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Review Article

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.[2,3] 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.[4-6] 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.[7] 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.[8-12] PBD and BTI are also rescue management strategies for recurrent achalasia. However, the durability of both interventions is limited. Repeat treat-

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ment for relapsing symptoms is required in up to 45% of patients after 2 years.[5,13] Furthermore, previous myotomy is considered to be a relative contraindication to PBD.[14,15] 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%.[16-30] 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,[31] 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-

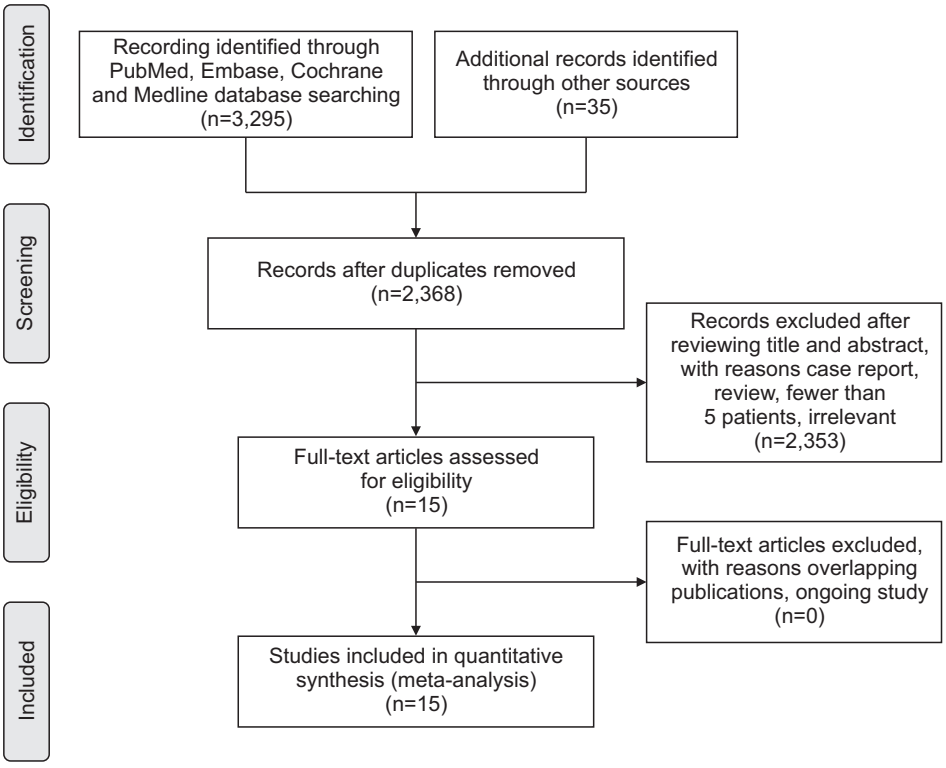


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart.

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.[32,33] 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.[34] 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,

Table 1. Baseline Characteristics of Included Studies

Author (year)	Country	Design	Duration	No. of patients	Group	Age, yr	Male sex, No. (%)
Tyberg *et al.* (2016)[16]	USA	Prospective	Mar 2014–Aug 2015	46	46 PTF	49.3±16.78	20 (45.0)
Tyberg *et al.* (2018)[21]	USA	Prospective	Jan 2012–Jan 2017	51	51 PTF	54.2	24 (47.0)
Onimaru *et al.* (2013)[25]	Japan	Prospective	Sep 2008–Dec 2012	10	10 PTF	52	5 (50.0)
Vigneswaran *et al.* (2014)[26]	USA	Prospective	Oct 2010–Jun 2013	5	5 PTF	69.6	4 (80.0)
Zhou *et al.* (2013)[28]	China	Prospective	Mar 2011–Dec 2011	12	12 PTF	51.1	5 (41.7)
Ling *et al.* (2014)[17]	China	Prospective	May 2010–Sep 2012	51	21 PTF	43.2±12.7	8 (38.1)
					30 Naïve	42.5±11.3	10 (33.3)
Ngamruengphong *et al.* (2017)[18]	USA	Retrospective	Dec 2009–Sep 2015	180	90 PTF with HM	54±15	44 (48.9)
					90 PTF without HM	53±14	38 (42.2)
Tang *et al.* (2017)[19]	China	Retrospective	Jul 2011–Jan 2014	61	22 PTF	34.9±7.7	14 (63.6)
					39 Naïve	38.5±11.3	20 (51.3)
Kristensen *et al.* (2017)[20]	Denmark	Retrospective	Jan 2012–May 2016	66	14 PTF with HM	43.5 (22–75)	7 (50.0)
					52 PTF without HM	49.5 (18–77)	26 (50.0)
Orenstein *et al.* (2015)[23]	USA	Retrospective	May 2011–Sep 2013	40	16 PTF	NA	NA
					24 Naïve	NA	NA
Nabi *et al.* (2018)[24]	India	Retrospective	Jan 2013–Nov 2016	502	242 PTF	42.4±13.6	137 (56.6)
					260 Naïve	38.0±13.6	142 (54.6)
Sharata *et al.* (2013)[27]	USA	Retrospective	Oct 2010–May 2012	40	12 PTF	55±17	5 (41.7)
					28 Naïve	48±21	12 (42.9)
Zhang *et al.* (2018)[22]	USA	Retrospective	Oct 2009–Oct 2016	318	46 PTF*	55 (17–85)	24 (52.2)
					272 PTF†	54 (10–94)	155 (57.0)
Jones *et al.* (2015)[29]	USA	Retrospective	Aug 2012–Oct 2014	45	15 PTF	64.4±12	3 (20.0)
					30 Naïve	46.2±17.2	25 (83.3)
Liu *et al.* (2019)[30]	China	Retrospective	Aug 2010–Dec 2014	849	245 PTF	38 (6–98)	132 (53.9)
					604 Naïve	38 (8–77)	291 (48.2)

