

Journey into the Esophageal Complications: Decoding Systemic Sclerosis with Cutting-Edge Endoscopy, Manometry, and Ambulatory pH-Study

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Purpose: Systemic Sclerosis (SSc) is a rare connective tissue disorder characterized by autoimmunity, fibrosis, and vasculopathy that affects the skin and internal organs, including the gastrointestinal tract, particularly the esophagus. This article highlights the characteristics and clinical symptoms of esophageal involvement in patients with SSc.

Patients and Methods: This study was conducted between November 2022 to August 2023, including 26 already diagnosed cases of SSc in the Department of Rheumatology and Rehabilitation and Kurdistan Center for Gastroenterology and Hepatology-Sulaymaniyah, Iraq. Esophageal involvement was investigated using esophageal manometry, esophagogastroduodenoscopy (EGD), and 24-hour impedance-pH monitoring.

Results: Females were significantly predominant ($P = 0.019$) regarding the symptoms; 76.9% of the patients had heart burn, 76.9% dysphagia, 73.1% water brush, and 69.2% regurgitation. In total, 69.2% of the patients showed erosive gastrointestinal reflux disease (GERD) on EGD, 76.9% had decreased lower esophageal sphincter pressure (DLESP) and decreased distal esophageal peristaltic contractions (DDEPC) on esophageal manometry, and 84.6% had reflux on pH monitoring. Raynaud's phenomenon is the most common and typically the earliest clinical manifestation of SSc. The presence of erosive GERD was found to significantly increase the risk of developing dysphagia ($B = 4.725$, $P = 0.014$, $OR = 3.482$) and regurgitation ($B = 3.521$, $P = 0.006$, $OR = 4.030$).

Conclusion: It is crucial to take gender-specific considerations into account when diagnosing and managing esophageal complications in patients with systemic sclerosis (SSc). Additionally, employing various diagnostic assessments to detect esophageal involvement during SSc is essential. Erosive GERD has been identified as a risk factor that contributes to the development of dysphagia and regurgitation in individuals with SSc.

Keywords: esophageal involvement, esophageal manometry, esophagogastroduodenoscopy, 24-hour Impedance-pH Monitoring, systemic sclerosis

Introduction

Scleroderma is a rare connective tissue disorder recognized as an autoimmune disorder with a complex and unknown pathogenesis. The term "Scleroderma" originated in 1836 when Fantonetti, a Milanese physician, employed it to describe skin alterations in an adult individual.¹ There are two major forms of scleroderma: localized scleroderma, and systemic sclerosis. Localized scleroderma is a skin and subcutaneous tissue disease that leads to patches of thickened skin.² Systemic sclerosis (SSc), associated with severe morbidity and mortality, is characterized by gradual fibrosis of the skin and internal organs.³ Despite its relatively low prevalence, SSc has the highest mortality rate of all rheumatic diseases.⁴ SSc is classified into diffuse cutaneous SSc and limited cutaneous SSc. Diffuse cutaneous SSc shows a poor prognosis

because of early and rapid organ involvement, whereas limited cutaneous SSc shows a better prognosis with slower disease progression and visceral involvement later in the disease course.⁵

Systemic sclerosis (SSc) is a complex disease that affects not only the skin but also various organs, often leading to serious complications in the lungs and kidneys. In addition, some individuals experience musculoskeletal and cardiac problems. Gastrointestinal tract manifestations, including esophageal involvement, are observed in most patients.^{6,7} However, there is limited understanding of the pathogenesis and risk factors for the development and predictors of esophageal disease progression in patients with SSc. Vasculopathy,⁸ oxidative stress, fibrosis because of collagen deposition,⁹ and autoantibody generation because of a dysregulated immune system may cause esophageal dysfunctions.¹⁰ Epigenetic regulation plays an important role in the occurrence and development of systemic sclerosis, which involves DNA methylation, histone modification and non-coding RNA regulation. Many genes related to the interferon pathway undergo epigenetic changes and appear to be associated with different antibodies in SSc.¹¹ Capillary abnormalities, such as the enlargement and/or disappearance of capillary loops, occur early in the majority of SSc patients.^{12,13} Recently, videocapillaroscopy is used for measuring absolute nailfold capillary number and density of fingers.¹⁴ Additionally, studies have shown that continuous fibrosis and myopathy affect the function and structure of the esophageal sphincter and motility, in which gastric juice refluxes to the esophagus and damages the squamous epithelium. The gastrointestinal reflux is asymptomatic but gradually symptoms start, such as heartburn, dysphagia, and regurgitation.^{15,16} Today, respiratory involvement (pulmonary fibrosis and pulmonary artery hypertension) is among the leading causes of SSc-related deaths.¹⁷

