Predictive Ability for Reflux Esophagitis by Gastroesophageal Barium Reflux and Angle of His Seen in Upper Gastrointestinal Series

TAKAYUKI HASHIMOTO*1) 2), KOUTATSU MARUYAMA*1) 3), YOSHI YAMAJI*1) 4), HIROO WADA*1), AI IKEDA*1), KOU MORICHIKA*5), TAKESHI TANIGAWA*1)

*1)Department of Public Health, Juntendo University Graduate School of Medicine, Tokyo, Japan, *2)Yushikai Nogi Hospital, Tochigi, Japan, *3)Laboratory of Community Health and Nutrition, Special Course of Food and Health Science, Department of Bioscience, Ehime University Graduate School of Agriculture, Ehime, Japan, *4) Life-Care Clinic Nozomi, Tochigi, Japan, *5)Ochanomizu-Sougo Clinic, Tokyo, Japan

Objective: This study aimed to examine the ability of barium-confirmed gastroesophageal reflux and the angle of His assessed using upper gastrointestinal series (UGIS) to predict the presence of reflux esophagitis (RE).

Design: A total of 1,628 middle-aged Japanese individuals who underwent a radiographic and endoscopic examination between January 2000 and December 2012 were recruited.

Methods: The receiver operating characteristic (ROC) curves and the area under the curves (AUCs) were used for RE diagnosis according to barium reflux, the angle of His, and their combination. The predictive sensitivity, specificity, and the Youden index were calculated according to the combination of the two indices, and the maximum value of the Youden index was considered as the optimal cutoff value for RE diagnosis.

Results: ROC analysis was performed to estimate the optimal cutoff values of the Youden index for barium reflux and the angle of His. The AUCs for RE diagnosis according to barium reflux, the angle of His, and their combination were 0.76, 0.64, and 0.80, respectively. The optimal cutoff value was an angle of His of 45-46° with barium reflux. The sensitivity, specificity, and the Youden index were 76.3%, 80.4%, and 0.56, respectively.

Conclusion: Our results suggest that barium reflux and the angle of His assessed using UGIS are useful for an early diagnosis of RE.

Key words: upper gastrointestinal series (UGIS), gastroesophageal reflux disease (GERD), reflux esophagitis (RE), angle of His

Introduction

Endoscopic esophagitis typically involves reflux esophagitis (RE) 1), and is the primary finding of gastroesophageal reflux disease (GERD). GERD involves the retrograde flux of gastric contents into the esophagus, which stimulates the esophageal mucosa.

Because RE is highly prevalent in Western countries and is known as a precancerous disease of the esophagus, esophageal screening is crucial 2)-6). In contrast, the prevalence of RE in Japan was previously reported to be low, but has recently increased, and RE is currently regarded as an important medical issue 7). Therefore, it is important to develop early diagnostic and treatment methods for RE in the Japanese population.

Various approaches, including questionnaires, the proton pump inhibitor (PPI) test, endoscopy, upper gastrointestinal series (UGIS), and 24 h pH monitoring, are used RE diagnosis; endoscopy is considered the standard diagnostic approach 8). UGIS is
less invasive and has a shorter examination time than endoscopy. Furthermore, UGIS with barium contrast helps objectively visualize the gastroesophageal morphology and gastroesophageal reflux (GER). The angle of His is determined as the incident angle of the lower esophagus in the cardiac region with respect to the stomach on UGIS, and it is associated with lower esophageal sphincter (LES) function. Our previous studies showed that the presence of barium-confirmed GER and the larger angle of His are associated with a higher prevalence of esophagitis; however, the population was too small to perform statistical analysis. This led to a hypothesis that barium reflux and the angle of His, as assessed using UGIS, can predict the presence of RE. Therefore, the present study aimed to examine the ability of barium reflux and the angle of His using UGIS to diagnose RE among the Japanese individuals undergoing health checkup.

