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ORIGINAL ARTICLE

Effectiveness of Thoracic Ultrasonography in the Evaluation of the Severity of Pulmonary Involvement in Patients With Systemic Sclerosis

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ABSTRACT

Objectives: This study aims to investigate the effectiveness of thoracic ultrasonography (USG) in a single session in the evaluation of the severity of pulmonary involvement in systemic sclerosis.

Patients and methods: A total of 48 consecutive systemic sclerosis patients (2 males, 46 females; mean age 50.8±11.9 years; range 21 to 76 years) followed-up in our center were included. A thoracic USG using a linear probe was performed for each patient to evaluate the parenchymal involvement by two pulmonary disease specialists. The number of B-lines (B-lines described USG sign of interstitial lung fibrosis) was recorded. Systolic pulmonary artery pressure was measured by means of using a phase probe to evaluate pulmonary hypertension in the same sequence. The same day, pulmonary function tests were conducted. Warrick score was calculated according high resolution computed tomography (HRCT) images which were evaluated independently from each other by a radiologist and a pulmonary disease specialist. Medsger severity scale was calculated for each patient according to the results of HRCT findings, pulmonary function test, and systolic pulmonary artery pressure.

Results: The number of B-lines detected on thoracic USG was correlated with the Warrick score (r=0.89; p=0.0001) and Medsger disease scale (r=0.55; p=0.0001) and negatively correlated with diffusing capacity of carbon monoxide (r= -0.56; p=0.0001) and forced vital capacity (r= -0.46; p=0.001). When HRCT was accepted as the gold standard; the sensitivity, specificity, positive predicted value, and negative predicted value for thoracic USG were 100%, 84.2%, 90.6%, and 100%, respectively. If thoracic USG was used instead of HRCT for the evaluation of Medsger scale, the results changed in only one of the 48 patients.

Conclusion: Thoracic USG showed good correlation with HRCT findings for the evaluation of pulmonary parenchymal involvement in systemic sclerosis. Therefore, USG might be a noninvasive and useful tool for the long-term follow-up of systemic sclerosis patients after initial examination with USG and HRCT.

Keywords: High resolution computed tomography; Medsger scale; systemic sclerosis; thoracic ultrasonography.

Systemic sclerosis (SSc) is an autoimmune disease characterized by vascular injury caused by tissue fibrosis, skin fibrosis, as well as heart, pulmonary, kidney, and gastrointestinal system involvement.[1] It is classified as either limited or diffuse according to the extent of skin involvement.[2]

Lung involvement may be seen in several different types of SSc. Particularly, interstitial abnormalities which are more common on high resolution computed tomography (HRCT) are observed in 90% of the patients with SSc.[3] On the other hand, pulmonary hypertension is reported in 13% to 35% of the patients.[4,5]

High resolution computed tomography is the gold standard for showing interstitial involvement in SSc. However, HRCT carries risk due to

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radiation exposure. One study has shown that radiation increases a female's risk of cancer more than a male.[6] In SSc, which affects females predominantly, the repetition of HRCTs might increase risk of cancer. Radiation exposure may be reduced by low-dose computed tomography; however, this is not as widely available as ultrasonography (USG).[7]

In lung evaluations, USG has been neglected for a long time because they can retain air. Indeed, air-filled lungs may not normally give an acoustic image. However, when exudate, blood, cells, or fibrotic tissue change place with air in pathological situations, USG may detect some images in the lungs.[8]

Ultrasonography has also been begun to be used in the evaluation of interstitial fibrosis particularly in patients with connective tissue diseases. USG is a cheap, safe, non-ionizing method which can be applied easily on bedside. B-lines may be seen particularly in interstitial pulmonary disease and are identified as "lung comets" in USG. These are images that take origin from thickening of interlobular septa and may be used as a biomarker to show fibrosis.[9]

Measuring disease activity is challenging in SSc. Many measurement systems have been developed for this purpose including the Medsger disease severity scale (MDSS). MDSS includes pulmonary function tests, HRCT, and echocardiography.[10]

In this study, we aimed to investigate the effectiveness of thoracic USG in a single session in the evaluation of the severity of pulmonary involvement in SSc.

