

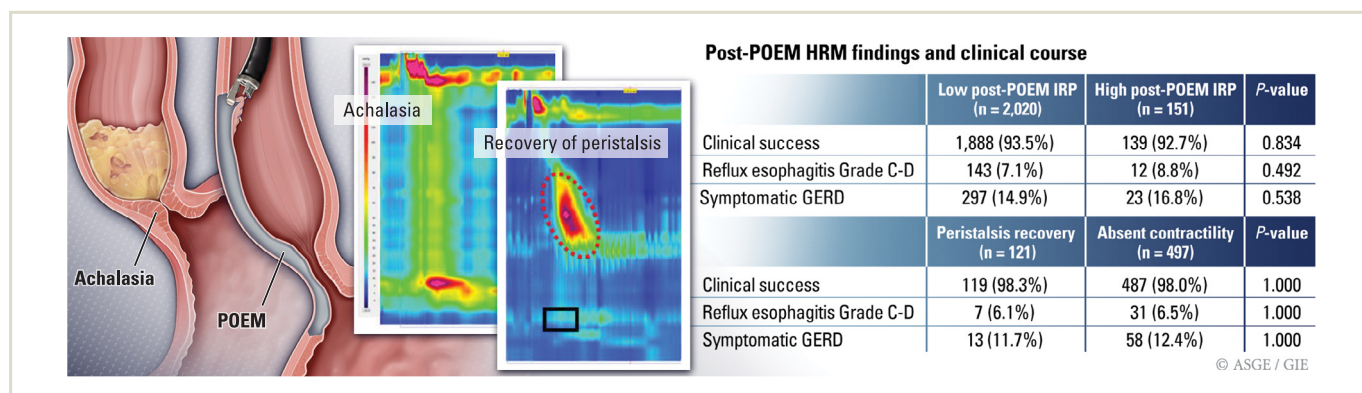


Impact of peroral endoscopic myotomy on high-resolution manometry findings and their association with the procedure's outcomes

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GRAPHICAL ABSTRACT



Background and Aims: Peroral endoscopic myotomy (POEM) is conducted for patients with esophageal motility disorders based on high-resolution manometry (HRM) findings. However, the impact of POEM on HRM findings and the associations between post-POEM HRM and outcomes have not been clarified.

Methods: In a multicenter, observational, cohort study, patients with achalasia treated by POEM received follow-up HRM. Associations between patient characteristics, POEM procedures, and post-POEM HRM findings, including integrated relaxation pressure (IRP) and distal contractile integral (DCI), were investigated. Furthermore, POEM procedure outcomes were compared with post-POEM HRM findings.

Results: Of 2171 patients, 151 (7.0%) showed residual high post-POEM IRP (≥ 26 mm Hg; Starlet [Starmedical Ltd, Tokyo, Japan]). In a multivariate analysis, high pre-POEM IRPs (odds ratio [OR], 24.3) and gastric myotomy >2 cm (OR, .22) were found to be positive and negative predictive factors of high post-POEM IRPs, respectively. Peristalsis recovery (DCI ≥ 500 mm Hg/cm/s, at least 1 swallow; Starlet) was visible in 121 of 618 patients (19.6%) who had type II to III achalasia. High pre-POEM IRP (OR, 2.65) and DCI ≥ 500 (OR, 2.98) predicted peristalsis recovery, whereas esophageal dilation (OR, .42) predicted a risk of no recovery. Extended myotomy did not reveal a significant impact on peristalsis recovery. High or low post-POEM IRP and DCI did not increase the incidence of clinical failure, reflux esophagitis, or symptomatic GERD.

Conclusions: Extended gastric myotomy decreased IRP values, whereas peristalsis recovery depended on the characteristics of achalasia. A residual high post-POEM IRP does not necessarily mean clinical failure. Routine HRM follow-up is not recommended after POEM. (Gastrointest Endosc 2023;97:673-83.)

(footnotes appear on last page of article)

Achalasia is an esophageal motility disorder (EMD) characterized by impaired lower esophageal sphincter (LES) relaxation and absence of normal esophageal peristalsis.¹ High-resolution manometry (HRM) was developed in the early 2000s,^{2,3} and parameters such as integrated relaxation pressure (IRP) and distal contractile integral (DCI) are used to define LES function and esophageal body contraction, respectively. The Chicago classification, based on HRM findings, is the criterion standard for the diagnosis of EMDs and categorizes achalasia into 3 subgroups based on esophageal contraction: type I, with 100% failed peristalsis; type II, with pan-pressurization; and type III, with spastic contraction.⁴ In 2010, we reported the efficacy of peroral endoscopic myotomy (POEM) for achalasia,⁵ and POEM is currently an established treatment option.^{6,7}

The pathology of achalasia is unclear, although a reduced or absent Auerbach plexus in the esophageal muscularis propria has been reported.¹ The degree of ganglion damage differs across achalasia types. Therefore, post-treatment esophageal motility recovery depends on patient characteristics.^{8,9} Short symptom duration, high pretreatment IRP, and types II and III achalasia have been reported as indicators of peristalsis recovery after treatment, although discrepancies were present in these reports.¹⁰⁻¹² Despite their relevance as indicators of residual LES function impairment, patient characteristics associated with high postintervention IRP values have not been fully investigated.

Interventions also change esophageal motility. An advantage of POEM is that the length and direction of myotomy can be adjusted.⁵ A meta-analysis including 1261 patients revealed that the direction of myotomy does not affect post-POEM LES pressure and clinical outcomes.¹³ However, the association between myotomy length and post-POEM HRM findings has not been fully investigated. Regarding outcomes, IRP values after pneumatic dilation (PD) were reported to be higher in cases of clinical failure than in cases of clinical success.¹⁴⁻¹⁶ However, the frequency of post-POEM residual high IRP values has not been compared between cases of clinical failure and success. A report on 52 patients with achalasia indicated that more cases with clinical failure showed an increase in IRP compared with those before POEM.¹⁷ The association between post-POEM HRM findings and POEM outcomes should be elucidated by a study with a larger sample size. Although HRM is considered standard before POEM, the necessity and value of HRM after POEM has not yet been determined and warrants further investigation.

