6-14-2024

Feasibility and Safety of Peroral Endoscopic Myotomy With Fundoplication in Patients With Achalasia: A Systematic Review and Meta-Analysis

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Annals of Gastroenterology (2024) **37,** 403-409

Feasibility and safety of peroral endoscopic myotomy with fundoplication in patients with achalasia: a systematic review and meta-analysis

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Abstract

Background Achalasia can cause disabling symptoms that may substantially impair the quality of life. Peroral endoscopic myotomy (POEM) has shown promising results in the management of achalasia. In this meta-analysis we have evaluated the feasibility and safety of single-session POEM with fundoplication (POEM+F) in patients with achalasia.

Methods We reviewed several databases from inception to July 08, 2022, to identify studies evaluating the feasibility and/or safety of single-session POEM+F for patients with achalasia. Our outcomes of interest included the technical success of POEM+F, adverse events, esophagitis and wrap integrity on follow-up upper endoscopy, total procedure time, and fundoplication time. Pooled rates with 95% confidence intervals (CI) for outcomes were calculated using a random effect model. Heterogeneity was assessed using the I^2 statistic.

Results We included 4 studies with 90 patients. Pooled rates (95%CI) of technical success and adverse events were 92% (83-96%) and 5% (2-11%), respectively. Pooled rates (95%CI) of esophagitis and wrap integrity on follow-up upper endoscopy were 18% (11-30%) and 85% (43-98%) respectively. Pooled mean procedure time and fundoplication time were 113.2 (98.7-127.6) and 55.3 (43.7-66.8) min, respectively.

Conclusions This meta-analysis demonstrates the feasibility and safety of POEM+F in patients with achalasia. More studies with long-term follow up are required to further validate these findings.

Keywords Peroral endoscopic myotomy, fundoplication, achalasia, meta-analysis

Ann Gastroenterol 2024; 37 (4): 403-409

Introduction

Achalasia is a neurodegenerative disorder that can cause disabling symptoms, such as dysphagia, regurgitation and chest pain, and may increase the risk of developing squamous cell cancer of the esophagus [1]. It is a rare disorder, with an estimated prevalence of 1.8-12.6 per 100,000 persons per year [2]. Mechanical interruption of the lower esophageal sphincter using pneumatic dilation (PD) or Heller myotomy (HM) are the most commonly used treatments. HM has better long-term outcomes compared to PD [3,4]. High relapse rates warrant additional treatment after PD, limiting its usefulness.

Since its introduction in 2009, peroral endoscopic myotomy (POEM) has shown promising results in the management of achalasia and has become the first-line treatment at many centers. One side-effect of a successful POEM procedure is iatrogenic gastroesophageal reflux disease (GERD) which can occur in up to 28% of patients [5]. HM is often performed with a simultaneous fundoplication, which decreases the risk of GERD. The incidence of GERD is much higher after POEM compared to HM with fundoplication [6]. Reduction

Conflict of Interest: None

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Received 24 September 2023; accepted 19 March 2024; published online 14 June 2024

DOI: https://doi.org/10.20524/aog.2024.0890

in GERD is one potential area for improvement in the current technique of POEM. POEM with fundoplication (POEM+F) has been introduced, which can potentially lower the risk of post-POEM GERD. Inoue *et al* published a case series of 21 patients who underwent POEM+F and found that it was technically feasible in all patients, while no immediate or delayed complications were reported [7]. Since then, several other studies have evaluated the feasibility of POEM+F and have reported promising results [8-10]. In this meta-analysis we have evaluated the feasibility and safety of POEM+F.

