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Type II achalasia with focal elevated pressures: A distinct manometric and clinical sub-group

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Abstract

Background: Type II achalasia (Ach2) is distinguished from other achalasia sub-types by the presence of panesophageal pressurization (PEP) of ≥30 mmHg in ≥20% swallows on high-resolution manometry (HRM). Variable manometric features in Ach2 have been observed, characterized by focal elevated pressures (FEPs) (focal/segmental pressures ≥70 mmHg within the PEP band) and/or high compression pressures (PEP ≥70 mmHg). This study aimed to examine clinical and physiologic variables among sub-groups of Ach2.

Methods: This retrospective single center study performed over 3 years (1/2019–1/2022) included adults with Ach2 on HRM who underwent endoscopic ultrasound (EUS), functional lumen imaging probe (FLIP), and/or barium esophagram (BE) prior to therapy. Patients were categorized into two overarching sub-groups: Ach2 without FEPs and Ach2 with FEPs. Demographic, clinical, and physiologic data were compared between these sub-groups utilizing unpaired univariate analyses.

Key Results: Of 53 patients with Ach2, 40 (75%) were without FEPs and 13 (25%) had FEPs. Compared with the Ach2 sub-group without FEPs, the Ach2 sub-group with FEPs demonstrated a significantly thickened distal esophageal circular muscle on EUS (1.4 mm [SD 0.9] vs. 2.1 [0.7]; $p = 0.02$), higher prevalence of tertiary contractions on BE (46% vs. 100%; $p = 0.0006$), lower esophagogastric junction distensibility index (2.2mm^2/mmHg [0.9] vs 0.9 [0.4]; $p = 0.0008$) as

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AUTHOR CONTRIBUTIONS

Eric E. Low involved in study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and statistical analysis. Syed Abbas Fehmi involved in acquisition of data, critical revision of the manuscript for important intellectual content, and approval of final manuscript. Aws Hasan, Michael Chang, Wilson Kwong, Mary L. Krinsky, and Gobind Anand involved in acquisition of data and approval of final manuscript. Madeline Greytak involved in critical revision of the manuscript for important intellectual content and administrative, technical, or material support. Alexander Kaizer involved in critical revision of the manuscript for important intellectual content, statistical analysis, and approval of final manuscript. Dustin A. Carlson and John E. Pandolfino involved in analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and approval of final manuscript. Rena Yadlapati involved in analysis and interpretation of data, critical revision of the manuscript for important intellectual content, approval of final manuscript, and study supervision.

well as higher distensive pressure (31.0 mmHg [9.8] vs. 55.4 [18.8]; $p = 0.01$) at 60 cc fill on FLIP, and higher prevalence of chest pain on Eckardt score ($p = 0.03$).

Conclusions and Inferences: We identified a distinct sub-group of type II achalasia on HRM, defined as type II achalasia with focal elevated pressures. This sub-group uniquely exhibits spastic features and may benefit from personalized treatment approaches.

Keywords

achalasia; manometry; esophagus; contraction; EUS

1 | INTRODUCTION

Achalasia is the most well-characterized esophageal motility disorder, defined globally by impaired lower esophageal sphincter (LES) relaxation and absent peristalsis on high-resolution manometry (HRM).[1] The Chicago Classification (CC), now in its fourth iteration, describes three distinct subtypes of achalasia based on HRM (type I, type II, and type III); the identification of distinct subtypes of achalasia has impacted treatment recommendations and clinical outcomes.[2]

Type II achalasia (Ach2) is the most frequently diagnosed subtype of achalasia and postulated to represent an earlier stage of achalasia.[3] In Ach2, the esophagus generates simultaneous pressurization across a common cavity while the upper esophageal sphincter and lower esophageal sphincter are closed. Manometrically, this is observed as panesophageal pressurization (PEP) at an isobaric contour of 30 mmHg or greater. Sub-groups of Ach2 cases have been noted to exhibit varying patterns of increased pressure within the panesophageal pressure band on HRM, including high compression pressures as well as focal elevated pressures (FEPs), which may be characteristic of distinct manometric and clinical sub-groups. Observed manometric variations include: (1) high levels of focal/segmental pressures (≥70 mmHg) within the isobaric PEP band representing FEPs, (2) higher isobaric contour PEP bands (≥70 mmHg) representing high compression pressures, or (3) a combination of both higher isobaric PEP bands and presence of FEPs on HRM.

The most recent iteration of the CC suggested consideration of Ach2 cases with an "embedded spasm" as representative of a possible spastic phenotype.[1] However, the definition of an "embedded spasm" on HRM lacks consensus with variable interpretation in clinical practice, and literature to support a clinical distinction of a spastic phenotype beyond case reports does not exist. Consequently, recognizing Ach2 with an "embedded spasm" was not a formal recommendation in CC. Therefore, the aim of our study was to examine clinical and physiologic variables among a cohort of patients with Ach2 with variable manometric features on HRM.

2 | MATERIALS AND METHODS

2.1 | Study design and subject selection

We performed a retrospective single center study of adult patients meeting diagnostic criteria for Ach2 per the Chicago Classification v4.0 on high-resolution impedance manometry

(HRIM) over 3 years (January 2019–January 2022).[1] Patients with Ach2 were included if they had undergone at least one of the following evaluations prior to achalasia directed therapy: endoscopic ultrasound (EUS) of the esophageal circular muscle, functional lumen imaging probe (FLIP), or barium esophagram (BE). The Institutional Review Board approved this study.

