

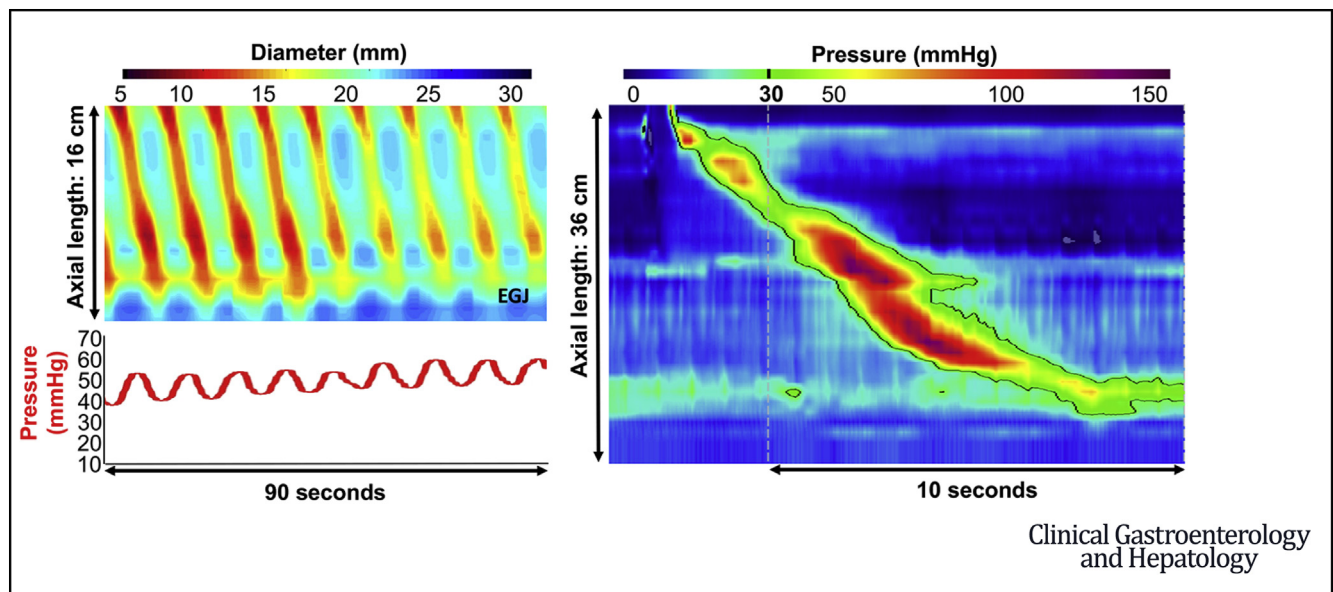
ALIMENTARY TRACT

Normal Functional Luminal Imaging Probe Panometry Findings Associate With Lack of Major Esophageal Motility Disorder on High-Resolution Manometry



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BACKGROUND & AIMS:

A normal esophageal response to distension on functional luminal imaging probe (FLIP) panometry during endoscopy might indicate normal esophageal motor function. We aimed to investigate the correlation of normal FLIP panometry findings with esophageal high-resolution manometry (HRM) and outcomes of discrepant patients.

METHODS:

We performed a retrospective study using data from a registry of patients who completed FLIP during sedated endoscopy. We identified 111 patients with normal FLIP panometry findings (mean age, 42 y; 69% female) and corresponding HRM data. A normal FLIP panometry was defined as an esophagogastric junction (EGJ) distensibility index greater than 3.0 mm²/mm Hg, an absence of repetitive retrograde contractions, and a repetitive antegrade contraction pattern that met the Rule-of-6s: ≥ 6 consecutive antegrade contractions of ≥ 6 -cm in length, at a rate of 6 ± 3 contractions per minute. HRM findings were classified by the Chicago classification system version 3.0.

RESULTS:

HRM results were classified as normal motility in 78 patients (70%), ineffective esophageal motility in 10 patients (9%), EGJ outflow obstruction in 20 patients (18%), and 3 patients (3%) as other. In patients with EGJ outflow obstruction based on HRM, the integrated relaxation pressure normalized

Abbreviations used in this paper: DCI, distal contractile integral; DES, distal esophageal spasm; EGJ, esophagogastric junction; EGJ-DI, esophagogastric junction distensibility index; EGJOO, esophagogastric junction outlet obstruction; FLIP, functional luminal imaging probe; GERD, gastroesophageal reflux disease; HRM, high-resolution manometry; IEM, ineffective esophageal motility; IRP, integrated relaxation pressure; MRS, multiple rapid swallow; PPI, proton pump inhibitor; RAC, repetitive antegrade contraction; RDC, rapid drink challenge; RRC, repetitive retrograde

contraction; Rule-of-6s, duration of at least 6 consecutive antegrade contractions that spanned at least 6 cm in axial length occurring with a rate of 6 ± 3 contractions per minute; TBE, timed barium esophagram.



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on adjunctive swallows in 16 of 20 patients (80%), and in 8 of 9 patients (88%) who completed a barium esophagram and had normal barium clearance. Thus, although 23 of 111 patients (21%) with normal FLIP panometry had abnormal HRM findings, these HRMs often were considered to be false-positive or equivocal results. All patients with an abnormal result from HRM were treated conservatively.

CONCLUSIONS:

In a retrospective cohort study, we found that patients with normal FLIP panometry results did not have a clinical impression of a major esophageal motor disorder. Normal FLIP panometry results can exclude esophageal motility disorders at the time of endoscopy, possibly negating the need for HRM in select patients.

Keywords: EGJOO; Dysphagia; Peristalsis; Impedance; Spasm.

The functional luminal imaging probe (FLIP) uses high-resolution impedance panometry to measure esophageal luminal parameters and their relationship to distension pressure (distensibility) during sustained volumetric distension. In addition to evaluating esophagogastric junction (EGJ) opening and distensibility, esophageal contractility in response to distension can be observed via the comprehensive esophageal functional evaluation provided with FLIP panometry. Thus, FLIP panometry carries the potential to evaluate esophageal motility at the time of sedated endoscopy.^{1,2}

Although esophageal high-resolution manometry (HRM) is thought to be a gold standard for defining esophageal motility, HRM carries several notable limitations. HRM and its clinical classification scheme are susceptible to both false-positive and false-negative clinical classifications, making it an imperfect gold standard. The EGJ outflow obstruction (EGJOO) classification within the Chicago Classification version 3.0 in particular is problematic because the integrated relaxation pressure (IRP) is susceptible to pressure artifacts, often leading to a falsely positive diagnosis of a major esophageal motility disorder.^{3–5} In addition, even patients with clinical achalasia may have normal lower-esophageal sphincter relaxation pressure on HRM.⁶ Last, because HRM is placed transnasally and performed while the patient is awake over an extended time period, it often is tolerated poorly and generally disliked by patients.