Data are presented as mean±SD or median (range).
PTF, previous treatment failure; HM, Heller myotomy.
*Previous surgical and endoscopic treatment failure; †Previous endoscopic treatment failure.

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
						E	G	T	
Tyberg *et al.*[16]	46 PTF	46 POEM	10 I, 16 II, 5 III, 15 other EDD	NA	90	NA	NA	NA	NA
Tyberg *et al.*[21]	51 PTF	43 LHM, 8 laparotomy HM	13 I, 29 II, 6 III, 3 other EDD	51 Posterior	NA	NA	NA	NA	NA
Onimaru *et al.* [25]	10 PTF	10 LHM+PBD	6 II, 4 III	7 Posterior 1 Right anterior 2 Right	118.2	9.2	3.2	12.4	NA
Vigneswaran *et al.*[26]	5 PTF	5 LHM	NA	NA	139.0±29.6	NA	NA	9.0	1.6±0.2
Zhou *et al.*[28]	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)†	4.1±1.3
Ling *et al.*[17]	21 PTF	21 PBD	5 I, 13 II, 3 III	21 Posterior	42.4±8.3	NA	NA	10.3±1.5	NA
	30 Naïve	None	6 I, 22 II, 2 III	30 Posterior	34.3±7.4	NA	NA	9.6±1.2	NA
Ngamruengphong *et al.*[18]	90 PTF with HM	40 PBD, 10 BTI	26 I, 23 II, 10 III, 31 unspecified	2 Anterior 86 Posterior 2 Missing data	102.8±41	8.7±4.4	2.9±1.2	11.6	3.54±1.7
	90 PTF without HM	23 PBD, 7 BTI	20 I, 29 II, 10 III, 31 unspecified	42 Anterior 48 Posterior	102.6±61	9.7±3.9	3±1.3	12.7	3.59±2.5
Tang *et al.*[19]	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	6.2±1.3
	39 Naïve	None	13 I, 26 II	NA	62.0±21.0	7.4±3.3	3.1±1.6	10.5±3.9	6.5±1.6
Kristensen *et al.*[20]	14 PTF with HM	13 BTI or PBD	9 I, 5 missing data	NA	74 (35–149)‡	9 (6–13)‡	3 (2–5)‡	NA	2 (1–4)‡
	52 PTF without HM	15 BTI or PBD	7 I, 25 II, 3 III, 17 missing data	NA	61 (35–126)‡	9.5 (6–13)‡	4 (2–5)‡	NA	2 (1–4)‡
Orenstein *et al.*[23]	16 PTF	6 BTI, 4 PBD, 3 BTI+PBD, 3 LHM	NA	NA	102	NA	NA	NA	NA
	24 Naïve	None	NA	NA	118	NA	NA	NA	NA
Nabi *et al.*[24]	242 PTF	205 PBD, 30 LHM, 4 BTI, 3 POEM	91 I, 140 II, 11 III	186 Anterior 56 Posterior	74.9±30.6	9.4±2.4	3.1±0.5	12.5	3 (2-5)†
	260 Naïve	None	82 I, 169 II, 9 III	210 Anterior 50 Posterior	67.0±27.1	9.0±2.5	3.08±0.5	12.08	3 (2-5)†
Sharata *et al.*[27]	12 PTF	10 BTI, 2 PBD	9 Unspecified , 3 other EDD	NA	134±43	NA	NA	NA	NA
	28 Naïve	None	22 Unspecified, 6 other EDD	NA	131±41	NA	NA	NA	NA
Zhang *et al.*[22]	46 PTF§	14 HM+PBD, 19 HM+BTI	30 I, 5 II, 6 III, 5 unspecified	8 Anterior 38 Posterior	82 (32–166)‡	NA	NA	11 (5–23)‡	1 (1–5)‡
	272 PTF‖	29 PBD, 54 BTI	53 I, 147 II, 32 III, 26 unspecified, 14 other EDD	137 Anterior 135 Posterior	72 (21–240)‡	NA	NA	12 (3–27)‡	2 (1–30)‡

