Digestive and Liver Disease 58 (2026) 488–492

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Alimentary Tract

Evaluation of the diagnostic accuracy of two esophageal biopsy sites compared to three in histological follow-up of eosinophilic esophagitis – A multicentric study

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ARTICLE INFO

Article history:
Received 17 October 2025
Accepted 23 January 2026
Available online 17 February 2026

Keywords:
Diagnosis
Endoscopy
Esophagus
Immune-mediated
Eosinophils

ABSTRACT

Introduction and Aim: Guidelines recommend sampling 2–3 esophageal locations (4–6 biopsies) during EoE follow-up, but the optimal scheme is uncertain. We assessed whether two biopsies (distal, proximal) reliably classify activity versus three sites (distal, middle, proximal).

Methods: Retrospective analysis of EoE follow-up endoscopies (2020–2024, tertiary centers) with three-site histology. Active disease was defined as ≥15 eos/0.3 mm² in ≥1 site; sub-analyses used ≥6 and ≥1 eos/0.3 mm². We compared active/inactive classification for two-site (distal+proximal) versus three-site sampling.

Results: Among 634 histologic evaluations, 306 three-site sets and 293 two-site sets were positive at ≥15 eos/0.3 mm²; all 328 three-site negatives remained negative with two sites. Thus, omitting the middle site would miss 2.0 % of active disease. Two-site performance: accuracy 98.0 %, sensitivity 96 %, specificity 100 %, PPV 100 %, NPV 96 %, AUC 0.98 (95 % CI, 0.97–0.99), Cohen's κ 0.98. At ≥6 eos/0.3 mm², sensitivity 97 %, accuracy 98.6 %, AUC 0.98 (95 % CI, 0.98–0.99). At ≥1 eos/0.3 mm², sensitivity 99 %, AUC 0.99 (95 % CI, 0.98–0.99).

Conclusions: In EoE follow-up, two-site (distal+proximal) biopsies provide classification nearly equivalent to three-site sampling, with only a 2 % miss rate for active disease when the middle site is omitted. This approach may reduce procedure time, patient discomfort, and costs while maintaining excellent diagnostic performance.

1. Introduction

Eosinophilic esophagitis (EoE) is a chronic, progressive, T-helper type 2 immune-mediated disorder characterized by eosinophil-predominant inflammation and symptoms of esophageal dysfunction, occurring in the absence of secondary causes [1–4]. EoE remains among the leading causes of dysphagia in the outpatient setting, with an increasing prevalence trend in the last decades [5,6].

As the incidence is increasing, as well as the burden of the disease, a punctual and precise diagnosis is pivotal to avoid possible complications or more severe form of disease [7–9]. Indeed, clinical

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https://doi.org/10.1016/j.dld.2026.01.219

symptoms and endoscopic appearance in EoE often fail to reliably indicate the underlying histological activity [10–13]. As a result, carefully structured esophageal biopsy protocols are essential to achieve an accurate diagnosis and to monitor inflammation levels effectively [1,3,14]. These biopsies provide a more detailed view of mucosal health, ensuring that disease activity is precisely assessed, even when visual and symptomatic indicators may be misleading [15]. The number and location of biopsies needed for EoE diagnosis are well-established in most international consensus guidelines [1,3], yet there remains ongoing debate about the optimal biopsy protocol during follow-up endoscopies. Specifically, whether biopsy samples should be taken from two sites—the distal and either the middle or proximal esophagus—or whether four or six specimens should be to collected has not been fully investigated [16,17].

Although the variability in esophageal eosinophilia distribution, often referred to as a 'patchy esophagus,' is well-known [18–20], recent studies have shed light on its potential implications for refining biopsy strategies. Sorge et al. observed that while EoE typically involves the entire esophagus (64.4 % of cases), isolated distal or proximal involvement can still occur (27.5 % and 8.1 %, respectively), underscoring the need to consider multiple biopsy sites to avoid misdiagnosis [21]. This patchy eosinophil distribution aligns with findings from Godat et al., who reported a distal-to-proximal gradient in eosinophil density in many cases, though highest disease activity sometimes presented in the proximal esophagus [22].