Methods

1. Subjects
The study included 1,231 male and 792 female individuals who underwent UGIS as part of an annual medical checkup at the Ochanomizu-Sougo Clinic between January 2000 and December 2012. The examinees did not have severe gastrointestinal-related diseases, i.e., gastric cancer, esophagus varix, or esophageal achalasia. Those who did not undergo upper endoscopy (n=365) and those with a history of esophageal, stomach, or duodenal surgery (n=30) were excluded. Therefore, data from a total of 976 male and 652 female examinees were analyzed. The study was approved by the Ethics Committee of Juntendo University (No. 2015109).

2. Diagnosis of RE
RE was diagnosed by a board certified gastroenterologist (KM) of the Japanese Society of Gastroenterology after an inquiry accompanying the assessment of the upper gastrointestinal tract. KM graded the RE of all examinees using images obtained through a GIF-Q200 9.8 mm endoscope (OLYMPUS®, Tokyo, Japan) within 2 weeks after UGIS. The examinees were classified into grades ranging from A to D according to the Los Angeles classification. Grade A examinees exhibited mucous membrane injury such as inflammation with a length of 5 mm or less; Grade B examinees exhibited at least one mucous membrane injury with a length of 5 mm or longer but without adhesion over the injuries; Grade C examinees exhibited adhesion of mucous membrane injuries over 75% or less of the mucous circumference; and Grade D examinees cases exhibited adhesion of mucous membrane injuries over 75% or more of the mucous circumference. Examinees without a mucous membrane injury were diagnosed as not having RE.

3. UGIS measurements
UGIS was performed by a trained radiological technologist (TH) using an X-ray television system (KXO-50N, TOSHIBA, Tokyo, Japan), 120–180 ml of a 180–220 w/v% high-density, low-viscosity barium contrast medium (Barytgen®, FUSHIMI, Kagawa, Japan), and 5.0 g of a foaming agent (BAROS EFFERVESCENT GRANULES®, HORII, Osaka, Japan) for double contrast (sodium bicarbonate + tartaric acid), in accordance with the New Gastrointestinal X-ray Imaging Guidelines. No examinees underwent pre-test treatment with an anticholinergic (scopolamine butylbromide) injection. Body weight, height, and body mass index (BMI) were measured at the time of UGIS.

A radiological technologist confirmed the presence of reflux in cases where X-ray films revealed the presence of barium reflux. Reflux of gastric barium to the lower thoracic esophagus was determined using double-contrast gastrography in the supine position (Figure-1) and a barium-filled image in the prone position. Each UGIS examination took approximately 10 min.

In the present study, the angle of His was defined as the angle at the cardiac notch formed by a tangent line connecting the angular part of the stomach with the gastric base in the cardia and intersecting a line extending from the center of the lower esophageal transverse diameter to the center of the esophageal hiatus in upright images of the barium-filled stomach (Figure-2). Measurements were obtained by TH using a ruler and a semicircular protractor.

4. Statistical analysis
Mean differences in age, the angle of His, and BMI
were evaluated using Student’s t-test, and differences in sex distribution and the presence of barium reflux between the RE and non-RE groups were compared using the Chi-square test. The presence of RE according to barium reflux, quintiles of the angle of His, and their combination were evaluated using receiver operating characteristic (ROC) analysis and the area under the curve (AUC). Furthermore, the prediction sensitivity and specificity and the Youden index were calculated according to the combination of barium reflux (binary variable) and quintiles of the angle of His. The maximum value of the Youden index was regarded as the optimal cutoff value for the prediction of RE. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), and the level of significance was two-sided p<0.05.

Results

The mean (SD) age and BMI of all examinees were 57.9 (13.2) years and 22.5 (2.3) kg/m², respectively. Of the 1,628 examinees, 524 (32.1%) were diagnosed with RE, Grade A (94.6%), Grade B (4.6%), Grade C (0.4%), Grade D (0.4%), and 740 (45.5%) had barium reflux. In the presence of barium reflux, increases in age, BMI, and the angle of His were significantly associated with the severity of RE (data not shown). The RE group included individuals who were older and had a higher mean BMI than those in the non-RE group. Additionally, this group included a higher proportion of male individuals and individuals with barium reflux than those in the non-RE group (Table-1).

