Esophagus Involvement in Systemic Sclerosis Ultrasound Parameters and Association with Clinical Manifestations

Li Ma
  Peking Union Medical College Hospital   https://orcid.org/0000-0001-5380-0499

Qingli Zhu
  Peking Union Medical College Hospital

Yan Zhang
  Peking Union Medical College Hospital

Jianchu Li
  Peking Union Medical College Hospital

Yuxin Jiang
  Peking Union Medical College Hospital

Dong Xu
  Peking Union Medical College Hospital

Xiaofeng Zeng
  Peking Union Medical College Hospital

Yong Hou (✉ houyongjia@hotmail.com)
  Peking Union Medical College hospital, Chinese Academy of Medical Sciences   https://orcid.org/0000-0002-9534-6965

He Liu
  Peking Union Medical College Hospital

Abstract

Background: The esophagus involvement in systemic sclerosis (SSc) is very common yet underestimated due to the lack of suitable evaluation tools. This study aims to explore the usefulness of ultrasound (US) in the assessment of esophagus involvement and to identify its relationship with clinical and CT manifestations.

Methods: We performed esophageal US in 38 SSc patients and 38 controls. US parameters including the abdominal esophagus length, esophagus wall thickness, shear-wave elastography, gastro-esophageal (His) angle, and reflux were compared. Relationships between distinguishable US parameters and clinical/CT parameters, such as gastro-esophageal reflux disease questionnaire (GERDQ), modified Rodnan skin score (mRSS), interstitial lung disease (ILD) score, the largest esophagus diameter (Dmax), and esophagus dilation percentage (%Eop), were evaluated.

Results: Abdominal esophagus length was shorter in the SSc group than the control group (2.69 cm vs 3.06 cm, P=0.018), while His angle and the angle change before and after drinking water were larger in the SSc group than the control group (121°vs 108°, P=0.000; 7.97°vs 2.92°, P=0.025). Reflux was more frequently seen in the SSc group than the control group (7/38 vs 0/38; P=0.017). As for correlation with clinical and CT parameters, His angle was higher in patients with GERDQ ≥ 8 than GERDQ < 8 (116.5°vs 125.6°, P=0.035). Patients with reflux showed higher ILD score than patients without (15.8 vs 9.6, P=0.043). Furthermore, abdominal esophagus length was negatively correlated with %Eop and Dmax (r=-0.573, P<0.001; r=-0.476, P=0.003),

Conclusion: US parameters of the esophagus can distinguish SSc patients from controls, as well as had correlations with clinical and CT characteristics. Our study firstly shows that US can be used as a noninvasive and convenient method to evaluate the esophagus involvement in SSc.

Introduction

Systemic sclerosis (SSc) is a rare rheumatic disease characterized by fibroproliferative alterations in the microvasculature, leading to fibrosis in the skin and internal organs(1, 2). The esophagus is the most commonly affected organ in SSc, which was reported to have occurred in 75–90% of SSc patients(1, 3, 4). The esophagus dysfunction is a result of reduced lower esophageal sphincter (LES) pressure and weakened peristalsis(3). Esophagus dysfunction can cause malabsorption and compromise patients' quality of life (5).

Up to 50% of the patients with esophagus involvement are asymptomatic, while those with upper gastrointestinal (GI) complaints are too subjective to scale(4, 6). For this reason, the esophagus involvement is often ignored, leading to delayed treatment(7). On the other hand, there are currently no convenient screening strategies for esophagus dysfunction in SSc patients(8). Several diagnostic methods, such as 24-hour pH monitoring, barium esophagography, esophageal manometry, upper GI endoscopy, have been applied to identify objective evidence for gastroesophageal reflux disease (GERD),

including reflux esophagitis, hiatal hernia, gastritis, strictures, or Barret's esophagus(9, 10). Unfortunately, none of these methods can be a single perfect test for routine clinical evaluation due to their invasiveness, complex procedure, and high expense(11). Esophageal dilation is another common manifestation in SSc that can be evaluated by chest CT and positively correlated with interstitial lung diseases (ILD), a severe and lethal disease(12). However, it is not clear at which stage of esophagus involvement the esophageal dilation would occur. Besides, the radiation of CT hinders its application as a screening tool.

Ultrasound (US) is a non-invasive, feasible tool that can evaluate the abdominal part of the esophagus as well as the gastro-esophageal junction. There have been several published reports confirming the value of the US in evaluating GERD in infants and children(13). By observing the length and wall thickness of the abdominal esophagus, gastro-esophageal angle (His angle), and reflux, US can reach an 80–90% accuracy as compared to 24-hour pH monitoring(14, 15). The new generations of US machines provide a high resolution in deeper organs, as well as offer shear-wave elastography (SWE) technique to quantify organ hardness, enabling the evaluation of adults' esophagus. To our knowledge, the usefulness of US on the evaluation of esophagus involvement in SSc patients has not been reported previously. Here, we designed a pilot study to validate the US parameters in the evaluation of esophagus involvement and explored the association with clinical manifestations.

