

Comparison of Patients with Eosinophilic Esophagitis with Extremely High and Low Esophageal Eosinophil Counts

K.M. O'Shea¹, M. Rochman¹, T. Shoda¹, N. Zimmermann¹, J. Caldwell¹ and M.E. Rothenberg¹

¹Division of Allergy and Immunology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH 45229-3039, USA.



Introduction

Eosinophilic esophagitis (EoE) is an inflammatory disease characterized by eosinophil infiltration into the esophageal mucosa with a peak count of ≥ 15 eosinophils per high-powered field (eos/hpf) following endoscopic biopsy. However, the range of esophageal eosinophilia can vary markedly from patient to patient. A key question in the field is to understand the relationship of eosinophil levels with disease features, especially since eosinophil-targeted therapies are now available. Patients with extremely high levels of esophageal eosinophilia have not previously been studied. It is unknown whether these patients exhibit different characteristics compared with EoE patients that have esophageal eosinophilia that is near the threshold of disease diagnosis. Given this, we aimed to establish whether any significant clinical, endoscopic, histologic, or transcriptomic features differ between patients with extremely high levels of esophageal eosinophilia and those with levels near the threshold of disease diagnosis.

Methods

Subject selection

Amongst a registry of patients with EoE, we identified a group of patients with the highest recorded levels of esophageal eosinophilia (eos/hpf >350), referred to as EoE-Hi. We subsequently identified a second group that had relatively low levels of esophageal eosinophilia (15-24 eos/hpf), referred to as EoE-Low. There were 74 patients in the registry with eosinophil counts of 15-24 eos/hpf on a distal esophageal biopsy. A random number generator was used to select the 14 patients that comprised the EoE-Low group.

Analysis

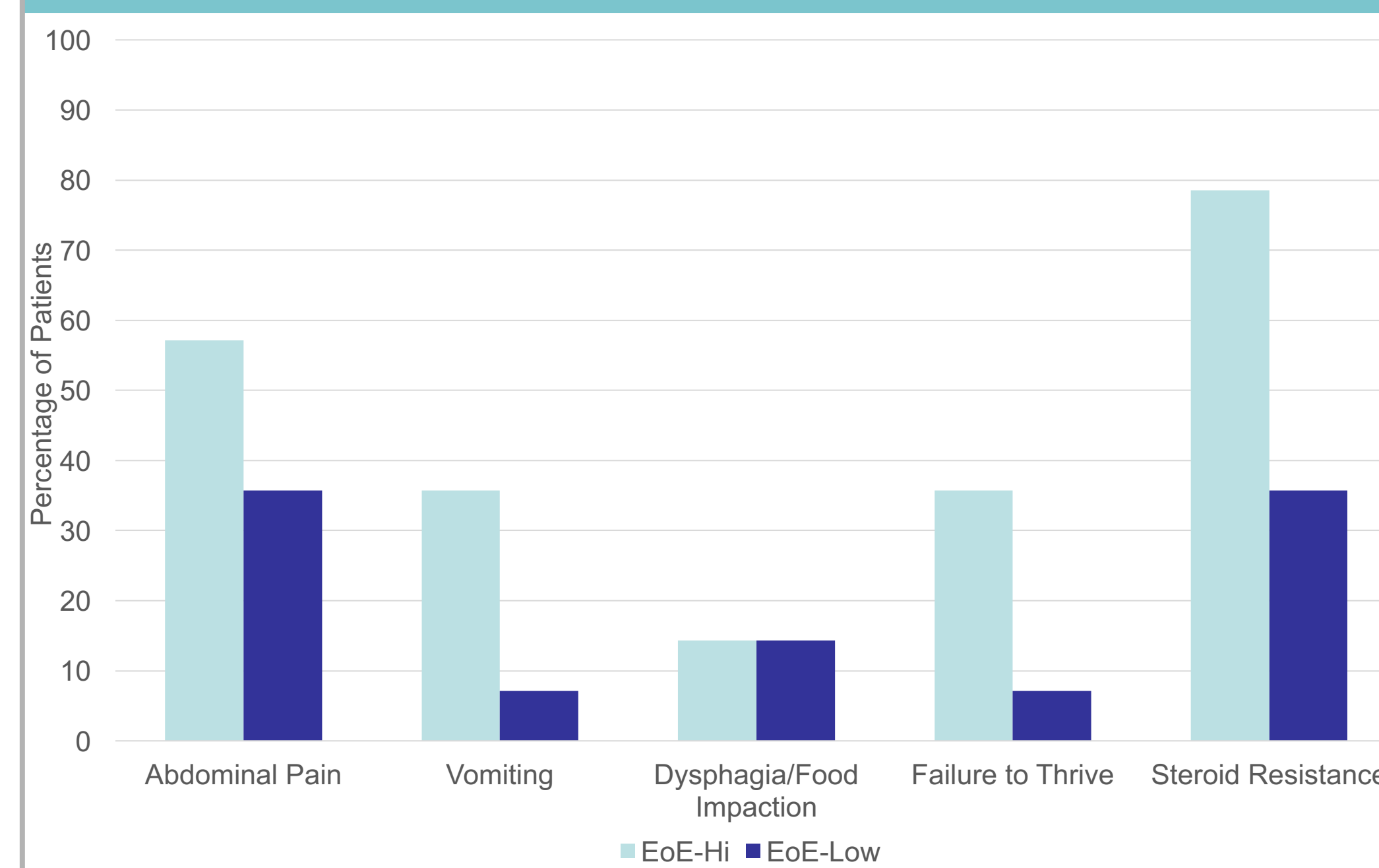
Phenotypic and clinical characteristics were gathered on the basis of electronic medical records and detailed questionnaires as part of a research registry. Endoscopic characteristics were assessed on the basis of findings from EGD operative reports. Histologic characteristics were classified on the basis of the histologic scoring system. Molecular analysis was performed using the 96-gene EoE Diagnostic Panel (EDP).