This variability in the distribution of eosinophilic inflammation has important implications for the diagnostic accuracy of esophageal biopsies. In clinical practice, however, evidence is limited regarding the optimal biopsy strategy during follow-up endoscopies, and no consensus exists on how many sites must be sampled to reliably detect ongoing disease activity. Because additional biopsy sites increase both procedure time and tissue burden without necessarily improving diagnostic yield, it is crucial to determine whether a simplified protocol can perform comparably to the standard approach. Therefore, the present study aims to evaluate whether a two-site strategy (distal and proximal esophagus) provides diagnostic accuracy equivalent to the traditional three-site protocol (distal, middle, and proximal) during follow-up assessment of eosinophilic esophagitis.

2. Methods

A retrospective analysis was conducted on esophagogastroduodenoscopies with three-site biopsies from patients with EoE performed between January 2020 and October 2024 at four Italian tertiary centers. Included patients were adults (≥18 years old) with a previously confirmed histological diagnosis of EoE according to current diagnostic guidelines, undergoing follow-up endoscopy to reassess disease activity [1,3,23,24]. At least two samples from three different sites of esophagus (distal, middle and proximal) were considered adequate for inclusion.

Exams with incomplete three-site biopsy samples or imprecise eosinophil counts were excluded (32 total exams with incomplete three-site bioptic samples were not included, as reported in STROBE Fig. 1). Data were collected from medical records, including demographic and anthropometric characteristics, disease duration, ongoing specific EoE therapy, and endoscopic severity assessment using the endoscopic reference score (EREFS: edema, rings, exudates, furrows, strictures) [25].

Disease activity was histologically defined as the presence of ≥15 eos/0.3 mm^2 in at least one biopsy site. We also evaluated more strict levels of eosinophilic infiltration using cutoffs of ≥6 and ≥1 eos/0.3 mm^2 [26]. The histological response to therapies based on two-site biopsies (distal and proximal esophagus) was compared to the standard three-site protocol (distal, middle, and proximal esophagus). Additional sub-analyses compared the three-site biopsy protocol with another two-site approaches (i.e., distal + middle vs. proximal + middle).

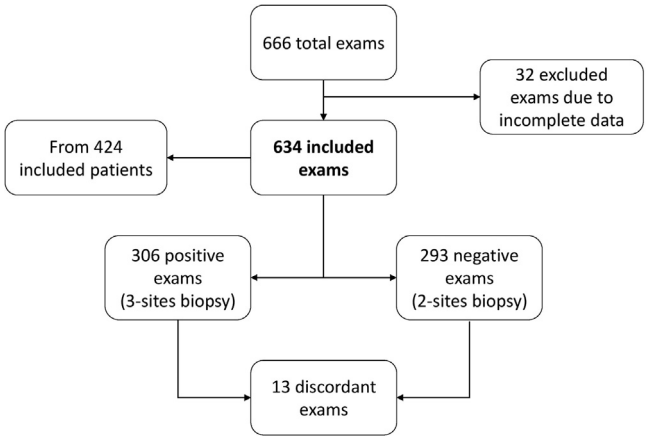

Fig. 1. STROBE flow diagram of the study. "Positive" and "negative" exams refer to histological activity of remission according to presence of ≥15 eos/0.3 mm^2 in ≥1 site.

Table 1
Therapy at the moment of follow-up endoscopy.

Total (n = 634)	Therapy (n, %)
PPI	162 (25.5)
Orodispersive budesonide	383 (60.4)
Oral viscous budesonide	69 (10.9)
Fluticasone	2 (0.4)
Prednisone	1 (0.2)
Elimination diet	4 (0.7)
Mepolizumab	9 (1.4)
Upadacitinib	1 (0.2)
Dupilumab	3 (0.5)

Abbreviations: PPI: proton pump inhibitors;.

