High prevalence of esophagitis in patients with severe ineffective esophageal motility: need for a new diagnostic cutoff

Hang Viet Dao[a,b], Long Bao Hoang[b], Minh-Hue Thi Luu[b], Hoa Lan Nguyen[c], Robert Goldberg[c], Jeroan Allison, Minh-An Thi Dao[d,e], Tomoaki Matsumura[f], Long Van Dao[a,b]

Hanoi Medical University, Hanoi, Vietnam; The Institute of Gastroenterology and Hepatology, Hanoi, Vietnam; University of Massachusetts Medical School, Worcester, Massachusetts, USA; University of Queensland, Herston, Australia; Graduate School of Medicine, Chiba University, Chiba, Japan

Abstract

Background A new classification criterion for diagnosing ineffective esophageal motility (IEM) was proposed at the 2018 Stanford symposium, but limited data exists about the utility of this criterion.

Methods We conducted a cross-sectional study among 3826 patients treated at the Institute of Gastroenterology and Hepatology, Hanoi, Vietnam, between March 2018 and May 2020. Patients were classified as having normal motility, mild IEM, severe IEM, or absent contractility based on the Chicago classification version 3.0 and the new IEM criterion (severe IEM was defined as having >70% ineffective swallows). We examined the association between these 4 motility subgroups and the presence of erosive esophagitis and Barrett's esophagus, using multivariate logistic regression analysis.

Results The mean age of the study sample was 44.7 years and 66.3% were women. The prevalence of symptoms, hiatal hernia, and *Helicobacter pylori*-positive patients was similar in the 4 study groups. The 4-second integrated relaxation pressures and lower esophageal sphincter resting pressures were lower in patients with severe IEM and absent contractility. Severe IEM and absent contractility, but not mild IEM, were significantly associated with Los Angeles (LA) grade B-D esophagitis (relative risk ratio [RRR] for severe IEM 1.81, 95% confidence interval [CI] 1.17-2.80; and RRR for absent contractility 2.37, 95%CI 1.12-5.04). None of the hypomotility subgroups were associated with LA grade A esophagitis and Barrett's esophagus.

Conclusions Patients with severe IEM have a high prevalence of severe erosive esophagitis. These findings suggest the need for a more meaningful classification criterion for IEM.

Keywords Ineffective esophageal motility, esophageal hypomotility, manometry, erosive esophagitis

Ann Gastroenterol 2022; 35 (5): 483-488

Conflict of Interest: None

Correspondence to: Hang Viet Dao, Hanoi 100000, Vietnam, e-mail: daoviethang@hmu.edu.vn

Received 26 January 2022; accepted 11 May 2022; published online 11 July 2022

DOI: https://doi.org/10.20524/aog.2022.0733

Introduction

In the past decade, high-resolution manometry has become an important tool for the study of esophageal motility disorders. The most commonly utilized criterion for determining the presence of esophageal motility disorders is the Chicago Classification version 3.0 [1]. In this classification system, hypomotility disorders include ineffective esophageal motility (IEM), fragmented peristalsis, and absent contractility. While absent contractility (complete loss of esophageal peristalsis) is clearly associated with an increased risk of gastroesophageal reflux disease (GERD) [2,3], IEM appears to have less clinical significance because the findings concerning its association with GERD are inconclusive [4]. The 2018 Stanford symposium suggested that the IEM population might be heterogeneous, including both healthy individuals and persons at higher risk for GERD [4], reinforcing the need for a more detailed classification schema for those with hypomotility disorders. These investigators proposed a new classification criterion for IEM, which separates the condition into mild (having ≥50% to ≤70% ineffective swallows), and severe IEM (having >70% ineffective swallows) [4]. The Chicago Classification version 4.0 proposed in 2020 also modified the diagnostic criteria for IEM as having >70% ineffective swallows or ≥50% failed swallows [5]. It has been suggested that patients with severe IEM have more abnormal reflux exposure and dysphagia [6,7]. Since significant hypomotility is associated with impairment of normal bolus clearance [7], patients with severe hypomotility may be at higher risk for developing erosive esophagitis [8] and Barrett's esophagus [9].

