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The Effect of Peroral Endoscopic Myotomy in Achalasia Patients with Prior Endoscopic Intervention: A Systematic Review and Meta-Analysis

Chunyu Zhong[a] Bowen Ni[b] Sixiu Liu[b] Shali Tan[a] Muhan Lü[a] Yan Peng[a] Li Liu[c, d] Xiaowei Tang[a]

[a]Department of Gastroenterology, Affiliated Hospital of Southwest Medical University, Luzhou, China; [b]School of Clinical Medicine, Southwest Medical University, Luzhou, China; [c]Department of Digestive Endoscopy, The First Affiliated Hospital with Nanjing Medical University, Nanjing, China; [d]Department of General Surgery, The First Affiliated Hospital with Nanjing Medical University, Nanjing, China

Keywords
Achalasia · Peroral endoscopic myotomy · Endoscopic intervention · Systematic review · Meta-analysis

Abstract
Background: Peroral endoscopic myotomy (POEM) has been reported to be effective in achalasia patients with prior failed endoscopic intervention (PFI). We performed this meta-analysis to compare and summarize the clinical outcome of POEM in patients with or without prior endoscopic intervention. ***Method:*** We searched relevant studies published up to March 2020. Meta-analysis for technical success, clinical success, Eckardt score, lower esophageal sphincter (LES) pressure, clinical reflux, and adverse event were conducted based on a random-effects model. ***Results:*** Eight studies enrolling 1,797 patients who underwent POEM were enrolled, including 1,128 naïve achalasia patients and 669 patients with PFI. In the PFI group, the pooled estimated rate of technical success was 97.7% (95% confidence interval [CI], 95.8–98.8%), the pooled clinical success rate was 91.0% (95% CI, 88.0–93.4%), and the pooled adverse events rate was 23.5% (95% CI, 10.6–44.1%). The Eckardt score significantly decreased by 5.95 points (95% CI, 5.50–6.40, $p < 0.00001$) and the LES pressure significantly reduced by 19.74 mm Hg (95% CI, 14.10–25.39, $p < 0.00001$) in the PFI group. There were no difference in the technical success, clinical success, and adverse events rate between the treatment-naïve group and PFI group, with a risk ratio of 1.0 (95% CI, 0.99–1.01, $p = 0.89$), 1.02 (95% CI, 0.98–1.06, $p = 0.36$), and 0.88 (95% CI, 0.67–1.16, $p = 0.38$), respectively. ***Conclusions:*** POEM is an effective and safe treatment for achalasia patients with prior endoscopic intervention. Randomized clinical trials are needed to further verify the efficiency and safety of the POEM in those patients.

Introduction

Achalasia is a primary esophageal disorder characterized by the esophageal neuromuscular motor dysfunction and impaired lower esophageal sphincter (LES) relaxation [1, 2]. The clinical manifestations include dyspha-

Chunyu Zhong, Bowen Ni, and Sixiu Liu have contributed equally to this study.

karger@karger.com
www.karger.com/dsu

Xiaowei Tang
Department of Gastroenterology
Affiliated Hospital of Southwest Medical University
Street Taiping No. 25, Region Jiangyang, Luzhou 646099 (China)
solitude5834@hotmail.com

gia, chest pain, weight loss, regurgitation, and even cough and pulmonary infection caused by aspiration [3]. It occurs rarely, with an estimated incidence of 0.5–1.6 per 100,000 and a prevalence of 9–11 per 100,000 [4].

Traditional treatment methods for patients with confirmed achalasia include medical therapy, botulinum toxin injection (BTI), pneumatic dilation (PD), and laparoscopic Heller myotomy (LHM). All treatment options for achalasia focus on destruction or forced relaxation of the LES, accompanied by advantages and disadvantages [5]. Drug therapy has been largely discontinued due to its poor results. BTI is safe and effective for most patients in the short term, but only 29% of patients with remission were observed during the intermediate follow-up [6]. As for PD, there is evidence that the short-term success rates were achieved in >90%, but the recurrence rate is about 20% in 2 years, 30% in 5 years, and 40% in 10 years [7–9]. LHM is regarded as the gold standard for treating achalasia with satisfied long-term effect [10]. Peroral endoscopic myotomy (POEM) is a novel minimally invasive method for achalasia and has been continued to grow in popularity worldwide. Since other endoscopic treatments have a high recurrence rate, it has been reported that up to 40% of patients undergoing POEM had undergone at least 1 previous intervention before POEM [11]. Previous interventions have been reported to increase the difficulty of LHM and are associated with poor results [12, 13].

Currently, a number of clinical studies have demonstrated that POEM is effective and safe for achalasia patients with prior failed endoscopic intervention (PFI) [11, 14–20]. Therefore, we conducted this meta-analysis to compare clinical outcomes between patients with and without prior endoscopic intervention.

Methods

The recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were followed in this meta-analysis [21].

Search Strategy

A broad literature examination between January 2010 to April 2020 was performed to identify the studies related to POEM for esophageal achalasia. PubMed, Embase, Cochrane library, and other sources were searched using the keywords "achalasia," "peroral endoscopic myotomy," and "POEM" (see online suppl. Table 1; see www.karger.com/doi/10.1159/000512627 for all online suppl. material). The key word "prior endoscopic intervention" is not included in our search to ensure a comprehensive literature available for POEM.

Inclusion and Exclusion Criteria

To be included in the study, articles must attain the following inclusion criteria: (1) population: patients were diagnosed with achalasia; (2) intervention: POEM; (3) compared: patients with and without prior endoscopic intervention; and (4) outcome: technical and clinical success, postoperative Eckardt score and LES pressure, operative time, hospital stay, adverse events, and clinical reflux. Studies were excluded if (1) they were animal studies, (2) studies had <5 patients per study arm, (3) articles were reviewed, abstracted, and case reported, and (4) overlapping publications.

Study Selection

The selection of articles was conducted independently by 2 reviewers. Any disagreements between reviewers were resolved by discussing with a third reviewer. The title and abstract of identified studies were first reviewed. If the studies were still eligible after screening, the full-text articles were reviewed in accordance with our inclusion and exclusion criteria. Finally, we identified and included the literature for our meta-analysis and extracted the data into tables, while we recorded the information relating to the methodological quality of each study.

