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Delay in Diagnosis of Eosinophilic Esophagitis Increases Risk for Stricture Formation, in a Time-Dependent Manner

Running head:

Strictures in eosinophilic esophagitis

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ABSTRACT

Background & Aims: Development of strictures is a major concern for patients with eosinophilic esophagitis (EoE). At diagnosis, EoE can present with an inflammatory phenotype (characterized by whitish exudates, furrows, and edema), a stricturing phenotype (characterized by rings and stenosis), or a combination of these. Little is known about progression of stricture formation; we evaluated stricture development over time in the absence of treatment and investigated risk factors for stricture formation.

Methods: We performed a retrospective study using the Swiss EoE Database, collecting data on 200 patients with symptomatic EoE (153 men; mean age at diagnosis, 39±15 y old). Stricture severity was graded based on the degree of difficulty associated with passing of the standard adult endoscope.

Results: The median delay in diagnosis of EoE was 6 y (inter-quartile range, 2–12 y). With increasing duration of delay in diagnosis, the prevalence of fibrotic features of EoE, based on endoscopy, increased from 46.5% (diagnostic delay, 0–2 years) to 87.5% (diagnostic delay, >20 y; P=.020). Similarly, the prevalence of esophageal strictures increased with duration of diagnostic delay, from 17.2% (diagnostic delay, 0–2 years) to 70.8% (diagnostic delay, >20 y; P<.001). Diagnostic delay was the only risk factor for strictures at the time of EoE diagnosis (odds ratio, 1.08; 95% confidence interval, 1.040–1.122; P<.001).

Conclusions: The prevalence of esophageal strictures correlates with the duration of untreated disease. These findings indicate the need to minimize delay in diagnosis of EoE.

Keywords: esophagus, complications, inflammation, remodeling

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INTRODUCTION

Eosinophilic esophagitis (EoE) has recently been defined by an expert panel as "a chronic, immune/antigen-mediated, esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation".[1]

There is evidence that EoE incidence increased over the last decades with current prevalence rates in the Unites States and Europe of about 1 affected individual among 2,000 inhabitants in the pediatric as well as in the adult population.[2-6] Adult EoE patients primarily suffer from dysphagia, often culminating in food impaction necessitating endoscopic bolus removal.[7-9]

The endoscopic presentation of EoE is quite variable. Recently, the endoscopic features of EoE have been graded by Hirano *et al*.[10] For the purposes of this study, characteristic features of EoE were classified into two categories, the inflammatory and the fibrotic group of EoE features. According to this classification, whitish exudates, edema and linear furrows represent the items of acute inflammation.[11] Normal esophageal diameter is another hallmark characteristic associated with the inflammatory group of endoscopic features. The fibrotic features of EoE are rings, strictures, and crêpe-paper esophagus. Most patients present with a mix of these inflammatory and fibrotic features at the time of EoE diagnosis.[1,12]

There is a lack of data evaluating stricture development over time in EoE. We know from natural history studies in Crohn's disease that patients initially present with an inflammatory phenotype and that complications (strictures and/or fistulas) develop over time.[13,14] It is presently unknown whether, similar to Crohn's disease progression, EoE is initially characterized by the occurrence of inflammatory features, and, as inflammation persists, fibrotic features, including strictures, develop over time. The lack of data on stricture formation in EoE may be related to the fact that EoE is diagnosed with a longer diagnostic delay (time period from appearance of first symptoms to diagnosis, median 5 years in EoE) when compared with Crohn's disease (median 0.75 years).[7,15] During this long diagnostic

delay, unbridled eosinophil-predominant inflammation is allowed to persist, such that patients may present with strictures at the time of diagnosis. Given the imminent risk of food bolus impactions, purely observational studies of untreated EoE patients are rare for reasons related to ethical standards.[7] Therefore, we examined the relationship between the duration of untreated disease, which corresponds to the diagnostic delay (time period from symptom onset to EoE diagnosis), and the appearance of endoscopic alterations at time of EoE diagnosis.

We aimed to examine whether the length of diagnostic delay positively correlates with the frequency of encountering strictures in EoE patients at the time of diagnosis. An additional aim of the present study was to determine the kinetics of the appearance of inflammatory and fibrotic endoscopic features over time. We also aimed to identify risk factors for stricture development.

