**Efficacy and Safety of Peroral Endoscopic Myotomy in Achalasia Patients with Failed Previous Intervention: A Systematic Review and Meta-analysis**

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Peroral endoscopic myotomy (POEM) has emerged as a rescue treatment for recurrent or persistent achalasia after failed initial management. Therefore, we aimed to investigate the efficacy and safety of POEM in achalasia patients with failed previous intervention. We searched the MEDLINE, Embase, Cochrane, and PubMed databases using the queries “achalasia,” “peroral endoscopic myotomy,” and related terms in March 2019. Data on technical and clinical success, adverse events, Eckardt score and lower esophageal sphincter (LES) pressure were collected. The pooled event rates, mean differences (MDs) and risk ratios (RR) were calculated. A total of 15 studies with 2,276 achalasia patients were included. Overall, the pooled technical success, clinical success and adverse events rate of rescue POEM were 98.0% (95% confidence interval [CI], 96.6% to 98.8%), 90.8% (95% CI, 88.8% to 92.4%) and 10.3% (95% CI, 6.6% to 15.8%), respectively. Seven studies compared the clinical outcomes of POEM between previous failed treatment and the treatment naïve patients. The RR for technical success, clinical success, and adverse events were 1.00 (95% CI, 0.98 to 1.01), 0.98 (95% CI, 0.92 to 1.04), and 1.17 (95% CI, 0.78 to 1.76), respectively. Overall, there was significant reduction in the pre- and post-Eckardt score (MD, 5.77; p<0.001) and LES pressure (MD, 18.3 mm Hg; p<0.001) for achalasia patients with failed previous intervention after POEM. POEM appears to be a safe, effective and feasible treatment for individuals who have undergone previous failed intervention. It has similar outcomes in previously treated and treatment-naïve achalasia patients. *(Gut Liver 2021;15:153-167)*

**Key Words:** Esophageal achalasia; Meta-analysis; Pyloromyotomy; Safety; Treatment failure

**INTRODUCTION**

Achalasia is an esophageal motility disorder, caused by the absence of myenteric neurons and the subsequent impaired lower esophageal sphincter (LES) relaxation. Patients present with dysphagia, regurgitation, chest pain, and weight loss.¹ Treatment options include Heller myotomy (HM), pneumatic balloon dilation (PBD), and botulinum toxin injection (BTI). Although HM is considered the first-line therapy due to its superior long-term outcomes, a failure rate of approximately 10% to 20% is observed.²³ Similarly, despite a 90% PBD success rate, recurrence of symptoms occurs post-procedure in 20%, 30%, and 40% of patients in 2, 5 and 10 years, respectively.⁴⁵ Lastly, BTI is safety and efficacious in the majority of patients; however, symptomatic relief is short term with only 29% of patients reporting continued success during intermediate follow-up.⁶ In cases of symptom recurrence after primary intervention, surgical myotomy is often technically challenging. Additionally, a high risk of adverse events is documented. Reported rates of gastrointestinal perforation range from 1.5% to 20% and are typically due to the formation of scars, fibrosis and adhesions resulting from previous surgical or endoscopic interventions.⁸¹² PBD and BTI are also rescue management strategies for recurrent achalasia. However, the durability of both interventions is limited. Repeat treat-
ment for relapsing symptoms is required in up to 45% of patients after 2 years. Furthermore, previous myotomy is considered to be a relative contraindication to PBD. Recently, peroral endoscopic myotomy (POEM) has emerged as a treatment for recurrent or persistent achalasia after failed initial management. It can avoid shortcomings of other treatments mentioned above. Several studies have demonstrated a promising clinical success rate of greater than 90%. However, some of these studies in this setting are limited by their small numbers. Therefore, the aim of this systematic review and meta-analysis was to determine the efficacy and safety of POEM as a therapy in those who have undergone failed endoscopic or surgical treatments. We also compared the efficacy and safety of POEM in patients who had previously failed endoscopic or surgical therapies with those who underwent the POEM as a primary treatment.

METHODS

1. Search strategy and study selection

Utilizing Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, the following databases were searched from interception to March 2019: MEDLINE, Embase, Cochrane, and PubMed. The keywords “achalasia,” “esophageal achalasia,” “peroral endoscopic myotomy,” “per-oral endoscopic myotomy,” “Heller myotomy,” “POEM,” “Pneumatic dilation,” “HM,” and the related terms provided in Supplementary Table 1 were used. The references of published articles were also manually reviewed to ensure the inclusion of all relevant studies. Articles published in the Chinese language were reviewed by coauthor X.T. However, none met our inclusion criteria. Two authors (S.T. and C.Z.) screened all titles, abstracts and full texts independently. Any discrepancies were discussed with a third investigator (X.T.).

