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Esophageal Distensibility as a Measure of Disease Severity in Patients with Eosinophilic Esophagitis

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Abstract

Background & Aims—The aim of this study was to assess whether measurements of esophageal distensibility, made by high-resolution impedance planimetry, correlated with important clinical outcomes in patients with eosinophilic esophagitis.

Methods—Seventy patients with eosinophilic esophagitis (50 male, ages 18–68) underwent endoscopy with esophageal biopsy collection and high-resolution impedance planimetry using the functional lumen-imaging probe. The patients were followed prospectively for an average of 9.2 months (range 3–14 months), and the risk of food impaction, requirement for dilation; symptom severity during the follow-up period was determined from medical records. Esophageal distensibility metrics and the severity of mucosal eosinophilia at baseline were compared between patients presenting with and without food impaction and those requiring or not requiring esophageal dilation. Logistic regression and stratification assessments were used to assess the predictive value of esophageal distensibility metrics in assessing risk of food impaction, the need for dilation, and continued symptoms.

Results—Patients with prior food impactions had significantly lower distensibility plateau (DP) values than those with solid food dysphagia alone. Additionally, patients sustaining food impaction and requiring esophageal dilation during the follow-up period had significantly lower DP values than those who did not. The severity of mucosal eosinophilia did not correlate with risk for food impaction, the requirement for dilation during follow up, or DP values.

Conclusions—Reduced esophageal distensibility predicts risk for food impaction and the requirement for esophageal dilation in patients with eosinophilic esophagitis. The severity of

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No financial interest for Frédéric Nicodème, Ikuo Hirano, Joan Chen, Kenika Robinson, Zhiyue Lin, Yinglian Xiao, Nirmala Gonsalves, Mary J Kwasny, Peter J Kahrilas, or John E Pandolfino.

Author contributions:

Zhiyue Lin contributed to the data analysis and interpretation, manuscript drafting, editing and final approval. Peter J. Kahrilas contributed to the conception and study design, data interpretation, manuscript drafting, editing, critical revision and final approval. Yinglian Xiao and Frédéric Nicodème contributed to data analysis and interpretation, and manuscript revision and final approval. Nirmala Gonsalves and Ikuo Hirano contributed to data collection and analysis, and final approval. John E. Pandolfino contributed to the conception and study design, obtained funding, data interpretation, manuscript editing, critical revision and final approval.

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mucosal eosinophilia was not predictive of these outcomes and had a poor correlation with esophageal distensibility.

Keywords

eosinophilic esophagitis; high resolution impedance planimetry; esophageal ; distensibility; functional luminal-imaging probe; dysphagia

INTRODUCTION

Eosinophilic esophagitis (EoE) is a disease of increasing prevalence ¹ possibly related to a higher incidence of allergic diseases and to a greater awareness in specific patient populations ^{2,3}. Patients present with a spectrum of esophageal symptoms ⁴, however, the dominant symptoms in adults are dysphagia, food impaction and, less commonly, chest pain ⁵. These symptoms are thought to result from the consequences of an allergic immune response that involves T-cell mediated hypersensitivity and IgE mediated pathways, leading to eosinophil activation with the consequence of tissue remodeling and fibrosis ⁶.

The current clinical paradigm for diagnosing and assessing EoE is focused on endoscopic biopsies. Specifically, the greatest observed density of eosinophils per high power field (/hpf) is used as a diagnostic test: patients with a positive biopsy (≥ 15 eosinophils /hpf) should receive a trial PPI and be biopsied again to affirm the diagnosis of EoE (second eosinophil count ≥ 15 /hpf). Patients with a density of eosinophils <15 /hpf after PPI therapy are categorized as PPI-responsive esophageal eosinophilia (PPI-R-EE). The density of eosinophils is also used as a clinical indicator of disease activity ². However, that approach largely ignores the dominant clinical and pathological feature of the disease, which is of luminal stiffening and narrowing associated with esophageal wall thickening ⁷, edema, fibrosis and stricture. Although endoscopic features are utilized to assess disease activity ⁸, the endoscopic assessment is hampered by poor reproducibility and an inability to directly measure abnormalities in esophageal wall biomechanics related to tissue remodeling. Recently, our group has refined a modified high-resolution impedance planimetry technique to quantify the pressure-geometry relationship in the esophagus ⁹. The functional lumen-imaging probe (FLIP) utilizes high-resolution impedance planimetry to render a 3-dimensional approximation of intraluminal esophageal anatomy during volumetric distention. Our initial results suggested that EoE patients had reduced esophageal distensibility compared to controls. However, we were unable to determine whether esophageal distensibility could inform clinical outcome and function as a biomarker of EoE disease activity.