METHODS

Swiss EoE Database

We performed a retrospective analysis of the Swiss EoE database (SEED) and an extensive review of all patient records. The SEED has been founded in 1989 by the senior author (AS) and currently includes data on 783 EoE patients from all over Switzerland. The data are stored in the Swiss EoE Clinic located in Olten, Switzerland. Of 783 patients, 323 patients (41.3 %) are followed-up and treated on a regular basis in the Swiss EoE Clinic by the senior author. In order to minimize the limitations of the retrospective design of this study, only data gathered in structured manner on 323 patients, who personally attended the Swiss EoE Clinic, were used to carry out most of the analysis. The data on the remaining 460 EoE patients (58.7 %), who were diagnosed externally by other gastroenterologists in Switzerland, were only used to examine the occurrence of strictures over time.

Patients, whose data were included into the SEED, had to meet the following criteria: 1) report the presence of symptoms of esophageal dysfunction, 2) exhibit predominant eosinophilic esophageal inflammation, 3) either test negative by 24-hour pH-metric study or have esophageal eosinophilia that did not resolve following a completion of at least a 6-week double-dose PPI trial. Data of patients with histologically-diagnosed eosinophilic gastroenteritis were not included into SEED. For the purposes of inclusion into SEED, four biopsies from the distal esophagus (defined as the part lying > 5 cm above the gastro-esophageal junction) and four biopsies from the proximal esophagus were taken during each upper endoscopy from every patient. Between 1989 and 2007, the diagnostic criterion for EoE was met, if ≥ 24 eosinophils per high power field (hpf) were observed in any of the fields examined. From the time of publication of the first consensus recommendation (2007), the diagnostic criterion for EoE was met, if ≥ 15 eosinophils per high power field (hpf) were observed in any of the fields examined.[16] In the SEED, items pertaining to demographics, disease-specific characteristics, EoE family history, history of allergies, EoE-related

laboratory abnormalities, history of endoscopies, histologic findings, medications and complications, are recorded.

In addition, the records of all patients included in the analysis presented in this manuscript were reviewed under the supervision of AMS and AS, and a new database was created in EpiData (version 3.1, The EpiData Association, Denmark). This database incorporates a total of 98 items, of which 22 are related to EoE patient history and 76 related to symptoms, endoscopic, laboratory and histologic findings assessed and therapeutic decisions made during each visit. For the purposes of this study, diagnostic delay was defined as the time period from appearance of first symptoms to establishment of EoE diagnosis.

In addition to the above-mentioned criteria for SEED inclusion, patients were only included into this study if a complete data set consisting of the following documents was obtained: a standardized symptom assessment questionnaire completed during each visit, a record of complete laboratory work-up of samples obtained on the day of patient interview and endoscopy, an endoscopy report containing a structured description and photographic documentation of the endoscopic findings and a histology report on the biopsies taken from the proximal and distal esophagus.

Description of Endoscopic Findings

Since 1989, the following endoscopic signs were consistently described: edema (defined as reduced vascular pattern), white exudates (defined as white spots of the esophageal surface), furrows (defined as vertical lines), rings, crêpe-paper esophagus (lacerations), and strictures. The endoscopic features described in Swiss EoE Clinic visit records were identical to those that were used by Hirano *et al.* for a novel grading system for endoscopic esophageal features of EoE.[10]

For the purposes of this study, strictures were defined as narrowing of the esophageal diameter, irrespective of the length of the stricture. Stricture severity was classified as described elsewhere.[17] Briefly, a stricture was classified as low-grade if it could be passed with a standard endoscope (measured 9 mm in outer diameter) with some resistance, often

inducing lacerations (also described as crêpe-paper esophagus). A stricture was classified as intermediate-grade if it could not be passed with a 9-mm outer diameter endoscope, but could be passed with a 6-mm outer diameter endoscope. A stricture was classified as high-grade if it could not be passed with a 6-mm outer diameter endoscope. If multiple strictures were found, the diameter of the narrowest stricture was reported. The length and location of strictures were recorded. Stricturing rings were assigned a length of 0.5 cm.

Histologic Analyses

The biopsies of all SEED patients followed up at the Swiss EoE Clinic were evaluated by CB. For the purposes of histologic examination, 4-µm sections were cut from the paraffin blocks and stained with H&E, van Gieson, Alcian blue and Periodic acid-Schiff stain. All histologic examinations were performed using a standard pathology microscope (Zeiss Axiophot, Plan-Neofluar 40, ocular magnification 10 ×, area of microscopic field 0.260 mm^2). At least 10 sections of each esophageal biopsy specimen were surveyed, and the eosinophils in the most densely infiltrated area were counted (peak eosinophil count). The extent of subepithelial fibrosis was visualized using the van Gieson stain and semiquantiatively graded as either absent, mild/moderate, or severe.