Clinical symptoms related to SSc are not sufficient to diagnose esophageal involvement; however, esophageal manometry is used to evaluate esophageal motility disorders.¹⁸ In addition, endoscopy could be used to identify histological alterations in the mucosa of the esophagus¹⁹ and the 24 hour pH study has a successful sensitivity for the diagnosis of gastroesophageal reflux.²⁰ Data on SSc and esophageal involvement in Kurdish patients are limited. Hence, we used a range of diagnostic techniques (endoscopy, esophageal manometry, and ambulatory pH study) to explore practical and effective indicators of esophageal disorders. Thus, this study underscores the importance of multidisciplinary approaches for diagnosis and management.

Materials and Methods

Patients

For this study, 26 patients were enrolled from the Department of Rheumatology and Rehabilitation and the Kurdistan Center for Gastroenterology and Hepatology, Sulaymaniyah, Iraq. The study was conducted from November 2022 to August 2023 and was approved by the Ethical Committee of the College of Science-Biology Department/Salahaddin University and complied with the Declaration of Helsinki. Patients were diagnosed by experienced rheumatologists according to the 2013 American College of Rheumatology.²¹ Inclusion criteria: patients included based on having thickening of skin on fingers proximal to the metacarpophalangeal or metatarsophalangeal joints, telangiectasia, pulmonary arterial hypertension, Raynaud phenomenon, visceral involvement, and autoantibody. It is then classified as either limited cutaneous SSc or diffuse cutaneous SSc according to the classification created by LeRoy et al,²² in which limited cutaneous SSc includes skin involvement distal to the elbows and knees and diffuse cutaneous SSc includes skin involvement of the proximal limbs and/or trunk. Exclusion criteria: patients with diabetes and autoimmune connective tissue diseases including, systemic lupus erythematosus and rheumatoid arthritis were excluded from this study. Patients with sicca symptoms were also excluded to avoid the probability of having Sjögren syndrome.

Written informed consent was obtained from all patients, and data were collected (sex, SSc subtypes, Heartburn, Dysphagia, water brush, Regurgitation, and Odynophagia). The presence of Raynaud phenomenon was identified by asking the patients whether their fingers turn blue when exposed to cold or during emotional stressors. Moreover, extractable nuclear antigen test was done to determine anti-centromere antibody (ACA) and anti-topoisomerase I antibody (ATA). The patients then underwent upper gastrointestinal endoscopy, Esophageal Manometry (EM), and 24-hour pH monitoring for the evaluation of esophageal involvement. The drugs used by the patients were reviewed. Drugs

known to suppress acid or alter esophageal motility (proton pump inhibitors, H₂-receptor blockers, antacids, prokinetics, and calcium channel blockers) were discontinued in patients 2 weeks prior to the study.

The Extractable Nuclear Antigen Test (ENA)

Following proper sample collection and serum preparation, the procedure was carried out by adding 10 μ L of serum into the first well of 8 well Alegria test strip, then inserting the strip into Sys tray and placing the tray into its position of Alegria instrument, and the run was started. All other steps were done automatically through an ELISA-based, automated, in-vitro test system with fully automated random access Alegria analyzer (ORGENTEC Diagnostika, Germany). Antibodies present in positive samples bind to the antigen coated on the surface of the two reaction wells, forming an antibody antigen complex. The intensity of the formed blue color correlates with the concentration of the antibody-antigen-complex and can be measured photometrically at 650 nm. For ACA, Normal: <10 U/mL and Elevated: \geq 10 U/mL. However, Normal: < 15 U/mL, Borderline: 15–25 U/mL, and Elevated: > 25 U/mL are considered for ATA.

