

Clinical Features Distinguish Eosinophilic and Reflux-induced Esophagitis

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ABSTRACT

Background and Objectives : Diagnosing eosinophilic esophagitis (EoE) depends on intraepithelial eosinophil count of ≥ 15 eosinophils per high-power field (HPF); however, differentiating EoE from gastroesophageal reflux disease (GERD) continues to be a challenge because no true “criterion standard” criteria exist. Identifying clinical and endoscopic characteristics that distinguish EoE could provide a more comprehensive diagnostic strategy than the present criteria. The aim of the study was to determine symptoms and signs that can be used to distinguish EoE from reflux esophagitis.

Methods: Adult and pediatric patients with EoE were identified by present diagnostic guidelines including an esophageal biopsy finding of ≥ 15 eosinophils/HPF. Patients with GERD were age-matched one to one with patients with EoE. Clinical, endoscopic, and histologic information at the time of diagnosis was obtained from the medical record and compared between pairs by McNemar test. A conditional logistic regression model was created using 6 distinguishing disease characteristics. This model was used to create a nomogram to differentiate EoE from reflux-induced esophagitis.

Results: Patients with EoE were 75% men and 68% had a history of atopy. Many aspects of EoE were statistically distinct from GERD when controlling for age. Male sex, dysphagia, history of food impaction, absence of pain/heartburn, linear furrowing, and white papules were the distinguishing variables used to create the logistic regression model and scoring system based on odds ratios. The area under the curve of the receiver-operator characteristic curve for this model was 0.858.

Conclusions: EoE can be distinguished from GERD using a scoring system of clinical and endoscopic features. Prospective studies will be needed to validate this model.

Key Words: eosinophilic esophagitis, esophagus, gastroesophageal reflux

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Eosinophilic esophagitis (EoE) has emerged as an important gastrointestinal (GI) disorder during the last 15 years, affecting approximately 15% of patients with dysphagia (1,2). A 2007 Consensus Report (3) and 2011 update (4) have defined EoE based on general symptoms and signs of esophagitis, ruling out gastroesophageal reflux disease (GERD), and peak eosinophil count on biopsy (≥ 15 intraepithelial eosinophils per maximally affected high-power field [HPF]). The pathognomonic characteristic of EoE is intense intraepithelial eosinophil infiltration, but it is also accompanied by a wide variety of other features including clinical, endoscopic, and histologic findings (4). EoE presents a diagnostic challenge because eosinophils are also a feature of acid-induced esophagitis, especially in children (5). Overlap may exist between EoE and GERD, with severe GERD exceeding 15 eosinophils/HPF, and the 2 diseases may also coexist in some patients (6,7). Endoscopic biopsies may not always be representative because sampling errors may occur. Rebiopsy of patients after intervention has been proposed to confirm diagnosis, but variation in histology may occur over time or with seasonal changes (8,4). Although the diagnostic criteria are internationally recognized, improved strategies to identify EoE using clinical and endoscopic features to complement histologic findings would be useful to better define EoE.

EoE has been associated with many characteristics that are common but not exclusive to patients with EoE (9). These include adolescent age, male sex, atopic disorders, dysphagia, food impaction, pain, odynophagia, and vomiting (10). In some cases, EoE is discovered in the absence of endoscopic abnormalities (11). Endoscopic findings may include trachealization (ringed esophagus), linear furrows, white papules, and strictures (3). Contrast radiographic studies of patients with EoE may demonstrate an abnormal barium esophagram (3). Additionally, histologic characteristics include marked basal zone hyperplasia and elongated vascular papillae (3). It may thus be possible to identify a set of symptoms and signs that are highly likely to distinguish EoE from acid-related esophagitis.

A validated questionnaire could increase the certainty of a diagnosis of EoE. Previous studies have proposed questionnaires for EoE diagnosis based on validated surveys developed for GERD diagnosis. Such scoring systems provide a basis for diagnosing EoE beyond histopathology, but do not overcome the problem of differentiating GERD from EoE. Although both adult (1,12,13) and pediatric (14–16) questionnaires for EoE have been proposed, no scoring system has yet been independently validated. Patients with EoE (17) tend to be younger than patients with GERD (18,19). In fact, the presenting symptoms of EoE may vary with age (9). Thus, when comparing large patient cohorts with EoE and GERD, matching patients by age is important to decrease the potential for age-related bias.

