Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.6715-20
Intern Med 60: 2537-2543, 2021
http://internmed.jp

【 ORIGINAL ARTICLE 】

The Evaluation of Esophageal Endoscopic Findings in Patients with Functional Esophagogastric Junction Outflow Obstruction

Yorinari Ochiai, Daisuke Kikuchi, Kosuke Nomura, Takayuki Okamura, Junnosuke Hayasaka, Yugo Suzuki, Nobuhiro Dan, Yutaka Mitsunaga, Masami Tanaka, Hiroyuki Odagiri, Satoshi Yamashita, Akira Matsui and Shu Hoteya

Abstract:

Objective Esophagogastric junction outflow obstruction (EGJOO) is a diagnosis of unclear significance that has become increasingly common with recent advances in high-resolution manometry (HRM). EGJOO can be divided into mechanical or functional obstruction. Functional EGJOO is considered an incomplete phenotype or an early stage of achalasia. However, little is known about the endoscopic findings in patients with functional EGJOO. Thus, we aimed to elucidate the endoscopic findings in patients with functional EGJOO and to identify patients at high risk for achalasia.

Methods This was a single-center retrospective study. A total of 259 patients underwent esophagogastroduodenoscopy (EGD) along with HRM for upper gastrointestinal symptoms without any obstructive lesions or stricture between July 2013 and September 2019 in our institute. Among them, 31 patients were diagnosed with EGJOO. After excluding patients who had undergone previous endoscopic treatment, those who were diagnosed with eosinophilic esophagitis and those who had undergone EGD at other institutes, 23 patients were finally included with a diagnosis of functional EGJOO. The endoscopic findings were evaluated by three endoscopists.

Results Five patients (21.7%) had an esophageal rosette sign (ERS). No patients had grade IV gastroesophageal flap valve, esophageal mucosal breaks, or abnormal retention of liquid or food in the esophagus. Manometric findings revealed that the median distal contractile integral value was significantly higher in patients with an ERS (n=5) than in those without it (n=18).

Conclusion There were some patients with functional EGJOO who had an ERS, which is the characteristic endoscopic finding in achalasia.

Key words: esophagogastric junction outflow obstruction, functional, esophageal rosette sign, endoscopy, achalasia

(Intern Med 60: 2537-2543, 2021)
(DOI: 10.2169/internalmedicine.6715-20)

Introduction

Esophagogastric junction outflow obstruction (EGJOO) is a diagnosis made by high-resolution manometry (HRM) and is characterized by incomplete relaxation of the esophagogastric junction (EGJ) in combination with preserved peristalsis (Fig. 1) (1, 2). Conversely, esophageal achalasia is diagnosed by demonstrating impaired EGJ relaxation and the absence of peristalsis (1). EGJOO is said to encompass a heterogeneous group of patients with primary or idiopathic (functional) and secondary (mechanical) outflow obstruction (3). In addition, functional EGJOO is considered an incomplete phenotype or an early stage of achala-

Department of Gastroenterology, Toranomon Hospital, Japan
Received: November 12, 2020; Accepted: January 14, 2021; Advance Publication by J-STAGE: March 8, 2021
Correspondence to Dr. Yorinari Ochiai, y.ochiai.1987@gmail.com

