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Clinical Characteristics, Diagnostic Challenges, and Therapeutic Outcomes in Non-eosinophilic Esophagitis Eosinophilic Gastrointestinal Diseases in Comparison with Eosinophilic Esophagitis: A Retrospective Cohort Study

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ABSTRACT

Eosinophilic gastrointestinal diseases (EGIDs) are chronic, T_H2-mediated conditions. Eosinophilic esophagitis (EoE) is the most common type, while non-EoE EGIDs affect other gut segments.

This retrospective study of 111 patients (50 EoE and 61 non-EoE) from 2011 to 2022 compared the clinical aspects of these 2 types.

Dysphagia and food impaction dominated in EoE, while abdominal pain, nausea, and diarrhea were more common in non-EoE EGIDs. Atopic comorbidities were frequent. Diagnostic delays>1 year were more common in EoE (72% vs 47.5%). The overall clinical response rate was 88.29%, with most patients using food avoidance (90.99%) and proton pump inhibitors (94.59%). Clinical relapses occurred in 38.88% over the mean follow-up of 4.62 years and were unaffected by therapy type. Failure to thrive was seen in 26.7%, with no significant intergroup difference.

This study highlights a prolonged diagnostic delay in EoE vs non-EoE EGIDs. Both groups showed similar, favorable response rates, underscoring a need for greater awareness. Prospective studies with standardized measures are required to optimize management.

Keywords: Delayed diagnosis treatment outcome; Eosinophilic colitis; Eosinophilic esophagitis; Eosinophilic gastroenteritis; Eosinophilic gastrointestinal disease; Food allergy

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INTRODUCTION

Eosinophilic gastrointestinal diseases (EGIDs) are chronic T helper 2 (T_H2)-mediated inflammatory conditions characterized by a heterogeneous group of disorders marked by eosinophilic infiltration of different segments of the gastrointestinal (GI) tract, resulting in a range of gastrointestinal symptoms depending on the specific segment affected.[1] Recurrent gastrointestinal symptoms, eosinophilic infiltration in the gastrointestinal tract, and the exclusion of other potential causes are the three main components of an EGIDs diagnosis.[22] Non-EoE EGIDs, including eosinophilic gastritis (EoG), eosinophilic gastroenteritis (EGE), and eosinophilic colitis (EoC), are far rarer and less well-characterized, posing significant diagnostic and therapeutic challenges due to their nonspecific symptom profiles.

Despite increasing studies on EGIDs, our understanding of their causes, pathogenic factors, disease progression, treatment, and long-term effects remains limited. Eosinophilic esophagitis (EoE) is the most well-characterized form, with an estimated prevalence of 50 cases per 100 000 individuals, while non-EoE EGIDs have a prevalence of less than 10 cases per 100 000.[3–5]

After being initially identified by Kaijser in 1937,[6] EGIDs were later classified into three categories by Klein et al in 1970: mucosal, muscular, and serosal, according to the extent of eosinophilic infiltration in the intestinal tract.[7] Mucosal inflammation correlates with diarrhea, malabsorption, and hemorrhage, while muscular inflammation may manifest as obstruction, and serosal disease may present as eosinophilic ascites.[2]

EGIDs are caused by genetic, environmental, and immunologic factors. The updated ESPGHAN and ACG guidelines provide insights into standardizing care and emerging therapeutic approaches. Clinical presentation varies depending on the affected GI segment: EoE patients experience dysphagia, food impaction, and chest pain; Eosinophilic Gastritis (EoG) and Eosinophilic Gastroenteritis (EGE) patients present with abdominal pain, nausea, vomiting, diarrhea, and weight loss; and Eosinophilic Colitis (EoC) patients exhibit colonic inflammation.[8–10]

Elimination of food allergens is effective in treating eosinophil infiltration in EoE, with 74% improvement in symptoms and histological resolution.[11] EGE and EoC may be linked to other allergens, as half of the patients have high blood eosinophil counts and positive skin prick tests.[12] EGE patients have distinct gastric transcriptomes with over 90% homology to eosinophilic esophagitis, although some exhibit common autoimmune features without atopy.[13] Gastrointestinal dysbiosis may also contribute to the condition. Whether these changes in the gut microbiota are a cause or an effect of the illness is still under debate.[14,15]

Glucocorticoid and nutritional interventions are the conventional therapies for EGIDs, with many patients achieving clinical remission after initial treatment. However, many experience disease recurrence, glucocorticoid dependence, or serious complications like luminal strictures and failure to thrive (FTT).[16] FTT, a commonly used concept, lacks a universally accepted definition and shows variability among different anthropometric criteria, making it challenging to detect nutritional growth delay.[17]

EoE is the most prevalent EGID, although there is a growing awareness of other EGIDs affecting different parts of the gastrointestinal tract (non-EoE).[18] Consensus diagnostic criteria and accepted therapeutic approaches for other EGIDs are currently absent in the literature, with the exception of EoE. Previous studies on non-EoE EGIDs have mostly consisted of case series due to the condition's rarity. The objective of this retrospective cohort study is to contribute to the current understanding of this condition, with a particular focus on its clinical aspects.