Materials And Methods

Study Participants

Thirty-eight patients and 38 controls participated in this cross-sectional study. For the patient group, subjects must fulfill the American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) 2013 criteria for SSc, and only subjects with diffuse cutaneous systemic sclerosis (dcSSc) or limited cutaneous systemic sclerosis (lcSSc) were included(16, 17). All patients were consecutively recruited at the Rheumatology Department of Peking Union Medical College Hospital between September 2018 and October 2019. For the control group, volunteers with no known underlying connective tissue diseases (CTD) or vascular diseases, including Raynaud's phenomenon, diabetes, and hypertension, nor the upper gastrointestinal symptoms, were recruited. Patients and controls were matched by age and sex. The study was approved by the ethics committee of Peking Union Medical College Hospital and followed institutional guidelines. All participants gave written informed consent, and the body photo used in this article was consented by one volunteer (Z.M.).

Clinical and serological assessment

At entry, all patients with SSc underwent clinical and serological assessment. Data were collected including the patient's age, gender, and disease duration. Disease duration was defined as the time between the first non-Raynaud symptom attributed to SSc and the date of US examination. The modified Rodnan skin score (mRSS) was determined by evaluating 17 skin sites in each patient, including the face, upper arms, forearms, dorsum of the hands, fingers, chest, abdomen, thighs, forearms, and feet as

previously described(18). The symptoms of GERD were assessed by GERD questionnaire (GERDQ) as previously described(19). A GERDQ ≥ 8 is considered to have GERD. The mRSS score and GERDQ were evaluated by an experienced physician specialized in rheumatology, who was trained at the EULAR Scleroderma Trials and Research group course(20). The serological markers, such as antinuclear antibody (ANA), anti-centromere antibody (ACA), Scl-70, was tested in the high-level rheumatological laboratory and recorded. The pulmonary function was performed for every patient, with forced vital capacity (FVC) and carbon monoxide diffusing capacity, single breath (DLCO, SB) recorded. Systolic pulmonary arterial pressure (PASP) pressure was measured by echocardiography through estimating right atrial pressure and measuring tricuspid regurgitation velocity. Pulmonary hypertension was defined as the PASP > 40mmHg.

Ultrasound examinations

Participants were asked to fast for at least 8 h before US examination. The examinations were conducted by one radiologist (L.H.) who had experience with > 100 gastric US examinations using a SuperSonic Aixplorer machine (SuperSonic Imaging. SA, France) with the convex (C5-2) transducer. The radiologist was blinded to the diagnosis, clinical symptoms, relevant laboratory data, and any imaging or endoscopy results. The abdominal part of the esophagus and the gastro-esophageal junction was examined as previously described (Fig. 1)(21). In short, the transducer was placed sagittally in the midline or a little left-leaning under the xiphoid, to reveal the abdominal esophagus longitudinally through the window of the left lobe of the liver. The length of the abdominal esophagus was measured from the point at which the esophagus traversed the diaphragm to the gastro-esophageal junction, which was identified on sonograms by a small triangular pad of gastric folds radiating from the cardia. The esophageal wall thickness was measured on the anterior wall at the midpoint of the abdominal esophagus. The His angle was delimited by the tangent line passed from the left fornix of the stomach and the long axis of the abdominal esophagus(13). The SWE was obtained by placing the SWE box on the abdominal esophagus, and the image was frozen after the colored signal was stable. A round "Q-box" region of interest was positioned inside the SWE image and within the anterior wall of the abdominal esophagus. Then the mean elastic modulus within the "Q-box" was shown on the screen. Each measurement was performed three times, and the mean value was used for further analysis. After the measurements above, the participants were asked to intake the 300ml of warm water. Reflux was carefully observed immediately after water intake for 5 minutes at the gastro-esophageal junction. And measurements of the length of the abdominal esophagus, the esophageal wall thickness, SWE, and His angle were performed for the second time. Videos were recorded during the examination.

To test the intra-observer reproducibility of the measurements, the same radiologist (L.H.) reviewed saved videos one month later and repeated all measurements. To assess interobserver reproducibility, another independent radiologist (M.L.), who had experience with > 50 gastric US examinations, reviewed saved videos and repeated all measurements.