PATIENTS AND METHODS

The study consisted of 48 SSc patients (2 males, 46 females; mean age 50.8±11.9 years; range 21 to 76 years) diagnosed at Trakya University Medical Faculty, Department of Rheumatology between December 2013 and January 2014. All SSc patients were classified according to American College of Rheumatology 1980 criteria.[11] The study protocol was approved by the Medical Faculty of Trakya University Ethics Committee. A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data about patients' demographic and clinical features, laboratory findings, and pulmonary function tests were obtained from hospital records. All of the patients were evaluated by a team consisting of a pulmonary disease specialist, a cardiologist, and a rheumatologist.

Exclusion criteria included patients with pulmonary neoplasm, interstitial fluid, asthma, chronic obstructive pulmonary disease, kyphoscoliosis, dyspnea in need of oxygen, and connective tissue diseases other than SSc.

Pulmonary parenchymal (number of B-lines) and pulmonary vascular (pulmonary artery pressure) evaluations with thoracic USG were carried out by a pulmonary disease specialist with a Sonosite Medromaxx brand portable USG device (Sonosite Inc., Bothell, WA, USA). The specialist was unaware of any radiological and clinical findings of the patients. For interobserver evaluation, the number of B-lines were repeated the same day with the same device by a second pulmonary disease specialist who was also unaware of the clinical and radiological findings.

Using USG, patient's anterior chest wall was evaluated in the supine position while the posterior chest wall was evaluated in the sitting position with a linear probe (L38E/5-10 MHz, SonoSite, Inc.). Systolic pulmonary artery pressure (sPAP) over tricuspid regurgitation was calculated with the modified Bernoulli equation formula with a sector probe (P17/1-5 MHz, Sonosite Inc.). We obtained B-lines which consisted of a total of 14 bilaterally involved lung intercostal spaces (LIS). For the anterior chest, the authors considered the second LIS along the parasternal lines, the fourth LIS along the midclavicular, the anterior axillary, and the midaxillary lines. For the posterior chest, the eighth LIS along the paravertebral, the subscapular, and the posterior axillary lines were selected. The reason for choosing these regions was to detect more ultrasonographic B-lines and also because these are the regions that can be evaluated by a USG. The number of B-lines was recorded for every LIS (Figure 1). When the number of B-lines were ≥3 in a region or >5 in adjacent spaces, they were accepted as positive. If there was a fully white appearance in a region, it was accepted to be 10 B-lines.[12] The B-lines total sum of all LIS was recorded. According to the semiquantitative method, we recorded as

follows: 0= normal (B-lines <5); 1= mild (B-lines 6-15); 2= moderate (B-lines 16-30); 3= prominent (B-lines >30).[9]

In an ultrasonographic evaluation, bilateral symmetric areas containing more than three B-lines were accepted as positive for interstitial involvement. The ones with localized findings on a single site were accepted as negative.

High resolution computed tomography scans were performed with a 64-slice multidetector computed tomography (Aquillion, Toshiba Medical Systems, USA). Patients were examined in the supine position during a maximal inspiration. A standard HRCT of the entire chest was performed and used as the standard of reference (tube potential 120 kV; reference tube current-time product 40 or 120 mAs). Data were reconstructed with filtered back projection, a slice thickness of 1 mm, and an increment of 0.9 mm.

If the patients had been performed a HRCT in the last three months for routine evaluation, no new HRCT imaging was conducted. The patients who had not been performed a HRCT in the last three months underwent HRCT and USG simultaneously. The duration between USG and HRCT was median 0 days (range 0 to 73 days).