MATERIALS AND METHODS

Patient Selection

We retrospectively enrolled 126 patients with EGID. However, documentation was unavailable for 13 patients, and 2 patients declined to participate. Finally, 111 patients with EGID were included in the study; all were diagnosed by pathology and referred to the Hepato-Gastroenterology or Allergy-Immunology Department at Rasool Akram Hospital, a referral center for allergy in Tehran (capital of Iran), between 2011 and 2022. Patients were divided into two groups: 50 patients with EoE-EGID and 61 patients with non-EoE-EGID. Patients with histological evidence of eosinophilia in multiple segments of the GI tract were categorized as non-EoE-EGID. Specifically, 8 patients had concomitant esophageal and gastroduodenal

involvement but were classified in the non-EoE EGID group. The criteria established by Talley et al[19] for EGID included gastrointestinal (GI) symptoms, eosinophilic infiltration in one or more areas of ascites or GI biopsy tissues, and the absence of other illnesses that could cause elevated eosinophil counts. Eosinophilic infiltration was defined as an eosinophil count >15 per high-power field (HPF) in the esophagus; >25 per HPF in the gastric biopsies; >30 per HPF in the duodenal biopsies; >50 per HPF in the right colon; >35 per HPF in the transverse colon; and >25 per HPF in the left colon biopsies.[20,21] While initial patient identification relied on the foundational histological criteria proposed by Talley et al, our diagnostic approach is consistent with the latest contemporary guidelines, like the ESPHGAN/NASPGHAN update, which emphasize clinicopathological correlation and the exclusion of secondary causes of eosinophilia.[8,10]

The inclusion criteria were defined as follows: (1) a thorough assessment encompassing clinical features, endoscopic findings, and histopathological analysis confirming the diagnosis of eosinophilic gastroenteritis (EGE); (2) a minimum follow-up period of six months; and (3) provision of signed informed consent.[19]

Exclusion criteria included: (1) definitive evidence of parasitic infections, inflammatory bowel disease, hypereosinophilic syndrome, connective tissue disorders, malignant tumors, drug allergies, or other conditions associated with elevated eosinophil levels; and (2) absence of follow-up data.

Baseline clinical data were retrospectively collected from medical records and included the following: demographic characteristics, presenting symptoms, symptom duration prior to diagnosis, follow-up duration, personal or family history of allergies, history of food intolerance or specific food allergies, allergic conditions (e.g., allergic rhinitis, asthma, and urticaria), initial clinical manifestations (e.g., abdominal pain, diarrhea, nausea, vomiting, distension, gastrointestinal bleeding, weight loss, fever, and rash), as well as endoscopic and pathological findings.

FTT in children is a multifaceted condition characterized by insufficient growth or the inability to sustain growth. Various standardized methodologies are employed to evaluate and assess FTT in children aged 1 to 18 years. Due to resource limitations and the lack of relevant patient data, we utilized the Weight-for-Height/Length (Body Mass Index (BMI)-for-Age) method to evaluate FTT. This approach identifies children as at risk of FTT if their BMI is below the fifth percentile when compared to age- and sex-specific standards. We used the World Health Organization (WHO) BMI percentile tables for accuracy and consistency.[22]

Clinical response was defined as the complete resolution or significant improvement of all primary EGID-related symptoms as reported by the patient and documented in the clinical chart at the first follow-up visit (typically 8–12 weeks post-initiation of therapy). Clinical relapse was defined as the recurrence of previously resolved primary EGID-related symptoms, requiring a change or escalation in therapy, as documented during any subsequent follow-up beyond the initial response period. A responder was a patient who achieved a clinical response within the defined timeframe. A non-responder was a patient who did not achieve a clinical response despite therapy and required alternative treatment strategies.

Follow-up and Classification

The treatment and outcome of each patient were reviewed from medical records and updated via outpatient services or telephone calls. Due to the difficulty of performing multiple endoscopies, especially in children, many doctors are in favor of using clinical symptoms, although currently, studies are questioning the use of clinical symptoms without histological findings.

We used two different definitions. Patients report subjective clinical symptoms, such as pain or fatigue, which guide initial assessments. However, physicians rely on objective clinical findings from examinations, imaging, or laboratory tests to confirm and understand underlying conditions. Combining subjective symptoms with objective findings is essential for accurate diagnosis and treatment. Clinical remission or relapse is defined based on only clinical symptoms that the patient or the parents say, but disease remission or relapse is when clinical findings are confirmed by pathological findings focusing on the tissue eosinophils. In our study, because of the unavailability of endoscopy of the patients and their lack of consent for re-endoscopy in a significant number of patients, the treatment success rate was based on the clinical symptoms reported by the patient.

Considering that the most common site of involvement among EGID patients is the esophagus, the cohort was classified into two groups: eosinophilic esophagitis (EoE) and patients with involvement of

other parts of the gastrointestinal tract other than the esophagus (non-EoE). Additionally, based on subjective findings during follow-up, we divided the patients into two groups: responder vs. non-responder and relapsers vs. non-relapsers.

Statistical Analysis

Continuous variables were expressed as means and standard deviations for those fitting a normal distribution and were compared between groups using Student's t-test. Medians and quartiles [M (Q1, Q3)] were used for variables not fitting a normal distribution, and the comparison analysis was conducted by the Mann-Whitney U test. Categorical variables were reported as numbers and percentages and compared between groups using the chi-square test. Relapse-free survival (RFS) was calculated from the data of the patient's initial diagnosis of EGID at our center until the date of disease relapse or the last follow-up. A two-tailed $p<0.05$ was considered statistically significant.

