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Original Article

Abnormal Gastroesophageal Flap Valve Is Associated With High Gastresophageal Reflux Disease Questionnaire Score and the Severity of Gastroesophageal Reflux Disease in Vietnamese Patients With Upper Gastrointestinal Symptoms

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Background/Aims
There have been no studies investigating the distribution of abnormal gastroesophageal flap valve (GEFV) among patients with dyspepsia, non-erosive reflux disease (NERD), and reflux esophagitis (RE) in the same set of patients. The aims of this study are to investigate (1) the association between GEFV and gastroesophageal reflux disease questionnaire (GERDQ) score, and (2) the distribution of abnormal GEFV in Vietnamese patients presenting with upper gastrointestinal symptoms.

Methods
Three hundred and thirty-one patients recruited in this prospective cross-sectional study were classified into 3 groups: reflux esophagitis (RE), non-erosive reflux disease (NERD) (GERDQ score ≥ 8, no endoscopic mucosal injury), and dyspepsia (GERDQ score < 8, no endoscopic mucosal injury). The GEFV was graded endoscopically according to the Hill classification. GEFV grades I and II were regarded as normal, while grades III and IV were regarded as abnormal GEFV.

Results
There were 215 (65.0%) patients with dyspepsia, 55 (16.6%) patients with NERD, and 61 (18.4%) patients with RE. Abnormal GEFV was an independent risk factor for GERD (OR, 2.93; CI 95%, 1.76-4.88) and RE (OR, 3.41; CI 95%, 1.78-6.53). The mean GERDQ score of patients with abnormal GEFV was significantly higher than that of patients with normal GEFV (5.7 ± 2.4 vs 4.9 ± 2.7, P = 0.011). The prevalence of abnormal GEFV gradually increased in patients with dyspepsia (27.4%), NERD (43.6%), grade A RE (56.8%), and grades B/C RE (80.0%) (P < 0.001).

Conclusions
Abnormal GEFV was significantly associated with high GERDQ score. Its prevalence gradually increased in patients with dyspepsia, NERD, and RE, respectively.
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Key Words
Dyspepsia; Esophagitis; Gastroesophageal reflux; Vietnamese

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Introduction

The endoscopic gastroesophageal flap valve (GEFV) grading system proposed by Hill et al[1] allows evaluation of the stepwise relaxation of the gastroesophageal junction. The association between GEFV and gastroesophageal reflux disease (GERD) has been already reported in several previous studies.[2-7] However, most of these studies were conducted on patients with reflux esophagitis (RE)[2-5] and there were very few studies on patients with dyspepsia and non-erosive reflux disease (NERD).[6,7] There have been no studies investigating the distribution of abnormal GEFV among patients with dyspepsia, NERD and different grades of RE in the same set of patients. Such studies are important as they can help to shed light on the role of GEFV in the pathophysiology of GERD spectrum.

In clinical practice, differentiating between dyspepsia and GERD may be very challenging. Several types of questionnaires have been suggested for the diagnosis of GERD. A previous study reported that the scores of quality of life and utility evaluation survey technology (QUEST) questionnaire had a positive correlation with GEFV grades.[7] But a recent study showed that this questionnaire was complicated to complete.[8] The gastroesophageal reflux disease questionnaire (GERDQ) has been developed as a useful tool to improve and standardize symptom-based diagnosis in patients with GERD.[9] This questionnaire has been validated in Vietnamese patients but has not been applied to investigate the association between abnormal GEFV and GERD. Our study aims to assess: (1) the association between GEFV abnormality and GERDQ score, and (2) the distribution of abnormal GEFV in Vietnamese patients presenting with dyspepsia, NERD, and RE.