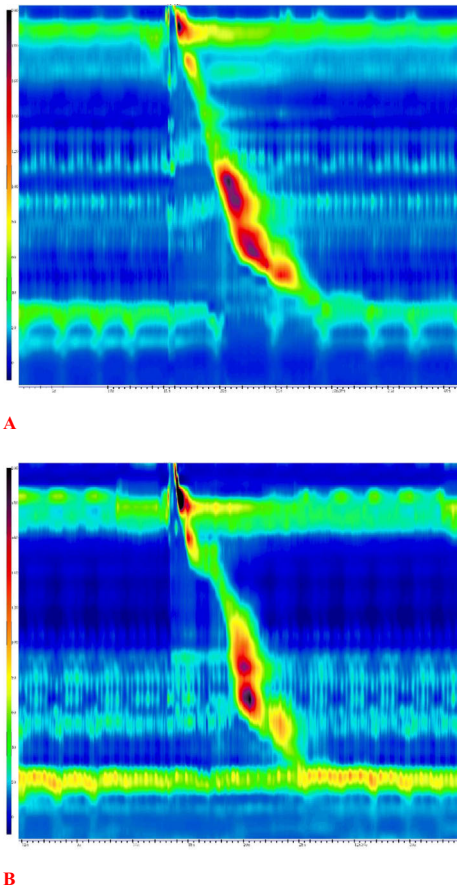

Figure 1. Representative images of high-resolution manometry. (A) A patient without obstruction. The EGJ pressure decreases when swallowing (IRP=11.5 mmHg). (B) A patient with esophagogastric outflow obstruction. The EGJ pressure remains high when swallowing (IRP=42.2 mmHg). EGJ: esophagogastric junction, IRP: integrated relaxation pressure

sia that is difficult to differentiate from achalasia, as both disorders present with dysphagia, regurgitation, chest pain, and weight loss (4).

EGJOO is a diagnosis of unclear significance that has become increasingly common with recent advances in HRM. However, the etiology of this disease has not been clearly determined (3). One reason for this is the current definition recommended by the Chicago classification version 3.0 (CC, version 3.0) (5). The findings for functional EGJOO consist of the absence of a mechanical etiology, which is accompanied by clinical uncertainty. To differentiate functional from mechanical EGJOO, it is essential to perform esophagogastroduodenoscopy (EGD), which is almost always performed prior to HRM (6). However, little has been reported regarding the esophageal endoscopic findings in patients with functional EGJOO. Furthermore, using EGD to identify patients at high risk of developing achalasia among those with functional EGJOO would be helpful in daily practice.

The present study clarified the endoscopic findings in patients with functional EGJOO diagnosed by HRM and identified patients at high risk for achalasia using EGD.

Materials and Methods

Study design

The study was a single-center retrospective study.

Patients

A total of 259 patients underwent EGD with HRM for upper gastrointestinal symptoms without any obstructive lesions or stricture from July 2013 to September 2019 in our institute. Manometric diagnoses were conducted based on the CC, version 3.0. Among them, 31 patients were diagnosed with EGJOO. We excluded eight patients (two patients after previous endoscopic treatments, two patients with eosinophilic esophagitis and four patients who underwent EGD at other institutes). As a result, 23 patients were finally included with a diagnosis of functional EGJOO (Fig. 2).

Definition of functional EGJOO

EGJOO is defined as a condition in which patients showed impaired EGJ relaxation and preserved esophageal peristalsis that is diagnosed using manometry based on the CC, version 3.0. Among them, the patients without any endoscopic abnormalities that explained the manometric changes were considered to have functional EGJOO.

The evaluation of symptoms

Symptoms were recorded using questionnaires and assessed using the Eckardt scores (7).

HRM

The catheter was inserted nasally, positioned to extend over both the upper and lower esophageal sphincter (LES), and fixed to the nose with tape. After 5 minutes of rest, 10 mouthfuls of water (5 mL per mouthful) were swallowed in the supine position. HRM was carried out using a Starlet® HRM system (Star Medical, Tokyo, Japan). This system has a catheter with a 36-channel solid-state sensor spaced at 1-cm intervals (Unisensor, Attikon, Switzerland). Esophageal motility was described according to the CC, version 3.0. The upper limit of normal for the integrated relaxation pressure (IRP) was set at 26 mmHg, and the normal range for distal contractile integral (DCI) was set between 1,500 and 13,000 mmHg·s·cm, which also accounted for the differences in IRP and DCI based on the type of HRM catheter used (8).

