New endoscopic classification of esophageal mucosa in achalasia: A predictor for submucosal fibrosis

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Abstract

Background/Aim: In this study, we aim to investigate the predicting ability of one new endoscopic classification of esophageal mucosa in achalasia (EMIA) for submucosal fibrosis (SMF) affecting the success of peroral endoscopic myotomy (POEM).

Patients and Methods: The endoscopic and clinical data of achalasia patients undergoing POEM from 2012 to 2016 were investigated retrospectively. According to the endoscopic images or videos, EMIA and SMF grades were recorded. The relation between EMIA and SMF gradings was assessed by Spearman's rank correlation, and the predictive factors of SMF were identified by logistic regression analysis.

Results: A total of 568 achalasia patients who underwent POEM were enrolled. For EMIA classification, there were 40 (7.0%), 373 (65.7%), 139 (24.5%), 14 (2.5%), 1 (0.2%), and 1 (0.2%) case (s) for grades a, b, c, d, e1, and f4, respectively. POEM procedures were aborted in 16 patients, and 93.8% (15/16) were due to severe SMF. Because grades e and f were rare and the related SMF was obvious, these two grading cases were excluded from the following analysis. Correlation between EMIA and SMF gradings was significant (Spearman r = 0.62, $P < 0.01$). Multivariate logistic analysis, including age, sex, disease duration, Ling classification, previous treatment, and EMIA classification, demonstrated that the EMIA classification (grades c to d) was an independent predictor for advanced SMF (odds ratio = 26.547, 95% confidence interval: 15.809–44.578, $P < 0.01$).

Conclusions: The new endoscopic EMIA classification is an independent predictor of advanced SMF during POEM. The classification may be used for assessment of the difficulty and success of POEM.

Keywords: Achalasia, endoscopic classification, peroral endoscopic myotomy, submucosal fibrosis

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INTRODUCTION

Achalasia is one type of primary esophageal motility disorder, which is characterized by absent esophageal peristalsis and incomplete relaxation of the lower esophageal sphincter (LES).[1-5] Therefore, achalasia patients usually complain of dysphagia, regurgitation, retrosternal pain, and weight loss.[1-3] However, the etiology of the disease remains unclear, probably involving infection, autoimmunity, and heredity.[3-5] Consequently, the current management is mainly focused on relieving the esophageal outflow obstruction by lowering LES pressure to improve quality of life.[3,6,7] At present, the available interventional therapies include botulinum toxin injection (BTI), pneumatic balloon dilation (PBD), endoscopic stent placement (ESP), Heller myotomy (HM), and peroral endoscopic myotomy (POEM).[6,7]

POEM, based on submucosal tunneling techniques, has been established as the primary and preferred treatment for achalasia at many centers.[2,7-10] The indications of POEM for achalasia have expanded from simple ones to those with sigmoid esophagus and failed remission of previous therapies, including BTI, PBD, ESP, HM.[2,9] However, submucosal fibrosis (SMF) remains an obstacle to successful operation of POEM procedures.[2] Severe SMF precludes the establishment of submucosal tunnel, and then can result in prolonged duration, unexpected complications, and even procedure failure.[2,6,11,12] Because the operator's experience can affect operation outcomes, it is possible to select operators according to the skill required for a given operation by predicting the degree of SMF before POEM. However, there are no reports about predicting the degree of SMF before POEM.

Based on reviewing and analyzing the endoscopic pictures of 1869 achalasia patients, we proposed one new endoscopic classification of esophageal mucosa in achalasia (EMIA) in 2015. The EMIA classification is based on the changes of the mucosal and submucosal vasculature, and recorded as grades a to f. The detailed grades are shown in [Figure 1]. Grades e and f are further divided into four subgroups, respectively, according to the ulcer or scar involvement of esophageal circumference. However, the clinical significance of the classification is unknown. This study aimed to determine the usefulness of EMIA classification in assessment of SMF, and identify predictive factors of SMF in achalasia patients.

PATIENTS AND METHODS

This retrospective study was approved by the Medical Ethics Committee of Chinese PLA general hospital. The endoscopic and clinical data of achalasia patients who underwent POEM from January 2012 to December 2016 in our department were retrospectively reviewed. All of the patients signed the informed consent before POEM. All the POEM procedures were performed under general anesthesia and the standard procedures were recorded in previous report.[13] According to the aim of the study, patients with clear images or videos of esophageal mucosa before POEM and submucosal layer after injection during POEM were enrolled. The baseline characteristics, including previous treatment history, were extracted from clinical records. The related images or videos were collected and examined by two expert endoscopists who had more than 5 years of POEM operation experience, respectively. If the two endoscopists had different opinions, they would discuss it to come to a final decision. They were blinded to the patient information and history.

