

# Long-term quality of life after peroral endoscopic myotomy remains compromised in patients with achalasia type III

## Authors

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## ABSTRACT

**Background and study aims** Peroral endoscopic myotomy (POEM) is an excellent endoscopic treatment for achalasia. Clinical and manometric parameters are used for evaluation and follow-up. However, clinical success does not guarantee high quality of life (QoL) scores, generating doubts about their direct relationship. We aimed to evaluate QoL scores before and after POEM at medium and long term, to evaluate differences between achalasia subtypes and find which factors related to low QoL scores.

**Patients and methods** Achalasia-confirmed patients undergoing POEM between February 2012 and November 2016, and completing at least 1 year of follow-up, were included. Assessment before and at 1, 6, 12, 24, 36 and 48 months after POEM employed manometry, barium series, Eckardt score, and the AE-18 health-related QoL scale. Demographic, clinical, and procedure characteristics were documented, with comparisons between subgroups. Multiple logistic regression analysis was done.

**Results** 65 of 88 patients were included (38 women, 27 men; median age 47 years, interquartile range [IQR] 20–81), and 50 (76.9%) completed 4 years of follow-up. Eckardt score improved (median, preprocedure 10 vs. post-procedure 2;  $P=0.002$ ) and this persisted. There was initial improvement in median integrated relaxation pressure (IRP) (29.4 mmHg [16–55] vs. 10.3 mmHg [3–18];  $P=0.000$ ) and median QoL scores (40 vs. 68 at 1 month;  $P=0.002$ ); however IRP increased and QoL scores decreased. Men with confirmed type III achalasia had low QoL scores.

**Conclusions** All patients had significant clinical improvement after POEM, with medium- to long-term persistence. Though quality of life and IRP initially improved, they deteriorated in the long term. Male sex and type III achalasia seem to be associated with low QoL scores.

## Introduction

Achalasia is characterized by loss of coordinated esophageal peristalsis and failure of the lower esophageal sphincter (LES) to completely relax. High resolution manometry distinguishes three subtypes [1,2]. The Eckardt score evaluates clinical symptoms, but not quality of life [3]. The treatment aim is to decrease the LES pressure and the integrated relaxation pressure (IRP), in order to improve symptoms [4]. Medical and endoscopic therapeutic options have limited efficacy [5]. Laparoscopic Heller myotomy is considered the gold standard of treatment [6], but peroral endoscopic myotomy (POEM) has gained popularity because of its excellent safety and efficacy [7–12].

Success is defined as Eckardt score <3, IRP <15 mmHg, and >80% emptying of contrast at 5 minutes in TBE. When these

have been achieved, the patient's quality of life should be improved. Excellent clinical outcomes have been reported in the short, medium, and long term, but there is little information about long-term quality of life [13–15]. Moreover, 10%–15% of patients treated with laparoscopic Heller myotomy show a medium-term decrease in quality of life (QoL) scores following early success [4, 16], thus generating doubts about the direct relationship between procedural success and good quality of life. In addition, there is no information about any differences based on achalasia subtype [12, 16].

Among different methods used for the evaluation quality of life in achalasia [17–19], the Short Form Health Survey (SF-36) shows low specificity [20–22], whereas the disease-specific AE-18 questionnaire shows high sensitivity and specificity [23–25].

Our primary objective was to evaluate quality of life before and in the medium and long term after the POEM procedure. Secondary endpoints were: to evaluate the relationship of quality of life to the classical evaluation methods of Eckardt score, IRP, and timed barium esophagogram (TBE); to explore differences between subtypes; and to find whether there are factors associated with low QoL scores at long-term evaluation.

## Patients and methods

### Patients

We included patients diagnosed with achalasia who underwent a POEM procedure between February 2012 and November 2016 at a tertiary care medical center in Mexico City.

The diagnosis of achalasia was based on high resolution manometry, upper endoscopy, TBE, and clinical assessment. We excluded patients who were not POEM candidates (with presence of severe coagulopathy, end-stage cardiopulmonary disease, premalignant esophageal conditions, or portal hypertension), those with pseudoachalasia or previous laparoscopic Heller myotomy treatment, and those who could not complete at least 1 year of follow-up.

The ethics committee of our institution approved the protocol. Informed consent was obtained from all patients before the procedure.

### Pre-POEM evaluation

Before the procedure, diagnosis and classification of achalasia (type I, type II, or type III); was done based on the Chicago classification [26]. A 36-channel solid-state catheter system with circumferential sensors spaced 1 cm apart (ManoScan ESOsystem; Given Imaging, Covidien; Dublin, Ireland) was used. All patients underwent upper endoscopy, chest computed tomography (CT), Chagas disease testing, and TBE (at 1, 2 and 5 minutes). Clinical evaluation was done using the Eckardt scale [27], and quality of life was scored using the AE-18 questionnaire [25].

The Eckardt scale assesses clinical symptoms in achalasia using the following scores: weight loss (0, none; 1, <5 kg; 2, 5–10 kg; 3, >10 kg), dysphagia (0, none; 1, occasionally; 2, daily; 3, each meal), retrosternal pain (0, none; 1, sometimes; 2, daily; 3, each meal), and regurgitation (0, none; 1, sometimes;

2, daily; 3, each meal). The scoring goes from 0 to 12 points; post-treatment scores of <3 and >9 points, respectively, represent success and failure.

