

GERD after Peroral Endoscopic Myotomy: Assessment of Incidence and Predisposing Factors

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- BACKGROUND:** Peroral endoscopic myotomy (POEM) is an effective intervention for achalasia, but GERD is a major postoperative adverse event. This study aimed to characterize post-POEM GERD and identify preoperative or technical factors impacting development or severity of GERD.
- STUDY DESIGN:** This is a retrospective review of patients who underwent POEM at our institution. Favorable outcome was defined as postoperative Eckardt score of 3 or less. Subjective GERD was defined as symptoms consistent with reflux. Objective GERD was based on a DeMeester score greater than 14.7 or Los Angeles grade C or D esophagitis. Severe GERD was defined as a DeMeester score greater than 50.0 or Los Angeles grade D esophagitis. Preoperative clinical and objective data and technical surgical elements were compared between those with and without GERD. Multivariate logistic analysis was performed to identify factors associated with each GERD definition.
- RESULTS:** A total of 183 patients underwent POEM. At a mean \pm SD follow-up of 21.7 ± 20.7 months, 93.4% achieved favorable outcome. Subjective, objective, and severe objective GERD were found in 38.8%, 50.5%, and 19.2% of patients, respectively. Of those with objective GERD, 24.0% had no reflux symptoms. Women were more likely to report GERD symptoms ($p = 0.007$), but objective GERD rates were similar between sexes ($p = 0.606$). The independent predictors for objective GERD were normal preoperative diameter of esophagus (odds ratio [OR] 3.4; $p = 0.008$) and lower esophageal sphincter (LES) pressure less than 45 mmHg (OR 1.86; $p = 0.027$). The independent predictors for severe objective GERD were LES pressure less than 45 mmHg (OR 6.57; $p = 0.007$) and obesity (OR 5.03; $p = 0.005$). The length of esophageal or gastric myotomy or indication of procedure had no impact on the incidence or severity of GERD.
- CONCLUSION:** The rate of pathologic GERD after POEM is higher than symptomatic GERD. A nonhypertensive preoperative LES is a predictor for post-POEM GERD. No modifiable factors impact GERD after POEM. (J Am Coll Surg 2023;236:58–70. © 2022 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American College of Surgeons. This is an open-access article distributed under the terms of the [Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 \[CCBY-NC-ND\]](https://creativecommons.org/licenses/by-nc-nd/4.0/), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.)

Achalasia is a primary esophageal motility disorder that can manifest with varied patterns of esophageal contractility. However, the cardinal feature of this disease is the failure

of deglutitive lower esophageal sphincter (LES) relaxation, resulting in an esophagogastric junction (EGJ) outflow obstruction, subsequent esophageal bolus retention, and

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Abbreviations and Acronyms

DES	=	diffuse esophageal spasm
EGD	=	esophagogastroduodenoscopy
EGJ	=	esophagogastric junction
EGJOO	=	esophagogastric junction outlet obstruction
HMD	=	Heller myotomy with Dor fundoplication
LES	=	lower esophageal sphincter
POEM	=	peroral endoscopic myotomy

stasis. Therefore, the management of achalasia is targeted to relieve this obstruction. Pneumatic dilation, laparoscopic Heller myotomy, and more recently, peroral endoscopic myotomy (POEM) are the durable interventions performed to achieve this goal.

POEM is a safe and effective endoscopic treatment, utilized to alleviate obstructive physiology at the EGJ or distal esophagus. Patients with achalasia and a few other esophageal motility disorders (eg esophagogastric junction outlet obstruction [EGJOO], jackhammer esophagus, and diffuse esophageal spasm [DES]) benefit from this procedure. POEM was developed to mimic the Heller myotomy through an endoscopic platform, thereby avoiding body wall trauma and preserving extraesophageal anatomy. This less invasive procedure is rapidly being adopted by clinicians in the US. A recent study shows a 19-fold increase in use of POEM during an 8-year period.¹ Several studies have compared the outcomes of POEM to that of

Heller myotomy with Dor fundoplication (HMD), and found equivalent efficacy with comparable safety^{2,3}; however, investigators have expressed concern about the high rate of GERD after POEM.

The clinical challenge in achalasia management is the relief of dysphagia without inducing debilitating gastroesophageal reflux. Surgical or endoscopic disruption of the LES compromises the competency of the EGJ against acidic gastric refluxate. Therefore, the development of GERD after myotomy is a frequent problem. The reported prevalence of reflux symptoms or objectively proven GERD after treatment in patients with achalasia ranges from 5% to 60%.⁴⁻⁶ This wide variability is related to the definition, method of reflux measurement, and, most importantly, the type of treatment. Since the POEM procedure does not include the creation of a concurrent antireflux mechanism, it is associated with the highest rate of iatrogenic GERD among definitive procedures. A prospective cohort study of POEM outcomes reported rates of subjective GERD, endoscopic esophagitis, and abnormal distal esophageal acid exposure at 43%, 60%, and 56%, respectively.⁴ Although several studies have reported the rate of GERD after POEM, there is limited data on the factors predicting the occurrence or severity of reflux after POEM. Therefore, we designed the current study to characterize GERD after POEM using both subjective and objective parameters and to determine potential preoperative criteria or technical elements that may predict the development of GERD or its severity.

METHODS

Study population

This was a retrospective review of prospectively collected data of patients who underwent POEM at Allegheny Health Network hospitals (Pittsburgh, PA) between January 2013 and June 2021. This study was evaluated and approved by the IRB of the Allegheny Health Network (IRB No. 2021-239). Patients with a diagnosis of achalasia subtypes, EGJOO, DES, or jackhammer esophagus; who were 18 years or older; and had at least 6 months of follow-up after surgery were included in this study. Demographic, clinical, quality of life questionnaire, intraoperative, and objective testing data were assessed for impact on the development and severity of GERD after POEM.