Endoscopic classifications and definitions

The EMIA classification was based on the endoscopic images of esophageal mucosa. According to the changes of the esophageal mucosal and submucosal vasculature, six grades were recorded [Figure 1]. The smooth mucosa with clear vascular texture was defined as grade a; grade b was defined as rough mucosa with vague vascular texture; grade c meant that the mucosa was granular without obvious vascular texture; grade d was defined when the mucosa was pachyntic, striated, or like sulcus; grade e was defined when there was ulcer in the mucosa; and grade f was recorded when there was scar in the mucosa. Grades e and f were further classified into four subtypes according to the involvement of esophageal circumference: (1) ulcer/scar ≤1/4; (2) 1/4 < ulcer/scar ≤ 1/2; (3) 1/2 < ulcer/scar ≤3/4; (4) ulcer/scar > 3/4. The subtypes determine the feasibility of submucosal tunnel establishment.

To evaluate the degree of SMF, one new SMF classification system was proposed based on the submucosal images at the time of submucosal injection during POEM [Figure 2]. Fibrosis assessed during POEM was classified as follows: SMF-0, no fibrosis, the fibrous filaments were dispersed throughout the transparent submucosal layer, and the mucosa was easy to be lifted; SMF-1, mild fibrosis, the fibers were grouped in bundles in the submucosal layer, and the mucosa could be lifted; SMF-2, moderate fibrosis, the irregular fibers fused in the lower transparent submucosa, and the mucosa was difficult to lift; SMF-3, severe fibrosis, the mucosa was completely adherent to the muscularis propria and the lifting effect was negative. If there were more than one type from the images of the same patient, the severe one was recorded in this study. Advanced fibrosis was defined when the SMF was graded as SMF-2 or SMF-3.

The endoscopic morphology of esophageal lumen was recorded as Ling classification, which had been reported in previous studies.[14] According to multiring structure, crescent-like structure, and diverticulum, the classification was recorded as Ling I, Ling IIa, Ling IIb, Ling IIc, or Ling III in this study. This classification was recorded in the endoscopic reports in our center from 2012; therefore, the endoscopic records could provide the related data. In the statistical analysis, the esophageal lumen was recorded as two types: straight and tortuous. The former one included Ling I, Ling IIa, and the other one was composed of Ling IIb, Ling IIc, and Ling III.

For POEM procedures, success was defined as the completion of myotomy and closure of the mucosal incision. If not, the procedure was defined as aborted. Major adverse events (mAEs) were defined as perioperative
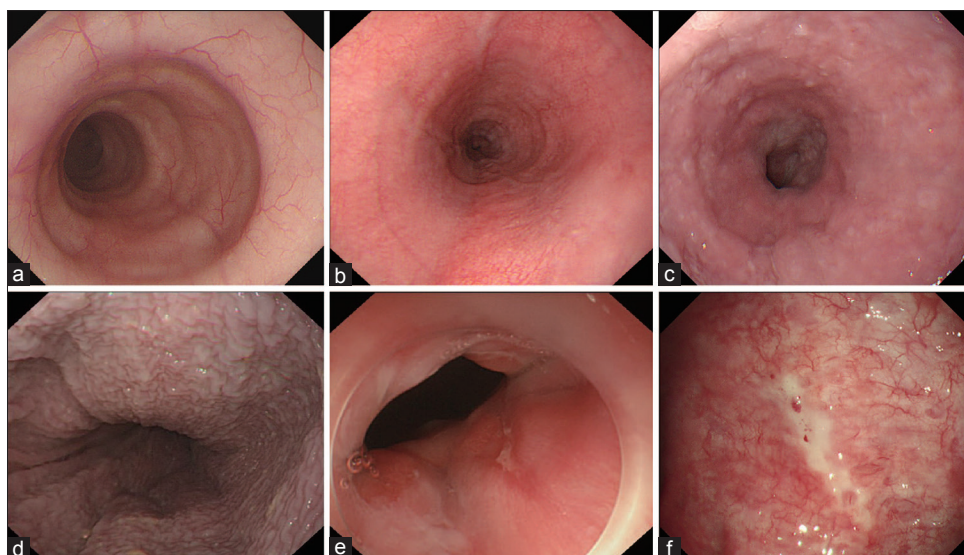
Figure 1: EMIA classification: (a) EMIA-a, normal mucosa with clear vascular texture; (b) EMIA-b, rough mucosa with vague vascular texture; (c) EMIA-c, granular mucosa without obvious vascular texture; (d) EMIA-d, the mucosa is pachyntic, striated or like sulcus; (e and f) Ulcer (EMIA-e)/Scar (EMIA-f) in the mucosa
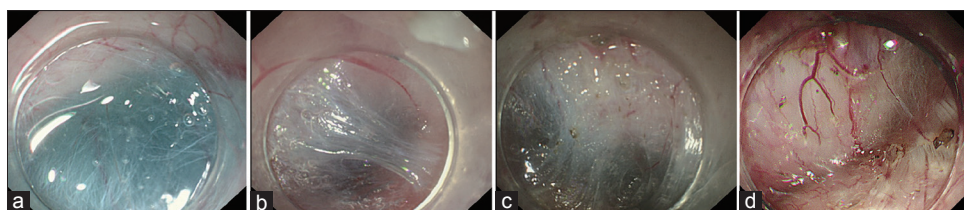