The AE-18 questionnaire consists of 18 items grouped in four subscales (physical functioning [PF], psychological functioning [PS], social functioning [SF], and sleep [S]). The answers to each item are measured on a 5-point Likert scale. Scores for each item range from 1 ("always") to 5 ("never"). The maximum points for each domain are: PF 20, PS 20, SF 30 and S 20 with, therefore, a maximum score of 90 points; higher scores correspond to a better quality of life.

### POEM procedure

Prophylactic third-generation cephalosporin antibiotics were given before the procedure. General anesthesia was used. A regular endoscope was used (EG590WR; Fujinon, Tokyo, Japan), along with a transparent cap model (DH-28GR, Fujinon), an electrosurgical unit (ERBE VIO-200D; Tübingen, Germany), and an I-type hybrid knife (ERBE). Closure was done with hemoclips (Boston Scientific, Natick, Massachusetts, USA).

The POEM technique was applied as reported by Inoue et al. [7]. First, a revision and documentation of the esophagogastric junction (EGJ) level was done. Then an injection was done 13–15 cm above the EGJ, with a longitudinal mucosal incision of 15 mm in the 2-o'clock direction. This was followed by submucosal tunnelization down to 3–4 cm below the EGJ, myotomy of the circular inner muscle beginning 2 cm below the incision site, and complete EGJ myotomy including 2–3 cm on the gastric side. Confirmation was based on three indicators: first, loss of resistance to passage of the scope at EGJ level; second, comparison between the EGJ distance from the incisors and the measure of the farthest myotomy point through the tunnel; and third, observation of the EGJ opening in retroflexed view at medium insufflation. An ultraslim scope was not available. Finally, closure was done using clips. A longer myotomy (20 cm, including the EGJ and the gastric portion below) was performed in patients with type III achalasia.

All the five POEM steps were done by the same operator with POEM expertise and three endoscopists.

### Post-POEM procedure

After procedure, patients received nothing by mouth for 24 hours, and pain management and antibiotics were continued. Esophagography was done at 24 hours to rule out tunnel complications. If no complications were detected, patients received a liquid diet followed by a soft diet for the next 2 or 3 days, and were then discharged. If a complication was detected, it was addressed appropriately.

### Follow-up

High resolution manometry, upper endoscopy, esophageal pH monitoring (Digitrapper), and clinical assessment for reflux disease, quality of life, and Eckardt score were scheduled at 1, 6, 12, 24, 36, and 48 months after POEM.

Success was considered to have been attained when IRP was <15 mmHg, Eckardt score was <3, and there was adequate passage of contrast ( $\geq 80\%$  at 5 minutes) in TBE. Quality of life was

considered to be low when patients reported less than 75 % for the AE-18 score ( $\leq 68$  points). At the first assessment of reflux (1 month after POEM), if this was confirmed to be present by either a DeMeester score of  $> 14.73$  or esophagitis of any grade, proton pump inhibitor (PPI) medication was initiated for 8 weeks. If reflux disease was confirmed at 6 months, PPIs were prescribed indefinitely. Recurrence was defined as when, after an initial success, clinical and manometrically assessed failure appeared during follow-up.

We hypothesized that QoL score did not have a direct relationship with successful procedure at long-term evaluation.

## Statistical analyses

The sample size was calculated based on the formula for difference of proportions for paired measurements (QoL score before and after POEM). According to previous studies [21, 25, 28, 29], the QoL score in an achalasic patient is compromised to a mean of 40 % of the possible total score (36/90 points). After the procedure, the expected increase is 35–45 percentage points (to scores of 67/90 to 76/90 points). Thus we assumed a mean improvement of 40 percentage points, and assumed a 20 % drop-out rate (patients who did not reach the 4th year), with a significance alpha level of 0.05 (type I error of 5 %) and a beta of 0.20 (type II error of 20 %). Using an online statistically validated program for sample size calculation (EpiInfo, USA), we calculated a minimum sample of 48 patients.

The clinical characteristics of patients, procedural data, and clinical assessment, were documented. Quantitative findings were expressed as medians and interquartile ranges (IQRs). Qualitative data were expressed as frequencies and percentages.

Bivariate analyses were done using the Kruskal–Wallis test (for comparisons between achalasia subtypes and quantitative data), and the Mann–Whitney *U* test when  $P < 0.05$  was found or the Pearson  $\chi^2$  test for qualitative data. Evaluation of changes over time in Eckardt, AE-18, and DeMeester scores and in IRP were done using the Friedman test (repeated measures in one sample), and when  $P < 0.05$ , the Wilcoxon test was performed.

A multiple logistic regression model was applied that considered the presence of low QoL score ( $< 68$  points) as final outcome. After univariate analysis between independent variables and low QoL score, the multiple logistic regression model was constructed, and results were expressed in odds ratios (ORs)

**► Table 1** Peroral endoscopic myotomy (POEM) in patients with achalasia. Characteristics of patients, procedure, and achalasia and quality of life (QoL) scores.

