

# Is Per-oral Endoscopic Myotomy (POEM) More Effective than Pneumatic Dilation and Heller myotomy? A Systematic Review and Meta-Analysis: Supplements

## S1. PICO questions

### Population

Adults and children with achalasia who are candidates for surgery. The motility disorder must have been objectively established by esophageal manometry

- Exclude secondary esophageal motility disorders, such as secondary to esophagogastric cancer, large hiatal hernia (>3cm), post-radiotherapy
- Population subgroups of interest (pending available literature)
  - Achalasia subtypes (subtypes 1, 2 and 3)
  - Esophageal anatomy – linear vs. sigmoid
  - Prior intervention (Botulinum toxin, dilation or myotomy)
  - Adults vs. children
  - Surgeon experience (foregut surgeons with previous experience in Heller)

**Intervention:** Peroral endoscopic myotomy (POEM)

### Comparators

- Heller myotomy [KQ1]
- Pneumatic Dilation [KQ2]

### Outcomes

- Dysphagia rates
- Pain scores
- Reflux symptoms, including:
  - Heartburn
  - Regurgitation
  - Belching
- Bloating
- Rectal flatulence
- Quality of life, patient satisfaction
- Cost
- Length of hospital stay
- Perforation rates
  - Detected
  - Undetected
- Reoperation rates

### Study design

- Systematic reviews (with or without meta-analysis)
- RCTs
- Non-randomized comparative studies (experimental or observational)
- Non-comparative (experimental or observational) studies *if* no evidence found from aforementioned study designs – exclude case reports

## **S2. PubMed search string used during the literature search.**

(((((POEM OR (peroral endoscopic myotomy) OR (per-oral endoscopic myotomy) OR (peroral esophageal myotomy) OR (per-oral esophageal myotomy) OR (laparoscopic esophageal myotomy) OR (laparoscopic oesophagealmyotomy) OR (pneumatic dilation) OR (pneumatic dilation) OR (Heller myotomy)) AND (achalasia OR "Jackhammer esophagus" OR (distal esophageal spasm)) AND "English"[Language]))) NOT (("address"[Publication Type] OR "autobiography"[Publication Type] OR "bibliography"[Publication Type] OR "biography"[Publication Type] OR "book illustrations"[Publication Type] OR "case reports"[Publication Type] OR "classical article"[Publication Type] OR "clinical conference"[Publication Type] OR "clinical trial, veterinary"[Publication Type] OR "collected work"[Publication Type] OR "comment"[Publication Type] OR "congress"[Publication Type] OR "consensus development conference"[Publication Type] OR "consensus development conference, NIH"[Publication Type] OR "corrected and republished article"[Publication Type] OR "dataset"[Publication Type] OR "dictionary"[Publication Type] OR "directory"[Publication Type] OR "duplicate publication"[Publication Type] OR "editorial"[Publication Type] OR "ephemera"[Publication Type] OR "expression of concern"[Publication Type] OR "festschrift"[Publication Type] OR "government document"[Publication Type] OR "historical article"[Publication Type] OR "interactive tutorial"[Publication Type] OR "interview"[Publication Type] OR "lecture"[Publication Type] OR "legal case"[Publication Type] OR "legislation"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "patient education handout"[Publication Type] OR "periodical index"[Publication Type] OR "personal narrative"[Publication Type] OR "pictorial work"[Publication Type] OR "portrait"[Publication Type] OR "retracted publication"[Publication Type] OR "retraction of publication"[Publication Type] OR "video audio media"[Publication Type] OR "webcasts"[Publication Type])))

### **S3. Excluded references after full text review.**

1. Akintoye E, Kumar N, Obaitan I, Alayo QA, Thompson CC (2016) Peroral endoscopic myotomy: a meta-analysis. *Endoscopy* 48:1059-1068
2. Allaix ME, Patti MG (2016) Toward a Tailored Treatment of Achalasia: An Evidence-Based Approach. *J Laparoendosc Adv Surg Tech A* 26:256-263
3. Andolfi C, Fisichella PM (2019) Meta-analysis of clinical outcome after treatment for achalasia based on manometric subtypes. *Br J Surg* 106:332-341
4. Arora Z, Thota PN, Sanaka MR (2017) Achalasia: current therapeutic options. *Ther Adv Chronic Dis* 8:101-108
5. Awaiz A, Yunus RM, Khan S, Memon B, Memon MA (2017) Systematic Review and Meta-Analysis of Perioperative Outcomes of Peroral Endoscopic Myotomy (POEM) and Laparoscopic Heller Myotomy (LHM) for Achalasia. *Surg Laparosc Endosc Percutan Tech* 27:123-131
6. Barbieri LA, Hassan C, Rosati R, Romario UF, Correale L, Repici A (2015) Systematic review and meta-analysis: Efficacy and safety of POEM for achalasia. *United European Gastroenterol J* 3:325-334
7. Boeckxstaens GE (2016) Achalasia: From Bench to Peroral Endoscopic Myotomy. *Dig Dis* 34:476-482
8. Campos GM, Vittinghoff E, Rabl C, Takata M, Gadenstatter M, Lin F, Ciovica R (2009) Endoscopic and surgical treatments for achalasia: a systematic review and meta-analysis. *Ann Surg* 249:45-57
9. Chan SM, Wu JC, Teoh AY, Yip HC, Ng EK, Lau JY, Chiu PW (2016) Comparison of early outcomes and quality of life after laparoscopic Heller's cardiomyotomy to peroral endoscopic myotomy for treatment of achalasia. *Dig Endosc* 28:27-32
10. Chandrasekhara V, Desilets D, Falk GW, Inoue H, Romanelli JR, Savides TJ, Stavropoulos SN, Swanstrom LL (2015) The American Society for Gastrointestinal Endoscopy PIVI (Preservation and Incorporation of Valuable Endoscopic Innovations) on peroral endoscopic myotomy. *Gastrointest Endosc* 81:1087-1100.e1081
11. Chavez YH, Ciarleglio MM, Clarke JO, Nandwani M, Stein E, Roland BC (2015) Upper esophageal sphincter abnormalities: frequent finding on high-resolution esophageal manometry and associated with poorer treatment response in achalasia. *J Clin Gastroenterol* 49:17-23
12. Crespin OM, Liu LWC, Parmar A, Jackson TD, Hamid J, Shlomovitz E, Okrainec A (2017) Safety and efficacy of POEM for treatment of achalasia: a systematic review of the literature. *Surg Endosc* 31:2187-2201
13. DeMeester SR (2015) Optimizing Patient Selection and Outcomes for Surgical Treatment of GERD and Achalasia. *Curr Treat Options Gastroenterol* 13:1-15
14. DeMeester SR (2017) Per-oral endoscopic myotomy for achalasia. *J Thorac Dis* 9:S130-s134

