A clinical prediction tool identifies cases of eosinophilic esophagitis without endoscopic biopsy: A prospective study

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Abstract

Objectives—Eosinophilic esophagitis (EoE) is difficult to distinguish from gastroesophageal reflux (GERD) and other causes of dysphagia. We assessed the utility of a set of clinical and endoscopic features for predicting EoE without obtaining esophageal biopsies.

Methods—We prospectively enrolled consecutive adults undergoing outpatient upper endoscopy at University of North Carolina from 7/2011–12/2013. Incident cases of EoE were diagnosed per consensus guidelines. Non-EoE controls had either GERD- or dysphagia-predominant symptoms. A predictive model containing clinical and endoscopic, but no histologic data was assessed. Receiver operator characteristic (ROC) curves were constructed and the area under the curve (AUC) was calculated.

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Results—A total of 81 EoE cases (mean age 38 years; 60% male; 93% white; 141 eos/hpf) and 144 controls (mean age 52, 38% male; 82% white; 3 eos/hpf) were enrolled. A combination of clinical (age, sex, dysphagia, food allergy) and endoscopic (rings, furrows, plaques, hiatal hernia) features was highly predictive of EoE. The AUC was 0.944, with sensitivity, specificity, and accuracy of 84%, 97%, and 92%. Similar values were seen after limiting controls to those with only reflux or dysphagia, or to those with esophageal eosinophilia not due to EoE.

Conclusions—We validated a set of clinical and endoscopic features to predict EoE with a high degree of accuracy, and allow identification of those at very low risk of disease. Use of these predictors at the point-of-care will avoid the effort and expense of low-yield histological examinations for EoE.

Introduction

Eosinophilic esophagitis (EoE) is a clinicopathologic condition defined by symptoms of esophageal dysfunction and eosinophilic infiltration of the esophageal mucosa, in the absence of other causes (1–3). Despite this definition, distinguishing patients with EoE from patients with gastroesophageal reflux disease (GERD) symptoms remains clinically challenging. While dysphagia is the hallmark of EoE (1, 4, 5), many non-EoE conditions can cause dysphagia. Additionally, other symptoms in EoE patients including heartburn, reflux, and chest pain, can mimic GERD (6–8). Because of this substantial overlap (9, 10), it is not surprising that EoE has been found in 1% to 8% of patients with symptoms of GERD (11–16). Moreover, an elevated eosinophil count on esophageal biopsy, the presumed hallmark of EoE, is not specific; high levels of esophageal eosinophils can be found in both diseases (9, 10, 15–22). The differentiation between EoE and GERD is critical, however, as evaluation, treatment, and prognosis for the two conditions are divergent. Improved techniques to separate these two entities are required.

We previously performed a study comparing clinical, endoscopic, and histologic features of EoE and GERD patients (23). While no individual feature was pathognomic, on multivariable analysis, a set of factors independently distinguished EoE from GERD, and had substantial utility for diagnosis of EoE as measured with receiver operator characteristic (ROC) curve analysis. However, this study was retrospective, encompassed a time frame when features of EoE might not have been universally recognized, did not assess patients with symptoms of dysphagia who did not have EoE, and included full histopathologic data in the model, which limited clinical utility.

The aim of the present study was to determine prospectively whether a set of clinical and endoscopic features could be used as a prediction tool to distinguish patients with EoE from patients with GERD- or dysphagia-predominant symptoms not caused by EoE without obtaining esophageal biopsies. We hypothesized that a multivariable model would

differentiate EoE cases from non-EoE controls with a high degree of accuracy as measured by the area under the receiver operating characteristic curve (AUC).

Methods

Study design and patient population

This was a prospective study performed at University of North Carolina from July, 2011 through December, 2013. Consecutive adult patients (age 18–80 years) referred for outpatient esophagogastroduodenoscopy (EGD) were eligible for recruitment if they had symptoms of esophageal dysfunction, such as dysphagia, food impaction, heartburn, reflux, or chest pain, that could suggest EoE clinically. Subjects were excluded if they had a known (prevalent) diagnosis of EoE or a different eosinophilic gastrointestinal disorder (EGID), GI bleeding, active anticoagulation, known esophageal cancer, prior esophageal surgery, known esophageal varices, medical instability or multiple comorbidities precluding enrollment in the clinical opinion of the endoscopist, or inability to read or understand the consent form. Subjects provided informed consent and were enrolled prior to the endoscopy. Endoscopy could be performed by any of the gastroenterologists at UNC. A total of 15 attending physicians performed study endoscopies; the majority (73%) were performed by a single endoscopist (ESD). This study was approved by the UNC Institutional Review Board and registered on clinicaltrials.gov (NCT 01988285).

