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Clinical, endoscopic, and histologic findings distinguish eosinophilic esophagitis from gastroesophageal reflux disease

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Abstract

Background & Aims—Features of eosinophilic esophagitis (EoE) and gastroesophageal reflux disease (GERD) overlap; because they cannot be differentiated based on eosinophil counts alone, it can be a challenge to distinguish between these disorders. We aimed to characterize the clinical, endoscopic, and histologic features of EoE and GERD and identify factors that might be used to differentiate them.

Methods—We performed a retrospective case-control study on data collected from 2000 to 2007. Cases were patients of any age with EoE, as defined by recent consensus guidelines; controls were patients of any age with GERD. Clinical and endoscopic data were collected and all esophageal biopsy specimens were reassessed by gastrointestinal pathologists. Cases and controls were compared, unconditional logistic regression was performed to develop a model to predict EoE, and receiver operator characteristic curves were constructed.

Results—Data from 151 patients with EoE and 226 with GERD were analyzed. Compared to GERD, features that independently predicted EoE included younger age; symptoms of dysphagia; documented food allergies; observations of esophageal rings, linear furrows, white plaques, or exudates by upper endoscopy; an absence of a hiatal hernia, observed by upper endoscopy; a higher maximum eosinophil count; and the presence of eosinophil degranulation, observed in biopsy specimens. The area under the curve for this model was 0.934.

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Dellon: study concept and design; data acquisition; analysis; interpretation; manuscript drafting/revision
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Fritchie, Rubinas, & Woosley: performed all histology/recounts; critical revision
Shaheen: study concept and design; supervision; interpretation; critical revision

Conclusions—We identified a set of readily available and routinely measured variables that differentiate EoE from GERD. Use of this type of analysis with patients suspected to have EoE might lead to more accurate diagnoses.

Introduction

Eosinophilic esophagitis (EoE) is an emerging condition characterized by a constellation of clinical, endoscopic, and histopathologic features.[1] In the context of the correct symptoms, such as dysphagia, food impaction, heartburn, and in children, failure to thrive,[2–6] and endoscopic findings, such as rings, linear furrows, or white plaques,[5, 7–9] a demonstration of prominent esophageal eosinophilia on biopsy can suggest the diagnosis.[10, 11] Recently published consensus guidelines have proposed formal diagnostic criteria,[1] but because many of the clinical findings related to EoE may be non-specific, in practice it can be challenging to confirm the diagnosis of EoE.

The most common disorder which must be distinguished from EoE is gastroesophageal reflux disease (GERD).[1, 12, 13] This differentiation is critical, as evaluation, treatment, and prognosis for the two conditions are widely divergent. The symptoms of both conditions overlap substantially,[14, 15] potentially related pathogenic mechanisms have been proposed,[12] and elevated eosinophil counts, the presumed hallmark of EoE, are not specific.[14–16] Moreover, much of the literature on EoE is based on analyses of series of, or comparisons between groups of, EoE patients. Only limited published data exist comparing EoE patients to those without EoE,[17–20] and comparing EoE to GERD.[21–24]

The aims of this study were to thoroughly characterize clinical, endoscopic, and histologic features in a large number of patients with EoE of any age, compare them to GERD patients, and determine factors that could reliably differentiate the two conditions. We hypothesized that a combination of specific symptoms, esophageal mucosal abnormalities, and pathologic findings beyond simple eosinophil counts would predict a diagnosis of EoE.

Methods

Study design and patients

We conducted a retrospective case-control study at the University of North Carolina (UNC) Hospitals. All patients were selected from the UNC EoE clinicopathologic database, which contains information on patients with esophageal eosinophilia from any cause from January 2000 through December 2007. This resource was originally constructed by searching the UNC pathology database for every esophageal biopsy obtained over this time frame and then narrowing the search to those reports with any mention of the term “eosinophil”.

Cases were patients of any age with EoE, as defined by the recent consensus guidelines.[1] Specifically, patients needed to have ≥ 15 eosinophils in at least one high-powered field (eos/hpf) and at least one typical symptom of esophageal dysfunction (i.e. dysphagia, food impaction, heartburn, or feeding intolerance), with other causes of esophageal eosinophilia excluded, and without a response to acid-suppression. When available (n = 79), response to acid-suppression was assessed by esophageal biopsy; otherwise, response was assessed by symptoms. Because these diagnostic guidelines were published at the end of this study period, they were applied in a retrospective fashion to every potential case identified, and the data sources specified below were utilized to confirm case status. In addition, only incident cases were included, and these were categorized by esophageal biopsy date.

Controls were patients of any age with GERD who also underwent esophagogastroduodenoscopy (EGD)and biopsy over this time course. GERD patients were

defined by at least one typical symptom (i.e. heartburn, regurgitation, pain, failure to thrive) which was the main indication for EGD, consistent biopsy findings (inflammation), and a clinical evaluation which excluded other possible causes. They could have either erosive or non-erosive disease. There were no restrictions on esophageal eosinophil counts in the GERD patients, and controls were also categorized by their esophageal biopsy date. Patients with confirmed Barrett's esophagus were not included in the study population, nor were patients newly diagnosed with Barrett's as a consequence of the upper endoscopy included in this study. Cases and controls were not matched.

Data sources and variables

Clinical data were abstracted from the UNC electronic medical record. Covariates of interest included: demographic factors (date of birth, gender, race); symptoms (dysphagia, food impaction, heartburn or regurgitation, chest pain, abdominal pain, nausea, vomiting, crying, failure to thrive); coexisting atopic disease (allergic rhinitis or sinusitis, documented food allergy (demonstrated by either symptomatic evidence of allergy with reintroduction of a food or by testing directed by an Allergist), asthma); medication use at the time of endoscopy; selected lab values as available (peripheral eosinophil count, IgE level, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)); and results from ambulatory pH monitoring and esophageal manometry.

Endoscopic data was extracted from our electronic database, ProvationMD (Provation Medical, Minneapolis, MN), with attention to the EGD indication as well as endoscopist-reported esophageal findings. These included: a normal esophagus (no findings), rings, strictures, a narrow-caliber esophagus, linear furrows, delicate or easily torn mucosa (so-called "crêpe-paper" mucosa), white plaques or exudates, erythema, erosions, decreased vascularity, esophagitis, ulceration, hiatal hernia, as well as any other pertinent finding. We also determined the overall case volume of EGDs for each of the study years, as well as the number and type of cases during which esophageal biopsies were performed.

Histopathologic interpretation

Once appropriate cases and controls were identified, all original pathology slides were retrieved from archival status and re-examined. Each slide was re-read by one of three study pathologists (KJF, TCR, JTW) according to a protocol our group has previously validated which has excellent inter- and intra-observer reliabiltiy.[25, 26] In brief, each glass slide was blinded, scanned and converted to a digital slide, and viewed with Aperio ImageScope (Aperio Technologies, Vista, CA). The eosinophil density (eosinophils/um^2) was then determined for five areas: the area of maximum eosinophilia, the area that was judged to be the next-most densely infiltrated with eosinophils, and three areas that were representative of the biopsy specimen overall. For purposes of comparison to previously published studies, eosinophil density was converted to eos/hpf for an assumed hpf size of 0.24 mm^2, the size of an average field as reported in the literature.[6]

In addition, for each of the five areas, the presence of degranulating eosinophils (defined as eosinophilic granules in the proximity of a eosinophil, but not in isolation),[10, 11] the presence of eosinophilic microabscesses (defined as clusters of ≥ 4 eosinophils),[10] the mucosal and biopsy distribution of eosinophils, the presence of spongiosis, and the presence of laminal propria fibrosis was noted. For analysis, if any of these findings were present in one area, then that biopsy was analyzed as having that specific finding. Finally, because pathologists may use a variety of indicators when assessing a biopsy specimen, each pathologist made a global (but blinded) determination of whether their findings were consistent with EoE "in the correct clinical context".

