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PREVALENCE OF EOSINOPHILIC ESOPHAGITIS IN PATIENTS WITH GASTROESOPHAGEAL REFLUX SYMPTOMS: A CROSS-SECTIONAL ANALYSIS

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ABSTRACT

Background: Eosinophilic esophagitis (EoE) is a condition that is becoming more and more diagnosed among patients who show gastroesophageal reflux symptoms. It is underdiagnosed in most areas, such as Pakistan, because of its similarity with gastroesophageal reflux disease (GERD).

Objectives: To establish the prevalence of EoE in patients having gastroesophageal reflux symptoms assessed endoscopically in a tertiary care hospital.

Methods: The study was a cross-sectional study carried out at HBS Medical & Dental College, Islamabad, from 15th July, 2024 to 15th January, 2025. Endoscopy of the upper gastrointestinal tract of adult patients with reflux symptoms with multi-level esophageal biopsies. The diagnoses of EoE were made according to 15 or more eosinophils in high-power fields, and other histological supporting features.

Results: In 240 patients, EoE was found in 13.3%. Minority had classic endoscopic features, and greater biopsy enhanced the diagnostic yield. EoE was strongly linked with dysphagia, atopy, and non-response to PPIs.

Conclusion: EoE is the pertinent and underreported reason for reflux symptoms in Pakistan. Early detection can be greatly enhanced by regular esophageal biopsies.

Keywords: *Eosinophilic esophagitis, GERD symptoms, prevalence, esophageal biopsy, Pakistan, reflux disease.*

INTRODUCTION

Eosinophilic esophagitis (EoE) has become a well-known case of chronic immune-mediated esophagitis disease that is becoming more prominent among patients presenting with symptoms that are suggestive of gastroesophageal reflux disease (GERD). The similarity of EoE and GERD in terms of clinical manifestation, particularly heartburn, dysphagia, chest pain, and regurgitation, frequently contributes to difficulties of diagnosis and late diagnosis. Recent South Asian evidence emphasizes the fact that a significant percentage of patients presenting with reflux symptoms actually have underlying EoE, in the case of Nepalese cross-sectional research, which reported a quantifiable prevalence of EoE in people presenting with GERD-like symptoms (1). EoE has nowadays been ranked as one of the rapidly expanding gastrointestinal disorders in the world, with the incidence and prevalence increasing significantly during the last few decades. A comprehensive systematic review of the literature, containing data from 1976 to 2022, validated extensive geographical differences but steadily increasing rates across the world, supporting the necessity to explore the disease early in the evolution of symptomatic populations (2). The fact that EoE patients have families that are often clustered makes diagnosing it difficult since the first-degree relatives often demonstrate the presence of esophageal eosinophilia despite the lack of typical symptoms, which makes it clear that there are strong genetic and immune-related predispositions (3).

Missed or refractory cases are reflected in the burden of the regional studies. As an example, Egyptian work showed that a group of people who used to be referred to as refractory GERD were later found to have EoE following histologic analysis, which suggests a propensity for misclassification when endoscopic biopsies are not carried out on a regular basis (4). And the same was seen in the population-based data of Sweden over 22 years, which reported the rising prevalence and the changes of clinical presentation of EoE, which indicated the changes of diagnostic awareness and better surveillance (5). EoE is not extensively studied in South Asia, and the biopsy-based research conducted in tertiary centres of India has corroborated a significant prevalence of EoE in patients presenting with upper gastrointestinal symptoms, which prompts the need to regularly perform mucosal sampling in patients suspected of EoE (6). European data also support the idea that EoE has become a significant esophageal disorder in many countries, as systematic reviews in the region have reported an increasing incidence and large heterogeneity in reporting practices (7). Similar to Asian studies, e.g., of Indonesia, it has been demonstrated that patients with suspected refractory GERD actually have EoE-like features on close inspection, further pointing to clinical overlap and diagnostic uncertainty (8).