Materials and Methods

Patients

We conducted a prospective cross-sectional study on patients with upper gastrointestinal symptoms from March 2015 to July 2015 at the University Medical Center, Hochiminh City, Vietnam. We included patients who (1) were at least 18 years of age, (2) had upper gastrointestinal symptoms, and (3) underwent upper gastrointestinal endoscopy. We excluded patients who (1) used antibiotics or proton pump inhibitors (PPIs) within 4 weeks, or (2) had at least one of the following conditions: advanced esophageal or gastric cancer, active upper gastrointestinal bleeding, or prior history of up-

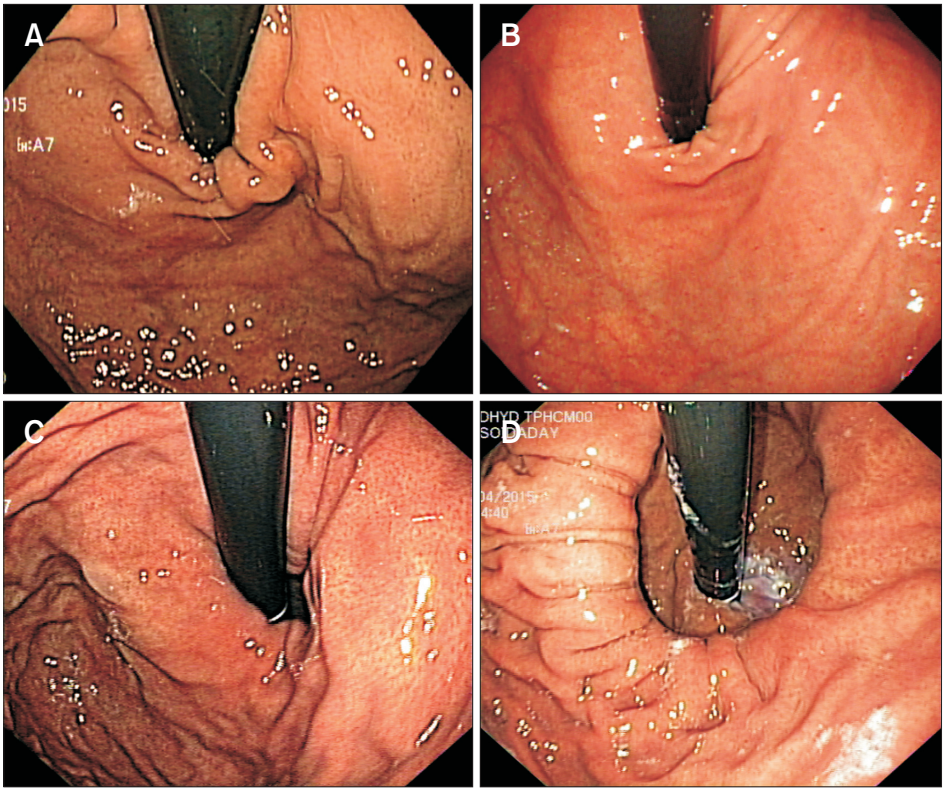

Figure 1. Endoscopic gastroesophageal flap valve assessment. Grade I: gastroesophageal flap valve (GEFV) with a prominent fold or ridge of tissue along the lesser curvature closely apposed to the endoscope. Grade II: GEFV with a less prominent ridge, opening rarely with respiration and closing promptly. Grade III: fold not prominent; the endoscope was not gripped tightly by the tissues and often failed to close around the endoscope. Grade IV: fold absent with the lumen of the esophagus gaping open, allowing squamous epithelium to be viewed from below.

per gastrointestinal surgery. This study was approved by the Ethics Committee of the University of Medicine and Pharmacy, Hochiminh City, Vietnam (No. 1511-15/DHYD-HD).

Pre-endoscopic Evaluation

Before undergoing upper gastrointestinal endoscopy, all patients filled out the GERDQ score.[9] The history of smoking and alcohol consumption was recorded. The body mass index (BMI) and waist–hip ratio were calculated for all patients. Obesity was defined as BMI > 25 kg/m^2, and central obesity was defined as waist–hip ratio ≥ 0.9 in male or ≥ 0.85 in female according to the World Health Organization criteria.[10]

