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Efficacy and safety of peroral endoscopic myotomy in the management of recurrent achalasia after failed Heller myotomy: a systematic review and meta-analysis

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Abstract

Background Heller myotomy (HM) is an established treatment for achalasia but can fail in up to 10-20% of patients. Peroral endoscopic myotomy (POEM) may be an appropriate treatment for patients with failed HM.

Methods We searched several databases to identify non-comparative studies evaluating the efficacy and/or safety of POEM after failed HM and comparative studies comparing the efficacy and/or safety of POEM in patients with and without prior HM. Outcomes assessed included clinical success, technical success, adverse events, post-treatment gastroesophageal reflux disease (GERD), and presence of esophagitis on endoscopy. We calculated weighted pooled rates with 95% confidence intervals (CI) for all outcomes in patients undergoing POEM with prior HM. We calculated pooled odds ratios with 95%CI to compare the outcomes between patients with and without previous HM who underwent POEM.

Results We included 11 observational studies with 1205 patients. Weighted pooled rates (95%CI) for overall clinical success and technical success in patients with failed HM were 87% (81-91%) and 97% (94-99%), respectively. Weighted pooled rates (95%CI) for major adverse events, new-onset GERD and presence of esophagitis on endoscopy were 5% (2-10%), 33% (26-41%), and 38% (22-58%), respectively. There were no differences in clinical success, adverse events, post-treatment GERD and esophagitis between patients with and without previous HM.

Conclusions POEM is safe and effective in patients with failed HM and should be considered in patients with recurrent achalasia after HM. Outcomes of POEM are comparable in patients with and without prior HM.

Keywords Heller myotomy, efficacy, peroral endoscopic myotomy, meta-analysis

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Introduction

Heller myotomy (HM) and pneumatic dilation (PD) are commonly used treatment modalities for achalasia. Although PD can achieve immediate relief of symptoms, relapse rates can approach 18% by 2 years and 41% by 5 years [1]. HM, generally accompanied by some form of fundoplication, is appropriate for patients who are good candidates for surgery. HM can achieve symptom relief in up to 90% of patients [2], with 10-year remission rates of up to 80% [3]. Possible reasons for persistent or recurrent symptoms after HM include incomplete myotomy, surgical site fibrosis, fundoplication disruption, and an excessively tight fundoplication [5]. Management of patients with failed HM is challenging, as treatment options are limited; PD and repeat HM have both been evaluated [6,7]. Although PD is associated with good long-term outcomes in patients with failed HM, repeat dilations may still be required as the relapse rate is substantial [7,8]. Repeat HM is associated

Conflict of Interest: None

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with a better remission rate than PD for recurrent achalasia after HM [5].

Since its introduction in 2009, peroral endoscopic myotomy (POEM) has gained popularity in the treatment of achalasia and is used in some centers as a first-line treatment of achalasia. Compared to HM, POEM has the advantages of rapid recovery and avoiding abdominal incisions. One meta-analysis found that POEM was more effective than HM in relieving dysphagia in patients with achalasia [9]. Studies have evaluated the role of POEM in the management of recurrent achalasia after failed HM and some studies compared the outcomes of POEM in patients with and without prior HM. In this systematic review and meta-analysis, we evaluated the efficacy and safety of POEM for the treatment of recurrent achalasia after failed HM.

Materials and methods

Data sources and search strategy

We followed the guidelines for Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) [10] and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) [11]. We conducted a comprehensive search of several databases, including PubMed & MEDLINE, Embase, Web of Science Core Collection and the Cochrane Central Register of Controlled Trials, from inception to January 29, 2020. An experienced medical librarian (WL-S) performed the search. No language limitation was applied. The search included keywords and database-specific controlled subject terms for the concepts: peroral endoscopic myotomy, Heller's myotomy, and retreatment/prior treatment failure. Two authors (FK and SS) conducted an initial screening by independently reviewing the titles and abstracts of the articles retrieved by the search and excluded those that did not address our question of interest. Full texts of remaining articles, including references, were reviewed. The search strategy is illustrated in Fig. 1.

