

TITLE:

**Reappraisal of the Eosinophilic Esophagitis Endoscopic Reference Score (EREFS):
Subscoring Inflammatory and Fibrotic Findings Improves the Assessment of Disease Activity**

AUTHORS

Pierfrancesco Visaggi^{1,2}, Irene Solinas¹, Gaia Pellegatta³, Federico Testi, Gaia Cairoli, Mauro Mitilini, Valeria Poletti³, Giacomo Marcozzi³, Emanuele Marciano², Stefano Siboni, Alessandro Repici³, Edoardo V. Savarino^{4,#}, and Nicola de Bortoli^{1,#}

AFFILIATIONS:

1. University of Pisa
2. Humanitas Research Hospital
3. University of Padua

Background:

The eosinophilic esophagitis (EoE) endoscopic reference score (EREFS) is the validated scoring system for endoscopic findings of EoE. EREFS findings are currently scored cumulatively and correlate modestly with histological disease activity (HDA), symptoms, and adaptive behaviors. However, inflammatory and fibrotic findings may reflect different aspects of EoE, but this has never been evaluated.

Methods:

We investigated the correlation of EREFS inflammatory and fibrotic subscores with HDA, symptoms and adaptive behaviors. In three tertiary referral centres for EoE, consecutive adults (>18 years) undergoing upper endoscopy for suspected or follow up EoE were prospectively enrolled. EREFS was scored as follows: edema 0-1; rings 0-3; exudates 0-2; furrows 0-2; stricture 0-1. The EREFS inflammatory sub-score (EREFS-i) combined the scores of edema, exudates and furrows. The EREFS fibrotic sub-score (EREFS-f) combined the scores of moderate-severe rings (score ≥ 2) and stricture. Subsequently, at least six esophageal biopsies were collected to assess HDA based on peak eosinophil count/high-power field (PEC/HPF) (active EoE PEC ≥ 15 /HPF; EoE in remission: PEC < 15/HPF). Symptoms were assessed using the dysphagia symptoms questionnaire (DSQ). Adaptive behaviors were assessed using the Pisa EoE Adaptation Questionnaire v1.0 (PiEAQ) [reference 1]. Clinical characteristics were recorded. Kruskal-Wallis Rank Sum Test and Pearson's Chi-squared were used for comparisons. ROC curve analysis was used to calculate the diagnostic accuracy (AUC). Spearman's test and linear regression models were used to assess relationships between variables. Significance threshold was $p < 0.05$.

Results: 121 patients were included. 58% had active EoE, 42% were in histological remission. Baseline clinical data are reported in **Table 1**. The EREFS total score had modest AUC for predicting HDA (0.68) and did not show significant correlation with DSQ and PiEAQ. In contrast, EREFS-i had AUC of 0.73, with 88.2% sensitivity and 51.4% specificity for predicting HDA, being significantly more accurate compared to the EREFS-f ($p < 0.001$; **Figure 1**). There was a significant correlation between EREFS-i and PEC/HPF with Spearman's $Rho = 0.5$ ($p < 0.001$), with linear regression showing that an increase of 1 point of any inflammatory feature corresponded to an increase of 12 eosinophils/HPF ($p < 0.0001$). In contrast, EREFS-f correlated significantly with the use of adaptive behaviors assessed with PiEAQ [Spearman's Rho of 0.6 ($p < 0.001$); **Figure 2**], with linear regression showing that an increase of 1 point of any fibrotic feature corresponded to an increase of one adaptive behavior ($p = 0.001$). EREFS, EREFS-i, and EREFS-f had nonsignificant negative correlation with DSQ ($p > 0.05$ for all).

Conclusions:

We confirmed that, while total EREFS provides a global assessment of endoscopic disease severity, it lacks correlation with histological and clinical disease activity. However, we demonstrated that EREFS-i correlates significantly with PEC and predicts PEC/HPF and that EREFS-f correlates significantly with the use of adaptive behaviors assessed with PiEAQ, which represent known clinical markers of disease activity. Neither EREFS-i nor EREFS-f correlated significantly with DSQ. In conclusion, we showed that, compared to the total EREFS, EREFS sub-scores improve the correlation between endoscopy findings with histology and clinical disease activity markers.

