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Original Article

Esophageal Dilatation as a Predictor of Systemic Sclerosis in Patients with Interstitial Lung Disease

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Abstract

OBJECTIVE: To determine the predictive value of esophageal dilatation as observed in high-resolution computed tomography (HRCT) for the diagnosis of systemic sclerosis (SSc) in patients with interstitial lung disease (ILD).

METHODS: Our sample consisted of patients diagnosed with SSc and proven interstitial lung involvement with available HRCT exams (n = 20). Individuals with other forms of rheumatic ILD were included as a control group (n = 20). Two blinded radiologists independently reviewed the images for the presence of esophageal dilatation, measured at 3 different levels. Interobserver agreement was tested with Lin's concordance correlation coefficient (CCC). Independent t-test was used to compare maximum esophageal diameters between groups. Friedman's test was used to evaluate differences between the 3-level measurements. Receiver operating characteristic analysis was performed.

RESULTS: There was a substantial correlation between both readers (CCC = 0.9802-0.9919). Esophageal dilatation was significantly associated with SSc (P = .0012). The optimal calculated cut-off value to differentiate SSc from other ILDs was 18.5 mm (sensitivity and specificity of 70 and 90%, respectively; area under the curve 0.819), measured 1 cm above the diaphragmatic hiatus.

CONCLUSION: HRCT may have a discriminative role in the presence of both ILD and esophageal dilatation for the diagnosis of SSc. Our results suggest that a cut-off value for the esophageal diameter of 18.5 mm might propose the diagnosis of SSc with reasonable confidence.

KEYWORDS: Systemic sclerosis, esophagus, interstitial lung disease, high-resolution computed tomography
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INTRODUCTION

Systemic sclerosis (SSc) is a generalized autoimmune disorder affecting the connective tissue. Lung involvement is the primary cause of death, both from pulmonary hypertension and interstitial lung disease (ILD).[1-3] However, even if often overlooked, the most frequently affected internal organ is the esophagus, in up to 90% of the patients.[4] Early in the course of the disease, there is smooth muscle atrophy, which is replaced by fibrous tissue. These changes may lead to severe dysmotility of the distal esophagus, dilatation and absent body peristalsis, and reduced pressure of the lower esophageal sphincter.[5,6] There is growing evidence that gastroesophageal reflux with the recurrent microaspiration of gastric contents may be a critical contributor to the development of ILD in patients with SSc.[6-8]

Various tests are available for the evaluation of the esophagus, including manometry, pH monitoring, scintigraphy, endoscopy, and barium esophagram. Still, the correlation between complaints and abnormal findings is weak, and up to 40% of patients with SSc and documented esophageal disease may be asymptomatic.[9,10]

High-resolution computed tomography (HRCT) is a valuable screening tool for the assessment of ILD and is now included in the ACR-EULAR joint classification criteria to identify SSc.[11] A patulous esophagus is a frequent incidental finding and considered a cardinal feature of the disease.[12-14] Nevertheless, its significance remains unclear.

We hypothesized that the presence of esophageal dilatation with associated signs of ILD on an HRCT scan, regardless of indication, could be used to propose an earlier diagnosis of SSc. Therefore, our purpose was to determine the predictive value of esophageal dilatation as observed in HRCT for diagnosing SSc in patients with ILD and defining an optimal cut-off value to differentiate SSc from other ILD-associated connective tissue diseases.

MATERIAL AND METHODS

A list was obtained of 20 consecutive confirmed cases of SSc with proven lung involvement, being followed by experienced rheumatologists in our institution and which had HRCT results available at the time. The control group consisted of consecutive individuals with other forms of rheumatic ILD (Table 1).

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Table 1. Control Group by ILD Condition

Non-SSc ILD	
Rheumatoid arthritis	15
ANCA-associated vasculitis	1
Ankylosing spondylitis	1
Sjögren's disease	1
Antisynthetase syndrome	1
Polymyositis	1
Total	20

SSc, systemic sclerosis; ILD, interstitial lung disease; ANCA, antineutrophil cytoplasmic antibody.