Data Extraction and Definition

From each article, reviewers independently abstracted (1) baseline date of included studies: first author, year of publication, country, study design, duration, group, number of patients, age, gender, achalasia type, sigmoid type, and follow-up; (2) preoperative and operative data: duration of symptoms, previous treatment, submucosal tunnel length, myotomy length, type of myotomy, orientation of myotomy, operative time, and hospital stay; (3) clinical outcomes: technical success rate, clinical success rate, pre- and postoperative Eckardt score, pre- and postoperative LES pressure, clinical reflux (reflux esophagitis at esophagogastroduodenoscopy and symptomatic reflux), and adverse events (major events and minor events).

Technical success was defined as completion of the whole POEM procedure. Clinical success was defined as Eckardt score ≤3 during follow-up after POEM procedure. Clinical reflux included symptomatic reflux (heartburn or regurgitation) and reflux esophagitis at esophagogastroduodenoscopy. Major adverse events were defined as hemodynamic instability, necessitating premature termination of POEM, bleeding requiring blood transfusion, prolonged hospital stay, or readmission after discharge, and mucosal injuries that could not be closed with regular hemostatic clips [18, 20]. Minor adverse events were described gas-related events that could be managed with needle decompression, pleural effusion, pneumonia, atelectasis, delayed esophageal hematoma, and mucosal injuries that could be comfortably closed with regular hemostatic clips and temporary cessation of the procedure [18, 20]. Gas-related events not requiring any intervention were not considered as adverse events [18, 20].

Assessment of the Study Quality

The Newcastle-Ottawa Quality assessment tool was utilized [22]. A total of 9 points of the scale evaluates the quality of the included studies from 3 aspects: selection, outcome, and comparability. High-quality studies got a score of >6, medium-quality studies of 5–6, and low-quality studies of <5 (online suppl. Table 2).

Statistical Analysis

The statistical analyses of this meta-analysis were conducted using Comprehensive Meta-Analysis software version 2 and Review

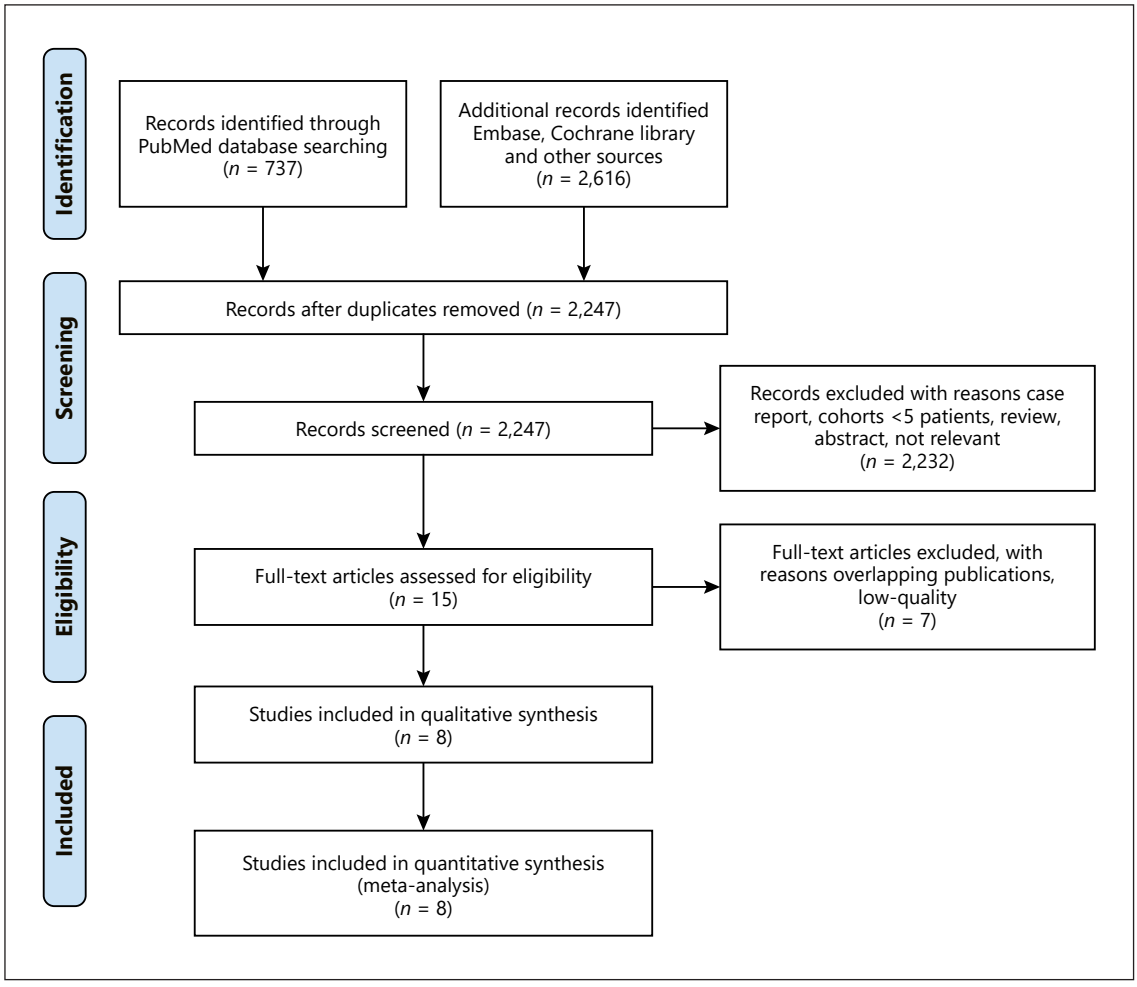

Fig. 1. PRISMA statement of the study. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Manager 5.3 and, with a level of significance set at p of <0.05. Effect sizes for continuous variables were expressed as mean difference (MD) with 95% confidence interval (CI), while that of dichotomous variables were expressed as risk ratio (RR) with 95% CI. All meta-analyses of our study selected the random effects models [23]. Whenever data were expressed as a median and range, they were converted to standard deviation (SD) before analysis. Heterogeneity was assessed using I^2 statistics. The I^2 score values of <50 and >50 were reflective of low- and high heterogeneity, respectively.

Results

Study Characteristics

From 3,353 potentially relevant citations, 2,247 studies were screened for eligibility criteria after removing duplicates. After screening the titles and abstracts, 15 studies fulfilled criteria for the eligibility assessment. Finally, 8 full-text articles matched the eligibility criteria and were included for qualitative analysis (meta-analysis) [11, 14–20]. Figure 1 depicted the PRISMA flow diagram of the literature selection process.