2.2 | HRIM evaluation

All HRIM evaluations utilized a catheter (4.2 mm diameter; Medtronic Inc.,) equipped with 36 pressure transducers spaced 1 cm apart and 18 impedance electrodes spaced 2 cm apart. Once the catheter was placed, and a baseline period was recorded confirming catheter placement, a minimum of ten 5 ml wet swallows in the supine position were performed. If patient tolerated, additional swallows were performed including five wet swallows in the seated position, up to three multiple rapid swallows, and a rapid drink challenge. Impedance contours were evaluated imposed on the esophageal pressure topography (EPT). Impedance increases by 500 ohms from baseline measurement were measured and considered suggestive of contact pressure with the catheter.[4]

2.3 | Definition of Ach2 with variable manometric features

Ach2, consistent with the CCv4.0, was defined as an abnormal median IRP and absent contractility (100% failed peristalsis) with PEP in 20% or more swallows.[1] All cases of Ach2 were categorized into one of four sub-groups based on distinct manometric patterns: (A) Ach2 without FEPs and PEP <70 mmHg (i.e., traditional Ach2), (B) Ach2 without FEPs and PEP ≥70 mmHg, (C) Ach2 with FEPs & PEP ≥70 mmHg, and (D) Ach 2 with FEPs and PEP <70 mmHg. PEP ≥70 mmHg was defined as panesophageal pressure band(s) where the isobaric pressure is ≥70 mmHg on 2 or more swallows; these higher pressures represent higher compression. A FEP (focal elevated pressure) was defined as a focal or segmental area of pressurization ≥70 mmHg within the panesophageal pressure band, but not extending the length of the panesophageal band, on 2 or more swallows where the esophageal body contacts the HRM catheter (Figure 1). All HRIM studies were reviewed independently by two team members (EL, RY), and a patient was included in a specified sub-group above if both team members agreed on the HRIM criteria.

2.4 | EUS

EUS was routinely performed by an advanced endoscopy specialist for patients with achalasia in accordance with an adopted, standardized protocol to (a) evaluate for pseudo-achalasia and (b) measure esophageal muscle thickness to assist with myotomy length planning for definitive therapy (i.e., peroral endoscopic myotomy [POEM]). Variable EUS performance in our study cohort relates to differences in patient adherence and clinical follow-up patterns and is not reflective of differences in manometric morphology or clinical features as endoscopists performing the EUS procedure were blinded to HRM tracings. Data from EUS evaluations were collected for patients who underwent EUS prior to potential surgical or endoscopic intervention for achalasia. A radial EUS endoscope was utilized, and measurements of the circular muscle thickness were described at the esophagogastric junction (EGJ) and at every centimeter proximally to the EGJ until the muscle thickness reached 1 mm or less, which defined a normal circular muscle thickness.[5–9] Average circular

muscle thickness was computed for the distal esophagus at 3 different lengths from the EGJ: (1) EGJ to 3 cm proximal (the typical extent of a short esophageal myotomy during per-oral endoscopic myotomy [POEM][10,11]), (2) 4 cm–7 cm proximal (the typical extent of a standard esophageal myotomy during POEM[11]), and (3) 8 cm–10 cm proximal (a length beyond standard esophageal myotomy during POEM). Prior studies have demonstrated an average circular muscle thickness in the distal esophagus ranging from 0.6 to 1.2 mm among healthy control subjects, with normal manometry.[6–9] Additionally studies evaluating circular muscle thickness in type III achalasia have shown an average muscle thickness in the distal esophagus ranging from 1.7 to 2.3 mm.[5,6] For the purpose of this study, and based on the available literature, we defined a thickened circular muscle layer in the distal esophagus equal to 1.6 mm or greater.

2.5 | Barium esophagram

Data from barium esophagram were collected for patients that underwent barium esophagram. Barium swallows were evaluated for the presence of tertiary contractions.[12,13] Tertiary contractions were classified as “moderate-to-severe” if the contractions resulted in curling, corkscrew, or a beading appearance of the esophagus.[13] Otherwise, mild indentations or disruptions in the esophagus were classified as mild (Figure 2).

2.6 | FLIP

Real-time FLIP evaluation was performed by a motility specialist using a standardized protocol as a part of per-therapy evaluation. At the time of procedure, the endoscopist was blinded to HRM tracings. FLIP data were collected from all those who underwent FLIP prior to therapy, and variability in study performance relates to clinical adherence and follow-up patterns. FLIP procedures were performed using a 16 cm FLIP (EF322; Medtronic Inc) catheter. Catheters were placed transorally during a sedated upper endoscopy and adequate position was confirmed on planimetry under 30 cc fill. EGJ distensibility index (DI), pressure, and diameter were reported at balloon catheter fill volumes of 40 cc, 50 cc, 60 cc, and 70 cc after the balloon was held in place for 60 s at each fill volume. Real-time measurements at 60 cc fill volume were collected and used in our analyses.

2.7 | Clinical evaluation and therapeutic outcomes

Data collection of clinical metrics included the Eckardt score,[14] as well as therapeutic outcomes following achalasia therapy.

2.8 | Data management and statistical comparisons and analysis

Participant data were securely maintained in REDCap. First, summary statistics of demographic, radiographic, and physiologic tests were described for all four manometrically distinct Ach2 sub-groups as mean values with standard deviation for continuous variables or as frequencies for categorical variables (Tables 1 and 2). Next, one-way ANOVA with Tukey tests as well as Chi-squared or Fisher’s exact tests were computed to identify potential differences among the four sub-groups regarding radiographic and physiologic metrics (Table 2).

Based on the results from these comparative analyses, similarities were identified between two overarching sub-groups: (1) Ach2 *without* FEPs [i.e., patients with (A) Ach2 without FEPs and PEP <70 mmHg (i.e., traditional Ach2) or (B) Ach2 without FEPs and PEP ≥70], and (2) Ach2 *with* FEPs [i.e., patients with (C) Ach2 with FEPs and PEP ≥70 or (D) Ach 2 with FEPs and PEP <70]. As such, *post-hoc* summary statistics were computed for these two sub-groups. Unpaired Student T-tests were used to estimate the statistical significance for continuous variables between these two sub-groups. Chi-squared or Fisher's exact tests were used when appropriate to estimate statistical significance for categorical variables between the two sub-groups.

For all comparisons, p-values of <0.05 were considered statistically significant. Analyses were conducted using Statistical Analysis System 9.4 (SAS Institute Inc.).

3 | RESULTS

3.1 | Baseline characteristics

A total of 53 patients met inclusion criteria and are included in this analysis: mean age 55.0 years (SD 18.9), mean BMI 25.5 kg/m^2 (SD 4.7), and 29 (55%) males.

3.2 | Characteristics of four manometric sub-groups of Ach2

Thirty-six (68%) met criteria for sub-group (A) Ach2 without FEPs and PEP <70 mmHg (i.e., traditional Ach2), 4 (8%) met criteria for sub-group (B) Ach2 without FEPs and PEP ≥70, 8 (15%) met criteria for sub-group (C) Ach2 with FEPs and PEP ≥70, and 5 (9%) patients met criteria for sub-group (D) Ach 2 with FEPs and PEP <70 (Table 1, Figure 2)

Radiographic and physiologic characteristics were compared among the four sub-groups (Table 2, Figure 2).