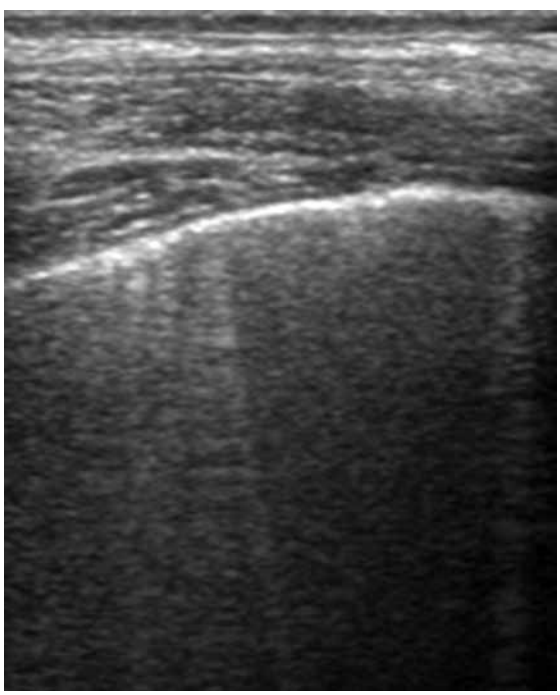

Figure 1. B-line in ultrasonography.

High resolution computed tomography images were evaluated by a radiologist who was unaware of the clinical features of the patients. For interobserver evaluation, pulmonary disease specialists who performed USG examined HRCTs and calculated Warrick score after the study ended (Table 1).[13] HRCT was calculated semiquantitatively as follows: 0= normal; 1= mild (<8 points); 2= moderate (8-15 points); and 3= severe (>15).[9]

Symmetrical bilateral interstitial involvement on HRCT was accepted as positive for pulmonary parenchymal involvement.

Standard respiratory function tests were applied to all patients using a standard computerized spirometry system (Sensor medics, V max 22 PFT SYSTEM, USA). A diffusing capacity of the lungs for carbon monoxide (DLCO) was performed and the actual DLCO level was corrected according to hemoglobin levels. The results were presented according to expected values in terms of percentage.

In all patients, echocardiographic examinations (Vivid 7 Pro, GE, Horten, Norway, 2-4 MHz phased-array transducer) were performed by one cardiologist. During echocardiography, a single-lead electrocardiogram recorded simultaneously. Doppler measurements were performed in accordance with the American Society of Echocardiography guidelines.[14] A continuous-wave Doppler was used to measure the peak velocity of the tricuspid regurgitation jet at end-expiration. The transtricuspid pressure gradient was calculated by using a modified Bernoulli equation.[15] Estimated pulmonary arterial systolic pressure was derived from adding the transtricuspid pressure gradient to the right atrial (RA) pressure, in the absence of a right ventricular

Table 1. Warrick score[13]

Severity score	
Parenchymal changes	
Ground glass opacity	1
Irregular margins	2
Septal/subplevral lining	3
Honeycomb	4
Subplevral cyst	5
Lung segment number	
1-3	1
4-9	2
>9	3

obstruction and pulmonary stenosis. Estimated RA pressure was calculated according to the respiratory motion of the inferior vena cava. If the diameter of the vena cava decreased by 50% or more with inspiration, the RA pressure was accepted to be below 10 mmHg. If inspiratory collapse was less than 50%, RA pressure was accepted to be above 10 mmHg.

The lung involvement was handled under a separate title within MDSS, in which the disease activity of the SSc was assessed; and a grouping was performed ranging from 0 to 4, namely normal, mild, moderate, severe, and end stage. In the normal disease, DLCO and forced vital capacity (FVC) were ≥80%, there was no fibrosis on radiography, and the sPAP was <35 mmHg. In the mild disease, DLCO and FVC were between 70% and 79%, there was fibrosis on radiography, there were bibasilar rales, and the sPAP was 35-49 mmHg. In the moderate disease, DLCO and FVC were between 50% and 69%, and the sPAP was 50-64 mmHg. In the severe disease, DLCO and FVC were <50% and the sPAP was >65 mmHg. In the end stage disease, oxygen support was needed.[16]

Statistical analysis

Continuous variables were calculated as mean ± standard deviation and the categorical variables are presented as number and percentage. In univariate comparisons, the Chi-square or t-test was applied. The correlation between the parameters was conducted with non-parametric Spearman analysis or Pearson analysis. Interobserver reliability was assessed using intraclass correlation analysis. A receiver operating characteristic curve was drawn to detect area under the curve values. All statistical analyses were performed with PASW Statistics version 17.0 software (SPSS Inc., Chicago, IL, USA).

