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Original Scientific Paper

ESOPHAGEAL DIAMETER ON HIGH-RESOLUTION COMPUTED TOMOGRAPHY – A POTENTIAL USEFUL MARKER FOR INTERSTITIAL LUNG DISEASE SEVERITY IN PATIENTS WITH SYSTEMIC SCLEROSIS

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SUMMARY – Patients with systemic sclerosis (SSc) are at an increased risk of developing interstitial lung disease (ILD) and esophageal dysfunction, with frequently present esophageal dilatation. Our study aimed to investigate the relationship between esophageal diameter (ED) analyzed on high-resolution computed tomography (HRCT) with lung function tests and ILD evaluated with Warrick score. Thirty-nine patients with SSc were enrolled in this study. ED and Warrick score were evaluated by HRCT. The relationships between Warrick score, lung function, and ED were analyzed. Multivariate regression analysis was used to determine the effect of individual predictors on SSc-ILD. ILD was present in 25 (64%) patients. ED >10 mm in one or more of the measured locations on HRCT was present in 25 (64%) patients and 19 (76%) of these patients had concurrent ILD. Subjects with esophageal dilatation had a higher Warrick score and lower lung function tests. The measurement of ED was able to predict the presence of ILD in 69% of patients. Results suggest that evaluation of ED during regular HRCT follow-up could be useful in patients with SSc due to the association of esophageal dilatation with worse lung function tests and a more severe form of ILD.

Keywords: *Systemic sclerosis; Esophagus; Lung diseases, interstitial; Computed tomography; Lung function tests*

Introduction

Systemic sclerosis (SSc) is a disease of unknown etiology with microvascular and fibrous skin lesions, while it also affects internal organs. The incidence is three to twelve cases *per* million people. Interstitial lung disease (ILD) is one of the most prevalent causes

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of death in patients with SSc[1]. Like in some other lung diseases[2,3], lung disease in SSc could be associated with esophageal dysfunction and consequently aspiration of gastric acid and lung damage[4], but the results of earlier studies are conflicting[5,6]. Appropriate treatment depends on early identification of lung affection. Evaluation of the severity of this disease is performed with lung function tests and high-resolution computed tomography (HRCT), which is especially important for the prevention of severe forms of lung disease. Normally, the lung interstitium is not visible on a chest x-ray[7], and even though it might show interstitial abnormalities, it is not sensitive enough to make the ILD diagnosis. Warrick score measured on HRCT has until now been used in several studies on SSc and ILD to examine the extent and type of ILD lesions[8-10]. Five lesion types are evaluated by Warrick severity score, i.e., ground-glass opacities, septal/subpleural lines, irregular pleura, honeycombing, and subpleural cysts. The extent score is defined by the total of bronchopulmonary segments affected by each lesion. The global Warrick score (ranging from 0 to 30) is the sum of extent and severity score. A minimal global score of 7 is prognostic for abnormal lung function tests. In patients with a global score of 7 or higher, pulmonary abnormalities should be considered prognostic of significant pulmonary disease[11]. Until now, no general consensus on ILD monitoring with HRCT has been established. The regular CT follow-up of patients with SSc usually does not include measurement of esophageal diameter (ED).

This study aimed to investigate ED analyzed on HRCT, lung function, and ILD severity and extension evaluated with Warrick score in patients with SSc.

Patients and Methods

In this retrospective study, 39 patients were selected to fulfill the 2013 ACR/EULAR criteria for SSc classification[12]. Exclusion criteria were lung disease not specific to patients with SSc and/or other autoimmune disease that could contribute to pathological values of pulmonary function tests. Forced vital capacity (FVC), lung diffusing capacity for carbon monoxide (DLCO), Warrick score for evaluation of ILD (extent, severity, and global scores), as well as data on patient subjective gastroesophageal symptoms (heartburn, gastric acid/content regurgitation, dysphagia, and/or epigastric pain) were retrospectively evaluated. During their regular follow-up, all evaluated patients underwent thoracic HRCT scans that included non-contrast scans taken in maximal inspiration. CT examinations were performed on a 128-slice Siemens Definition MDCT machine (Siemens, Erlangen, Germany). ED was measured in a soft-tissue window on axial slices at three locations, i.e., atop the aortic arch (location 1), between the right inferior pulmonary vein and the arch of the aorta (location 2), whereas the third point of measurement was between the right inferior pulmonary vein and diaphragmatic hiatus (location 3), all according to previously published data[13]. Five types of lung lesions were evaluated: ground-glass opacities; pleural irregularities; septal/subpleural lines; honeycombing; and subpleural cysts. According to their sum, the severity score was calculated, with a range from 0 (without any lesions) to 15 if all lesions were present. The extent score of all lesions was assessed depending on the number of affected bronchopulmonary segments (1-3 segments, score 1; 4-9 segments, score 2; and >9 segments; score 3) affected by each lung abnormality, with a range of 0-15. HRCT was analyzed by the same thoracic radiologist with expertise in diffuse lung disease blinded to the lung function test results.