Figure 2: SMF classification after submucosal injection: (a) SMF-0, fibrous filaments are dispersed throughout the transparent submucosal layer, and the mucosa is easy to be lifted; (b) SMF-1, the fibers are grouped in bundles in the submucosal layer, and the mucosa can be lifted; (c) SMF-2, the irregular fibers fuse in the lower transparent submucosa, and the mucosa is difficult to lift; (d) SMF-3, the mucosa is completely adherent to the muscularis propria and the lifting effect is negative

adverse events that required additional interventions or intensive care unit stay, including pneumothorax and/or hydrothorax requiring drainage, delayed bleeding requiring interventions and/or blood transfusion, delayed mucosal barrier failure, and clinical inflammation requiring interventions (antibiotics or drainage) with prolonged hospital stay (>5 days).[15]

Statistical analysis

Quantitative variables were recorded as mean ± standard deviation (SD) or median (range), and were assessed using analysis of variance or Kruskal–Wallis test, as appropriate. Categorical variables were recorded as counts and percentages, and were evaluated by the Chi-square or Fisher's exact test, as appropriate. The interobserver agreement was assessed by kappa value. Correlations were assessed by Pearson or Spearman correlation coefficient, as appropriate. A logistic regression model was performed to identify the predictive factors for advanced fibrosis. Statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) version 17.0 software. P value <0.05 was considered statistically significant.

RESULTS

Clinical characteristics

A total of 647 achalasia patients who underwent POEM in our hospital from 2012 to 2016 were assessed. Among them, 79 cases were excluded due to lack of clear mucosal or submucosal images for endoscopic classification. The detailed clinical characteristics of the 568 cases included are shown in [Table 1]. The median age was 43 years, and the median disease duration was 5 years. A total of 140 (24.6%) patients had received previous treatment, and 19 (3.35%) cases had previously undergone more than one intervention.

EMIA classification and analysis of related outcomes

For EMIA classification, there were 40 (7.0%), 373 (65.7%), 139 (24.5%), 14 (2.5%), 1 (0.2%), and 1 (0.2%) case (s) for grades a, b, c, d, e, and f, respectively. For grades e and f, there was only one case in each group and SMF was obvious. Therefore, the two gradings were not included in the following analysis. The kappa values at the first separate assessment between the two endoscopists were 1.00, 0.95,

0.95, and 1.00 for grades a, b, c, and d, respectively. The disagreement was presented in 16 cases, and finally the cases were recorded as grade b or c after mutual discussion. The differences of clinical characteristics in the four EMIA grades are shown in [Table 2].

Any two grades were further compared for the significant variables. In sex distribution, there were more men in grade c than in grades a and b ($P < 0.05$), and there were no significant differences in grade d and any one of the other grades ($P > 0.05$). There was a tendency toward an increase in age from grades a to d, and any two grades presented significant difference ($P < 0.05$), as shown in [Figure 3a]. The median disease duration in grade d was longer than any one of the other grades ($P < 0.05$), as shown in [Figure 3b]. The percentage of the tortuous esophageal lumen in grades c and d was higher than that in grades a and b ($P < 0.05$), and the endoscopic morphology of esophageal lumen had a weak correlation with EMIA grades (Spearman r = 0.158, $P < 0.01$), as shown in [Figure 4a].