FLIP panometry, on the other hand, can evaluate esophageal motility during sedated endoscopy. FLIP panometry has shown promise in identifying major esophageal motility disorders, achalasia in particular.¹ Thus, we hypothesized that a normal FLIP panometry would be associated with a normal esophageal motility evaluation and predictive of a favorable clinical course with conservative management. In this study, we aimed to investigate the correlation of normal FLIP panometry with HRM in patients undergoing an esophageal motility evaluation and the resulting clinical course for any patients with discrepant FLIP panometry and HRM.

Methods

Subjects

Adult patients presenting to the Esophageal Center of Northwestern University for evaluation of esophageal symptoms between November 2012 and September 2019 who completed HRM and FLIP during upper endoscopy were evaluated prospectively and data were maintained in an esophageal motility registry. Additional clinical evaluation (ie, barium esophagram) was obtained and management decisions were made at the discretion of the primary treating gastroenterologist. This prospective database was reviewed retrospectively to identify patients with a normal FLIP panometry study (defined later) that also had a corresponding HRM study. Patients with previous upper gastrointestinal surgery, previous pneumatic dilation, previous botulinum toxin injection, eosinophilic esophagitis, severe reflux esophagitis (LA classification C or D), hiatal hernia larger than 3 cm, or evidence of mechanical obstruction on endoscopy (ie, esophageal stricture) were excluded. There is overlap in this study cohort with previous reports.¹

Clinical data, including demographics, patient symptoms,^{7,8} prescribed treatments, timed barium esophagram (TBE), and endoscopy results were attained from patient electronic medical records. The study protocol was approved by the Northwestern University Institutional Review Board.

Functional Luminal Imaging Probe Study Protocol and Analysis

Evaluation was completed after a minimum 6-hour fast. Subjects underwent upper endoscopy in the left lateral decubitus position. Conscious sedation with 3 to 14 mg midazolam and 50 to 300 mcg fentanyl was administered during the procedure. Other sedative medications, for example, propofol (in addition to midazolam and fentanyl), were used with anesthesiologist assistance at the discretion of the performing endoscopist in some cases.

The 16-cm FLIP (EndoFLIP EF-322N; Medtronic, Inc, Shoreview, MN) was calibrated to atmospheric pressure before transoral probe placement. With the endoscope withdrawn, the FLIP was positioned within the esophagus such that 1 to 3 impedance sensors were observed beyond the EGJ, with this positioning maintained throughout the FLIP study. Stepwise 5-mL or 10-mL balloon distensions beginning with 20 mL and increasing to a target volume of 60 or 70 mL then were performed; each stepwise distension volume was maintained for 30 to 60 seconds (variations in FLIP study protocol evolved during the study period).

FLIP data were exported and analyzed as previously described using a customized program developed at Northwestern, which is available for download at <http://www.wklytics.com/nmgi>.^{1,9-11} Analysis of a single FLIP study using the program takes approximately 5 minutes. The EGJ-distensibility index (DI) was calculated by dividing the median EGJ-midline cross-sectional area by the median intraballoon pressure over the duration of the 60-mL distension volume: median cross-sectional area/median pressure = EGJ-DI in mm²/mm Hg. Esophageal body contractions were identified by a transient decrease of 5 mm or greater in the luminal diameter in 3 or more adjacent impedance planimetry channels. The axial length of contractions was determined by the number of consecutive impedance planimetry channels (1-cm spacing), with a decrease in luminal diameter. The direction of contractions (antegrade or retrograde) was categorized based on a tangent line placed at the onset of contraction. Specific patterns of the contractile response to distension were categorized further as repetitive if contractions of similar directionality occurred consecutively at a consistent time interval and then by contraction direction: repetitive antegrade contractions (RACs) or repetitive retrograde contractions (RRCs). The rate of repetitive contractions was derived by dividing the number of repetitive contractions by duration (time) of repetitive contraction pattern and then normalized to reflect the rate of contractions as the number of contractions per minute.

A normal FLIP panometry was defined as follows: (1) EGJ-DI greater than 3.0 mm²/mm Hg,¹² (2) absence of RRCs, and (3) presence of a RAC pattern that met the following criteria: duration of at least 6 consecutive antegrade contractions that spanned at least 6 cm in axial length occurring with a rate of 6 ± 3 contractions per minute (Rule-of-6s).¹³ FLIP panometry studies were reviewed by 3 physicians (A.J.B., J.E.P., and D.A.C.), with consensus achieved for all included studies.

High-Resolution Manometry Protocol and Analysis

After a minimum 6-hour fast, HRM studies were completed using a 4.2-mm outer diameter, solid-state assembly with 36 circumferential pressure sensors at

What You Need to Know

Background

A normal esophageal response to distension on functional luminal imaging probe (FLIP) panometry during endoscopy might indicate normal esophageal motor function.

Findings

In a retrospective cohort study, we found that patients with normal FLIP panometry results did not have a clinical impression of a major esophageal motor disorder.

Implications for patient care

Normal findings from FLIP panometry can be used to exclude esophageal motility disorders at the time of endoscopy, possibly reducing the need for high-resolution manometry evaluation of some patients.