All patients underwent HRCT using a multidetector CT equipment (LightSpeed, GE Healthcare, Milwaukee, WI, USA or BrightSpeed, GE Healthcare, Milwaukee, WI, USA). The scanning was performed in suspended inspiration through the entire chest in a supine position. The images were retrospectively and independently reviewed by 2 radiologists using a standard picture archiving and communication system workstation (Centricity Radiology RA 1000, GE Healthcare). The coronal esophageal diameter was measured on the axial plane using a soft-tissue window, considering only the internal limits of the inner mucosa, as shown in Figure 1. Initially, all images were displayed with a standard mediastinal window setting (window width 400 HU, window center 40 HU). The window settings were adjusted to the reviewers' preferences. Measurements were performed at 3-specific levels: the mid-arch of the aorta (L1), the main carina (L2), and 1 cm above the diaphragmatic hiatus (L3). The presence of hiatus hernia is recognized by the convergence of gastric folds above and below the diaphragm. In these cases, the third diameter was estimated immediately above the gastroesophageal transition. In agreement with previous studies, esophageal dilatation was diagnosed if the luminal diameter of the esophagus exceeded 10 mm.[13-15] Interobserver agreement between the 2 readers' esophageal measurements was tested using Lin's concordance correlation coefficient (CCC). Group comparisons were performed by using an independent *t* test, and a *P*-value of less than .05 was considered significant. Differences between the 3-level measurements were evaluated based on Friedman test. A receiver operating characteristic (ROC) curve was calculated to test the ability of HRCT to differentiate patients with and without SSc. The area under the curve (AUC) is a suitable measure to summarize a diagnostic model's discrimination power and thus represent its accuracy, ranging from 0.5 (no discrimination) to 1.0 (perfect discrimination). Sensitivity and specificity values were estimated, along with the Youden index, to determine the optimal cut-off value. All of the procedures were conducted strictly following the Declaration of Helsinki. Since this is a retrospective observational study, in which collected data was stripped of all personal identifiers, informed consent was not obtained.

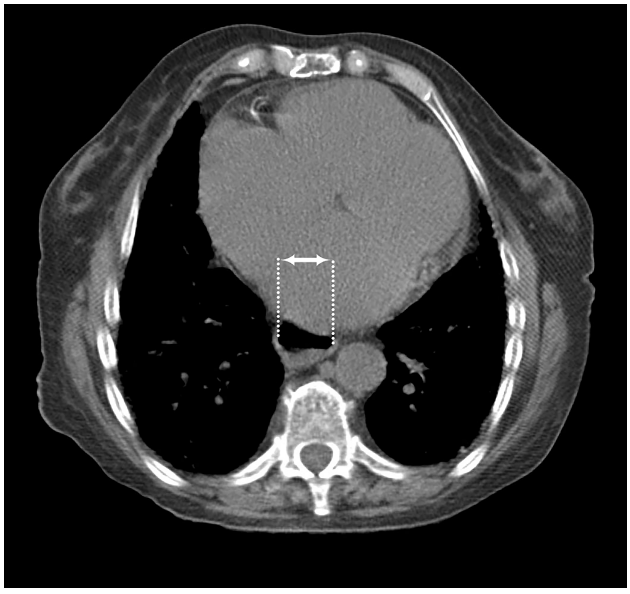

Figure 1. Example of how the measurements in the axial plane were performed.

Main Points

- A patulous esophagus is a frequent finding on HRCT in patients with SSc and, even though its relationship with esophageal dysmotility has been already recognized, previous studies have failed to consistently determine its significance, partly because of different methods and small cohort sizes.
- Our analysis tested the discriminating power of a dilated esophagus with a control group of patients with ILD unrelated to SSc. We found the typical threshold used for dilatation in the measurement of the esophageal diameter was far too low, and obtained a more ideal cut-off value of 18.5 mm.
- An esophageal diameter ≥18.5 mm may better distinguish between SSc and other diagnoses in HRCT scans ordered for the evaluation of interstitial lung disease.

RESULTS

There was a substantial correlation between both examiners for the measurements (CCC = 0.9802-0.9919). Mean, standard deviation, and results of the *t* test for independent samples are detailed in Table 2. Our results showed that better discrimination and increased significance level (*P* = .0002) was attained by using the esophageal measurement near the gastroesophageal junction (L3) with a 95% CI (0.95) of 16.49-27.81 for the SSc group and 6.71-12.25 for the control group, with a mean difference of 12.68 mm. The mean difference of the widest esophageal diameter (WED), regardless of the level of measurement, was 10.4 mm, with a CI (0.95) of 17.69-28.57 for the SSc group and 10.28-15.18 for the control group, with an associated *P*-value of .0012. In contrast, higher in patients with SSC, the mean WED in the control group was above the previously established normal upper limit of 10 mm. These measurements are graphically displayed in Figure 2, and a slight overlap between both groups is evident. Incidentally, a sliding hiatal hernia was evident on the HRCT scans of 2 patients in the study group and 5 control group patients. The Friedman test showed significant differences between L3 and both L1 and L2 measurements (*P* = .00342) and nonsignificant differences

