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It is correct. However, I think it will be better to highlight (in Bold) the subtitles such as:

Full-thickness versus circular myotomy
Anterior versus posterior myotomy
Long versus short myotomy
Naïve versus PTF
HM verus Non-HM
Type I versus Type II
Type I versus Type III
Type II versus Type III
Age (≥ 60 years versus < 60 years)

5. Please provide disclosure (conflict of interest) statement.

Raquel Cristina Lins Mota, MD: none

Eduardo Guimarães Hourneaux de Moura, MD, MSc, PhD: Consultant for Boston Scientific and Olympus

Diogo T. H. de Moura, MD, MSc, PhD: none

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Vitor O. Brunaldi, MD: none

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6. AUTHOR: Reference numbers have been reordered to appear sequentially. Please check and confirm this was done correctly.

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Can you please delete references 56 and 57 from the main text (conclusion section) and from the reference list. Thank you.

Risk factors for gastroesophageal reflux after POEM for achalasia: a systematic review and meta-analysis

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Abstract

Introduction

Peroral endoscopic myotomy (POEM) demonstrated similar efficacy to surgical myotomy in the management of achalasia. However, gastroesophageal reflux disease (GERD) is common after POEM. The aim of this study is to identify factors associated with GERD after POEM.

Method

After searching electronic databases, randomized trials and observational studies including patients with achalasia or other spastic esophageal disorders, treated by POEM, and providing GERD data were selected. GERD was evaluated by 3 methods: pH monitoring, endoscopic findings, and symptoms. For each method, an analysis was performed comparing the outcomes related to the following independent variables: full-thickness (FT) vs circular myotomy, anterior vs posterior, long myotomy vs short myotomy, naive vs previous treatment failure, previous Heller myotomy (HM) vs non-previous-HM, Type I vs II, Type I vs III, and Type II vs III.

Results

2869 publications were identified, and 25 studies met criteria for inclusion in

the qualitative analysis. Of these, 18 were included in the meta-analysis. According to the endoscopic findings, circular and anterior myotomy demonstrated a lower trend of GERD with borderline significance ($p = 0.06$; $p = 0.07$, respectively). In the pH monitoring and symptom analyses, circular myotomy, anterior myotomy, treatment naive, and non-HM patients were associated with a lower occurrence of GERD; however, no statistically significant difference was found. When comparing achalasia subtypes, no statistical difference was found in all analyses.

Conclusion

This systematic review and meta-analysis suggest that a circular anterior approach may limit post-POEM GERD and should be considered in appropriate patients.

AQ1

Keywords

Achalasia
Endoscopy
Surgery
GERD
Myotomy
POEM

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00464-020-07412-y) contains supplementary material, which is available to authorized users.

Achalasia is a rare primary esophageal motility disorder, characterized by incomplete relaxation of the lower esophageal sphincter (LES) and aperistalsis of the esophageal body [1, 2]. These changes are attributed to degeneration of the myenteric plexus, resulting in dysfunctional esophageal motility and subsequent esophageal stasis. Achalasia may be infectious, autoimmune, drug-induced, or most frequently idiopathic [2]. The main manifestations of this disease include dysphagia, regurgitation, chest pain, and weight loss and it poses risk of aspiration pneumonia and esophageal squamous cell carcinoma in the long-term [3, 4]. The diagnosis is based on high-resolution manometry

(HRM), which subdivides achalasia into 3 types, and barium esophagram which often shows a classic bird's beak sign [5]. Treatment is not curative, and consists of techniques that decrease the LES pressure, either by endoscopic, pharmacological, or surgical approaches [3, 6].

AQ2

In 2010, Inoue et al. [7] demonstrated satisfactory results of a new endoscopic technique called Peroral Endoscopic Myotomy (POEM). POEM is a minimally invasive and safe technique to reduce LES pressure, with success rates approaching 90% [6, 8]. It involves endoscopic creation of a submucosal tunnel, with subsequent myotomy of the distal esophagus, which is extended a few centimeters below the esophageal-gastric junction (EGJ) into the gastric wall [5, 9]

POEM is a therapeutic modality that provides efficacy and improvement in quality of life similar to surgical myotomy [8, 10, 11]. For this reason, POEM has quickly gained acceptance, even without long-term follow-up and randomized trials comparing to other techniques. Unfortunately, decreasing LES pressure leads not only to symptom relief but may be associated with an increase in lower esophageal acid exposure and possibly symptomatic gastroesophageal reflux disease (GERD) [1]. This problem may be related to the performance of myotomy of the LES with no concomitant antireflux procedure.

AQ3

Since the introduction of POEM into clinical practice, there have been several procedural modifications in an attempt to make the procedure safer, more effective, and reproducible. These modifications include myotomy approach (full-thickness when all muscle layers are cut; partial-thickness when only the circular layer is cut), location of the tunneling (anterior wall between 1 and 2 o'clock position; posterior wall between 5 and 6 o'clock position), and length of myotomy (long if ≥ 7 cm; or short if < 7 cm). These approaches typically vary according to operator experience and preference; however, patient characteristics can occasionally impact these technical aspects. Although these refinements have technically facilitated the procedure, their impact on adverse events, especially GERD, are unknown or controversial. In fact, based on objective observations, the occurrence of GERD after POEM ranges from 10 to 57% and appears to be the major limitation of the procedure [12, 13, 14, 15]. Therefore, the aim of this systematic review and meta-analysis is to identify

risk factor for GERD after POEM, with regard to procedure technique, patient characteristics, and achalasia subtype.

Methods

Protocol and registration

This systematic review and meta-analysis was performed according to the Preferred Items for Systematic Review and Meta-Analysis (PRISMA) [16] and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group [17] recommendations**.** The study was also registered at the International Prospective Register of Systematic Reviews (PROSPERO) database [18] (number CRD 42019117733). Additionally, this study was approved by the Ethics Research Committee of Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo.

Eligibility criteria

Observational studies and clinical trials with patients > 18 years old, providing information on the occurrence of post-POEM GERD, were searched, without language restriction. If the same author submitted more than one study related to the topic, the most recent publication with the largest population would be included in the analysis, and the other rejected to avoid duplicate data. Animal studies and studies with incomplete data were excluded. Patients diagnosed with achalasia as defined by Chicago Classification [19] treated by POEM with or without previous treatments were included.

The primary outcomes were incidence of GERD assessed objectively on pH monitoring, esophagogastroduodenoscopy (EGD), and based on symptoms. All variables related to the POEM technique, including length of myotomy (long versus short), thickness of myotomy (full-thickness versus circular), and orientation of myotomy (anterior versus posterior), were evaluated. Variables related to patient characteristics such as age, ethnicity, body mass index (BMI), presence of comorbidities, previous treatments failure (PTF) [(naive versus PTF)], and previous surgical myotomy failure (HM versus Non-HM) were also analyzed. Additionally, achalasia subtypes (Type I versus Type II, Type I versus Type III, and Type II versus Type III). An additional analysis was also performed to evaluate whether there is a difference in the frequency of GERD after POEM between Asian and Western populations.

Information sources

The electronic databases searched were MEDLINE, Embase, LILACS, and Cochrane Library. Moreover, gray literature was assessed in references from the articles, book chapters, and theses. Last search was performed in February 2019. The search strategy was *"(cardiospasm OR achalasia OR megaesophagus) AND (POEM OR peroral myotomy OR endoscopic myotomy OR peroral myotomy OR endoscopy myotomy)*."

Selection of studies

The articles were initially selected after an assessment of the titles and abstracts in order to evaluate the relevance of the full text. This process was carried out by three independent reviewers. Disagreements between the reviewers were resolved after a discussion and consensus with the participation of the leading authors. To summarize the study selection processes, an adapted PRISMA flow diagram was used.