Esophagogastroduodenoscopy (EGD)

EGD was performed on 26 patients in the Endoscopy Department of the Kurdistan Center for Gastroenterology and Hepatology by an endoscopist using a video endoscopic system (GIF – Q 240; Olympus, Japan). The patients fasted for at least 8 hours prior to the procedure. EGD was used to examine esophageal strictures, hiatus hernias, Barrett's esophagus (BE), and esophageal malignancies (biopsy taken in suspected cases of Barrett's disease and malignancy and sent for histopathological examination).

High Resolution-Manometry

The procedure was performed in the Manometry Department of the Kurdistan Center for Gastroenterology and Hepatology by a well-trained esophageal laboratory nurse. Manometry was performed using a high-resolution impedance manometry machine (UNI-ESO–W5025, R2.0; SANDHIL SCIENTIFIC, USA). The instrument comprises a 38-channel manometry system used to record esophageal motility, which contains 32 solid-state circumferential pressure sensors spaced at 1-cm intervals, each of which detects pressure over a length of 2.5 mm in 12 radially dispersed sectors. The main esophageal manometry findings in SSc patients are decreased lower esophageal sphincter pressure (DLESP) and distal esophageal peristaltic contraction (DDEPC).

Twenty-Four-Hour Impedance-pH Monitoring

Twenty-four-hour pH Monitoring was performed at the pH-study Department of Kurdistan Center for Gastroenterology and Hepatology using a combined multichannel intraluminal impedance–pH monitoring machine (REF: Z 07–2000–B; SANDHIL SCIENTIFIC, USA). In each patient, an intraesophageal catheter provided with nine sensors (three impedance sensors) was placed trans-nasally and remained in place for 24 h. Both acid (refluxate with pH < 4) and non-acid reflux (refluxate with pH \geq 4) were evaluated, and reflux episodes were detected by impedance and categorized as acid or non-acid by pH.

Statistical Analysis

The information got from the patients and the three procedures (EGD, Manometry, and pH monitoring) was inserted into an Excel sheet for later analysis. Statistical analyses were performed using the GraphPad Prism version 9. Both relative and absolute frequencies were used to represent patient characteristics. The age of the patients is represented as mean \pm SD. The Chi-square test was used to determine the association of sex, disease duration, and SSc subtypes with esophageal involvement in patients with SSc. The association between esophageal symptoms and clinical findings was investigated using binary logistic regression. We employed the Hosmer-Lemeshow test to evaluate the accuracy of our binary logistic regression model. This required comparing the actual results with the expected ones to identify any significant discrepancies. If the p-value of the Hosmer-Lemeshow test is greater than the chosen significance level (typically 0.05), it suggests that there is no evidence of a lack of fit, indicating that the model accurately fits the data. A p-value less than 0.05 was considered to be statistically significant.

Results

Patients

In total, 26 patients were enrolled in the study. Esophageal involvement was more common among females in a male-to-female ratio of 1:12. The mean age of the patients was 43.3 ± 12.1 years. Most patients have limited cutaneous SSc (65.4%). Twenty out of 26 patients (92.3%) had esophageal involvement (confirmed by at least one of these investigations; endoscopy or manometry or PH-study). Twenty-one patients with SSc had symptoms of esophageal involvement, while the rest were asymptomatic. ENA test showed that all patients (65.4%) with limited cutaneous SSc tested ACA positive and the patients with diffuse cutaneous SSc (34.6%) tested ATA positives. Regarding Raynaud phenomenon, most of the patients (92.3%) experienced the color changing of fingers to blue, especially when exposed to cold or during stress (Table 1).

Table 2 presents the symptoms of patients with SSc with esophageal involvement. Nearly all the patients experienced heartburn, dysphagia, water brushing, and regurgitation. However, only 42.3% of the patients had odynophagia.