Case definitions and clinical data

EoE cases were diagnosed per consensus guidelines (1–3). They were required to have at least one typical symptom of esophageal dysfunction, an esophageal biopsy demonstrating 15 eosinophils per high-power field (eos/hpf) after an 8 week trial of a proton-pump inhibitor (PPI; 20–40 mg twice daily of any of the available agents, prescribed at the discretion of the clinician), and other causes of esophageal eosinophilia excluded. Accordingly, baseline data for the EoE cases were obtained after the PPI trial and at the time of the confirmatory endoscopy, but prior to knowledge of the biopsy results and before any EoE-specific treatment was prescribed. Subjects who were enrolled and found to have esophageal eosinophilia but who were not on a PPI were prescribed a high-dose PPI trial. If symptoms and esophageal eosinophilia 15 eos/hpf persisted, EoE was diagnosed and they were included in the study. If symptoms and eosinophilia resolved (<15 eos/hpf), they were diagnosed with PPI-responsive esophageal eosinophilia (PPI-REE) and were not included in this analysis. PPI-REE was excluded for several reasons. First, because the major aim of the study was to predict EoE case status at endoscopy and prior to biopsy, we used the consensus diagnostic guidelines as the gold standard, and these guidelines require exclusion of PPI-REE. Second, previous work by us and others compared EoE and PPI-REE subjects, and found that clinical, endoscopic, and histologic features did not distinguish these groups (24–28). Finally, pH testing was not a component of this study, as it has not been shown to predict PPI-REE status or reflux as a cause of esophageal eosinophilia (25, 26, 29).

Non-EoE controls were subjects with symptoms of esophageal dysfunction as noted above who, after endoscopy and biopsy, did not meet clinical and histologic criteria for EoE. PPI use was not proscribed in this group and was at the discretion of the referring provider.

Controls with dysphagia-predominant and GERD-predominant symptoms (ie heartburn, reflux, chest pain) without consideration of clinical PPI response were recruited in equal numbers to allow for secondary analyses as noted below. This distinction was based on symptoms at the time of presentation for endoscopy, and represents a control group previously used for such studies, given that they are at risk for EoE and would otherwise meet disease definition if they had accompanying appropriate histological findings (30).

Standardized case report forms and a prospectively administered questionnaire were used to collect clinical data, including demographics, medical history, symptoms, allergic conditions, indications for endoscopy, endoscopic findings, and final diagnoses. Food allergies were provided by patient self-report, and could reflect either overt allergic reactions or sensitization. During endoscopy, esophageal biopsies for research use were obtained (two from the proximal, one from the mid, and two from the distal esophagus) to maximize EoE diagnostic sensitivity (31, 32). Gastric and duodenal biopsies were also collected for research purposes to exclude concomitant eosinophilic gastroenteritis. Additional clinical biopsies were taken as indicated at the discretion of the endoscopist.

The study pathologists quantified the esophageal eosinophil counts using our previously validated methodology (33). In brief, slides were masked to case/control status, digitized, and reviewed with Aperio ImageScope (Aperio Technologies, Vista, CA). Five microscopy fields from each of the five biopsies were examined to determine the maximum eosinophil density (eosinophils/mm^2 [eos/mm^2]). In order to compare results to prior studies, eosinophil density was converted to an eosinophil count (eos/hpf) using a hpf size of 0.24 mm^2, the most commonly reported field size in the literature (5). In addition to eosinophilic counts, associated histologic findings were also recorded. These included the presence of eosinophilic microabscesses (clusters of 4 eosinophils), eosinophil degranulation, basal layer hyperplasia (when evaluable in properly oriented specimens), spongiosis, and lamina propria fibrosis (if adequate subepithelial stroma was present (32, 34).

Statistical analysis

Distributions of all clinical, endoscopic, and histologic variables of interest were summarized and described. To compare the EoE cases and non-EoE controls, we used Chi-square for categorical variables, and t-tests or Wilcoxon rank-sum test for continuous variables as appropriate for bivariate analysis.