Statistical analysis

Statistical analysis was performed using Stata version 9 (Statacorp, College Station, TX). Descriptive statistics were used to summarize characteristics of the study population. The number of incident cases of EoE diagnosed each year of the study was determined, and this number was standardized by the total number of EGDs performed each year, the number of cases with esophageal biopsies, and the number of esophageal biopsies performed during procedures evaluating dysphagia in order to determine whether observed trends were potentially due to increased detection.

Bivariate analysis was used to compare the case and control groups. Chi-square was used for categorical variables, and t-test or ANOVA were used for continuous variables. To examine seasonal variation of diagnosis, the month of diagnosis was categorized to create typical seasons: winter was December through February; spring was March through May; summer was June through August; and fall was September through November. Proportions within groups were compared with the chi-square goodness-of-fit test, and proportions between groups were compared with chi-square.

Multivariate analysis with unconditional logistic regression was used to develop predictive models. The main outcome was a diagnosis of EoE (yes/no). Results of the bivariate analysis, as well as results of multivariate modelling within sets of clinical, endoscopic, and histologic characteristics, informed the initial candidate variable selection for the model. Then, the model was reduced with a backwards elimination strategy, *a priori* retaining variables that were significant at a $p < 0.10$ level or were felt to be clinically important. Receiver operator characteristic (ROC) curves were constructed, and the area under the curve (AUC) calculated. Reliability and stability of the final predictive model were tested with the Hosmer-Lemeshow goodness-of-fit test, an examination of classification statistics, and bootstrap stepwise regression (to assess the frequency at which the chosen variables would be selected to remain in the model). The analysis was then repeated with the study population stratified by adult (age ≥ 18 years) or child (age < 18) status. Because a component of eosinophil count was included in the case definition but was a potential predictor variable, we also conducted a sensitivity analysis with and without this variable in the final model, as well as an assessment of incorporating the mean eosinophil count, which is not part of the case definition, in the model. Patients with missing data were excluded from both the bivariate and multivariate analysis.

This study was approved by the UNC Institutional Review Board, and complied with published criteria for conducting and reporting observational studies.[27]

Results

Study subjects

Of the 456 candidate patients identified in the database for this study, 151 were found to have EoE meeting our case definition, and 226 had GERD meeting our control definition. Of the EoE patients, 79 (52%) had persistent eosinophilia on esophageal biopsy while on acid suppression (69 with a PPI and an additional 10 with an H_2-receptor antagonist); the remainder did not have a symptom response to acid suppression. There were 22 patients who had either EoE or GERD, but the medical record contained insufficient data to make a definite determination, and there were 37 patients whose EoE or GERD status could not be determined. Of the remaining 20 patients, esophageal eosinophilia was explained in 4 by achalasia, and 1 each by graft-versus-host-disease, celiac disease, and a parasitic infection; the other 13 had no esophageal disease.

Missing data accounted for $\leq 12\%$ of all observations with exceptions as noted in Table 1. In all cases, missing data were non-differentially distributed between the EoE and GERD groups.

Increasing incidence of EoE

Over the eight year time frame of this study, the number of cases of EoE diagnosed at our center increased dramatically in both pediatric and adult populations (Figure 1A). No cases were found in 2000, while 60 were identified in 2007. While there were increases in EGD and esophageal biopsy volume (65% and 77% increases respectively from 2002 to 2007), as well as increases in biopsies performed in patients undergoing EGD for an indication of dysphagia (104% increase from 2002 to 2007), the increase in the number of EoE cases diagnosed (750% increase from 2002 to 2007) far outpaced this (Figure 1B). This suggests that increased recognition alone was not the responsible for the observed trends in diagnosis.

Clinical characteristics: EoE vs GERD

There were multiple differences in clinical characteristics between the EoE and GERD groups (Table 1). Cases of EoE were younger than GERD cases (25 vs 33 years; $p = 0.001$) and were comprised of a higher proportion of males (77% vs 58%; $p < 0.001$). Symptoms were also different, with cases of EoE having more dysphagia and food impaction, and GERD patients noting more heartburn and abdominal pain. Interestingly, the proportion of patients reporting heartburn was high in both groups (46% of EoE patients vs 56% of GERD patients; $p = 0.009$). For EoE patients, the type of symptom varied by age (see Figure 2A). Non-specific symptoms were seen in younger patients, while more “typical” symptoms of food impaction or dysphagia were seen in comparatively older patients. Specifically, when comparing symptoms between pediatric and adult populations, failure to thrive, vomiting, and heartburn were significantly more common in children than in adults, and food impaction and dysphagia were significantly more common in adults (see Figure 2B).

Atopic diseases, such as allergic rhinitis or dermatitis, documented food allergies, and asthma, were also more common in the EoE group. In addition, the season of diagnosis varied between the groups ($p = 0.02$). Cases of EoE were most commonly diagnosed during summer months ($p = 0.007$), while there was no seasonal trend with GERD ($p = 0.87$).

Endoscopic characteristics: EoE vs GERD

The endoscopic findings also differed substantially between the EoE and GERD groups (Table 2). The most common EGD indication in the EoE group was dysphagia (58%), while heartburn (32%) and abdominal pain (30%) were the most common in the GERD group.

Overall, the esophagus was reported to be normal in 21% of EoE patients and in 27% of GERD patients ($p = 0.16$). Rings, strictures, a narrowed esophagus, linear furrows, crêpe-paper mucosa, and white plaques were all more common in the EoE group, while hiatal hernias were more common in the GERD group. Interestingly, the proportion of patients with esophagitis was similar in the EoE and GERD groups (35% vs 42%; $p = 0.21$). For EoE patients, the EGD findings varied by age (Figure 2C). A normal appearing esophagus and inflammatory-type findings were seen in younger patients, while more “classic” findings were seen in comparatively older patients (mean age range 31–37 years). Specifically, when comparing endoscopic findings between pediatric and adult populations, a normal appearance, white plaques, erythema, or erosive esophagitis were significantly more common in children than in adults, and esophagela narrowing, strictures, crêpe-paper mucosa, and rings were significantly more common in adults (see Figure 2C).

Histopathologic characteristics: EoE vs GERD

Histopathologic features distinguished the EoE and GERD groups as well (Table 3). The mean of the maximum eosinophil counts in the EoE group was 121, compared with 34 in the GERD group ($p < 0.001$), and the mean count in 5 hpfs in the EoE group was 76 compared with 16

in the GERD group ($p < 0.001$). In general, there was no variation in eosinophil count by clinical symptom in either group, or by endoscopic findings with the exception of white plaques. In the EoE group, patients with white plaques had a maximum eosinophil count of 197 compared with a count of 114 in patients without this finding ($p = 0.005$).

