Prevalence and clinical importance of gastroesophageal reflux in Chinese patients with systemic sclerosis

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ABSTRACT

Objectives. *To estimate the prevalence of gastroesophageal reflux (GER) and its clinical relevance with other manifestations in Chinese patients with systemic sclerosis (SSc).*

Methods. *A prospective cross-sectional study of 205 Chinese patients with SSc was conducted at Peking Union Medical College Hospital (PUMCH). GER was diagnosed as mild heartburn or regurgitation ≥2 days per week, or moderate/severe heartburn or regurgitation ≥1 day a week. PAH was defined as pulmonary artery systolic pressure (PASP) >45mmHg at rest as estimated by transthoracic echocardiography (TTE). Demographic, clinical, and laboratory data were calculated between GER and non-GER groups, and relative examinations including a six-minute walk test, pulmonary function test and modified Rodnan skin score (mRSS) were also performed.*

Results. *The prevalence of GER was 43.90% (90/205) among 205 Chinese patients with SSc. The presence of Raynaud phenomenon (98.9% vs. 92.2%), fingertip ulcers (56.7% vs. 51.3%), pulmonary arterial hypertension (PAH) (18.89% vs. 6.96%, respectively), and all gastrointestinal tract manifestations occurred significantly more frequent in patients with GER than in patients without GER, respectively (p<0.05). There were no differences in the development of any autoantibody between GER patients and non-GER patients (p>0.05). Echocardiography showed that the left ventricular ejection fraction (LVEF) was lower (62.27±10.48 vs. 70.09±5.26, respectively) and pericarditis was more frequent (22.6% vs. 11.0%, respectively) in SSc-related GER than in SSc patients without GER, respectively. The New York Heart Association (NYHA) functional class of SSc-related GER was worse than patients without GER (p=0.015). A pulmonary function test showed that forced vital capacity FVC% (78.93±17.90 vs. 84.55±17.45, respectively, p=0.042), forced expiratory volume FEV1% (77.12±15.65 vs. 84.30±16.25, respectively, p=0.004), and diffusing capacity DLCO% (4.76±1.76 vs. 5.63±2.12, respectively, p<0.001) were lower, and the FVC%/DLCO% ratio (1.46±0.42 vs. 1.28±0.27, respectively, p=0.001)was higher in SSc-related GER than non-GER patients (p<0.05). We also found that GER was an independent risk factor of PAH in SSc patients (p=0.030, OR=7.532).*

Conclusions. *GER is common in Chinese patients with SSc, and patients with GER are susceptible to microvascular damage. Therefore, SSc patients presenting with GER should be screened for PAH.*

Introduction

Systemic sclerosis (SSc) is a connective tissue disorder that is characterised by excessive collagen production resulting in skin and visceral fibrosis of various organs, such as the gastrointestinal tract, lungs, kidneys, and heart (1-2). Gastrointestinal tract dysfunction is one of the most common problems in SSc and is found in both diffuse and limited subgroups. Although any section of the gastrointestinal tract can be involved, esophageal disease occurs in nearly all patients with SSc. In addition, 75%–90% of patients with SSc have abnormal esophageal motility (3-5), and the most common complication of esophageal motility abnormalities in SSc is gastroesophageal reflux (GER). Clinically, GER of SSc patients is characterised by gastresophageal reflux disease (GERD) symptoms and sometimes dysphagia (4).

GER is defined as the retrograde movement of gastric contents across the lower esophageal sphincter (LES) into the esophagus. Histological examination of esophageal biopsy specimens has revealed the replacement of normal

smooth muscle by smooth muscle atrophy, which leads to motor activity abnormalities in patients with SSc (6). In patients with SSc, gravity plays a major role in esophageal acid clearance time. GER is related to both the low pressure in the LES and abnormal peristalsis, which together lead to decreased acid clearance and prolonged acid-mucosal contact time (7).

Pulmonary arterial hypertension (PAH) is a major cause of death in patients with SSc (8). Several studies suggest that GER is associated with pulmonary impairment, and in particular asthma, interstitial lung disease (ILD), and PAH (9-10). In general, GER does not cause significant mortality, but the symptoms of GER often impair a patient's quality-of-life. Importantly, GER can also increase the risk of cardiopulmonary symptoms of SSc patients due to acid reflux occurring at night and sleep deprivation. However, it is not clear whether GER can worsen PAH in SSc patients, which would consequently affect prognosis.