Materials and methods

Data sources and search strategy

We followed the guidelines of Preferred Reporting items for Systematic Review and Meta-Analysis (PRISMA) to conduct this systematic review and meta-analysis. An experienced medical librarian (WL-S) conducted a comprehensive search of Embase (Embase.com, Elsevier), MEDLINE (PubMed platform, National Center for Biotechnology Information, National Library of Medicine), Cochrane Central Register of Controlled Trials (CochraneLibrary.com, Wiley, and the Web of Science Core Collection (Web of Science platform, Clarivate) from inception to July 28, 2022. There was no limitation of language in conducting the search. The search included keywords and database-specific controlled subject terms for the concepts peroral endoscopic myotomy, fundoplication, and achalasia. Full search strategies for all databases are provided in Supplementary Table 1. Two authors (FK and SS) independently reviewed the titles and abstracts of the articles retrieved and excluded those that did not address our question of interest. Full texts of the remaining articles, including references were reviewed. The screening results are illustrated in the form of a PRISMA flowchart in Fig. 1.

Inclusion and exclusion criteria

Two authors (FK and MAK) independently reviewed original studies based on predetermined inclusion criteria, detailed below. We included full length publications and abstracts evaluating the feasibility and/or safety of single-session POEM+F for patients with achalasia. Case reports, small case series with fewer than 5 patients, and studies with animal models were excluded. If there were multiple publications from the same cohort, we included only the most recent publication and/or the publication with most information. All articles were downloaded into Endnote X9 (Clarivate, Philadelphia, PA, USA), a bibliographic citation manager. Duplicate citations were removed by successive iterations of EndNote's duplicate detection algorithms and manual inspection.

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 author (TK); agreement was reached by consensus. Data extracted included year of publication, number of patients, number of females, mean or median age, type of achalasia based on the Chicago classification, duration of disease, inclusion criteria, exclusion criteria, technical success, adverse events, pre-POEM and post-POEM Eckardt score, total procedure time, fundoplication time, esophagitis on follow-up endoscopy, and wrap integrity on follow-up endoscopy.

Quality assessment

We assessed the quality of studies using Methodological Index for Nonrandomized Studies (MINORS) criteria [11]. Non-comparative studies were scored on 8 items of the MINORS criteria and each item was scored from 0-2 (0 if not reported; 1 when reported but inadequate; and 2 when reported and adequate). The global ideal score for non-comparative studies is 16. The quality of studies was classified as poor (score ≤5), fair (score 6-10), or high quality (≥11), as described previously [12,13]. Two authors (UF and ZI) independently performed the quality assessment and any disagreement was discussed with a third reviewer (FK). The quality assessment of studies is summarized in Supplementary Table 2.

Statistical analysis

Our primary outcome of interest was the technical success rate of POEM+F. Secondary outcomes of interest were adverse events, esophagitis on follow-up upper endoscopy, wrap integrity on follow-up upper endoscopy, total procedure time and fundoplication time. We calculated pooled rates with 95% confidence intervals (CI) for outcomes of interest and data were transformed using logit transformations. For the outcome of procedure time, we calculated pooled mean procedure time with 95%CI. We used a DerSimonian and Laird random effect model for our analyses. Heterogeneity was assessed