Eosinophil degranulation was more commonly present in the EoE group compared with the GERD group (94% vs 52%; $p < 0.001$), as was the presence of eosinophil microabscesses (67% vs 19%; $p < 0.001$). The distribution of eosinophils also varied between the groups. In the EoE group, the mucosal distribution was almost always diffuse (92% compared with 77% in the GERD group; $p = 0.004$), and the biopsy distribution was also diffuse (65% vs 21%; $p < 0.001$). Spongiosis was more commonly seen in the EoE group (89% vs 59%; $p < 0.001$). When subepithelial tissue was present in the biopsy samples, significant lamina propria fibrosis was not seen in either group.

Predictive modelling

Nine key variables were retained in our final predictive model (Table 4). These were: age at biopsy/diagnosis, dysphagia as a symptom; the presence of a documented food allergy; the presence of rings on EGD; the presence of linear furrows on EGD, the presence of white plaques or exudates seen on EGD; the presence of a hiatal hernia on EGD; the maximum eosinophil count; and the presence of eosinophil degranulation on the biopsy specimen. All were significant at the $p = 0.05$ level with the exception of age, linear furrows, and white plaques.

This model had excellent predictive ability when an ROC curve was constructed (Figure 3), with an AUC = 0.934. The model was also reliable by a number of measures: the Hosmer-Lemeshow goodness-of-fit test yielded a $p = 0.72$ indicating a good fit; the model correctly classified 89% of the subjects in the study; and a post-hoc bootstrap stepwise regression confirmed that the same variables would be selected. The sensitivity analysis demonstrated only a slight decrement of the AUC (to 0.91) when the maximum eosinophil count was removed from the model, and no change in the AUC (0.934) when mean eosinophil count was substituted.

When we stratified the study population by age status (adult vs child), for adults the same key variables as listed above were retained in the model, with the AUC improving to 0.971. For children, the same model yielded a lower AUC of 0.914. A second predictive model for children was developed which included 8 key variables: male gender, the presence of heartburn, atopic disease, food allergy, asthma, linear furrows on endoscopy, the maximum eosinophil count, and eosinophil degranulation. The AUC for this model was 0.957.

Discussion

Because the clinical features and histologic findings of EoE are non-specific and can overlap with GERD, and because distinguishing these two entities is critical for appropriate patient care, we performed a case-control study comparing patients with EoE to those with GERD. The goal was to determine factors that could reliably differentiate the two groups of patients. We found that individual clinical factors (such as age and gender, symptoms of dysphagia and food impaction, the presence of atopic disease, and the season of diagnosis), endoscopic findings (such as rings, strictures, linear furrows, and white plaques), and histopathologic features (such as maximum eosinophil count, the presence of eosinophil degranulation or microabscesses, and the mucosal or biopsy distribution of eosinophils) differed substantially between the EoE and study groups. While previous studies[28–36] have identified similar features in series of EoE patients, our study represents the most thorough examination of these characteristics in a rigorous comparison with an appropriate control group. Moreover, because any one of these individual factors does not have the ability to separate EoE from GERD alone

(indeed, in our study, the prevalence of erosive esophagitis was the same in each group), our modeling strategy identified a set of 9 easily measured factors in this patient population that distinguished EoE from GERD with a high degree of discrimination. Importantly, multiple factors above and beyond the eosinophil count, which can be non-specific,[14–16] are included.

Previous studies have attempted to isolate factors differentiating subjects with EoE from other patient groups. Two similar studies, both prospective assessments of patients presenting for EGD for evaluation of dysphagia, compared patients found to have EoE with the heterogeneous group that did not have it.[19, 20] Prasad and colleagues found that the 33 adult EoE patients identified tended to be younger, present with food impaction, and have typical (rings, furrows, strictures, white plaques) endoscopic features.[19] Mackenzie and colleagues found that the EoE patients (n = 31) also tended to be younger, and have more food allergies and asthma.[20] Two retrospective studies of pediatric populations are also pertinent. Franciosi and colleagues compared a very large series of patients with EoE (n = 335) to clinic-based geographically matched controls in the greater Philadelphia area, as well as to 2000 United States census data, in an analysis primarily limited to demographic data.[17] Aceves and colleagues reviewed their pathology database and compared EoE patients (n = 102) to non-EoE controls with mild esophageal eosinophilia who were presumed to have GERD (n = 102).[18] They performed a detailed histologic analysis and found the EoE patients had more basal zone hyperplasia, as well as more eosinophil degranulation and microabscesses. Similar findings were reported in adult patients by Parfitt and colleagues, in an analysis of 41 patients with EoE and 116 patients who did not have EoE and were also presumed to have GERD.[23]

Several other smaller studies have directly compared histologic features of esophageal biopsies in EoE and GERD patients. Steiner and colleagues reported prominent basal zone hyperplasia in pediatric patients with EoE as compared with GERD, with the diagnosis of GERD confirmed by pH monitoring.[21] Additional investigators have recently applied immunohistochemical techniques to stain for mast cell tryptase[22, 24] and eosinophil-granule related markers such as eosinophil peroxidase,[22, 37] in an attempt to more readily distinguish EoE and GERD. Despite these multiple reports, none had previously attempted to combine the pertinent clinical, endoscopic, and histologic features in a model to predict the presence of EoE.

When interpreting the results of our study, there are several limitations to consider. First, because this is a retrospective study, it is subject to potential misclassification bias and the effect of missing data. Because we recognized these potential limitations during the design of the study, we took specific steps to make sure cases and controls were defined carefully in an *a priori* fashion. Though we identified multiple possible cases of EoE, we only included in this study those which we considered to be definitive cases of EoE. In addition, we confirmed that more than half of the patients in the EoE group had their esophageal biopsies performed on acid suppression and that the remainder did not have a symptomatic improvement with acid suppression. Because the symptomatic assessment was determined retrospectively from the medical records, this could have introduced bias. However, we also went beyond the consensus guideline diagnostic criteria[1] to ensure all other potential causes of esophageal eosinophilia were excluded. We extensively searched all available databases to minimize missing data, and while there were variables with data missing, this was non-differentially distributed between the cases and controls. None of the variables appearing in the final predictive model had more than 10% of the data missing, with the exception of food allergy (28%).

It is also possible that our GERD control group is heterogenous. As can be seen from the range of symptoms and endoscopic findings in this group, there were patients with dyspepsia, as well as patients with both erosive and non-erosive disease included in this group. Additionally, because patients of all ages were included in this study, it is important to remember that typical symptoms of GERD in young children (reflux, vomiting/spitting up, abdominal pain, failure

to thrive) are different than the more typical symptoms in adults. Nevertheless, all of the GERD patients met the same *a priori* definition for study inclusion, and all had evidence of inflammation on biopsy. The fact that the eosinophil count for the GERD group is higher than generally reported in the literature[38, 39] is directly attributable to our case finding strategy and this disease definition. However, this is also the group of patients in whom it is most challenging to distinguish from EoE patients in practice, making it the most informative to use as a control.