The aim of the study was to identify the distinct demographic, clinical, endoscopic, and histologic characteristics that could be used to distinguish EoE from GERD. We retrospectively

compared patients with EoE at the time of diagnosis with age-matched patients with GERD. We hypothesize that there is a set of symptoms and signs that result from the unique immune processes of EoE and can be used to distinguish EoE from reflux esophagitis. In the present study, we have found a set of characteristics to be highly associated with EoE when compared with age-matched patients with GERD. Using independent odds ratios obtained from a conditional logistic regression model, we propose a scoring system based on these characteristics that is predictive of a diagnosis of EoE.

METHODS

Patient Identification

An electronic search of the pathology records at the tertiary care center in Kingston, Canada, was performed for “esophagus AND (eosinophil OR eosinophils OR eosinophilia OR eosinophilic)” in the final diagnosis section of all pathology reports from January 1, 1997 to December 31, 2009. EoE was defined, based on the 2007 consensus report (3) and 2011 update (4), as ≥ 15 eosinophils per maximal HPF, symptoms of esophagitis, and absence of other causes of esophagitis. Four hundred eleven cases were identified by the initial search. A total of 232 cases did not meet the criteria for the diagnosis of EoE and were excluded. As a result of increasing awareness of EoE, our pathologists often include a statement such as “no esophageal eosinophils,” which was flagged in our electronic search of the keywords “esophagus” and “eosinophil.” This accounts for the cases excluded after the initial search. Subsequently, any suggestion of having concurrent EoE and GERD resulted in exclusion from the study ($n = 3$). For example, pH probe results suggesting GERD and ≥ 15 eosinophils/HPF, or patients diagnosed as having GERD who had previous or subsequent biopsies showing ≥ 15 eosinophils/HPF, were excluded from the study. Patients ($n = 9$) were also excluded if they had evidence of other upper GI tract pathology, such as eosinophilic gastroenteritis, Barrett esophagus, or Crohn disease. From the search results, 167 (41 pediatric and 126 adult) cases of isolated EoE were identified. The medical record of each case was then reviewed to identify the initial clinical presentation and endoscopy findings for each case. Biopsy slides from the selected cases were then blinded and reevaluated to confirm the presence of ≥ 15 intraepithelial eosinophils per maximal HPF. The Queen’s University Health Sciences research ethics board approved the present study.

Age Matching

A matching GERD cohort was identified by searching all pathology reports for “esophagus AND reflux” in the final diagnosis section during the same time period as the EoE cohort ($n = 564$). Selection of GERD cases was based on symptoms of esophagitis, pathology demonstrating distal esophagitis with < 15 eosinophils/HPF, and exclusion of other causes of esophagitis (20,21). Thus, only patients who underwent upper GI endoscopy and were biopsied during this time period were considered for the present study. We acknowledge that only a subset of patients with GERD have endoscopic procedures and biopsies. It is important to note that the control patients with GERD were included in the present study, as they all had significant enough clinical findings to warrant endoscopy, likely had a more severe form of GERD, thus enabling better comparison to patients with EoE.

An age-matched, case-control pairing was performed. One control GERD case of a matching age (within 18 months) was selected from the GERD cohort for one-to-one matching with each EoE case. This age matching approach minimizes the bias introduced by comparing an older GERD population (19,22) with a primarily adolescent and young adult EoE population (17). The entire biopsy tissue area from each GERD case was reevaluated and confirmed to have histology representative of GERD, but not EoE. A total of 163 of the 167 patients with EoE were matched with GERD control patients when using the criterion of age within 18 months (Fig. 1). The 4 patients with EoE that were not matched (ages 5, 24, 27, and 28) by this process were excluded from any subsequent matched data analysis, including determining the conditional logistic regression model.

Demographic, Clinical, Endoscopic, and Histologic Information

Patient information, including clinical and laboratory findings, were collected by review of medical records. This information was based on symptoms and signs present at the time of diagnosis. Information recorded during chart review included sex, date of birth, presenting symptoms, atopic comorbidities, endoscopic findings, level of biopsies, blood eosinophil count, and upper GI radiographic studies. Atopy was defined as a clinical history of type I hypersensitivity including positive skin prick tests, abnormal immunoglobulin E ImmunoCAP test, anaphylaxis, or diagnosis by