Table 2. Mean, Standard Deviation and Statistical Results of all Esophageal Measurements

	Mean ± SD	CI (0.95)	Mean $_{SSc}$ − Mean $_{non\text{-}SSc}$	*P*
L1				
SSc	14.88 ± 9.41	10.48-19.28	7.95	.0025
Non-SSc	6.93 ± 5.2	4.5-9.36		
L2				
SSc	17.15 ± 11.15	11.93-22.37	7.15	.0148
Non-SSc	10 ± 5.13	7.6-12.4		
L3				
SSc	22.15 ± 12.09	16.49-27.81	12.68	.0002
Non-SSc	9.48 ± 5.92	6.71-12.25		
WED				
SSc	23.13 ± 11.63	17.69-28.57	10.4	.0012
Non-SSc	12.73 ± 5.24	10.28-15.18		
AED				
SSc	18.06 ± 10.23	13.27-22.85	9.26	.0009
Non-SSc	8.8 ± 4.21	6.83-10.77		
L1				
SSc	14.88 ± 9.41	10.48-19.28	7.95	.0025
Non-SSc	6.93 ± 5.2	4.5-9.36		
L2				
SSc	17.15 ± 11.15	11.93-22.37	7.15	.0148
Non-SSc	10 ± 5.13	7.6-12.4		
L3				
SSc	22.15 ± 12.09	16.49-27.81	12.68	.0002
Non-SSc	9.48 ± 5.92	6.71-12.25		
WED				
SSc	23.13 ± 11.63	17.69-28.57	10.4	.0012
Non-SSc	12.73 ± 5.24	10.28-15.18		
AED				
SSc	18.06 ± 10.23	13.27-22.85	9.26	.0009
Non-SSc	8.8 ± 4.21	6.83-10.77		

CI were calculated based on a confidence of 95%.
L corresponds to the three-level measurements (L1, aortic arch; L2, main carina; L3, above the diaphragmatic hiatus).
WED, widest esophageal diameter; AED, average esophageal diameter; SSc, systemic sclerosis.

between L1 and L2. In our sample of 20 patients with SSc, 80% had esophageal dilatation on HRCT, with measurements ranging from 13 to 44 mm. An example is shown in Figure 3. A comparison of the 3-level measurements in the group with SSc showed that luminal distention was likely to be higher just above the lower esophageal sphincter. These diameters were significantly different from the other levels ($P < .05$). The optimal calculated cut-off value to differentiate SSc from other types of rheumatic ILD (utilizing ROC curve analysis) was 18.5 mm (sensitivity and specificity of 70 and 90%, respectively; AUC 0.819), measured 1 cm above the diaphragmatic hiatus. The specificity was 100% above 22 mm. Conversely, applying the 10 mm threshold proposed by previous authors to our study population yielded significantly lower sensitivity (60%) and specificity (70%). The ROC curve analysis of all measurements is presented in Table 3.

DISCUSSION

Our results show that a patulous esophagus in HRCT is useful in discriminating between SSc and other diagnoses in the presence of ILD. This finding may be used as an additional radiological sign and also a marker of the functional status of the esophagus in SSc, as it has been found to correlate strongly with dysmotility in other studies.[14]

SSc carries significant morbidity and mortality. Therefore, an early diagnosis is of utmost importance as an adequate therapeutic approach may help reduce symptoms and slow disease progression.

The esophagus is the most frequently involved internal organ and is often imaged as part of chest HRCT studies ordered because of a suspected or known ILD. In our study, a higher