Patients with Extremely High Eosinophil Counts Have a Unique Phenotype

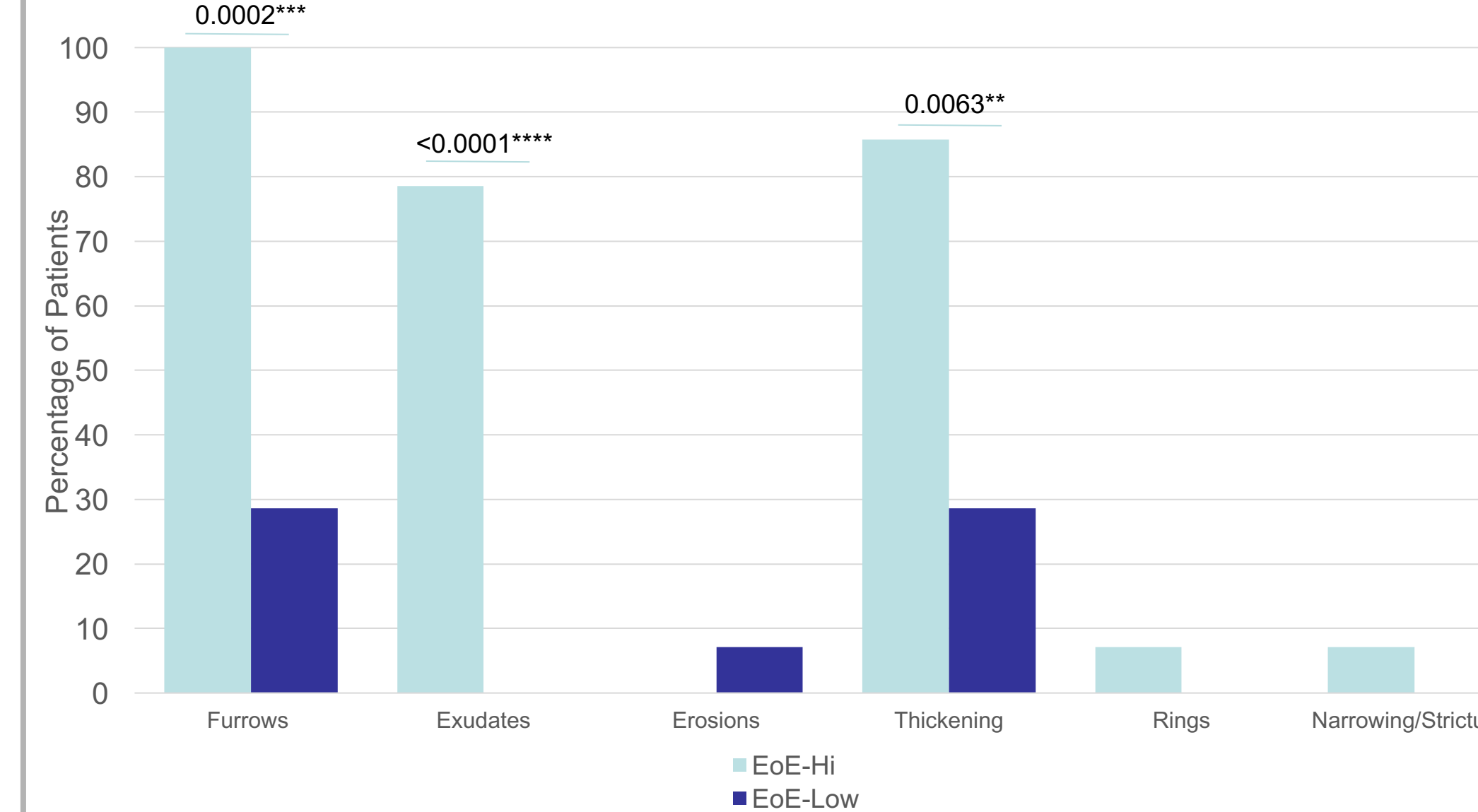
	Eos/hpf >350 (n=14)	Eos/hpf 15-24 (n=14)	P-value
Male sex, no (%)	78.6	78.6	>0.9999
Age at Biopsy (y), mean \pm SD	13.4 \pm 2.7	6.3 \pm 0.9	0.0205
Age at Diagnosis (y), mean \pm SD	7.3 \pm 2.9 (n=11)	4.4 \pm 0.8 (n=12)	0.3313
Duration of Disease*(y), mean \pm SD	10.9 \pm 0.9 (n=12)	6.4 \pm 0.6 (n=12)	0.0008
Eosinophils/hpf (mean \pm SD)	433.3 \pm 96.6	18.6 \pm 2.9	<0.0001
Absolute Eosinophilia (mean \pm SD)	686.2 \pm 97.8 (n=13)	481.5 \pm 74.7 (n=13)	0.1094
IgE (mean \pm SD)	426.3 \pm 150.4 (n=9)	338.8 \pm 245.1 (n=5)	0.7521
History of other EGIDs ⁺ , no. (%)	3 (23.1) (n=13)	0	0.2276
Atopic Co-morbidities, no. (%)	14 (100)	9 (64.3)	0.0407
Atopic Dermatitis	10 (71.4)	6 (42.8)	0.2519
Allergic Rhinitis	13 (92.8)	7 (50)	0.0329
Asthma	9 (64.3)	8 (57.1)	>0.9999
Food Allergy	9 (64.3)	6 (42.8)	0.4495
History of Anaphylaxis	5 (35.7)	4 (28.6)	>0.9999

EGID, eosinophilic gastrointestinal disorder; EoE, eosinophilic esophagitis; HPF, high-power field; IgE, immunoglobulin E; PPI, proton-pump inhibitor; SD, standard deviation
*Duration of Disease is defined as the time interval between age at diagnosis and age at time of biopsy.
⁺In addition to a diagnosis of EoE, 2 patients in the EoE-Hi group have diagnoses of eosinophilic colitis and 1 patient has a diagnosis of eosinophilic gastroenteritis.