CT

The chest CT was performed on all SSc patients. Images were obtained using a C-100 scanner (GE Imatron, San Francisco, CA, USA) with a section thickness of 5 mm at full inspiration. For the esophagus, the images were set to the mediastinal window (window width 396 HU, window level 44 HU). The largest linear measurement of the esophageal air column was recorded as the largest esophagus diameter (Dmax)(22). The number of sections with the esophagus air column more than 10 mm was divided by the total number of the esophageal sections to give a percentage of the open or dilated esophagus over the whole esophagus, namely esophagus dilation percentage (%Eop)(23). A fluid level was recorded if there was an air-fluid level at any place in the esophagus. The ILD score was evaluated as previously described(23). In short, the CT images were set to lung windows (window width 1465 Hounsfield Units (HU), window level – 498 HU). Lungs were divided into 6 zones, and each zone was scored from 0 to 3 by severity in each of the following categories: ground glass, fibrosis (reticular or scarring), honey-combing, and consolidation. The esophagus parameters and ILD score were assessed by an experienced radiologist who was blinded to clinical and laboratory data.

Statistics

We performed statistical analysis using SPSS software version 23 (IBM Corp., Armonk, NY, USA). Descriptive statistics were reported as number (percent) for categorical variables, or median (range) for continuous variables. Intra-observer and inter-observer reproducibility were evaluated using intraclass correlation coefficient (ICC) analysis which was graded as follows: poor (< 0.20), moderate (0.20 to 0.40), fair (0.40 to 0.60), good (0.60 to 0.80), or very good (0.80–1.00). The independent t-test was used to compare continuous variables and categorical variables were compared with Pearson chi-square test or Mann-Whitney U test. Correlations between variables were analyzed using Pearson's correlation for two variables with normal distribution, or Spearman's correlation for two variables with non-normal distribution. A P value < 0.05 was considered statistically significant. An experienced biomedical statistician reviewed the statistical methods used in this study.

Results

Patient characteristics

Thirty-eight SSc patients and 38 age- and sex-matched controls were recruited in the study. The baseline characteristics of all participants are shown in Table 1. There were 8% (3/38) males in both groups. The average age was 51.3 ± 12.6 in the SSc group and 52.2 ± 12.9 in the control group, with no statistical difference (P = 0.76). For SSc patients, the average disease duration was 11.2 ± 6.6 years, GERDQ score was 8.3 ± 2.7, and mRSS was 4.6 ± 3.9. The FVC was averagely 87.8% of predicted, and DLCO was averagely 63.7% of predicted. In all, 16 (42%) patients were positive for Scl-70, 33 (87%) were positive for ANA, and 7(18%) were positive for ACA. No patients had pulmonary hypertension.

Table 1
Baseline characteristics of enrolled participants

	Patient (n = 38)	Control (n = 38)	P
Male, n (%)	3 (8%)	3 (8%)	1
Age (years), mean ± SD	51.3 ± 12.6	52.2 ± 12.9	0.76
SSc Characteristics			
Disease duration(years), mean ± SD	11.2 ± 6.6		
GERDQ score, mean ± SD	8.3 ± 2.7		
mRSS, mean ± SD	4.6 ± 3.9		
FVC (actual/predicted, %), mean ± SD	87.8 ± 17.2		
DLCO SB (%), mean ± SD	63.7 ± 13.7		
Scl-70, n (%)	16 (42%)		
ANA, n (%)	33 (87%)		
ACA, n (%)	7(18%)		
Pulmonary hypertension, n (%)	0		

Abbreviations: SD, standard deviation; SSc, systemic sclerosis; MRSS, the modified Rodnan skin score; GERDQ, gastro-esophageal reflux disease questionnaire; ANA, antinuclear antibody; ACA, anti-centromere antibody; DLCO SB, carbon monoxide diffusing capacity, single breath; FVC, forced vital capacity.

Comparison of ultrasound parameters between SSc and control groups

The differences of US parameters between the SSc and control groups are shown in Table 2. The abdominal esophagus length was shorter in the SSc group than the control group (before drinking water, 2.69 cm vs 3.06 cm, P = 0.018; after drinking water, 2.64 cm vs 3.03 cm, P = 0.016), with no significant change before and after drinking water. His angle was larger in the SSc group than in the control group both before and after drinking water (before drinking water, 121°vs 108°, P = 0.000; after drinking water, 129°vs 111°, P = 0.000). Also, the angle change was larger in the SSc group (7.97°vs 2.92°, P = 0.025). There were 7 out of 38 patients who showed reflux after drinking water, and no one in the control group showed reflux (P = 0.017). There were no differences in esophagus wall thickness (P = 0.890 and 0.185, before and after drinking water) and SWE (P = 0.703 and 0.416, before and after drinking water) between the two groups, both before and after drinking water.