15. Docimo S, Jr., Mathew A, Shope AJ, Winder JS, Haluck RS, Pauli EM (2017) Reduced postoperative pain scores and narcotic use favor per-oral endoscopic myotomy over laparoscopic Heller myotomy. *Surg Endosc* 31:795-800
16. Dunst CM, Kurian AA, Swanstrom LL (2014) Endoscopic myotomy for achalasia. *Adv Surg* 48:27-41
17. Esposito D, Maione F, D'Alessandro A, Sarnelli G, De Palma GD (2016) Endoscopic treatment of esophageal achalasia. *World J Gastrointest Endosc* 8:30-39
18. Estremera-Arevalo F, Albeniz E, Rullan M, Areste I, Iglesias R, Vila JJ (2017) Efficacy of peroral endoscopic myotomy compared with other invasive treatment options for the different esophageal motor disorders. *Rev Esp Enferm Dig* 109:578-586
19. Evensen H, Kristensen V, Larssen L, Sandstad O, Hauge T, Medhus AW (2019) Outcome of peroral endoscopic myotomy (POEM) in treatment-naïve patients. A systematic review. *Scand J Gastroenterol* 54:1-7
20. Familiari P, Greco S, Volkanovska A, Gigante G, Cali A, Boskoski I, Costamagna G (2015) Achalasia: current treatment options. *Expert Rev Gastroenterol Hepatol* 9:1101-1114
21. Fernandez-Ananin S, Fernandez AF, Balague C, Sacoto D, Targarona EM (2018) What to do when Heller's myotomy fails? Pneumatic dilation, laparoscopic remyotomy or peroral endoscopic myotomy: A systematic review. *J Minim Access Surg* 14:177-184
22. Fisichella PM, DeMeester SR, Hungness E, Perretta S, Soper NJ, Rosemurgy A, Torquati A, Sachdeva AK, Patti MG (2015) Emerging Techniques in Minimally Invasive Surgery. *Pros and Cons. J Gastrointest Surg* 19:1355-1362
23. Fisichella PM, Ferreres A, Patti MG (2015) Peroral Endoscopic Myotomy for Achalasia. *JAMA Surg* 150:806-807
24. Franklin AL, Petrosyan M, Kane TD (2014) Childhood achalasia: A comprehensive review of disease, diagnosis and therapeutic management. *World J Gastrointest Endosc* 6:105-111
25. Fuchs KH, Schulz T, Varga G, Babic B, Breithaupt W (2015) The potential and perspective of peroral endoscopic esophageal myotomy for achalasia. *World J Surg* 39:1598-1602
26. Greene CL, Chang EJ, Oh DS, Worrell SG, Hagen JA, DeMeester SR (2015) High resolution manometry sub-classification of Achalasia: does it really matter? Does Achalasia sub-classification matter? *Surg Endosc* 29:1363-1367
27. Hamer PW, Holloway RH, Crosthwaite G, Devitt PG, Thompson SK (2016) Update in achalasia: what the surgeon needs to know. *ANZ J Surg* 86:555-559
28. Herbella FA, Moura EG, Patti MG (2017) Achalasia 2016: Treatment Alternatives. *J Laparoendosc Adv Surg Tech A* 27:6-11
29. Illes A, Farkas N, Hegyi P, Garami A, Szabo I, Solymar M, Petervari E, Balasko M, Par G, Sarlos P, Bajor J, Szucs A, Czimmer J, Szemes K, Vincze A (2017) Is Heller myotomy better than balloon dilation? A meta-analysis. *J Gastrointest Liver Dis* 26:121-127

30. Islam S (2017) Achalasia. *Semin Pediatr Surg* 26:116-120
31. Kahrilas PJ, Bredenoord AJ, Carlson DA, Pandolfino JE (2018) Advances in Management of Esophageal Motility Disorders. *Clin Gastroenterol Hepatol* 16:1692-1700
32. Kahrilas PJ, Bredenoord AJ, Fox M, Gyawali CP, Roman S, Smout A, Pandolfino JE (2017) Expert consensus document: Advances in the management of oesophageal motility disorders in the era of high-resolution manometry: a focus on achalasia syndromes. *Nat Rev Gastroenterol Hepatol* 14:677-688
33. Kahrilas PJ, Katzka D, Richter JE (2017) Clinical Practice Update: The Use of Per-Oral Endoscopic Myotomy in Achalasia: Expert Review and Best Practice Advice From the AGA Institute. *Gastroenterology* 153:1205-1211
34. Kahrilas PJ, Pandolfino JE (2017) Treatments for achalasia in 2017: how to choose among them. *Curr Opin Gastroenterol* 33:270-276
35. Khan MA, Kumbhari V, Ngamruengphong S, Ismail A, Chen YI, Chavez YH, Bukhari M, Nollan R, Ismail MK, Onimaru M, Balassone V, Sharata A, Swanstrom L, Inoue H, Repici A, Khashab MA (2017) Is POEM the Answer for Management of Spastic Esophageal Disorders? A Systematic Review and Meta-Analysis. *Dig Dis Sci* 62:35-44
36. Khashab MA, Benias PC, Swanstrom LL (2018) Endoscopic Myotomy for Foregut Motility Disorders. *Gastroenterology* 154:1901-1910
37. Kotilea K, Mahler T, Bontems P, Deviere J, Louis H (2018) Management of esophageal motility disorders in children : a review. *Acta Gastroenterol Belg* 81:295-304
38. Krill JT, Naik RD, Vaezi MF (2016) Clinical management of achalasia: current state of the art. *Clin Exp Gastroenterol* 9:71-82
39. Kumar A, Wig JD, Kochhar R, Gupta NM, Nagi B (1994) An audit of pneumatic dilation and oesophagomyotomy in patients with achalasia cardia. *Trop Gastroenterol* 15:152-156
40. Maradey-Romero C, Gabbard S, Fass R (2014) Treatment of esophageal motility disorders based on the chicago classification. *Curr Treat Options Gastroenterol* 12:441-455
41. Marano L, Pallabazzer G, Solito B, Santi S, Pigazzi A, De Luca R, Biondo FG, Spaziani A, Longaroni M, Di Martino N, Boccardi V, Patrì A (2016) Surgery or Peroral Esophageal Myotomy for Achalasia: A Systematic Review and Meta-Analysis. *Medicine (Baltimore)* 95:e3001
42. Mu D, Li YY, Zhang MM, Zhang Y, Li Z, Li YQ (2017) POEM for special patient cohorts: A review. *J Dig Dis* 18:265-272
43. Pandolfino JE, Gawron AJ (2015) Achalasia: a systematic review. *JAMA* 313:1841-1852
44. Parsa N, Khashab MA (2018) POEM in the Treatment of Esophageal Disorders. *Curr Treat Options Gastroenterol* 16:27-40