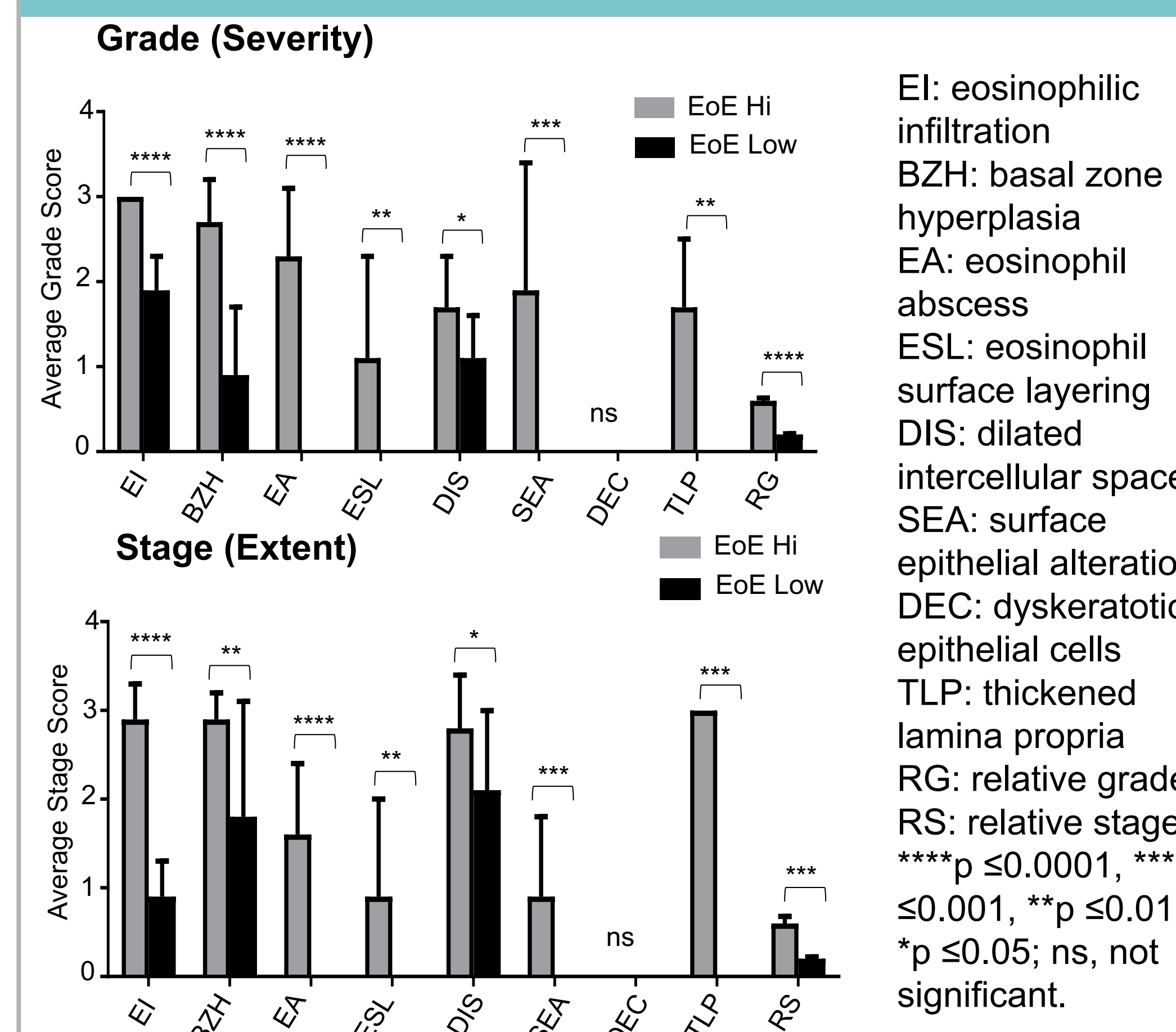
Trends for More Severe Symptoms in EoE-Hi Group



Patients in the EoE-Hi Group have a Greater Incidence of Furrows, Exudates and Thickening on Endoscopy

