

Quality of life in patients with achalasia: Associations with Eckardt score and objective treatment outcomes after peroral endoscopic myotomy



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ABSTRACT

Background and study aims Knowledge on self-reported quality of life (QoL) in achalasia and QoL improvements after peroral endoscopic myotomy (POEM) is limited. Furthermore, the clinical role of QoL in achalasia follow-up has not been evaluated. The present study aimed to examine QoL in achalasia patients before and after POEM and assess associations between QoL, Eckardt score (ES) and objective results.

Patients and methods This was a single-center prospective study of treatment-naïve achalasia patients with 12-month follow-up after POEM including manometry, upper endoscopy, 24-hour pH registration, and timed barium esophagogram. QoL data were registered using European Organisation for Research and Treatment of Cancer core questionnaire (QLQ-C30) and esophageal module (QLQ-OES18). Comparison with a reference population was performed to assess impact of achalasia on QoL and effect of therapy. Mixed models for repeated measures were applied.

Results Fifty patients (26 females) with a median age of 47 years (18–76) were included. Before treatment, all QoL domains were significantly impaired compared with an age- and gender-adjusted reference population ($P < 0.05$). No significant QoL-differences were found after POEM, except for fatigue and nausea/vomiting. Clinically relevant QoL improvement was observed in $\geq 50\%$ of the patients in all QoL domains, except for physical and role functioning. QoL was significantly associated with ES ($P < 0.05$) but not with objective results.

Conclusions Achalasia is associated with severe QoL impairment. Following POEM, a significant and clinically relevant QoL improvement is observed. QoL is associated with ES, but not with objective results after POEM.

Introduction

Achalasia is a rare, primary esophageal dysmotility disorder of unknown etiology. Lymphocytic destruction of ganglion cells in the esophagus and the lower esophageal sphincter (LES) causes loss of inhibitory neuromuscular control. The resulting physiological disturbances include esophageal aperistalsis and impaired LES relaxation, which together are achalasia-defining features [1].

The treatment is palliative and aims at reducing the increased LES pressure, thereby alleviating symptoms by improving esophageal clearance and preventing the development of esophageal decompensation. Primary therapeutic modalities include pneumatic balloon dilation (PD), laparoscopic Heller myotomy (LHM), and peroral endoscopic myotomy (POEM).

Treatment evaluation in achalasia includes both objective and subjective measures. Objective tests such as timed barium esophagogram (TBE) and high-resolution manometry (HRM) offer superior predictive value to symptoms, and are central in the post-treatment evaluation [2–5]. The Eckardt score (ES) is the most frequently used patient-reported outcome (PRO) measure, incorporating dysphagia, regurgitation and chest pain as well as weight loss [3].

The symptom burden associated with achalasia affects several aspects of the patients' quality of life (QoL). Validated QoL questionnaires are sensitive in capturing the patient perspectives, and have been recommended in achalasia follow-up [6]. There are, however, few prospective studies on the effects on QoL after treatment, and there is limited knowledge on QoL in achalasia before and after therapy, when compared with a reference population [7–9]. Furthermore, statistically significant QoL improvements after treatment have been reported, but QoL may still remain impaired [10], and less is known about the clinically relevant improvements of QoL [9, 11].

Validated QoL questionnaires include measures beyond the four metrics of ES, and may hence represent a more valuable symptomatic evaluation than ES. Only limited associations between ES and objective results have been reported, suggesting that an alternative PRO measure is needed [2, 12]. While studies have found that ES and QoL are strongly associated, the associations between QoL and objective results after POEM have to our knowledge not been systematically examined [7, 13, 14].

The aims of the present study were to: 1) examine QoL in achalasia patients at time of diagnosis and changes over time after POEM; 2) compare patient QoL scores with a reference population; and 3) explore associations between QoL and objective outcomes and between QoL and ES.

Patients and methods

Study design and patients

The present study was a single-center prospective study on consecutive treatment-naïve achalasia patients undergoing POEM with 12-month follow-up. Detailed results on outcome and predictive factors have recently been presented elsewhere [2]. All achalasia patients diagnosed at Oslo University Hospital were evaluated for eligibility, and the inclusion period was from

March 2016 to November 2018. The diagnosis of achalasia was based on HRM-findings according to the Chicago classification [15] supplemented by TBE [16] and upper endoscopy (EGD).