Thus, the aim of this study was to assess whether esophageal distensibility metrics correlated with susceptibility to food impaction and/or the subsequent requirement for esophageal dilation during follow-up. In addition, we sought to compare esophageal distensibility to the severity of mucosal eosinophilia as an outcome measure by correlating each with symptom severity during follow-up clinical evaluation.

METHODS

Subjects

Seventy-seven patients (55 males, [18–68]), who presented to the Esophageal Center at Northwestern from July 2009 to May 2012 with food impaction, dysphagia, chest pain or heartburn and histology reporting ≥ 15 eosinophils/high power field (hpf – magnification 0.196 mm^2) ¹⁰, were enrolled to assess the biomechanical properties of the esophageal wall ⁹. After a trial of PPI therapy, a second endoscopy with repeated biopsies and high-

resolution impedance planimetry using the FLIP device was performed to classify the patients as EoE (eosinophil count $\geq 15/\text{hpf}$) or PPI-R-EE eosinophils $<15/\text{hpf}$). Each patient was cared for by one of the four esophagologists after the FLIP protocol and managed at that physician's discretion. Symptoms were assessed at 12-month follow-up (a shorter follow-up was utilized if patients required immediate intervention). None of the subjects had a history of gastrointestinal surgery or malignancy. A group of 10 normal controls underwent endoscopy to confirm lack of endoscopic findings consistent with EoE and FLIP protocol for comparison. The study protocol was approved by the Northwestern University Institutional Review Board and informed consent was obtained from each subject.

FLIP system

The FLIP assembly^{9,11,12} was built on a 240 cm long catheter with a 3-mm outer diameter. An infinitely compliant bag (up to a volume limit of 50 ml) sealed to the distal 14 cm of the probe was fabricated to assume a 10-cm long cylindrical shape between tapering ends. The minimal-to-maximal range of cross-sectional area (CSA) measurable was 10–491 mm². The 8 cm segment within the bag designed for impedance planimetry measurement was comprised of 16 ring electrodes spaced 5-mm apart. The assembly also contained a solid-state pressure transducer for determining intrabag pressure. Measurements were sampled at 10 Hz.

Study protocol

Subjects underwent endoscopy with a 9.9-mm outer diameter diagnostic gastroscope (Olympus® GIF type H180J, Olympus Corporation, Tokyo, Japan), in left lateral decubitus position to evaluate for EoE findings, esophagogastric junction (EGJ) location, and to help position the FLIP. Moderate sedation with 5–10 mg midazolam and 0–200 µg fentanyl was administered during the procedure. Still images taken during endoscopy were graded by a blinded investigator (JC) for the major EoE structural features of the grading system proposed by Hirano, et al.⁸. Ring score was graded 0 (none), 1 (mild for subtle circumferential ridges), 2 (moderate for distinct rings that do not impair passage of a standard diagnostic adult endoscope), or 3 (severe for distinct rings that do not permit passage of a diagnostic endoscope); Focal stricture score was graded 0 (absent) or 1 (present); Exudates score was graded 0 (none), 1 (mild for lesions involving $<10\%$ of the esophageal surface area), or 2 (severe for lesions involving $>10\%$ of the esophageal surface area); Furrows score was graded 0 (absent) or 1 (present).

After endoscopy, the FLIP probe was placed transorally across the EGJ⁹. Volume distension was performed to localize the EGJ and then position the FLIP with the distal recording site 3 cm proximal to the EGJ. Esophageal CSAs were measured during 2-ml stepwise distensions beginning with 2 ml and increasing to a maximum of 40 ml (each step recorded for 5–20 seconds). When measurements were interrupted by peristalsis, steps were prolonged or repeated. To prevent unintended dilation of a stiff or poorly compliant esophagus, the recording unit stopped infusing and displayed an alarm message if intrabag pressure exceeded 60 mmHg.