The endoscopic evaluation

EGD was performed using the GIF-Q260, GIF-H260, or GIF-H290Z endoscope (Olympus, Tokyo, Japan), either in a fully conscious state or under conscious sedation achieved using pethidine hydrochloride. We evaluated the EGJ morphology in all patients for the presence of three endoscopic findings based on previous studies: esophageal rosette sign (ERS) (9), gastroesophageal flap valve (10), and esophageal

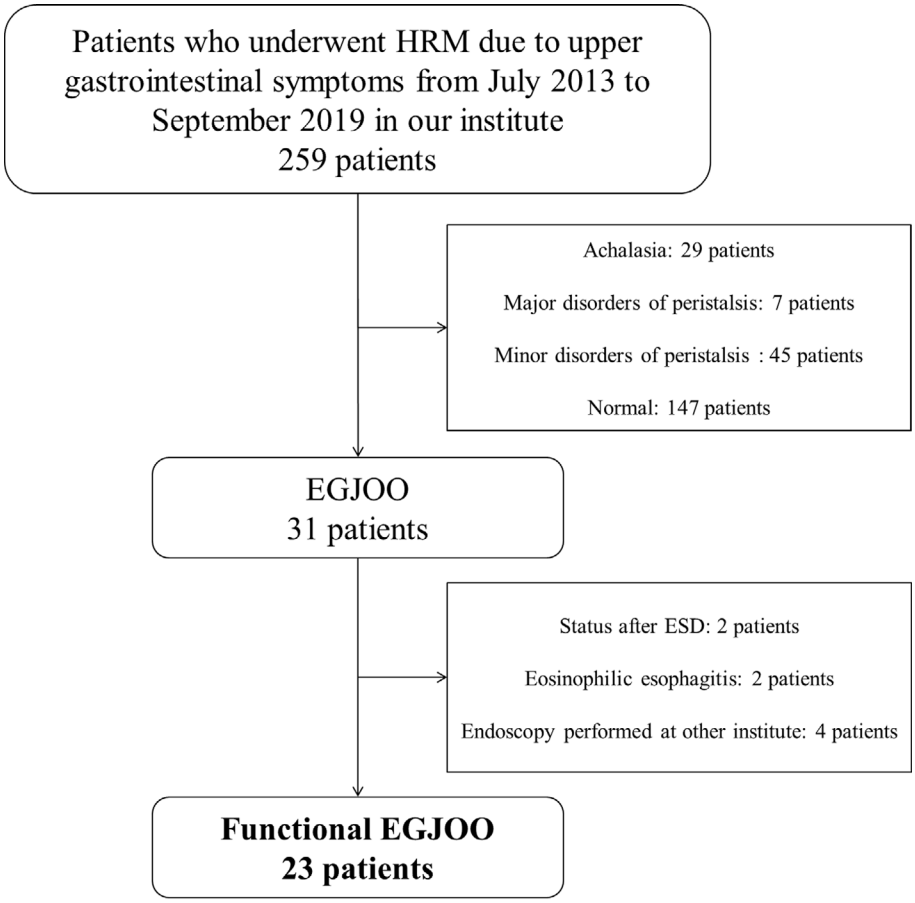

Figure 2. **Flowchart of the study design. HRM: high-resolution manometry, EGJOO: esophagogastric junction outflow obstruction, ESD: endoscopic submucosal dissection**

mucosal breaks. ERS was defined as the non-visibility of the full extent of the esophageal palisade vessels above the EGJ and the appearance of rosette-like folds at the luminal center of the lower esophagus, after a deep inspiration by the patients while air was pumped into the lower esophagus by endoscopy (Fig. 3). The presence of a grade IV gastroesophageal flap valve was indicative of esophageal hiatal hernia in this study (Fig. 4). The mucosal breaks were defined as per the Los Angeles classification (11). Aside from the above-mentioned EGJ morphology, abnormal retention of liquid or food in the esophagus, which is often seen in patients with achalasia, and the presence of features suggestive of atrophic gastritis were also evaluated.

Three endoscopists reviewed the observations of 23 patients retrospectively and evaluated their endoscopic findings; the evaluators were blinded to patient information. If the diagnosis did not match among the three endoscopists, the final diagnosis was decided after deliberation.