Albeit rare, achalasia is a major EMD with an incidence of 1.0 per 100,000 persons per year.¹⁸ A single-center study did not achieve sufficient statistical power required for the study purpose. Therefore, a multicenter study was planned, including facilities with HRM and POEM procedures.

The study aimed first to identify patient characteristics and POEM procedures predictive of residual high post-POEM IRP values and recovery of esophageal peristalsis. Second, we aimed to elucidate the associations between

post-POEM HRM findings and POEM outcomes, including clinical success, reflux esophagitis (RE), and symptomatic GERD.

METHODS

Patients

This study was part of a more extensive retrospective clinical study of EMDs, including achalasia, the Japanese Achalasia Multicenter Study.^{19,20} The facilities included in the Japanese Achalasia Multicenter Study were those with more than 50 patients with achalasia from 2010 to 2020. Patients with EMDs, diagnosed using standard methods including HRM, esophagogram, and gastroscopy, and treated by POEM were enrolled. This study was conducted at 13 high-volume centers.

The study was approved by the ethics committees of all involved institutions ([Supplementary Table 1](#), available online at www.giejournal.org) and was conducted according to the tenets set by the Declaration of Helsinki. Informed consent was obtained in the form of an opt-out system on a website. All authors had access to the study data and reviewed and approved the final manuscript.

Data collection

A study-specific Excel spreadsheet (Microsoft, Redmond, Wash, USA) was made to collect validated case data from each hospital. The survey items included the following patient characteristics: age at POEM, duration of symptoms, sex, body mass index, Eckardt score (ES), prior treatment for achalasia, HRM diagnosis, IRP, DCI, esophageal dilation, and type of achalasia. The POEM procedure information included esophageal and gastric myotomy length, myotomy direction (anterior, 9-3 o'clock; posterior, 3-9 o'clock), and adverse events. The outcomes of POEM were assessed at the 3-month follow-up and included the ES, HRM findings, RE, and symptomatic GERD. To prevent data omissions or entry errors and to reduce missing values, we used the multiple-choice rules in Excel to input categorical variables (eg, type of achalasia: straight, sigmoid, unknown) and free input for continuous variables. The sheet was filled using data retrieved from the electronic medical records and endoscopic records, which were then sent to the representative's facility. The representative evaluated omissions and errors in the input values for the data sent from each hospital. Data to be corrected were communicated by the site physician(s) of each hospital with detailed comments. Such communication was conducted more than 3 times per hospital through Excel sheets sent by email.

Variables

The ES was used to assess symptom severity.¹⁴ This was composed of the sum of the 3-point scores for dysphagia, regurgitation, chest pain, and weight loss. A higher score reflects more severe symptoms of achalasia (maximum of