Once the FLIP protocol was completed, the catheter was removed and the endoscope was reintroduced to obtain biopsy specimens. At least 5 specimens were obtained in total from both the distal (at least 2 within 5 cm of the SCJ) and mid-proximal esophagus (at least 2 approximately 15 cm above the SCJ). In instances where there was significant disease activity in the proximal esophagus, biopsies were performed in the region extending from 11 cm above the mid-portion of the EGJ to 19 cm above the EGJ.

Data analysis

Distension volume, intrabag pressure, and 16 channels of impedance planimetry raw data were exported to MATLAB™ (The Math Works, Natick, MA) for analysis using a customized program with four functions: 1) Minimize vascular and respiratory artifacts using a median filter of the intrabag pressure, 2) Isolate the recording pressure between esophageal contractions using a nonlinear pulse detection technique, 3) Identify the distensibility plateau (DP) after modeling the esophageal distensibility from the pressure-CSA relationship with a polynomial regression method and extraction of the slope of the best-fit line of the initial phase of distention and curve fitting, and 4) Filter out signals related to respiration, vascular pulsation, and esophageal contractions using a wavelet decomposition of data.

Distensibility was plotted as a function of pressure for the narrowest CSA along the FLIP for each subject to derive three distensibility metrics: the distensibility slope (DS), and the DP. The values for each metric were compared to those calculated for a set of 10 previously reported control subjects⁹. The treating physicians were blinded to the distensibility data as this was independently assessed using a customized MATLAB program.

The primary endpoints of interest were: 1) history of food impaction at presentation confirmed by endoscopy, 2) occurrence of food impaction during follow up, 3) requirement for dilation during follow-up, and 4) symptom assessment at 12-month follow-up (or shorter follow-up if patients required immediate intervention). Two blinded investigators (KR/JC) graded symptoms retrospectively. Symptom outcome scores were presented as: 0-complete resolution with no change in therapy or food impaction, 1-mild improvement with no food impaction, 2-moderate symptoms (continued symptoms with intervention required), 3-severe symptoms and/or food impaction). The severity of mucosal eosinophilia was calculated as the average maximal eosinophil density from distal and proximal esophageal biopsies. Food impaction was defined based on patient report or the need for immediate endoscopy.

Statistical analysis

Results are presented as median and interquartile range. Clinical measures between groups were compared using Wilcoxon rank sum tests. Spearman's rank correlation was used to evaluate for significant association between eosinophil density, distensibility markers, and symptom severity at follow-up. Logistic Regression models were fit to determine which demographic or clinical measure best associated with a history of food impaction, sustained food impaction, need for dilation, and symptom severity at follow-up. Models were first fit with a stepwise procedure and then further examined after adjusting for potential confounders. Analyses were performed in SASv9.2 (Cary, NC) and were run at a type-I error rate of 5%.

RESULTS

Baseline clinical data

Seventy patients were included for analysis (4 patients had technically limited studies and 3 subjects were lost to follow-up). Baseline characteristics are shown in Table 1. All the patients had a trial of PPI therapy before the FLIP was performed. At the time of the second endoscopy with the FLIP procedure, 21 patients were noted to have <15 eosinophils/hpf in both the proximal and distal biopsy locations and classified as PPI-R-EE. The remaining 49 patients fitted criteria for the diagnosis of EoE².

Prior to the endoscopy with the FLIP protocol, 26 patients had a history of food impaction, 37 had dysphagia and no food impaction, 5 had chest pain alone and 2 had only heartburn. The majority of patients had endoscopic findings of EoE with rings and furrows being the most common findings (Table 1). The treatment after the PPI trial was variable: 10 discontinued PPI therapy, while 54 were on PPIs, 7 were on swallowed steroids, and 4 were on restricted diets. Of the patients with <15 eosinophils on both proximal and distal biopsies, 16 were on PPI therapy, 4 were on swallowed steroids and one patient was on diet restriction, PPI, and swallowed steroids.

Esophageal distensibility

Table 2 resumes esophageal distensibility metrics for normal controls and patients with PPI-R-EE and EoE. Comparisons of the distensibility curves are presented in Figure 1. Values for each metric were significantly less than for control subjects, but there was no significant difference between patients with and without abnormal eosinophilia (Figure 1A). There was no correlation between mean eosinophil density and DP ($r_s = -0.10$, $p=0.42$), or DS ($r_s = -0.02$, $p=0.89$). There was a correlation between ring score and DP ($r_s = -0.52$, $p<0.001$) and DS ($r_s = -0.33$, $p<0.001$). However, the range of DP among the ring scores was highly variable (Grade-0, [151–321] mm²; Grade-1 [185–247] mm²; Grade-2, [123–187] mm²; Grade-3 [70–106] mm²).

