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ORIGINAL ARTICLE

Eosinophilic Esophagitis Histologic Scoring System: Correlation with Histologic, Endoscopic, and Symptomatic Disease and Clinical Use

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Abstract

Background The eosinophilic esophagitis histologic scoring system (EoEHSS) was developed to enhance the diagnostic standard of peak eosinophil count (PEC) in evaluating disease activity in EoE.

Aims (1) Correlate the EoEHSS and PEC to measures of symptomatic and endoscopic disease activity, (2) Correlate EoEHSS grade and stage subcomponents to clinical, radiology, and endoscopic markers of fibrotic disease, (3) Evaluate EoEHSS remission in asymptomatic patients with PEC < 15 eosinophils per high powered field (eos/hpf).

Methods Secondary analysis of prospective cohort data of 22 patients with EoE that underwent dietary therapy and endoscopy at 3 time points. Active disease was defined by EoEHSS grade or stage > 0.125, symptomatic disease by EoE symptom activity index > 20, endoscopic disease by endoscopic reference score > 2, and histologic disease by PEC ≥ 15 eos/hpf. EoEHSS remission was defined by esophageal inflammation (EI) grade of 0–1, EI stage of 0, total grade ≤ 3, and total stage ≤ 3.

Results EoEHSS grade and stage did not correlate with symptomatic disease but did with endoscopic and histologic disease. PEC showed similar correlation pattern. Abnormal grade and stage had strong sensitivity (87–100%) but poor specificity (11–36%) to detect symptomatic, endoscopic, and histologic disease activity. Lamina propria fibrosis was evaluated in 36% of biopsies and did not correlate with minimum esophageal diameter. Out of 14 patients who were in complete symptomatic, endoscopic, and histologic remission, 8 met criteria for EoEHSS remission.

Conclusion The positive and negative correlations of EoEHSS to specific measures of symptomatic, histologic, and endoscopic activity suggest that it provides complementary information in EoE.

Keywords Eosinophilic esophagitis · Eosinophilic esophagitis histologic scoring system · Peak eosinophil count · Six food elimination diet

Abbreviations

EoE	Eosinophilic esophagitis
EESAI	Eosinophilic esophagitis symptom activity index
EREFS	Eosinophilic endoscopic reference score
EoEHSS	Eosinophilic esophagitis histologic scoring system
PEC	Peak eosinophil count
SFED	Six food elimination diet
FED	Food elimination diet
PPI	Proton pump inhibitor
GERD	Gastroesophageal disease
HPF	High powered field
PRO	Patient reported outcomes

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VDQ Visual dysphagia questionnaire
AMS Avoidance, modification, slow-eating score

Introduction

Eosinophilic esophagitis (EoE) has been associated with multiple histologic findings, with the peak eosinophil count (PEC) considered most characteristic. However, PEC correlation with symptoms and endoscopic findings in EoE has been inconsistent. A novel eosinophilic esophagitis histologic scoring system (EoEHSS) was developed by Collins et al. which consider a variety of histologic features of EoE in addition to the PEC which better allows for evaluation of both severity and extent of EoE [1]. These features are given a grade (degree of activity) and stage (degree of specimen involved) and scored 0–3. The EoEHSS has been shown to correlate well with the PEC and has very good inter and intrareader consistency [2] Correlation of EoEHSS with endoscopic and symptomatic response has been modest [3, 4].

It has been proposed that remission can be defined by the EoEHSS as a peak eosinophil count of < 15 eosinophils/hpf, and total grade and stage scores ≤ 3 [5]. This definition of remission has not been thoroughly evaluated. Furthermore, it has been suggested that EoEHSS features of lamina propria fibrosis, basal zone hyperplasia, surface epithelial alterations, and dyskeratotic epithelial cells are markers of disease severity [6]. Whether these features correlate with clinical, radiologic, and endoscopic indicators of fibrotic disease has not yet been evaluated.

We recently published a trial in which an esophageal cytosponge was used to evaluate dietary therapy in EoE. Participants were evaluated at 3 time points: before the six-food elimination diet (SFED), after remission on the SFED, and after food reintroduction with EGD and biopsy. We sought to utilize this existing cohort to evaluate the EoEHSS on the pathology specimens of this group. We aimed to (1) correlate the EoEHSS and PEC to measures of symptomatic and endoscopic disease activity, (2) evaluate EoEHSS remission scores in asymptomatic patients with peak eosinophil count (PEC) < 15 eos/hpf, and (3) evaluate the ability of EoEHSS grade and stage subcomponents to predict esophageal narrowing.

Methods

Study Design and Study Participants

This study was performed as a secondary analysis of prospective cohort data which involved cytosponge directed food reintroduction in patients responsive to a 6–8 food elimination diet (FED) [7]. The study was approved by the Mayo Foundation Institutional Review Board IRB #15-004741 on 10/29/2015. All subjects provided written informed consent. Subjects were prospectively recruited from the Esophageal Clinic at Mayo Clinic Rochester between 1/1/2016 and 12/31/2018 where they were seen by one of three providers (JA, DK, KR). All subjects were between 18 and 65 years of age, had dysphagia, and an esophageal biopsy showing a PEC of ≥ 15 eos/hpf after 8 weeks of twice daily PPI therapy indicating PPI nonresponsive disease. Patients with an esophageal stricture precluding passage of a 9–10 mm endoscope, an esophageal mass, or LA grade C or D esophagitis at endoscopy were excluded. Steady dose PPI medications were continued only when used to treat coexistent gastroesophageal reflux (GERD). Esophageal dilation was performed as part of clinical management only prior to the pre-SFED endoscopy and biopsy. All authors had access to the study data and reviewed and approved the final manuscript.