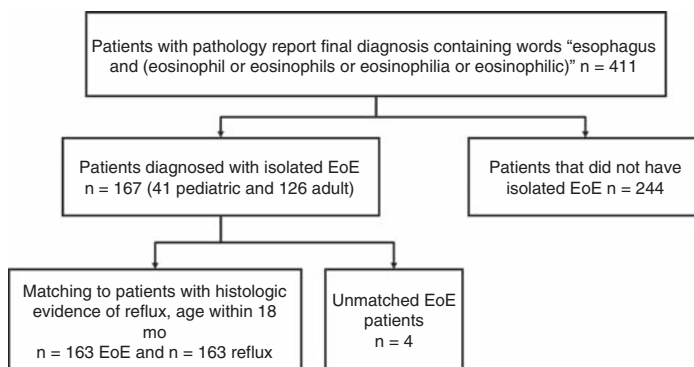


FIGURE 1. Process of patient identification. Patients were initially identified by search of the pathology database and were then screened by review of both biopsies and medical records for a diagnosis of eosinophilic esophagitis (EoE). Age matching was then performed one to one, such that 326 patients were ultimately selected for analysis, 163 patients with EoE and 163 patients with gastroesophageal reflux disease.

an allergist of allergic asthma, allergic rhinitis, or food allergy. Endoscopic features included were trachealization (defined as multiple rings seen at any level of the esophagus), linear furrows, white papules, stricture, and normal endoscopy. Archived esophageal tissue specimens from endoscopies in which EoE was first diagnosed were evaluated for histopathologic criteria; these included maximal intraepithelial eosinophil count, basal zone thickness, and elongation of vascular papillae. Basal zone hyperplasia and vascular papilla elongation were assessed in well-oriented sections, as we have previously reported (23). The basal zone was scored as: 0% to 25% (normal), 26% to 50%, 51% to 75%, or 76% to 100% of the total thickness of the epithelium (23). For vascular papilla length, scores given were 0% to 33% (normal), 34% to 67%, and 68% to 100% of the total thickness of the epithelium (23).

Many patients in the present study had an upper GI radiographic study. A double-contrast barium swallow was done first. Patients were then asked to swallow three barium-coated marshmallows (approximately 1 × 1 × 1 cm) under fluoroscopy. An ordinal value was given to quantify the results based on descriptors used in the radiology report and studies of EoE with similar methodology (24,25). Scores were 0 = normal, 1 = mild, 2 = moderate, 3 = severe.

Statistical Analysis

Graphpad Prism version 4.0 (GraphPad, La Jolla, CA) was used to perform statistics, except for the conditional logistic regression model, which was created using SPSS version 17.1 (SPSS Inc, Chicago, IL), and the nomogram, which was originally created using the Orange Software Suite version 2.0. $P < 0.05$ was considered to be statistically significant. McNemar test was used to evaluate “yes/no” matched data from contingency tables. P values from this test were calculated using the continuity correction. For unmatched data analysis, a contingency table was created and analyzed by Fisher exact test. Linear correlation was evaluated using Spearman rank correlation coefficient. Confidence intervals (CI) were evaluated at 95%. For each disease characteristic investigated, data were only used for development of the regression model if available for both members of the pair. If one of the pairs was missing from the information being evaluated, that category data was excluded from both pairs automatically in the creation of the model. Interactions were not included in the model because the relations between the disease characteristics were not clinically relevant and did not significantly alter the model when using a backwards elimination strategy informed by the results of McNemar test. The odds ratios determined by conditional logistic regression were then used to establish a nomogram, with a score that would predict the relative odds of a patient having EoE versus GERD based on the selective set of clinical and endoscopic characteristics.

RESULTS

Clinical Characteristics

The clinical, endoscopic, and histologic data for the age-matched EoE and GERD cohorts are summarized in Table 1. The matched odds ratios and P values in this table are based on the results of the McNemar test. The proportion of men in the EoE cohort (75%) was significantly greater than the proportion of men in the GERD cohort (52%, $P < 0.0001$).

The most common age range to be diagnosed as having EoE in the present study patients was the second decade of life, although patients were diagnosed as having EoE at ages ranging

from 1 to 79 years (Fig. 2A). Male sex was more common for patients with EoE in all age groups.

Atopic Features

When stratified by age, the prevalence of atopic disease in patients with EoE was more than half of the patients in each decade of life (Fig. 2B). Atopic patients with EoE were found in every decade of life except the eighth, for which there was only 1 patient. In the EoE cohort, 68% of patients had a history of atopy. Age-matched patients with GERD had significantly lower incidence of atopy (43%, $P = 0.03$). Separating patients into adult and pediatric (younger than 18 years) groups did not alter these findings.