The presence of significant ILD was defined in patients with a global Warrick score ≥7[11]. Patients were clustered in a group without esophageal widening (ED ≤10 mm) and a group with esophagus wider than 10 mm according to the three abovementioned measured locations on HRCT.

The study was conducted in accordance with ethical standards and it was approved by the hospital Ethics Committee (approval no.: 2020/2409-04).

Statistical analysis

Categorical data were expressed as absolute and relative frequencies. The normality of distribution of numerical variables was tested by the Shapiro-Wilk test. Numerical data were expressed by median and interquartile range (IQR). Differences between two independent groups were tested by Mann-Whitney's U test. The correlations between numerical variables were evaluated by Spearman's correlation coefficient

ρ (rho). With regression analysis we determined the effect of individual predictors on ILD in patients with SSc. All p values were two-sided. The level of significance was set at alpha=0.05. The analysis was conducted using the MedCalc® Statistical Software version 20.111 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2022).

Results

Thirty-nine patients were included in this retrospective study. We analyzed patient medical records who were in regular follow-up by a rheumatologist between October 2020 and January 2022. Clinical and demographic characteristics of all patients are shown in Table 1. Thirty-five (90%) patients were women. Median age was 64 years (IQR 27-77). ILD with a global Warrick score ≥7 was present in 25 (64%) patients with SSc. ED of more than 10 mm in one or more of the three measured locations on HRCT was present in 25 (64%) patients, and 19 of them (76%) had concurrent ILD. The presence of ILD in patients with ED equal to or lower than 10 mm was significantly lower, measured in 6 (24%) patients. The median global Warrick score of the patients was 8 (IQR 4-15). The median severity score was 4 (IQR 3-6) and extent score was 4 (IQR 2-8). Furthermore, ground-glass opacities on HRCT were present in 24 (65%), irregular pleura in 24 (65%), septal/subpleural lines in 27 (73%), honeycombing in 4 (11%), and subpleural cysts in 9 (24%) patients. Twenty-seven (69%) patients had at least one gastroesophageal symptom (heartburn, gastric acid/content regurgitation, dysphagia, and/or epigastric pain). Thirty-five (89%) patients were taking proton-pump inhibitors.

Comparisons of ED at HRCT locations 1, 2 and 3 in relation to age, DLCO%, FVC%, severity, extent, and global Warrick score are shown in Tables 2, 3 and 4, respectively. The largest number of patients (n=26) had esophageal dilatation when measurements were obtained on the second HRCT point (between the right inferior pulmonary vein and aortic arch). There was no relation between patient age and ED. Patients with an ED wider than 10 mm measured at all three points on HRCT had higher severity and extent Warrick scores and lower values of FVC% and DLCO% (Tables 2, 3 and 4). Patients with gastroesophageal symptoms had lower DLCO values, median 55% (IQR 43-68) (p=0.02, Mann-Whitney U test), and wider ED measured on HRCT between the right inferior pulmonary vein and diaphragmatic hiatus, median 16 mm (IQR 8.25-25 mm) (p=0.03, Mann-Whitney U test)

Table 1. Characteristics of patients with systemic sclerosis

Parameter	**n (%)**
Gender: Female Male	 35 (90%) 4 (10%)
*Age (yrs)	64 (27-77)
Patients with significant ILD – global Warrick score ≥7	25 (64%)
Patients with ED >10 mm	25 (64%)
*Esophageal diameter at location 1 (mm) atop the aortic arch	7 (6-11)
*Esophageal diameter at location 2 (mm) between the right inferior pulmonary vein and the aortic arch	13 (8-17)
*Esophageal diameter at location 3 (mm) between the right inferior pulmonary vein and the diaphragmatic hiatus	14 (7-20)
Patients with ILD with >10 mm esophageal diameter	19 (76%)
Patients with ILD with ≤10 mm esophageal diameter	6 (24%)
*Global Warrick score	8 (4-15)
*Severity Warrick score	4 (3-6)
*Extent Warrick score	4 (2-8)
Ground-glass opacities	24 (65%)
Irregular pleura	24 (65%)
Septal/subpleural lines	27 (73%)
Honeycombing	4 (11%)
Subpleural cysts	9 (24%)
DLCO (%)	58,5 (13-88)
FVC (%)	96,3 (17-138)
Patients with reduced DLCO	35 (90%)
Patients with reduced FVC	6 (15%)
Patients with gastroesophageal symptoms	27 (69%)
Patients on proton pump inhibitor therapy	35 (89%)