45. Patel K, Abbassi-Ghadi N, Markar S, Kumar S, Jethwa P, Zaninotto G (2016) Peroral endoscopic myotomy for the treatment of esophageal achalasia: systematic review and pooled analysis. *Dis Esophagus* 29:807-819
46. Patti MG, Andolfi C, Bowers SP, Soper NJ (2017) POEM vs Laparoscopic Heller Myotomy and Fundoplication: Which Is Now the Gold Standard for Treatment of Achalasia? *J Gastrointest Surg* 21:207-214
47. Ponds FA, Fockens P, Neuhaus H, Beyna T, Frieling T, Chiu P, Wu JC, Costamagna G, Familiari P, Wong VW, Kahrilas P, Pandolfino JE, Smout AJ, Bredenoord AJ (2017) Peroral endoscopic myotomy (POEM) versus pneumatic dilation in therapy-naive patients with achalasia: Results of a randomized controlled trial. *Gastroenterology* 152:S139
48. Ramchandani M, Nageshwar Reddy D, Nabi Z, Chavan R, Bapaye A, Bhatia S, Mehta N, Dhawan P, Chaudhary A, Ghoshal UC, Philip M, Neuhaus H, Deviere J, Inoue H (2018) Management of achalasia cardia: Expert consensus statements. *J Gastroenterol Hepatol* 33:1436-1444
49. Repici A, Fuccio L, Maselli R, Mazza F, Correale L, Mandolesi D, Bellisario C, Sethi A, Khashab MA, Rosch T, Hassan C (2018) GERD after per-oral endoscopic myotomy as compared with Heller's myotomy with fundoplication: a systematic review with meta-analysis. *Gastrointest Endosc* 87:934-943.e918
50. Roman S, Kahrilas PJ (2015) Distal esophageal spasm. *Curr Opin Gastroenterol* 31:328-333
51. Schaheen LW, Sanchez MV, Luketich JD (2018) Peroral Endoscopic Myotomy for Achalasia. *Thorac Surg Clin* 28:499-506
52. Schlottmann F, Lockett DJ, Fine J, Shaheen NJ, Patti MG (2018) Laparoscopic Heller Myotomy Versus Peroral Endoscopic Myotomy (POEM) for Achalasia: A Systematic Review and Meta-analysis. *Ann Surg* 267:451-460
53. Schlottmann F, Patti MG (2018) Laparoscopic Heller Myotomy versus Per Oral Endoscopic Myotomy: Evidence-Based Approach to the Treatment of Esophageal Achalasia. *Am Surg* 84:496-500
54. Schlottmann F, Shaheen NJ, Madanick RD, Patti MG (2017) The role of Heller myotomy and POEM for nonachalasia motility disorders. *Dis Esophagus* 30:1-5
55. Shah ED, Chang AC, Law R (2019) Valuing innovative endoscopic techniques: per-oral endoscopic myotomy for the management of achalasia. *Gastrointest Endosc* 89:264-273.e263
56. Sharp NE, St Peter SD (2016) Treatment of Idiopathic Achalasia in the Pediatric Population: A Systematic Review. *Eur J Pediatr Surg* 26:143-149
57. Smith I, Kahaleh M (2018) An Update on Current Management Strategies for Achalasia and Future Perspectives. *J Clin Gastroenterol* 52:277-286
58. Stavropoulos SN, Modayil R, Friedel D (2015) Per oral endoscopic myotomy for the treatment of achalasia. *Curr Opin Gastroenterol* 31:430-440

