The effect of prior treatment on clinical outcomes in patients with achalasia undergoing peroral endoscopic myotomy

Authors
Zu-Qiang Liu*, Quan-Lin Li*, Wei-Feng Chen, Xiao-Cen Zhang, Qiu-Ning Wu, Ming-Yan Cai, Wen-Zheng Qin, Jian-Wei Hu, Yi-Qun Zhang, Mei-Dong Xu, Li-Qing Yao, Ping-Hong Zhou

Institution
Endoscopy Center and Endoscopy Research Institute, Zhongshan Hospital, Fudan University, Shanghai, China

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Corresponding author
Ping-Hong Zhou, MD, PhD, Endoscopy Center and Endoscopy Research Institute, Zhongshan Hospital, Fudan University, 180 FengLin Road, Shanghai, 200032, P. R. China
Fax: +86-21-64038472
zhou.pinghong@zs-hospital.sh.cn

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ABSTRACT

Background Peroral endoscopic myotomy (POEM) is a treatment option for patients with previous surgical or endoscopic treatment. We aimed to evaluate the influence of prior treatment on perioperative and follow-up outcomes in patients undergoing POEM.

Methods From August 2010 to December 2014, a total of 1384 patients with achalasia underwent POEM at our center. We retrospectively reviewed 849 patients who completed follow-up. Patients with an Eckardt score ≥ 4 after POEM were considered to have a clinical failure. We compared variables between patients with and without prior treatment. We analyzed risk factors for perioperative major adverse events, and clinical reflux and failure during follow-up.

Results 245 patients (28.9 %) had undergone prior treatment, and 34 patients (4.0 %) experienced a major adverse event associated with the POEM procedure. During a median follow-up of 23 months (range 1 – 71), clinical reflux occurred in 203 patients (23.9 %) and clinical failure was recorded for 94 patients (11.1 %). Patients with prior treatment had a longer procedure duration ($P = 0.001$) and longer hospital stay after POEM ($P = 0.001$). Prior treatment was not an independent risk factor for major adverse events or clinical reflux (odds ratio [OR] 1.19, $P = 0.65$; OR 1.26, $P = 0.19$; logistic regression), but it did increase the rate of clinical failure during follow-up (hazard ratio 1.90, $P = 0.002$; Cox regression).

Conclusions POEM was performed safely with a low rate of major adverse events in patients with achalasia who had undergone prior surgical or endoscopic treatment. However, prior treatment increased the risk of clinical failure after POEM.

Introduction

Achalasia is a primary esophageal motility disorder that presents with symptoms reflecting esophageal aperistalsis and impaired lower esophageal sphincter (LES) relaxation, including dysphagia, regurgitation, chest pain, and weight loss [1]. Traditional treatment options for achalasia include botulinum toxin injection, pneumatic balloon dilation, and laparoscopic Heller myotomy [2]. Peroral endoscopic myotomy (POEM) is a novel endoscopic therapy; it is less invasive than conventional myotomy, which requires an extraluminal surgical approach [2, 3]. Recently, POEM has demonstrated promising advantages for the treatment of achalasia [4 – 6]. However, all types of treatment may be associated, to a greater or lesser extent, with clinical failure.

* These authors contributed equally to this work.

POEM is a potential treatment option for patients in whom a previous intervention for achalasia has failed. Orenstein et al. reported that up to 40 % of patients undergoing POEM had undergone at least one previous intervention before POEM [7]. Several authors recently reported preliminary results of their studies exploring the performance or early outcomes of POEM for patients with prior interventions [8 – 10]. However, these studies are limited by their small case volume, and most of them focused on perioperative outcomes. Only a few studies have described long-term outcomes of POEM in patients with previous treatment, but results of these studies have been conflicting [11 – 14]. Therefore, systematic evaluation of short- and long-term outcomes of POEM is essential for patients with prior treatment. The aim of the current study was to evaluate perioperative outcomes, as well as outcomes during long-term follow-up, in patients with prior treatment undergoing POEM.

Methods

Patients

From August 2010 to December 2014, a total of 1384 patients with achalasia underwent POEM at the Endoscopy Center and Endoscopy Research Institute, Zhongshan Hospital, Shanghai, China. Among them, 849 patients who completed follow-up were enrolled in the study (▶ **Fig. 1**). (Study patients who had been included in previously published studies with more than 50 patients are shown in ▶ **Supplemental Table e1**, available online). Of these patients, 245 had undergone prior treatment, which included botulinum toxin injection, dilation, esophageal stent placement, Heller myotomy, and POEM. This retrospective study was approved by our local research ethics committee.

Preoperative evaluation of achalasia included determination of the standardized Eckardt score [15], esophageal high resolution manometry (HRM), esophagogastroduodenoscopy (EGD), and a barium swallow. Demographic and clinical information, including patient age, sex, and disease duration, as well as the presence or absence of sigmoid esophagus, submucosal fibrosis, or remnant contents, was collected.

