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Joana Sobral Cardoso da Silva

Achalasia: Laparoscopic Heller myotomy with fundoplication versus peroral
endoscopic myotomy – A systematic review and meta-analysis

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FMUP

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E sob a Coorientação de:

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Doutor José Pedro Coimbra de Vargas Lobarinhas Barbosa

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Eu, Joana Sobral Cardoso da Silva abaixo assinado, nº mecanográfico 201705520, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro ter actuado com absoluta integridade na elaboração do meu trabalho de Dissertação ou Monografia.

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DESIGNAÇÃO DA ÁREA DO PROJECTO

CIÊNCIAS MÉDICAS E DA SAÚDE, MEDICINA CLÍNICA

TÍTULO DISSERTAÇÃO

Achalasia: Laparoscopic Heller myotomy with fundoplication versus peroral endoscopic myotomy – A systematic review and meta-analysis

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Dedicatória:

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Achalasia: Laparoscopic Heller myotomy with fundoplication versus peroral endoscopic myotomy – A systematic review and meta-analysis

Running Head: Laparoscopic Heller myotomy versus POEM

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Keywords: Achalasia, Laparoscopic Heller myotomy, POEM, Gastroesophageal reflux

Abstract

Background: There are various therapeutic options for achalasia. Nevertheless, peroral endoscopic myotomy (POEM) and laparoscopic Heller myotomy with fundoplication (LHM) are distinguished by their efficacy and low incidence of complications.

Objective: Compare POEM and LHM regarding several outcomes in patients with achalasia.

Materials and Methods: This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. An exhaustive literature search was performed using PubMed, Web of Science, and Cochrane Library databases. Studies comparing several outcomes between POEM and LHM in patients with achalasia were included. Data on clinical success, operative time, intraoperative complications, length of stay, reintervention rates, postoperative pain, overall complications, occurrence of GERD symptoms, use of proton pump inhibitors and esophagitis were extracted. Quality assessment of the included studies was performed using the MINORS scale.

Results: We included twenty retrospective observational studies with a combined total of 5139 participants. The results demonstrated that there was no statistically significant difference in terms of intraoperative complications, postoperative complications, reintervention rate, occurrence of GERD symptoms, GERD HRQL, use of proton pump inhibitors, and esophagitis between POEM and LHM groups. Conversely, POEM was associated with higher clinical success and shorter operative time, length of stay, and postoperative pain.

Conclusion: This meta-analysis concludes that both POEM and LHM, are effective and safe treatments for achalasia. However, POEM demonstrates better results regarding clinical success, operative time, length of stay, postoperative pain, and a tendency towards lower recurrence.

Introduction:

Achalasia, which is distinguished by abnormal esophageal peristalsis and ineffective relaxation of the lower esophageal sphincter (LES), is classified as a primary motor disorder of the esophagus. Although there are plenty of theories concerning its pathophysiology, the precise etiology has not been identified in its entirety.^{1,2}

It is a rare disease, exhibiting an annual average incidence of 1 in 100.000 cases and a prevalence of 10 in 100.000. The incident rate escalates as age increases, with the mean age of diagnosis surpassing fifty years. Additionally, it is indifferent to ethnicity and affects both sexes.³

All therapeutic alternatives aim to alleviate the patient's symptoms by decreasing the tone of the lower esophageal sphincter and promoting esophageal emptying. Furthermore, it is imperative that the treatments halt the disease's progression and, as a result, avert its later complications.³

Therefore, pharmacological, endoscopic, or surgical interventions may be utilized. Pharmacological intervention is considered the least effective and should be reserved for patients who don't meet the required clinical criteria to undergo endoscopic or surgical treatment. Endoscopic treatment can be organized into four distinct options: Pneumatic dilation, sclerotherapy, injection of botulinum toxin and peroral endoscopic myotomy (POEM). Total esophagectomy and Heller myotomy with fundoplication comprise the surgical treatment.^{4,5}

Over the years, laparoscopic Heller myotomy with fundoplication (LHM) has been considered the gold-standard treatment due to its long-term efficacy and low associated morbidity. Since its creation in 1913, this surgical technique has come a long way from laparotomy lacking an anti-reflux mechanism to its present form, laparoscopic myotomy combined with fundoplication.^{6,7}

However, in 2010, Inoue et al. published a study in which 17 adults with the diagnosis of achalasia were evaluated and subjected to POEM. There was a substantial reduction in symptomatology and LES pressure observed in all patients. By creating an endoscopic submucosal tunnel, this technique permits the extent of the dissection to be modified in accordance with the type of achalasia that has been identified. Hence, a benefit of POEM in comparison to the laparoscopic approach is the possibility for a more extensive myotomy, which could result in a significant improvement of dysphagia.⁸

Consequently, over the past decade, POEM has emerged as a viable substitute for laparoscopic Heller myotomy with fundoplication due to its reduced invasiveness. Nevertheless, a concern that has been raised regarding this endoscopic method is the potential for iatrogenic gastroesophageal reflux disease to develop since POEM lacks an anti-reflux mechanism in contrast to the surgical alternative.⁹

Therefore, a comparison of the outcomes of patients diagnosed with achalasia who underwent laparoscopic Heller myotomy with fundoplication or POEM is the objective of this meta-analysis. The assessed results include the efficacy of each procedure as determined by symptomatology, with the Eckardt score being the preferred measurement, the postoperative pain, the occurrence of gastroesophageal reflux following each procedure, the length of time required for procedures and hospital stays, and potential complications and relapses.

Methods:

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹⁰

Search strategy/Information sources:

Two authors independently searched the following databases for relevant literature: PubMed, Web of Science and Cochrane Library.

The search query that was entered into PubMed was: “(((Achalasia[Title/Abstract]) OR (Achalasia treatment[Title/Abstract])) AND ((Laparoscopic heller myotomy[Title/Abstract]) OR (Heller Myotomy[Title/Abstract]) OR (LHM[Title/Abstract]) OR (Surgical Myotomy[Title/Abstract])) AND ((Peroral endoscopic myotomy[Title/Abstract]) OR (POEM[Title/Abstract]) OR (Surgical Endoscopy[Title/Abstract]))”).

We used the following query in the Cochrane Library and Web of Science: “(((Achalasia) OR (Achalasia treatment)) AND ((Laparoscopic heller myotomy) OR (Heller Myotomy) OR (LHM) OR (Surgical Myotomy)) AND ((Peroral endoscopic myotomy) OR (POEM) OR (Surgical Endoscopy)))”.

Studies published from January 2010 to December 2022 were included. The selection of this time restriction was because the initial publication about POEM was published by Inoue et al in 2010.

Study selection and eligibility criteria:

After reviewing the literature, two independent authors selected articles based on their titles and abstracts. Observational clinical studies comparing the results of POEM and LHM surgery in adult patients with achalasia were included. After deliberation among reviewers, disagreements were resolved by consensus.

Subsequently, the authors assessed the full texts and excluded articles that fit the exclusion criteria: Pediatric studies, animal studies, case reports, conference abstracts, reviews, comments, and articles not pertaining to the research question. Language restrictions were not applied.

Data extraction:

Two authors were involved in data extraction. Data extraction included study information (author, published year, study period, study design, sample size and surgical approach), patients baseline characteristics (age, gender, achalasia subtype and Eckardt score before surgery), surgical outcomes (operative time, intraoperative complications) and postoperative outcomes (length of stay, readmission rates, Eckardt score, GERD symptoms, esophagitis according to Los Angeles classification, use of proton pump inhibitors, postoperative complications according to Clavien-Dindo grade and use of analgesic medication).

Quality assessment

The Methodological Index for Non-Randomized Studies (MINORS) checklist, comprising 12 items, was utilized by two independent reviewers to assess the quality of our included studies. A cumulative score of 24 is achievable for each study, with a score of 2 (reported and adequate), 0 (not reported), or 1 (reported but inadequate) assigned to each item specified in the checklist.¹¹

Statistical analysis

We used Review Manager (Version 5.4.1) to perform our data analysis. The risk ratio (RR) was used for dichotomous variables, and the mean difference (MD) was used for continuous variables. The RR and MD were considered to be statistically significant at a p value less than 0.05. The results of some studies were expressed as the median and range. We estimated the mean and standard deviation in accordance with the method described by Wan et al.¹² To evaluate heterogeneity, the Chi-squared (χ^2) test and the I-squared (I^2) measure were applied. We utilized a random effects model due to the heterogeneity of clinical outcomes among the included studies.

