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Original article

Comparison of Endoscopic and Histological Scoring Systems in Adults with Eosinophilic Esophagitis and Their Correlation with Inflammatory Activity

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Abstract

Background: Eosinophilic esophagitis (EoE) is a chronic inflammatory disease mediated by allergic mechanisms, with increasing prevalence in both adults and children. Disease activity is assessed using endoscopic (EREFS) and histological (PHEEo) scoring systems, although their concordance and discriminatory capacity remain under debate. **Objectives:** To evaluate the relationship between EREFS, PHEEo scores, and peak eosinophil count (PEC), and to develop a predictive model of EoE activity based on combined endoscopic and histological components. **Methods:** A multicenter study including 94 adult patients with confirmed EoE was conducted. Disease was classified as active (EoE-A; n = 49, ≥15 eosinophils per high-power field) or inactive (EoE-I; n = 45, <15 eosinophils per high-power field). Pearson correlation coefficients and receiver operating characteristic (ROC) curve analyses were applied, with 95% confidence intervals estimated using bootstrap techniques and comparison of areas under the curve (AUCs) performed using DeLong's method. **Results:** The diagnostic performance of the histological score PHEEo was superior to the endoscopic score EREFS (AUC: 0.90; 95% CI: 0.83–0.96 vs. 0.62; 95% CI: 0.52–0.74). The combined model (PEC) achieved an AUC of 1.00, indicating overfitting and the need for external validation. Correlation between EREFS and PHEEo was weak (r = 0.03; 95% CI: −0.18 to 0.23), whereas PHEEo and PEC showed a moderate association (r = 0.62; 95% CI: 0.48–0.73). These findings confirm that endoscopic and histological markers provide complementary, non-mutually exclusive, and non-redundant information. **Conclusions:** The histological score PHEEo more accurately discriminates inflammatory activity in EoE than the endoscopic score EREFS. An integrated model combining specific endoscopic and histological findings improves predictive performance and may optimize the assessment of active disease. However, the perfect performance of the combined model suggests overfitting and requires prospective validation before routine clinical implementation.

Keywords

Eosinophilic esophagitis; hypersensitivity; adult; endoscopy; methods; histological techniques.

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic, inflammatory, recurrent allergic disease mediated by the immune system through activation of type 2 helper T (Th2) cells, and its main pathological feature is the predominant infiltration of eosinophils into the esophageal mucosa[1]. Clinically, EoE presents with symptoms related to esophageal dysfunction, such as dysphagia and episodes of food impaction, and it may affect individuals of all ages. Over recent decades, its prevalence has increased significantly[2]. The diagnosis of EoE is based on a consensus criterion requiring the presence of at least 15 eosinophils per high-power field (Eos/HPF) in esophageal biopsies, which is considered the diagnostic gold standard[3].

Although endoscopic findings such as edema, concentric rings, exudates, furrows, and strictures are suggestive of EoE, they are not entirely specific[4]. To standardize their assessment, the EREFS (Endoscopic REFerence System) endoscopic scoring system is used, providing a validated quantification of five key EoE features: edema, rings, exudates, furrows, and strictures[5]. Previous studies have demonstrated acceptable interobserver and intraobserver agreement for these endoscopic scores[6,7]. However, controversy remains regarding the relationship between endoscopic scores and eosinophil counts. While some studies have shown that endoscopic scores reliably predict both the diagnosis of EoE and histological response to treatment[8–10], others have indicated that these scores may not adequately reflect the histological activity of the disease[11,12].

Recently, a histological scoring system for EoE (EoEHSS) was developed and validated to comprehensively assess mucosal alterations through eight pathological features, including the severity of eosinophilic inflammation, measured by peak eosinophil count (PEC)[13]. This system has been shown to outperform PEC in distinguishing between treated and untreated patients with EoE, and some of its components have been associated with disease-specific endoscopic patterns[14]. Although both endoscopic and histological scores are validated tools for assessing EoE activity[15], the relationship between these two metrics and their combined value for predicting disease activity in adults has not yet been adequately documented. A strong correlation between these scores would allow them to be used as indirect markers of tissue pathology in EoE.

In this context, the aim is to establish the relationship between the endoscopic score (EREFS), the histological score (EoEHSS), and peak eosinophil count (PEC) in EoE activity, as well as how these parameters may be combined into a predictive model to more accurately assess the clinical activity of the disease.

PATIENTS AND METHODS

Study Participants and Case Definition

This multicenter retrospective cohort study included patients older than 18 years with a diagnosis of EoE who underwent endoscopic evaluation with biopsy sampling between January 2019 and December 2023. This cohort had previously been described in a larger study published recently[16]. The diagnosis of EoE was established according to the 2018 AGA Consensus recommendations[17], which require the presence of symptoms of esophageal dysfunction and significant eosinophilic inflammation in at least one esophageal biopsy sample following eight weeks of treatment with proton pump inhibitors, after excluding other causes of esophageal eosinophilia.

In this study, active eosinophilic esophagitis (aEoE) was defined as the presence of ≥15 eosinophils per high-power field (Eos/HPF), whereas inactive eosinophilic esophagitis (iEoE) was characterized by <15 Eos/HPF[18,19]. Patients were excluded from the analysis if they did not have at least six biopsy specimens adequate for histological evaluation, if proximal and distal esophageal biopsies were not differentiated, or if they had coexisting conditions that could interfere with the diagnosis, such as other eosinophilic gastrointestinal disorders (e.g., eosinophilic colitis or gastroenteritis), inflammatory bowel disease, connective tissue disorders, esophageal varices, or a history of esophageal surgery.