Table 2
Comparison of ultrasound parameters between SSc and control group

	SSc group	Control group	*P*
Abdominal esophagus length (cm)*			
Before drinking water	2.69	3.06	0.018
After drinking water	2.64	3.03	0.016
Esophagus wall thickness (mm)*			
Before drinking water	3.47	3.49	0.890
After drinking water	3.66	3.91	0.185
His angle (°)			
Before drinking water	121	108	0.000
After drinking water	129	111	0.000
Angle change	7.97	2.92	0.025
SWE (kPa)*			
Before drinking water	5.52	6.20	0.703
After drinking water	4.58	3.56	0.416
reflux	7/38	0/38	0.017
*There is no significant difference before and after drinking.			
Abbreviations: SSc, systemic sclerosis; His angle, the gastro-esophageal angle; SWE, shear-wave elastrography			

These results suggested that abdominal esophagus length, His angle, and reflux are characteristic parameters in SSc patients, while esophagus wall thickness and SWE had no significant differences in our study.

Intra-observer and inter-observer reproducibility

For intra-observer reproducibility, the intraclass correlation coefficient of abdominal esophagus length, esophagus wall thickness, His angle, SWE and reflux was 0.760 (95% confidence interval [CI]: 0.646–0.841, good), 0.206 (95% CI: -0.019-0.411, moderate), 0.883 (95% CI: 0.822–0.924, very good), 0.352 (95% CI: -0.157-0.713, moderate), and 1(very good). For inter-observer reproducibility, the intraclass correlation coefficient of abdominal esophagus length, esophagus wall thickness, His angle, and reflux was 0.818

(95% CI: 0.728−0.881, very good), 0.803 (95% CI: 0.705−0.870, very good), and 0.613 (95% CI: 0.368−0.778, good) (Table 3).

Table 3
Intra-observer and Inter-observer Reproducibility

	Intra-observer Reproducibility	Inter-observer Reproducibility
	ICC (95%CI)	ICC (95%CI)
Abdominal esophagus length	0.760 (0.646−0.841)	0.818 (0.728−0.881)
Esophagus wall thickness	0.206 (-0.019-0.411)	/
His angle	0.883 (0.822−0.924)	0.803 (0.705−0.870)
SWE	0.352 (-0.157-0.713)	/
reflux	1	0.613 (0.368−0.778)
Abbreviations: ICC, intraclass correlation coefficient; CI, confidence interval; His angle, the gastro-esophageal angle; SWE, shear-wave elastography		

These results indicated that abdominal esophagus length, His angle, and reflux had a good intra-observer and inter-observer reproducibility. SWE and esophagus wall thickness had a poor intra-observer reproducibility.

Correlation between ultrasound parameters and clinical/CT manifestations in SSc patients

The correlation between ultrasound parameters (abdominal esophagus length, His angle, and reflux) with clinical factors (mRSS, GERDQ) and CT parameters (Dmax, %Eop, ILD score) was analyzed. We found that His angle was higher in SSc patients with GERDQ score ≥ 8 than GERDQ score < 8 (116.5°vs 125.6°, P = 0.035, Fig. 2). The ILD score was higher in SSc patients with reflux on ultrasound than without (15.8 vs 9.6, P = 0.043, Fig. 3). The abdominal esophagus length was negatively correlated with %Eop (r=-0.573, P < 0.001) and Dmax (r=-0.476, P = 0.003) on CT (Fig. 4). None of the US parameters were correlated with mRSS.

These results indicated that US parameters were associated with clinical and CT manifestations in SSc patients.

Discussion

As the esophagus is a commonly involved organ of SSc, a practical and convenient screening tool to objectively evaluate the existence and severity of esophagus status is still lacking. The novelty of our

study is that we first reported a spectrum of US parameters that can be used to detect the esophagus involvement in SSc patients, and that these new parameters correlated to SSc clinical and CT markers.

The US parameters we used in this study are summarized from literature which mostly reported the US evaluation of GERD in infants and children(13). In the literature, abdominal esophagus length is a commonly adopted parameter, and is shorter in GERD patients as compared to normal controls in our and previous studies(2, 21, 24). The underlying reason is complicated, possibly due to the fibrosis and contracture of the esophagus wall in SSc. It has been reported that the reflux detected by US has high sensitivity and positive predictive value with reference to pH monitoring in children(14, 25). In our study, we found reflux a discriminating parameter between SSc and control group, yet the sensitivity is to be determined.

His angle was reported to be a stable, age-independent parameter, which is larger in GERD patients than controls(26, 27). We found that His angle was larger in SSc patients than controls, which confirmed the previous findings(28). Moreover, the angle change before and after water intake was larger in patients than in controls, which is not reported previously. This can be explained by that the stiffness of the esophagus and stomach wall in SSc decreases the elasticity, making it harder to maintain the original form under pressure, and reflected as a bigger angle change.