2. Eligibility criteria and data collection

Two reviewers (X.F. and Y.R.) assessed the articles independently based on the predefined inclusion criteria and exclusion criteria. All prospective, retrospective, case-control and cohort studies and other clinical trials were included if they featured patients: (1) diagnosed with achalasia and (2) who had undergone POEM after failed previous treatment(s). Manuscripts were excluded if: (1) they described non-human studies, (2) were single-arm studies with treatment-naïve patients undergoing POEM or (3) were case-reports less than five patients, commentaries, reviews, editorials, conference abstracts or surveys. For overlapping publications from the same center, only the most recent and comprehensive publication was considered for inclusion. Two reviewers (Y.P. and X.T.) collected the following data independently: baseline characteristics (author name, year of publication, country, study design, study duration, group, sample size, patient age, and sex distribution); clini-
cal characteristics (initial achalasia treatment, achalasia subtype, myotomy orientation, myotomy length, procedure time, and length of hospital stay) and clinical outcomes (technical success, clinical success, incidence of symptomatic reflux and reflux esophagitis). Also, major and minor adverse events were recorded to determine the safety of POEM. Pre- and post-procedure Eckardt scores and LES pressures were also included.

3. Quality assessment
The Newcastle-Ottawa Quality Assessment Scale for non-randomized studies was used by two investigators (X.L. and J.X.) to assess the risk of bias in the included studies. This scale rates three study aspects: selection, comparability and outcome. The maximum attainable score is 9. Each study was rated as “high quality” (score ≥7), “medium quality” (score of 5 or 6) or “low quality” (score ≤4).

4. Endpoint definition and statistical analysis
The primary outcomes were efficacy (as measured by technical and clinical success) and safety (indicated by presence and severity of adverse events) of POEM after failure of endoscopic or surgical intervention for achalasia. Technical success was defined as successful completion of the entire procedure. Clinical success was defined as an Eckardt score ≤3 during the study follow-up period. Procedure-related and post-procedure adverse events were included. Adverse events were divided into major and minor according to the NOSCAR white paper. Major adverse events were defined as events requiring additional intervention during or after POEM including endoscopic or surgical interventions, bleeding requiring transfusion, readmission within 30 days, prolonged hospital stay (>5 days) and clinical inflammation. Air-related outcomes and fluid collections were considered to be major adverse events when requiring drainage. Adverse events which were managed conservatively were defined as minor adverse events. The secondary endpoints of the study were the mean reduction in Eckardt scores and LES pressures, the difference in procedure time and hospital stay between the patients with and without previous intervention(s), and gastroesophageal reflux disease (GERD) incidence during follow-up. All statistical analyses were conducted using Comprehensive Meta-Analysis version 2 (Biostat, Englewood, NJ, USA), Cochrane Review Manager 5.3 (London, England).
Table 2. Clinical Characteristics of Included Studies