In this cross-sectional study of patients with normal motility or hypomotility, we examined the relationship between motility categories and endoscopic findings, including erosive esophagitis and Barrett's esophagus. We combined the conventional Chicago Classification version 3.0 with the IEM criterion proposed in the Stanford symposium to separate IEM into 2 entities (severe or mild). Our hypothesis is that patients with severe IEM would have a greater burden of these esophageal injuries compared to those with mild IEM. Such findings, if present, suggest the need to expand the diagnostic paradigm for hypomotility disorders in the Chicago Classification version 3.0.

Patients and methods

We conducted a cross-sectional study among patients who had a diagnosis of normal motility, IEM, or absent contractility based on the Chicago Classification version 3.0 on high-resolution manometry (HRM) at the Institute of Gastroenterology and Hepatology, Hanoi, Vietnam, between March 2018 and May 2020. To exclude changes in esophageal motility due to the use of various treatment practices, only the first HRM measurements of those who had not received any treatment for motility disorders in the past 3 months were analyzed.

Data collection

Demographic information was obtained from electronic medical records. Body mass index (BMI) and clinical symptoms were collected in a routine patient form completed before patients underwent HRM. Clinical symptoms relevant to motility disorders and GERD were categorized into 3 main groups: typical symptoms (heartburn, regurgitation), obstructive symptom (dysphagia), and other atypical symptoms. The clinical severity of GERD was assessed using the GERD Questionnaire (GERDQ) [10] and the Frequency Scale from the Symptoms of GERDQ (FSSG) [11]. A clinical diagnosis of GERD was made when the GERDQ or FSSG total score was ≥8 [10,11]. We also collected data on the history of systemic diseases, such as systemic sclerosis, mixed connective tissue disorder or CREST syndrome, and performed a thorough clinical examination. Patients with symptoms that suggested these conditions would be referred to a dermatologist for more specialized investigations.

HRM

Indications for HRM included suspected esophageal motility disorders, refractory GERD, extraesophageal reflux symptoms, systemic disease with esophageal symptoms, and the need for determining the location of the lower esophageal sphincter (LES) prior to 24-h pH-impedance monitoring. HRM would be canceled or delayed if the patient had a history of gastroesophageal surgery or esophageal tumors, had active upper gastrointestinal bleeding on endoscopy, or had taken medications that affect esophageal motility (e.g., prokinetics, calcium channel blockers, nitrates, opiates, anticholinergics) during the past 48 h [12].

We used the Solar GI (Laborie) HRM system with 22-channel water-perfusion catheters. The results were interpreted based on the Chicago Classification version 3.0, with a 4-sec integrated relaxation pressure (IRP4s) of <19 mmHg being considered normal (according to the specification of the manufacturer). An esophageal swallow was classified into either normal, ineffective, failed, or fragmented swallow. The normal range of LES resting pressure was 10-45 mmHg; values below 10 mmHg were considered as LES hypotension [13]. The peristaltic reserve was assessed using the distal contractile integral (DCI) ratio, calculated by dividing the multi-rapid swallow DCI by the average DCI of single wet swallows [14].

After excluding patients with either a hypermotility disorder or impaired relaxation capacity (LES resting pressure ≥45 mmHg or IRP4s ≥19 mmHg), we categorized patients into those with normal motility, mild IEM (≥50% to ≤70% ineffective swallows), severe IEM (>70% ineffective swallows),

[a]Internal Medicine Faculty, Hanoi Medical University, Hanoi, Vietnam (Hang Viet Dao, Long Van Dao); [b]The Institute of Gastroenterology and Hepatology, Hanoi, Vietnam (Hang Viet Dao, Long Bao Hoang, Minh-Hue Thi Luu, Long Van Dao); [c]Department of Population and Quantitative Health Sciences, University of Massachusetts Medical School, Worcester, Massachusetts, USA (Hoa Lan Nguyen, Robert Goldberg, Jeroan Allison); [d]School of Public Health, University of Queensland, Herston, Australia (Minh-An Thi Dao); [e]Epidemiology Department, Hanoi Medical University, Hanoi, Vietnam (Minh-An Thi Dao); [f]Department of Gastroenterology, Graduate School of Medicine, Chiba University, Chiba, Japan (Tomoaki Matsumura)

Funding sources: This work was supported by funding from the Vietnam Ministry of Science and Technology and the D43 project, a collaborative project between Hanoi Medical University (Hanoi, Vietnam) and the University of Massachusetts Medical School (Worcester, MA, USA)

and absent contractility (100% failed peristalsis). The criteria for mild and severe IEM were adopted from the 2018 Stanford symposium [4]. Patients with fragmented peristalsis were too few to be included in the analysis.