Endoscopic Examination

Upper gastrointestinal endoscopy was performed using flexible video endoscopy Olympus scope GIF-160 or GIF-Q180 (Olympus Co. Ltd, Tokyo, Japan) under topical anesthesia in each patient. All endoscopic procedures were performed by experienced endoscopists who were blinded from GERDQ score. The esophagus, stomach, and duodenum were examined with optimal visualization. The severity of RE was graded according to Los Angeles classification.[11] The degree of gastric mucosal atrophy was classified as closed or open type according to the Kimura–Takemoto classification,[12] and divided into 3 groups: none or mild (C-0, C-1, C-2), moderate (C-3, O-1), and severe (O-2, O-3). The GEFV was inspected with a retroflexed endoscope and graded I to IV according to the Hill classification (Fig. 1).[1] One endoscopist (T.T.N.) evaluated the endoscopic GEFV of all patients in this study. In addition, the GEFV grade in each patient was also evaluated by one another endoscopist from the Department of endoscopy, University Medical Center, Hochiminh City who (1) has an experience to perform upper gastrointestinal endoscopy with at least 5000 procedures over the last 5 years and (2) has attended a previous local training workshop on GEFV evaluation. The GEFV grade in each patient was then decided based on the agreement of these two doctors. If the agreement could not be reached, the still endoscopic images were used to discuss with a senior endoscopist (D.T.Q.) to make the final agreement.

Definitions

Patients were classified into 3 groups on the basis of upper endoscopic findings and GERDQ score: RE (presence of endoscopic mucosal injury), NERD (GERDQ score ≥ 8, no endoscopic mucosal injury), and dyspepsia (GERDQ score < 8, no endoscopic mucosal injury). GERD was defined as RE plus NERD. GEFV grades I and II were regarded as representing normal GEFV, while grades III and IV were regarded as representing abnormal GEFV. Sliding hiatus hernia was diagnosed when the apparent separation between the squamocolumnar junction and the diaphragmatic impression is greater than 2 cm.[13] Patients were considered *Helicobacter pylori* infection when local validated rapid urease test was positive within 1 hour.

Statistical Methods

Categorical variables were analyzed using Pearson's chi-squared test, and continuous variables were analyzed using Student's *t* test or one-way analysis of variance. The Spearman's rank correlation coefficient was used to measure the strength and direction of association between ordinal variables. Univariable and multivariable analyses using logistic regression were performed to identify the risk factors for GERD and RE. Patients' age, sex, BMI, alcohol drinking, and smoking status, *H. pylori* infection status and GEFV

Table 1. Baseline Demographics and Clinical Characteristics of Patients in the Study

Variables	Dyspepsia (n = 215)	NERD (n = 55)	RE (n = 61)	*P*-value
Male gender (n [%])	88 (40.9)	30 (54.5)	41 (67.2)	0.001
Age (mean ± SD, yr)	36.4 ± 11.9	38.1 ± 9.7	39.7 ± 12.3	0.120
BMI (mean ± SD, kg/m^2)	21.4 ± 2.9	21.8 ± 2.9	23.3 ± 3.4	< 0.001
Obesity[a] (n [%])	26 (12.1)	9 (16.4)	20 (32.8)	0.001
WHR (mean ± SD)	0.80 ± 0.06	0.83 ± 0.06	0.85 ± 0.07	< 0.001
Central obesity[a] (n [%])	58 (27)	16 (29.1)	21 (34.4)	0.524
Smoking (n [%])	43 (20)	17 (30.9)	28 (45.9)	0.001
Alcohol drinking (n [%])	72 (33.5)	22 (40)	29 (47.5)	0.120
H. pylori infection (n [%])	102 (47.4)	28 (50.9)	9 (14.8)	< 0.001

[a]Obesity was defined as body mass index (BMI) > 25kg/m^2 and central obesity was defined as waist–hip ratio (WHR) ≥ 0.9 in male or ≥ 0.85 in female according to the World Health Organization criteria (Adapted from WHO[10]).
NERD, non-erosive reflux disease; RE, reflux esophagitis; *H. pylori*, *Helicobacter pylori*.

grades were included in the multivariate logistic regression analysis (age was dichotomized as it was nonlinear). All tests were two-sided and performed at the 5% level of significance. Statistical calculations were performed with SPSS version 19.0 for Windows software (IBM, Armonk, NY, USA).