Table 1 The Patient's Characteristics

Characteristics (n = 26)		Frequency
Gender	Male	2 (7.7%)
	Female	24 (92.3%)
Age, Mean \pm SD		43.3 \pm 12.1
SSc subtype	Limited	17 (65.4%)
	Diffuse	9 (34.6%)
Esophageal involvement	Yes	24 (92.3%)
	No	2 (7.7%)
Esophageal symptoms	Symptomatic	21 (80.8%)
	Asymptomatic	5 (19.2%)
ENA profile	Positive ATA	34.6%
	Positive ACA	65.4%
Raynaud phenomenon	Yes	24 (92.3%)
	No	2 (7.6%)

Note: The age is represented by mean \pm SE.

Abbreviations: ACA, anti-centromere Ab; ATA, anti-topoisomerase I Ab; ENA, extractable nuclear antigen; SD, standard deviation; SSc, systemic sclerosis.

Table 2 The Symptoms Experienced by SSc Patients Related to Esophageal Involvement

Symptoms (n = 26)	Frequency
Heart burn	20 (76.9%)
Dysphagia	20 (76.9%)
Water brush	19 (73.1%)
Regurgitation	18 (69.2%)
Odynophagia	11 (42.3%)

The EGD procedure performed for all patients indicated that erosive gastrointestinal reflux disease (GERD) was seen in two-thirds (69.2%) of the patients. A minority of the patients had Barrett's Esophagus and esophageal strictures (7.7% and 3.8%, respectively). However, the pathological results showed normal tissue, and no malignancy was observed in any patient (Table 3).

The results obtained by high-resolution manometry and 24-hour impedance-pH monitoring of patients are shown in Table 4. Most of the patients (76.9%) faced the DLESP and DDEPC at the same time. Moreover, three other patients only had DDEPC, and the remaining three patients had normal esophageal manometry. In addition, the findings by pH monitoring indicated the presence of reflux in 84.6% of the SSc patients.

Table 5 illustrates the relationship between various variables and esophageal involvement, including sex, disease duration, and the SSc subtype. The results showed a significant relationship ($P = 0.019$) between sex and esophageal involvement, with esophageal involvement being more prevalent among females (95.83%). Nonetheless, the relationship between disease duration and SSc subtypes with esophageal involvement was not significant ($P = 0.668$ and 0.634 , respectively). The study analyzed the association between clinical findings (erosive GERD, DLESP + DDEPC, and reflux) and esophageal symptoms (heartburn, dysphagia, and regurgitation) and found that having any of the clinical findings increases the likelihood of experiencing these symptoms (Table 6). Specifically, erosive GERD was identified as a major risk factor for the development of dysphagia ($B = 4.725$, $P = 0.014$, $OR = 3.482$) and regurgitation ($B = 3.521$, $P = 0.006$, $OR = 4.030$) in patients with SSc. The findings suggest that individuals with SSc and erosive GERD are more prone to experiencing these symptoms in comparison to those without the condition.

Table 3 The Results of EGD Procedure of the Study Subjects

EGD Findings (n = 26)	Frequency
Erosive GERD	18 (69.2%)
Barrett's esophagus	2 (7.7%)
Esophageal stricture	1 (3.8%)
Esophageal cancer	0 (0.0%)

Abbreviations: EGD, Esophagogastroduodenoscopy; GERD, gastrointestinal reflux disease.

Table 4 The Comprehensive Results Obtained from Esophageal Manometry and pH Monitoring

Manometry Findings (n = 26)	Frequency
DLESP + DDEPC	20 (76.9%)
DDEPC	3 (11.5%)
Normal	3 (11.5%)
pH Monitoring findings	Frequency
Reflux	22 (84.6%)
No reflux	4 (15.4%)

Abbreviations: DLESP, decreased lower esophageal sphincter pressure; DDEPC, decreased distal esophageal peristaltic contractions.