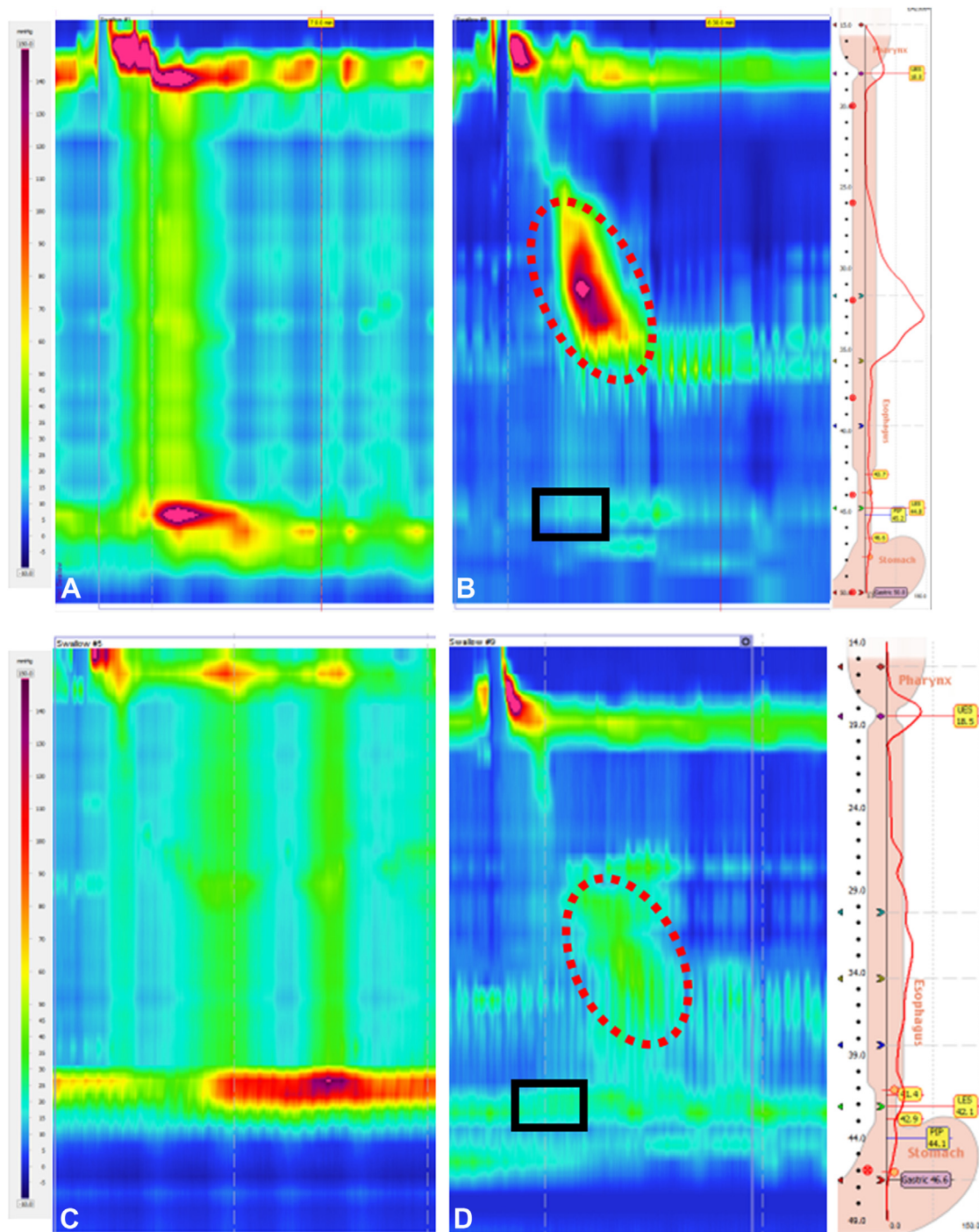


Figure 1. Cases of achalasia (**A**, **C**, and **E**) were treated with peroral endoscopic myotomy, and high-resolution manometry findings changed to normal (**B**), ineffective motility (**D**), and absent contractility (**F**). Integrated relaxation pressure (IRP) is shown as a *black solid-line square* and distal contractile integral as a *red dotted-line circle*. Residual high IRP values (34.0 mm Hg \geq 26; Starlet) are visible in **D**.

12), whereas a lower score indicates milder symptoms (minimum of 0). HRM diagnosis was based on the Chicago classification criteria v3.0.⁴ To assess deglutitive LES relaxation, IRP was measured and \geq 26 mm Hg on Starlet (Star-medical Ltd, Tokyo, Japan) was defined as a high IRP value, meaning incomplete LES relaxation.²¹ The IRP values were

the lowest 4-s cumulative pressure values that occurred during a 10-s post-deglutition time window in the electronically generated e-sleeve signal through the anatomic zone defining the esophagogastric junction (Fig. 1).⁴ The DCI, which is a parameter of contractile vigor in HRM, was calculated as the product of amplitude, duration, and

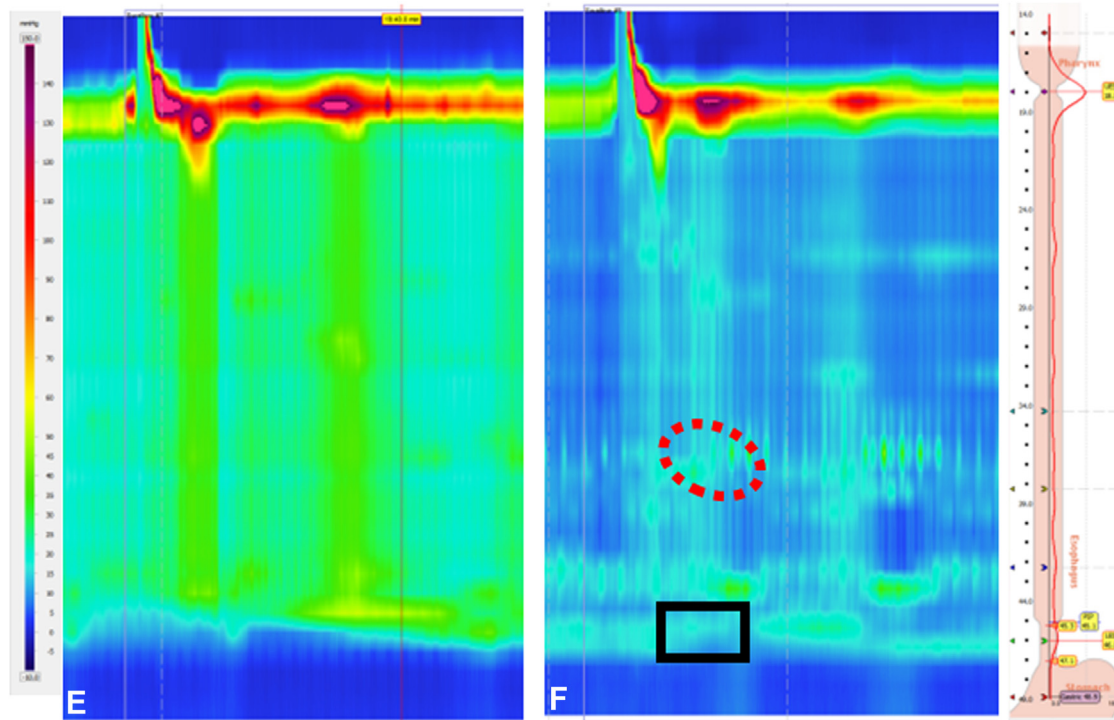


Figure 1. Continued.

span of distal esophageal contraction. IRP and DCI values between several HRM systems were converted to Starlet criteria using a previously reported formula.^{22,23} Starlet is the major HRM system in Japan²⁴ and was mostly used in this study. On the esophagogram, the type of achalasia was defined as straight or sigmoid. The degree of esophageal dilation was classified as grade I (<3.5 cm), grade II (3.5-6 cm), or grade III (>6 cm) according to the diameter of the esophageal lumen²⁵; grades II and III were defined as esophageal dilation.

Clinical success was defined as a postoperative ES of ≤ 3 in cases with a pre-POEM ES of ≥ 4 or a decreased ES in cases with a pre-POEM ES of < 4 , without reintervention.²⁶ RE was classified according to the Los Angeles 4-degree classification, from A to D.²⁷ Symptomatic GERD was defined as a GerdQ score of > 7 after POEM.²⁸

Analysis 1: Analysis of the predictive factors of high post-POEM IRP values

Among patients with EMDs registered, patients with achalasia who underwent HRM examination after POEM were enrolled in analysis 1. Residual high IRP values post-POEM were defined as those ≥ 26 mm Hg and low values as those < 26 mm Hg (on Starlet) based on the diagnostic criteria of impaired LES relaxation. Patient characteristics and POEM procedures were compared between the groups with high and low IRP values after POEM. Furthermore, multivariate analysis was conducted to identify predictive factors of IRP values that remained high after POEM.