59. Talukdar R, Inoue H, Nageshwar Reddy D (2015) Efficacy of peroral endoscopic myotomy (POEM) in the treatment of achalasia: a systematic review and meta-analysis. *Surg Endosc* 29:3030-3046
60. Tefas C, Ababneh R, Tantau M (2018) Peroral Endoscopic Myotomy Versus Heller Myotomy for Achalasia: Pros and Cons. *Chirurgia (Bucur)* 113:185-191
61. Teitelbaum EN, Boris L, Arafat FO, Nicodeme F, Lin Z, Kahrilas PJ, Pandolfino JE, Soper NJ, Hungness ES (2013) Comparison of esophagogastric junction distensibility changes during POEM and Heller myotomy using intraoperative FLIP. *Surg Endosc* 27:4547-4555
62. Teitelbaum EN, Rajeswaran S, Zhang R, Sieberg RT, Miller FH, Soper NJ, Hungness ES (2013) Peroral esophageal myotomy (POEM) and laparoscopic Heller myotomy produce a similar short-term anatomic and functional effect. *Surgery* 154:885-891; discussion 891-882
63. Teitelbaum EN, Soper NJ, Pandolfino JE, Kahrilas PJ, Boris L, Nicodeme F, Lin Z, Hungness ES (2014) An extended proximal esophageal myotomy is necessary to normalize EGJ distensibility during Heller myotomy for achalasia, but not POEM. *Surg Endosc* 28:2840-2847
64. Teitelbaum EN, Soper NJ, Pandolfino JE, Kahrilas PJ, Hirano I, Boris L, Nicodeme F, Lin Z, Hungness ES (2015) Esophagogastric junction distensibility measurements during Heller myotomy and POEM for achalasia predict postoperative symptomatic outcomes. *Surg Endosc* 29:522-528
65. Tuason J, Inoue H (2017) Current status of achalasia management: a review on diagnosis and treatment. *J Gastroenterol* 52:401-406
66. van Lennep M, van Wijk MP, Omari TIM, Benninga MA, Singendonk MMJ (2018) Clinical management of pediatric achalasia. *Expert Rev Gastroenterol Hepatol* 12:391-404
67. Wei M, Yang T, Yang X, Wang Z, Zhou Z (2015) Peroral esophageal myotomy versus laparoscopic Heller's myotomy for achalasia: a meta-analysis. *J Laparoendosc Adv Surg Tech A* 25:123-129
68. Wong I, Law S (2017) Peroral endoscopic myotomy (POEM) for treating esophageal motility disorders. *Ann Transl Med* 5:192
69. Zaninotto G, Bennett C, Boeckxstaens G, Costantini M, Ferguson MK, Pandolfino JE, Patti MG, Ribeiro U, Jr., Richter J, Swanstrom L, Tack J, Triadafilopoulos G, Markar SR, Salvador R, Faccio L, Andreollo NA, Cecconello I, Costamagna G, da Rocha JRM, Hungness ES, Fisichella PM, Fuchs KH, Gockel I, Gurski R, Gyawali CP, Herbella FAM, Holloway RH, Hongo M, Jobe BA, Kahrilas PJ, Katzka DA, Dua KS, Liu D, Moonen A, Nasi A, Pasricha PJ, Penagini R, Perretta S, Sallum RAA, Sarnelli G, Savarino E, Schlottmann F, Sifrim D, Soper N, Tatum RP, Vaezi MF, van Herwaarden-Lindeboom M, Vanuysel T, Vela MF, Watson DI, Zerbib F, Gittens S, Pontillo C, Vermigli S, Inama D, Low DE (2018) The 2018 ISDE achalasia guidelines. *Dis Esophagus* 31
70. Zhang Y, Wang H, Chen X, Liu L, Wang H, Liu B, Guo J, Jia H (2016) Per-Oral Endoscopic Myotomy Versus Laparoscopic Heller Myotomy for Achalasia: A Meta-Analysis of Nonrandomized Comparative Studies. *Medicine (Baltimore)* 95:e2736

#### S4. Disclosures including conflict(s) of interest and funding reported by study authors.

Hungness 2013	Olympus America, Inc. granted instruments used during the POEM procedures, but was not involved in the study design, data collection, analysis, or manuscript preparation. John E. Pandolfino has consulting agreements with Given Imaging and Crospon. Nathaniel J. Soper is on the scientific advisory boards of TransEnterix and Miret Surgical. Eric S. Hungness, Ezra N. Teitelbaum, Byron S. Santos, Fahd O. Arafat, and Peter J. Kahrilas have no conflicts of interest or financial ties to disclose.
Khashab 2017	No financial support. COI: Mouen Khashab is consultant for Boston Scientific and Olympus America. Vivek Kumbhari is a consultant for Boston Scientific and Apollo Endosurgery. Anthony Kalloo is a founding member, equity holder and consultant for Apollo Endosurgery. All other authors have no relevant conflicts of interest to disclose.
Kumbhari 2015	M. Khashab is a consultant for Boston Scientific, Xlumena and Olympus America and has received research support from Cook Medical. H. Inoue is a founding member, equity holder, and consultant for Apollo Endosurgery. No other financial relationships relevant to this article were disclosed.
Miller 2017	Jeffrey M. Marks has Consultant for US Endoscopy, GI Supply, Merck, GORE, Apollo Endosurgery, Olympus, Fujifilm.
Peng 2017	Shandong Provincial Natural Science Foundation of China (No. ZR2013HL018) and Shandong Provincial Medicine and Health Science and Technology Program (No. 2015WS0366).
Ponds 2019	This study was made possible with financial support from Fonds NutsOhra (FNO grant 1202-022) and an ESGE Research Grant. The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Dr Fockens reported receiving personal fees from Cook Endoscopy, Olympus, Ethicon Endosurgery, and Fujifilm, consulting for Medtronic, and receiving research support from Boston Scientific and Ovesco outside the submitted work. Dr Beyna reported receiving grants, personal fees, and nonfinancial support from Olympus, and Boston Scientific, personal fees and nonfinancial support from Medtronic, personal fees from Falk Foundation, and grants and nonfinancial support from Erbe USA outside the submitted work. Dr. Wu reported receiving personal fees from AstraZeneca, Takeda, Reckitt Benckiser, and Menarini outside the submitted work. Dr. Costamagna reported receiving personal fees and nonfinancial support from Olympus, grants from Boston Scientific, and grants and nonfinancial support from Cook Medical outside the submitted work. Dr Kahrilas reported receiving grants from the National Institutes of Health during the conduct of the study. Dr Pandolfino reported receiving personal fees from Medtronic, Diversatek, Torax, Ironwood, and Takeda and a grant from Impleo outside the submitted work. Dr. Bredenoord reported receiving grants and personal fees from Norgine, grants and personal fees from Laborie, personal fees from Medtronic, personal fees from Diversatek, grants from Nutricia, personal fees from Regeneron, personal fees from Celgene, grants and personal fees from Bayer, and personal fees from Dr. Falk outside the submitted work and grants from Fonds NutsOhra and ESGE Research during the conduct of the study. No other disclosures were reported.
Schneider 2016	Dr. Schneider's fellowship is supported by the Ryan Hill Foundation and the Foundation for Surgical Fellowships.
Wang 2016	This study was funded by Development and Reform Commission of Hunan Province (XFGTZ2014713)
Werner 2019	Various public foundations and Olympus Europa supported the trial. None of the sponsors had any role in the design of the trial or in the analysis or interpretation of the data.