Clinical data and follow-up

Patients with a history of food impaction had significantly lower distensibility metrics, but no difference in eosinophil density, compared to those without (Table 2) (Figures 1B and 2A). The ring score was associated with a significant difference in food impaction rate at presentation (Grade-0, 0%; Grade-1, 22.5%; Grade-2, 47%; Grade-3, 100%). Interestingly, DP was significantly lower in patients with Grade-1 and Grade-2 ring scores ($p<0.001$ and $p<0.05$ respectively) who presented with food impaction compared to those without (Grade-1: 161 mm² [112–188] vs. 235 mm² [202–263]; Grade-2: 131 mm² [106–151] vs. 180 mm² [160–250]). Twelve patients had a food impaction during the follow-up period with seven requiring emergent endoscopy. DP for these patients was 152 mm² [101–193], significantly lower than those who didn't have a food impaction on follow-up (Figure 1B and 2B). There was no significant correlation between food impaction risk on follow-up and ring score.

Twenty-five patients had dilation (7 dilation only, 18 dilation with an additional change in medical therapy). These patients had significantly lower values for esophageal distensibility metrics, but no difference in eosinophil density, than those who did not. The association between the follow-up symptom score and distensibility metrics (DP, DS) was stronger than the association between the follow-up symptom score and eosinophil density (Table 2).

Predictors of outcome

When stepwise logistic models were fit to determine factors associated with a history of food impaction with possible predictors including age, gender, treatment type (including none), mean eosinophil density, DP, and DS, the only significant association that was found was with DP. Similarly, for food impaction occurring during follow-up, esophageal dilation within 12 months, and symptom severity at follow-up, DP was the only predictor of these events. Although demographics and eosinophil density were not predictive of any of these events, models were fit adjusting for these variables to assess the impact on the relationship between outcome and DP. The only relationship that was no longer significant after adjusting for potential covariates was symptom severity at follow-up (Table 3). Using stratified groups based on the distribution of observed DP values revealed that patients with a DP greater than 225 mm² were less likely to have a history of a food impaction or to

sustain one during follow-up. Additionally, these patients were also less likely to undergo esophageal dilation and less likely to be symptomatic at follow-up compared to the other groups (Table 4).

DISCUSSION

This study assessed whether measurements of esophageal distensibility with the FLIP during endoscopy correlated with clinically relevant outcomes in EoE patients. The major findings were that reduced esophageal distensibility ($DP < 225 \text{ mm}^2$) was associated with an increased risk of food impaction and requirement of esophageal dilation during a 4–12 month follow-up. Additionally, there was a relationship between DP and symptom score during follow-up suggesting that this parameter may have utility as an outcome measure. Another interesting finding was that baseline mucosal eosinophil density was not correlated with esophageal distensibility and that this histologic parameter did not appear to predict risk of food impaction or requirement of dilation during follow-up. DP was also a better predictor of food impaction risk than were endoscopy findings. Thus, these data suggest that an assessment of esophageal distensibility could complement the current clinical paradigm centered on histologic assessment of disease activity and potentially be utilized as a biomarker of fibrostenotic disease status in future clinical trials.

The FLIP utilizes high-resolution impedance planimetry^{9,12–14} to quantify the distensibility of the esophagus as a function of progressive increases in intraluminal diameter and was shown recently to be useful in predicting the effectiveness of achalasia treatments¹⁵. Although we previously reported that esophageal distensibility was reduced in EoE compared to control subjects⁹, there were no data correlating this measurement with important clinical outcome, such as food impaction, requirement for medical intervention or dilation, and symptom score. The current findings suggest that DP, in particular, is a much more robust predictor of complications than mucosal eosinophil density. Food impaction was an uncommon presentation or occurrence during follow-up when DP was greater than 225 mm^2 but very substantial if DP was less than 125 mm^2 . The 125 mm^2 threshold is interesting in that it correlates with the 12.5 mm barium tablet test (DP of 123 mm^2) as a target for treatment of rings and stricture¹⁶. However, our data also suggest that food impaction risk was still significant above the diameter of the barium tablet and that a reasonable target diameter may be closer to a DP of 225 mm^2 , corresponding to a diameter of 17 mm. However, prospective studies need to be performed in which esophageal distensibility is assessed before and after treatment before threshold values can be confidently defined.