Over the past few years, several studies have assessed the occurrence and implications of GER in SSc patients throughout the world. However, the epidemiology and characteristics of GER in SSc patients remain unclear, especially in China. As one Chinese centre of EULAR Scleroderma Trials and Research group (EUSTAR), we followed the international protocol to collect data of Chinese patients with SSc. In this current study, we aimed to prospectively evaluate the impact of GER (defined on the basis of symptoms) in China.

Patients and methods

Patients

Data from 205 Chinese SSc patients were collected from February 2009 to September 2010 from one EULAR Scleroderma Trial and Research group (EUSTAR) centre in China. All patients fulfilled the American College of Rheumatology (ACR) (8) or LeRoy and Medsger criteria (11) for SSc. This study was approved by the medical ethics committee of Peking Union Medical College Hospital and ethics committee of EUSTAR, followed by the entry of the Minimal Essential Data Set (MEDS) (12-13). Scleroderma subsets were labelled as "diffuse SSc" (dcSSc), which was defined as skin thickening that extends proximal to the elbows and knees or includes the trunk, "limited SSc" (lcSSc), which was defined as skin thickening that is confined to the elbows, knees, or face, and "sine scleroderma" (ssSSc), which was defined as SSc with major organ involvement but without the characteristic skin changes of scleroderma (14). Conditions that are characterised by the presence of clinical and serological manifestations suggestive of systemic autoimmune diseases but not fulfilling the classification criteria for defined connective tissue disease (CTD) are common in clinical practice and are indicated as undifferentiated connective tissue diseases (UCTDs) (15). Patients who fulfilled the ACR criteria for scleroderma but simultaneously presented with typical features of one or more of other CTDs, such as systemic lupus erythematosus, Sjögren's syndrome, dermatomyositis, polymyositis, or rheumatoid arthritis were classified as overlapping syndrome.

GER definition

Reflux symptoms were defined as the presence of heartburn and/or regurgitation. Heartburn was subjectively assessed as 'burning behind the breastbone' and 'pain behind the breastbone', and regurgitation was assessed as 'acid taste in your mouth' and 'unpleasant movement of materials upwards from the stomach' (16). GER was diagnosed as mild heartburn and/or regurgitation ≥2 days per week, or moderate/severe heartburn and/or regurgitation ≥1 day a week, as stated by the Montreal Definition of GERD (17). Some of the patients who did not respond to acid suppressant treatment received a double-contrast barium swallow, upper endoscopy, esophageal manometry, and esophageal pH monitoring.

PAH definition

Although right heart catheterisation (RHC) is the gold standard for diagnosing PAH (18), transthoracic echocardiography (TTE) has also been validated as an acceptable screening tool of PAH in patients with CTD (19-20). The World Health Organisation (WHO) defines PAH as a mean pulmonary artery pressure (PAP) >25 mmHg at rest by RHC in the presence of normal pulmonary capillary wedge pressure. To increase the specificity of SSc-related PAH, we defined PAH as pulmonary artery systolic pressure (PASP) >45mmHg at rest as estimated by TTE (20-21). Chronic lung complications, such as interstitial lung disease or chronic obstructive pulmonary disease, were excluded by chest x-ray or computerised tomography due to possible affects on PAP.

Data collection

All investigators received a training program and used the same protocol-directed methods to provide uniform evaluations and record data. Demographics, symptoms, and signs were collected from all patients. Laboratory findings, including leukocyte, immunoglobulin, complement, and autoantibody measurements were also calculated. The concentration of autoantibodies, including anti-ANA, anti-dsDNA, anti-Sm, anti-SSA, anti-SSB, anti-RNP, anti-Scl70, and ACA antibodies was determined. Each patient received a six minute walk test (6MWD), TTE, pulmonary function test and modified Rodnan skin score (mRSS) assessment.

Statistical analysis

A case control study was used to compare parameters between GER and non-GER groups. Data were analysed with the SPSS 17.0 statistics package (IBM, USA). Variables were summarised as counts and percentages or as medians and ranges. The chi-square test and Fisher's exact test were used to compare categorical data, and the Independent Samples t-test was used to compare quantitative data between the groups. A model of binary logistic regression was used to analysis the risk factor. P values less than 0.05 were considered to be statistically significant.