Patients, n	65
Age, median (IQR), years	47 (20–81)
Sex, n (%)	
▪ Women	38 (58.5 %)
▪ Men	27 (41.5 %)
Esophagus type, n (%)	
▪ Normal	13 (20.6 %)
▪ Slightly dilated	11 (16.9 %)

▪ Moderately dilated	27 (41.7 %)
▪ Severe dilated	7 (10.7 %)
▪ Megaesophagus	7 (10.7 %)
Symptoms, n (%)	
▪ Dysphagia	58 (89.2 %)
▪ Weight loss	43 (66.1 %)
▪ Thoracic pain	30 (46.1 %)
▪ Reflux symptoms	22 (33.8 %)
Time before achalasia diagnosis, median (IQR), months	36 (14–120)
Achalasia subtype, n (%)	
▪ Type I	19 (29.2 %)
▪ Type II	34 (52.3 %)
▪ Type III	12 (18.5 %)
POEM duration time, median (IQR), minutes	70 (43–104)
Tunnel length, median (IQR), cm	15 (10–27)
Myotomy length, median (IQR), cm	13 (7–25)
Adverse events in POEM, n (%)	
▪ Minor bleeding during the procedure	20 (30.7 %)
▪ Subcutaneous emphysema	15 (23.1 %)
▪ Pneumoperitoneum	10 (15.3 %)
▪ Mallory–Weiss tear	4 (6.1 %)
▪ Mucosotomy	3 (4.8 %)
Length of stay, median (IQR), days	3 (1–4)
Eckardt score, median (IQR)	
Pre-POEM	10 (7–12)
Post-POEM	2 (0–5)
AE-18 total score, median (IQR)	
▪ Pre-POEM	40 (28–53)
▪ Post-POEM	56 (45–64)
IRP pressure, median (IQR), mmHg	
▪ Pre-POEM	29.4 (16–55)
▪ Post-POEM	10.3 (3–18)

IQR, interquartile range; IRP, integrated reflux pressure.

with 95 % confidence interval (95 %CI) and *P* values. Differences were considered significant when  $P < 0.05$ . SPSS 22.0 for Mac (IBM) was used for statistical analysis.

## Results

### Baseline characteristics of patients (► Table 1)

We conducted a retrospective analysis of a prospectively collected database from 88 patients who underwent POEM between February 2012 and November 2016. A total of 23 were

► **Table 2** Comparisons between patients with different esophageal achalasia subtypes.

	Type I n = 19	Type II n = 34	Type III n = 12	P
Age, median (IQR), years	49 (26–81)	45.5 (20–78)	54 (24–69)	0.64 <sup>1</sup>
Sex, n (%)				0.15 <sup>2</sup>
▪ Women	15 (78.9%)	16 (47.1%)	7 (58.3%)	
▪ Men	4 (21.1%)	18 (52.9%)	5 (41.7%)	
Type of esophagus, n (%)				0.12 <sup>2</sup>
▪ Normal	5 (26.3%)	7 (20.6%)	1 (8.3%)	
▪ Slightly dilated	2 (10.5%)	7 (20.6%)	2 (16.7%)	
▪ Moderately dilated	11 (57.9%)	11 (32.4%)	5 (41.7%)	
▪ Severely dilated	0 (0%)	5 (13.7%)	2 (16.7%)	
▪ Megaesophagus	1 (5.3%)	4 (11.8%)	2 (16.7%)	
Symptoms, n (%)				0.51 <sup>2</sup>
▪ Dysphagia	17 (89.4%)	30 (88.2%)	11 (91.6%)	
▪ Weight loss	15 (78.9%)	18 (52.9%)	10 (83.3%)	
▪ Thoracic pain	9 (15.8%)	16 (47.0%)	5 (41.6%)	
▪ Reflux symptoms	7 (36.8%)	10 (29.4%)	5 (41.6%)	
Time to achalasia diagnosis, median (IQR), months	20 (4–99)	25 (4–120)	20 (4–46)	0.40 <sup>1</sup>
Eckardt score, median (IQR), points				
▪ Pre-peroral myotomy (POEM)	9 (8–12)	10 (7–12)	12 (9–12)	0.005 <sup>3</sup> Type I vs. type II: P = 0.52 Type I vs. type III: P = 0.004 Type II vs. type III: P = 0.05
▪ Post-POEM 1-month	3 (1–4)	2 (0–5)	2 (2–4)	0.10 <sup>1</sup>
Integrated relaxation pressure (IRP), median (IQR), mmHg				
▪ Pre-POEM	22.5 (16–45)	31.5 (16–55)	36.1 (22–55)	0.08 <sup>1</sup>
▪ Post-POEM 1-month	11.5 (4–15)	10.5 (4–18)	8.7 (3–17)	0.33 <sup>1</sup>
AE-18 total score, median (IQR)				
▪ Pre-POEM	40 (30–53)	42 (29–52)	32 (28–43)	0.000 <sup>3</sup> Type I vs. type II: P = 1.0 Type I vs. type III: P = 0.003 Type II vs. type III: P = 0.000
▪ Post-POEM 1-month	57 (45–63)	58 (49–64)	52 (48–56)	0.000 <sup>3</sup> Type I vs. type II: P = 1.0 Type I vs. type III: P = 0.007 Type II vs. type III: P = 0.000
POEM time median (IQR), minutes	70 (49–104)	74.5 (43–102)	62.5 (49–99)	0.15 <sup>1</sup>
Tunnel length, median (IQR), cm	14 (10–16)	14 (10–19)	21 (16–27)	0.000 <sup>3</sup> Type I vs. type II: P = 1.0 Type I vs. type III: P = 0.000 Type II vs. type III: P = 0.000
Myotomy length, median (IQR), cms	12 (9–15)	13 (7–18)	18 (15–25)	0.000 <sup>3</sup> Type I vs. type II: P = 1.0 Type I vs. type III: P = 0.000 Type II vs. type III: P = 0.000