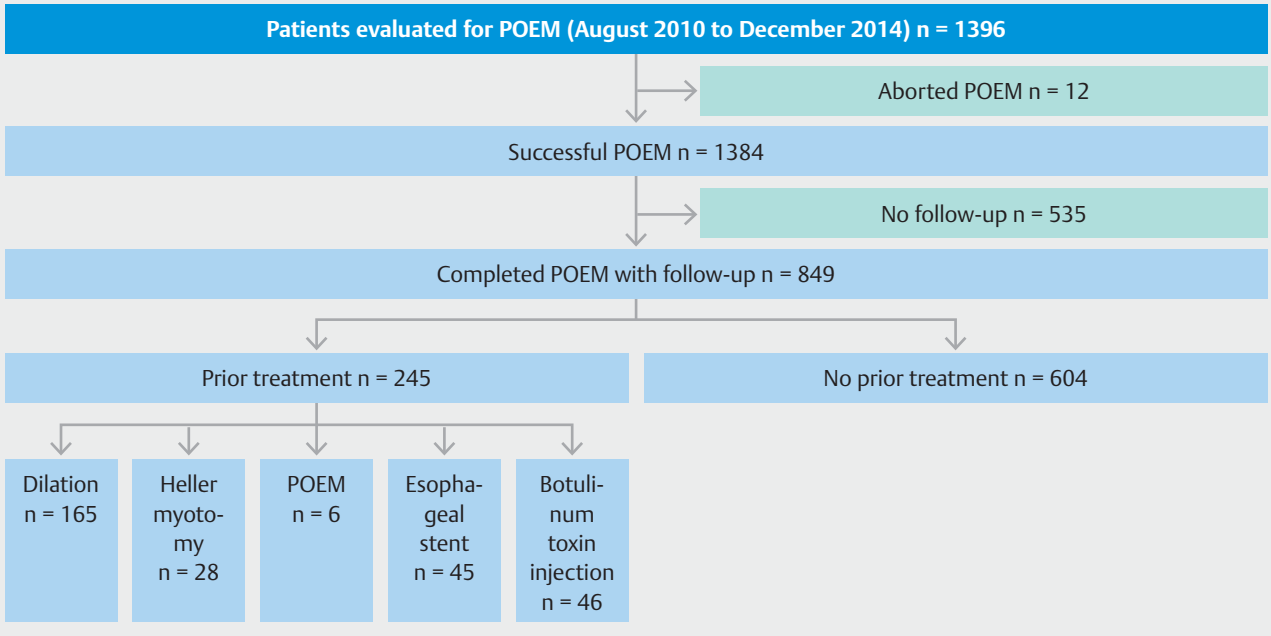
POEM procedure

The standard POEM procedure was performed as previously described [3]. It generally consisted of four major steps: 1) submucosal injection at the 5 – 6-o'clock position entry point, and a 1.5-cm longitudinal mucosal incision; 2) submucosal tunneling; 3) myotomy, from 2 cm proximal to the mucosal entry point to 2 – 4 cm beyond the cardia; and 4) closure of the mucosal entry site (▶ **Fig. 2**). In special circumstances, when fibrosis or adhesions were present because of prior treatment, the myotomy was located in an area of normal (fibrosis-free) tissue.

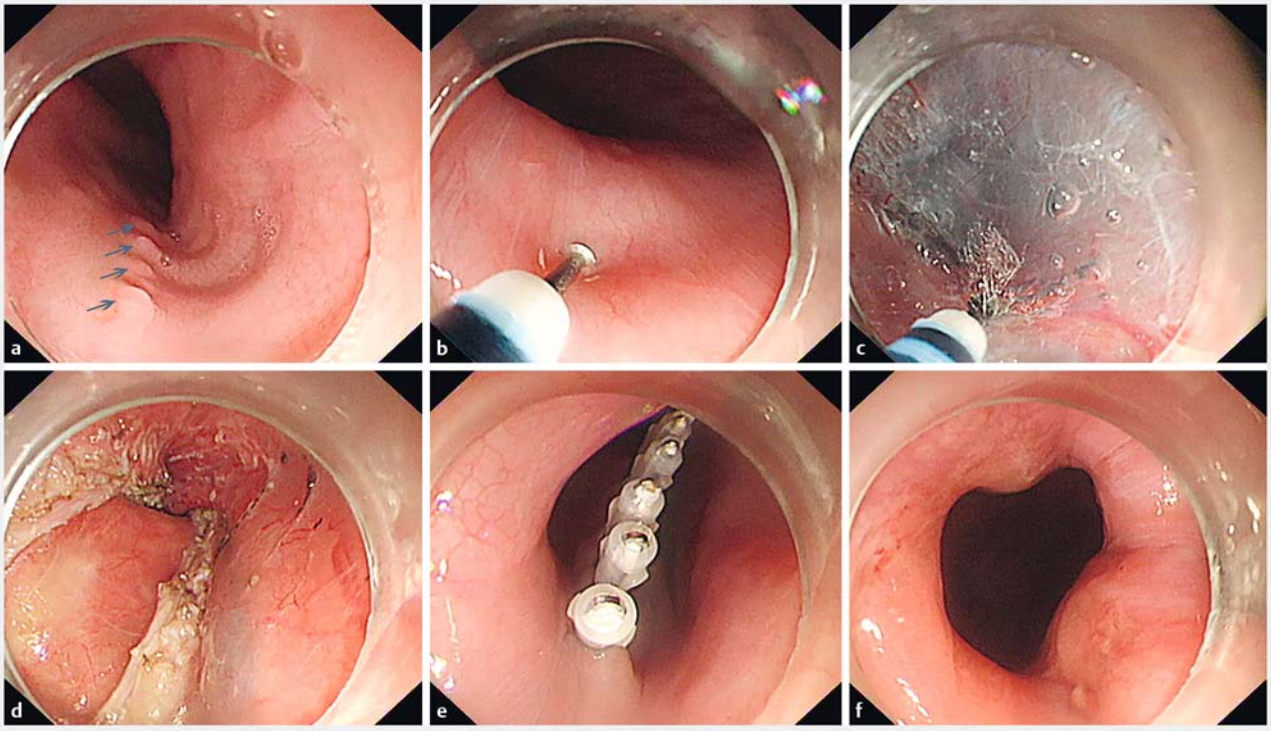
All patients received general anesthesia and endotracheal intubation. A waterjet-assisted knife was used in the vast majority of patients. Prophylactic antibiotic treatment was initiated 30 minutes before the procedure and continued until the second postoperative day. Patients remained fasted until the evening of the first postoperative day; thereafter, a liquid diet was allowed, as tolerated. After the procedure, patients regularly received proton pump inhibitors for 2 months for anti-reflux treatment.