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Inclusion and exclusion criteria

Two authors (FK and MAK) independently reviewed original studies based on inclusion criteria established *a priori*. We included single-arm non-comparative studies that evaluated the efficacy and/or safety of POEM in patients with prior failed HM. We also included comparative studies that compared the efficacy and/or safety of POEM in patients with and without prior HM. Case reports, case series with fewer than 5 patients, guidelines, editorials, review articles and studies with animal models were excluded. We only included full publications as well as abstracts. All articles were downloaded into Endnote X9.0, a bibliographic database manager. Duplicate citations were removed.

Data extraction

Two authors (FK and MAK) independently assessed the eligibility of included studies and designed data extraction forms for this study. They then collected data independently using these forms and discussed any discrepancies with a third reviewer (MKI); agreement was reached by consensus. Data extracted included year and country of publication, type of study, patient demographics, number of patients, technical success, clinical success, major adverse events, pre-and post-treatment Eckardt score [13], operative time, length of stay, duration of follow up, post-treatment new onset gastroesophageal reflux disease (GERD) based on patients' reporting of symptoms, presence of esophagitis on esophagogastroduodenoscopy (EGD), and GERD confirmed by 24-h pH monitoring.

Quality assessment

We assessed the quality of comparative studies using the Newcastle-Ottawa Scale (NOS). The NOS assesses the quality of observational studies based on selection, comparability and exposure/outcome, and allocates a maximum of 4, 2, and 3 points, respectively. Studies that score more than 7 are considered high quality, those that score between 5 and 7 are considered moderate quality, and those that score below 5 are considered low quality. We performed quality assessment of non-comparative studies using a modified version of the NOS, which allocates a maximum of 6 points [14]. On this modified score, high quality studies score over 3 while low quality studies score 3 or below. Two authors (ZK and RT) independently performed the quality assessment and any disagreement was discussed with a third reviewer (CWH).

Data synthesis and statistical analysis

The primary outcome of interest for POEM with prior failed HM was clinical success, defined as a post-treatment Eckardt score of ≤3. Secondary outcomes of interest were technical success (defined as successful completion of the procedure), procedure time, major adverse events, post-