Baseline characteristics of the included studies are showed in Table 1. Overall, these studies were published between 2013 and 2020. Three studies were performed in the USA, 3 in China, 1 in India, and 1 in Korea. Most of the studies were retrospective and only 1 study was prospective.

Patients Baseline Characteristics

Eight studies enrolling 1,797 patients underwent POEM procedure. Among them, 1,128 treatment-naïve achalasia patients were compared with 669 patients with

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Table 1. The baseline characteristics of included studies

Study	Year of publication	Country	Study design	Duration	Groups	Patient, *n*	Age, years	Gender (M:F)	Achlasia type, I/II/III	Sigmoid type	Follow-up, months
Sharata et al. [14]	2013	United States	Retrospective	Oct 2010–May 2012	Treatment-naïve	28	48±21	12:16	–	1	6
					PFI	12	55±17	5:7	–	1	6
Ling et al. [15]	2014	China	Prospective	May 2010–Sept 2012	Treatment-naïve	30	42.5±11.3	10:20	6/22/2	–	14.4±2.4
					PFI	21	43.2±12.7	8:13	5/13/3	–	13.2±3.6
Orenstein et al. [11]	2014	United States	Retrospective	May 2011–Sept 2013	Treatment-naïve	24	–	–	–	–	10.1
					PFI	16	–	–	–	–	9
Jones et al. [16]	2015	United States	Retrospective	Aug 2012–Oct 2014	Treatment-naïve	30	46.2±17.2	25:5	–	–	10
					PFI	15	64.4±12	3:12	–		12
Tang et al. [17]	2017	China	Retrospective	Jul 2011–Jan 2014	Treatment-naïve	39	38.5±11.3	20:19	–	–	12
					PFI	22	34.9±7.7	14:8	–	–	12
Nabi et al. [18]	2018	India	Retrospective	Jan 2013–Nov 2016	Treatment-naïve	260	38.0±13.6	142:118	82/169/9	21	20 (range 1–45)
					PFI	242	42.4±13.6	137:105	91/140/11	36	20 (range 1–45)
Liu et al. [19]	2019	China	Retrospective	Aug 2010–Dec 2014	Treatment-naïve	604	38 (range 8–77)	291:313	144/309/31	31	23 (range 1–71)
					PFI	245	38 (range 6–98)	132:113	65/132/13	32	23 (range 1–71)
Yeniova et al. [20]	2020	Korea	Retrospective	Nov 2011–Mar 2018	Treatment-naïve	113	43.19±14.95	54: 59	37/48/16	8 (7.6%)	6
					PFI	96	44.19±16.41	44: 52	43/34/9	10 (11.6%)	6

M:F, male to female; PFI, prior failed endoscopic intervention.

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Table 2. The preoperative and operative data in included studies

Study	Groups	Duration of symptoms, months	Previous treatment, *n*	Submucosal tunnel length, cm	Myotomy length, cm	Type of myotomy (FTMG:CMG)	Orientation of myotomy	Operative time, min	Hospital stay, days
Sharata et al. [14]	Treatment naïve	55±64	–	–	–	–	–	131±41	–
	PFI	77±107	BTI 10, PD 2	–	–	–	–	134±43	–
Ling et al. [15]	Treatment naïve	–	–	–	9.6±1.2	–	–	34.3±7.4	–
	PFI	–	PD 21 (4 had twice)	–	10.3±1.5	–	–	42.4±8.3	–
Orenstein et al. [11]	Treatment naïve	–	–	–	–	–	–	118	–
	PFI	–	BTI 6, PD 4, LHM 3, and BTI + PD 3	–	–	–		102	–
Jones et al. [16]	Treatment naïve	–	–	–	–	–	–	101.6±29	1 (range 0–1)
	PFI	–	BTI 7, PD 5, and LHM 3	–	-	–	–	103.3±26.7	1 (range 0–12)
Tang et al. [17]	Treatment naïve	6.5±4.8	–	13.4±3.1	Esophagus 7.4±3.3 Stomach 3.1±1.6	–	–	62.0±21.0	6.5±1.6
	PFI	6.4±5.4	BTI 2, PD 18 BTI + PD 2	13.4±4.6	Esophagus 6.7±2.6 Stomach 3.1±1.1	–	–	60.8±30.9	6.2±1.3
Nabi et al. [18]	Treatment naïve	36.6±29.26	–	–	Esophageal 9.0±2.5 Stomach 3.08±0.5	–	Anterior 210 Posterior 50	67.0±27.1	3 (range 2–5)
	PFI	55.3±47.04	BTI 4, PD 205, LHM 23 POEM 3, LHM + PD 7	–	Esophageal 9.4±2.4 Stomach 3.1±0.5	–	Anterior 186 Posterior 56	74.9±30.6	3 (range 2–5)
Liu et al. [19]	Treatment naïve	<10 years 491 ≥10 years 113	–	–	–	497:107	–	<60 min 441 ≥60 min 163	<2 days 324 ≥2 days 280
	PFI	<10 years 163 ≥10 years 82	BTI 46, PD 165, LHM 28 POEM 6, and Stent 45	–	–	184:61	–	<60 min 166 ≥60 min 79	<2 days 107 ≥2 days 138
Yeniova et al. [20]	Treatment naïve	4.45±5.67	–	11.84±2.57	Esophagus 7.22±2.27 Stomach 1.81±0.59	15:98	Anterior 64 Posterior 49	74.08±31.93	7.23±1.51
	PFI	7.92±9.28	BTI 33, PD 37, LHM 2, POEM 7, BTI + PD 9, BTI + PD + POEM 1, PD + POEM 2, BTI + POEM 2, and PD + LHM 3	11.90±2.35	Esophagus 7.11±1.97 Stomach 1.82±0.54	18:78	Anterior 56 Posterior 35 Other 5	76.52±32.27	7.28±1.46

FTMG, full-thickness myotomy group; CMG, circular myotomy group; PFI, prior failed endoscopic intervention; BTI, botulinum toxin injection; PD, pneumatic dilatation; LHM, laparoscopic Heller myotomy, POEM, peroral endoscopic myotomy; IRQ, interquartile range.