Outcome measurements

Outcome measures were divided into perioperative outcomes and outcomes during follow-up. Perioperative outcomes were defined as perioperative major adverse events, including con-



▶ **Fig. 1** Patient eligibility flow chart. POEM, peroral endoscopic myotomy.



▶ **Fig. 2** Peroral endoscopic myotomy (POEM) procedure for a patient who had undergone a previous POEM procedure. **a** Mucosal scars (arrows) of prior POEM. **b** Submucosal injection. **c** Submucosal tunneling. **d** Full-thickness myotomy. **e** Closure of the mucosal entry site. **f** Opening of the esophagogastric junction after the procedure.

version to laparoscopic or open procedure, blood transfusion, intensive care unit stay after the procedure, invasive operation postoperatively, hospital readmission after discharge, and hospital stay of more than 5 days [16].

The outcomes during follow-up included clinical reflux and clinical failure. Clinical reflux has been defined previously, and included symptomatic reflux and reflux esophagitis [17, 18]. Clinical reflux was diagnosed if the patient experienced positive results of either reflux or reflux esophagitis, which were confirmed by further investigation. Symptomatic reflux was diagnosed by GerdQ questionnaire, which comprises six items of gastroesophageal reflux disease, including four positive predictors (heartburn, regurgitation, sleep disturbance cause by heartburn and regurgitation, and use of over-the-counter medication in addition to prescribed treatment), and two negative predictors (epigastric pain and nausea). Patients were required to reflect on symptoms during the preceding week. Scores of 0 to 3 were used for the positive predictors and 3 to 0 (reversed order, where 3 was none) for the negative predictors. The GerdQ score was calculated as the total score of the items, ranging from 0 to 18. A score of 8 or more was defined as symptomatic reflux. Reflux esophagitis was diagnosed and graded by EGD based on the Los Angeles classification.

Once clinical reflux had been confirmed, patients took double-dose proton pump inhibitors for anti-reflux treatment. Patients with an Eckardt score ≥ 4 after POEM were considered to have a clinical failure [17]. The overall follow-up duration was defined as the time from the procedure to clinical failure or the last follow-up.

Follow-up

Patients were scheduled for follow-up at 1 month, 3 months, 6 months, and 1 year postoperatively, and yearly thereafter. Evaluation of clinical response was based on the Eckardt score. Barium swallow was performed to objectively assess treatment efficacy and clinical failure. EGD was regularly performed because it provided both outcome assessment and cancer screening. HRM was also advised, especially in patients with dysphagia.

Patients who lived a long distance from our institution or who were unwilling to return for follow-up underwent detailed telephone interviews, which included questions about symptoms, as well as examinations and treatments at other hospitals. The last follow-up was performed in October 2016.

Statistical analyses

Categorical variables were compared using the chi-squared test, and continuous variables were compared using the Student's *t* test. Logistic regression analysis was used to assess variables associated with major adverse events and clinical reflux, and Cox's regression analysis was used for variables associated with clinical failure. Multivariate analysis was performed for variables with $P < 0.1$ during univariate analysis. Kaplan-Meier analysis and the log-rank test were also used to

evaluate variables associated with clinical failure. Variables were considered statistically significant if the *P* value was <0.05. Statistical analyses were conducted using SPSS software version 21.0 (IBM Corp., Armonk, New York, USA).

Results

Patient and procedural characteristics

Patient and POEM procedural characteristics are listed in ▶**Table 2**. A total of 849 patients underwent POEM, including 423 males and 426 females. Median age was 38 years (range 6–98 years). A total of 694 patients (81.7%) underwent HRM, including 209 patients of Type I, 441 patients of Type II, and 44 patients of Type III. The median pre-POEM Eckardt score was 7 (range 4–12) and median pre-POEM LES resting pressure on HRM was 29 mmHg (range 15–78 mmHg). A total of 63 patients (7.4%) had a sigmoid esophagus. Full-thickness myotomy was performed in 681 patients (80.2%). The median procedure duration was 45 minutes (range 14–202 minutes), and the duration was more than 60 minutes in 242 patients (28.5%). Air insufflation was used in 213 patients.

Prior treatment

Overall, 245 patients (28.9%) had undergone prior treatment. The treatment was dilation in 165 patients, botulinum toxin injection in 46 patients, esophageal stent placement in 45 patients, Heller myotomy in 28 patients, and POEM in 6 patients (▶**Table 3**). Only one prior treatment was performed in 202 patients, whereas 43 patients had undergone more than one prior treatment (▶**Table 3**). Undergoing prior treatment was significantly associated with insufflation ($P<0.001$), disease duration ($P<0.001$), sigmoid esophagus ($P<0.001$), submucosal fibrosis ($P=0.03$), full-thickness myotomy ($P=0.02$), procedure duration ($P=0.001$), length of hospital stay ($P=0.001$), and endoscopist experience ($P=0.002$) (▶**Table 2**). Pre-POEM Eckardt score, pre-POEM LES resting pressure, and achalasia subtype were comparable between patients with vs. without prior treatment ($P=0.43$, 0.88, 0.29, respectively) (▶**Table 2**).