DLCO = diffusing capacity for carbon monoxide; FVC = forced vital capacity; ILD = interstitial lung disease; ED = esophageal diameter; *expressed as median (interquartile range (IQR))

Table 2. Differences in observed values in relation to esophageal diameter measured at location 1 (atop the aortic arch) on high-resolution computed tomography

	ED ≤10 mm (n=26)	**ED >10 mm (n = 13)**	**Difference†**	**95% CI**	**p**
Age (yrs)	61 (55-71)	63 (46.8-67.5)	-1.5	-11 to 8	0.79
DLCO (%)	67 (53-69)	52 (32.5-62.5)	-13	-27 to -1	0.02*
FVC (%)	106 (99-112)	87 (69-95)	-19	-33 to -9	0.005*
Severity Warrick score	3.5 (2-6)	6.0 (4-11)	3	0 to 6	0.03*
Extent Warrick score	2 (1-6)	6 (5.5-9.8)	4	2 to 6	0.002*
Global Warrick score	6 (3-12)	12 (9.5-20)	7	3 to 12	0.008*

DLCO = diffusing capacity for carbon monoxide; FVC = forced vital capacity; ED = esophageal diameter; CI = confidence interval; expressed as median (interquartile range, IQR), Mann Whitney U test; †Hodges-Lehmann median difference; *statistically signifcant at the p<0.05 level

Table 3. Differences in observed values in relation to esophageal diameter measured at location 2 (between the right inferior pulmonary vein and aortic arch) on high-resolution computed tomography

	ED ≤10 mm (n=13)	**ED >10 mm (n=26)**	**Difference†**	**95% CI**	**p**
Age (yrs)	59 (55-62)	64 (54-70)	5	-5 to 12	0.34
DLCO (%)	67 (61.5-76.8)	55.5 (41-68)	-13	-25 to -2	0.02*
FVC (%)	106 (103.5-110.5)	95 (82-107)	-13	-25 to -2	0.03*
Severity Warrick score	3 (1.5-5)	6 (3-11)	3	0 to 6	0.03*
Extent Warrick score	2 (0.75-4)	6 (2-9)	3	0 to 6	0.01*
Global Warrick score	4 (2.25-8.25)	12 (5-19)	5	1 to 12	0.02*

DLCO = diffusing capacity for carbon monoxide; FVC = forced vital capacity; ED = esophageal diameter; CI = confidence interval; expressed as median (interquartile range, IQR), Mann Whitney U test; †Hodges-Lehmann median difference; *statistically signifcant at the p<0.05 level

Table 4. Differences in observed values in relation to esophageal diameter measured at location 3 (between the right inferior pulmonary vein and diaphragmatic hiatus) on high-resolution computed tomography

	ED ≤10 mm (n=16)	**ED >10 mm (n=23)**	**Difference†**	**95% CI**	**p**
Age (yrs)	59.5 (55-70)	63 (53-69)	2	-6 to 10	0.66
DLCO (%)	67.5 (61-77.5)	52 (38.75-67)	-16	-26 to -6	0.004*
FVC (%)	106 (103-111)	95 (74.5-106.25)	-15	-28 to -4	0.01*
Severity Warrick score	3 (1-5)	6 (3.25-11)	3	1 to 6	0.006*
Extent Warrick score	2 (0.5-4)	6 (4-9.75)	4	2 to 6	0.001*
Global Warrick score	4.5 (1.5-8)	12 (7.25-22)	8	3 to 12	0.002*

DLCO = diffusing capacity for carbon monoxide; FVC = forced vital capacity; ED = esophageal diameter; CI = confidence interval; expressed as median (interquartile range, IQR), Mann Whitney U test; †Hodges-Lehmann median difference; *statistically signifcant at the p<0.05 level

