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Development and Validation of Web-based Tool to Predict Lamina Propria Fibrosis in Eosinophilic Esophagitis

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Abstract

Background: Approximately half of esophageal biopsies from patients with eosinophilic esophagitis (EoE) contain inadequate lamina propria, making it impossible to determine the lamina propria fibrosis (LPF).

Aims: To develop and validate a web-based tool to predict LPF in esophageal biopsies with inadequate lamina propria.

Methods: Prospectively collected demographic and clinical data, as well as scores for seven relevant EoEHSS epithelial features, from EoE patients participating in the Consortium of Eosinophilic Gastrointestinal Disease Researchers observational study were used to build the models. Using the least absolute shrinkage and selection operator method, variables strongly associated with LPF were identified. Logistic regression was used to develop models to predict grade and stage of LPF. The grade model was validated using an independent dataset.

Results: Of 284 subjects in the discovery dataset, median age (quartiles) was 16 (8–31) years, 68.7% were male, and 93.4% were White. Age of the patient, basal zone hyperplasia, dyskeratotic epithelial cells, and surface epithelial alteration were associated with presence of LPF. The AUC for the grade model was 0.84 (95% CI: 0.80–0.89) and for stage model was 0.79 (95% CI: 0.74–0.84). Our grade model had 82% accuracy in predicting the presence of LPF in an external validation dataset.

Conclusion: We developed parsimonious models (grade and stage) to predict presence of LPF in esophageal biopsies with inadequate lamina propria, and validated our grade model. Our predictive models can be easily used in the clinical setting to include LPF in clinical decisions and determine its impact on treatment outcomes.

Keywords

Eosinophilic esophagitis; Esophageal biopsies; Histology; Lamina propria fibrosis; Prediction model

INTRODUCTION

Eosinophilic esophagitis (EoE) is an allergen mediated chronic inflammatory condition affecting the esophagus (1). It is estimated to affect 1 in 2000 individuals in the United States (US) (2). Children affected by EoE typically present with feeding difficulties, vomiting, and abdominal pain due to the inflammatory phenotype (3,4). A delay in diagnosis or sub-optimal treatment may lead to persistent eosinophilic inflammation, and involvement of the sub-epithelium and lamina propria fibrosis which in turn can result in esophageal remodeling or the fibrostenotic phenotype (5,6). As such, adolescents and adults with EoE typically present with dysphagia and esophageal food impaction requiring endoscopic interventions (7,8).

The EoE diagnostic guidelines recommend multiple esophageal mucosal biopsies from two or more levels in order to optimize the diagnostic yield (9,10). Subsequently, the esophageal biopsies are assessed for the intensity of eosinophilic inflammation by the peak eosinophil count per high power field (eos/hpf). With the recognition that the disease severity does not strongly depend on the intensity of the eosinophilic infiltration alone, the EoE histology scoring system (EoEHSS) was developed to quantify the grade (degree) and stage (extent) of EoE-relevant histologic changes in epithelium and sub-epithelium (11,12). However, nearly half of the esophageal mucosal biopsies obtained in routine clinical practice by using standard forceps inadequately sample the sub-epithelium (13). This makes it impossible to assess the extent of lamina propria fibrosis (LPF) - a key histologic feature of the esophageal remodeling process (12). As such, developing approaches to predict LPF in esophageal biopsies with inadequate lamina propria sampling can facilitate clinical decision making and inform treatment choices to more accurately assess treatment response, prevent future complications, and improve the clinical outcomes.

We previously reported a high concordance between the presence of surface epithelial alteration and dyskeratotic epithelial cells, and the presence of LPF in children with EoE (14). Based on these observations, we hypothesized that in EoE the level of involvement of certain esophageal epithelial features can predict LPF in situations where it is impossible to determine the status of lamina propria. Therefore, the aims of this study were to construct and validate computational models to accurately predict LPF in esophageal biopsies with inadequate lamina propria. We additionally sought to share our prediction model with the healthcare community as a web-based tool to facilitate management of their EoE patients.

Methods:

Ethical considerations

All participants provided consent to partake in the Outcome Measures for Eosinophilic Gastrointestinal Diseases across Ages (OMEGA) study and for future use of their samples and data, as per both central Institutional Review board (IRB) and local IRB requirements. The present study is a secondary analysis of these data and was approved by the IRB at Cincinnati Children’s Hospital Medical Center (CCHMC) and at the Vanderbilt University Medical Center.