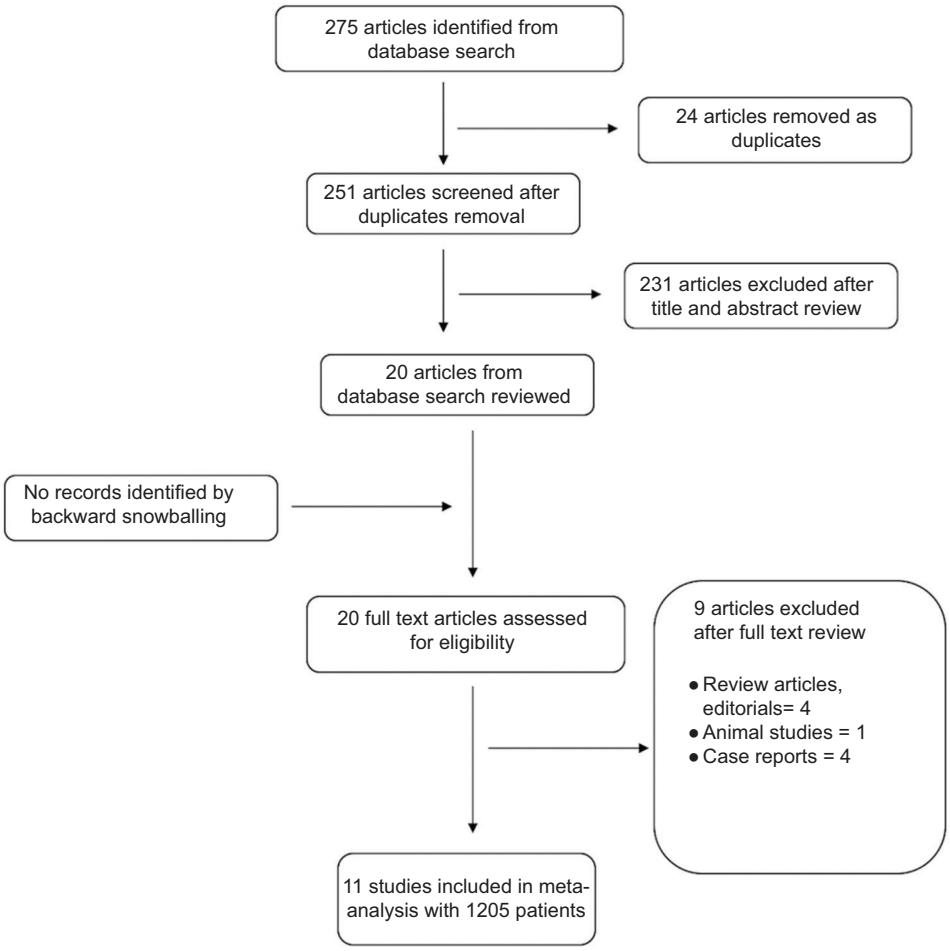

Figure 1 PRISMA flowchart

treatment new onset symptomatic GERD (based on patients' reporting of symptoms) and presence of esophagitis on EGD. The major adverse events that we included in our analysis were those that required intervention or were determined to be moderate or severe according to the American Society for Gastrointestinal Endoscopy (ASGE) lexicon system [4] or as described in the Natural Orifice Surgery Consortium for Assessment and Research (NOSCAR) white paper [15]. For single arm, non-comparative studies, we calculated weighted pooled rates with 95% confidence intervals (CI) for technical and clinical success, major adverse events and rate of post-procedure new onset symptomatic GERD. For comparative studies, we calculated pooled odds ratios (OR) with 95%CI to compare clinical success, risk of new onset symptomatic GRED, esophagitis on endoscopy, and adverse events between groups with and without prior HM. We calculated standard mean difference (SMD) with 95%CI to compare operative times between groups. Some studies reported operative times as mean ± standard deviation (SD) and others as median and interquartile range (IQR). According to the Cochrane handbook, "when sample sizes are large and the distribution of the outcome is similar to the normal distribution, the width of the interquartile range will be approximately 1.35 standard deviations" [26]. We used this approach to calculate SMD.

We used a fixed effect model for most of our analyses. However, we used a random effects model when significant heterogeneity was encountered in data, as recommended by the Cochrane handbook. Heterogeneity was assessed by the I^2 statistic. The statistical analysis was performed using Review Manager (RevMan, version 5.3 for Windows; The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark, 2014) and comprehensive meta-analysis (CMA) software.

Results

Search strategy yield and quality assessment

The search strategy yielded 275 articles (Fig. 1), from which we removed 24 duplicates. Of the remaining 251 articles, 231 were removed after title and abstract review. No relevant articles were identified from a search of bibliographies in the retrieved publications. We reviewed the full texts of 20 articles, from which we ultimately included 11 studies comprising 1205

Table 1 Characteristics of studies

Study, year [Ref]	Country	Type of study	Total number of patients	Males	Inclusion criteria	Exclusion criteria	Quality assessment NOS score
Zhang *et al,* 2018 [16]	USA	Prospective	318	179	Patients undergoing POEM at Winthrop University Hospital. Patients with prior HM were identified and analyzed as a subgroup.	Patients with uncorrectable coagulopathy and severe lung disease requiring oxygen supplementation as well as steroid-dependent patients and patients with expected survival <12 months	7
Ngamruengphong *et al*, 2017 [4]	Multicenter	Retrospective	180	82	Adult patients (age ≥18 years) with achalasia and Eckardt scores of 3 or higher who underwent POEM	Patients with a history of prior POEM, patients with esophageal cancer, and patients with a history of esophageal surgery (other than HM).	7
Kristensen *et al,* 2017 [17]	Denmark	Prospective	66	33	Patients who underwent POEM for achalasia	Patients who did not fulfill the initial 3-month follow up, patients in whom the procedure could not be completed for technical reasons, re-POEMs and patients with Jackhammer esophagus	6
Tyberg *et al,* 2017 [18]	Multicenter	Prospective	51	24	Patients who underwent POEM post-HM from 13 centers in 9 countries were included	NR	5
Fumagalli *et al,* 2015 [19]	Italy	Retrospective	6	3	Patients who had previously undergone myotomy for achalasia and subsequently underwent a repeated myotomy for persistent or recurrent dysphagia	Esophageal varices, coagulopathy, active esophagitis, gastroesophageal malignancy	
Vigneswaran *et al,* 2014 [20]	USA	Prospective	5	4	Patients with recurrent dysphagia symptoms after failed Heller myotomy for achalasia	Esophageal varices, coagulopathy, active esophagitis, pregnancy, known gastroesophageal malignancy, age less than 18 years	2
Onimaru *et al,* 2013 [21]	Japan	Prospective	10	5	Patients with persistent or recurrent achalasia who previously underwent surgical myotomy as a first-line treatment. All failed surgical myotomy patients received PBD as the first line rescue treatment, and in patients with no symptomatic relief after PBD, POEM was considered as a second line rescue treatment	NR	3