Results

Prevalence of GER

Among 205 Chinese patients with SSc that participated in this study, 90 patients had GER symptoms. The

prevalence of GER was 43.90% in our study cohort. Most of these SSc-GER cases initially presented with Raynaud phenomenon (76.67%) or arthritis/arthralgia (14.41%), and only six cases (6.67%) initially presented with GER. There was no significant difference in the initial symptoms and classification of SSc between SSc patients with and without GER (p>0.05; Table I). Among 90 symptom-defined GER with SSc, 44 (48.89%) patients received a UGI examination, eight patients had detectable gastroesophageal reflux, 15 patients manifested with weakened esophageal motility, and eight patients had an expansion of the esophagus. There were 17 (18.89%) patients who received an endoscopic examination and 12 patients were diagnosed with reflux esophagitis (RE). Among them, one patient conformed to the Los Angeles (LA) classification-grade A (LA-A), two patients conformed to LA-B, five patients conformed to LA-C, and four patients conformed to LA-D with one patient experiencing an upper gastrointestinal haemorrhage. The other five endoscopic negative patients were considered to have non-erosive reflux disease (NERD). Every patient received HRCT of the chest in our study, and only 11 (12.22%) patients experienced an expansion of the esophagus, and one patient had limited thickening of the esophageal wall. There was only one patient who received esophageal manometry and esophageal pH monitoring, and the results showed that the resting tone of the lower esophageal sphincters and the contractile pressures in the body of the esophagus were decreased. Moreover, the DeMeester = 15.12 and the UGI showed weakening of esophageal motility, but the endoscopy was negative.

Table I. Prevalence of disease presentation between GER and non-GER groups.

	GER	Non-GER	p-value
Number of patients	90 (43.9%)	115 (56.3%)	NA
Gender (F/M)	81/9	107/8	0.455
Age at onset (years)	36.28 ± 12.16	37.04 ± 14.00	0.682
Age at diagnosis (years)	46.52 ± 11.06	45.30 ± 12.87	0.474
Disease duration (years)	10.24 ± 8.58	8.20 ± 7.23	0.066
Initial symptoms			
Raynaud phenomenon	69 (76.67%)	95 (82.61%)	0.285
arthritis/ arthralgia	13 (14.44%)	12 (10.43%)	
myasthenia	1 (1.11%)	4 (3.48%)	
others	7 (7.78%)	4 (3.48%)	
Classification			
dcSSc	48 (53.33%)	62 (53.91%)	0.828
lcSSc	33 (36.67%)	38 (33.04%)	
ssSSc	1 (1.11%)	2 (1.74%)	
UCTD	1 (1.11%)	4 (3.48%)	
overlapping syndrome	7 (7.78%)	9 (7.83%)	

F: female; M: male.

Table II. Comparison of clinical manifestations between GER and non-GER groups.

	GER	non-GER	p-value
Raynaud phenomenon	89 (98.9%)	106 (92.2%)	***0.045***
Arthritis/ arthralgia	51 (56.7%)	59 (51.3%)	0.482
Fingertip ulcers	32 (35.6%)	24 (20.9%)	***0.027***
Myasthenia	35 (38.9%)	31 (27.0%)	0.073
Dysphagia	41 (45.6%)	16 (13.9%)	***0.000***
Fullness	25 (27.8%)	12 (10.4%)	***0.002***
Constipation	19 (21.1%)	7 (6.1%)	***0.002***
Vomit	17 (18.9%)	0 (0.0%)	***0.000***
ILD	47 (52.2%)	57 (49.6%)	0.779
PAH	17 (18.89%)	8 (6.96%)	***0.009***
Emptysis	2 (2.2%)	0 (0.0%)	0.192
Dyspnea	15 (16.7%)	14 (12.2%)	0.421
Cough	31 (34.4%)	21 (18.3%)	***0.010***
Palpitation	28 (31.1%)	15 (13.0%)	***0.002***
Effort-dyspnea	56 (62.2%)	44 (38.3%)	***0.001***
Oedema	18 (20.0%)	15 (13.0%)	0.187
Renal crisis	2 (2.2%)	2 (1.7%)	1.000
Hypourocrinia	5 (5.6%)	2 (1.7%)	0.244

ILD: interstitial lung disease; PAH: pulmonary arterial hypertension.