Data Source

We analyzed the demographic, clinical, and histologic data collected as part of the OMEGA study – a multicenter, observational study, aimed at understanding the natural history of EoE and other non-EoE eosinophilic gastrointestinal diseases (EGIDs) such as eosinophilic gastritis and colitis. This study was conducted from 2015 through 2019 under the auspices of the Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR) - a national collaborative network of 13 academic centers caring for adults and children with EGIDs (15,16).

Model Development

Subjects with a diagnosis of EoE who were aged 3 years or older were included in the discovery dataset. Diagnosis of EoE was based on the published criteria of having symptoms of esophageal dysfunction and presence of a peak of ≥ 15 eos/hpf in at least one of their multiple esophageal biopsies (9). Patients could be at any point in their EoE course (newly diagnosed, active off treatment, successfully treated, or treatment-refractory), and with any level of disease activity. Subjects with a history of intestinal surgery other than G tube placement, planned or recent enrollment in blinded investigational studies, esophageal stricture < 3 mm, other identifiable potential causes for esophageal eosinophilia. Individuals with any physicial, mental or social condition or history that might have interfered with study procedures or the ability of the subject to adhere to and complete the study were excluded. However, this did not directly impact the present study as we performed secondary analysis of the data already collected in the original study.

The esophageal biopsies were collected during a clinically indicated esophagogastroduodenoscopy (EGD) and were taken at the discretion of the gastroenterologist performing the endoscopy. The location of acquisition of the esophageal biopsies was noted. The biopsies were processed locally, and the slides were then scanned using the 2-dimensional Aperio Digital Pathology Slide Scanner (Leica Biosystems, Illinois). The scanned images were sent to the CCHMC. The CEGIR Central Review Pathology committee accessed the images stored on a CCHMC server.

The Pathology committee comprised of 3 pathologists with expertise in EoE. They assessed the scanned images for the grade and stage of tissue pathology per the EoEHSS. The EoEHSS assesses eight EoE relevant histologic features: eosinophilic inflammation (EI), basal zone hyperplasia (BZH), eosinophilic abscess (EA), eosinophilic surface layering (ESL), dilated intercellular spaces (DIS), surface epithelial alteration (SEA), dyskeratotic epithelial cells (DEC), and lamina propria fibrosis (LPF) when adequate lamina propria was available for evaluation. Each feature is scored on a 4-point scale (0 to 3) for severity (grade) or extent (stage) of the abnormality, with 0 representing normal features and 3 denoting most severe or extensive pathology (11). EoEHSS has been shown to have excellent inter- and intra-observer reliability (17,18).

To develop our prediction model we used the initial biopsy with adequate lamina propria from EoE patients after being included in the OMEGA study. This allowed us to ascertain the reliability of our data, and eliminate the confounding effect of intra-individual corelationship in patients who underwent esophagogastroduodenoscopy (EGD) with biopsies at multiple time points. We used the peak score for each of the eight epithelial features irrespective of the location of the sampling in the esophagus. This allowed us to develop prediction models based on the epithelial features and optimized for real-world clinical application. We excluded subjects in whom lamina propria could not be assessed due to insufficient sampling as their information would not have contributed towards model development.

External Validation

The external validation dataset comprised of demographic, clinical, and histologic information of children aged 3 – 18 years with EoE undergoing EGD with biopsies at Monroe Carrell Jr. Children's Hospital at Vanderbilt between 2017 and 2018. Details of this study have been previously published (14). Briefly, in this study multiple biopsies were collected from the proximal and distal esophagus from children with EoE undergoing EGD for clinical care at the discretion of their pediatric gastroenterologist. Each of the biopsies were examined. The fragment with most prominent and abnormal histologic and architectural changes and the highest amount of eosinophilic infiltration in a given subject was scored for the EoEHSS grade score. This was the same protocol as used by the CEGIR pathologists. The EoEHSS stage score was not collected in this study.

Statistical analysis

Descriptive statistics including counts and percentages for categorical variables, and medians and quartiles for continuous variables, were used to summarize the characteristics of subjects included in the discovery and validation datasets.