Peripheral blood eosinophilia was not helpful in distinguishing EoE from GERD. Although blood eosinophil count was significantly greater in the EoE cohort, both EoE and GERD cohort average blood eosinophil levels were within the normal range. Seven of 82 matched patients with EoE and 2 of 82 matched patients with GERD had a peripheral blood level $> 0.7 \times 10^9$ eosinophils/L. Using matched analysis, the amount of patients with EoE presenting with peripheral blood eosinophilia was not significantly different from the GERD cohort (Fig. 3A, $P = 0.18$). Our tertiary care center considers an abnormal absolute eosinophil count to be $> 0.7 \times 10^9$ eosinophils/L. No consensus exists in the literature with regard to the definition of peripheral blood eosinophilia. Some studies have considered peripheral blood eosinophilia to be any value $> 0.5 \times 10^9$ eosinophils/L (26). There was no statistically significant difference in the incidence of eosinophilia between the EoE and GERD cohorts when using either cut-off value to define peripheral blood eosinophilia.

Peripheral blood eosinophilia has been proposed as a possible surrogate marker of esophageal eosinophilia (27). Thus, the level of correlation between esophageal eosinophil count and peripheral blood eosinophil level was investigated. These data were analyzed unpaired to investigate the possibility of blood eosinophil level alone being a predictor of the severity of esophageal eosinophilia in a particular disease state; neither EoE (Fig. 3B) nor GERD (Fig. 3C) peripheral blood eosinophil level correlated with maximal esophageal intraepithelial eosinophil count/HPF.

Based on the month in which the diagnostic endoscopy was performed, patients were more likely to be diagnosed as having GERD during the winter months (December–February). During the remaining months of the year, patients were no more likely to be diagnosed as having EoE or GERD.

Endoscopic and Radiologic Findings

Four endoscopic features were significantly different between patients with EoE and age-matched patients with GERD. Trachealization, linear furrows, and white papules were significantly more likely to be found in the patients with EoE and a normal endoscopic appearance was more likely to be found in patients presenting with GERD. Barium-coated marshmallow esophagram was assessed for 105 EoE and 80 patients with GERD and was ranked as normal, mild, moderate, or severe. The proportion of patients with normal to severe dysmotility was similar in both disease states when analyzed age-matched and unmatched. The incidence of esophageal strictures was statistically similar between the cohorts.

Histologic Characteristics

In EoE, the mean $\pm$ standard deviation of eosinophils per maximal HPF was 76 ± 56 and ranged from 15 to 308. The

TABLE 1. Age-matched comparison of individual signs and symptoms of EoE and GERD

	EoE, n = 163	GERD, n = 163	Matched odds ratio (95% confidence interval)	P
Clinical characteristics				
Age at diagnosis, mean $\pm$ SD	31.8 $\pm$ 17.7	31.8 $\pm$ 17.7		0.83
Male, n (%)	122 (75)	85 (52)	2.61 (1.59–4.42)	<0.0001
Symptomatology, n (%)				
Dysphagia	108 (74)	65 (45)	3.26 (1.93–5.78)	<0.0001
History of food impaction	51 (35)	10 (7)	5.56 (2.71–12.85)	<0.0001
Pain/heartburn	49 (34)	103 (71)	0.23 (0.12–0.40)	<0.0001
Odynophagia	5 (3)	7 (5)	0.71 (0.18–2.61)	0.77
Vomiting	23 (16)	29 (20)	0.73 (0.36–1.45)	0.42
No symptoms	6 (4)	6 (4)	1.00 (0.27–3.74)	0.77
Atopic disease				
History of atopy, n (%)	30 (68)	19 (43)	3.20 (1.12–11.17)	0.03
Food allergy, n (%)	15 (34)	3 (7)	13.00 (1.95–552.47)	0.0033
Asthma, n (%)	14 (32)	14 (32)	1.00 (0.35–2.84)	0.81
Atopic dermatitis, n (%)	6 (14)	1 (2)	6.00 (0.73–275.99)	0.13
Allergic rhinitis, n (%)	10 (23)	2 (5)	9.00 (1.25–394.48)	0.03
Drug allergy, n (%)	1 (2)	5 (11)	0.20 (0.00–1.79)	0.22
Environmental allergy, n (%)	19 (43)	6 (14)	7.50 (1.74–67.59)	0.004
Blood eosinophil count ($\times 10^9/L$), mean $\pm$ SD	0.35 $\pm$ 0.29	0.22 $\pm$ 0.18		0.0005
Season diagnosed, n (%)				
Winter (December–February)	27 (17)	47 (29)	0.39 (0.19–0.77)	0.005
Spring (March–May)	44 (27)	40 (25)	1.13 (0.67–1.98)	0.71
Summer (June–August)	38 (23)	38 (23)	1.00 (0.59–1.70)	0.90
Autumn (September–November)	54 (33)	38 (23)	1.67 (0.98–2.89)	0.06
Endoscopic and radiologic findings				
Trachealization, n (%)	58 (41)	18 (13)	4.64 (2.39–9.87)	0.004
Linear furrows, n (%)	67 (48)	11 (8)	12.20 (4.95–38.91)	<0.0001
White papules, n (%)	23 (16)	3 (2)	7.67 (2.32–39.89)	0.0002
Stricture, n (%)	14 (10)	6 (4)	2.60 (0.87–9.32)	0.10
Normal endoscopy, n (%)	38 (27)	67 (48)	0.45 (0.27–0.75)	0.001
Barium esophagram score, mean $\pm$ SD	0.52 $\pm$ 0.82	0.70 $\pm$ 0.93		0.20
Histology				
Intraepithelial eosinophils/HPF, mean $\pm$ SD	75 $\pm$ 56	3 $\pm$ 4		<0.0001
Basal zone thickness, mean % thickness $\pm$ SD	83 $\pm$ 21	59 $\pm$ 25		<0.0001
Elongated vascular papillae, mean % thickness $\pm$ SD	60 $\pm$ 14	54 $\pm$ 18		0.004