Ethics

The study was approved by the local ethics committee. Prior to inclusion into the SEED, a written informed consent was obtained from all patients.

Statistical Analysis

Data from EpiData were imported into a statistical package program (STATA® version 12, College Station, Texas, USA). Data distribution was analyzed using Normal-QQ-Plots. Results of quantitative data are presented as either mean ± SD and range (for parametric data) or median plus interquartile range (IQR) (for non-parametric data). Categorical data

were summarized as the percentage of the group total. Differences in quantitative data distributions between the groups were assessed by the Student's t-test (for parametric data) and by the Wilcoxon rank-sum test (for non-parametric data). Univariate logistic regression modeling was performed to identify risk factors for the outcome "presence of stricture(s) at the time of EoE diagnosis". As dependent variables for the outcome, the following items were evaluated: gender (coded as "male" and "female", binary variable), allergies (coded as "present" and "absent", binary variable), diagnostic delay (in years, continuous variable), age at EoE symptom onset (in years, continuous variable), EoE family history (coded as "present" and "absent", binary variable), blood eosinophilia at EoE diagnosis (defined as > 0.3 G/L, coded as "present" and "absent", binary variable), elevated levels of IgE (defined as IgE level of > 100 kU/L, coded as "present" and "absent", binary variable), and severe histologic activity (defined as peak eosinophil count of > 100 per hpf, coded as "present" and "absent", binary variable). For the purposes of this study, a p-value of < 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

The flow chart of the study population is shown in **Supplementary Figure 1**. Of 783 patients included into SEED, 323 were diagnosed by the senior author according to standardized protocols for assessment of clinical, endoscopic, histologic, and laboratory disease activity. Data on 123 patients were excluded due to either incomplete or missing information (records of 41, 37, 26, and 19 patients were missing data on the endoscopic features of EoE, symptom severity, laboratory workup, and histology, respectively). The remaining 200 EoE patients had complete datasets on clinical, endoscopic, histologic, and laboratory disease activity and were included for further analysis. The demographic and disease-specific characteristics of the patients included in this study are presented in **Table 1**. Of 200 patients, 153 patients were male (76.5 %) with median age at diagnosis of 39 years (IQR 28 - 50). Dysphagia was the leading symptom exhibited by 189 EoE patients (94.5 %), followed by chest pain affecting 71 patients (35.5 %). Allergies were identified in 132 patients (66.0 %). An endoscopic bolus removal was performed in 56 (28.0 %) patients; 28 patients underwent this procedure prior to and 28 at the time of EoE diagnosis. Median diagnostic delay was 6 years (IQR 2 - 12). Sixty patients (30.0 %) had EoE symptom onset between 0 and ≤ 20 years of age, whereas 140 patients had symptom onset at > 20 years of age. Twenty-two patients (11.0 %) were diagnosed with EoE between 10 and ≤ 20 years of age. Diagnostic delay was longest in the young patient population (≤ 20 years of age) and decreased with increasing age (**Figure 1**).

Of 783 patients included into SEED, 460 EoE patients were diagnosed externally by other gastroenterologists in Switzerland. Due to the limited and non-standardized data available for this group of patients, only data for the occurrence of strictures over time, which was available for 359 patients, was used in this manuscript. Of these 349 patients, 277 (79.4%) were male with median age at EoE diagnosis of 38 years (IQR 26-53 years). Dysphagia was

the predominant symptom in 336 patients (96.3%). Median diagnostic delay was 5 years (IQR 2-10).

Endoscopic, Histologic, and Laboratory Characteristics at EoE Diagnosis

The key endoscopic, histologic, and laboratory findings at the time of EoE diagnosis are illustrated in **Table 2**. Strictures were found in 75 patients (37.5 %). Further details on the number and other characteristics of esophageal strictures are provided in **Table 3**. Patients had a median of 1 stricture (IQR 1 - 1, range 1 - 3).

Features of active inflammation (edema, furrows, and whitish exudates) were found in 159 patients (79.5 %) and features of fibrotic activity (strictures, rings and crêpe-paper esophagus) were detected in 126 patients (63.0 %) at EoE diagnosis. An endoscopic dilation of stricture(s) was performed in 27 patients (13.5 %). No perforation was observed in dilated patients. Fifty eight patients (29.0 %) had peripheral blood eosinophilia (> 0.35 G/L), and 124 patients (62.0 %) had elevated IgE levels (> 100 kU/L).