► **Table 2** (Continuation)

	Type I n=19	Type II n=34	Type III n=12	P
Adverse effects in POEM (%)				0.81 <sup>2</sup>
▪ Subcutaneous emphysema	1 (5.3%)	4 (11.8%)	1 (8.3%)	
▪ Minor bleeding during procedure	3 (15.8%)	1 (2.9%)	2 (16.7%)	
▪ Pneumoperitoneum	0 (0%)	2 (5.9%)	1 (8.3%)	
▪ Pneumomediastinum	1 (5.3%)	2 (5.9%)	0 (0%)	
▪ Mallory–Weiss tear	2 (10.5%)	3 (8.8%)	0 (0%)	
▪ Mucosotomy	1 (5.3%)	2 (5.9%)	1 (8.3%)	
▪ None	11 (57.9%)	20 (58.8%)	7 (58.3%)	
Length of stay, median (IQR), days	3 (1–6)	3 (1–6)	3 (1–6)	0.72 <sup>3</sup>
IQR, interquartile range. <sup>1</sup> Kruskal–Wallis test <sup>2</sup> Pearson $\chi^2$ test <sup>3</sup> Kruskal–Wallis and Mann–Whitney U				

excluded (18 previous treatment, 5 lost to follow-up before 1 year). Thus 65 were included (38 women [58.5%], 27 men [41.5%]; median age 47 years [IQR 20–81]).

Regarding the esophagus, moderate dilatation was the most common finding (17/65 [26.1%]). The median time to achalasia diagnosis, namely from initial signs and symptoms to the final manometric confirmation, was 36 months (IQR 14–120). Type II achalasia was the most common subtype, in 34/65 (52.2%), and dysphagia was the most common symptom 58/65 (89.2%).

The median Eckardt score reduced from 10 pre-POEM to 2 after the procedure. The median pre-POEM AE-18 total score was 40, and this increased to 56 after POEM. The operating time was 70 minutes (43–104). All POEM procedures were considered to be satisfactory (all steps were completed). All adverse events were minor and well-controlled; the most common was intraprocedural bleeding which occurred in 20 patients (30.7%). No major adverse event occurred. The median length of stay was 3 days.

### Patient differences according to achalasia subtypes before and after POEM procedure.

There were no differences between achalasia subtypes in relation to age, gender, type of esophagus, symptoms, time to diagnosis, procedure time, length of stay, or adverse events.

Before POEM, patients with type III achalasia had the worst Eckardt and AE-18 total scores, and 1 month after the procedure, they continued to show the lowest AE-18 total score compared with others.

There were no differences in IRP between achalasia subtypes before and after POEM, but myotomy and tunnel lengths were longer in those with type III (► **Table 2**).

### Relationship between AE-18 score, Eckardt score, and IRP

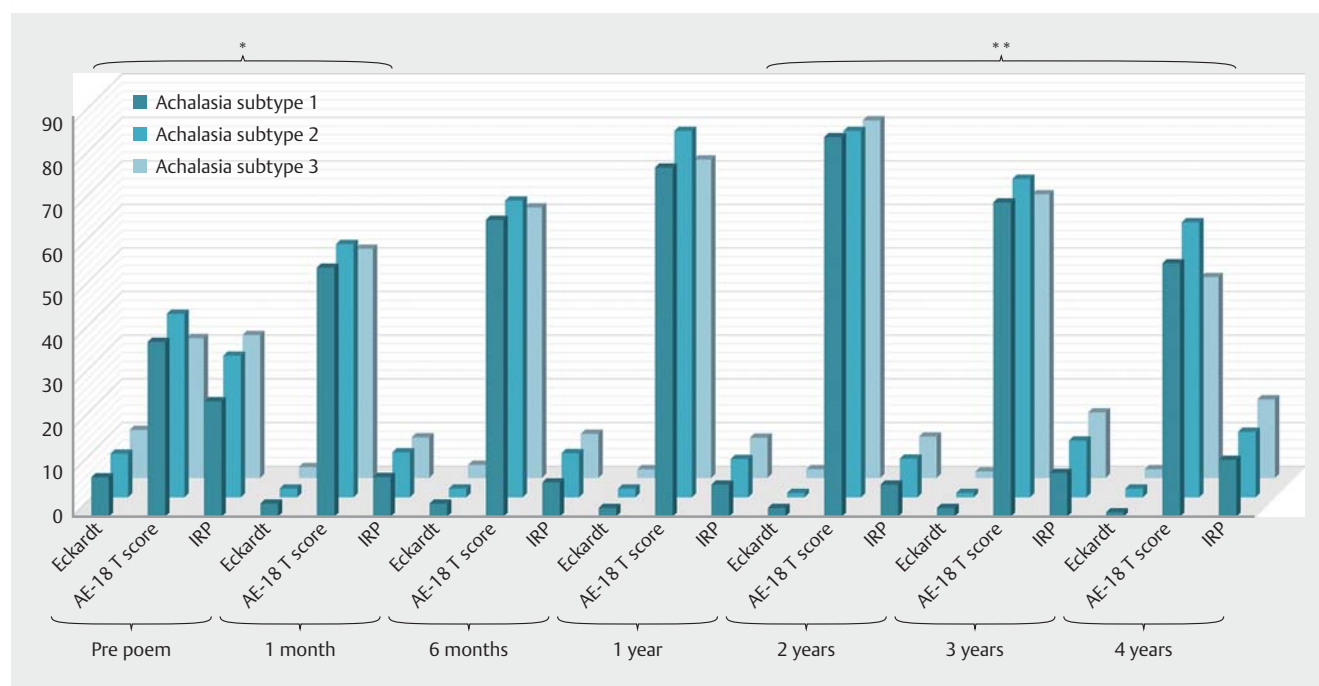
Follow-up was completed in 65 patients at 1 year (100%), in 59 at 2 years (90.7%), in 55 at 3 years (84.6%), and in 50 at 4 years (76.9%).