RESULTS

Search Results and Characteristics of the Included Studies

The initial search of PubMed, Web of Science, and the Cochrane Library platforms found 318, 796, and 74 studies, for a total of 1188 potentially relevant articles. There were 252 duplicates removed out of the total. After reading their titles and abstracts, we selected 49 full-text articles to assess for eligibility, a total of 20 studies met the eligibility criteria for the qualitative and quantitative analyses. Figure 1 presents a flowchart illustrating the reasons for excluding the remaining articles at each step of the process.

These studies include a total of 5139 participants, of which 1394 underwent POEM and 3745 underwent LHM. All studies were retrospective observational studies.¹³⁻³² Detailed information on study characteristics and details of the patients was presented in Table 1 and 2.

Quality Assessment:

The median score in the MINORS scale was 18, with a range of 16–20, as indicated in Table 1. As a result, all included studies were deemed adequate for inclusion in the quantitative analysis.

Surgical outcomes

Operative time: This outcome was reported by twelve studies, involving a total of 892 patients. It was significantly shorter in the POEM group, when compared with the LHM. Mean operation time was 116.8 minutes in the POEM group and 150.5 minutes in the LHM group. (MD -33.80, $P < .0001$ [95% CI: -46.07, -21.53], $I^2=90\%$, $P<.00001$). (Fig. 2).

Intraoperative complications: Eight studies reported this outcome. The rate of intraoperative complications was 11.1% (40/359) in the POEM group and 8.94% (27/302) in the LHM group. This difference was not statistically significant (RR 1.21, $p = 0.48$ [95% CI: 0.72, 2.04], $I^2 = 0\%$, $p = 0.44$).

Postoperative outcomes

Clinical success: In the included studies, clinical success was defined as an Eckardt score of three or lower. It was reported in eight studies. Clinical success rate was 91.2% (250/274) in the POEM group and 82.3% (246/299) in the LHM group. The POEM group had a significantly higher clinical success when compared with the LHM. (RR 1.08, $p = 0.010$ [95% CI: 1.02, 1.14], $I^2 = 0\%$, $p = 0.76$). (Fig. 3)

Eckardt score: Ten studies reported the postoperative Eckardt score's mean and standard deviation instead of using the clinical success criterion of being equal to or less than 3. There was no statistically significant difference between the POEM group and the LHM group. (MD -0.08, $p = 0.76$ [95% CI: -0.63, 0.46], $I^2 = 86\%$, $p < 0.00001$).

Overall complications: The overall complication rate was 7.7% (91/1178) in the POEM group and 5.7% (195/3431) in the LHM group. The meta-analysis did not demonstrate a statistically significant difference among the 15 studies that reported this outcome. (RR 0.89, $p = 0.62$ [95% CI: 0.57, 1.40], $I^2 = 43\%$, $p = 0.04$). (Fig. 4)

Surgical complications (grades I and II in the CD classification): Ten studies reported postoperative complications corresponding to CD grades 1 and 2. This rate was 5.4% (52/971) in the POEM group and 4.2% (130/3114) in the LHM group. This difference was not statistically significant. (RR 0.78, $p = 0.34$ [95% CI: 0.47, 1.30], $I^2 = 39\%$, $p = 0.10$).

Surgical complications (grade III in the CD classification): This outcome was included in 13 studies and demonstrated no statistically significant difference between both groups. In the POEM group, it was 2.7% (15/634), and in the LHM group, it was 1.1% (32/2813). (RR 1.20, $p = 0.82$ [95% CI: 0.26, 5.48], $I^2 = 37\%$, $p = 0.20$).

Surgical complications (grade IV in the CD classification): This outcome was included in 3 studies and demonstrated no statistically significant difference between the 2 groups. In the POEM group, it was 2.8% (21/757), and in the LHM group, it was 1.2% (34/2843). (RR 1.18, $p = 0.77$ [95% CI: 0.40, 3.43], $I^2 = 39\%$, $p = 0.18$).

Reintervention rate: Seven studies were included, and reintervention rate was comparable between both groups. Reintervention rate was 10.7% (36/335) in the POEM group and 17.4% (58/334) in the LHM group. (RR 0.62, $p = 0.06$ [95% CI: 0.37, 1.02], $I^2 = 29\%$, $p = 0.20$). (Fig. 5)

Postoperative pain: Through the duration of analgesic medication use, postoperative pain was evaluated in two studies. According to our research, the POEM group experienced significantly less pain following surgery. Mean duration of analgesic medication use was 1.6 days in the POEM group and 2.3 days in the LHM group. (MD -0.91, $p = 0.03$ [95% CI: -1.71, -0.11], $I^2 = 0\%$, $p = 0.64$). (Fig. 6)

Length of stay (LOS): This outcome was reported in 14 studies. The mean length of hospital stay was 2.1 days in the POEM group and 2.7 days in the LHM group. The POEM group had a significantly lower length of stay. (MD -0.55, $p = 0.0001$ [95% CI: -0.83, -0.27], $I^2 = 83\%$, $p < 0.00001$). (Fig. 7)

Occurrence of GERD symptoms: Six studies reported this outcome. The rate of GERD symptoms was 21% (43/204) in the POEM group and 18.1% (40/221) in the LHM group. There was no statistically significant difference. (RR 0.94, $p = 0.75$ [95% CI: 0.37, 1.02], $I^2 = 0\%$, $p = 0.72$).

GERD HRQL: Four studies applied the GERD HRQL questionnaire both prior to and following the procedures. After the procedures, the mean of these questionnaires was comparable between the groups. (MD 1.46, $p = 0.13$ [95% CI: -0.41, 3.33], $I^2 = 0\%$, $p = 0.58$).

Use of proton pump inhibitors: Five studies assessed the postoperative use of proton pump inhibitors. PPI use was 25.4% (36/184) in the LHM group and 25.5% (47/184) in the POEM group. There is no statistically significant difference between both groups. (RR 0.92, $p = 0.65$ [95% CI: 0.64, 1.31], $I^2 = 0\%$, $p = 0.97$).

Esophagitis: This outcome was included in five studies. In the POEM group, the incidence of esophagitis was 21.3% (29/136), whereas in the LHM group, it was 13.9% (16/115). There was no statistically significant difference observed. (RR 1.43, $p = 0.39$ [95% CI: 0.63, 3.23], $I^2 = 40\%$, $p = 0.16$). (Fig. 8)

Esophagitis LA grades A and B: The occurrence of grade A and B esophagitis, as classified by the Los Angeles classification of reflux esophagitis, was reported in five studies. The rate of esophagitis LA grades A and B was 17.7% (23/130) in the POEM group and 10.8% (12/111) in the LHM group. This difference was not statistically significant. (RR 1.57, $p = 0.29$ [95% CI: 0.69, 3.58], $I^2 = 26\%$, $p = 0.25$).

Esophagitis LA grades C and D: The occurrence of grade C and D esophagitis, as classified by the Los Angeles classification of reflux esophagitis, was reported in four studies. The rate of esophagitis LA grades C and D was 6.5% (6/93) in the POEM group and 4.9% (4/82) in the LHM group. This difference was not statistically significant. (RR 1.48, $p = 0.51$ [95% CI: 0.46, 4.70], $I^2 = 0\%$, $p = 0.63$).

Discussion:

In recent years, the treatment of achalasia has been the subject of several studies. While there are numerous therapeutic options available for this pathology, LHM and POEM are particularly noteworthy due to their sustained efficacy and a minimal occurrence of associated complications. Costantini et al published an article comparing the various therapeutic options for achalasia. Regarding POEM and LHM, they report that both have excellent long-term efficacy, safe techniques, and can be used in all types of achalasia. However, POEM has the advantage of being a less invasive procedure and absence of skin incisions.³³ Sharma et al reinforce the idea that POEM is an equally effective procedure as LHM, but less invasive, with less pain after the procedure and, consequently, lower costs.³⁴ So, this systematic review and meta-analysis encompass the latest studies directly comparing LHM with POEM, presenting numerous results that could elucidate existing literature and guide future research.

