Lung ultrasound in patients with rheumatoid arthritis and the definition of significant interstitial lung disease

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Abstract

Background. In recent years, a growing interest has grown around interstitial lung disease (ILD) in patients with rheumatoid arthritis (RA). While high resolution computed tomography (HRCT) of the chest remains the diagnostic method of choice, increasing attention has been directed towards lung ultrasound (LUS) in the diagnosis of ILD in connective tissue diseases. However, in patients with RA it is not yet clear how to interpret, in quantitative terms, the presence of B-lines, the LUS artifact indicative of ILD. The aim of this study was to determine the cut-off number of LUS B-lines that identifies a significant RA-ILD.

Methods. A cross sectional study was conducted on consecutive RA patients with suspected RA-ILD. The inclusion criteria were clinical (dyspnea, velcro sounds), instrumental (suggestive anomalies on conventional radiography, DLco reduction), or in presence of at least two of the following risk factors for RA-ILD: smoking habit, male sex, advanced age, and ACPA presence.

Patients underwent LUS (carried out in 14 defined intercostal spaces), chest HRCT, pulmonary function tests, and clinical evaluation. The diagnosis of RA-ILD was based on a semi-quantitative evaluation of chest HRCT using a computer-aided method (CaM). The discriminative validity of the LUS versus HRCT has been studied by using the receiver operating characteristic (ROC) curve analysis.

Results. 72 consecutive RA patients (21 male, 51 female) were evaluated, with a mean age of 63.0 (SD 11.5 years). The mean estimate of pulmonary fibrosis using the CaM was 11.20% (SD 7.48) at chest HRCT, while at LUS the mean number of B-lines was 10.65 (SD 15.11). A significant RA-ILD, as measured by the CaM at HRCT, was detected in 25 patients (34.7%). The presence of 9 B-lines was found to be the optimal cut-off at ROC curve analysis. This LUS cut-off defines the presence of significant RA-ILD with a sensitivity of 70.0%, a specificity of 97.62%, and a positive likelihood ratio of 29.4.

Conclusion. The present study provided data to determine the number of B-lines to identify a significant RA-ILD. LUS may represent a useful technique to select RA patients to be assessed by chest HRCT.

Introduction

Among the extra-articular comorbidities in the course of rheumatoid arthritis (RA), lung involvement, defined as RA-interstitial lung disease (RA-ILD), is among those that have raised most interest in recent years [1]. The definition of the RA-ILD pathogenesis is intricate, since in addition to the immunological mechanisms, lung damage can be caused by iatrogenic (e.g. drugs) or infectious causes [2]. It is estimated that RA-ILD affects about 20% of patients assessed through chest high resolution tomography (HRCT), however the percentages vary depending on the diagnostic methods used, and the most prevalent HRCT pattern is represented by the usual interstitial pneumonia (UIP) [3]. A diagnosis of RA-ILD is important for prognostic purposes since being able to intervene in the early and pre-clinical stages of the disease could mean a decisive improvement in the morbidity and mortality of these patients. With the currently available medications, it is possible to personalize the treatment in order to improve pulmonary involvement [4]. Although RA-ILD represents a frequent extra-articular involvement, to date there are no