Disease-related quality of life measures

All patients were asked to complete validated questionnaires preoperatively and then again at 6 and 12 months postoperatively. The validated questionnaires included the

GERD Health-Related Quality of Life (GERD-HRQL) and Eckardt symptom score. The GERD-HRQL consists of 16 questions with scores from 0 to 5, specifically addressing GERD symptoms.⁷ The Eckardt score stages severity of achalasia and consists of 4 questions, each with scores from 0 to 3, for an aggregate score of 0 to 12, assessing weight loss, dysphagia, retrosternal pain, and regurgitation. A total Eckardt score greater than 3 was considered abnormal.⁸

Preoperative clinical and objective evaluation

All patients underwent a comprehensive clinical evaluation with a focus on their foregut symptoms and their use of antisecretory medications. They also completed GERD-HRQL and Eckardt questionnaires. The routine preoperative objective assessment included several tests. A videoesophagram was used to evaluate gross pharyngeal and esophageal motility, delineate the anatomy, and assess for masses, mucosal lesions, hiatal hernia, stricture, esophageal dilation, distal esophageal tapering, or stasis. An esophagogastroduodenoscopy (EGD) assessed esophageal dilation, tortuosity, esophagitis, stasis of liquid or residual food, resistance at the EGJ, and other anatomic considerations such as Hill classification and presence and size of hiatal hernia. High-resolution impedance manometry utilized a 4.2-mm ManoScan ESO catheter (Medtronic, Minneapolis, MN) with 36 pressure sensors spaced 1 cm apart to record baseline resting measurements, followed by ten standard swallows of saline that were separated by at least 20 seconds. Tracings were analyzed using ManoView software (Medtronic, Minneapolis, MN) to assess manometric characteristics of upper and lower esophageal sphincter (LES), esophageal body, and bolus clearance. An integrated relaxation pressure greater than 15 mmHg defined impaired LES relaxation and resting pressure greater than 45 mmHg defined hypertensive LES. Diagnosis of achalasia subtypes, EGJOO, DES, and jackhammer esophagus were made per Chicago Classification version 3.0 criteria.⁹ Esophageal pH monitoring was done using a Bravo pH capsule (Medtronic, Minneapolis, MN) placed 6 cm above the EGJ during EGD. Patients taking proton pump inhibitors held their medications 10 days before pH testing. Abnormal distal esophageal acid exposure was defined as a DeMeester score greater than 14.7.^{10,11}

Surgical technique

Patients were placed on a clear liquid diet for at least 24 hours before surgery. Preoperative prophylactic antimicrobial therapy included a single dose of ampicillin-sulbactam

and fluconazole within 30 minutes of mucosotomy. The patients were placed in the supine position and general anesthesia was administered. An EGD was performed. The desired length of esophageal myotomy was determined based on diagnosis, manometric findings, and endoscopic evaluation. The site for the anterior esophageal mucosotomy was identified 2 cm above the proximal extent of the intended myotomy. Orise solution (Boston Scientific, Natick, MA) was injected at the 12-o'clock position to create a submucosal cushion and a 1.5 to 2 cm mucosotomy was performed using a triangle tip electro-surgical knife. The endoscope was inserted, and a submucosal tunnel was created with a combination of blunt dissection, carbon dioxide insufflation, hydrodissection, and careful use of a triangle tip electro-surgical knife. The tunnel was extended past the EGJ, 2 to 3 cm onto the gastric cardia. A proximal to distal circular myotomy was performed, taking care to preserve the longitudinal muscle layers of the esophagus and stomach. Easy passage of the endoscope through the EGJ and retroflexed evaluation of the valve confirmed an adequate myotomy. The submucosal tunnel was then irrigated with gentamycin solution and the mucosal incision was closed using endoscopic Resolution 360 Clips (Boston Scientific, Natick, MA).

All patients were evaluated with a water-soluble contrast esophagogram on the first postoperative day. They were then discharged on a clear liquid diet and placed on a 2-week regimen of triple antacid therapy consisting of an H2 receptor antagonist, a proton pump inhibitor, and sucralfate.

Follow-up protocol

Subjective outcomes were evaluated at 2 weeks, 6 weeks, 6 months, 1 year, and then annually after surgery. Patients were maintained with triple acid-reducing therapy for 2 weeks after surgery and then only proton pump inhibitors until 6 months after surgery. The GERD-HRQL and Eckardt questionnaires were completed while patients were off antisecretory medications at 6 months, 12 months, and then annually after surgery. Objective testing was repeated at 12 months after surgery and annually thereafter in the form of EGD and Bravo pH monitoring while off antisecretory medications.

Outcome and definitions

Favorable outcome after POEM was defined as an Eckardt score of 3 or less after surgery. Subjective GERD after POEM was defined as patient-reported perceived symptoms consistent with GERD. Objective GERD after POEM was defined as either a DeMeester score greater

than 14.7 or a Los Angeles grade C or D esophagitis. Severe objective GERD was defined as a DeMeester score greater than 50 or Los Angeles grade D esophagitis.

Statistical analysis

Values were expressed as mean \pm SD for continuous variables and frequency and percentage for categorical variables. Univariate logistic analysis was performed for predicting binary outcomes of subjective, objective, and severe objective GERD with respect to potential preoperative predictors. A multivariable logistic model for predicting each of the 3 outcomes was fitted using a stepwise selection that mandated a variable that was statistically significant or borderline significant in the univariate analysis. They were required to have a significant threshold of 0.30 and 0.10 to be opted and retained in the model, respectively. Due to the size of sample, Firth's penalized likelihood approach was applied to the univariate and multivariable logistic analyses. A statistically significant association between a predictor and an outcome was established if the p-value was 0.05 in a Wald chi-square test or the 95% CI of the OR did not cross 1.0.

Bar graph was used to visualize the relationship between predicted probability of a binary outcome and LES resting pressure mean using a logistic model with Firth's penalized likelihood approach. A Kruskal-Wallis test was performed to examine difference for the predicted probability of the outcome among grouped LES resting pressure mean. A p-value less than 0.05 was considered statistically significant. All statistical analyses were performed using SAS software (v 9.4; SAS Institute, Cary, NC).

RESULTS

Study population and overall outcomes

A total of 183 patients underwent POEM during the study period. Baseline demographic and clinical characteristics of the study population are shown in Table 1. At a mean \pm SD follow-up of 21.7 \pm 20.7 months, Eckardt scores improved from 7.2 \pm 1.9 to 1.4 \pm 1.6 ($p < 0.0001$), with 171 (93.4%) patients achieving favorable outcome, defined by an Eckardt score of 3 or less. Of the 12 patients with unfavorable outcome, 10 required additional procedures (Heller myotomy and Dor fundoplication in 6 and esophagectomy in 4 patients).