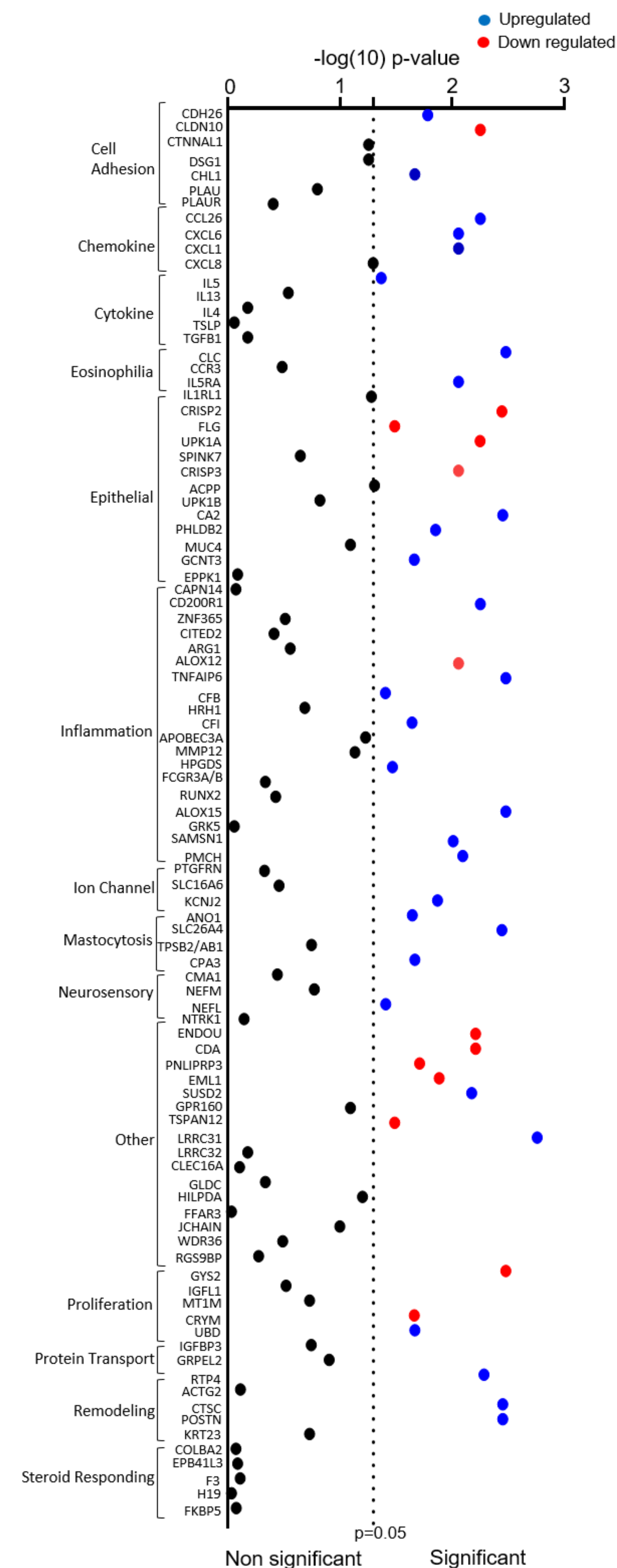


Total Score for Each of Individual Histologic Parameter was Higher (More Severe) in the EoE-Hi Group