(*Contd...*)

Table 1 (*Continued*)

Study, year [Ref]	Country	Type of study	Total number of patients	Males	Inclusion criteria	Exclusion criteria	Quality assessment NOS score
Zhou *et al*, 2012 [22]	China	Prospective	12	5	Patients ≥18 years who had recurrence/ persistence of symptoms after primary Heller myotomy, with an Eckardt symptom score of ≥4	severe cardiopulmonary disease or other serious disease leading to unacceptable surgical risk, pseudoachalasia, and megaesophagus (diameter >7 cm)	4
Parikh *et al*, 2018 [25]	USA	Prospective	138	NR	Achalasia patients who underwent POEM with at least 2 months post treatment follow up	NR	
Chavan *et al*, 2017 Abstract [23]	India	Retrospective	26	NR	All patients who underwent POEM with history of failed HM	NR	
Landi *et al*, 2017 [24]	Italy	Prospective	393	NR	Patients who underwent POEM because of recurrent symptoms after a failed HM	NR	

POEM, peroral endoscopic myotomy; HM, Heller myotomy; NR, not reported; PBD, pneumatic balloon dilation

patients [4,16-25]. Eight were full publications [4,16-22] and 3 were abstracts [23-25]. Of these, 6 [18-23] (110 patients) were non-comparative and comprised only patients with prior failed HM. The other 5 [4,16,17,24,25] were comparative studies comprising 193 patients with, and 902 without, prior HM. The characteristics of the included studies are summarized in Tables 1 and 2. The quality assessment of studies is summarized in Table 1.

Meta-analysis

Clinical success

9 studies with 1001 patients [4,16,18-24] reported data on this outcome. Weighted pooled rates (95%CI) were 87% (81-91%), Cochran Q test P=0.17, I^2=31% (Fig. 2A). Three studies [4,16,24] with 882 patients compared clinical success in patients with and without prior HM. We found no difference in clinical success between the 2 groups; pooled OR (95%CI) 2.30 (0.83-6.43), Cochran Q test P=0.15, I^2=47% (Fig. 2B).

Technical success

Nine studies with 1001 patients [4,16,18-24] reported data on this outcome. Weighted pooled rates (95%CI) were 97% (94-99%), Cochran Q test P=0.96, I^2=0% (Fig. 3).

Major adverse events

We included 7 studies with 582 patients [4,16,18-22]. Weighted pooled rates (95%CI) were 5% (2-10%), P=0.26, I^2=22% (Fig. 4). In 2 studies [4,16] with 498 patients that compared adverse events in patients with and without prior HM, we found no difference between the 2 groups: pooled OR (95%CI) 0.52 (0.12-2.33), Cochran Q test P=0.68, I^2=0%.

Post-treatment GERD and esophagitis

We included 5 studies with 969 patients [4,16,17,22,24]. Weighted pooled rates for new onset symptomatic GERD (based on patients' reporting of symptoms) were 33% (26-41%), I^2=37% (Supplementary Fig. 1). Three studies [4,16,22] evaluated the presence of esophagitis on EGD after POEM: weighted pooled rates were 38% (22-58%), I^2=52% (Supplementary Fig. 2).

Four studies [4,16,17,24] compared the rates of GERD between patients with and without prior HM and found no significant difference between the 2 groups; pooled OR (95%CI) 1.28 (0.83-1.96) Cochran Q test P=0.38, I^2=2% (Supplementary Fig. 3A). Two studies [4,16] compared rates of esophagitis (confirmed by EGD) between patients with and without prior HM and found no significant difference between the 2 groups, pooled OR (95%CI) 1.09 (0.60-1.98), Cochran Q test P=0.17, I^2=47% (Supplementary Fig. 3B). Overall, there was no significant difference in the rates of symptomatic GERD and esophagitis between patients with and without prior HM.

Only one study reported data on GERD confirmed by 24-h pH monitoring: rates of GERD in patients with and without prior HM were 50% and 48% respectively.