| Author            | Group                  | Previous treatment | Subtype *           | Direction of myotomy | Procedure time, mean±SD, min | Myotomy length, mean±SD, cm | Hospital stay, mean±SD, day |
|-------------------|------------------------|--------------------|---------------------|-----------------------|-------------------------------|-----------------------------|-----------------------------|
| Tyberg et al.     | 46 PTF                 | 46 POEM            | 10 I, 16 II, 5 III, 15 other EDD | NA                   | 90                           | NA                          | NA                          |
| Tyberg et al.     | 51 PTF                 | 43 LHM, 8 laparotomy HM | 13 I, 29 II, 6 III, 3 other EDD | 51 Posterior         | NA                           | NA                          | NA                          |
| Onimaru et al.    | 10 PTF                 | 10 LHM+PBD        | 6 II, 4 III         | 7 Posterior           | 118.2                        | 9.2                         | 3.2                         | 12.4                        |
| Vigneswaran et al.| 5 PTF                  | 5 LHM              | NA                  | NA                    | 139.0±29.6                  | NA                          | NA                          | NA                          |
| Zhou et al.       | 12 PTF                 | 3 Laparotomy HM, 3 open thoracotomy HM, 6 LHM | NA                  | 12 Posterior          | 36.4±9.3                     | 8.0 [6–10]                  | 2.1 [2–3]                  | 10.1 [8–13]                  |
| Ling et al.       | 21 PTF                 | 21 PBD             | 5 I, 13 II, 3 III   | 21 Posterior          | 42.4±8.3                     | NA                          | NA                          | NA                          |
| Ngamruengphong et al.| 90 PTF with HM       | 40 PBD, 10 BTI    | 26 I, 23 II, 10 III, 31 unspecified | 2 Posterior           | 102.8±61                     | 8.7±4.4                     | 2.9±1.2                     | 11.6                        |
|                 | 90 PTF without HM     | 23 PBD, 7 BTI     | 20 I, 29 II, 10 III, 31 unspecified | 42 Posterior          | 102.6±61                     | 9.7±3.9                     | 3±1.3                       | 12.7                        |
|                 |                        |                    |                     |                       |                              |                             |                             | 3.59±2.5                    |
| Tang et al.       | 22 PTF                 | 18 PBD, 2 BTI, 2 BTI+PBD | 5 I, 17 II         | NA                    | 60.8±30.9                    | 6.7±2.6                     | 3.1±1.1                     | 9.8±2.9                     |
| Kristensen et al. | 14 PTF with HM         | 13 BTI or PBD     | 9 I, 5 missing data | NA                    | 62.0±21.0                    | 7.4±3.3                     | 3.1±1.6                     | 10.5±3.9                    |
|                 | 52 PTF without HM      | 15 BTI or PBD     | 7 I, 25 II, 3 III, 17 missing data | NA                  | 74 [35–149]                  | 9.5 [16–13]                  | 3 [2–5]                     | NA                          |
| Orenstein et al. | 16 PTF                 | 6 BTI, 4 PBD, 3 BTI+PBD, 3 LHM | NA              | 102                     | NA                           | NA                          | NA                          | NA                          |
|                 | 24 Naive               | None              | NA                  | 118                   | NA                           | NA                          | NA                          | NA                          |
| Nabi et al.       | 242 PTF                | 205 PBD, 30 LHM, 4 BTI, 3 POEM | 91 I, 140 II, 11 III | 186 Posterior         | 74.9±30.6                    | 9.4±2.4                     | 3.1±0.5                     | 12.5                        |
|                 | 260 Naive              | None              | 82 I, 169 II, 9 III | 210 Posterior         | 67.0±27.1                    | 9.0±2.5                     | 3.08±0.5                    | 12.08                       |
|                 |                        |                    |                     |                       |                              |                             |                             | 3 [2–5]                     |
| Sharata et al.    | 12 PTF                 | 10 BTI, 2 PBD     | 9 Unspecified, 3 other EDD | NA                    | 134±43                       | NA                          | NA                          | NA                          |
|                 | 28 Naive               | None              | 22 Unspecified, 6 other EDD | NA                    | 131±41                       | NA                          | NA                          | NA                          |
| Zhang et al.      | 46 PTF                 | 14 HM+PBD, 19 HM+BTI | 30 I, 5 II, 6 III, 5 unspecified | 8 Posterior           | 82 [32–166]                  | NA                          | NA                          | 11 [5–23]                  |
|                 | 272 PTF                | 29 PBD, 54 BTI    | 53 I, 147 II, 32 III, 26 unspecified, 14 other EDD | 137 Posterior         | 72 [21–240]                  | NA                          | NA                          | 12 [3–27]                  |
UK) and GraphPad Prism version 5.00 (San Diego, CA, USA). Pooled effects with 95% confidence intervals (CI) were calculated for technical success, clinical success and adverse events. The mean difference (MD) was calculated for Eckardt score, LES pressure, procedure time and length of hospital stay. We also compared the efficacy and safety of POEM in patients who had previously failed endoscopic or surgical therapies with those who underwent POEM as a primary treatment for achalasia. Risk ratios (RR) were derived for technical success, clinical success and adverse events. The heterogeneity between the studies was assessed using the $I^2$ test and Cochran's Q statistic in which a $p<0.1$ indicates substantial heterogeneity. $I^2$ values of around 25%, 50% and 75% were considered as low, moderate and high heterogeneity, respectively. When $I^2$ was greater than 50% and/or the Cochran's Q test provided a $p<0.1$, we ran analyses with the random-effect model, otherwise we used the fixed-effect model. Publication bias was assessed using funnel plots and the Egger's regression test. In addition, we performed subgroup analyses according to follow-up time and adverse events (major and minor adverse events), and a sensitivity analysis to confirm whether a single study caused an effect. A two-sided $p<0.05$ was regarded as statistically significant.

### RESULTS

#### 1. Study characteristics and quality

Using the search strategy, 3,330 records were identified. After exclusion criteria, 15 studies were eligible (Fig. 1). The baseline characteristics of the included studies are summarized in Table 1. The 15 studies were all conducted between September 2008 and January 2017. Three multicenter studies, all lead by USA investigators, were included. The 12 single-center studies were conducted in Japan (n=1), USA (n=5), China (n=4), Denmark (n=1), and India (n=1). Among these studies, six were prospective. No randomized control trials met inclusion criteria.

A total of 2,276 patients were included in our study. One thousand-fifteen were treatment-naïve and 1,261 patients had undergone previous treatment(s) for achalasia. The mean ages of patients ranged from 34.9 to 69.6 years. Overall, five studies were single arm studies with failed endoscopic or/and surgical interventions. Seven studies compared the clinical outcomes of POEM between previous failed treatment and the treatment naïve patients.

Table 2 shows the clinical characteristics of the included studies. Information on achalasia subtype was available for 2,197 patients (type I n=579, type II n=1,108, type III n=145, and unspecified type n=321). There were 44 pa-
tients with other esophageal dysmotility disorders. Submu-
cosal myotomies (354/1,169; 45.7%) were posterior. The 
mean procedure time, total myotomy length and hospital 
stay ranged from 36.4 to 139 minutes, 9.0 to 12.7 cm and 
1 to 6.2 days, respectively. The assessment of risk of bias 
of individual studies is shown in the Table 3. Follow-up time 
ranged from 5 to 28 months (Table 4).

