score of 0 and the highest score of 10 and the highest frequency score of 0 (61 cases equivalent to 49.6%) was equal to score 1.

The study of lung involvement segments was evaluated based on HRCT findings and 23 patients (18.7%) had a score of one (involvement of 1-3 lung segments) and 39 patients (31.7%) had a score of two (4-9 lung segments) and involvement of more than 9 segments, was not observed in any patients.

ILD evidence in HRCT study was observed in 37 subjects (approximately 30%) of the subjects and 86 participants in the study (approximately 70%) were diagnosed as normal.

The frequency of ILD based on age, sex, smoking history, number of B Line and using of medication has been evaluated in Table 2. Among these factors, as can be seen in the table, the frequency of ILD was significantly different in terms of number of B Line (0.05). > P).

**Table 2:** Frequency of ILD in terms of demographic and sonographic factors

Variable	Condition	ILD Diagnosis		Result of the test
		Positive ( $\geq 7$ ) Frequency (percentage)	Negative ( $< 7$ ) Frequency (percentage)	
Age	$\leq 38$	18 (30)	42(70)	0.891 Chi-Squared test
	$>38$	19 (31.1)	42 (68.9)	
Gender	Male	0 (0)	3 (100)	0.555 Fisher's exact test
	Female	37 (30.8)	83 (69.2)	
Smoker	Yes	0 (0)	1 (100)	0.987 Fisher's exact test
	No	37 (31.4)	81 (68.6)	
Number of B-line	$<5$ (normal)	13 (20)	52 (80)	B Line
	6-15 (mild)	12 (26.7)	33 (73.3)	
	16-30 (moderate)	12 (92.3)	1 (7.7)	
Medication	Prednisolone + methotrexate + folic acid + hydroxychloroquine	8 (42.1)	11 (57.9)	0.343 Fisher's exact test
	methotrexate + folic acid	6 (25)	18 (75)	
	Hydroxychloroquine + folic acid + methotrexate	20 (33.9)	39 (66.1)	
	Methotrexate + hydroxychloroquine+ prednisolone and other drugs	3 (16.7)	15 (83.3)	

Table 3 assessed the sensitivity and specificity of ultrasound (normal / abnormal b-line) in the diagnosis of ILD disease (based on HRCT) and obtained 64.8% and 60.47%, respectively. The values of PPV,

Variable	Condition	Frequency	Mean score (SD)	Result of the test P-value
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NPV, LR +, and LR- were estimated at 41.38%, 80%, 1.64, 0.58, and diagnostic accuracy was 61.79%, respectively.

**Table 3:** Frequency of ILD depending on whether the ultrasound is normal or abnormal

Reality		ILD		Total
		Negative (<7) (numbers)	Positive (>=7) (numbers)	
Diagnostic test				
B Line	Negative (normal)	52	13	65
	Positive	34	24	58
Total		86	37	123

The sensitivity, specificity, and diagnostic accuracy of the ultrasound were assessed separately by the Bline rating system. The sensitivity of ultrasound in both mild and moderate classes was 48%, but the specificity of ultrasound in mild and moderate classes was 61% and 98%, respectively, and according to the formula, the diagnostic accuracy of ultrasound for mild and moderate classes were calculated 58% and 82%, respectively.

In the study of the relationship between HRCT and Bline number, a direct and significant relationship was obtained using Spearman correlation with a correlation coefficient of 0.514.

Age	≤ 38	60	2.2(3.12)	0.186 T-test
	> 38	61	2.96(3.22)	
Gender	Male	3	2(1.73)	0.634 T-test
	Female	120	2.56(3.2)	
Smoker	Yes	1	4(0)	0.662 T-test
	No	118	2.58(3.21)	
Medication	Prednisolone + methotrexate + folic acid + hydroxychloroquine	19	3.73(3.58)	0.283 One-way ANOVA analysis
	methotrexate + folic acid	24	1.91(2.85)	
	Hydroxychloroquine + folic acid + methotrexate	59	2.59(3.29)	
	Methotrexate + hydroxychloroquine+ prednisolone and other drugs	18	2.16(2.74)	

**Table 4:** Frequency of HRCT findings in terms of demographic factors

In Table 5, the number of B Lines in sonography in the subjects studied based on age, gender, history of smoking and drugs used, and according to the results, the relationship between B line and age (0.004 P-value) and drugs history (= 0.046 P-value) was significant.

**Table 5:** Frequency of B Line status in terms of demographic factors

Variable	Condition	B Line			Test result
		<5 (normal) Numbers (frequency)	6-15 (Mild) Numbers (frequency)	16-30 (Moderate) Numbers (frequency)	
Age	≤ 38	41(68.3)	13(21.7)	6(10)	0.004
	> 38	24(39.3)	30(49.2)	7(11.5)	Chi-Squared test
Gender	Male	0(0)	3(100)	0(0)	0.119
	Female	65(54.2)	42(35)	13(10.8)	Fisher's exact test
Smoker	Yes	0(0)	1(100)	0(0)	0.462
	No	64(54.2)	41(34.7)	13(11)	Fisher's exact test
Medication	Prednisolone + methotrexate + folic acid + hydroxychloroquine	6(31.6)	7(36.8)	6(31.6)	0.046 Fisher's exact test
	methotrexate + folic acid	16(66.7)	6(25)	2(8.3)	
	Hydroxychloroquine + folic acid + methotrexate	34(57.6)	20(33.9)	5(8.5)	
	Methotrexate + hydroxychloroquine+ prednisolone and other drugs	9(50)	9(50)	0(0)	