RESULTS

Clinical Characteristics

We initially selected 126 patients for the study. However, documentation was unavailable for 13 patients, and 2 patients declined to participate. Ultimately, 111 patients with EGIDs were included; 66 were male, and 45 were female. Clinical characteristics of the total, EoE, and non-EoE EGID groups are shown in Table 1. It is important to note that while 14 EoE patients had documented gastritis and 16 had duodenitis, the eosinophil counts in their gastric and duodenal biopsies did not meet the contemporary histological thresholds for a concomitant diagnosis of eosinophilic gastritis or eosinophilic duodenitis, respectively. At enrollment, the median age of patients was 10 years, with a range of 1.5 to 21 years old. The median (interquartile range (IQR)) time interval from symptom onset to diagnosis was 1.5 (3) years (diagnostic gap). The most frequent presenting symptoms were abdominal pain in 72.07% of cases, followed by gastroesophageal reflux (59.46%), vomiting (54.95%), nausea (54.05%), anorexia (50.45%), and restlessness (45.05%).

Other Allergic Disease

Among the various atopic disorders, rhinitis was the most common, accounting for 39.64% of cases. Atopic dermatitis, asthma, and urticaria followed, with prevalence rates of 27.03%, 17.12%, and 17.12%, respectively. A positive family history of allergic disease was identified in 70.27% of the cases.

Endoscopic Findings

Following endoscopy, the most frequently observed macroscopic lesions were esophagitis (65.77%), gastritis (34.32%), duodenitis (32.43%), erythema (29.73%), and nodularity (25.23%). Histologic samples were available for all patients. Biopsy findings indicated pathological eosinophilic infiltration in the esophagus, stomach, duodenum, and colon in 45%, 1.8%, 39.6%, and 13.5% of the cases, respectively. The estimated median (interquartile range) peak tissue eosinophil count/HPF in the esophagus, stomach, duodenum, and colon were 35 (33.8), 75.5 (23.5), 41.5 (21.8), and 63 (46), respectively.

Clinical Data Based on EoE and Non-EoE Classification

The patients were classified into two groups: 50 patients diagnosed with eosinophilic esophagitis (EoE) and 61 patients with involvement of other parts of the gastrointestinal (GI) tract (non-EoE). A summary of the clinical features of the two groups at diagnosis is presented in Table 1. The prevalence of gastroesophageal reflux was higher among patients in the EoE group (78% vs 44.26%, p=0.001). Conversely, a higher prevalence of bloody stools was seen in the non-EoE group (19.67% vs 2%, p=0.006). Furthermore, the EoE group had a higher prevalence of reported rhinitis (52% vs 29.51%, p=0.027) and asthma (30% vs. 17.12%, p=0.002). During endoscopy, esophagitis and edema were more frequently observed in the EoE group compared to the non-EoE group (84% vs 50.82%, p=0.001, and 8% vs 0%, p=0.038). Pathology examination also revealed that superficial layering of eosinophils was more prominent in the non-EoE group than in the EoE group (39.34% vs 10%, p=0.001). All the clinical symptoms are described in Table 1.

Table 1. Clinical characteristics.

Variable	Category	Total count (%)	EoE count (%)	Non-EoE count (%)	*p*
Demographic	Sex				
	Female	45 (40.54%)	17 (34%)	28 (45.9%)	0.282
	Male	66 (59.46%)	33 (66%)	33 (54.1%)	0.282
	Age of onset	Median (IQR) 2.5(5)	2 (4.5)	3 (5)	0.145
	Age of diagnosis	Median (IQR) 5(6)	4.75(4)	5.5(7)	0.339
	Age of registration	Median (IQR) 10 (5.5)	9.75(4.5)	9.75(7)	0.541
	Follow up (years)	Median (IQR) 4.5 (2.5)	4.7(2.5)	4(2.5)	0.0001
	Eosinophil count	Median (IQR) 42(31)	35(33.75)	50(28)	0.0003
	Diagnostic delay				0.016
	1 year or less	46 (41.44%)	14 (28%)	32 (52.46%)	
	> 1 year	65 (58.56%)	36 (72%)	29 (47.54%)	
	Body mass index				0.727
	Underweight	90 (81.08%)	42 (84%)	48 (78.69%)	
	Normal	17 (15.32%)	7 (14%)	10 (16.39%)	
	Overweight	4 (3.6%)	1 (2%)	3 (4.92%)	
Skin test	Prick test				
	Positive	80 (89.89%)	40 (95.24%)	40 (85.11%)	0.163
	Patch test				
	Positive	24 (64.86%)	9 (56.25%)	15 (71.43%)	0.541
Clinical status	Clinical disease relapse[c]				
	Yes	48 (43.24%)	26 (52%)	22 (36.07%)	0.135
	Clinical response[c]				
	Yes	98 (88.29%)	46 (92%)	52 (85.25%)	0.377
Treatment	Food avoidance	101 (90.99%)	46 (92%)	55 (90.16%)	1
	Antihistamine	58 (52.25%)	26 (52%)	32 (52.46%)	1
	Systemic steroid (tablet)	26 (23.42%)	10 (20%)	16 (26.23%)	0.585
	Local steroid (MDI spray, oral respule)	30 (27.03%)	10 (20%)	20 (32.79%)	0.195
	PPI (proton pump inhibitor)	105 (94.59%)	47 (94%)	58 (95.08%)	1
Clinical symptoms	Nausea	60 (54.05%)	29 (58%)	31 (50.82%)	0.573
	Vomiting	61 (54.95%)	32 (64%)	29 (47.54%)	0.123
	Stomachache	80 (72.07%)	33 (66%)	47 (77.05%)	0.281
	Anorexia	56 (50.45%)	27 (54%)	29 (47.54%)	0.627
	Dysphagia	21 (18.92%)	12 (24%)	9 (14.75%)	0.32
	Diarrhea	25 (22.52%)	8 (16%)	17 (27.87%)	0.207
	Constipation	38 (34.23%)	15 (30%)	23 (37.7%)	0.516
	Bloody stool	13 (11.71%)	1 (2%)	12 (19.67%)	0.006
	Restlessness	50 (45.05%)	26 (52%)	24 (39.34%)	0.254
	Colic	26 (23.42%)	14 (28%)	12 (19.67%)	0.421
	Reflux	66 (59.46%)	39 (78%)	27 (44.26%)	0.001
	Growth difficulty	32 (28.83%)	13 (26%)	19 (31.15%)	0.7