3.2.1 | EUS—Of 44 (83%) total patients that underwent EUS, there were significant differences in proportion of patients among sub-groups with a thickened circular muscle (>1.6 mm) measured from the EGJ to 3 cm proximal ($p < 0.0001$) and the most proximal segment at 8–10 cm from the EGJ on EUS ($p = 0.0002$). Notably, sub-group (C) Ach2 with FEPs and PEP ≥70 mmHg had a greater proportion of thickened circular muscle from EGJ to 3 cm (100%), than sub-group (A) Ach2 without FEPs and PEP <70 (24%) or sub-group (B) Ach2 without FEPs and PEP ≥70 (0%).

3.2.2 | BE—Of 50 (94%) total patients that underwent BE, there was a significant difference in the proportion of patients with tertiary contractions among sub-groups ($p = 0.0001$). A higher proportion of tertiary contractions on BE was seen in both sub-group (C) Ach2 with FEPs and PEP ≥70 mmHg (100%) and sub-group (D) Ach 2 with FEPs and PEP <70 (100%) when compared independently to sub-group (A) Ach2 without FEPs and PEP <70 (44%).

3.2.3 | FLIP—Of 32 (60%) total patients that underwent FLIP, there were significant differences in findings on FLIP at a 60 cc fill volume among sub-groups including mean EGJ-DI ($p = 0.005$), FLIP pressure ($p = 0.0003$) and presence of contractility in response

to distension ($p = 0.0001$). For instance, mean EJG-DI at a balloon fill of 60 cc was significantly lower in both sub-group (C) Ach2 with FEPs and PEP ≥70 mmHg (1.0 mm^2/mmHg [SD 0.6]) and sub-group (D) Ach 2 with FEPs and PEP <70 (0.9 mm^2/mmHg [SD 0.1]) when compared independently to sub-group (B) Ach2 without FEPs and PEP ≥70 (2.7 mm^2/mmHg [SD 0.4]).

No significant differences were seen in any of the diagnostic tests between sub-groups without FEPs (sub-group A or B). Similarly, no significant differences were seen in any of the diagnostic tests between sub-groups with FEPs (sub-group C or D) (Table 2).

Based on manometric sub-group comparisons, further analyses in this study were performed between two overarching sub-groups of Ach2: (1) Ach2 *without* FEPs (including sub-groups A and B), and (2) Ach2 *with* FEPs (including sub-groups C and D).

3.3 | Comparisons of physiologic and clinical data between Ach2 with or without FEPs

Thirteen (25%) patients met criteria for Ach2 with FEPs and 40 (75%) met criteria for Ach2 without FEPs. There were no significant differences in baseline characteristics between these two sub-groups (Table 3) with the exception of a significantly higher baseline Eckardt chest pain sub-score in the Ach2 with FEPs sub-group (1.4 [SD 1.1]) than the Ach2 without FEPs sub-group (0.7 [SD 1.0]; $p = 0.03$)

3.3.1 | Endoscopic ultrasound—On EUS, the proportion of patients with a thickened circular muscle was significantly greater in the Ach2 with FEPs sub-group than the Ach2 without FEPs sub-group at each level (EGJ to 3 cm proximal: 10/11 (91%) vs. 7/33 (21%) [$p < 0.0001$]; 4 cm to 7 cm proximal to EGJ: 6/11 (55%) vs. 4/33 (12%) [$p = 0.008$]; 8 cm to 10 cm proximal to EGJ: 7/11 (64%) vs. 3/33 (9%) [$p = 0.0007$], respectively). (Table 4).

3.3.2 | Barium esophagram—On BE, the proportion of patients with tertiary contractions was significantly greater in the Ach2 with FEPs sub-group (13/13 (100%)) than Ach2 without FEPS sub-group (17/37 [46%]; $p = 0.0006$). The majority of tertiary contractions in patients with Ach2 with FEPs were moderate-to-severe (10/13; 77%) compared with only 1/17 (6%) in patients with Ach2 without FEPs. (Table 4).

3.3.3 | FLIP—At a standard 60 cc fill volume, comparing the Ach2 with FEPs sub-group versus Ach2 without FEPs sub-group the mean EGJ-DI was significantly lower (0.9 mm^2/mmHg [SD 0.4] vs. 2.2 mm^2/mmHg [SD 0.9]; $p = 0.0008$), the mean EGJ diameter was significantly smaller (7.2 mm [SD 2.2] vs. 9.0 mm [SD 1.4]; $p = 0.01$), and the mean distensive pressure was significantly higher (55.4 mmHg [SD 18.8] vs. 31.0 mmHg [SD 9.8]; $p = 0.01$). Contractility in response to distension was observed in 5/7 (71%) of patients with Ach2 with FEPs compared with only 1/25 (4%) of patients with Ach2 without FEPs ($p = 0.0006$). (Table 4).

3.3.4 | HRIM—On HRIM, impedance contours were evaluated imposed on EPT. 8 of 13 (62%) subjects with Ach2 with FEPs demonstrated an impedance increase by 500 ohms in relation to FEPs (Figure 3). Comparatively, 2 of the 40 (5%) subjects with Ach2 without

FEPs demonstrated an impedance increase by 500 ohms in relation to PEP ($p < 0.0001$). (Table 4).

3.4 | Treatment outcomes among patients with Ach2 with FEPs

Of the 13 patients with Ach2 with FEPs, 9 individuals underwent first line therapy for achalasia—4 POEM, 4 laparoscopic Heller myotomy (LHM), and 1 pneumatic dilation (PD). Three out of 4 individuals who underwent POEM had an extended, tailored myotomy performed. Esophageal myotomy lengths included 14 cm, 16 cm, and 20 cm, and were tailored to the proximal border of the FEP within the PEP on HRIM in conjunction with circular muscle thickness on EUS. Pre-therapy Eckardt scores improved post-POEM for each patient: 5 pre- to 0 post-POEM at 12 months follow-up for the subject undergoing a 14 cm esophageal myotomy, 8 pre- to 0 post-POEM at 12 months follow-up for the subject undergoing a 16 cm esophageal myotomy, and 4 pre- to 0 post-POEM at 6 months follow-up for the subject undergoing a 20 cm esophageal myotomy. None of the individuals required retreatment or developed post-POEM gastroesophageal reflux disease.