Analysis 2: Analysis of the predictive factors of post-POEM peristalsis recovery

Among the patients in analysis 1, data on post-POEM DCI on HRM were collected in consecutive patients during 2020 (the last year of the study period) (analysis 2). To analyze post-POEM contraction, patients were categorized into 3 groups based on post-POEM DCI values and diagnostic criteria of hypomotility conditions (ie, ineffective esophageal motility [IEM] and absent contractility [AC])⁴: a normal DCI group with a DCI ≥ 1000 mm Hg/cm/s in $\geq 50\%$ swallows, an IEM group with a DCI < 1000 in $\geq 50\%$ swallows, and an AC group with a DCI < 500 in all swallows on Starlet. In this study, post-POEM DCI values were used to define these 3 groups because patterns such as contraction or peristalsis are difficult to visualize clearly after POEM. Three types of comparisons were made (normal vs IEM, normal vs AC, and IEM vs AC) for patient characteristics and POEMs. Furthermore, recovery of esophageal peristalsis after POEM was defined as normal or IEM findings (DCI ≥ 500 mm Hg/cm/s, at least 1 swallow) on HRM, and predictive factors were investigated by multivariate analysis.

Analysis 3: Association between post-POEM IRP and DCI values and outcomes of POEM

To analyze the associations between post-POEM IRP and DCI values and treatment efficacy, RE, and symptomatic post-POEM GERD, we compared the outcomes of POEM, using the ES, clinical success, RE, and symptomatic GERD after POEM, with post-POEM IRP and DCI values.

Statistical analysis

All data are expressed as medians (interquartile ranges) or numbers of patients and percentages. The Mann-Whitney U test was used to analyze continuous values, whereas the Pearson χ^2 test was used to analyze categorical data. For comparing 3 groups, a multiple-comparison test using the Tukey-Kramer method was also performed. In univariate and multivariate analyses, continuous values (age at POEM, duration of symptoms, body mass index, ES, pre-POEM IRP, pre-POEM DCI, and length of esophageal and gastric myotomy) were treated as categorical, according to common cutoff points or median approximation, to facilitate interpretation. Univariate and multivariate analyses were used to ascertain the factors associated with residual high IRP values and recovery of esophageal peristalsis after POEM, and odds ratios (ORs) and 95% confidence intervals (CIs) were computed. Statistical significance was set at $P < .05$. All statistical analyses were performed using JMP Pro 15.1.0 (SAS Institute, Cary, NC, USA).

RESULTS

A total of 3583 patients with EMDs were registered in 13 hospitals. Among them, 2171 patients with achalasia accomplished HRM examination at a median of 69 days (interquartile range, 63-90) after POEM and were enrolled in analysis 1. DCI after POEM was analyzed in 618 patients with achalasia who were enrolled in analysis 2 (Table 1, Supplementary Fig. 1, available online at www.giejournal.org).

Predictive factors of residual high post-POEM IRP values

In analysis 1, of 2171 patients with reviewable IRPs after POEM, 151 patients (7.0%) had high post-POEM IRP values (≥ 26 mm Hg; Starlet HRM). Compared with 2020 patients with low post-POEM IRP values, patients with high post-POEM IRP values had higher pre-POEM IRPs (37.5 vs 27.5 mm Hg), higher pre-POEM DCIs (397.9 vs 178.1 mm Hg/cm/s), and a higher proportion of type II and III achalasia (58.2 vs 46.0%). Regarding POEM procedures, esophageal myotomy length showed a statistical difference between the groups, although the median values were the same at 9.0 cm (Table 2).

The predictive factors of residual high post-POEM IRP values are shown in Table 3. In univariate analysis, a pre-POEM IRP of ≥ 26 mm Hg (OR, 3.08; 95% CI, 2.05-4.62) was statistically significant. Subsequent multivariate analysis showed that pre-POEM IRPs of ≥ 26 mm Hg (OR, 24.3; 95% CI, 3.06-193.0) and gastric myotomy length of > 2 cm (OR, .22; 95% CI, .05-.99) were positive and negative predictive factors for residual high post-POEM IRP, respectively.

Predictive factors of post-POEM peristalsis recovery

In 618 patients with reviewable DCIs after POEM, 26 (4.2%), 95 (15.3%), and 497 (80.4%) patients were classified into the normal DCI, IEM, and AC groups, respectively (Table 4). Among patient demographics, statistical significance was not observed between the 3 groups. Diagnosis on HRM and morphology on esophagography revealed more differences in the characteristics of the 3 groups. Types II and III achalasia were found in 26 patients (100%) in the normal group, 56 (59.0%) with IEM, and 189 (38.1%) with AC; a consistent statistical difference was observed between the groups. Pre-POEM IRP was lower in the AC group (27.3 mm Hg), whereas pre-POEM DCI was higher in the normal DCI group (3514.1 mm Hg/cm/s), and a consistent significant difference was observed between the groups. Esophageal dilation was significantly increased from normal to IEM and AC in 2 (7.7%), 47 (49.4%), and 330 (66.4%) patients, respectively. In contrast, among POEM procedures, gastric myotomy length was significantly different between the normal and AC groups, although the median value was almost equal.

Predictive factors of post-POEM peristalsis recovery are shown in Table 5. In univariate analysis, age ≥ 65 years (OR, 1.53; 95% CI, 1.02-2.31), prior treatment (OR, .57; 95% CI, .33-.99), an IRP of ≥ 26 mm Hg (OR, 4.64; 95% CI, 2.68-8.03), and a DCI of ≥ 500 mm Hg/cm/s (OR, 5.07; 95% CI, 3.14-8.17) were associated with peristalsis recovery. In multivariate analysis, an IRP of ≥ 26 mm Hg (OR, 2.65; 95% CI, 1.39-5.07) and a DCI of ≥ 500 mm Hg/cm/s (OR, 2.98; 95% CI, 1.70-5.20) were predictive factors for peristalsis recovery, whereas esophageal dilation (OR, .42; 95% CI, .24-.71) predicted no recovery of peristalsis.