Esophagogastroduodenoscopy (EGD) and *Helicobacter pylori* (*H. pylori*) testing

Endoscopic results were collected from patient's electronic medical records. We collected data on the presence of erosive esophagitis, Barrett's esophagus, and hiatal hernia. The severity of erosive esophagitis was evaluated using the Los Angeles (LA) classification [15]. According to the 2021 American College of Gastroenterology guidelines, LA grade B in the presence of typical symptoms and proton-pump inhibitor response, and LA grade C-D are diagnostic of GERD, whereas LA grade A is not sufficient for a definitive diagnosis of GERD [16]. Therefore, we grouped patients with LA grades B to D esophagitis into a single subgroup, making up 3 subgroups of patients with esophagitis (no esophagitis, LA grade A esophagitis, and LA grades B-D esophagitis). Barrett's esophagus on endoscopy was categorized as either short-segment (<3 cm in length) or long-segment (≥3 cm in length), and hiatal hernia was diagnosed on EGD if a Hill grade III or IV gastroesophageal flap valve was found in the retroflex view [17,18]. All of the procedures were performed and evaluated by endoscopists who had more than 5 years of experience. We reviewed the images of several categories of endoscopic results, including LA grades C-D esophagitis, long-segment Barrett's esophagus, and results without LA classification.

Per routine practice, *H. pylori* was tested for during endoscopy using the rapid urease test. Patients who tested negative were then tested again using the urea breath test to avoid false-negative urease test results. Patients were considered to be *H. pylori*-positive when at least one test result was positive and *H. pylori*-negative when both tests were negative.

Statistical analysis

The study population characteristics were expressed as percentages for categorical variables and means (standard deviation) or medians (interquartile range/min–max) for continuous variables. We compared differences in several patient characteristics between the 4 motility subgroups (normal, mild IEM, severe IEM, and absent contractility) using the chi-square test, one-way analysis of variance (ANOVA), or Kruskall-Wallis test where appropriate. The primary outcomes of the study were erosive esophagitis and Barrett's esophagus. To examine the association of hypomotility subgroups (mild IEM, severe IEM, and absent contractility) with erosive esophagitis, we used multinominal logistic regression. To examine the association with Barrett's esophagus, we used binary logistic regression. All the regression models were adjusted for potentially confounding characteristics, including male sex, older age, higher BMI, lower LES resting pressures [19-23], positive *H. pylori* state [19,24], and abnormal multiple rapid swallows [25]. Data were cleaned and analyzed using the Python programming language version 3.8.6.

Results

Study population characteristics

Between March 2018 and May 2020, a total of 3826 eligible patients were recruited and included in our analysis. The mean age of this study population was 44.7 years, two-thirds were women, and more than one-third were overweight (BMI ≥23 kg/m^2). The proportion of patients with normal motility, mild IEM, severe IEM and absent contractility were 41.8%, 21.7%, 32.4% and 4.1%, respectively. The prevalences of typical symptoms and dysphagia were higher in patients with absent contractility than in the IEM and normal groups, but not significantly different. Erosive esophagitis was present in 44.4% of patients (41.0% LA grade A and 3.4% LA grade B-D).

All 4 groups were similar in terms of clinical GERD severity and the prevalence of symptoms (Table 1), as well as the prevalence of hiatal hernia and *H. pylori* infection (Table 2). However, the mean IRP4s and LES resting pressure were lower in patients with severe IEM and absent contractility. In addition, fewer patients in the hypomotility subgroups had DCI ratio >1. LA grade B-D esophagitis and short-segment Barrett's esophagus were more common in patients with severe IEM and absent contractility.

Association of hypomotility with erosive esophagitis and Barrett's esophagus

In examining the association between hypomotility disorders and the presence of erosive esophagitis, severe IEM and absent contractility were not associated with LA grade A esophagitis but were significantly associated with LA grade B-D esophagitis (relative risk ratio (RRR) for severe IEM 1.81, 95% confidence interval (CI) 1.17-2.80; and RRR for absent contractility 2.37, 95%CI 1.12-5.04) (Table 3). Mild IEM was not associated with any grade of esophagitis. None of the hypomotility disorders was associated with Barrett's esophagus (Table 3).