The ROC curves and AUCs for RE according to barium reflux, the angle of His, and their combination are shown in Figure-3. The AUCs for RE diagnosis according to barium reflux, the angle of His, and their combination were 0.76, 0.64, and 0.80, respectively.

The sensitivity, specificity, and the Youden index according to the combination of barium reflux and quintiles of the angle of His are presented in Table-2. The presence of barium reflux and a larger angle of His tended to show high specificity. According to the Youden index, the optimal cutoff value was barium reflux with an angle of His of 45–46°, with sensitivity, specificity, and the Youden index of 76.3%, 80.4%, and 0.56, respectively.
In this study, individuals with RE were more likely to have barium reflux and a greater angle of His. According to the Youden index, the presence of barium reflux and an angle of His of 45-46° were relatively sufficient to detect RE.

Various esophagitis screening tools have been developed, particularly for RE. Previous studies have reported that the sensitivity and specificity of the Questionnaire for the Diagnosis of Reflux Disease (QUEST) were 70-72% and 46-54% respectively, and those of the Frequency Scale for the Symptoms of GERD (FSSG) were 62% and 59%, respectively. Additionally, the sensitivity and specificity of the PPI test, which is another less invasive method for diagnosing RE, were 75-80% and 55-74%, respectively. Thus, the sensitivity and specificity of the PPI test were better than those of the questionnaire. Our screening method involving a combination, had better results and was more appropriate because the PPI test is costlier and requires consultation with clinicians.

A useful method used to diagnose typical or atypical RE without obvious mucosal injury to the esophagus is 24 h pH monitoring, and the AUC of

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<tr>
<th>Table 1</th>
<th>Clinical characteristics according to reflux esophagitis among 1,628 medical examinees</th>
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<tr>
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<td>RE (n=524)</td>
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<tr>
<td>Gender, Male / Female</td>
<td>346/178</td>
</tr>
<tr>
<td>Age, years</td>
<td>61.6 ± 12.4</td>
</tr>
<tr>
<td>BMI kg/m²</td>
<td>23.3 ± 2.7</td>
</tr>
<tr>
<td>Barium reflux</td>
<td>423 (80.7)</td>
</tr>
<tr>
<td>Angle of His, degrees</td>
<td>53.9 ± 11.4</td>
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Age, BMI and angle of His were shown as mean ± SD. Barium reflux was shown as number (%).
p-value: Student’s t-test or Chi-square test

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<th>Table 2</th>
<th>Sensitivity, specificity, and youden index to detect reflux esophagitis according to the combination of barium reflux and angle of His</th>
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<td>Quintiles of His, degrees</td>
<td>(-)</td>
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<tr>
<td>Sensitivity, %</td>
<td>100</td>
</tr>
<tr>
<td>Specificity, %</td>
<td>0</td>
</tr>
<tr>
<td>Youden index</td>
<td>0</td>
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**Discussion**

In this study, individuals with RE were more likely to have barium reflux and a greater angle of His. According to the Youden index, the presence of barium reflux and an angle of His of 45-46° were relatively sufficient to detect RE.

Various esophagitis screening tools have been developed, particularly for RE. Previous studies have reported that the sensitivity and specificity of the Questionnaire for the Diagnosis of Reflux Disease (QUEST) were 70-72% and 46-54%, and those of the Frequency Scale for the Symptoms of GERD (FSSG) were 62% and 59%, respectively. Additionally, the sensitivity and specificity of the PPI test, which is another less invasive method for diagnosing RE, were 75-80% and 55-74%, respectively. Thus, the sensitivity and specificity of the PPI test were better than those of the questionnaire. Our screening method involving a combination, had better results and was more appropriate because the PPI test is costlier and requires consultation with clinicians.