Operative time

Five studies [4,16,17,24,25] compared operative time between patients with and without prior HM. We found that

Table 2 Data on outcomes of interest

Study, year [Ref]	Number of patients	Technical success	Clinical success	Follow up (months)Mean±SD or Median (IQR)	Adverse events	Operative time Mean±SD or Median (IQR)	LOS Mean±SD or Median (IQR)	Post- treatment GERD symptoms	Esophagitis on EGD (LA class A, B, C and D)	24-hour pH study	Pre-treatment Eckardt score	Post-treatment Eckardt score
Comparative studies												
Zhang *et al*, 2018 [16]	Prior HM: 46 No prior HM: 272	46	44 255	28 (14-29) 23 (10-34)	0 8	82 (60-102) 72 (53-102)	1 (1-2) 2 (1-2)	15 77	12/26 50/147	12/24 69/144	7 (6-8) 8 (7-9)	1 (0-1) 0 (0-1)
Parikh *et al*, 2018 [25] Abstract	Prior HM: 29 No prior HM: 109	NR	NR	NR	NR	110 91-130) 97.5 (79.5, 110.5)	NR	NR	NR	NR	NR	NR
Landi *et al*, 2017 [24] abstract	Prior HM: 14 No prior HM: 379	14 370	11 346	14.6±13.9 18.7±14.3	0 4	69±29 64±24	3 3	7 96	NR	NR	6.4±1.8 7.9±2.2	1.9±1.6 0.9±1.3
Ngamruengphong *et al*, 2017 [4]	Prior HM: 90 No prior HM: 90	88 90	61/76 72/77	9(4-14) 8.5 (1.3-18.5)	2 3	102.8±41 102.6±61	3.54±1.7 3.59±2.5	21/70 24/76	18/41(A=14, B=3, C=1, D=0) 23/44(A= 13, B=6, C=3, D=1	NR	7.1±2.7 6.9±2.3	2.09±2.5 1.08±1.2
Kristensen *et al*, 2017 [17]	Prior HM: 14 No prior HM: 52	NR	NR	NR	NR	74 (35-149) 61 (35-126)	2 (1-4) 2 (1-4)	4/7 11/25	NR	NR	7 (2-11) 7 (3-12)	5 (3-10) 2 (0-4)
Non-comparative studies												
Tyberg *et al*, 2017 [18]	Prior HM: 51	51	48	24.4	2	NR	NR	NR	NR	NR	NR	NR
Fumagalli *et al*, 2015 [19]	Prior HM: 6	6	6	8.9 (3.1-16)	0	62 (60-112)	2.5 (2-3)	NR	NR	NR	4.5 (2-7)	0 (0-1)
Vigneswaran *et al*, 2014 [20]	Prior HM: 5	5	5	5	1	139.0±29.6	1.6±0.2	NR	NR	NR	6.8 (5-10)	0.6
Onimaru *et al*, 2013 [21]	Prior HM: 10	10	10	3	0	118.2	NR	NR	NR	NR	6.5±1.3	1.1±1.3
Zhou *et al*, 2012 [22]	Prior HM: 12	12	11	10.4±3.1	2	36.4±9.3	4.1±1.3	1	1, LA Class B	NR	9.2 ± 1.1	1.3 ± 1.3
Chavan *et al*, 2017 [23] abstract	26	25	22/22	12	0	NR	NR	NR	NR	NR	6.5 ± 1.4	1.3 ± 0.6

IQR, interquartile range; LOS, length of hospital stay; SD, standard deviation; EGD, esophagogastroduodenoscopy; HM, Heller myotomy; GERD, gastroesophageal reflux disease, NR, not reported

operative time was longer in patients with prior HM: SMD (95%CI) 0.212 (0.03-0.39), I^2=0%.

Discussion

We found that POEM is a safe and effective option for patients with recurrent achalasia after HM and that outcomes of POEM in these patients are comparable to those without prior HM. Traditionally, PD and repeat HM have been mainstays of treatment in patients with failed HM. Kumbhari *et al* reported that the rate of remission in patients receiving PD (with repeat dilations as required) after failed HM at a median follow up of 30 months was 95% [8]. However, the need for repeat dilations, with the consequent increased risk of adverse events, most notably perforation, limits the usefulness of PD in this patient population. Repeat HM is often performed in these patients, but can be technically challenging because of adhesions from previous surgery [22], and also carries a risk of serious adverse events [27].