We first investigated if the grade and stage scores could be used interchangeably by examining the agreement between peak grade and peak stage scores. Differences between grade and stage scores were calculated for each pair, and we *a priori* determined that to be used interchangeably, at least 80% of the grade-stage pairs for each of the features had to be in agreement. Next, we computed two Spearman's correlation matrix, one each for grade and stage score, to investigate the relationship between each of the features in all subjects, as well as in subjects stratified by their LPF status (LPF=0 or absent , and LPF=1, 2, or 3 or present).

Given the high-dimensional nature of the data, we used the least absolute shrinkage and selection operator (LASSO) method, to simultaneously select the variables and estimate their regression coefficients. LASSO is a type of analysis that uses shrinkage to force some regression coefficients to be zero. It is particularly well-suited for automating certain parts of the model selection such as the variable selection or parameter elimination (19,20). As such, LASSO allowed us to develop a simple and sparse prediction model (i.e. a model with fewer predictor variables) while retaining the highest ability to predict LPF in biopsies with inadequate lamina propria.

The predictor variables comprised of patient characteristics (including age at biopsy collected used in model development, gender, race), clinical factors (environmental allergies, duration of EoE monitored defined as age at biopsy collected used in model development – age at diagnosis of EoE, and ongoing EoE treatment), and the seven epithelial features were fit into LASSO models to predict absence or presence of LPF (absence=0, presence=1). The area under the receiver operating characteristic curve (AUC) was calculated to assess how well the parsimonious models classified the presence or absence of LPF.

We performed sensitivity analysis to determine the robustness of our prediction model. Herein, we assessed the strength of agreement between the epithelial features, particularly the features selected in our prediction models, in the esophageal biopsies collected from

proximal, mid, and distal esophagus. Futhermore, as treatment can interfere with lamina propria fibrosis, we examined the effect of treatment status (treatment naïve vs. on treatment) and individual treatment approaches (topical steroids, elimination diet, empiric elimination diet, and elemental diet) on the predictors. Finally, the prediction model for grade of LPF was externally validated using our single-center EoEHSS grade scores in children with EoE.

All analyses were performed in R Statistical Software (version 4.0, R foundation for Statistical Computing, Vienna, Austria).

Results:

CEGIR data

In all, 419 subjects providing 1253 esophageal biopsies (proximal: 511, mid: 156, and distal: 586) were in the CEGIR dataset. Of these, the lamina propria was adequately sampled and assessed in 284 subjects who provided 614 biopsies (proximal: 255, mid: 77, and distal: 282). The peak value for each epithelial feature per EoEHSS per subject was included in the discovery dataset to construct the prediction models (Figure 1).

Cohort Characteristics—In the discovery dataset, 93.4% were White, 68.7% were male, and the median (quartiles) age was 16 (8 – 31) years. More than half (58%) of the subjects in the discovery datset were in the pediatric age group (≤ 18 years old). The external validation dataset comprised of 87 children. A majority of them were White (75.9%), male (77.0%) and the median (quartiles) age was 10 (7–13) years. Similar proportion of subjects in discovery (54%) and validation (47%) dataset had EoE for ≥ 24 months. A significantly higher proportion of subjects in the discovery dataset were on swallowed topical steroids when compared to the validation dataset (60.9% vs. 12.6%) (Table 1). The peak grade and stage score among proximal, mid and distal esophageal biopsies included on the analyses is summarized in Supplementary Table 1.

Agreement and Correlation between grade and stage score—The probabilities of agreement between grade and stage score for each of the features did not meet our *a priori* threshold of ≥ 80% to be used interchangeably. The peak grade and stage score agreement was less than 80% for EI (53%), BZH (74%), DIS (52%) and LPF (68%). For DIS and EI, the grade score was higher than the stage score (26% and 33%, respectively) (Supplementary Table 2).

The correlation between the peak grade and peak stage score was high (≥ 0.88) for EI, BZH, EA, ESL, SEA, DEC, and LPF, and was low (0.58) for DIS. On stratified analysis, in subjects with LPF=0, a moderate correlation was noted between BZH and EI for grade score (0.66) and a strong correlation was noted between BZH and EI (0.71) for the stage score. Moderate correlation was also noted between grade and stage score respectively for ESL and EI (0.51 and 0.53), BZH (0.54 and 0.52) and EA (0.53 and 0.51). In contrast, the only modest correlation was noted for grade score between BZH and EI (0.52) (Supplementary Figure 1). Based on these findings, we determined that the grade and stage scores could not be used interchangeably to develop a prediction model.