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Table 1. Continued...

Variable	Category	Total Count (%)	EoE count (%)	Non-EoE count (%)	*p*
Atopic disease	Asthma	19 (17.12%)	15 (30%)	4 (6.56%)	0.002
	Rhinitis	44 (39.64%)	26 (52%)	18 (29.51%)	0.027
	Eczema	30 (27.03%)	16 (32%)	14 (22.95%)	0.393
	Urticaria	19 (17.12%)	9 (18%)	10 (16.39%)	1
	Drug allergy	7 (6.31%)	4 (8%)	3 (4.92%)	0.699
	Family history of allergy	78 (70.27%)	35 (70%)	43 (70.49%)	1
Endoscopy (macroscopic findings)	Esophagitis	73 (65.77%)	42 (84%)	31 (50.82%)	0.001
	Sliding hernia	19 (17.12%)	8 (16%)	11 (18.03%)	0.976
	Gastritis	38 (34.23%)	14 (28%)	24 (39.34%)	0.293
	Duodenitis	36 (32.43%)	16 (32%)	20 (32.79%)	1
	Nodularity	28 (25.23%)	10 (20%)	18 (29.51%)	0.353
	Erythema	33 (29.73%)	11 (22%)	22 (36.07%)	0.16
	Edema	4 (3.6%)	4 (8%)	0 (0%)	0.038
	Furrows	3 (2.7%)	2 (4%)	1 (1.64%)	0.587
Pathology (histological findings)	Eosinophilic microabscesses	6 (5.41%)	2 (4%)	4 (6.56%)	0.688
	Superficial layering of eosinophils	29 (26.13%)	5 (10%)	24 (39.34%)	0.001
	Subepithelial fibrosis	15 (13.51%)	6 (12%)	9 (14.75%)	0.886

Data are presented as numbers (%). A p value <0.05 was considered statistically significant. Clinical response and clinical disease relapse of patients are considered based on the clinical symptoms reported by the patients themselves.
EoE: Eosinophilic Esophagitis; IQR: interquartile range; non-EoE: non-Eosinophilic Esophagitis.

Skin Allergy Test

We performed a skin prick test on 89 patients (89.88% positive) and a patch test on 37 patients (64.86% positive). Patients were then divided into four groups based on the results: both tests negative, only patch positive, only prick positive, and both tests positive. The results have been displayed in Table 1. Only prick test positivity was more prevalent in the EoE group (62% vs. 45.9%), whereas positivity for both patch and prick was more common in the non-EoE group (31.15% vs. 20%). The prick test showed a higher rate of positive results in the EoE group (95.24% vs. 85.11%, p=0.163), while the patch test showed a higher rate of positive results in the non-EoE group (71.43% vs. 56.25%, p=0.541); however, neither difference was statistically significant. In the EoE group, nuts, egg white, and milk (54.76%, 52.38%, and 47.62%, respectively), and in the non-EoE group, nuts, milk, and egg white (51.06%, 53.19%, and 34.04%, respectively) were the most common sensitized food allergens identified by prick test. In both EoE and non-EoE groups, nuts (43.75% and 31.82%, respectively) were the most frequently positive allergen in the patch test.

Tissue Eosinophil and Fibrosis

We also conducted a logistic regression analysis to investigate the correlation between eosinophil count and fibrosis in the initial endoscopic biopsy samples. We were not able to spot any significant association between eosinophil count and fibrosis among all patients (odds ratio: 1.01; 95% CI: 0.99–1.02; p=0.331), EoE patients (odds ratio: 1.01; 95% CI: 1.00–1.03; p=0.115), or the non-EoE group (odds ratio: 1.01; 95% CI: 0.97–1.02; p=0.712).