Table 3. The clinical outcomes of included studies

Study	Groups	Technical success	Clinical success	Preoperative Eckardt score	Postoperative Eckardt score	Preoperative LES pressure, mm Hg	Postoperative LES pressure, mm Hg	Clinical reflux	
								Reflux esophagitis at esophagogastroduodenoscopy	Symptomatic reflux
Sharata et al. [14]	Treatment naïve	28/28 (100%)	28/28 (100%)	6	1	40.25	–	–	–
	PFI	12/12 (100%)	12/12 (100%)	5	1	47.15	–	–	–
Ling et al. [15]	Treatment naïve	30/30 (100%)	–	6.8±1.7	0.5±0.8	32.9±13.7	6.7±5.4	–	–
	PFI	21/21 (100%)	18/21 (87.5%)	7.3±2.1	0.7±0.6	31.2±14.2	7.1±6.8	4/21 (19.0%)	4/21 (19.0%)
Jones et al. [16]	Treatment naïve	30/30 (100%)	–	–	–	–	–	–	–
	PFI	15/15 (100%)	–	–	–	–	–	–	–
Tang et al. [17]	Treatment naïve	39/39 (100%)	36/39 (92.3%)	7.3±1.8	1.2±1.1	39.9±14.4	14.5±5.6 (n = 28)	3/35 (8.6%)	7/35 (20%)
	PFI	22/22 (100%)	21/22 (95.5%)	7.4±2.4	1.2±1.1	41.1±15.7	13.4±5.3 (n = 12)	2/17 (11.8%)	4/17 (23.5%)
Nabi et al. [18]	Treatment naïve	255/260 (98.1%)	206/223 (92.4%)	7.1±1.6	1.10±0.74 (n = 175)	34.6±13.9	12.5±4.47 (n = 125)	29/131 (22.1%)	22/134 (16.4%)
	PFI	235/242 (97.1%)	186/201 (92.5%)	7.0±1.4	1.11±0.74 (n = 151)	36.3±12.1	13.0±5.02 (n = 148)	24/116 (20.7%)	26/146 (17.8%)
Liu et al. [19]	Treatment naïve	604/604 (100%)	574/604 (95.0%)	7 (range 4–12)	1.37 (rang 0–7)	30 (range 15–78)	11.1 (range 4–43.1)	80/462 (17.3%)	89/604 (14.7%)
	PFI	245/245 (100%)	217/245 (88.6%)	8 (rang 4–12)	1.69 (rang 0–10)	27 (range 15–71)	12.2 (range 6.4–32.2)	46/202 (22.8%)	46/245 (18.8%)
Yeniova et al. [20]	Treatment naïve	113/113 (100%)	107/113 (94.6%)	6.42±2.35	1.32±1.45	37.70±17.81	15.38±10.18	14/113 (12.4%)	41/113 (36.2%)
	PFI	96/96 (100%)	91/96 (94.7%)	6.39±2.65	1.37±1.37	26.44±19.19	15.49±10.46	18/96 (18.8%)	47/96 (49%)

LES, lower esophageal sphincter; PFI, prior failed endoscopic intervention.

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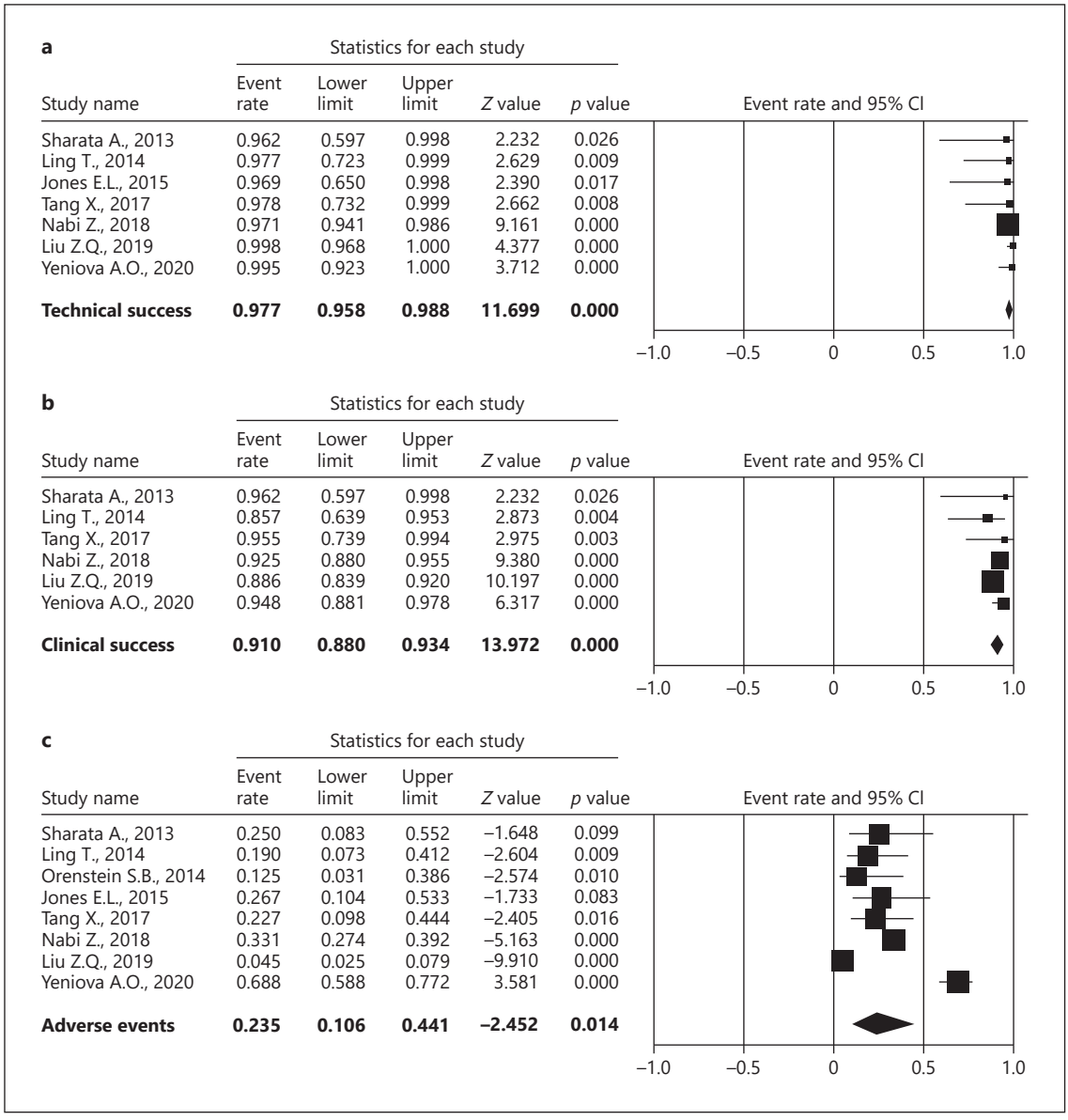

Fig. 2. a Forest plot of overall technical success of POEM for patients with prior endoscopic intervention. **b** Forest plot of overall clinical success of POEM for patients with prior endoscopic intervention. **c** Forest plot of overall adverse event of POEM for patients with prior endoscopic intervention. POEM, peroral endoscopic myotomy; CI, confidence interval.