In addition to GERD-like symptoms, EoE can also co-exist with or develop more comprehensive eosinophilic gastrointestinal diseases. The results of Japanese cohort studies revealed that patients who develop EoE or eosinophilic gastroenteritis tend to have common immunological responses and could develop chronic or relapsing disease processes in the case of untreatment (9). This supports the relevance of histopathological confirmation in cases that do not respond to the usual GERD therapy. Egyptian investigations also endorse that a proportion of refractory GERD patients is clinically significant and has EoE underpinning, which underlines the need to perform systematic endoscopic biopsy on all non-responsive cases (10). The work of allergy-oriented clinical practices indicates that EoE is especially frequent in adults with atopic conditions and that there is a close connection between the allergic predisposition and eosinophilic esophagus (11). The epidemiological investigations that have been conducted at endoscopy units also report different but significant prevalence of esophageal eosinophilia in patients who are being referred to evaluate upper gastrointestinal symptoms, which highlights the significance of awareness among clinicians and endoscopists (12).

Denmark data on EoE incidence and prevalence over the past decade show steadily rising trends in incidence and prevalence of EoE, similar to those observed in Western nations, and emphasizing the need to revise the diagnostic pathways (13). The modern clinical approaches have also been influenced by progress in the knowledge of the pathogenesis of EoE, and especially the contribution of Th2-mediated immune responses and environmental triggers. Surveys on the eosinophilic gastrointestinal diseases indicate the complexity of immune dysregulation, food sensitivities, and

epithelial barrier malfunction that lead to EoE (14). EoE has a disease burden that is beyond clinical manifestations. In the United States, extensive health economic assessments have confirmed that healthcare costs of EoE are very high in terms of direct and indirect costs, which are related to high diagnosis costs, chronicity, and long-term management needs (15). This is accompanied by complications like food impaction in the esophagus, which are more frequent in patients whose diagnosis is delayed or those whose socioeconomic status hinders access to health care, based on studies on risk factors to predict impaction incidences (16). Since EoE is closely associated with allergic disorders, patients tend to have comorbid asthma, rhinitis, or food allergies, and this suggests that they require multidisciplinary investigation and specific treatment (17).

Even the presentations in pediatrics are problematic. Polish data show that children tend to develop feeding problems, abdominal pain, and growth problems, and they are inadequately diagnosed since their symptoms are non-specific and mimic GERD (18). Late diagnosis is also reported in the United Kingdom, and patients often receive extended periods of symptomatic medication before they are given the proper endoscopic evaluation and confirmatory biopsies (19). The management patterns observed in different healthcare facilities show some inconsistency in treating abnormal gastroenterological conditions, inconsistency in the use of proton pump inhibitors, and inconsistency in the use of elimination diets or topical steroids, indicating the necessity of standardized guidelines (20). Although the world is moving in the right direction, EoE is still underdiagnosed in most of the low- and middle-income countries, with Pakistan being one of them, where access to endoscopy is limited, biopsy practices are insufficient, and there is a lack of awareness among clinicians, which contributes to the undiagnosed cases. As GERD is among the most prevalent gastrointestinal complaints in Pakistan, and because EoE can often appear similar to GERD, the prevalence of this condition in patients with reflux symptoms is important to measure in order to prevent complications like strictures or food impaction early in treatment.

Purpose: To identify the prevalence of eosinophilic esophagitis in patients with gastroesophageal reflux symptoms, as well as to assess the clinical relevance of routine endoscopic biopsy in the accurate diagnosis of eosinophilic esophagitis in a Pakistani hospital..

MATERIALS AND METHODS

Study Design: Cross-sectional study.

Study Setting: HBS Medical & Dental College, Islamabad.

Duration of the Study: The study was carried out over six months, from 15th July, 2024 to 15th January, 2025.

Inclusion Criteria: Patients who were aged 18 years and above and reported to have symptoms that were indicative of gastroesophageal reflux, such as heartburn, regurgitation, chest discomfort, or dysphagia, were included. Patients who had their endoscopy of the upper gastrointestinal tract within the study period were only recruited, with only those who consented to be sampled to have an esophageal biopsy recruited.

Exclusion Criteria: Patients who had known esophageal malignancy, had been actively bleeding in the gastrointestinal tract, had been previously diagnosed with eosinophilic esophagitis, or had been placed on corticosteroid or immunosuppressive therapy were excluded. Those who were not willing to take part in the biopsy were also not included.