Figure 1. Accuracy of Inflammatory vs Fibrotic EREFS findings for predicting histological disease activity

Figure 1.

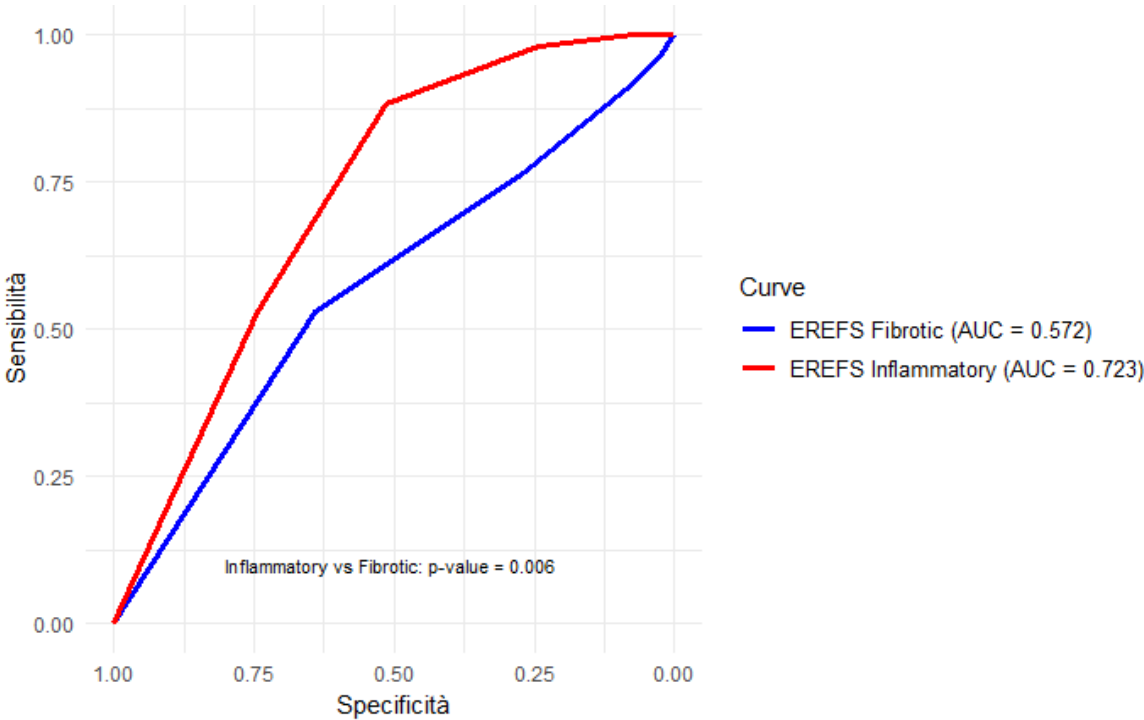
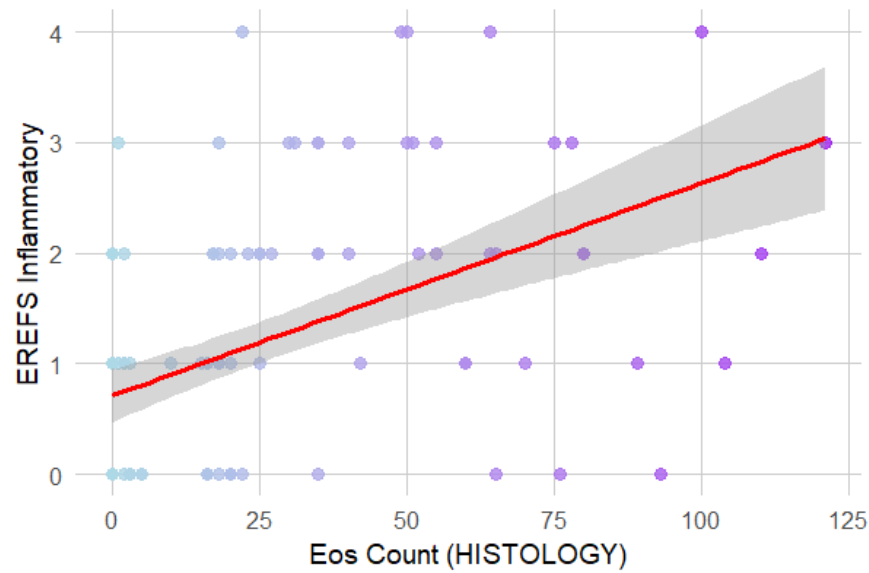


Figure 2.