Four subjects underwent LHM with Dor fundoplication. Two of the four subjects experienced treatment failure with recurrence of symptoms: one had a pre-therapy Eckardt score of 9 which only improved to 8 following surgery at 6 months follow-up, prompting retreatment with PD, and the other had a pre-therapy Eckardt score of 6 which reduced to a score of 4 at 6 months follow-up. The other two patients have experienced treatment success at 2 months follow-up with a decrease in pre-therapy Eckardt score of 11 (for both) to less than 3 post-surgery.

One subject underwent PD with a pre-therapy Echardt score of 4. This patient had treatment failure with recurrence of symptoms including dysphagia and chest pain (Eckardt score of 4) at 1 month following therapy.

4 | DISCUSSION

This study of 53 patients with type II achalasia identified clinical, radiographic, and physiologic distinctions between patients with and without focal elevated pressures within the panesophageal pressure band, suggesting that there may be a distinct sub-group of type II achalasia on HRM, defined as type II achalasia with focal elevated pressures (FEPs). Individuals with this sub-grouping, compared with type II achalasia without focal elevated pressures, demonstrated a significantly thickened distal esophageal circular muscle, higher prevalence of tertiary contractions on BE, higher distensive pressures and contractility in response to distension on FLIP, and higher prevalence of chest pain. Additionally, impedance contour increases were seen correlating with focal elevated pressures on manometry for a majority subjects with type II achalasia and FEPs, suggesting contact pressure with the HRM catheter at these areas.[4] Given this constellation of findings, we postulate that type II achalasia with focal elevated pressures may be a distinct sub-group which demonstrates lumen occluding contractions (LOCs) and is more akin to a spastic achalasia, either distinctly or in evolution (e.g., from type III to type II achalasia), in which there is increased spasticity at the LES and distal esophagus.[15] These findings are hypothesis

generating and may have important implications for treatment strategies and understanding mechanism of disease.

The etiology and pathophysiology of achalasia is not well understood. Some studies suggest that achalasia results from inflammation and degradation of neurons in the esophagus, possibly due to an autoimmune disorder or other inflammatory process.[16,17] Moreover, achalasia subtypes are postulated by some to represent a spectrum of disease progression, with progressive loss in neuronal function. Two studies[18,19] suggest that type III achalasia, a disease state where impaired neuronal inhibitory postganglionic neuron function rather than neuronal loss has been hypothesized, progresses to type II and finally to type I achalasia, both which demonstrate progressive plexopathy.[19] Clinical observations also suggest an overlap between some type II and type III achalasia.[20] To the best of our knowledge, our study is the first-of-its-kind to study distinct sub-groups of patients with type II achalasia and features of focal elevated pressures within panesophageal pressure bands. Our results suggest that a subset of patients with type II achalasia exhibiting these focal elevated pressures are distinct from the traditional type I or type II achalasia, potentially arising from a distinct pathophysiologic mechanism and falling along the spectrum of spastic achalasia or representing a spectrum of residual function.

This distinct type II sub-group (i.e. type II achalasia with focal elevated pressures) may exist due to esophageal muscle thickness and spasticity, particularly relating to the esophageal circular muscle.[7–9] In normal esophageal physiology, a peristaltic wave resulting from coordinated, anterograde esophageal circular muscle contractions after swallowing in conjunction with longitudinal muscle shortening acts to propel liquid and/or solid content toward the stomach.[21–23] Prior studies of esophageal muscle thickness in achalasia have identified greater esophageal muscle thickness, particularly the circular muscle, among type III achalasia than type II and type I achalasia.[5,6,24] The increased thickness may be either causative of, or resulting from spasticity of the circular muscle. Our study suggests that individuals with type II achalasia with focal elevated pressures may similarly have a thickened, spastic circular muscle. We also described an additional distinct type II achalasia manometric pattern of elevated compression pressures, where isobaric pressures are ≥70 mmHg. Prior studies of esophageal muscle thickness in type II achalasia suggest that panesophageal pressurization in type II achalasia may arise from longitudinal muscle contraction elevating luminal cavity pressure and resulting in non-occluding contractions. We hypothesize that these unique focal elevated pressures within the panesophageal pressure band may result from circular muscle contractions causing contact pressure on the HRM catheter (i.e., lumen occluding contractions), as evident by vigorous and prevalent contractions on barium esophagram, prevalent contractions in response to distention on FLIP, and impedance increases correlating with the focal elevated pressures.[25] Moreover, we hypothesize that a spectrum of spasticity among type II achalasia patients exists, where longitudinal muscle spasticity results in increased isobaric panesophageal pressurization without significant luminal distortion and circular muscle thickness and spasticity results in focal/segmental isobaric intensities on HRM and significant luminal narrowing/distortion. Additional studies are needed to test this hypothesis, particularly looking at longitudinal muscle physiology in these manometric sub-groups as well as concurrent radiologic/physiologic and manometric features.

The identification and definition of achalasia subtypes have led to improved treatment outcomes.[2] Currently, first-line therapies for type I and type II achalasia include any of the following: LHM, POEM, or PD. However, for type III achalasia POEM is the first-line therapy, as patients with type III achalasia have improved outcomes with longer, tailored myotomy.[26,27] This is likely due to the esophageal muscle spasticity in type III achalasia which can be targeted with proximal extension of the myotomy along the esophageal body. Our study demonstrated individuals with type II achalasia with focal elevated pressures have a significantly thickened circular muscle several centimeters proximal to the EGJ. Fifty five percent of individuals had a thickened circular muscle at 4–7 cm proximal to the EGJ, and 64% had a thickened circular muscle at 8–10 cm proximal to the EGJ. This suggests that likely more than half of the patients with type II achalasia with focal elevated pressures would maintain a thickened circular muscle above the proximal myotomy margin if these subjects underwent short (typically 3–4 cm myotomy in the esophagus[10,11]) or even standard length myotomy (typically 7–8 cm myotomy in the esophagus[11]). Without a personalized treatment approach, these patients may be at higher risk of treatment failure or adverse outcomes such as a blown out myotomy.[28] In our review of treatment outcomes in this sub-group, we found that all three patients with focal elevated pressures who underwent an extended, tailored myotomy had excellent outcomes. However, the majority of those who underwent treatment focused at the LES alone—two who underwent LHM and one who underwent PD—had poor resolution of symptoms and treatment failure. More studies are needed to evaluate outcomes specific to this sub-group.