Results

There were 331 patients in our study. The baseline demographics and clinical characteristics of patients in the study are described in Table 1. There were 116 (35%) patients diagnosed with GERD. RE was identified in 61 (18.4%) patients: 51 (15.4%) in grade A, 9 (2.7%) in grade B, 1 (0.3%) in grade C, and no patient in grade D. There were 120 (36.2%) patients with abnormal GEFV and 15 (4.5%) patients with hiatus hernia (Table 2). The rates of hiatal hernia according to GEFV from grade I to grade IV were 0.0% (0/36), 0.0% (0/175), 7.9% (9/114), and 100.0% (6/6), respectively (Spearman's rank correlation coefficient = 0.32; $P < 0.001$).

In multivariable analysis, abnormal GEFV was an independent risk factor for GERD (OR, 2.93; CI 95%, 1.76-4.88) and RE (OR, 3.41; CI 95%, 1.78-6.53) (Tables 3 and 4). Obesity was a risk factor of RE (OR, 2.59; CI 95%, 1.15-5.85), but the statisti-

Table 2. Endoscopic Characteristics of Patients in the Study

Variables	Dyspepsia (n = 215)	NERD (n = 55)	RE (n = 61)	*P*-value
Gastroesophageal flap valve (n [%])				< 0.001
Grade I	25 (11.6)	7 (12.7)	4 (6.6)	
Grade II	131 (60.9)	24 (43.6)	20 (32.8)	
Grade III	58 (27.0)	23 (41.8)	33 (54.1)	
Grade IV	1 (0.5)	1 (1.8)	4 (6.6)	
Endoscopic suspected Barrett's esophagus (n [%])	6 (2.8)	1 (1.8)	1 (1.6)	0.832
Hiatus hernia (n [%])	4 (1.9)	3 (5.5)	7 (11.5)	0.004
Peptic ulcer diseases (n [%])				0.512
Gastric ulcer	1 (0.5)	0	1 (1.6)	
Duodenal ulcer	6 (2.8)	1 (1.8)	0	
Atrophic gastritis (n [%])				0.830
None/mild	210 (97.7)	53 (96.4)	59 (96.7)	
Moderate	5 (2.3)	2 (3.6)	2 (3.3)	
Severe	0	0	0	

NERD, non-erosive reflux disease; RE, reflux esophagitis.

Table 3. Risk Factors for Gastroesophageal Reflux Disease: Multivariable Analysis

	Odds ratio	95% confidence interval	*P*-value
Gender (male)	1.68	0.78-3.62	0.190
Age (≥ 60)	4.32	1.05-17.77	0.043
Obesity[a]	1.93	0.97-3.86	0.062
Central obesity[a]	1.46	0.79-2.68	0.226
Smoking	2.51	1.23-5.1	0.010
Alcohol drinking	0.71	0.35-1.44	0.358
Abnormal gastroesophagel flap valve	2.93	1.76-4.88	< 0.001
H. pylori infection	0.49	0.29-0.82	0.007
Moderate gastric atrophy	1.48	0.32-6.75	0.626

[a]Obesity was defined as body mass index (BMI) > 25kg/m^2 and central obesity was defined as waist-hip ratio (WHR) ≥ 0.9 in male or ≥ 0.85 in female according to the World Health Organization criteria (Adapted from WHO[10]). *H. pylori*, *Helicobacter pylori*.

Table 4. Risk Factors for Reflux Esophagitis: Multivariable Analysis

	Odds ratio	95% confidence interval	*P*-value
Gender (male)	1.87	0.7-5.01	0.210
Age ≥ 60	3.46	0.62-19.35	0.163
Obesity[a]	2.59	1.15-5.85	0.024
Central obesity[a]	1.64	0.76-3.55	0.216
Smoking	2.45	1.06-5.69	0.041
Alcohol drinking	0.73	0.31-1.73	0.471
Abnormal gastroesophagel flap valve	3.41	1.78-6.53	< 0.001
H. pylori infection	0.16	0.07-0.36	< 0.001
Moderate gastric atrophy	1.56	0.2-12.37	0.673

[a]Obesity was defined as body mass index (BMI) > 25kg/m^2 and central obesity was defined as waist–hip ratio (WHR) ≥ 0.9 in male or ≥ 0.85 in female according to the World Health Organization criteria (Adapted from WHO[10]). *H. pylori*, *Helicobacter pylori*.