Demographics

In this study, 205 Chinese patients with SSc were studied and 188 patients (91.26%) were female. The age at onset was 36.97±12.94 (9-76) years and age at diagnosis was 45.84±12.06 (18-78) years. The disease duration was 8.87±6.92 (1–39) years. Among the 90 SSc-GER patients, the disease duration before GER was 4.13±5.37 (0-22) years, and the disease duration of GER was 6.11±6.04 (1–44) years. There was no significant difference in age, gender, or disease duration between SLE patients with and without GER (Table I).

Clinical manifestations

The clinical characteristics between GER and non-GER cases with SSc were compared. The presence of Raynaud phenomenon (p=0.045), fingertip ulcers (p=0.027), PAH (p=0.009), cough (p=0.010), palpitation (p=0.002), effort dyspnea (p=0.001), and all gastrointestinal tract manifestations (p<0.05) were significantly more frequent in SSc patients with related GER compared to patients without GER, whereas no significant difference was observed in other systemic manifestations between both groups (Table II)

Laboratory findings

The presence of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), immunoglobulin, and complement as well as anti-dsDNA and anti-ENA antibodies were compared between patients with and without GER, and only complement C3 was significantly lower in the GER group (p=0.024). There were no differences between the two groups in any of the autoantibodies measured (Tables III and IV).

Table III. Comparison of laboratory data between GER and non-GER groups.

	GER	non-GER	*p*-value
ESR (mm/1h)	42.4% (36/49)	33.7 (34/67)	0.229
CRP (mg/L)	58.2% (39/28)	50.0% (37/37)	0.398
IgG >17 g/L	38.3% (31)	35.0% (35)	0.846
IgG <7 g/L	1.2% (1)	2.0% (2)	
IgA >3.8g/L	18.8% (15)	16.0 (16)	0.407
IgA <0.7g/L	0.0% (0)	2.0% (2)	
IgM >2.5g/L	11.3 (9)	6.1% (6)	0.384
IgM <0.6g/L	8.8% (7)	12.1% (12)	
CH50 >55U/ml	60.3% (41)	46.3% (38)	0.174
CH50 <25U/ml	0.0% (0)	1.2% (1)	
C3 <60mg/dl	76.5 (52)	90.8% (79)	***0.024***
C4 <12mg/dl	80.0% (52)	89.5% (77)	0.181

Table IV. Comparison of autoantibodies between GER and non-GER groups.

	GER	non-GER	*p*-value
ANA	89.8% (79/9)	88.7% (102/13)	1.000
ANA(1:1280)	54.5% (48/40)	53.0% (61/54)	0.921
ANA(H)	33.3% (30/88)	31.3% (36/79)	0.766
ANA(N)	31.3% (28/60)	35.7% (41/74)	0.552
ANA(S)	44.4% (40/48)	45.2% (52/63)	1.000
ANA(H+N)	22.2% (20/68)	23.5% (27/88)	0.868
dsDNA	1.1% (1/87)	2.9% (3/100)	0.626
ENA	5.6% (5/85)	6.7% (7/98)	0.776
anti-Sm	2.2% (2/87)	4.8% (5/100)	0.456
anti-RNP	23.6% (21/68)	21.3% (25/90)	0.866
anti-SSA	20.2% (18/71)	13.9% (16/99)	0.259
anti-SSB	1.1% (1/88)	0.9% (1/114)	1.000
Scl-70	46.0% (23/27)	54.8% (51/42)	0.381
ACA	15.9% (10/52)	15.3% (11/61)	1.000
AMA	22.2% (4/14)	16.7% (3/15)	1.000

ANA: H, homogeneous; N: nucleolar; S. speckled.

Table V. Comparison of relative examinations between GER and non-GER groups.

	GER	non-GER	*p*-value
Echocardiography			
LVEF	62.27 ± 10.48	70.09 ± 5.26	***0.026***
PASP (mmHg)	43.68 ± 48.18	32.91 ± 15.19	0.061
Diastolic dysfunction	20.7% (17/65)	15.5% (15/82)	0.435
Pericarditis	22.6% (19/65)	11.0% (11/89)	***0.045***
6MWD(m)	456.81 ± 98.56	490.43 ± 85.35	***0.016***
NYHA functional class			
I	60.6% (43)	80.6% (75)	***0.015***
II	35.2% (25)	16.1% (15)	
III	4.2% (3)	3.2% (3)	
mRSS	6.31 ± 4.64	5.98 ± 4.42	0.641

LVEF: left ventricular ejection fraction; PASP: pulmonary artery systolic pressure; 6MWD: 6-minute walk distance; mRSS: modified Rodnan skin score.