Table 5. Correlation of esophageal diameter at three measured locations on high-resolution computed tomography with lung function and Warrick score (Spearman's correlation coefficient Rho)

	DLCO	FVC	Severity Warrick score	Extent Warrick score	Global Warrick score
ED location 1 p	-0.367 0.02 *	-0.516 <0.001 *	0.435 0.01*	0.552 <0.001 *	0.497 <0.001 *
ED location 2 p	-0.397 0.01 *	-0.405 0.01 *	0.437 0.01*	0.535 <0.001*	0.503 <0.001*
ED location 3 p	-0.412 0.01*	-0.486 <0.001*	0.546 <0.001*	0.61 <0.001*	0.592 <0.001*

DLCO = diffusing capacity for carbon monoxide; FVC = forced vital capacity; ED = esophageal diameter; location 1 = atop the aortic arch; location 2 = between the right inferior pulmonary vein and aortic arch; location 3 = between the right inferior pulmonary vein and diaphragmatic hiatus; *statistically signifcant at the p<0.05 level

as compared to patients without gastroesophageal symptoms.

We found positive correlations with ED measured at any of the three HRCT locations with global, severity, and extent Warrick score, and negative correlations with FVC% and DLCO% (Table 5). In patients with ILD, multivariate regression analysis demonstrated that the independent factor predicting ILD was diameter of the esophagus at location 3 on HRCT between the right inferior pulmonary vein and diaphragmatic hiatus (OR=1.18, 95% CI=1.04 to 1.33, β regression coefficient=0.16). This model correctly predicted the presence of ILD in 69% of patients.

Discussion

Study results suggest that measuring ED on HRCT is a useful radiological marker in patients with SSc-ILD. Early detection of esophageal dilatation in patients with SSc could be an important finding considering that patients with wider ED measured at any of the three different points on HRCT have higher Warrick score (global, severity, and particularly extent score) and lower lung function results. ED wider than 10 mm measured on HRCT between the right inferior pulmonary vein and diaphragmatic hiatus had the strongest correlations with Warrick score and DLCO. This third and lowest point of measurement could be clinically relevant for earlier screening and evaluation of gastroesophageal reflux disease and consequential ILD, considering that patients with wider esophagus at lower level have more acid reflux which could affect the lung parenchyma. This hypothesis should be tested with further research which should involve more invasive tests and a greater number of study subjects. Early detection of ILD with HRCT is important for prevention of development of more severe forms of lung disease. However, during follow-up, routine measurement of ED with CT usually is not performed in patients with SSc. The incidence of lung lesions in patients with SSc is difficult to determine on CT but according to published data, 55%-84% of patients have lung abnormalities[1,14]. Results of our study showed that 64% of patients had significant ILD. Warrick score is valuable for research purposes because of detailed information about lung lesions which provides but also for the uniform evaluation of ILD by radiologists in different institutions.

It is important to highlight that interstitial lesions on HRCT have different significance. Honeycombing has worse prognosis than ground-glass opacities[15]. Our results of interstitial lesions are similar to the research by Cozzi *et al.*, where ground-glass opacities were seen in 60%, irregular pleural margins in 56%, and septal/subpleural lines in 68% but honeycombing in 16% of SSc patients[16].

Given the frequency of ILD and gastroesophageal disorders in patients with SSc, these two diseases are increasingly associated[17]. Patients with esophageal structural and functional disease affection manifest gastroesophageal symptoms[19]. In retrospective data analysis, we found that 27 (69%) of our patients had at least one gastroesophageal symptom (heartburn,

gastric content regurgitation, dysphagia, and/or epigastric pain). Previous studies have shown that higher levels of pepsin are present in the bronchoalveolar lavage fluid in patients with gastroesophageal reflux and obliterative bronchiolitis after lung transplantation[2], which could imply that reflux can cause lung damage. A similar hypothesis that esophageal malfunction can predispose to the development of ILD is suggested in the study by Takekoshi *et al.*[18]. Other studies imply that gastroesophageal reflux can also lead to exacerbation or development of some chronic pulmonary diseases[3,19].

According to the results reported by Savarino *et al.*, patients with SSc-ILD also had severe reflux estimated as a greater number of episodes of reflux and levels of acid extending to the proximal esophagus[17]. Gastroesophageal reflux symptoms are relevant predictors of the FVC decline in patients with SSc-ILD[20]. Our patients with gastroesophageal symptoms had lower values of DLCO and more pronounced esophageal dilatation.