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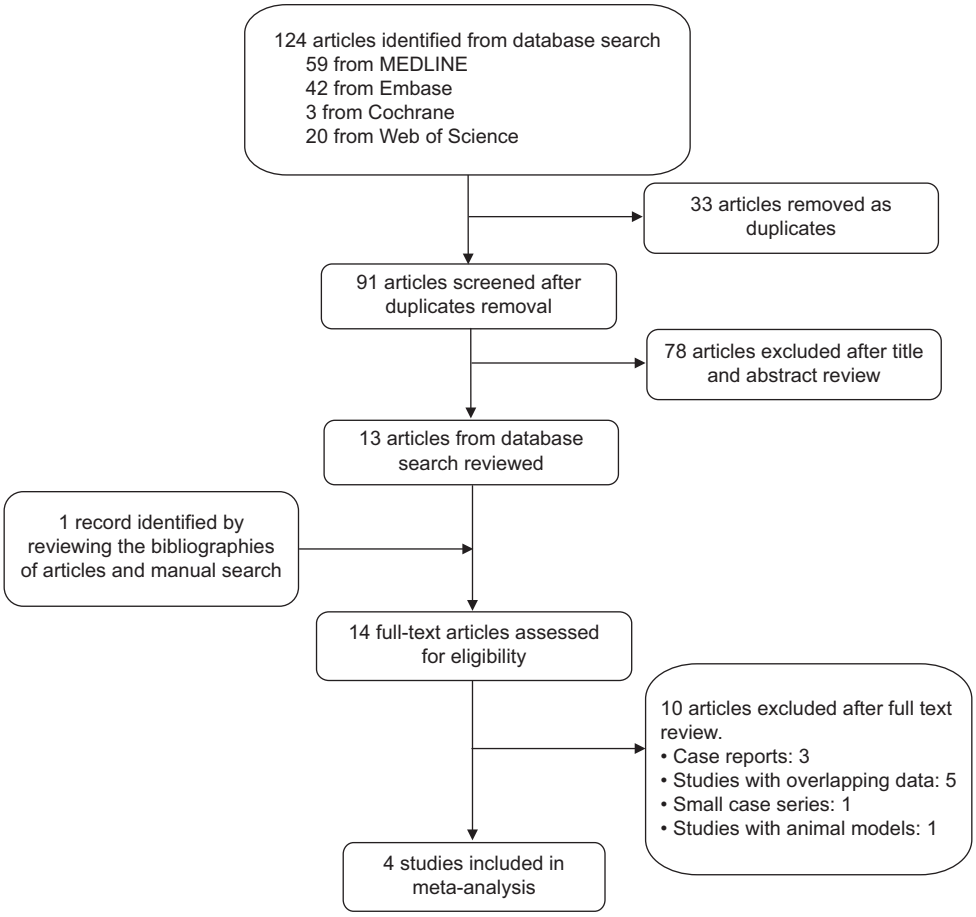

Figure 1 PRISMA flowchart

using the I^2 statistic. I^2 values of 30-60% represented moderate heterogeneity; values of 60-75% represented substantial heterogeneity, and values of 75-100% represented considerable heterogeneity. We did not assess for publication bias, because the total number of studies included in our meta-analysis was fewer than 10. The statistical analysis was performed using Comprehensive Meta-Analysis (CMA) software.

Results

The search strategy yielded 124 articles; from these, 33 duplicates were removed (Fig. 1). Of the remaining 91 articles, 78 were removed after title and abstract review. One additional article was identified by reviewing the bibliographies of articles and by manual search. We reviewed the full texts of 14 articles. Three case reports and 1 case series with fewer than 5 patients were excluded. Five studies had overlapping data and hence were excluded. We ultimately included 4 studies with 90 patients in the final analysis [7,9,10,14]. Three were full publications and 1 was an abstract. The characteristics of the included studies are summarized in Table 1.

Technical success

Four studies with 90 patients were included in this analysis. The pooled rate (95%CI) of technical success was 92% (83-96%), I^2=0% (Fig. 2).

Adverse events

Four studies with 109 patients were included in this analysis. The pooled rate (95%CI) of adverse events was 5% (2-11%), I^2=0% (Fig. 3).

Esophagitis and wrap integrity on follow-up upper endoscopy

Two studies with 63 patients reported data on esophagitis on follow-up upper endoscopy. The pooled rate (95%CI) of esophagitis on follow-up upper endoscopy was 18% (11-30%), I^2=0% (Fig. 4). Two studies with 41 patients reported data on wrap integrity. The pooled rate of wrap integrity on follow-up upper endoscopy was 85% (43-98%), I^2=70% (Fig. 5).