Eckardt scores were maintained after the procedure at a median of 2, up to the 4th year. However, QoL scores deteriorated over time; the median scores were: pre-POEM, 40/90 (44.4%); 1 month, 56/90 (62.2%); 6 months, 66/90 (73.3%); 1 year, 79/90 (87.7%); 2 years, 83/90 (92.2%); 3 years, 78/90 (86.6%), and 4 years, 68/90 (75.5%). Thus after year 2, there was a decrease in QoL scores, in spite of conservation of the Eckardt scores. Analysis between subgroups at 4 years showed that patients with type II achalasia had the highest median QoL scores; those with type III disease had the lowest, with statistically significant differences compared with type I ( $P=0.001$ ) or type II ( $P=0.003$ ).

Median myotomy length was type I 12 cm, type II 13 cm, and type III 18 cm, including 2–3 cm on the gastric side.

IRP showed a decrease of 65% from pre-POEM to post-POEM levels, from 29.4 mmHg (16–55) to 10.3 mmHg (3–18). This was partially maintained until the 3rd year, when we saw increases in the IRP (10.3 mmHg [3–18] at 1 month vs. 13.6 mmHg [6–19] at 3 years;  $P=0.03$ ). This became more pronounced at year 4 (10.3 mmHg [3–18] at 1 month vs. 14.7 mmHg [8–22] at 4 years;  $P=0.000$ ).

Patients with type III disease (12/65, 18%), had the lowest IRP in the short term after POEM with a median 8.7 mmHg (3–17), which was not different from IRP for other subtypes ( $P=0.33$ ). At the 3rd year, the IRP had increased in patients with all subtypes: type I, 8.9 mmHg (6–12); type II, 10.1 mmHg (5–15); and type III, 14.1 mmHg (8–19). There were statistically significant differences between type III and the others (type I vs. type III,  $P=0.001$ ; type II vs. type III,  $P=0.003$ ). At



► **Fig. 1** Comparison between achalasia subtypes in relation to Eckardt, AE-18 total score and integrated relaxation pressure (IRP) before and after peroral endoscopic myotomy (POEM) at early, medium-term, and long-term evaluation. \* $P=0.000$ , Friedman test and Wilcoxon test, for comparisons between pre-POEM and post-POEM at 1 month for Eckardt, AE-18 and IRP results. \*\* $P=0.000$ , Friedman test and Wilcoxon test, for comparisons between post-POEM at 2 years versus 3 or 4 years in AE-18 and IRP, but not in Eckardt score.

the 4th year, the IRP had increased again: type I, 9.6 mmHg (8–13); type II, 12.9 mmHg (9–15); and type III, 15.9 mmHg (11–22). Type III was associated with the highest IRP pressures (type I vs. type III,  $P=0.002$ ; type II vs. type III,  $P=0.001$ ). Among type III patients, 60% had an IRP > 15 mmHg, and this corresponded to a low QoL score (► **Fig. 1**).

### Changes in AE-18 subscales, reflux disease, and TBE

In the shorter term after the procedure (<1 year), scores on all the AE-18 subscales improved, reaching their maximum between 6 months and 2 years after POEM. However, at the 3rd year, we observed a decrease in the median scores in all subscales, despite maintenance of the Eckardt scores (<3). At the 4th year the social functioning subscale showed the greatest increase (27%), compared with the others (psychological functioning 15%, sleep 11%, and physical functioning 9%). Compared with pre-POEM levels, the final improvements at the 4th year were low for physical functioning (1%), moderate for psychological functioning (3%) and sleep (5%), and good for social functioning (11%). There were no differences associated with achalasia subtypes ( $P=0.35$ ).