**S5. Risk of bias detailed assessments for 20 observational studies addressing POEM (per oral endoscopic myotomy) versus HM (laparoscopic Heller myotomy).**

Study	Selection Bias	Incomplete Outcome Data	Selective Outcome Reporting	Performance Bias	Detection Bias	Overall
Bhayani 2014	Low	High	Low	Low	Low	High
Caldaro 2015	High	High	High	High	High	High
dePascale 2017	Low	High	Low	Low	High	High
Fumagalli 2016	Low	Low	Low	Low	High	High
Greenleaf 2018	Low	Low	Low	Low	Low	Low
Hanna 2018	High	Low	Low	High	High	High
Hungness 2013	High	High	High	Low	High	High
Khashab 2017	High	High	High	High	Unclear	High
Kumagai 2015	Low	High	High	High	High	High
Kumbhari 2015	High	High	High	High	High	High
Leeds 2017	High	High	Low	Unclear	High	High
Miller 2017	High	High	High	High	High	High
Peng 2017	High	Low	Low	High	High	High
Podboy 2020	Low	High	Low	Low	Low	High
Ramirez 2018	Unclear	Low	Low	Unclear	High	High
Sanaka 2018	High	High	Low	Low	High	High
Schneider 2016	Low	High	High	High	High	High
Ujiki 2013	High	High	High	High	High	High
Ward 2017	Low	Low	Low	Low	Low	Low
Wirsching 2019	High	High	Low	High	High	High

**S6. Cochrane Risk of Bias Tool 2.0 domains, signaling questions and answers, and judgements for Werner 2019.**

Domain	Randomization	Deviation from intended interventions	Missing outcome data	Measurement of outcome	Selection of reported results	
<b>Signaling questions</b>	1.1 Was the allocation sequence random?	<b>Y</b>	2.1 Were participants aware of their intervention? <b>Y</b>	3.1 Were data available for all, or nearly all, participants? <b>Y (N)</b> <b>(reflux, esophagitis, LESP, abnormal pH)</b>	4.1 Was the method of measuring the outcome inappropriate? <b>N</b>	5.1 Was trial analysed in accordance with a pre-specified plan? <b>Y</b>
	1.2 Was the allocation sequences concealed?	<b>Y</b>	2.2 Were personnel aware of the intervention? <b>Y</b>	3.2 <b>Reflux, esophagitis, LESP, abnormal pH:</b> Evidence that the result was not biased by missing outcome data? <b>N</b>	4.2 Could measurement or ascertainment of the outcome differ between groups? <b>N</b>	5.2 Is the result likely selected from multiple eligible outcome measurements? <b>PN</b>
	1.3 Did baseline differences suggest a problem with randomization?	<b>N</b>	2.3 Were important non-protocol interventions balanced? <b>Y</b>	3.3 <b>Reflux, esophagitis, LESP, abnormal pH:</b> Could missingness depend on its true value? <b>Y</b>	4.3 Were outcome assessors aware of the interventions received? <b>PY</b>	5.3 Is the result likely selected from multiple eligible analyses of the data? <b>PN</b>
			2.4 Were there failures in implementation affecting the outcomes? <b>PN</b>	3.4 <b>Reflux, esophagitis, LESP, abnormal pH:</b> Is it <i>likely</i> that missingness depended on its true value? <b>PN</b>	4.4 Could assessment have been influenced by knowledge of intervention? <b>PN (PY)</b> <b>(subjective outcomes)</b>	
			2.5 Was there non-adherence affecting the outcomes? <b>NA</b>		4.5 <b>Subjective outcomes:</b> Is it <i>likely</i> assessment was influenced? <b>PN</b>	
<b>Judgement</b>	<b>Low Risk of Bias</b>	<b>Low Risk of Bias</b>	<b>Low RoB (primary outcome) Some Concern<sup>a</sup> (reflux, esophagitis, LESP, abnormal pH)</b>	<b>Low Risk of Bias (objective) Some Concern<sup>b</sup> (subjective outcomes)</b>	<b>Low Risk of Bias</b>	

Y- Yes, N- No, PY – Probably Yes, PN – Probably No

- a. At 2-year follow-up, only 78% and 72% of patients received EGD for POEM and LHM respectively, only 63% & 51% underwent pH testing, and only 69% & 65% underwent LESP testing. Given patients chose not to undergo testing, it is reasonable to assume the absence of data could be due to the true value. Patient reported reflux had excellent follow up at 2 years (96% & 94%, POEM & LHM), but the observed events are smaller than the missing participant
- b. Blinding of patients was not possible, and patients were the outcome assessors for all subjective outcomes, suggesting assessment could theoretically be influenced by this knowledge (4.4). Considering “objective assessment corroborated the primary finding,” it is unlikely that assessment truly was influenced by this knowledge (4.5).