EoE = eosinophilic esophagitis; GERD = gastroesophageal reflux disease; HPF = high-power field; SD = standard deviation.

proportion of epithelium occupied by the basal zone was significantly greater in patients with EoE, as was elongation of vascular papilla.

Diagnosing EoE by Score

By evaluating the odds ratios and *P* values determined by comparison of individual disease features by McNemar test (evaluated in Table 1), as an approximation of that particular characteristic's ability to predict EoE, a conditional logistic regression model was created using a backwards elimination strategy. The final model consisted of 6 characteristics (sex, dysphagia, pain/heartburn, history of food impaction, linear furrowing, and white papules; Table 2). In addition, the selection of characteristics for the model was informed by the knowledge that for 326 rows of data, having 6 to 11 covariates in the model, is optimal (28). Male sex, dysphagia, history of food impaction, linear furrowing, and white papules were associated with increased odds of EoE diagnosis. Pain/heartburn was associated with increased odds of GERD diagnosis. Missing data accounted 8.0% (*n* = 13

pairs) of the cases for the 6 characteristics in the final conditional logistic regression model.

A nomogram (Fig. 4) was created from the odds ratios determined by the conditional logistic regression model. The characteristic with the highest odds ratio (white papules) was given an arbitrary value of 100 points and subsequent characteristics were given point values proportional to their odds ratio. A receiver-operator characteristic curve (Fig. 5) was plotted for the nomogram-based scores of the 301 cases in the study that were not missing data for the 6 characteristics analyzed. The area under the curve was 0.858 with a 95% confidence interval of 0.816 to 0.900 (*P* < 0.0001).

DISCUSSION

The major finding of the present study is the identification of 6 disease characteristics that could potentially differentiate EoE from GERD beyond the present diagnostic strategy, which is dependent on biopsy and eosinophil count. The six disease characteristics likely represent the clinical manifestation of a unique immune process that contributes to the pathophysiology of EoE.

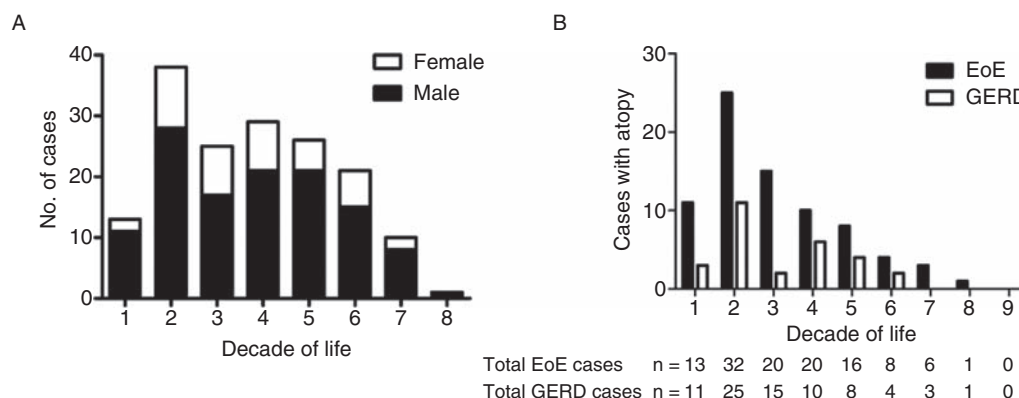


FIGURE 2. A, Sex distribution of the eosinophilic esophagitis (EoE) cohort by decade of life, at the time of diagnosis. B, The distribution, by decade of life, of the number of cases with concurrent atopy in the EoE and gastroesophageal reflux disease (GERD) cohorts.