Further research is required on whether early treatment of gastroesophageal manifestations in selected patients could influence the concomitant development or postponement of ILD. Patients are generally advised on dietary measures, avoiding alcohol, sitting upright 3 hours after a meal, and raising their head while sleeping. Fundoplication is an operative procedure that is done infrequently in the treatment of gastroesophageal reflux[21]. The results of our study correspond to the previously published data by Richardson *et al.*, in which the same ED measuring method was used, however, with a different CT scoring system[13]. Similar results to ours were also obtained by Salaffi *et al.*, who demonstrated a relationship between ILD and ED on HRCT in patients with SSc. The authors determined optimal cut-off value of the widest ED ≥11 mm for the presence of significant ILD. In this study, however, the authors did not consider the relationship between Warrick score and lung function tests separately for all three HRCT measuring points of ED[9], and furthermore our results showed that measurement of ED at location 3 was able to predict the presence of ILD in 69% of patients. Contrary to the abovementioned results, in a study by Gilson *et al.*, only diffuse SSc was predictive of pulmonary function reduction in early SSc[22]. In a study by Pandey *et al.*, there was no significant difference in HRCT lung abnormalities between patients with and without esophageal dilatation[6].

A limitation of this research was a relatively small number of patients. Considering that this was a retrospective study, causality could not be claimed. Patients with more severe disease may have both the respiratory system and esophagus involved. Considering conflicting and limited data regarding the association between esophageal dilatation and ILD, our findings may contribute to further larger studies and understanding of these rare clinical conditions. ILD and gastroesophageal symptoms significantly affect the quality of life of the SSc patients[23], and a multidisciplinary approach is needed for patient monitoring[24]. There should be a focus on conducting longitudinal research for better understanding of the connection between esophageal involvement and the severity and extent of ILD, as well as its effect on pulmonary function.

Conclusion

The ILD extent and severity scores measured on HRCT of the thorax are associated with esophageal dilatation. Patients with wider ED have lower lung function test results. The measurement of ED was able to predict the presence of SSc-ILD in 69% of patients. Considering the conflicting results from the literature, our results suggest usefulness of evaluation of ED during regular HRCT follow-up in patients with SSc due to its association with worse lung function tests and more severe form of ILD.

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Sažetak

PROMJER JEDNJAKA NA KOMPJUTORIZIRANOJ TOMOGRAFIJI VISOKE REZOLUCIJE – POTENCIJALNO KORISTAN MARKER ZA TEŽINU INTERSTICIJSKE BOLESTI PLUĆA U BOLESNIKA SA SISTEMSKOM SKLEROZOM

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Bolesnici sa sistemskom sklerozom (SSc) imaju povećani rizik za razvoj intersticijske bolesti pluća (*interstitial lung disease*, ILD) i disfunkciju jednjaka, uz često prisutnu dilataciju jednjaka. Cilj ove studije je bio utvrditi povezanost promjera jednjaka analiziranog kompjutoriziranom tomografijom visoke rezolucije (*high-resolution computed tomography*, HRCT) s testovima plućne funkcije i ILD utvrđenom Warrickovim zbrojem. U studiju je bilo uključeno 39 bolesnika. Promjer jednjaka i Warrickov zbroj su procijenjeni na HRCT-u prsišta. Analiziran je odnos između Warrickovog zbroja, testova plućne funkcije i promjera jednjaka. Multivarijatnom regresijskom analizom je utvrđen utjecaj prediktora na SSc-ILD. ILD je bila prisutna u 25 (64%) bolesnika. Promjer jednjaka >10 mm na jednoj ili više izmjerenih lokacija na HRCT-u je bio prisutan u 25 (64%) bolesnika, od kojih je 19 (76%) bolesnika imalo istodobnu ILD. Ispitanici s dilatacijom jednjaka su imali viši Warrickov zbroj i nižu plućnu funkciju. Mjerenje promjera jednjaka je omogućilo predviđanje ILD u 69% bolesnika. Uzimajući u obzir dosadašnje proturječne rezultate iz literature naši rezultati ukazuju na to da bi procjena promjera jednjaka tijekom redovitog praćenja HRCT-om mogla biti korisna u bolesnika sa SSc zbog povezanosti dilatacije jednjaka s nižom plućnom funkcijom i težim oblikom ILD.

Ključne riječi: *Sistemska skleroza; Jednjak; Bolesti pluća, intersticijske; Kompjutorizirana tomografija; Testovi plućne funkcije*