Endoscopy

All pre- and post-SFED endoscopies were performed by Mayo staff or fellows with a staff gastroenterologist in attendance. Biopsies were obtained with biopsy cable with open forceps size of 7 mm from the distal, mid, and proximal esophagus and placed in the same bottle. All endoscopies following completion of the food reintroduction protocol were performed by one author (JA). EoE endoscopic reference score (EREFS) was calculated [8]. We considered an EREFS > 2 to be active disease. The inflammatory EREFS was evaluated separately for the presence of edema, exudates, and furrows with a total possible score of 0–3 [4].

Histology

EoEHSS was not evaluated as part of primary study, and slides were re-read for the purpose of this study [7]. All patients had a total of 8 biopsies per endoscopy with at least 2 specimens obtained within 4 cm of the squamocolumnar junction. All pathology slides were reviewed by a single-expert GI pathologist (MC). The area of greatest eosinophil density under medium (200X) power was determined, and generally multiple high-power fields were examined to determine a peak eosinophil count (400X, 0.3 mm^2). The peak eosinophil count per HPF was reported from the area of greatest eosinophil density. A peak eosinophil count of ≥ 15 eos/hpf defined active histologic disease. All specimens were graded 0–3 and staged 0–3 with 0 indicating the absence of the feature and 3 indicating the most severe form of the feature or the greatest extent of the feature, for multiple histologic features of the EoEHSS. The EoEHSS has been well defined in previous publications [1]. In

summary, 8 histologic features are graded and staged from 0 to 3: esophageal inflammation (EI), basal zone hyperplasia (BZH), eosinophil abscess (EA), eosinophil surface layering (ESL), dilated intracellular spaces (DIS), dyskeratotic epithelial cells (DEC), surface epithelial alterations (SEA), and lamina propria fibrosis (LPF). The grade and stage were calculated as the mean over the 8 feature scores. If the sample was inadequate for evaluation of lamina propria fibrosis, the mean was based on the 7 remaining features. Histology remission was defined as grade score ≤ 0.125 (score for eosinophil inflammation must be ≤ 1), and stage score ≤ 0.125 (score for eosinophil inflammation must $= 0$) [5].

Symptom Assessment

The Eosinophilic Esophagitis Symptom Activity Index with Patient Reported Outcomes (EESAI PRO) instrument was used, and cutoff of > 20 indicated active symptoms [9].

Radiographic Assessment

The minimal esophageal diameter was measured at a structured barium esophagram. All esophagrams were performed prior to Mayo esophageal dilation. The specifics of the technique have been previously well described [10]. We considered an esophageal minimal diameter of < 15 mm to be abnormal and representing esophageal fibrosis.

Study Timeline

All patients underwent EGD with biopsies at 3 time points: (1) pre-SFED, (2) after response to SFED or extended SFED, and (3) after food reintroduction. Symptom scores (EESAI), endoscopic score (EREFS), and EoEHSS were evaluated at all three time points.

Statistical Analysis

The analytical dataset consisted of 66 observations: 22 subjects with 3 instances of measurement as described above. For bivariate analyses of continuous data, R^2 was used to quantify the strength of the relationship and scatterplots were used to visualize the association. For bivariate analyses of discrete data, Tjur's pseudo-R^2 was used to quantify the strength of the relationship [11]. P values were based on mixed effects models with a random effect for each subject modeled to account for the correlation of observations within each subject. In addition, P values within analyses groups were adjusted for multiple tests using Hochberg's step-up method [12]. The groups used for Hochberg corrections were the following bivariate analyses: EoEHSS with EESAI, EoEHSS with EREF, EoEHSS with PEC, EESAI and EREF with PEC, and EoEHSS with esophageal diameter.

Results

Demographics

The patient demographics are summarized in Table 1. The patient cohort was majority female (55%) with a mean age of 40 years and a large proportion had seasonal allergies (64%), heartburn (46%), and regurgitation (55%). In addition, most patients had a history of food impaction and esophageal dilation (73%). There was a general trend consistent with diffuse narrowing of the esophagus with mean minimum diameter of 13 mm (normal > 15) and mean maximum diameter of 20 mm (normal > 20 mm).

Esophageal dilation was performed in 16 of the 22 (72.7%) patients with 15 of those 16 (93.8%) dilations occurring during index endoscopy and 1 occurring before enrollment. The 16 patients that were dilated had minimum diameter ranging from 7 to 15 mm. The 6 patients that were not dilated had minimum esophageal diameter ranging from 15 to 20 mm.

Correlation Between EoEHSS and Disease Activity

EoEHSS was compared to alternative measures of disease activity including symptoms (EESAI), endoscopic findings (EREFS), and histology (PEC). EoEHSS grade and

Table 1 Demographics

	Overall ($N = 22$)
Age	
Median (Q1, Q3)	40.5 (31.2, 50.5)
Mean (SD)	40.3 (10.9)
Women	12 (55%)
Seasonal allergies	14 (646%)
Asthma	5 (23%)
Eczema	3 (14%)
Any allergy	16 (73%)
Heartburn	10 (45%)
Regurgitation	12 (55%)
Hx of food impaction	16 (73%)
Hx of ER food removal	7 (32%)
Max. esophageal diameter	
Median (Q1, Q3)	20 (16, 22)
Mean (SD)	19.6 (4.5)
Min. esophageal diameter	
Median (Q1, Q3)	12 (10, 15)
Mean (SD)	12.9 (3.7)

stage > 0.125 had high sensitivity of 91.3% and 87.0% for detecting active symptomatic disease by EESAI. There were 27 patient cases of symptomatic remission with EESAI ≤ 20. Of these 27, only 6 were in remission by EoEHSS grade (specificity 22%) and 3 were in remission by EoEHSS stage (specificity 11%). EoEHSS grade was evaluated as continuous and dichotomous variable and showed weak positive association ($R^2 = 0.051$ [continuous], 0.033 [dichotomous]) with EESAI that was nonsignificant ($P = 0.33$) (Fig. 1a). EoEHSS stage similarly had weak positive correlation to EESAI as a continuous ($R^2 = 0.010$) and dichotomous ($R^2 = 0.002$) variable that was nonsignificant ($P = 0.68$) (Fig. 1b).