Data collection process

The following information was obtained from each study: authors, year of publication, country, study design, demographic data, body mass index (BMI), details of POEM technique, disease classification, previous therapies, pre and post Eckardt score, method of identification and criteria for GERD, preoperative EGD and pH monitoring, follow-up duration, and time of postoperative GERD evaluation. In studies with incomplete data, authors were contacted by email to obtain additional information. Collected data included (a) variables related to the surgical technique including full-thickness versus circular myotomy, anterior versus posterior myotomy, and long versus short myotomy; (b) patients characteristics such as naïve versus PTF, HM prior to POEM versus Non-HM prior to POEM, age (< 60 and ≥ 60 years old), and achalasia subtypes. The data regarding relative frequency of GERD was obtained separately for each comparison group by three criteria: (a) presence of symptomatic reflux, as specified by a validated scoring system (GERD questionnaire (GerdQ) [20] or Frequency Scale For the Symptoms (FSSG)) [21]; (b) presence of reflux esophagitis on EGD according to the Los Angeles Classification [22] (LA); (c) esophageal acid exposure defined as over 5% of total time with esophageal pH < 4 on 24 h esophageal pH monitoring and/or DeMeester score > 14.72 over the 24-h period.

Risk of bias

We identified and evaluated the risk of bias for all studies according to the New Castle-Ottawa Quality Assessment Scale [23] criteria, which assesses selection, comparability of cohorts based on the design, analysis and outcomes. We considered a study scoring ≥ 7 as a high-quality study. The quality of evidence was analyzed according to the Grading of Recommendations Assessment, Development and Evaluation Working Group (GRADE) methodology [24]. Evidence for all comparisons performed between potential predictors and outcome (GERD after POEM) measured by the three different methods were analyzed individually.

Summary measures and synthesis of results

Dichotomous variables were analyzed by computing risk difference (RD) and Mantel–Haenszel Test. The random effect model was preferred. We used a 95% confidence interval and heterogeneity was calculated using the method of Higgins (I^2). If heterogeneity > 50% was detected, the Egger Test [25] was then used to identify publication bias and outlier studies, which were then removed to adjust heterogeneity to < 50%. The relationship between sample size and effect for each outcome was graphically analyzed using a forest plot. Funnel plots were used to assess risk of publication bias or inconsistency between the study outcomes. The analysis was performed using the software RevMan 5 (Review Manager Version 5.3.5, Cochrane Collaboration, London, UK) [26]. Quantitative analyses were only performed using RevMan 5 software for comparisons in which 3 or more studies could be included.

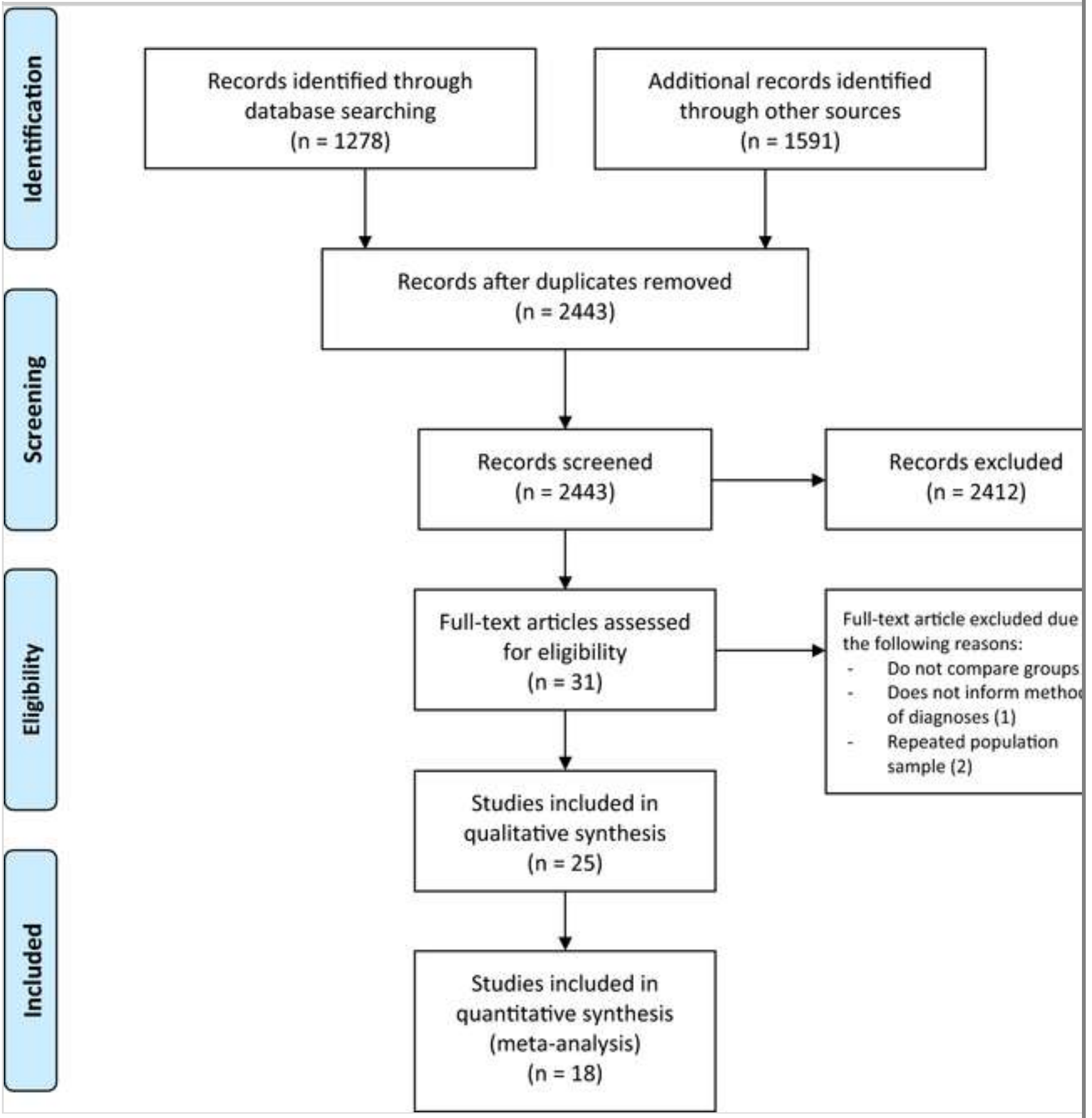
Results

Study selection

In the initial search, 2869 studies were screened and assessed for eligibility by evaluating titles and abstracts. Of these, 426 duplicated studies were removed, and 2443 titles and abstracts were analyzed. Finally, 31 studies were judged as potentially relevant and were analyzed in full text. After applying eligibility criteria, 25 studies were included in the systematic review. Of these, 18 were included in the quantitative analysis. This process is summarized in Fig. 1.

Fig. 1

PRISMA flow diagram



Studies characteristics

Of the 25 studies included in the systematic review, 5 were randomized clinical trials (RCT) [3, 27, 28, 29, 30], 1 case–control [30], and 19 were cohort studies [1, 5, 6, 9, 10, 12, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43]. Seventeen of these studies were from Asia. Five cohort studies were excluded from the meta-analysis. Of these, 3 [33, 34, 35] did not report GERD data categorized by potential predictors, one [36] was the only study to report age as a potential predictor (not allowing comparison) and one did not provide data on GERD frequency diagnosed by objective methods [4]. The studies of *Nabi Z, 2018* and

Ramchandani M, 2018 are from the same cohort and those from *Kumbhari V. 2017* and *Ngamruengphong, S, 2017* have some overlap. Because of this we excluded one of each pair of reports from the quantitative analysis.