Table 2. Comparison of high resolution computed tomography, ultrasonography, and Medsger scale

	HRCT		USG		Medsger	
	n	%	n	%	n	%
Normal	4	8.3	7	14.6	8	16.7
Mild	17	35.4	12	25	15	31.2
Moderate	8	16.7	8	16.7	17	35.4
Severe	19	39.6	21	43.7	8	16.7
Total	48	100	48	100	48	100

HRCT: High resolution computed tomography; USG: Ultrasonography.

RESULTS

Of the SSc patients, 15 (31%) were classified as diffuse and 33 (69%) as limited. The mean disease duration was 4.6±3.8 years. The average FVC and DLCO were 82.75±15 and 72.6±21, respectively.

The most common pathological findings on HRCT were septal/subpleural lining (81.3%), ground-glass opacity (77.1%), irregular pleural thickening (66.7%), honeycombing (35.4%), and subpleural cyst (12%). Interobserver reliability for the Warrick score was very good in HRCT evaluation (r=0.87; p=0.0001). Warrick score was positively correlated with MDSS (r=0.46; p=0.001) and negatively with DLCO (r= -0.42; p=0.003) and FVC (r= -0.35; p=0.014).

In ultrasonographic evaluation, interobserver reliability was excellent (r=0.96; p=0.001). The number of B-lines in USG positively correlated with MDSS (r=0.55; p=0.0001) and Warrick score (r=0.89; p=0.0001) (Table 2, Figure 2). B-lines were negatively correlated with DLCO (r= -0.56; p=0.0001) and FVC (r=0.46; p=0.001).

In three patients, while HRCT was negative, USG was positive. When HRCT was accepted as the gold standard, the sensitivity and specificity for USG were 100% and 84.2%, respectively. Furthermore, the positive predicted value, negative predicted value, and accuracy were 90.6%, 100%, and 93.7%, respectively (Table 3).

A significant correlation was detected when B-lines and the involvement on HRCT were

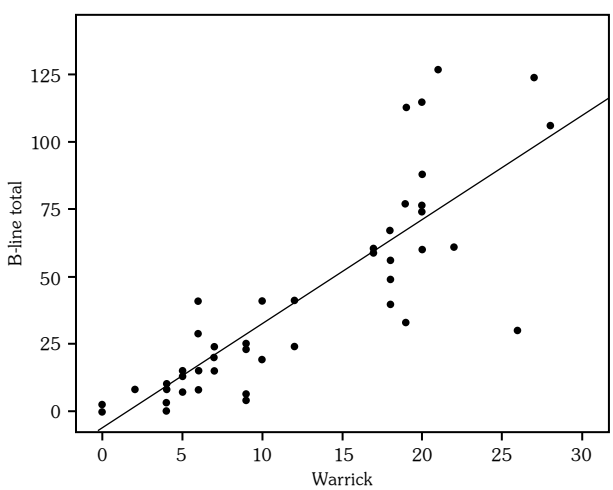

Figure 2. Correlation of Warrick score and B-line.

Table 3. Comparison of high resolution computed tomography and ultrasonographic involvement

	HRCT		*Total*
	Positive	Negative	
USG positive	29	3	32
USG negative	0	16	16
Total	29	19	48

HRCT: High resolution computed tomography; USG: Ultrasonography.

evaluated. For HRCT-positivity, the B-line optimum cutoff point was >24 (area under the curve= 0.948, 95% confidence interval 0.84 to 0.99, p=0.0001) (Figure 3).

Systolic pulmonary artery pressure measured with echocardiography and sPAP measured with an ultrasound phase-probe were correlated (r=0.83; p=0.001). The average sPAP and average ejection fraction were 23.3±8.1 mmHg and 65.4±6, respectively. In 12 patients, the sPAP was >25 mmHg. Two patients had pericardial effusion.

An evaluation of HRCT involvement in the Medsger scale and ultrasonographic involvement with the sPAP revealed that the Medsger scale changed only in one patient. While sPAP measured with USG was 37 mmHg, the Medsger scale was 1 instead of 0 since sPAP measured in the cardiology laboratory was under 35 mmHg.