Study endpoints

The primary endpoint was set as the presence of abnormal morphology on EGD based on the presence of the following three endoscopic findings: ERS, gastroesophageal flap valve and esophageal mucosal breaks, and abnormal retention of liquid or food in the esophagus. We set the secondary endpoint as the clinical differences between the patients with ERS and those without.

Statistical analyses

The chi-squared and Fisher's exact test were used for the inter-group comparison of qualitative variables, and the Mann-Whitney U test was used for the comparison of quantitative variables. All statistical analyses were performed using the SPSS software program for Windows, version 25.0 (IBM, Armonk, USA). A p value <0.05 was considered statistically significant.

Ethical approval

This study was retrospective in nature and was performed according to the ethical principles of the Declaration of Helsinki for medical research involving human subjects. The protocol was approved by the Ethics Committee of Toranomon Hospital.

Results

Patient characteristics

Patient characteristics are shown in Table 1. The median (interquartile range; IQR) age of the 23 patients was 66 (54-72) years old, and 5 (21.7%) patients were men. The most common major symptom was dysphagia, which was seen in

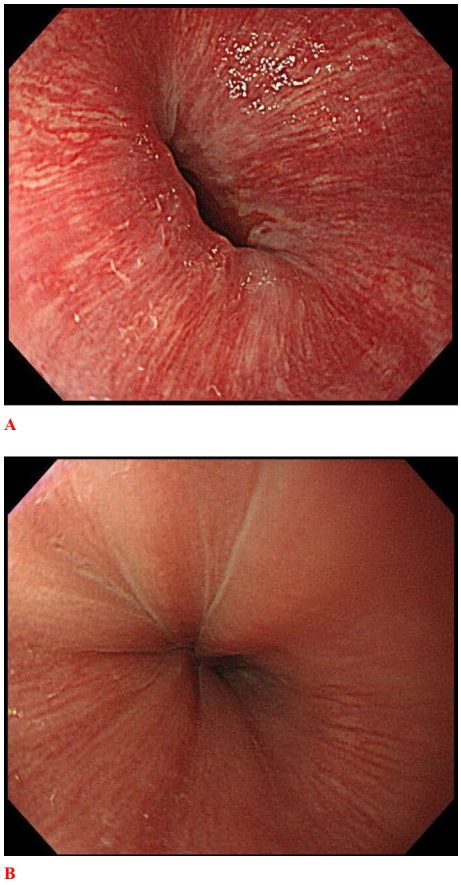

Figure 3. **Representative images of the esophagogastric junction. (A) Normal. (B) Esophageal rosette sign.**

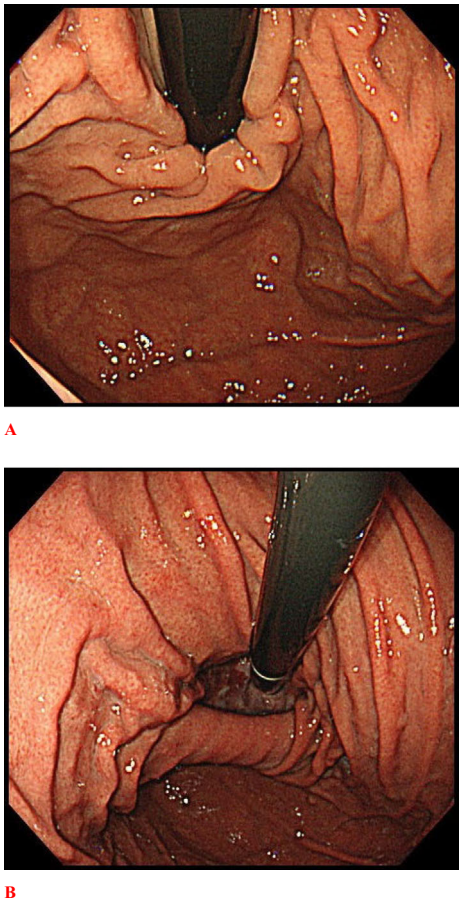

Figure 4. **Representative images of the gastroesophageal flap valve. (A) Grade I gastroesophageal flap valve. (B) Grade IV gastroesophageal flap valve.**

13 patients (56.5%). The median (IQR) duration of symptoms and the Eckardt scores were 18 (5-48) months and 2 (1-3) points, respectively. Twelve patients (52.2%) had no evidence of atrophy in the stomach. HRM revealed that the median (IQR) IRP was 31.2 (28.6-34.4) mmHg, which was higher than the upper limit of normal. Other metrics related to the manometric diagnosis based on the CC, version 3.0, were within normal limits.