Prior treatment and perioperative major adverse events

Major adverse events occurred in 34 patients (4.0%). Among these, 19 patients had a pneumothorax requiring drainage, 6 patients had a hydrothorax requiring drainage, 4 patients had delayed mucosa barrier failure, 2 patients had delayed bleeding requiring intervention or transfusion, and 3 patients had other miscellaneous major adverse events (▶**Supplemental Table e4**, available online). Eleven of the 34 patients had undergone prior treatment, including 7 with dilation, 3 with esophageal stent placement, 2 with botulinum toxin injection, and 1 with surgery. No statistical difference in major adverse events was found between patients with vs. without prior treatment ($P=0.65$).

Multivariate logistic regression analysis demonstrated that major adverse events were independently associated with endoscopist experience (odds ratio [OR] 0.23, $P=0.02$) and procedure duration (OR 3.82, $P<0.001$) (▶**Table 5**). Prior treatment was not a risk factor for major adverse events (OR 1.19, $P=0.65$), even when the number of prior treatments increased (only one treatment: OR 1.18, $P=0.68$; more than one treatment: OR 1.23, $P=0.78$).

Prior treatment and clinical reflux during follow-up

During a median follow-up 23 months (range 1–71 months), clinical reflux occurred in 203 patients (23.9%), 135 (15.9%) of whom had symptomatic reflux (▶**Supplemental Table e6**, available online). Of the 664 patients who underwent follow-up EGD, 126 patients (19.0%) were reported to have reflux esophagitis. A total of 100 patients were evaluated for severity of esophagitis, 6 (6.0%) of whom were reported to have severe esophagitis (Los Angeles classification Grade D). Patients with prior treatment had a clinical reflux rate of 26.9%, which was comparable with that in patients who had not undergone prior treatment ($P=0.19$). Multivariate logistic regression analysis demonstrated that prior treatment was not an independent risk factor for clinical reflux (OR 1.26, $P=0.19$) (▶**Table 7**).

Prior treatment and clinical failure during follow-up

Of the 849 patients with follow-up data, 664 patients returned for clinical follow-up and 185 patients received detailed telephone interviews. The median follow-up time for clinical failure was the same as for clinical reflux (23 months, range 1–71 months). Clinical failure occurred in 94 patients (11.1%) during follow-up. Clinical failure rates at 1, 2, and 5 years after POEM were 6.8%, 8.5%, and 11.1%, respectively. The rates at 1, 2, and 5 years were 11.4%, 13.5%, and 18.0% in patients with prior treatment, and 5.0%, 6.5%, and 8.3% in patients without prior treatment ($P=0.001$, 0.001, <0.001, respectively) (▶**Supplemental Table e8**, available online). Patients with prior treatment had a higher mean postoperative Eckardt score compared with patients without (1.69 vs. 1.37, $P=0.005$). A total of 438 patients (51.6%) underwent post-POEM HRM, among whom the post-POEM LES resting pressure was not statistically different between patients with and without prior treatment (12.2 vs. 11.1 mmHg; $P=0.23$).

Univariate log-rank tests demonstrated that clinical failure was associated with disease duration (hazard ratio [HR] 1.94, $P=0.002$), sigmoid esophagus (HR 2.07, $P=0.02$), and prior treatment (HR 2.16, $P<0.001$) (▶**Table 9**, ▶**Fig. 3**). Multivariate analysis demonstrated that disease duration and prior treatment were independent factors associated with clinical failure (HR 1.62, $P=0.03$; HR 1.90, $P=0.002$, respectively) (▶**Table 9**). In addition, when the number of prior treatments was considered, the risk of clinical failure was higher in patients with more than one prior treatment (HR 3.15, 95%CI 1.64–6.06; $P<0.001$) than in those with only one prior treatment (HR 1.96, 95%CI 1.26–3.03; $P=0.003$) (▶**Table 9**, ▶**Fig. 4**). Thus, prior treatment clearly increases the risk of clinical failure.

Outcome measures between patients with prior dilation and those with other prior treatments

Owing to the high proportion of prior dilation treatments, patients were stratified into two groups for further analysis: 1) those who underwent dilation, and 2) those who underwent

▶ **Table 2** Patient and procedure characteristics.