This is the first-of-its-kind study examining sub-groups of type II achalasia utilizing well characterized comprehensive physiologic and radiographic data. There are limitations to consider. First is that simultaneous radiographic/physiologic and manometric measurements were not performed to definitively tell if the focal elevated pressures within the panesophageal pressure band represent lumen occluding contractions. However, based on BE contractions and FLIP contractions in response to distention, we hypothesize that these focal elevated pressures are suggestive of lumen narrowing (i.e., LOCs). Further, a majority of the HRIM tracings for FEPs demonstrated evidence of increased impedance by at least 500 ohms which also supports contact pressure and lumen closure.[4] Future studies should focus on simultaneously comparing imaging or physiologic studies with HRM data. Secondly, there were variations in diagnostic study performance rates among EUS, BE, and FLIP. These variations were not reflective of differences in manometric morphology or clinical features but relate to variations in clinical adherence and follow-up patterns which are unavoidable to predict. All data available was used for each patient, no data was censored or excluded. Another limitation pertains to smaller sample size of the sub-groups, which may reduce the power to make meaningful comparisons; nonetheless, several significant statistical differences were noted. Given the retrospective nature of data collection, we were unable to assess treatment outcomes in a rigorous fashion. Additionally, definitions for thickened circular muscle on EUS or severity of tertiary contractions on BE are not well established; to address this limitation we a priori established these definitions based on available literature and each manometry study was reviewed by two study team members. Lastly, FLIP measurements for this study were collected in real-time, and tracings

from data files were not re-reviewed. Future studies with evaluating specific FLIP metrics such as type of contractile response to distension are needed.

5 | CONCLUSION

We identified a distinct sub-group of type II achalasia on HRM, defined as type II achalasia with focal elevated pressures. Individuals with type II achalasia with focal elevated pressures were more likely, compared with those without focal elevated pressures, to have a thickened esophageal circular muscle on EUS, prominent tertiary contractions on BE, higher distensive pressure and contractility in response to distension on FLIP, and present with a higher burden of chest pain. This subset of type II achalasia patients with focal elevated pressures may represent a unique sub-group with spastic features and may benefit from personalized treatment approaches. More studies are needed to evaluate physiologic properties as well as treatment outcomes among patients with type II achalasia with focal elevated pressures.

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CONFLICT OF INTEREST

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Key Points

- Variable manometric patterns of type II achalasia have been observed on high resolution esophageal manometry, including focal elevated pressures (FEPs) which are characterized by focal or segmental pressures ≥70mmHg within the panesophageal pressure band.
- Type II achalasia with FEPs represent a distinct sub-group of type II achalasia which exhibit spastic features, akin to type III achalasia.
- Patients with type II achalasia with FEPs may therefore benefit from personalized treatment approaches.

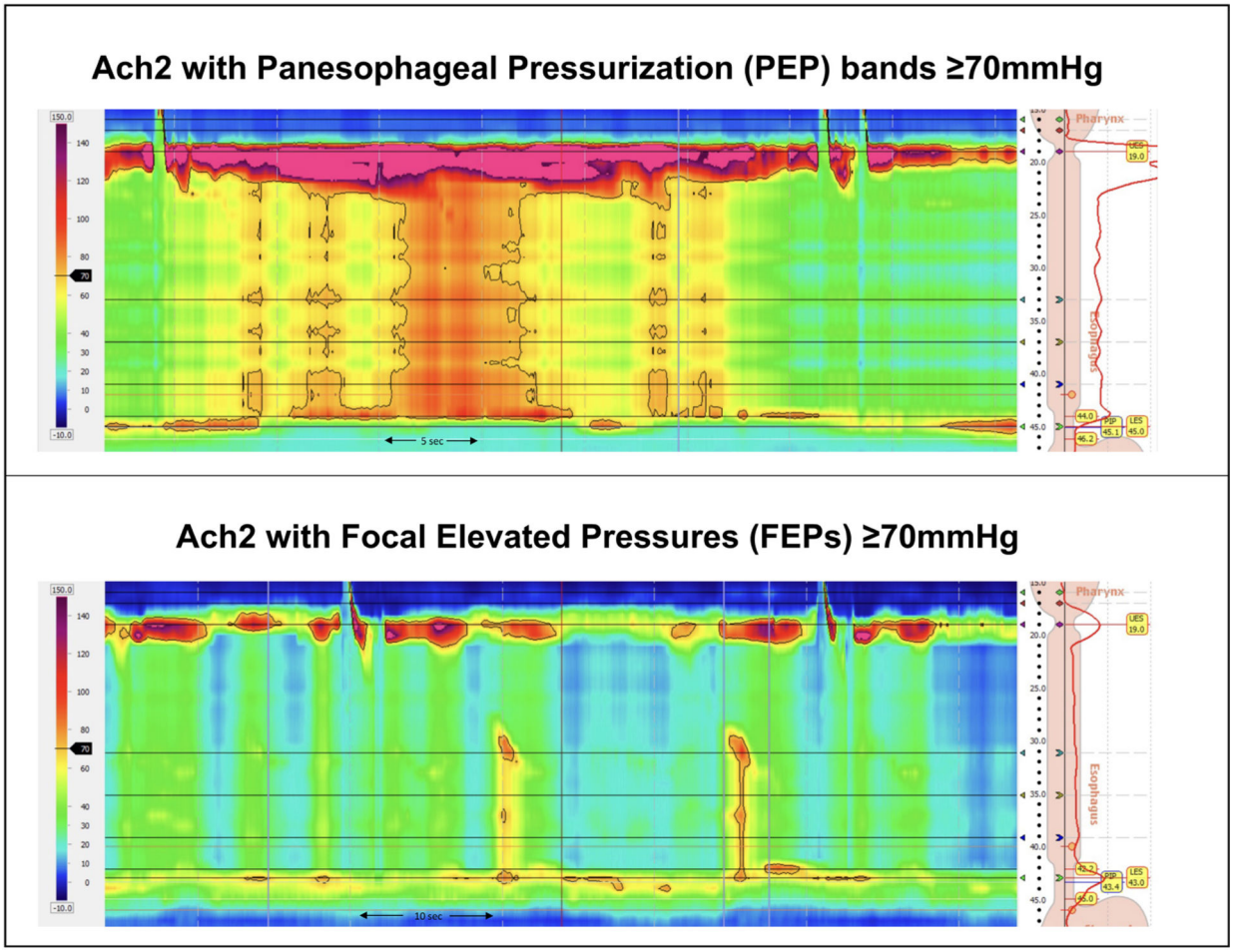

FIGURE 1.