Data Collection

Demographic data (age, sex) and details regarding clinical presentation (initial symptoms), allergic comorbidities (eczema, allergic rhinitis, asthma), and exposure to ongoing treatments (such as proton pump inhibitors, oral and topical antiallergic agents, and topical corticosteroids) were collected. All information was recorded in a previously de-identified MS Excel database to ensure patient privacy.

Endoscopic Findings

During endoscopy, esophageal findings were evaluated using the EREFS scoring system, which includes the following parameters: edema (0–2), rings (0–3), exudates (0–2), furrows (0–2), and strictures (0–1). In addition, relevant secondary features, such as the appearance known as crepe-paper esophagus, were recorded. The total EREFS score was calculated by summing the individual values of each component, yielding a range from 0 to 10. Higher scores indicate greater severity of endoscopic findings (**Figure 1**).

Esophageal Biopsies and Histological Evaluation

At least six esophageal biopsy samples were obtained from each patient: three from the proximal esophagus and three from the distal esophagus. Sampling was prioritized in areas with features suggestive of EoE, such as furrows or exudates, and specimens were classified as proximal or distal according to their anatomical origin. All biopsies were processed using hematoxylin and eosin staining and evaluated for peak eosinophil count (PEC) and the degree of abnormality in eight pathological features according to the EoEHSS system: eosinophilic inflammation, basal zone hyperplasia, eosinophilic microabscesses, superficial layering of eosinophils, dilated intercellular spaces, surface

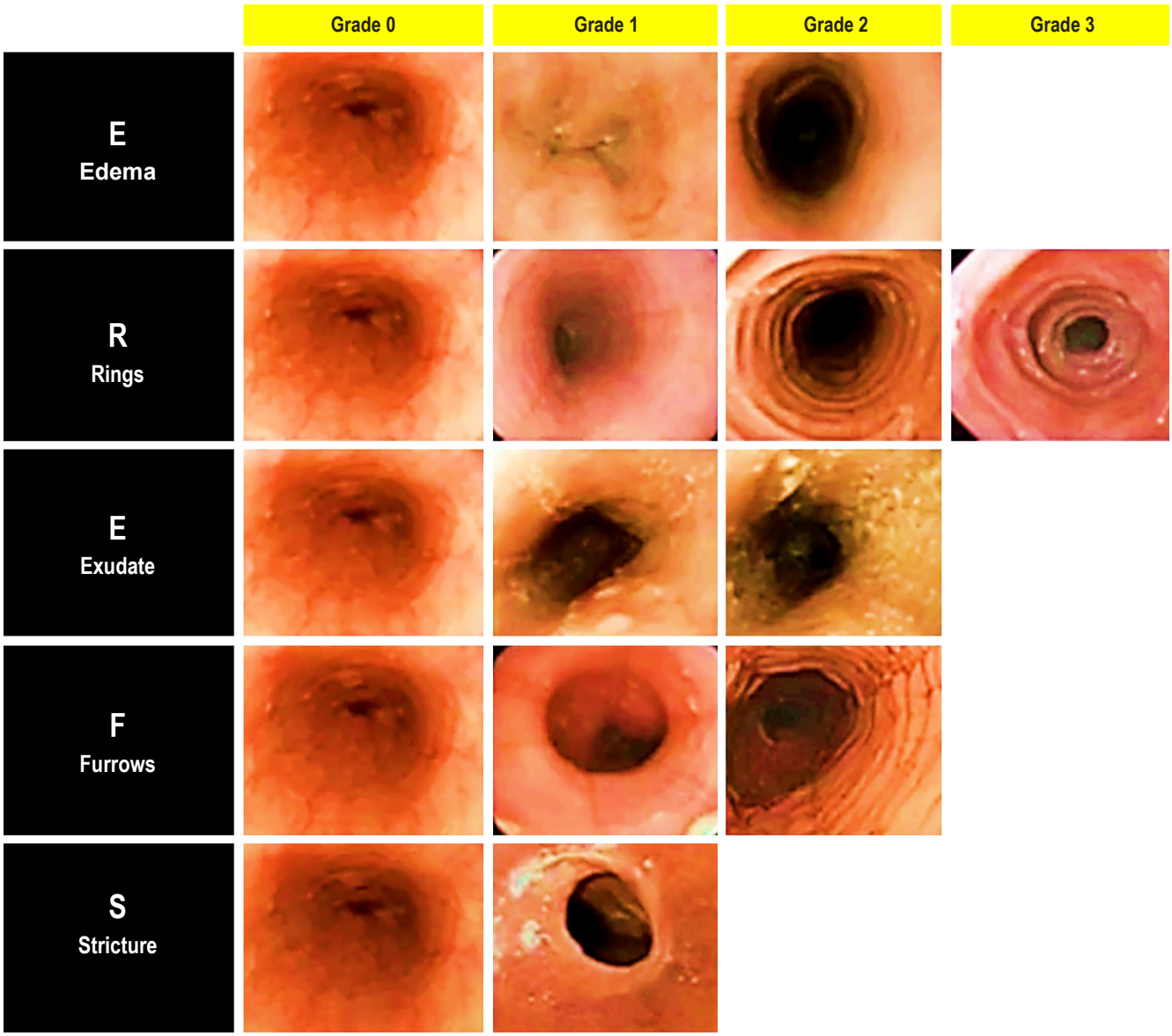


Figure 1. Endoscopic findings of eosinophilic esophagitis according to the EREFS classification and its progressive grades (0–3). Author's file.

epithelial alterations, dyskeratotic cells, and lamina propria fibrosis. Each feature received a score from 0 to 3, with a maximum score of 24 per biopsy. If any feature was not assessable (for example, fibrosis in the absence of lamina propria), the maximum score was adjusted proportionally. For instance, if the lamina propria was absent, the maximum score was reduced to 21. The final score for each biopsy was calculated as the quotient between the total sum of scores and the adjusted maximum score, thereby ensuring a standardized and comparable assessment (**Figure 2**).