Relative examinations

Echocardiography showed that left ventricular ejection fraction (LVEF) was lower in SSc-related GER patients than non-GER patients, and pericarditis was more frequent in patients who had GER. Pulmonary artery systemic pressure (PASP) was higher in patients with SSc-related GER, but no difference between SSc-related GER and non-GER was observed. The New York Heart Association (NYHA) functional class showed that the cardiac function in patients with SSc-related GER was worse than patients who did not have GER. In addition, there were no differences in mRSS between patients with SSc-related GER and non-GER patients (Table V). Pulmonary function test shows that forced vital capacity (FVC)%, forced expiratory volume (FEV1)%, and diffusing capacity (DLCO)% were lower and the FVC%/DLCO% ratio was higher in SSc-related GER than non-GER patients (Table VI).

The relationship between GER and PAH

Binary logistic regression analysis indicated that GER (OR=7.532) was an independent risk factor of PAH in patients with SSc (p=0.030), with 68.00% sensibility and 59.44% specificity.

Discussion

The major symptoms of SSc-related GER are heartburn and acid reflux, which is the same as GERD. In general, esophageal dysfunction affects 50%–90% of patients with SSc (22-24). Some studies have shown a prevalence of esophageal dysmotility in SSc patients (25-26), but most were asymptomatic. In fact, no clear clinical data have shown GER in SSc patients. The prevalence of GER was 43.90% in our study cohort, which suggests that GER is a common complication of SSc. These data also suggest that GER contributes to gastrointestinal dysfunction and correlates with other gastrointestinal symptoms. No significant correlations were found between gastrointestinal manifestations and gender or age at diagnosis in previous studies (3, 27-28). Our findings were similar to these studies. Moreover, we found no significant correlation between GER and the age of outset or disease duration. Domsic *et al*. reported that patients with dcSSc tend to have more significant visceral organ involvement, and patients with lcSSc are more likely to develop PAH. However, both subsets of patients commonly have gastrointestinal involvement (29). In addition, we found no relationship between SSc-related GER and the five clinical subtypes of SSc, including lcSSc and dcSSc, in our study.

Important features of tissue lesions in stages of scleroderma are microvascular damage, slowly developing fibrosis, and mononuclear-cell infiltrates (1, 30). Endothelial cell abnormalities and the effects on the surrounding microvascu-

Table VI. Comparison of the pulmonary function test between GER and non-GER groups.

	GER	non-GER	*p*-value
TLC (L)	4.18 ± 1.13	4.39 ± 1.05	0.255
TLC%	86.45 ± 17.94	91.32 ± 16.04	0.070
FVC (L)	2.44 ± 0.66	2.62 ± 0.68	0.100
FVC%	78.93 ± 17.90	84.55 ± 17.45	***0.042***
FEV1 (L)	2.79 ± 6.34	4.45 ± 20.35	0.505
FEV1%	77.12 ± 15.65	84.30 ± 16.25	***0.004***
FEV1/FVC (%)	84.32 ± 8.76	84.68 ± 11.94	0.858
FEV1/FVC%	103.46 ± 10.79	110.36 ± 64.59	0.371
DLCO	4.76 ± 1.76	5.63 ± 2.12	***0.009***
DLCO%	56.74 ± 17.42	67.85 ± 18.91	***0.000***
FVC%/DLCO%	1.46 ± 0.42	1.28 ± 0.27	***0.001***
VA (L)	2.14 ± 1.80	2.09 ± 1.34	0.899
VA%	21.60 ± 15.90	33.54 ± 31.45	0.251

lature are the focal points in the pathogenesis of systemic sclerosis disease and may be the early sentinel event for this disorder (31). Patients with SSc display blood vessel morphological changes, including the obliteration of vessels and reduced capillary density, intimal proliferation, and fibrosis (32). Raynauds phenomenon, which reflects involvement of the vascular system in SSc, is usually the earliest clinical sign of the disease. As the disease progresses, complications with vascular involvement can be observed, such as digital ulcers, watermelon stomach, PAH, or renal crisis. In this study, most of these events were more frequent in patients with SSc-related GER than patients without GER, even those with PAH.