The study discovered that multiple clinical and endoscopic findings are associated with EoE and the presence of these findings increases the statistical confidence with which the patient can be said to have EoE. Male sex, dysphagia, a history of food impaction, linear furrowing, and white papules were the clinical and endoscopic findings independently associated with EoE. Pain (including heartburn) was independently associated with a diagnosis of GERD. The finding of a normal appearing esophagus in 48% of the GERD group may not be representative of the GERD population as a whole because patients with a typical clinical presentation of erosive esophagitis are not always biopsied. Findings found to be significantly associated with EoE in previous studies including peripheral blood eosinophilia (27) and esophageal dysmotility (29) were not found to contribute to differentiating EoE and GERD in the present study population.

The nomogram was based on the conditional logistic regression model determined by our data set. The purpose of the study was not to replace the histopathologic component of the EoE diagnosis, but to improve our understanding of the value of other clinical and endoscopic information that may aid in differentiating EoE and GERD. It is important to note that, based on the present model, a male patient with dysphagia and no pain or heartburn would have a score of 98 and a reasonably high probability of having EoE and not GERD. This result is noteworthy because these

particular disease characteristics do not require endoscopy or biopsy. Future prospective studies can expand on the present findings to create a more comprehensive diagnosis of EoE that may supplement present practices of evaluation for patients with suspected EoE.

We aimed to build upon the findings of Dellon et al who performed a similar study, which was case-controlled, but not age-matched (30). Similar to our study, this group also found that dysphagia and linear furrows supported a diagnosis of EoE compared with GERD. Six other studies have investigated questionnaires as a method to predict EoE (Table 3) (1,12–16,31–35). A symptom score based on a modified questionnaire for pediatric acid-peptic disease (31) has been used retrospectively to evaluate the safety and efficacy of budesonide treatment (15) and prospectively to identify symptoms associated with EoE (14). The latter study found that dysphagia and early satiety were predictive of EoE in children. Two other scoring systems adapted from GERD questionnaires (32–34) have found that allergic asthma, male sex, trachealization (12), and dysphagia (1) were independent predictors of EoE in prospective study of adult subjects undergoing endoscopy. Many of these characteristics were significantly associated with EoE when considered individually in our patient cohort as well. Another study, using the same questionnaire as Veerappan et al (12), found no significant difference in symptom

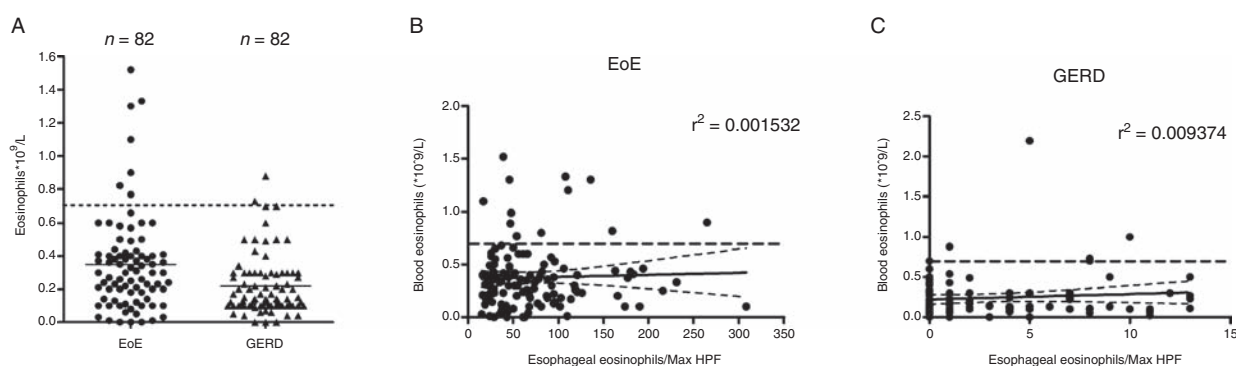


FIGURE 3. A, Distribution of matched peripheral blood eosinophil level comparing eosinophilic esophagitis (EoE) and gastroesophageal reflux disease (GERD) cohorts (n = 82 for each group). The dotted line represents the threshold value (0.7×10^9 eosinophils/L) for eosinophilia at our center. B, No significant correlation was found between unmatched intraepithelial esophageal eosinophils per maximal high-power field (HPF) and peripheral blood eosinophil level in EoE (n = 119, $P = 0.673$) or GERD (C; n = 110, $P = 0.314$) patients.