Statistical analyses were performed to assess the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy of the two-site approaches compared to the three-site protocol. Cohen's kappa was used to evaluate inter-method agreement, and the McNemar test was applied to compare classification outcomes.

This study involved a retrospective analysis of anonymized clinical and histological data collected during routine care. In accordance with institutional policies for non-interventional retrospective studies, formal ethics committee approval and specific informed consent for study participation were not required. All patients had previously provided general consent for the use of their anonymized clinical data for research purposes at the time of their clinical evaluation. The study was conducted in accordance with national regulations and the principles of the Declaration of Helsinki.

3. Results

The overall population included in the study was 424 patients with a median age of 33 years (IQR 24.0 – 47.0), predominantly men (342, 80.7 %) and, with a median disease duration of 2 years (IQR 0.9–4.1).

A total of 634 endoscopies were considered and the therapies administered at the time of the endoscopic examination were the following: 383 (60.4 %) examinations were on orodispersible budesonide therapy, 162 (25.5 %) were on PPI therapy and 69 (10.9 %) were on viscous budesonide preparation therapy. Details are summarized in Table 1. The Median EREFS score was 2.0 (IQR

1.0–3.0). As reported in STROBE Fig. 1, 32 examinations were not excluded due to incomplete data.

Among the 634 histological results analyzed, 306 three-site biopsies (distal, middle, proximal) and 293 two-site biopsies (distal, proximal) were positive for disease activity (≥15 eos/ 0.3mm^2). This indicates that 13 (2.0 %) of active cases were missed when omitting the middle esophageal biopsies. The two-site biopsy approach (distal + proximal esophagus) demonstrated a diagnostic performance with an overall accuracy of 98.0 %, achieving a sensitivity of 96 %, specificity of 100 %, positive predictive value (PPV) of 100 %, and negative predictive value (NPV) of 96 %. The area under the receiver operating characteristic curve (AUC) was 0.98 (95 % CI 0.97–0.99). Cohen's kappa was 97.95, signifying almost perfect agreement between the two-site and three-site methods.

When the cut-off was lowered to 6 eosinophils per 0.3 mm², the two-site protocol reached a sensitivity of 97 % and an AUC of 0.99 (95 % CI 0.98–0.99), with an overall accuracy to 98.6 % (Table 2). The missed cases with this threshold would have been 9 (1.4 %). However, at a threshold of 1 eosinophil per 0.3 mm², sensitivity was 99 %, with a corresponding AUC of 0.99 (95 % CI 0.98–1.00), and an overall accuracy of 99 %, reflecting a number of missed cases of 5 (0.8 %).

The diagnostic performance of two other possible biopsy site combinations (distal + middle and middle + proximal) was also evaluated. Sensitivity, negative predictive value (NPV), and area under the curve (AUC) for these combinations are presented in Table 3.

When comparing the 13 discordant cases — those positive only due to the mid-esophageal biopsy — with concordant cases identified as positive by both the three-site and the two-site (distal + proximal) protocols, no statistically significant differences were observed. Age (40.0 years, IQR 24.5–49.0 vs 33.0 years, IQR 22.0–48.0, $p = 0.200$), male sex prevalence (84.6 % vs 81.7 %, $p = 0.952$), disease duration (2.0 years, IQR 1.0–3.0 vs 2.0 years, IQR 1.0–3.0; $p = 0.581$), EREFS score (1.0, IQR 0–3.0 vs 2.0, IQR 1.0–3.0; $p = 0.282$), and PPI use (23.1 % vs 25.1 %, $p = 0.997$) were all comparable between groups. Finally, the overall esophageal distribution in active patients (≥15 eos/0.3 mm²) was diffuse across all segments in 247 (80.7 %) of cases. Among the remaining positive cases, the distribution was as follows: only proximal (6.9 %), distal + middle (5.9 %), middle + proximal (3.9 %), distal + proximal (1.4 %), only distal (1.1 %), and only middle involvement (0.1 %), as shown in Fig. 2.