Impact of post-POEM IRP values and peristalsis recovery for treatment outcomes

The association between post-POEM IRP values, peristalsis recovery, and treatment outcomes is shown in Table 6. Statistical significance was not observed for persistent symptoms and clinical success between the groups with high and low IRP values. Interestingly, RE and symptomatic GERD were not associated with low IRP values. Furthermore, recovery of peristalsis was not associated with clinical success, RE, or symptomatic GERD. Notably, the presence of persistent chest pain was more apparent in patients with AC than in those with peristalsis recovery (18.9% vs 9.9%, $P = .022$).

DISCUSSION

In this large-scale, multicenter study, residual high IRP values and peristalsis recovery were observed in 7.0% and 19.6% of patients after POEM, respectively. High pre-POEM IRP values and POEM procedures such as gastric myotomy of ≤ 2 cm were predictive of residual

TABLE 1. Study dataset of patient characteristics and POEM procedures

	Patients with confirmed IRP after POEM (n = 2171)	Patients with confirmed DCI after POEM (n = 618)
Patient characteristics		
Age, y	49.0 (37.0-64.0)	55.0 (42.0-68.8)
Duration of symptoms, y	4.7 (2.0-10.6)	4.0 (1.1-10.4)
Sex, male	1056 (48.6)	309 (50.0)
Body mass index, kg/m ²	20.8 (18.7-23.3)	21.0 (18.8-23.6)
Eckardt score	6.0 (4.0-7.0)	6.0 (4.0-7.0)
Prior treatment		
Pneumatic dilation	405 (18.7)	115 (18.6)
Heller myotomy	65 (3.0)	16 (2.6)
POEM	5 (.2)	3 (.5)
Other*	2 (.1)	0 (.0)
Diagnosis		
Type I	1074 (49.5)	296 (47.9)
Type II	819 (37.7)	222 (35.9)
Type III	128 (5.9)	49 (7.9)
Achalasia on esophagography	150 (6.9)	50 (8.1)
IRP, mm Hg	28.0 (19.1-39.0)	29.1 (19.9-40.7)
DCI, mm Hg/cm/s	179.1 (27.3-882.5)	179.7 (27.3-882.5)
Esophageal dilation	1313 (60.4)	379 (61.3)
Sigmoid type	455 (21.0)	180 (29.1)
POEM procedures		
Esophageal myotomy, cm	9.0 (7.0-12.0)	9.0 (6.0-11.0)
Gastric myotomy, cm	3.0 (2.0-3.0)	2.0 (2.0-3.0)
Direction, posterior	1777 (81.9)	549 (88.8)
Adverse events	135 (6.2)	37 (6.0)

Values are median (interquartile range) or n (%). Missing values in the analysis are as follows: Eckardt score, 38; IRP, 150; DCI, 1642; esophageal myotomy, gastric myotomy, and direction, 4.

POEM, Peroral endoscopic myotomy; IRP, integrated relaxation pressure; DCI, distal contractile integral.

*Other treatments included botulinum toxin injection and undetailed surgery.

high post-POEM IRP values. Peristalsis recovery was negatively associated with esophageal dilation but positively associated with high pre-POEM IRP and DCI values. Importantly, low post-POEM IRP values did not increase the prevalence of RE and symptomatic GERD, and residual post-POEM IRP values also maintained clinical success.

In our study, residual high IRP values after POEM were less frequent than those found in a previous report that showed IRP normalization in 80% of patients after POEM and laparoscopic Heller myotomy.²⁹ Other reports did not mention the frequency of high IRP values but rather only documented median or mean IRP values.^{6,7,30-32} In contrast, peristaltic recovery rates were previously reported as 25.0% to 60.9%,^{8,11,12} which were higher compared with our results. The lower frequency of high IRP values and peristalsis recovery in our study possibly means that the expert doctors at the study's high-volume centers achieved better results with myotomy than those in previous studies; indeed, clin-

ical failure was only observed in 6.6% of patients. In this study, peristalsis recovery was classified as normal and IEM based on the post-POEM DCI values, and the proportion of normal classification (4.2%) was lower than that of the previous report.¹² This could be attributed to the higher prevalence of type I achalasia in our study, with an absent ganglion.^{33,34}

A pre-POEM IRP of ≥ 26 mm Hg was predictive of a residual high post-POEM IRP value, indicating that the presence and severity of impaired LES before POEM was associated with residual high IRP values after POEM. Myotomy was conducted longitudinally; therefore, the circumferential pressure without myotomy remained,²⁴ differentiating POEM from circumferential PD. Furthermore, extended gastric myotomy may cause a reduction in IRP values, matching previous findings of laparoscopic Heller myotomy.³⁵ Further, we identified predictive factors of peristalsis recovery after POEM, where previous efforts with a small sample size failed.¹² Because

TABLE 2. Patient characteristics and POEM procedures in patients with high and low IRPs after POEM (n = 2171)

	Overall	Low post-POEM IRP (n = 2020)	High post-POEM IRP (n = 151)	P value
Patient characteristics				
Age, y	49.0 (37.0-64.0)	50.0 (37.0-65.0)	48.0 (37.0-62.5)	.704
Duration of symptoms, y	4.7 (2.0-10.6)	4.7 (2.0-10.7)	4.0 (1.8-9.8)	.142
Sex, male	1056 (48.6)	979 (48.5)	77 (51.0)	.606
Body mass index, kg/m ²	20.8 (18.7-23.3)	20.8 (18.7-23.3)	20.8 (18.8-23.6)	.822
Eckardt score	6.0 (4.0-7.0)	6.0 (4.0-7.0)	6.0 (4.0-8.0)	.750
Prior treatment	477 (22.0)	450 (22.3)	27 (17.9)	.247
Types II and III achalasia	947 (43.6)	862 (46.0)	85 (58.2)	.004
IRP, mm Hg	28.0 (19.1-39.0)	27.5 (18.8-37.9)	37.5 (25.8-54.2)	<.001
Distal contractile integral, mm Hg/cm/s	179.1 (27.3-882.5)	178.1 (26.1-860.9)	397.9 (92.9-1077.8)	.183
Esophageal dilation	1313 (60.4)	1230 (60.9)	83 (55.0)	.177
Sigmoid type	455 (21.0)	429 (21.2)	26 (17.2)	.286
POEM procedures				
Esophageal myotomy, cm	9.0 (7.0-12.0)	9.0 (6.0-11.3)	9.0 (7.0-13.0)	.021
Gastric myotomy, cm	3.0 (2.0-3.0)	3.0 (2.0-3.0)	3.0 (2.0-3.0)	.204
Direction, posterior	1777 (81.9)	1662 (82.4)	115 (76.2)	.068
Adverse events	135 (6.2)	125 (6.2)	10 (6.6)	.969

Values are median (interquartile range) or n (%). Bold P values denote statistical significance. The prevalence of types II and III achalasia is analyzed among types I, II, and III achalasia. Missing values in the analysis are as follows: duration of symptoms, 43; Eckardt score, 44; previous treatment, 281; IRP, 152; distal contractile integral, 1776; sigmoid type, 4; esophageal myotomy, gastric myotomy, and direction, 10.