### **S7. Components of the Eckardt Symptom Score and Stages [45].**

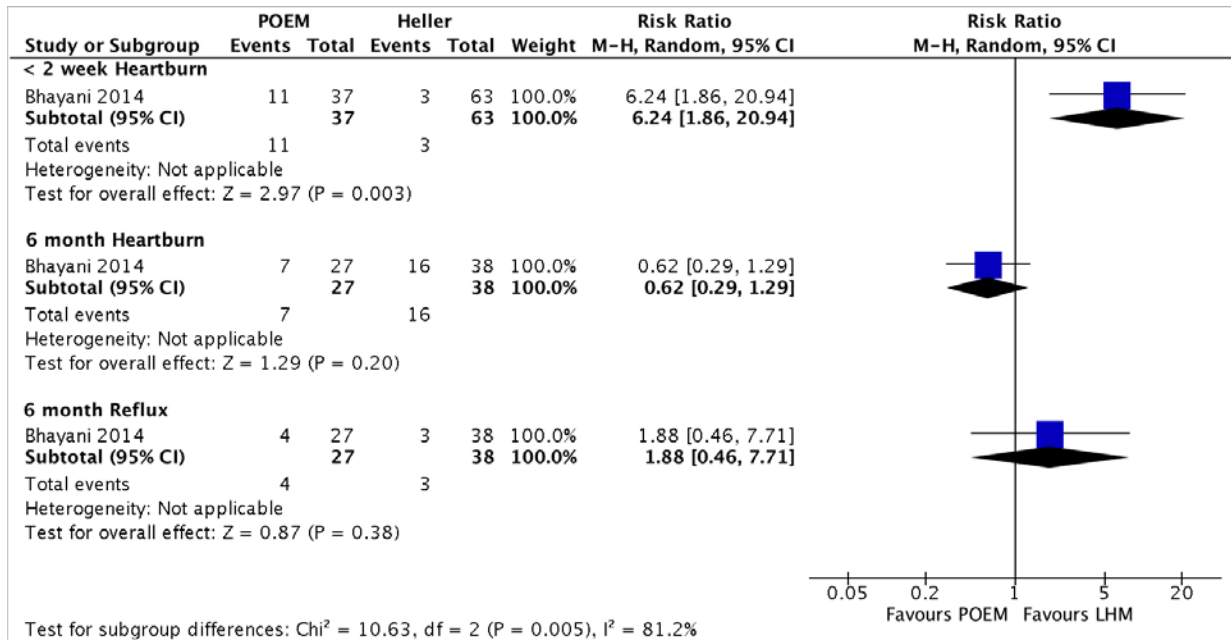
Eckardt Score and Components.

Score	Weight Loss (kg)	Dysphagia	Retrosternal Pain	Regurgitation
0	none	None	None	None
1	< 5	Occasional	Occasional	Occasional
2	5 - 10	Daily	Daily	Daily
3	>10	Each Meal	Each Meal	Each Meal

Eckardt Stages and associated scores and implication.

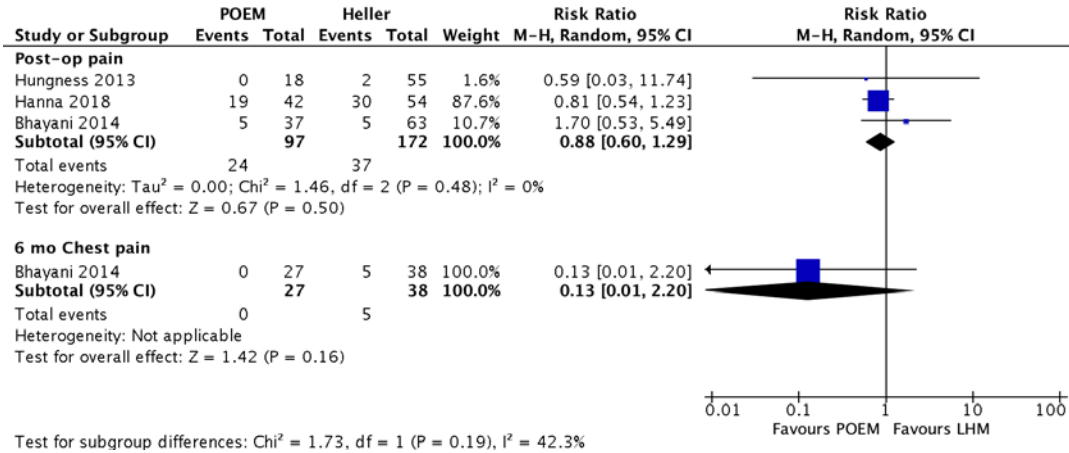
Stage	Eckardt Score	Clinical Implication
0	0 - 1	Remission
I	2 - 3	Remission
II	4 - 6	Treatment Failure
III	> 6	Treatment Failure

## S8. Gastroesophageal reflux (GER) symptoms as reported in Bhayani et al. [25]

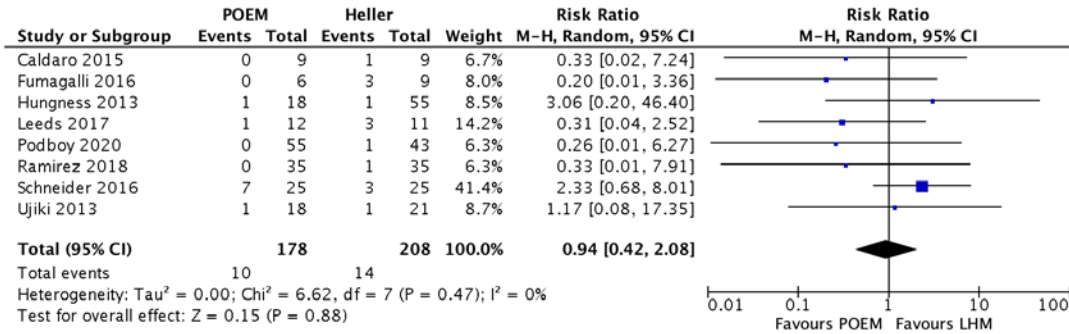


**S9. Observational data for per oral endoscopic myotomy (POEM) versus laparoscopic Heller myotomy (LHM) on pain (A), perforation (B), return to OR for postoperative complications (C), unexpected ICU stay (D), and length of hospital stay (E).**