Evolution of Endoscopic Features Over Time

The analysis of the types of the endoscopic features present at the time of EoE diagnosis stratified according to the length of diagnostic delay is shown in **Figure 2**. In this report, whitish exudates, furrows and/or edema were considered as inflammatory features, whereas corrugated rings, strictures and/or crêpe paper esophagus were considered as fibrotic features. **Figure 2** shows that the prevalence of fibrotic endoscopic features at the time of EoE diagnosis either alone or in combination with inflammatory features increased with increasing duration of diagnostic delay from 46.5 % (diagnostic delay 0 - 2 years) to 87.5 % (diagnostic delay > 20 years) (p = 0.020, Cochran-Armitage trend test). Furthermore, the prevalence of purely inflammatory features decreased with increasing duration of diagnostic delay period (p = 0.019). The prevalence of esophageal strictures positively correlated with the presence of endoscopic fibrotic features (Spearman's rho 0.3226, p < 0.001) and subepithelial fibrosis (rho 0.1927, p < 0.001).

The Prevalence of Strictures at EoE Diagnosis Significantly Correlates with the Duration of Diagnostic Delay

We evaluated the prevalence of strictures at the time of EoE diagnosis stratified according to the length of the diagnostic delay periods. These findings are shown in **Table 4**. An increase in the stricture prevalence was observed over time, such that a group with a diagnostic delay of 0 - 2 years had a stricture prevalence of 17.2 %, while a group with diagnostic delay of > 20 years exhibited a stricture prevalence of 70.8 %. The Cochran-Armitage trend test revealed a significant increase in the prevalence of strictures with the increasing length of diagnostic delay period (p < 0.001). **Figure 3** illustrates the "stricture-free" survival of the EoE patients over the diagnostic delay period encompassing > 20 years. We were also interested if EoE in the group of 60 patients with symptom onset between 0 to ≤ 20 years of age progressed differently from the disease in the group of 140 patients with symptom onset at > 20 years of age with respect to stricture formation. Therefore, we performed logistic regression modeling evaluating gender, presence of allergies, length of diagnostic delay period, presence of EoE family history, presence of blood eosinophilia, and elevated IgE levels as risk factors for the presence of strictures at the time of EoE diagnosis. These results are depicted in **Supplementary Table 1**. We found that the length of diagnostic delay was the only factor associated with the presence of strictures at the time of EoE diagnosis in the ≤ 20 years of age symptom onset group (OR 1.116, 95% CI 1.041 - 1.195, p = 0.002) as well as in the group of patients with EoE symptom onset > 20 years of age (OR 1.088, 95% CI 1.032 - 1.148, p = 0.002). We conclude that the population with symptom onset at ≤ 20 years of age does not seem to be different from the group with EoE symptom onset of > 20 years of age regarding stricture formation.

We also evaluated whether the relationship between the prevalence of strictures at the time of EoE diagnosis and the duration of untreated EoE can also be observed in the externally-diagnosed EoE patients, for whom data on the diagnostic delay were available (359/460 patients [78.0 %]). We observed the following stricture prevalence at the time of diagnosis for each corresponding diagnostic delay period: 18/155 patients (11.6 %) for

diagnostic delay period of 0 - 2 years; 8/60 patients (13.3 %) for diagnostic delay period of > 2 - 5 years; 6/30 patients (20.0 %) for diagnostic delay period of > 5 - 8 years; 13/43 patients (30.2 %) for diagnostic delay period of > 8 - 11 years; 4/15 patients (26.7 %) for diagnostic delay period of > 11 - 14 years; 6/11 patients (54.5 %) for diagnostic delay period of > 14 - 17 years; 8/19 patients (42.1 %) for diagnostic delay period of > 17 - 20 years; 9/16 patients (56.3 %) for diagnostic delay period of > 20 years. Using the Cochran-Armitage trend test, we found that the prevalence of strictures at the time of EoE diagnosis increased with the increasing length of diagnostic delay period (p < 0.001) also in the externally diagnosed EoE patients.