The 25 studies were heterogeneous in their design and used different diagnostic criteria for GERD. However, most of the studies measured GERD by more than one diagnostic method. The time at which post-POEM evaluation of GERD occurred varied from 1 to 36 months and few studies reported preprocedural EGD results regarding reflux esophagitis. Some considered the presence of esophagitis pre-POEM an exclusion criterion, but no studies reported pH monitoring before POEM. Any grade of Los Angeles Classification [22] was considered as diagnostic of GERD upon EGD in all studies. The time of evaluation for each diagnostic method also varied within studies. We obtained data on the frequency of GERD ranging from 3 to 12 months after POEM. Most patients with a previous history of HM underwent POEM with a posterior and full-thickness myotomy technique. The main criteria used to diagnose GERD were the same in all studies. The characteristics of the included studies are summarized in Table 1.

Table 1

Characteristics of the studies included

Study	Country	Design	*N*	Comparison	Criteria of GERD
Khashab MA, 2018	USA	RCT	150	Anterior vs posterior	pH monitoring
Nabi Z, 2018	India	Retrospective cohort	502	Naive vs PTF	pH monitoring, EGD, symptoms
Tan Y, 2018	China	RCT	63	Anterior vs posterior	pH monitoring, EGD, symptoms
Ramchandani M, 2018	India	RCT	60	Anterior vs posterior	pH monitoring, EGD
Zhang X, 2018	USA	Retrospective cohort	318	HM vs non-HM	pH monitoring, EGD, symptoms
Zu QL, 2018	China	Retrospective cohort	849	Naive vs PTF	EGD, symptoms

Kumbhari V, 2017	USA	Case–control	282	Anterior vs posterior/ full-thickness vs circular/ naive vs PTF	pH monitoring
Ngamruengphong S, 2017	USA	Retrospective cohort	180	HM vs non-HM	EGD, symptoms
Li C, 2017	China	Retrospective cohort	33	Full-thickness vs circular	EGD, symptoms
Kristensen HΦ, 2017	Denmark	Retrospective cohort	66	HM vs non-HM	Symptoms
Mondragón OVH, 2017	Mexico	Cohort	66	Chicago classification	pH monitoring,
Duan T, 2017	China	Retrospective cohort	123	Full-thickness vs circular	pH monitoring, EGD, symptoms
Gao Q, 2017	China	RCT	100	Long vs short myotomy	Non-specified
Aslan F, 2017	Turkey	Retrospective cohort	225	Anterior vs posterior	EGD
Tang X, 2017	China	Retrospective cohort	113	≥ 60 yo vs < 60 yo	EGD
Wang XH, 2016	China	Retrospective cohort	56	Full-thickness vs circular	pH monitoring, EGD, symptoms
Shiwaku H, 2016	Japan	Retrospective cohort	152	Anterior vs posterior	pH monitoring, EGD, symptoms
Familiari P, 2016	Italy	Retrospective cohort	103	Chicago classification/ HM vs non-HM	pH monitoring, EGD, symptoms
Gong W, 2016	China	Retrospective cohort	97	Long vs short myotomy	Non-specified
Familiari P, 2016	Italy	RCT	73	Long vs short myotomy	Non-specified
Wang J, 2015	China	Prospective cohort	46	Full-thickness vs circular	pH monitoring
		Prospective			pH

Tang X, 2015	China	cohort	77	Naive vs PTF	monitoring
Tang X, 2015	China	Prospective cohort	68	Chicago classification	pH monitoring
Zhou PH, 2013	China	Prospective cohort	12	HM	EGD, symptoms
Q L Li, 2013	China	Prospective cohort	234	Full-thickness vs circular	EGD, symptoms

NA not available, *RCT* randomized controlled trial, *vs* versus, *m* months, *yo* years ol
esophagogastroduodenoscopy, *PTF* previous treatment failure, *N* total number of stu
participants

[a]The time to evaluate GERD ranged from 3 to 12 months among the 3 diagnostic me
within the same study

Risk of bias within and across studies

The majority of studies analyzed were observational. There were 5 randomized controlled trials (RCT) and 1 case control study. To aggregate all these studies under the same analysis strategy, we opted to consider them all observational. For the RCTs and case control study, we collected data on prognostic factors from the intervention group only. According to the Newcastle-Ottawa Quality Assessment Scale criteria, 2 out of the 24 studies scored < 7 (Table 2). The certainty of the results was low for all assessments. Full-tables and figures with this analysis are included in the supplementary data (Tables 1 to 8 in the supplementary data).

Table 2

Newcastle-Ottawa Quality Assessment Scale results according to the study design

Cohort studies				
Study	**Selection**			
	Representativeness of the exposed cohort Total: 1	**Selection of the non-exposed cohort Total: 1**	**Ascertainment of exposure Total: 1**	
Kashab MA, 2018	1	1	1	

Nabi Z, 2018	1	1	1	
Tan Y, 2018	1	1	1	
Ramchandani M, 2018	1	1	1	
Zhang X, 2018	1	1	1	
Zu QL, 2018	1	1	1	
Ngamruengphong S, 2017	1	1	1	
Li C, 2017	1	1	1	
Kristensen HØ, 2017	1	1	1	
Mondragón OVH 2017	1	1	1	
Duan T, 2017	1	1	1	
Gao Q, 2017	1	1	1	
Aslan F, 2017	1	1	1	
Tang X, 2017	1	1	1	
Wang XH, 2016	1	1	1	
Shiwaku H, 2016	1	1	1	
Familiari P, 2016	1	0	1	
Gong W, 2016	1	1	1	
Familiari P, 2016	1	1	1	
Wang, J, 2015	1	1	1	
Tang X, 2015	1	1	1	
Tang X, 2015	1	1	1	
Zhou PH, 2013	1	1	1	
Q L Li, 2013	1	1	1	

Case–control study

STUDY	**Is the case definition adequate? Total: 1**	**Representativeness of the cases Total: 1**	**Selection of Controls Total: 1**	

Kumbhari V, 2017	1	1	1	

Meta-analysis results

Table 3 summarizes the results of this meta-analysis.

Table 3

Summary of meta-analysis results

Comparison	Risk difference	*p* value	Favors
Post-POEM GERD risk according to pH monitoring			
Full-thickness versus circular	0.04 (− 0.08, 0.15)	*p = 0.51*	Circular
Anterior versus posterior	− 0.08 (− 0.20, 0.04)	*p = 0.17*	Anterior
Naive versus PTF	−0.00 (− 0.08, 0.08)	*p = 0.98*	Naive
Type I versus Type II	− 0.04 (− 0.15, 0.07)	*p = 0.45*	Type I
Post-POEM GERD risk according to endoscopic findings			
Full-thickness versus circular	0.05 (0.00, 0.10)	*p = 0.06*	Circular
Anterior versus posterior	− 0.09 (− 0.20, 0.01)	*p = 0.07*	Anterior
HM versus non-HM	0.03 (− 0.11, 0.17)	*p = 0.69*	Non-HM
Post-POEM GERD risk according to symptom assessment			
Full-thickness versus circular	0.03 (− 0.03, 0.09)	*p = 0.31*	Circular
HM versus non-HM	0.07 (− 0.13, 0.28)	*p = 0.47*	Non-HM
Post-POEM GERD risk according to non-specific assessment			
Long versus short	− 0.05 (− 0.18, 0.08)	*p = 0.47*	Long