Table 5. Gastroesophageal Reflux Disease Questionnaire Score of Patients With Normal and Abnormal Gastroesophageal Flap Valve

	Normal GEFV (n = 211)	Abnormal GEFV (n = 120)	*P*-value
GERDQ score (mean ± SD)	4.9 ± 2.4	5.7 ± 2.7	0.011
GERDQ score (n [%])			
< 8	177 (83.9)	84 (70.0)	0.003
≥ 8	34 (16.1)	36 (30.0)	

GEFV, gastroesophageal flap valve; GERDQ, gastroesophageal reflux disease questionnaire.

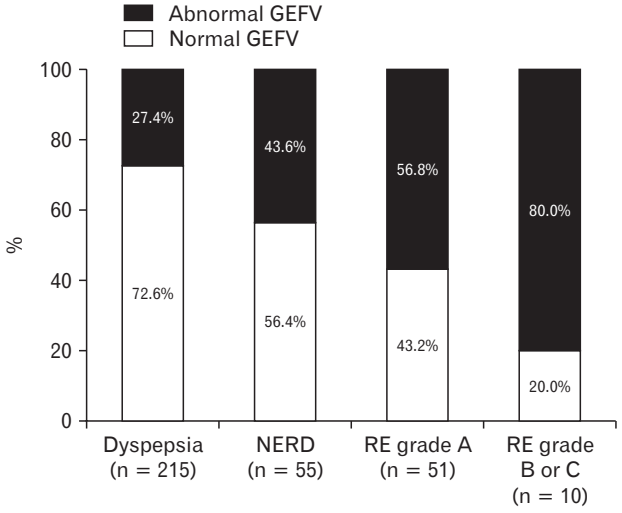

Figure 2. Abnormal gastroesophageal flap valve (GEFV) prevalence in upper gastrointestinal disorders. NERD, non-erosive reflux disease; RE, reflux esophagitis. Pearson's chi-squared test, $P < 0.001$.

cal significance was marginal for GERD. *H. pylori* infection was a significant preventive factors for GERD (OR, 0.49; CI 95%, 0.29-0.82) and RE (OR, 0.16; CI 95%, 0.07-0.36).

The mean GERDQ score of patients with abnormal GEFV was significantly higher than that of patients with normal GEFV: 5.7 ± 2.7 vs 4.9 ± 2.4, respectively ($P = 0.011$) (Table 5). Figure 2 summarises the distribution of abnormal GEFV among patients with upper gastrointestinal disorders. The prevalence of abnormal GEFV gradually increased in subgroups of patients with dyspepsia (59/215, 27.4%), NERD (24/55, 43.6%), grade A RE (29/51, 56.8%), and grades B/C RE (8/10, 80%) ($P < 0.001$).

Discussion

There were very few Asian data about the prevalence of abnormal GEFV. Iwamoto et al[7] reported that the prevalence of abnormal GEFV in Japan was 13.5% with a total GERD prevalence of 27.0% among patients undergoing endoscopic examination. In another study in Taiwan, Lin et al[6] reported that the prevalence of abnormal GEFV was 27.3% with a total GERD prevalence of 41.3% among subjects undergoing routine check-ups. Our study showed that abnormal GEFV is an independent risk factor of GERD in multivariable analysis (OR, 2.93; CI 95%, 1.76-4.88; $P < 0.001$). This finding helps to partially explain why GERD prevalence increases in parallel with the prevalence of abnormal GEFV in the 2 above-mentioned populations.

Some previous Asian studies reported that abnormal GEFV was a risk factor of RE, and associated with RE severity in adults as well as in pediatric patients.[2-4,7] Our study also confirmed this finding in Vietnamese population. It is well known that the prevalence of RE in Caucasian population is higher than that in Asian population.[14] A recent study on Russian Caucasians and Koreans patients showed that abnormal GEFV was an independent risk factor of RE regardless of ethnicity.[5] Interestingly, the prevalences of abnormal GEFV and RE in the former population were both significantly higher than those in the later (44.2% vs 28.5%, $P < 0.001$; 20.2% vs 9.8%, $P < 0.001$, respectively). Although hiatus hernia has been identified as an independent risk factor of GERD, its prevalence in Asian populations is substantially lower than those reported in Western populations.[15] In our study, there were only 15 (4.5%) patients with hiatus hernia. All of these patients were with GEFV types III and IV. Therefore, abnormal GEFV could be a more sensitive risk factor of GERD in Asian populations compared to hiatus hernia.