TABLE 2. Results of the conditional logistic regression analysis for each parameter

Parameter	Odds ratio	95% Confidence interval	P
Male sex	1.82	0.86–4.72	0.106
Dysphagia	2.02	1.74–16.68	0.003
Pain/heartburn	0.4	2.36–28.23	0.001
History of food impaction	5.39	0.19–0.86	0.018
Linear furrowing	8.16	0.70–4.70	0.217
White papules	9.61	1.33–69.28	0.025

score when adult patients with EoE were stratified by the presence of nonspecific esophageal motility disorder (13). This finding is similar to our own finding that dysmotility, as subjectively assessed by barium swallow, does not aid in differentiating EoE from GERD. Pentiuk et al (16) developed a questionnaire that was based on symptom frequency and severity, and found that scores did not correlate with esophageal eosinophilia; thus, we did not attempt to evaluate symptom frequency or severity in our study.

Logistic models can be useful for evaluating case-control studies, provided certain assumptions are met (36,37). Notably, case-controlled logistic regression models cannot be used to calculate positive or negative predictive values, which depend on prevalence. Because the cases and controls were matched in the present study in a one-to-one ratio, the disease prevalence in this population is artificial (50% of patients had EoE and 50% had GERD). The relation between EoE and the covariates determined in the present study is not necessarily causal. Other covariates that were not available for the present study may also influence

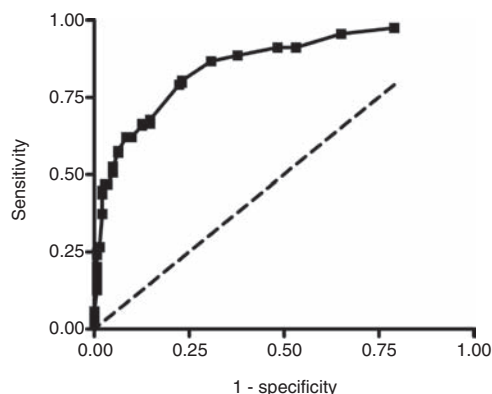


FIGURE 5. Receiver-operator characteristic curve pertaining to the ability of the conditional logistic regression model to predict eosinophilic esophagitis versus gastroesophageal reflux disease in the population studied. The model was based on 6 clinical and endoscopic characteristics. Area under the curve was 0.858 with a 95% confidence interval of 0.816 to 0.900 ($P < 0.0001$).

identification of EoE over GERD. We cannot discount the possibility that the strength of the logistic regression model in the present study is based in part on the fact that little data were missing from the characteristics used. For example, even though some atopic characteristics were significantly different when analyzed individually in Table 1, these characteristics did not contribute when included in the conditional logistic regression analysis. The missing data in these categories may have decreased their influence on the model and subsequent odds ratios.