Predictive models based on beta values derived from our previous study population of EoE cases and GERD controls (23) were generated and applied to the current prospectively recruited independent population. In brief, the prior study identified a number of factors on multivariate analysis that predicted EoE case status. The primary model of interest that we examined in the present study contained clinical and endoscopic, but no histologic data, so that EoE case status could be predicted without esophageal biopsy. Beta values and the associated ROC AUC data derived for this model from the dataset from the prior study are listed in Supplemental Table 1. Other models of secondary interest included: 1) a model with full clinical, endoscopic, and histologic data; 2) a model that did not contain the dysphagia and eosinophil count components of the EoE disease definition; and 3) a model

with only clinical, but no endoscopic or histologic, data. These beta values and AUC results from the prior dataset are listed in Supplemental Table 2.

These prior beta values were then used to construct a multivariate logistic regression model to predict EoE case status in the present study population. Diagnosis of EoE by the consensus guidelines was the gold standard. ROC curves were constructed and AUCs were calculated to determine the utility of the models. The AUCs were further contextualized by calculating the sensitivity, specificity, positive and negative predictive values (PPV; NPV), and accuracy. For the primary analysis, all non-EoE controls comprised a single group. Several *a priori* secondary analyses were also performed. The models were reanalyzed first limiting the non-EoE control group to those with dysphagia-predominant symptoms, and then to those with GERD-predominant symptoms. They were also reanalyzed limiting the control group to those subjects with an elevated eosinophil count at the 7 eos/hpf, and then also at the 10 eos/hpf levels. This allowed us to focus on the group of subjects for whom there would be the most diagnostic confusion. Finally, these analyses were also performed with the models of secondary interest.

The planned ROC analysis for the primary analysis determined the necessary sample size. By enrolling at least 60 EoE cases and 120 controls (half with dysphagia-predominant and half with GERD-predominant symptoms), we would have >80% power to detect a true AUC value of >0.90, a highly clinically relevant test performance level (35, 36). All analyses were performed with Stata version 9 (Statacorp, College Station, TX).

Results

Patient flow and characteristics

After screening 586 subjects referred for outpatient upper endoscopy, 276 were enrolled, yielding 81 EoE cases and 144 non-EoE controls (70 with dysphagia-predominant and 74 with GERD-predominant symptoms); 51 patients with either PPI-REE or a clinically indeterminant phenotype were not analyzed for the purposes of this study (Figure 1).

There were clinical differences between the EoE and controls groups (Table 1). EoE cases were younger (38 vs 52 years; p < 0.001), more likely to be male (60% vs 38%; p = 0.001) and white (93% vs 82%; p = 0.03), and almost all had dysphagia (98%). Rates of atopy were high in both the EoE and control group (69% vs 58%; p = 0.09), though food allergies were more common in EoE (43% vs 15%; p < 0.001). Common diagnoses in the control group included GERD (47%), esophageal stricture or Schatzki's ring (18%), functional disorders (17%), and esophageal dysmotility (13%). Additionally, while all of the EoE patients were on twice daily therapy at enrollment, 97 of controls (67%) were on PPI, of whom 58 (40%) were on twice daily dosing.

There were also multiple endoscopic and histologic differences between the two groups (Table 2). Very few (4%) of the endoscopic exams were normal in EoE cases. As would be expected in an EoE group, rings (78% vs 10%), furrows (86% vs 6%), and plaques (47% vs 3%), were more common (p < 0.001 for all). In contrast, hiatal hernias were less common in the EoE group (14% vs 54%; p < 0.001). Stricture and dilation rates were comparable

between the two groups. On histology, the mean eosinophil counts for the cases and controls were 141 ± 119 eos/hpf and 3 ± 6 eos/hpf, respectively ($p < 0.001$). Associated histologic findings including eosinophil degranulation, microabscesses, basal zone hyperplasia, spongiosis, and lamina propria fibrosis were more common in the EoE cases.

Predictive modeling

For the primary predictive model analysis (clinical and endoscopic, but no histologic data, so that EoE case status could be predicted without esophageal biopsy), we used the beta values derived from an independent patient population in our prior study (Supplemental Table 1) (23). The variables included in this model were age, sex, dysphagia, food allergy, rings, furrows, plaques, and hiatal hernia. When these were applied to the prospectively enrolled patient population in the present study, the AUC of the predictive model was 0.944 (Figure 2). The model correctly classified 92% of subjects, with a sensitivity of 84%, specificity of 97%, and PPV and NPV of 93% and 91%, respectively (Table 3). On sub-analysis, the model performed similarly well. The AUC was 0.948 for the GERD-predominant control sub-group, 0.940 for the dysphagia-predominant controls, 0.892 for controls with 10 eos/hpf, and 0.905 for controls with 7 eos/hpf. Similar results were also noted after stratifying the control group for baseline PPI status (for PPI users, AUC = 0.944; for non-PPI users, AUC = 0.965).