Statistical Analysis

Descriptive statistical methods were used to characterize the study cohort. Correlations between endoscopic scores (EREFS) and peak eosinophil count (PEC), between endoscopic and histological scores (EoEHSS), and between histological score and PEC were assessed using Spearman's rho correlation coefficient (r). Both the total scores of the EREFS and EoEHSS systems and those of their individual components were analyzed. To adjust for

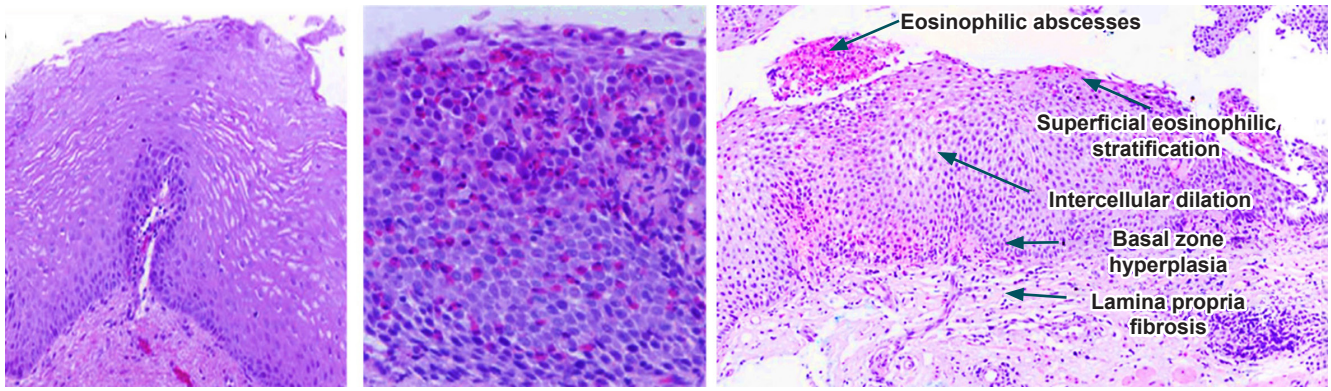


Figure 2. Histological findings in hematoxylin and eosin-stained biopsies, ranging from normal epithelium and eosinophilic infiltration (≥15 eosinophils per high-power field) to eosinophilic abscesses, basal hyperplasia, intercellular dilation, and lamina propria fibrosis, characteristic of the chronic inflammatory process. Author's file.

the effect of multiple comparisons, the Bonferroni correction was applied.

The magnitude of the correlation coefficient was interpreted as follows: 0.00–0.30 as negligible, 0.31–0.50 as weak, 0.51–0.70 as moderate, 0.71–0.90 as high, and 0.91–1.00 as very high. In addition, receiver operating characteristic (ROC) analysis was used to calculate the area under the curve (AUC) and generate plots representing sensitivity (true-positive rate) versus 1 – specificity (false-positive rate). Accuracy at different cutoff points for each component of the EREFS and EoEHSS systems was evaluated according to EoE activity status (active EoE versus inactive EoE).

Prospectively, it was planned to identify individual components with high AUC values (AUC ≥0.71) in order to develop an integrated panel of endoscopic and histological findings aimed at predicting EoE activity. For this combined panel, sensitivity, specificity, and correct classification rate values were calculated. All statistical analyses were performed using IBM SPSS software, version 26.0 (Armonk, New York).

RESULTS

Characteristics of Patients

A total of 94 adult patients with confirmed EoE were included (49 active EoE [≥15 eos/HPF], 45 inactive EoE). Mean age was 33 ± 8 years, and 69% were male. Fifty-three percent had atopic comorbidities (allergic rhinitis 20%, allergic conjunctivitis 19%). Dysphagia (18%) and reflux (16%) were the predominant symptoms. Ninety percent were receiving proton pump inhibitors (PPIs) (**Table 1**).

Endoscopic Findings (EREFS)

A total of 154 endoscopies were analyzed. Mean EREFS score was significantly higher in active EoE (4.5 ± 2.4) than in inactive EoE (3.5 ± 2.2; p = 0.016). Furrows were the most frequent finding (78% overall; 94% in active EoE versus 42% in inactive EoE, p <0.001). A normal endoscopic appearance (EREFS = 0) was observed in 6% of active EoE cases compared with 18% of inactive EoE cases (p = 0.07). The presence of friability, known as the crepe-paper sign, was also evaluated during biopsy collection, and no significant differences were found between the groups. The total EREFS score was significantly higher in patients with active EoE than in those with inactive EoE (4.5 ± 2.4 versus 4.2 ± 2.7; p ≤0.016) (**Table 2**).

Histological Evaluation (EoEHSS and PEC)

Mean peak eosinophil count (PEC) was 40 ± 12 eos/HPF in active EoE versus 4 ± 2 eos/HPF in inactive EoE (p <0.001). Mean EoEHSS score was 0.7 ± 0.1 versus 0.3 ± 0.2 (p <0.001). All histological features were significantly more prevalent in active EoE, particularly eosinophilic inflammation (96% versus 4%), eosinophilic abscesses (57% versus 7%), and epithelial stratification (35% versus 2%) (all p <0.001) (**Table 3**).