Discussion

In this large observational study, we examined the association between esophageal lesions and the 4 HRM subgroups (normal motility, mild IEM, severe IEM, and absent contractility). Severe IEM and absent contractility were associated with more severe (LA grade B-D) esophagitis, independently of LES hypotension, hiatal hernia and impaired contraction reserve, but were not associated with LA grade A esophagitis and Barrett's esophagus.

Table 1 Study population characteristics according to the presence of motility disorders

Characteristics	Normal (n=1600)	Mild IEM (n=829)	Severe IEM (n=1239)	Absent contractility (n=158)	P-value
Age (year), mean (SD)	44.6 (11.8)	45.4 (11.9)	44.4 (12.3)	44.6 (14.7)	0.26[b]
Male, n (%)	573 (35.8)	276 (33.3)	383 (30.9)	58 (36.7)	0.04[a]
BMI (kg/m^2), mean (SD)	22.0 (2.6)	21.9 (2.4)	21.6 (2.5)	21.2 (2.5)	<0.001[b]
BMI group, n (%)					0.007[a]
Underweight (BMI <18.5)	121 (7.6)	64 (7.7)	118 (9.5)	24 (15.2)	
Normal (BMI 18.5-22.9)	857 (53.6)	499 (60.2)	755 (60.9)	81 (51.3)	
Overweight (BMI ≥23)	622 (38.9)	266 (32.1)	366 (29.5)	53 (33.5)	
Symptoms, n (%)					
Typical symptoms	1134 (70.9)	608 (73.3)	907 (73.2)	122 (77.2)	0.22[a]
Dysphagia	413 (25.8)	215 (25.8)	345 (27.8)	55 (34.8)	0.07[a]
Atypical symptoms	250 (15.6)	106 (12.8)	168 (13.6)	18 (11.4)	0.14[a]
GERD clinical scores					
GERDQ, median [IQR]	7.0 [6.0-9.0]	7.0 [6.0-9.0]	7.0 [6.0-9.0]	7.0 [6.0-9.0]	0.76[c]
FSSG, median [IQR]	11.0 [7.0-17.0]	11.0 [7.0-17.0]	12.0 [7.0-17.0]	12.5 [7.0-19.0]	0.15[c]
FSSG reflux, median [IQR]	5.0 [3.0-9.0]	6.0 [3.0-9.0]	6.0 [3.0-9.0]	6.0 [3.0-9.0]	0.22[c]
FSSG motility, median [IQR]	6.0 [3.0-9.0]	6.0 [3.0-9.0]	6.0 [3.0-10.0]	6.0 [3.0-11.0]	0.17[c]

Typical symptoms included heartburn and regurgitation. Atypical symptoms included nausea, vomiting, bloating, non-cardiac chest pain, weight loss, chronic cough, chronic pharyngitis, dyspnea and globus. Characteristics were compared among groups using [a]chi-square tests for categorical variables and [b]one-way analysis of variance (ANOVA) or [c]Kruskall-Wallis tests for continuous variables

BE, Barrett's esophagus; BMI, body mass index; DCI, distal contractile integral; GERD, gastroesophageal reflux disease; FSSG, frequency scale for the symptoms of GERD; GERDQ, GERD questionnaire; IEM, ineffective esophageal motility; IQR, interquartile range; SD, standard deviation

Table 2 Characteristics on endoscopy and high-resolution manometry according to the presence of motility disorders