Diagnostic Gap

The diagnostic gap, defined as the time between the appearance of symptoms and the confirmation of a diagnosis, was categorized into two groups: those with a gap of less than one year and those with a gap of one year or more. The data revealed that 58.56% of patients were diagnosed at or beyond a 1-year diagnostic gap, compared to 41.44% of patients diagnosed within a 1-

year gap. A higher proportion of the EoE group had a diagnostic gap of 1 year or more in comparison to the non-EoE group (72% vs. 47.54%, p=0.016). The study additionally investigated the diagnosis gap in individuals presenting with various clinical symptoms (Figure 1). The results demonstrated that patients who initially experienced bloody stool had a significantly shorter diagnostic gap (p=0.002). Furthermore, it was demonstrated that those who had nausea and vomiting as their primary symptom had a longer diagnostic gap (p=0.014 and p=0.001). No statistically significant correlation was observed with other clinical symptoms.

We also investigated changes in the diagnostic gap across ages of disease onset (Figure 2). Linear regression analysis revealed that the diagnostic gap decreased significantly as the age of onset increased, with a p value of 0.0002.

Treatments and Outcomes

Among the 111 patients originally enrolled in the trial, 105 patients (94.59%) were administered proton pump inhibitors (PPIs), 101 (90.99%) received food avoidance, 58 (52.25%) received antihistamines, 30 patients (27.03%) received local budesonide, and 26 patients (23.42%) received oral short-course glucocorticoids. Regarding treatment combinations, 37 patients (33.33%) were administered dietetic therapy together with PPI, 18 (16.22%) received PPIs together with antihistamines and dietetic therapy, and 18 patients (16.22%) were on PPIs, antihistamine, local Budesonide (Pulmicort, AstraZeneca, Cambridge, UK), and dietetic therapy. Furthermore, Figure 3 illustrates various treatment strategies in relation to clinical response and clinical recurrence. The combination of diet, PPIs, and oral short-course corticosteroid drug combination group had the lowest clinical response rate, whereas the combination of diet, PPIs, oral short-course corticosteroid, and antihistamine drug combination group had the greatest clinical relapse rate. These findings in our survey suggest that adding more medications does not significantly alter the prognosis. Among the 111 patients, 98 (88.29%) achieved a clinical response. We define clinical response as the alleviation of the symptoms that patients initially experienced. Although patients with EoE had a higher clinical response rate (92%) compared to non-EoE patients (85.25%), there was no statistically significant distinction between the two groups (p=0.377). Furthermore, there was no statistically significant relationship between fibrosis development and clinical response among all patients (p=0.221), the EoE group (p=1), or the non-EoE group (p=0.052).

Long-term Prognosis and Its Predictive Factors

All patients survived, with a mean follow-up period of 4.62 years, and 38.88% (49/126) of all patients experienced clinical relapse after diagnosis. Among four treatment options: antihistamines, PPI, oral budesonide respules, and oral short-course corticosteroids, none statistically affected the disease relapse (p=0.668, 0.253, 0.316, and 0.504, respectively).

Failure to Thrive

Among 105 patients aged 1.5 to 18 years, 28 (26.7%) were identified as having FTT, defined by a BMI below the 5th percentile based on age- and sex-specific standards. Of 46 patients with EOE, 14 (30.5%) met the criteria for FTT, while in the non-EOE group, 14 (23.7%) of 59 patients were classified as having FTT. The frequency of FTT did not differ significantly between the EOE and Non-EOE groups (p=0.58). This indicates that FTT is similarly distributed between the two groups (Figure 4).

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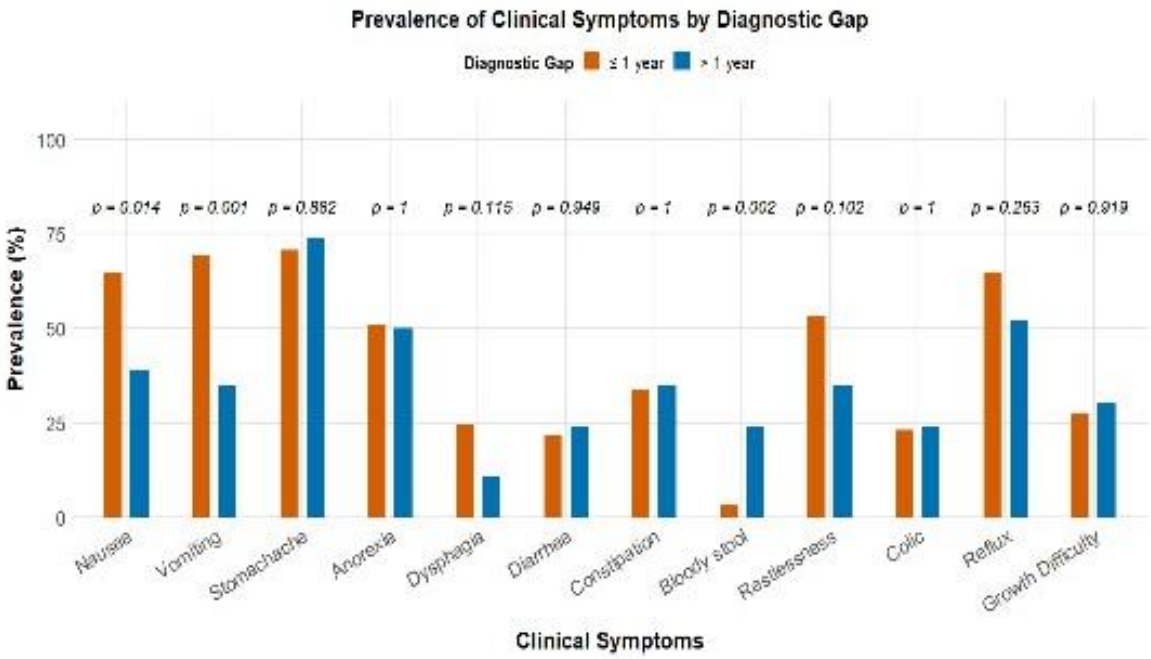

