



# Transabdominal ultrasound elastography of the esophagogastric junction predicts reflux esophagitis

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## Abstract

**Purpose** Abdominal ultrasound (US) can visualize the esophagogastric junction (EGJ) as a hyperechoic area in the dorsal portion of the lateral segment of the liver. We prospectively evaluated the EGJ using US elastography (US-EG) in patients with reflux esophagitis (RE) to examine prediction of distal esophageal function.

**Methods** Of 108 patients undergoing US-EG and esophagogastroduodenoscopy, 102 in whom the EGJ was observed for  $\geq 15$  s were included. The subjects were divided into a RE group ( $n = 41$ , Grade M/A/B:24/13/4 according to modified Los Angeles Classification) and a non-RE group ( $n = 61$ ). Direct strain elastography (LOGIQ E9, GE Healthcare), which gives a semi-quantitative elasticity index within a region of interest including the lateral segment, was used as a standard for measurement of the change in stiffness (CS) at the EGJ.

**Results** The number of CS as determined by US-EG was 6.0 (5.5–6.7) in the RE group and 8.6 (6.6–10.0) in the non-RE group ( $P < 0.0001$ ). In ROC analysis, the AUC was 0.8415 for diagnosis of RE using the number of CS. At a cut-off of 7.7, the sensitivity, specificity, and accuracy for diagnosis were 92.7, 65.6, and 74.5%, respectively.

**Conclusion** The presence of RE can be predicted based on US-EG.

**Keywords** Reflux esophagitis · Transabdominal-ultrasound · Elastography

## Introduction

The prevalence of gastroesophageal reflux disease (GERD) has increased in Asian countries, including Japan, as in Western countries [1], and is now common in routine practice. The major pathology of GERD is reflux of gastric acid contents into the esophagus, which may be caused by breakdown of antireflux defense mechanisms in the esophagogastric junction (EGJ). Esophageal motility is correlated with the severity of reflux esophagitis (RE) [2], which suggests that esophageal motility dysfunction might cause this breakdown.

GERD is classified into RE with endoscopic findings and non-erosive reflux esophagitis (NERD) without endoscopic findings [3, 4]. In turn, RE is classified into symptomatic and asymptomatic types. Endoscopic evaluation of the EGJ for diagnosis of GERD focuses on the presence or absence of RE, hiatal hernia, and Barrett epithelium, and diagnosis of Barrett adenocarcinoma, but this approach is not physiological and does not include evaluation of esophageal motility. Esophageal manometry can be used to evaluate esophageal motility, but the measurement is complicated and invasive, which limits its use to only a small number of specialized centers. In contrast, transabdominal ultrasound is a simple and noninvasive technique that has been widely used in various fields, including recent studies showing its utility in treatment of digestive diseases [5–7]. Furthermore, combination of transabdominal ultrasound with elastography, which can estimate the stiffness of a target, may be useful to diagnose tumors in the mammary gland [8], thyroid [9], and abdominal organs [10, 11], and to quantify even skeletal muscle stiffness [12].

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Observation of the EGJ using noninvasive transabdominal ultrasound elastography (US-EG) may be clinically useful if esophageal motility can be estimated indirectly. Against this backdrop, a prospective study was designed to investigate whether US-EG can predict RE (symptomatic or asymptomatic) and non-RE as the primary endpoint, and to analyze relationships between factors that may influence esophageal motility and US-EG findings as the secondary endpoint.