In the evaluation of reflux disease, at 1 month post-POEM, 24/65 patients (37%) had a positive pHmetry finding confirming reflux disease, 11 showed clinical manifestations (17%), and 10/65 (15%) showed esophagitis (grade A 6/10 [60%], grade B 2/10 [20%], grade C 1/10 [10%], and grade D 1/10 [10%]). PPI treatment was initiated in patients with endoscopic findings of reflux, at single dose in 6/10 (60%) or double dose in 4/10 (40%). At 6 months, 18% of patients had positive findings

on pHmetry, 14% had esophagitis and 10% had clinical manifestations. PPI was initiated indefinitely in those with endoscopic findings of reflux. Reflux was confirmed in 8% at 1 year, in 6% at 2 years, and in 5% at 3 years, by pHmetry. Finally, at 4 years, 5% of patients continued to have positive findings on pHmetry, all of these had grade A esophagitis, and only 2% of patients had clinical symptoms. No relationship with QoL score was found (► **Fig. 2**).

Emptying at TBE was excellent in up to 60% of patients at the 4th year (► **Table 3**), with no differences between subtypes or with no relationship to QoL scores.

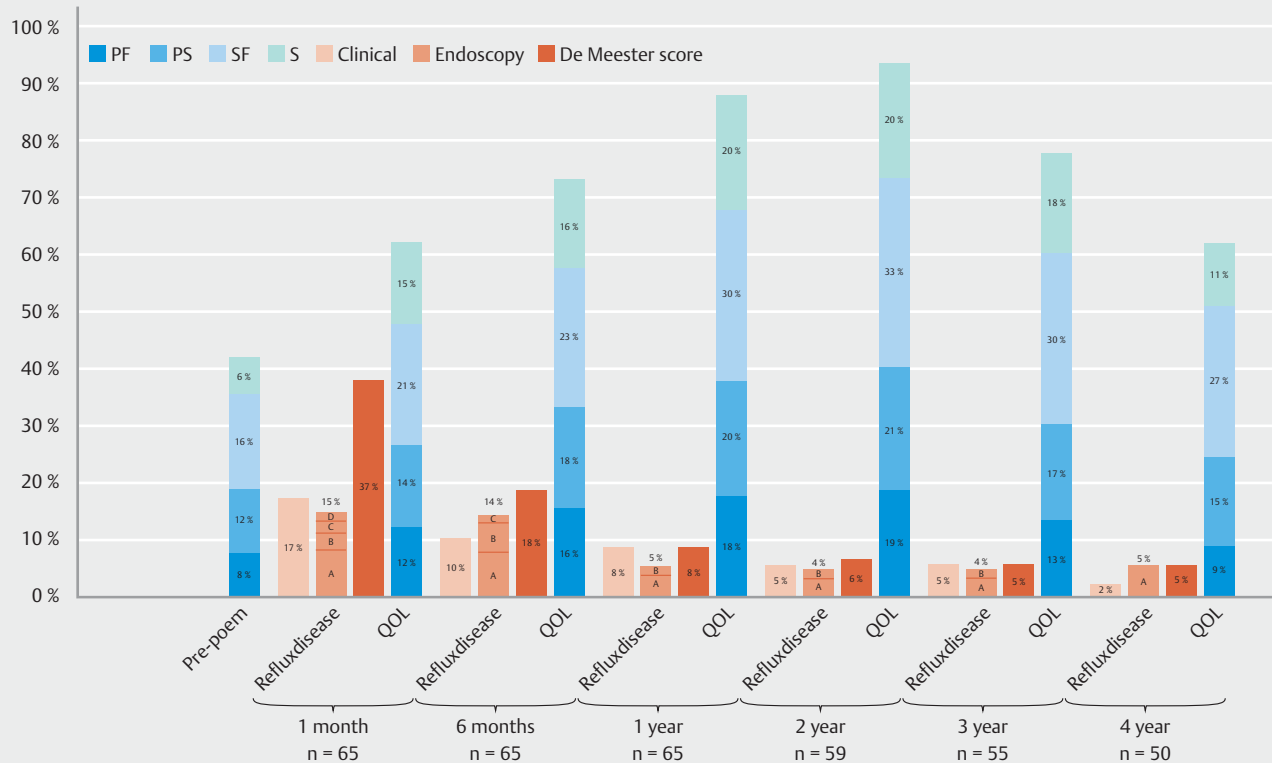
### Low vs. high QoL scores

At 1 month 7/65 patients (10.7%) had manometric failure (> 15 mmHg), 6/65 (9.2%) showed clinical failure (Eckardt score > 3), and 3 (4.6%) met both criteria. At 1 year, 4/65 (6.1%) had manometric failure and 5/65 (7.6%) had clinical failure; 2 of these patients were amongst the 3 patients with treatment failure on both criteria at 1 month, so POEM was considered to have failed in these patients. Dilation treatment was offered; patients meeting only one POEM failure criterion were followed up.

At 2 years, 6/59 patients (8.4%) had manometric failure, 6/59 (8.4%) showed clinical failure, and 4/59 (6.7%) had shown recurrence (with initial response after POEM and then showing clinical and manometric failure). Of these 4 patients, 2 had undergone a repeat POEM, and 2 received dilation.