Table 1 Characteristics of studies

Author year [ref.]	Study design	Location of studies	Number of patients	Number of females	Age Mean or median	Duration of symptoms, months mean (SD)	Baseline Eckardt score, mean (SD)	Chicago classification I/II/III	Duration of disease (months)	Inclusion criteria	Exclusion criteria
Shrigiriwar *et al* 2022 [14]	Retrospective	USA, India	6	1	50±4.8	28 (11.4	8.8 (1.1)	0/6/0	28 (11.4)	Patients with symptomatic and manometrically confirmed achalasia were included.	Body mass index (BMI) ≥30, prior esophageal or gastric surgery, prior achalasia treatment including HM, POEM or pneumatic balloon dilation, large hiatal hernias (axial length>2 cm or Hill grade>2) and sigmoid achalasia
Inoue *et al* 2020 [7]	Retrospective	Japan	21	11	45.4 (14.0)	86.4 (88.8)	5.7 (1.8)	13/15/1	7.2 (7.4)	Patients scheduled to undergo POEM for achalasia were offered POEM+F. Achalasia was diagnosed based on clinical symptoms and high-resolution manometry using the Chicago 3.0 classification	Patients with significant cardiac comorbidities or gastric surgery
Patil *et al* 2020 [9]	Retrospective	India	20	6	32 (25-41)	25.2 (18-44.4)	7.2 (1.2)	2/18	25.2 (18-44.4)	Patients with a definite diagnosis of achalasia scheduled to undergo POEM were offered POEM+F	Past history of upper gastrointestinal surgery, failed POEM with an anterior approach, sigmoid esophagus, and ASA physical status>II
Tyberg *et al* 2022 [10]	Retrospective	USA, India	43	21	42.8 (13.9)	NA	NA	2/37/4	NA	NA	NA

NA, not available; POEM+F, peroral endoscopic myotomy plus fundoplication

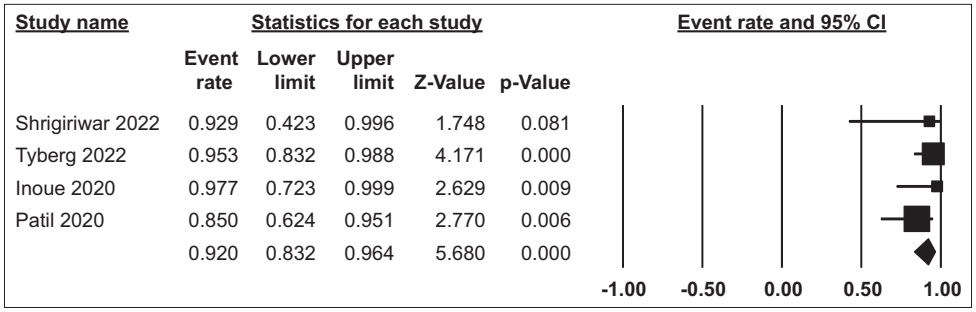

Figure 2 Technical success of peroral endoscopic myotomy with fundoplication
CI, confidence interval

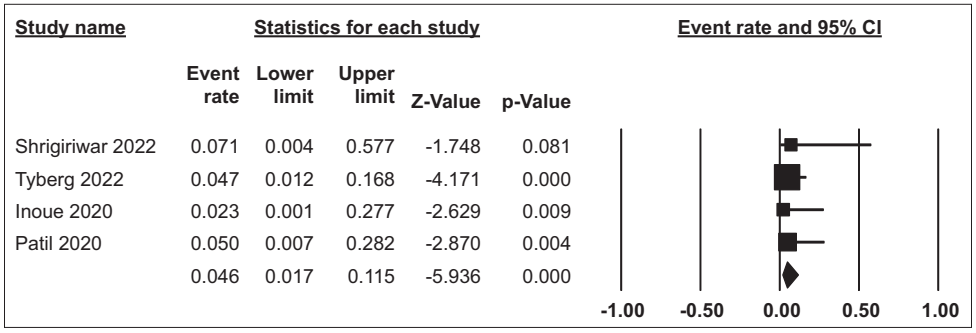

Figure 3 Adverse events of peroral endoscopic myotomy with fundoplication
CI, confidence interval