Table 2. continued

Author	Group	Previous treatment	Subtype*	Direction of myotomy	Procedure time, mean±SD, min	Myotomy length, mean±SD, cm			Hospital stay, mean±SD, day
						E	G	T	
Jones *et al.*[29]	15 PTF	7 BTI, 5 PBD, 3 HM	42 Unspecified, 3 other EDD (total)	15 Anterior	102±29	NA	NA	NA	1 [0–12]‡
	30 Naïve	None		30 Anterior	103±27	NA	NA	NA	1 [0–1]
Liu *et al.*[30]	245 PTF	165 PBD, 28 HM, 6 POEM, 45 esophageal stent, 46 BTI	65 I, 132 II, 13 III, 35 unspecified	NA	<60, 166	NA	NA	NA	<2, 107
					≥60, 79				≥2, 138
	604 Naïve	None	144 I, 309 II, 31 III, 120 unspecified	NA	<60, 441	NA	NA	NA	<2, 324
					≥60, 163				≥2, 280

E, esophageal; G, gastric; T, total; PTF, previous treatment failure; POEM, peroral endoscopic myotomy; EDD, esophageal dysmotility disorder; NA, not available; LHM, laparoscopic Heller myotomy; HM, Heller myotomy; PBD, pneumatic balloon dilation; BTI, botulinum toxin injection.
*Chicago classification; †Mean (range); ‡Median (range); §Previous surgical and endoscopic treatment failure; ||Previous endoscopic treatment failure.

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. Submucosal myotomies (534/1,169; 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 technical success of POEM for patients with prior endoscopic or/and 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 heterogeneity (Q=9.99, p=0.62, I^2=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, I^2=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 removing one study at a time was performed and confirmed the outcomes of the main analyses. However, when removing either the study by Zhang *et al.*[22] or Ngamruengphong *et al.*,[18] a considerable reduction in heterogeneity occurred, changing the I^2 from 16.14% to 0%. There was no publication 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/and surgical treatment. A total of 83 (6.9%) adverse events occurred (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, I^2=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 demonstrated that the largest change occurred when the study conducted by Zhang *et al.*[22] was removed. The heterogeneity decreased 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 Supplementary Fig. 1C (Egger' s regression test p=0.39).

Table 3. Newcastle-Ottawa Quality Assessment Scale for Included Studies

Study	Selection				Outcome assessment			Comparability		Quality of study
	1	2	3	4	1	2	3	1	2	
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.

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

Author	Group	% (No./No.)			Follow-up, mean (range), mo
		Technical success	Clinical success	Symptomatic reflux and reflux esophagitis	
Tyberg *et al.*[16]	46 PTF	100 (46/46)	85 (41/46) (3-mo FU)	NA	12.2 (1–32)
Tyberg *et al.*[21]	51 PTF	100 (51/51)	94 (48/51) (1-yr FU)	NA	24.4 (12–52)
Onimaru *et al.*[25]	10 PTF	100 (10/10)	NA	NA	18.3
Vigneswaran *et al.*[26]	5 PTF	100 (5/5)	NA	NA	4.9
Zhou *et al.*[28]	12 PTF	100 (12/12)	91.7 (11/12) (5–14 mo FU)	Reflux esophagitis 8.3 (1/12)	10.4 (5–14)
Ling *et al.*[17]	21 PTF	100 (21/21)	92.3 (19/21) (postoperative), 87.5 (18/21) 1-yr FU	Reflux esophagitis 19.0 (4/21)	13.2
	30 Naïve	100 (30/30)	NA	NA	14.4
Ngamruengphong *et al.*[18]	90 PTF (with HM)	98 (88/90)	81.2 (69/85)	Symptomatic reflux 30 (21/70) Reflux esophagitis 44 (18/41)	9 (4–14)*
	90 PTF (without HM)	100 (90/90)	94.8 (77/82) (total n=167) (≥3-mo FU)	Symptomatic reflux 32 (24/76) Reflux esophagitis 52 (23/44)	8.5 (1.3–18.5)*
Tang *et al.*[19]	22 PTF	100 (22/22)	95.5 (21/22)	Reflux esophagitis 23.5 (4/17)	12
	39 Naïve	100 (39/39)	92.3 (36/39) (1-yr FU)	Reflux esophagitis 20 (7/35)	12
Kristensen *et al.*[20]	14 PTF (with HM)	NA	NA	NA	24
	52 PTF (without HM)	NA	NA	NA	24
Orenstein *et al.*[23]	16 PTF	NA	NA	NA	9.0
	24 Naïve	NA	NA	NA	10.1
Nabi *et al.*[24]	242 PTF	97.1 (235/242)	92.5 (186/201) (6-mo FU) 91.2 (145/159) (1-yr FU) 84.2 (85/101) (2-yr FU) 76.3 (29/38) (3-yr FU)	Symptomatic reflux 17.8 (26/146) Reflux esophagitis 20.7 (24/116)	20 (1–45)†
	260 Naïve	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) Reflux esophagitis 22.1 (29/131)	20 (1–45)†
Sharata *et al.*[27]	12 PTF	100 (12/12)	100 (12/12)	NA	6
	28 Naïve	100 (28/28)	100 (28/28) (postoperative)	NA	6
Zhang *et al.*[22]	46 PTF‡	100 (46/46)	95.7 (44/46)	Reflux esophagitis 46.2 (12/26)	28 (3–46)†
	272 PTF§	100 (272/272)	95.1 (255/272) (>3 mo)	Reflux esophagitis 34.0 (50/147)	23 (3–78)†
Jones *et al.*[29]	15 PTF	100 (15/15)	NA	NA	12†
	30 Naïve	100 (30/30)	NA	NA	10†
Liu *et al.*[30]	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) Reflux esophagitis 22.8 (46/202) Symptomatic reflux 14.7 (89/604)	23 (1–71)†
	604 Naïve	100 (604/604)	95.0 (574/604) (1-yr FU) 93.5 (565/604) (2-yr FU) 91.7 (554/604) (5-yr FU)	Reflux esophagitis 17.3 (80/462)	23 (1–71)†