EoEHSS grade and stage were similarly compared with the EREFS score. All 20 cases that demonstrated endoscopically active disease (EREFS > 2) had active disease by EoEHSS grade and stage (100% sensitivity). In evaluating endoscopic remission, 40 cases had EREFS < 2 and of those

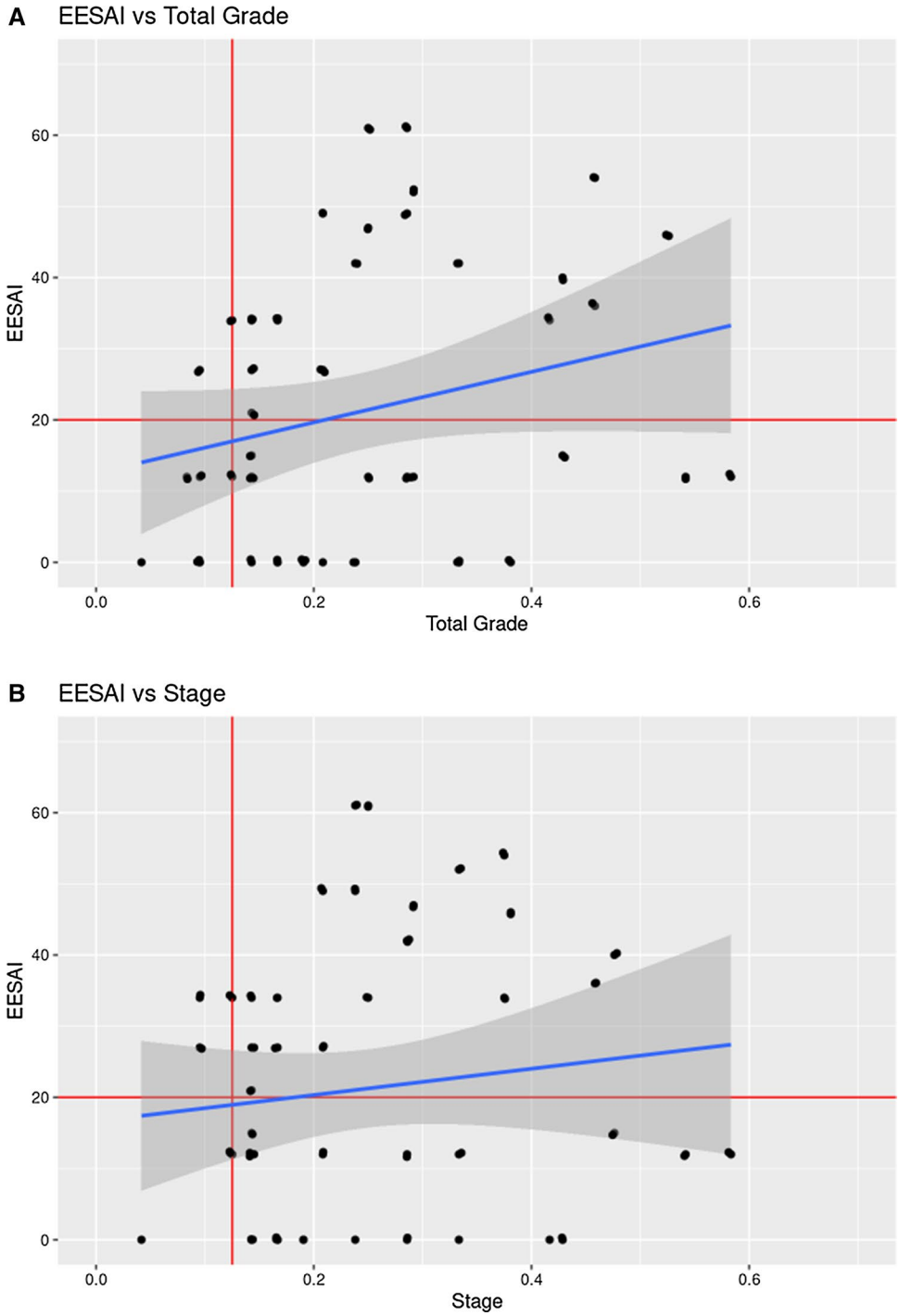

Fig. 1 **a** EoEHSS grade vs. EESAI. Weak positive correlation ($R^2 = 0.051$) denoted by blue line that was nonsignificant ($P = 0.33$) with gray crossing *x*-axis. **b** EoEHSS stage vs. EESAI. Weak positive correlation ($R^2 = 0.010$) denoted by blue line that was nonsignificant ($P = 0.68$) with gray crossing *x*-axis

only 10 had remission by EoEHSS grade (specificity 25%) and 8 by stage (specificity 20%). EoEHSS grade had a modest positive correlation to EREFS ($R^2 = 0.194$, $P = 0.003$; Fig. 2a) as did stage ($R^2 = 0.167$, P = 0.002) (Fig. 2b).

Lastly, EoEHSS grade and stage were evaluated in comparison to PEC. All 33 cases of histologically active disease defined by PEC ≥ 15 eos/hpf had active disease by EoEHSS grade and stage (100% sensitivity). There were 33 cases of histologic remission based on a PEC < 15 eos/hpf and of those 12 were in remission by EoEHSS grade (specificity 36%) and 10 by stage (specificity 30%). When evaluated as a continuous variable, EoEHSS grade and stage showed strong positive correlation ($R^2 = 0.602$, 0.600; both $P < 0.001$) with PEC (Fig. 3a and b).