A final limitation is that because this is a single center experience, with a referral center for esophageal diseases and pathologists specifically interested in gastrointestinal disorders, the results may not be generalizable to other settings. However, our findings argue against this. We found many of the characteristics previously reported to be associated with EoE present in our case group, and have corroborated other recently reported findings such as the seasonal variation in the diagnosis of EoE. Our observation that symptoms of EoE vary by age has been reported.[40] Our finding that the endoscopic findings also vary with age, with more inflammatory findings early in the disease and more fibrotic findings coming at an older age, is striking and suggests a potentially progressive course of the condition.

There are several other strengths of this paper. First, this is the largest case-control study of EoE vs GERD reported in the literature, and the only one to specifically develop a predictive model of EoE. We were able to extract data on multiple thoroughly characterized clinical and endoscopic features, and all pathology slides were re-reviewed using a previously validated protocol.[25, 26] In the context of a rigorous case definition and a rich database, we identified a set of relatively simple, and routinely collected, factors that, when taken together, reliability predict EoE in this patient population. Of note, this model will need to be validated in other populations of EoE patients before it can be routinely used in practice.

In conclusion, we have presented the results of a large case-control study comparing the clinical, endoscopic, and histologic features of EoE and GERD. Nine factors were found to reliably predict EoE and distinguish it from GERD, including: age, dysphagia; documented food allergy; esophageal rings, linear furrows, and white plaques or exudates on EGD; the absence of a hiatal hernia on EGD; the maximum eosinophil count; and the presence of eosinophil degranulation on the biopsy specimen. By focusing on this group of factors, which can be readily determined during a new patient evaluation, rather than on a simple eosinophil count, EoE and GERD were reliably distinguished in our cohort. Our model, after validation, may help improve the diagnosis of this condition, and facilitate earlier effective therapy for subjects with EoE patients.

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Abbreviations

AUC, area under the curve
CRP, C-reactive protein
EGD, esophagogastroduodenoscopy
EoE, eosinophilic esophagitis
eos/hpf, eosinophils per high-powered field
ESR, erythrocyte sedimentation rate
GERD, gastroesophageal reflux disease
HPF, high-powered field
mm^2, square millimeters
PPI, proton-pump inhibitor

ROC, receiver operator characteristic
um^2, square microns
UNC, University of North Carolina