The esophageal wall thickness and esophageal SWE failed to show good repeatability in our study. Although SWE can theoretically give quantitative measurements to reflect esophageal fibrosis, it is highly affected by the heartbeat, breath, and complicated tissue texture during our practice. Further research is needed to find a suitable way to use SWE.

In our study, US parameters had a fair-to-good correlation with CT parameters (Dmax, %Eop). No previous studies had reported the correlation between the two imaging modalities. Our study proved that although evaluating esophagus from different perspectives, US and CT can be complementary tools to reflect esophagus condition in SSc. GERDQ is considered as an auxiliary method in GERD diagnosis, which has a positive correlation with His angle in our study. These results imply that US is able to evaluate the esophagus status in SSc patients.

Accumulating evidence has suggested that esophageal disease may be an independent contributor to ILD, a condition that is strongly associated with increased morbidity and mortality(6, 9, 29). Previous studies have shown a negative correlation between esophagus dilation and pulmonary function test(6, 9, 29). Our study demonstrated that SSc patients with reflux on US tend to have higher ILD scores than patients with no reflux, confirming the relationship between esophagus dysfunction and ILD in SSc. We did not find correlations between US parameters and pulmonary function test indicators, possibly due to the small sample size.

Our results failed to find the association between US parameters and mRSS. Since the enrolled SSc patients were not naïve, the skin thickness is under the influence of the long-term medication, which disturbs the original condition of the skin.

There are several limitations to our study. First, we did not compare US parameters with classical examination methods for GERD, such as 24-hour pH monitoring, barium esophagography, esophageal manometry, or upper GI endoscopy, due to their complexity and invasiveness leading to the limited use in China. Another obvious limitation is that the sample size is relatively small despite our promising findings, which leaves the validation of our preliminary results for future studies.

Conclusion

In this pilot study, we found that abdominal esophagus length, His angle, and reflux assessed by US had significant differences between SSc patients and controls, and also had associations with the largest esophagus diameter on CT, GERDQ, and mRSS in SSc. Therefore, US has the potential to be a pragmatic tool for detecting the esophagus involvement in SSc.

Declarations

Ethics approval and consent to participate

The study protocol was reviewd and approved by the ethics committee of Peking Union Medical College Hospital and followed institutional guidelines. All participants gave written informed consent.

Consent for publication

The body photo used in this article was consented for publication by one volunteer (Z.M.).

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

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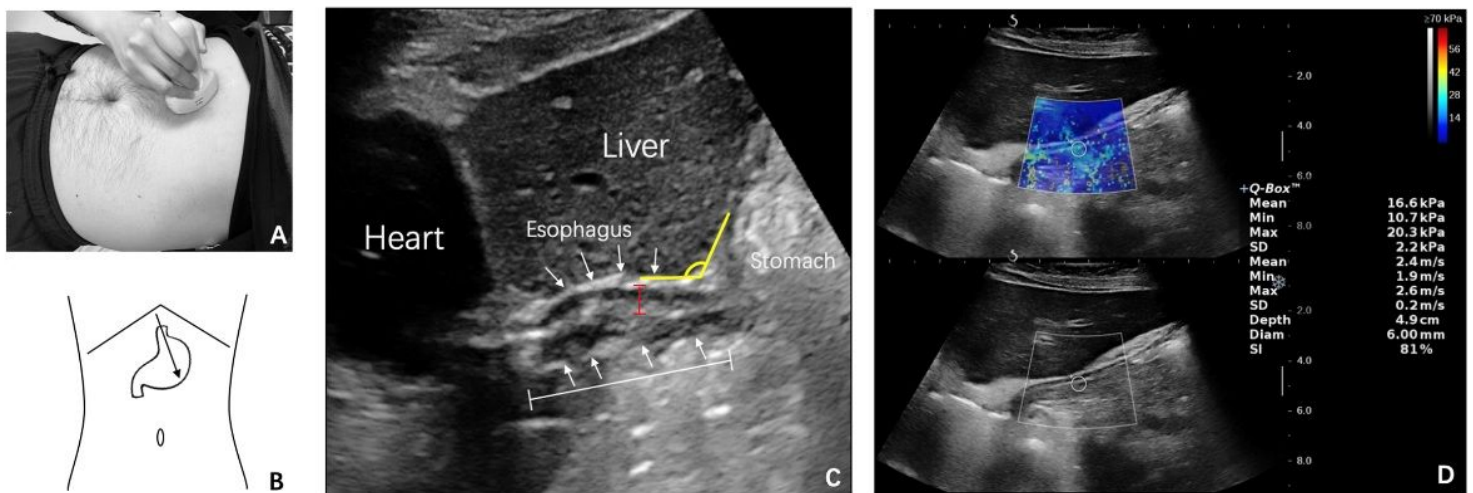
Figures