At 3 years, 4/55 patients (7.2%) had shown recurrence and were treated with dilation ( $n=1$ ) or repeat POEM ( $n=3$ ). At 4





► **Fig. 2** Changes in quality of life subscales and reflux disease at early, medium-term and long-term evaluation. QOL, quality of life; PF, physical functioning; PS, psychological functioning; SF, social functioning; S, sleep.

► **Table 3** Timed barium esophagogram (TBE) findings during follow-up after peroral endoscopic myotomy in patients with achalasia.

TBE emptying	Pre-POEM (n = 65)	Post-POEM					
		1 month (n = 65)	6 months (n = 65)	12 months (n = 65)	24 months (n = 59)	36 months (n = 55)	48 months (n = 50)
Very compromised (<50%)							
n/n	65/65	0/65	0/65	0/65	0/59	0/55	2/50
%	100%	0%	0%	0%	0%	0%	4%
Moderately compromised (50%–80%)							
n/n	0/65	20/65	12/65	13/65	17/65	20/55	18/50
%	0%	30.7%	18.4%	20%	28.8%	36.3%	36%
Not compromised (>80%)							
n/n	0/65	45/65	53/65	52/65	42/59	35/55	30/50
%	0%	69.3%	81.6%	80%	71.2%	63.7%	60%

years, 11/50 (22%) had manometric failure and 14/50 (28%) clinical failure, and 10/50 patients (20%) had recurrence of achalasia, of whom 60% had type III disease. Of these 10 patients, 8/10 (80%) were treated with repeat POEM and 2/10 (20%) with dilation. Good outcomes were observed in patients with rescue treatment.

At the 4th year 16/50 patients (32%) had low QoL scores. After univariate analysis of multiple predictor variables, in the multiple logistic regression model, only male sex (OR 1.901, 95%CI 1.512–3.101;  $P=0.04$ ) and type III disease (OR 11.31, 95%CI 1.55–16.90;  $P=0.04$ ) showed a statistically significant relationship with low QoL score independently of other factors. This means that the risk of having a low QoL score at 4 years after POEM is increased by 90% in men and 10-fold in patients with type III achalasia (► **Table 4**).

## Discussion

In the evaluation of a medical or surgical intervention, quality of life should be considered for two principal reasons. First, when quality of life (QoL) scores decrease, symptoms often occur, representing the main reason for consultation. Secondly, because even the presence of clinical and objective improve-

ment as measured by different tools does not guarantee good quality of life [12, 14, 28].

In this paper, our primary objective was to evaluate QoL score maintenance in a cohort of patients after they had undergone the POEM procedure. Early improvement was seen, but was not maintained over time. POEM was developed in 2008 and has gained popularity because of its safety and efficacy in more than 90% of cases, compared to laparoscopic Heller myotomy [15, 29]. Clinical and manometric criteria for success have been used as the cornerstone of evaluation, and most studies report on these two endpoints, but quality of life is rarely considered. This is because most of the information we have comes from surgical treatment [30–32], and not from POEM, which is a relatively new treatment. In a multicenter international study, Ngamruengphong et al. [33] evaluated outcomes from 201 post-POEM patients followed for a median of 31 months (IQR 26–38). The patient group was heterogeneous, because 39.5% of patients had received previous non-POEM treatment. The clinical evaluation was based only on Eckardt score. They found that POEM is a safe and effective procedure that provides high clinical success and excellent long-term outcomes, but that there was recurrence in 6% of patients after 2 years. We found a similar result at 2 years with 4/59 recur-

► **Table 4** Multiple logistic regression model for evaluation of low quality of life (QoL) scores following peroral endoscopic myotomy (POEM).

Variable	Univariate analysis				Multivariate analysis		
	OR	95%CI	P value		OR	95%CI	P value
Age	1.144	0.753–1.730	0.534				
First 30 POEM*	1.121	0.041–1.601	0.450				
Sex (male)	2.910	1.941–3.212	0.031		1.901	1.512–3.101	0.042
Dilated esophagus	3.942	0.731–4.405	0.936				
POEM time	4.432	0.737–6.473	0.780				
Myotomy length	0.572	0.381–0.990	0.045				
Eckardt score pre-POEM	3.441	0.455–4.334	0.231				
AE-18 total pre-POEM	0.881	0.405–3.781	0.521				
IRP pre-POEM	10.12	1.010–14.81	0.050				
Achalasia type I	3.062	0.902–5.472	0.490				
Achalasia type II	5.201	0.470–8.410	0.645				
Achalasia type III	10.51	1.210–21.53	0.043		11.31	1.551–16.91	0.040
Eckardt post-POEM, 1-month	8.410	0.901–10.74	0.186				
AE-18 T post-POEM, 1-month	0.602	0.550–1.910	0.291				
IRP post-POEM, 1-month	2.101	0.292–8.901	0.430				
Clinical reflux disease, 1-month	2.401	0.810–5.101	0.421				
De Meester score, 1-month	3.451	0.145–25.34	0.921				
Esophagitis, 1-month	5.101	0.102–10.13	0.781				

OR, odds ratio; CI, confidence interval; IRP, integrated reflux pressure.