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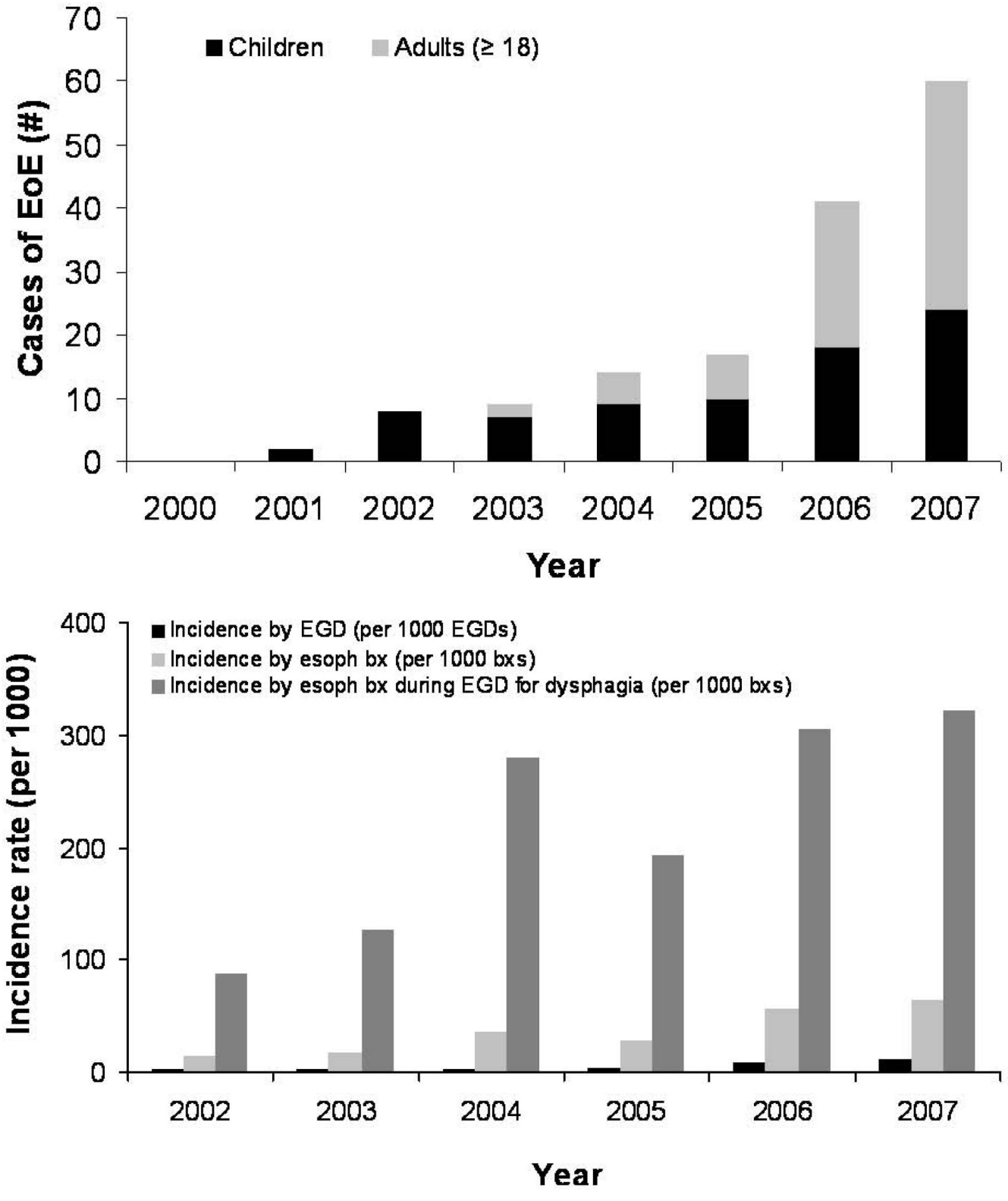
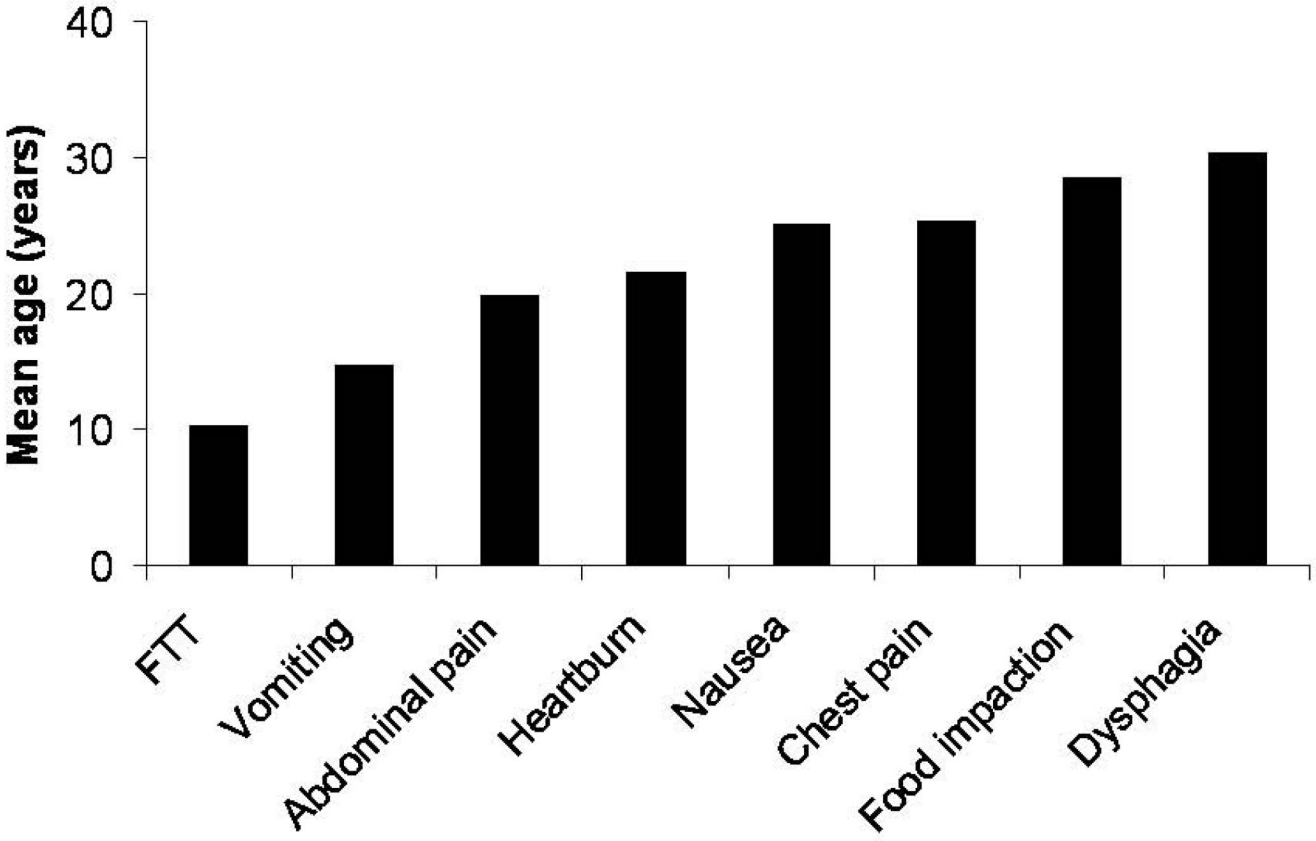
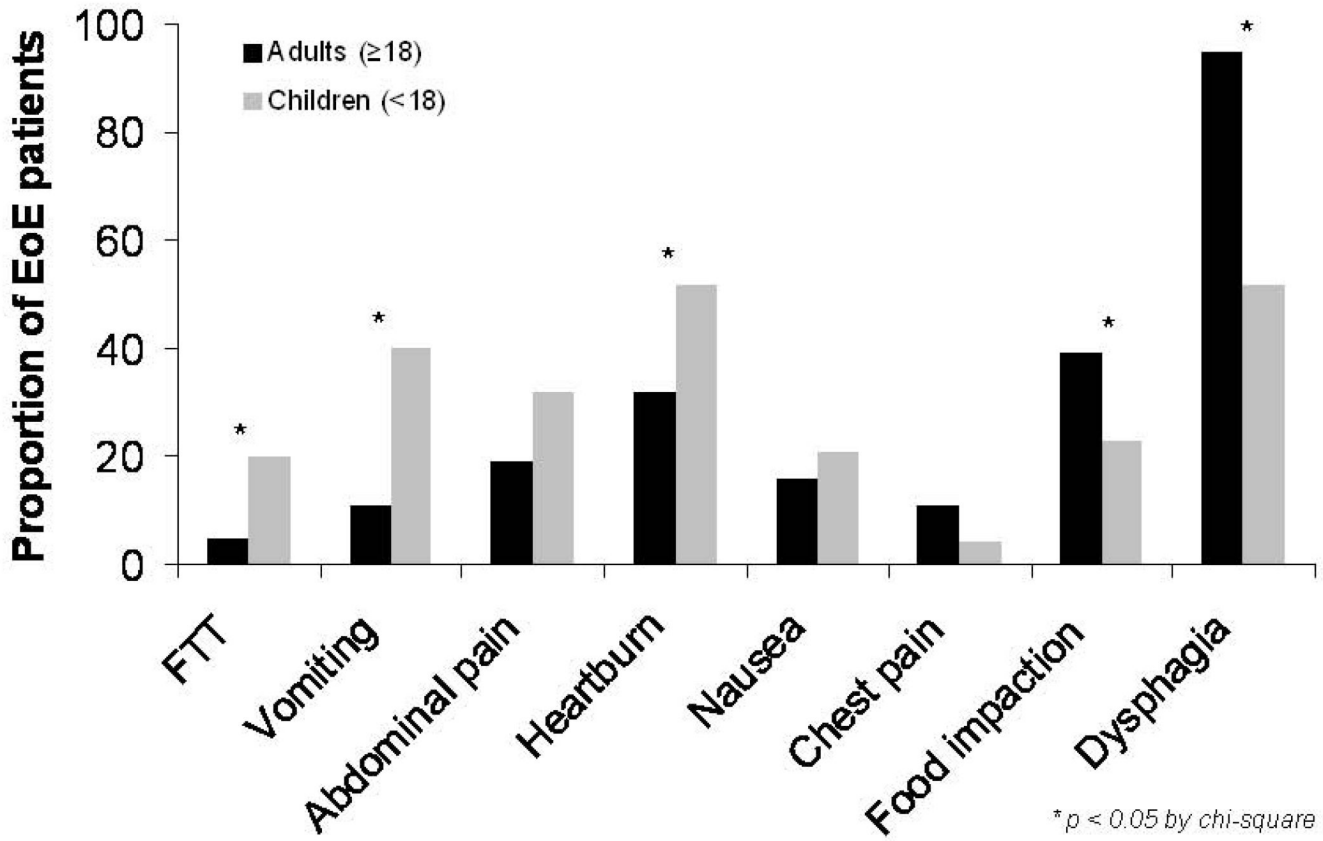
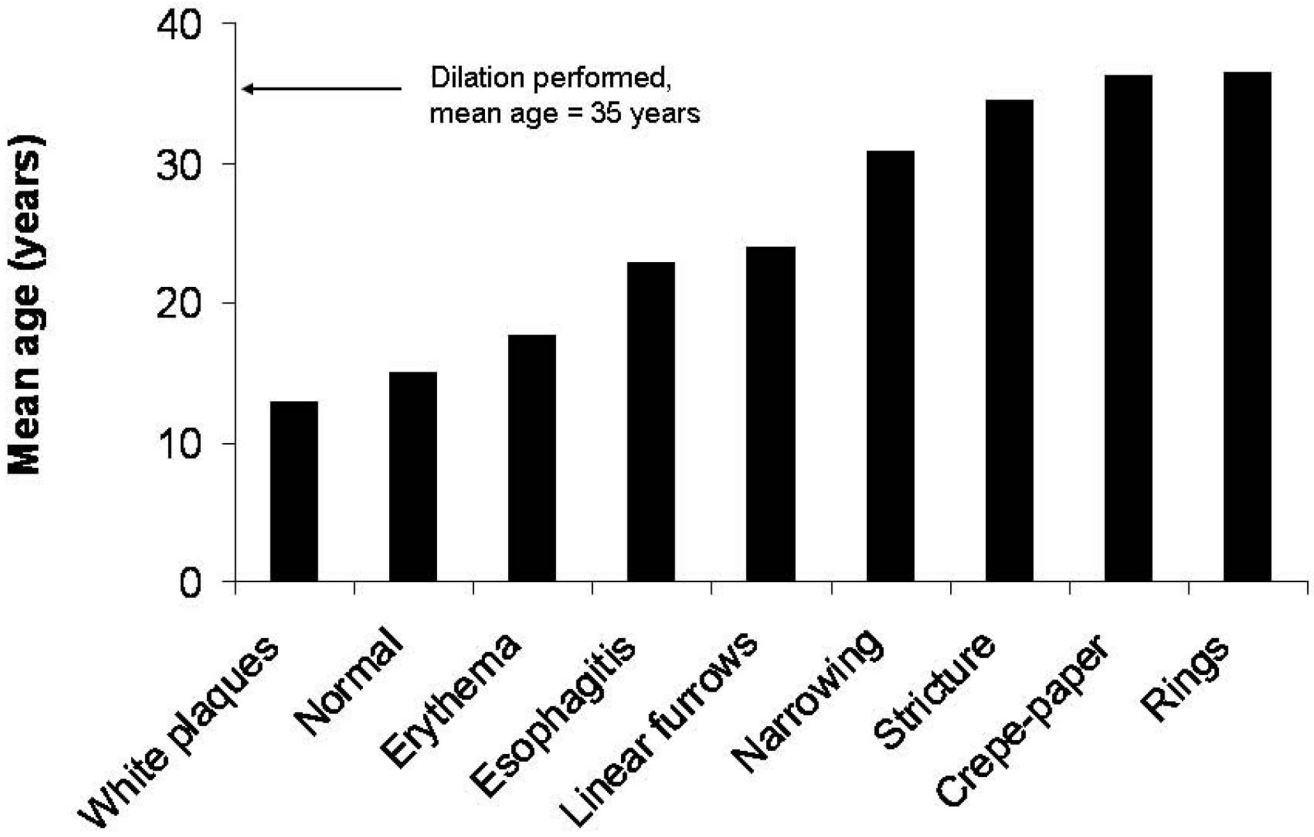