The analysis of the secondary models of interest also showed similar results. The beta values and variables used for these models are listed in Supplemental Table 2, and ROC curves are displayed in the Supplemental Figure. For the model with full clinical, endoscopic, and histologic data, the AUC was 0.981. For the model that did not contain the dysphagia and eosinophil count components of the EoE disease definition, the AUC was 0.973. For the model with only clinical, but no endoscopic or histologic, data, the AUC was not as good at 0.862. Even though dysphagia was a strong factor in all of the models, there was a clinically and statistically significant gain in the predictive power as measured by the AUC between the model of clinical factors alone and our primary model of clinical and endoscopic factors ($p < 0.01$). This is reflected by an increase in the proportion of EoE cases correctly classified from 76% to 92%.

Discussion

Despite publication of consensus diagnostic criteria for EoE (1–3), there are no pathognomic symptoms or signs of the disease, and therefore EoE remains challenging to distinguish from other causes of esophageal eosinophilia, particularly GERD, both before and after esophageal biopsy (5, 10, 16, 18, 23). Our previous work identified a set of clinical, endoscopic, and histologic features, that, when taken together, were highly predictive of EoE case status (23). However, the methodology of that study was limited by its retrospective nature and requirement for full biopsy information.

The present prospective study aimed to validate a set of clinical and endoscopic features that could distinguish EoE from non-EoE controls with symptoms of esophageal dysfunction, including symptoms of dysphagia and GERD, without esophageal biopsy by using previously derived beta values and applying them to a newly recruited independent

population. We found that eight easily obtainable measures, including younger age, male sex, presence of dysphagia and food allergies, presence of esophageal rings, furrows, and plaques, and lack a hiatal hernia, predicted EoE diagnosis with a very high degree of accuracy. The results held on additional analyses examining dysphagia-predominant and GERD-predominant controls, and in controls with elevated eosinophil counts not due to EoE. Moreover, we also validated a highly accurate model that could be used when full histologic data are available. Taken together, these models have a high degree of clinical utility, both to minimize the need for biopsy in low-yield patients, and to help distinguish EoE from other clinical conditions when there is a diagnostic conundrum.

There has been intense interest in methods to distinguish EoE from GERD, including analysis of tissue biomarkers (20, 22, 37–43), non-invasive biomarkers (44–47), and most recently, genetic expression profiling (48). While there have also been recent efforts to validate symptom and quality of life measures (49–53), the goal of these investigations has not been to use the symptom scores to diagnose EoE per se. There have been only a few prior attempts to generate clinical prediction tools to identify EoE cases. Aceves and colleagues studied 35 children with EoE and 27 with GERD, and found that the presentation between the groups was similar, but that dysphagia and anorexia/early satiety were more common in EoE and correlated with endoscopic and histologic findings (54). von Arnim and colleagues analyzed clinical and laboratory features of 23 adults with EoE and 20 with GERD, and after logistic regression found that three factors – peripheral eosinophilia, history of food impaction, and PPI-refractory heartburn symptoms – were predictive of EoE with sensitivity of 91% and specificity of 100% (55). Mulder and colleagues identified 163 adult and pediatric EoE cases, and an equal number of GERD controls (56). Using methodology similar to our prior study (23), they generated a predictive model containing six characteristics – sex, dysphagia, chest pain/heartburn, food impaction, furrows, and plaques – which was able to distinguish EoE from GERD with an AUC of 0.858. With the exception of the study by Aceves, the others have been retrospective, and none have attempted to validate the findings in an independent population.

In this study, we present a clinically relevant predictive model. Being able to recognize patients with symptoms of esophageal dysfunction who are most likely to have EoE, as well as those in whom there is a very low likelihood of EoE, based on clinical and endoscopic factors alone, allows a clinical decision to be made as to whether to obtain an esophageal biopsy. Several prospective studies have shown that esophageal eosinophilia or EoE will be found in up to 3–7% of patients undergoing endoscopy for any reason (57, 58), in up to 23% undergoing endoscopy for dysphagia (24, 59–61), and in 1–8% undergoing endoscopy for PPI-refractory heartburn symptoms (11–14, 62). Because of this, current guidelines recommend obtaining esophageal biopsies in all patients with dysphagia to assess for EoE, as well considering biopsy in patients with PPI-refractory GERD (2, 3, 63). In such a paradigm, there will be far more negative than positive biopsies, particularly in patients with GERD-predominant symptoms. In one analysis, the prevalence of EoE in heartburn patients had to be at least 8%, the top of the reported range, for biopsy to be cost-effective (64). Moreover, a recent study of shows EoE health care-related costs are approaching $1 billion annually, a remarkable amount for a relatively uncommon disease (65). Therefore, it is imperative to minimize costs when the biopsy yield is low. Our study provides a model that