We found that the overall technical success rate for POEM after failed HM was 97% (94-99%) comparable to the reported rate of 98% in patients without prior HM [28]. The overall clinical success rate for POEM after failed HM was 87% (81-91%), equivalent to the figure of 86.9% for repeat HM. Wang *et al* reported that the rate of recurrent achalasia with repeat HM after failed HM was 86.9% [5]. The clinical success rate of POEM after failed HM appears comparable to that of POEM without prior HM. We also found that the clinical success rate for POEM was comparable between patients with and without prior HM, pooled OR (95%CI) 2.30 (0.83-6.43). However, this analysis had only moderate heterogeneity (I^2=47%), which limits the validity of its results.

The overall rate of major adverse events was 5% and there were no cases of esophageal perforation. A previous systematic review of 7 studies evaluating the feasibility and safety of laparoscopic repeat HM reported intraoperative esophageal or gastric perforation in 16% of patients, with 4% requiring conversion to an open procedure [27]. HM is also more invasive and is associated with longer procedure and recovery times than POEM.

The analysis of procedure time was limited, as some studies reported this as mean ± SD and others as median (IQR). However, procedure time was typically longer in patients with prior HM compared to those without, probably because of fibrosis and adhesions from prior surgery. Contrary to other studies, Ngamruengphong *et al* [4] reported that procedure time was the same in both groups. However, they included a higher proportion of patients in the prior HM group who had undergone previous attempts at PD, compared to patients without prior HM (44% vs. 25%), which may explain this discrepancy.

One of the strengths of our work is the inclusion of both single-arm and comparative studies to estimate the overall efficacy and safety of POEM after failed HM, as well as comparative efficacy and safety compared to patients without prior HM. Analyses of most of the outcomes that we assessed had low heterogeneity.

This meta-analysis also has some limitations. To date, no randomized controlled trial has compared POEM in patients with and without prior HM. Consequently, our meta-analysis only included observational studies, which entail risks of measured and unmeasured confounding [29]. In many of the included studies, patients received other treatments, including botulinum toxin injections and PD that could have affected the performance of POEM. In a study by Onimaru *et al*, all patients underwent PD as first-line rescue treatment after failed HM, and patients with no response to PD underwent POEM. The analysis of our primary outcome of interest (clinical success)

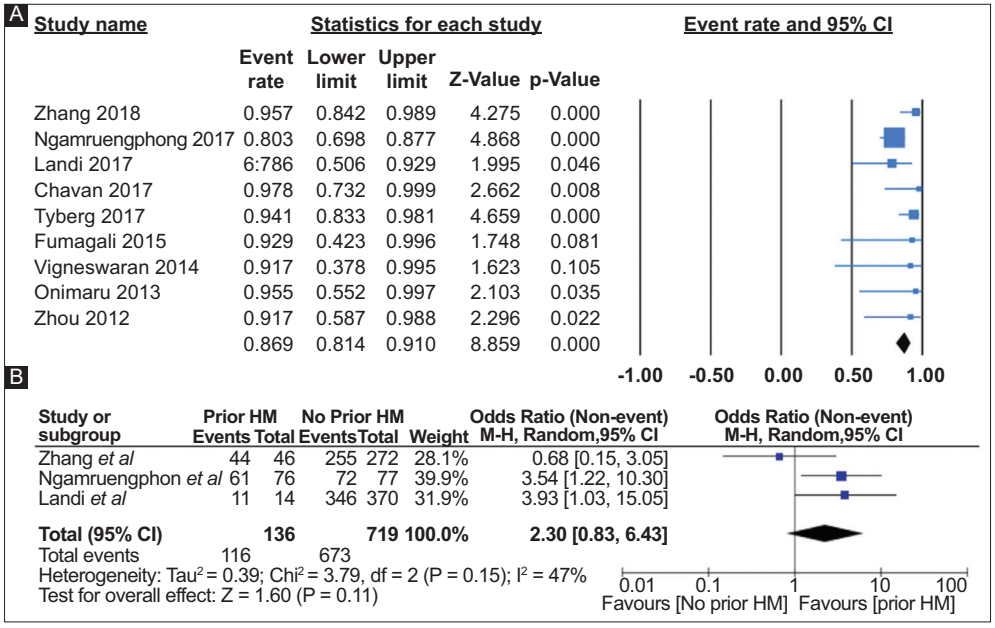

Figure 2 Clinical success of peroral endoscopic myotomy (POEM) after failed Heller myotomy (HM) (overall and comparative). (A) Overall clinical success of POEM after failed HM. (B) Comparison of clinical success of POEM in patients with and without prior HM
CI, confidence interval