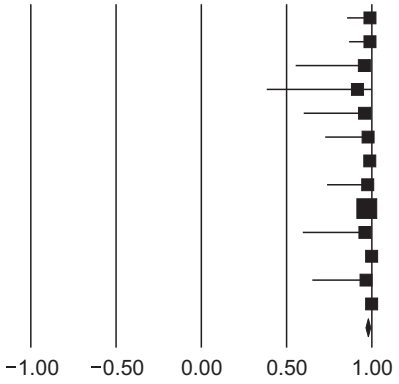
PTF, previous treatment failure, FU, follow-up; NA, not available; HM, Heller myotomy.
*Median (interquartile range); †Median (range); ‡Previous surgical and endoscopic treatment failure; §Previous endoscopic treatment failure.

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, I^2=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, I^2=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 were 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, I^2=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,

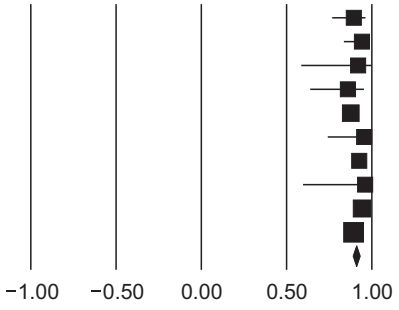
A Technical success

Study name	Event rate	Lower limit	Upper limit	p-value
Tyberg A *et al.* 2016	0.989	0.851	0.999	0.001
Tyberg A *et al.* 2018	0.990	0.864	0.999	0.001
Onimaru M *et al.* 2013	0.955	0.552	0.997	0.035
Vigneswaran Y *et al.* 2014	0.917	0.378	0.995	0.105
Zhou PH *et al.* 2013	0.962	0.597	0.998	0.026
Ling T *et al.* 2014	0.977	0.723	0.999	0.009
Ngamruengphong S *et al.* 2017	0.989	0.957	0.997	0.000
Tang X *et al.* 2017	0.978	0.732	0.999	0.008
Nabi Z *et al.* 2018	0.971	0.941	0.986	0.000
Sharata A *et al.* 2013	0.962	0.597	0.998	0.026
Zhang X *et al.* 2018	0.998	0.975	1.000	0.000
Jones EL *et al.* 2015	0.969	0.650	0.998	0.017
Liu ZQ *et al.* 2019	0.998	0.968	1.000	0.000
	0.980	0.966	0.988	0.000



B Clinical success

Study name	Event rate	Lower limit	Upper limit	p-value
Tyberg A *et al.* 2016	0.891	0.764	0.954	0.000
Tyberg A *et al.* 2018	0.941	0.833	0.981	0.000
Zhou PH *et al.* 2013	0.917	0.587	0.988	0.022
Ling T *et al.* 2014	0.857	0.639	0.953	0.004
Ngamruengphong S *et al.* 2017	0.874	0.815	0.917	0.000
Tang X *et al.* 2017	0.955	0.739	0.994	0.003
Nabi Z *et al.* 2018	0.925	0.880	0.955	0.000
Sharata A *et al.* 2013	0.962	0.597	0.998	0.026
Zhang X *et al.* 2018	0.940	0.908	0.962	0.000
Liu ZQ *et al.* 2019	0.886	0.839	0.920	0.000
	0.908	0.888	0.924	0.000



C Adverse event

Study name	Event rate	Lower limit	Upper limit	p-value
Tyberg A *et al.* 2016	0.174	0.089	0.311	0.000
Tyberg A *et al.* 2018	0.157	0.080	0.284	0.000
Onimaru M *et al.* 2013	0.045	0.003	0.448	0.035
Vigneswaran Y *et al.* 2014	0.200	0.027	0.691	0.215
Zhou PH *et al.* 2013	0.250	0.083	0.552	0.099
Ling T *et al.* 2014	0.023	0.001	0.277	0.009
Ngamruengphong S *et al.* 2017	0.106	0.068	0.160	0.000
Tang X *et al.* 2017	0.045	0.006	0.261	0.003
Orenstein SB *et al.* 2015	0.188	0.062	0.447	0.022
Nabi Z *et al.* 2018	0.058	0.035	0.095	0.000
Sharata A *et al.* 2013	0.250	0.083	0.552	0.099
Zhang X *et al.* 2018	0.025	0.013	0.049	0.000
Jones EL *et al.* 2015	0.267	0.104	0.533	0.083
Liu ZQ *et al.* 2019	0.045	0.025	0.079	0.000
	0.103	0.066	0.158	0.000