Major intraoperative complications were seen in 5 (2.7%) patients and consisted of full-thickness perforation requiring endoscopic clipping in 2 (1.1%) and development of pleural effusions requiring drainage in 3 (1.6%). A total of 40 (21.9%) patients required Veress

Table 1. Baseline Demographics and Clinical Characteristics

Characteristic	Study population (n = 183)
Age, y, mean \pm SD	58.1 \pm 18
Sex, n (%)	
Male	95 (51.9)
Female	88 (48.1)
BMI, kg/m ² , mean \pm SD	28.7 \pm 18
Obesity, BMI \geq 30 kg/m ² , n (%)	68 (37.2)
Diagnosis, n (%)	
Achalasia type I	13 (7.1)
Achalasia type II	110 (60.1)
Achalasia type III	20 (10.9)
EGJOO	20 (10.9)
Jackhammer esophagus	18 (9.8)
Diffuse esophageal spasm	2 (1.1)
Duration of symptoms, y, mean \pm SD	5.9 \pm 4.7
Proton pump inhibitor usage, n (%)	29 (15.8)
Eckardt Score, mean \pm SD	
Weight loss	1.7 \pm 1.0
Dysphagia	2.3 \pm 0.7
Chest pain	1.1 \pm 0.9
Regurgitation	2.1 \pm 0.8
Total score	7.2 \pm 1.9

EGJOO, esophagogastric junctional outlet obstruction.

needle decompression for capnoperitoneum. None of these patients had ventilatory or hemodynamic instability. These intraoperative complications were not associated with postoperative sequelae.

A total of 71 (38.8%) patients reported symptoms of GERD after POEM. Of the 183 patients who underwent POEM, a group of 99 patients had routine postoperative objective testing in the form of EGD (n=99) and Bravo pH monitoring (n=60). Objective GERD was found in 50 (50.5%) of these patients. There were 19 (19.2%) patients who had severe GERD, defined by Los Angeles grade D esophagitis or a DeMeester score greater than 50. Postoperative Eckardt scores for each of the 3 GERD definitions are shown in Table 2. Patients with objective GERD had lower postoperative Eckardt regurgitation and total scores, as well as a higher rate of favorable outcome.

Subjective GERD after POEM

The results of the univariate analysis comparing the preoperative demographic, clinical, and physiologic parameters of patients with symptomatic GERD to those without are shown in Table 3. Patients with symptomatic GERD were more likely to be female and have a higher regurgitation

Table 2. Postoperative Eckardt Scores and Outcomes

Variable	GERD	No GERD	p Value
Subjective GERD (n=183)			
Weight loss	0.1±0.3	0.1 ± 0.4	0.8363
Dysphagia	0.6±0.7	0.5 ± 0.7	0.1794
Chest pain	0.5±0.7	0.3 ± 0.6	0.1064
Regurgitation	0.4±0.7	0.3 ± 0.6	0.3122
Total score	1.6±1.7	1.2 ± 1.6	0.1367
Total score >3, n (%)	6 (8.5)	6 (5.4)	0.4163
Objective GERD (n=99)			
Weight loss	0.0±0.2	0.2 ± 0.6	0.1647
Dysphagia	0.5±0.6	0.8 ± 0.8	0.0824
Chest pain	0.4±0.6	0.6 ± 0.7	0.1182
Regurgitation	0.3±0.5	0.7 ± 0.9	0.0137*
Total score	1.2±1.2	2.3 ± 2.3	0.0118*
Total score >3, n (%)	2 (4.0)	9 (18.4)	0.0499*
Severe objective GERD (n=99)			
Weight loss	0.1±0.2	0.1 ± 0.5	0.7377
Dysphagia	0.5±0.8	0.7 ± 0.7	0.4571
Chest pain	0.3±0.6	0.5 ± 0.7	0.1841
Regurgitation	0.2±0.4	0.6 ± 0.8	0.1227
Total score	1.1±1.1	1.9 ± 2.0	0.1104
Total score >3, n (%)	0 (0.0)	11 (13.8)	0.2232

All data given as mean ± SD, except where indicated otherwise as n (%).

*Statistically significant.

score on their preoperative GERD-HRQL questionnaires. They were also less likely to have a dilated esophagus on the preoperative endoscopy.

Multivariable logistic analysis showed that independent predictors of subjective GERD after POEM were female sex and a preoperative GERD-HRQL regurgitation score less than 3 (Table 4).

Objective GERD after POEM

The results of the univariate analysis comparing the preoperative demographic, clinical, and physiologic parameters of patients with objectively proven GERD to those without are shown in Table 5. Of the 50 patients with objectively proven GERD, there were 12 (24.0%) who denied reflux symptoms.

Patients with objective GERD had lower preoperative mean LES resting pressures. LES overall length, intraabdominal length, and relaxation pressures had no impact on GERD. Patients with objective GERD were also less likely to have a dilated esophagus on preoperative EGD. The prevalence of objective GERD was similar between men and women. Furthermore, among patients with objectively proven GERD, females were not more likely

to report subjective GERD (22 [78.6%] vs 16 [72.7%]; $p = 0.7432$). The other demographic and clinical parameters and indications for the procedure were similar between groups. The indication for the procedure had no impact on the degree of esophageal acid exposure after POEM (Fig. 1).

Multivariable logistic analysis showed that independent predictors of objective GERD after POEM were a nonhypertensive LES resting pressure on high-resolution impedance manometry and lack of esophageal dilation on endoscopy during preoperative work-up (Table 6). Multivariable analysis also showed that patients with a lower postoperative Eckardt score were more likely to have objective GERD (OR 0.713 [95% CI 0.534 to 0.953]; $p = 0.0222$).

Severe objective GERD

A subanalysis was performed to assess factors contributing to severe GERD after POEM. The univariate comparison of patients with severe GERD to those with less severe GERD is shown in Table 7. Patients with severe GERD had greater BMIs and were more likely to be obese (BMI>30 kg/m²). They were also more likely to have a nonhypertensive preoperative LES resting pressure and higher percentage of incomplete bolus clearance.

Multivariable logistic analysis showed that the independent predictors of severe objective GERD after POEM were a nonhypertensive LES resting pressure on preoperative high-resolution impedance manometry and obesity (BMI>30 kg/m²) (Table 8).

Impact of the length of myotomy on GERD

The mean length of the overall myotomy in the entire population was 14.0 ± 3.8 cm. The length of esophageal myotomy was 11.7 ± 3.8 cm and the length of extension to the gastric cardia was 2.3 ± 0.6 cm. The overall length of myotomy or the length of esophageal or gastric myotomy had no impact on the rate of subjective, objective, or severe objective GERD (Fig. 2).

Probability of GERD based on preoperative LES resting pressure

The predicted probability of subjective, objective, and severe objective GERD based on preoperative LES resting pressure is shown in Figure 3. There was a stepwise decrease in probability of objective and severe objective GERD for each 10 mmHg increase in resting pressure ($p < 0.001$ for both analyses). This trend was not observed for subjective GERD.