Regarding operative time, our research shows that it was significantly shorter in POEM when compared with LHM. This result contradicts the current literature, since the most recent meta-analyses on the subject concluded that the operative time was comparable between the two procedures.^{35,36} According to some studies, the difference stems from the fact that POEM is an endoscopic procedure while LHM is a surgical intervention. Additionally, LHM requires a fundoplication, which lengthens the surgical procedure.¹⁴

Our results show that there was no statistically significant difference in intraoperative complications between POEM and LHM. A significant proportion of these complications were injuries to the esophageal or gastric mucosa that occurred during the procedures and were promptly repaired. None of the studies identified any perioperative mortality or conversion to an alternative procedure. This is consistent with the available literature and demonstrates the safety of both treatments.³⁶

The clinical success, defined as an Eckardt score of three or lower, was significantly higher in the POEM group, when compared with the LHM group. However, the follow-up duration was relatively short in most studies. We decided to use the Eckardt score to compare the clinical improvement of the procedures since it considers the occurrence of dysphagia, regurgitation, chest pain, and weight loss, all of which are useful to assess the disease severity.³⁷

In addition, some studies published the mean and standard deviation of the postoperative Eckardt score and we chose to report this outcome to complement the clinical success mentioned above. Therefore, there was no statistically significant difference between the POEM group and the LHM group. However, significant heterogeneity was identified in postoperative Eckardt score. There is currently no consensus in the literature on this matter. Marano et al found that the Eckardt score postoperative was similar between the two procedures. However, Sharma et al. published that POEM has greater clinical success than LHM based on several studies that only evaluated POEM over long periods of time.

Hence, our findings suggests that POEM could provide a more significant clinical improvement than LHM during the initial months. Nevertheless, further research comparing the two procedures with longer follow-up periods is required to assess this outcome.

Regarding overall postoperative complications, they were comparable between both groups. These results were also observed in other meta-analyses and reveal that POEM is a safe procedure and comparable to LHM.^{35,36} Additionally, the CD classification has been applied in multiple studies to distinguish the severity of different postoperative complications. We conducted separate comparisons of complications classified as grades 1 and 2, as well as complications classified as grades 3 and 4, and found no statistically significant differences between both procedures. Most of the grade 3 complications documented in multiple studies were perforations or esophageal leakage requiring surgical intervention. Cases of sepsis, mediastinitis, and acute respiratory distress syndrome (all of which necessitated intensive care unit admission) constituted complications of grade 4 identified in three studies. There were no deaths related to the procedures.

Concerning reintervention due to clinical failure, it did not differ considerably between both procedures, although there was a trend to lower recurrence in the POEM group. Most of the patients who required reintervention were due to the recurrence of dysphagia after the procedures. Therefore, this result reaffirms that POEM and LHM have similar clinical success.

Furthermore, our study found that postoperative pain was significantly lower in the POEM group. This finding is novel in the current literature, since the meta-analyses conducted by Marano and Awaiz et al. concluded that postoperative pain was comparable for both procedures.^{35,36} Several studies indicate that POEM is a less painful procedure than LHM because it doesn't require skin incisions.^{17,26} Nevertheless, this result was documented in two studies, as most of the studies incorporated in this meta-analysis assessed postoperative pain using distinct methodologies. To confirm this result, further research applying a standardized method of measurement is necessary.

In comparison to the LHM group, the POEM group exhibited a significantly reduced length of stay. Similar results have been reported in recent meta-analyses.^{35,36,38} Even though the costs associated with the procedures are not accounted for in this meta-analysis, this result is significant in this regard.

Nevertheless, numerous studies highlight that the main drawback of POEM is gastroesophageal reflux, since it doesn't involve any antireflux procedure in contrast to surgical myotomy.^{1,33,39} In this meta-analysis, postoperative gastroesophageal reflux was assessed using four outcomes. Following both procedures, postoperative GERD symptoms were comparable. Some studies applied the GERD HRQL questionnaire and found no statistically significant difference. Also, clinical records regarding esophagitis and the use of PPIs were similar between the two groups. So, our research did not identify any statistically significant differences between the two procedures regarding postoperative gastroesophageal reflux. While POEM lacks an associated anti-reflux mechanism, several studies suggest that the dissection executed during this technique is less disruptive and maintains a certain level of lower esophageal sphincter functionality, thereby decreasing the occurrence of gastroesophageal reflux.^{14,27,34,38} However, further research is needed to compare the two techniques directly and to determine the incidence of postoperative gastroesophageal reflux using the same method.

There were some limitations to this study. The studies included were observational and non-randomized, the average follow-up time was less than a year, some outcomes analyzed showed high heterogeneity, and most studies included were from the United States, which may not represent

global reality. Regarding the operative time, we must emphasize that LHM is a surgical procedure involving fundoplication, whereas POEM is an endoscopic technique.

Conclusion:

In conclusion, this meta-analysis provides evidence that POEM, like LHM, is a safe and efficient treatment for achalasia. Nevertheless, POEM exhibits better results in terms of operative time, length of stay, postoperative pain, and a tendency towards lower recurrence. One noteworthy finding is that POEM exhibits superior clinical success compared to LHM during the initial months. There is a need for additional research to assess this matter over the long term.

Hence, we believe that POEM may soon be regarded as the treatment of choice for achalasia, rather than exclusively type III achalasia.

Authors' Contributions:

Joana Sobral: Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (supporting); validation (equal); visualization (equal); writing—original draft (lead); and writing—review and editing (equal).

Miguel Machado: Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (lead); validation (equal); visualization (equal); writing—original draft (supporting); and writing—review and editing (equal).

José Pedro Barbosa: Data curation (equal); formal analysis (equal); investigation (supporting); methodology (supporting); resources (lead); validation (equal); visualization (supporting); and writing—review and editing (supporting).

José Barbosa: Conceptualization (equal); investigation (supporting); supervision (lead); validation (supporting); visualization (supporting); and writing—review and editing (supporting).

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The authors have no conflicts of interest to disclose.

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Table 1 - Summary of studies included in the meta-analysis:

Author:	Year	Study design	Region	Study period	Intervention (n)	Comparison (n)	Sample size (n)	MINORS
Hungness et al.	2012	ROS	United States	2004 – 2012	POEM (n = 18)	LHM (n = 55)	73	17
Bhayani et al.	2014	ROS	United States	2007 – 2012	POEM (n = 37)	LHM (n = 64)	101	19
Kumbhari et al.	2014	ROS	Multinational	2000 – 2013	POEM (n = 49)	LHM (n = 26)	75	16
Chan et al.	2016	ROS	China	2001 – 2014	POEM (n = 33)	LHM (n = 23)	56	17
Docimo et al.	2016	ROS	United States	2006 – 2015	POEM (n = 44)	LHM (n = 122)	166	20
Schneider et al.	2016	ROS	United States	2004 – 2016	POEM (n = 25)	LHM (n = 25)	50	18
Ward et al.	2017	ROS	United States	2011 – 2016	POEM (n = 41)	LHM (n = 24)	65	18
Leeds et al.	2017	ROS	United States	2014 – 2017	POEM (n = 12)	LHM (n = 11)	23	18
de Pascale et al.	2017	ROS	Italy	2012 – 2015	POEM (n = 32)	LHM (n = 42)	74	17
Peng et al.	2017	ROS	China	2009 – 2012	POEM (n = 13)	LHM (n = 18)	31	20
Ramirez et al.	2017	ROS	Argentina	2010 – 2016	POEM (n = 35)	LHM (n = 35)	70	16
Shea et al.	2019	ROS	United States	2009 – 2018	POEM (n = 44)	LHM (n = 97)	141	17
Shemmeri et al.	2019	ROS	United States	2005 – 2017	POEM (n = 71)	LHM (n = 114)	185	16
Wirsching et al.	2019	ROS	United States	2014 – 2017	POEM (n = 23)	LHM (n = 28)	51	19
Ward et al.	2020	ROS	United States	2015 – 2019	POEM (n = 54)	LHM (n = 46)	100	19
Attar et al.	2020	ROS	United States	2010 – 2020	POEM (n = 126)	LHM (n = 33)	159	18
Kahaleh et al.	2020	ROS	Latin America	2015 – 2020	POEM (n = 69)	LHM (n = 64)	133	20
Podboy et al.	2020	ROS	United States	2010 – 2015	POEM (n = 55)	LHM (n = 43)	98	17
Trieu et al.	2021	ROS	United States	2013 – 2017	POEM (n = 580)	LHM (n = 2850)	3430	19
Shally et al.	2022	ROS	United States	2014 – 2021	POEM (n = 33)	LHM (n = 25)	58	17

LHM, Laparoscopic Heller Myotomy; POEM, Peroral Endoscopic Myotomy; ROS, retrospective observational study

Table 2 - Baseline characteristics of included patients:

Author:	Age (LHM)		Age (POEM)		Sex (LHM)			Sex (POEM)		
	Mean	SD	Mean	SD	M	F	Pt	M	F	Pt
Hungness et al., 2012	49.75	12.5	41.75	12.9	29	26	55	13	5	18
Bhayani et al., 2014	57	20	56	16	31	33	64	19	18	37
Kumbhari et al., 2014	51.6	17.9	58.3	18.8	13	13	26	29	20	49
Chan et al., 2016	38.4	14.3	48.2	15.17	11	12	23	12	21	33
Docimo et al., 2016	50.9	17.89	52.2	20.75	63	59	122	27	17	44
Schneider et al., 2016	53.25	6.87	58.75	1.78	12	13	25	13	12	25
Ward et al., 2017	61.5	19.3	63	17.9	14	10	24	25	16	41
Leeds et al., 2017	52.7	12.4	52	16.9	6	5	11	4	8	12
de Pascale et al., 2017	49.75	13.56	53.25	15.73	19	23	42	20	12	32
Peng et al., 2017	44.7	21.6	37.5	13	8	10	18	8	5	13
Ramirez et al., 2017	45	NA	50	NA	20	15	35	15	20	35
Shea et al., 2019	NA	NA	NA	NA	NA	NA	97	NA	NA	44
Shemmeri et al., 2019	NA	NA	NA	NA	NA	NA	114	NA	NA	71
Wirsching et al., 2019	57.25	17.89	58.5	10.37	12	16	28	11	12	23
Ward et al., 2020	54.1	16.8	56.9	16.7	13	33	46	19	35	54
Attar et al., 2020	58	19	64	16	19	14	33	62	64	126
Kahaleh et al., 2020	45.6	10.5	47.3	15.9	30	34	64	29	40	69
Podboy et al., 2020	57.93	2.4	59.18	2.4	10	33	43	22	33	55
Trieu et al., 2021	54.28	18.497	56	19.37	NA	NA	2850	NA	NA	580
Shally et al., 2022	59.5	5.6	57.25	4.09	NA	NA	25	NA	NA	33

F, female; LHM, Laparoscopic Heller Myotomy; M, male; NA, not available; POEM, Peroral Endoscopic Myotomy; Pt, patients; SD, standard deviation