Figure 1.

A: New cases of eosinophilic esophagitis diagnosed by year of the study time frame. Black bars indicate pediatric cases (age < 18) and grey bars indicate adult cases (age ≥ 18). **B:** Annual incidence rate of EoE over the study time frame, after accounting for procedure volume. The black bar indicates the rate (number of new diagnoses per year) per 1000 EGDs performed. The light grey bar indicates the rate per 1000 esophageal biopsies performed. The dark grey bar indicates the rate per 1000 esophageal biopsies during EGDs performed for an indication of dysphagia.







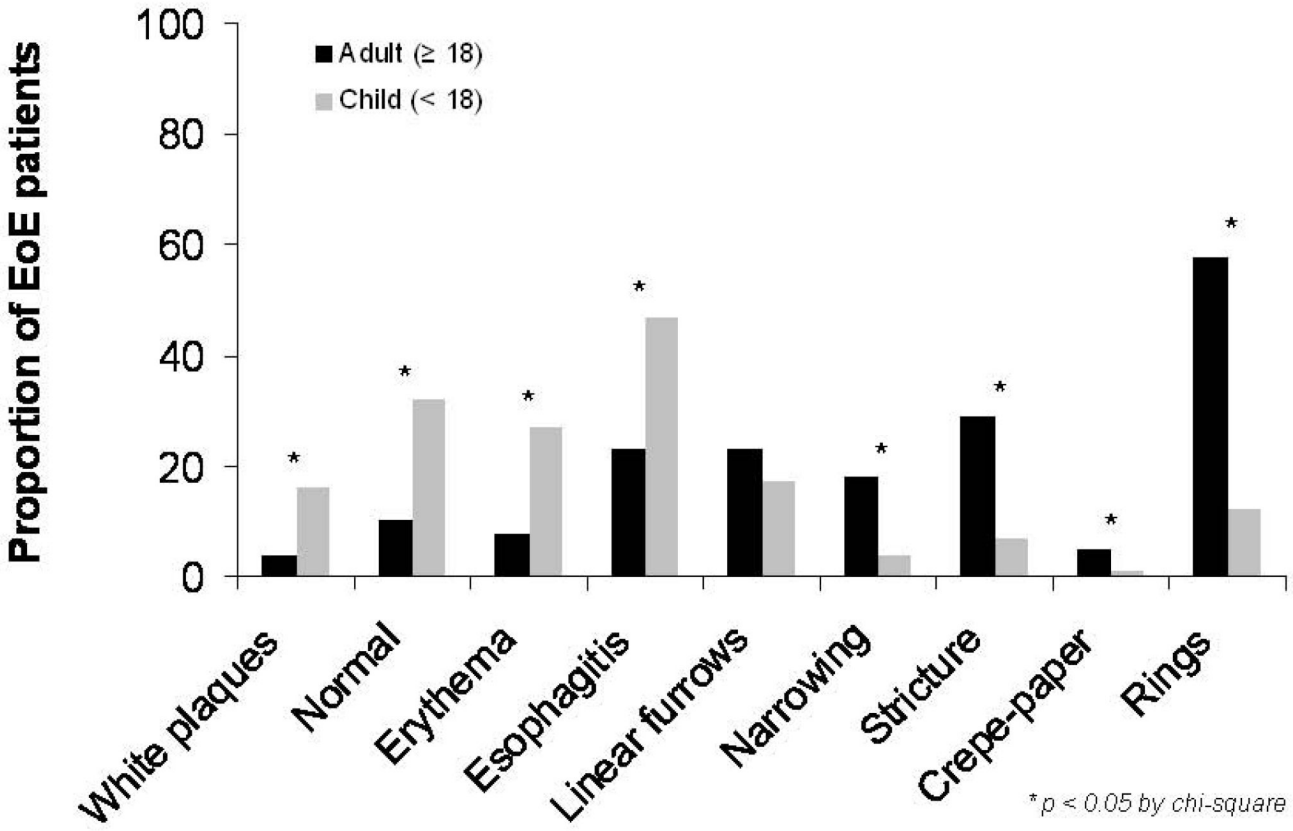


Figure 2.

A: Symptoms in the eosinophilic esophagitis group as stratified by mean age. Non-specific-type symptoms are seen in younger age groups while more "typical" symptoms are seen in the older patients. **B:** Symptoms in the EoE group as stratified by adult (age ≥ 18 years) or child (age < 18) status. The stars represent significant differences in the prevalence of symptom types between the groups. **C:** Endoscopic findings in the EoE group as stratified by mean age. Either a normal esophagus or more inflammatory-type findings are reported in younger age groups, while more "classic" or fibrotic findings are seen in older patients. **D:** Endoscopic findings in the EoE group as stratified by adult or status. The stars represent significant differences in the prevalence of endoscopic findings between the groups.