Table 5 Association of the Sex, Disease Duration, and SSc Subtypes with Esophageal Involvement

Variables	Esophageal Involvement		P value
	Present (n = 24)	Absence (n = 2)	
Sex			
Male	1 (4.16%)	1 (50%)	0.019*
Female	23 (95.83%)	1 (50%)	
Disease duration			
1–5 years	8 (33.33%)	1 (50%)	0.668 ns
7–12 years	9 (37.5%)	1 (50%)	
13–18 years	7 (29.1%)	0 (0%)	
SSc subtypes			
Limited	16 (66.66%)	1 (50%)	0.634 ns
Diffuse	8 (33.33%)	1 (50%)	

Notes: Chi-square was used to find the P value. *p < 0.05.

Abbreviations: SSc, systemic sclerosis; ns, not significant.

Table 6 Association Between Clinical Findings with Esophageal Symptoms: Binary Logistic Regression

Dependent Variables	Independent Variables	B	Sig for Regression	OR	Sig for Hosmer-Lemeshow test
Heart burn	Erosive GERD	1.469	0.998	1.213	0.914
	DLESP + DDEPC	2.286	0.998	1.002	
	Reflux	0.706	0.675	0.985	
Dysphagia	Erosive GERD	4.725	0.014*	3.482	0.918
	DLESP + DDEPC	2.542	0.414	1.271	
	Reflux	0.962	0.091	1.254	
Regurgitation	Erosive GERD	3.521	0.006**	4.030	0.892
	DLESP + DDEPC	1.813	0.192	1.163	
	Reflux	1.226	0.883	1.253	

Notes: *p < 0.05. **p < 0.01.

Abbreviations: GERD, gastrointestinal reflux disease; DLESP, decreased lower esophageal sphincter pressure; DDEPC, decreased distal esophageal peristaltic contractions.

Discussion

In this study, 26 patients with confirmed SSc were included to provide recommendations for the regular monitoring and early detection of esophageal involvement in SSc patients, aiming to improve prognosis and management outcomes. Our results showed that the high prevalence of SSc among females and female patients was significantly associated with a higher risk for esophageal involvement compared to males, which is in line with the results of a systematic review conducted in 2018 and a cross-sectional study in 2021.^{23,24} Female predominance may be because of the effects of estrogen fluctuations, especially during menopause and pregnancy. Estrogen contributes to SSc because of its pro-fibrotic

effect.²⁴ Most patients have limited SSc, which is more common, as shown in other studies.^{25,26} In our study, the presence of ATA antibodies and ACA antibodies in diffuse cutaneous SSc and limited cutaneous SSc, respectively align with the results of the other study.²⁷ The studies revealed that secondary raynaud's phenomenon is the most common and typically the earliest clinical manifestation of SSc. This is why it is prevalent among SSc patients, which is consistent with our findings.^{28,29}

Besides skin thickness in systemic sclerosis, the internal organs are included, such as the esophagus.³⁰ This was true for this study, in which esophageal involvement was identified in most patients with symptoms related to esophageal abnormalities. The most common symptoms were heartburn, dysphagia, water brushing, and regurgitation. Moreover, erosive GERD was predominant among the patients, as identified by EGD. These problems result from retrograde reflux of acid from the stomach because of an abnormality of the esophageal sphincter in systemic sclerosis.^{16,31} Studies have reported the association of systemic sclerosis and cancer, and long-term exposure of the esophageal lining with gastric acid in SSc patients may lead to cancer,^{32–34} however none of the enrolled patients were diagnosed with esophageal cancer, which may be because of the small sample size and also requires a long period for cancer development.

The abnormalities were recorded using esophageal manometry, in which the patients frequently suffered from both abnormal esophageal sphincter pressure and contraction (DLESP and DDEPC), as has been reported in other studies.^{35,36} In addition, reflux was reported in most patients using pH monitoring, and Arif et al (2015) also reported a high prevalence of reflux in his study.³⁷ Consistent with the other study employing videofluorography, signs of esophageal reflux were reported in most patients.³⁸

In our study, the disease duration was not significantly associated with esophageal involvement. Esophageal involvement was more prevalent among those with limited SS with 7–12 years of disease duration. However, there was no significant association between esophageal manifestations and disease duration or SSc subtype of SSc, which is in agreement with the results of a previous study.³⁹ Furthermore, our analysis revealed a notable association between clinical findings, particularly erosive GERD, and esophageal symptoms. This correlation is corroborated by a study showing that dysphagia, heartburn, and regurgitation are prevalent presentations of GERD.⁴⁰ These findings greatly enhance our current knowledge of the clinical characteristics and connections pertaining to esophageal manifestations in patients with SSc. Moreover, the study adds adequate information on esophageal complications using different techniques. These findings highlight the significance of further research in this field.