Parsimonious model to predict Lamina propria fibrosis—Using the LASSO approach, age of the patient, BZH, DEC, and SEA were identified as the variables that were associated with LPF, for both grade and stage (Supplementary Table 3). These variables were fit into separate prediction models. The AUC for grade model was 0.84 (95% CI: 0.80–0.89) and the AUC for stage model was 0.79 (95% CI: 0.74–0.84) (Figure 2). The link to the web-based prediction tool is: https://ls2021.shinyapps.io/pre_lpf/

Sensitivity analysis

Agreement between epithelial features: In all, 47 subjects had esophageal biopsies collected from proximal, mid, and distal sites. The epithelial features identified by LASSO as predictors of LPF were in strong agreement across all levels for the grade scores [BZH: 57–66%; DEC: 91%; and SEA: 81–85%] and the stage scores [BZH: 60–70%; DEC: 89–94%; and SEA: 81–85%] (Supplementary Table 4)

Effect of treatment on model performance: In all, 58 (20%) patients were treatment naïve and 226 (80%) patients were on treatment. Of the ones on treatment, 72 (32%) were on topical steroids alone, 21 (9%) were on elimination diet alone, 19 (8%) were on empiric elimination diet alone, and 2 (<1%) were on elemental diet alone. Approximately 50% of individuals were on a combination treatment.

Neither the treatment status nor exposure to swallowed topical steroids confounded the ability of the predictors (i.e., Age, BZH, DEC, and SEA) to predict LPF. Given the small number of patients, we were unable to conduct meaningful analysis to examine the effect of dietary therapy on our prediction model.

External Validation: We used grade scores from 87 subjects in the Vanderbilt dataset to validate our LPF grade prediction model. Our model correctly predicted absence of LPF (grade LPF = 0) in 60 (80%) and presence of LPF (grade LPF = 1) in 27 (85%) with a cumulative accuracy of 82%. The AUC was 0.78 (95% CI: 0.60 – 0.95) (Supplementary Figure 2). As the stage scores were unavailable, we were unable to validate the prediction model for the stage of LPF in this study.

Discussion:

In EoE, almost half of the esophageal mucosal biopsies obtained using standard forceps inadequately sample the sub-epithelial space. This makes it impossible to assess the sub-epithelial involvement including the lamina propria fibrosis. Using a large and diverse dataset we developed highly accurate computational models to predict the presence or absence of LPF, individually for grade and stage, in esophageal biopsies with inadequate lamina propria. Our models included patient characteristics and epithelial features as assessed per the EoEHSS. The predictor epithelial features were in strong agreement across the biopsy sites, and the performance of our model was not confounded by treatment status and exposure to swallowed topical steroids. The grade model was externally validated using our single-center dataset which comprised of children with EoE and its total accuracy was 82%.

A drawback of assessing esophageal biopsies from EoE patients per the EoEHSS for both grade and stage of tissue pathology is that it is time consuming and thus impractical in clinical practice setting in contrast to the research setting. This holds true even though the grade and stage scores have been previously thought to track together (21). In this study, we found that the correlation between grade and stage score was high but the agreement between the two scores did not meet our predetermined threshold. This suggests that there can be incongruence between the grade and stage of tissue pathology in EoE, and these metrics may need to be assessed separately.

Previously, in a single-center study involving only pediatric EoE patients we reported that peak grade score of DEC (r =0.75), SEA (r = 0.70), ESL (r = 0.60) and EI (r = 0.59) and EA (r = 0.52) were associated with LPF in biopsies with adequate lamina propria sampling (14). We also reported that the presence of SEA and DEC strongly corelated with presence of LPF. In our present study involving multi-center data comprised of both pediatric and adult EoE patients, we found that BZH, DEC and SEA were highly associated with LPF in biopsies with adequate lamina propria. We were unable to confirm our previous finding related to the association between ESL, EI, and EA and the presence of LPF.

In our analysis, the duration of EoE monitored was not identified as one of the optimal variables to predict the LPF. Based on the cross-sectional data, the current disease paradigm suggests that the fibrostenotic complications can occur in EoE in a time-dependent manner (3,5). Perhaps, future prospective studies will be able provide more data on the natural history of EoE and the factors associated with fibrostenotic complications. Likewise, the markers of esophageal eosinophilia (EI and EA) were also not selected as optimal variables predictive of LPF. This highlights the ongoing dilemma about the role of eosinophils as a histologic marker of EoE activity (22), and the unmet need to identify more reliable histologic markers of tissue involvement in EoE. Our findings suggest that BZH, DEC, and SEA may serve as efficient histologic markers of EoE activity.