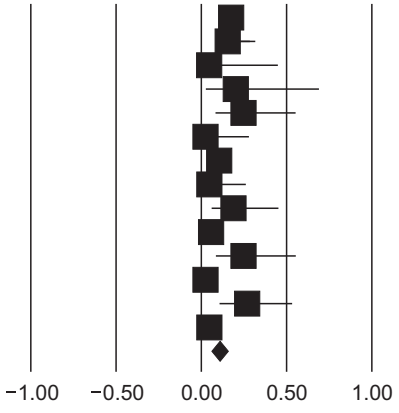


Fig. 2. Overall efficacy and safety of peroral endoscopic myotomy in patients with previous intervention(s). (A) Technical success; (B) clinical success (less than 12 months of follow-up); (C) adverse events.
CI, confidence interval.

I^2=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, I^2=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

Table 5. Safety of Peroral Endoscopic Myotomy

Author	Major adverse events		Minor adverse events	
	PTF	Naïve	PTF	Naïve
Tyberg *et al.*[16]	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 Mucosal perforation	-
Ling *et al.*[17]	0	0	0	0
Ngamruengphong *et al.*[18]	1 Pneumonia 1 Mediastinitis 5 Symptomatic pneumoperitoneum 1 Symptomatic pneumothorax 1 Symptomatic subcutaneous emphysema 1 Pleural effusion requiring chest drain	-	7 Mucosotomy 1 Delayed bleeding 1 Submucosal hematoma	-
Tang *et al.*[19]	0	0	1 Bleeding	2 Bleeding
Kristensen *et al.*[20]	NA	-	NA	-
Orenstein *et al.*[23]	1 Capnoperitoneum alleviated with angiocatheter evacuation 1 Mallory-Weiss tear requiring blood transfusion 1 Mucosal tear requiring a stent	1 Capnoperitoneum alleviated with angiocatheter evacuation	0	1 Mucosal tear
Nabi *et al.*[24]	1 Capnothorax requiring decompression 2 Enlargement of mucosal incision	2 Capnopericardium 1 Capnothorax requiring decompression 1 Enlargement of mucosal incision 1 30-Day readmission	11 Mucosal injury	8 Mucosal injury
Sharata *et al.*[27]	1 Bleeding requiring endoscopic re-intervention 1 Mucosotomy dehiscence needing endoscopic suture 1 Capnoperitoneum needed Veress needle decompression	1 Full-thickness esophageal perforation requring endoscopic and surgical re-intervention 1 Capnoperitoneum needed Veress needle decompression	0	0
Zhang *et al.*[22]	5 Prolonged stay >5 day 3 Readmission within 30 days related to POEM (1 diarrhea; 1 bleeding; 1 fever)	-	NA	-
Jones *et al.*[29]	4 Pneumoperitoneum needed needle decompression	12 Pneumoperitoneum needed needle decompression	NA	NA
Liu *et al.*[30]	6 Pneumothorax requiring drainage 2 Hydrothorax requiring drainage 1 Delayed mucosa barrier failure 1 Delayed bleeding requiring intervention or transfusion 1 Other miscellaneous major adverse event	13 Pneumothorax requiring drainage 4 Hydrothorax requiring drainage 3 Delayed mucosa barrier failure 1 Delayed bleeding requiring intervention or transfusion 2 Other miscellaneous major adverse events	NA	NA

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

7.21 minutes (95% CI, 4.04 to 10.39; p<0.001, I^2=0%) and 0.09 days (95% CI, –0.53 to 0.71; p=0.77, I^2=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, I^2=96%) and LES pressure was significantly reduced by 18.3 mm Hg (95% CI, 12.73 to 23.86; p<0.001, I^2=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, I^2=90%) and 20.16 mm

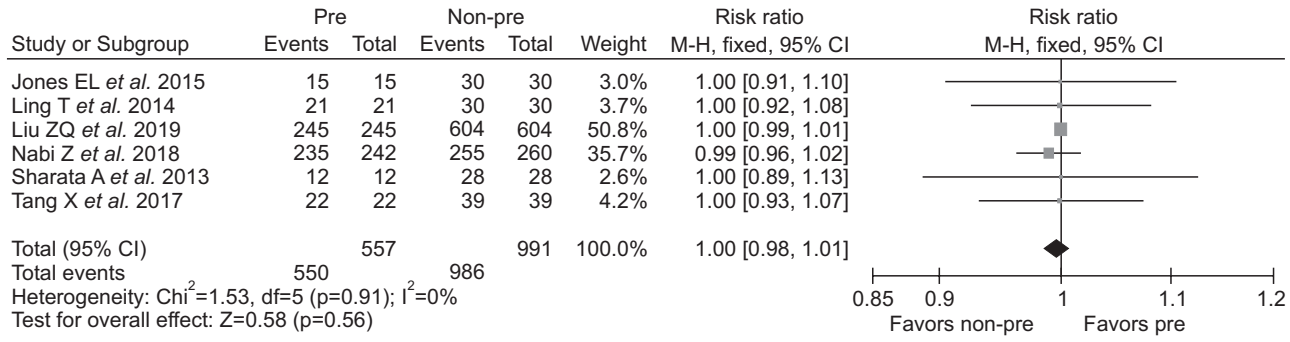


Fig. 3. Meta-analysis of technical success between patients with and without previous intervention(s).
M-H, Mantel-Haenszel; CI, confidence interval.