## Materials and methods

### Subjects

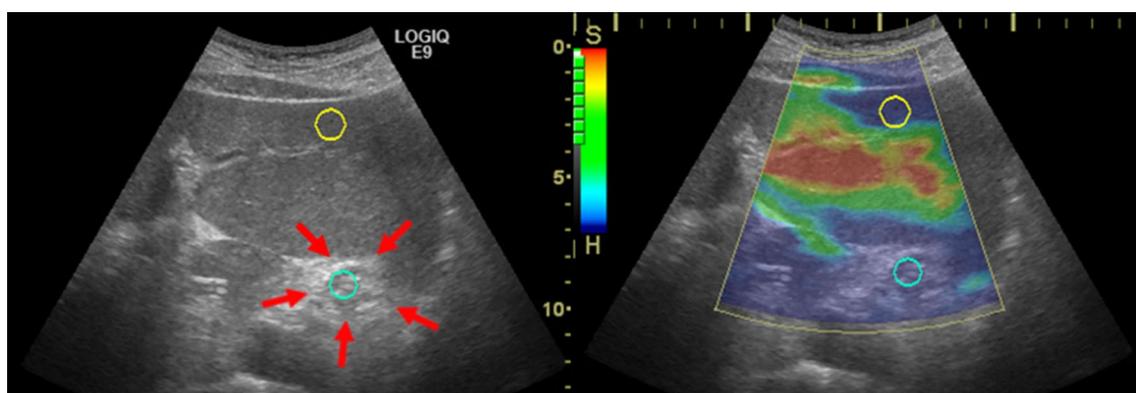
The subjects were patients aged  $\geq 18$  years old who underwent esophagogastroduodenoscopy (EGD) and US. Exclusion criteria included patients who could not hold their breath for  $\geq 15$  s, could not maintain a supine position, had serious complications including chronic liver diseases (NASH, viral hepatitis), which had the possibility of liver fibrosis and malignant tumor, or had a severe psychiatric disorder based on clinical information. Of 108 patients undergoing US-EG and EGD, 102 in whom the EGJ was observed for  $\geq 15$  s were included in this study. US was performed in subjects who fasted from 9 p.m. on the previous day and did not take medicine in the morning. US was performed first, followed by EGD. In addition to routine tests, a continuous transverse epigastric scan was performed for  $\geq 15$  s with deep inspiration. The subjects were divided into RE and non-RE groups based on the modified Los Angeles Classification [13], in which Grade N is defined as normal mucosa; Grade M as minimal changes to the mucosa, such as erythema and/or whitish turbidity; Grades A and B as non-confluent mucosal breaks of no longer than 5 mm and more than 5 mm, respectively; and Grades C and D as less

than 75% and at least 75% circumferential mucosal breaks, respectively. Grade N subjects were defined as the non-RE group ( $n=61$ ), and all others comprised the RE group ( $n=41$ , Grade M/A/B:24/13/4 cases).

The study was approved by the institutional review board of our hospital and was registered in UMIN-CTR (UMIN000016143) prior to commencement. All subjects provided written informed consent to study participation.

### Strain elastography

Real-time elastographic examinations of direct strain elastography with pressure by cardiovascular pulsation were performed with a 5-MHz convex-type probe (C1–5) on a LOGIQ E9 (GE Healthcare, USA) by a radiologist specialized in abdominal sonography. The radiologist who performed the strain measurements was blinded to other clinical information and the results of EGD. Although the color parameter in elastography is a relative value, blue indicates hard and red indicates soft. On B-mode image, hyperechoic areas continuous from the stomach on the dorsal side of the liver were defined as the EGJ. In our study, EGJ means the thickened wall of the lower esophagus. After fitting the semi-quantitative strain elastography image box to fully cover the EGJ and lateral segment of the liver, the examiner kept the same area of the lesion in the field of view and stored the data for  $\geq 15$  s. We set a region of interest (ROI) in the EGJ (Fig. 1). To reduce the influence of the measurement, we set a standard ROI in the liver free of vessels as a stable control. The size of the ROI at the EGJ was made as large as possible, and strain values of tissues were measured by setting equal- or near equal-sized ROI in the EGJ and liver. Semi-quantitative strain values with color change were defined as a change over time in the stiffness of the EGJ in our study. The change in stiffness (CS) of the EGJ for  $\geq 15$  s



**Fig. 1** Transverse epigastric scan of the hepatic left lobe and EGJ. B-mode image of the lateral segment of the liver with the EGJ (red arrows) on the dorsal side. Elastography image. Blue circle: region of interest (ROI) of the EGJ; yellow circle: ROI of the lateral segment of

the liver. These were defined as standard ROIs because the EGJ and lateral segment of the liver were visible on the same screen and stiffness of the liver was stable

was determined based on stored data. The number of CS as determined by US-EG was calculated using Qanalysis (GE Healthcare), a built-in software that produces a stiffness information graph for the ROI.