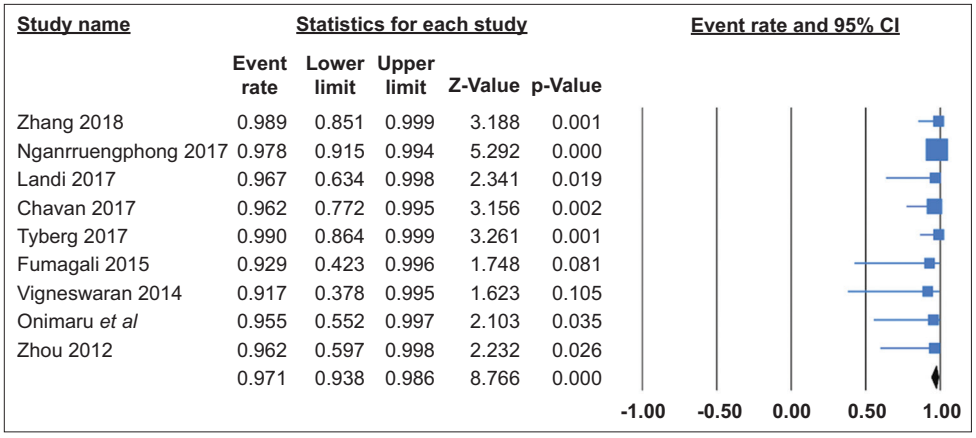

Figure 3 Overall technical success of peroral endoscopic myotomy after failed Heller myotomy
CI, confidence interval

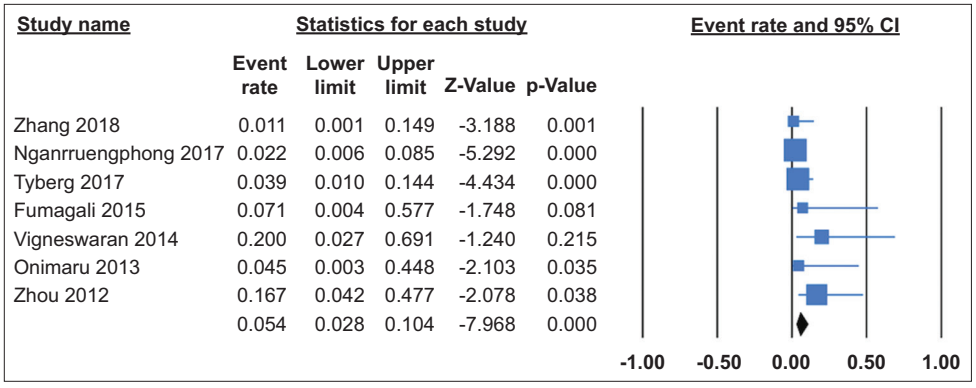

Figure 4 Adverse events with peroral endoscopic myotomy after failed Heller myotomy
CI, confidence interval

Summary Box

What is already known:

- Management of patients with failed Heller myotomy (HM) is challenging and treatment options are limited
- Pneumatic dilation (PD) can be used in these patients but its usefulness is limited by a high relapse rate
- Repeat HM is associated with increased risk of complications
- Peroral endoscopic myotomy (POEM) may be a suitable option in patients with failed HM

What the new findings are:

- POEM is a safe and effective option in patients with recurrence of symptoms after prior HM
- Outcomes of POEM in patients with prior HM are comparable to outcomes in patients without prior HM
- POEM should be considered in patients with failed HM

was limited by moderate heterogeneity. Follow-up periods varied across different studies, which may have led to clinical heterogeneity in the analysis. Only few comparative studies reported data on all of the outcomes we assessed and the data may not be sufficiently powered to draw firm conclusions. Finally, most of the included studies did not report the efficacy and safety of POEM in individual achalasia subtypes.

In conclusion, this systematic review and meta-analysis supports the role of POEM in patients with no improvement in achalasia symptoms or recurrence of symptoms after HM.