POEM, Peroral endoscopic myotomy; IRP, integrated relaxation pressure.

TABLE 3. Predictive factors for residual impaired lower esophageal sphincter relaxation after peroral endoscopic myotomy (n = 2171)

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% confidence interval)	P value	Odds ratio (95% confidence interval)	P value
Age ≥ 65 y	.87 (.59-1.29)	.488	.99 (.39-2.54)	.984
Duration of symptoms ≥ 5 y	.92 (.66-1.28)	.609	1.63 (.69-3.86)	.264
Sex, male	1.11 (.80-1.54)	.549	1.06 (.45-2.48)	.893
Body mass index ≥ 25 kg/m ²	1.00 (.63-1.60)	.996	.71 (.20-2.57)	.599
Eckardt score ≥ 6	.81 (.58-1.13)	.213	.82 (.34-1.98)	.658
Prior treatment	.76 (.50-1.17)	.209	.88 (.26-3.00)	.836
Integrated relaxation pressure ≥ 26 mm Hg	3.08 (2.05-4.62)	<.001	24.3 (3.06-193.0)	.003
Distal contractile integral ≥ 500 mm Hg/cm/s	1.71 (.77-3.78)	.185	.86 (.34-2.17)	.751
Esophageal dilation	.78 (.56-1.09)	.152	.74 (.30-1.85)	.525
Sigmoid type	.77 (.50-1.19)	.243	1.29 (.44-3.79)	.647
Esophageal myotomy > 10 cm	1.19 (.84-1.68)	.337	2.01 (.86-4.70)	.108
Gastric myotomy > 2 cm	1.01 (.72-1.42)	.940	.22 (.05-.99)	.049
Direction, posterior	.68 (.46-1.01)	.054	.60 (.16-2.31)	.458
Adverse events	1.08 (.55-2.09)	.831	.61 (.07-4.97)	.641

Bold P values denote statistical significance. Residual impaired lower esophageal sphincter relaxation was defined as an integrated relaxation pressure of ≥ 26 on Starlet high-resolution manometry after peroral endoscopic myotomy.

the absence of normal peristalsis is a typical pathology of classic achalasia,³⁶ its recovery is difficult with type I achalasia and occurs more often in cases with types II and III achalasia.

High DCI values before POEM do not completely decline after POEM, similar to the results with post-POEM IRP values. Low IRP values and severe esophageal dilation have been

TABLE 4. Patient characteristics and POEM procedures in patients with and without recovery of esophageal peristalsis after POEM (n = 618)

	Overall	Normal (n = 26, 4.2%)	IEM (n = 95, 15.3%)	Absent contractility (n = 497, 80.4%)	P value*	P value†	P value‡
Patient characteristics							
Age, y	55.0 (42.0-68.8)	62.0 (48.8-74.8)	61.0 (44.0-71.0)	53.0 (41.0-68.0)	.731	.186	.305
Duration of symptoms, y	4.0 (1.1-10.4)	2.4 (.6-6.1)	4.1 (1.7-10.3)	4.4 (1.3-10.7)	.105	.070	.997
Sex, male	309 (50.0)	14 (53.9)	49 (51.6)	246 (49.5)	1.000	.817	.795
Body mass index, kg/m ²	21.0 (18.8-23.6)	20.2 (17.5-23.7)	21.2 (19.0-23.6)	20.9 (18.8-23.6)	.300	.441	.672
Eckardt score	6.0 (4.0-7.0)	6.0 (4.0-8.3)	6.0 (5.0-8.0)	6.0 (4.0-7.0)	.888	.748	.889
Prior treatment	134 (21.7)	2 (7.7)	16 (16.8)	116 (23.3)	.395	.063	.208
Types II and III achalasia	271 (43.8)	26 (100)	56 (59.0)	189 (38.1)	<.001	<.001	<.001
Integrated relaxation pressure, mm Hg	29.1 (19.9-40.7)	43.5 (30.0-72.9)	36.7 (27.2-48.6)	27.3 (18.2-37.8)	.127	<.001	<.001
Distal contractile integral, mm Hg/cm/s	179.7 (27.3-882.5)	3514.1 (1649.4-4688.5)	667.0 (204.1-1934.0)	120.4 (18.5-576.0)	<.001	<.001	<.001
Esophageal dilation	379 (61.3)	2 (7.7)	47 (49.4)	330 (66.4)	<.001	<.001	.003
Sigmoid type	180 (29.1)	6 (23.1)	23 (24.2)	151 (30.4)	.905	.567	.277
POEM procedures							
Esophageal myotomy, cm	9.0 (6.0-11.0)	9.0 (7.0-10.5)	9.0 (7.0-11.0)	8.0 (6.0-11.0)	.992	.922	.714
Gastric myotomy, cm	2.0 (2.0-3.0)	2.0 (2.0-3.0)	2.0 (2.0-3.0)	2.0 (2.0-2.0)	.163	.037	.841
Direction, anterior	549 (88.8)	5 (19.2)	6 (6.3)	57 (11.5)	.104	.378	.200
Adverse events	37 (6.0)	2 (7.7)	6 (6.3)	29 (5.8)	.802	.696	.856

Values are median (interquartile range) or n (%). Bold P values denote statistical significance. The prevalence of type III achalasia was analyzed among types I, II, and III achalasia. Missing values in the analysis are as follows: integrated relaxation pressure, 51; distal contractile integral, 97.