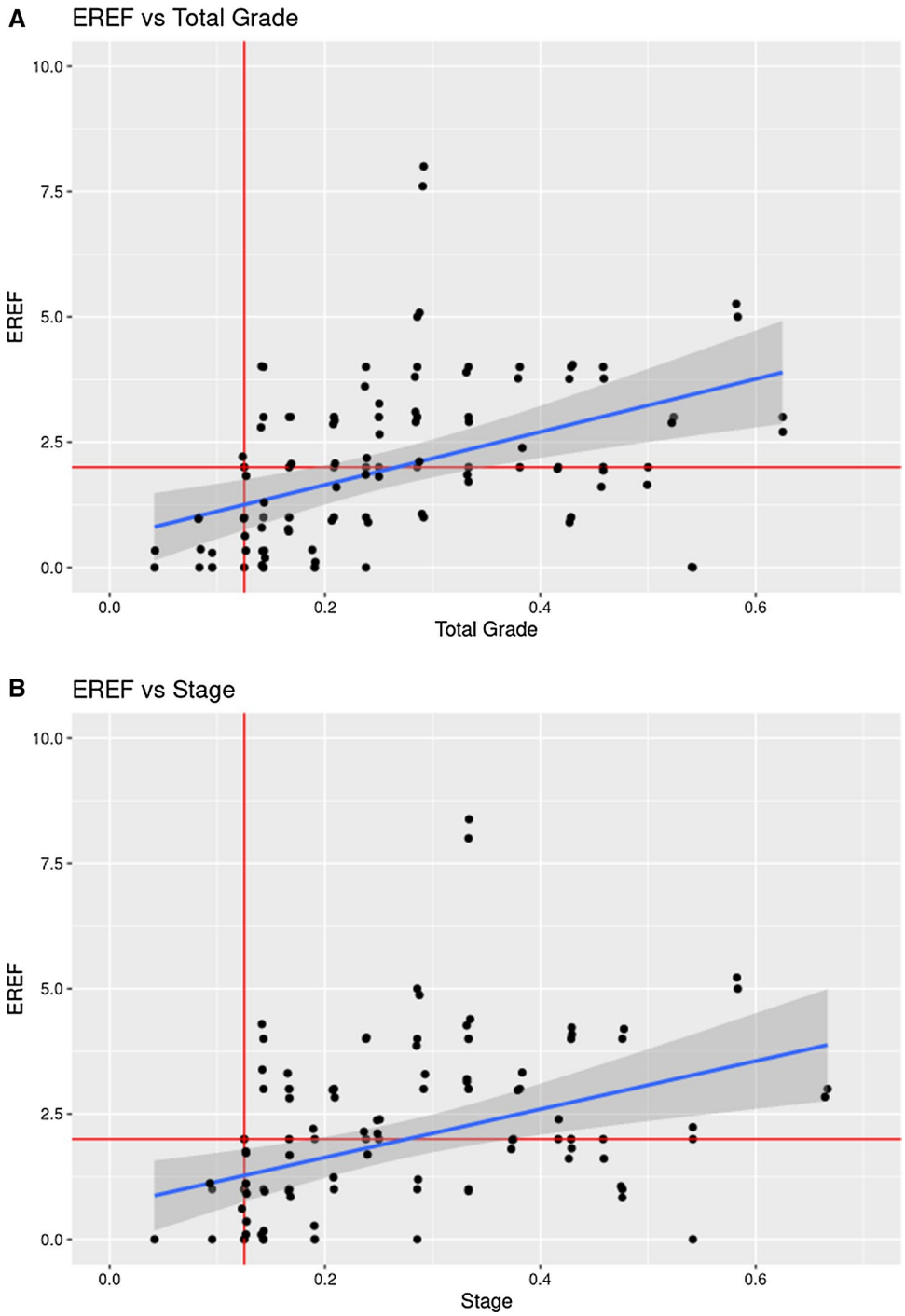

Fig. 2 **a** EoEHSS grade vs. EREFS. Modest positive correlation ($R^2 = 0.194$) denoted by blue line that was significant ($P = 0.003$). **b** EoEHSS stage vs. EREFS. Modest positive correlation ($R^2 = 0.167$) denoted by blue line that was significant ($P = 0.002$)

