GERD questionnaire for diagnosis of gastroesophageal reflux disease in systemic sclerosis

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ABSTRACT

Objective. *Gastroesophageal reflux disease (GERD) is clinically-identified in patients with systemic sclerosis (SSc). The GERD-questionnaire (GERD-Q) score is a sensitive, non-invasive, diagnostic screening tool for diagnosis of GERD in general patients, but it has been not investigated for use in SSc.*
Our aim was to evaluate the proper cut-off GERD-Q score, sensitivity and specificity for a diagnosis of GERD in SSc patients.

Method. *A cross-sectional study using the GERD-Q was performed during May 2012–January 2013 on patients over 18 with the diffuse SSc subset. Both esophago-gastro-duodenoscopy (EGD) and 24-hr pH-monitoring (24hr-pH) were performed as the gold standard tests for both symptomatic and asymptomatic GERD.*

Results. *A total of 75 SSc patients completed the GERD-Q, EGD and 24hr-pH. We identified 22 males (29.3%), 53 females (70.7%) with a mean age of 54.2 years. The respective number of symptomatic and asymptomatic GERD was 69 and 6 cases. For a GERD diagnosis, a cut-off GERD-Q score of 4 provided the best balance between sensitivity and specificity (96.9% and 50%, respectively). Of 48 participants (69.6%) with symptomatic GERD (i.e. positive for both EGD and 24hr-pH), 65 (94.2%) were positive for either EGD or 24hr-pH, and 4 (5.8%) were negative for both EGD and 24hr-pH. A respective majority (83%) vs. one-third of the asymptomatic group had reflux as detected by 24hr-pH vs. EGD.*

Conclusion. *A GERD-Q score of 4 or higher indicates a high sensitivity for a diagnosis of GERD in SSc. It can thus be used as a non-invasive screening tool for diagnosing GERD in cases where EGD and 24hr-pH are unavailable.*

Introduction

Systemic sclerosis (SSc) is a chronic multi-system disorder of unknown etiology. SSc is characterised by thickening of the skin (scleroderma) and distinctive involvement of multiple internal organs; most notably the lungs, gastrointestinal tract, heart, and kidneys (1). The definite initiating mechanisms are not fully understood and remain controversial. Discussions on the development of SSc include: a) infection-caused stimuli (*e.g.* cytomegalovirus, Epstein-Barr virus or parovirus B19); b) environmental factors (*i.e.* exposure to silica or to organic solvents); and, c) genotypic modalities (*i.e.* comparing certain susceptibility constellations) (1).

The gastrointestinal tract is one of the most commonly involved sites and oesophageal involvement occurs in 75-90% of patients (2, 3). Gastroesophageal reflux disease (GERD) is a common oesophageal involvement in SSc. The prevalence of GERD in Asian is reported around 6-47% (4-6). Oesophageal damage is prominent in its distal two-thirds. Histologic examination of oesophageal tissue reveals that the replacement of normal smooth muscle by collagenous fibrosis and smooth muscle atrophy, leads to abnormalities in motor activity (3). Patients with SSc, moreover, cannot undergo invasive procedures (even minor ones) due to potential associated complications and their anatomical disease-affected structures (*i.e.* narrowing of the oral orifice and pulmonary involvement). There have been various studies on SSc patients (3, 7, 8) such as GIT 2.0 reflux and distention/bloating (D/B) scales which were applied for evaluating upper gastrointestinal tract involvement in SSc but it has very low specificity (0–20%) for assessment (9). Recently, there is a limited research on the GERD questionnaire

(GERD-Q), particularly vis-à-vis clinical symptoms for identifying the correlation between clinical scoring and the gold standard (Esophago-Gastro-Duodenoscopy; EGD and 24-hr impedance pH monitoring) for diagnosis of GERD in SSc patients. Our study aimed to evaluate the proper cut-off score of GERD-Q; its sensitivity and specificity for diagnosis of GERD in SSc patients.

Material and method

A cross-sectional study using the GERD-Q for SSc patients over 18 with the diffuse subset was performed between May 2012 and January 2013. Seventy-five patients were enrolled, both those symptomatic and asymptomatic for upper gastrointestinal tract. None of the enrolled patients was (at the time) taking proton pump inhibitors or histamine receptor antagonists 2 weeks prior to study. We excluded patients who had: a) an overlap with other connective tissue disease; b) limitation and/or at high risk for EGD (*i.e.* patients with severe cardiopulmonary disease, patients with too small oral orifice unable to secure mouth guard during endoscopic procedure); and, c) being pregnant and/or lactating