Figure 1. Diagnostic gap based on presenting symptom. The *y*-axis represents the prevalence of each symptom in patients with a diagnostic gap of more than one year (blue bars) and those with a diagnostic gap of one year or less (red bars). The results revealed that patients who initially presented with bloody stool had a significantly shorter diagnostic gap (*p*=0.002). In contrast, those with nausea and vomiting as primary symptoms exhibited a longer diagnostic gap (*p*=0.014 and *p*=0.001).

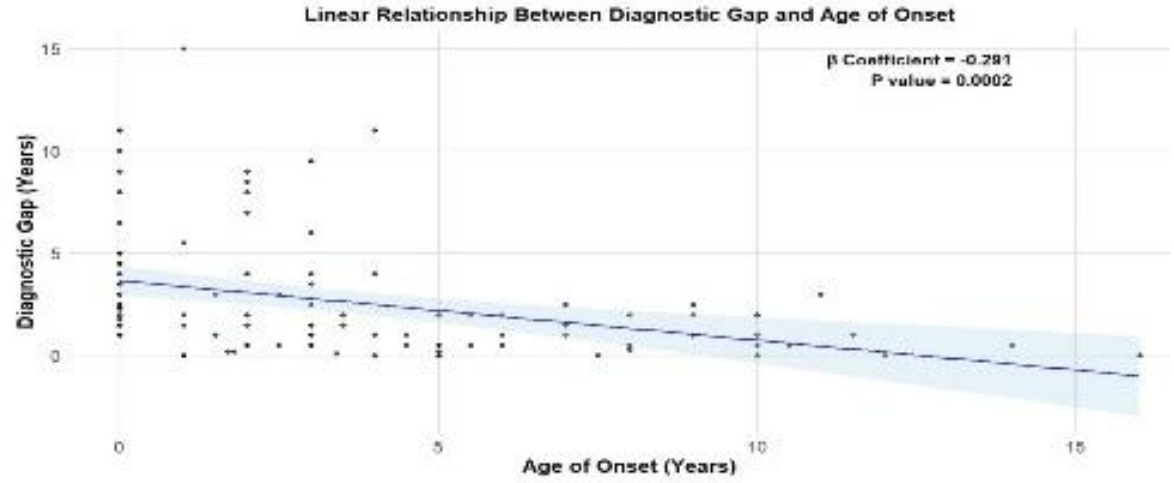

Figure 2. Diagnostic gap and age of onset. *p* value: 0.0002; β coefficient: -0.291. The *x*-axis represents the age of onset, while the *y*-axis shows the diagnostic gap. The regression line indicates the trend or correlation between the two variables, highlighting any potential association. The plot also includes data points that reflect individual cases, and the corresponding regression equation or statistical details (such as *p* value and β coefficient) are provided to assess the strength of the relationship. This analysis aims to explore whether an earlier age of onset is associated with a longer diagnostic delay.