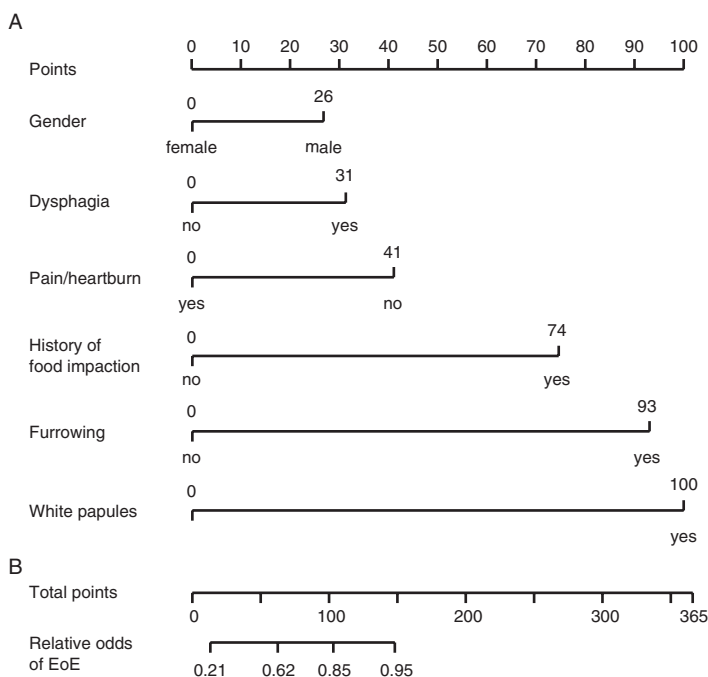


FIGURE 4. Nomogram based on the odds ratios from the conditional logistic regression model. A, The number of points for a given characteristic is proportional to the odds ratio for that characteristic. Note that the absence of pain/heartburn adds points to the total score. B, The sum of the points for each characteristic can be used to predict the relative odds that a patient has eosinophilic esophagitis (EoE) and not gastroesophageal reflux disease (GERD) (assuming an equal distribution of EoE and patients with GERD).

TABLE 3. Details of the previous studies that make use of scoring systems to investigate EoE

Reference	Patients who completed questionnaire	Age group	No. symptoms questions	Symptom frequency score	Symptom severity score	Endoscopic score	Histologic score	Study type	Adapted from
Veerappan et al (12)	385 EGD (25 EoE)	Adult	8	1–3	1–3	Not included	Not included	Prospective	Vigneri et al (32)
Bassett et al (13)	32 EoE	Adult	6	1–3	1–3	Not included	Not included	Prospective	Vigneri et al (32)
MacKenzie et al (1)	261 Dysphagia/food impaction EGD (31 EoE)	Adult	Dysphagia and GERD validated questionnaires	Included	Included	Not included	Not included	Prospective	Aanen et al (33) and DiSario et al (34)
Aceves et al (15)	20 EoE	Pediatric	7 sets	Not included	1–2	4 categories, 1–2	Not included	Retrospective	Dohil et al (31)
Aceves et al (14)	100 (35 EoE, 27 GERD, 24 allergic nonEoE, 14 nonallergic nonEoE)	Pediatric	7 sets	Not included	1–2	4 categories, 1–2	8 features, of 18	Prospective	Aceves et al (15), added histology scoring
Penttinen et al (16)	49 EoE	Pediatric	10 for frequency, 8 for severity	1–5	1–3	Not included	Not included	Prospective	Konikoff et al (35)

EGD = esophagogastroduodenoscopy; EoE = eosinophilic esophagitis; GERD = gastroesophageal reflux disease.

One of the strengths of the present study is that it controls for the high proportion of pediatric patients with EoE when compared with the generally older GERD population (22). EoE characteristics may change with age (9). The selection method used in the present study limited age-related bias, especially when determining the significance of atopic status to the diagnosis because pediatric patients in general are more likely to have atopic disease (38). We found that even when controlling for age, patients with EoE have an increased likelihood of having atopic disease.

One of the limitations of the present study is that it is retrospective by design. A prospective study is being performed to evaluate the model, as a follow-up to the present study. An important aspect of future studies will be evaluating not only esophageal eosinophil count as an endpoint, but also the patient's response to treatment. One recent change to the diagnostic criteria for EoE that has emerged is that the original diagnostic strategy could be supplemented with a trial of proton pump inhibitor (PPI) therapy to rule out severe GERD and possible "PPI-responsive EoE" (4). Interventions, including PPI therapy, were not evaluated in the present study because the patients were evaluated at the time of initial presentation, not following a trial therapy.

A potential confounding factor in the design of the present study is the possible overlap between the EoE and GERD patient groups. Unfortunately, no true criterion standard exists to define EoE at this time, so we are left with using esophageal eosinophil counts and the criteria set out in the published consensus statements (3,4). In this retrospective review, not all of the patients underwent repeat endoscopy, especially those who fulfilled criteria for GERD that responded to PPI therapy. This issue will be addressed by a prospective study to evaluate the scoring system.

Future studies will be needed to assess the contribution of intraepithelial eosinophil number per HPF to the ability to distinguish EoE from GERD. Intraepithelial eosinophil count could not be included in our conditional regression model because it was used to define the cases and the controls. Based on previous epidemiologic studies (39), it is likely that both age and esophageal eosinophil count will contribute to the diagnosis in future prospective studies. The criteria for the scoring system will need to be updated when this information is available.

In conclusion, our study has identified 6 symptoms and signs that can be used in a scoring system to aid in distinguishing EoE from GERD. The disease characteristics were determined by case-controlled, age-matched comparison of EoE and patients with GERD. This scoring system will need to be validated by prospective studies before it can be used in clinical practice.

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