Risk Factors for Stricture Formation

Using logistic regression modeling, we evaluated whether some patients are at higher risk than others to develop strictures. The dependent variables for the outcome "presence of stricture(s) at the time of EoE diagnosis" are described in the methods section. The results of the logistic regression modeling are shown in **Supplementary Table 2**. Using univariate logistic modeling, we found that length of diagnostic delay (OR 1.080 per year, 95% CI 1.040 - 1.122, p < 0.001) was the only factor significantly associated with the presence of strictures at the time of EoE diagnosis. Of note, age at EoE symptom onset was not associated with the presence of strictures at the time of EoE diagnosis (OR 0.988, 95% CI 0.969 - 1.006, p = 0.195).

We hypothesized that persistent inflammatory activity could accelerate stricture formation in EoE patients. To evaluate a relationship between peak eosinophil counts in esophageal biopsies and stricture formation, we calculated the Spearman's correlation coefficient. However, the presence of strictures at the time of EoE diagnosis correlated neither with the proximal (Spearman's rho 0.048, p = 0.580) nor with the distal peak eosinophil counts (Spearman's rho 0.099, p = 0.248). Of note, tissue eosinophilia at a single time point, such as at the time of EoE diagnosis, is not likely to reflect the overall histologic disease activity over the entire course of the disease.

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DISCUSSION

Stricture formation is a major complication of EoE. We were able to demonstrate that patients are more likely to present with purely inflammatory endoscopic EoE features early in the disease course and then progress to develop fibrotic endoscopic features, in addition to inflammatory features. Also, the risk of developing esophageal strictures is significantly associated with the length of diagnostic delay, a time period from appearance of first symptoms to establishment of EoE diagnosis. We further showed that diagnostic delay is longest in young patients (median of 10 years in the symptom onset group from 0 to 10 years) and gradually decreases with age.

So far, the natural history of untreated EoE has not been extensively investigated. In a first study, published 10 years ago, Straumann *et al.* examined an adult cohort of 30 EoE patients, who were not treated with any anti-inflammatory therapy over a mean time period of 7.2 years.[7] This study demonstrated that tissue eosinophilia as well as symptoms persisted for years and, therefore, provided the first evidence that EoE is a chronic disease. In addition, this study showed for the first time that subepithelial fibrosis might develop over time. Later on, in studies by Aceves *et al.* and Mishra *et al.*, it was demonstrated that untreated chronic eosinophil-predominant inflammation may lead to esophageal remodeling with fibrosis and stricture formation.[18,19] After these initial findings and the work that followed, it became evident that EoE should be treated.[8,9,18,19] Due to the rareness of purely observational studies, our understanding of the natural history of EoE remains limited.

For the purposes of this study, we made use of the EoE patients' ability to cope for years with their symptoms prior to seeking medical attention and subsequent establishment of diagnosis. We analyzed the length of this self-reported pre-diagnostic period and various clinical characteristics at the time of EoE diagnosis in order to learn more about stricture development in the absence of therapeutic interventions. In our cohort, a median diagnostic delay of 6 years was observed. This length of diagnostic delay is comparable to the mean duration of symptoms before diagnosis of 4 years observed by Kanakala *et al.* in the United Kingdom.[20] We found that the length of diagnostic delay was positively correlated with the

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prevalence of esophageal strictures. This finding provides evidence that the individual's disease course is a continuum - a march from a disease predominantly inflammatory in nature to a disease with endoscopic fibrotic features including strictures in addition to existing inflammation. Our findings are comparable to those obtained during a study on a natural history of Crohn's disease conducted by Cosnes *et al.* The authors found that initially present inflammatory uncomplicated disease (defined as absence of strictures and/or fistulas) over time evolves into a penetrating and/or stricturing disease.[13] Despite the fact that there are many differences between EoE and Crohn's disease, fibrosis, being a universal repair mechanism, is common to these two conditions.[21]

We were also interested to identify potential disease, environmental and patient-inherent risk factors for stricture formation. Our study demonstrates that the length of diagnostic delay is the major risk factor for stricture formation. It is well established that strictures contribute to symptom generation as well as occurrence of potentially dangerous food bolus impactions.[17,22]

In Switzerland, approximately 250 board-certified gastroenterologists, working in university hospitals, general hospitals and private practices provide gastroenterological care. These physicians are educated in the diagnostic and therapeutic management of EoE patients. Furthermore, health insurance in Switzerland is mandatory, and residents have easy access to medical care. Nonetheless, despite these favorable conditions for early EoE diagnosis, median diagnostic delay observed in this study cohort was 6 years. Analysis according to the decade of symptom onset revealed longest diagnostic delays in patients ≤ 20 years of age. The long diagnostic delay in children/young adults might be related to the fact that an upper endoscopy needs to be performed under general anesthesia, and, hence, physicians are more reluctant to refer children for endoscopy. In addition, physicians perceive dysphagia as an alarm symptom of esophageal cancer in the adult population, which leads to a faster referral for upper endoscopy and a shorter diagnostic delay in adults.