1-cm intervals (Medtronic, Inc). The HRM assembly was placed transnasally and positioned to record from the hypopharynx to the stomach with approximately 3 intragastric pressure sensors. After a 2-minute baseline recording, the HRM protocol was performed with ten 5-mL liquid swallows in a supine position.^{3,14} This was followed by 5 upright swallows and 1 or more provocative maneuvers in the upright position, including solid swallows, multiple rapid swallows (MRS), and a rapid drink challenge (RDC) (variations in HRM study protocol evolved during the study). Five boluses of 2 mL water were swallowed less than 4 seconds apart during MRS,^{15,16} and 200 mL water was swallowed over 30 seconds during RDC.^{17,18}

Manometry studies were analyzed using ManoView version 3.0 analysis software (Medtronic, Inc) to measure the IRP, distal contractile integral (DCI), and distal latency according to the Chicago Classification version 3.0.^{3,14} Esophageal motility disorders were generated from 10 supine swallows according to the Chicago Classification version 3.0. A median IRP greater than 15 mm Hg was applied as the criterion for the diagnosis of EGJOO. Failed (DCI, <100 mm Hg*s*cm) or weak (DCI, 100–450 mm Hg*s*cm) swallows were applied as a criterion for classification of ineffective esophageal motility (IEM). Distal latency less than 4.5 seconds was applied to classify distal esophageal spasm (DES). On MRS, contractile augmentation was considered if the DCI of the post-MRS peristaltic wave was greater than the median value of the 10 supine swallow DCI values.¹⁵

When available, impedance tracings with channels placed at 5, 10, 15, and 20-cm proximal to the EGJ were analyzed based on previous methods.¹⁹ Complete bolus clearance was defined as bolus entry at the 20-cm channel and bolus exit at the 15-cm, 10-cm, and 5-cm channels. Normal bolus transit was defined as complete bolus clearance in more than 70% of swallows.

Esophagram

A TBE was obtained in patients at the discretion of the patients' treating physicians. In patients who had a TBE, the barium column height above the EGJ was measured from images obtained at 1, 2, and 5 minutes after ingestion of 200 mL barium. If there was no contrast retention, a 12.5-mm barium tablet also was administered, and images were obtained at timed intervals until passed into the stomach.

Statistical Analysis

Descriptive statistics were applied. Results were reported as percentage, means \pm SD, range, or median and interquartile range, depending on data distribution.

Results

Subjects

During the study period between November 2012 and September 2019, 111 (16%) of 718 consecutive patients with esophageal symptoms, nonobstructive endoscopy, and corresponding HRM had normal FLIP panometries (Supplementary Figure 1). Demographic and baseline assessment data are listed in Table 1. HRM was performed on the same day as or the day after FLIP in 86% of patients. The longest interval between FLIP and HRM was 7 months. There were no interval treatments between FLIP and HRM beyond acid-suppressive therapy. The 111 patients with normal FLIPs had a median EGJ-DI at a 60-mL fill volume of 5.5 mm²/mm Hg (interquartile range, 4.6–7.3 mm²/mm Hg).

Table 1. Normal Functional Luminal Imaging Probe Panometry Patient Characteristics Based on HRM Diagnosis

| | Total cohort (N = 111) | HRM classification | | | | |
|--|---------------------------|-----------------------------|------------------|-------------------|---|-----------------------------|
| | | Normal motility (n = 78) | IEM (n = 10) | EGJOO (n = 20) | Absent contractility ^a (n = 2) | DES ^a (n = 1) |
| Age, y, means \pm SD | 42 \pm 15 | 42 \pm 15 | 35 \pm 12 | 45 \pm 18 | 34, 66 | 44 |
| Sex, female, n (%) | 77 (69.4) | 57 (73.1) | 6 (60) | 13 (65) | 1 (50) | 0 (0) |
| Indication, n (%) | 78 (70.3) | | | | | |
| Dysphagia | 15 (13.5) | 54 (69.2) | 7 (70) | 15 (75) | 1 (50) | 1 (100) |
| Reflux symptoms | 11 (9.9) | 12 (15.4) | 1 (10) | 2 (10) | | |
| Dysphagia and reflux symptoms | 5 (4.5) | 8 (10.3) | 1 (10) | 2 (10) | | |
| Chest pain Systemic sclerosis | 2 (1.8) | 4 (5.1) | 1 (10) | 1 (5) | 1 (50) | |
| Patient-reported symptom scores | | | | | | |
| GERDQ, ⁷ n (%) completed median [IQR] | 84 (75.7%) | 56 (71.8%) | 8 (80%) | 17 (85%) | 2 (100%) | 1 (100%) |
| 9 [7–10] | | 9 [6–10] | 8 [7–10] | 9 [8–11] | 9, 13 | 10 |
| BEDQ, ⁸ n (%) completed median [IQR] | 79 (71.2) | 53 (68) | 8 (80) | 16 (80) | 1 (50) | 1 (100) |
| 10 [5–17] | | 8 [4–19] | 11 [7–18] | 11 [5–17] | — ^e , 10 | 20 |
| Sedation ^b | | | | | | |
| Midazolam, mg, range | 3–14 | 3–14 | 8–12 | 4–12 | 6–9 | 10 |
| Fentanyl, mcg, range | 50–300 | 50–300 | 125–200 | 75–250 | 125–175 | 200 |
| MAC, n (%) | 13 (12.7) | 8 (10.3) | 2 (20) | 3 (15) | | |
| Objective endoscopy findings, n (%) | | | | | | |
| LA grade A esophagitis | 4 (3.6) | 3 (3.9) | 1 (10) | | 1 (50) | |
| LA grade B esophagitis | 8 (7.2) ^c | 7 (9) ^c | | | | |
| Widely patent rings ^d | 4 (3.6) ^c | 4 (5.1) ^c | | | | |
| Hiatal hernia on HRM, n (%) | | | | | | |
| No hernia | 88 (79.3) | 63 (80.7) | 8 (80) | 14 (70) | 2 (100) | 1 (100) |
| Small hernia, 1–3 cm | 23 (20.7) | 15 (19.2) | 2 (20) | 6 (30) | | |
| IRP, mm Hg, median [IQR] | 9.9 [7–13.1] | 9.3 [6.9–11.9] | 5.2 [2–8.3] | 20.9 [17.7–25.5] | 5.5, 14 | 9 |
| EGJ-DI, mm ² /mm Hg, median [IQR] | 5.5 [4.6–7.3] | 5.8 [4.7–7.4] | 6.2 [5–10] | 4.9 [3.8–6.5] | 3.1, 5 | 3.7 |
| Maximum EGJ diameter, mm, median [IQR] | 23.4 [21–27.5] | 24 [21.6–28] | 23.7 [21.2–26.8] | 21 [18.4–25.3] | 19.5, 19.7 | 20.6 |

BEDQ, brief esophageal dysphagia questionnaire; DES, distal esophageal spasm; EGJ, esophagogastric junction; EGJ-DI, esophagogastric junction distensibility index; EGJOO, esophagogastric junction outflow obstruction; GERDQ, gastroesophageal reflux disease questionnaire; HRM, high-resolution manometry; IEM, ineffective esophageal motility; IEM, ineffective esophageal motility; IQR, interquartile range; IRP, integrated relaxation pressure; MAC, monitored anesthesia care. ^aIndividual values for each of the 2 patients are listed given the small sample size.