Table 2
Accuracy of two sites biopsies (distal + proximal esophagus).

	Cut-off 15 eos/ 0.3mm2	Cut-off 6 eos/ 0.3mm2	Cut-off 1 eos/ 0.3mm2
Sensitivity	96 %	97 %	99 %
Specificity	100 %	100 %	100 %
Positive Predictive Value	100 %	100 %	100 %
Negative Predictive Value	96 %	97 %	99 %
Area Under the Curve	0.98	0.98	0.99

Table 3
Comparison of accuracies of different two sites biopsies (distal + proximal, distal + middle, middle + proximal).

	Distal-proximal	Distal-middle	Middle-proximal
Sensitivity	96 %	97 %	90 %
Specificity	100 %	100 %	100 %
Positive Predictive Value	100 %	100 %	100 %
Negative Predictive Value	96 %	97 %	92 %
Area Under the Curve	0.98	0.98	0.95

4. Discussion

With the increasing prevalence of EoE and the corresponding rise in endoscopic examinations, the optimal biopsy approach for follow-up patients remains a topic of ongoing debate. Despite established guidelines for initial diagnosis, practices for follow-up procedures performed to assess disease activity and therapeutic response are still heterogeneous across clinical centers. This variability reflects both the patchy distribution of eosinophilic infiltration in the esophagus and the lack of consensus on the minimal number and locations of biopsies needed to ensure reliable follow-up assessment [17,21–23].

Our study addresses this gap by evaluating the diagnostic accuracy of a two-site biopsy protocol (distal and proximal esophagus) compared to the standard three-site approach (distal, middle, and proximal esophagus). The findings demonstrate that the two-site protocol achieves high diagnostic accuracy (98 %) with a sensitivity of 96 % and a specificity of 100 %, with 15 eos/0.3mm2 cut-off. These results might suggest that omitting biopsies from the middle esophagus resulted in a low histological case-missing rate (2 %), without allowing conclusions regarding symptom-related clinical impact. In the sub-analysis of discordant cases, no substantial differences were observed between endoscopically active and inactive disease. However, data on the inflammatory versus fibrotic components of the EREFS score were insufficient. It is possible—though purely speculative—that the presence of inflammatory markers of active disease, rather than fibrotic features, might have guided targeted biopsies and thereby reduced the total number of biopsies needed. Given the heterogeneous distribution of eosinophils in the esophagus, increasing the number of biopsies and sampling locations undoubtedly enhances the likelihood of detecting areas of eosinophilic infiltration. However, this approach must be weighed against the practical constraints of clinical practice, particularly in an era where achieving sustainable endoscopy is an important goal [27,28]. Nielsen et al. demonstrated that taking more than six esophageal biopsies does not provide any additional diagnostic benefit in diagnosing EoE [29]. In our study, which focused on follow-up evaluations of patients with an established diagnosis of EoE, the diagnostic accuracy was comparable to Nielsen et al. [29]. In real-world scenarios, where the frequency of follow-up endoscopic examinations is rising, procedures are often conducted within limited time frames and without dedicated sessions for EoE patients. This necessitates a streamlined and efficient approach that maintains diagnostic accuracy while accommodating the logistical constraints of busy endoscopy units. Nevertheless, given the high frequency of endoscopic monitoring required for accurate diagnosis and management, EoE contributes a substantial economic burden. The annual healthcare costs for EoE patients in US are estimated at a median of $3304, significantly higher than the $1001 median for controls, with endoscopic procedures alone contributing approximately $157 per year per patient [30]. When scaled to the national level, the total annual burden in 2024 was estimated at $1.32 billion, highlighting the substantial and growing economic impact of the disease [31]. In the setting of the rising incidence of EoE and its management beyond tertiary referral centers, the generalizability of biopsy-sparing strategies warrants caution. Although reducing the number of biopsies may offer practical advantages, our findings should not be interpreted as supporting a generalized reduction in biopsy sampling. Rather, they provide histological evidence derived from a selected follow-up population with established EoE. Given the retrospective design of the study and the lack of detailed endoscopic characterization distinguishing inflammatory from fibrotic features, firm recommendations for broader clinical practice cannot be made.