Primary endpoint

Five patients (21.7%) had ERS, whereas there were no patients with grade IV gastroesophageal flap valve, esophageal mucosal breaks, or the abnormal retention of liquid or food in the esophagus (Table 2).

Secondary endpoint

The comparison between patients with and without ERS is shown in Table 3. There were no significant differences in the patient characteristics, such as the age, gender, and symptoms. Among the HRM findings, the median value of mean DCI was significantly higher in patients with ERS (4,865 mmHg·s·cm) than in those without ERS (3,597 mmHg·s·cm) (p=0.046). In addition, median values of IRP and mean LES pressure were higher in patients with ERS (35.1 and 63.4 mmHg) than in those without ERS (30 and 49.3 mmHg), respectively. However, they were not statistically significant (both p=0.067).

Discussion

The present study mainly investigated the esophageal endoscopic findings of functional EGJOO, diagnosed by HRM. Esophageal obstructive lesions or strictures were ruled out by EGD. ERS was seen in 21.7% of the patients. There were no patients with grade IV gastroesophageal flap valve, esophageal mucosal breaks, or abnormal retention of liquid or food in the esophagus. With regard to HRM, the median DCI value was significantly higher in patients with ERS than in those without it. Even though the findings were not significant, the median values of IRP and mean LES pressure in patients with ERS were higher than in those without it.

The diagnosis of EGJOO is based solely on the interpretation of HRM. The purpose of further workup is to differentiate the patients into subgroups (mechanical or functional) and to better characterize the nature of any potential obstruction, which cannot be made with HRM (6). EGD and barium esophagogram are reportedly first-line investigations and are likely to have complementary roles (6). However, the previous literature has predominantly reported the find-

Table 1. Patient Characteristics.

Patients, n	23
Age (years), median (IQR)	66 [54-72]
Gender, male (%)	5 (21.7)
Main symptom, n (%)	
Dysphagia	13 (56.5)
Heartburn	3 (13)
Chest pain	2 (8.7)
Globus sensation	4 (17.4)
Others	1 (4.4)
Symptom duration (months), median (IQR)	18 [5-48]
Eckardt score, median (IQR)	2 [1-3]
No atrophy in the stomach, n (%)	12 (52.2)
Follow-up period after first HRM (days), median (IQR)	484 [130-1,080]
IRP (mmHg), median (IQR)	31.2 [28.6-34.4]
Mean LES pressure (mmHg), median (IQR)	54 [43.2-61.3]
UES basal pressure (mmHg), median (IQR)	64 [38.9-81.6]
DCI mean (mmHg·s·cm), median (IQR)	4,025 [2,324-4,865]
DCI max (mmHg·s·cm), median (IQR)	5,386 [4,255-6,579]
DL (s), median (IQR)	6.9 [6.2-7.4]

IQR: interquartile range, HRM: high-resolution manometry, IRP: integrated relaxation pressure, LES: lower esophageal sphincter, UES: upper esophageal sphincter, DCI: distal contractile integral, DL: distal latency

Table 2. Esophageal Endoscopic Findings in Patients with Functional Esophagogastric Junction Outflow Obstruction.

Endoscopic findings	Patients, n (%)
Esophageal rosette sign	5 (21.7)
Gastroesophageal flap valve (grade IV)	0
Esophageal mucosal breaks	0
Abnormal retention of liquid or food in the esophagus	0

Table 3. The Comparison between Patients with ERS and Those without It.