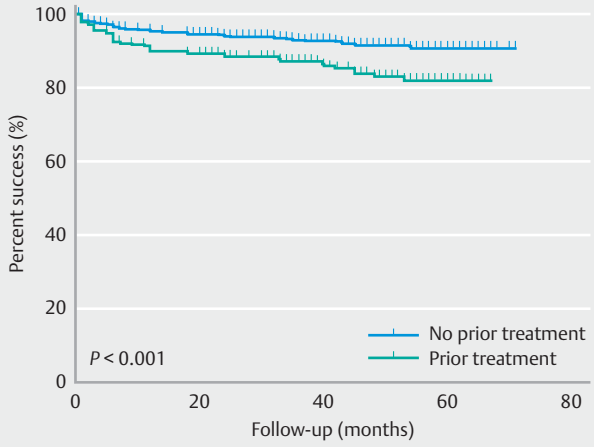
Variables	N	No prior treatment	Prior treatment	*P*
Total number, n (%)	849	604 (71.1)	245 (28.9)	–
Male, n (%)	423	291 (48.2)	132 (53.9)	0.13
Age, median (range), years	38 (6 – 98)	38 (8 – 77)	38 (6 – 98)	0.83
Pre-POEM Eckardt score, median (range)	7 (4 – 12)	7 (4 – 12)	8 (4 – 12)	0.43
Pre-POEM LES resting pressure on HRM, median (range), mmHg	29 (15 – 78)	30 (15 – 78)	27 (15 – 71)	0.88
Achalasia subtype, n (%)				0.29
▪ Type I	209	144 (23.8)	65 (26.5)	
▪ Type II	441	309 (51.2)	132 (53.9)	
▪ Type III	44	31 (5.1)	13 (5.3)	
▪ Unspecified	155	120 (19.9)	35 (14.3)	
Insufflation, n (%)				< 0.001
▪ Air	213	131 (21.7)	82 (33.5)	
▪ CO_2	636	473 (78.3)	163 (66.5)	
Disease duration, n (%)				< 0.001
▪ < 10 years	654	491 (81.3)	163 (66.5)	
▪ ≥ 10 years	195	113 (18.7)	82 (33.5)	
Sigmoid esophagus, n (%)				< 0.001
▪ No	786	573 (94.9)	213 (86.9)	
▪ Yes	63	31 (5.1)	32 (13.1)	
Remnant contents, n (%)				0.72
▪ No	793	563 (93.2)	230 (93.9)	
▪ Yes	56	41 (6.8)	15 (6.1)	
Submucosal fibrosis, n (%)				0.03
▪ No	797	574 (95.0)	223 (91.0)	
▪ Yes	52	30 (5.0)	22 (9.0)	
Full-thickness myotomy, n (%)				0.02
▪ No	168	107 (17.7)	61 (24.9)	
▪ Yes	681	497 (82.3)	184 (75.1)	
Procedure duration, n (%)				0.001
▪ < 60 minutes	607	441 (73.0)	166 (67.8)	
▪ ≥ 60 minutes	242	163 (27.0)	79 (32.2)	
Hospital length of stay, n (%)				0.001
▪ < 2 days	431	324 (53.6)	107 (43.7)	
▪ ≥ 2 days	418	280 (46.4)	138 (56.3)	
Endoscopist experience, n (%)				0.002
▪ ≤ 100	100	58 (9.6)	42 (17.1)	
▪ > 100	749	546 (90.4)	203 (82.9)	

HRM, high resolution manometry, LES, lower esophageal sphincter, POEM, peroral endoscopic myotomy.

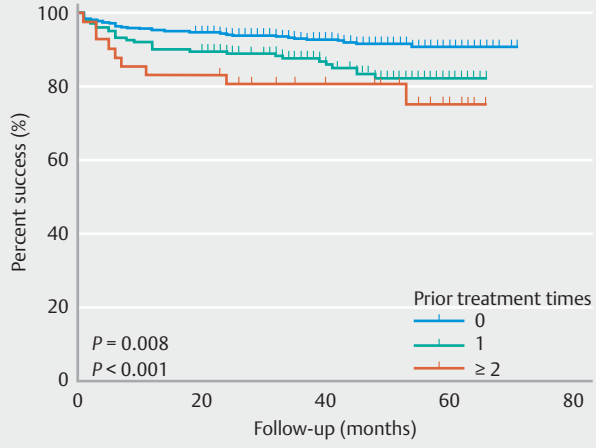
▶ **Table 3** Prior treatment for achalasia.

Variables	Number
Patients	245
Type	
▪ Balloon or bougie dilation	165
▪ Botulinum toxin injection	46
▪ Esophageal stent	45
▪ Heller myotomy	28
▪ POEM	6
Number of prior treatments	
▪ 1	202
▪ ≥2	43

POEM, peroral endoscopic myotomy.



▶ **Fig. 3** Prior treatment increased the risk of clinical failure ($P<0.001$).



▶ **Fig. 4** When the number of prior treatments was considered, the risk of clinical failure was higher in patients with more than one prior treatment compared with those with only one prior treatment.

botulinum toxin injection, Heller myotomy, POEM, or esophageal stent placement. Patients with prior dilation had a higher rate of sigmoid esophagus compared with patients who had undergone botulinum toxin injection/Heller myotomy/POEM/esophageal stent placement ($P=0.03$; Supplemental ▶ **Table e10**, available online). Other patient and POEM procedural characteristics were comparable between the two groups (all $P>0.05$). In addition, there were no statistical differences in perioperative outcomes and outcomes during follow-up between the two groups (▶ **Supplemental Table e11**, available online).

Discussion

Traditional treatment methods for achalasia include botulinum toxin injection, pneumatic balloon dilation, and Heller myotomy [2]. In past decades, these kinds of treatments cured multitudes of patients with achalasia throughout the world. However, the success rates of these procedures varied. For instance, reported success rates ranged from 50 % to 85 % at 2 years after pneumatic dilation [19 – 21]. With the development of natural orifice transluminal endoscopic surgical procedures, POEM became a good alternative because of its safety and feasibility [3]. However, even the POEM procedure was reported to have a clinical failure rate of more than 10 % after 3 years [22].

POEM was previously recommended as a rescue treatment for recurrent achalasia. As reported in earlier studies, up to 40 % of patients undergoing POEM had received other treatment before the procedure [7]. A few studies explored the short-term efficacy of POEM for patients with prior treatment for achalasia [8 – 10]. In our 2013 prospective study of 12 patients with recurrent symptoms after primary Heller myotomy, we found that POEM produced short-term symptom relief in more than 90 % of patients, with no major adverse events [8]. In 2016, Jones et al. retrospectively analyzed 45 patients who underwent POEM for achalasia [9]. Among these, 15 patients had undergone prior treatment, including seven with botulinum toxin injection, five with pneumatic dilation, and three with Heller myotomy. The study demonstrated that patients who had undergone treatment prior to undergoing POEM had similar early outcomes, including procedure duration, length of hospital stay, and incidence of reflux, when compared with patients without previous therapy.