guidelines or recommendations indicating how to diagnose it. However, it is recognized that chest HRCT remains the gold standard. HRCT allows for a detailed assessment of lung parenchymal abnormalities, and those of airways as well [5]. A further advantage of chest HRCT is the possibility to estimate the ILD quantitatively. Post-processing modifications are also possible on chest HRCT images that allow a quantitative estimation of RA-ILD. Through dedicated software, this assessment is rapid and reliable [6]. The two major limitations to a wide use of chest HRCT are the use of ionizing radiation and the limited availability of machines. Therefore, the use of HRCT should be wisely considered on an individual patient basis. A technique that can certainly be more widely available and reproducible is lung ultrasound (LUS). In recent years, LUS has become increasingly important in the study of ILD associated with connective tissue diseases (CTD-ILD) [7, 8]. Through the detection of artifacts that identify a pulmonary "interstitial syndrome", namely the B lines, LUS has emerged as a complementary method to HRCT. Although the mechanisms underlying B-lines are not yet fully understood, this "laser-like" artifact has demonstrated good diagnostic accuracy, and in particular the number of B-lines correlates with the extent of the fibrotic pattern in the CTD-ILD [9]. Since CT imaging should not be frequently repeated because of its radiation hazards, it seems appropriate to use LUS to improve timing to perform chest HRCT. An interpretative problem is to determine how many B-lines are indicative of a significant ILD. In this regard, in systemic sclerosis (SSc), a study has already been conducted that determined the B-lines cut-off indicative of significant SSc-ILD using the chest HRCT as gold standard criterion [10]. The determination of this type of cut-off is missing for the RA-ILD. Based on these considerations, the aim of this study was to identify the number of B-lines capable of identifying the presence of a significant ILD, defined at chest HRCT, in patients with RA.

Methods

Patients

For the purposes of this study, patients referring to a third level centre for the diagnosis and treatment of RA were consecutively included from June 2018 to January 2020. Patients with RA diagnosed in accordance with the 2010 American College of Rheumatology/European League Against Rheumatism criteria were included [11]. Alongside the diagnosis of RA, additional inclusion criteria defining a category of patients at risk of RA-ILD have been added. In detail, the risk of ILD was defined by clinical criteria, i.e. the presence of dyspnea and/or velcro sounds, instrumental criteria, i.e. the presence of suggestive abnormalities in the chest X-ray and/or a reduction in carbon monoxide diffusion lung capacity (DLco), or the presence of at least two risk factors for RA-ILD, i.e. smoking habit, male sex, advanced age (>65 years), presence of anti-citrullinated peptide antibodies (ACPA). None of the enrolled patients had a previous diagnosis of RA-ILD. Patients with a positive history of fibrosing lung diseases other than suspected RA-ILD, severe congenital or acquired thoracic deformities, previous lung surgery, heart failure, and a recent or current history of low respiratory tract infections were excluded.

Patients at risk of RA-ILD underwent a clinical examination performed by an experienced rheumatologist (MDC), and on the same day LUS was performed by an expert rheumatologist with 10 years of experience

in chest ultrasound (MT). Within two weeks of the clinical evaluation and LUS, patients underwent pulmonary function tests (PFTs) with DLco evaluation and chest HRCT.

Patients signed informed consent for the procedures performed in this study and the study protocol was approved by the local ethics committee.

Lung ultrasound examination

LUS examination was conducted by an operator who was aware of the diagnosis of RA, but blinded to the clinical (e.g. disease duration, dyspnea, serological status, velcro sounds, current therapy), chest HRCT, and PFTs data. In this study a simplified protocol including 14 lung intercostal spaces (LIS) already used for CTD-ILD was adopted [12]. This protocol, initially described by our group [12], was also used by other researchers to assess pulmonary involvement in patients with SSc [13]. Simplified LUS protocols, i.e. with a reduced number of evaluated LIS, have also been shown to correlate with HRCT scores for idiopathic pulmonary fibrosis [14]. Starting from the posterior thoracic region, the 14 LIS studied were the eighth in the paravertebral, subscapular, and posterior axillary lines, the fourth in the middle axillary, anterior axillary, and hemiclavicular lines, and the second in the parasternal line. All the LIS were bilaterally examined through longitudinal scans. The B-lines were counted and added up. When more B-lines appeared confluent, the semi-quantitative rule already proposed was applied for which in each single space the percentage of white screen was divided by 10, so for example a 40% of white screen corresponds to 4 B-lines, 50% to 5 B-lines and so on [15]. In Figure 1 is depicted an illustrative B-line. The examination was carried out with a linear probe from 4 to 13 MHz of a MyLab Class C, Esaote S.p.A., Genoa, Italy. Chest high-resolution computed tomography interpretation Chest HRCT images were acquired and evaluated through OsiriX MD 7. This software is a DICOM viewer for Mac operating systems. Using this computer-aided method (CaM), for each chest HRCT a semi-automatic lung segmentation was obtained. First of all it was calculated in total lung volume, then a second lung volume was calculated by applying -700 Hounsfield units (HU) as cut-off for the presence of normal lung tissue (the attenuation between -800 and -900 HU is that of the normal lung parenchyma, while values between -500 and -700 are considered in the ILD range). It was therefore possible to calculate the percentage of pulmonary parenchyma affected by ILD. This method has demonstrated good reliability in the evaluation of SSc-ILD [6, 16], and it is also valid for RA-ILD [3].