In Fig. 2, the upper row shows the relative values of the EGJ and liver, and the standard ROI, and the lower row shows the relative value ratio. We measured the number of CS in the EGJ, and the graph shows this number with the liver defined as one. Each patient had different breath-hold times at deep inspiration; therefore, data were normalized to CS numbers over a period of 30 s. CS is influenced by factors such as pulsation and peristaltic motion of the surrounding gastrointestinal tract. Even when there was no peristaltic motion, there were small changes in stiffness. Observations were made in B mode and 0.2 was used as a threshold change, even in a state without factors other than peristaltic motion. A value less than 0.2 was not counted in our study. EGD was performed by one endoscopist specialized in upper gastrointestinal endoscopy. In EGD, in addition to upper gastrointestinal screening, EGJ assessment of conditions such as esophageal hiatus hernia and reflux esophagitis and the presence or absence of chronic gastritis and Barrett esophagus was performed. The correlation of the number of CS as determined by US-EG was evaluated with clinical information and endoscopic findings.

**Statistical analysis**

Continuous variables are expressed as the median (range or interquartile range) where indicated. A Kruskal–Wallis test and a Mann–Whitney *U* test were used for continuous variables. A Chi square test was used for categorical variables. Spearman’s correlation coefficients of the number of CS were calculated for intraobserver agreement. A receiver operating characteristic (ROC) curve was generated and the

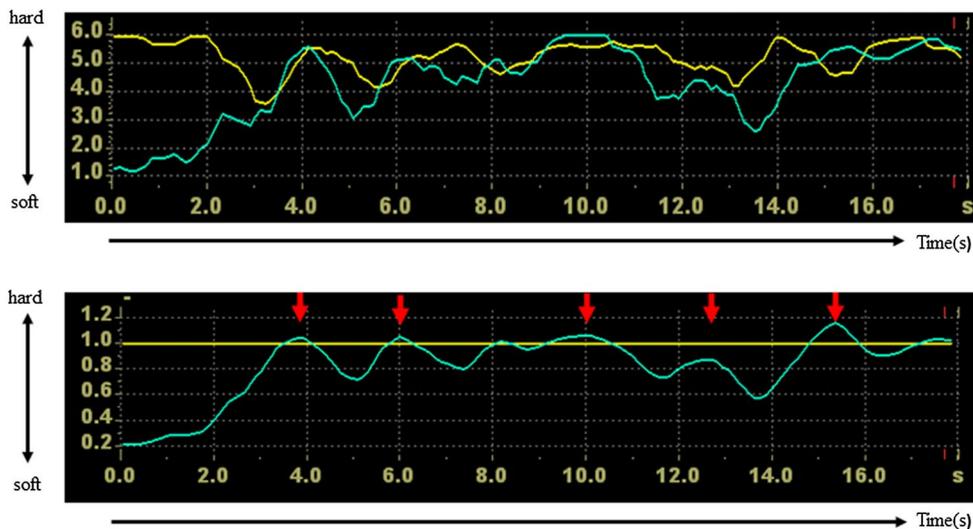
area under the curve (AUC) was calculated to determine the cut-off value for the number of CS as determined by US-EG for RE diagnostic ability. Low, moderate, and high accuracy were defined as AUC=0.5–0.7, 0.7–0.9, and 0.9–1.0, respectively. Cut-off values were determined to maximize the Youden index (sensitivity + specificity – 1). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for these cut-off values. SPSS ver. 22.0 (SPSS, Chicago, IL, USA) was used for all analyses. All tests were two-tailed, and *P* < 0.05 was considered to be significant.

Single and multiple regression analyses were used for univariate and multivariate analyses of factors related to the number of CS as determined by US-EG. These analyses were performed to evaluate relationships between the number of CS and factors that may influence esophageal motility: age (≥ 65 years old), gender, BMI (≥ 25 kg/m<sup>2</sup>), diabetes, use of a proton pump inhibitor (PPI), upper abdominal symptoms, presence or absence of RE, hiatal hernia, short segment Barrett esophagus (SSBE), and chronic gastritis.