2. Technical success
Thirteen studies with 1,179 patients reported the tech-
nical success of POEM for patients with prior endoscopic 
or/surgical treatment. Technical success ranged from 
97.1% to 100% and was achieved in 1,170 (99.2%) patients 
(Table 4). Pooled technical success was 98.0% (95% CI, 
96.6% to 98.8%) with no statistically significant hetero-
geneity (Q=9.99, p=0.62, I²=0%) (Fig. 2A). Sensitivity 
analysis was performed removing one study at a time, and 
confirmed the same outcomes of the main analyses. There 
was no publication bias amongst the studies as shown in 
the Supplementary Fig. 1A (Egger’s regression test p=0.38).

3. Clinical success
Ten studies with 1,095 patients reported the clinical 
success of POEM for patients with prior endoscopic or/
and surgical treatment. Clinical success ranged from 81% 
to 100% in these studies. Clinical success was achieved in 
999 patients (91.2%) at 3-month follow-up (Table 4). The 
pooled clinical success in patients with greater than three 
months’ follow-up was 90.8% (95% CI, 88.8% to 92.4%) 
with a low degree of heterogeneity (Q=10.73, p=0.29, 
I²=16.14%) as shown in Fig. 2B. Subgroup analysis was 
undertaken on the basis of duration of follow-up. Four 
studies reported clinical success with 1-year follow-up. Two 
studies reported 2- and 3-year follow-ups. The pooled 
results of clinical success rates for 1-, 2-, and 3-year follow-
ups were 89.9% (95% CI, 86.9% to 92.3%), 85.8% (95% 
CI, 81.7% to 89.1%) and 81.2% (95% CI, 76.2% to 85.4%), 
respectively (Supplementary Fig. 2). Sensitivity analysis re-
moving one study at a time was performed and confirmed 
the outcomes of the main analyses. However, when remov-
ing either the study by Zhang et al. or Ngamruengphong 
et al., a considerable reduction in heterogeneity occurred, 
changing the I² from 16.14% to 0%. There was no publica-
tion bias amongst the studies as shown in Supplementary 
Fig. 1B (Egger’s regression test p=0.49).

4. Adverse events
Fourteen studies with 1,195 patients reported the adverse 
events of POEM for patients with prior endoscopic or/
surgical treatment. A total of 83 (6.9%) adverse events oc-
curred (Table 5). The pooled adverse events rate was 10.3% 
(95% CI, 6.6% to 15.8%) with a high degree of heterogeneity 
(Q=45.67, p<0.001, I²=71.54%), as shown in Fig. 2C. The 
pooled major and minor adverse events rates were 6.4% 
(95% CI, 3.6% to 11.1%) and 7.0% (95% CI, 5.2% to 9.5%) as 
shown in Supplementary Fig. 3. Sensitivity analysis demon-
strated that the largest change occurred when the study con-
ducted by Zhang et al. was removed. The heterogeneity de-
creased from 71.54% to 60.74%. The effect sized changed 
from 10.3% to 11.8% (95% CI, 7.9% to 17.3%). There was 
no publication bias amongst the studies as shown in Sup-
plementary Fig. 1C (Egger’s regression test p=0.39).

| Study                        | Selection | Outcome assessment | Comparability | Quality of study |
|------------------------------|-----------|--------------------|---------------|-----------------|
| Tyberg et al.16              | +         | +                  | +             | Medium quality  |
| Ling et al.17                | +         | +                  | +             | High quality    |
| Tang et al.19                | +         | +                  | +             | High quality    |
| Ngamruengphong et al.18      | +         | +                  | +             | High quality    |
| Kristensen et al.20          | +         | +                  | +             | High quality    |
| Tyberg et al.21              | +         | +                  | +             | Medium quality  |
| Orenstein et al.23           | +         | +                  | +             | High quality    |
| Nabi et al.24                | +         | +                  | +             | High quality    |
| Onimaru et al.25             | +         | +                  | +             | Medium quality  |
| Vigneswaran et al.26         | +         | +                  | +             | Medium quality  |
| Sharata et al.27             | +         | +                  | +             | High quality    |
| Zhang et al.22               | +         | +                  | +             | High quality    |
| Zhou et al.28                | +         | +                  | +             | Medium quality  |
| Jones et al.29               | +         | +                  | +             | High quality    |
| Liu et al.30                 | +         | +                  | +             | High quality    |

Selection: 1, representativeness of the exposed cohort; 2, selection of the nonexposed cohort; 3, ascertainment of exposure; 4, outcome of interest not present at start of study. Outcome assessment: 1, assessment of outcome; 2, adequacy of duration of follow-up; 3, adequacy of completeness of follow-up. Comparability: 1, study controls for confounder; 2, study controls for any additional factors.
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5. Meta-analysis