SMF classification during POEM and its relation with EMIA classification

There were no cases with SMF-0 throughout the POEM procedures. The cases in SMF classification were as follows: 412 (72.54%) in SMF-1, 132 (23.24%) in SMF-2, and 24 (4.23%) in SMF-3. The kappa values at the first separate assessment between the two endoscopists were 0.99, 0.99, and 1.00 for SMF-1, SMF-2, and SMF-3, respectively. The disagreement was presented in two cases, and finally the cases were recorded as SMF-2 after mutual discussion. The distribution of the SMF grades in EMIA grades is shown in [Figure 4b]. Spearman's rank order correlation analysis indicated EMIA grades positively correlated with SMF grades (r = 0.62, $P < 0.01$).

To confirm the role of EMIA classification in predicting SMF, multivariate logistic regression analysis was performed. The small number of SMF-3 cases made the established model unstable; therefore we defined two groups based on POEM findings: The first (SMF-1) had mild fibrosis and the second (SMF-2 and SMF-3) had advanced fibrosis. The enrolled factors included sex, age,

Table 1: Clinical characteristics of the enrolled 568 patients

Characteristics	Values
Age, median (range), years	43 (7–9)
Sex, Male/Female	269/299
Disease duration, median (range), years	5 (0.1–44)
Ling classification	
Ling I/IIa/IIb/IIc/III	158/148/131/109/22
Previous treatment*	140
Botulinum toxin injection (BTI)	52
Pneumatic balloon dilation (PBD)	85
Endoscopic stent placement (ESP)	11
Peroral endoscopic myotomy (POEM)	6
Heller myotomy (HM)	5
EMIA classification	
Grade a/b/c/d/e1/f4	40/373/139/14/1/1
SMF classification	
Grade 0/1/2/3	0/412/132/24
POEM procedure, *n* (%)	
Success	552 (97.2)
Abortion	16 (2.8)
Major adverse events, *n* (%)	4 (0.72)
Pneumothorax requiring drainage	2 (0.36)
Infection requiring antibiotics and drainage	2 (0.36)
Mucosal defect, *n* (%)	30 (5.43)

*There were 19 cases that underwent combined treatment before POEM: BTI and PBD (*n*=13), BTI and ESP (*n*=2), PBD and ESP (*n*=1), PBD and POEM (*n*=2), PBD and HM (*n*=1). Botulinum toxin injection (BTI)

Table 2: Differences of clinical characteristics in the four EMIA grades

Variables	Grade a	Grade b	Grade c	Grade d	*P*
Sex, *n* (%)					0.012
Male	13 (32.50)	167 (44.77)	80 (57.55)	8 (57.14)	
Female	27 (67.50)	206 (55.23)	59 (42.45)	6 (42.86)	
Age (years), median	46.5	52	55	62.5	<0.01
Disease duration (years), median	4	5	4	8	0.033
Ling classification, *n* (%)					<0.01
Straight (Ling I+IIa)	29 (72.50)	211 (56.57)	62 (44.60)	4 (28.57)	
Tortous (Ling IIb+IIc+III)	11 (27.50)	162 (43.43)	77 (55.40)	10 (71.43)	
Chicago classification*, *n* (%)					0.702
Type I	1 (3.03)	27 (9.47)	6 (5.94)	0 (0.00)	
Type II	29 (87.88)	225 (78.95)	83 (82.18)	6 (85.71)	
Type III	2 (6.06)	23 (8.07)	7 (6.93)	0 (0.00)	
Unknown	1 (3.03)	10 (3.51)	5 (4.95)	1 (14.29)	
SMF classification, *n* (%)					<0.01
SMF-1	39 (97.5)	333 (89.3)	40 (28.8)	0	
SMF-2	1 (2.5)	36 (9.7)	93 (66.9)	1 (7.1)	
SMF-3	0	4 (1.0)	6 (4.3)	13 (92.9)	
Success, *n* (%)	40 (100)	371 (99.46)	136 (97.84)	4 (28.57)	<0.01
Major adverse events, *n* (%)	1 (2.5)	2 (0.54)	1 (0.74)	0 (0)	0.582
Mucosal defect, *n* (%)	0 (0)	23 (6.2)	7 (5.15)	0 (0)	0.397