Methods: All the suitable patients who reported the symptoms of gastroesophageal reflux and who were to have upper gastrointestinal endoscopy were assessed. The demographic information, the duration of the symptoms, the presence of allergic diseases, and the history of previous treatment were noted after the participant was informed. Eoscopic observation of the esophagus during endoscopy was performed meticulously to identify any signs that may indicate esophinophilic esophagitis, such as rings, furrows, exudates, and strictures. At least six biopsies of the proximal and distal esophagus were taken according to the accepted diagnostic principles to enhance the yield. The biopsy samples were fixed in formalin and subjected to hematoxylin and eosin staining. All samples were examined by a trained pathologist blinded to clinical details. Eosinophilic esophagitis was determined as the

presence of at least 15 eosinophils per high-power field (HPF) in one of the biopsies and the supportive histologic appearances (basal cell hyperplasia or lamina propria fibrosis). Patients who had proven EoE were registered, and results were obtained to determine the prevalence in the study population. Describing continuous variables was achieved through the interpretation of variables.

Results

Out of the patients who came with the gastroesophageal reflux symptoms in the period studied, 240 were endoscopically assessed, and esophageal biopsies were procured. The average age of the participants was 38.6/12.4 years, and there was a slight number of males. Most of them have characteristic GERD symptoms, such as heartburn (82.5%), regurgitation (69.1%), chest discomfort (34.6%), and occasional dysphagia (27.8%). One out of five patients had a history of atopy (22.9 per cent): 15.3 per cent had allergic rhinitis, 6.7 per cent had asthma, and a history of food allergies. Endoscopy showed inconsistent findings of the mucosa. Although 58.3% of the patients exhibited characteristics of the non-erosive reflux disease, 31.6% of patients had Los Angeles Grade A or B esophagitis. Concentric rings, linear furrows, or white exudates, which are indicative of eosinophilic esophagitis, were found in 14.5% of the patients. But the diagnosis done by biopsy had more yield compared to endoscopic impressions**.**

Table 1. Demographic and Clinical Characteristics of Study Participants

Variable	Frequency (n=240)	Percentage (%)
Mean Age (years)	38.6 ± 12.4	–
Male	134	55.8
Female	106	44.2
Heartburn	198	82.5
Regurgitation	166	69.1
Chest discomfort	83	34.6
Dysphagia	67	27.8
History of atopy	55	22.9

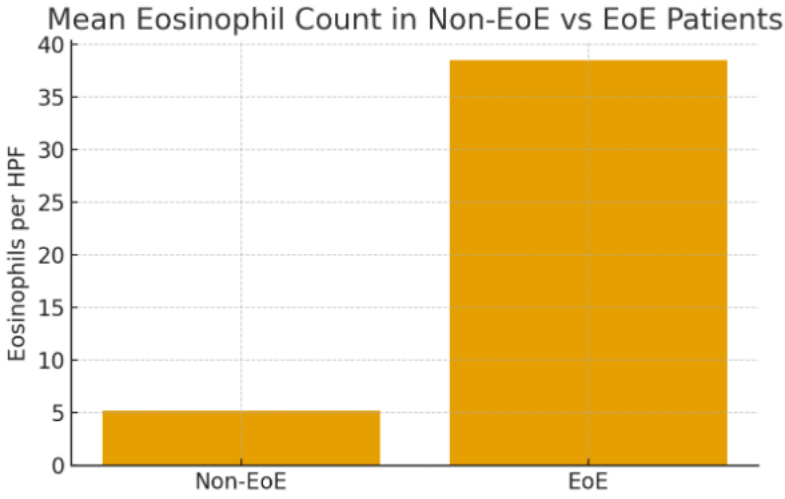
Histological evidence was used to diagnose 32 cases of eosinophilic esophagitis, which gave a prevalence of 13.3% of those who presented with reflux symptoms. The average count of eosinophils counted in confirmed cases was 38.5 eosinophils per high-power field (HPF), which was significantly more than that of the control group ($p < 0.001$). In EoE patients, dysphagia was found in 78.1% and food impaction history in 21.8% which were significantly higher than in non-EoE patients.