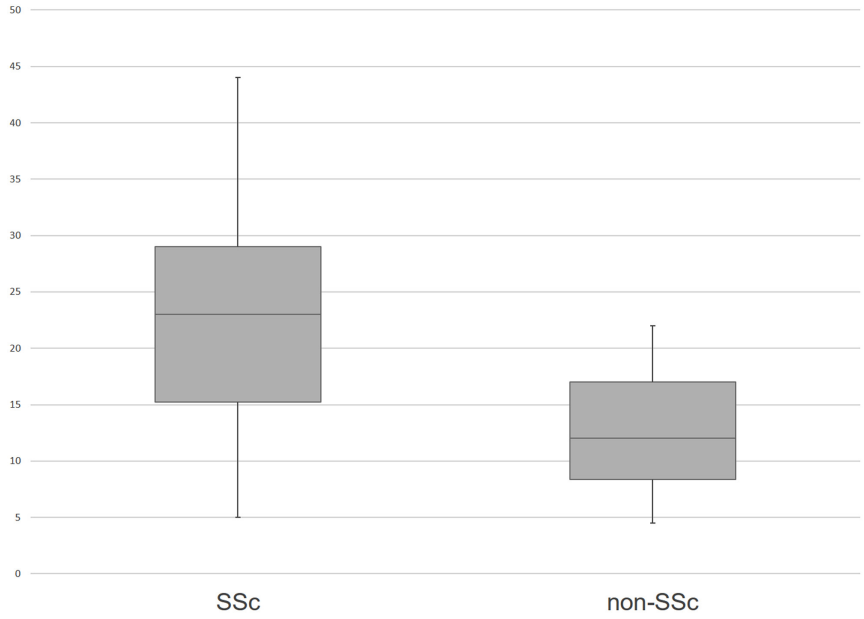

Figure 2. Box-and-whisker plot for the comparison of WED (mm) in both groups. The center horizontal line represents the median. The bottom and top edges of the box indicate the 25th and 75th percentiles. The vertical line is the data range. There was a statistically significant difference between both groups (P = .0012), despite a small overlap. SSc, systemic sclerosis.

degree of luminal dilatation was predominantly found in the distal third of the esophagus, presumably because of the higher amount of smooth muscle fibers in this location.[15] Using a threshold diameter of 10 mm as previous studies have, we obtain a comparable 80% prevalence of esophageal dilatation in SSc patients.[13-15] However, we found that threshold insufficient, which may account for the conflicting results described before.[14,16] Using the 10 mm cut-off, we find an overlap between SSc and the control group. Other authors tried to circumvent this issue, treating esophageal

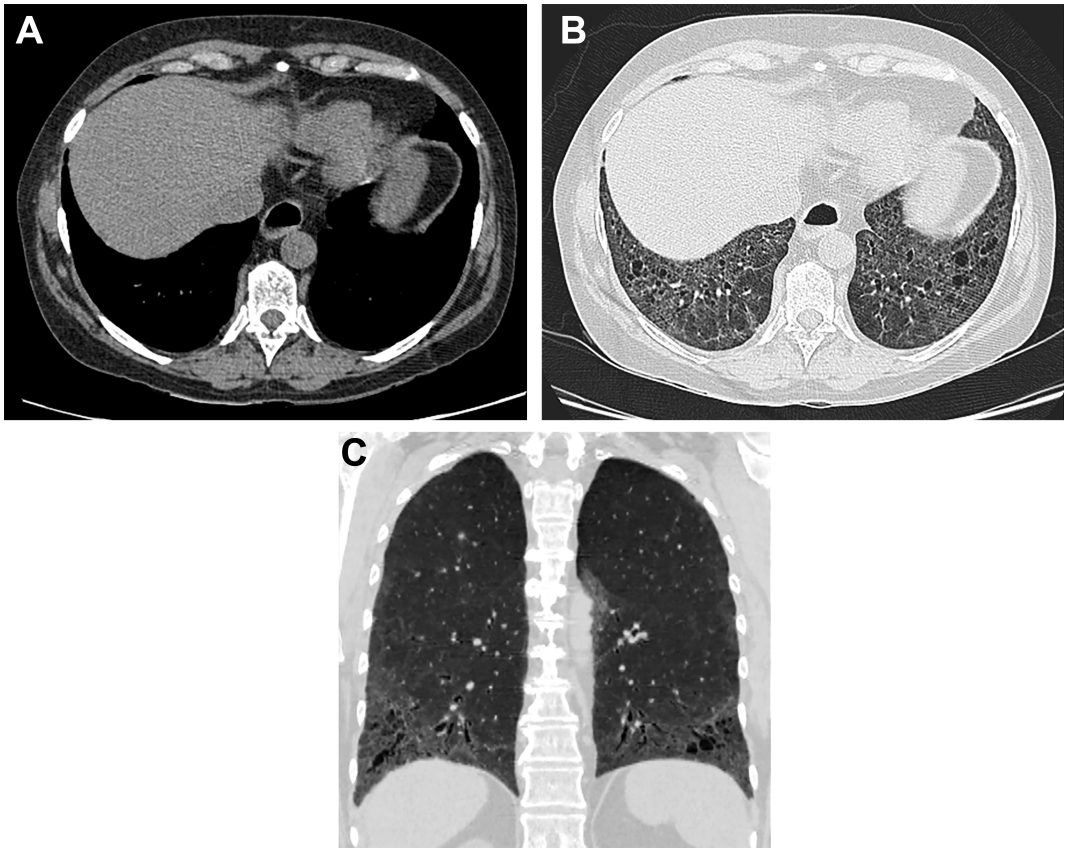

Figure 3. A 49-year-old woman with SSc. Soft-tissue (A) and lung (B) window HRCT axial images at the level of measurement in the lower third of the esophagus, 1 cm above the diaphragmatic hiatus. The esophagus is dilated with an air-fluid level, the lumen diameter measuring 21 mm. Interstitial lung disease is evident at the lung bases, better depicted in the coronal MinIP reconstruction (C), in a pattern suggestive of nonspecific interstitial pneumonia (NSIP).