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<th>Figure 3</th>
<th>ROC curves and AUC to detect RE according to barium reflux, angle of His and their combination</th>
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The AUCs for RE diagnosis was 0.76 by barium reflux (A) and 0.64 by the angle of His (B). The AUC of the ROC curve for RE was 0.80 (C).
the ROC curve, sensitivity, and specificity of this method were 0.89, 80%, and 81.2%, respectively. However, this method is impractical for use as a screening test because it requires the 24 h placement of a catheter. Therefore, compared with the aforementioned screening methods, this method, which involves measurements of the angle of His and barium reflux using UGIS, is an easy, less invasive, and practical approach for RE diagnosis.

Although barium reflux measured using UGIS was defined as a surrogate index of GER in another study, our previous studies have indicated that GER was not observed in some patients with RE. Indeed, barium reflux was absent in 19% of individuals with RE. In general, barium reflux assessed using UGIS is only exclusively detectable for several seconds on fluoroscopic examination; thus, barium reflux is not always found during examination, even in individuals with RE. However, the sensitivity and specificity of barium reflux measurements using UGIS were found to be comparable to those of the other screening tools for RE diagnosis.

Because transient relaxation is the primary mechanism underlying GER, the functional assessment of LES, including the effects of movement of the diaphragmatic crura on the lower esophagus, is important. A previous study has reported that the proportion of GER during LES relaxation is higher among GERD patients than among non-GERD patients (34.0–65.0% vs. 13.0–35.0%) in patients with RE.

A previous study has described that interactions of the angle of His, ring-shaped muscle of the esophagus, oblique muscle of the stomach, cardiac rosette, phrenoesophageal ligament, and diaphragmatic crura potentially influence LES pressure. Other studies have reported that destruction of the angle of His due to abdominal surgery results in functional impairment of the lower esophagus in patients with RE. Additionally, our previous study on approximately 350 health checkup examinees showed that RE individuals have a higher prevalence of barium reflux and a larger mean angle of His. Therefore, barium reflux and a large angle of His could be considered as major characteristics of RE.

The strength of this study is that it enrolled annual checkup examinees without any manifestations; therefore, sampling bias was small and study findings are generalizable compared with those of patient–based studies. Nevertheless, the limitations of this study should be discussed. First, there was a restriction with regard to the fluoroscopy time in health checkup examination; thus, a detailed examination of hernias was difficult. With regard to hiatal hernia, which is an important characteristic of GERD, we could not obtain appropriate images in all examinees. The second limitation was that a direct comparison of multiple modalities in RE detection was not possible because no other RE screening tool was concomitantly used in the same examinee.

UGIS is a major screening modality for digestive organ diseases. According to a nation-wide survey by the Japanese Society of Gastrointestinal Cancer Screening, approximately 6,800,000 individuals annually undergo upper gastrointestinal tract examinations involving UGIS. UGIS offers excellent accuracy and processing ability that has been established for over half a century, and it remains the most commonly used method to examine upper gastrointestinal tract in Japan.

In the present study, the prevalence of RE was 32.1%, and it was nearly equivalent to those reported in other studies on Japanese individuals that followed the original Los Angeles classification before revision. RE is a factor that increases the risk of precancerous diseases, and approximately 30% of Japanese adults are exposed to this risk. Therefore, an early detection and the treatment of RE are important. Additional assessments of gastroesophageal barium reflux and the angle of His using UGIS will lead to an early diagnosis of RE.

In conclusion, we found that barium reflux and the angle of His assessed using UGIS reasonably predicted the presence of RE.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

3) Morichika K, Ishi K, Hashimoto T, Kusano M: Three cases of adenocarcinoma in Barrett’s epithelium in patients with reflux esophagitis. Juntendo Medical

15) Armstrong D, Bennett JR, Blum AL, et al.

14) Morichika K, Hashimoto T, Kusano M,

13) Hashimoto T, Kusano M: Obesity and reflux esophagitis.