Figure 1

The measurements of US parameters. (A) (B) The transducer was placed a little left-leaning under the xiphoid, to reveal the longitudinal abdominal esophagus and gastro-esophageal junction. (C) The US image showing the abdominal esophagus and gastro-esophageal junction. The esophagus is delineated as a linear structure (arrows) with the hypoechogenic wall and hyperechogenic lumen. The measurements of abdominal esophagus length (white lines), esophageal wall thickness (red lines), and His angle (yellow lines) are illustrated. C. SWE was obtained by placing the SWE box (trapezoid) on the abdominal esophagus, and the image was frozen after the colored signal was stable. A Q-box region of interest (circle) was positioned within the anterior wall of the abdominal esophagus. The mean elastic

modulus within the Q-box was shown on the screen. Each measurement was performed three times. His angle, the gastro-esophageal angle; SWE, shear-wave elastography.
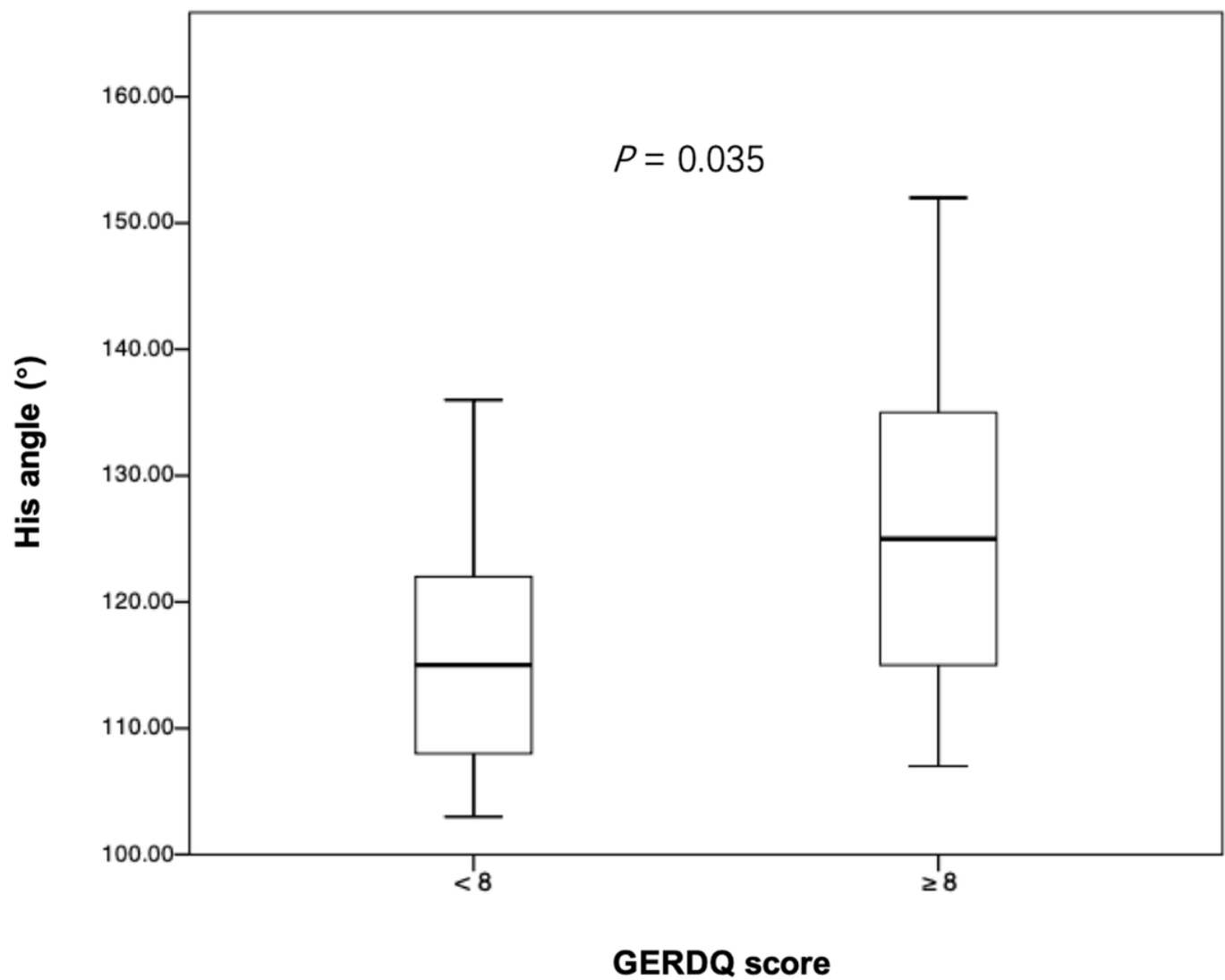