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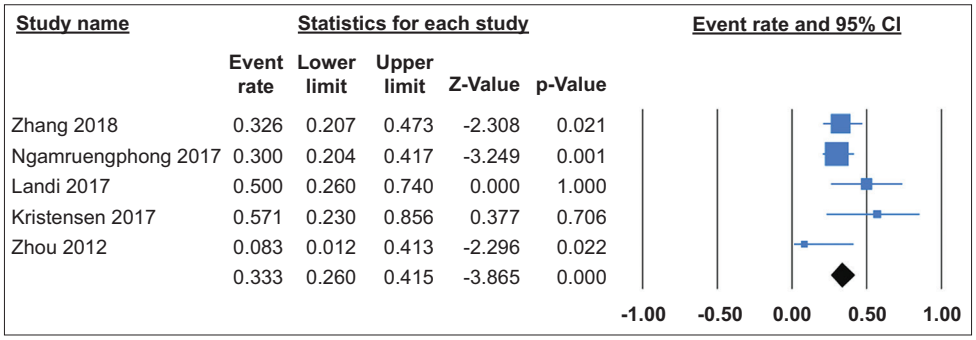
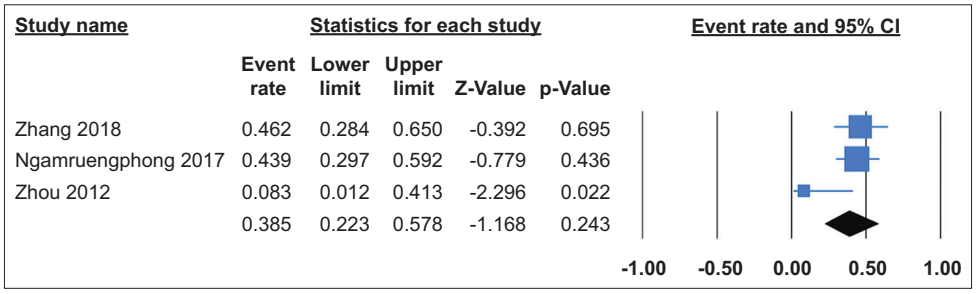
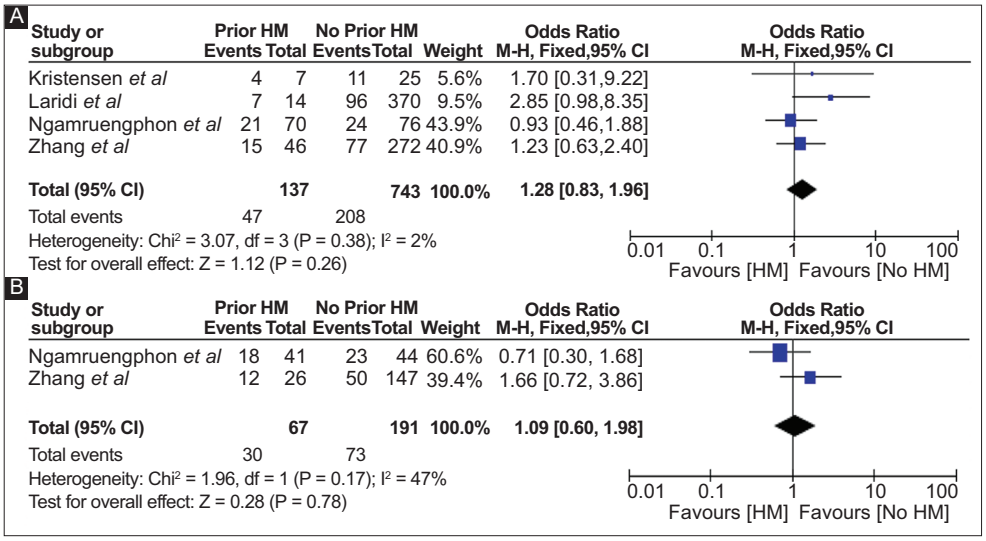
Supplementary material



Supplementary Figure 1 Overall risk of gastroesophageal reflux disease with peroral endoscopic myotomy after failed Heller myotomy
CI, confidence interval



Supplementary Figure 2 Overall risk of esophagitis with peroral endoscopic myotomy after failed Heller myotomy
CI, confidence interval



Supplementary Figure 3 (A) Risk of gastroesophageal reflux disease in patients with prior Heller myotomy (HM) vs. no prior HM (B) Risk of esophagitis in patients with prior HM vs. no prior HM
CI, confidence interval