Overall, six studies with 1,548 patients compared the technical success of POEM between achalasia patients with and without previous treatment. The pooled RR for technical success was 1.00 (95% CI, 0.98 to 1.01), p=0.56, Cochran Q test p=0.91, I²=0% (Fig. 3). For clinical success, the pooled RR at 1-year follow-up was 0.98 (95% CI, 0.92 to 1.04), p=0.46, Cochran Q test p=0.10, I²=56% (Fig. 4A). The results for 2- and 3-year follow-ups were 0.93 (95% CI, 0.89 to 0.98) and 0.89 (95% CI, 0.84 to 0.95) (Fig. 4B and C). Seven studies with 1,588 patients compared the safety of POEM in achalasia patients with and without previous treatment. The adverse events rate for patients with prior treatment versus treatment naïve patients was 6.3% and 5.3%. The pooled RR was 1.17 (95% CI, 0.78 to 1.76), p=0.45, Cochran Q test p=0.60, I²=0% (Fig. 5A). There were also no significant difference in major and minor adverse events between the two groups. The RR for major and minor adverse events were 1.14 (95% CI, 0.71 to 1.82; p=0.60) and 0.99 (95% CI, 0.85 to 1.16; p=0.94), respectively (Fig. 5B and C). The presence of GERD diagnosed via esophagogastroduodenoscopy (EGD) was documented for 963 patients. The RR for reflux esophagitis at EGD was 1.18 (95% CI, 0.91 to 1.53), p=0.21, Cochran Q test p=0.51.

### Table 4. Clinical Outcomes of Included Studies during Follow-up

| Author           | Group          | % (No./No.) | Follow-up, mean (range), mo |
|------------------|----------------|-------------|-----------------------------|
| Tyberg et al.    | 46 PTF         | 100 (44/46) | 85 (41/46) [3-mo FU]         |
| Tyberg et al.    | 51 PTF         | 100 (51/51) | 94 (48/51) [1-yr FU]         |
| Onimaru et al.   | 10 PTF         | 100 (10/10) | NA                          |
| Vigneswaran et al.| 5 PTF         | 100 (5/5)   | NA                          |
| Zhou et al.      | 12 PTF         | 100 (12/12) | 91.7 (11/12) [5–14 mo FU]    |
| Ling et al.      | 21 PTF         | 100 (21/21) | 92.3 (19/21) [postoperative], 87.5 (18/21) | 1-yr FU |
| Ngamruengphong et al. | 90 PTF (with HM) | 98 (88/90) | 81.2 (69/85) | Symptomatic reflux 30 (21/70) |
|                  | 90 PTF (without HM) | 100 (90/90) | 94.8 (77/82) [total n=167] | Symptomatic reflux 44 (18/41) |
| Tang et al.      | 22 PTF         | 100 (22/22) | 95.5 (21/22) |
|                  | 39 Naive       | 100 (39/39) | 92.3 (36/39) [1-yr FU]       |
| Kristensen et al. | 14 PTF (with HM)| NA         | NA                          |
|                  | 52 PTF (without HM) | NA       | NA                          |
| Orenstein et al. | 16 PTF         | NA          | NA                          |
| Nabi et al.      | 242 PTF        | 97.1 (235/242) | 92.5 (186/201) [6-mo FU] 191.2 (145/159) [1-yr FU] 90.7 (116/183) [1-yr FU] 87.5 (112/128) | [2-yr FU] 87.1 (27/31) [3-yr FU] | Symptomatic reflux 17.8 (26/146) |
|                  | 260 Naive      | 98.1 (255/260) | 92.4 (206/223) [6-mo FU] 90.7 (166/183) [1-yr FU] 87.5 (112/128) | [2-yr FU] 87.1 (27/31) [3-yr FU] | Symptomatic reflux 16.4 (22/134) |
| Sharata et al.   | 12 PTF         | 100 (12/12) | NA                          |
|                  | 28 Naive       | 100 (28/28) | 100 (28/28) [postoperative] | NA | 6 |
| Zhang et al.     | 46 PTF         | 100 (44/46) | 95.7 (44/46) |
|                  | 272 PTF²       | 100 (272/272) | 95.1 (255/272) | I>3 mo | Reflux esophagitis 46.2 (12/26) |
| Jones et al.     | 15 PTF         | 100 (15/15) | NA                          |
|                  | 30 Naive       | 100 (30/30) | NA                          |
| Liu et al.       | 245 PTF        | 100 (245/245) | 88.6 (217/245) | [1-yr FU] 86.5 (212/245) | [2-yr FU] 82 (201/245) | [5-yr FU] | Symptomatic reflux 18.8 (46/245) |
|                  | 604 Naive      | 100 (604/604) | 95.0 (574/604) | [1-yr FU] 93.5 (565/604) | [2-yr FU] 91.7 (554/604) | [5-yr FU] | Symptomatic reflux 17.3 (80/462) |