Full-thickness versus circular myotomy

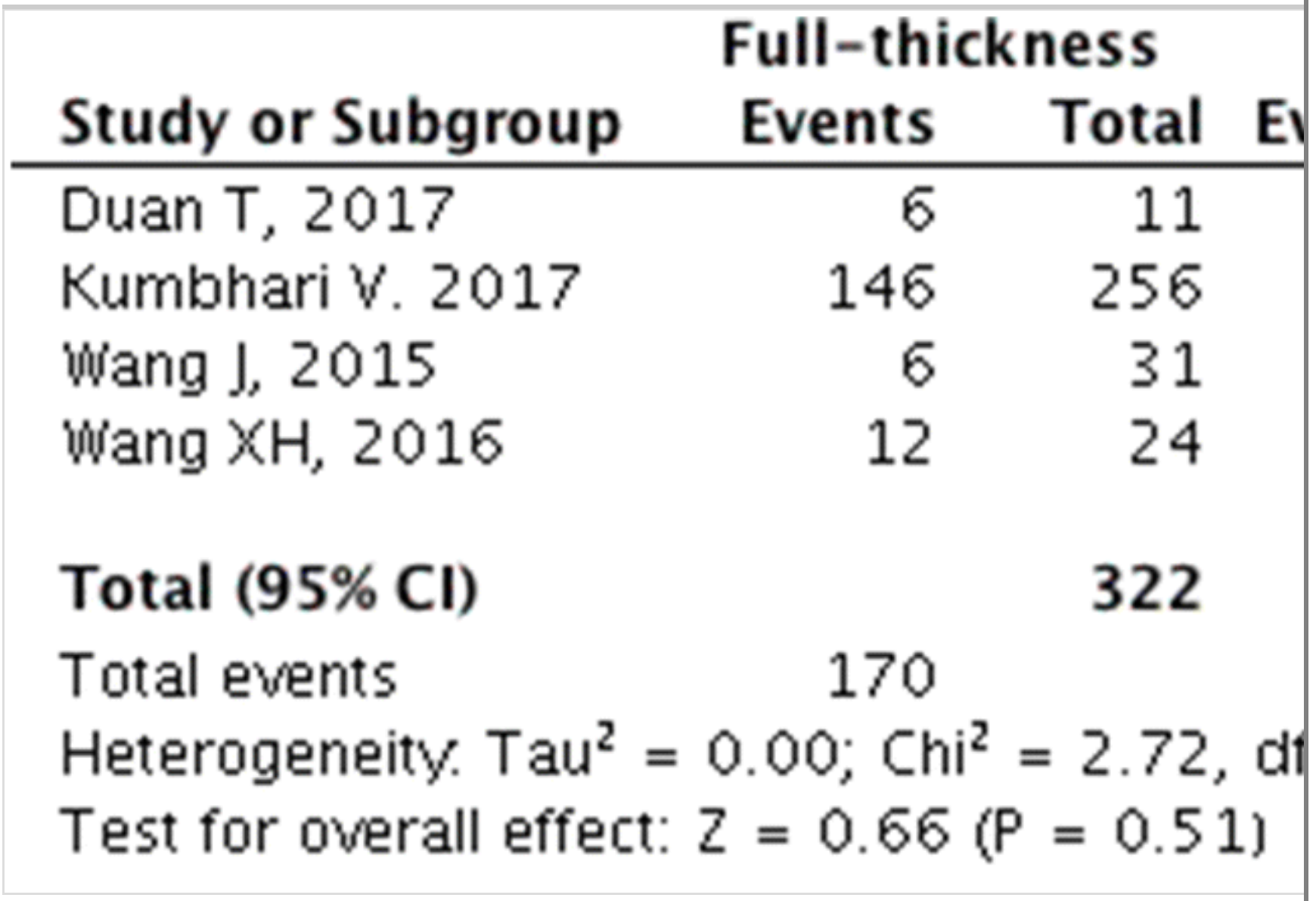
pH monitoring

Four observational studies including 322 subjects in the full-thickness group and 81 subjects in the circular group were included in this analysis [10, 32, 39, 44]. GERD was reported in 170 (53%) patients who underwent full-thickness

POEM versus 35 (43%) in those undergoing circular myotomy. None of the studies individually demonstrated a statistically significant difference between these two techniques. Accordingly, the meta-analysis showed no significant difference (*IC: 0.04 [− 0.08, 0.15]*, $p = 0.51$, $I^2 = 0\%$) (Fig. 2).

Fig. 2

Risk difference of GERD after POEM (measured by pH monitoring) between full-thickness and circular myotomy

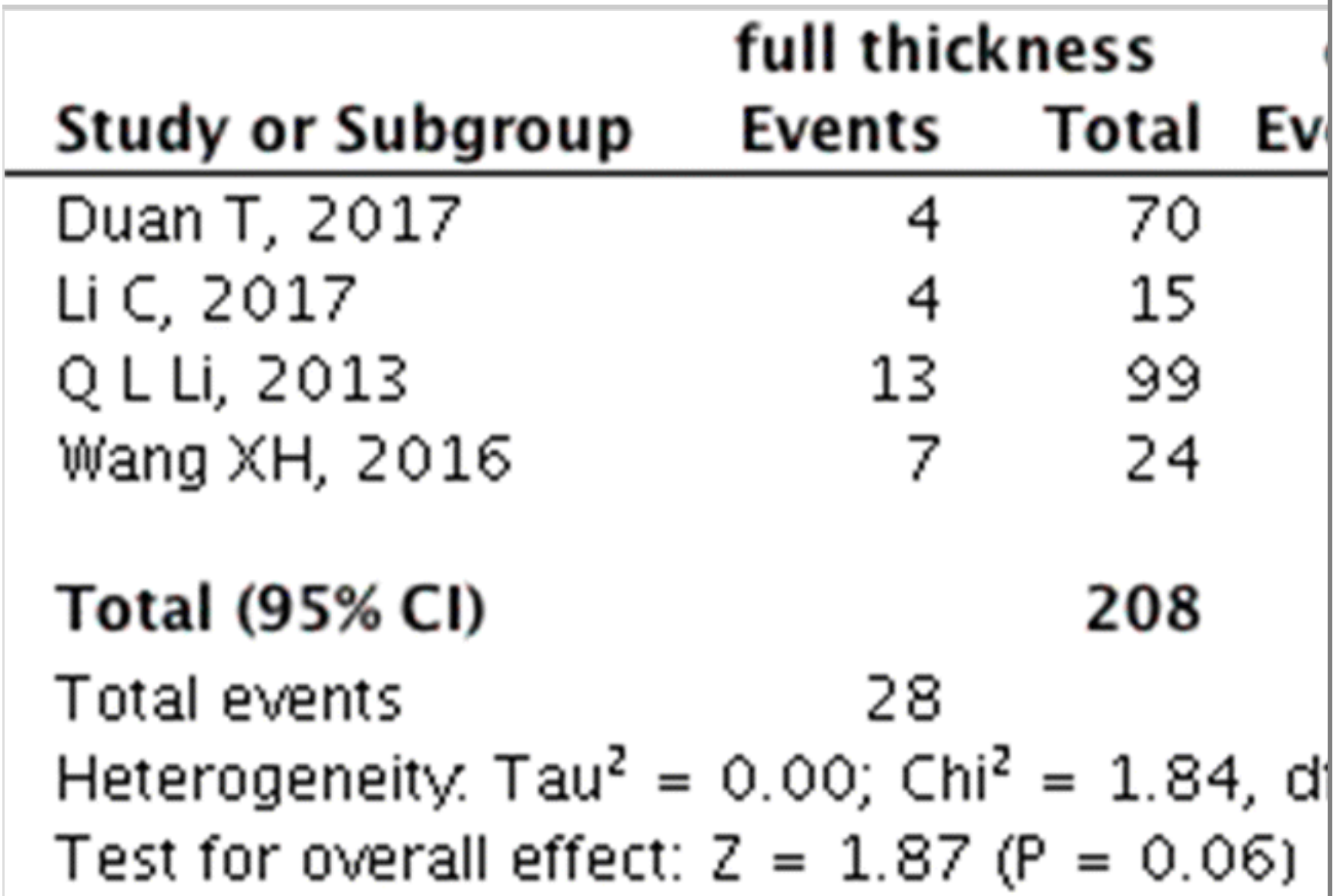


Endoscopic findings

Four observational studies including 208 subjects in the full-thickness group and 218 subjects in the circular group were included in this analysis. GERD was reported in 28 (13%) patients who underwent full-thickness POEM versus 17 (8%) in those undergoing circular myotomy [9, 10, 37, 43]. None of the studies individually demonstrated a statistically significant difference between these two techniques. The meta-analysis indicated a lower rate of GERD in the circular group with borderline significance (*IC: 0.05 [− 0.00, 0.10]*, $p = 0.06$, $I^2 = 0\%$) (Fig. 3).