*The classification just included the patients without previous treatment, which affected the outcomes of esophageal manometry
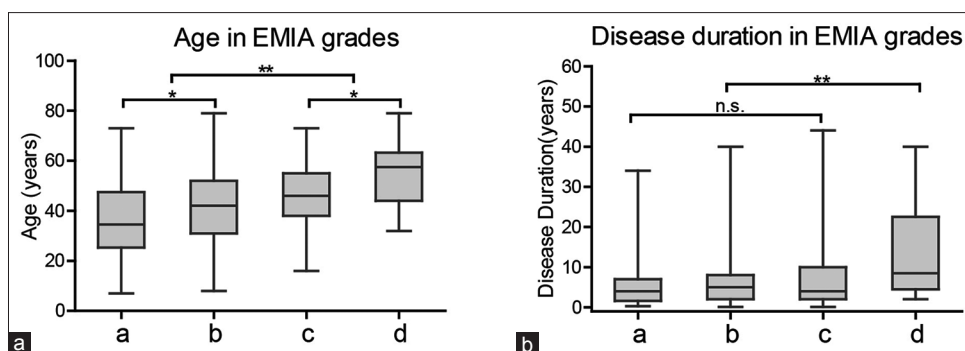
Figure 3: Difference of age and disease duration in four EMIA grades: (a) significant increase of median age from grade a to d ($P < 0.05$); (b) the median disease duration in grade d is longer than any one of the former three grades ($P < 0.05$)
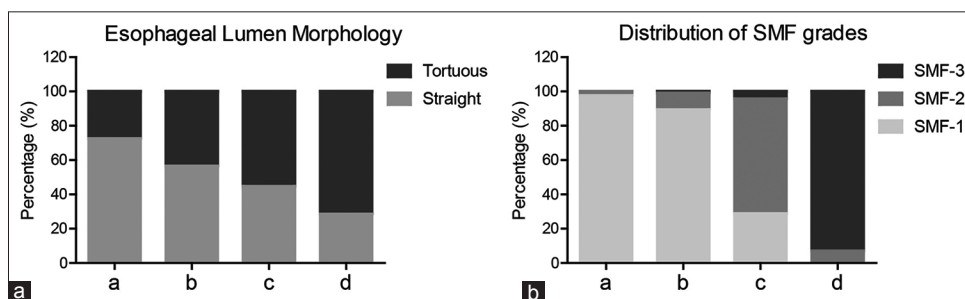

Figure 4: Distribution of endoscopic morphology of esophageal lumen and SMF grades in four EMIA grades: (a) endoscopic morphology of esophageal lumen has a weak correlation with EMIA grades (Spearman r = 0.158, $P < 0.01$); (b) SMF grades are strongly related to EMIA grades (Spearman r = 0.62, $P < 0.01$)

disease duration, Ling classification (straight and tortuous types), previous treatment, and EMIA classification. The multivariate analysis demonstrated EMIA classification (grades c to d) was an independent predictor of advanced SMF (odds ratio = 26.547, 95% confidence interval 15.809–44.578, $P < 0.01$), as shown in [Table 3].

POEM outcomes and relation with EMIA classification

Of the enrolled 568 patients, POEM procedures were successfully completed in 552 and were aborted in 16. Reasons for abortion were severe SMF in 15 (93.8%) cases and bleeding from cardiac mucosal laceration in 1 (6.2%) case. For EMIA classification, there were 40 (100%), 371 (99.46%), 136 (97.84%), 4 (28.57%), 1 (100%) and 0 (0%) cases that were successfully operated in grade a, b, c, d, e1 and f4, respectively. The success rate decreased from grade a to d [Table 2], and grade d showed a significantly lower success rate than the other three grades ($P < 0.05$).

In 552 patients undergoing successful POEM procedures, 4 (0.7%) patients experienced mAEs: 2 cases with pneumothorax requiring drainage, one with mediastinitis requiring antibiotics and drainage, and one with infection of submucosal tunnel requiring endoscopic flushing using antibiotics. These four patients had a long hospital stay (from 10 to 30 days) after POEM, but there was no mortality or need for conversion to surgery or intensive

Table 3: Logistic regression analysis of predictive factors for advanced SMF

Variable	Odds ratio	95% Confidence interval	*P*
EMIA classification			
Grades a to b	1.000	Reference	
Grades c to d	26.547	15.809–44.578	<0.01

care management. Mucosal defects were demonstrated in 30 (5.43%) patients and were successfully closed endoscopically during POEM procedures: 14 were closed with clips, 11 with fibrin glue, and 4 with clips and fibrin glue. There were no differences in the distribution of major adverse events and mucosal defects in EMIA classification ($P > 0.05$) [Table 2].