Our study has several important strengths, but also a number of limitations. It is the first long-term study demonstrating that EoE patients are more likely to present with inflammatory

esophageal endoscopic features earlier in the disease course and mostly develop fibrotic endoscopic features, in addition to inflammatory features, as disease progresses. One major limitation of this study is its retrospective design. We tried to minimize the drawbacks associated with such study design by using strict inclusion and exclusion criteria, by applying the same methodology for the assessment of symptoms, endoscopic and histologic abnormalities,[1,16] and by systematic re-evaluation of all raw data. The presence of strictures was assessed based on the degree of difficulty with which an endoscope (with either 9-mm or 6-mm diameter) could pass through the esophagus. Thus, the presence of strictures is likely under-estimated in this study. We neither radiologically measured esophageal diameter nor determined the distensibility of the esophagus.[23] Determination of the distensibility of the esophagus with the EndoFlip device, as recently described by Kwiatek *et al.*, has the potential to detect more subtle esophageal narrowings.[23] Estimation of the length of diagnostic delay in our study was based on patient's reported outcomes, which is a subject to a recall bias. While there is consensus among the members of scientific community and regulatory agencies that symptoms should be assessed by patients themselves [24,25], the extent of correlation between patient-reported outcomes and endoscopic and histologic findings has not yet been determined and needs to undergo further evaluation.[26-29] We addressed the potential issue of a referral bias by comparing the results of time-dependent stricture development in the group of 200 patients diagnosed by the senior author (AS) with the group of 460 externally diagnosed EoE patients. Although the assessment of endoscopic features at the time of EoE diagnosis was not standardized in this external cohort, we found, similarly to the results in the "core" cohort of 200 patients, that the prevalence of strictures at the time of EoE diagnosis significantly increased with ongoing duration of untreated disease. Therefore, we believe that referral bias did not majorly influence our results regarding stricture formation.

In conclusion, our analysis of a large group of untreated EoE patients demonstrates that the prevalence of strictures is directly correlated with the length of diagnostic delay. In addition, EoE patients are more likely to present with inflammatory endoscopic features early

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in the disease course and mostly develop fibrotic endoscopic features, in addition to the inflammatory features, as disease progresses. Measures should be undertaken to reduce the diagnostic delay in EoE.

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Author names in bold designate shared co-first authorship.

FIGURE LEGEND

Figure 1: Diagnostic delay (time from first symptoms to diagnosis) in relation to age at EoE symptom onset (in decades). The horizontal line in the box represents the median; the box includes values from the 25th to 75th percentile. The figure shows that diagnostic delay is longest in patients with symptom onset ≤ 20 years of age, and that diagnostic delay gradually decreases with increasing age of the patient.

Figure 2: Types of the endoscopic features present at the time of EoE diagnosis stratified according to the length of diagnostic delay period. The frequency of patients exhibiting purely inflammatory endoscopic features at the time of EoE diagnosis decreased with the increasing length of diagnostic delay period, and the frequency of patients exhibiting a combination of inflammatory and fibrotic endoscopic features increased with increasing length of diagnostic delay period.

Figure 3: Percentage of patients without strictures over the diagnostic delay period encompassing > 20 years.

TABLES

Table 1: Demographic and disease-specific characteristics of included EoE patients.

Characteristic	Frequency
Number of patients	200
Males	153 (76.5 %)
Age at symptom onset (median, IQR) (years)	31, 17 - 44
Age at EoE diagnosis (median, IQR) (years)	39, 28 - 50
Diagnostic delay (median, IQR, range) (years)	6, 2 - 12, 0 - 40
Symptoms leading to EoE diagnosis - Dysphagia - Chest pain - Regurgitations - Abdominal pain - Vomiting - Weight loss	 189 (94.5 %) 71 (35.5 %) 9 (4.5 %) 3 (1.5 %) 2 (1.0 %) 1 (0.5 %)
Family history for EoE	24 (12.0 %)
Concomitant allergies - Rhinoconjunctivitis - Asthma - Neurodermitis - Oral allergy syndrome - Food allergies	132 (66.0 %) 85 (42.5 %) 74 (37.0 %) 8 (4.0 %) 9 (4.5 %) 41 (20.5 %)
Endoscopic bolus removal - Prior to EoE diagnosis - At time of EoE diagnosis	56 (28.0 %) 28 (14.0 %) 28 (14.0 %)
Concomitant gastroesophageal reflux disease - Barrett Esophagus	23 (11.5 %) 4 (2.0 %)

Table 2: Endoscopic, histologic, and laboratory characteristics of EoE patients at the time of diagnosis.