Although several previous studies have focused on short-term outcomes after POEM in patients with prior treatment [7 – 10], long-term clinical failure and reflux rates have only recently been reported (since 2017)[11 – 14]. One study performed by Kristensen et al. enrolled 66 patients undergoing POEM, 14 of whom had undergone previous Heller myotomy [11]. The authors found that the non-Heller group had more symptom relief at 3, 12, and 24 months after POEM than those

▶ **Table 5** Risk factors for perioperative major adverse events.

Variables	Univariate analysis			Multivariate analysis*		
	OR	95%CI	*P*	OR	95%CI	*P*
Sex, Male vs. Female	0.54	0.26 – 1.10	0.09	0.57	0.26 – 1.22	0.15
Age, ≥ 60 vs. < 60 years	1.81	0.68 – 4.81	0.24	NA	NA	NA
Insufflation, Air vs. CO_2	6.88	3.29 – 14.37	< 0.001	2.12	0.57 – 7.96	0.26
Pre-POEM Eckardt score, ≥ 7 vs. < 7	0.77	0.38 – 1.57	0.48	NA	NA	NA
Disease duration, ≥ 10 vs. < 10 years	1.42	0.67 – 3.02	0.36	NA	NA	NA
Sigmoid esophagus, Yes vs. No	1.71	0.58 – 5.01	0.33	NA	NA	NA
Procedure duration, ≥ 60 vs. < 60 minutes	3.82	1.90 – 7.69	0.001	3.82	1.81 – 8.08	< 0.001
Submucosal fibrosis, Yes vs. No	2.82	1.04 – 7.61	0.04	1.97	0.58 – 6.64	0.28
Full-thickness myotomy, Yes vs. No	0.16	0.08 – 0.32	< 0.001	0.44	0.17 – 1.17	0.10
Remnant contents, Yes vs. No	0.88	0.21 – 3.77	0.86	NA	NA	NA
Endoscopist experience > 100	0.09	0.04 – 0.18	< 0.001	0.23	0.07 – 0.76	0.02
Prior treatment, Yes vs. No	1.19	0.57 – 2.48	0.65	NA	NA	NA

CI, confidence interval; NA, not applicable; OR, odds ratio; POEM, peroral endoscopic myotomy.
* Compared using logistic regression analysis.

▶ **Table 7** Risk factors for clinical reflux during follow-up.

Variables	Univariate analysis			Multivariate analysis*		
	OR	95%CI	*P*	OR	95%CI	*P*
Sex, Male vs. Female	0.88	0.64 – 1.20	0.41	NA	NA	NA
Age, ≥ 60 vs. < 60 years	0.84	0.47 – 1.49	0.54	NA	NA	NA
Insufflation, Air vs. CO_2	0.87	0.60 – 1.26	0.47	NA	NA	NA
Pre-POEM Eckardt score, ≥ 7 vs. < 7	1.07	0.76 – 1.50	0.70	NA	NA	NA
Disease duration, ≥ 10 vs. < 10 years	1.30	0.90 – 1.87	0.16	NA	NA	NA
Sigmoid esophagus, Yes vs. No	1.30	0.73 – 2.30	0.37	NA	NA	NA
Procedure duration, ≥ 60 vs. < 60 minutes	0.88	0.62 – 1.26	0.49	NA	NA	NA
Submucosal fibrosis, Yes vs. No	1.07	0.56 – 2.04	0.85	NA	NA	NA
Full-thickness myotomy, Yes vs. No	1.49	0.98 – 2.29	0.07	1.49	0.98 – 2.29	0.07
Remnant contents, Yes vs. No	0.59	0.29 – 1.23	0.16	NA	NA	NA
Major adverse event, Yes vs. No	0.54	0.21 – 1.41	0.21	NA	NA	NA
Endoscopist experience > 100	1.29	0.77 – 2.17	0.33	NA	NA	NA
Prior treatment, Yes vs. No	1.26	0.89 – 1.77	0.19	NA	NA	NA

CI, confidence interval; NA, not applicable; OR, odds ratio; POEM, peroral endoscopic myotomy.
* Compared using logistic regression analysis.

who had undergone the previous procedure. Another study reported by Ngamruengphong et al. showed similar findings from a review of 180 patients from 13 tertiary centers [12]. The rate of clinical success in patients with prior Heller myotomy was lower than that in patients who had not undergone Heller myotomy (81% vs. 94%; $P = 0.01$). However, similar studies from Nabi et al. and Zhang et al. showed conflicting results. Nabi et al. reported a series of 502 patients with achalasia undergoing POEM, with 260 patients (51.8%) in the treatment-naïve group and 242 patients (48.2%) in the prior treatment

▶ **Table 9** Risk factors for clinical failure during follow-up.