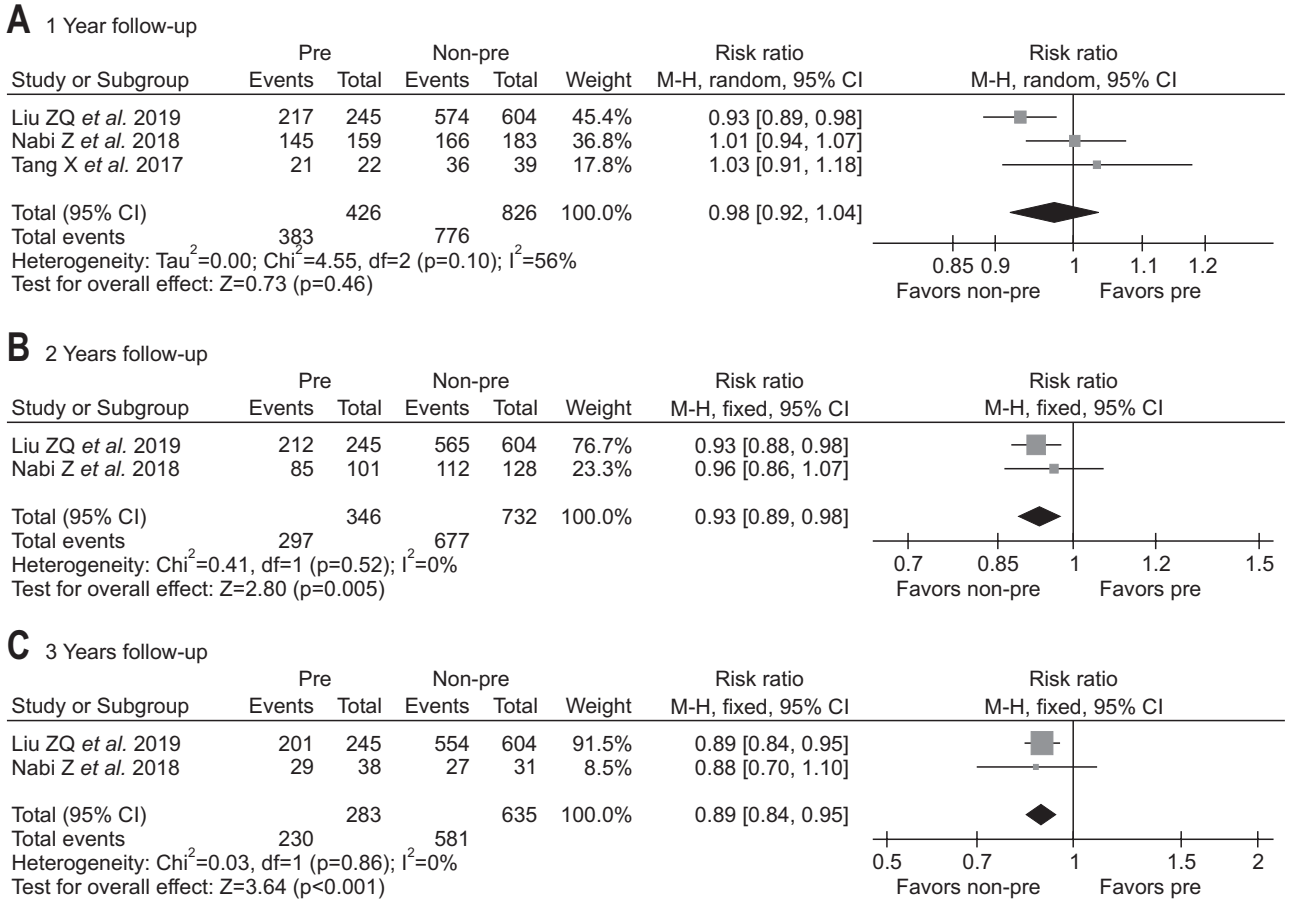


Fig. 4. Meta-analysis of clinical success between patients with and without previous intervention(s). (A) One-year follow-up; (B) 2-year follow-up; (3) 3-year follow-up.
M-H, Mantel-Haenszel; CI, confidence interval.

Hg (95% CI, 14.76 to 25.56; p<0.001, I^2=87%), respectively.