**Results**

A total of 108 patients were registered between July 2011 and May 2015. Of these patients, CS was measurable by US-EG in 102 (52 females and 50 males, median age: 66 years old). Six patients were excluded from the study because they could not hold their breath for > 15 s (*n* = 2), had a large hepatic cyst (*n* = 1) or hepatic tumor (*n* = 1), or the EGJ could not be visualized due to severe obesity (*n* = 2). The patients were classified into a RE group (*n* = 41, 16 males, median age 68 years old) and a non-RE group (*n* = 61, 34 males, median age 64 years old) based on endoscopic findings. There were no significant differences in background

**Fig. 2** Sequential display of the change in stiffness (CS) in the yellow and blue regions of interest (ROIs) and measurement of the number of CS by transabdominal ultrasound elastography (US-EG). Smaller changes (<0.2) during measurement were excluded from the analysis. In this case, five (red arrows) in 18 s were defined as 8.3 over 30 s



characteristics between the two groups (Table 1). In all patients, CS was calculated two times, and Spearman's correlation coefficient ( $r_s$ ) was 0.8891 ( $P < 0.0001$ ). Spearman's correlation coefficient ( $r_s$ ) with  $> 0.8$  relating to the number of CS was considered to indicate very good intraobserver agreement.

GERD symptoms were present in 13 subjects in the RE group and 12 in the non-RE group, and eight subjects in each group were taking PPIs. The number of CS as determined by US-EG in 30 s was significantly lower in the RE group as compared with the non-RE group [6.0 (5.5–6.7) vs. 8.6 (6.6–10.0),  $P < 0.0001$ , Fig. 3]. In the RE group, there were no significant differences in the number of CS as determined by US-EG among Grades (Fig. 4): the numbers in patients with Grades M, A, and B were 6.0 (5.4–6.8), 6.0 (5.6–7.0) and 5.5 (5.0–6.1), respectively. In univariate analysis, age ( $P = 0.0314$ ) and presence or absence of RE ( $P < 0.0001$ ) were identified as factors that were significantly related to the number of CS as determined by US-EG. In multivariate analysis with addition of parameters with  $P < 0.2$  [diabetes ( $P = 0.1854$ ) and use of PPIs ( $P = 0.1542$ )], only presence or absence of RE was significant ( $P < 0.0001$ ) (Table 2). The AUC was calculated to examine the RE diagnostic ability using the number of CS as determined by US-EG. A good AUC of 0.8415 was obtained. At a cut-off of 7.7, the sensitivity, specificity, and accuracy for diagnosis were 92.7, 65.6, and 74.5%, respectively (Fig. 5).

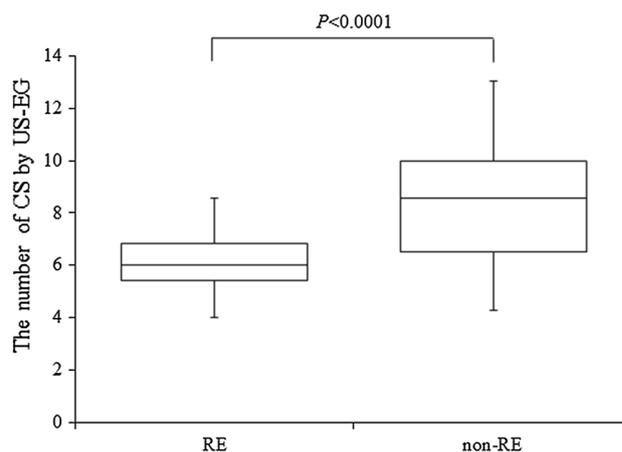
## Discussion

GERD is caused by frequent acid reflux or retention in the lower esophagus. The EGJ plays an important role in prevention of reflux, and the lower esophageal sphincter (LES) and crura of the diaphragm are responsible for prevention of acid reflux in the EGJ [14]. The EGJ pressure is varied by contraction of the LES and crura of the diaphragm, and GERD is caused by abnormal peristalsis of the LES and dysfunction of the crura [15–17].