Variable manometric features among type II achalasia patients. (1A) Panesophageal isobaric pressurization exceeding ≥70 mmHg are seen representing elevated panesophageal compression. (1B) Pressurization exceeding ≥70 mmHg are focal/segmental in the mid-to-distal esophageal body, representing focal elevated pressures (FEPs). The panesophageal pressurization exceeds 30 mmHg, however, is less than 70 mmHg, as is seen with the traditional compression pressures in type II achalasia

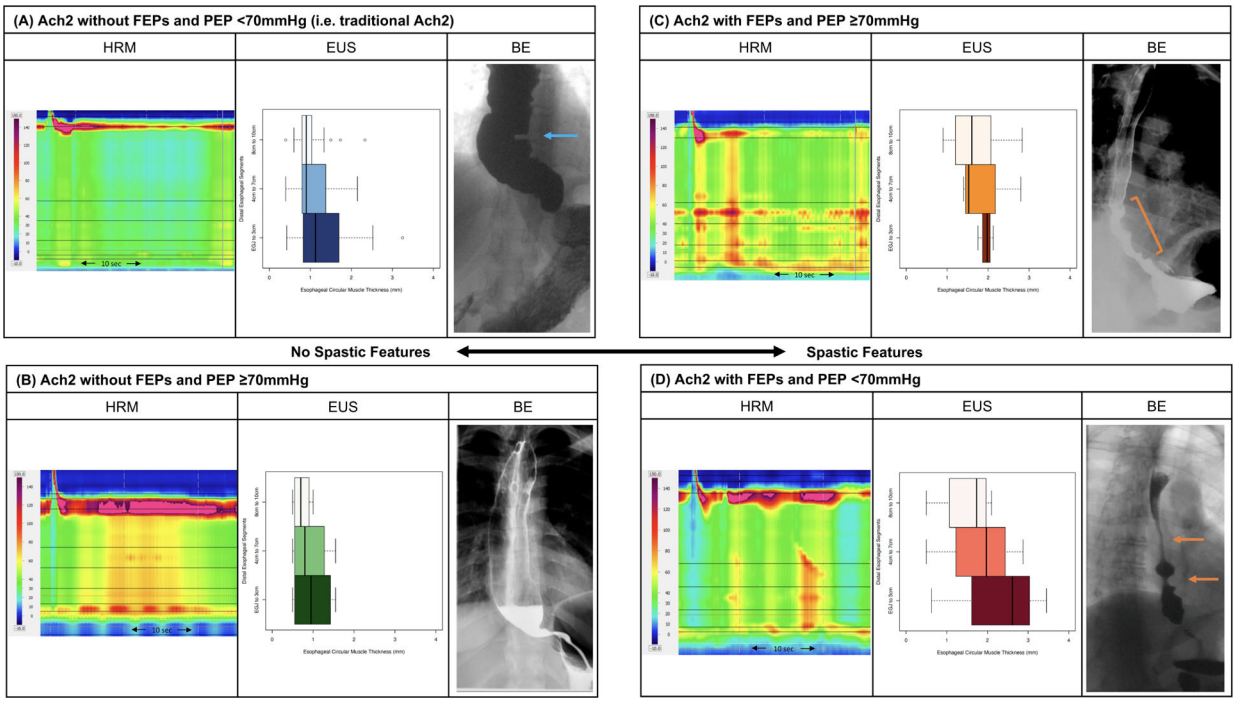

FIGURE 2.

Hypothesized Spectrum of Spastic Features Among Manometric Patterns of Type II Achalasia Examples of the four distinct manometric patterns of type II achalasia. Each panel displays an example of the characteristic HRM pattern, a violin plot depicting median circular muscle thickness (with interquartile range [box] and standard deviation [bars]) at three lengths from the EGJ as determined on EUS, and representative image on BE. (A) The HRM findings are representative of Ach2 without FEPs and PEP <70 mmHg. The violin plot shows a median circular muscle thickness of 1.1 mm from the EGJ to 3 cm proximal. This median thickness then remains <1 mm to the most proximal measured esophageal segment (four outliers were not shown on this plot). The BE example shows evidence of a mild tertiary contraction, characterized by a mild non-lumen obliterating distortion of the esophageal lumen (blue arrow). (B) The HRM findings are the representative of Ach2 without FEPs & PEP ≥70 mmHg. The violin plot shows a median circular muscle thickness <1 mm in all distal esophageal segments. The BE example shows no evidence of tertiary contractions. (C) The HRM findings are the representative of Ach2 with FEPs and PEP ≥70 mmHg. The violin plot shows a median circular muscle thickness of 2 mm from the EGJ to 3 cm proximal. The median muscle thickness then remains >1.5 mm to the most proximal measured segment. The BE example shows a non-dilated esophagus with moderate-to-severe tertiary contractions, characterized by significant curling of the esophageal lumen (orange bar). (D) The HRM findings are the representative of Ach2 with FEPs & PEP <70 mmHg. The violin plot shows a median circular muscle thickness of 2.6 mm from the EGJ to 3 cm proximal. The median muscle thickness then remains >1.7 mm to the most proximal measured segment. The BE example shows a non-dilated esophagus with moderate-to-severe tertiary contractions, characterized by near complete obliteration of the esophageal lumen (orange arrows)