Correlations Between Scoring Systems

Peak eosinophil count (PEC) showed a high correlation with the EoEHSS histological score (r = 0.70; p <0.001), which remained significant after Bonferroni correction

Table 1. Demographic, Clinical, and Therapeutic Characteristics of the Cohort (n = 94)

Characteristics		Active EoE n = 49 (%)	Inactive EoE n = 45 (%)	Total n = 94 (%)
Age in years, mean ± SD		35 ± 8	31 ± 8	33 ± 8
Duration of symptoms, mean ± SD		21 ± 5	19 ± 5	20 ± 5
Eosinophil count, mean ± SD		37 ± 13	4 ± 2	21 ± 19
Sex	Female	14 (29)	15 (33)	29 (31)
	Male	35 (71)	30 (67)	65 (69)
Atopy	No	21 (22)	14 (15)	35 (37)
	Rhinitis	10 (11)	9 (10)	19 (20)
	Conjunctivitis	8 (9)	10 (11)	18 (19)
	Dermatitis	4 (4)	7 (7)	11 (12)
	Asthma	6 (6)	5 (5)	11 (12)
Symptoms	Asymptomatic	17 (35)	29 (64)	46 (49)
	Dysphagia	12 (25)	5 (11)	17 (18)
	Reflux	10 (20)	5 (11)	15 (16)
	Epigastric pain	7 (7)	3 (7)	10 (11)
	Food impaction	3 (3)	3 (7)	6 (6)
Management	PPI alone	23 (47)	22 (49)	45 (48)
	PPI plus diet	13 (27)	16 (36)	29 (31)
	PPI plus steroids	7 (14)	3 (7)	10 (11)
	PPI plus dilation	3 (6)	1 (2)	4 (4)
	No PPI	3 (6)	3 (7)	6 (6)

SD: standard deviation; EoE: eosinophilic esophagitis; PPI: proton pump inhibitors. Author's own research.

Table 2. Endoscopic Reference Score of the Cohort (n = 94)

Item		Active EoE n = 49	Inactive EoE n = 45	Total n = 94	*p*-Value
Exudates	0	9	12	21	0.622
	1	20	17	34	
	2	20	16	39	
Rings	0	11	8	19	**0.033**
	1	11	21	29	
	2	12	11	25	
	3	15	5	21	
Edema	0	14	13	25	0.576
	1	35	32	69	
Furrows	0	3	26	21	**0.001**
	1	46	19	73	
Strictures	0	47	44	91	0.532
	1	2	1	3	
Friability	0	21	19	40	0.558
	1	28	26	54	
EREFS	0-1	9	11	20	**0.013**
	2-3	6	8	13	
	4-5	15	17	23	
	>5	19	9	38	

EoE: eosinophilic esophagitis. Author's own research.

(p <0.001), whereas its correlation with the EREFS endoscopic score was weak (r = 0.21; p = 0.036) and lost significance after Bonferroni correction (p = 0.11) and Fisher's exact test (p = 0.31); the correlation between EoEHSS and EREFS was weak (r = 0.05; p = 0.629). Among individual components (versus PEC), strong correlations were observed with eosinophilic inflammation (r = 0.76), furrows (r = 0.45), and eosinophilic abscesses (r = 0.46) (all p <0.001); moderate correlations with dyskeratosis (r = 0.22) and fibrosis (r = 0.26); and weak or nonsignificant correlations with rings, edema, and strictures (**Figures 3–5**). Consequently, EoEHSS and PEC were strongly correlated with the inflammatory activity of EoE, whereas EREFS showed only a weak correlation.

Predictive Model for Active Eosinophilic Esophagitis

Whether the relationship between endoscopic findings (EREFS) and histological involvement (EoEHSS) was influenced by eosinophilic esophagitis activity (active EoE), defined according to the conventional PEC cutoff of ≥15 eos/HPF, was evaluated. The AUC of EoEHSS (0.90; 95% confidence interval [CI] 0.84–0.96) exceeded that of EREFS (0.62; 95% CI 0.52–0.72; p <0.001). A combined model (eosinophilic inflammation + furrows + eosinophilic abscesses + epithelial stratification + dyskeratosis) achieved:

- AUC: 0.93 (95% CI: 0.89–0.97).
- Sensitivity: 83% (95% CI: 74%–90%).
- Specificity: 95% (95% CI: 88%–98%).
- Accuracy: 90% (p <0.001) (**Table 4**, **Figures 6** and **7**).

Table 3. Histological Evaluation Based on the EoE Histological Scoring System and Peak Eosinophil Count

Evaluation		Active EoE n = 49 (%)	Inactive EoE n = 45 (%)	Total n = 94 (%)	*p*-Value
Eosinophilic inflammation	<15	2 (4)	43 (96)	45 (48)	**0.001**
	≥15	47 (96)	2 (4)	49 (52)	
Basal hyperplasia	No	4 (8)	13 (29)	17 (18)	**0.009**
	Yes	45 (92)	32 (71)	77 (82)	
Eosinophilic abscesses	No	21 (43)	42 (93)	63 (67)	**<0.001**
	Yes	28 (57)	3 (7)	31 (33)	
Eosinophil stratification	No	32 (65)	44 (98)	76 (81)	**<0.001**
	Yes	17 (35)	1 (2)	18 (19)	
Intercellular space dilation	No	4 (8)	12 (27)	16 (17)	**0.017**
	Yes	45 (92)	33 (73)	84 (83)	
Superficial epithelial alteration	No	33 (67)	42 (93)	75 (80)	**0.002**
	Yes	16 (33)	3 (7)	19 (20)	
Dyskeratosis	No	8 (16)	21 (47)	29 (31)	**0.001**
	Yes	41 (84)	24 (53)	65 (69)	
Lamina propria fibrosis	No	24 (49)	35 (78)	59 (63)	**0.004**
	Yes	25 (51)	10 (22)	35 (37)	
Histological score	Mean ± SD	0.7 ± 0.1	0.3 ± 0.2	0.5 ± 0.3	**<0.001**
Eosinophil count	Mean ± SD	40 ± 12	4 ± 2	23 ± 20	**<0.001**

SD: standard deviation; EoE: eosinophilic esophagitis; Eos: eosinophils. Author's own research.