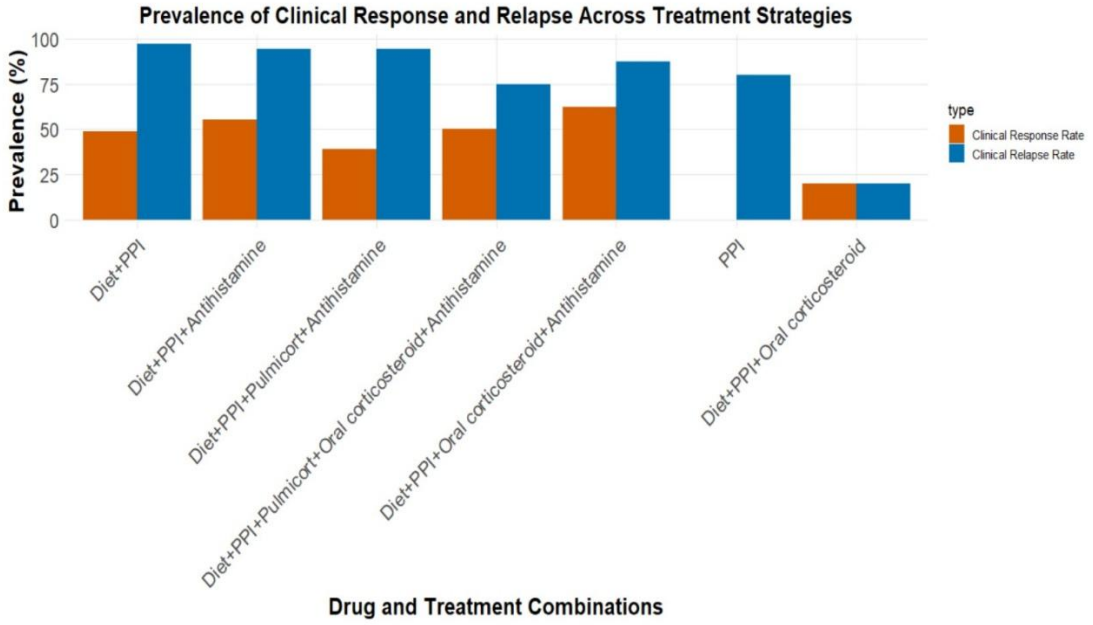

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Figure 3. Clinical response and relapse based on the drugs used in treatment. The treatment regimens for the condition under study vary, with the most common approach being a combination of Diet and PPI, used in 37 cases (33.33%). Other frequent treatment combinations include Diet + PPI + Antihistamine and Diet + PPI + Antihistamine + Pulmicort, each utilized in 18 cases (16.22%). A more intensive regimen involving Diet + PPI + Pulmicort + Oral corticosteroid + Antihistamine was used in 12 cases (10.81%), while Diet + PPI + Oral corticosteroid + Antihistamine was used in 8 cases (7.21%). PPI alone was the least common option, accounting for 5 cases (4.5%), and the combination of Diet + PPI + Oral corticosteroid also appeared in 5 cases (4.5%).

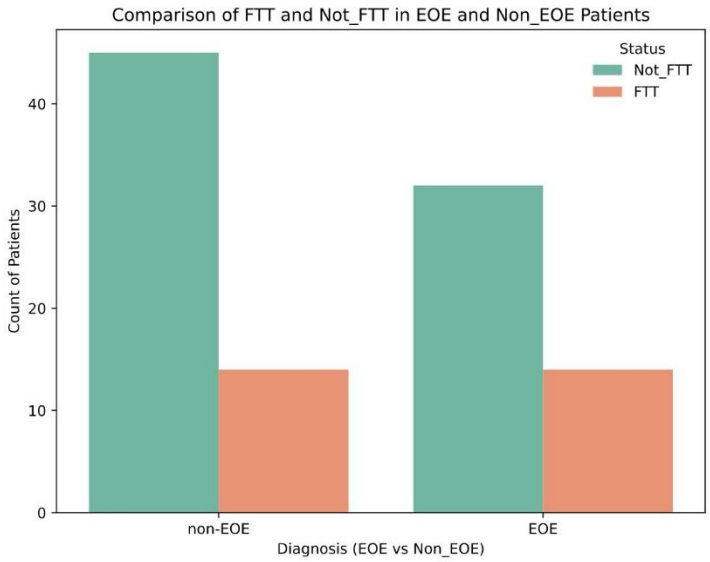

Figure 4. The bar chart compares the frequency of failure to thrive (FTT) and non-FTT status among patients with eosinophilic esophagitis (EOE) and non-EOE conditions. The *x*-axis represents the diagnosis groups (EOE and non-EOE), while the *y*-axis shows the count of patients.

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DISCUSSION

EGID patients' initial symptoms, diagnostic gap, pathologic findings, allergy tests, treatment, and prognoses are crucial predictors, although they are often overlooked due to the non-specific, heterogeneous nature of symptoms.[23] This retrospective cohort study provides the first report on the characteristics, clinical and laboratory data, and follow-up of 111 confirmed EGID patients in Tehran, Iran, from 2011–2022. However, due to the lack of a national registry, the prevalence of EGID in Iran cannot be estimated.

This study found significant differences in sex distribution between patients with EoE and non-EoE EGIDs. Males dominated the EoE cohort, accounting for 66% of the group, while non-EoE showed no apparent sex disparity. This finding aligns with previous literature suggesting a higher prevalence of EoE among males.[24,25]

One of the challenges associated with EGID disease is the delayed diagnosis, which can result in considerable costs for patients, particularly children. In 2018, a large multi-center study by Chehade et al found that the time between symptom onset and diagnosis increased with age: a median of 4.0 years in adults, 2.0 years in 11–17-year-olds, and 1.0 years in children.[26] In our study, the median diagnosis delay was 1.5 years from symptom onset, with children and adolescents experiencing a shorter interval between diagnosis and alternative diagnoses. This may be explained by factors such as a lower probability of receiving alternative diagnoses and more frequent use of gastric and duodenal sampling during pediatric endoscopies.[27,28]

The study reveals that the diagnostic gap in children under 11 decreases linearly with age due to factors like non-specific symptoms, inadequate parental history, and lack of consent for endoscopy and biopsy preparation. EoE-EGID patients experience longer diagnostic delays, and more common conditions are often suspected before EGIDs, possibly because of nonspecific symptoms or misdiagnosis with other differential diagnoses such as GERD, food refusal, and reflux.

In addition, some studies identified clinical characteristics linked to a reduced diagnostic gap. The characteristics that showed a strong correlation with increased diagnostic delay were non-smoking status, multiple episodes of food impaction, having undergone previous endoscopy without biopsies, and being assessed by two or more physicians.[29] Our investigation revealed that patients presenting initially with bloody stool experienced a significantly shorter diagnostic interval (p=0.002). It was also found that individuals exhibiting nausea and vomiting as their initial symptom experienced a significantly longer diagnostic time (p<0.01). No substantial correlations were seen for other clinical symptoms (Table 1).