Conclusion

The heterogeneous expression of this rare condition poses a challenge to both patients and clinicians. Predicting the development of serious internal organ complications is therefore important. Clinicians frequently encounter difficulties in promptly diagnosing systemic sclerosis during the initial phase. The exact cause of systemic sclerosis is a mystery; however, we concluded that females were at high risk for SSc and were significantly more susceptible to esophageal involvement. Furthermore, we deduced that the presence of multiple signs and symptoms, such as erosive GERD on EGD, DLESP, and DDEPC during esophageal manometry, concurrent with reflux identified on pH monitoring, may serve as indicative markers for esophageal involvement in patients with SSc. These abnormalities in the esophagus of the patients contribute to the high incidence of dyspeptic symptoms (heartburn, dysphagia, water brush, and regurgitation) among the patients. We realized that the disease duration and subtype of SSc were not associated with esophageal involvement. The occurrence of erosive GERD has been recognized as a risk factor that contributes to the emergence of dysphagia and regurgitation in individuals diagnosed with SSc.

Ethics Statement and Consent to Participate

This study was approved by the ethics committee of Salahaddin University (registration no.: R131-019; 102 approved on June 24, 2022) and followed the Declaration of Helsinki. All participants provided consent prior to the study. If they could not sign the questionnaire because of their inability, we asked their legal companions.

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Author Contributions

All authors made a significant contribution to the work reported, whether that was in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas. They took part in drafting, revising, or critically reviewing the article. They gave final approval of the version to be published. They agreed on the journal to which the article had been submitted; and they agreed to be accountable for all aspects of the work.