In response to the second objective, the integrated panel of five markers (2 endoscopic + 3 histological) predicted active EoE with high accuracy, outperforming each system individually. In the diagnostic performance analysis (**Figure 6**), peak eosinophil count (PEC) achieved an area under the curve (AUC) of 1.00, followed by the histological score (EoEHSS) with 0.90 (95% CI: 0.83–0.96) and the endoscopic score (EREFS) with 0.62 (95% CI: 0.52–0.74). The difference between EoEHSS and EREFS was statistically significant (p <0.001), demonstrating the superiority of the histological component for identifying active disease.

In the analysis of individual components (**Figure 7**), eosinophilic inflammation showed the greatest discriminative capacity (AUC = 0.96), whereas longitudinal furrows (AUC = 0.76) and eosinophilic abscesses (AUC = 0.75) were the most relevant endoscopic findings. These results demonstrate that histological variables carry greater diagnostic weight than endoscopic findings, and that combining both domains could optimize the prediction of inflammatory activity in EoE.

DISCUSSION

The relationship between endoscopic scores (EREFS), histological scores (EoEHSS), and PEC was evaluated in 94 adults with EoE. In addition, selected components were integrated to develop a predictive panel for active EoE. The initial hypothesis—that EREFS, by capturing the most severe endoscopic findings, would closely correlate with histological changes—was not fully confirmed.

The correlation between EREFS and EoEHSS was poor, and the association observed with PEC was weak, ruling out the isolated use of endoscopy as a substitute for histo-

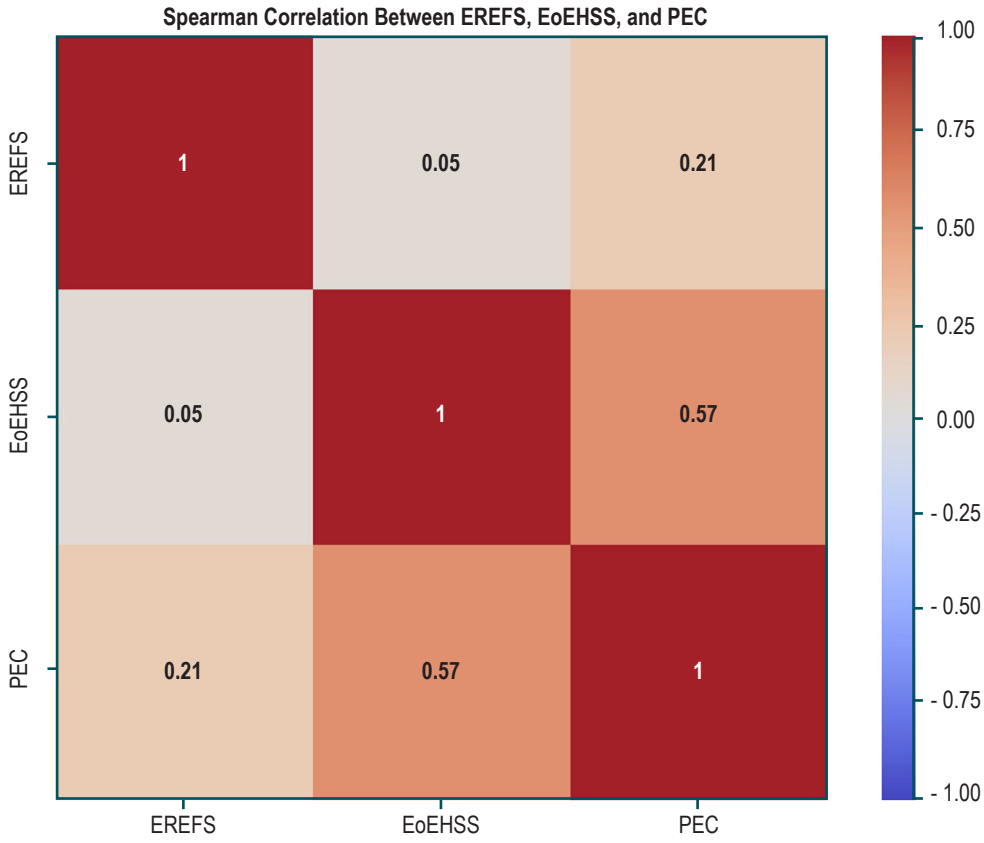


Figure 3. Heat map illustrating Spearman correlation (r; *p-value*) between endoscopic score, histological score, and peak eosinophil count. 0.91–1.00: very high; 0.71–0.90: high; 0.51–0.70: moderate; 0.31–0.50: weak; 0.00–0.30: negligible. Author's file.