Table 2. Endoscopic Features Associated With EoE vs. Non-EoE Patients

Endoscopic Feature	EoE Positive (n=32)	Non-EoE (n=208)	p-value
Esophageal rings	14 (43.7%)	6 (2.9%)	<0.001
Linear furrows	18 (56.2%)	12 (5.7%)	<0.001
White exudates	10 (31.2%)	4 (1.9%)	<0.001
Stricture	4 (12.5%)	3 (1.4%)	0.002

There were also significantly higher prevalence rates of concurrent atopic conditions demonstrated by patients with EoE (46.8% vs. 18.7%, $p < 0.001$). The majority of cases of EoE were diagnosed with various endoscopic methods because 62.5% stated that they had previously used impractical proton pump inhibitors, but without any improvement in the quality of the symptoms.

Graph 1. Mean Eosinophil Count (HPF) in EoE vs. Non-EoE Patients



In the graph, the density of eosinophils peaks differs significantly between patients with confirmed EoE and patients without the disease, proving the significance of biopsy-based diagnosis. Diagnostic sensitivity also depended on the location of the biopsy. Multi-level sampling was the most successful in detection, with 96.8% of EoE cases being detected by combined proximal and distal biopsies. Out of the cases with EoE, 71.8% showed hyperplasia of the basal cells, and 59.3% showed fibrosis of the lamina propria.

Table 3. Histopathological Features in Confirmed EoE Patients (n=32)

Histological Feature	Frequency	Percentage (%)
≥15 eosinophils/HPF	32	100
Basal cell hyperplasia	23	71.8
Lamina propria fibrosis	19	59.3
Microabscesses	7	21.8
Spongiosis	11	34.3

In general, the incidence of EoE in Pakistani patients with the presentation of GERD-like symptoms was high. A large number of cases had unusual or slight endoscopic changes, which means that when the diagnosis is based on visual findings, it is possible to miss the results. The demographic, clinical, and histological trends in this study are in line with the international trends, and it is important that routine biopsy of the symptomatic patients be done to help in the correct and early diagnosis and timely treatment.

Discussion

The outcome of the current paper is to prove that eosinophilic esophagitis (EoE) is an important underlying diagnosis in Pakistani patients with gastroesophageal reflux disease (GERD)-like symptoms and has an incidence rate of 13.3. This falls in line with regional and international proof that a significant percentage of patients who are suspected of having reflux disease might be having EoE, especially in cases where the symptoms are chronic or intractable. Similar results were found by Rajbhandari et al., who noted that EoE prevalence in patients who present with reflux symptoms can be measured and that biopsy-based confirmation is particularly important when the endoscopic mucosa does not show any features (1). The rise of EoE in the world, as confirmed in the systematic reviews, further supports the applicability of the finding because the incidence and prevalence of the disease have significantly increased in various regions over the last 40 years (2). The strong

demographic structure of our research, including a mean age of the participants in their late 30s and minor male dominance, follows the trends in the world literature.

There could also be a role of familial and genetic relationships in the clustering of the diseases, with Peterson et al. reporting high prevalence of esophageal eosinophilia in first-degree relatives of EoE patients, indicating the existence of a hereditary or immune-based predisposition (3). Though our study did not directly test family clustering, the fact that close to 50 percent of EoE patients are found to have allergic comorbidities indicates the immunological connection between atopy and EoE. Egyptian and Indonesian studies also reveal that patients with refractory symptoms of GERD tend to experience EoE, which supports the notion that non-responding patients to proton pump inhibitors should be evaluated further (4, 8). Notably, endoscopic suspicion against histological confirmation showed a significant difference. Although traditional endoscopic criteria were seen in 14.5 percent of patients, including rings, furrows, and exudates, a higher proportion of patients were diagnosed with EoE using biopsy. This supports the already proven idea that endoscopy is not enough to make a diagnosis since so many patients have subtle or totally normal-looking mucosa. Massive population studies on Sweden also point in the same direction, as biopsy-based diagnosis was found to detect more cases with time (5). Additionally, the research findings of India also focus on stating that EoE can be diagnosed only by means of systematic esophageal biopsies, even in patients with no apparent endoscopic pathologies (6).