Fig. 3

Risk difference of GERD after POEM (measured by EGD) between full-thickness and circular myotomy



Symptom assessment

Four observational studies including 212 subjects in the full-thickness group and 220 subjects in the circular group were included in this analysis [9, 10, 37, 43]. GERD was reported in 37 (17%) patients who underwent full-thickness POEM versus 32 (15%) those undergoing circular myotomy. None of the studies individually demonstrated a statistically significant difference between these two techniques. Likewise, the meta-analysis did not show a significant difference between groups (*IC: 0.03 [-0.03, 0.09]*, $p = 0.31$, $I^2 = 0\%$) (Fig. 4).

Fig. 4

Risk difference of GERD after POEM (measured by symptoms assessment) between full-thickness and circular myotomy

Study or Subgroup	full-thickness Events	Total	Ev
Duan T, 2017	4	70	
Li C, 2017	6	19	
Q L Li, 2013	19	99	
Wang XH, 2016	8	24	
Total (95% CI)		**212**	
Total events	37		
Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.97, df			
Test for overall effect: Z = 1.02 (P = 0.31)			

Anterior versus posterior myotomy

pH monitoring

Five studies were included in this analysis [3, 27, 30, 38, 44]. Of these studies, 3 were RCTs [3, 27, 30] and 2 were observational studies [38, 44]. This analysis included 495 subjects in the anterior group and 196 subjects in the posterior group. GERD was reported in 213 (43%) patients who underwent anterior myotomy versus 70 (36%) in those who underwent posterior myotomy. One of these studies demonstrated a statistically significant difference between the outcomes comparing these two techniques [38], favoring the anterior approach. However, the meta-analysis showed no significant difference (*IC: − 0.08 [− 0.20, 0.04]*, $p = 0.17$, $I^2 = 44\%$) (Fig. 5).

Fig. 5

Risk difference of GERD after POEM (measured by pH monitoring) between anterior and posterior myotomy

Study or Subgroup	anterior Events	Total	Ev
Khashab MA, 2018	36	73	
Kumbhari V. 2017	158	274	
Ramchandani M, 2018	4	25	
Shiwaku H., 2016	7	93	
Tan Y, 2018	8	30	
Total (95% CI)		**495**	
Total events	213		
Heterogeneity: Tau² = 0.01; Chi² = 7.08, df			
Test for overall effect: Z = 1.37 (P = 0.17)			

Endoscopic findings

Three studies were included in this analysis [3, 28, 38]. Of them, 2 were RCTs [3, 28] and 1 was an observational study [38]. This analysis included 148 subjects in the anterior group and 111 subjects in the posterior group. GERD was reported in 75 (51%) of patients who underwent anterior myotomy versus 59 (53%) of those who underwent posterior myotomy. One of these studies [38] demonstrated a statistically significant difference between the outcomes comparing these two techniques favoring the anterior approach. The meta-analysis showed a lower rate of GERD in the anterior group with borderline significance (*IC: − 0.09 [− 0.20, 0.01]*, $p = 0.07$, $I^2 = 0\%$) (Fig. 6).

Fig. 6

Risk difference of GERD post POEM (measured by EGD) between anterior and posterior myotomy

Study or Subgroup	anterior Events	Total	Ev
Ramchandani M, 2018	6	25	
Shiwaku H., 2016	64	93	
Tan Y, 2018	5	30	
Total (95% CI)		**148**	
Total events	75		
Heterogeneity: Tau² = 0.00; Chi² = 1.50, df			
Test for overall effect: Z = 1.84 (P = 0.07)			

Symptoms assessment

Only two studies [28, 38] reported GERD by symptoms assessment in this subgroup. Of these, there was one RCT [28] and one observational study [38]. The overall sample included 123 subjects in the anterior group and 84 subjects in the posterior group. GERD was reported in 16 (13%) patients who underwent anterior POEM versus 13 (15%) in those who underwent posterior POEM. None of the studies individually demonstrated a statistically significant difference between the outcomes. No meta-analysis was performed for this outcome.

Long versus short myotomy

pH monitoring

Three studies compared long versus short myotomy [29, 30, 39]. However, only one study provided information on the frequency of GERD diagnosed by pH monitoring [30]. This study was observational and included 23 subjects in the long myotomy group and 26 subjects in the short myotomy group. In this specific comparison GERD was reported in 10 (43%) patients from the long myotomy group versus 17 (65%) patients of the short myotomy group with no statistical difference.

Endoscopic findings and Symptom assessment

Three studies compared these two techniques [29, 30, 39]. None of these provided information on the frequency of GERD according to endoscopic findings or symptom assessment.

Nonspecific assessment

Three studies were included in this analysis [29, 30, 39]. Out of these studies, 2 were RCT [29, 30] and 1 was an observational study [39]. They provided the frequency of GERD without mentioning how it was assessed. This analysis included 150 subjects in the long myotomy group and 124 subjects in the short myotomy group. GERD was reported in 33 (22%) patients who underwent long myotomy versus 37 (30%) who underwent short myotomy. Pooled data from the meta-analysis did not find a significant difference between these techniques (*IC: − 0.05 [− 0.018, 0.08]*, $p = 0.47$, $I^2 = 48\%$) (Fig. 7).

Fig. 7

Risk difference of GERD (nonspecific assessment) post POEM between long and short myotomy

	long		sh
Study or Subgroup	**Events**	**Total**	**Events**
Familiari P, 2016	16	38	25
Gao Q, 2017	6	53	6
Gong W., 2016	11	59	6
Total (95% CI)		**150**	
Total events	33		37
Heterogeneity: Tau² = 0.01; Chi² = 3.82, df =			
Test for overall effect: Z = 0.72 (P = 0.47)			