**Table 1** Characteristics of patients with and without reflux esophagitis (RE)

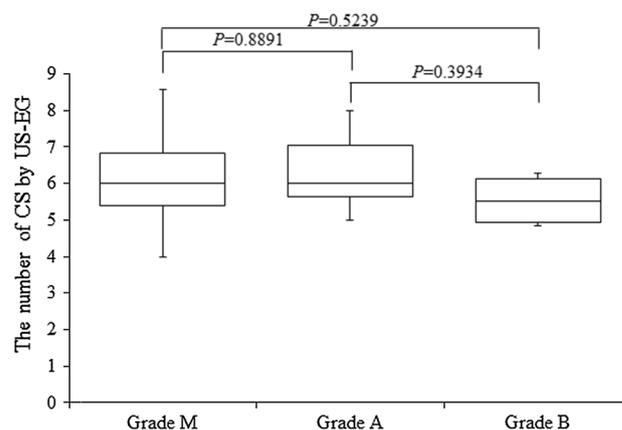
Item	RE group ( $n = 41$ )	Non-RE group ( $n = 61$ )	$P$
Age (years)	68 (35–87)	64 (30–84)	0.0828
Gender (M:F)	16:25	34:27	0.0978
Height (cm)	158.5 (140–184)	161.6 (138.2–179.0)	0.1909
Weight (kg)	56.0 (41.0–92.0)	55.8 (38.0–90.0)	0.7246
Body mass index (%)	21.7 (17.4–32.9)	21.6 (15.2–28.5)	0.9224

Data are shown as median (range)



**Fig. 3** Comparison of the number of the change in stiffness (CS) by transabdominal ultrasound elastography (US-EG) in the reflux esophagitis (RE) and non-RE groups. The numbers of CS normalized to a period of 30 s in the RE and non-RE groups were 6.0 (5.5–6.7) and 8.6 (6.6–10.0), respectively, with a significantly lower number in the RE group

Furthermore, esophagus peristalsis has two types, i.e., primary peristaltic waves that are initiated by swallowing and secondary peristaltic waves that result from distention of the esophagus [18]. Secondary peristalsis is a reflexive movement initiated by distension of the esophageal wall, which may induce gastric content reflux into the esophagus [19]. In patients with GERD, the time from onset of reflux to the start of secondary peristaltic movement is prolonged and secondary peristaltic contraction waves are decreased, which results in exacerbation of esophageal acid exposure [20]. Esophageal tension also plays an important role in preventing reflux [21]. When both the esophagus and the EGJ were in the same image, all observed CS at the esophagus

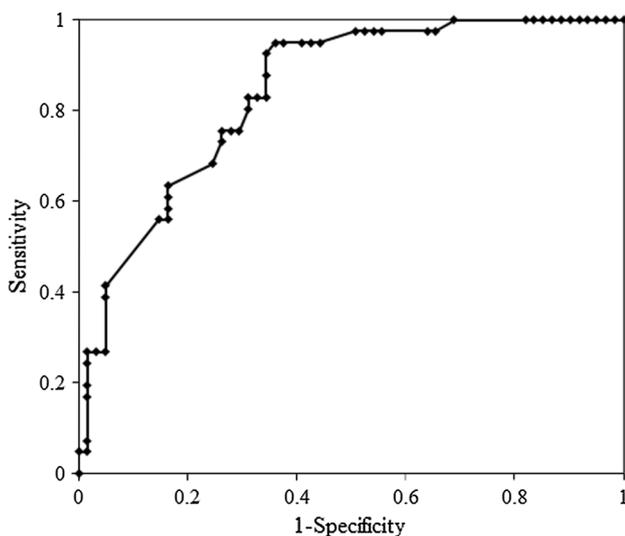


**Fig. 4** Comparison of the number of the change in stiffness (CS) by reflux esophagitis (RE) Grade. There were no significant differences in the number of CS by Grade: the numbers for Grades M, A, and B were 6.0 (5.4–6.8), 6.0 (5.6–7.0), and 5.5 (5.0–6.1), respectively