PTF, previous treatment failure; FU, follow-up; NA, not available; HM, Heller myotomy.
*Median (interquartile range); †Median (range); ‡Previous surgical and endoscopic treatment failure; §Previous endoscopic treatment failure.
I² = 0% (Table 4, Supplementary Fig. 4A). The RR for GERD symptoms was 1.19 (95% CI, 0.90 to 1.57), p = 0.22, Cochran Q test p = 0.45, I² = 0% (Table 4, Supplementary Fig. 4B). We also compared the procedure time between the patients with and without previous intervention. The MD for procedure time and length of hospital stay were
7.21 minutes (95% CI, 4.04 to 10.39; p<0.001, I²=0%) and 0.09 days (95% CI, –0.53 to 0.71; p=0.77, I²=58%) (Table 2, Supplementary Fig. 5). Thirteen studies reported the change in the Eckardt score in the cohort with previous intervention. Ten studies evaluated the change in LES pressure after POEM. The mean Eckardt score was significantly decreased by 5.77 points (95% CI, 5.07 to 6.47; p<0.001, I²=96%) and LES pressure was significantly reduced by 18.3 mm Hg (95% CI, 12.73 to 23.86; p<0.001, I²=95%) (Fig. 6A and C, Supplementary Table 2). The mean Eckardt score and LES pressure in patients with prior treatment were 7.25±0.14 points and 38.65±1.28 mm Hg, respectively. After POEM, these decreased to 1.07±0.10 and 16.28±0.65, respectively (Fig. 6B and D). When we excluded the studies that did not report the standard deviation, significant changes in Eckardt score and LES pressure were still found. The overall MDs in Eckardt score and LES pressure were 5.74 (95% CI, 5.04 to 6.44; p<0.001, I²=90%) and 20.16 mm Hg (95% CI, 14.81 to 25.51; p<0.001, I²=92%).

### Table 5. Safety of Peroral Endoscopic Myotomy

| Author             | Major adverse events                  | Minor adverse events                  |
|--------------------|---------------------------------------|---------------------------------------|
|                    | PTF | Naïve | PTF | Naïve |
| Tyberg et al.¹⁴    | 0   | -     | 8   | Bleeding |
| Tyberg et al.²¹    | 2   | Mediastinitis | 6 | Mucosal defects |
| Onimaru et al.²⁵   | 0   | -     | 0   | -     |
| Vigneswaran et al.²⁶ | 1   | Esophageal leak and mediastinal abscess | - | 0     |
| Zhou et al.²⁸      | 1   | Pneumothorax | 1 | Pneumoperitoneum |
|                    | 1   | -     | 1   | Mucosal perforation |
| Ling et al.¹⁷      | 0   | 0     | 0   | 0     |
| Ngaamruengphong et al.¹⁶ | 1   | Pneumonia | 1 | Mediastinitis |
|                    | 5   | Symptomatic pneumoperitoneum | 1 | Symptomatic pneumothorax |
|                    | 1   | Symptomatic subcutaneous emphysema | 1 | Pleural effusion requiring chest drain |
| Tang et al.¹⁹      | 0   | 0     | 1   | Bleeding |
| Kristensen et al.²⁰ | NA | -     | 2   | Bleeding |
| Orenstein et al.²³ | 1   | Capnoperitoneum alleviated with angiocatheter evacuation | 1 | Capnoperitoneum alleviated with angiocatheter evacuation |
|                    | 1   | Mallory-Weiss tear requiring blood transfusion | 0   | 1 Mucosal tear |
|                    | 1   | Mucosal tear requiring a stent |
| Nabi et al.²⁴      | 1   | Capnopericardium | 2 | Capnoperitoneum requiring decompression |
|                    | 2   | Enlargement of mucosal incision | 1 | Enlargement of mucosal incision |
|                    | 1   | 30-Day readmission |
| Sharata et al.²⁷   | 1   | Bleeding requiring endoscopic re-intervention | 1 | Full-thickness esophageal perforation requiring endoscopic and surgical re-intervention |
|                    | 1   | Mucosotomy dehiscence needing endoscopic suture | 1 | Capnoperitoneum needed Veress needle decompression |
| Zhang et al.²²     | 5   | Prolonged stay >5 day | 11 | Mucosal injury |
|                    | 3   | Readmission within 30 days related to POEM (1 diarrhea; 1 bleeding; 1 fever) | 8 | Mucosal injury |
| Jones et al.²⁹     | 4   | Pneumoperitoneum needed needle decompression | 12 | Pneumoperitoneum needed needle decompression |
| Liu et al.³⁰       | 6   | Pneumothorax requiring drainage | 13 | Pneumothorax requiring drainage |
|                    | 2   | Hydrothorax requiring drainage | 4 | Hydrothorax requiring drainage |
|                    | 1   | Delayed mucosa barrier failure | 3 | Delayed mucosa barrier failure |
|                    | 1   | Delayed bleeding requiring intervention or transfusion | 1 | Delayed bleeding requiring intervention or transfusion |
|                    | 1   | Other miscellaneous major adverse event | 2 | Other miscellaneous major adverse events |

PTF, previous treatment failure; NA, not available; POEM, peroral endoscopic myotomy.
**DISCUSSION**

With the advent of minimally invasive era, POEM has become a promising technique with excellent clinical outcomes for the treatment of achalasia patients with or without failed previous treatment. However, it is technically challenging for several, multifactorial reasons. Irrespective of type of previous intervention for achalasia, endoscopic or surgical, esophageal scarring and fibrosis may result. This may lead to difficulty in delineating tissue planes and reduce the efficacy of submucosal injection, leading to an increase in technical success rates.