There are very few studies investigating the distribution of abnormal GEFV on patients with dyspepsia and NERD.[6,7] NERD accounts for the majority of GERD patients in clinical practice. It is a heterogeneous group which consists of patients who have no endoscopic RE but (1) increased acid exposure time, or (2) normal acid exposure time but positive symptom-associated probability, or (3) normal acid exposure time and negative symptom-associated probability (functional heartburn).[16] Studying the distribution of abnormal GEFV among patients with dyspepsia, NERD, and RE may help to predict the subgroups of NERD with actually having increased reflux events. In a previous study, Koch et al reported that there was a significant positive correlation between increased GEFV

grade and DeMeester score, total number of reflux events and acid reflux events.[17] Our study showed that GERDQ score in patients with abnormal GEFV was significantly higher compared to patients with normal GEFV (5.7 ± 2.4 vs 4.9 ± 2.7, $P = 0.011$) (Table 5). The prevalence of abnormal GEFV also gradually increased among patients with dyspepsia, NERD, grade A, and grades B/C RE, respectively (Fig. 2). In the dyspepsia group of our study, there were 59 (27.4%) out of 215 patients having abnormal GEFV. According to the finding from the above-mentioned study by Koch et al,[17] these patients might already have a higher number of acid reflux and reflux events compared with the rest patients in the dyspepsia group, but not yet enough to fulfill the definition of GERD. However, they are more likely to develop GERD in the future when other risk factors of GERD involve. In clinical practice, we have found some patients changing symptoms from dyspepsia to typical reflux during follow-up. The changes of other risk factors of GERD in these patients such as aging, smoking status, obesity may play important roles on the development of GERD.

H. pylori infection is a "protective" factor for GERD as shown in our study and a recent study in Korea,[5] while the infection is considered an important cause of dyspepsia.[18] Inoue et al[19] reported that Japanese patients after successful eradication of the bacteria were more likely to suffer from RE. This study also showed that the pH level of gastric juice after eradication therapy was lower in the group of patients with successful eradication than in the group with failed therapy. In addition, the incidence of RE after *H. pylori* eradication was significantly higher in patients with abnormal GEFV compared to patients with normal GEFV (33.3% vs 16.3%, $P = 0.04$). Therefore, the current evidence suggests that abnormal GEFV is an important risk factor for a diverse spectrum of gastroesophageal reflux phenomenon: from an episode with increased reflux events but not yet fulfilled the definition of GERD to a real GERD.

On the other end of the spectrum, 8 (80%) out of 10 patients with grades B/C RE in our study had abnormal GEFV, suggesting that abnormal GEFV contributes an important role on severe RE. Some studies also reported that abnormal GEFV was associated with poor response to PPI treatment, more PPIs usage during on demand therapy after remission and surgery indication for either failed medical management or complications.[3,20,21]

Our study has some limitations. Firstly, it is a single-center study with relatively small number of patients. Secondly, the number of patients with severe RE (ie, grades C and D) in our study is small. As a consequence, the prevalence of abnormal GEFV in severe RE has not been fully investigated in this study.

In conclusion, our study showed that abnormal GEFV was an independent risk factor of GERD and significantly associated with high GERDQ score in Vietnamese patients with upper gastrointestinal symptoms. The prevalence of abnormal GEFV increased gradually among patients with dyspepsia, NERD, and RE.

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Conflicts of interest: None.

Author contributions: Duc T Quach and Toru Hiyama designed the research study and wrote the paper; Trang T Nguyen and Duc T Quach performed the research, collected data, and analyzed the data; and all authors approved the final version of the manuscript.