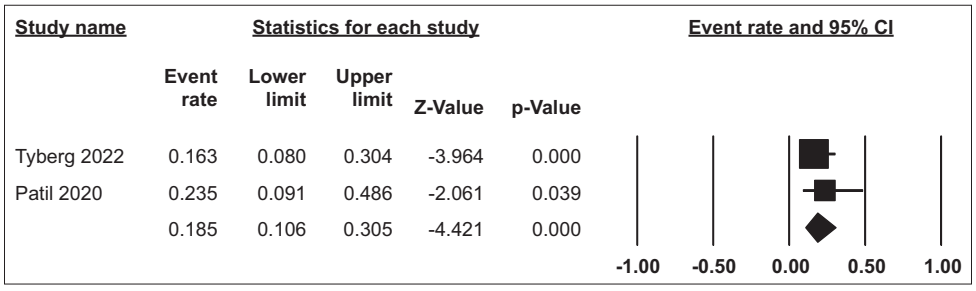

Figure 4 Esophagitis on upper endoscopy after peroral endoscopic myotomy with fundoplication
CI, confidence interval

Procedure time

Three studies with 47 patients reported data on procedure time and fundoplication time. The pooled mean procedure time (in min) was 113.2, 95%CI 98.7-127.6; I^2=91% (Supplementary Fig. 1). The pooled mean fundoplication time was 55.3, 95%CI 43.7-66.8; I^2=91% (Supplementary Fig. 2).

Discussion

This meta-analysis found that POEM+F is a feasible and safe option in patients with achalasia. POEM is the preferred treatment for achalasia at many centers, given its proven advantages over HM and PD. One meta-analysis comparing POEM with HM showed that the short-term efficacy of POEM was superior to that of HM [15]. However erosive esophagitis was more common in the POEM group compared to HM [15]. In a recent network meta-analysis comparing POEM, HM and PD, POEM was ranked first in terms of treatment efficacy, followed by HM [16].

One of the major drawbacks of POEM is the greater risk of GERD and erosive esophagitis after the procedure. One meta-analysis comparing POEM and HM found that the risk of esophagitis after HM was lower compared to POEM [15]. The lower rate of GERD and esophagitis after HM is reasonable, because it is often accompanied by partial or complete fundoplication. The traditional POEM procedure is not accompanied by fundoplication. We found that the rate (95%CI) of esophagitis after POEM+F was 18% (11-30%), somewhat lower compared to the reported rate of esophagitis after traditional POEM without fundoplication [15]. There were a total of 11 cases of esophagitis: 8 patients had Los

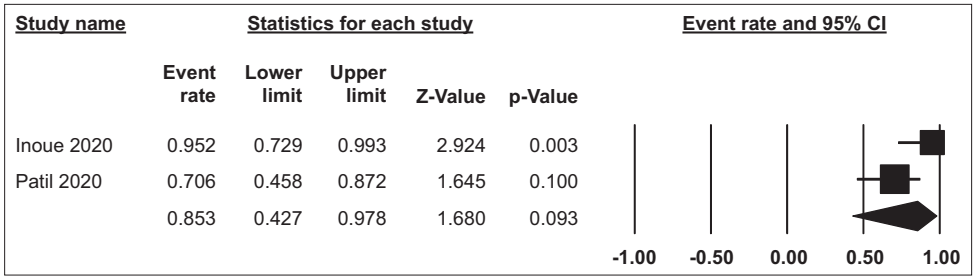

Figure 5 Wrap integrity on upper endoscopy after peroral endoscopic myotomy with fundoplication
CI, confidence interval

Angeles class A esophagitis, 2 patients had class B, and 1 patient had class C esophagitis. There were no cases of class D esophagitis.

We found that the pooled rate (95%CI) of wrap integrity on follow-up upper endoscopy was 85% (95%CI 43-98%). The rates of wrap integrity varied across the studies. In the study by Inoue *et al,* 95% of the patients were found to have intact wrap on follow-up endoscopy [7]. However, in the study by Patil *et al*, 59% of the patients had intact wrap on endoscopy 3 months after the procedure [9]. Wrap integrity is a crucial factor in the prevention of post-POEM GERD. The patients who were found to have loose wrap after the procedure developed GERD.

We found that the rate (95%CI) of technical success of POEM+F was 92% (83-96%). The procedure could not be completed in 5/90 patients, 3 in the study by Patil *et al* [9] and 2 in the study by Tyberg *et al* [10]. In the study by Patil *et al* [9], fundoplication was not successful in 3 patients: the peritoneal cavity could not be entered because of difficulty in localization, despite adequate dissection post myotomy.