can do just that. Because of the very high specificity and NPV, it can accurately identify patients unlikely to have EoE, and therefore not require esophageal biopsy. To aid in this process, we have created an on-line calculator that can be used at the point-of-care to provide the probability of an EoE diagnosis (https://gicenter.med.unc.edu/cedas/eoe_clinical_calculator.html).

This study does have limitations. We did not use validated measures to characterize severity of symptoms or endoscopic findings. While those measures are now available (49, 50, 66), they did not exist when this study was designed. With the modeling strategy that we employed, only the presence or absence of symptoms and endoscopic signs was required, a metric that is easy to use clinically. Given the excellent performance characteristics of the model, it is unlikely that more complicated assessment of symptom severity would have markedly improved its performance. Second, we did not analyze patients with PPI-REE. The overall aim of this study was to distinguish EoE from GERD and other esophageal conditions, and we and others have previously shown that clinical and endoscopic characteristics do not distinguish EoE from PPI-REE (24–28), so we did not repeat that analysis here. We would emphasize, however, that these predictive models are most appropriately used for patients after a PPI trial. Related to this, two-thirds of controls were on PPI. While there was no way to know whether a patient with GERD symptoms on PPI who had an endoscopy and normal biopsies had prior esophageal eosinophilia, we suspect that this type of misclassification would be rare, and if present would have biased the results towards the null. Third, this was an adult population, so we cannot comment on whether the same factors would have utility in a pediatric population. However, because we have provided the beta values from our results, it would be possible to assess the utility of this model in an independent pediatric population. Finally, we did not perform standardized food allergy testing in this patient population. The food allergy variable in the model relies on patient self-report, and could include either overt food allergies or food sensitizations. However, our dichotomous patient self-report mimics clinical practice by allowing a practitioner to fill in the needed data for the model after asking a simple yes/no question.

This study also has a number of strengths. It is the largest prospective study to assess a clinical predictive tool for EoE. It applied beta values developed from a prior study population to validate the results in the present independent subject group. The screening and enrollment strategy was comprehensive and focused on a clinically relevant population, patients undergoing endoscopy for symptoms of esophageal dysfunction, from which the majority of EoE cases come, and in whom the vast majority of difficulty in making an EoE diagnosis occurs. While there might be some referral bias for patients seen in an outpatient endoscopy unit at a tertiary care institution, the broad inclusion criteria, the use of the consensus guidelines for diagnosis of EoE, and the variety of underlying causes of symptoms in the control group, should make the results relatively generalizable. Therefore, we feel that the resultant model has substantial clinical utility. It distinguishes EoE from non-EoE controls with a high degree of accuracy, and the operating characteristics of the model impact a relevant clinical decision, whether or not to obtain esophageal biopsies. Given that high costs from endoscopy and biopsy constitute a substantial portion of the overall costs of EoE patients (65), the question of whether to biopsy has special relevance in this population. Moreover, we performed several pre-specified sub-analyses that show that

the model performs equally well in patients with dysphagia-predominant or GERD-predominant symptoms, as well as the subset of control patients who have elevated esophageal eosinophil counts. Finally, we also analyzed several secondary models, and when full clinical, endoscopic, and histologic data are available, these models also perform very well.

In conclusion, we have performed a prospective study that validated a set of clinical and endoscopic features, including younger age, male sex, presence of dysphagia and food allergy, presence of esophageal rings, furrows, and plaques, and lack of hiatal hernia, predicts EoE with a high degree of accuracy. Using these predictors at the point-of-care to aid with clinical decision making (https://gicenter.med.unc.edu/cedas/eoe_clinical_calculator.html) will avoid the effort and expense of low-yield histological examination for EoE, and also provide guidance in cases where differentiating EoE from other conditions is challenging.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

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Study highlights

What is current knowledge?

- Differentiating eosinophilic esophagitis (EoE) from gastroesophageal reflux disease (GERD) and other causes of dysphagia remains clinically challenging, but the distinction is critical, as evaluation, treatment, and prognosis for the two conditions are divergent.

- There are currently no prospectively validated models to predict EoE case status to use in routine clinical practice.

What is new here?