Characteristics	Normal (n = 1,600)	Mild IEM (n = 833)	Severe IEM (n = 1,239)	Absent contractility (n = 158)	P-value
Endoscopy					
Esophagitis, n (%)					0.006[a]
No esophagitis	894 (55.9)	449 (54.2)	695 (56.1)	89 (56.3)	
Esophagitis, LA grade A	665 (41.6)	359 (43.3)	489 (39.5)	58 (36.7)	
Esophagitis, LA grade B-D	41 (2.6)	21 (2.5)	55 (4.4)	11 (7.0)	
Barrett's esophagus, n (%)					0.03[a]
No BE	1,522 (95.1)	792 (95.5)	1,159 (93.5)	146 (92.4)	
BE, short segment	56 (3.5)	27 (3.3)	70 (5.6)	10 (6.3)	
BE, long segment	22 (1.4)	10 (1.2)	10 (0.8)	2 (1.3)	
Hiatal hernia, n (%)	67 (4.2)	32 (3.9)	41 (3.3)	5 (3.2)	0.65[a]
Positive *H. pylori* test, n (%)	477 (29.8)	254 (30.6)	378 (30.5)	43 (27.2)	0.83[a]
High-resolution manometry					
UES resting pressure, median [min-max]	42.8 [2.7-257.9]	43.3 [3.3-194.3]	42.9 [2.1-199.8]	43.9 [-6.4-203.9]	0.83[b]
LES resting pressure, median [min-max]	19.6 [0.9-62.8]	17.2 [1.5-73.0]	14.5 [-0.7-59.8]	11.2 [0.4-42.0]	<0.001[b]
LES resting pressure <10 mmHg, n (%)	168 (10.5)	136 (16.4)	301 (24.3)	64 (40.5)	<0.001[a]
IRP4s, median [min-max]	5.4 [-1.0-18.7]	5.1 [-4.7-18.0]	4.6 [-3.0-18.8]	3.9 [-0.3-17.9]	<0.001[b]
DCI ratio <1, n (%)	996 (62.3)	499 (60.2)	736 (59.4)	70 (44.3)	<0.001[a]

Characteristics were compared among groups using [a]chi-square tests for categorical variables or [b]Kruskall-Wallis tests for continuous variables

BE, Barrett's esophagus; DCI, distal contractile integral; IEM, ineffective esophageal motility; H. pylori, Helicobacter pylori; IRP, integrated relaxation pressure; LA, Los Angeles classification of esophagitis; LES, lower esophageal sphincter; UES, upper esophageal sphincter

We found that there was a relationship between the severity of hypomotility and the prevalence of LA grade B-D esophagitis: the RRR was higher in patients with severe IEM and absent contractility. A 2018 study of 188 patients who underwent HRM and pH monitoring examined the cutoff to classify IEM using the Chicago Classification version 3.0, showing that patients with a higher proportion of ineffective and failed swallows were associated with higher total acid exposure time on pH monitoring [26]. Other studies have failed to find an association between IEM and GERD, although IEM was associated with prolonged acid exposure time and impaired esophageal clearance capacity [27-29]. Therefore, the observed

Table 3 Differences in the risk of esophagitis and Barrett's esophagus among patients with motility disorders

Motility disorder (Reference: Normal)	Esophagitis*		Barrett's esophagus** OR (95%CI)
	LA grade A RRR (95%CI)	LA grade B-D RRR (95%CI)	
Mild IEM	1.10 (0.92-1.31)	1.02 (0.59-1.77)	0.88 (0.59-1.32)
Severe IEM	0.98 (0.84-1.15)	1.81 (1.17-2.80)	1.25 (0.90-1.74)
Absent contractility	0.88 (0.62-1.26)	2.37 (1.12-5.04)	1.30 (0.68-2.49)

*Results from multinominal regression model. **Results from logistic regression model. The base outcome group for esophagitis was no esophagitis. All regression models were adjusted for age, sex, body mass index, Helicobacter pylori infection, hiatal hernia, lower esophageal sphincter hypotension, and distal contractile integral ratio <1

CI, confidence interval; IEM, ineffective esophageal motility; LA, Los Angeles classification of esophagitis; OR, odds ratio; RRR, relative risk ratio

higher prevalence of esophagitis in patients with severe IEM could be due to more impaired reflux clearance, suggesting that severe IEM should be distinguished from mild IEM because the patients might have different risks of developing esophagitis.

We also found that, compared with normal patients, the mean LES resting pressure and IRP4s, and the percentage of those with contraction reserve, were lower in patients with hypomotility, with a trend towards being lower in patients with more severe conditions. The adequacy of LES pressure and esophageal motility are major mechanisms that prevent reflux events. The combination of LES hypotension and esophageal hypomotility, as well as hiatal hernia, could predispose to the development of GERD [30].