At this point, the cut-off of the percentage of fibrosis indicative of significant RA-ILD was deduced from a previously published case history in which the chest HRCT of patients with RA was evaluated using both a conventional visual method (Warrick's score) and the CaM [3]. The definition of significant RA-ILD has therefore been exclusively related to the chest HRCT findings. Briefly describing the results of that work, it was found that 29 out of 151 patients (19.2%) showed a significant RA-ILD estimated through Warrick's score. Comparing Warrick's score to CaM for the detection of a significant RA-ILD, the analysis of the receiver operating characteristic (ROC) curve showed that a significant RA-ILD measured by the Warrick's score (Warrick's score >7 applied as dichotomous criterion) [17], corresponds to 10.7% (Youden index) at the CaM. This cut-off identifies a significant RA-ILD with a sensitivity of 96.55%, a specificity of 80.33%,

and a positive likelihood ratio (LR+) of 4.91 (Supplementary material). In the present study, reference was therefore made to percentages above 10.7% as indicative of a significant RA-ILD at chest HRCT.

Statistical analysis

Data are presented as mean and standard deviation (SD) and as median and interquartile range. First of all, a correlation analysis (Pearson's rank correlation test) was made between the number of B-lines, the percentage of fibrosis evaluated with the CaM method at HRCT, and the PFTs measurements, specifically the first second forced expiratory volume (FEV1), forced vital capacity (FVC), and DLco.

Therefore, in order to answer the main objective of the study, i.e. to establish the number of B-lines at the LUS that identifies the presence of significant RA-ILD, an analysis of the receiver operating characteristic (ROC) curve was conducted, applying as a dichotomous criterion the presence of 10.7% of fibrosis evaluated with the CaM at the chest HRCT. The area under the ROC curve (AUC-ROC) was evaluated considering that an AUC-ROC between 0.50 and 0.70 has a poor accuracy, between 0.70 and 0.90 is considered "useful for some purposes", values above 0.90 identify a high accuracy [18]. The cut-off of the number of B-lines for significant RA-ILD was evaluated in the Youden index.

In addition, through one-way analysis of variance (ANOVA), the number of B-lines in relation to gender and in relation to current therapy were compared (grouping patients treated with csDMARDs vs those treated with bDMARDs or tsDMARDs). Statistical analyses were performed using MedCalc 18.0.0.

Results

A total of 72 patients (21 male, 51 female) with RA and suspected associated ILD were evaluated, with a mean age of 63.0 (SD 11.5 years), and a mean disease duration of 106.82 (SD 111.34) months. The serological status revealed a mean ACPA titre of 327.6 (SD 633.3) U/ml, and a rheumatoid factor of 324.6 (SD 748.7) U/ml. Thirty-eight (52.8%) patients had an erosive disease with an average CDAI of 17.60 (SD 9.46). Twenty-three (31.9%) patients were exposed to cigarette smoke, 18 (25%) were still smoking, and overall the number of pack years was 5.56 (SD 9.21) (Table 1).