POEM, Peroral endoscopic myotomy; IEM, ineffective esophageal motility.

*Statistical analyses were performed between patients with normal and IEM.

†Statistical analyses were performed between patients with normal and absent contractility.

‡Statistical analyses were performed between patients with IEM and absent contractility.

TABLE 5. Predictive factors of recovery of esophageal peristalsis after peroral endoscopic myotomy (n = 618)

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% confidence interval)	P value	Odds ratio (95% confidence interval)	P value
Age ≥65 y	1.53 (1.02-2.31)	.039	1.67 (.99-2.83)	.055
Duration of symptoms ≥5 y	.91 (.61-1.36)	.645	1.55 (.91-2.64)	.105
Sex, male	1.11 (.75-1.65)	.612	1.45 (.88-2.40)	.145
Body mass index ≥25 kg/m ²	.78 (.45-1.37)	.390	.68 (.33-1.41)	.298
Eckardt score ≥6	1.01 (.68-1.50)	.972	.71 (.42-1.19)	.192
Prior treatment	.57 (.33-.99)	.047	.73 (.36-1.51)	.402
Integrated relaxation pressure ≥26 mm Hg	4.64 (2.68-8.03)	<.001	2.65 (1.39-5.07)	.003
Distal contractile integral ≥500, mm Hg/cm/s	5.07 (3.14-8.17)	<.001	2.98 (1.70-5.20)	<.001
Esophageal dilation	.34 (.23-.52)	<.001	.42 (.24-.71)	.001
Sigmoid type	.72 (.46-1.14)	.165	.84 (.44-1.60)	.587
Esophageal myotomy >10 cm	.84 (.53-1.31)	.438	.74 (.42-1.29)	.289
Gastric myotomy >2 cm	1.43 (.93-2.18)	.101	1.00 (.56-1.80)	1.000
Direction, posterior	1.18 (.61-2.27)	.627	1.00 (.45-2.23)	.997
Adverse events	1.14 (.51-2.57)	.747	.99 (.34-2.84)	.977

Bold P values denote statistical significance. Recovery of esophageal peristalsis was defined as normal or ineffective esophageal motility on high-resolution manometry after peroral endoscopic myotomy.

TABLE 6. Post-POEM high-resolution manometry findings and clinical course

	Low post-POEM IRP (n = 2020)	High post-POEM IRP (n = 151)	P value
Eckardt score	1.0 (.0-1.0)	1.0 (.0-1.0)	.688
Dysphagia	805 (39.9)	62 (41.3)	.730
Chest pain	489 (24.2)	41 (27.3)	.377
Regurgitation	235 (11.6)	18 (12.0)	.895
Clinical success	1888 (93.5)	139 (92.7)	.834
Reflux esophagitis			
Grades A-D	1326 (66.3)	101 (74.3)	.060
Grades C-D	143 (7.1)	12 (8.8)	.492
Symptomatic GERD	297 (14.9)	23 (16.8)	.538
	Recovery of peristalsis (n = 121)	Absent contractility (n = 497)	P value
Eckardt score	.0 (.0-1.0)	.0 (.0-1.0)	.100
Dysphagia	32 (26.4)	172 (34.6)	.106
Chest pain	12 (9.9)	94 (18.9)	.022
Regurgitation	12 (9.9)	46 (9.3)	.862
Clinical success	119 (98.3)	487 (98.0)	1.000
Reflux esophagitis			
Grades A-D	71 (62.3)	278 (58.0)	.459
Grades C-D	7 (6.1)	31 (6.5)	1.000
Symptomatic GERD	13 (11.7)	58 (12.4)	1.000

Values are median (interquartile range) or n (%). Bold P values denote statistical significance. Recovery of esophageal peristalsis was defined as normal or ineffective esophageal motility findings on high-resolution manometry. Missing values in the analysis are as follows: Eckardt score and clinical success, 1; reflux esophagitis, 35; symptomatic GERD 44. POEM, Peroral endoscopic myotomy; IRP, integrated relaxation pressure.

observed, particularly in advanced achalasia,³⁷ considered to be a type with reduced or absent ganglion cells,³⁸ and peristalsis is considered difficult to restore. It has been reported that myotomy of the lower esophagus was less likely to produce contractile pressure^{8,39}; however, extended myotomy length to the oral side, beyond 10 cm, may not be relevant to peristalsis recovery.

Residual high post-POEM IRP values did not impair clinical success, meaning that the reduction of IRP levels to the normal range is not the goal of POEM. Reduced IRP values ultimately indicate the accomplishment of the 1-direction myotomy procedure, providing improved flow of fluids and solids after POEM. Thus, IRP value reduction is of greater importance than post-POEM IRP value alone. HRM has circumferential pressure sensors that detect high pressure from the nonmyotomy line.²⁴ PD expands the esophagus circumferentially, meaning that IRP levels within the normal range should be the goal. The significance of residual high IRP values after POEM is different from that of PD; therefore, in cases of post-POEM clinical failure, indication of retreatment should be carefully considered after comprehensive assessment by HRM, gastroscopy, and esophagography because residual high IRP value does not always mean bad flow. Moreover, low IRP values after POEM were not associated with the prevalence of RE and symptomatic GERD. Post-POEM RE and symptomatic GERD are also difficult to predict based on patient characteristics and

POEM procedures,⁴⁰ because the mechanisms may include esophageal hypersensitivity. In our study, we found more chest pain in patients with post-POEM AC, which was not related to residual esophageal contractions; patient characteristics or POEM procedures are possibly associated with chest pain.⁴¹ Therefore, a second myotomy for persistent symptoms, including chest pain, targeting the residual contractions may not be necessary. Weak correlations between severity of hypomotility and symptoms have been reported, and the same is possibly true in post-POEM conditions.^{42,43} In summary, after POEM, follow-up using medical interviews and endoscopy is suggested instead of HRM.