In pediatric patients, clinical presentations range from mild, nonspecific symptoms like abdominal pain, vomiting, and dyspepsia to more severe manifestations like failure to thrive and even food impaction. Previous research by Votto found that 20% of all patients with EGID had failure to thrive (26% of EoE and 10% of non-EOE patients, respectively). Children with EoE who had FTT or feeding difficulties experienced a longer time to diagnosis compared to those without such problems, with statistically significant differences. In non-EoE-EGID patients, those with FTT also showed delayed diagnosis, but the difference was not statistically significant.[30] Our findings are consistent with the studies conducted by Paguet et al, who presented that among 62 individuals, 15 (24%) patients met at least one of the six criteria for FTT. Due to the absence of a definitive clinical definition for FTT in children with EoE, these findings support maintaining a higher index of suspicion for FTT during the assessment of this demographic.[31]

Endoscopic examinations provide visual assessment and allow for biopsies to detect eosinophilia and other histopathologic changes. Endoscopy was performed on all study participants; however, some patients may not have undergone colonoscopy depending on their clinical presentation. Of the total, 23 patients had no abnormal findings on gross endoscopic examination, and 103 had at least one abnormal finding on endoscopy or colonoscopy. Among EOE patients, 84% had esophagitis compared to 50% of non-EOE patients, which was significant with a p value of 0.001. A previous study examined 153 EOE and 151 non-EOE patients. Abnormal esophageal findings were observed in 98 percent of EOE patients and only 20 percent of non-EOE patients.[25] In the Li et al study, 55 patients with EGE underwent endoscopy, of which 14.5% had no macroscopic endoscopic abnormalities. The duodenum was the most commonly involved site (74.1%), with frequent presentation including hyperemia (57.4%), erosion (24.1%), and ulceration (9.3%).[16]

This study supports prior findings that a significant proportion of EoE patients have a history of allergies,

with 64.3% in the current sample showing atopic conditions.[16,32] Asthma and rhinitis were notably more prevalent in this group, highlighting the diagnostic value of allergy history in patients with nonspecific gastrointestinal symptoms. While common allergens like milk, wheat, and nuts often yield positive test results, these results indicate sensitization rather than confirmed clinical relevance. Moreover, atopic symptoms and EoE may not always progress together,[33,34] even though more than 80% of adult patients demonstrate positive skin prick test results.[35]

Topical glucocorticoids have also been shown to be effective in treating EoE; however, their usefulness for treating non-EoE-EGID remains unclear. Compared to individuals with non-EoE-EGID, EoE patients find it far easier to effectively control disease activity. Managing disease activity in non-EoE-EGID patients is often more challenging, even with a combination of medication regimens.[3] The primary treatments used were food avoidance, local steroids, and PPIs, with clinical improvement seen in 92% of EoE patients and 88.29% of non-EoE patients. Comparison of different medications showed no significant benefit in treatment response or relapse reduction. Notably, adding oral corticosteroids did not improve outcomes but may significantly increase side effects (Figure 3). These findings were consistent with those reported in other publications.[28,36]

The study's main limitation is the absence of pathological findings post-treatment. Only 35 out of 111 patients consented to follow-up endoscopy, underscoring the importance of assessing both clinical and pathologic responses in managing eosinophilic gastroenteritis. Pathologic relapses can occur silently and is often detected only through follow-up endoscopies and biopsies. A treatment plan that only targets symptoms alone may miss ongoing inflammation, potentially leading to long-term damage or complications even in the absence of symptoms.[37,38] Another limitation of our study was the simultaneous initiation of three treatment modalities (diet, topical steroid, and PPI). This concurrent rather than staggered initiation prevented analysis of the individual effectiveness of each treatment. Third, the retrospective nature of this study and the use of telephone follow-up for a subset of patients introduce the potential for recall and reporting bias, as symptom assessment relied on patient self-report and clinical documentation rather than validated patient-reported outcome (PRO) instruments or symptom diaries.

This paper highlights notable variations in clinical presentation, endoscopic findings, allergy profiles, and treatment outcomes between EoE and non-EoE subtypes, providing a comprehensive clinical overview of eosinophilic gastrointestinal diseases (EGIDs) in Iranian pediatric patients. Our data also suggest that broad pharmacological combinations do not improve long-term outcomes beyond diet therapy and PPI treatment. Despite increased awareness, diagnostic delays remain common (particularly in EoE), underscoring the need for earlier suspicion and biopsy-based evaluation, especially in patients with persistent upper gastrointestinal symptoms. Patients with unexplained gastrointestinal symptoms, particularly those with atopic conditions, should be suspected of having EGID. Allergists and immunologists refer patients with consistent clinical histories to a gastroenterologist for esophagogastroduodenoscopy or colonoscopy. Immunologists evaluate all potential causes, initiate diet therapy, administer PPI medications, and monitor treatment response.

STATEMENT OF ETHICS

Written informed consent was obtained from all participants or their legal guardians, and the study was reviewed and approved by the Iran University of Medical Sciences ethics committee (IR.IUMS.FMD.REC.1401.067).

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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DATA AVAILABILITY

The datasets generated and/or analyzed during the current study are not publicly available due to patient privacy and ethical restrictions but are available from the corresponding author on reasonable request. Requests should be submitted via email and will be considered based on a sound scientific proposal, subject to a data sharing agreement in line with the ethical approvals governing this research.

AI ASSISTANCE DISCLOSURE

No AI assistance was used in this study.

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