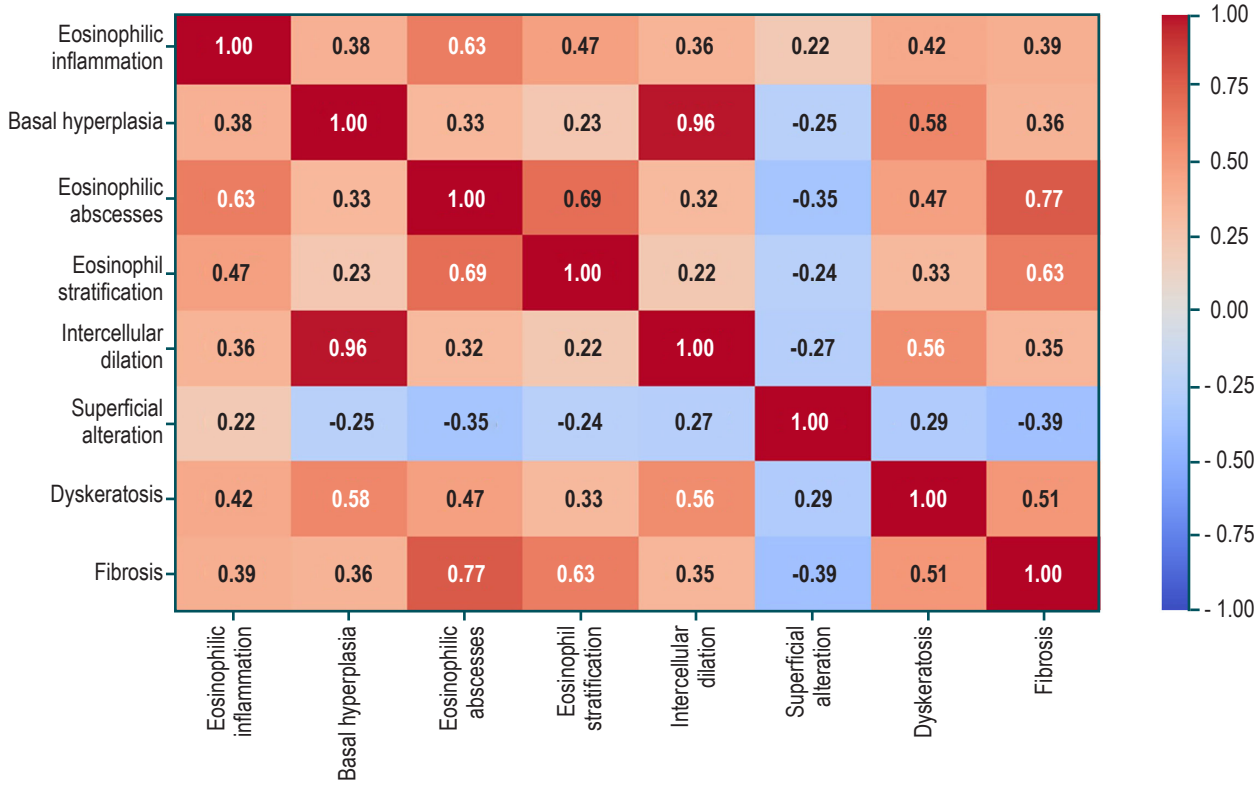


Figure 4. Heat map illustrating Spearman correlation (r; *p-value*) between histological score and peak eosinophil count. Author's file.

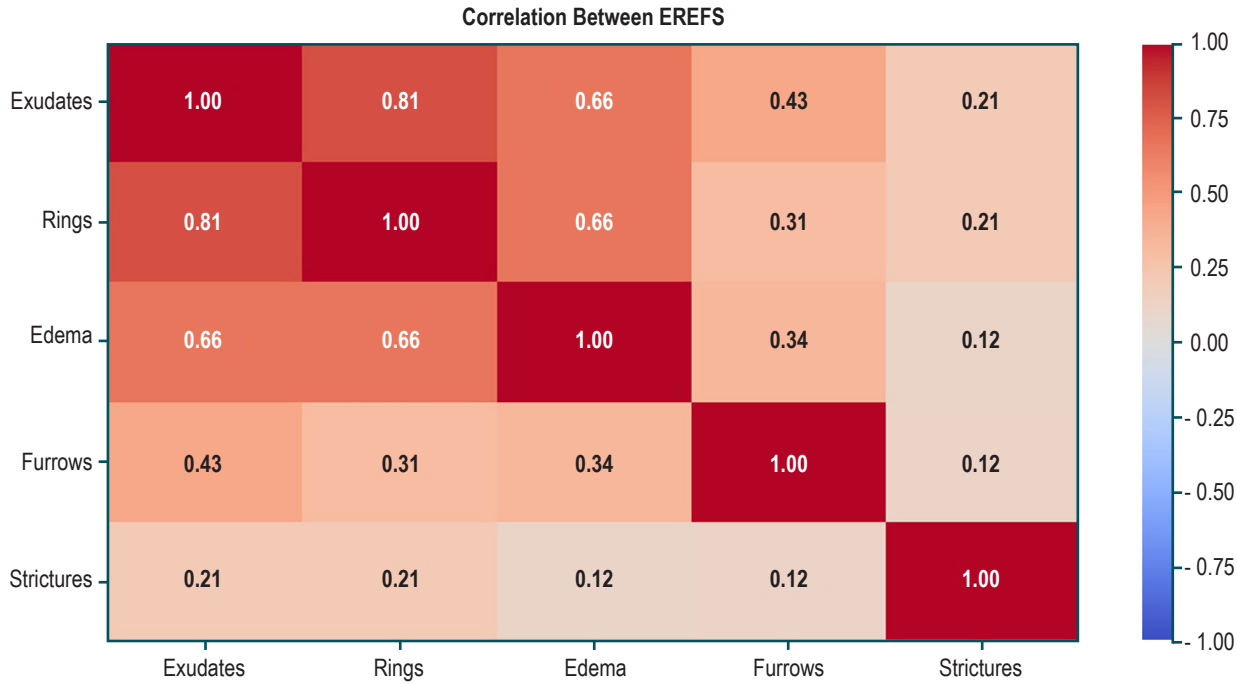


Figure 5. Heat map illustrating Spearman correlation (r; *p-value*) between endoscopic score and peak eosinophil count. Author's file.