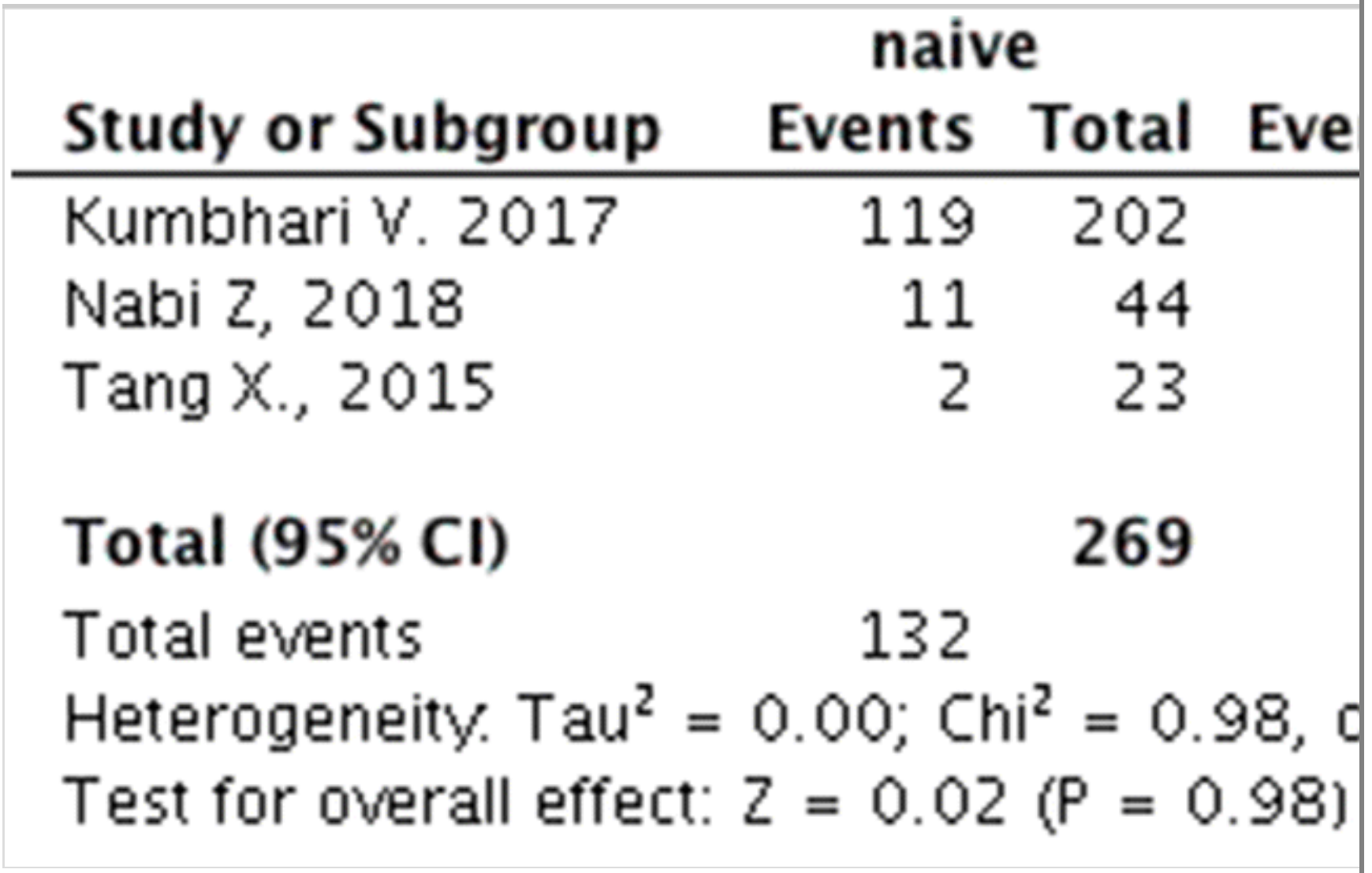
Naive versus PTF

pH monitoring

Three observational studies including 269 subjects in the naive group and 187 subjects in the PTF group were included in this analysis [40, 41, 44]. GERD was reported in 132 (49%) patients from the naive group versus 66 (35%) patients from the PTF group. None of the studies individually demonstrated a statistically significant difference between the outcomes comparing these two groups and the meta-analysis also showed no significant difference (*IC: − 0.00 [− 0.08, 0.08]*, $p = 0.98$, $I^2 = 0\%$) (Fig. 8).

Fig. 8

Risk difference of GERD post POEM (measured by pH monitoring) between naive and PTF group



Endoscopic findings

Only one observational study [40] comparing these two categories of patients provided information on the frequency of GERD assessed by endoscopic findings. This study included 131 subjects in the naive group and 116 subjects

in the PTF group. GERD was reported in 29 (22%) patients in the naive group versus 24 (20%) patients in the PTF group. The study concluded that the occurrence of GERD by endoscopic erosions was similar in both groups ($p = 0.88$).

Symptom assessment

Only one observational study [40] comparing these two categories of patients provided information on the frequency of GERD by symptoms assessment. This study included 134 subjects in the naive group and 146 subjects in the PTF group. GERD was reported in 22 (16%) patients in the naive group versus 26 (18%) patients in the PTF group. The study did not demonstrate a statistically significant difference between these two groups ($p = 0.87$).

HM versus Non-HM

pH monitoring

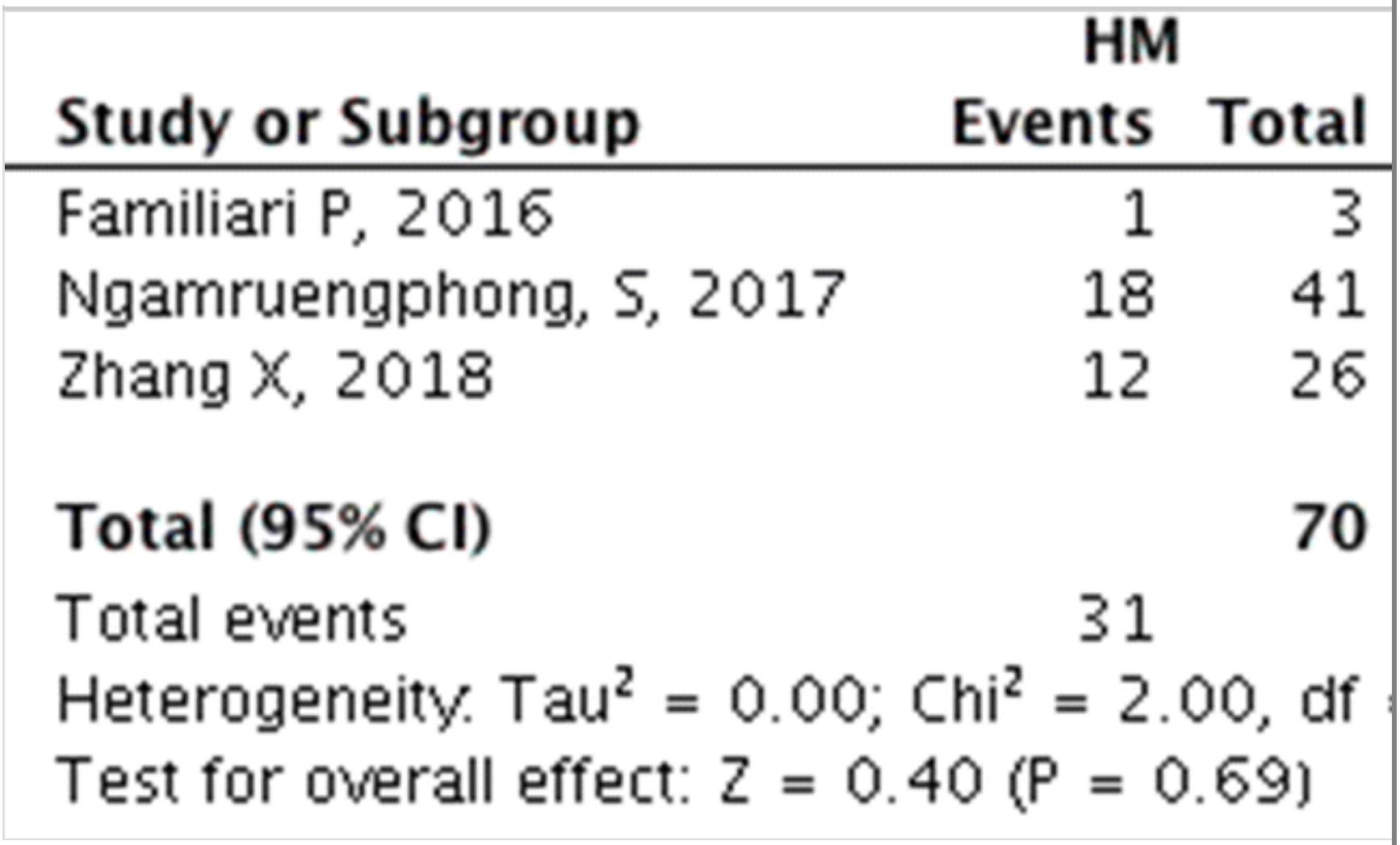
Two observational studies [1, 31] comparing these two groups provided information on the frequency of GERD assessed by pH monitoring. The overall sample included was 27 subjects with HM prior to POEM and 244 subjects with no-HM prior to POEM. GERD was reported in 14 (52%) of those undergoing HM prior to POEM versus 119 (49%) patients who did not undergo HM prior to POEM. None of the studies individually demonstrated a statistically significant difference between the outcomes comparing these two groups. No meta-analysis was performed for this outcome.