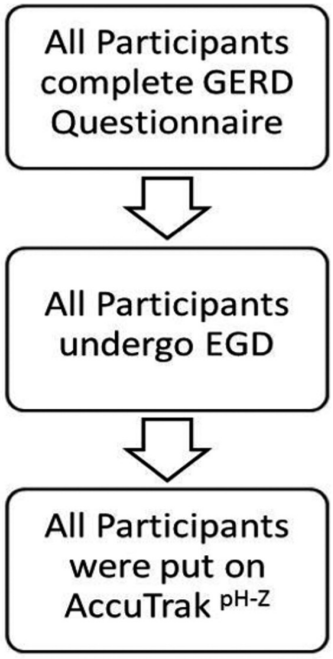

Fig. 1. Evaluation steps.
GERD gastroesophageal reflux disease, EGD oesophagogastroduodenoscope.

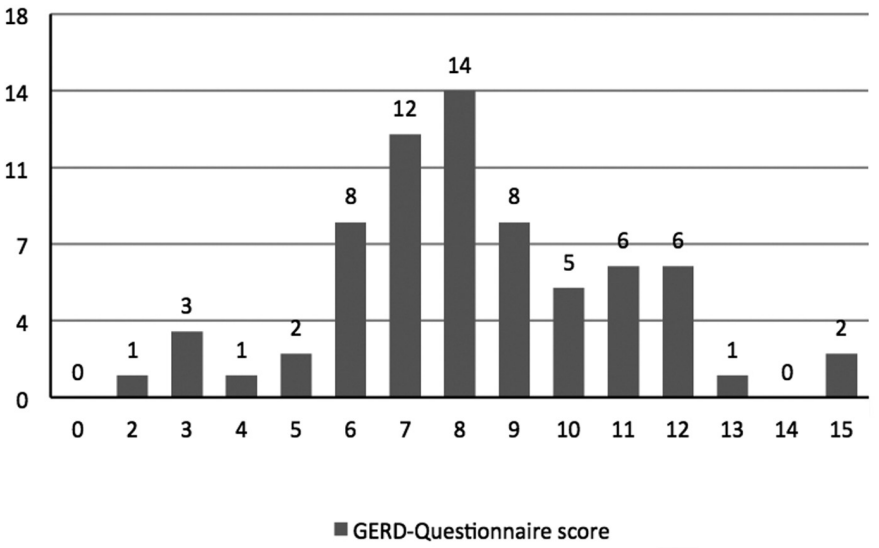

Fig. 2. Distribution of GERD-Q scoring.

All participants completed the GERD-Q first then underwent EGD and finally the patients were put on AccuTrac^{pH-Z} 24-hr ambulatory impedance pH monitoring (Fig. 1).

GERD questionnaires

The GERD-Q was originally derived from an exploratory analyses, based on the Diamond Study (10, 11) and was self-evaluated by the patients.

Esophagogastroduodenoscopy (EGD)

EGD was performed on all participants prior to 24-hr impedance pH monitoring. EGD results and oesophagitis grading were a consensus of 2 of 3 endoscopists. Oesophagitis was graded in accordance with the Los Angeles Classifications (LA classification).

24-hr impedance pH monitoring

AccuTrac^{pH-Z} 24-hr ambulatory impedance pH monitoring was applied to all participants for 24 hours while allowing participants to continue their usual activities.

Symptomatic GERD is defined when the patient complaints of heart burn and/or regurgitation. Diagnosis of GERD was based on findings of one or more of the following (10, 12-14): a) A classification grading A-D oesophagitis at endoscopy; b) DeMeester Score >14.72; c) Normalised Reflux Episode Activity >95 percentile; and, d) a Reflux Symptom Association Probability >95%.

The data were analysed using STATA version 11.2 (StataCorp., College Station, TX, USA). The continuous data were presented as means ± SD while the categorical data were presented as numbers and percentages. The ROC curve was run and the sensitivity and specificity were calculated. All statistical tests were two-tailed. A p-value of <0.05 was considered statistically significant.

The study was designed by the authors and approved by the Human Research Ethics Committee at Khon Kaen University as per the Helsinki Declaration and the Good Clinical Practice Guidelines (HE541391). All the patients signed informed consent before being enrolled in the study.

Result

A total of 75 eligible SSc participants were enrolled: 22 males (29.3%) and 53 females (70.7%). The mean age was 54.2±9.8 years (range, 31–80). The median duration of disease at the time of the study was 5 years (IQR 2-6). Half of the participants had disease duration of <5 years. The mean BMI was 21.1±3.7 kg/m^2.

The average score from the GERD-Q was 13±2.7 (range, 2–15). The distribution of the total score is presented in Figure 2.

Oesophagitis from the EGD exam (LA classification A-D) was present in almost 80% of those symptomatic

Table I. A comparison of endoscopic findings and results of the 24-hr impedance pH monitoring between asymptomatic and symptomatic GERD patients.