Inclusion criteria were: confirmed achalasia, ES >3, treatment-naïve, age ≥18 years, decision of POEM in a multidisciplinary team meeting, American Society of Anesthesiologists (ASA) score ≤3 [17] and written informed consent.

Data collection

A predefined post-POEM follow-up protocol was used with telephone interviews after one week and 3 and 6 months. Before treatment and after 12 months, a standard comprehensive evaluation including HRM, TBE, EGD and 24-hour ambulatory pH registration (24-h pH) was performed, except in cases of treatment failure where earlier post-POEM evaluation was required. ES and QoL were registered simultaneously. QoL registration at baseline and at 12 months was performed by the patients, while registrations at 3 and 6 months were performed by telephone interviews by the same physician (HE).

Patient-reported QoL data were assessed using European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life core questionnaire EORTC QLQ-C30 [18] supplemented with selected symptoms from the esophageal module EORTC QLQ-OES18 [19]. The QLQ-C30 contains five functional scales, one global QoL scale, three symptom scales and six single items, that are scored on a 1 (not at all) to 4 (very much) scale denoting the severity of the problem. The global QoL scale assessing overall health and overall QoL is scored from 1 (poor) to 7 (excellent). All scores are transformed to 0–100 scales, with higher scores on the functional and global QoL scales representing better functioning/higher global QoL, whereas higher score on the symptom scales and single items indicate more problems. The EORTC QLQ-OES-18 represents common symptoms with relevance to QoL in patients with esophageal cancers, some that are identical to those found in achalasia.

In the present study, the following scales and items were selected as they were regarded as particularly relevant to achalasia patients: From the QLQ-C30; four functioning scales; physical, social, role, and emotional, one global QoL scale, three symptom scales; fatigue, nausea and vomiting and pain and one single item; appetite loss. From the QLQ-OES18; one functional scale; dysphagia and three symptom scales; reflux, choked when swallowing and eating disturbances.

TBE was performed as described by Neyaz et al. [16]. The ManoScan ESO High-Resolution Manometry System (Medtronic, Minneapolis, Minnesota, United States) was applied. HRM was performed and analyzed according to the Chicago classification, v 3.0, and achalasia was classified in subtypes I, II and III [15]. Twenty-four-hour pH recording was performed using Digitrappher pH testing System (Medtronic, Minneapolis, Minnesota, United States). Detailed results on TBE, HRM, 24 h pH registration and upper endoscopy have been reported elsewhere [2].

Definitions and variables

The following definitions and variables were applied:

Clinically relevant change in QoL: ≥ 10 [20].

Favorable post-POEM esophageal clearance: 1-minute TBE reduction rate ≥ 0.5 [2, 21].

Normal post-POEM esophageal diameter: ≤ 3 cm [22].

Favorable HRM response: Lower esophageal sphincter relaxation pressure (LESrp) < 10 mm Hg [3]. Negative 24-hour pH measurement: Distal esophageal acid exposure time $< 6\%$ [23].

Negative upper endoscopy: No esophagitis according to the Los Angeles Classification [24]

Achalasia stage: Sigmoid and non-sigmoid achalasia [25]

Achalasia subtypes I, II and III [15]

Symptom duration: Time (years) with clinical symptoms until POEM treatment

Reference population

A representative sample ($n = 1965$) from the Norwegian normal population, was available for comparison of QoL (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire [EORTC QLQ-C30]) [18]. Estimates from this reference population have previously been presented elsewhere [20].

Ethics

Data from standard clinical follow-up were prospectively included in the study database, which was approved for use in research by the institutional review board at Oslo University Hospital (personvern@oslo-universitetssykehus.no, case number 2016/5437). All patients signed informed consent. The study adheres to the Declaration of Helsinki. Data on outcome evaluation and predictive outcome have recently been presented elsewhere [2].

Statistical analyses

Continuous variables were described with mean and standard deviation (SD) when normally distributed or with median and range if the variables followed a skewed distribution. Categorical data were presented as counts and percentages.

Crude comparison between pairs of variables were performed using chi-square test (categorical data) or Mann-Whitney Wilcoxon and Wilcoxon signed rangs test (continuous data).