Since LPF can be an early feature even in the absence of overt endoscopic findings such as esophageal narrowing or stricture (23), a variety of approaches are being used to indirectly or directly predict the presence of LPF or fibrosis deeper in the esophageal layers in EoE patients. For instance, application of EndoFLIP® - a novel approach using high resolution impedance planimetry to determine regional variations in pressure in a cross-sectional area of a hollow organ such as esophagus has revealed that esophagus is less distensible in EoE patients compared to controls and decreased esophageal distensibility was associated with future food impactions (24–26). Likewise, using specialized forceps to obtain deep esophageal biopsies allowed sampling of subepithelial space in more than 90% of adult EoE patients (27). However, these approaches are invasive and can be unsafe particularly in children. They may also require specialized equipment that are not widely available and incur considerable expense. Likewise, molecular markers of epithelial-stromal crosstalk and fibrosis in EoE such as upregulation of periostin and transforming growth factor β1 induced plasminogen activator inhibitor-1 in active EoE and its correlation with LPF have shown promise in research setting, but their utility in clinical practice remains to be studied (28,29). On the other hand, our parsimonious predictive models can be easily used to reliably predict presence or absence of LPF (grade and stage) by inputting the patient's age and maximum

score (grade and stage scores separately) for specific epithelial features which are routinely assessed by pathologists in both clinical and research settings. Our model is available at: https://ls2021.shinyapps.io/pre_lpf/

Our study has limitations. Although we used data from a relatively large and diverse group of EoE patients for analysis, we do not know if the presence of impenetrable LPF affected procurement of LP in esophageal biopsies in the original dataset. Given that EoE patients often have delayed diagnosis or symptoms dating back years prior to diagnosis, we were unable to use the exact duration of EoE in our models instead we used duration of EoE monitored. Next, we did not have sufficient data to develop highly accurate models to predict presence of LPF with more granularity. So at this point, our models can be used to predict presence or absence of LPF (dichotomous outcome) as opposed to providing a break down grade or stage of LPF by sub-scores (0–3) per the EoEHSS. Likewise, we also had limited data to assess the impact dietary therapy on the performance of our prediction model. Our models were developed on the data that were already collected as part of an observational study. There is need to test the models longitudinally to assess their performance in real-world clinical setting. The validation dataset was only able to focus on grade score in children with EoE, as the stage was not available. Additional studies are needed to validate our model using the stage score in children as well as grade and stage scores in adults.

Despite these limitations, our study has several strengths. We used a large, diverse, prospectively collected, and multi-institutional dataset to develop our prediction models, highlighting the value of CEGIR's collaborative infrastructure to develop novel approaches to facilitate a better understanding of the disease natural history and improve clinical outcomes in patients with EoE (30–34). By using LASSO, we were able to optimally use our high-dimensional data for variable selection and model building. Furthermore, this approach has been shown to be superior to usual methods of automatic variable selection such as forward, backward, and stepwise selection for such tasks (35). Since the model is based on the grade and the stage of selected epithelial features at a given time point, predictive ability of our model will be independent of the ongoing EoE therapy. Mirroring a real clinical practice scenario, we corroborated the high accuracy of our prediction model (grade) in an independent single-center dataset which included only pediatric EoE patients wherein the EoEHSS scoring was done by an independent pathologist. Taken together, these illustrate the generalizability and clinical applicability of our prediction model. Finally, we have made the prediction tool freely available for the clinical community. We envision that either pathologists could use this to expand on their report, or clinicians can use the pertinent patient information and data from their pathology report to inform their management of EoE patients.