Table 3. Subjective GERD: Impact of Baseline Demographic, Clinical, and Physiological Characteristics

Variable	Subjective GERD (n=71)	No subjective GERD (n=112)	Odds ratio (95% CI)	p Value
Sex, n (%)			2.264 (1.234-4.155)	0.0083*
Male	28 (39.4)	67 (59.8)		
Female	43 (60.6)	45 (40.2)		
Age, y, mean ± SD	55.9 ± 15.4	59.6 ± 19.4	0.989 (0.973-1.006)	0.1899
BMI, kg/m ² , mean ± SD	29.1 ± 6.7	28.5 ± 7.0	1.012 (0.969-1.056)	0.5944
Obesity (BMI ≥30 kg/m ²), n (%)	30 (42.2)	38 (33.9)	1.422 (0.771-2.622)	0.2594
Duration of symptoms, y, mean ± SD	6.4 ± 4.9	5.6 ± 4.5	1.033 (0.969-1.100)	0.3187
PPI usage, n (%)	17 (58.6)	12 (41.4)	2.582 (1.150-5.798)	0.0216*
Diagnosis, n (%)				
Type 1	7 (9.9)	6 (5.4)	-	-
Type 2	40 (56.3)	70 (62.5)	0.498 (0.157-1.583)	0.2375
Type 3	9 (12.7)	11 (9.8)	0.716 (0.176-2.907)	0.6402
EGJOO	8 (11.3)	12 (10.7)	0.589 (0.144-2.411)	0.4620
Jackhammer	7 (9.9)	11 (9.8)	0.565 (0.134-2.392)	0.4383
DES	0 (0.0)	2 (1.8)	0.173 (0.004-8.355)	0.3753
Eckardt score				
Weight loss, mean ± SD	1.6 ± 0.8	1.7 ± 1.1	0.923 (0.680-1.253)	0.6075
Dysphagia, mean ± SD	2.3 ± 0.7	2.3 ± 0.8	1.131 (0.753-1.700)	0.5522
Chest pain, mean ± SD	1.2 ± 0.8	1.0 ± 0.9	1.249 (0.895-1.743)	0.1910
Regurgitation, mean ± SD	2.2 ± 0.7	2.1 ± 0.8	1.116 (0.754-1.651)	0.5840
Total score, mean ± SD	7.4 ± 1.8	7.1 ± 1.9	1.079 (0.918-1.268)	0.3544
GERD-HRQL, n (%)†				
Heartburn >3	8 (22.9)	12 (20.3)	1.175 (0.428-3.226)	0.7549
Difficulty swallowing >3	26 (74.3)	44 (74.6)	0.972 (0.374-2.528)	0.9530
Regurgitation >3	7 (20.0)	28 (47.5)	0.291 (0.111-0.762)	0.0119*
Endoscopic feature, n (%)				
Esophageal tortuosity	6 (8.5)	10 (8.9)	0.969 (0.337-2.783)	0.9531
Esophageal dilation	26 (36.6)	59 (52.7)	1.910 (1.040-3.508)	0.0371*
Manometric feature				
LES total length, cm, mean ± SD	3.0 ± 0.8	3.1 ± 0.9	0.848 (0.594-1.211)	0.3645
LES intraabdominal length, cm, mean ± SD	1.7 ± 1.0	1.7 ± 0.9	0.982 (0.716-1.347)	0.9100
Mean LES resting pressure, mmHg, mean ± SD	45.9 ± 17.3	46.1 ± 19.1	1.000 (0.983-1.016)	0.9532
LES resting pressure mean mmHg >45, n (%)	33 (46.5)	56 (50.0)	0.870 (0.480-1.578)	0.6469
Mean LES residual pressure, mmHg, mean ± SD	28.3 ± 11.9	27.9 ± 12.8	1.002 (0.978-1.026)	0.8576
Percent incomplete bolus clearance, mean ± SD	87.6 ± 29.7	90.0 ± 25.7	0.997 (0.986-1.008)	0.5539
Percent panesophageal pressurization, mean ± SD	59.6 ± 43.6	65.7 ± 43.2	0.997 (0.990-1.004)	0.3521

*Statistically significant.

†Only clinically relevant items were included.

EGJOO, esophagogastric junctional outflow obstruction; HRQL, health-related quality of life; LES, lower esophageal sphincter; PPI, proton pump inhibitor.

DISCUSSION

Iatrogenic gastroesophageal reflux has been a significant tradeoff in the surgical management of achalasia since Ernst Heller first described his famous surgery in 1914.¹² Reflux rates as high as 55% to 100% after surgical myotomy prompted the addition of a partial fundoplication to the procedure 50 years later.¹³ This addition became

standard practice and substantially mitigated the problem of GERD after myotomy.¹⁴ In fact, a prospective randomized trial found that 48% of patients had abnormal distal esophageal acid exposure after laparoscopic myotomy alone, compared with only 9% when a Dor fundoplication was added to the myotomy.¹⁵ However, the advent of the endoscopic approach to myotomy in 2010 brought a

Table 4. Independent Predictors of Subjective GERD Using Multivariable Logistic Model

Variable	Estimate ± SE	Odds ratio (95% CI)	p Value
Female sex	1.335 ± 0.495	3.799 (1.441-10.016)	0.0070
Preoperative GERD-HRQL regurgitation item <3	1.314 ± 0.536	3.720 (1.300-10.641)	0.0143

HRQL, health-related quality of life.

resurgence of postoperative GERD, and it remains a problem today.^{1,16} We found that 38.8% of patients reported symptoms of GERD after POEM. The rate of objectively proven GERD was even higher at 50.5%. These findings highlight the necessity for thorough preoperative counseling and comprehensive postoperative objective testing and reflux management.

Our high rate of GERD after POEM is consistent with reported rates in the literature. The POEM white paper by Stavropoulos et al.^{17,18} and a publication by Inoue et al.¹⁹ reported post-POEM GERD prevalence at long-term follow-up to be 20% to 46% and 20%, respectively. Similarly, a prospective cohort study of POEM outcomes reported that 43% of patients had subjective GERD, 60% had endoscopic esophagitis, and 56% had a positive DeMeester score.⁴ Furthermore, a meta-analysis of 1,542 POEM patients from 17 studies found that the pooled rates of subjective GERD, endoscopic esophagitis, and abnormal esophageal acid exposure were 19.0%, 29.4%, and 39.0%, respectively.⁵ These studies highlight the fact that GERD after POEM affects a substantial proportion of patients, and that rates of objective GERD are often higher than subjective GERD.