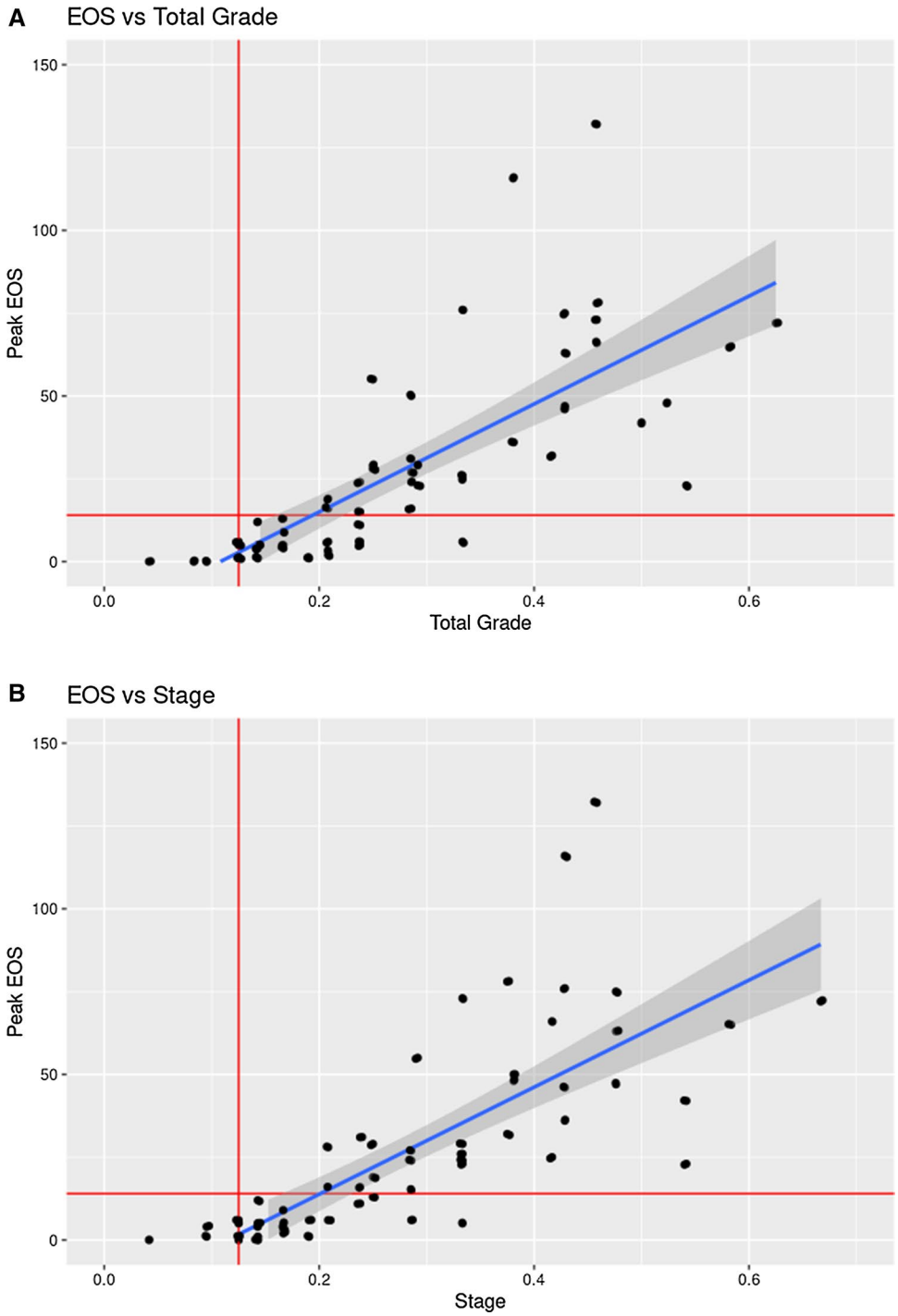

Fig. 3 **a** EoEHSS grade vs. PEC. Strong positive correlation ($R^2 = 0.602$) denoted by blue line that was significant ($P < 0.001$). **b** EoEHSS stage vs. PEC. Strong positive correlation ($R^2 = 0.600$) denoted by blue line that was significant ($P < 0.001$)

Correlation Between PEC and Disease Activity

When comparing EREFS to PEC, of the 20 patients with endoscopically active disease, 15 had histologic disease (75% sensitivity). Of the 40 patients in endoscopic remission, only 23 were in histologic remission (specificity 58%) based on PEC. There were 23 cases of symptomatic disease with EESAI > 20, with 12 histologically active based on PEC (sensitivity 52%). Of the 27 patients in symptomatic remission, 16 of them were in histologic remission by PEC (specificity 59%). PEC had modest correlation with EREFS ($R^2 = 0.1$, $P = 0.009$; Fig. 4a) and weak correlation with EESAI ($R^2 = 0.08$, $P = 0.22$; Fig. 4b).

Evaluation of EoEHSS in Patients in Remission

We also evaluated how frequently remission based on EoEHSS occurred at each of the 3 timepoints of the study. At

