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Exploring a predictive model for screening eosinophilic esophagitis in children with dysphagia

Julio César Moreno-Alfonso[1,2]; Rocío del Campo-Pedrosa[3]; Amit Beher[4]; Ada Molina Caballero[1]; Alberto Pérez Martínez[1]; María Concepción Yárnoz Irazábal[2,5]

1: Pediatric Surgery Department. Hospital Universitario de Navarra. Calle Irunlarrea, 3. C.P. 31008. Pamplona, Navarra; Spain.

2: Doctoral School of Health Sciences. Universidad Pública de Navarra (UPNA). Pamplona, Navarra; Spain.

3: Department of Mechanical Engineering, University of La Rioja, C.P. 26006. Logroño, La Rioja; Spain.

4: Pediatric Surgery Department. Klinikum Kassel GmbH, Kassel, Hessen; Germany.

5: General and Digestive Surgery Department. Hospital Universitario de Navarra. Calle Irunlarrea, 3. C.P. 31008. Pamplona, Navarra; Spain.

Corresponding author:

Julio César Moreno-Alfonso

email: juliomoreno.md@gmail.com

ORCID: https://orcid.org/0000-0002-0414-2888

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Dear Editor,

Eosinophilic esophagitis (EoE) is frequently associated with dysphagia and requires esophagoscopy with biopsies for diagnosis, as no reliable diagnostic biomarkers currently exist (1). While inflammatory indices derived from complete blood counts have been investigated in esophageal dysfunction, their role in screening for EoE remains unexplored (2). This study evaluates the utility of different predictive models for screening EoE through a diagnostic study of patients <15 years old undergoing esophagoscopy for suspected EoE in a pediatric hospital between 2015 and 2022 (Reg. 3318-0000206). Children with histologically confirmed EoE and those with normal biopsies were included, while patients diagnosed with other esophageal conditions (e.g., gastroesophageal reflux disease, esophagitis) were excluded. The area under the curve (AUC) was used to compare the peripheral eosinophil count and the eosinophil-to-lymphocyte ratio (ELR), eosinophil-to-monocyte ratio (EMR), and eosinophil-to-neutrophil ratio (ENR) between EoE and non-EoE (NEoE) patients; the ratios were calculated as the quotient between the aforementioned cells. The optimal cut-off points were determined, and logistic regression was used to identify the best-performing predictive model, which was internally validated using bootstrap techniques (n=1,000).

During the study period, 501 diagnostic endoscopies were performed, 46 of which were for suspected esophageal dysfunction. Ultimately, 24 patients with EoE and 17 with NEoE were included. The best predictive model included ELR and ENR, yielding a sensitivity of 88%, negative predictive value (NPV) of 79%, and false positive rate of 12% (**Table 1**).

The definitive diagnosis of EoE is established based on symptoms of esophageal dysfunction and biopsies showing >15 eosinophils/high-power field in the absence of other causes of

esophageal eosinophilia (3). Peripheral eosinophilia has been reported in EoE, particularly in untreated patients, although its sensitivity for detecting active esophagitis is low (4,5). Konikoff *et al*. demonstrated that peripheral eosinophilia correlates with esophageal eosinophil density (r=0.56, p=0.0001) and is elevated in active EoE compared to healthy controls (440 vs. 140 eosinophils/mm^3; p=0.05) (6). Recent studies have analyzed the role of eosinophilic indices in EoE diagnosis, showing promising results. The ELR, with a cut-off of 0.243 and an AUC of 0.767, exhibited a sensitivity of 54%, specificity of 94%, positive predictive value (PPV) of 93%, and NPV of 59% (2). However, this study did not evaluate the role of these indices in screening. Our findings align with these results, as combined eosinophilic indices proved to be valuable predictive models. Direct comparison remains challenging, as this is the first study assessing these biomarkers for EoE screening.