An important question is: are the outcomes of POEM+F acceptable in the context of achalasia treatment? We found that POEM+F was not associated with a substantial increase in the risk of adverse events. In our meta-analysis, the pooled rate of adverse events of POEM+F was 5% (95%CI 2-11%). A previous meta-analysis [17], comparing POEM and PD, found that the pooled rates of adverse events of POEM were as follows: mucosal injury (4.5%), perforation (0.3%), significant bleeding (0.4%), subcutaneous emphysema (6.5%), pneumothorax (1.4%), and pneumomediastinum (1.8%). The overall technical success rate of POEM+F does seem to be slightly lower than the reported technical success rate of POEM alone. The rate of technical success of POEM+F was 92% (95%CI 83-96%) in our meta-analysis. A previous meta-analysis reported that the technical success rate of POEM was 97% [17]. Finally, we found that the rate of esophagitis after POEM+F was lower than the reported rates of esophagitis after POEM alone. In our meta-analysis, the rate of esophagitis after POEM+F was 18% (95%CI 11-30%). A previous meta-analysis [6] found that the rate of esophagitis after POEM alone was 29.4% (95%CI 18.5-43.3%). In light of these findings, we feel that the observed outcomes of POEM+F are acceptable in the context of achalasia treatment.

This is the first meta-analysis to evaluate the feasibility and safety of POEM+F. There was low heterogeneity in most of the analyses, apart from the analyses of wrap integrity and fundoplication time. However, this meta-analysis had several limitations. Only 4 studies with 90 patients met the inclusion criteria and the overall sample size of this meta-analysis was too small to allow firm conclusions. The small sample size may limit the generalizability of these findings. All the studies included were observational in nature, and were thus at risk of measured and unmeasured confounding [18]. The definitions of outcomes were not uniformly provided across the studies. There was substantial heterogeneity in the analysis of wrap integrity, and considerable heterogeneity in the analysis of procedure time and fundoplication time. As noted above, the rates of wrap integrity on follow-up endoscopy varied across studies, which may have contributed to heterogeneity. Differences in the number of operators, skills, experience and level of expertise may also have contributed to this heterogeneity. Slight variations in POEM+F technique could have contributed to heterogeneity and variations in rates of wrap integrity on follow-up endoscopy. All the studies included in this meta-analysis used endoloop and clips. However, in the study by Inoue *et al* [7], multiple simulations were carried out by grasping and pulling the anterior gastric wall towards the gastroesophageal junction at different sites in order to identify the ideal distal anchoring site on the gastric wall that would correspond to the starting point of the fundoplication. The site that created the most prominent identifiable wrap with closure of the gastroesophageal junction hiatus, as seen from the retroflexed scope, was selected for placement of the distal anchor with clip. Inoue *et al* [7] did not use the endoscopic hand suturing technique in the study that was included in our meta-analysis. However, they later refined this technique, using endoscopic hand-suturing instead of endoloop and clips in a published case report [19]. In view of the significant heterogeneity, the results for wrap integrity, procedure time and fundoplication times should be interpreted carefully. Future large-scale studies with a standardized fundoplication technique will be required before firm conclusions can be drawn.

Despite these limitations, this meta-analysis demonstrates the feasibility and safety of POEM+F in patients with achalasia and supports its use as a potential minimally invasive alternative to laparoscopic HM plus fundoplication. More studies with long-term follow-up are required to further validate these findings.