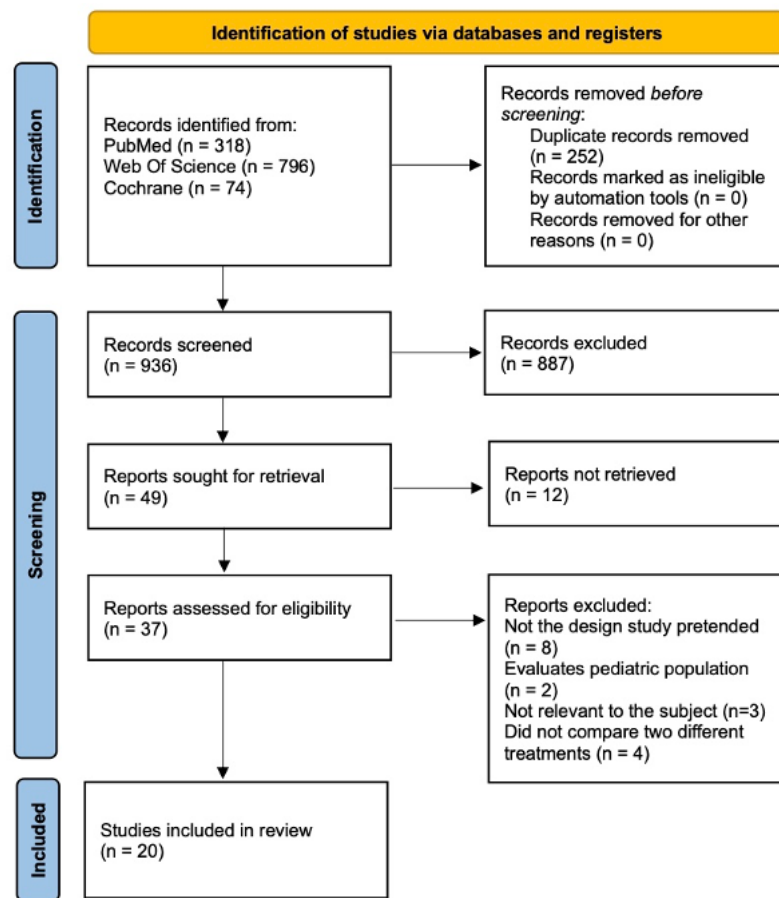


Figura 1 - PRISMA Flowchart

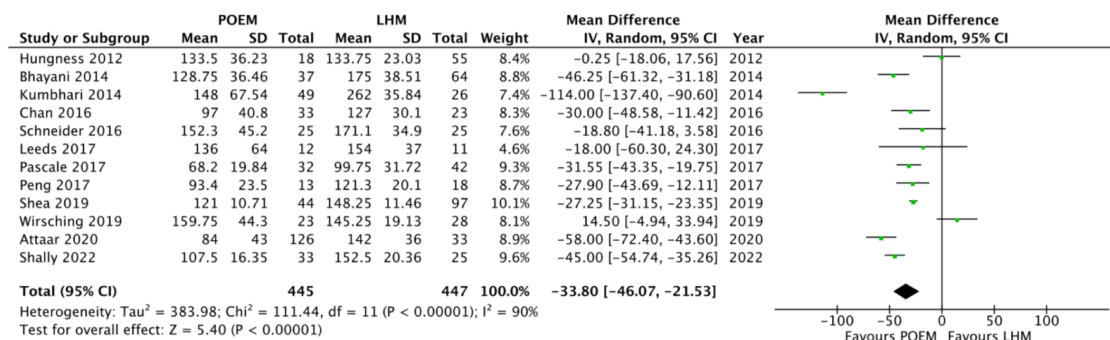


Figure 2 - Operative Time

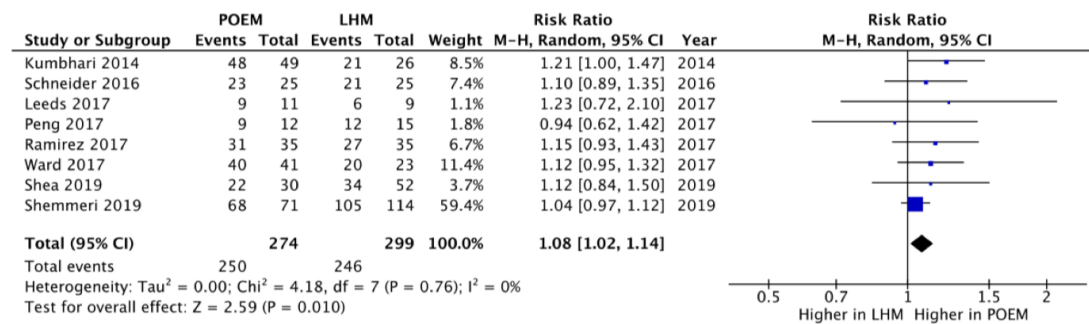


Figura 3 - Clinical Success

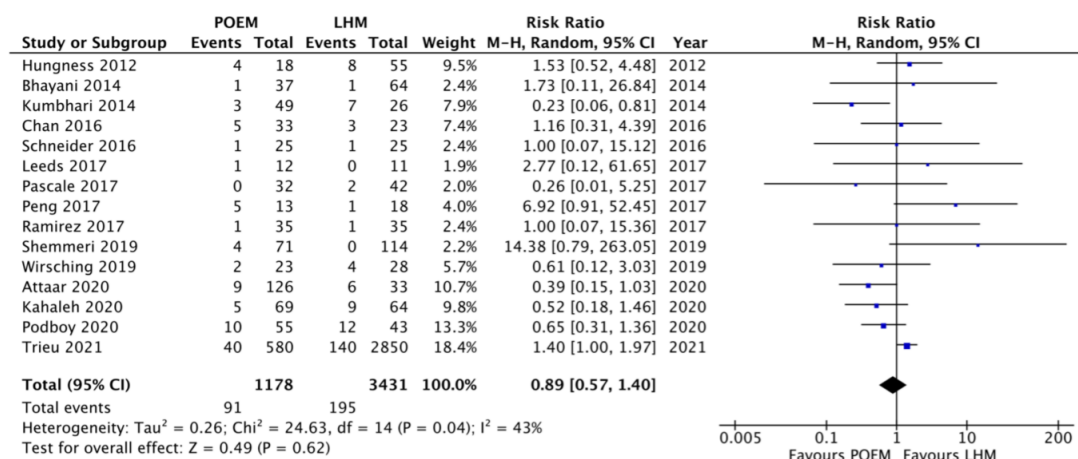


Figura 4 - Overall complications

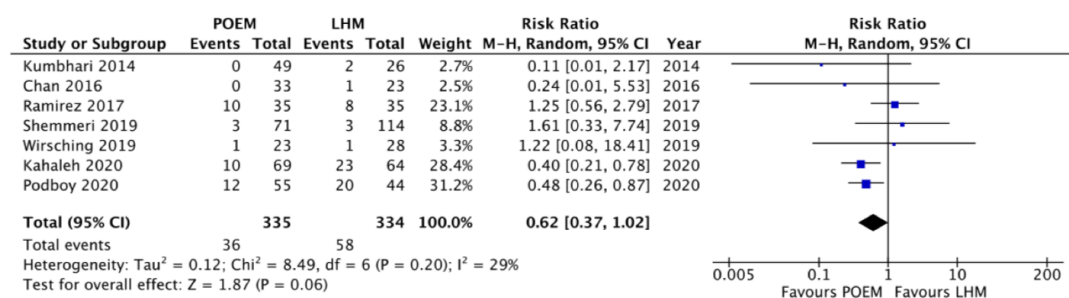


Figura 5 - Reintervention rate

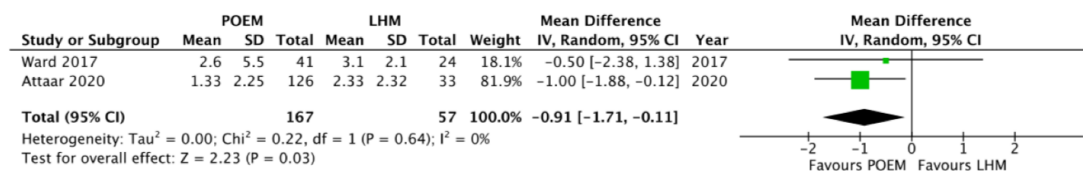


Figura 6 - Postoperative pain

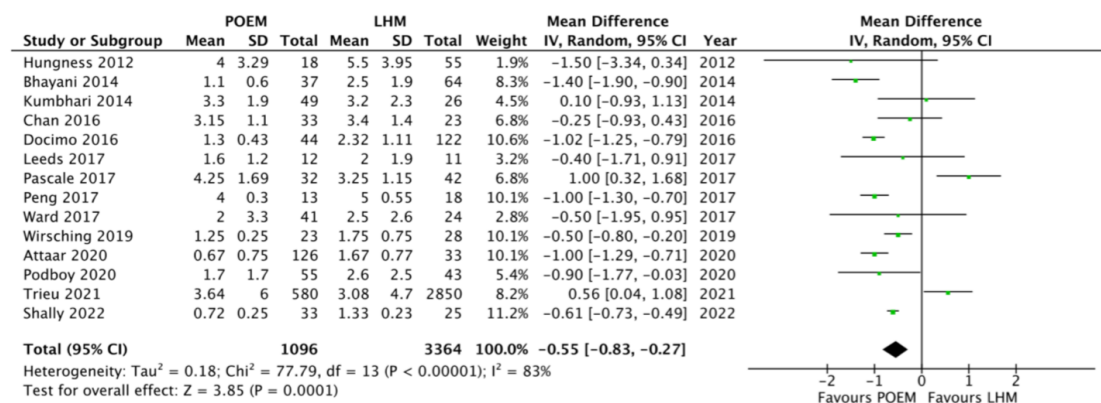


Figura 7 - Length of stay

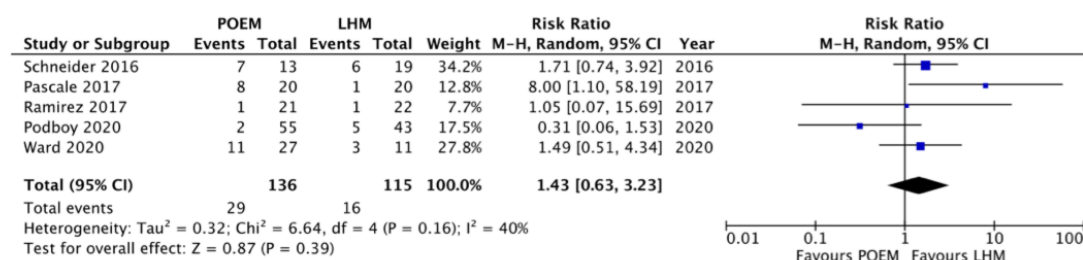


Figura 8 – Esophagitis

Supplemental File – Forest Plots:

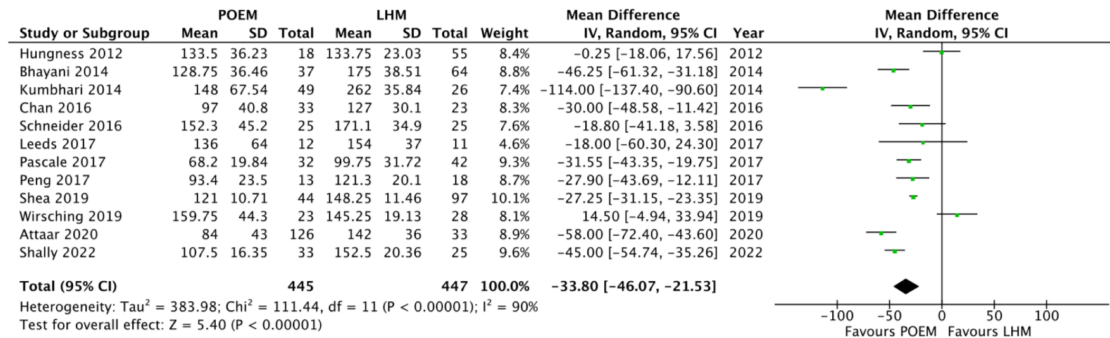


Figure 1 - Operative Time

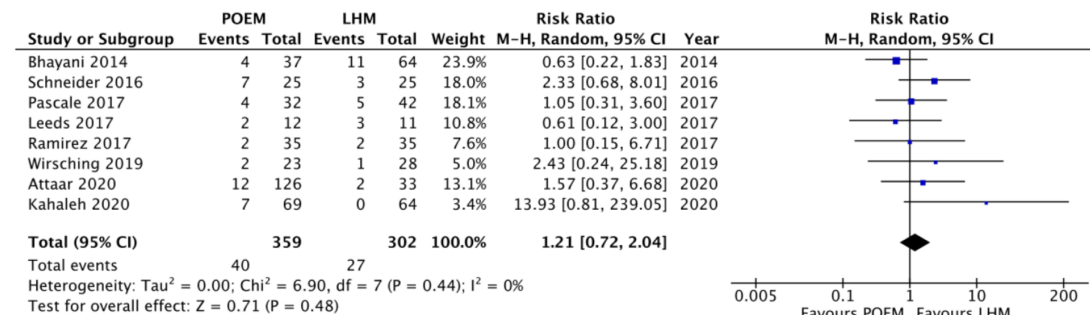


Figure 2 - Intraoperative Complications

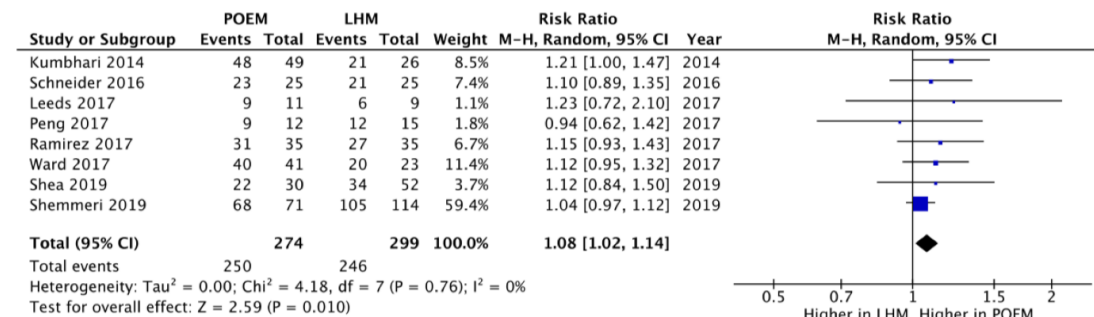


Figure 3 - Clinical Success

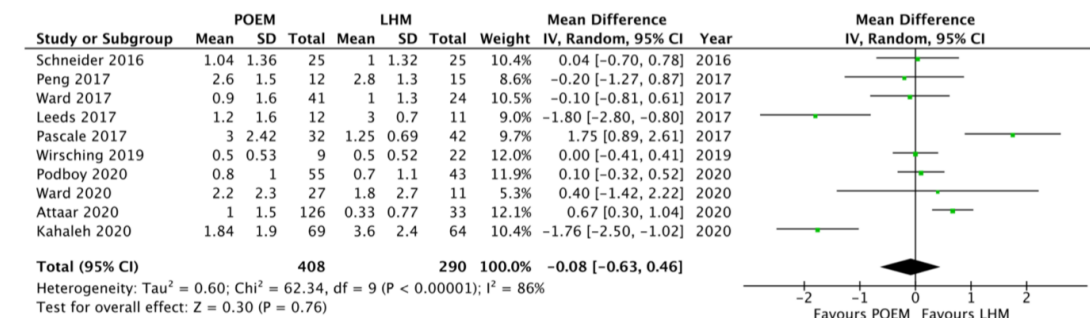


Figure 4 - Eckardt Score

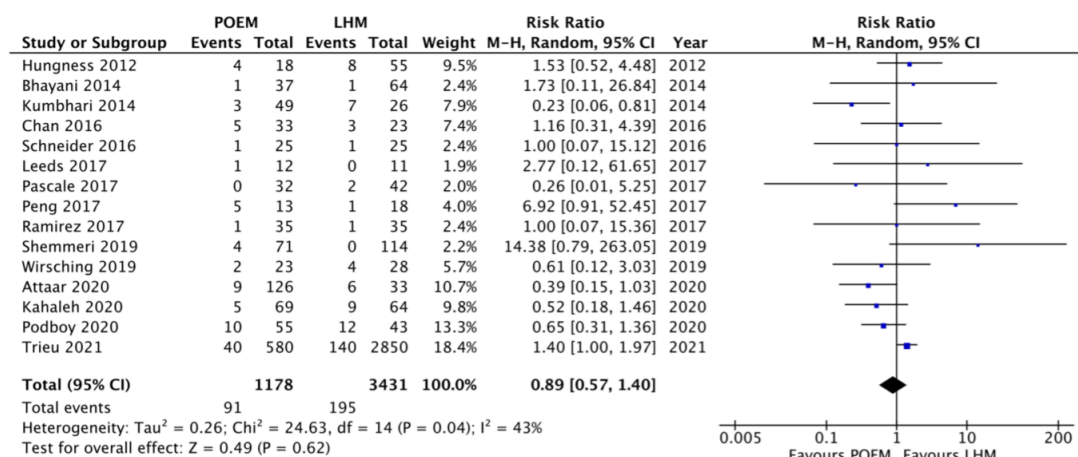


Figura 5 - Overall complications

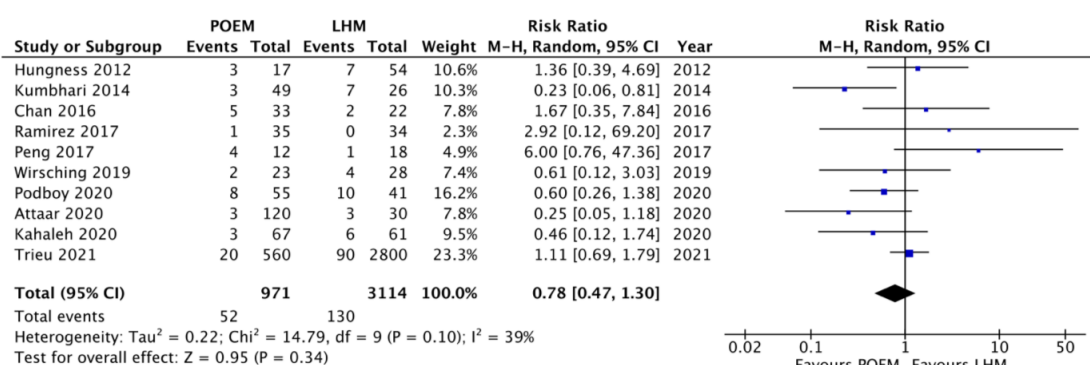


Figura 6 - Grades I and II in the CD classification

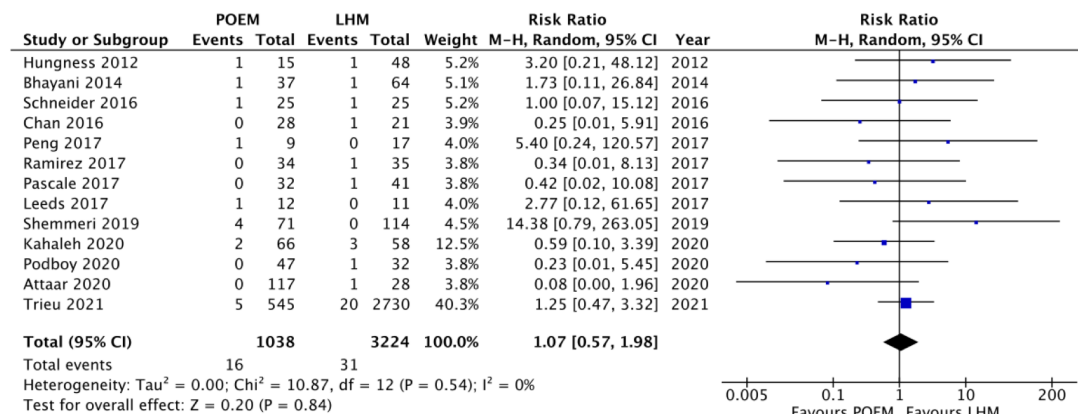


Figura 7 - Grade III in the CD classification

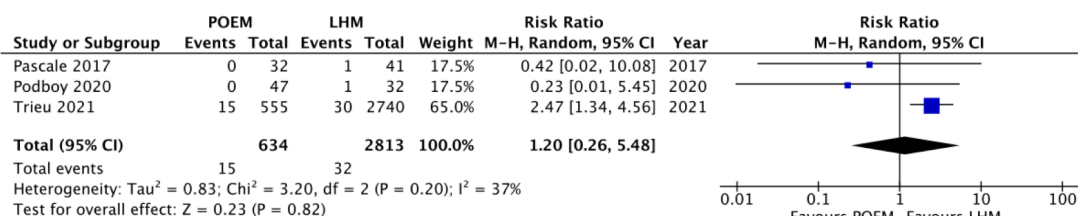


Figura 8 - Grade IV in the CD classification

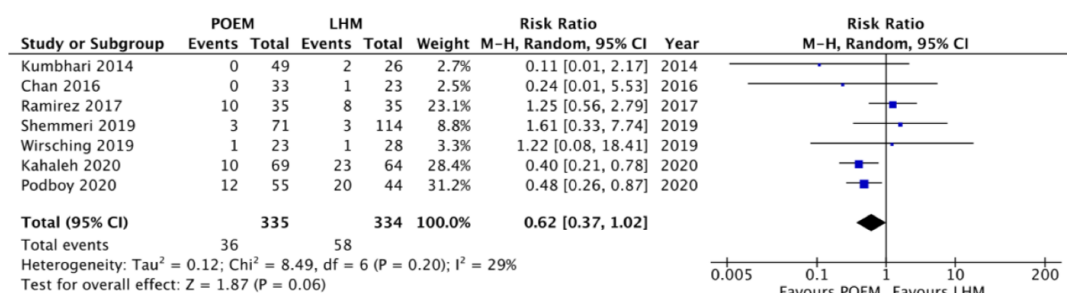


Figura 9 - Reintervention rate

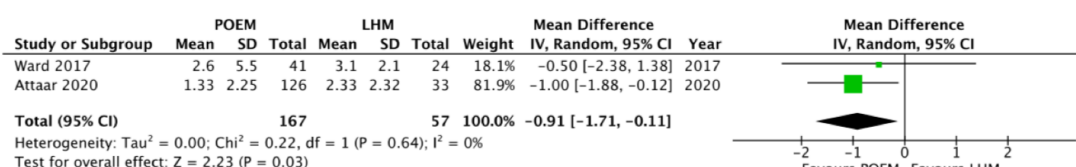


Figura 10 - Postoperative pain

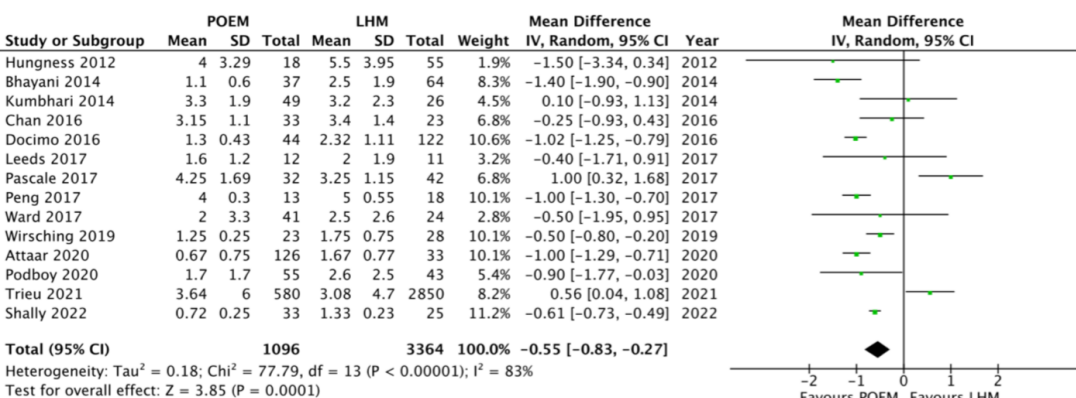


Figura 11 - Length of stay

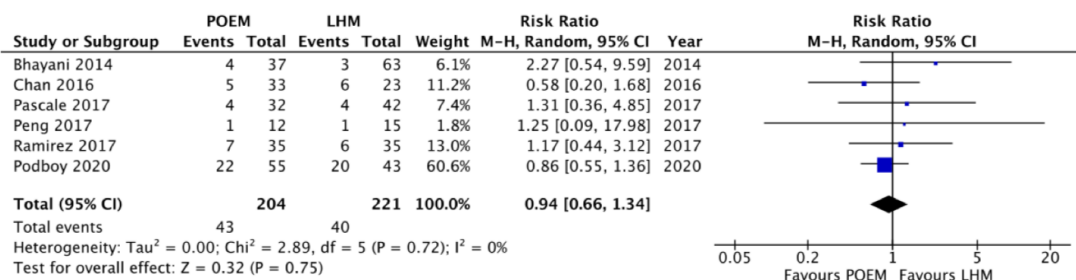


Figura 12 - Occurrence of GERD symptoms

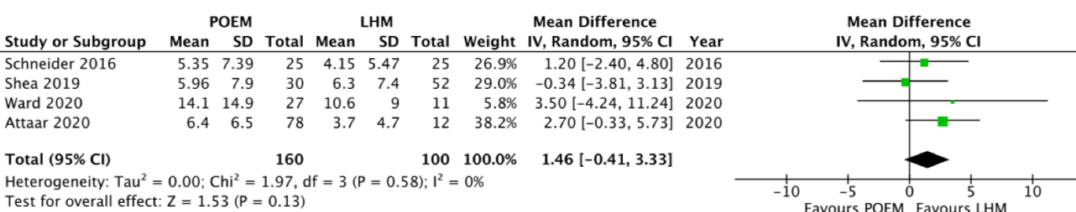


Figura 13 - GERD HRQL

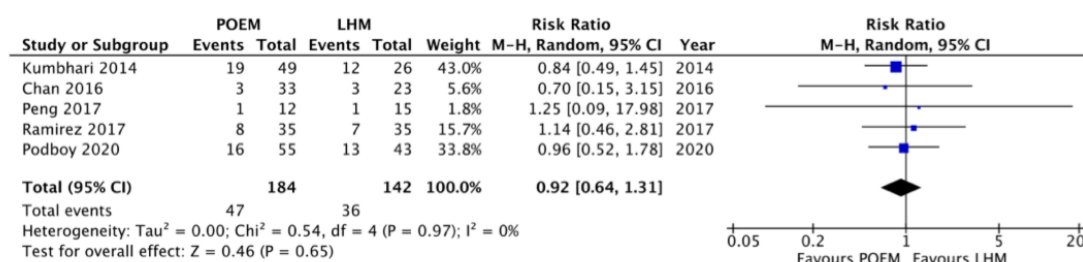


Figura 14 - Use of proton pump inhibitors

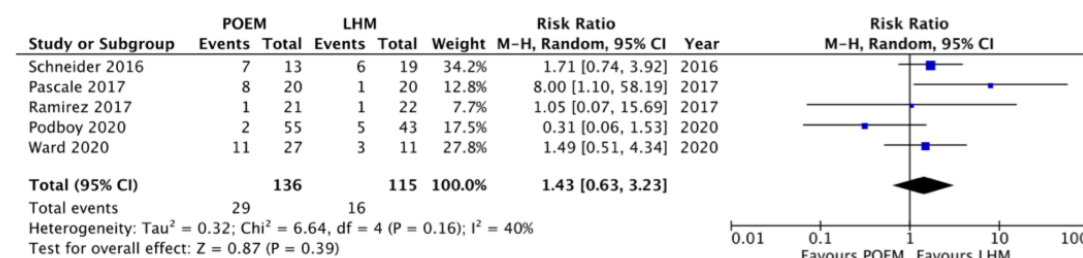


Figura 15 – Esophagitis

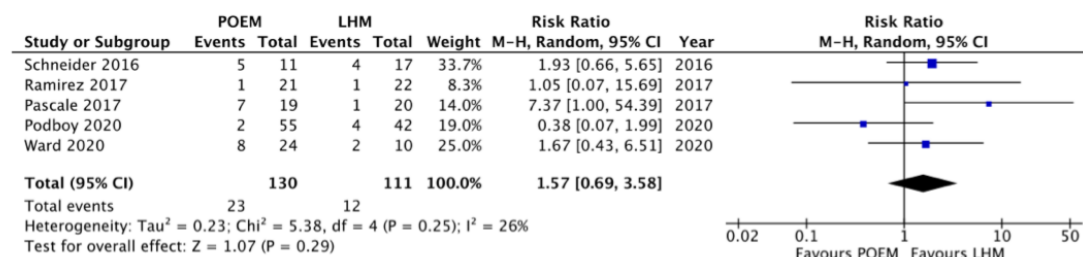


Figura 16 - Esophagitis LA grades A and B

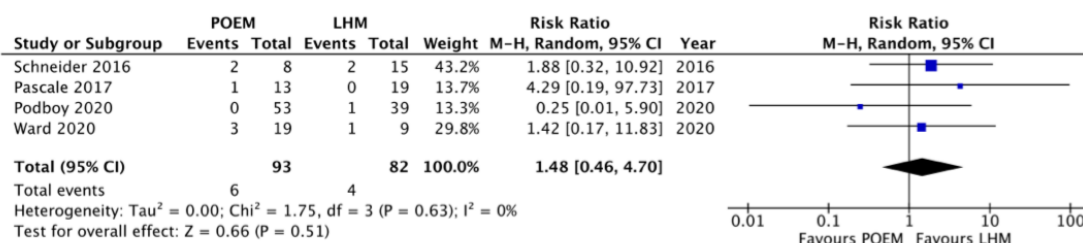


Figura 17 - Esophagitis LA grades C and D



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page and paragraph/ table #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both. - MANDATÓRIO	Página 1 “Achalasia: Laparoscopic Heller myotomy with fundoplication versus peroral endoscopic myotomy – A systematic review and meta-analysis”
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. – SEGUIR RECOMENDAÇÕES DA REVISTA	Página 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. – MANDATÓRIO <i>O rationale corresponde à justificação da importância da revisão sistemática</i>	Página 3 “Consequently, over the past decade, POEM has emerged as a viable substitute for laparoscopic Heller myotomy with fundoplication due to its reduced invasiveness. Nevertheless, a concern that has been raised regarding this endoscopic method is the potential for iatrogenic gastroesophageal reflux disease to develop since POEM lacks an anti-reflux mechanism in contrast to the surgical alternative.”
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). - MANDATÓRIO	Página 3 “Therefore, a comparison of the outcomes of patients diagnosed with achalasia who underwent laparoscopic Heller myotomy with fundoplication or POEM is the objective of this meta-analysis. The assessed results include the efficacy of each procedure as determined by symptomatology, with the Eckardt score being the preferred measurement, the postoperative pain, the occurrence of gastroesophageal reflux following each procedure, the length of time required for procedures and hospital stays, and potential complications and relapses.”