\* In order to evaluate any learning curve effect, the first 30 patients were compared with the subsequent patients for QoL scores.



ces (6.7%), but this increased to 10/50 (20%) at 4 years, possibly because of a longer follow-up time. Vigneswaran et al. [28], evaluated quality of life scores retrospectively in a group of post-POEM patients at an early time (less than 1 year), and they described excellent outcomes. Chan et al. [22], and Ward et al. [29] compared QoL between achalasia patients treated with LHM vs. POEM. These were also early comparisons, and the generic SF-36 scale was used for evaluation. As expected, good QoL results were found, but not until a minimum of 6 months after the procedure. No information about longer-term follow-up was provided. Therefore, we think that one of the strongest points of our paper is that our cohort has the longest evaluation time after a POEM procedure, in that follow-up in 76.9% of our patients reached 4 years, and 100% of patients had a minimum of 1 year of follow-up. This is why we propose that quality of life evaluation in the medium and long term should be considered, because although early evaluation shows excellent results, further observation is needed.

Our results confirm early improvements in Eckardt score and TBE findings that were maintained over time; however, improvements in QoL scores and IRP were not maintained. IRP increased from a median of 10.3 mmHg (3–18) at 1 month after POEM to a median of 14.7 mmHg (8–22) at the 4th year. Among the patients with deterioration in QoL score and IRP, most had type III disease and 60% had an IRP greater than 15 mmHg. This is relevant because it corresponds to changes in QoL scores that were also not maintained after year 2. After this point, we observed an increase in IRP, and a decrease in QoL scores, to a final median of 68, but, as with IRP, most of these patients had type III achalasia. However, if our study had lasted only 2 years, the changes and results would have paralleled those of other authors who have shown good outcomes in quality of life in the shorter term [22, 28, 29, 33]. Our longer follow-up revealed a nonlinear behavior in QoL scores and IRP, that perhaps more accurately represents the course of both these variables in this disease, and may account for the 6% of patients in the study by Ngamruengphong et al. [33], who initially responded at 6 months but relapsed at year 2 of follow-up.

We had a higher proportion of patients with type III achalasia (18%) than in other studies, possibly because of ethnicity. This affected our results, because most of the patients showing treatment failure at the 4th year had type III disease. Kumbhari et al. [34] compared early outcomes between laparoscopic Heller myotomy and POEM in 75 patients with type III disease. As expected, POEM had better results, because a longer myotomy was performed (as in our patients with type III disease), but unfortunately the follow-up in the POEM group was shorter (8.6 vs. 21.5 months); Sharata et al. [8], have addressed the role of POEM in spastic disorders (including type III achalasia), and they reported a lower efficacy (71%), but with at least 1 year of follow-up. Their data, therefore, supports the idea that a more real clinical outcome in patients with achalasia could be observed with a longer follow-up period. In our study, we do not know whether the increase in IRP that corresponded to low QoL scores depended on the presence of scar tissue at the EGJ level, as in patients that have been treated with laparoscopic Heller myotomy, or whether it is due to a different pa-

thophysiology in which repair is begun, creating a new sphincter that consequently increases the basal and IRP pressures, and differing from the other achalasia subtypes [2, 3, 18, 20].

For evaluation of quality of life, we used the AE-18 questionnaire because of its high specificity for achalasia and its availability. This scale evaluates four different areas: physical functioning, psychological, social, and sleep. In our cohort, we had a median delay of 36 months between initial symptoms and diagnosis. This is not different from international reports [1, 14, 15], and could be the reason for the impairment shown on the physical functioning and sleep subscales, perhaps because chronically impaired passage of food through the EGJ causes weight loss, malnutrition, and an increase in reflux symptoms, mostly in the supine position. It is evident that psychological and social functioning are least affected because, out of embarrassment, patients “learn to live with” this disease. In our patients, sleep and physical functioning had the lowest scores before and after treatment despite an initial improvement. This improvement was not maintained after year 2 and the decline corresponded to the increase in IRP, although we found no associations with any achalasia subtypes.

Moreover, in the evaluation of reflux disease, 37% of our patients had positive pHmetry findings at 1 month after the procedure and 18% at 6 months; in most cases there was mild esophagitis and there was no relationship to symptoms. In patients initially treated with PPI after POEM and followed up for 48 months, reflux was successfully controlled with PPI in all except 5%. Failure may have been due to lack of compliance or to a need for dose adjustment. No relationship was found between reflux, TBE, and QoL scores.

In order to explain factors associated with low QoL scores, a multiple logistic regression model was constructed. We found that male sex and type III achalasia had a statistically significant relationship with low QoL scores independently of other factors, including any influence of learning curve. (We investigated whether there was any association between the first 30 POEMs and QoL scores.) We believe this to be the most important finding of our work, because by considering only those two parameters we could identify patients at risk of having low QoL scores in the long term after POEM. However, these results do not permit us to make practical recommendations in terms of modification of treatment. Therefore, to confirm these results, new research in this direction is needed and longer follow-up must be done, so that specific suggestions may be made about improvements during or after the POEM procedure.

In conclusion, at early evaluation after the POEM procedure, clinical and QoL score improvements are found in most patients, but in the medium and long term (after the second year), unknown factors associated with male sex and type III achalasia induce an increase in IRP and a decrease in QoL scores. Longer follow-up is needed, but these findings must be taken into account during evaluation, treatment, and follow-up of these patients.

## Competing interests

None

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