Summary Box

What is already known:

- Peroral endoscopic myotomy (POEM) has shown promising results in the management of achalasia and has become first line treatment at many centers.
- One side effect of POEM is iatrogenic gastroesophageal reflux disease (GERD)
- POEM with fundoplication (POEM+F) can potentially lower the risk of post-POEM GERD

What the new findings are:

- POEM with fundoplication (POEM+F) is associated with high rate of technical success and low rate of post-POEM esophagitis.
- POEM+F is a feasible and safe option in patients with achalasia

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Supplementary material

Supplementary Table 1 Full search strategies (all searched performed 28 July 2022)

Embase (Embase.com, Elsevier)

No.	Query	Results
#1	'peroral endoscopic myotomy'/exp OR 'per oral endoscopic myotom*' OR 'peroral endoscopic myotom*' OR 'poem' OR 'poem+f' OR 'poemf' OR ((peroral OR oral OR esophag* OR pharyng* OR transpharyng*) AND ('natural orifice endoscopic surgery' OR 'natural orifice transluminal endoscopic surgery'/exp OR 'natural orifice transluminal endoscopic surgery'))	5142
#2	'stomach fundoplication'/exp OR 'transoral incisionless fundoplication'/exp OR 'fundal plication*' OR 'fundic wrap*' OR 'fundo plication*' OR fundoplicat* OR 'stomach fundus plication' OR 'poem+f' OR 'poemf'	13704
#3	#1 AND #2	385
#4	'esophagus achalasia'/exp OR achalasia* OR cardiospasm* OR cardiospasmus* OR megaesophagus	15702
#5	#3 AND #4	330
#6	#5 NOT ([animals]/lim NOT [humans]/lim)	323
#7	#6 NOT ('conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it OR 'tombstone'/it OR 'case report'/de OR 'meta analysis'/de OR 'meta analysis topic'/de OR 'systematic review'/de OR 'systematic review topic'/de)	202
#8	same OR 'single session' OR tandem OR simultane* OR concomitant OR plus OR 'endoscopic myotomy with fundoplic*' OR 'poem with fundoplicat*' OR 'poem+f' OR 'poemf'	3470442
#9	#7 AND #8	42

MEDLINE (PubMed, National Center for Biotechnology Information, National Library of Medicine)

No.	Query	Results
1	(Per-oral-endoscopic-myotom* OR Peroral-endoscopic-myotom* OR "POEM" OR "POEM+F" OR "POEMF" OR ((Peroral OR Oral OR esophag* OR pharyng* OR transpharyng*) AND (Natural-Orifice-Endoscopic-Surgery OR natural-orifice-transluminal-endoscopic-surgery OR "Natural Orifice Endoscopic Surgery"[Mesh: NoExp])))	3,142
2	"Fundoplication"[Mesh] OR fundal-plication* OR fundic-wrap* OR fundo-plication* OR fundoplicat* OR stomach-fundus-plication OR "POEM+F" OR "POEMF"	7,693
3	#1 AND #2	153
4	"Esophageal Achalasia"[Mesh] OR achalasia* OR cardiospasm* OR cardiospasmus* OR Megaesophagus	9,773
5	#3 AND #4	121
7	#5 NOT ("animals"[mesh] NOT "humans"[mesh]) NOT ("case reports"[Publication Type] OR "comment"[Publication Type] OR "editorial"[Publication Type] OR "guideline"[Publication Type] OR "introductory journal article"[Publication Type] OR "meta analysis"[Publication Type] OR "news"[Publication Type] OR "retracted publication"[Publication Type] OR "review"[Publication Type] OR "systematic review"[Publication Type])	59

Cochrane Central Register of Controlled Trials (CochraneLibrary.com platform, Wiley, Issue 7 of 12, July 2022)

ID	Search	Hits
#1	(Per-oral-endoscopic-myotom* OR Peroral-endoscopic-myotom* OR "POEM" OR "POEM+F" OR "POEMF" OR ((Peroral OR Oral OR esophag* OR pharyng* OR transpharyng*) AND (Natural-Orifice-Endoscopic-Surgery OR natural-orifice-transluminal-endoscopic-surgery OR [mh ^"Natural Orifice Endoscopic Surgery"])))	684
#2	[mh "Fundoplication"] OR fundal-plication* OR fundic-wrap* OR fundo-plication* OR fundoplicat* OR stomach-fundus-plication OR "POEM+F" OR "POEMF"	763
#3	#1 AND #2	13
#4	[mh "Esophageal Achalasia"] OR achalasia* OR cardiospasm* OR cardiospasmus* OR Megaesophagus	438
#5	#3 AND #4	12

(Contd...)