In our study, objective GERD was more prevalent than subjective GERD, and among those with objective GERD, one in 4 were asymptomatic. A similar discordance between symptoms and objective GERD was observed by Karyampudi et al.²⁰ They compared patients with objective GERD after POEM to patients with nonachalasia GERD, and found that those with achalasia were less likely to report reflux symptoms.²⁰ A potential explanation for this contrast is that these achalasia patients have a degree of visceral desensitization that prevents them from perceiving reflux. It is well documented that degeneration of efferent neurons plays a role in the pathogenesis of achalasia; however, circumstantial evidence suggests that esophageal afferent pathways may similarly degenerate in patients with achalasia.^{21,22} Rate et al.²³ used esophageal electromyography to measure responses to esophageal balloon distension, electric stimulation, and transcranial magnetic stimulation. They found that patients with

achalasia had diminished or absent responses to all 3 types of stimuli, suggesting degeneration of the long-tract afferent neurons.²³ Other studies have attributed the decreased ability to detect reflux to chronic esophageal irritation due to food stasis and fermentation.²⁴ Some authors have hypothesized that mucosal denervation during submucosal tunneling and myotomy may result in esophageal hyposensitivity after POEM.²⁰ Further research is necessary to fully understand this pathophysiological difference between those with and without reflux symptoms despite objective GERD; however, our findings and the results of these studies suggest that symptoms are not a reliable index of pathologic reflux after POEM. Therefore, postoperative objective testing should be obtained regardless of symptoms, and these patients should be closely followed.

We found that female patients were more than 3 times as likely to report reflux symptoms after POEM; however, the rate of objective GERD was similar between men and women. Furthermore, among those with objectively proven GERD, the rate of subjective GERD was similar between sexes. These findings suggest that female patients are more likely to perceive esophageal symptoms with subclinical stimulus. These results are consistent with studies showing that among healthy volunteers undergoing esophageal balloon distention tests, women have a significantly lower distention detection and pain perception threshold.²⁵ Variable expression of signaling receptors in the esophageal mucosa, such as the *transient receptor potential vanilloid subfamily member-1 (TRPV1)* receptor have been linked to differences in visceral sensitivity. This mucosal receptor is more frequently expressed in female patients with nonerosive reflux disease, but less frequently expressed in those with esophagitis.^{26,27} The different distributions of *TRPV1* receptors in these populations is a likely explanation for the higher rate of subjective GERD among women in our cohort, despite similar rates of objective GERD. The findings of these studies suggest increased vigilance and objective testing is necessary when following male patients, regardless of symptoms.

The LES resting pressure is a key component of the reflux barrier. Dodds et al.²⁸ studied 12-hour manometry and pH recordings and found that, on average, patients with GERD have less than half the LES resting pressure of healthy volunteers. We found that a mean LES resting pressure less than 45 mmHg on preoperative manometry is an independent predictor for both objective and severe objective GERD after POEM. Additionally, the probability of objective and severe objective GERD increased in a stepwise fashion with each additional 10 mmHg decrease in preoperative resting pressure (Fig. 3). This is a novel finding in the literature on POEM outcomes.^{29,30}

Table 5. Objective GERD: Impact of Baseline Demographic, Clinical, and Physiologic Characteristics

Variable	Objective GERD (n=50)	No objective GERD (n=49)	Odds ratio (95% CI)	p Value
Sex, n (%)			0.810 (0.363-1.805)	0.6060
Male	22 (44.0)	19 (38.8)		
Female	28 (56.0)	30 (61.2)		
Age, y, mean ± SD	57.1 ± 15.7	57.1 ± 17.8	1.000 (0.977-1.024)	0.9908
BMI, kg/m ² , mean ± SD	28.9 ± 6.6	28.7 ± 7.2	1.004 (0.948-1.064)	0.8875
Obesity (BMI ≥30 kg/m ²), n (%)	21 (42.0)	16 (32.7)	1.479 (0.652-3.357)	0.3488
Duration of symptoms, mean ± SD	5.8 ± 3.7	5.8 ± 5.3	1.000 (0.917-1.091)	0.9982
Preoperative PPI use, n (%)	10 (20.0)	8 (16.3)	1.266 (0.454-3.532)	0.6525
Diagnosis, n (%)				
Type 1	6 (12.0)	2 (4.1)	-	-
Type 2	28 (56.0)	28 (57.1)	0.385 (0.075-1.970)	0.2516
Type 3	5 (10.0)	8 (16.3)	0.249 (0.037-1.674)	0.1527
EGJOO	6 (12.0)	6 (12.2)	0.385 (0.057-2.615)	0.3286
Jackhammer	5 (10.0)	5 (10.2)	0.385 (0.053-2.793)	0.3449
Eckardt score, mean ± SD				
Weight loss	1.8 ± 0.8	1.4 ± 0.9	1.520 (0.959-2.411)	0.0750
Dysphagia	2.3 ± 0.6	2.3 ± 0.8	0.845 (0.480-1.485)	0.5580
Chest pain	1.0 ± 0.9	1.1 ± 0.8	0.920 (0.577-1.467)	0.7262
Regurgitation	2.1 ± 0.6	2.1 ± 0.8	1.119 (0.643-1.947)	0.6920
Total score	7.2 ± 1.9	6.9 ± 1.7	1.073 (0.863-1.334)	0.5245
GERD-HRQL, n (%)†				
Heartburn >3	7 (25.9)	4 (21.1)	1.260 (0.313-5.070)	0.7446
Difficulty swallowing >3	21 (77.8)	15 (78.9)	0.961 (0.231-3.989)	0.9559
Regurgitation >3	9 (47.4)	9 (33.3)	0.568 (0.170-1.890)	0.3561
Endoscopic feature, n (%)				
Esophageal tortuosity	2 (4.0)	6 (12.2)	0.345 (0.070-1.710)	0.1926
Esophageal dilation	14 (28.0)	27 (55.1)	3.077 (1.337-7.084)	0.0082*
Manometric feature				
LES total length, cm, mean ± SD	3.0 ± 0.9	3.2 ± 0.8	0.787 (0.488-1.270)	0.3273
LES intraabdominal length, cm, mean ± SD	1.7 ± 1.0	1.7 ± 1.0	1.039 (0.689-1.567)	0.8547
Mean LES resting pressure, mmHg, mean ± SD	41.1 ± 16.5	49.4 ± 20.6	0.977 (0.955-0.999)	0.0395*
LES resting pressure mean mmHg >45, n (%)	16 ± 32.0	29 ± 59.2	3.009 (1.323-6.845)	0.0086*
Mean LES residual pressure, mmHg, mean ± SD	25.8 ± 12.2	27.7 ± 12.7	0.988 (0.957-1.020)	0.4590
Percent incomplete bolus clearance, mean ± SD	87.0 ± 31.7	92.7 ± 20.1	0.992 (0.977-1.008)	0.3395
Percent panesophageal pressurization, mean ± SD	58.6 ± 45.1	61.6 ± 41.2	0.998 (0.989-1.008)	0.7311

*Statistically significant.