- We performed a prospective study of adults undergoing outpatient upper endoscopy, identified EoE cases and non-EoE controls, and assessed a predictive model containing clinical and endoscopic, but no histologic data.

- A set of clinical (younger age, male sex, dysphagia, food allergy) and endoscopic (rings, furrows, plaques, and lack of hiatal hernia) features were highly predictive of EoE. The AUC was 0.944, with sensitivity, specificity, and accuracy of 84%, 97%, and 92%.

- These operating characteristics held in the subset of controls with esophageal eosinophilia, as well as for models incorporating all clinical, endoscopic, and histologic features.

- This validated combination of clinical and endoscopic predictors can be used at the point-of-care to aid with clinical decision making.
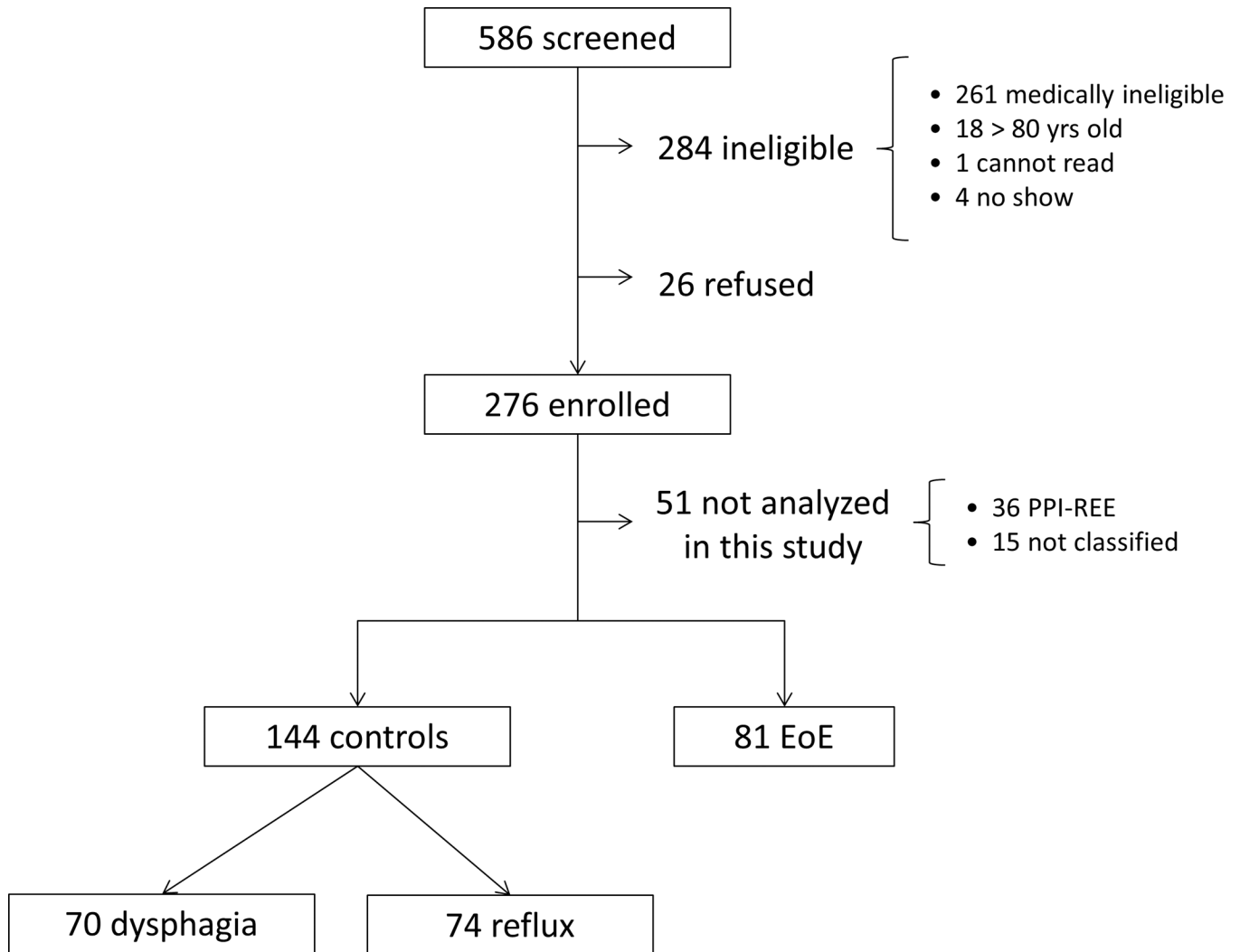
Figure 1.
Patient flow and enrollment in this study. Of the 261 who were ineligible, 61 had non-esophageal symptoms (ie abdominal pain, diarrhea, weight loss, etc), 23 had anemia or GI bleed, 24 had a malignancy, 36 had prior upper GI surgery, 9 had known esophageal dysmotility, 51 had known causes of their symptoms and were undergoing therapeutic endoscopy (ie prior esophageal stricture; treatment of Barrett's esophagus, etc), and 57 had medical contraindications (varices, coagulopathy, multiple medical comorbidities, etc). Of the 15 who were not classified, 4 had prevalent EoE, 2 had a new diagnosis of eosinophilic gastroenteritis, 2 had a new diagnosis of esophageal cancer, and 7 did not complete a PPI trial to complete the EoE diagnostic algorithm during the study time frame.