With regard to treatment, 31 (43.1%) patients were treated with a biological disease-modifying anti-rheumatic drug (bDMARD), respectively 10 (13.9%) with etanercept, 9 (12.5%) with abatacept, 5 (6.9%), 3 (4.2%) with golimumab, 1 (1.4%) with certolizumab pegol, and 1 (1.4%) with rituximab. One (1.4%) patient was treated with the targeted synthetic DMARD (tsDMARD) tofacitinib. Forty-four (61.1%) were taking a conventional synthetic (csDMARD), in 34 (47.2%) cases it was methotrexate. Fifteen (20.8%) patients were on biological association treatment plus csDMARD. Applying the 10.7% cut-off at CaM, it was found in the present sample that 25 out of 72 patients (34.7%) had significant RA-ILD. The mean estimate of pulmonary fibrosis using the CaM was 11.20% (SD 7.48) at chest HRCT, while at LUS the mean number of B-lines was 10.65 (SD 15.11) (Table 1).

The correlation analysis revealed a good positive correlation ($r = 0.559$, $p < 0.0001$) between the number of B-lines and the percentage of chest HRCT fibrosis measured by the CaM. In addition, significant negative correlations have emerged between the number of B lines and DLco ($r = -0.375$, $p = 0.001$) and FVC ($r = -0.338$, $p = 0.003$) (Table 2).

Applying the cut-off of 10.7% for chest HRCT as estimate of significant RA-ILD, the presence of 9 B-lines (Youden index) was found to be the optimal cut-off at ROC curve analysis. This LUS cut-off defines the presence of significant fibrosis with a sensitivity of 70.0%, a specificity of 97.62%, and a positive likelihood ratio of 29.4. The estimated AUC-ROC was 0.838 ($p < 0.0001$) (Table 3, Figure 2).

ANOVA found that male patients had a significantly higher mean B-lines number than female patients (14.85 ± 20.57 vs 8.27 ± 12.25 , $p = 0.001$), while at the limits of statistical significance it was found that patients treated with bDMARDs or tsDMARDs had a higher mean B-lines number than patients treated with csDMARDs (12.96 ± 17.78 vs 7.97 ± 12.68 , $p = 0.044$).

Discussion

To the best of our knowledge, this is the first study that identified the B-lines cut-off number, documented at LUS, indicative of a significant RA-ILD. Being able to diagnose the presence of RA-ILD at an early stage, through repeatable and non-invasive methods, should be a prerogative of the rheumatologist. The recognition of comorbidities, and in particular pulmonary conditions, has been shown to be a fundamental element for prognostic purposes already in the early stages of the disease [19]. The mean time between RA-ILD diagnosis and RA diagnosis is 4.9 years, and at RA-ILD diagnosis a significant reduction in DLco is already present, with oxygen-therapy needed in half of the subjects [20]. ILD is a frequent extra-articular involvement, which can deteriorate rather rapidly [21], and imposes a severe burden on affected patients. The therapeutic armamentarium for treating this condition is fortunately becoming richer, although to date there are no specific recommendations on how to treat RA-ILD [22].

Different are the attempts to diagnose RA-ILD without the use of methods that use ionizing radiation, including the use of algorithms that elaborate velcro sounds at chest auscultation [23].

In the effort to diagnose RA-ILD as early as possible, without using X-rays, LUS certainly offers interesting possibilities. While detailed information on pulmonary parenchyma cannot be derived from the LUS examination, the identification of the B-lines artifact is very sensitive and specific for the diagnosis of "interstitial syndrome". The detection of interstitial syndrome should lead to further diagnostic investigations with more detailed imaging techniques such as chest HRCT. The problem is in the quantitative interpretation of the artifact, i.e. how many B-lines correspond to an interstitial syndrome corresponding to a significant RA-ILD. In this study we have documented that the quantitative cut-off of 9 B-lines corresponds, with a sensitivity of 70% and a specificity of 97%, to a significant RA-ILD documented in chest HRCT. The determination of this cut-off certainly offers greater interpretability to LUS measurements.