^bThe majority of patients received midazolam and fentanyl with conscious sedation; MAC typically involved the use of propofol.

^cOne patient had both LA grade B esophagitis and a widely patent ring and was included in both totals/percentages.

^dWidely patent rings were considered clinically insignificant.

^eItem not completed.

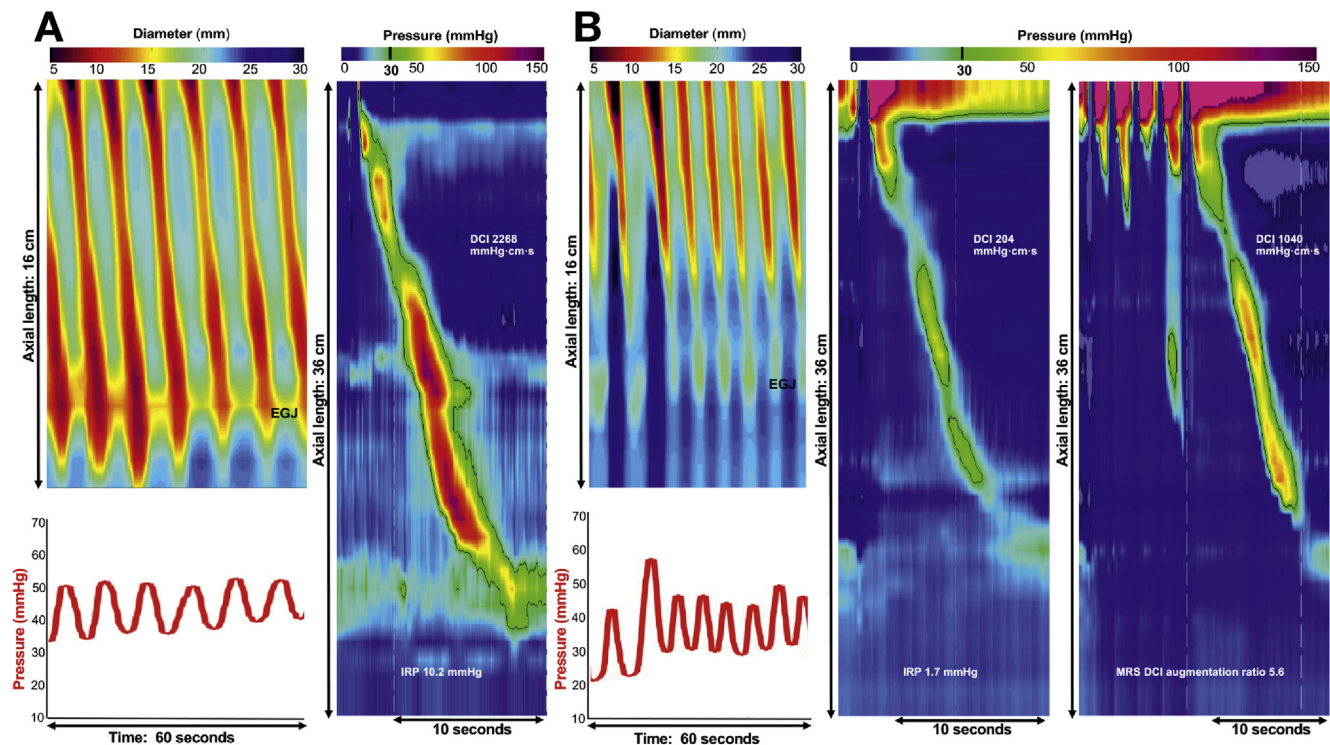


Figure 1. Examples of normal functional luminal imaging probe (FLIP) panometry among patients without a major motor disorder on high-resolution manometry (HRM). Patient examples (A, B) of normal FLIP panometry (top left: topography, bottom left: intraball pressure) with corresponding HRM (right). (A) A single supine swallow from HRM is shown, the median integrated relaxation pressure on 10 supine swallows was 12.2 mm Hg and the HRM diagnosis was normal motility. (B) The HRM diagnosis on supine swallows was ineffective esophageal motility with 10 of 10 ineffective supine swallows (middle). Multiple rapid swallows (right) showed contractile reserve with normal augmentation.¹⁵ EGJ, esophagogastric junction. DCI, distal contractile integral.

High-Resolution Manometry Findings Among Patients With Normal Functional Luminal Imaging Probe Panometry

Among the total patient cohort of 111, the motility classification based on the Chicago Classification version 3.0 of HRM was normal motility in 78 (70.3%) patients, IEM in 10 (9%) patients, EGJOO in 20 (18%) patients, absent contractility in 2 (1.8%) patients, and DES in 1 (0.9%) patient (Table 1). Thus, 79.3% of patients with FLIP panometry did not have a major esophageal motor disorder on corresponding HRM (Figure 1).

Patients With Abnormal High-Resolution Manometry and Normal Functional Luminal Imaging Probe Panometry

Esophagogastric junction outflow obstruction on high-resolution manometry. Among the 20 patients with increased supine IRP and thus EGJOO on HRM, 17 (85%) had normal bolus transit on the supine swallows (Table 2). In addition, 16 (80%) had an IRP less than 12 mm Hg on adjunctive maneuvers such as upright swallows, MRS, or RDC (Table 2). Ten of 20 patients with EGJOO on HRM underwent TBE: 8 showed normal emptying (Figure 2), 1 showed temporary delay of the

barium tablet but no retention, and 1 had an incomplete study. The other 10 patients with EGJOO did not have TBE despite often being recommended. The overall clinical impression was not of an achalasia variant in any of these 20 patients with EGJOO on HRM, and thus none underwent botulinum toxin injection, pneumatic dilation, or lower-esophageal sphincter myotomy at our center. Of those with available clinical follow-up evaluation (3 patients were lost to follow-up evaluation), 4 of 17 patients had empiric dilation performed with a 54-french bougie dilator (1 patient) or 20 mm through-the-scope balloon (3 patients). None who were dilated showed any sign of mucosal disruption, but 1 patient had symptomatic improvement. Three patients had strong vascular signals noted on HRM, prompting referral for endoscopic ultrasound, which was normal in 1 patient and showed mild extrinsic compression by the aorta in the other patient who completed it. In addition, 1 patient was diagnosed with dysphagia lusoria by cross-sectional imaging. The remainder were treated with a proton pump inhibitor (PPI) for presumed gastroesophageal reflux disease (GERD), a neuromodulator and/or behavioral medicine, pharmacologic smooth muscle relaxant, observation alone, or a combination of the above (Table 2).