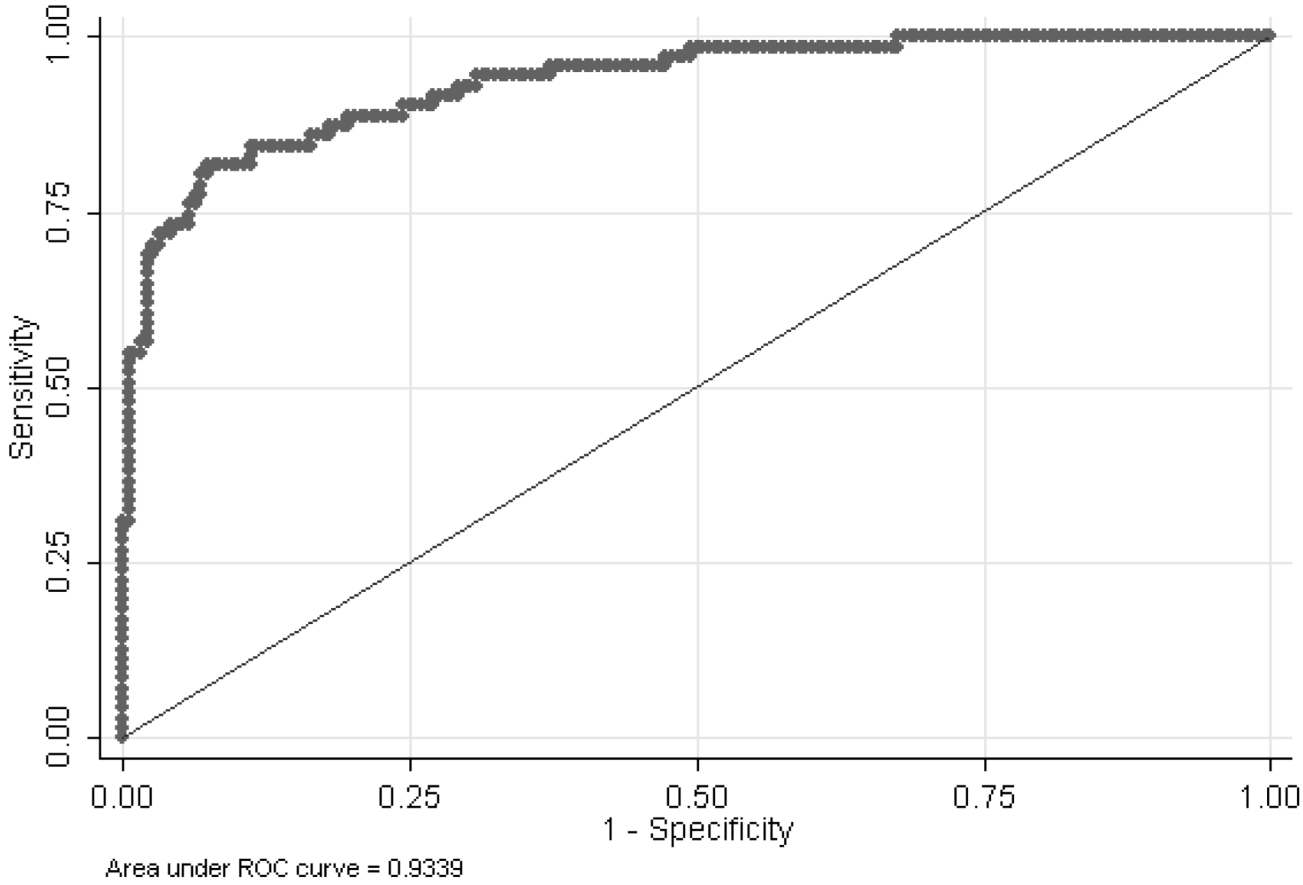


Figure 3.

Receiver operator characteristic (ROC) curve for the final predictive model differentiating EoE from GERD. Variables in the model include: age at biopsy/diagnosis; dysphagia as a symptom; the presence of a documented food allergy; the presence of rings on EGD; the presence of linear furrows on EGD, the presence of white plaques or exudates seen on EGD; the presence of a hiatal hernia on EGD; the maximum eosinophil count; and the presence of eosinophil degranulation on the biopsy specimen.

Table 1

Patient characteristics*

	EoE cases (n = 151)	GERD controls (n = 226)	p value†
Mean age at biopsy (± SD, range)	24.9 ± 18.3 (0.7–77)	32.5 ± 24.7 (0.5–87)	0.001
Adults ≥ 18 years (n, %)	73 (48)	124 (55)	0.21
Male subjects (n, %)	116 (77)	130 (58)	< 0.001
Race (n, %)			0.01
White	122 (81)	185 (83)	
Black	21 (14)	26 (12)	
Hispanic	0 (0)	8 (4)	
Asian	1 (1)	0 (0)	
Native American	2 (1)	3 (1)	
Other	5 (3)	0 (0)	
Symptoms (n, %)‡			
Dysphagia	109 (73)	57 (28)	< 0.001
Food impaction	41 (30)	6 (3)	< 0.001
Heartburn	57 (42)	122 (56)	0.009
Chest pain	10 (8)	26 (13)	0.13
Abdominal pain	35 (26)	108 (52)	< 0.001
Nausea	25 (19)	38 (19)	0.99
Vomiting	36 (27)	68 (33)	0.23
Crying	0 (0)	3 (1)	0.16
Failure to thrive	17 (13)	18 (9)	0.24
Atopic disease (n, %)			
Allergic rhinitis/dermatitis	48 (37)	27 (14)	< 0.001
Food allergy	22 (26)	5 (3)	< 0.001
Asthma	39 (30)	25 (12)	< 0.001
Season of diagnosis (n, %)#			0.02
Winter (December-February)	27 (18)	69 (26)	
Spring (March-May)	31 (21)	67 (26)	
Summer (June-August)	55 (36)	60 (23)	
Fall (September-November)	38 (25)	67 (25)	
Medications (n, %)**			
Proton-pump inhibitors	69 (50)	123 (59)	0.08
H2 receptor antagonists	20 (15)	34 (17)	0.64
Inhaled steroids	20 (15)	16 (8)	0.05
Leukotriene antagonists	8 (6)	8 (4)	0.41
Lab values (mean ± SD, range)			
Peripheral eosinophils (10^9/L)	0.49 ± 0.40 (0–2.3)	0.25 ± 0.17 (0–0.8)	< 0.001
IgE level (kU/L)	270 ± 348 (14–1254)	174 ± 319 (7–1045)	0.46
ESR (mm/hour)	9.0 ± 11.1 (0–47)	9.1 ± 9.0 (0–45)	0.96
CRP (mg/dL)	1.3 ± 2.2 (0–6)	0.9 ± 1.8 (0–4)	0.63
pH probe (n, %)			0.001
Normal	12 (86)	3 (25)	
Acid reflux (by criteria)	0 (0)	8 (67)	
Borderline result	2 (14)	1 (8)	
Esophageal manometry (n, %)			0.28
Normal	2 (50)	7 (78)	
Ineffective esophageal motility	0 (0)	1 (11)	
Non-specific	2 (50)	1 (11)	

*Missing data accounted for ≤ 12% of all observations with the following exceptions: chest pain (13%); nausea (13%); crying (13%); failure to thrive (13%); the presence of allergic rhinitis or dermatitis (14%); food allergy (28%); asthma (13%); and peripheral eosinophil count (47%). In all cases, missing data were non-differentially distributed between the EoE and GERD groups. For clinical variables not routinely obtained in practice, there were more missing data: IgE level (92%); ESR (73%); CRP (95%); pH probe (94%); and esophageal manometry (96%).