Variables	Univariate analysis			Multivariate analysis*		
	HR	95%CI	*P*	HR	95%CI	*P*
Sex, Male vs. Female	1.12	0.75 – 1.68	0.58	NA	NA	NA
Age, ≥ 60 vs. < 60 years	1.05	0.53 – 2.09	0.89	NA	NA	NA
Insufflation, Air vs. CO_2	0.71	0.43 – 1.16	0.17	NA	NA	NA
Pre-POEM Eckardt score, ≥ 7 vs. < 7	1.22	0.78 – 1.92	0.39	NA	NA	NA
Disease duration, ≥ 10 vs. < 10 years	1.94	1.28 – 2.96	0.002	1.62	1.04 – 2.52	0.03
Sigmoid esophagus, Yes vs. No	2.07	1.15 – 3.72	0.02	1.47	0.80 – 2.72	0.22
Procedure duration, ≥ 60 vs. < 60 minutes	0.99	0.63 – 1.54	0.95	NA	NA	NA
Submucosal fibrosis, Yes vs. No	1.87	0.97 – 3.61	0.06	1.72	0.89 – 3.32	0.11
Full-thickness myotomy, Yes vs. No	1.21	0.79 – 2.32	0.47	NA	NA	NA
Remnant contents, Yes vs. No	0.90	0.39 – 2.05	0.80	NA	NA	NA
Major adverse event, Yes vs. No	0.69	0.22 – 2.18	0.53	NA	NA	NA
Endoscopist experience > 100	1.16	0.63 – 2.15	0.64	NA	NA	NA
Prior treatment, Yes vs. No	2.16	1.44 – 3.24	< 0.001	1.90	1.26 – 2.88	0.002
Number of prior treatments, 1 vs. 0	1.96	1.26 – 3.03	0.002	NA	NA	NA
Number of prior treatment, ≥ 2 vs. 0	3.15	1.64 – 6.06	< 0.001	NA	NA	NA

CI, confidence interval; NA, not applicable; HR, hazard ratio; POEM, peroral endoscopic myotomy.
* Compared using Cox regression analysis.

failure group [13]. Zhang et al. reviewed 318 consecutive patients including 46 patients with prior Heller myotomy [14]. Both of these studies showed comparable clinical failure in the two groups. Therefore, previous studies on long-term outcomes of POEM in patients with prior treatment are limited and contradictory. Given these conflicting data, systematic evaluation of long-term outcomes between these groups is highly necessary.

In the current study, we comprehensively compared perioperative outcomes in patients with vs. without prior treatment for achalasia. Our study demonstrated that patients with prior treatment had longer disease duration and were more likely to have sigmoid esophagus and submucosal fibrosis (▶ **Table 2**). Therefore, inflammation in the area of prior treatment is expected to be high in these patients. The presence of inflammation and fibrosis could increase the technical challenge of POEM, leading to longer procedure duration and length of hospital stay after POEM (▶ **Table 2**) [8]. Nevertheless, our study indicated that patients with prior treatment receiving POEM had a similar rate of perioperative major adverse events when compared with patients without prior treatment; that is, when the procedure is performed by experienced operators who are highly proficient, the rate of major adverse events could be unaffected by previous treatment. Therefore, we recommend that patients with prior treatment undergo POEM at centers that have experience in the procedure.

The current study represents the largest database of single-center data on the long-term outcome of POEM to date. We found that patients with prior treatment had a comparable risk of clinical reflux but a higher risk of clinical failure after POEM. Patients with prior treatment had a clinical reflux rate of 26.9% compared with 22.7% in patients without prior treatment (P = 0.19). All patients with clinical reflux experienced symptom relief with proton pump inhibitors, and no patient required rescue surgery. In addition, patients with prior treatment had clinical failure rates at 1, 2, and 5 years of 11.4%, 13.5%, and 18.0%, compared with 5.0%, 6.5%, and 8.3% in patients without prior treatment. The difference in clinical failure between the two groups was significant, although the differences between the 1 – and 2-year clinical failure rates were not large in the respective groups. However, by the 5-year follow-up, the difference in failure rates between the two groups had increased (18.0% vs. 8.5%), suggesting that the longer the follow-up, the greater the difference in clinical failure between patients with vs. without prior treatment. In addition, we found that patients with more than one prior treatment had a higher risk of clinical failure than those with only one prior treatment (▶ **Table 9**, ▶ **Fig. 4**). Therefore, we conclude that patients in whom prior treatment failed would have a greater risk of failure again, especially during long-term follow-up. This finding is similar to that observed in the latest study reported by Ngamruengphong et al., where the rate of clinical success was lower in patients with prior Heller myotomy than in patients without (81% vs. 94%) [12].

Patients with prior treatment had longer duration, and more sigmoid esophagus and submucosal fibrosis (▶ **Table 2**), that is,

more serious disease with severe inflammation and technical challenges. Therefore, it is expected that the severe inflammation and fibrosis of the cardia could lead to severe technical challenges and inadequate tunneling or myotomy, which might increase the risk of clinical failure in these patients.

In our study, not all patients who underwent successful POEM had available follow-up information (849/1384, 61.3 %). The high rate of loss to follow-up might be caused by the large database of the study. In this Chinese patient population, many patients from less economically developed regions did not return for further follow-up and many patients changed their phone numbers during the follow-up period. This was the main limitation of our study. However, the median follow-up in the study was 23 months (range 1 – 71 months). Actually, all patients with follow-up of less than 19 months experienced clinical failure. Although the loss to follow-up was high, patients without clinical failure had the shortest follow-up of 19 months. Therefore, the rate of clinical failure in our study was credible. Furthermore, we found that even in patients with prior treatment, the long-term clinical failure rates at our center were acceptable when compared with the rates after Heller myotomy [23 – 25].

Other limitations of this study include its retrospective design and relative lack of objective measurements, such as postoperative HRM. In addition, because the study was performed at a center that has one of the highest POEM case volumes in the world, the conclusions drawn from this study might not be applicable to all centers. Large prospective multicenter studies with longer follow-up are required to validate our results.

Conclusions

POEM was successfully and safely performed, with a low rate of major adverse events and comparable clinical reflux, in patients who underwent prior surgical or endoscopic treatment. However, previous treatment increased the technical challenges of the POEM procedure, leading to a longer procedure duration. In addition, the rate of clinical failure in patients with prior treatment was higher than in patients without prior treatment. Because of the increased technical challenges and clinical failure rates, patients with prior treatment should undergo POEM only at experienced centers.