Findings	Asymptomatic GERD n= 6	Symptomatic GERD n=69
Endoscopic findings		
Oesophagitis	2 (33.3%)	55 (79.7%)
LA class A	0	11
LA class B	2	27
LA class C	0	14
LA class D	0	4
No oesophagitis	4 (66.7%)	14 (20.3%)
24-hr impedance pH monitoring		
Positive pH monitoring	5 (83.3%)	58 (84.1%)
Negative pH monitoring	1 (16.7%)	11 (15.9%)

GERD: gastroesophageal reflux disease.

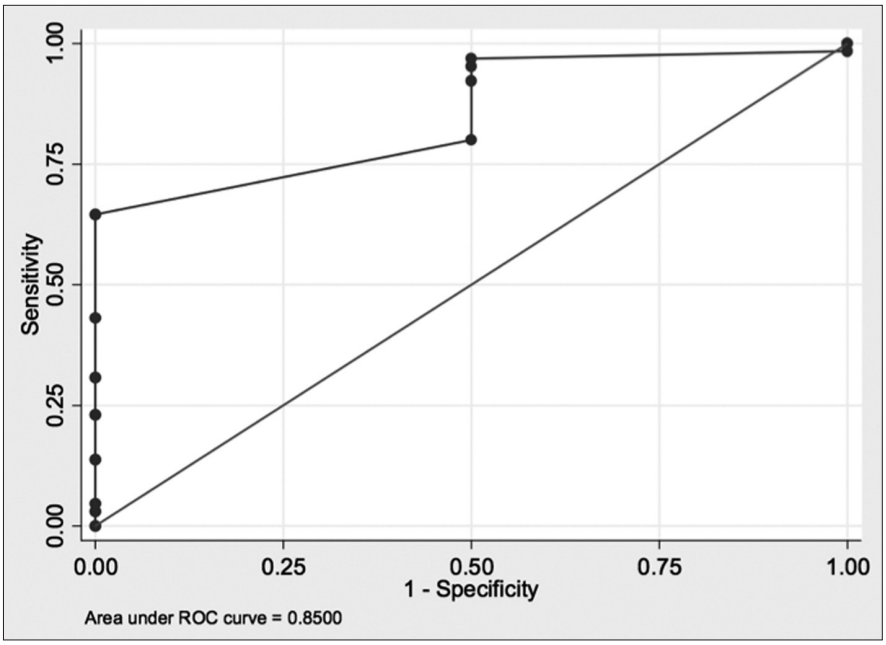

Fig. 3. ROC Curve.

for GERD and in one-third of those asymptomatic for GERD. The positive 24-hr impedance pH monitoring was equally present in both groups (Table I). The details of oesophagitis grading and 24-hr impedance pH monitoring of asymptomatic and symptomatic GERD patients are presented in Table I.

Forty-eight (69.6%) of patients with symptomatic GERD were positive for both EGD and 24-hr pH monitoring, while 65 (94.2%) were positive for either EGD or 24-hr pH monitoring, and 4 (5.8%) were negative for both EGD and 24-hr pH monitoring. By comparison, 2 participants (33.3%) with asymptomatic GERD were positive for both EGD and 24-hr pH monitoring, 5 (83.3%) were positive for either EGD or pH monitoring and only 1 (16.7%) had negative result for both.

Scoring data were analysed to test for any correlation between GERD-Q scoring and the gold standard test for GERD by EGD and/or 24-hr pH monitoring. According to the rationale for using the GERD-Q (*i.e.* to test persons with symptomatic GERD), 6 asymptomatic participants were excluded. After evaluating the ROC curve (Fig. 3), the respective sensitivity and specificity of GERD-Q for diagnosis of GERD was inferred (Table II). A GERD-Q score of 4 had a sensitivity of 96.9% (95%CI 89.3–99.6), specificity of 50.0% (95%CI 6.8–93.2), positive predictive value (PPV) of 96.9% (95%CI 89.3–99.6) and negative predictive value (NPV) of 50.0% (95%CI 6.8–93.2). A respective specificity, sensitivity, PPV and NPV of 100% (95%CI 39.8-100.0), 64.6% (95%CI 51.8–76.1), 100% (95%CI 91.6–100) and 14.8% (95%CI 4.2–33.7) was achieved when the score was ≥8.

Discussion

GERD-Q was developed as an exploratory part of the Diamond Study in which the upper gastrointestinal symptoms correlated with several objective markers of GERD (10, 11, 15). A cut-off GERD-Q score of 8 yielded a sensitivity of 65% and a specificity of 71% for symptoms defining GERD vs. an investigational-based diagnosis of the same. More recently, validation of the GERD-Q for diagnosis of GERD in a primary care setting showed that a cut-off score of 9 gave the best balance with regard to sensitivity (65%; 95% CI:58–74) and specificity (64%; 95% CI:41–83) for GERD. Those 2 studies, however, were conducted among non-SSc patients (11).