†P values calculated with t-test for continuous variables and with chi-square for categorical variables

‡Patients may have had more than one symptom

#For seasons of diagnosis, the listed p value is the overall comparison between the two groups. Within the EoE group, p for trend = 0.007, and within the GERD group, p for trend = 0.87, both calculated with the chi-squre goodness of fit test.

**Medications were recorded if they were being used at the time of endoscopy and biopsy. At total of 79 of the 151 patients with EoE were on either a PPI or an H2-receptor antagonist at the time of endoscopy.

Table 2

Endoscopic characteristics

	EoE cases (n = 151)	GERD controls (n = 226)	p value*
EGD main indication (n, %)			< 0.001
Dysphagia	48 (32)	21 (9)	
Dysphagia and other	28 (19)	18 (8)	
Dysphagia and heartburn	11 (7)	13 (6)	
Heartburn/reflux	20 (13)	31 (14)	
Heartburn and other	6 (4)	28 (12)	
Food impaction alone	6 (4)	2 (1)	
Abdominal pain (any)	17 (11)	67 (30)	
Weight loss/failure to thrive	5 (3)	3 (1)	
Nausea and/or vomiting	5 (3)	13 (6)	
Chest pain	2 (1)	3 (1)	
Anemia/GI bleeding	0 (0)	17 (8)	
Peptic ulcer disease	0 (0)	1 (0)	
Prior upper GI neoplasm	0 (0)	2 (1)	
Odynophagia	2 (1)	2 (1)	
Feeding intolerance	1 (1)	0 (0)	
EGD done for any dysphagia (n, %)	87 (58)	52 (23)	< 0.001
EGD done for any heartburn (n, %)	37 (25)	72 (32)	0.12
EGD findings (n, %)†			
Normal	31 (21)	62 (27)	0.16
Rings	51 (34)	7 (3)	< 0.001
Stricture	26 (18)	17 (8)	0.003
Narrowed esophagus	16 (11)	1 (0)	< 0.001
Linear furrows	30 (20)	3 (1)	< 0.001
“Crêpe-paper” mucosa	4 (3)	0 (0)	0.01
White plaques	15 (10)	7 (3)	0.005
Erythema	26 (18)	25 (11)	0.07
Erosions	8 (5)	10 (4)	0.67
Decreased vascularity	7 (5)	6 (3)	0.28
Esophagitis	52 (35)	94 (42)	0.21
Ulcerations	2 (1)	7 (3)	0.28
Hiatal hernia	10 (7)	59 (26)	< 0.001
Other findings (n, %)			0.004
Schatzki’s ring	9 (6)	9 (4)	
External compression	1 (1)	0 (0)	
Nodule	3 (2)	7 (3)	
Lichenification	1 (1)	1 (0)	
Irregular z-line	0 (0)	14 (6)	
Patulous LES	0 (0)	2 (1)	
Polyp	0 (0)	3 (1)	
Prior fundoplication	3 (2)	8 (4)	
Candidal esophagitis	0 (0)	3 (1)	
Web	3 (2)	1 (0)	
Tortuous esophagus	1 (1)	1 (0)	
Acute food impaction	3 (2)	1 (0)	
Pseudodiverticula	0 (0)	1 (0)	
Granularity and/or friability	4 (3)	7 (3)	
“Boggy” esophagus	7 (5)	2 (1)	
No other finding	116 (77)	157 (69)	
Dilation performed (n, %)	31 (21)	12 (5)	< 0.001

*P values calculated with chi-square for categorical variables

†Patients may have had more than one EGD finding

Table 3

Histologic characteristics

	EoE cases (n = 151)	GERD controls (n = 226)	p value*
Biopsy location (n, %)			< 0.001
Gastroesophageal junction	5 (3)	26 (12)	
Distal esophagus	13 (9)	38 (17)	
Mid esophagus	7 (5)	12 (5)	
Proximal esophagus	3 (2)	1 (0)	
Multiple levels	51 (34)	24 (11)	
Not specified	72 (48)	125 (55)	
Max eosinophil density (eos/mm^2)			
Mean (± SD, range)	505 ± 456 (63–2536)	140 ± 207 (0–1570)	< 0.001
Median (IQR)	374 (208–606)	72 (10–182)	< 0.001
Max eosinophil count†			
Mean (± SD, range)	121 ± 110 (15–609)	34 ± 50 (0–377)	< 0.001
Median (IQR)	90 (50–145)	17 (2–44)	< 0.001
Mean eosinophil density (of 5 hpfs)			
Mean (± SD, range)	317 ± 265 (6–1471)	69 ± 102 (0–660)	< 0.001
Median (IQR)	243 (143–412)	32 (5–86)	< 0.001
Mean eosinophil count (of 5 hpfs)†			
Mean (± SD, range)	76 ± 64 (1–353)	16 ± 24 (0–158)	< 0.001
Median (IQR)	53 (34–99)	8 (1–21)	< 0.001
Histologic findings (n, %)			
Degranulation present	106 (94)	115 (52)	< 0.001
Microabscess present	76 (67)	43 (19)	< 0.001
Eosinophil mucosal distribution			0.004
Basal	5 (5)	25 (16)	
Superficial	4 (4)	12 (8)	
Diffuse	102 (92)	121 (77)	
Eosinophil biopsy distribution			< 0.001
Patchy	39 (35)	151 (79)	
Diffuse	74 (65)	41 (21)	
Basal layer present	110 (97)	219 (99)	0.40
Spongiosis present	101 (89)	132 (59)	< 0.001
Subepithelial tissue present	91 (81)	173 (78)	0.58
Lamina propria fibrosis present	1 (1)	3 (2)	0.69
Biopsy consistent with EoE‡	100 (92)	72 (36)	< 0.001

*P values calculated with t-test for continuous variables and with chi-square for categorical variables

†Calculated for a hpf area = 0.24 mm^2

‡Determined by the pathologists on examination of the biopsy specimen alone in the absence of clinical information

Table 4

Multivariate model predicting EoE*

Predictor	Odds ratio	95% CI	p value
Age at biopsy†	0.98	0.95 – 1.00	0.09
Dysphagia (symptom)	11.8	3.77 – 36.8	< 0.001
Food allergy (documented)	11.2	2.79 – 45.0	0.001
Rings seen on EGD	9.9	1.93 – 51.1	0.006
Linear furrows seen on EGD	6.4	0.62 – 65.5	0.12
White plaques seen on EGD	5.4	0.49 – 58.5	0.17
Hiatal hernia present on EGD	0.21	0.04 – 1.00	0.05
Maximum eosinophil count‡	1.01	1.01 – 1.02	< 0.001
Degranulating eosinophils	4.81	1.52 – 15.2	0.008

*Multivariate logistic regression with a backwards elimination strategy was used to develop model variables.

†Odds ratio represents the odds of being a case for a 1 year increase in age at biopsy.

‡Odds ratio represents the odds of being a case for a one cell increase in eosinophil count.