PRISMA 2009 Checklist

METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. – FACULTATIVO	Não aplicável.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. – MANDATÓRIO <i>É altamente recomendado, de acordo com as boas práticas da Cochrane, que não sejam aplicados critérios de exclusão baseados na língua e/ou data de publicação dos estudos.</i>	Página 4 “Studies published from January 2010 to December 2022 were included. The selection of this time restriction was because the initial publication about POEM was published by Inoue et al in 2010. (...) Subsequently, the authors assessed the full texts and excluded articles that fit the exclusion criteria: Pediatric studies, animal studies, case reports, conference abstracts, reviews, comments, and articles not pertaining to the research question. Language restrictions were not applied.”
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. – MANDATÓRIO <i>Em consonância com as boas práticas da Cochrane, é mandatório que se verifique pesquisa em pelo menos duas bases de pesquisa bibliográfica (idealmente, deverão ser pesquisadas duas bases generalistas e uma específica da área). No caso de revisões sistemáticas de estudos experimentais/ensaio clínicos aleatorizados, é altamente recomendado que uma das bases pesquisadas corresponda à CENTRAL ou a bases de ensaios clínicos como a ClinicalTrials.gov.</i> <i>Estudos de revisão da literatura em que a pesquisa decorra numa única base de dados não serão classificados como revisões sistemáticas.</i>	Página 4 “Two authors independently searched the following databases for relevant literature: PubMed, Web of Science and Cochrane Library.”
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. – MANDATÓRIO <i>A query de pesquisa deve ser obrigatoriamente disponibilizada. A utilização de filtros de pesquisa da InterTASC é altamente recomendada (https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home)</i>	Página 4 “The search query that was entered into PubMed was: “(((Achalasia[Title/Abstract]) OR (Achalasia treatment[Title/Abstract])) AND ((Laparoscopic heller myotomy[Title/Abstract]) OR (Heller Myotomy[Title/Abstract]) OR (LHM[Title/Abstract]) OR (Surgical Myotomy[Title/Abstract])) AND ((Peroral endoscopic myotomy[Title/Abstract]) OR (POEM[Title/Abstract]) OR (Surgical Endoscopy[Title/Abstract]))).” We used the following query in the Cochrane Library and Web of Science:



PRISMA 2009 Checklist

			"(((Achalasia) OR (Achalasia treatment)) AND ((Laparoscopic heller myotomy) OR (Heller Myotomy) OR (LHM) OR (Surgical Myotomy)) AND ((Peroral endoscopic myotomy) OR (POEM) OR (Surgical Endoscopy)))".
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). – MANDATÓRIO <i>As fases de selecção dos estudos primários devem ser descritas. Em consonância com as boas práticas da Cochrane, é mandatório que o processo de selecção envolva duas fases (fase de rastreio, em que os registos são seleccionados por título e abstract, e fase de inclusão, na qual se procede à leitura integral dos full texts). Em cada uma destas fases, o processo de selecção deve mandatoriamente envolver dois investigadores actuando de forma independente.</i>	Página 4 "Two authors independently searched the following databases for relevant literature: PubMed, Web of Science and Cochrane Library. (...) After reviewing the literature, two independent authors selected articles based on their titles and abstracts (...) Subsequently, the authors assessed the full texts and excluded articles that fit the exclusion criteria"
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. – MANDATÓRIO <i>Trata-se de descrever de que forma se procedeu à extracção de dados dos estudos primários. Em consonância com as boas práticas da Cochrane, tal processo deverá envolver dois investigadores de forma independente.</i>	Página 4 "Two authors were involved in data extraction (...)"
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. – MANDATÓRIO <i>Trata-se de descrever as variáveis para as quais foi obtida informação.</i>	Página 4 "Data extraction included study information (author, published year, study period, study design, sample size and surgical approach), patients baseline characteristics (age, gender, achalasia subtype and Eckardt score before surgery), surgical outcomes (operative time, intraoperative complications) and postoperative outcomes (length of stay, readmission rates, Eckardt score, GERD symptoms, esophagitis according to Los Angeles classification, use of proton pump inhibitors, postoperative complications according to Clavien-Dindo grade and use of analgesic medication)."
Risk of bias in individual studies / Risk of bias across studies	12/15	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. – MANDATÓRIO <i>Em todas as revisões sistemáticas, deverá existir um processo de avaliação da</i>	Página 4 "The Methodological Index for Non-Randomized Studies (MINORS) checklist, comprising 12 items, was utilized by two independent reviewers to



PRISMA 2009 Checklist

		<i>qualidade dos estudos primários. No caso de revisões sistemáticas de estudos experimentais/ensaio clínico aleatorizados, a aplicação dos critérios de risco de viés (Risk of Bias) da Cochrane é altamente recomendada. No caso de revisões sistemáticas de estudos observacionais, poderão ser seguidos os critérios ROBINS ou os critérios dos National Institutes of Health (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools).</i>	assess the quality of our included studies” Página 5 “The median score in the MINORS scale was 18, with a range of 16–20, as indicated in Table 1. As a result, all included studies were deemed adequate for inclusion in the quantitative analysis.”
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). – FACULTATIVO. APENAS NECESSÁRIO SE FOR FEITA META-ANÁLISE	Página 5 “The risk ratio (RR) was used for dichotomous variables, and the mean difference (MD) was used for continuous variables.”
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis. – FACULTATIVO. APENAS NECESSÁRIO SE FOR FEITA META-ANÁLISE	Página 5 “To evaluate heterogeneity, the Chi-squared (χ^2) test and the I-squared (I^2) measure were applied. We utilized a random effects model due to the heterogeneity of clinical outcomes among the included studies.”
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. – FACULTATIVO. APLICÁVEL APENAS SE FOR FEITA META-ANÁLISE	Não aplicável
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. – MANDATÓRIO	Figura 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. – MANDATÓRIO	Tabelas 1 e 2
Risk of bias within and across studies	19/ 22	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). – MANDATÓRIO	Página 5 “The median score in the MINORS scale was 18, with a range of 16–20, as indicated in Table 1. As a result, all included studies were deemed adequate for inclusion in the quantitative analysis.”
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. – FACULTATIVO. APLICÁVEL APENAS SE FOR FEITA META-ANÁLISE	“Supplemental File”
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency. – FACULTATIVO. MANDATÓRIO APENAS SE FOR FEITA META-ANÁLISE	Desde os últimos 4 parágrafos da página 5 até ao segundo parágrafo da página 7



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Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). – FACULTATIVO. APLICÁVEL APENAS SE FOR FEITA META-ANÁLISE	Não aplicável
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). – MANDATÓRIO	Desde o último parágrafo da página 7 até ao segundo parágrafo da página 9.
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). – MANDATÓRIO	Página 9 “There were some limitations to this study (...)”
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research. – MANDATÓRIO	Página 9 “In conclusion, this meta-analysis provides evidence that POEM, like LHM, is a safe and efficient treatment for achalasia. Nevertheless, POEM exhibits better results in terms of operative time, length of stay, postoperative pain, and a tendency towards lower recurrence. One noteworthy finding is that POEM exhibits superior clinical success compared to LHM during the initial months. There is a need for additional research to assess this matter over the long term. Hence, we believe that POEM may soon be regarded as the treatment of choice for achalasia, rather than exclusively type III achalasia.”
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. – SEGUIR RECOMENDAÇÕES DA REVISTA	Página 10 “No funding was received for this project.”

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Manuscript Submission Guidelines and Policies for *Journal of Laparoendoscopic & Advanced Surgical Techniques*

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Journal article with more than 3 authors	Pfister EL, DiNardo N, Mondo E, et al. Artificial miRNAs reduce human mutant Huntington throughout the striatum in a transgenic sheep model of Huntington's disease. <i>Hum Gene Ther</i> 2018;29(6):663–673; doi: 10.1089/hum.2017.199 [insert article-specific DOI if available].
Edited Book	Herzog RW, Zolotukhin S, (eds). <i>A Guide to Human Gene Therapy</i> . World Scientific Publishing Co. Pte. Ltd.: Singapore; 2010.
Chapter in an Edited Book	Nicklin SA, Baker AH. Adenoviral Vectors. In: <i>A Guide to Human Gene Therapy</i> . (Herzog RW, Zolotukhin S. eds.) World Scientific Publishing Co. Pte. Ltd.: Singapore; 2010; pp. 21-36.

Authored Book	Isaacson W. The Code Breaker: Jennifer Doudna, Gene Editing, and the Future of the Human Race. Simon & Schuster: New York, NY; 2021.
Website	Last name, first/middle initial(s) of author(s) [if available]. U.S. Food and Drug Administration. What is Gene Therapy? Silver Spring, MD; 2018. Available from: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/what-gene-therapy . [Last accessed: month/date/year].
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