Supplementary Table 1 *(Continued)*

Cochrane Central Register of Controlled Trials (CochraneLibrary.com platform, Wiley, Issue 7 of 12, July 2022)

ID	Search	Hits
#6	same OR "single session" OR tandem OR simultane* OR concomitant OR plus OR "endoscopic myotomy with fundoplication" OR "poem with fundoplication" OR "poem+f" OR "poemf"	259167
#7	#5 AND #6	4
	Trials matching "#7 - #5 AND #6"	3

Web of Science Core Collection (Web of Science Platform, Clarivate, Editions=Arts & Humanities Citation Index, Emerging Sources Citation Index [previous 5 years], Conference Proceedings Citation Index, Science Citation Index-EXPANDED, and Social Science Citation Index)

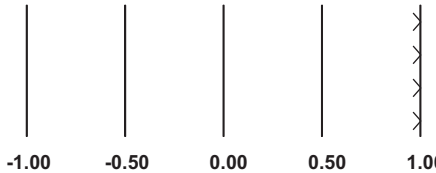
(Per-oral-endoscopic-myotom* OR Peroral-endoscopic-myotom* OR "POEM" OR "POEM+F" OR "POEMF" OR ((Peroral OR Oral OR esophag* OR pharyng* OR transpharyng*) AND (Natural-Orifice-Endoscopic-Surgery OR natural-orifice-transluminal-endoscopic-surgery))) (Topic) AND fundal-plication* OR fundic-wrap* OR fundo-plication* OR fundoplicat* OR stomach-fundus-plication OR "POEM+F" OR "POEMF" (Topic) AND achalasia* OR cardiospasm* OR cardiospasmus* OR Megaesophagus (Topic) AND same-session OR "single session" OR tandem OR simultane* OR plus OR concomitant OR "endoscopic myotomy with fundoplication" OR "poem with fundoplication" OR "poem f" OR "poemf" (Topic) AND Review Article or Editorial Material or Case Report (Exclude – Document Types) and Web of Science Core Collection (Database)	20

Supplementary Table 2 Methodological Index for Non-Randomized Studies (MINORS) Score for Methodological Quality Assessment of Included Studies

Author [ref.]	Clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoints appropriate to the aim of the study	Unbiased assessment of the study endpoint	Follow-up period appropriate to the aim of the study	Loss to follow up less than 5%	Prospective calculation of the study size	An adequate control group	Contemporary groups	Baseline equivalence of groups	Adequate statistical analyses	Total Score
Shrigiriwar *et al* [14]	2	2	2	2	0	2	2	0	N/A	N/A	N/A	2	14
Inoue *et al* [7]	2	2	2	1	0	1	2	0	N/A	N/A	N/A	N/A	10
Patil *et al* [9]	2	2	2	1	0	1	2	0	N/A	N/A	N/A	N/A	10
Tyberg *et al* [10]	2	2	2	2	0	2	2	0	1	2	1	2	18

N/A, not available

Study name	Mean	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Shrigiriwar 2022	101.000	2.205	4.860	96.679	105.321	45.815	0.000
Inoue 2020	119.000	4.408	19.430	110.360	127.640	26.996	0.000
Patil 2020	121.000	4.808	23.113	111.577	130.423	25.169	0.000
	113.221	7.365	54.249	98.785	127.657	15.372	0.000



Supplementary Figure 1 Mean procedure time for peroral endoscopic myotomy with fundoplication
CI, confidence interval

Study name	Mean	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Shrigiriwar 2022	48.400	2.082	4.335	44.319	52.481	23.246	0.000
Inoue 2020	51.300	4.037	16.298	43.388	59.212	12.707	0.000
Patil 2020	66.400	3.175	10.082	60.177	72.623	20.912	0.000
	55.308	5.898	34.789	43.747	66.868	9.377	0.000

Supplementary Figure 2 Fundoplication time
CI, confidence interval