Association between baseline QoL, selected possible predictive factors, selected objective measures and QoL assessed at 3, 6, and 12 months were modeled using generalized linear models for repeated measures (GLM). Possible statistical dependencies among individuals being measured several times were modeled using unstructured covariance matrix. Due to a limited sample size and to avoid overfitting, the analyses were conducted in two steps:

1) Separate GLM models were fitted for all the QoL variables as the dependent and the following possible predictive factors: gender, age, achalasia subtype, achalasia stage (sigmoid vs non-sigmoid) and symptom duration as covariates.

2) Variables that were statistically significant in step 1) were added to the models investigating the strength of association between the QoL variables and selected objective measures.

The results were expressed as regression coefficients (B) with 95% confidence intervals (CI).

The proportions of patients with clinically relevant improvement were reported as the estimated proportions with 95% CI constructed using Agresti-Coull approximation. Association between ES and QoL was depicted using kernel weighted polynomial smoothing using Gaussian kernel function [26], and applying the Stata command “*kdensity*.”

All the analyses were considered exploratory so no correction for multiple testing was done. $P < 0.05$ was considered statistically significant. All analyses were performed using SPSS ver 26 and Stata ver 17.

Results

In total, 50 treatment-naïve achalasia patients (26 females) with a median age of 47 years (18–76) and a median symptom duration of 4 years (1–30) were included in the study. All 50 patients adhered to the predefined follow-up protocol. Twelve-month QoL data were available in 42 patients. The distribution of age and gender was similar ($P > 0.05$) in the patients and the reference population.

At the 12-month control, TBE reduction rate was favorable in 36 of the patients (75%), a normal esophageal diameter was seen in 35 (71%) and 22 (45%) had a LESrp < 10 mm Hg, while 34 (72%) and 25 (51%) of the patients had a negative 24-hour pH registration and a negative upper endoscopy, respectively [2].

After POEM, statistically significant QoL improvements were observed for all analyzed domains, except for physical functioning (► **Table 1**). Clinically relevant improvements were observed in 50% or more of the patients for all QoL domains except for physical functioning and role functioning (► **Table 2**). Compared with the reference population, pre-treatment QoL scores were significantly impaired in the achalasia patients for all examined domains. Twelve months after treatment, QoL scores were similar between the achalasia patients and the reference population, except that achalasia patients reported lower levels of fatigue, but scored higher on nausea and vomiting (► **Fig. 1a**, ► **Fig. 1b**).

Global QoL after POEM was significantly associated with pre-treatment global QoL score, but was not associated with objective results (► **Table 3**). On further analyses, post-POEM QoL scores were associated with QoL pre-treatment scores for all QoL domains, except for appetite loss and eating disturbances. Reduced post-POEM esophageal diameter was significantly associated with improved social functioning and reduced nausea and vomiting and eating disturbances, while a negative post-POEM upper endoscopy (no sign of reflux esophagitis) was significantly associated with increased eating disturbances (all $P < 0.05$). No further statistically significant associations were found between the selected objective measures and QoL (**Table S1**). When adjusted for gender, age, symptom duration, achalasia stage and subtype, the only association that remained

► **Table 1** Quality of life in patients with achalasia (n = 50) in the period from baseline (before treatment) until 12 months.

	Study population				
	baseline	3 months	6 months	12 months ¹	P value
Physical functioning	84.9 (19.1) ²	96.7 (8.3)	94.6 (11.1) ²	90.5 (17.1)	0.09
Social functioning	62.2 (30.5) [†]	95.0 (13.2)	93.2 (15.2) ²	84.9 (23.5)	<0.01
Role functioning	70.4 (33.2) ²	94.7 (13.7)	93.3 (15.8)	87.3 (22.9)	<0.01
Emotional functioning	69.0 (26.0) ³	91.8 (12.8)	91.5 (15.4)	88.3 (15.1)	<0.01
Global QoL	45.7 (24.3) ³	73.7 (19.8)	72.2 (16.6)	76.8 (20.7)	<0.01
Fatigue	47.6 (30.7) ²	10.2 (16.5)	13.1 (18.3)	20.1 (19.1)	<0.01
Pain	38.1 (29.7) ²	9.3 (15.5)	11.0 (17.4)	13.9 (22.7)	<0.01
Nausea, vomiting	35.0 (29.3) ²	5.3 (11.9)	4.0 (9.3)	6.7 (12.8)	<0.01
Appetite loss	36.7 (34.2) ²	4.0 (12.8)	8.7 (20.0)	6.3 (16.8)	<0.01
Dysphagia	40.3 (26.5) ³	4.7 (12.9)	5.3 (11.5)	6.4 (14.1)	<0.01
Reflux	29.5 (32.1) ³	8.0 (13.6)	7.0 (13.5)	13.1 (23.2)	<0.01
Eating disturbances	67.1 (22.6) ³	9.7 (16.8)	12.0 (17.2)	20.2 (24.7)	<0.01
Choked when swallowing	32.5 (32.9) ³	3.3 (12.1)	2.0 (8.0)	12.8 (23.7)	<0.01