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References

- Rodnan GP, Benedek TG. An historical account of the study of progressive systemic sclerosis (diffuse scleroderma). *Ann Internal Med.* 1962;57:305–319. doi:10.7326/0003-4819-57-2-305
- Marabotto E, Savarino V, Savarino E. Towards a more precise classification of esophageal motility disorders in patients with systemic sclerosis. *Neurogastroenterol Mot.* 2022;34(7):e14416. doi:10.1111/nmo.14416
- Denton CP, Khanna D. Systemic sclerosis. *Lancet.* 2017;390(10103):1685–1699. doi:10.1016/s0140-6736(17)30933-9
- Bairkdar M, Rossides M, Westerlind H, Hesselstrand R, Arkema EV, Holmqvist M. Incidence and prevalence of systemic sclerosis globally: a comprehensive systematic review and meta-analysis. *Rheumatology.* 2021;60(7):3121–3133. doi:10.1093/rheumatology/keab190
- Emmanuel A. Current management of the gastrointestinal complications of systemic sclerosis. *Nat Rev Gastroenterol Hepatol.* 2016;13(8):461–472. doi:10.1038/nrgastro.2016.99
- Varga J, Abraham D. Systemic sclerosis: a prototypic multisystem fibrotic disorder. *J Clin Invest.* 2007;117(3):557–567. doi:10.1172/jci31139
- Allanore Y, Simms R, Distler O, et al. Systemic sclerosis. *Nature Rev Dis Prim.* 2015;1:15002. doi:10.1038/nrdp.2015.2
- Apostolidis SA, Stifano G, Tabib T, et al. Single Cell RNA Sequencing Identifies HSPG2 and APLNR as markers of endothelial cell injury in systemic sclerosis skin. *Front Immunol.* 2018;9:2191. doi:10.3389/fimmu.2018.02191
- Zhang R, Kumar GS, Hansen U, et al. Oxidative stress promotes fibrosis in systemic sclerosis through stabilization of a kinase-phosphatase complex. *JCI Insight.* 2022;7(8). doi:10.1172/jci.insight.155761
- Fuschiotti P. T cells and cytokines in systemic sclerosis. *Current Opin Rheumatol.* 2018;30(6):594–599. doi:10.1097/bor.0000000000000553
- Yu J, Tang R, Ding K. Epigenetic modifications in the pathogenesis of systemic sclerosis. *Int J Gen Med.* 2022;15:3155–3166. doi:10.2147/ijgm.S356877
- Wildt M, Wuttge DM, Hesselstrand R, Scheja A. Assessment of capillary density in systemic sclerosis with three different capillaroscopic methods. *Clin Exp Rheumatol.* 2012;30(2 Suppl 71):1.
- Smith V, Scirè CA, Talarico R, et al. Systemic sclerosis: state of the art on clinical practice guidelines. *RMD Open.* 2018;4(Suppl 1):e000782. doi:10.1136/rmdopen-2018-000782
- Cutolo M, Trombetta AC, Melsens K, et al. Automated assessment of absolute nailfold capillary number on videocapillaroscopic images: proof of principle and validation in systemic sclerosis. *Microcirculation.* 2018;25(4):e12447. doi:10.1111/micc.12447
- Kimmel JN, Carlson DA, Hinchcliff M, et al. The association between systemic sclerosis disease manifestations and esophageal high-resolution manometry parameters. *Neurogastroenterol Mot.* 2016;28(8):1157–1165. doi:10.1111/nmo.12813
- Kumar S, Singh J, Rattan S, DiMarino AJ, Cohen S, Jimenez SA. Review article: pathogenesis and clinical manifestations of gastrointestinal involvement in systemic sclerosis. *Aliment Pharmacol Ther.* 2017;45(7):883–898. doi:10.1111/apt.13963
- Pătrîntău DE, Sárközi HK, Lupuşor E, et al. A multidisciplinary approach as a goal for the management of complications in systemic scleroderma: a literature review and case scenario. *Diagnostics.* 2023;13(21):1.
- Liu P, Chai J, Dai L, et al. Development of a diagnostic model focusing on esophageal dysmotility in patients with systemic sclerosis. *Diagnostics.* 2022;12(12):3142. doi:10.3390/diagnostics12123142
- Park JW, Kim J, Kang EA, Kim MJ, Kim JS, Lee EB. Endoscopic features of upper gastrointestinal tract in patients with systemic sclerosis compared to the healthy control. *Journal of Rheum Dis.* 2019;26(1):66–82. doi:10.4078/jrd.2019.26.1.66
- Li B, Yan J, Pu J, Tang J, Xu S, Wang X. Esophageal dysfunction in systemic sclerosis: an update. *Rheumatol Therap.* 2021;8(4):1535–1549. doi:10.1007/s40744-021-00382-0
- van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. *Ann Rheum Dis.* 2013;72(11):1747–1755. doi:10.1136/annrheumdis-2013-204424
- LeRoy EC, Black C, Fleischmajer R, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol.* 1988;15(2):202–205.
- Abbot S, Bossingham D, Proudman S, de Costa C, Ho-Huynh A. Risk factors for the development of systemic sclerosis: a systematic review of the literature. *Rheumatol Adv Pract.* 2018;2(2):rky041. doi:10.1093/rap/rky041
- De Angelis R, Giuggioli D, Bajocchi G, et al. Sex-related differences in systemic sclerosis: a multicenter cross-sectional study from the national registry of the Italian society for rheumatology. *J Rheumatol.* 2022;49(2):176–185. doi:10.3899/jrheum.210794