Ineffective esophageal motility on high-resolution manometry. The IEM classification was derived from 50% to 70% ineffective swallows in 5 of 10 patients, and

Table 2. HRM and TBE Findings in Patients With EGJOO on HRM and Their Clinical Management

| EGJOO patient | Maximum EGJ diameter, mm | Median supine IRP, mm Hg | Hiatal hernia size on HRM, cm | Normal bolus transit | IRP in upright position, mm Hg | IRP on RDC, mm Hg | IRP on MRS, mm Hg | TBE | Clinical management |
|---------------|--------------------------|--------------------------|-------------------------------|----------------------|--------------------------------|-------------------|-------------------|---------------------|---|
| 1 | 20 | 20.6 | 0 | N/A ^a | 9 ^b | N/A ^c | 6 ^b | Incomplete | Neuromodulator/behavioral medicine |
| 2 | 19.3 | 24.6 | 0 | Yes ^b | 11 ^b | 7.9 ^b | 7.5 ^b | Normal ^b | Dilation/neuromodulator/behavioral medicine |
| 3 | 21 | 19.5 | 1 | Yes ^b | 9 ^b | 1 ^b | 3.1 ^b | Normal ^b | PPI |
| 4 | 21 | 15.8 | 0 | Yes ^b | 11 ^b | N/A ^d | 5.3 ^b | N/A ^b | PPI |
| 5 | 21.8 | 17.5 | 0 | Yes ^b | 10 ^b | N/A ^c | 9 ^b | N/A ^c | Lost to follow-up evaluation |
| 6 | 21.6 | 18.5 | 2 | Yes ^b | 10 ^b | N/A ^d | N/A ^c | N/A ^c | Lost to follow-up evaluation |
| 7 | 33.8 | 21.1 | 2 | Yes ^b | 17 | 3.7 ^b | 10.8 ^b | Normal ^b | Neuromodulator/behavioral medicine |
| 8 | 25.3 | 20.4 | 2 | Yes ^b | 15 | N/A ^d | 8.7 ^b | Normal ^b | EUS recommended/not completed |
| 9 | 30.2 | 23 | 0 | Yes ^b | 26 | N/A ^d | 11 ^b | Normal ^b | Dilation alone |
| 10 | 18.2 | 26.2 | 2 | Yes ^b | 12 | N/A ^d | N/A ^c | Normal ^b | Observation |
| 11 | 21.7 | 29.1 | 0 | Yes ^b | 17 | N/A ^d | 11.8 ^b | Normal ^b | EUS: mild extrinsic compression by aorta |
| 12 | 18.4 | 25.9 | 0 | Yes ^b | 18 | N/A ^c | 10.4 ^b | N/A ^c | Lost to follow-up evaluation |
| 13 | 26.5 | 18.6 | 0 | Yes ^b | 13 | N/A ^d | 5.5 ^b | N/A ^c | SMR |
| 14 | 24 | 17.3 | 0 | Yes ^b | 23 | N/A ^d | 9.3 ^b | N/A ^c | Dilation/PPI |
| 15 | 33.2 | 28 | 0 | Yes ^b | 24 | N/A ^d | 2.1 ^b | N/A ^c | Dilation alone |
| 16 | 29.4 | 16.5 | 0 | Yes ^b | 13 | N/A ^d | 9 ^b | N/A ^c | PPI |
| 17 | 20.7 | 21.4 | 2 | Yes ^b | 18 | 14.1 | 16 | N/A ^c | PPI/neuromodulator/behavioral medicine |
| 18 | 16.7 | 16 | 0 | Yes ^b | 14 | N/A ^c | N/A ^c | Tablet delayed | PPI |
| 19 | 18.2 | 21.8 | 0 | No | 23 | N/A ^d | 11 ^b | Normal ^b | Dysphagia lusoria |
| 20 | 29.5 | 29.1 | 0 | No | 18 | N/A ^d | 14 | N/A ^c | EUS normal |

EGJ, esophagogastric junction; EGJOO, esophagogastric junction outflow obstruction; EUS, endoscopic ultrasound; HRM, high-resolution manometry; IRP, integrated relaxation pressure; MRS, multiple rapid swallows; N/A, not applicable. PPI, proton pump inhibitor; RDC, rapid drink challenge; SMR, smooth muscle relaxant; TBE, timed barium esophagram.

^aNo impedance on HRM.

^bHRM or TBE findings were considered normal; IRP was <12 mm Hg for upright position, RDC, and MRS.^{4,17}

^cNot performed.

^dRDC was not completed in 30 seconds.

80% or more ineffective swallows in 5 patients. In addition, contractile augmentation on MRS was observed in 6 of 6 patients who completed MRS, including 3 of 3 patients with 80% or more ineffective swallows (Figure 1). Five of 10 patients with IEM on HRM had a TBE with normal emptying. Four patients were treated with a PPI for presumed GERD. Three patients were treated with neuromodulators and/or behavioral medicine for a presumed functional component to their symptoms. Three patients were treated with a combination of PPI and neuromodulator/behavioral medicine, 1 of whom also received a cricopharyngeal dilation with 54-french bougie dilator for coexisting oropharyngeal dysphagia. No patients required further invasive interventions, including surgery.

Other motility disorders on high-resolution manometry. Both patients with absent contractility on supine

test swallows had weak peristalsis observed on provocative HRM maneuvers (Figure 3A). One of these patients had systemic sclerosis and the other patient had a history of metastatic multiple myeloma and was receiving chemotherapy and radiation; the latter had a TBE with normal emptying. The 2 patients with absent contractility on HRM were treated with PPI for presumed GERD and 1 also underwent empiric bougie dilation.