Values are mean (SD).
P value baseline vs 12 months.
¹ n = 42.
² n = 49.
³ n = 48.

► **Table 2** Proportions of achalasia patients with clinically relevant improvement in QoL.

QoL	Clinical improvement ¹
Physical functioning ²	26.8 [14.2–42.9]
Social functioning ³	57.5 [40.9–73.0]
Role functioning ²	46.3 [30.7–62.6]
Emotional Functioning ³	52.5 [36.1–68.5]
Global functioning ³	80.0 [64.4–90.9]
Fatigue ²	73.2 [57.1–85.8]
Pain ²	68.3 [51.9–81.9]
Nausea/vomiting ²	63.4 [46.9–77.9]
Appetite loss ²	58.5 [42.1–73.7]
Dysphagia ³	82.5 [67.2–92.7]
Reflux ³	50.0 [33.8–66.2]
Choked ³	51.3 [34.8–67.6]
Eating disturbance ³	85.0 [70.2–94.3]

(≥ 10) 12 months after treatment compared with baseline (before treatment).
¹ % [95% confidence interval].
² n = 41.
³ n = 40.

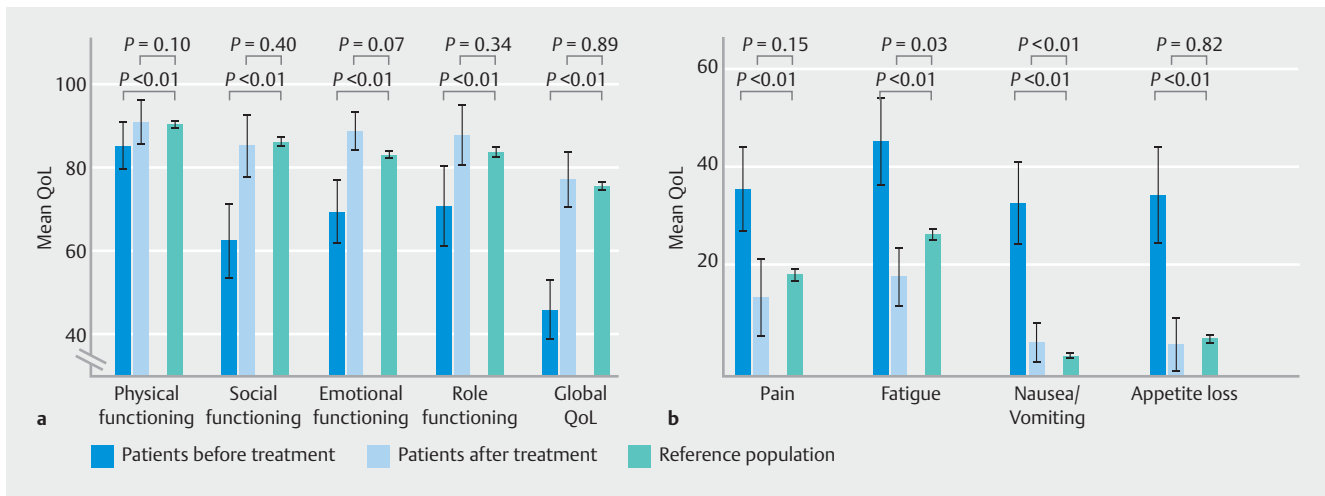
statistically significant was the association between post-POEM esophageal diameter and nausea and vomiting (data not shown).

Eckardt score and QoL (global QoL) were significantly associated ($P < 0.001$) before treatment and throughout the follow-up period (► **Fig. 2**).