25. Pokeerbux MR, Giovannelli J, Dauchet L, et al. Survival and prognosis factors in systemic sclerosis: data of a French multicenter cohort, systematic review, and meta-analysis of the literature. *Arthritis Res Ther.* 2019;21(1):86. doi:10.1186/s13075-019-1867-1
26. De Almeida Chaves S, Porel T, Mounié M, et al. Sine scleroderma, limited cutaneous, and diffused cutaneous systemic sclerosis survival and predictors of mortality. *Arthritis Res Ther.* 2021;23(1):295. doi:10.1186/s13075-021-02672-y
27. Bobeica C, Niculet E, Musat CL, et al. Paraclinical aspects in systemic sclerosis. *Int J Gen Med.* 2022;15:4391–4398. doi:10.2147/ijgm.S355662
28. Pauling JD, Saketkoo LA, Matucci-Cerinic M, Ingegnoli F, Khanna D. The patient experience of Raynaud's phenomenon in systemic sclerosis. *Rheumatology.* 2019;58(1):18–26. doi:10.1093/rheumatology/key026
29. Maciejewska M, Sikora M, Maciejewski C, Alda-Malicka R, Czuwara J, Rudnicka L. Raynaud's phenomenon with focus on systemic sclerosis. *J Clin Med.* 2022;11(9):2490. doi:10.3390/jcm11092490
30. Nagy G, Dobrota R, Becker MO, et al. Characteristics of ScleroID highlighting musculoskeletal and internal organ implications in patients afflicted with systemic sclerosis. *Arthritis Res Ther.* 2023;25(1):84. doi:10.1186/s13075-023-03063-1
31. Petronovich JJ, Bock JM. Systemic sclerosis and reflux. *Ear Nose Throat J.* 2013;92(4–5):192–194. doi:10.1177/014556131309200410
32. Maria ATJ, Partouche L, Goulabchand R, et al. Intriguing relationships between cancer and systemic sclerosis: role of the immune system and other contributors. *Front Immunol.* 2018;9:3112. doi:10.3389/fimmu.2018.03112
33. Fragoulis GE, Daoussis D, Pagkopolou E, Garyfallos A, Kitas GD, Dimitroulas T. Cancer risk in systemic sclerosis: identifying risk and managing high-risk patients. *Expert Rev Clin Immunol.* 2020;16(12):1105–1113. doi:10.1080/1744666x.2021.1847641
34. Zhang X, Yang X, Zhang T, Yin X, Man J, Lu M. Association of educational attainment with esophageal cancer, Barrett's esophagus, and gastroesophageal reflux disease, and the mediating role of modifiable risk factors: a Mendelian randomization study. *Front Public Health.* 2023;11:1022367. doi:10.3389/fpubh.2023.1022367
35. Markus J, Pinto RMC, Matoso AGB, Ranza R. Esophageal manometry in systemic sclerosis: findings and association with clinical manifestations. *Rev Assoc Med Bras.* 2020;66(1):48–54. doi:10.1590/1806-9282.66.1.48
36. Dao HV, Hoang LB, Luu HTM, et al. Clinical symptoms, endoscopic findings, and lower esophageal sphincter characteristics in patients with absent contractility. *Medicine.* 2022;101(43):e31428. doi:10.1097/md.00000000000031428
37. Arif T, Masood Q, Singh J, Hassan I. Assessment of esophageal involvement in systemic sclerosis and morphea (localized scleroderma) by clinical, endoscopic, manometric and pH metric features: a prospective comparative hospital based study. *BMC Gastroenterol.* 2015;15:24. doi:10.1186/s12876-015-0241-2
38. Fraticelli P, Pisani AM, Benfaremo D, et al. Videofluorography swallow study in patients with systemic sclerosis: correlation with clinical and radiological features. *Clin Exp Rheumatol.* 2019;119(4):108–114.
39. Raja J, Ng CT, Sujau I, Chin KF, Sockalingam S. High-resolution oesophageal manometry and 24-hour impedance-pH study in systemic sclerosis patients: association with clinical features, symptoms and severity. *Clin Exp Rheumatol.* 2016;100(5):115–121.
40. Foocharoen C, Chunlertrith K, Mairiang P, et al. Prevalence and predictors of proton pump inhibitor partial response in gastroesophageal reflux disease in systemic sclerosis: a prospective study. *Sci Rep.* 2020;10(1):769. doi:10.1038/s41598-020-57636-0

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