Interestingly, SSc-related GER is associated with changes in the cardiovascular system, especially left ventricular function. Only a few reports have explored the relationship between GER and cardiac function. Some studies have shown that 50% of patients with coronary artery disease (CAD) also have abnormal GER (33-34). Cardioesophageal reflex and chronic antianginal medications, especially nitrates and calcium channel blockers, may worsen LES pressure (35-37). Moreover, muscular atrophy may be a common feature shared by esophageal muscle and cardiac muscle, which leads to abnormalities in the esophagus and cardiovascular system, respectively. However, there is currently no evidence to support this hypothesis. Although the main pathophysiological mechanism of the concomitant dysfunction of two thoracic viscera is not clear, these data suggest that SSc-related GER is associated with vascular impairment.

Skin thickening is a universal feature of SSc and is caused by intercellular matrix formation and increased collagen in the dermis (38). In general, there is no relationship between the severity of cutaneous and gastrointestinal manifestations in SSc patients (29). In agreement with previous findings, we also found no difference in mRSS between GER and non-GER SSc patients.

Scleroderma is associated with the production of several autoantibodies, some of which are important diagnostic markers. Tests for autoantibodies against topoisomerase I (Scl-70), centromere-associated proteins, and nucleolar antigens can be useful in facilitating the diagnosis and formulating a prognosis (1). Using esophageal high-resolution manometry (HRM), Roman found that anti-Scl70 antibodies were more frequently positive in patients with impaired esophageal body motility, and patients with positive ACA had normal esophageal body motility (4). However, we did not find a relationship between any of these autoantibodies and SSc-related GER, as defined on the basis of symptoms.

The pathophysiology of SSc can be summarised as being based on imbalances in the cellular and humoral immune system, vascular dysfunction, and activation of resident connective tissue cells (39). Our results suggest that SSc-related GER is associated with microvascular damage, but not tissue fibrosis and dysfunction of the immune system. Roberts *et al*. showed that the major pathology of esophageal diseases in SSc is loss of smooth muscle with no evidence of tissue fibrosis or increased collagen deposition. In addition, vascular intimal proliferation is more frequently observed in the esophagus of SSc-related GER patients than in patients without GER (40).

Recently, some reports have shown a relationship between GER and pulmonary impairment in SSc (5, 41-42). In our study, GER was associated with PAH in SSc patients, but was not associated with ILD. In addition, asthma was not observed in GER or non-GER SSc patients. Moreover, we found several characteristics of SSc-related GER that conformed to PAH, such as NYHA functional class, pulmonary function test, and 6MWD, all of which involve vascular impairment that is accompanied by symptoms such as Raynauds phenomenon and digital ulcers. The FVC% is believed to physiologically correlate with the extent of fibrosis and is commonly used to define the severity of fibrosis and to follow patients with ILD (43). Low DLCO is an important risk factor in the development of PAH (44), and an increased FVC%/DLCO% ratio has been used to predict and assess PAH in SSc patients (19, 45-46). Our results also showed that the FVC%/DLCO% ratio is higher in patients with SSc-related GER, which is in agreement with our finding that GER is associated with PAH but not ILD in SSc patients. Furthermore, we confirmed that GER is indeed an independent risk factor of PAH in SSc. Early symptoms of PAH are rarely observed and the prognosis of PAH is very poor. Symptoms of GER predict vascular dysfunction and should indicate the need for PAH screening in SSc patients, which will ultimately improve PAH diagnosis in these patients.

Clinical experts agree with the EULAR/EUSTAR recommendation of proton pump inhibitors (PPIs) for the management of SSc-related GER (47), which is the same recommendation as GERD but does not treat the underlying cause of disease. PPIs are effective in the control of the reflux symptoms of SSc (48), but there is no evidence that this treatment can alleviate reflux symptoms over a long period of time or

prevent the progression of GER (49). Therefore, further investigation is required to determine whether treating the underlying vascular dysfunction can alleviate and prevent GER in SSc patients.

In conclusion, this is the first report to determine the prevalence of GER in Chinese patients with SSc. Our study has demonstrated that GER frequently occurs in SSc patients, and these patients are susceptible to microvascular damage. Importantly, we found that GER is a major independent risk factor of PAH in SSc patients. Therefore, future studies should determine whether GER can predict PAH within a cohort study, and whether targeting the underlying vascular dysfunction can prevent not only PAH, but also GER in SSc patients.

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