The current disease paradigm suggests that EoE is a chronic, progressive condition and can lead to esophageal remodeling due to lamina propria fibrosis. As such, recognizing signs of fibrosis can provide information on the severity and progression of the disease. Finding lamina propria fibrosis even when the eosinophilia is controlled could lead to escalation of treatment, a careful search for strictures (e.g., using barium swallow, EndoFLIP, balloon sizing of the esophagus), or more close monitoring. We envision that our prediction tool

would be used in both clinical and research settings. In clinical setting, we anticipate that this will help the clinicians to better understand their patients symptoms, chart the course of their disease, prepare for complications associated with LPF such as persistent dysphagia, future food impactions, and the need for esophageal dilation(s), and inform themselves and the patient about the treatment options if there is LPF (e.g., escalating care by considering topical steroids if the patient is on a PPI alone, improving compliance in a non-compliant patient). It will also alleviate the need to collect deeper esophageal biopsies or biopsies with larger forceps to obtain adequate lamina propria and assess its health. In the research setting, we foresee that our prediction tool will aid the researchers to correlate the esophageal distensibility (as measured by EndoFLIP) with LPF, become a part of the therapeutic trials so that the effect of the new drug can be estimated on the health of lamina propria in the setting where adequate lamina propria is unavailable.

In conclusion, we developed prediction models based on the grade or stage of alterations in epithelial features to predict grade or stage of LPF in esophageal samples with inadequate lamina propria. Prospective use of models in routine clinical practice, patient-oriented research, and therapeutic drug trials will allows us to assess its performance, and further document the impact of LPF on disease progression and clinical outcomes in EoE.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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STUDY HIGHLIGHTS

WHAT IS KNOWN

- In eosinophilic esophagitis (EoE), lamina propria fibrosis (LPF) is central to esophageal remodeling and fibrostenotic complications
- However, almost half of esophageal mucosal biopsies do not contain adequate lamina propria, thereby making it impossible to ascertain LPF
- Developing an easy and widely applicable approach to predict LPF in esophageal biopsies with inadequate lamina propria sampling can contribute towards improving clinical outcomes in EoE

WHAT IS NEW HERE

- Using patient characteristics and the peak grade and stage score for each of the features of the EoE histology scoring system, we developed parsimonious models to predict the presence of LPF (grade and stage) in esophageal biopsies with inadequate lamina propria.
- The area under the ROC curve of our model to predict of LPF (grade) was 0.84 (95% CI: 0.80–0.89), and that for the LPF (stage) was 0.79 (95% CI: 0.74–0.84).
- Our grade model predicted presence of LPF with 82% accuracy in an independent dataset (external validation).
- The prediction model is made available as a web-based tool: https://ls2021.shinyapps.io/pre_lpf/