References

1. Hill LD, Kozarek RA, Kraemer SJ, et al. The gastroesophageal flap valve: in vitro and in vivo observations. Gastrointest Endosc 1996;44:541-547.
2. Navarathne NM, Abeysuriya V, Ileperuma A, Thoufeek UL. Endoscopic observations around the gastroesophageal junction in patients with symptomatic gastroesophageal reflux disease in South Asia. Indian J Gastroenterol 2010;29:184-186.
3. Kayaoglu HA. Correlation of the gastroesophageal flap valve grade with the surgery rate in patients with gastroesophageal reflux disease. Surg Endosc 2013;27:801-807.
4. Chang KC, Wu JF, Hsu WC, Lin BR, Chen HL, Ni YH. Impacts of endoscopic gastroesophageal flap valve grading on pediatric gastroesophageal reflux disease. PLoS One 2014;9:e107954.
5. Ko SH, Baeg MK, Jung HS, Kim P, Choi MG. Russian Caucasians have a higher risk of erosive reflux disease compared with East Asians: a direct endoscopic comparison. Neurogastroenterol Motil Published Online First: 12 Dec 2016. doi: 10.1111/nmo.13002.
6. Lin BR, Wong JM, Chang MC, et al. Abnormal gastroesophageal flap valve is highly associated with gastroesophageal reflux disease among subjects undergoing routine endoscopy in Taiwan. J Gastroenterol Hepatol 2006;21:556-562.
7. Iwamoto M, Kato, K, Mizuno, S, et al. Evaluation of gastro-oesophageal flap valve is useful for diagnosing gastro-oesophageal reflux disease. Aliment Pharmacol Ther symp Ser 2006;2:141-146.
8. Nonaka T, Kessoku T, Ogawa Y, et al. Comparative study of 2 different questionnaires in Japanese patients: the quality of life and utility evaluation survey technology auestionnaire (QUEST) versus the frequency scale for

the symptoms of gastroesophageal reflux disease questionnaire (FSSG). J Neurogastroenterol Motil 2013;19:54-60.
9. Jones R, Junghard O, Dent J, et al. Development of the GerdQ, a tool for the diagnosis and management of gastro-oesophageal reflux disease in primary care. Aliment Pharmacol Ther 2009;30:1030-1038.
10. WHO. Waist circumference and waist–hip ratio: report of a WHO expert consultation, Geneva, 8-11 December 2008.
11. Lundell LR, Dent J, Bennett JR, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut 1999;45:172-180.
12. Kimura K, Satoh K, Ido K, Taniguchi Y, Takimoto T, Takemoto T. Gastritis in the Japanese stomach. Scand J Gastroenterol Suppl 1996;214:17-20; discussion 21-13.
13. Kahrilas PJ, Kim HC, Pandolfino JE. Approaches to the diagnosis and grading of hiatal hernia. Best Pract Res Clin Gastroenterol 2008;22:601-616.
14. Wu JC. Gastroesophageal reflux disease: an Asian perspective. J Gastroenterol Hepatol 2008;23:1785-1793.
15. Kang JY, Ho KY. Different prevalences of reflux oesophagitis and hiatus hernia among dyspeptic patients in England and Singapore. Eur J Gastroenterol Hepatol 1999;11:845-850.
16. Chen CL, Hsu PI. Current advances in the diagnosis and treatment of nonerosive reflux disease. Gastroenterol Res Pract 2013;2013:653989.
17. Koch OO, Spaun G, Antoniou SA, et al. Endoscopic grading of the gastroesophageal flap valve is correlated with reflux activity and can predict the size of the esophageal hiatus in patients with gastroesophageal reflux disease. Surg Endosc 2013;27:4590-4595.
18. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of *Helicobacter pylori* infection-the Maastricht V/Florence Consensus Report. Gut 2017;66:6-30.
19. Inoue H, Imoto I, Taguchi Y, et al. Reflux esophagitis after eradication of *Helicobacter pylori* is associated with the degree of hiatal hernia. Scand J Gastroenterol 2004;39:1061-1065.
20. Cheong JH, Kim GH, Lee BE, et al. Endoscopic grading of gastroesophageal flap valve helps predict proton pump inhibitor response in patients with gastroesophageal reflux disease. Scand J Gastroenterol 2011;46:789-796.
21. Xirouchakis E, Kamberoglou D, Kalos D, Zambeli E, Doulgeroglou V, Tzias V. The effect of gastroesophageal flap valve appearance on the management of patients with symptoms of gastroesophageal reflux disease. Dig Dis Sci 2009;54:328-332.