PFI. In treatment-naïve group, the mean age ranged from 38.0 to 48.0 years, and 554 (50.2%) patients were male. In PFI group, the mean age ranged from 34.9 to 64.4 years, and 343 (52.4%) patients were male. As shown in Table 2, in PFI group, 108 patients previously underwent BTI, 457 underwent PD, 59 underwent LHM, 16 underwent POEM, and 45 underwent stent. Among them, 29 patients underwent more than 1 endoscopic intervention.

Operative Data

Table 2 shows the detailed operative data of POEM procedure. The myotomy length reported in 4 studies, ranged from 9.6 to 12.1 in the treatment-naïve group, 9.8–12.5 in the PFI group. Operative time reported in 8 studies, which ranged from 34.3 to 131 and 42.4–134 min in 2 groups, respectively. The operative time in the treatment-naïve group was significantly shorter than in the PFI group (MD 6.37, 95% CI, 3.74–9.71, $p < 0.00001$, I^2 =

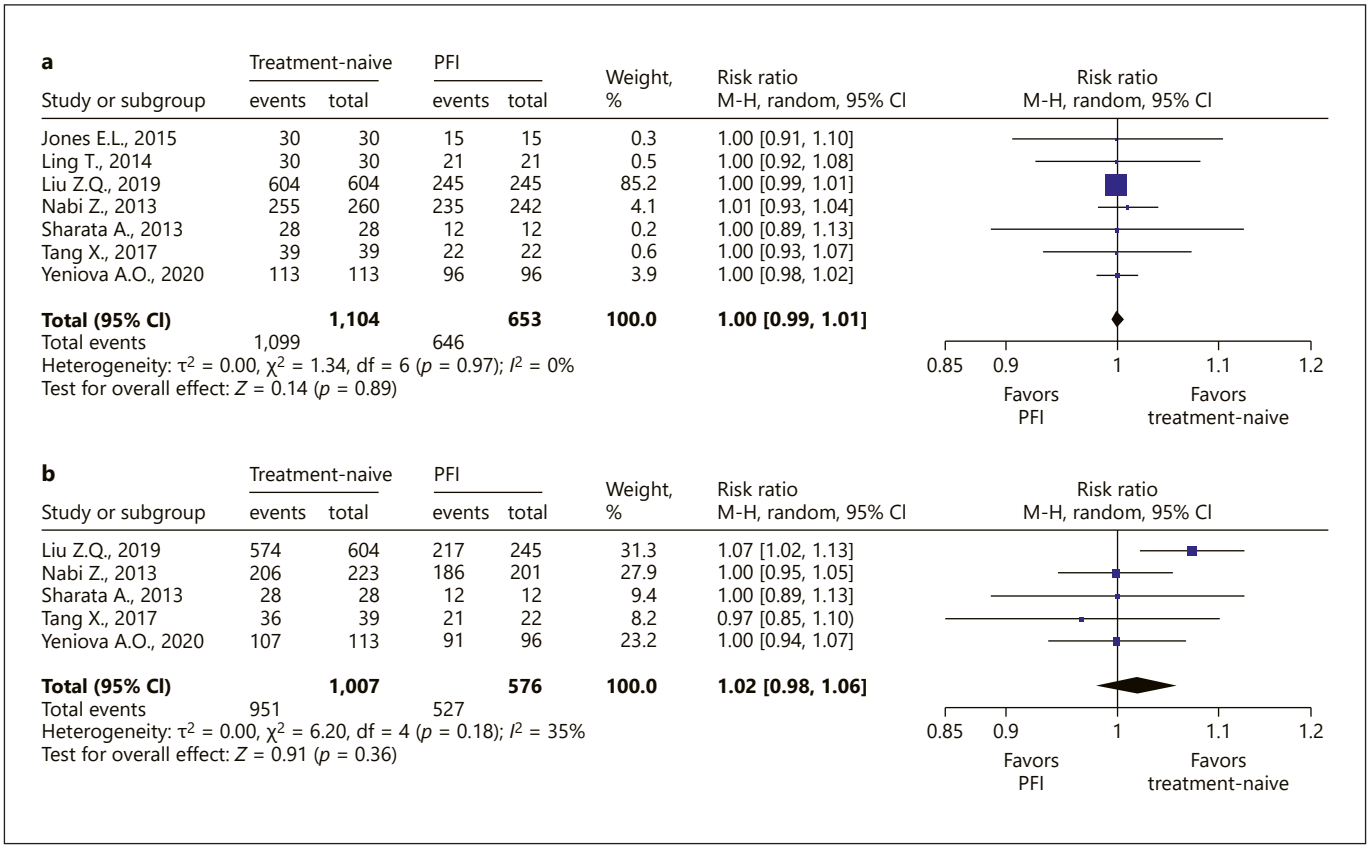

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Fig. 3. a Meta-analysis of technical success between patients with and without prior endoscopic intervention. **b** Meta-analysis of clinical success between patients with and without prior endoscopic intervention. RR, risk ratio; PFI, prior failed endoscopic intervention.

0%) (online suppl. Fig. 1a). The hospital stay was reported in 5 studies, there was no significant difference in 2 groups (MD 0.00, 95% CI, −0.12–0.13, $p = 0.95$, $I^2 = 0\%$) (online suppl. Fig. 1b).

Clinical Outcome

The clinical outcomes of POEM are provided in Table 3. The pooled technical success rate was 97.7% (95% CI, 95.8–98.8%, $I^2 = 0\%$) and pooled clinical success was 91.0% (95% CI, 88.0–93.4%, $I^2 = 9.8\%$) in the PFI group (Fig. 2a, b). As shown in Figure 3, there were no significant difference in technical success and clinical success rates between the treatment-naïve group and PFI group, with an RR of 1.0 (95% CI, 0.99–1.01, $p = 0.89$, $I^2 = 0\%$) and 1.02 (95% CI, 0.98–1.06, $p = 0.36$, $I^2 = 35\%$), respectively.