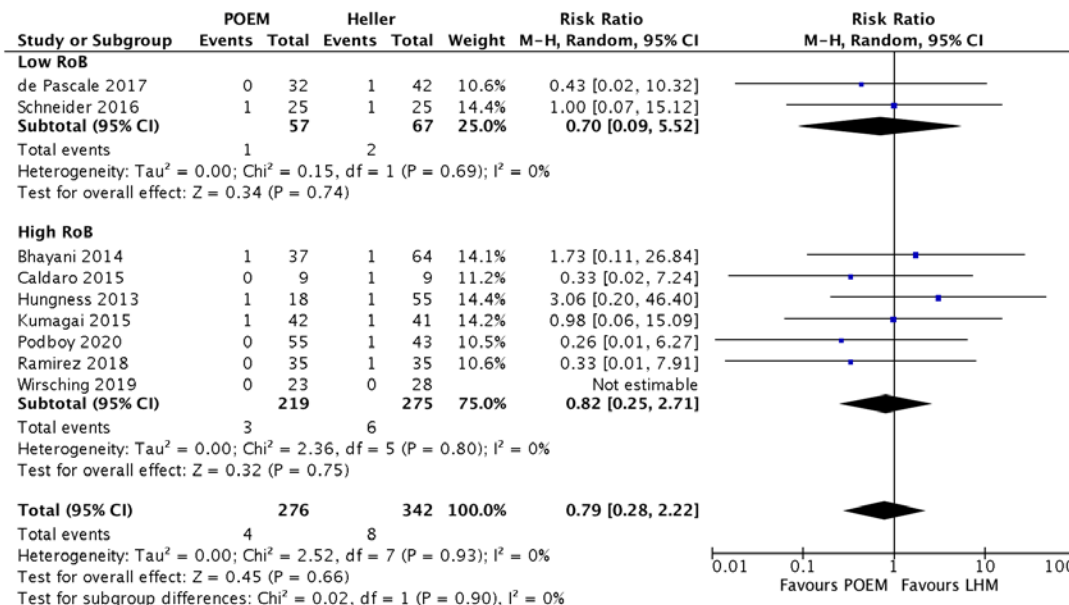
**A.**



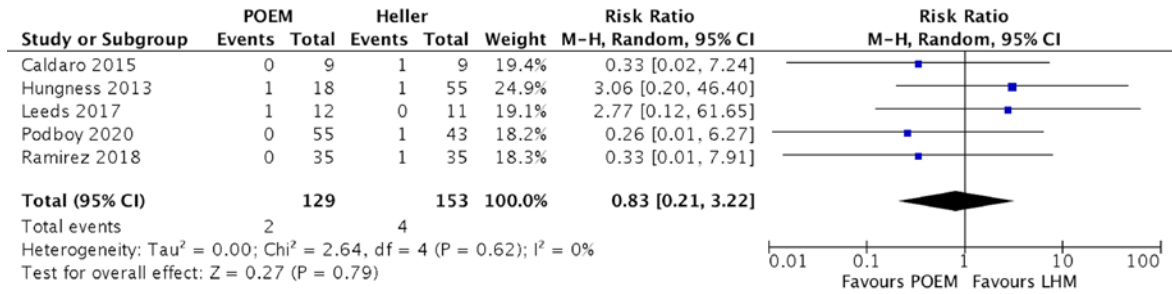
**B.**



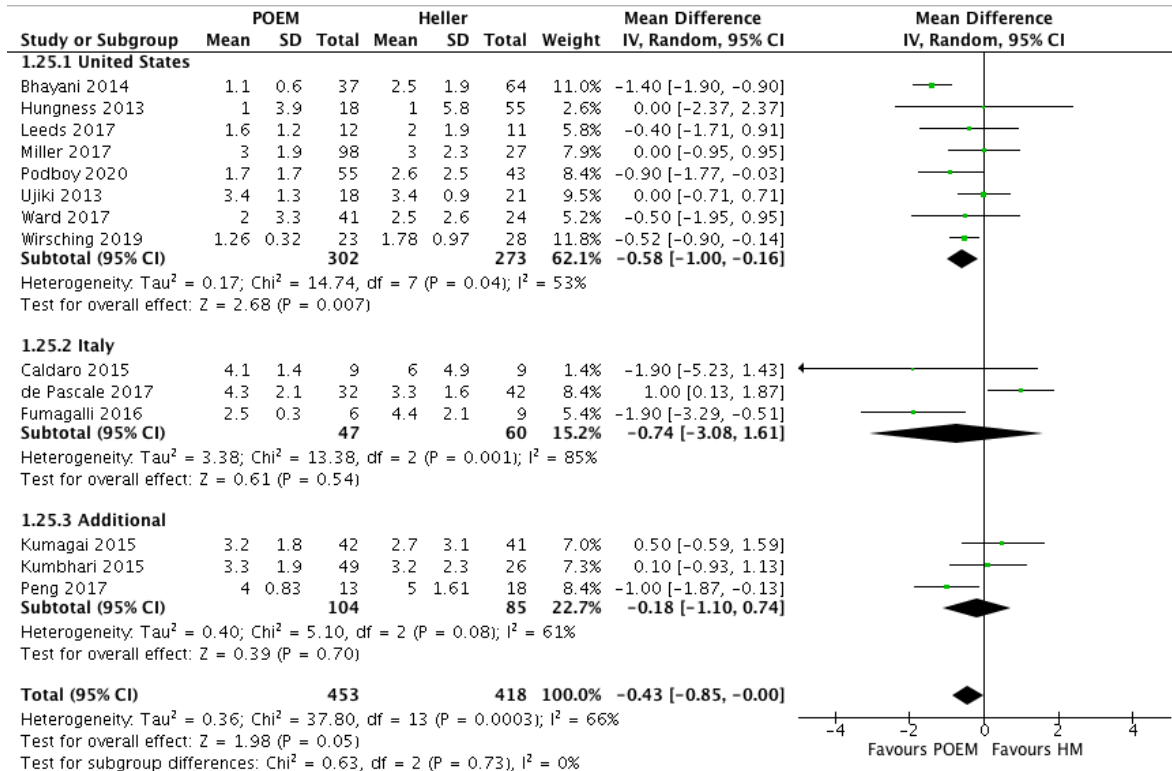
**C.**



**D.**



**E.**



**S10. Cost estimates from observational studies comparing per oral endoscopic myotomy (POEM) and Heller myotomy (HM). All values are in dollars.**

Study	POEM	HM	Description of Cost
Greenleaf 2018	10763.21	8923.43	USD, Pre-procedure, Index admission, & post-procedure costs
Hanna 2018	3473	3024	USD, Operative costs (room time and supplies)
Khashab 2017	14481	17782	USD, index admission (operative costs, inpatient stay charges)
Miller 2017	12120	11582	USD, "cost per cure" at first year
Wirsching 2019	14201	13328	USD, overall cost (hospital and clinic costs)