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

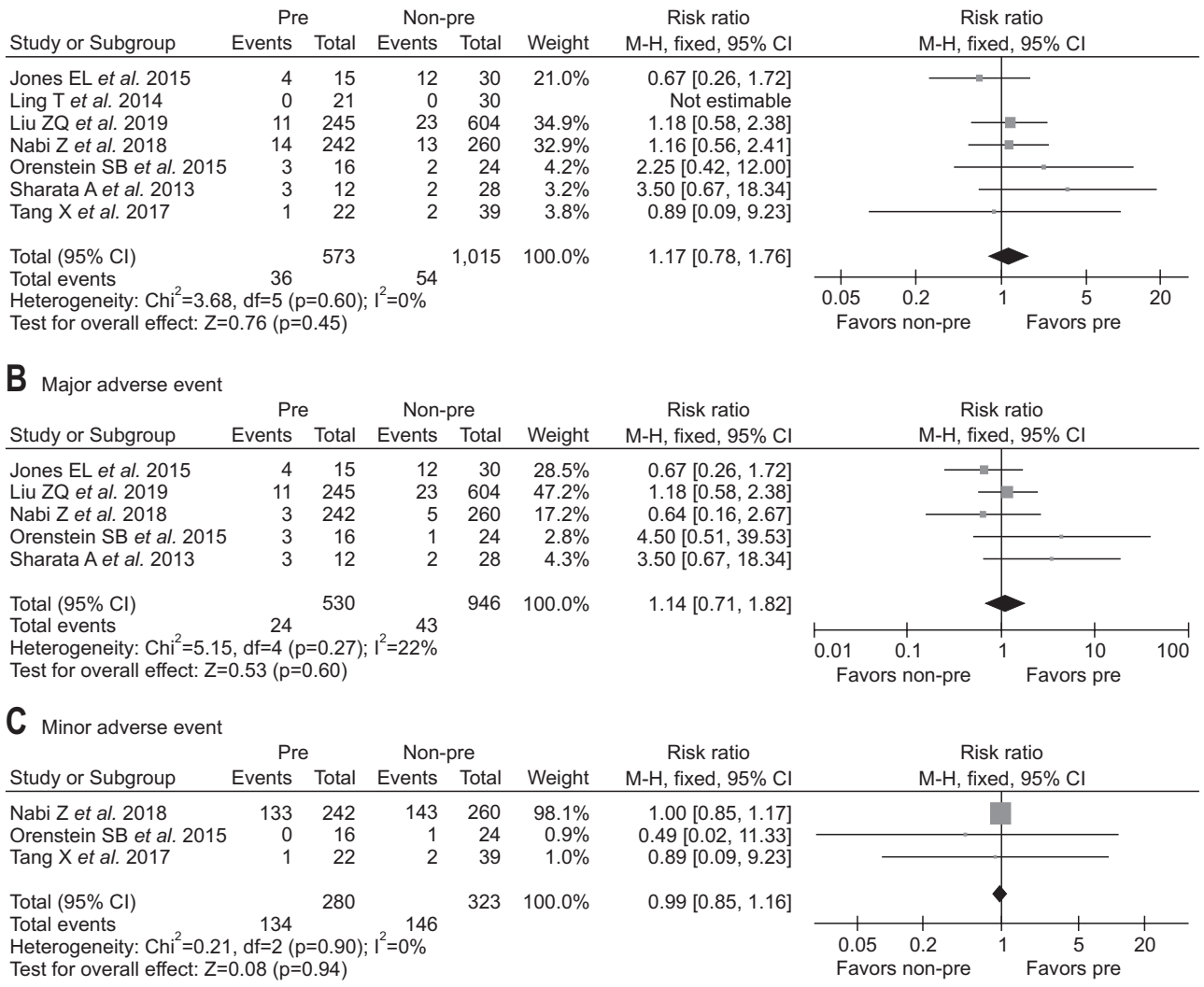


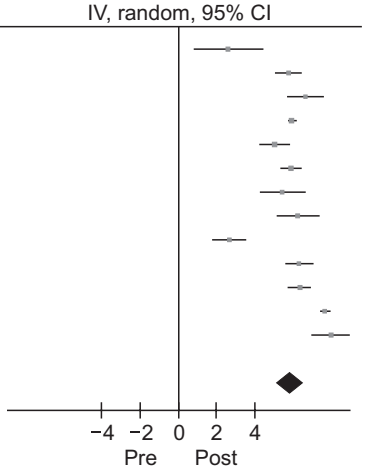
Fig. 5. Meta-analysis of adverse events between patients with and without previous intervention(s). (A) Overall adverse events; (B) major adverse events; (3) minor adverse events.
M-H, Mantel-Haenszel; CI, confidence interval.

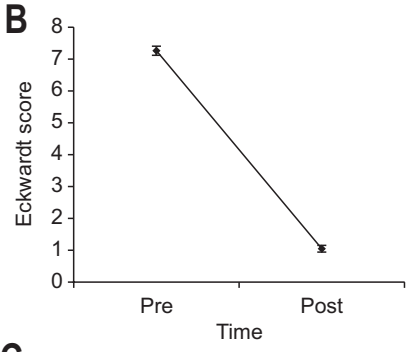
increased likelihood of complications such as perforation and bleeding. Due to this potentially increased difficulty of POEM after previous interventions for achalasia, we performed this meta-analysis to explore the efficacy and safety of POEM for patients with and without prior treatment. In our present 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-naïve patients. Our result is consistent with several published studies.[24,28] 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.*,[30] a significantly longer hospital stay after POEM was found in patients with