Of all included studies, 6 studies reported pre- and postoperative Eckardt score and 5 studies reported pre- and postoperative LES pressure. The Eckardt score significantly decreased by 5.95 points (95% CI, 5.50–6.40, $p < 0.00001$, $I^2 = 73\%$), and the LES pressure significantly reduced by 19.74 mm Hg (95% CI, 14.10–25.39, $p < 0.00001$, $I^2 = 94\%$) in the PFI group (Fig. 4).

There were 5 studies reported the clinical reflux. Among the studies, the prevalence of reflux esophagitis at esophagogastroduodenoscopy varied from 8.6 to 22.1% in the treatment-naïve group and 11.8–22.8% in the PFI group. The prevalence of symptomatic reflux varied from 14.7 to 36.2% in the treatment-naïve group and 17.8–49% in the PFI group. There was no significant difference of reflux esophagitis rate between the treatment-naïve group and PFI group, with an RR of 0.81 (95% CI, 0.64–1.04, $p = 0.10$, $I^2 = 0\%$). But the occurrence of symptomatic reflux was significantly different between the 2 groups, with an RR of 0.79 (95% CI, 0.64–0.97, $p = 0.02$, $I^2 = 0\%$) (online suppl. Fig. 2).

Table 4 showed the clinical success rate in different follow-up times. Among them, clinical outcomes at 6-month follow-up were reported in 3 studies, 1-year follow-up in 3 studies, 2-year follow-up in 2 studies, and ≥3-year follow-up in 3 studies. In the PFI group, the pooled

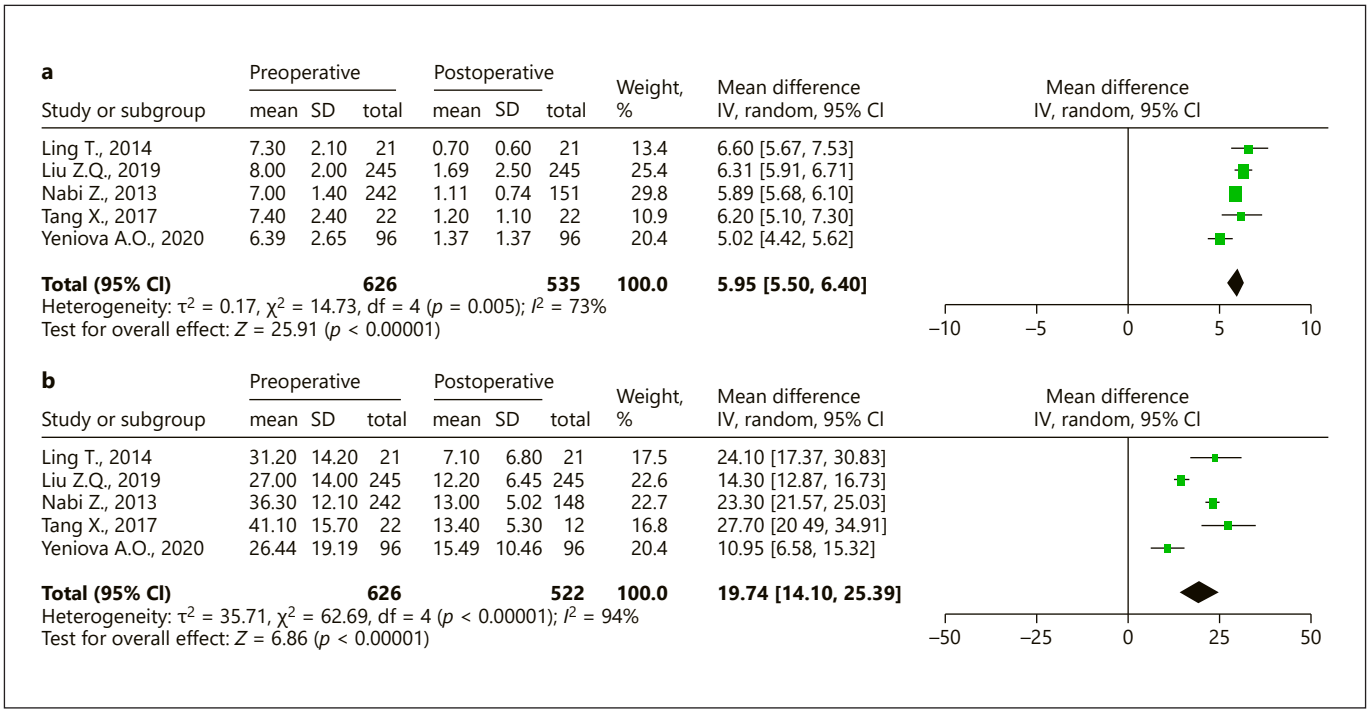

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Fig. 4. a Meta-analysis of the changes of Eckardt score before and after POEM in patients with prior endoscopic intervention. **b** Meta-analysis of the changes of LES pressure before and after POEM in patients with prior endoscopic intervention. POEM, peroral endoscopic myotomy; LES, lower esophageal sphincter.

Table 4. The clinical success rate in different follow-up times of included studies

Study	Groups	6 months	1 year	2 years	≥3 years
Sharata et al. [14]	Treatment naïve	28/28 (100%)	–	–	–
	PFI	12/12 (100%)	–		
Ling et al. [15]	Treatment naïve	–	–	–	–
	PFI	–	18/21 (87.5%)	–	–
Tang et al. [17]	Treatment naïve	–	36/39 (92.3%)	–	–
	PFI	–	21/22 (95.5%)	–	–
Nabi et al. [18]	Treatment naïve	206/223 (92.4%)	166/183 (90.7%)	112/128 (87.5%)	27/31 (87.1%)
	PFI	186/201 (92.5%)	145/159 (91.2%)	85/101 (84.2%)	29/38 (76.3%)
Liu et al. [19]	Treatment naïve	–	574/604 (95.0%)	565/604 (93.5%)	554/604 (91.7%)
	PFI	–	217/245 (88.6%)	212/245 (86.5%)	201/245 (82.0%)
Yeniova et al. [20]	Treatment naïve	107/113 (94.6%)	–	–	–
	PFI	91/96 (94.7%)	–	–	

PFI, prior failed endoscopic intervention.