DISCUSSION

In our study, the number of B-lines was positively correlated with the Warrick score and Medsger disease scale and negatively correlated with pulmonary function tests. When HRCT was accepted as the gold standard; the sensitivity, specificity, positive predicted value, and negative predicted value for USG was 100%, 84.2%, 90.6%, and 100%, respectively. If thoracic USG was used instead of HRCT for the evaluation of Medsger scale, the results changed in only one of the 48 patients.

Recently, USG, which is a non-invasive method, has been begun to be used in the evaluation of pulmonary parenchymal involvement. Gargani et al.[7] performed one of the first studies evaluating USG in SSc, comparing HRCT Warrick score and the number of B-lines in USG, and demonstrated

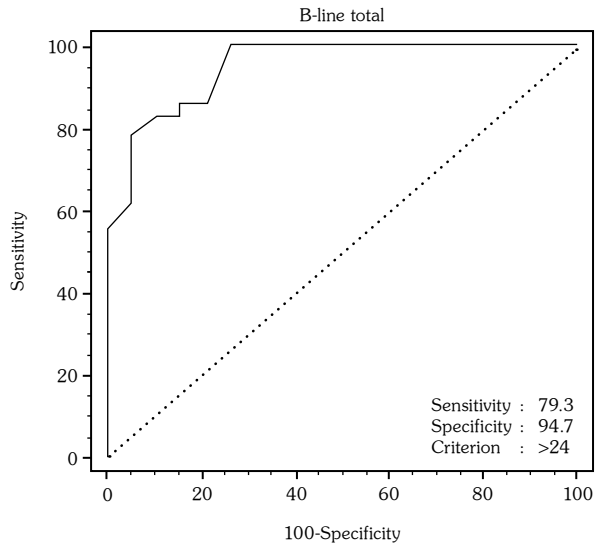

Figure 3. B-line evaluation according to high resolution computed tomography involvement.

that HRCT score and USG were correlated. In another study, detailed USG and simplified USG were performed through 14 intercostal spaces and these were found to be correlated as in our study. Both USG methods were correlated with Warrick score.[9] We also detected a correlation between the number of B-lines in USG and the Warrick score calculated in HRCT.

In another study in which USG was used for detection of early stage sclerosis, USG was found to be more sensitive than HRCT. Even though it did not show any findings in HRCT in the early stages of the disease, USG was considered to be useful.[12] Similar to our study, USG sensitivity, specificity, negative predicted value, and positive predicted value were 100%, 55%, 100%, and 78%, respectively. Another recent study compared HRCT and USG through 10 intercostal spaces in SSc. HRCT and USG findings were categorized as normal, mild, moderate, and severe as in our study and compared. USG sensitivity, specificity, positive predicted value, and negative predicted value were 72%, 88%, 95%, and 51.7%, respectively.[17]

Pulmonary involvement leads to decreased lung volumes and gas transfer across the alveolocapillary barrier and the alterations in pulmonary function provide prognostic information. In patients with SSc, the decrement in DLCO and HRCT were correlated.[18]

In studies with USG, the B-lines and DLCO were correlated.[7] In our study, both the Warrick score and the number of B-lines were negatively correlated with FVC and DLCO.

In our study, the MDSS was correlated with the number of B-lines and the Warrick score. When both the interstitial involvement and pulmonary artery pressure were evaluated with thoracic USG in the same session, the Medsger scale changed only in one patient.

The only limitation of our study is the lack of intraobserver reliability assessment because of technical reasons. In our study, we used separate probes for vascular evaluation and parenchymal evaluation. However, we could perform parenchymal evaluation with the same phase probe that we used in the evaluation of pulmonary artery pressure. In this way, we would not have to change the probe to evaluate the presence of B-line and pulmonary artery pressure. But we preferred this application since counting the number of B-line with the linear probe was easier.

In conclusion, we have shown that the evaluation of the severity of pulmonary involvement in SSc patients may be assessed with USG without being exposed to radiation in a single session. After initial examination with USG and HRCT, USG might be a noninvasive and useful tool for the long-term follow-up of SSc patients.

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Declaration of conflicting interests

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