An attempt in this sense, namely to identify a significant number of B-lines, has already been made in the context of SSc-ILD. A work of our group revealed that the presence of 10 B-lines identifies the presence of a significant SSc-ILD with an LR+ of 12.52 [10]. Thus, for both RA and SSc the number of B-lines expression of a significant ILD is very similar. The cut-off derived from our study is applicable to the method that investigates 14 LIS. Intuitively, a LUS study conducted on more LIS will provide a higher number of B-lines in the presence of significant RA-ILD. However, the method proposed on 14 LIS has demonstrated a high sensitivity and specificity [24]. Investigating more spaces, some works have studied up to 72 LIS [25], could be excessively time-consuming and difficult to apply in daily clinical practice.

One of these works that studied 72 LIS had already identified a B-lines cut-off for RA-ILD, suggesting the value of 10. However, this cut-off has been arbitrarily defined without using HRCT chest data as an external criterion [25]. In the present work we have instead demonstrated the correlation between LUS and chest HRCT and therefore established the best cut-off point based on an automatic segmentation method. However, despite the cut-off value of 9 indicates the best diagnostic performances of LUS according to HRCT findings, it cannot overcome intrinsic limitations of LUS which offers a sensitivity of 70% and may miss a number of RA patients with ILD. Rheumatologists should be aware of this and consider LUS findings as an additional piece of information to reach a correct diagnosis. Moreover, although LUS is increasingly widespread, the main drawback of this imaging technique is that it requires adequate training and cannot be left to inexperienced hands.

Among the other results that have emerged, it should be noted the presence, at the limits of significance, of a higher mean number of B-lines in patients with a more aggressive treatment strategy (bDMARDs or tsDMARDs vs csDMARDs). It can be speculated that the higher number of B-lines does not depend on the therapy itself but on the fact that patients currently being treated with a more aggressive treatment strategy had a higher disease activity in the months or years before. This is in agreement with the results of a recent study involving a large number of patients in which it was described that the incidence of RA-ILD is higher in patients with active joint disease [26]. In addition, male patients had a higher mean number of B-lines. Male patients would seem to be at greater risk of developing RA-ILD, as observed by other authors [27, 28]. One limitation of this study is the recruitment in a single centre, in patients with arbitrarily defined risk factors for RA-ILD, even if they are derived from the literature. This may have generated a selection bias: virtually the diagnosis of RA-ILD can be made at earlier stages and it has not been possible to determine the duration of interstitial lung involvement. As a strength of the research, the number of cases is good compared to previous studies using LUS in CTD-ILD [29].

Conclusion

LUS applications are promising and widely applicable in RA-ILD diagnosis. In this study, the B-lines number indicative of a significant RA-ILD was defined, using as external criterion the data from the chest HRCT, currently considered the gold standard method. LUS is not intended to replace the use of chest HRCT, but it is proposed as a useful method to identify RA patients to be assessed with chest HRCT, avoiding expensive, potentially uninformative, ionizing radiation exposure.

Declarations

Ethics approval and consent to participate

All patients agreed to participate in the study by signing informed consent, and the procedures conducted in the study were approved by the local Ethics Committee (Comitato Unico Regionale – number 2015 0458 AS).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

MDC performed the clinical data collection, and was the major contributor in writing the manuscript. MT performed the lung ultrasounds, while MC analyzed and interpreted the chest high-resolution computed tomographies. FS performed the statistical analysis. MDC, FS and MDC gave substantial contributions to the conception and design of the work. All authors read and approved the final manuscript.

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Tables

Table 1. Descriptive statistics of the 72 patients investigated.