Figure 2.
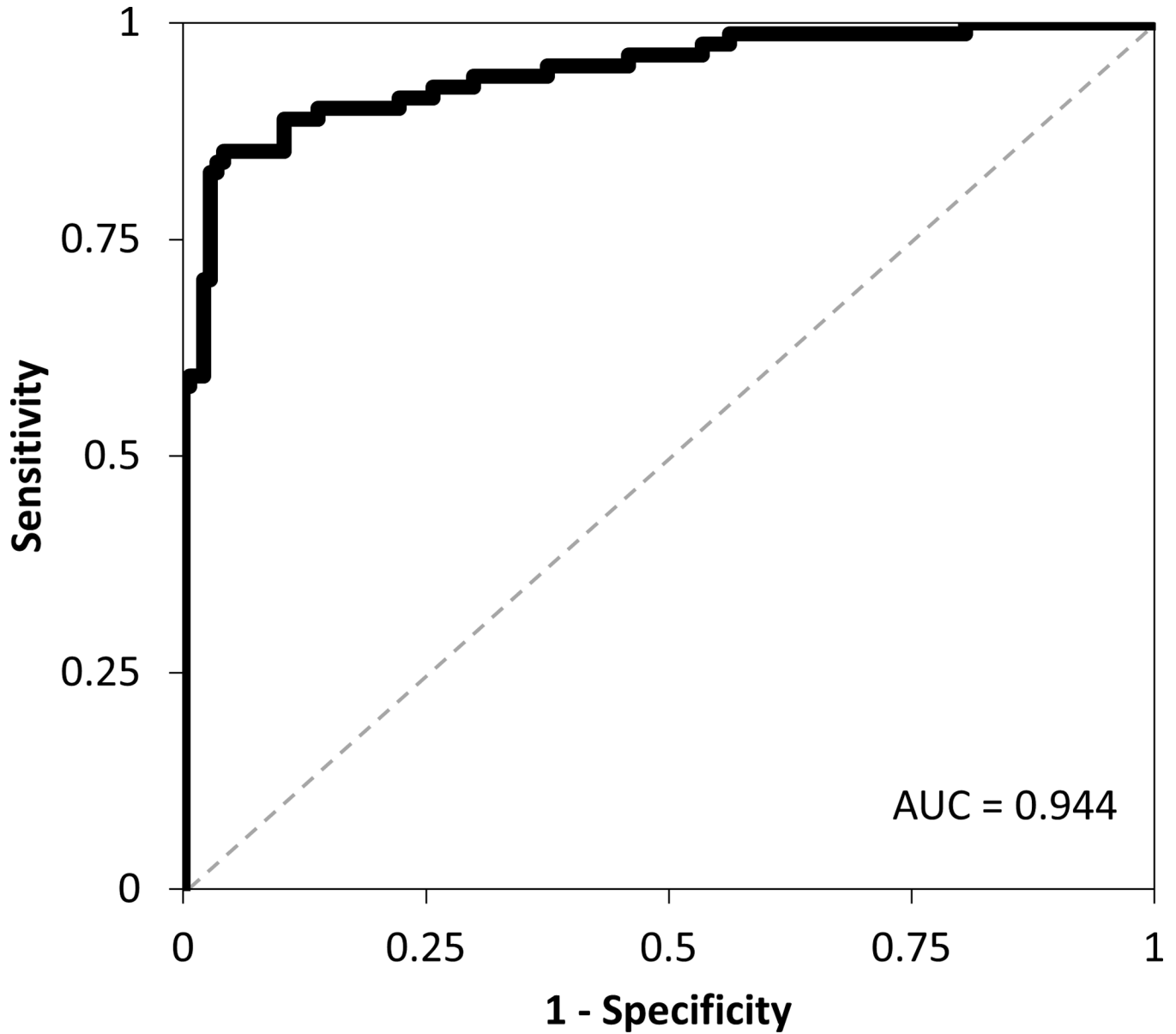Receiver operating characteristic (ROC) curve for predicting EoE case status prior to esophageal biopsy using consensus guidelines as the gold standard. The dotted gray line represents a test that performs no better than chance, which by definition has an area under the curve (AUC) of 0.5. For this figure, the primary model of interest with clinical and endoscopic, but no histologic features, was used.