Correlation between eosinophil counts on histology and EREFS inflammatory findings



Correlation between adaptive behaviors (PiEAQ) and EREFS fibrotic findings

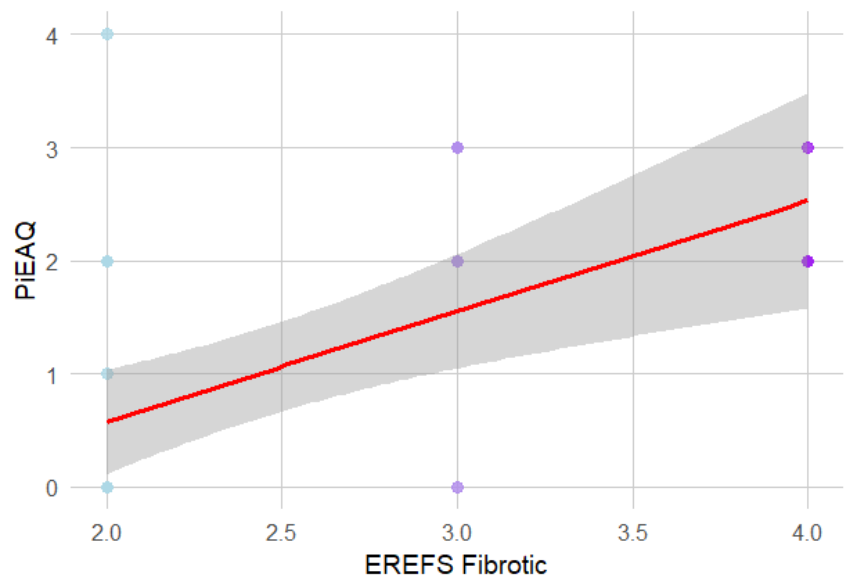


Table 1

Characteristic	N = 121
Sex (M/F)	82/39
Age	40 (31, 50)
Eos_Count_HISTOLOGY	16 (0, 35)
EREFS_Score_Total	2.00 (0.00, 3.00)
EREFS_Inflammatory	1.00 (0.00, 2.00)
EREFS_Fibrotic	1.00 (0.00, 2.00)
Diagnostic_Delay_months (INTERVAL SYMPROMS-DIAGNOSIS)	60 (24, 135)
Rhinitis	63 / 115 (55%)
Asthma	36 / 115 (31%)
Atopic Dermatitis	16 / 115 (14%)
Dysphagia	73 / 116 (63%)
History of Food Impaction	55 / 116 (47%)
Heartburn	34 / 116 (29%)
Chest Pain	11 / 95 (12%)
Regurgitation	19 / 116 (16%)
Histological Remission(<15eos/HPF)	51 / 121 (42%)
DSQ	14 (0 – 42)
PiEAQ score	0 (0 – 2)
EREFS total score	2 (0-3)
Edema(0-1)	
0	62 / 121 (51%)
1	59 / 121 (49%)
Rings(0-3)	
0	55 / 121 (45%)
1	36 / 121 (30%)
2	25 / 121 (21%)
3	5 / 121 (4.1%)
Exudates(0-2)	
0	91 / 121 (75%)
1	23 / 121 (19%)
2	7 / 121 (5.8%)
Furrows(0-2)	
0	80 / 121 (66%)
1	37 / 121 (31%)
2	4 / 121 (3.3%)
Stricture(0-1)	
0	109 / 121 (90%)
1	12 / 121 (9.9%)