Table 4. Diagnostic Metrics (AUC, Sensitivity, Specificity) of the Systems and Combined Model

Variable	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy (95% CI)	AUC	*p*-Value
Eosinophilic inflammation	0.959 (0.898-0.984)	0.956 (0.893-0.982)	0.957 (0.896-0.983)	0.957	**<0.001**
Combined model	0.837 (0.739-0.962)	0.956 (0.792-1.0)	0.929 (0.833-1.0)	0.932	**<0.001**
EoEHSS	0.918 (0.845-0.959)	0.778 (0.684-0.850)	0.851 (0.765-0.909)	0.902	**<0.001**
Furrows	0.939 (0.871-0.972)	0.578 (0.477-0.673)	0.766 (0.671-0.840)	0.758	**<0.001**
Eosinophilic abscesses	0.571 (0.471-0.667)	0.933 (0.864-0.969)	0.745 (0.648-0.822)	0.752	**<0.001**
Eosinophil stratification	0.347 (0.258-0.447)	0.978 (0.924-0.994)	0.649 (0.548-0.738)	0.662	**<0.001**
Dyskeratosis	0.837 (0.749-0.898)	0.467 (0.369-0.567)	0.660 (0.559-0.747)	0.652	**0.003**
Fibrosis	0.510 (0.411-0.609)	0.778 (0.684-0.850)	0.638 (0.538-0.728)	0.644	**0.007**
Superficial alteration	0.327 (0.240-0.427)	0.933 (0.864-0.969)	0.617 (0.516-0.709)	0.630	**0.004**
EREFS	0.694 (0.595-0.778)	0.422 (0.327-0.523)	0.564 (0.463-0.660)	0.624	0.339
Basal hyperplasia	0.918 (0.845-0.959)	0.289 (0.207-0.387)	0.617 (0.516-0.709)	0.604	**0.019**
Intercellular dilation	0.918 (0.845-0.959)	0.267 (0.188-0.364)	0.606 (0.505-0.699)	0.593	**0.035**
Rings	0.500 (0.401-0.599)	0.276 (0.196-0.374)	0.373 (0.282-0.473)	0.589	0.178
Exudates	0.690 (0.590-0.774)	0.414 (0.320-0.515)	0.552 (0.451-0.648)	0.546	0.585
Strictures	0.041 (0.016-0.102)	0.978 (0.924-0.994)	0.489 (0.391-0.589)	0.509	1.000
Edema	0.714 (0.616-0.796)	0.289 (0.207-0.387)	0.511 (0.411-0.609)	0.502	1.000

Eos: eosinophils; CI: confidence interval. Author's own research.

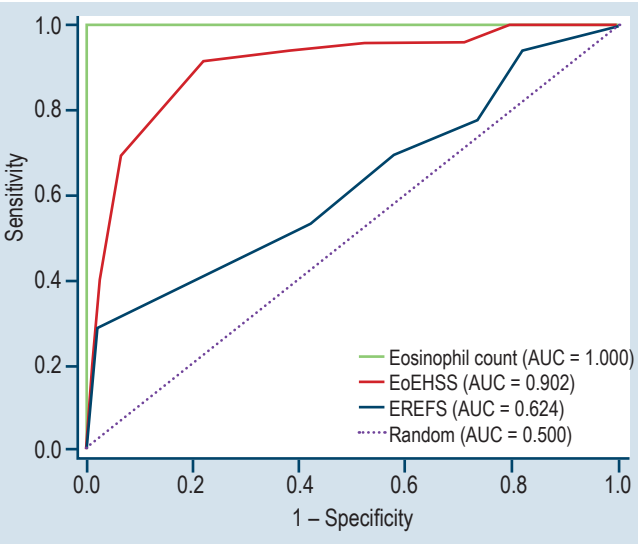


Figure 6. ROC curves for the endoscopic and histological references PEC, EoEHSS, and EREFS. Author's file.

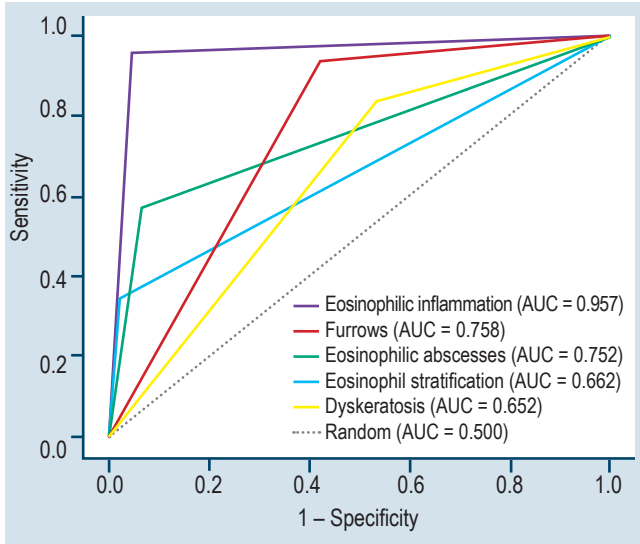


Figure 7. ROC curves for the most relevant individual histological and endoscopic components.

logy. This association was more pronounced in active EoE than in the inactive form. This discrepancy contrasts with reports in the literature describing stronger associations, mainly in pediatric populations[20], whereas in studies involving adults the relationship has also been modest[21], which may be influenced by this cohort being more inflammatory than fibrostenotic.

The demographic characteristics of the cohort (69% male, 53% with atopy) are consistent with the current epidemiology of adult EoE[22]. Twenty-five percent presented with an endoscopically normal esophagus, in agreement with series reporting between 20% and 30% normal endoscopies despite confirmed eosinophilia[23]. The predominant endoscopic phenotypes were inflammatory (furrows 78%, exudates) and, to a lesser extent, fibrostenotic (rings 81%, strictures 3%), which aligns with the current phenotypic classification[24]. Furrows showed the most robust correlation with PEC, replicating findings from Asian and Western cohorts[5,10].