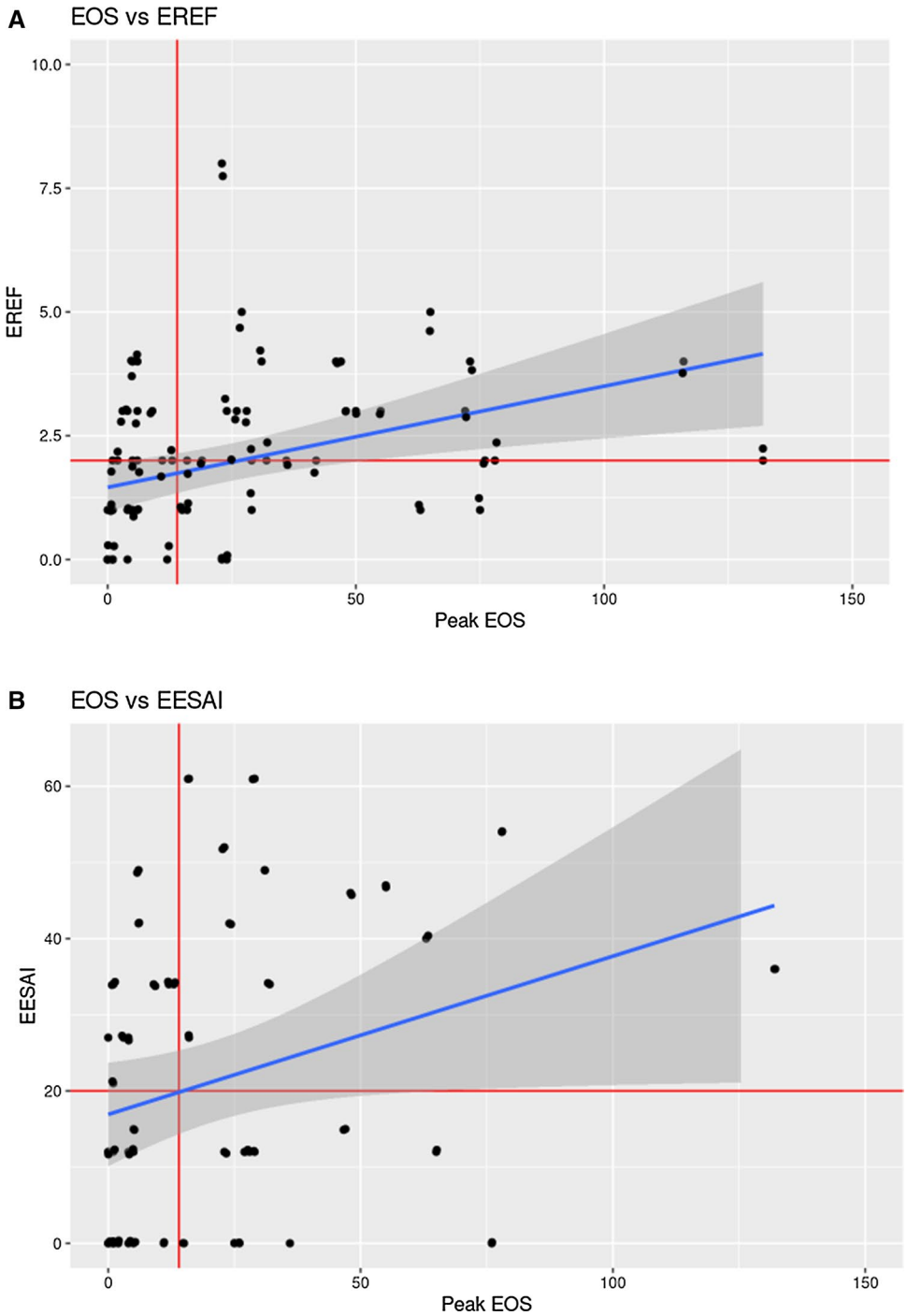

Fig. 4 **a** PEC vs. EREFS. Modest positive correlation ($R^2 = 0.1$) denoted by blue line that was significant ($P = 0.009$). **b** PEC vs. EESAI. Modest positive correlation ($R^2 = 0.08$) denoted by blue line that was non-significant ($P = 0.22$)

pre-SFED, no patients were in remission based on EoEHSS. At post-SFED, 14 patients (64%) were in EoEHSS remission. Of those 14, all were in histologic remission based on PEC, 13/14 (93%) were in endoscopic remission based on EREFS, and 9/14 (64%) were in symptomatic remission based on EESAI. Lastly at the 4-week timepoint, 6 (30%) patients were in remission based on EoEHSS, with all 6 being in histologic remission based on PEC and 5/6 (83%) in endoscopic and symptomatic remission based on EREFS and EESAI, respectively.

There were 14 cases of complete histologic, endoscopic, symptomatic remission across all 3 study timepoints, with 8 (57.1%) being at the post-SFED timepoint and 6 (42.9%) at 4 weeks post-food reintroduction. Of the 14 cases of complete remission, 6 (43%) did not meet criteria for EoEHSS remission. When the subcomponent of dilated intracellular

spaces was excluded from the grade and stage, all 14 cases met EoEHSS remission criteria.

EoEHSS Subcomponents and Esophageal Narrowing/ Fibrostenotic Disease

Correlation of EoEHSS grade and stage as well as the subcomponents to minimum esophageal diameter and presence of a narrow caliber esophagus (defined as minimum diameter < 15 mm by structured esophagram) was assessed. LPF could only be evaluated in 38% of biopsies. LPF and EoEHSS grade and stage showed essentially no correlation to minimum esophageal diameter with R^2 0.002 and 0.006, respectively ($P = 0.97$). Table 2 displays correlation between EoEHSS grade and stage subcomponents and narrow caliber esophagus. BZH correlated poorly with narrow caliber esophagus with R^2 0.007 and 0.002, respectively, and $P = 0.97$. Correlation with DEC could not be evaluated while SEA did not correlate with a narrow caliber esophagus (R^2 0.02 and 0.05, $P = 0.97$). The component of ESL within stage showed a weak correlation with the presence of a narrow caliber esophagus (R^2 0.25, OR 12.8) but did not reach statistical significance ($P = 0.55$) (Fig. 5). Similarly, the component of ESL within grade also demonstrated weak correlation with narrow caliber esophagus (R^2 0.21, OR 2.5) and did not reach statistical significance ($P = 0.97$) (Fig. 5). Consequently, with each point from 0 to 3 given to a patient case in the subcategory of surface layering within EoEHSS stage, the patient is 12.8 × more likely to have a narrowed esophagus.

Comparison of the 4 proposed subcomponents that may relate to or predict esophageal narrowing (LPF, BZH, DEC, and SEA) was made to clinical and endoscopic indicators of fibrotic disease (history of food impaction, history of ER removal, and prior esophageal dilation). Of the 22 patients, 16 underwent esophageal dilation prior to the current study. When correlating subcomponents with dilation, all had weak and nonsignificant correlation, with grade LPF having strongest correlation ($R^2 = 0.03$, $P = 0.95$). The same trend was seen with ER removal, and grade/stage LPF had strongest correlation ($R^2 = 0.13$, $P = 0.99$). When evaluating subcomponents in patients that reported food stuck > 5 min, grade SEA had strongest correlation ($R^2 = 0.24$, $P = 0.36$) (Table 3).

We also examined whether EoEHSS grade and stage as well as LPF correlated with endoscopic disease, specifically rings and strictures from EREFS. Of the 66 patient cases evaluated, there were 9 cases of moderate–severe rings (grade 2–3) and 10 cases of stricture with 2 overlapping yielding 17 cases of moderate–severe rings or stricture. Of those 17, 15 (88%) had active disease by EoEHSS grade and stage. LPF could be evaluated in 24 cases overall with 6 cases of LPF 1–3 by grade or stage. Of those 6, we observed grade 2–3 rings or stricture in 2 cases (33%).

Discussion

This study evaluated the EoEHSS in a group of 22 patients with 66 total EGDs undergoing dietary therapy for EoE. Patients were evaluated for symptomatic and endoscopic

Table 2 EoEHSS grade and stage subcomponents vs minimum esophageal diameter and narrowed esophagus (minimum diameter < 15 mm)