†Only clinically relevant items were included.

EGJOO, esophagogastric junctional outflow obstruction; HRQL, health-related quality of life; LES, lower esophageal sphincter; PPI, proton pump inhibitor.

However, our results are consistent with studies of Heller myotomy without fundoplication. Rice et al.³¹ compared outcomes from 61 Heller myotomies without fundoplication to 88 HMDs and found that lower preoperative LES resting pressures was a predictor for postoperative GERD only in the group without fundoplication. Based on these findings, achalasia patients with lower preoperative resting pressures should be counseled that they are at high risk

for GERD and six and a half times more likely to develop severe GERD. The decision to pursue POEM in these patients should be made with the understanding that they are likely trading dysphagia for GERD.

Patients with no GERD symptoms after POEM in our study were more likely to have a dilated esophagus on preoperative endoscopic evaluation. Esophageal dilation in achalasia is an indication of advanced disease, which

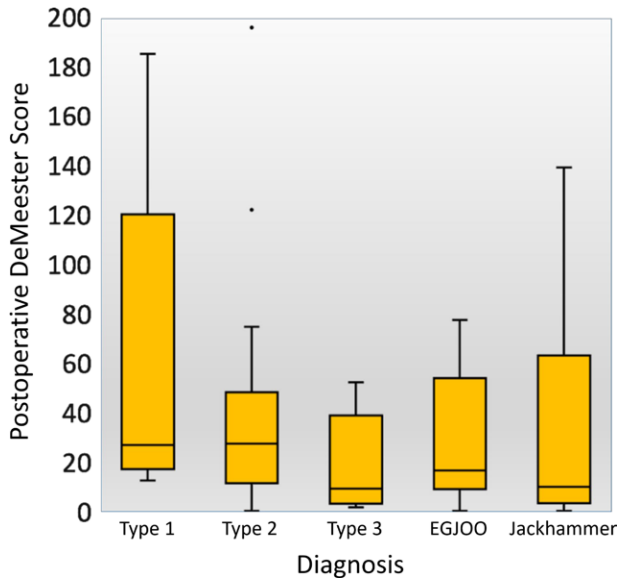


Figure 1. Postoperative DeMeester score by indication of procedure. The black middle line denotes the median DeMeester score for achalasia types 1, 2, and 3, esophagogastric junction outlet obstruction (EGJOO), and jackhammer esophagus. The gold box contains the interquartile range. The black whiskers mark the 5th and 95th percentiles, and values beyond these upper limits are marked with dots.

Table 6. Independent Predictors of Objective GERD using Multivariable Logistic Model

Variable	Estimate \pm SE	Odds ratio (95% CI)	p Value
No esophageal dilation	1.229 \pm 0.465	3.419 (1.374-8.509)	0.0082
Preoperative LES resting pressure \leq 45	0.621 \pm 0.280	1.861 (1.075-3.221)	0.0265

LES, lower esophageal sphincter.

is more likely to be associated with a profound decrease in sensation. This desensitization may explain the less frequent symptomatic GERD in patients with a dilated esophagus. In contrast, we found a dilated esophagus to be a predictor for less objective and severe objective GERD. This unexpected finding has not been reported in the literature previously. As a cylinder, the luminal diameter of the esophagus is inversely proportional to the height above the LES that a given volume of refluxate will reach. Therefore, in patients with dilated esophagus, a larger volume of refluxate will remain undetected below the pH sensor that is conventionally placed 6 cm above the EGJ. Additionally, less mucosal surface area is exposed to acid, reducing the likelihood of grade C or D esophagitis; however, the determination of endoscopic dilation is subjective and may be

operator dependent. Further investigation into the relationship between esophageal caliber and iatrogenic GERD using more objective measurements of esophageal dilation, such as esophagram, is warranted.

Patients with achalasia are unlikely to be obese³²; however obesity was found to be an independent predictor for severe objective GERD after POEM in our study. The relationship between BMI and the severity of GERD is well documented.³³ Studies have demonstrated that obesity defined by a BMI greater than 30 kg/m² is an independent risk factor for developing GERD.³⁴ Additionally, obesity is also a major risk factor for hiatal hernia, which promotes GERD.³⁵ Moreover, obese patients have greater intra-abdominal pressures and increased frequency of transient lower esophageal sphincter relaxation (TLESR) in the postprandial period, further exacerbating GERD.^{36,37} Failure of the LES to relax in achalasia constitutes an unwavering reflux barrier. After myotomy this barrier is disrupted and the effects of obesity become unmitigated, which explains our finding that obese patients are six and a half times more likely to develop severe GERD. Achalasia patients with a high BMI should be counseled that they are at increased risk of postoperative GERD, and may be better candidates for a procedure that includes an antireflux mechanism and the opportunity for hiatal hernia repair, like HMD.

The association between hiatal hernia and GERD is well established, and hiatal hernia repair is a fundamental step in all antireflux surgeries. The rate of hiatal hernia in this study population was very low, limiting our ability to evaluate the impact of preoperative hernia on the development of GERD after POEM. This low rate is due to our practice's approach, as patients with achalasia who are found to have hiatal hernia are less likely to be considered for the POEM procedure. They will mainly undergo laparoscopic Heller myotomy with repair of the hiatal hernia.

A major advantage of POEM is the ability to tailor technique, for example, calibrating myotomy length, to the patient's diagnosis and manometric features. Modifications in POEM technique have also been attempted to reduce rates of GERD. However, studies on the effect of the length, depth, and orientation of the myotomy on postoperative GERD report inconsistent results. Previous studies have suggested that the length of myotomy may influence GERD.³⁸ A meta-analysis of 36 studies comprising 2,373 patients found that studies with the highest rates of esophagitis had significantly longer myotomy lengths.⁶ By contrast, we did not find that variations in esophageal, gastric, or total myotomy length had any impact on the

Table 7. Severe Objective GERD: Impact of Baseline Demographic, Clinical, and Physiologic Characteristics