The 1 patient (<1% of this normal FLIP panometry cohort) with DES on HRM completed a TBE that had normal esophageal conformation (ie, no corkscrew appearance), no tertiary contractions, a 9-cm contrast column at 1 minute that cleared by 2 minutes, and normal passage of a barium tablet (Figure 3B). The patient was offered a smooth muscle relaxant but was lost to follow-up evaluation.

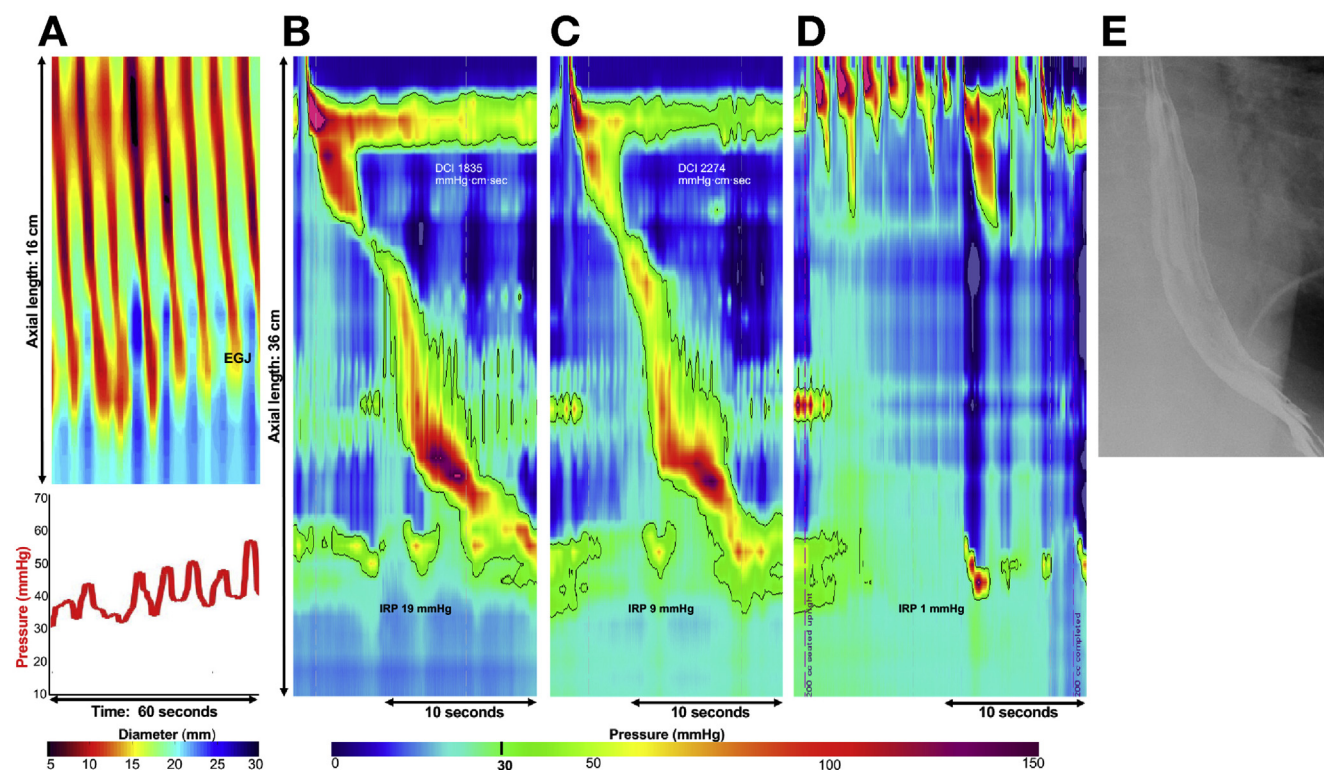


Figure 2. Example of normal functional luminal imaging probe (FLIP) panometry with esophagogastric junction outlet obstruction on corresponding high-resolution manometry (HRM). (A) Normal FLIP panometry (*top*: topography, *bottom*: intraball pressure). On supine swallows (such as in panel B, single supine swallow), the median integrated relaxation pressure (IRP) was 19 mm Hg. However, normal IRP values (ie, <12 mmHg) were observed on (C) single test swallows performed in the upright position, on multiple rapid swallows (not shown, IRP = 3 mmHg), and (D) on rapid drink challenge.^{4,17} (E) Timed barium esophagram showed no retention at 1 minute; there was a clear esophagogastric junction (EGJ) opening. DCI, distal contractile integral.

Discussion

In this cohort study of 111 patients with normal FLIP panometry, as defined by EGJ-DI greater than 3.0 mm²/mm Hg and normal contractile response (absence of RRCs and meeting the RAC Rule-of-6s), 79% did not have a major esophageal motor disorder on HRM. Among the remaining 21% with apparent disagreement with HRM, patients with normal FLIP panometry carried overall clinical impressions of not having a major esophageal motor disorder and subsequently were treated conservatively without the need for surgical interventions.

We recently described the normal esophageal response to controlled volumetric distension among asymptomatic volunteers by describing normal EGJ opening using the EGJ-DI as well as the normal contractile response to sustained distension.⁹ Compared with normal volunteers, patients with achalasia consistently showed a reduced EGJ-DI.^{1,13} The normal contractile response is a unique pattern of RACs, which likely represent a secondary peristalsis-like reaction that is repetitive in response to the sustained distension.⁹ Conversely, RRCs were not observed in asymptomatic volunteers, but may be observed in esophageal disorders such as spastic achalasia.¹⁰ We more recently refined the

criteria of the normal contractile response to distension by applying the RAC Rule-of-6s, defined as a RAC pattern with at least 6 consecutive antegrade contractions spanning at least 6 cm in axial length occurring at a rate of 6 ± 3 per minute. A contractile response meeting the RAC Rule-of-6s was found in 95% of asymptomatic controls and in less than 1% of achalasia patients.¹³