**S11. Risk of bias detailed assessments for 7 observational studies addressing POEM (per oral endoscopic myotomy) versus PD (pneumatic dilation).**

Study	Selection Bias	Incomplete Outcome Data	Selective Outcome Reporting	Performance Bias	Detection Bias	Overall
Kim 2019	High	High	High	Low	High	High
Meng 2017	Low	Low	Low	Low	Low	Low
Miller 2017	High	High	High	High	High	High
Sanaka 2016	High	Low	Low	Low	Low	High
Tan 2016	High	High	High	Low	High	High
Wang 2016	Unclear	High	High	High	High	High
Zheng 2019	Low	Low	Low	Unclear	Low	Low

**S12. Cochrane Risk of Bias Tool 2.0 Domains, signaling questions and answers, and judgements for Ponds 2019.**

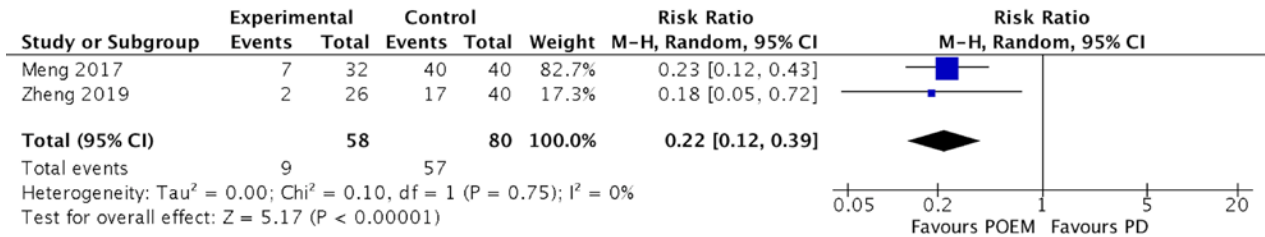
Domain	Randomization	Deviation from intended interventions	Missing outcome data	Measurement of outcome	Selection of reported results
<b>Signaling questions</b>	1.1 Was the allocation sequence random? <b>Y</b>	2.1 Were participants aware of their intervention? <b>Y</b>	3.1 Were data available for all, or nearly all, participants? <b>1° Outcome (2 yr symptom resolution)</b> <b>Y</b>	4.1 Was the method of measuring the outcome inappropriate? <b>N</b>	5.1 Was the trial analyzed in accordance with a pre-specified plan? <b>Y</b>
	1.2 Was the allocation sequences concealed? <b>Y</b>	2.2 Were personnel aware of the intervention? <b>Y</b>	<b>(2° outcomes)</b> <b>PN</b>	4.2 Could measurement or ascertainment of the outcome differ between groups? <b>N</b>	5.2 Is the result likely selected from multiple eligible outcome measurements? <b>N</b>
	1.3 Did baseline differences suggest a problem with randomization? <b>N</b>	2.3 Were important non-protocol interventions balanced? <b>PY</b>	3.2 <b>(2° outcomes)</b> Evidence that the result was not biased by missing outcome data? <b>PN</b>	4.3 Were outcome assessors aware of the interventions received? <b>PY</b>	5.3 Is the result likely selected from multiple eligible analyses of the data? <b>N</b>
		2.4 Were there failures in implementing affecting the outcomes? <b>N</b>	3.3 <b>(2° outcomes)</b> Could missingness depend on its true value? <b>NI</b>	4.4 Could assessment of the outcome have been influenced by knowledge of intervention? <b>PN</b>	
	2.5 Was there non-adherence affecting the outcomes? <b>NA</b>	3.4 <b>(2° outcomes)</b> Is it <i>likely</i> that missingness in the outcome depended on its true value? <b>Y</b>			
<b>Judgement</b>	<b>Low Risk of Bias</b>	<b>Low Risk of Bias</b>	<b>1° outcome: Low Risk of Bias; 2° outcomes: High Risk of Bias<sup>a</sup></b>	<b>Low Risk of Bias</b>	<b>Low Risk of Bias</b>

- a. While the primary outcome of treatment success at 2years by Eckardt score had >95% outcome data for both intervention groups, the outcome data for secondary outcomes was at best 91% for POEM and 52% for PD without description or explanation for missing data.

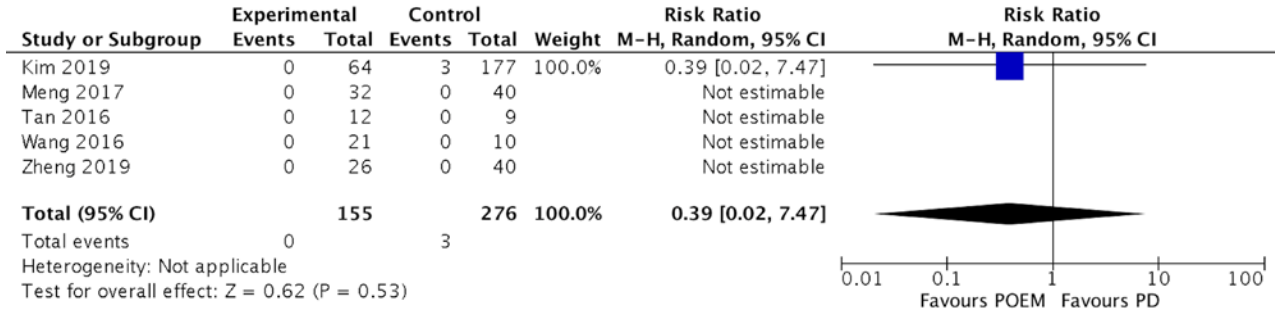


**S13. Observational data for per oral endoscopic myotomy (POEM) versus pneumatic dilation) on binary dysphagia (A) perforation (B)**

**A.**



**B.**



**S14. Cost estimates from observational studies comparing per oral endoscopic myotomy (POEM) and pneumatic dilation (PD). All values are in dollars.**

Study	POEM	PD	Description
Miller 2017	12120	7175	USD, "Cost per cure" at first year
Wang 2016	2620.3	1212.6	USD, Hospitalization costs