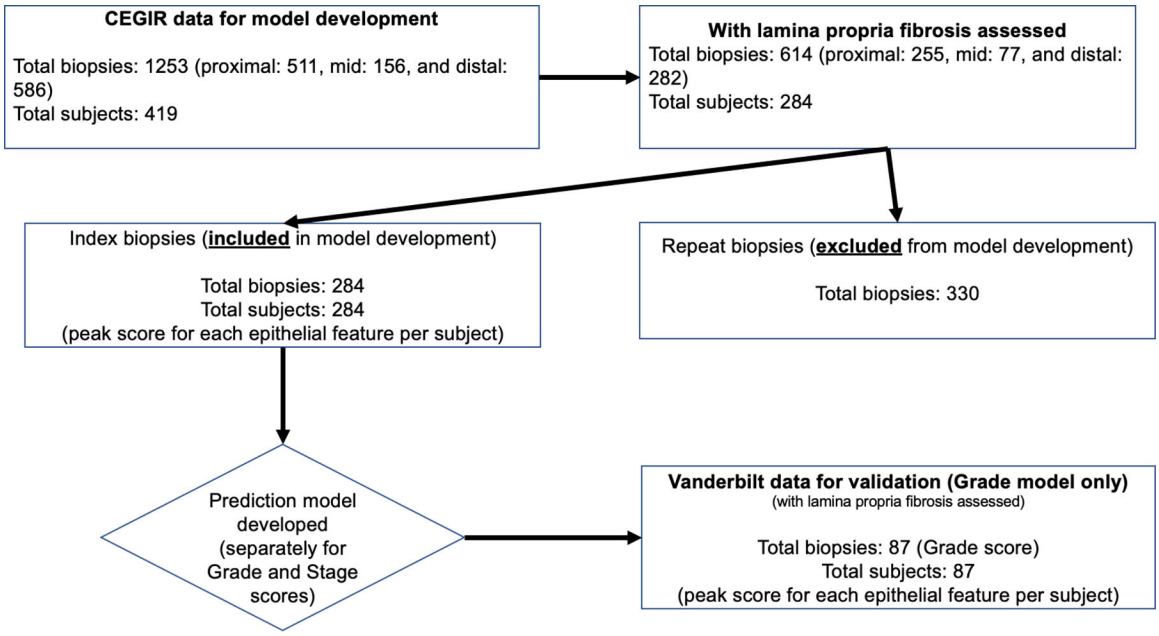

Figure 1:
Schematic illustration of the study

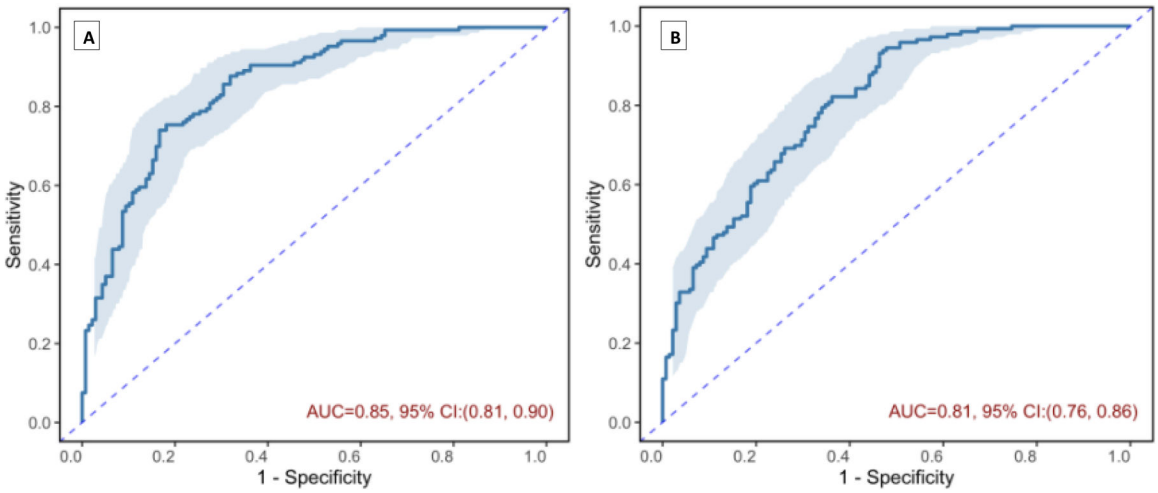

Figure 2:

Area under the curve of prediction models (A) Grade, (B) Stage of lamina propria fibrosis

Table 1:

Characteristics of the subjects included in the discovery dataset and validation dataset

		CEGIR data (Discovery dataset) N=284	Vanderbilt data (Validation dataset) N= 87
Age (years)			
Median (Quartile)		16 [8, 31]	10 [7, 13]
Male (n, %)		195 (68.7)	67 (77.0)
Race (n, %)	White	256 (90.1)	66 (75.9)
	African American	11 (3.9)	14 (16.1)
	Asian	1 (0.4)	0 (0)
	Others/Unknown	16 (5.7)	7 (8.0)
Environmental allergy (n, %)	Yes	120 (42.3)	
	No	54 (19.0)	
	Unknown	110 (38.7)	
Duration of EoE (n, %)	≤ 6 months	31 (10.9)	27 (31.0)
	6 – 12 months	31 (10.9)	12 (13.8)
	12 – 24 months	29 (10.2)	7 (8.0)
	> 24 months	154 (54.2)	41 (47.1)
	Unknown	39 (13.7)	
Ongoing treatment (n, %)	Swallowed topical steroids	173 (60.9)	11 (12.6)
	Elimination diet	93 (32.7)	
	Empiric elimination diet	83 (29.2)	
	Elemental diet	27 (9.5)	
	Other	41 (14.4)	
Subjects from each of the centers (n, %)	Cincinnati Children's Hospital	61 (31.5)	
	Children's Hospital Colorado	54 (19.0)	
	Children's Hospital of Philadelphia	6 (2.1)	
	Laurie Children's Hospital of Chicago	11 (3.9)	
	Northwestern University	16 (5.6)	
	Riley Children's Hospital	2 (0.7)	
	Rady Children's Hospital	28 (9.9)	
	Tuft's Medical Center	19 (6.7)	
	University of California San Diego	6 (2.1)	
	University of Colorado Denver	15(5.3)	
	University of Illinois at Peoria	5 (1.8)	
	University of North Carolina	31 (10.9)	
	University of Pennsylvania	30 (10.6)	

EoE: Eosinophilic esophagitis; CEGIR: Consortium of Eosinophilic Gastrointestinal Disease Researchers