The mild discordance between HRM and FLIP panometry interpretation is explained in part by the HRM assessment of primary peristalsis vs the FLIP panometry assessment of a secondary peristalsis-like response to sustained volumetric distention. For instance, FLIP panometry has shown esophageal contractility in achalasia patients when void on HRM.¹⁰ Variance in FLIP panometry and HRM also was seen in asymptomatic volunteers with normal HRM in 85%, with EGJOO in 10%, and with IEM in 5% of the defining cohort of normal FLIP panometry parameters.⁹ In this study, a similar discordant distribution of HRM was seen in symptomatic patients with normal FLIP panometry: 70.3% normal, 18% EGJOO, 9% IEM, and 2.7% other. In addition, upon review of the HRMs of the 20 patients with EGJOO (Table 2), HRM parameters generally were normal beyond the supine IRP, such as IRP on adjunctive maneuvers or bolus transit on impedance. In addition, 8 of 9

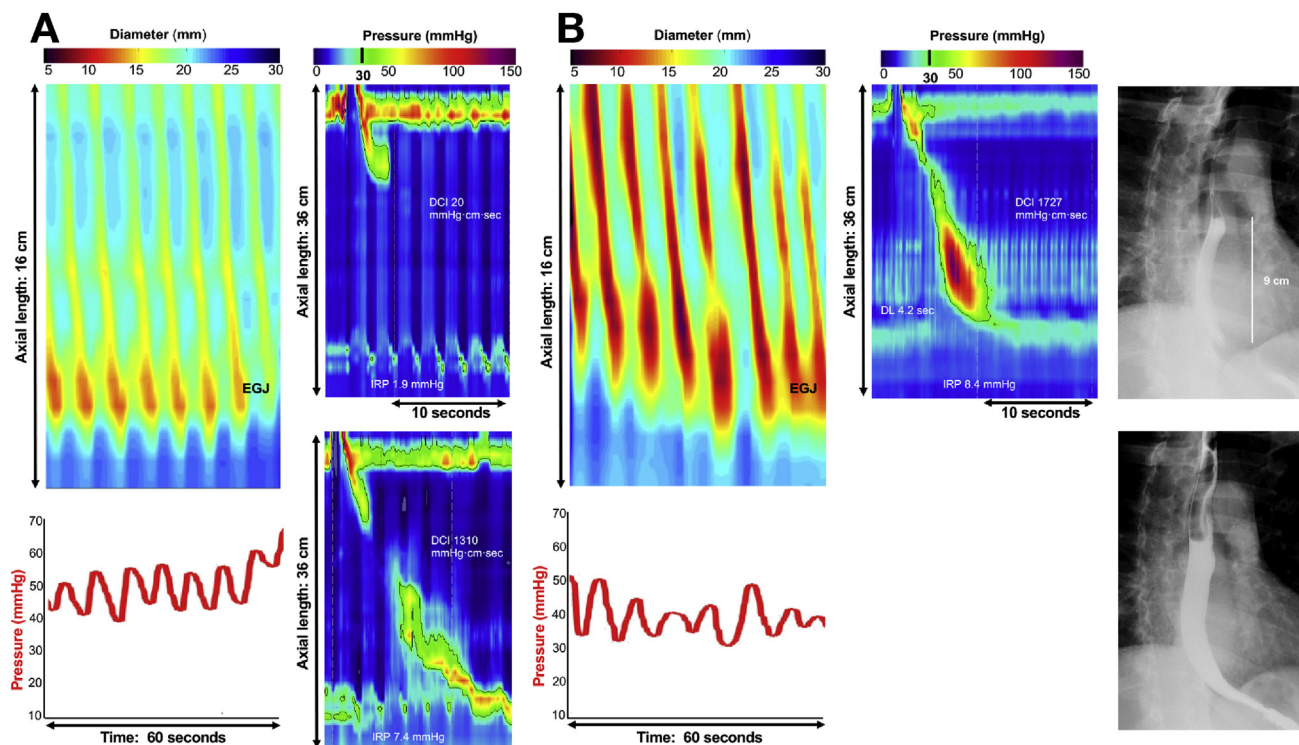


Figure 3. Examples of normal functional luminal imaging probe (FLIP) panometry among patients with (A) absent contractility and (B) distal esophageal spasm on high-resolution manometry (HRM). Normal FLIP panometries are shown on the *left* (top: topography, bottom: intraballoon pressure). (A) A classification of absent contractility was derived from 10 failed supine swallows on HRM (top right). However, weak and fragmented peristalsis was elicited on provocative maneuvers, such as with a solid (graham cracker) swallow (bottom right). (B) Patient example with normal FLIP panometry (left), but DES on corresponding HRM (center). Although a transient delay in contrast passage was observed (1-minute column, top right), the esophagus otherwise appeared normal (eg, no corkscrew configuration) (bottom right). DCI, distal contractile integral; EGJ, esophagogastric junction.

patients who completed TBE had normal emptying. These findings questioned the clinical significance of the EGJO diagnosis on HRM, but instead suggest that increased IRP on HRM may be related to misleading pressure artifact. Likewise, both patients with absent contractility on supine HRM had evidence of weak peristalsis on provocative HRM swallows (Figure 3A). The patient with DES on HRM had borderline distal latencies but otherwise overall normal appearance on HRM (Figure 3B). Thus, chasing isolated HRM parameters can be problematic because it does not consider the entire clinical picture.

The fact that patients with RACs had a high likelihood of having normal function on manometry makes physiologic sense because the secondary peristalsis-like response triggered by sustained volumetric distention would require intact neurologic function in the esophageal body. Distention can trigger extrinsic vagal-vagal reflexes that induce peristalsis, and distention also can trigger peristalsis via the intrinsic enteric nervous system without extrinsic influence. Thus, it would be logical that primary peristalsis triggered by extrinsic innervation would be associated with normal peristalsis because the neurologic and myogenic function of the esophageal body is intact during secondary peristalsis. In contrast, it

is possible that patients who have normal primary peristalsis may have impaired secondary peristalsis because the esophagus may have abnormal thresholds for triggering peristalsis. In addition, there may be paradoxical responses in which the lower esophageal sphincter either contracts or does not relax during distention owing to aberrant reflexes or a lack of triggering by an absent contractile response. We speculate that there may be a form of dysphagia related to an impaired contractile response to distention and subsequent reduced EGJ opening because we previously identified a subgroup of dysphagia patients with normal motility on HRM and patterns similar to achalasia patients during FLIP panometry.¹ Further research using pharmacologic interrogation may be helpful in describing these responses.