	Patients with ERS n=5	Patients without ERS n=18	p value
Age (years), median (IQR)	60 [47-74]	67 [56-72]	0.801
Gender, male (%)	0	5 (27.8)	0.545
Dysphagia, n (%)	4 (80)	9 (50)	0.339
Symptom duration (months), median (IQR)	5 [2.8-33.5]	18 [6.5-48]	0.172
Eckardt score, median (IQR)	2 [1-4.5]	2 [1-3]	0.638
No atrophy in the stomach, n (%)	2 (40)	10 (55.6)	0.640
IRP (mmHg), median (IQR)	35.1 [30.7-43.7]	30 [28.6-33.9]	0.067
Mean LES pressure (mmHg), median (IQR)	63.4 [49.9-71.5]	49.3 [42.4-59.2]	0.067
UES basal pressure (mmHg), median (IQR)	77 [46-95.8]	65.7 [40.2-88.1]	0.638
DCI mean (mmHg·s·cm), median (IQR)	4,865 [4,416-5,908]	3,597 [2,290-4,873]	0.046
DCI max (mmHg·s·cm), median (IQR)	6,269 [5,372-7,679]	5,299 [3,554-6,633]	0.150
DL (s), median (IQR)	6.5 [5.7-7.5]	6.9 [6.5-7.9]	0.403

ERS: esophageal rosette sign, IQR: interquartile range, IRP: integrated relaxation pressure, LES: lower esophageal sphincter, UES: upper esophageal sphincter, DCI: distal contractile integral, DL: distal latency

ings of mechanical obstruction, and very few studies have described the findings of functional obstruction. One study reported that hiatal hernia was seen in 31%, rings in 15%, esophagitis in 7%, and a mass in 2% of patients with mechanical obstruction (12). In contrast, 14.3% (2/14) of patients with functional EGJOO reportedly had abnormal EGD findings, such as resistance when passing through EGJ, residue in the esophageal lumen, and nonocclusive contraction. However, a multivariate logistic regression analysis revealed that functional EGJOO was not associated with endoscopic

parameters (13). In our retrospective study, we investigated patients with functional EGJOO, and 21.7% of these patients had the ERS. Iwakiri et al. reported that ERS, the appearance of rosette-like esophageal folds, was a characteristic endoscopic finding in primary achalasia due to the high prevalence of ERS in patients with achalasia compared to the control subjects (97.1% and 0%, respectively) (9). To our knowledge, no previous study has investigated the prevalence of ERS in patients with esophageal motor disorders except achalasia. Given that the prevalence of ERS was 0% in the normal control group, its prevalence in functional EGJOO cases can be considered relatively high.

Based on our results, patients with functional EGJOO could be divided into two groups: those with and those without ERS. On comparing the manometric findings between the two groups, the median value of mean DCI was significantly higher in the patients with ERS than in those without it. The median values of IRP and mean LES pressure in patients with ERS were also higher than in those without it, but not to a significant degree. These results show that patients with ERS had manometric findings similar to those with achalasia with respect to the IRP and mean LES pressure. Furthermore, the results observed for the median value of the mean DCI in this study might indicate the existence of compensation for esophageal clearance.

Functional EGJOO is considered to be an incomplete phenotype or an early stage of achalasia, and transformation of EGJOO to type II achalasia has been reported (14). Furthermore, a study reported that 3 of 34 patients with functional EGJOO developed achalasia at follow-up (3). No patients in our study were diagnosed with achalasia in the follow-up period. This might be because the median follow-up period was relatively short (484 days), especially in the patients with ERS (131 days). Although a small number of the patients who developed achalasia has been reported so far, we consider the presence of ERS to be useful not only for achalasia but also for functional EGJOO. ERS might be one of the more reliable findings for predicting which patients might develop achalasia. The further accumulation and assessment of similar cases is required.

Several treatments, such as per-oral endoscopic myotomy (POEM), botulinum toxin injection, Heller myotomy, pneumatic dilatation, smooth muscle relaxant therapy, and proton-pump inhibitor (PPI) therapy, have been suggested for EGJOO. However, a review reported that over 50% of patients were given no therapy, with response rates of 52.0-92.3% (6). Although EGJOO treatment should be tailored to the underlying etiology and presenting symptoms, we believe that EGJOO with ERS should be treated more proactively than that without ERS.