Characteristic	Frequency
Endoscopy	
Strictures	75 (37.5 %)
Corrugated rings	136 (68 %)
White exudates	105 (52.5 %)
Edema	151 (75.5 %)
Furrows	131 (65.5 %)
Crêpe-paper esophagus	44 (22 %)
Histology: median, interquartile range, range or frequency	
Proximal peak eosinophil count	35, 20-61, 0 - 167
Distal peak eosinophil count	28, 12-65, 0 - 192
Basal cell hyperplasia	188 (94 %)
Papillary elongation	192 (96 %)
Subepithelial fibrosis - Absent - Mild to moderate - Severe - No tissue to assess	 9 (4.5 %) 71 (35.5 %) 18 (9 %) 102 (51 %)
Dysplasia	0
Laboratory markers: median, interquartile range, range or frequency	
Blood eosinophil count (G/L)	0.324, 0.148 - 0.506, 0.0 - 1.214
Blood eosinophilia (> 0.35 G/L)	58 (29 %)
IgE (kU/L)	169, 55 - 344, 5 - 2500
Elevated levels of IgE (> 100 kU/L)	124 (62 %)

Table 3: Characterization of esophageal strictures found at the time of EoE diagnosis in 75 EoE patients.

Characteristic	Frequency or median, interquartile range, range
Number of strictures	
1	64 (85.4 %)
2	7 (9.3 %)
3	4 (5.3 %)
Stricture grading*	
Low grade	60 (80 %)
Intermediate	12 (16 %)
High grade	3 (4 %)
Stricture length (cm)	2.5, 2 - 4, 0.5 - 10
Stricture location	
Proximal esophagus	35 (46.7 %)
Distal esophagus	37 (49.3 %)
Proximal and distal esophagus	3 (4 %)

*The following definitions were applied for the stricture grading: a stricture was classified as low-grade if it could be passed with a standard endoscope (9 mm outer diameter) with some resistance, often inducing lacerations (crêpe-paper esophagus); a stricture was classified as intermediate-grade if it could not be passed with a 9-mm outer diameter endoscope, but could be passed with a 6-mm outer diameter endoscope; a stricture was classified as high-grade if it could not be passed with a 6-mm outer diameter endoscope.

Table 4: Prevalence of strictures in patients diagnosed with EoE after a diagnostic delay period

that ranged from 0 - > 20 years.

Diagnostic delay (years)	Number of patients	Number of patients with strictures at the time of EoE diagnosis	Stricture Prevalence (%)
0 - 2	58	10	17.2
>2 - 5	39	12	30.8
> 5 - 8	18	7	38.9
> 8 - 11	29	11	37.9
> 11 - 14	12	5	41.7
> 14 - 17	14	9	64.3
> 17 - 20	6	4	66.7
> 20	24	17	70.8

The stricture prevalence increases with increasing length of the diagnostic delay period, which

represents the duration of untreated EoE (Cochran-Armitage trend test, $p < 0.001$).