The limitations of this study were its descriptive and retrospective nature. FLIP panometry was intentionally not tested against HRM as the gold standard because HRM abnormalities do not always equate to patient outcomes and its metrics can carry limitations. This study instead showed agreement of HRM among patients selected by having a normal FLIP panometry in the majority and explored clinical outcomes in patients whose HRM and FLIP panometry did not agree. Although the

patients come from a prospectively collected clinical database, management decisions were at the discretion of the gastroenterologist so certain clinical information is missing (ie, TBE). In addition, effects of endoscopic sedation could impact results when HRM was completed after endoscopy; however, these HRM results were used clinically. Finally, the patient population was that of a tertiary referral center, therefore it may not be applicable to the general community. However, access to our FLIP panometry analysis software is offered and thus available for use at other centers.

In conclusion, FLIP panometry offers the potential to establish normal esophageal motility and function at the time of endoscopy and provide reassurance in supporting a conservative management strategy. Thus, a normal upper endoscopy and FLIP panometry substantially could reduce the probability for the presence of a major esophageal motor disorder and obviate the need for an HRM because there is good correlation with HRM and the esophagram. Instead, the initial clinical management strategy could be directed toward addressing gastroesophageal reflux or a functional syndrome. In addition, an abnormal FLIP panometry can better inform the diagnostic strategy because these patients will have a higher likelihood of having a major motor disorder. This could streamline the care of patients with esophageal symptoms and potentially avoid sending patients for unnecessary transnasal manometry. However, further longitudinal studies are needed to support this approach.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at <https://doi.org/10.1016/j.cgh.2020.03.040>.

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Reprint requests

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Conflicts of interest

These authors disclose the following: Dustin A. Carlson, Peter J. Kahrilas, and John E. Pandolfino hold shared intellectual property rights and ownership surrounding functional luminal imaging probe panometry systems, methods, and apparatus with Medtronic, Inc; Dustin A. Carlson has served as a speaker and consultant for Medtronic; Wenjun Kou has consulted for Crospon, Inc; and John E. Pandolfino holds stock options in Crospon, Inc, has served as a consultant for Given Imaging, Sandhill Scientific, Medtronic, Torax, and Ironwood, has received grants from Given Imaging and Impleo, and has been a speaker for Given Imaging, Sandhill Scientific, Takeda, Astra Zeneca, Medtronic, and Torax. The remaining authors disclose no conflicts.

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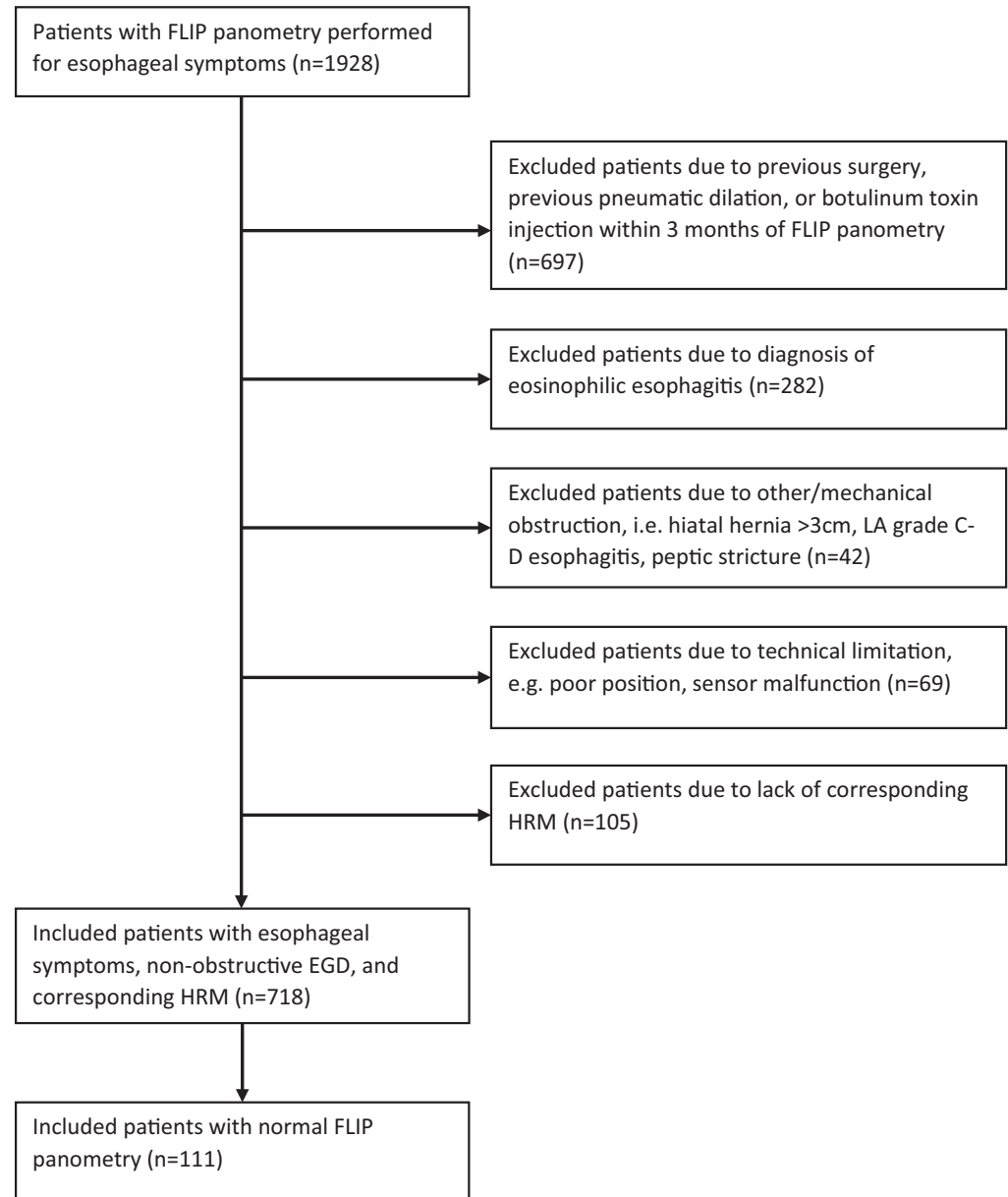
**Supplementary**

Figure 1. Flow diagram of cohort inclusion. EGD, esophagogastroduodenoscopy; FLIP, functional luminal imaging probe; HRM, high-resolution manometry.