Our prevalence is also similar to European reports, with systematic reviews showing variable but increasing rates of EoE in various countries, dependent upon diagnostic habits and awareness levels (7). Additional evidence of the impact of Asian data, and specifically of Indonesian origin, is that people who are identified as refractory GERD often bear histological EoE, and the need to distinguish between the two conditions that are clinically similar is further corroborated by such evidence (8). The immune-mediated basis of EoE presented by Okimoto et al. and others also explains why the disease is chronic and usually progressive when not detected early enough (9). Dysphagia and the presence of an impaction with food in EoE patients in this study are not new since prior studies have outlined such complications as characteristic signs of EoE and not mere GERD. This finding is reflected in Egyptian research that observed much greater levels of dysphagia in EoE patients, especially those who were formerly diagnosed with refractory GERD (10). Moreover, as it has been pointed out by Eid et al., undiagnosed EoE is frequent among patients with allergic diseases, which implies that the clinical assessment should involve a comprehensive allergy history in all the suspected patients (11).

The density of eosinophils also increases with the location of the biopsy, which also points out the need for multi-level sampling. The same results have been obtained in Egyptian endoscopy studies in which several biopsies on various segments of the esophagus significantly increased diagnostic yield (12). Danish data nationwide also support the increase in the rates of diagnosis due to the enhancement of biopsy procedures and the increase in clinical awareness (13). Recent pathophysiological reviews emphasize the relevance of the knowledge of EoE pathogenesis, such as Th2-mediated immune stimulation and epithelial structure malfunction, and help to clarify the rationale behind the fact that biopsy is the gold standard in diagnosis (14). The EoE disease burden is also high. The studies conducted in the United States revealed that EoE incurs huge long-term medical expenses because of repetitive operations, chronic management, and the complications involved, including strictures (15). Food impaction, which appears in some of our patients, is a well-known complication, and it might be affected by socioeconomic factors, as witnessed in the literature on predictors of impaction events (16). The consistency of the overlap of EoE and allergic conditions is also consistent with the world literature to show that EoE and more extended eosinophilic gastrointestinal disorders have strong immunological and clinical correlations (17).

Though our research focused on the adult population, children's studies in Europe also indicate the same, such as diagnostic difficulties and delays due to symptom overlap with GERD, implying that these patterns can be generalized across age lines (18). The existence of diagnostic delays as recorded in the United Kingdom further justifies the importance of having systematized diagnostic routes to

reduce the time to diagnosis (19). The differences in the treatment pattern, such as unreliable adherence to dietary therapy, steroids, and PPIs reported in the United States claims-based studies, highlight the importance of standard management guidelines (20). Altogether, our results have some significant implications. EoE is to be considered regularly in patients of the adult population with reflux-like symptoms, especially those with dysphagia, atopy, or non-response to acid suppression treatment. Endoscopic impression alone would be prone to underdiagnosis because of small or no mucosal abnormalities. Multi-site biopsy has an important effect on the accuracy of the diagnosis, and it must become the rule of thumb in cases of suspicion. Lastly, the trends of this study are in line with the global trends, which implies that EoE is not uncommon in Pakistan, but is underdiagnosed because of low levels of biopsy and clinical suspicion.

Conclusion

This paper brings out the fact that eosinophilic esophagitis is a serious and little-known disorder among Pakistani patients who come with a history of gastroesophageal reflux. The fact that the prevalence of 13.3 is what was seen in our analysis and globally indicates that there are a significant number of cases that were diagnosed as refractory GERD but are actually undiagnosed EoE. Confirmed EoE was largely linked to clinical characteristics, including dysphagia, a documented history of atopy, and an insensitive response to acid suppression therapy, which underscores the necessity to retain a high index of suspicion. Our results also show that endoscopic appearance is not sufficient in diagnosis because most patients had little or nonspecific mucosal changes. Repeat multi-level esophageal biopsies were also found to be much more accurate in diagnosis and are recommended to be added to the assessment regimen in GERD-like appearance. Several long-term complications that include strictures and food impaction should be avoided by identifying and managing them early enough before the condition escalates. In general, this paper justifies the necessity of creating awareness and combining diagnostic approaches to EoE in Pakistan.

Authors Contributions:

1st author Role: Suggested title, written abstract, Research Methodology, tool for data collection & conclusion summary of Article
2nd author Role: Data analysis & Research Biostatistics and Results, Article Revision & Correction of spelling & grammatical mistakes.
3rd author Role: Past Articles review & written introduction
4th author Role: written discussion of the Article.
5th author Role: Data Collection & References.
6th author Role: Data Collection and Article Revision

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