**Table 2** Univariate and multivariate analyses of factors related to number of CS by US-EG

Item	Median number of CS by US-EG		Univariate <i>P</i>	Multivariate	
				95% CI	<i>P</i>
Age (< 65: ≥ 65 55:47)	6.7	7.6	0.0314	− 1.1829 to 0.2222	0.1780
Gender (M:F 50:52)	6.6	7.6	0.4549		
Body mass index (≤ 25: > 25 16:86)	6.4	7.0	0.6417		
Diabetes mellitus (+ : − 18:84)	6.3	7.4	0.1854	− 1.3741 to 0.4625	0.3270
Proton pump inhibitor (+ : − 16:84)	6.4	7.0	0.1542	− 1.5301 to 0.3870	0.2395
Symptoms of upper abdomen (+ : − 25:77)	6.4	7.3	0.2127		
Reflux esophagitis (+ : − 41:61)	6.0	8.6	< 0.0001	− 2.9761 to 1.5504	< 0.0001
Hiatal hernia (+ : − 17:85)	7.0	7.0	0.5590		
Short segment Barrett esophagus (+ : − 10:92)	6.9	7.0	0.4647		
Chronic gastritis (+ : − 57:45)	6.6	7.5	0.2281		

CS the change in stiffness, US-EG transabdominal ultrasound elastography



**Fig. 5** Diagnosis of reflux esophagitis (RE) using the number of the change in stiffness (CS) as determined by transabdominal ultrasound elastography (US-EG). The area under the curve (AUC) was 0.8415. At a cut-off of 7.7, the sensitivity, specificity, and accuracy of diagnosis were 92.7, 65.6, and 74.5%, respectively

near the EGJ were less than 0.2. In the present study, we set the threshold at 0.2 over 15 s, because we could not rule out the possibility other than peristaltic movement for less than 0.2 in our experience in this study.

The common causes of onset of GERD symptoms are gastric and bile acid secretion, hiatal hernia, LES dysfunction, esophageal peristaltic dysfunction, and esophageal hypersensitivity [22]. This study focused on the EGJ alone, but many factors are related to GERD symptoms. Therefore, there were no significant differences in the number of CS as determined by US-EG in patients with and without GERD symptoms. In contrast, the number of CS as determined by US-EG was significantly lower in

patients with RE based on endoscopic findings, compared with non-RE patients. Esophageal motility decreases with age [23], and GERD is common in the elderly [24], but there was no effect of age on the number of CS observed in our multivariate analysis. From the standpoint of physical interpretation of what is observed here, the number of CS is small in the case of reflux esophagitis, which is considered to be dysfunction of the EGJ. Esophageal reflux was thought to be related to reduced number of CS in RE cases. CS shows the relative change in stiffness of our defined EGJ with reference to the liver, which shows less change in stiffness, and therefore a high CS means normal movements of the EGJ.

Severity assessment in GERD and diagnosis by exclusion of other disorders should be based on endoscopic screening, but this is only occasionally performed because endoscopy is invasive. Some cases are diagnosed based on subjective symptoms alone [25]. However, the treatment outcome varies markedly between RE and NERD, and EGD should be performed if GERD is suspected. The sensitivity and accuracy of diagnosis of RE based on the number of CS as determined by US-EG were 92.7 and 75.4%, respectively, and US is a simple and noninvasive procedure for abdominal screening. A complete analysis using elastography can be performed in 1–2 min after screening. US also noninvasively predicts onset of RE [26, 27], which is related to Barrett's esophagus, one of the major risk factors for esophageal adenocarcinoma [28–30], and may indicate a need to perform endoscopy.

The limitations of this study were as follows: the small sample size; possible inclusion of NERD cases in the non-RE group; performance of the procedure in a supine position, which may induce reflux; the influence of the crura of the diaphragm during deep inspiration to visualize the EGJ on the dorsal side of the liver, which may cause the result to reflect changes other than a decrease in distal esophageal

function; and indirect estimation of esophageal motility using US-EG.

There is no *ex vivo* basis for the number of CS associated with distal esophageal function. There was an overlap in the number of CS between the RE groups and non-RE groups, but we were able to identify a difference between these groups, although there was no significant difference among subjects with Grades M, A, and B. The lack of patients with Grade C and D was the final limitation.

## Conclusion

In conclusion, within these limitations, the presence of RE can be predicted noninvasively based on the number of CS measured by US elastography.

## Compliance with ethical standards

**Conflict of interest** The authors declare that there are no conflicts of interest. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

**Ethical statements** Informed consent to the protocol was obtained from all patients. The study was approved by our institutional ethics committee for human research.

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