Response	Explanatory	*R*-squared	Odds ratio	*P* value
Min Diam	LP Fibrosis (grade)	0.002	1.224	0.967
Min Diam	LP Fibrosis (stage)	0.006	1.229	0.967
Min Diam < 15	LP Fibrosis (grade)	0.072	2.550	0.967
Min Diam < 15	LP Fibrosis (stage)	0.057	1.621	0.967
Min Diam < 15	Stage basal cell (grade)	0.007	1.263	0.967
Min Diam < 15	Peak EOS (grade)	0	0.920	0.967
Min Diam < 15	Abscess (grade)	0.001	0.889	0.967
Min Diam < 15	Surface layering (grade)	0.213	2.454	0.967
Min Diam < 15	DIS (grade)	NA	NA	NA
Min Diam < 15	Surface alteration (grade)	0.049	1.978	0.967
Min Diam < 15	Apoptotic epith cells (grade)	NA	NA	NA
Min Diam < 15	Stage basal cell (stage)	0.002	1.121	0.967
Min Diam < 15	Peak EOS (stage)	0.004	1.155	0.967
Min Diam < 15	Abscess (stage)	0.001	0.889	0.967
Min Diam < 15	Surface layer (stage)	0.254	12.800	0.514
Min Diam < 15	DIS	0	0.968	0.967
Min Diam < 15	Surface alteration (stage)	0.02	1.768	0.967
Min Diam < 15	Apoptotic cell (stage)	NA	NA	NA

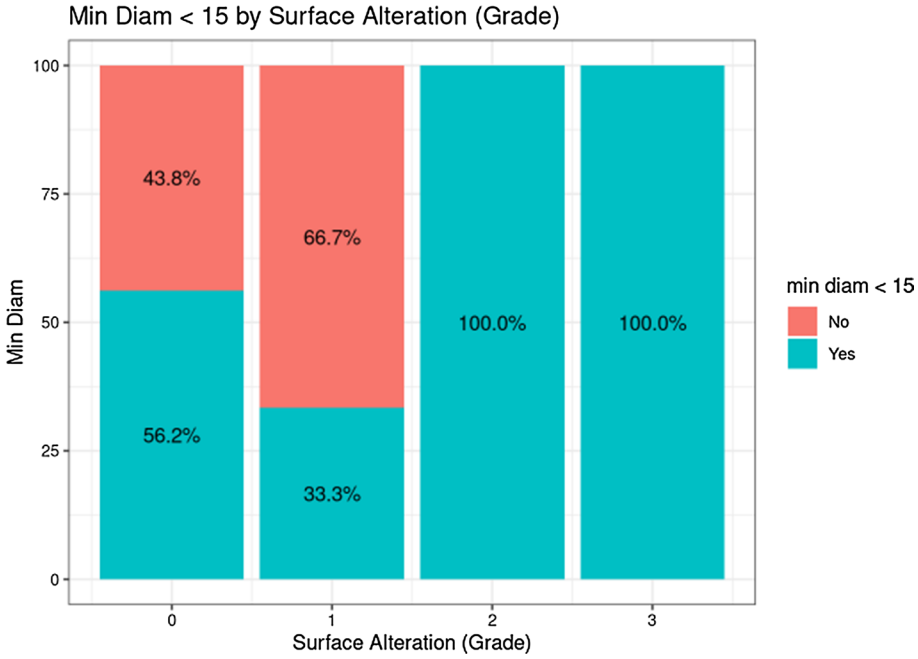

Fig. 5 Eosinophil surface layering (ESL) by grade compared to minimum diameter < 15 mm

Table 3 EoEHSS grade and stage subcomponents vs esophageal dilation, emergency room food removal, and food impaction

Response	Explanatory	*R* squared	*P* value
Dilated?	Basal layer hyperplasia (grade)	0	0.952
Dilated?	Surface alteration (grade)	0.007	0.952
Dilated?	Apoptotic epith cells	NA	NA
Dilated?	LP fibrosis (grade)	0.032	0.952
Dilated?	Basel layer hyperplasia (stage)	0.002	0.952
Dilated?	Surface alteration (stage)	0	0.952
Dilated?	Apoptotic epith cells (stage)	NA	NA
Dilated?	LP fibrosis (stage)	0.021	0.952
ER removal	Basal layer hyperplasia (grade)	0.093	0.814
ER removal	Surface alteration (grade)	0.017	0.997
ER removal	Apoptotic epith cells	NA	NA
ER removal	LP fibrosis (grade)	0.133	0.997
ER removal	Basel layer hyperplasia (stage)	0.106	0.814
ER removal	Surface alteration (stage)	0.001	0.997
ER removal	Apoptotic epith cells (stage)	NA	NA
ER removal	LP fibrosis (stage)	0.133	0.997
Food stuck	Basal layer hyperplasia (grade)	0.043	0.675
Food stuck	Surface alteration (grade)	0.242	0.359
Food stuck	Apoptotic epith cells	NA	NA
Food stuck	LP fibrosis (grade)	0.128	0.675
Food stuck	Basel layer hyperplasia (stage)	0.008	0.675
Food stuck	Surface alteration (stage)	0.174	0.392
Food stuck	Apoptotic epith cells (stage)	NA	NA
Food stuck	LP fibrosis (stage)	0.112	0.675

disease activity with standard validated instruments at the same time as histologic evaluation. Both the EoEHSS grade and stage were found to have high sensitivity (87–91%) but low specificity (11–22%) for symptomatic disease when evaluated in a binary fashion. As a continuous variable, EoEHSS grade and stage demonstrated weak associations with symptoms. The EoEHSS grade and stage were highly sensitive but not specific for endoscopically and histologically active disease. On a continuous scale, the EoEHSS grade and stage had modest correlation with endoscopic and histologic disease.