The lack of reliable biomarkers and outcome measures has been a problem in the study and management of EoE. A recent FDA meeting highlighted this fact (<http://www.naspghan.org>). The current paradigm has been heavily reliant on endoscopy, histology, and patient recorded outcomes and each of these tools has some utility in assessing disease activity. However, the correlation between these measures and clinical outcome and dysphagia is unclear. Our findings suggest that mucosal eosinophil density was not associated with risk of food impaction and we hypothesize that this doesn't parallel the fibrostenotic consequences of the inflammatory cascade mediated by activated eosinophils. This could explain the disconnect between symptom outcome and mucosal eosinophil density in recent trials¹⁷ and suggests that the fibrostenotic changes leading to reduced esophageal distensibility are more resistant to medical therapies. Another consideration is that, once triggered, the fibrostenotic changes are independent of the inflammatory influences of activated eosinophils. Regardless, our findings suggest that esophageal distensibility may be helpful as an independent marker of symptom outcome to complement mucosal eosinophil density and patient reported outcomes. Thus, a shift in the management

paradigm toward a dual approach of treating and preventing inflammation coupled with a separate targeted approach focused on improving distensibility via mechanical or medical intervention could be more effective in improving outcomes in patients with esophageal eosinophilia.

Esophageal distensibility could potentially be assessed with other tools such as endoscopy, barostat distention, and fluoroscopy. However, these techniques would have major limitations. Endoscopy is useful in the context of an overt stricture and in assessing the pathognomonic features of EoE (rings, strictures, exudates), but is not capable of measuring compliance as the insufflation pressure cannot be controlled and measurement of luminal diameter is hindered by magnification. Barostat distention could provide a measure of compliance, but provides no assessment of regional variability, limiting its utility in EoE. Lee, et al.¹⁸ utilized fluoroscopy to assess esophageal diameter as a marker for disease activity before and after treatment: they reported that the esophageal lumen was narrowed in EoE patients, however, fluoroscopy provides only diameter measurements without corresponding pressure measurements making it unsuitable to assess the mechanical properties of the esophageal wall, possible with FLIP.

Although findings from this study suggest that esophageal distensibility may be useful in studying EoE, this study had limitations. The treatments were heterogeneous and follow-up was not according to a predefined protocol. Hence, we could not evaluate which therapy was most effective in improving distensibility. However, we were still able to determine the predictive value of esophageal distensibility after PPI therapy by controlling for these confounders in regression analyses and there was no evidence that therapy before or during follow-up had any predictive value. Additionally, the primary intent of the study focused on the mechanical properties of the esophagus in patients with esophageal eosinophilia and the endpoints of food impaction and requirement for esophageal dilation were objective and easily determined. Another limitation was that the symptom score utilized was not validated and the outcomes were obtained by a retrospective chart review. However, the investigators were blinded to the distensibility data and the symptom scoring was taken directly from the clinic notes by other blinded investigators.

In summary, we report that esophageal distensibility was associated with relevant clinical outcomes in EoE and that this measurement should be viewed as a potential biomarker worthy of further evaluation. Esophageal distensibility did not correlate with mucosal eosinophil density, suggesting that these two variables have independent roles in the pathogenesis of EoE and should be targeted separately to improve outcomes. Future prospective trials utilizing well-defined patient groups with a validated patient reported outcome are needed to further define the utility of measuring esophageal distensibility in EoE.

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Abbreviations

EoE	eosinophilic esophagitis
CSA	cross-sectional area
EGJ	esophagogastric junction

FLIP functional luminal imaging probe

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1A

1B

Figure 1.

Comparison of the modeled averaged distensibility curves for subject groups. Panel A compares normal subjects to EoE patients and PPI-R-EE patients. Panel B compares patients with and without food impaction at both presentation and follow up.

Figure 2.

Comparison of the individual DP values for patients with and without food impaction on presentation (A) and follow-up (B). Note that almost all of the patients with a food impaction had DPs less than 225 mm². Additionally, many patients who did not endorse food impaction on presentation or develop food impaction during follow-up despite having reduced distensibility. The two patients with the lowest DP values (circled) had food impactions on presentation, but did not have food impaction on follow-up due to observing a very restricted diet.