Discussion

The present study demonstrates that patients with achalasia have markedly reduced QoL at time of diagnosis compared with a reference population. Treatment with POEM distinctly improves this situation, and after twelve months, QoL was similar in patients and the reference population. As such, validated QoL questionnaires represent the patients' own perceptions and provide important and supplemental health information to objective measures in achalasia patients. While changes in ES and QoL after POEM are significantly associated, QoL changes are only to a limited extent associated with objective outcome variables.

The marked differences in QoL in treatment-naïve achalasia patients and the reference population, illustrate the impact of achalasia. Swallowing difficulties are readily demonstrated in relevant symptom scores, and moreover, QoL data reveal the association between achalasia and impaired health, including mental, physical and social functioning. Following treatment with POEM, QoL improves, and at 12 months follow-up, QoL in achalasia patients is comparable to the reference population. In



► **Fig. 1** Quality of life (QoL) in achalasia patients before and 12 months after POEM compared to reference population. **a** QoL functioning and global QoL. **b** QoL symptoms.

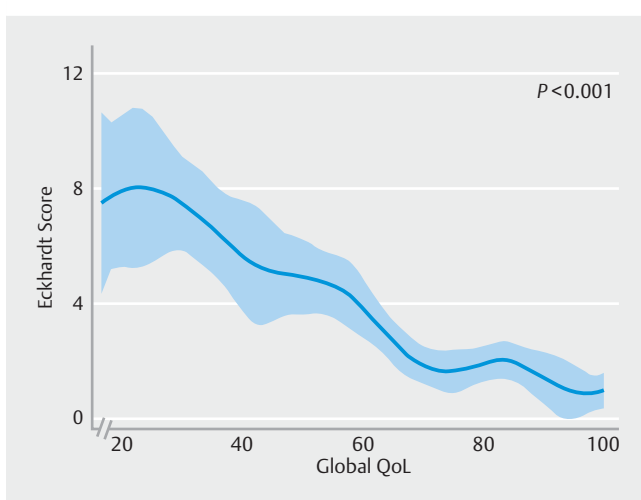
► **Table 3** Predictive factors for global quality of life after peroral endoscopic myotomy (POEM).

Predictive factor	Regression coefficient B [95 % CI]	P value
Baseline QoL (prior to treatment)	0.2 [0.0; 0.3]	<0.05
Timed barium esophagogram (TBE) ¹	3.8 [-4.5; 12.1]	0.37
Esophageal diameter ¹	2.1 [-6.3; 10.5]	0.62
Lower esophageal sphincter (LES) residual pressure ¹	0.5 [-5.5; 6.5]	0.87
Upper endoscopy ¹	-1.2 [-7.8; 5.4]	0.73
24 hour pH recording ¹	-0.5 [-7.9; 6.9]	0.90

Mixed model analyses for repeated measures.

Cut-offs: TBE reduction rate 0.5, esophageal diameter 3 cm, LES residual pressure 10 mmHg, upper endoscopy with no esophagitis, 24 hours pH 6 % acid exposure time.

¹ 12 months after POEM.



► **Fig. 2** Association between ES and global QoL depicted using kernel weighted polynomial smoothing.

in addition to the statistically significant change, it is important to consider the clinical relevance of the QoL changes, as this may provide more relevant information. When adhering to a standard cut-off value for clinical relevance [20], QoL improvement was evident in the majority of the patients for most of the analyzed items. For the highly relevant QoL domains global QoL, dysphagia and eating disturbances, clinically relevant improvement was observed in more than 80% of the patients. Interestingly, patients treated for achalasia reported less fatigue than the reference population. The present study does not provide an explanation, but the effect on fatigue may be a consequence of the relief of reduced achalasia symptoms after long-standing disease.

Due to the complex nature of achalasia and the impact on both physical and mental health, validated QoL questionnaires are recommended tools in treatment outcome evaluation [6, 7]. Consequently, post-treatment QoL improvements have been used to compare outcome of PD with LHM [27]. However, when assessing the importance of applying QoL in achalasia follow-up, the association with objective results is relevant. Main

goals in achalasia therapy and follow-up are persistent symptomatic effect and preventing disease progression toward end-stage achalasia. The predictive value of objective tests such as TBE and HRM has been repeatedly demonstrated [2, 3, 5, 22], and specific study protocols, e. g. rapid drink challenge (RDC), may further increase the importance of HRM [28]. In contrast to objective tests, the relevance of QoL is in this respect uncertain. To our knowledge, this is the first achalasia study to systematically assess the role of QoL outcomes by their associations to objective results.