Several limitations associated with the present study warrant mention. First, this was a retrospective study in a single institute, and the number of patients was relatively small. Second, the men-to-women ratio was biased toward women. Finally, the endoscopic findings were also evaluated retrospectively. However, this study was the first to elucidate the endoscopic findings in patients with functional EGJOO. We believe that our findings will help identify patients with functional EGJOO who are likely to develop achalasia.

Conclusion

In conclusion, the present study revealed the endoscopic findings of the EGJ morphology in patients with functional EGJOO. There were some patients who had ERS, which is often seen in achalasia.

The authors state that they have no Conflict of Interest (COI).

References

1. Scherer JR, Kwiatek MA, Soper NJ, Pandolfino JE, Kahrilas PJ. Functional esophagogastric junction obstruction with intact peristalsis: a heterogeneous syndrome sometimes akin to achalasia. J Gastrointest Surg **13**: 2219-2225, 2009.
2. Bredenoord AJ, Fox M, Kahrilas PJ, Pandolfino JE, Schwizer W, Smout AJ. Chicago classification criteria of esophageal motility disorders defined in high resolution esophageal pressure topography. Neurogastroenterol Motil **24** (Suppl): 57-65, 2012.
3. van Hoeij FB, Smout AJ, Bredenoord AJ. Characterization of idiopathic esophagogastric junction outflow obstruction. Neurogastroenterol Motil **27**: 1310-1316, 2015.
4. Furuzawa-Carballeda J, Coss-Adame E, Romero-Hernandez F, et al. Esophagogastric junction outflow obstruction: characterization of a new entity? Clinical, manometric, and neuroimmunological description. Neurogastroenterol Motil **32**: e13867, 2020.
5. Kahrilas PJ, Bredenoord AJ, Fox M, et al. The Chicago Classification of esophageal motility disorders, v3.0. Neurogastroenterol Motil **27**: 160-174, 2015.
6. Zikos TA, Triadafilopoulos G, Clarke JO. Esophagogastric junction outflow obstruction: current approach to diagnosis and management. Curr Gastroenterol Rep **22**: 9, 2020.
7. Eckardt VF, Aignherr C, Bernhard G. Predictors of outcome in patients with achalasia treated by pneumatic dilation. Gastroenterology **103**: 1732-1738, 1992.
8. Kuribayashi S, Iwakiri K, Kawada A, et al. Variant parameter values-as defined by the Chicago Criteria-produced by ManoScan and a new system with Unisensor catheter. Neurogastroenterol Motil **27**: 188-194, 2015.
9. Iwakiri K, Hoshihara Y, Kawami N, et al. The appearance of rosette-like esophageal folds ("esophageal rosette") in the lower esophagus after a deep inspiration is a characteristic endoscopic finding of primary achalasia. J Gastroenterol **45**: 422-425, 2010.
10. Contractor QQ, Akhtar SS, Contractor TQ. Endoscopic esophagitis and gastroesophageal flap valve. J Clin Gastroenterol **28**: 233-237, 1999.
11. Armstrong D, Bennett JR, Blum AL, et al. The endoscopic assessment of esophagitis: a progress report on observer agreement. Gastroenterology **111**: 85-92, 1996.
12. Okeke FC, Raja S, Lynch KL, et al. What is the clinical significance of esophagogastric junction outflow obstruction? evaluation of 60 patients at a tertiary referral center. Neurogastroenterol Motil **29**: 2017.
13. Matsubara M, Manabe N, Ayaki M, et al. Clinical significance of esophagogastroduodenoscopy in patients with esophageal motility disorders. Dig Endosc. Forthcoming.
14. Shin IS, Min YW, Rhee PL. Esophagogastric Junction Outflow Obstruction Transformed to Type II Achalasia. J Neurogastroenterol Motil **22**: 344-345, 2016.