Variable	Severe objective GERD (n=19)	No severe objective GERD (n=80)	Odds ratio (95% CI)	p Value
Sex, n (%)			1.620 (0.570-4.607)	0.3652
Male	6 (31.6)	35 (43.8)		
Female	13 (68.4)	45 (56.2)		
Age, y, mean ± SD	56.8 ± 16.9	57.2 ± 16.7	0.999 (0.969-1.029)	0.9275
BMI, kg/m ² , mean ± SD	32.6 ± 6.8	27.9 ± 6.6	1.096 (1.019-1.180)	0.0138*
Obesity (BMI ≥30 kg/m ²), n (%)	13 (68.4)	24 (30.0)	4.790(1.660-13.822)	0.0038*
Duration of symptoms, mean ± SD	6.4 ± 3.7	5.7 ± 4.8	1.037 (0.937-1.148)	0.4837
PPI usage, n (%)	3 (15.8)	15 (18.8)	0.897 (0.242-3.321)	0.8701
Diagnosis, n (%)				
Type 1	3 (15.8)	5 (6.3)	-	-
Type 2	10 (52.6)	46 (57.5)	0.355 (0.074-1.712)	0.1969
Type 3	1 (5.3)	12 (15.0)	0.189 (0.020-1.808)	0.1480
EGJOO*	1 (5.3)	11 (13.8)	0.205 (0.021-1.986)	0.1713
Jackhammer	4 (21.1)	6 (7.5)	1.088 (0.163-7.273)	0.9308
Eckardt score, mean ± SD				
Weight loss	1.8 ± 0.9	1.6 ± 0.9	1.344 (0.766-2.358)	0.3034
Dysphagia	2.3 ± 0.7	2.3 ± 0.7	0.891 (0.447-1.778)	0.7438
Chest pain	1.1 ± 0.8	1.1 ± 0.9	1.013 (0.565-1.816)	0.9664
Regurgitation	2.1 ± 0.6	2.1 ± 0.7	0.908 (0.455-1.811)	0.7835
Total score	7.2 ± 1.9	7.0 ± 1.8	1.036 (0.789-1.359)	0.7996
GERD-HRQL, n (%)†				
Heartburn	4 (36.4)	7 (20.0)	2.280 (0.525-9.897)	0.2713
Difficulty swallowing	10 (90.9)	26 (74.3)	2.510(0.358-17.569)	0.3541
Regurgitation	4 (36.4)	14 (56.0)	0.890 (0.225-3.527)	0.8681
Endoscopic feature, n (%)				
Esophageal tortuosity	0 (0.0)	8 (10.0)	0.219 (0.010-4.695)	0.3313
Esophageal dilation	5 (26.3)	36 (45.0)	2.162 (0.730-6.409)	0.1642
Manometric feature				
LES total length, cm, mean ± SD	3.3 ± 0.9	3.1 ± 0.8	1.316 (0.732-2.367)	0.3592
LES intraabdominal length, cm, mean ± SD	1.8 (1.1)	1.7 (0.9)	1.194 (0.707-2.015)	0.5080
Mean LES resting pressure, mmHg, mean ± SD	37.9 ± 15.1	46.9 ± 19.6	0.973 (0.944-1.003)	0.0816
LES resting pressure mean mmHg >45, n (%)	3 (15.8)	42 (52.5)	5.206(1.497-18.103)	0.0095*
Mean LES residual pressure, mmHg, mean ± SD	25.1 ± 9.6	27.1 ± 13.0	0.988 (0.948-1.030)	0.5763
Percent incomplete bolus clearance, mean ± SD	77.9 ± 41.6	92.6 ± 21.0	0.984 (0.969-0.999)	0.0428*
Percent panesophageal pressurization, mean ± SD	43.2 ± 47.4	64.1 ± 41.2	0.989 (0.978-1.001)	0.0643

*Statistically significant.

†Only clinically relevant items were included.

EGJOO, esophagogastric junctional outflow obstruction; HRQL, health-related quality of life; LES, lower esophageal sphincter; PPI, proton pump inhibitor

development of GERD (Fig. 2). Our results are consistent with the findings of the 10-year follow-up study to the original POEM cohort, which did not find that length of myotomy had any impact on GERD.³⁹ Length of myotomy onto the gastric body and the division of the sling fibers has significant impact on dismantling the LES complex. Grimes et al.³⁸ found that a gastric myotomy length greater than 2.5 cm increased the severity of GERD but

not the clinical efficacy of the procedure. However, 96% of the patients in this study underwent a posterior POEM so their results may not be generalizable to our population of anterior POEMs.³⁸ Prospective randomized trials are necessary given the contradictory results in the literature.

In a randomized pilot study, anterior and posterior approaches demonstrated similar efficacy, but the posterior approach had a higher incidence of esophagitis.⁴⁰

Table 8. Independent Predictors of Severe Objective GERD using Multivariable Logistic Model

Variable	Estimate \pm SE	Odds ratio (95% CI)	p Value
Obesity	1.616 \pm 0.581	5.033 (1.611-15.718)	0.0054
Preoperative LES resting pressure \leq 45 mmHg	1.882 \pm 0.700	6.567 (1.665-25.904)	0.0072

LES, lower esophageal sphincter

This esophagitis was theorized to be due to disruption of the clasp and sling fibers in the LES complex. Due to the anatomic configuration of these fibers, the posterior approach is more likely to completely cut them both, which may promote GERD after POEM.⁴¹ However, a subsequent anterior-vs-posterior approach, multicenter, blinded, randomized control trial was unable to identify any difference in safety, efficacy, or iatrogenic GERD between approaches.⁴² We did not evaluate this technical aspect, as our practice is to perform anterior myotomies for all of our POEMs. Another technical variation, proposed by Tanaka and associates,⁴³ is the identification of 2 penetrating vessels between the circular and oblique muscles of the gastric cardia as a marker for the furthest extent of the myotomy. This modification led to preservation of the oblique muscle and lower rates of endoscopic GERD.⁴³ Despite previous studies demonstrating some agency over iatrogenic GERD through adjusting surgical technique, in the current study, we were unable to determine any impactful technical variations in relation to GERD after endoscopic myotomy.

We found no modifiable preoperative or perioperative factors that can reduce the rate of GERD after POEM. However, despite high rates of GERD, we found that POEM is a highly effective and safe procedure. The rate of favorable outcome based on postoperative Eckardt score in this cohort was 93% with a major complications rate of just 0.3%. These results are consistent with a meta-analysis of 2,373 patients by Akintoye and associates⁶ that reported a pooled efficacy of 98%. These findings highlight one of the limitations of relying on Eckardt score alone as a metric in evaluating patients after POEM because it does not take into account postoperative GERD. In fact, our study demonstrated that patients with lower Eckardt scores were more likely to develop objective GERD, suggesting the better the sphincter disruption, the higher the risk of GERD. Therefore, careful risk stratification and patient selection is warranted to decide between HMD and POEM. Patients deemed to be better candidates for POEM should be counseled that GERD is a very common and often an inevitable consequence of POEM. They may develop asymptomatic GERD, and should be empirically tested and aggressively followed for medical GERD management, postoperatively.