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### Table: Technical Success

| Study or Subgroup | Pre | Non-pre | Risk ratio | Risk ratio |
|-------------------|-----|---------|------------|------------|
|                   | Events | Total | Events | Total | M-H, fixed, 95% CI | M-H, fixed, 95% CI |
| Jones EL et al. 2015 | 15 | 15 | 30 | 30 | 1.00 [0.91, 1.10] |
| Ling T et al. 2014 | 21 | 21 | 30 | 30 | 1.00 [0.92, 1.08] |
| Liu ZQ et al. 2019 | 245 | 245 | 604 | 604 | 1.00 [0.99, 1.01] |
| Nabi Z et al. 2018 | 235 | 242 | 255 | 260 | 0.99 [0.96, 1.02] |
| Sharata A et al. 2013 | 12 | 12 | 28 | 28 | 1.00 [0.89, 1.13] |
| Tang X et al. 2017 | 22 | 22 | 39 | 39 | 1.00 [0.93, 1.07] |
| Total (95% CI) | 557 | 991 | 100.0% | 1.00 [0.98, 1.01] |

**Fig. 3.** Meta-analysis of technical success between patients with and without previous intervention(s). M-H, Mantel-Haenszel; CI, confidence interval.

### Table: Clinical Success

| Study or Subgroup | Pre | Non-pre | Risk ratio | Risk ratio |
|-------------------|-----|---------|------------|------------|
|                   | Events | Total | Events | Total | M-H, fixed, 95% CI | M-H, fixed, 95% CI |
| Liu ZQ et al. 2019 | 217 | 245 | 574 | 604 | 0.93 [0.89, 0.98] |
| Nabi Z et al. 2018 | 145 | 159 | 166 | 183 | 1.01 [0.94, 1.07] |
| Tang X et al. 2017 | 21 | 22 | 36 | 39 | 1.03 [0.91, 1.18] |
| Total (95% CI) | 426 | 826 | 100.0% | 0.98 [0.92, 1.04] |

**Fig. 4.** Meta-analysis of clinical success between patients with and without previous intervention(s). (A) One-year follow-up; (B) 2-year follow-up; (C) 3-year follow-up. M-H, Mantel-Haenszel; CI, confidence interval.
A. Overall adverse event

| Study or Subgroup | Pre Events | Non-pre Events | Weight | Risk ratio M-H, fixed, 95% CI |
|-------------------|------------|----------------|--------|-----------------------------|
| Jones EL et al. 2015 | 4          | 15             | 21.0%  | 0.67 [0.26, 1.72]           |
| Ling T et al. 2014 | 0          | 21             | 100.0% | Not estimable               |
| Liu ZQ et al. 2019 | 11         | 245            | 34.9%  | 1.18 [0.58, 2.38]           |
| Nabi Z et al. 2018 | 14         | 242            | 32.9%  | 1.16 [0.56, 2.41]           |
| Orenstein SB et al. 2015 | 3       | 16             | 4.2%   | 2.25 [0.42, 12.00]          |
| Sharata A et al. 2013 | 3         | 12             | 3.2%   | 3.50 [0.67, 18.34]          |
| Tang X et al. 2017 | 1          | 22             | 3.8%   | 0.89 [0.09, 9.23]           |
| Total (95% CI)     | 573        | 1,015          |        | 1.17 [0.78, 1.76]           |

B. Major adverse event

| Study or Subgroup | Pre Events | Non-pre Events | Weight | Risk ratio M-H, fixed, 95% CI |
|-------------------|------------|----------------|--------|-----------------------------|
| Jones EL et al. 2015 | 4          | 15             | 28.5%  | 0.67 [0.26, 1.72]           |
| Liu ZQ et al. 2019 | 11         | 245            | 47.2%  | 1.18 [0.58, 2.38]           |
| Nabi Z et al. 2018 | 3          | 242            | 17.2%  | 0.64 [0.16, 2.67]           |
| Orenstein SB et al. 2015 | 3       | 16             | 2.8%   | 4.50 [0.51, 39.53]          |
| Sharata A et al. 2013 | 3         | 12             | 4.3%   | 3.50 [0.67, 18.34]          |
| Total (95% CI)     | 530        | 946            |        | 1.14 [0.71, 1.82]           |

C. Minor adverse event

| Study or Subgroup | Pre Events | Non-pre Events | Weight | Risk ratio M-H, fixed, 95% CI |
|-------------------|------------|----------------|--------|-----------------------------|
| Nabi Z et al. 2018 | 133        | 242            | 98.1%  | 1.00 [0.85, 1.17]           |
| Orenstein SB et al. 2015 | 0       | 16             | 0.9%   | 0.49 [0.02, 11.33]          |
| Tang X et al. 2017 | 1          | 22             | 1.0%   | 0.89 [0.09, 9.23]           |
| Total (95% CI)     | 280        | 323            |        | 0.99 [0.85, 1.16]           |

Fig. 5. Meta-analysis of adverse events between patients with and without previous intervention(s). [A] Overall adverse events; [B] major adverse events; [C] minor adverse events.