Endoscopic findings

Three observational studies including 70 subjects in HM prior to POEM and 291 subjects with non-HM prior to POEM were included in this analysis [1, 6, 31]. GERD was reported in 31 (44%) patients who underwent HM prior to POEM versus 93 (32%) who did not undergo HM prior to POEM. None of the studies individually demonstrated a statistically significant difference between the outcomes comparing these two groups. The meta-analysis showed no significant difference either ($IC: 0.03\ [-0.11, 0.17]$, $p = 0.69$, $I^2 = 0\%$) (Fig. 9).

Fig. 9

Risk difference of GERD post POEM (measured by EGD) between HM and non-HM group



Symptom assessment

Four observational studies including 133 subjects in HM prior to POEM and 500 subjects in non-HM prior to POEM were included in this analysis [1, 5, 6, 31]. GERD was reported in 47 (35%) patients who underwent to HM prior to POEM versus 138 (28%) who did not undergo prior HM. Two [5, 31] of the analyzed studies showed a trend towards a lower rate of GERD in the non-HM group and the other two demonstrated a trend towards a lower rate of GERD in the HM group. Pooled data from meta-analyses did not find a significant difference between groups (*IC: 0.07 [− 0.13, 0.28]*, $p = 0.47$, $I^2 = 75\%$) (Fig. 10).

Fig. 10

Risk difference of GERD post POEM (measured by symptoms assessment) between HM and non-HM group

Study or Subgroup	HM Events	Total
Familiari P, 2016	0	3
Kristensen H Ø., 2017	11	14
Ngamruengphong, S, 2017	21	70
Zhang X, 2018	15	46
Total (95% CI)		**133**
Total events	47	
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 12.00$, df		
Test for overall effect: $Z = 0.72$ ($P = 0.47$)		

Type I versus Type II

pH monitoring

Three observational studies including 94 subjects in the Type I group and 241 subjects in the Type II group were included in this analysis [1, 42, 44]. GERD was reported in 42 (45%) patients with Type I achalasia versus 121 (50%) patients with Type II achalasia. None of the studies individually demonstrated a statistically significant difference between the outcomes comparing these two subtypes of achalasia. The meta-analysis also showed no significant difference (*IC: − 0.04 [− 0.15, 0.07]*, $p = 0.45$, $I^2 = 0\%$) (Fig. 11).

Fig. 11

Risk difference of GERD post POEM (measured by pH monitoring) between Type I and Type II achalasia

Study or Subgroup	type I Events	Total	t Eve
Familiari P, 2016	13	26	
Kumbhari V. 2017	26	49	
Tang X, 2015 (2)	3	19	
Total (95% CI)		**94**	
Total events	42		1
Heterogeneity: Tau² = 0.00; Chi² = 0.55, c			
Test for overall effect: Z = 0.75 (P = 0.45)			

Endoscopic findings and symptom assessment

Three observational studies compared these two subtypes of achalasia [1, 42, 44]. Only one provided information on the frequency of GERD according to endoscopic findings or symptom assessment [1]. This study included 26 subjects in the Type I group and 46 subjects in the Type II group. GERD was reported in 5 (19%) patients with Type I achalasia versus 9 (20%) patients with Type II achalasia, assessed by endoscopic findings and 2 (8%) patients with Type I achalasia versus 7 (15%) patients with Type II achalasia, measured by symptom assessment. The study demonstrated no statistically significant difference between the outcomes comparing these two subtypes of achalasia.

Type I versus Type III

pH monitoring

Two observational studies [1, 44] compared these two subtypes of achalasia and provided information on the frequency of GERD measured by pH monitoring. The overall sample included 75 subjects in the Type I group and 23 subjects in the Type III group. GERD was reported in 28 (37%) patients with Type I achalasia versus 14 (61%) patients with Type III achalasia. None of the studies

individually demonstrated a statistically significant difference between the two subtypes of achalasia. No meta-analysis was performed for this outcome.

Endoscopic findings and symptom assessment

Two studies compared these two subtypes of achalasia [1, 44]. Only one provided information on the frequency of GERD according to endoscopic findings or symptom assessment [1]. This study included 26 subjects in the Type I group and 2 subjects in the Type III group. GERD was reported in 5 (19%) patients with Type I achalasia versus 0 patients with Type III achalasia, assessed by endoscopic findings and 2 (8%) patients with Type I achalasia versus 0 patients with Type III achalasia, measured by symptoms assessment. The study demonstrated no statistically significant difference between the outcomes comparing these two subtypes of achalasia.

Type II versus Type III

pH monitoring

Two observational studies [1, 44] compered these two subtypes of achalasia. The overall sample included 192 subjects in the Type II group and 23 subjects in the Type III group were included in this analysis. GERD was reported in 95 (49%) patients with Type II achalasia versus 14 (61%) patients with Type III achalasia. None of the studies individually demonstrated a statistically significant difference between the two subtypes of achalasia. No meta-analysis was performed.

Endoscopic findings and symptom assessment

Two studies compared these two subtypes of achalasia [1, 44]. Only one provided information on the frequency of GERD according to endoscopic findings or symptom assessment [1]. This study included 46 subjects in the Type II group and 2 subjects in the Type III group. GERD was reported in 9 (20%) patients with Type II achalasia versus 0 patients with Type III achalasia, assessed by endoscopic findings and 7 (15%) patients with Type II achalasia versus 0 patients with Type III achalasia, measured by symptoms assessment. The study demonstrated no statistically significant difference between the outcomes comparing these two subtypes of achalasia.

Age (≥ 60 years versus < 60 years)

Endoscopic findings

Only one study compared age-related patient groups and provided information on the frequency of GERD assessed by endoscopic findings [36]. This was an observational study and included 8 patients who were ≥ 60 years old and 50 patients who were < 60 years old. The proportion of GERD was 25% among those who were ≥ 60 years old and 22% among those who were < 60 years old, with no statistical difference between groups ($p = 0.90$).

pH monitoring and symptom assessment

Only one study compared age-related patient groups [36]. This study did not provide information on the frequency of GERD according to pH monitoring or symptom assessment.

Additional analysis

We intended to compare studies including Eastern and Western populations in the analysis for each of the comparisons performed in the main analysis. However, it was not possible because there were less than 3 studies that could be included in the same comparison group or there were no comparable outcomes.

Discussion

This is the first systematic review and metanalysis assessing risk factors of GERD after POEM for achalasia, including analyses based on pH monitoring, endoscopic findings, and symptoms. We found that patient-related factors, different achalasia subtypes, and variations in the myotomy technique do not differ in the incidence of post-POEM GERD.