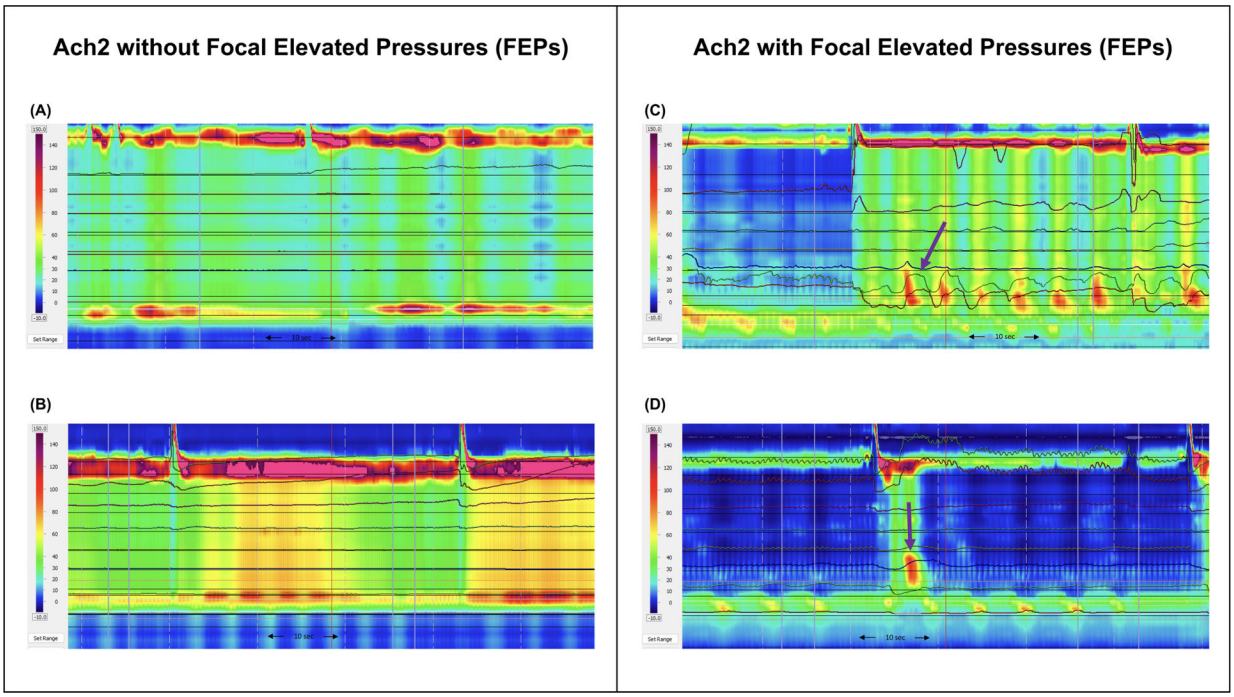

FIGURE 3.

Impedance Contour Tracings Imposed on Esophageal Pressure Topography for Type II Achalasia with and without Focal Elevated Pressures (FEPs) (A) and (B) HRM tracings are examples of type II achalasia without FEPs. In both examples, the impedance contour tracings show no change in the setting of panesophageal pressure (PEP) bands, which suggests an absence of esophageal luminal narrowing. (C) and (D) HRM tracings are examples of type II achalasia with FEPs. In both examples, the impedance contour tracings demonstrate an increase in impedance correlating to the FEPs (purple arrow). This may be suggestive of contact pressure on the catheter, and, therefore, lumen occluding contractions (LOCs)

TABLE 1

Demographic Characteristics

	(A) Ach2 without FEPs & PEP <70 (Traditional Ach2) *N* = 36	**(B) Ach2 without FEPs & PEP ≥70 *N* = 4**	**(C) Ach2 with FEPs & PEP ≥70 *N* = 8**	**(D) Ach2 with FEPs & PEP <70 *N* = 5**
Age (years), mean (SD)	55.3 (19.1)	40.3 (13.7)	59.4 (22.4)	57.2 (13.3)
Male Gender, *n (%)*	19 (52.8)	2 (50.0)	6 (75.0)	2 (40.0)
Hispanic Ethnicity, *n* (%)	13 (36.1)	3 (75.0)	4 (50.0)	1 (20.0)
Race, *n* (%)				
White	19 (52.8)	2 (50.0)	4 (50.0)	3 (60.0)
Black	3 (8.3)	1 (25.0)	0 (0)	0 (0)
Asian	2 (5.6)	0 (0)	0 (0)	0 (0)
Native Hawaiian or Other Pacific Islander	0 (0)	0 (0)	0 (0)	1 (20.0)
American Indian or Alaska Native	1 (2.8)	0 (0)	0 (0)	0 (0)
Other	11 (30.6)	1 (25.0)	4 (50.0)	1 (20.0)
BMI (kg/m^2), mean (SD)	25.3 (4.4)	23.1 (2.9)	25.8 (6.4)	28.2 (5.3)
Diabetes, *n* (%)	4 (11.1)	0 (0)	2 (25.0)	0 (0)
Opiate Exposure, *n* (%)	4 (11.1)	2 (100)	1 (12.5)	1 (20)
Eckardt Score, mean (SD)	6.3 (2.5)	7.8 (3.9)	8.0 (3.2)	7.2 (2.0)
Dysphagia[^]	2.5 (0.7)	2.8 (0.5)	2.6 (0.5)	2.6 (0.5)
Chest Pain[^]	0.6 (0.9)	1.5 (1.3)	1.6 (1.4)	1.0 (0)
Regurgitation[^]	1.5 (1.1)	1.8 (1.0)	2.0 (0.9)	1.8 (1.3)
Weight Loss[^]	1.7 (1.2)	1.8 (1.5)	1.8 (1.4)	1.8 (0.4)

Abbreviations: BMI, body mass index; SD, standard deviation.

% reflects the column percentage.

[^]Sub-category of the Eckardt score with a range of values from 0 to 3.