Table 1

Clinical characteristics of the EoE cases and non-EoE controls

	Non-EoE controls (n = 144)	EoE (n = 81)	p
Age at diagnosis (mean ± SD)	51.6 ± 13.5	38.1 ± 13.3	< 0.001
Male (n, %)	54 (38)	49 (60)	0.001
White (n, %)	118 (82)	75 (93)	0.03
Symptoms/EGD indication (n, %)			
Dysphagia	108 (75)	79 (98)	< 0.001
Heartburn	103 (72)	14 (17)	< 0.001
Abdominal pain	9 (6)	7 (8)	0.50
Nausea/vomiting	12 (8)	2 (2)	0.08
Atopic disorders (n, %)			
Asthma	33 (23)	22 (27)	0.48
Atopic dermatitis	10 (7)	5 (6)	0.82
Allergic rhinitis/sinusitis	69 (48)	50 (62)	0.05
Food allergies	21 (15)	35 (43)	< 0.001
Any atopic disease	83 (58)	56 (69)	0.09
Final diagnoses (n, %)			
GERD	67 (47)	-	-
Erosive	17 (12)	-	-
Non-erosive	45 (31)	-	-
BE	5 (3)	-	-
Stricture		-	-
Peptic	12 (8)	-	-
Radiation	2 (1)	-	-
Other	4 (3)	-	-
Schatzki's ring	9 (6)	-	-
Anti-reflux surgery site defect	3 (2)	-	-
Esophageal dysmotility		-	-
Achalasia	3 (2)	-	-
Spasm	7 (5)	-	-
Other	9 (6)	-	-
Zenker's diverticulum	1 (1)	-	-
Functional	25 (17)	-	-
Candidal esophagitis	2 (1)	-	-

Table 2

Endoscopic and histologic characteristics of the EoE cases and non-EoE controls

	Non-EoE controls (n = 144)	EoE (n = 81)	p
EGD findings at baseline (n, %)			
Normal	23 (16)	3 (4)	0.006
Rings	14 (10)	63 (78)	< 0.001
Stricture	26 (18)	20 (25)	0.24
Narrowing	5 (3)	25 (31)	< 0.001
Furrows	9 (6)	70 (86)	< 0.001
Crêpe-paper	3 (2)	6 (7)	0.05
White plaques/exudates	4 (3)	38 (47)	< 0.001
Decreased vascularity	5 (3)	47 (58)	< 0.001
Erosive esophagitis	22 (15)	2 (2)	0.003
Schatzki's ring	16 (11)	9 (11)	1.0
Hiatal hernia	78 (54)	11 (14)	< 0.001
Dilation performed	44 (31)	28 (35)	0.54
Baseline max eosinophil count (mean eos/hpf ± SD)	2.5 ± 6.3	140.5 ± 119.0	< 0.001
Median eosinophil count (IQR)	0 (0–2)	113 (58–166)	< 0.001
Baseline histology findings (n, %)[*]			
Eosinophil degranulation	17 (13)	71 (95)	< 0.001
Eosinophil microabscess	3 (2)	52 (69)	< 0.001
Basal zone hyperplasia	16 (13)	33 (45)	< 0.001
Spongiosis	53 (41)	68 (91)	< 0.001
Sub-epithelial stroma present	35 (27)	46 (61)	< 0.001
Lamina propria fibrosis	4 (11)	16 (35)	0.02

[*] data available for 203 subjects

Table 3

Diagnostic operating characteristics for the primary predictive model analysis

	Model with clinical and endoscopic, but no histologic, features
AUC	0.944
Sensitivity	84
Specificity	97
PPV	93
NPV	91
Correctly classified	92
AUCs from sub-analyses	
Reflux controls (n = 74)	0.948
Dysphagia controls (n = 70)	0.940
Controls with 10 eos/hpf (n = 11)	0.892
Controls with 7 eos/hpf (n = 15)	0.905