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Competing interests

None.

References

[1] Bechara R, Ikeda H, Inoue H. Peroral endoscopic myotomy: an evolving treatment for achalasia. Nat Rev Gastroenterol Hepatol 2015; 12: 410 – 426

[2] Bechara R, Onimaru M, Ikeda H et al. Per-oral endoscopic myotomy, 1000 cases later: pearls, pitfalls, and practical considerations. Gastrointest Endosc 2016; 84: 330 – 338

[3] Li QL, Zhou PH. Perspective on peroral endoscopic myotomy for achalasia: Zhongshan experience. Gut Liver 2015; 9: 152 – 158

[4] Ngamruengphong S, Inoue H, Chiu PW et al. Long-term outcomes of per-oral endoscopic myotomy in patients with achalasia with a minimum follow-up of 2 years: an international multicenter study. Gastrointest Endosc 2017; 85: 927 – 933

[5] Familiari P, Gigante G, Marchese M et al. Peroral endoscopic myotomy for esophageal achalasia: outcomes of the first 100 patients with short-term follow-up. Ann Surg 2016; 263: 82 – 87

[6] Von Renteln D, Fuchs KH, Fockens P et al. Peroral endoscopic myotomy for the treatment of achalasia: an international prospective multicenter study. Gastroenterology 2013; 145: 309 – 311

[7] Orenstein SB, Raigani S, Wu YV et al. Peroral endoscopic myotomy (POEM) leads to similar results in patients with and without prior endoscopic or surgical therapy. Surg Endosc 2015; 29: 1064 – 1070

[8] Zhou PH, Li QL, Yao LQ et al. Peroral endoscopic remyotomy for failed Heller myotomy: a prospective single-center study. Endoscopy 2013; 45: 161 – 166

[9] Jones EL, Meara MP, Pittman MR et al. Prior treatment does not influence the performance or early outcome of per-oral endoscopic myotomy for achalasia. Surg Endosc 2016; 30: 1282 – 1286

[10] Sharata A, Kurian AA, Dunst CM et al. Peroral endoscopic myotomy (POEM) is safe and effective in the setting of prior endoscopic intervention. J Gastrointest Surg 2013; 17: 1188 – 1192

[11] Kristensen HO, Kirkegard J, Kjaer DW et al. Long-term outcome of peroral endoscopic myotomy for esophageal achalasia in patients with previous Heller myotomy. Surg Endosc 2017; 31: 2596 – 2601

[12] Ngamruengphong S, Inoue H, Ujiki MB et al. Efficacy and safety of peroral endoscopic myotomy for treatment of achalasia after failed Heller myotomy. Clin Gastroenterol Hepatol 2017; 15: 1531 – 1537

[13] Nabi Z, Ramchandani M, Chavan R et al. Peroral endoscopic myotomy in treatment-naive achalasia patients versus prior treatment failure cases. Endoscopy 2018; 50: 358 – 370

[14] Zhang X, Modayil RJ, Friedel D et al. Per-oral endoscopic myotomy in patients with or without prior Heller's myotomy: comparing long-term outcomes in a large US. single-center cohort (with videos). Gastrointest Endosc 2018; 87: 972 – 985

[15] Ren Y, Tang X, Chen Y et al. Pre-treatment Eckardt score is a simple factor for predicting one-year peroral endoscopic myotomy failure in patients with achalasia. Surg Endosc 2017; 31: 3234 – 3241

[16] Zhang XC, Li QL, Xu MD et al. Major perioperative adverse events of peroral endoscopic myotomy: a systematic 5-year analysis. Endoscopy 2016; 48: 967 – 978

[17] Li QL, Wu QN, Zhang XC et al. Outcomes of per-oral endoscopic myotomy for treatment of esophageal achalasia with a median follow-up of 49 months. Gastrointest Endosc 2018; 87: 1405 – 1412

[18] 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

[19] Emami MH, Raisi M, Amini J et al. Pneumatic balloon dilation therapy is as effective as esophagomyotomy for achalasia. Dysphagia 2008; 23: 155 – 160

[20] Boeckxstaens GE, Annese V, des VarannesSB et al. Pneumatic dilation versus laparoscopic Heller's myotomy for idiopathic achalasia. N Engl J Med 2011; 364: 1807 – 1816

[21] Borges AA, Lemme EM, Abrahao LJ et al. Pneumatic dilation versus laparoscopic Heller myotomy for the treatment of achalasia: variables related to a good response. Dis Esophagus 2014; 27: 18 – 23

[22] Inoue H, Sato H, Ikeda H et al. Per-oral endoscopic myotomy: a series of 500 patients. J Am Coll Surg 2015; 221: 256 – 264

[23] Veenstra BR, Goldberg RF, Bowers SP et al. Revisional surgery after failed esophagogastric myotomy for achalasia: successful esophageal preservation. Surg Endosc 2016; 30: 1754 – 1761

[24] Kilic A, Schuchert MJ, Pennathur A et al. Long-term outcomes of laparoscopic Heller myotomy for achalasia. Surgery 2009; 146: 826 – 833

[25] Nau P, Rattner D. Laparoscopic Heller myotomy as the gold standard for treatment of achalasia. J Gastrointest Surg 2014; 18: 2201 – 2207

CORRECTION

The effect of prior treatment on clinical outcomes in patients with achalasia undergoing peroral endoscopic myotomy

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In the above-mentioned article, the number of the one prior treatment has been corrected to 202 patients.

This was corrected in the online version on August 28, 2020.