TABLE 2

Diagnostic Characteristics and Measurements

	(A) Ach2 without FEPs & PEP <70 (Traditional Ach2) *N = 36*	**(B) Ach2 without FEPs & PEP ≥70 *N = 4***	**(C) Ach2 with FEPs & PEP ≥70 *N = 8***	**(D) Ach2 with FEPs & PEP <70 *N* = 5**	***p*-Value**
Endoscopic Ultrasound	***n = 29***	***n = 4***	***N = 7***	***n = 4***	
Thickened Distal Esophagus, *n* (%)					
EGJ to 3 cm proximal	7 (24.1) $^{+}$	0 (0) $^{+}$	7 (100)	3 (75)	<0.0001 *
4 cm–7 cm proximal	4 (13.8) †	0 (0)	3 (42.9)	3 (75)	0.0013 *
8 cm–10 cm proximal	3 (10.3) $^{+,\dagger}$	0 (0)	4 (57.1)	3 (75)	0.0002 *
Circular Muscle Thickness in mm, mean (SD)					
EGJ to 3 cm proximal	1.4 (0.9)	1.0 (0.5)	2.0 (0.1)	2.3 (1.2)	0.07
4 cm–7 cm proximal	1.4 (1.2)	0.9 (0.5)	1.9 (0.5)	1.9 (1.0)	0.42
8 cm–10 cm proximal	1.1 (0.9)	0.8 (0.2)	1.7 (0.7)	1.6 (0.7)	0.16
Barium Esophagram	***n = 34***	***n = 3***	***n = 8***	***n = 5***	
Tertiary Contractions, *n* (%)	15 (44) $^{+,\dagger}$	2 (66.7)	8 (100)	5 (100)	0.0001 *
Moderate-to-Severe	1 (7.7)	0 (0)	6 (75)	4 (80)	
Mild	14 (93.3)	2 (100)	2 (25)	1 (20)	
High Resolution Manometry	***n = 36***	***n = 4***	***n = 8***	***n = 5***	
IRP (mmHg), mean (SD)	31.1 (8.4) $^{+}$	39.6 (5.4)	41.4 (12.8)	35.2 (11.5)	0.03 *
FLIP at 60 cc fill volume	***n = 21***	***n = 4***	***n = 4***	***n = 3***	
EGJ DI (mm^2/mmHg), mean (SD)	2.1 (0.9)	2.7 (0.4) $^{+,\dagger}$	1.0 (0.6)	0.9 (0.1)	0.005 *
EGJ Diameter (mm), mean (SD)	8.9 (1.5)	9.9 (0.4)	7.7 (2.8)	6.5 (1.1)	0.05
Pressure (mmHg), mean (SD)	31.4 (10.5) $^{+}$	28.8 (5.4) $^{+}$	62.7 (21.6)	45.7 (10.6)	0.0003 *
Contractility Present, *n* (%)	1 (4.8) $^{+,\dagger}$	0 (0) †	2 (50)	3 (100)	0.0001 *

*Statistically significant at alpha = 0.05 for overall group comparisons.

$^{+}$denotes statistically significant ($p < 0.05$) compared with Ach2 with FEPs & PEP ≥70.

†denotes statistically significant ($p < 0.05$) compared with Ach2 with FEPs and PEP <70.

TABLE 3

Demographic Characteristics Comparing Ach2 with and without focal elevated pressures (FEPs)

	Ach2 without FEPs *N* = 40	**Ach2 with FEPs *N* = 13**	***p*-value**
Age (years), mean (SD)	53.8 (19.1)	58.5 (18.7)	0.44
Male Gender, *n* (%)	21 (52.5)	8 (61.5)	0.57
Hispanic Ethnicity, *n* (%)	16 (40.0)	5 (38.5)	0.92
Race, *n* (%)			0.35
White	21 (52.5)	7 (53.9)	
Black	4 (10.0)	0 (0)	
Asian	2 (5.0)	0 (0)	
Native Hawaiian or Other Pacific Islander	0 (0)	1 (7.7)	
American Indian or Alaska Native	1 (2.5)	0 (0)	
Other	12 (30.0)	5 (38.5)	
BMI (kg/m^2), mean (SD)	25.0 (23.7)	26.7 (23.2)	0.27
Diabetes, *n* (%)	4 (10.0)	2 (15.4)	0.31
Opiate Exposure, *n* (%)	4 (10.0)	2 (15.4)	0.31
Eckardt Score, mean (SD)	6.5 (2.6)	7.7 (2.8)	0.16
Dysphagia[^]	2.5 (0.6)	2.6 (0.5)	0.70
Chest Pain[^]	0.7 (1.0)	1.4 (1.1)	0.03[*]
Regurgitation[^]	1.5 (1.0)	1.9 (1.0)	0.23
Weight Loss[^]	1.7 (1.2)	1.8 (1.1)	0.84

Abbreviations: BMI, body mass index; SD, standard deviation.

% reflects the column percentage.

[^]Sub-category of the Eckardt score with a range of values from 0 to 3.

[*]Statistically significant at an alpha = 0.05.

TABLE 4

Diagnostic Characteristics and Measurements Comparing Ach2 with and without Focal Elevated Pressures (FEPs)

	Ach2 without FEPs *N* = 40	**Ach2 with FEPs *N* = 13**	***p*-value**
Endoscopic Ultrasound	***n* = 33**	***n* = 11**	
Thickened Distal Esophagus, *n* (%)			
EGJ to 3 cm proximal	7 (21.2)	10 (90.9)	<0.0001*
4 cm–7 cm proximal	4 (12.1)	6 (54.6)	0.008*
8 cm–10 cm proximal	3 (9.1)	7 (63.6)	0.0007*
Circular Muscle Thickness in mm, mean (SD)			
EGJ to 3 cm proximal	1.4 (0.9)	2.1 (0.7)	0.02*
4 cm–7 cm proximal	1.3 (1.2)	1.9 (0.7)	0.14
8 cm–10 cm proximal	1.1 (0.8)	1.7 (0.7)	0.05
Barium Esophagram	***n* = 37**	***n* = 13**	
Tertiary Contractions, *n* (%)	17 (46.0)	13 (100)	0.0006*
Moderate-to-Severe	1	10	
Mild	16	3	
High Resolution Impedance Manometry	***n* = 40**	***n* = 13**	
IRP (mmHg), mean (SD)	32.0 (8.5)	39.1 (12.2)	0.02*
Impedance Increase, *n* (%)	2 (5)	8 (61.5)	<0.0001*
FLIP at 60 cc fill volume	***n* = 25**	***n* = 7**	
EGJ DI (mm^2/mmHg), mean (SD)	2.2 (0.9)	0.9 (0.4)	0.0008*
EGJ Diameter (mm), mean (SD)	9.0 (1.4)	7.2 (2.2)	0.01*
Pressure (mmHg), mean (SD)	31.0 (9.8)	55.4 (18.8)	0.01*
Contractility Present, *n* (%)	1 (4.0)	5 (71.4)	0.0006*

Abbreviations: EGD, esophagogastroduodenoscopy; EUS, endoscopic ultrasound; EGJ, esophagogastric junction; IRP, integrated relaxation pressure; DI, distensibility index.

% reflects the column percentage of those that underwent the specified diagnostic test.

*Statistically significant at an alpha = 0.05.