DISCUSSION

SMF is common in achalasia. According to the SMF classification in this study, 73%, 23% and 4% of the patients had mild, moderate and severe SMF, respectively. POEM has become the preferred therapy for achalasia.[2,7-9] Excessive SMF makes esophageal mucosa difficult to lift after submucosal injection, which leads to prolonged operation time, unexpected adverse events and even POEM failure.[6,11,12] In our study, of the 16 patients who did not undergo POEM successfully, 15 (96%) cases resulted from severe SMF by presenting negative lifting sign and even

diffuse submucosal bleeding. Only 4 patients experienced mAEs and the risk factors were not analyzed in this study. Notably, mediastinitis, as one of the worst adverse events, occurred in patients with severe SMF (SMF-3). Therefore, the prediction of fibrosis is very important for assessment of the operation difficulty and safety, and then the operator can be assigned according to the skills required for a given procedure to increase the safety and rate of success.

In this study, the SMF in achalasia patients were first graded according to the distribution and density of fibers and the lifting effect after submucosal injection. Based on the SMF gradings, the current analysis demonstrated that the EMIA classification was the significant independent predictor of advanced SMF. The gradings of EMIA classification also had positive relationship with the ones in SMF classification. The changes of intra-esophageal pressure and long-term food stasis may lead to chronic inflammation of the esophageal mucosa,[15,16] which explained patients graded d having significantly longer disease duration than the former three grades in the EMIA classification. Chronic inflammation causes fibrosis, and thus the EMIA gradings is highly correlated with SMF gradings. In previous studies, mucosal edema gradings were described and were reported to be related to SMF and severe perioperative adverse events.[2,15] The mucosal edema gradings were based on surface texture and cutting-edge abnormality. However, when mucosal incision is performed, the SMF can also be judged. The EMIA gradings can be determined from mucosal changes without mucosal incision. Therefore, the EMIA gradings are more suitable for predicting of SMF before POEM. Additionally, interobserver agreement was excellent for this classification ($\kappa > 0.9$). Notably, the completion rate of POEM procedures decreased from grade a to d. That trend can be explained by the relation between EMIA and SMF gradings and reflects the clinical significance of EMIA gradings. In terms of mAEs, there were no differences between the four EMIA gradings, but this study had limited statistical power owing to the small number ($n = 4$) of mAEs.

It is noteworthy that previous treatment was not a significant risk factor for SMF in multivariate analysis, which was different from previous reports.[2] All the patients ($n = 11$) who had prior POEM or HM displayed advanced SMF than other prior treatments. The small number might explain that this factor did not reach statistical significance. Shiwaku *et al.*[17] reported that the muscle tissue divided by the POEM procedure was completely replaced by fibrosis. However, many previous studies supported that previous treatment had no impact on the POEM outcomes.[6,18,19] Fibrosis after myotomy is common, but the fibrosis is often confined to the local myotomy site. Therefore, POEM

can be completed in other locations or by simultaneous myotomy and submucosal dissection.[6,20]

The modified POEM procedures have expanded the indications of POEM from patients with simple achalasia to those with sigmoid esophagus, fibrosis, and failed previous interventions.[2,3,21-23] When establishment of submucosal tunnel is difficult or impossible, simultaneous submucosal and muscle dissection, or free-tunnel POEM can be considered.[21,24] However, the procedures are time-consuming and technically difficult. Accordingly, the operation should be delegated to the skilled or experienced operator in such cases. In addition, the sigmoid-type achalasia used to be considered a contraindication to POEM.[23] However, the short tunnel established in the POEM procedures makes it possible for successful operation for distorted esophagus.[23] In the present study, we also found that there was a larger proportion of tortuous esophagus in EMIA-d than the former three grades, which might be related with the long disease duration. After multivariate analysis for advanced SMF, the esophageal morphology was not a risk factor. Meanwhile, there were no aborted POEMs attributed to esophageal morphology. Therefore, esophageal morphology was not a significant obstacle for completion of POEM procedures.

There were several limitations to this study. First, the study was retrospective and a single-center analysis. Secondly, the SMF was just assessed visually during POEM procedures, not by pathological findings. Thirdly, the EMIA and SMF grades were recorded mostly based on static endoscopic images, and just severe grades were recorded. Therefore, different grades in different locations were not assessed. To provide more reliable evidence for the benefit of EMIA classification, we are conducting a large prospective multicenter study.

In conclusion, SMF is common in achalasia patients, and the EMIA classification is an independent predictor of advanced SMF encountered during POEM. The classification may be used for assessment of the difficulty and success of POEM. Additional prospective studies on this new classification are required to confirm its clinical significance.

Conflicts of interest

There are no conflicts of interest.

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