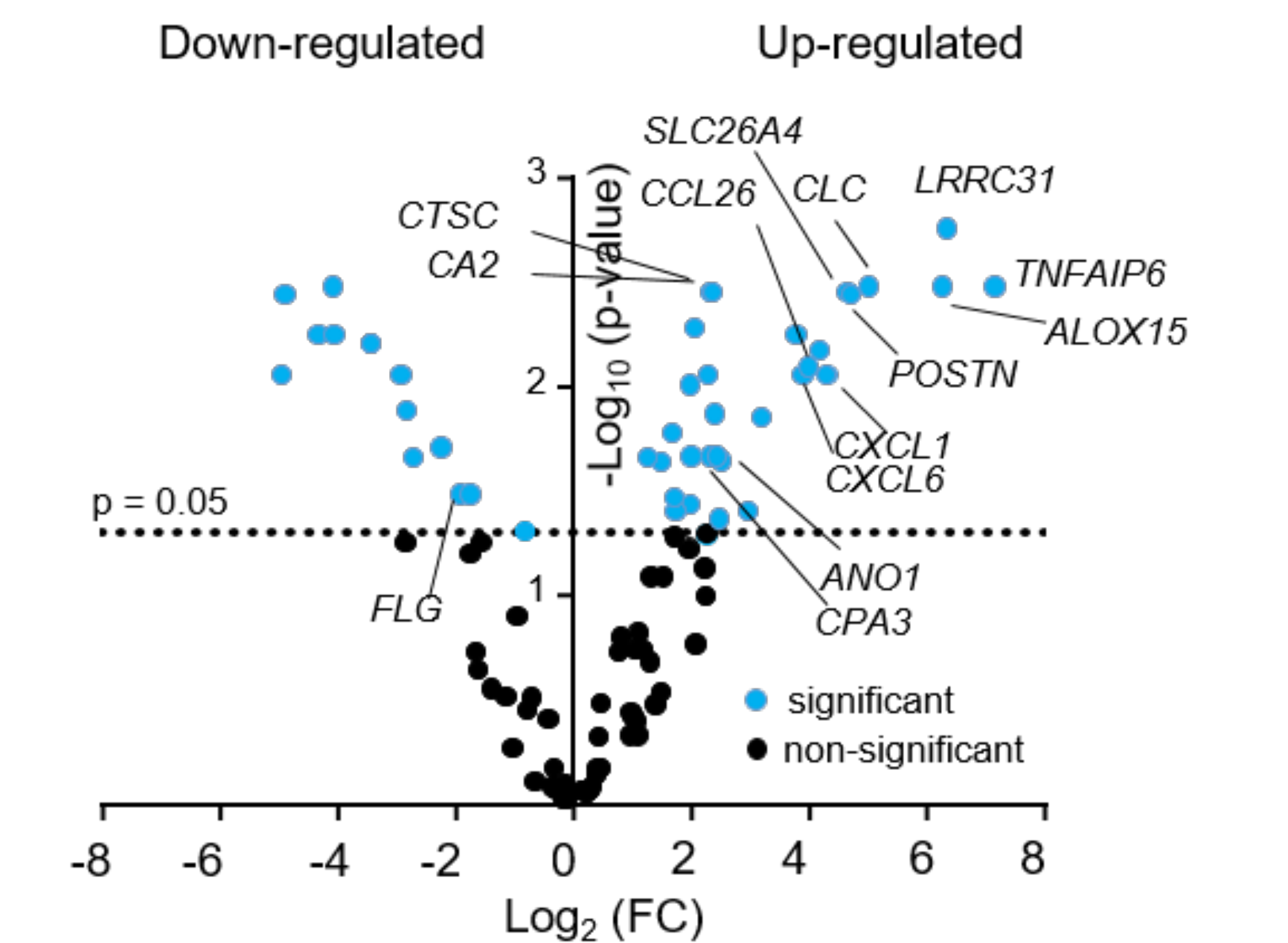
EI: eosinophilic infiltration
BZH: basal zone hyperplasia
EA: eosinophil abscess
ESL: eosinophil surface layering
DIS: dilated intercellular spaces
SEA: surface epithelial alteration
DEC: dyskeratotic epithelial cells
TLP: thickened lamina propria
RG: relative grade
RS: relative stage
****p \leq 0.0001, ***p \leq 0.001, **p \leq 0.01, *p \leq 0.05; ns, not significant.

Transcriptomic Analysis Revealed 30 Upregulated and 13 Downregulated Genes When Comparing EoE-Hi vs EoE-Low



When individual expression of the EoE Diagnostic Panel genes was compared between the 2 groups, there were 43 genes with significantly different expression (p < 0.05, fold change >2.0). This graph displays gene expression by category and negative log₁₀ p-value.

IL-13 Related Pathways Associate with Esophageal Eosinophil Levels



A volcano plot reflects a bidirectional fold change (log₂) and negative log₁₀ p-value (EoE-Hi vs. EoE-Low) for 96 genes. The 14 genes that previously have been reported to be regulated by IL-13 are labeled.

Summary

- Compared with patients with EoE with relatively low esophageal eosinophilia, patients with extremely high levels of esophageal eosinophilia present with:
 - increased incidence of atopic co-morbidities (specifically atopic rhinitis upon subcategorization)
 - older age at the time of esophageal biopsy
 - longer disease duration
 - more severe endoscopic effects
 - more severe histologic disease
 - a distinct molecular signature, especially enriched for IL-13-regulated genes.

- These patients may represent a unique endotype
- Patients with extremely high levels of esophageal eosinophilia may require more aggressive therapeutic intervention, including anti-IL-13-based agents.

References and Acknowledgements

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