It is not surprising that EoEHSS had low specificity for endoscopically and symptomatically active disease as histologic activity precedes symptomatic and grossly visible activity for most diseases. This has been well established in inflammatory bowel disease where active histologic disease activity is often seen in asymptomatic patients with grossly normal appearing mucosa at endoscopy [13]. Similarly, the EoEHSS continued to suggest active disease in patients where all other metrics suggested remission: In 14 patients, in remission by PEC, EREFS, and EESAI, 43% were indicated to have active disease by EoEHSS. Interestingly, this was primarily related to the persistence of DIS. If DIS was not considered, all patients in endoscopic, symptomatic, and PEC-based histologic remission would be considered in EoEHSS remission. This would be consistent with the expectation that some histologic changes would persist 6 weeks after successful therapy. The EoEHSS remission scores were based on a study of biopsies from children who had EoE at a single institution, as well as author experience [5]. The remission scores correlated with diminished gene

expression and reduced symptom scores. DIS often persists despite therapy, most commonly with reduced grade (generally 2–3) and stage scores, and few intraepithelial eosinophils (grade 1) are also common, and therefore, the remission score was set at 3 to avoid overtreatment. The cause for persistent DIS is a subject for research. However, the importance of DIS as a source of ongoing impaired barrier function [14, 15] supports retaining this feature as a part of the EoEHSS in order to ensure its evaluation in both pre- and post-therapy biopsies, especially in the setting of persistent symptoms despite reduced eosinophil inflammation. DIS was first recognized in gastroesophageal reflux disease and is similar to a feature of atopic dermatitis known as spongiosis, and therefore, clinicopathologic findings involving DIS may have significance for diseases in addition to EoE.

The recent EoE severity score gives severity points to the findings of BZH or LPF or to DEC or SEA if the lamina propria could not be evaluated [16]. In the current study where standard biopsy forceps were utilized, subepithelial fibrosis could only be evaluated in 36% of biopsy samples. This is similar to previous studies demonstrating only about 50% of biopsy specimens with standard forceps obtain adequate subepithelial tissue for examination [17]. No significant correlation of BZH, LPF, DEC, or SEA with minimal esophageal diameter by standardized barium study, a narrow caliber esophagus, or a clinical history of food impaction, ER removal, or esophageal dilation was uncovered. This finding is quite interesting as a narrow caliber esophagus and history of dilation, while not completely specific for advanced EoE, are certainly markers for fibrosis. Food impactions can occur in patients without gross stricturing disease, but food impaction is associated with a lack of esophageal distensibility, and therefore, a reasonable marker for fibrotic disease [10, 18]. In summary, although LPF was not found to correlate to esophageal narrowing in this study, it is still a reasonable marker for patients at risk of advanced disease. However, BZH, DEC, and SEA will need further evaluation as markers of advanced EoE.

The EoEHSS has previously been shown by Ma et al. to be highly responsive to patient improvement similar to PEC and more highly correlated than PEC with a visual analog scale of overall histologic activity [4]. Hiremath et al. found EoEHSS to correlate better with EREFS [3] as well. Hirano et al. found the EoEHSS to decrease with topical steroid therapy [19]. Finally, intra-reader variability with the EoEHSS has been strong [2]. The major clinical question would be: Is the EoEHSS better at evaluation of disease activity than PEC alone? Unfortunately, this study was not designed or powered to answer this question. Importantly, this study could not adequately evaluate the performance of the EoEHSS in patients with active symptomatic and/or endoscopic disease but histologic remission by PEC. This study does suggest that the EoEHSS may be more sensitive at identifying active disease than PEC, but that it often remains elevated in the face of improvement in endoscopic and symptomatic assessments which may explain ongoing symptoms. Data in the literature that support the use of the EoEHSS both clinically and academically include its use in a severity score index [6], correlations with symptoms using validated instruments that exceed PEC symptoms correlations [20], and as a source of pathology to explain ongoing symptoms after eosinophil reduction/depletion [21, 22]. EoEHSS features may be evaluated dichotomously, but semiquantitative measurements provide trend lines in patients who have serial biopsies that dichotomous scoring does not.

The strengths of the study were that it was performed at a center with considerable EoE experience, and all the pathology slides were read by an experienced GI pathologist (MC). Second, three endoscopies were performed on each patient allowing the comparison of active disease to remission in each patient. However, there are several limitations. Although 66 biopsy specimens were available for review, these were obtained as 3 specimens in each of the 22 patients. This was accounted for by using mixed linear models which properly handle correlated observations. Second, EoEHSS was compared to the EESAI and EREFS which are far from perfect predictors of disease activity. Both the EESAI and EREFS have only moderate accuracy in predicting histologic remission [23, 24]. Third, the study was performed at a tertiary care center and are, thus, subject to referral bias. However, this was likely minimized as patients within the cohort underwent multiple evaluations for dietary therapy and all lived within reasonable driving distance of our facility. At last, this is a small study with a female predominant population that participated in a prospective dietary trial and may not accurately represent the general EoE population. We, thus, suggest that this study is primarily utilized as a signal for further investigation.

In conclusion, we find the EoEHSS to be highly sensitive but nonspecific for the evaluation of active EoE disease. The current EoEHSS criteria for histologic remission fail to adequately recognize remission after treatment likely related to the delayed resolution of several of the grade and stage pathologic features, most notably DIS. Finally, individual features of EoEHSS correlated poorly with esophageal narrowing. We conclude the EoEHSS is a valuable instrument in the evaluation of EoE but suggest modifications of the EoEHSS may allow for improved recognition of inactive disease. Future larger prospective studies with are needed to better determine the role of EoEHSS in clinical practice.

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Author's contribution RA is a Resident Physician in Internal Medicine at the Mayo Clinic Rochester. He was instrumental in the design and conduct of the study, data collection, and writing of the manuscript. KR is a gastroenterologist in the Department of Gastroenterology and

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Data availability Deidentified individual patient data will be available for 5 years' time.

Declarations

Conflict of interest Jeffrey Alexander has financial interest in Meritage Pharmacia, consulting agreement with Lucid Diagnostics, and research assistance with Regeneron, Ellodi, Arena, and Cellgene pharmaceuticals. Dr Katzka has received research funding from Shire and Takeda and is a consultant for Regeneron and Takeda. Margaret H. Collins is a consultant for Allakos, Arena Pharmaceuticals/Pfizer, AstraZeneca, Calypso Biotech, EsoCap Biotech, GlaxoSmithKline, Receptos/Celgene/BMS, Regeneron Pharmaceuticals, Robarts Clinical Trials Inc./ Alimentiv, Inc. and Shire, a Takeda company.

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