## **Discussion**

Rheumatoid arthritis is a common and systemic disease for unknown reasons. Pulmonary involvement is common in patients with rheumatoid arthritis. Pulmonary ultrasound is a safe, easy, and accessible way to assess lung involvement (17). The aim of this study was to investigate the efficacy of lung ultrasound in the finding of interstitial lung disease (ILD) in patients with rheumatoid arthritis. In the present study, the role of pulmonary ultrasound in the diagnosis of interstitial lung tissue in patients with rheumatoid arthritis was examined. Because this diagnostic tool is available, cheap and safe compared to HRCT. In the study of demographic information in the present study, the frequency of female gender was higher than male (97.6% vs. 2.4%). Due to the autoimmune nature of rheumatoid arthritis, higher prevalence of female patients is expected, in line with our findings other studies in RA patients have reported a higher prevalence of females compared to males (18-20).

In the present study, ILD evidence in HRCT study was observed in 30% of the subjects. In a study by Cogliati et al. (21), out of 39 subjects, 13 patients (approximately 33%) and in a study of Moazedi-Fuerst et al. (22) 28% of patients showed ILD evidence in HRCT.

In the present study, there was no significant difference in RA-ILD patients compared to RA patients without pulmonary involvement in terms of age group, gender, smoking and drug use, which was similar to the results of Cogliati et al. However, the relationship between HRCT findings and lung B lines was significant and they were directly related to each other based on the results of the present study (21). The results of Cogliati et al.'s study also showed a direct and significant relationship between Warrick score and B Line with a correlation coefficient of 0.806 (21), which strongly supports the use of pulmonary ultrasound in ILD grading as well as long-term monitoring. In a 2016 meta-analysis, a direct and significant relationship was found between B Line ultrasound scores and Warrick scores in HRCT with a correlation coefficient of 0.783 (23). In the study of Tardella (24) and Torzillo et al. (25), this significant and direct correlation between ultrasound score and HRCT score was observed.

In our study, sensitivity and specificity, PPV and NPV of ultrasound in the diagnosis of ILD were estimated at 64.8% and 60.47%, 41.38% and 80%, respectively. In Cogliati et al.'s (21) study, the values of these indicators were 92% and 56%, respectively. The sensitivity index in this study was much higher than in our study, which may have been due to the use of Pocket-Size US Device (PS-USD) in their study as screening tools. In a 2016 meta-analysis in South Korea, the sensitivity and specificity of lung ultrasound were 91.5% and 81.3%, respectively (66), which was higher than the results of the present study. In the study by Aghdashi et al., The values of sensitivity, specificity, positive and negative predictive values of trans-thoracic ultrasound were 73.58%, 88.23%, 95.12% and 51.72%, respectively (26). In the study by Torzillo et al. (24), the sensitivity and specificity of pulmonary ultrasound performed

by an experienced physician were 92% and 56%, respectively, while the sensitivity and specificity of pulmonary ultrasound performed by the trained operator were 88% and 50%, respectively. In the present study, the values of positive likelihood ratio and negative likelihood ratio were estimated to be 1.64 and 0.58, respectively. In the meta-analysis of Song G et al. (23), these values were 4.1 and 0.176, respectively, and therefore the diagnostic accuracy of ultrasound in the present study was less than the meta-analysis performed in South Korea. However, in our study, the diagnostic accuracy of ultrasound in individuals in middle class in terms of the number of B line numbers was more than the total calculated value and more than the value of this parameter in the light class and about 80%, which can indicate higher accuracy of lung ultrasound in diagnosing ILD in patients with more lung involvement compared to Patients with mild involvement, however, need more extensive studies with a larger sample size to achieve definitive results in this area.

However, as can be seen, the results of various studies are different, which might be related to variation in the type of device used, operator experience, scanning methodology (number of areas or spaces examined, Optimal probe including convex, cardiac and linear and the number of times the pathological findings are evaluated, the difference in the target group or cut offs considered in the classification of patients in terms of the number of B Line. Despite these differences, most studies have considered ultrasound as an important, accessible, repeatable, non-invasive, and relatively easy diagnostic tool for the diagnosis and follow-up of interstitial lung disease.

According to the results of the present study, the relationship between B line and age was significant and the frequency was significantly higher at the age of 38 years. In a study by Bongartz et al. (27), those patients with rheumatoid arthritis who were older at the time of the onset of the disease were at higher risk for developing ILD. Based on the results of the present study, the relationship between B line and the drug history was significant that could be due to the limitations of studies in this field. For this reason, more studies are needed to obtain more accurate information about the effect of each drug used in these patients on disease progression of the interstitial tissue in the lungs.

### **Conclusion**

According to the results of this study, the sensitivity of lung ultrasound diagnosis was significantly lower than expected. However, the direct and significant relationship between Warrick score and B Line supported the possibility of using pulmonary ultrasound in ILD grading, especially in patients with more lung involvement, as well as long-term control of this disease in RA patients.

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