Table 5. Detailed analysis of adverse events

Study	Groups	Total	Major events	Minor events	Others
Sharata et al. [14]	Treatment naïve	2 (7.1%)	Full-thickness esophageal perforation 1	Gas-related events 1	–
	PFI	3 (25%)	Hematemesis 1, mucosotomy dehiscence 1	Gas-related events 1	–
Ling et al. [15]	Treatment naïve	6 (20%)	–	Gas-related events 6	–
	PFI	4 (19%)	–	Gas-related events 4	–
Orenstein et al. [11]	Treatment naïve	4 (16.7%)	Arrhythmias 2	Gas-related events 1, mucosal injury 1	–
	PFI	2 (12.5%)	Mucosal injury 1, Mallory-Weiss tear 1	–	–
Jones et al. [16]	Treatment naïve	12 (40%)	–	Gas-related events 12	–
	PFI	4 (27%)	–	Gas-related events 4	–
Tang et al. [17]	Treatment naïve	8 (20.5%)	0	Gas-related events 6, bleeding 2	–
	PFI	5 (22.7%)	0	Gas-related events 4, bleeding 1	–
Nabi et al. [18]	Treatment naïve	93 (35.8%)	Capnopericardium 2 capnothorax (requiring decompression) 1 Enlargement of mucosal incision 1 30-day readmission 1	Gas-related events 82, mucosal injury 8, and pleural effusion 1	–
	PFI	80 (33.1%)	Capnothorax (requiring decompression) 1 Enlargement of mucosal incision 2	Mucosal injury 11, gas-related events 68	–
Liu et al. [19]	Treatment naïve	23 (3.8%)	Bleeding 1 Other miscellaneous major adverse event 2	Gas-related event 13, hydrothorax requiring drainage 4 Delayed mucosa barrier failure 3	–
	PFI	11 (4.5%)	Bleeding 1 Other miscellaneous major adverse event 1	Gas-related event 6, hydrothorax requiring drainage 2 Delayed mucosa barrier failure 3	–
Yeniova et al. [20]	Treatment naïve	52 (46.0%)	Bleeding 2 (1.7%)	Gas-related events 14 (12.4%), pleural efusion 13 (11.5%) Pneumonia 1 (0.08%), atelectasis 6 (5.3%) Delayed esophageal hematoma 3 (2.6%) Mucosal injury 12 (10.6%) Temporary cessation of the procedure* 1 (0.08%)	0
	PFI	66 (68.7%)	Bleeding 4 (4.1%)	Gas-related events 19 (19.8%), pleural efusion 13 (13.5%), pneumonia 5 (5.2%), and atelectasis 11 (11.5%) Delayed esophageal hematoma 2 (0.2%) Mucosal injury 10 (10.4%)	2 (0.2%)

PFI, prior failed endoscopic intervention; POEM, peroral endoscopic myotomy. * Changed to open POEM because of severe fibrosis.

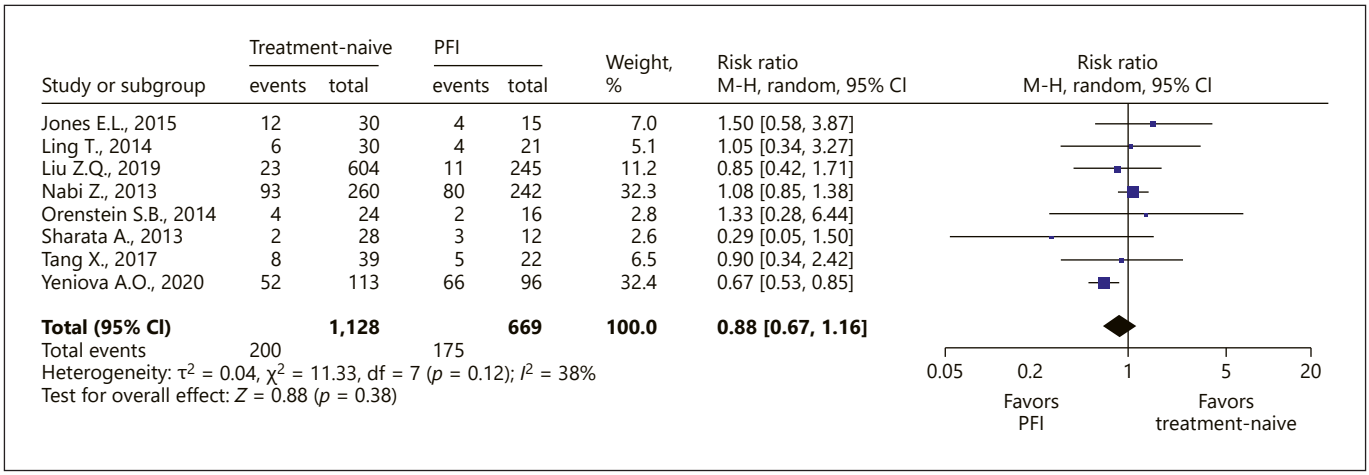

Fig. 5. Meta-analysis of pooled adverse events between patients with and without prior endoscopic intervention.

clinical success rate was 93.3% (95% CI, 89.9–95.6%) at 6-month follow-up, 89.5% (95% CI, 86.3–92.1%) at 1-year follow-up, 85.8% (95% CI, 81.7–89.1%) at 2-years follow-up, and 81.2% (95% CI, 76.2–85.4%) at ≥ 3-year follow-up (online suppl. Fig. 3). There were no significant difference in the clinical success rates between the treatment-naïve group and PFI group at 6-month and 1-year follow-up, with an RR of 1.00 (95% CI, 0.96–1.04, $p = 0.95$, $I^2 = 0\%$) and 1.02 (95% CI, 0.96–1.09, $p = 0.46$, $I^2 = 56\%$), respectively (online suppl. Fig. 4a, b). But there were significant difference in the clinical success rates between the treatment-naïve group and PFI group at 2- and ≥3-year follow-up, with an RR of 1.07 (95% CI, 1.02–1.13, $p = 0.004$, $I^2 = 0\%$) and 1.12 (95% CI, 1.05–1.19, $p = 0.0003$, $I^2 = 0\%$), respectively (online suppl. Fig. 4c, b).