	Mean	Standard deviation	Median	25 - 75 Percentiles
Age (years)	63.09	11.48	62.00	56.50 - 71.50
Disease duration (months)	106.82	111.34	66	
ACPA (titre, UI/ml)	327.63	633.33	98.00	1.92 - 445.25
RF (titre, UI/ml)	324.63	748.69	72.00	10.00 - 350.00
ESR (mm/h)	33.23	27.94	26.00	11.50 - 46.50
CRP (mg/dl)	1.89	2.39	1.10	0.40 - 2.55
CDAI	17.60	9.46	17.00	11.50 - 23.50
HAQ	1.39	0.69	1.55	0.76 - 2.00
Borg scale	3.54	1.86	4.00	2.00 - 5.00
FEV1 (% predicted)	96.24	15.27	98.00	88.50 - 107.50
FVC (% predicted)	100.99	19.59	101.00	87.00 - 114.50
DLco (% predicted)	77.60	19.79	77.15	67.00 - 89.00
Smoking status (pack years)	5.56	9.21	0.00	0.00 - 10.00
Chest HRCT CaM score (%)	11.20	7.48	8.17	6.75 - 13.20
B-lines (total number)	10.65	15.11	4.50	0.00 - 11.00

Abbreviations: ACPA=anti-citrullinated protein antibodies, RF=rheumatoid factor, ESR=erythrocyte sedimentation rate, CRP=C-reactive protein, CDAI=Clinical Disease Activity Index, HAQ=Health Assessment Questionnaire, FEV1=first second forced expiratory volume, FVC=forced vital capacity, DLco= carbon monoxide diffusion lung capacity, HRCT= high-resolution computed tomography, CaM=computer-aided method.

Table 2. Correlation table (Pearson's r) among the variables studied.

		B-lines (total number)	FEV1 (% predicted)	FVC (% predicted)	DLco (% predicted)
Chest HRCT CaM score (%)	correlation coefficient,	0.559	-0.096	-0.264	-0.270
	r	<0.0001	0.424	0.024	0.022
	significance level, p				
B-lines (total number)	correlation coefficient,		-0.181	-0.338	-0.375
	r		0.128	0.003	0.001
	significance level, p				
FEV1 (% predicted)	correlation coefficient,			0.794	0.447
	r			<0.0001	0.0001
	significance level, p				
FVC (% predicted)	correlation coefficient,				0.416
	r				0.0003
	significance level, p				

Abbreviations: FEV1=first second forced expiratory volume, FVC=forced vital capacity, DLco= carbon monoxide diffusion lung capacity, HRCT= high-resolution computed tomography, CaM=computer-aided method.

Table 3. Receiver operating characteristic curve analysis of the optimal cut-off point of number of B-lines detected by lung ultrasound for the presence of significant rheumatoid arthritis-interstitial lung disease.

Number of B-lines	Sensitivity	95% CI	Specificity	95% CI	+LR	-LR
>4	76.67	57.7 - 90.1	69.05	52.9 - 82.4	2.48	0.34
>7	76.67	57.7 - 90.1	85.71	71.5 - 94.6	5.37	0.27
>8	70.00	50.6 - 85.3	95.24	83.8 - 99.4	14.70	0.32
>9*	70.00	50.6 - 85.3	97.62	87.4 - 99.9	29.40	0.31
>11	53.33	34.3 - 71.7	97.62	87.4 - 99.9	22.40	0.48

Abbreviations and legend: CI=confidence interval, +LR=positive likelihood ratio, -LR=negative likelihood ratio, *=optimal cut-off point.

Figures

Figure 1

Example of B-line. Arrowheads: laser-like (or comet tail) artifact, asterisks: lung parenchyma, arrows: pleura.

Figure 2

Receiver operating characteristic (ROC) curve analysis to determine the number of B-lines at lung ultrasound defining a significant rheumatoid arthritis-interstitial lung disease, applying the 10.7% of fibrosis measured by computer-aided method at chest high-resolution computed tomography as external criterion.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementarymaterialLUSRA2020mar19th.pdf](#)