Figure 2

His angle in SSc patients with GERDQ < 8 and GERDQ ≥ 8. Patients with GERDQ ≥ 8 has a larger His angle than patients with GERDQ < 8, with a P value < 0.05. GERDQ, gastro-esophageal reflux disease questionnaire; His angle, the gastro-esophageal angle.
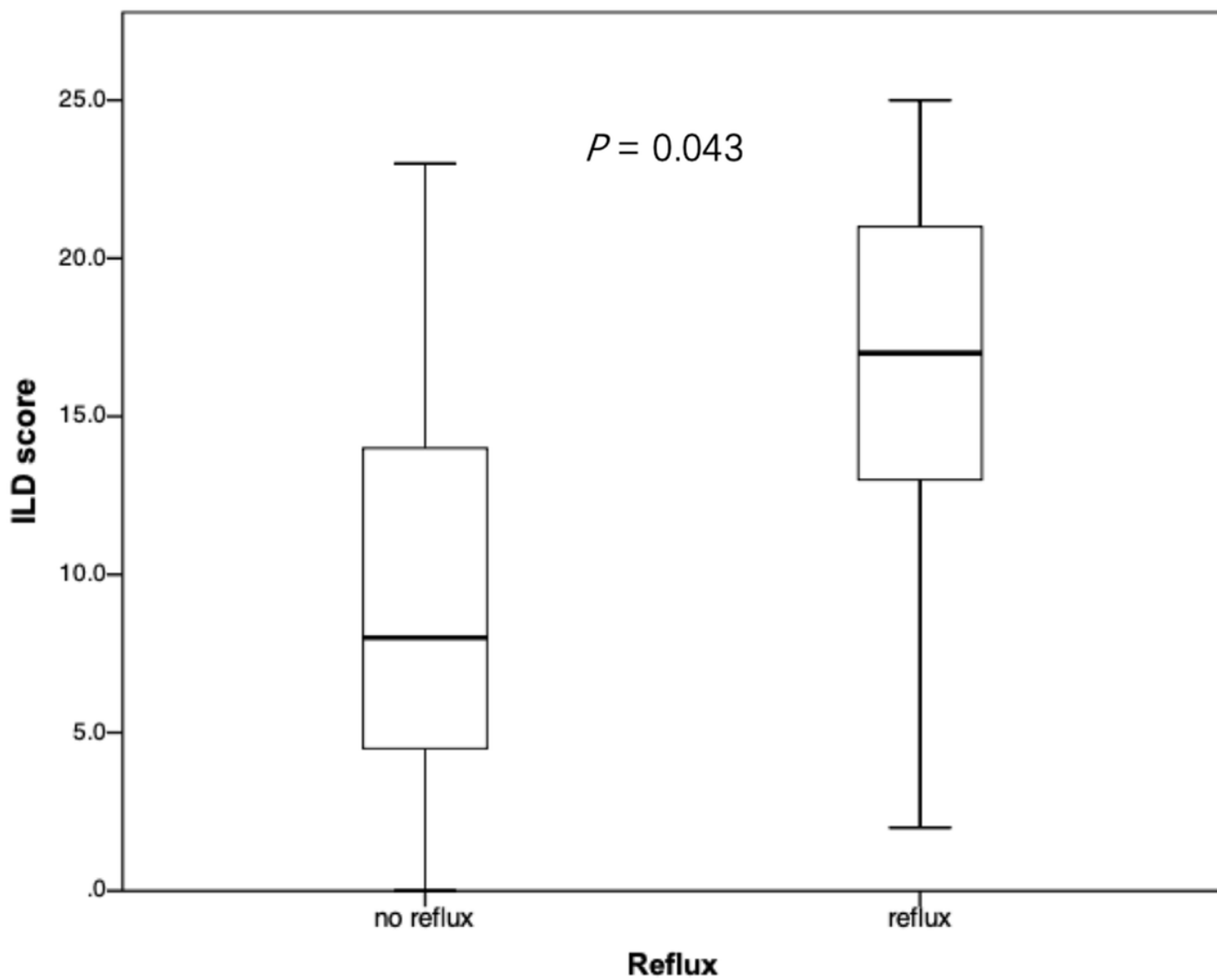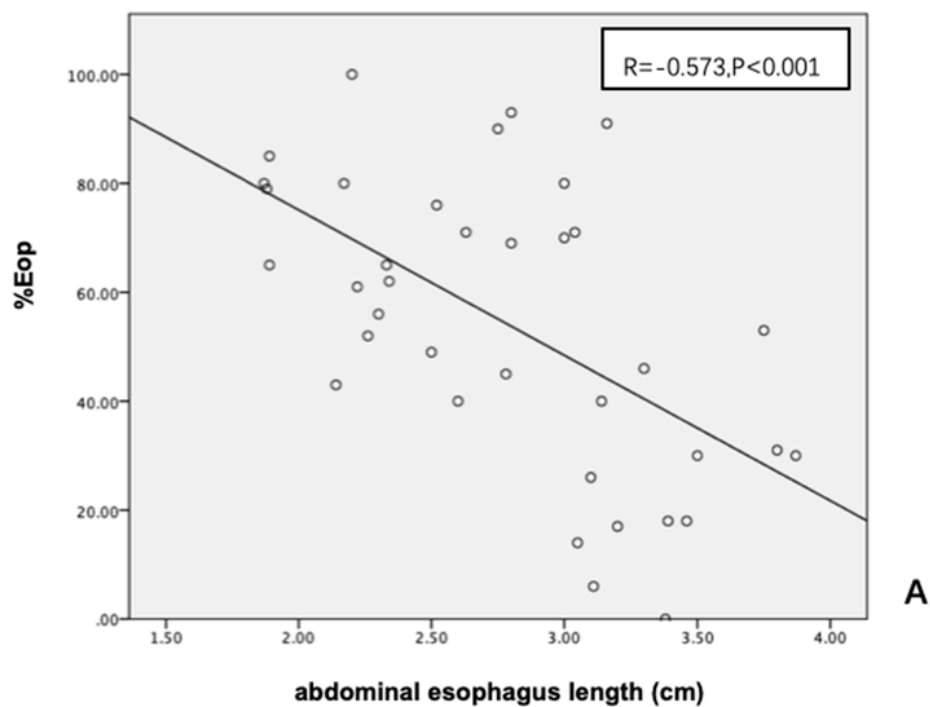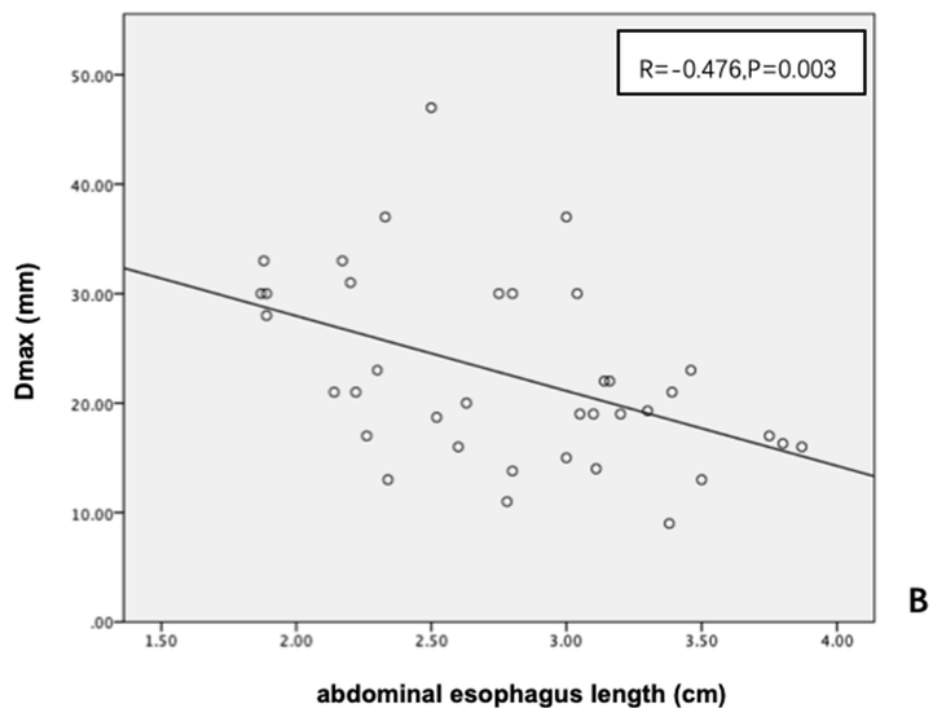
Figure 3

ILD score in SSc patients with/without reflux on US. ILD score is higher in patients with reflux than without reflux, with a P value < 0.05. ILD, interstitial lung disease.

Figure 4

The correlations between abdominal esophagus length and CT parameters. (A) abdominal esophagus length is negatively correlated to the esophagus dilation percentage (%Eop); (B) abdominal esophagus length is negatively correlated to the largest esophagus diameter (Dmax).