M-H, Mantel-Haenszel; CI, confidence interval.

increased likelihood of complications such as perforation and bleeding. Due to this potentially increased difficulty of POEM after previous interventions for achalasia, we performed this meta-analysis to explore the efficacy and safety of POEM for patients with and without prior treatment. In our present study, we demonstrated that POEM was equally efficacious and safe in achalasia patients with and without previous intervention. We found that POEM achieved high pooled technical (98.0%) and clinical (90.8%) success rates and reduced the Eckardt score (MD: 5.77, p<0.001) and LES pressure (MD: 18.3 mm Hg, p<0.001) significantly in patients who have undergone prior treatment. In addition, our meta-analysis demonstrated that the efficacy of POEM in the patients who had undergone prior intervention was comparable to that of the treatment-naive patients. Our result is consistent with several published studies. The favorable results provided by POEM are due to several reasons. POEM is a completely endoscopic and intraluminal approach which is unlikely to be affected by the scars and tissue adhesions resulting from previous treatment. Thus, efficacy is similar to treatment naïve patients. Additionally, POEM provides the opportunity to perform the myotomy in an opposite orientation. Thus, the new myotomy can be performed in a location without scars, resulting in good control of the myotomy length. Conversely, due to the presence of scars, fibrosis and tissue adhesions, the POEM procedure could potentially be more technically challenging, resulting in a longer procedure time and hospital stay. In the Liu et al., a significantly longer hospital stay after POEM was found in patients with
Fig. 6. Changes in the mean Eckardt score and lower esophageal sphincter (LES) pressure before and after peroral endoscopic myotomy (POEM) in patients with previous endoscopic or/surgical intervention. (A) Change in the mean Eckardt score. (B) Changes in the mean Eckardt score before and after POEM: the diamond corresponds to the mean Eckardt score, and the lines extending from them indicate the standard error above and below the mean. (C) Change in the mean LES pressure. (D) Changes in the mean LES pressure before and after POEM. IV, inverse variance; CI, confidence interval.
prior therapy when compared to the patients without prior treatment (<2 days: 43.7% vs 53.6%, ≥2 days: 56.3% vs 46.4%, p=0.001). Our study failed to demonstrate a longer length of hospital stay (MD: 0.09, p=0.77) after pooling all related data. Importantly, our analysis was performed with only three studies. In view of this small numbers of studies and sample size, we must interpret this outcome with caution.

When comparing the clinical success rate of POEM in patients with a greater than 2- and 3-year follow-ups, we found that results from the group of treatment naïve patients was superior to the that of the patients who had undergone previous endoscopic or/surgical interventions. However, an individual study by Nabi et al.24 with 502 patients and a greater than 2-year follow-up did not suggest a higher clinical success rate in treatment-naïve patients. Liu et al.25 reviewed 849 patients and demonstrated a superior 5-year clinical success rate in the treatment naïve cohort. They indicated that follow-up duration correlated with the difference in clinical failure between patients with and without prior treatment. They also found patients who had undergone more than one previous intervention had a higher risk than those with only one previous treatment. This may be attributed to severe inflammation and fibrosis formed by prior treatments. This difference may also be due to a difference in "symptom-reporting threshold" of patients whose symptoms recurred after prior treatments. Given this discrepancy in outcomes, systematic evaluation of long-term outcomes between the two groups is necessary in the future.

In our study, the most common adverse events related to the POEM procedure in patients with prior treatments were mucosal injury, bleeding, pneumothorax, and pneumoperitoneum. Theoretically, patients who have undergone surgical or/endoscopic treatment are more prone to incur adverse events because of inflammation and fibrosis. Nevertheless, in the current study, the adverse event rate was not significantly higher in those who had undergone previous interventions when compared to those without interventions. This may be due to all the POEM procedures being performed by experienced operators in our included studies.26 When evaluating the GERD rate during follow-ups, we found that the incidence of GERD diagnosed via EGD or questionnaires was not significantly different between the two groups (Supplementary Fig. 4).

Our study confirmed the safety of POEM for patients with previous interventions.

To our knowledge, this is the first systematic review and meta-analysis comparing the efficacy and safety of POEM in patients with and without previous treatments. There are a few limitations in the current study. First, only retrospective and prospective studies were included. No randomized controlled studies were found. Second, owing to the paucity of data in the included studies, we were unable to assess the efficacy and safety of POEM for patients with previous surgical or endoscopic interventions separately. Third, some studies included pediatric patients with achalasia and some patients with other esophageal dysmotility disorders. However, these patients accounted for a small percentage and our outcomes were unchanged after removing these studies. Fourth, we were unable to assess the quality of life in patients with prior treatments after POEM due to the limited number of studies reporting this results. Last, long-term (greater than 2 years) differences between the patients with and without prior intervention should be interpreted carefully as only two study reported these outcomes.

**CONCLUSION**

POEM appears to be a safe, effective and feasible treatment for those who have undergone previous failed endoscopic or surgical intervention. It has similar outcomes in previously treated and treatment-naïve achalasia patients. It may be an attractive option for the treatment of patients with this difficult condition. However, further studies with a long-term follow-up to determine the durability of rescue POEM are still warranted.

**CONFLICTS OF INTEREST**

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Study conception and design: X.T., Y.R. Acquisition of data and critical revision: X.L., J.X. Drafting of manuscript: S.T., C.Z. Revision of manuscript, and final approval of manuscript: X.F., Y.P., X.T.

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