A

Study or Subgroup	Pre Mean	Pre SD	Pre Total	Post Mean	Post SD	Post Total	Weight	Mean difference IV, random, 95% CI
Kristensen HØ *et al.*	6.80	2.60	14	4.20	1.70	9	5.6%	2.60 [0.84, 4.36]
Kristensen HØ *et al.* 2017	7.10	2.00	52	1.40	1.40	40	8.0%	5.70 [5.00, 6.40]
Ling T *et al.* 2014	7.30	2.10	21	0.70	0.60	21	7.5%	6.60 [5.67, 7.53]
Nabi Z *et al.* 2018	7.00	1.40	242	1.11	0.74	151	8.6%	5.89 [5.68, 6.10]
Ngamruengphong S *et al.*	7.10	2.70	90	2.12	2.50	85	7.9%	4.98 [4.21, 5.75]
Ngamruengphong S *et al.* 2017	6.90	2.30	90	1.06	1.20	82	8.3%	5.84 [5.30, 6.38]
Onimaru M *et al.* 2013	6.50	1.30	10	1.10	1.30	10	7.1%	5.40 [4.26, 6.54]
Tang X *et al.* 2017	7.40	2.40	22	1.20	1.10	22	7.1%	6.20 [5.10, 7.30]
Tyberg A *et al.* 2016	4.30	2.48	46	1.64	1.67	46	7.7%	2.66 [1.80, 3.52]
Tyberg A *et al.* 2018	7.98	2.11	51	1.72	1.50	51	8.0%	6.26 [5.55, 6.97]
Zhang X *et al.*	7.10	1.80	46	0.80	0.80	46	8.2%	6.30 [5.73, 6.87]
Zhang X *et al.* 2018	8.00	1.50	272	0.40	0.90	272	8.6%	7.60 [7.39, 7.81]
Zhou PH *et al.* 2013	9.20	1.10	12	1.30	1.30	12	7.5%	7.90 [6.94, 8.86]
Total (95% CI)			968			847	100.0%	5.77 [5.07, 6.47]

Heterogeneity: Tau^2=1.47; Chi^2=272.62, df=12 (p<0.001); I^2=96%
Test for overall effect: Z=16.14 (p<0.001)

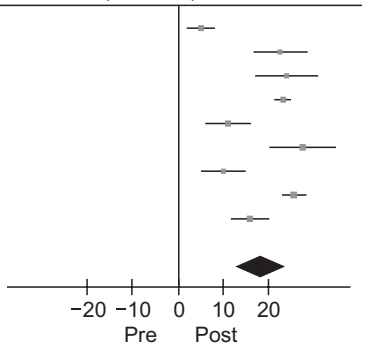




C

Study or Subgroup	Pre Mean	Pre SD	Pre Total	Post Mean	Post SD	Post Total	Weight	Mean difference IV, random, 95% CI
Kristensen HØ *et al.*	13.3	4.7	14	8.2	3.2	14	11.7%	5.10 [2.12, 8.08]
Kristensen HØ *et al.* 2017	39.8	19.7	52	17.1	8.6	52	10.7%	22.70 [16.86, 28.54]
Ling T *et al.* 2014	31.2	14.2	21	7.1	6.8	21	10.3%	24.10 [17.37, 30.83]
Nabi Z *et al.* 2018	36.3	12.1	242	13.0	5.02	148	12.0%	23.30 [21.57, 25.03]
Onimaru M *et al.* 2013	22.1	6.6	10	10.9	4.5	10	11.0%	11.20 [6.25, 16.15]
Tang X *et al.* 2017	41.1	15.7	22	13.4	5.3	12	10.1%	27.70 [20.49, 34.91]
Zhang X *et al.*	27.0	15.6	46	16.8	6.3	46	11.1%	10.20 [5.34, 15.06]
Zhang X *et al.* 2018	45.2	18.9	272	19.4	9.1	272	11.8%	25.80 [23.31, 28.29]
Zhou PH *et al.* 2013	29.4	5.8	12	13.5	4.3	12	11.4%	15.90 [11.81, 19.99]
Total (95% CI)			691			587	100.0%	18.30 [12.73, 23.86]

Heterogeneity: Tau^2=66.55; Chi^2=168.68, df=8 (p<0.001); I^2=95%
Test for overall effect: Z=6.45 (p<0.001)



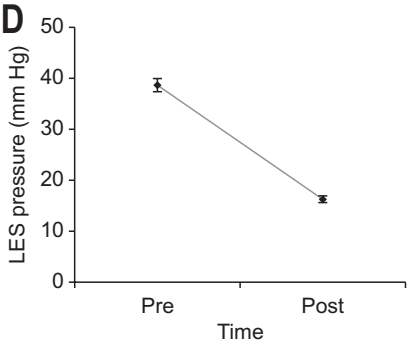


Fig. 6. Changes in the mean Eckardt score and lower esophageal sphincter (LES) pressure before and after peroral endoscopic myotomy (POEM) in patients with previous endoscopic or/and surgical intervention. (A) Change in the mean Eckardt score. (B) Changes in the mean Eckardt score before and after POEM: 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/and 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.*[30] 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/and 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.[30] 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). However, our result may be affected by various factors. For example, the GERD measurement results were only available in a minority of the total patients' number. Additionally, previous fundoplication may have an influence on preventing postoperative reflux. Importantly, there were no procedure-related deaths in any of the included studies. 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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