The Chicago Classification version 4.0 has changed the working definition of IEM recommended for use in the Chicago Classification version 3.0 from ≥50% ineffective swallows to ≥70% ineffective swallows or ≥50% failed swallows [5]. Although the value of the new classification criteria will need to be evaluated in different populations, these changes reflect the current opinion that the earlier cutoff might be too low to detect clinically meaningful changes [4]. It is also noteworthy that the percentage of ineffective or failed single swallows on HRM is not the only diagnostic criteria for IEM. Different protocols for HRM, such as multi-rapid swallows, rapid drink challenges, or use of a single wet swallow in other positions, as well as use of the findings from other diagnostic techniques, such as functional luminal imaging probes, have been proposed to more systematically identify disorders of hypomotility that are clinically relevant [4,5].

This is one of the first studies that has explored the association between different severity levels of hypomotility and esophagitis. The large sample size of our study provided precise estimates of this association. However, our results should be interpreted within certain limitations. Data on erosive esophagitis and Barrett's esophagus were collected retrospectively; therefore, there might be inconsistency in the ascertainment of these outcomes. We attempted to minimize this bias by independently reviewing the endoscopic images to the extent possible. Our HRM system did not use an integrated impedance catheter, so we could not provide further information about bolus transport and esophageal clearance in the study sample. We did not perform pH-impedance monitoring, a better method for diagnosing GERD, and thus did not have the gold standard criteria for diagnosing patients with nonerosive reflux disease. However, the pH-impedance study is an expensive and resource-intensive approach and cannot be utilized in all patients with suspected GERD.

In conclusion, patients with severe IEM detected on HRM had a higher rate of severe erosive esophagitis compared to patients with mild IEM. Our findings suggest the use of a new cutoff, such as >70% ineffective swallows, to distinguish between mild and severe IEM, or another modification of the definition of IEM to make it a more clinically meaningful diagnosis.

Summary Box

What is already known:

- Hypomotility disorders are common; ineffective esophageal motility (IEM) is the most prevalent, but its clinical relevance is unclear
- The 2018 Stanford symposium and subsequent Chicago classification version 4.0 proposed new cutoff values for diagnosing IEM
- Severe hypomotility is associated with impaired bolus clearance and a higher risk for developing erosive esophagitis and Barrett's esophagus

What the new findings are:

- Severe IEM and absent contractility, but not mild IEM, were associated with Los Angeles (LA) grade B-D esophagitis, currently considered as a finding of gastroesophageal reflux disease on endoscopy
- None of the hypomotility subgroups were associated with LA grade A esophagitis and Barrett's esophagus

References

1. Kahrilas PJ, Bredenoord AJ, Fox M, et al; International High Resolution Manometry Working Group. The Chicago Classification of esophageal motility disorders, v3.0. *Neurogastroenterol Motil*