The minimal discrepancy between the two approaches is further supported by the strong agreement observed in classification

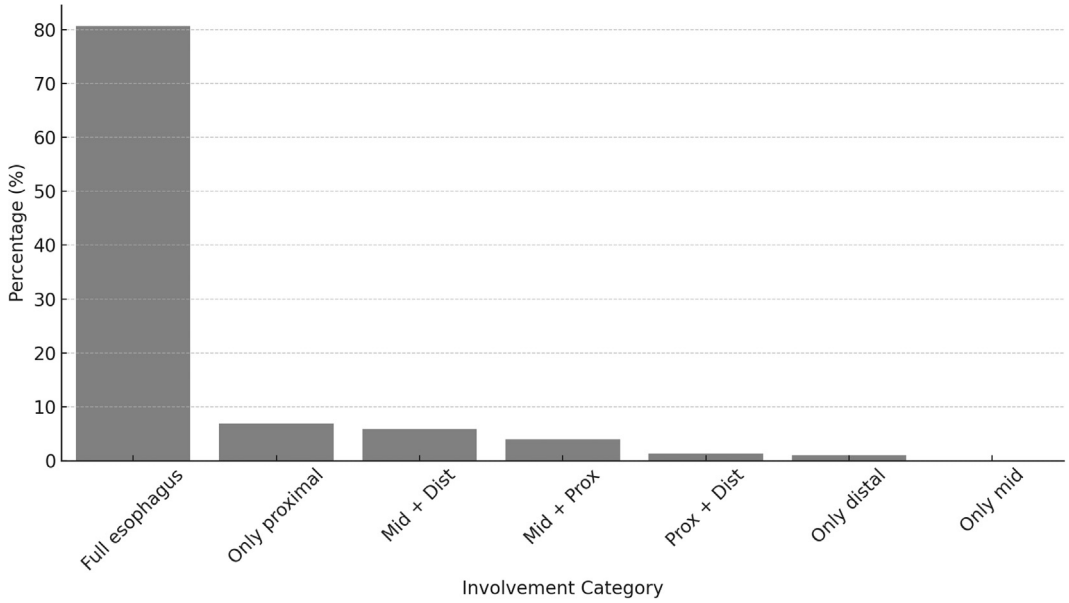

Fig. 2. Distribution of esophageal involvement in the different esophageal segments.

outcomes (Cohen's kappa=97.95). Additionally, the AUC of 0.98 for the two-site protocol reinforces its robustness, highlighting its potential as a simplified yet reliable alternative for monitoring EoE activity. Lowering the eosinophil threshold from 15 to 6 or even 1 eos/0.3 mm^2 resulted in a slight gain in sensitivity and negative predictive value, while maintaining perfect specificity and positive predictive value across all thresholds.

General characteristics of the population reflects the literature reported prevalence, with young adult males being predominant in this cohort. Most of the patients were receiving orodispersive budesonide, followed by PPI and viscous budesonide preparation. Type of ongoing therapy, age, gender, EREFS score, and median disease duration did not differ significantly in discordant cases. However, the very small number of discordant cases relative to the overall population limits the ability to draw definitive conclusions.

Regarding the distribution of the eosinophils in the esophagus, also defined as "patchy" in EoE, most studies agree that distal esophagus is always involved, while isolated middle and proximal involvement are less frequent, at 2.7 % and 2.3 %, respectively [18,20–22]. While the proximal esophagus is often described as slightly less involved than the middle, similar results were observed in our cohort, as showed in Fig. 2.