Table 1

Baseline data before intervention

Patient Characteristics	
Male n (%)	50 (71%)
Age-years, median (range)	38 (18–68)
Presenting Symptom n (%)	
Food impaction	26 (37%)
Dysphagia alone	37 (53%)
Chest Pain	5 (7%)
Heartburn	2 (3%)
Endoscopic findings[*] n (%) - may be multiple	
Rings:	66 (94%)
- Grade 1: mild	- 40 (57%)
- Grade 2: moderate	- 17 (24%)
- Grade 3: severe	- 9 (13%)
Focal Stricture (present):	34 (49%)
Exudates:	35 (50%)
- Grade 1: mild	- 31 (40%)
- Grade 2: severe	- 4 (6%)
Furrows:	56 (80%)
- Grade 1: mild	- 55 (79%)
- Grade 2: severe	- 1 (1%)
Primary treatment n (%) - may be multiple	
Discontinued PPI	10 (14%)
Continued PPI therapy,	54 (78%)
Swallowed topical steroids,	7 (10%)
Diet	4 (6%)

^{*} Endoscopic features were graded according to Hirano, et al.⁸

Table 2
Comparison of distensibility metrics and eosinophil density in subjects groups. Values given as Median [IQR].

		N	Distensibility plateau (DP) (mm ²)	Distensibility slope (DS) (mm ² /mmHg)	Eosinophil density (eosinophils/ hpf)
Normal Controls		10	308 [293–367]	11 [10–14]	-
	All patients	70	189 [140–240]*	4 [2–6]*	24 [5–45]
EoE		49	185 [130–239]*	4 [2–6]*	38 [23–50]
	PPI-R-EE	21	200 [150–262]*	6 [3–8]*	0 [0–3]
No impaction history	EoE	30	229 [183–250] §	5 [4–7] §	34 [22–47]
	PPI-R-EE	14	235 [190–300] §	7 [4–10] §	0 [0–2]
History of food impaction	EoE	19	113 [99–171]	2 [1–4]	40 [26–95]
	PPI-R-EE	7	110 [100–165]	3 [1–5]	0 [0–5]
No food impaction during follow-up	EoE	38	210 [148–243] §	5 [3–6] §	36 [20–52]
	PPI-R-EE	20	194 [150–270]	5 [3–9]	0 [0–2]
Food impaction during follow-up	EoE	11	145 [103–185]	3 [1–4]	38 [25–50]
	PPI-R-EE	1	230	7	7
No dilation	EoE	32	210 [142–246]	4 [3–6]	35 [20–46]
	PPI-R-EE	13	240 [175–301] §	6 [5–10] §	0 [0–1]
Dilation	EoE	17	172 [113–210]	3 [2–5]	40 [23–79]
	PPI-R-EE	8	135 [100–191]	3 [1–6]	1 [0–6]
Symptom score: Spearman correlation	All	70	–0.303 §	–0.379 §	0.239 §

PPI-R-EE, PPI responsive esophageal eosinophilia

Wilcoxon rank sum test used.

* Different with normal

§ Difference between subgroups

Table 3Odds ratios for 10 mm² change in DP for each variable

Outcome	Univariate OR (95%CI)	Adjusted OR (95% CI)
History of food impaction	0.38 (0.24, 0.60)	0.37 (0.23, 0.59)
Food impaction during follow-up	0.73 (0.56, 0.95)	0.73 (0.56, 0.96)
Esophageal dilation	0.76 (0.62, 0.93)	0.78 (0.63, 0.96)
12-month symptom severity	0.81 (0.68, 0.98)	0.83 (0.69, 1.01)

* Model adjusted for age, gender, and mean eosinophil count

Table 4

Stratified analysis of 3 groups based on distensibility plateau: Compare mean eosinophil count, risk of food impaction, food impaction on f/u, need for intervention, and symptom score between the groups.

Distensibility Plateau range	History of food impaction	Food impaction during follow-up	Esophageal dilation during follow-up	Symptomatic at 12 months
0–125 mm ²	12 (94%)	6 (38%)	10 (63%)	12 (75%)
126–225 mm ² ,	11 (35%)	5 (16%)	10 (32%)	18 (58%)
> 225 mm ²	0 (0%)	1 (4%)	5 (22%)	10 (43%)
Cochran-Armitage trend p-value	<0.001	0.008	0.011	0.050