In SSc, oesophageal involvements are common (2, 3). The prevalence of SSc in Northeastern Thailand is 1 per 100,000; peak age between 40-50 years with a female to male ratio of 2:1 (16, 17). Organ involvements were reported among Thai SSc sufferers in 1991: musculoskeletal was the most common extracutaneous involvement (69.6%), followed by gastrointestinal (54.3%), and respiratory system (43.3%). Of the gastrointestinal involvements, manifestations included dysphagia (32.6%), retrosternal burning pain (6.5%) and diarrhea (15.2%) (4).

The investigation of choice for evaluating oesophageal involvement is oesophagoscope and/or oesophagomanometry. Most patients, however, are unable to undergo this relatively invasive procedure due to a) their anatomical structures (*i.e.* narrowing of oral orifice) and b) complications of their disease (*e.g.* restrictive lung disease). We, therefore, determined to establish a non-invasive tool to aid in diagnosis of GERD in order to provide appropriate care to this group of patients.

Table II. Cut-off value of each GERD-Q score and detailed report of sensitivity and specificity.

Cut-off	Sensitivity (%)	Specificity (%)	Correctly classified (%)	LR+	LR-
≥ 2	100	0.00	94.20	1.0000	
≥ 3	98.46	0.00	92.75	0.9846	
≥ 4	96.92	50.00	94.20	1.9385	0.0615
≥ 5	95.38	50.00	92.75	1.9077	0.0923
≥ 6	92.31	50.00	89.86	1.8462	0.1538
≥ 7	80.00	50.00	78.26	1.6000	0.4000
≥ 8	64.62	100.00	66.67		0.3538
≥ 9	43.08	100.00	46.38		0.5692
≥ 10	30.77	100.00	34.78		0.6923
≥ 11	23.08	100.00	27.54		0.6923
≥ 12	13.85	100.00	18.84		0.8615
≥ 13	4.62	100.00	10.14		0.9538
≥ 15	3.08	100.00	8.70		0.9692

LR+ likelihood ratio positive; LR- likelihood ratio negative.

Our study demonstrated that the GERD-Q can be used as a screening tool for diagnosis of GERD. A cut-off score of 4 gave us the highest balance between sensitivity and specificity (96.9% and 50%, respectively). Moreover, 100% specificity was achieved for diagnosis of GERD when the score was 8 or more. This finding will be of value to non-gastroenterologists (particularly caregivers of patients with SSc) for making a clear diagnosis of GERD, and planning appropriate care.

More interestingly, in the asymptomatic group of participants, there were 2 participants (33.3%) positive for both EGD and 24-hr pH monitoring, 5 participants (83.3%) positive for either EGD or 24 hr pH monitoring and 1 participant (16.7%) yielded negative result for both tests. Although the number of participants is small, the results provide important trending data. We infer that despite being asymptomatic, significant numbers of patients can have GERD without clinical complaint. This result also suggests that GERD is even more common in SSc patients than we expected. Although the current data do not support treatment in this group, this new information reveals a high incidence of oesophageal involvement among SSc patients; such that once a clinical complaint occurs, a diagnosis is appropriate and appropriate treatment should be provided.

The lower cut-off GERD-Q Score in this population may be explained by the disease itself, which frequently causes reflux disease. Acid is only one component that leads to development of GERD. The pathogenesis of GERD is complex, resulting from an imbalance between defensive factors protecting the oesophagus (*i.e.* anti-reflux barriers, oesophageal acid clearance, tissue resistance) and aggressive factors refluxing from the stomach (*i.e.* gastric acidity, volume, and duodenal contents) (18). These factors among individuals will vary and this possibly contributed to the variation in the clinical presentations we observed.

There were some limitations to our study. First, we included only the diffuse SSc subset, so we cannot provide data regarding the limited SSc subset. Second, there was a limitation of data analysis owing to the small number of participants. Third, the content validity has not yet been determined for GERD-Q and there is lack of sensitivity of change. Notwithstanding, our study included asymptomatic SSc patients and pioneered the use of a non-invasive tool for diagnosis of GERD in SSc patients. The findings provide interesting data potentially leading to better patient care.

Conclusion

The current study demonstrated that a cut-off score of 4 on the GERD-Q for symptomatic patients provides the best balance of sensitivity and specificity (96.92% and 50%, respectively). In the asymptomatic group, there was a high incidence of reflux which exceeded our expectations.

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