Supplementary Table 1: Logistic regression modeling evaluating risk factors for the presence of strictures at EoE diagnosis stratified according to age at symptom onset. Duration of untreated EoE, corresponding to the diagnostic delay, was the only risk factor in both groups associated with presence of strictures at the time of EoE diagnosis.
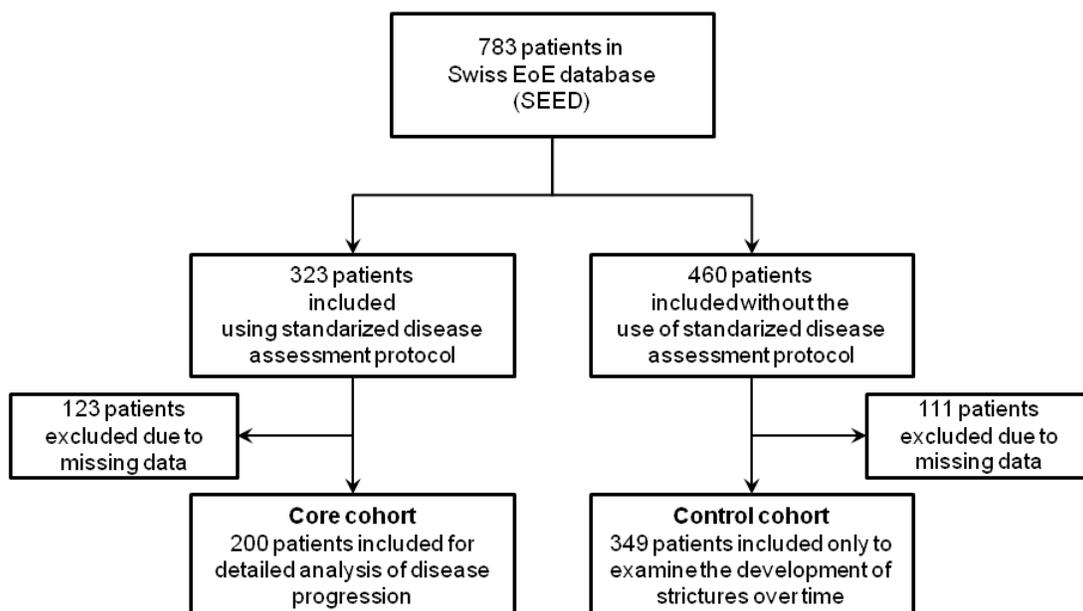
Candidate Risk factor for presence of stricture at the time of EoE diagnosis	Symptom onset 1 - ≤ 20 years		Symptom onset > 20 years	
	Univariate model		Univariate model	
	OR, 95% CI	p-value	OR, 95% CI	p-value
Gender <u>Male</u> Female	1.190 0.336-4.213	0.787	0.780 0.332-1.834	0.570
Allergies <u>Present</u> Absent	0.455 0.117-1.764	0.255	1.455 0.609-3.469	0.398
Diagnostic delay (years)	1.116 1.041-1.195	0.002	1.088 1.032-1.148	0.002
Family history of EoE <u>Present</u> Absent	0.677 0.176-2.604	0.570	1.101 0.294-4.123	0.887
Blood eosinophilia <u>Present</u> Absent	1.667 0.251-11.071	0.597	0.938 0.297-2.962	0.912
Elevated IgE levels <u>Present</u> Absent	1.678 0.570-4.936	0.347	1.773 0.533-5.898	0.351

Logistic regression modeling with the outcome "presence of stricture at the time of EoE diagnosis". Univariate logistic regression modeling was performed. The Odds Ratio (OR) is computed on the underlined outcome of the dependent variable of the logistic regression model. The variable "diagnostic delay" is entered as continuous variable.

Supplementary Table 2: Analysis of potential risk factors for stricture development in EoE patients.

Candidate Risk Factor	Univariate Model	
	OR, 95% CI	p-value
Gender: <u>Male</u> Female	0.953 0.476-1.909	0.892
Allergies <u>Present</u> Absent	0.968 0.474-1.978	0.928
Diagnostic delay (years)	1.080 1.040-1.122	<0.001
Age at onset of EoE symptoms (years)	0.988 0.969-1.006	0.195
Family history of EoE <u>Present</u> Absent	0.825 0.332-2.049	0.678
Blood eosinophilia <u>Present</u> Absent	1.111 0.421-2.935	0.832
Elevated IgE levels <u>Present</u> Absent	1.678 0.57-4.936	0.347
Peak eosinophil count <u>≥ 100 per hpf</u> < 100 per hpf	1.911 0.796-4.586	0.147

Logistic regression modeling with the outcome "presence of stricture at the time of EoE diagnosis". Univariate logistic regression modeling was performed. The Odds Ratio (OR) is computed on the underlined outcome of the dependent variable of the logistic regression model.

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                        ┌─────────────────────┐
                        │  783 patients in    │
                        │ Swiss EoE database  │
                        │      (SEED)         │
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783 patients in Swiss EoE database (SEED)

323 patients included using standarized disease assessment protocol	460 patients included without the use of standarized disease assessment protocol

123 patients excluded due to missing data			111 patients excluded due to missing data

Core cohort 200 patients included for detailed analysis of disease progression	**Control cohort** 349 patients included only to examine the development of strictures over time