This variability underscores the importance of strategic biopsy site selection to capture disease activity and minimize diagnostic oversight. From this standpoint, we sub analysed also the combination of distal and middle site and the combination of distal and proximal site, with the best accuracy present in the combination of proximal or middle and distal site (Table 3).

This study has the limitation of the retrospective design, which inherently carries the potential for biases, including variability in data quality and selection criteria. The lack of patient-reported symptoms of esophageal dysfunction represents a relevant limitation, given the central role of symptoms in the diagnosis and assessment of treatment response in EoE. Additionally, the exclusion of examinations with incomplete data (Fig. 1) may have introduced a selection bias. A further limitation is that EREFS findings were not used to guide biopsy acquisition. Consequently, we could not assess whether fewer biopsies might have been sufficient in patients with targeted sampling of inflammatory endoscopic features, which are associated with higher eosinophil counts. Nevertheless, performing six biopsies in all patients strengthens the validity of our findings, given that this approach has been shown to achieve an AUC close to 100 %. There could be inter-observer heterogeneity among pathologists and potential variability in biopsy technique across different centers. However, the multicentric nature of the study strengthens its external validity by incorporating data from diverse clinical settings, and the large sample size provides sufficient statistical power to support the robustness of the analysis and the reliability of the conclusions.

Future research should focus on validating these findings in prospective settings and exploring whether specific subgroups of EoE patients—such as those with atypical presentations or refractory disease—might benefit more from the three-site approach. This could be true until reliable non-invasive markers would allow to safely and precisely spare endoscopic and histological examination [32–34].

In conclusion, our findings suggest that a two-site biopsy protocol represents an accurate strategy for the assessment of disease activity in patients with treated EoE undergoing follow-up endoscopies. However, further prospective studies are needed to define which subsets of patients may safely undergo a reduced biopsy protocol and which still require comprehensive three-site sampling, particularly outside tertiary referral centers.

Funding

none

Declaration of competing interest

FC, MF, GB, AS, MC, MV, BM, GA, TP, DM, EGG has no conflict of interest. FG has served as speaker for Astellas, AstraZeneca, Beigene, BMS, Daiichi-Sankyo, GSK, Incyte, MSD, Pierre Fabre, Servier and has served as consultant for Beigene, GSK, MSD; LM has served as consultant for Astellas, Beigene, BMS, MSD, Beigene; RP has served as speaker for Sofar and Dr Falk; PV has served as speaker for Dr. Falk, JB Pharmaceuticals, Malesci; NdB Advisory board member for: AlfaSigma, Sanofi Genzyme, Dr.Falk; Lecture grants from Reckitt-Benkiser, Malesci, Dr. Flak, Sofar, Alfa-Sigma, Pharma-Line; EVS has served as speaker for Abbvie, Agave, AG-Pharma, Alfasigma, Aurora Pharma, CaDiGroup, Celltrion, Dr Falk, EG Stada Group, Fenix Pharma, Fresenius Kabi, Galapagos, Janssen, JB Pharmaceuticals, Innovamedica/Adacyte, Malesci, Mayoly Biohealth, Omega Pharma, Pfizer, Reckitt Benckiser, Sandoz, SILA, So-

far, Takeda, Tillots, Unifarco; has served as consultant for Abbvie, Agave, Alfasigma, Biogen, Bristol-Myers Squibb, Celltrion, Diadema Farmaceutici, Dr. Falk, Fenix Pharma, Fresenius Kabi, Janssen, JB Pharmaceuticals, Merck & Co, Nestlè, Reckitt Benckiser, Regeneron, Sanofi, SILA, Sofar, Synformulas GmbH, Takeda, Unifarco; he received research support from Pfizer, Reckitt Benckiser, SILA, Sofar, Unifarco, Zeta Farmaceutici; EM Dr Falk, Sanofi, Pharmaline, Alfasigma.

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