When comparing groups according to the orientation of the myotomy (anterior versus posterior), a lower frequency of GERD assessed by EGD was found in the anterior myotomy group with borderline significance ($p = 0.07$); nevertheless, we did not find the same results by pH monitoring or symptoms assessment, which may render this result meaningless. The likely explanation for a higher frequency of GERD in patients submitted to a posterior myotomy is the damage to the angle of His, located at approximately the 8 o'clock position, which is a natural antireflux mechanism [3, 28]. One way to avoid damage to the angle of His, thus reducing the occurrence of GERD, is to perform the

myotomy between the 5 and 6 o'clock position [3]. One RCT [3] found a greater frequency of GERD with posterior myotomy; however, a higher incidence of mucosal injury with anterior myotomy was observed. Additionally, this study found no differences in operative time, technical success, bleeding, or adverse events related to insufflation [3]. The higher incidence of mucosal damage in the anterior myotomy may be related to the acute tip angulation required to hook the circular muscle layer and the subsequent uncontrolled release of the knife upon cutting the muscle [45]. Based on our results, we believe that an anterior myotomy performed with caution is preferred; however, if a posterior myotomy is performed, the 5 to 6 o'clock position should be favored with careful attention to avoid the sling fibers of the angle of His.

Individually, the studies did not demonstrate significant difference between full-thickness and circular myotomy approaches. However, in the meta-analysis, a lower frequency of GERD by endoscopic criteria was found in the circular group with borderline significance ($p = 0.06$). These studies used the Los Angeles Classification (LA) [22] as the endoscopic criteria for GERD and most of the patients presented with esophagitis grade A and B. Some authors believe that complete myotomy is a prerequisite for sufficient and long-term reduction of pressure in the LES [9, 37]. An incomplete myotomy with possible fibrotic scarring may be considered one of the main reasons for the recurrence of achalasia symptoms [43]. However, several studies showed similar efficacy when comparing full-thickness and circular myotomy [9, 10, 43]. Selective myotomy of the circular fibers is often difficult to achieve because the longitudinal muscle fibers of the esophagus can be extremely thin, which often leads to unintentional incision of the longitudinal fibers. At the esophagogastric junction (EGJ), a clear separation of the circular muscle layer and longitudinal muscle layer during the myotomy is very difficult, resulting in damage to the freno-esophageal ligaments, which may contribute to post-POEM GERD [1]. Studies comparing these two techniques show that performing the circular myotomy technique increases the procedure time. However, there is no difference when we compare the occurrence of adverse events such as bleeding, pneumoperitoneum, or inadvertent injury to the esophageal mucosa [9, 10, 43].

Comparing POEM performed by long myotomy or short myotomy, we found only abstracts that identified GERD without specifying the diagnostic methods used. The meta-analysis of these studies showed no difference between the techniques related to post-POEM GERD. However, the method used for GERD diagnosis may not have been uniform between studies.

The impact of previous treatments of achalasia on the viability of POEM, its efficacy, and the adverse events rate was evaluated in several studies [4, 40, 46, 47]. The included studies showed no difference in the rate of post-POEM GERD assessed by pH monitoring in comparison between patients with or without prior non-surgical treatment for achalasia and prior treatment. The previous application of botulinum toxin (BTI) can obliterate the planes between the mucosa and the muscle, making the dissection more difficult. Both BTI and pneumatic endoscopic balloon dilation (PBD) induced esophageal inflammation and fibrosis in animal models. Due to this difficulty in separating dissection planes, a selective myotomy of the muscular layer can be more challenging; however, this does not appear to effect rates of post-POEM GERD [40].

We did not find a difference in the incidence of GERD measured by EGD or symptoms assessment when comparing groups with previous HM and non-HM. The studies included in the analysis by each diagnostic method were different and when analyzed individually, demonstrated no statistically difference in GERD rate between the two groups. HM has been considered the gold standard treatment for achalasia [6, 31]. Besides leading to a significant reduction in LES tone, which relieves symptoms, the possibility to make a fundoplication, whether partial or complete, reduces the risk of subsequent GERD. However, when HM fails, few treatment options are available. Re-do HM is technically challenging and carries a higher risk of adverse events and lower efficacy, compared to primary HM [6, 31]. Recently, POEM has been described as an opportune rescue therapy for those patients [6]. Several studies [6, 31, 40] have demonstrated a similar risk of GERD among patients undergoing POEM with prior HM and patients with no history of HM. The initial hypothesis was that patients who underwent previous HM might have a lower risk of GERD after POEM since they had a fundoplication. However, our results do not support this hypothesis.

Although there is evidence that achalasia subtype is related to response after POEM, we did not find a significant difference in the proportion of post-POEM GERD between type I versus type II subtypes of achalasia analyzed by pH monitoring [48].

As previously highlighted, the development of GERD is the major shortcoming for POEM. Interestingly, even before POEM procedure, several endoscopic therapies for GERD have emerged as alternatives to the surgical fundoplication. Ultimately, combining POEM with some endoluminal modality to treat GERD

might eventually mitigate this problem. Currently there are several endoscopic methods to treat GERD including plication of the gastroesophageal junction (GEJ), radiofrequency, and mucosal resection of the gastric cardia [49], among others [50, 51, 52]. A systematic review and meta-analysis of 16 RCTs [53] compared the efficacy of endoscopic procedures versus sham therapies, pharmacological or surgical approaches. The article showed better short-term efficacy of endoscopic procedures compared to sham and pharmacological or surgical treatments. However, the long-term efficacy of endoscopic GERD therapies is not well established [54]

This systematic review and meta-analysis is not exempt from limitations. The studies are heterogeneous in design and methods. However, the meta-analysis showed low statistical heterogeneity (< 50%) in all the analyses. Different approaches were employed to confirm the diagnosis of GERD. Additionally, the time of the post-POEM evaluation of GERD ranged from 3 to 36 months, which could have created comparisons at different times of follow-up. Moreover, not all studies used the three diagnostic methods: pH monitoring, endoscopic criteria, and symptoms assessment to define GERD, which did not allow a homogeneous comparison between the studies, divided by diagnostic method. Finally, the diagnostic criteria for GERD in all studies included differ from the 2018 Lyon Consensus [55] as they were performed prior to 2018. Lyon Consensus does not consider grade A and B esophagitis by the Los Angeles Classification [22] as diagnostic of GERD. Because of this, many patients who were included in the quantitative analyses as having GERD measured by EGD would not be diagnosed with GERD with current practice. Moving forward it would be ideal for centers to adopt these criteria aiming to standardize diagnosis and facilitating comparison between centers. In spite of these limitations that are somewhat inherent to many meta-analyses, we believe that our findings may have significant clinical implications for the endoscopic management of patients with achalasia.

To our knowledge, this is the first meta-analysis to assess the risk of GERD after POEM including relevant and objective comparisons. This study synthesizes all current knowledge regarding this controversial matter and may inform the management of patients with achalasia undergoing endoscopic myotomy.

AQ4

Conclusion

This systematic review and meta-analysis identified a lower frequency of post-POEM GERD with borderline statistical significance, as assessed by EGD, in patients undergoing circular myotomy and anterior myotomy. Myotomy length, achalasia subtype, history of previous treatment, and previous Heller myotomy did not influence the development of post-POEM GERD. These results suggest that a circular anterior approach may limit post-POEM GERD and might be considered in appropriate patients [56, 57].

AQ5

Publisher's Note

Electronic supplementary material

Below is the link to the electronic supplementary material.

Supplementary file1 (DOCX 44 kb)

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AQ6

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