Adverse Events

The detailed analysis of adverse events is shown in Table 5. A total of 200 adverse events occurred in the treatment-naïve group and 175 in the PFI group. The pooled adverse events rate was 23.5% (95% CI, 10.6–44.1%, $I^2 = 93.65\%$) (Fig. 2c). The total adverse events', major events', and minor events' rates were similar when comparing the treatment-naïve group and PFI group, with an RR of 0.88 (95% CI, 0.67–1.16, $p = 0.38$, $I^2 = 38\%$) (Fig. 5), 0.67 (95% CI, 0.31–1.47, $p = 0.32$, $I^2 = 0\%$), and 0.89 (95% CI, 0.73–1.10, $p = 0.29$, $I^2 = 12\%$) (online suppl. Fig. 5), respectively. There were no POEM-related deaths.

Quality of Included Studies and Publication Bias

Online suppl. Table 2 showed the quality assessment of each study according to the Newcastle-Ottawa Quality assessment tool. One study scored 9 (high quality) [17], 3 scored 8 (high quality) [15, 19, 20], 2 scored 7 (high quality) [14, 18], 1 study scored 6 (medium quality) [16], and 1 scored 4 (low quality) [11].

Discussion

Recently, with the development of natural orifice transluminal endoscopic surgical procedures, POEM has emerged as the novel strategy for the treatment of achalasia. A recent systematic review demonstrated that POEM was a promising option for achalasia with its relatively long-term efficacy [24], in which the overall clinical success rate of 92.9% and the overall rate of complications of 21.2% were reported during the long-term follow-up over 2 years. A latest randomized trial also illustrated that POEM was noninferior to LHM plus Dor's fundoplication in controlling symptoms of achalasia at 2-year follow-up [25]. Achalasia patients with prior endoscopic intervention are not uncommon before undergoing POEM procedure since as many as 65–91% of BTI or 50% of PD will eventually fail and additional treatments are required [26, 27]. A concern is that previous endoscopic intervention, like BTI and PD, may lead to submucosal fibrosis, resulting in POEM procedure more difficult and unsafe [14]. It has been reported that perioperative perforation during surgical myotomy occurred in up to 15% of patients with prior interventions [16]. Therefore, it is of great significance to compare the clinical outcome of POEM in achalasia patients with or without prior endoscopic intervention. According to our meta-analysis, it is demonstrated

that: (i) in PFI group, the pooled estimated rate of technical success was 97.7%, the pooled clinical success rate was 91.0%, and the pooled adverse events rate was 23.5%, which was not statistically significant with the treatment-naïve group; (ii) there were no significant difference in the clinical success rate between the treatment-naïve group and PFI group during the short-term follow-up (≤1 year), but the treatment-naïve group was superior to the PFI group in clinical success rate during the long-term follow-up (≥2 years); (iii) the operative time in the treatment-naïve group was significantly shorter than the PFI group, the hospital stay had no significant difference in 2 groups.

A latest meta-analysis has reported that the pooled clinical success rate of POEM as salvage therapy was 85.6%, which was similar to our study (91%) [28]. They concluded that POEM after failed conventional endoscopic or surgical therapy in patients with achalasia is an effective and safe treatment. But this study failed to conduct subgroup analysis to compare the efficacy and safety of POEM between patients with and without prior endoscopic or surgical therapy. Besides, subgroup analysis should be performed on the clinical outcomes between previously failed endoscopic intervention and previously failed surgical therapy, separately. Since post-LHM state is not the same as that of patients who failed in endoscopic treatment. When the LHM treatment failed, the POEM's orientation of myotomy is the posterior wall of the esophagus. While the endoscopic treatment failed in some patients, the area of LES will have submucosal scar and fibrosis. Therefore, it is necessary to separate and analyze the cases of POEM treatment after the prior failed endoscopic treatment.

Due to the fact that clinical reflux has a potential to develop into strictures, Barrett's esophagus, and even adenocarcinoma, clinical reflux after POEM procedure is still a serious concern that needs attention [29, 30]. Our study demonstrated that the incidence of symptomatic reflux was lower in the treatment-naïve group than in the PFI group. But there was no significant difference in the occurrence rate of reflux esophagitis at esophagogastroduodenoscopy between the 2 groups. Therefore, the previous endoscopic treatment has a little effect on the occurrence of clinical reflux after POEM procedure. A meta-analysis by Schlottmann et al. [31] reported that reflux symptoms were presented in 19% of patients, reflux esophagitis at esophagogastroduodenoscopy was presented in 22%, and reflux evidenced by pH monitoring was present in 48% of patients after POEM [31]. This rate is quite high; therefore, we should pay attention to the intervention of post-POEM clinical reflux. Current treatments include medicine (such as proton pump inhibitors and H2-blocking agents), endoscopic fundoplication after POEM and laparoscopic partial fundoplication [32, 33]. As for medicine treatment, many patients will need lifelong medicine treatment, which is clearly associated with severe side effects and some patients have poor efficacy [33]. Recently, Inoue et al. [32] reported that endoscopic fundoplication at the same time of POEM may help to mitigate the clinical reflux. Nurczyk et al. [33] reported that 3 post-POEM patients still experienced heartburn and regurgitation after drug treatment, and finally the reflux symptoms were completely resolved by laparoscopic partial fundoplication.

This study has several limitations. First, our article aimed to discuss the patients with prior endoscopic intervention, but actually included some patients with prior surgical intervention. Thus, in order to reduce its impact on the results, we included studies with no >20% of patients received prior LHM treatment. Second, only 2 studies have described long-term (≥2 years) outcomes of POEM in patients with previous endoscopic intervention; therefore, the long-term results were not convincing. More original research is needed to confirm the sustainable efficacy of POEM for achalasia with failed endoscopic interventions Third, there was a certain degree of heterogeneity among some outcomes, such as Eckardt score, LES pressure, clinical success at 1 year's follow-up, and adverse event. This was due to some studies reporting variable data of outcomes and the difference proportion of patients in each study. Finally, the studies we included were retrospective and prospective cohort studies without randomized controlled studies, which would result in selection bias and reporting bias.

Conclusions

POEM is an effective and safe treatment for achalasia patients with PFI. Randomized clinical trials are warranted to further verify the efficiency and safety of the POEM in achalasia patients with and without prior endoscopic intervention.

Statement of Ethics

Ethical approval was not required for this systematic review and meta-analysis because there were no participants and no living individuals included.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Study conception and design: Xiaowei Tang and Li Liu. Drafting of manuscript: Chunyu Zhong, Bowen Ni, and Sixiu Liu. Acquisition of data: Chunyu Zhong and Shali Tan. Revision of manuscript and final approval of manuscript: Muhan Lü, Yan Peng, and Xiaowei Tang.

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