The main innovation of this study was the precise characterization of the relationship between endoscopic and histological scores in EoE. Twenty-five percent of patients had an endoscopically normal esophagus despite detectable histological abnormalities, demonstrating that EoEHSS is more sensitive than PEC for identifying subtle mucosal changes and suggesting a discrepancy between microscopic inflammation and visible endoscopic findings. Furrows correlated significantly with basal hyperplasia and papillary elongation, whereas edema and exudates showed weak correlations. These associations were more pronounced in the active inflammatory phenotype (active EoE), supporting the concept that endoscopic findings mainly reflect advanced inflammation rather than mild submucosal processes. Consistent with recent literature, the correlation between endoscopy and histology in EoE is only moderate[25].

Currently, there are no universally accepted threshold values for endoscopic (EREFS) or histological (EoEHSS) scores that accurately predict EoE activity status. This lack of standardization limits their routine application in clinical practice and underscores the need for thresholds adapted to endoscopic phenotype and degree of tissue remodeling. In recent studies, an EREFS ≥2 demonstrated 79% sensitivity and 86% specificity for the diagnosis of active EoE (AUC = 0.73) in Korean adults[10]. Similarly, another study reported that an EREFS ≤2 was associated with histological remission following treatment, with 80% sensitivity and 83% specificity (AUC = 0.88)[26]. In contrast, histological scores derived from EoEHSS have shown better overall discriminative capacity (AUC ≈ 0.90) and a closer correlation with inflammatory activity[13].

Furthermore, a recent review highlights that the systematic integration of endoscopic and histological assessments is essential for stratifying EoE activity, since each modality captures distinct disease domains and their combination significantly reduces the risk of underdiagnosis[27]. These findings support the concept that isolated assessment using

either EREFS or PEC is insufficient, and that a combined endoscopic-histological approach constitutes a superior strategy for estimating disease activity and predicting therapeutic response.

This study has several limitations. Its retrospective design based on electronic medical record review makes misclassification bias plausible. We predominantly included patients with the inflammatory EoE phenotype; therefore, our findings may not be generalizable to adult patients with a fibrostenotic phenotype. Due to the lack of a biopsy protocol, it was not possible to determine how specific endoscopic changes could affect histological metrics. Only the degree of abnormality (grade score) was used to evaluate relationships; therefore, the extent of pathology (stage score) was not analyzed. Nevertheless, recent studies have demonstrated that grade and stage exhibit a very high correlation (r >0.90) and respond similarly to treatment, validating the use of grade as the primary metric in the histopathological evaluation of EoE[21]. Endoscopic evaluations were performed by different endoscopists and histological assessments by multiple pathologists (multicenter design), without centralized review by an expert pathologist; this increases interobserver variability and limits the applicability of the findings to routine adult and pediatric endoscopy practice.

Despite the above, this study also has several strengths. We included consecutive patients with EoE undergoing endoscopy, thereby minimizing selection bias. All EREFS scores were recorded at the time of endoscopy (EGD), eliminating recall bias or subsequent reassessment based on archived photographs. The sample size was sufficient to detect a 10% Spearman correlation with $\alpha = 0.05$ and a power of 0.80. PEC and EoEHSS scoring were performed simultaneously on biopsy samples, without relying on historical readings or previous reports of correlations between endoscopy and histology.

The main findings of the study are as follows:

- The EoEHSS histological score and PEC are strong markers highly correlated with inflammatory activity in adult EoE, maintaining statistical significance after correction for multiple comparisons ($r = 0.70$; $p < 0.001$).
- The EREFS endoscopic score shows a weak and nonsignificant correlation with histological activity ($r = 0.21$; $p = 0.11$ after Bonferroni correction); therefore, it should not be used as an isolated substitute for histological analysis when assessing active tissue inflammation.
- An integrated predictive model combining eosinophilic inflammation, endoscopic furrows, eosinophilic abscesses, epithelial stratification, and dyskeratosis achieved an AUC of 0.93, with 83% sensitivity and 95% specificity, substantially outperforming EREFS (AUC: 0.62) and EoEHSS (AUC: 0.90) individually.
- Multimodal evaluation (endoscopic plus selective histological assessment) is essential for accurate stratification of EoE activity and should guide therapeutic and follow-up decisions in clinical practice.
- These findings validate a more efficient diagnostic and prognostic approach in adults with EoE, laying the foundation for prospective studies incorporating this combined panel as a composite endpoint in clinical trials and longitudinal management.

CONCLUSIONS

In adults with EoE, isolated endoscopic assessment (EREFS) does not replace histological analysis: its correlation with inflammatory activity is weak and loses significance after statistical adjustments. In contrast, the EoEHSS histological score and peak eosinophil count are strongly correlated with active tissue inflammation. An integrated panel of five markers (eosinophilic inflammation, furrows, eosinophilic abscesses, epithelial stratification, and dyskeratosis) predicts active EoE with an AUC of 0.93, 83% sensitivity, and 95% specificity, outperforming any individual system. This multimodal model redefines EoE assessment, offering a precise, reproducible, and clinically actionable tool to guide treatment and follow-up in daily practice.

Conflict of Interest

The authors declare that they have no conflicts of interest relevant to the content of this article.

Statement on the Use of Artificial Intelligence

The authors declare that artificial intelligence tools were used in a limited manner, exclusively for paraphrasing and linguistic revision of the text. Under no circumstances were they used for data analysis, interpretation, or the formulation of scientific conclusions. The authors assume full responsibility for the content, integrity, and originality of the manuscript.

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