Table 3. ROC Curve Analysis of all Esophageal Measurements

	AUC	CI (0.95)	Cut-Off Value	Sensitivity (%)	Specificity (%)
L1	0.77	0.61-0.89	> 10	65	80
L2	0.71	0.54-0.84	> 10	70	65
L3	0.82	0.67-0.92	> 18.5	70	90
WED	0.79	0.63-0.9	> 22	55	100
AED	0.79	0.63-0.9	> 11.7	70	80

CI were calculated based on a confidence of 95%.
L corresponds to the 3-level measurements (L1, aortic arch; L2, main carina; L3, above the diaphragmatic hiatus).
WED, widest esophageal diameter; AED, average esophageal diameter; SSc, systemic sclerosis; AUC, area under the curve.

dilatation as a continuous variable with a favorable outcome.[17] Moreover, Schraufnagel et al.[18] recorded esophageal diameters in a healthy population. They noticed that the esophagus is likely to be dilated in its inferior portion near the diaphragm, suggesting that luminal distention of up to 15 mm should be considered normal.[18]

Dilatation of the lower esophagus can occur in other conditions such as primary or secondary achalasia, the latter most frequently related to gastric malignancies. In both forms of the disease, luminal distention is found above a narrowed distal segment, which tends to be smooth in primary achalasia and irregular in secondary achalasia. Lung parenchyma can often be abnormal in these patients, but ILD is seldom present. The radiologist should carefully evaluate these and other radiological manifestations before suggesting the diagnosis of SSc.

While the association between esophageal dilatation and ILD in the context of SSc has been previously investigated, to our knowledge, this is the first study to test the discrimination against a control group of patients with ILD unrelated to SSc, potentially allowing a suggested diagnosis based on the cut-off value. Prior studies mainly assessed the association between a patulous esophagus and the severity of ILD, most without a control group. For example, Vonk et al.[14] used a control group with 107 subjects with different unrelated pathologies, of which only 7 had ILD (nonspecific interstitial pneumonia and usual interstitial pneumonia). Furthermore, they did not find a correlation between esophageal dilatation and ILD, which could be related to the used cut-off.

We found that the cut-off value of 18.5 mm has higher accuracy and appears to be a more reliable predictor of SSc in patients with ILD, with adequate sensitivity and specificity. Comparatively, the specificity of a 10 mm cut-off value decreases from 90 to 60%, in exchange for a marginal gain in sensitivity (75% as opposed to 70%). Of the 3 esophageal levels, the distal measurement 1 cm above the diaphragmatic hiatus had the highest statistical power ($P = .0012$).

Some limitations need to be acknowledged, being a retrospective study analyzing data from a relatively small number of subjects. We also did not quantify the overall ILD burden, so we cannot infer a relationship between esophageal dilatation and the extent of disease. Nevertheless, that was not the primary purpose of our study. Other investigators have already focused on that aspect, showing that a wider esophagus is associated with more severe lung impairment in HRCT and worse pulmonary function (lower lung volumes and lower DLCO % predicted).[17,19]

CONCLUSION

HRCT may have a discriminative role in patients with ILD and esophageal dilatation, which has not been explored before. Based on our results, a cut-off value for the esophageal diameter of 18.5 mm, higher than previously reported, may be used to propose the diagnosis of SSc with reasonable confidence.

Ethics Committee Approval: Ethical approval for this study was obtained from Comissão de Ética para a Saúde do Hospital Garcia de Orta, EPE in July 2017.

Informed Consent: Informed consent was waived because of the retrospective nature of the study and since the analysis used anonymous clinical data.

Peer Review: Externally peer-reviewed.

Author Contributions: Supervision – M.R., AP.M.; Design – M.R., AP.M.; Resources – F.DF., AP.M.; Materials – F.DF.; Data Collection and/or Processing – F.DF., J.FC.; Analysis and/or Interpretation – F.DF., J.FC.; Literature Search – F.DF; Writing Manuscript – F.DF, J.FC. M.R.; Critical Review – M.R.

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