According to the findings in the present study, pre-treatment QoL level is a strong predictive factor for post-treatment QoL score, and this emphasizes the relevance of applying change in QoL for treatment evaluation. Therefore, all our models exploring associations between selected objective outcomes and QoL were adjusted for pre-treatment QoL. The large number of analyses performed illustrates the lack of significant associations between QoL and objective results after POEM. Absence of reflux esophagitis on post-POEM EGD was associated with increased eating disturbances, a finding in line with Werner et al, who identified post-POEM reflux esophagitis as a predictive factor for clinical success [29]. Also, the predictive value of a normalized esophageal diameter after achalasia therapy has been demonstrated [22]. In the present study, this finding was associated with increased social functioning as well as a reduction in esophageal symptoms. Although plausible, the demonstrated associations were sporadic and only borderline statistically significant and thus hardly sufficient to encourage a shift in PRO measure from ES to QoL measurements in general clinical practice.

In contrast to the limited associations between QoL and objective outcome, ES and Global QoL were strongly associated. The close relationship between ES and scores derived using generic QoL questionnaires as well as achalasia-specific QoL questionnaires, has been demonstrated previously [7, 13]. ES is easily applied, widely used in clinical studies and seems an appropriate PRO in regular follow-up of achalasia patients. However, while the widespread use of ES is still advocated, it should be emphasized that validated QoL questionnaires provide extensive information from the patient point of view on both the impact of achalasia, and the potential health improvements induced by therapy such as POEM. In the present study, patient physical functioning did not improve significantly after POEM. This finding has been previously reported [8], and illustrates how validated QoL questionnaires offer relevant patient information beyond the metrics of ES. Studies on QoL are therefore definitely needed in a research setting to better characterize and scrutinize the complex influence of achalasia on patients' health and the effects of treatment.

Strengths and limitations

The limited sample size in the present study was to some degree offset by the comprehensive follow-up of patients, repeated QoL data registration and the application of mixed model analyses for repeated measures. Furthermore, when studying the influence of achalasia itself on QoL and the effect of treatment, including only treatment-naïve patients provides results

that may be easier to interpret. However, 12-month QoL data were not complete, and a follow-up period of 12 months does not constitute a long-term QoL outcome after POEM, which has been evaluated only in a few previous studies [14].

QoL data were registered partly by patients and partly by one clinician, potentially representing a data registration bias, although the baseline and 12-month QoL recordings were all performed by the patients. EORTC QLQ-C30 and QLQ-OES18 were chosen as QoL questionnaires. The EORTC QoL questionnaires are validated, translated into Norwegian language, and previous studies applying the EORTC QLQ-C30 have established a large Norwegian reference cohort and demonstrated the stability of QoL over decades in the general Norwegian population [20, 30]. Furthermore, we have applied these questionnaires previously and therefore had the necessary knowledge and experience [31]. Although developed primarily for cancer patients, the EORTC QLQ-C30 and QLQ-OES18 combined offer a wide array of commonly reported symptoms and problems in the general population, and include items used in benign gastrointestinal diseases as well as esophagus-specific items. A disease-specific QoL questionnaire could have provided more valid QoL data [32], but an achalasia-specific validated Norwegian questionnaire currently is not available, and the use of EORTC QLQ-C30 allowed us to compare the achalasia patients with a Norwegian reference population.

Conclusions

Achalasia is associated with markedly reduced QoL. Following POEM, clinically relevant and statistically significant QoL improvements are observed. Notably, QoL is normalized twelve months after achalasia treatment, indicating a large, beneficial effect of the procedure. While objective outcomes after treatment are only to a limited extent associated with QoL, ES, and QoL are closely related. Validated QoL questionnaires capture the patient's own evaluation of symptoms and problems and provide patient information beyond ES. However, due to its demonstrated clinical value, simplicity and widespreadness, the use of ES as a supplement to the objective tests is still supported in the clinical follow-up of patients with achalasia.

Competing interests

The authors declare that they have no conflict of interest.

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