We acknowledge the limitations with this study including its retrospective nature and lack of postoperative objective testing in all patients. It is possible that patients who underwent testing had more severe symptoms, introducing an element of bias, which may have affected the different rates of subjective and objective GERD. However, when we compared postoperative GERD-HQRL total scores from those with subjective GERD who had objective

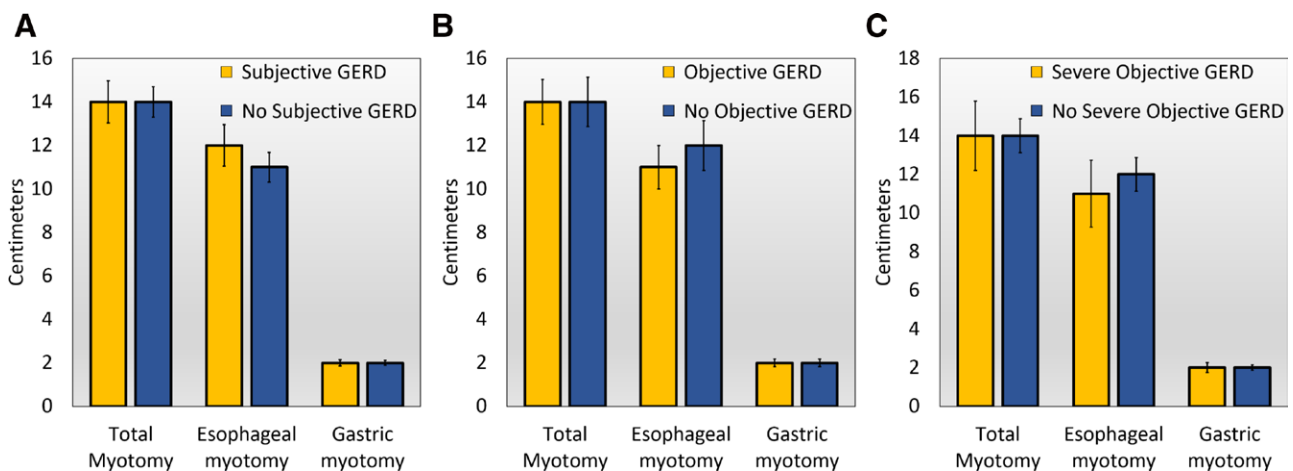


Figure 2. Myotomy lengths in each GERD type. Bar graphs showing differences in total, esophageal, and gastric myotomy lengths in centimeters between those with and without (A) subjective GERD, (B) objective GERD and (C) severe objective GERD. There were no significant differences in total, esophageal, or gastric myotomy lengths for any of the types of GERD ($p > 0.05$ for all comparisons).

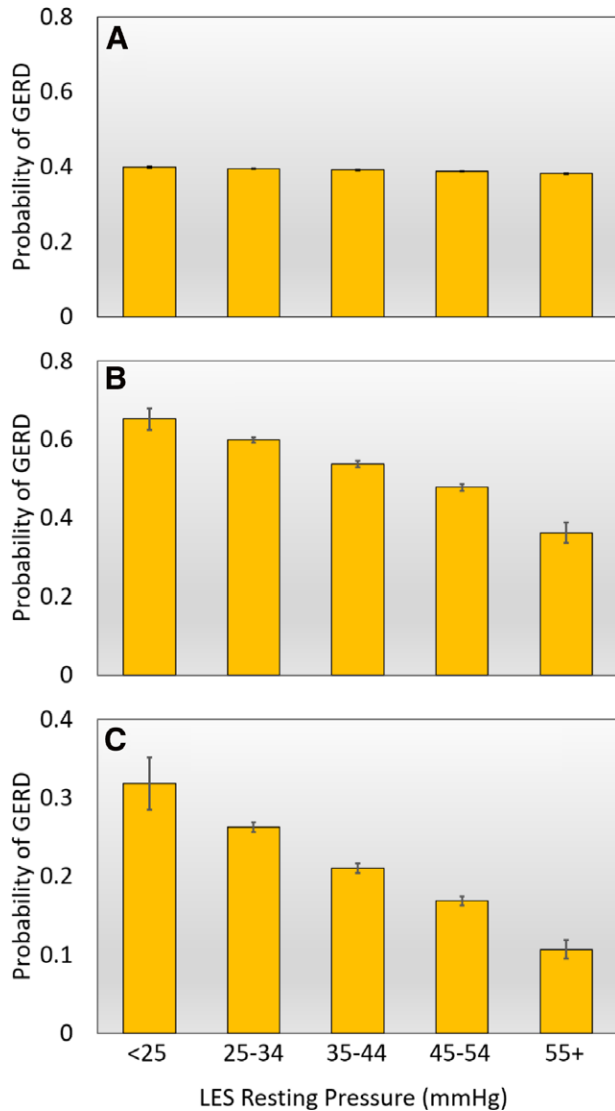


Figure 3. Probability of GERD based on preoperative lower esophageal sphincter (LES) resting pressures. Bar graphs showing the predicted probability of GERD (y-axis) for preoperative LES resting pressures grouped by 10-mmHg ranges (x-axis). (A) LES resting pressure had no impact on subjective GERD. (B) The probability of objective GERD increases in a stepwise fashion with each 10-mmHg decrease in resting pressure ($p < 0.0001$). (C) The probability of severe objective GERD increases in a stepwise fashion with each 10-mmHg decrease in resting pressure ($p < 0.0001$).

testing with those who did not, no significant difference was found (21.3 ± 19.3 vs 18.0 ± 8.7 ; $p = 0.7087$). This finding suggests that even if the potential bias exists, it had little impact on these results. Furthermore, our findings are consistent with publications from other large-volume centers and meta-analysis, which have demonstrated higher rates of objectively proven GERD compared with reported reflux symptoms after POEM.^{5,19}

CONCLUSIONS

We found that POEM is an effective and safe procedure, but half of patients demonstrate evidence of pathologic GERD on postoperative testing. Furthermore, 1 in 4 patients with objective GERD denied any GERD symptoms, likely due to esophageal desensitization, a common phenomenon in patients with achalasia. We also found that lower preoperative LES resting pressures increase the probability of developing GERD after POEM in a stepwise fashion. However, we were not able to identify any modifiable preoperative factors that reduce the risk of GERD. In particular, variations in surgical technique had no impact on iatrogenic GERD. Obesity was found to be an independent risk factor for development of severe objective GERD after POEM. As GERD symptoms are an unreliable marker of abnormal esophageal acid exposure in achalasia patients after POEM, we recommend objective testing in all patients after endoscopic myotomy to identify patients that require more aggressive reflux treatment and monitoring.

Author Contributions

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 Writing - review & editing: Eriksson, Jobe, Ayazi

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