This study had several limitations. First, this multicenter study aimed to analyze a large number of patients with achalasia using a retrospective design over 10 years; hence, dropout cases and missing values were observed, although the large-scale data may compensate for this. Because each institution's database did not include post-POEM DCI values before this study, these were collected from consecutive patients during the latest period to prevent selection bias and to avoid physicians' time demand, although the number was more limited than that for IRP analysis. Second, this study was conducted at high-volume centers with expert site practitioners; generalizability to other settings should be done carefully. Third, although clinical failure and GERD were evaluated using the ES and GerdQ score, respectively, the retrospective design may not completely differentiate

GERD-borne pseudo-clinical failure. Finally, post-POEM HRM findings and POEM outcomes were evaluated at the short-term follow-up. Future research should focus on distinguishing remaining abnormal contraction objectively to clarify the association between achalasia type and remaining motility. A functional luminal imaging probe has often been used to evaluate esophageal distensibility,⁴⁴ and the efficacy of a functional luminal imaging probe should be investigated before standardizing the procedure in this setting.

In conclusion, extended gastric myotomy decreased LES pressure, although peristalsis recovery depended on the phenotype of achalasia. The association between post-POEM HRM findings and POEM outcomes is limited; therefore, routine HRM follow-up is not necessary after POEM.

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Abbreviations: AC, absent contractility; CI, confidence interval; DCI, distal contractile integral; EMD, esophageal motility disorder; ES, Eckardt score; HRM, high-resolution manometry; IEM, ineffective esophageal motility; IRP, integrated relaxation pressure; LES, lower esophageal sphincter; OR, odds ratio; PD, pneumatic dilation; POEM, peroral endoscopic myotomy; RE, reflux esophagitis.

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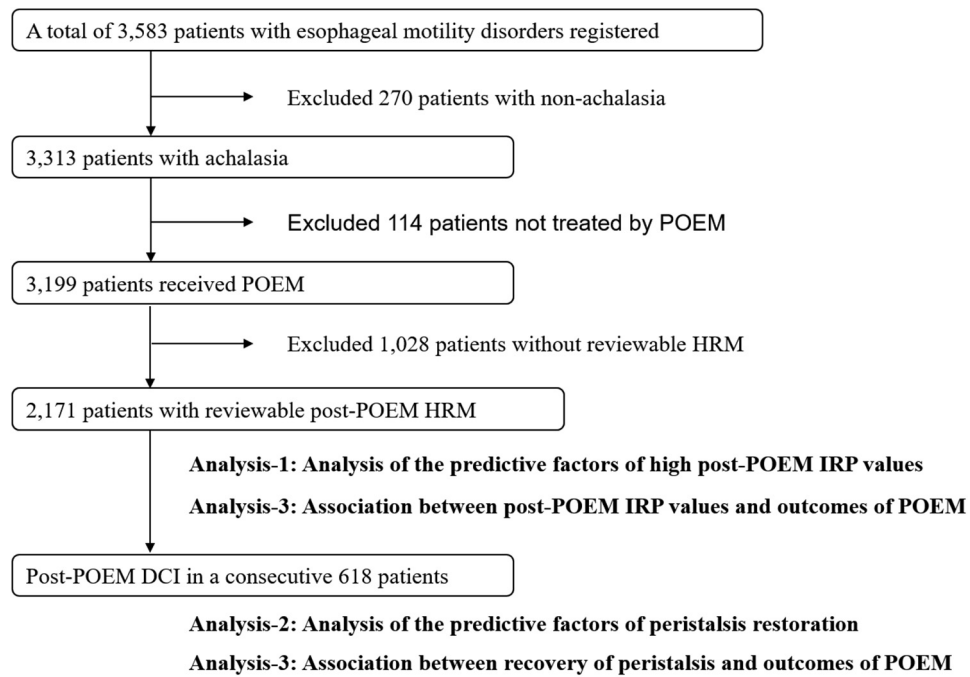
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Supplementary Figure 1. Study flowchart of 3583 patients with esophageal motility disorders registered at 13 hospitals in Japan. Among 3313 patients with achalasia, 3199 patients received peroral endoscopic myotomy (POEM). Follow-up HRM was conducted in 2171 patients, and integrated pressure (IRP) was measured. Distal contractile integral (DCI) was calculated in 618 patients. Analyses 1 and 2 were performed to analyze the associations between patient characteristics and POEM procedures and between IRP and DCI values. Analysis 3 was conducted to assess the associations between clinical outcomes and IRP and DCI values. *HRM*, High-resolution manometry.

SUPPLEMENTARY TABLE 1. Affiliations and ethics committee approval numbers for the participating facilities

	Prefecture	Institution	Department	Approval no. of ethics committee
1	Fukuoka	Graduate School of Medical Sciences, Kyushu University	Department of Medicine and Bioregulatory Science	2020-657
2	Niigata	Graduate School of Medical and Dental Sciences, Niigata University	Department of Gastroenterology	2020-0308
3	Tokyo	Showa University Koto-Toyosu Hospital	Digestive Diseases Center	20T7052
4	Hyogo	Kobe University Hospital	Department of Gastroenterology	B200195
5	Fukuoka	Fukuoka University Faculty of Medicine	Department of Gastroenterological Surgery	U21-03-002
6	Nagasaki	Nagasaki University Hospital	Department of Gastroenterology & Hepatology	21021504
7	Miyagi	Tohoku University School of Medicine	Division of Advanced Surgical Science and Technology	2020-1-1030
8	Osaka	Osaka Metropolitan University Graduate School of Medicine	Department of Gastroenterology	2020-282
9	Tochigi	Jichi Medical University	Division of Gastroenterology, Department of Medicine	20-126
10	Oita	Oita University	Department of Gastroenterology, Faculty of Medicine	2092
11	Fukushima	Fukushima Medical University Hospital	Department of Endoscopy	2020-256
12	Aomori	Hirosaki University Graduate School of Medicine	Department of Gastroenterology and Hematology	2020-216
13	Tottori	Tottori University Faculty of Medicine	Division of Gastroenterology and Nephrology	20A177