2015;**27**:160-174.
2. Martinucci I, de Bortoli N, Giacchino M, et al. Esophageal motility abnormalities in gastroesophageal reflux disease. *World J Gastrointest Pharmacol Ther* 2014;**5**:86-96.
3. Liu L, Li S, Zhu K, et al. Relationship between esophageal motility and severity of gastroesophageal reflux disease according to the Los Angeles classification. *Medicine (Baltimore)* 2019;**98**:e15543.
4. Gyawali CP, Sifrim D, Carlson DA, et al. Ineffective esophageal motility: Concepts, future directions, and conclusions from the Stanford 2018 symposium. *Neurogastroenterol Motil* 2019;**31**:e13584.
5. Yadlapati R, Kahrilas PJ, Fox MR, et al. Esophageal motility disorders on high-resolution manometry: Chicago classification version 4.0((c)). *Neurogastroenterol Motil* 2021;**33**:e14058.
6. Jain A, Baker JR, Chen JW. In ineffective esophageal motility, failed swallows are more functionally relevant than weak swallows. *Neurogastroenterol Motil* 2018;**30**:e13297.
7. Chugh P, Collazo T, Dworkin B, Jodorkovsky D. Ineffective esophageal motility is associated with impaired bolus clearance but does not correlate with severity of dysphagia. *Dig Dis Sci* 2019;**64**:811-814.
8. Fornari F, Callegari-Jacques SM, Scussel PJ, Madalosso LF, Barros EF, Barros SG. Is ineffective oesophageal motility associated with reflux oesophagitis? *Eur J Gastroenterol Hepatol* 2007;**19**:783-787.
9. Sanagapalli S, Emmanuel A, Leong R, et al. Impaired motility in Barrett's esophagus: A study using high-resolution manometry with physiologic challenge. *Neurogastroenterol Motil* 2018;**30**:e13330.
10. 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.
11. Kusano M, Shimoyama Y, Sugimoto S, et al. Development and evaluation of FSSG: frequency scale for the symptoms of GERD. *J Gastroenterol* 2004;**39**:888-891.
12. Trudgill NJ, Sifrim D, Sweis R, et al. British Society of Gastroenterology guidelines for oesophageal manometry and oesophageal reflux monitoring. *Gut* 2019;**68**:1731-1750.
13. Sloan S, Rademaker AW, Kahrilas PJ. Determinants of gastroesophageal junction incompetence: hiatal hernia, lower esophageal sphincter, or both? *Ann Intern Med* 1992;**117**:977-982.
14. Shaker A, Stoikes N, Drapekin J, Kushnir V, Brunt LM, Gyawali CP. Multiple rapid swallow responses during esophageal high-resolution manometry reflect esophageal body peristaltic reserve. *Am J Gastroenterol* 2013;**108**:1706-1712.
15. 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.
16. Katz PO, Dunbar KB, Schnoll-Sussman FH, Greer KB, Yadlapati R, Spechler SJ. ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease. *Am J Gastroenterol* 2022;**117**:27-56.
17. Kahrilas PJ, Kim HC, Pandolfino JE. Approaches to the diagnosis and grading of hiatal hernia. *Best Pract Res Clin Gastroenterol* 2008;**22**:601-616.
18. Sampliner RE. Practice guidelines on the diagnosis, surveillance, and therapy of Barrett's esophagus. The Practice Parameters Committee of the American College of Gastroenterology. *Am J Gastroenterol* 1998;**93**:1028-1032.
19. Labenz J, Jaspersen D, Kulig M, et al. Risk factors for erosive esophagitis: a multivariate analysis based on the ProGERD study initiative. *Am J Gastroenterol* 2004;**99**:1652-1656.
20. Ou JL, Tu CC, Hsu PI, et al. Prevalence and risk factors of erosive esophagitis in Taiwan. *J Chin Med Assoc* 2012;**75**:60-64.
21. Lin S, Li H, Fang X. Esophageal motor dysfunctions in gastroesophageal reflux disease and therapeutic perspectives. *J Neurogastroenterol Motil* 2019;**25**:499-507.
22. Chait MM. Gastroesophageal reflux disease: Important considerations for the older patients. *World J Gastrointest Endosc* 2010;**2**:388-396.
23. Ireland CJ, Thompson SK, Laws TA, Esterman A. Risk factors for Barrett's esophagus: a scoping review. *Cancer Causes Control* 2016;**27**:301-323.
24. Sharma N, Ho KY. Risk factors for Barrett's oesophagus. *Gastrointest Tumors* 2016;**3**:103-108.
25. Min YW, Shin I, Son HJ, Rhee PL. Multiple rapid swallow maneuver enhances the clinical utility of high-resolution manometry in patients showing ineffective esophageal motility. *Medicine (Baltimore)* 2015;**94**:e1669.
26. Rengarajan A, Bolkhir A, Gor P, Wang D, Munigala S, Gyawali CP. Esophagogastric junction and esophageal body contraction metrics on high-resolution manometry predict esophageal acid burden. *Neurogastroenterol Motil* 2018;**30**:e13267.
27. Leite LP, Johnston BT, Barrett J, Castell JA, Castell DO. Ineffective esophageal motility (IEM): the primary finding in patients with nonspecific esophageal motility disorder. *Dig Dis Sci* 1997;**42**:1859-1865.
28. Kasamatsu S, Matsumura T, Ohta Y, et al. The effect of ineffective esophageal motility on gastroesophageal reflux disease. *Digestion* 2017;**95**:221-228.
29. Dao HV, Matsumura T, Kaneko T, et al. Impact of ineffective esophageal motility on chemical clearance in patients with gastroesophageal reflux symptoms. *Dis Esophagus* 2020;**33**:doaa026.
30. Mello M, Gyawali CP. Esophageal manometry in gastroesophageal reflux disease. *Gastroenterol Clin North Am* 2014;**43**:69-87.