Despite the exploratory nature of our findings and methodological limitations related to sample size, our results suggest that the ELR + ENR model could serve as a useful clinical tool for screening patients with esophageal dysfunction. This model may help prioritize gastroenterology referrals and endoscopic evaluations when the predictive model is positive (ELR ≥0.25 + ENR ≥0.12) or consider less invasive initial studies in patients below this threshold (ELR <0.25 + ENR <0.12). Although the ELR + ENR model had lower specificity (62%) than the other predictive models (82%), it exhibited the highest NPV (79%) and lowest false negative rate (12.5%), minimizing missed diagnoses without significantly increasing unnecessary endoscopies. These findings could have significant implications in clinical practice, given the accessibility and low cost of obtaining cellular indices from complete blood counts. However, external validation through prospective studies is necessary, considering that cut-off values may be influenced by patient age, physiological variations in

leukocyte differentials, allergic history, or eosinophilia-related comorbidities.

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Table 1. Demographic and analytical characteristics of the studied population and predictive capacity of cellular indices models in eosinophilic esophagitis.

Variable	NEoE (n = 17)	EoE (n = 24)	*p* Value
Age (years)	12.9 (10.1 -14.3)	11.2 (9.4 -13.1)	0.213
Female n (%)	10 (58.8 %)	9 (37.5 %)	0.302
Male n (%)	7 (41.2 %)	15 (62.5 %)	
Lymphocytes	2324/mm^3 (2061-3448)	2998/mm^3 (2020-3362)	0.685
Neutrophils	3168/mm^3 (1976-3960)	2481/mm^3 (1998-2654)	0.184
Eosinophils	261/mm^3 (130-381)	636/mm^3 (375-954)	**0.005**
Monocytes	542/mm^3 (388-726)	515/mm^3 (440-561)	0.744
ELR	0.11 (0.07-0.17)	0.26 (0.16-0.33)	**0.003**
EMR	0.43 (0.31-0.77)	1.14 (0.78-1.89)	**0.004**
ENR	0.08 (0.05-0.14)	0.24 (0.14-0.39)	**0.002**

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Predictive model	ELR + EMR	ELR + ENR	EMR + Eosinophils	Eosinophils (6)*
AUC	0.793	**0.830**	0.779	_
Cut-off point	ELR= 0.25 EMR= 0.8	ELR= 0.25 ENR= 0.12	EMR= 0.8 Eosinophils= 492/mm^3	300/mm^3
Sensitivity	70%	**88**%	75%	75%
Specificity	82%	65%	**82.4**%	75%
PPV	85%	78%	**86**%	67%
NPV	67%	**79**%	70%	**82**%
LR+	4.0 (1.3-12)	2.4 (1.2-4.8)	**4.2** (1.4-12)	3
LR-	0.35 (0.18-0.69)	**0.19** (0.06-0.59)	0.30 (0.15-0.63)	0.33
PTP (+)	85% (66-94)	78% (64-87)	**86**% (68-94)	_
PTP (-)	33% (20-49%)	**21**% (8-45%)	30% (17-47)	_
FNR	29.1% (7/24)	**12.5**% (**3**/24)	25% (6/24)	_
FPR	**17.6**% (**3**/17)	35.2% (6/17)	**17.6**% (**3**/17)	_

Clinical value in screening	Model with the fewest endoscopies performed (n=**20**/41), but also the highest number of undiagnosed patients (n=7).	Most sensitive model with the lowest FNR. Therefore, although more endoscopies would be performed (n=27/41), fewer EoE patients (n=**3**) would be missed compared to other models.	Specific model with the highest PPV (86%). Only 21 out of 41 endoscopies would be performed, but **6** EoE patients would remain undiagnosed.	_

Bold values represent statistically significant differences or better performance of a metric. **AUC**: Area under the receiver operating characteristic curve; **PPV**: Positive predictive value; **NPV**: Negative predictive value; **LR+**: Positive likelihood ratio; **LR-**: Negative likelihood ratio; **PTP (+)**: Post-test probability for a positive result; **PTP (-)**: Post-test probability for a negative result; **FNR**: False negative rate; **FPR**: False positive rate. **(6)***: Comparison with peripheral blood eosinophil data from reference number 6.