

Clinical symptom tool that raises the index of suspicion for eosinophilic oesophagitis in adults and drives earlier biopsy for definitive diagnosis

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SUMMARY

Background

Eosinophilic oesophagitis (EoE) and gastro-oesophageal reflux disease (GERD) present with overlapping symptomatology and it is challenging to distinguish EoE from GERD clinically before endoscopy.

Aim

To investigate the prognostic value of a set of clinical symptoms and laboratory values in patients with EoE and GERD.

Methods

In this prospective, single-centre, observational study, we compared clinical and laboratory data from 202 patients with EoE or GERD (10 relevant characteristics). Those characteristics showing potential significance in a univariate analysis were then included in a multivariate analysis.

Results

The set of 10 characteristics (10-marker set) was able to distinguish between EoE and GERD with good reliability (correct assignment, i.e. agreement with subsequent EGD, of 94.4%). Reduction of the set to the six statistically and clinically most relevant markers continued to give good reliability (88.9%), and further stepwise reduction led to four-marker sets comprising history of atopy, history of food impaction, proton pump inhibitor refractory symptoms and either immunoglobulin E or peripheral eosinophilia, with correct assignment rates of 91.3% and 85.1% respectively.

Conclusions

We have developed a simple and easily applicable clinical/laboratory marker set that helps to distinguish EoE from GERD earlier in the treatment course, thus guiding the endoscopist to perform biopsies from the oesophagus to ensure the diagnosis. The application of the scoring system is expected to diagnose EoE earlier and avoiding delay of adequate treatment.

INTRODUCTION

Eosinophilic oesophagitis (EoE) is a chronic immune- or antigen-mediated disorder of the oesophagus. It is characterised by dysphagia and histologically demonstrable oesophageal eosinophilia, after exclusion of other causes of eosinophilic infiltration.^{1, 2} In the past two decades, increasing incidence and prevalence of this disorder have been noted,^{3–6} independently of the rising number of oesophagogastroduodenoscopies (EGDs) performed with oesophageal biopsies.⁷

Dysphagia, the leading symptom of EoE, ranges in clinical severity from mild swallowing disorders, for which the patient often unconsciously compensates by adaptation of eating habits, to dramatic effects such as food impaction, often requiring endoscopic intervention. Moreover, accompanying symptoms such as chest pain or reflux/heartburn can falsely suggest gastro-oesophageal reflux disease (GERD). It has been reported that 30–60% of EoE patients complain of heartburn and 8–44% of noncardiac chest pain.^{8, 9} Symptom heterogeneity is confusing; this leads to uncertainty regarding the next diagnostic step. It is unsurprising that there is a need for a clinical prediction tool, which facilitates an increased index of suspicion for EoE vs. GERD.

One of the reasons for delay in the diagnosis of EoE can be attributed to the circumstance that only few prospective clinical studies have been conducted to bring to light the common factors and the differences between EoE and GERD,^{8, 9, 10, 11} so that often EoE patients are initially treated as GERD patients and an index EGD is performed in case of treatment failure. Second, even when EGD is performed, EGD does not provide a reliable diagnostic criterion. Thus, a large-scale retrospective case–control study has revealed that 21% of EoE cases give a normal endoscopic picture.⁸ A prospective study has also shown that 42% of EoE cases do not manifest the typical endoscopic signs such as furrows, whitish plaques and/or rings. So, EoE would not have been diagnosed without a biopsy being taken.⁹ Third, even when EGDs with biopsies are performed, unless multiple stepwise biopsies are done (because of high index of suspicion for EoE), EoE may not be properly diagnosed because it is a patchy disease.¹² Because of the known varying distribution of eosinophilic inflammation in EoE at least four biopsies (preferably six: two each in the distal, middle and upper oesophagus) are essential, if confirmation of the currently accepted limit of >15 eosinophils per high-power field (HPF) is to be confirmed by the pathologist.¹³ The results of the histological examination represent, alongside the clinical symptoms, the most

important contribution to a diagnosis of EoE. All of this leads to delay in diagnosis and in treatment which can often lead to subsequent complications. For example, a retrospective study has shown that the average delay in diagnosis amounts to some 6 years, and that a delayed diagnosis of EoE is clearly associated with an increased prevalence of signs of fibrosis in the oesophagus and with the appearance of strictures and stenoses¹⁴ and furthermore has deleterious effects also upon the emotional and psychological state of the patients.^{15, 16}

Because of this we set out to develop a set of markers and to test its utility in a prospective observational study, in order to raise the index of suspicion of EoE before upper gastrointestinal endoscopy and in this way to guide the endoscopist to take multiple stepwise biopsies from the oesophagus. We advance the hypothesis that a multivariate model of clinical symptoms and markers is able to predict EoE pre-endoscopically with high accuracy.

METHODS

This prospective observation study was carried out at the university hospital of the Otto von Guericke University of Magdeburg, Germany, from 2011 to 2015. The study was designed and conducted in accordance with the Declaration of Helsinki and was approved by the local Ethics Committee. All patients consented in writing to performance of the EGD.

Patients were included as follows: (i) 48 patients with a first diagnosis of EoE from our tertiary-care out-patient department, (ii) 56 EoE patients from a clinical study at the baseline visit¹⁷ and (iii) 98 patients with symptoms suggesting underlying GERD from our out-patient department (total: 202 patients). Patients with a known history of Crohn's disease, coagulopathy, thrombocytopenia, liver cirrhosis with oesophageal varices, coeliac disease or parasitic infection and pregnant women were excluded.

EoE patients were diagnosed according to the consensus recommendations¹ and had to fulfil all of the following criteria: (i) one typical symptom of oesophageal dysfunction (dysphagia, food impaction, chest pain with or without swallowing/odynophagia, proton pump inhibitor (PPI)-refractory symptoms), (ii) >15 eosinophils/HPF in one biopsy from the oesophagus, (iii) prior PPI therapy (20–40 mg twice daily for at least 4 weeks) which did not improve the patient's symptoms and (iv) exclusion of other possible causes of EoE by stomach and duodenal biopsy. Patients who had not received PPI treatment were treated twice daily with 20–40 mg PPI

for at least ≥ 4 weeks before the index EGD and were interviewed about their symptomatic response before EGD with oesophageal biopsies was conducted. If symptoms improved, and the biopsy did not reveal oesophageal eosinophilia, then the patient was not included in this study as the presence of PPI-responsive oesophageal eosinophilia (PPI-REE) seemed likely.

GERD patients were grouped into those with typical endoscopic reflux lesions (erosive reflux disease, ERD) and those patients without endoscopic lesions, but with reflux symptoms (heartburn, regurgitations, acid eructation); the latter patients underwent impedance-combined oesophagogastric pH-monitoring for 24 h. Patients with a pathological result in the 24-h pH measurement were classified as having non-erosive reflux disease (NERD); in patients with endoscopic signs of Barrett's oesophagus, biopsies from the Barrett lesions were taken separately.

Every patient was interviewed and completed a questionnaire to elicit the patient's detailed medical history, and physical examination was performed. Symptoms of dysphagia (swallowing discomfort for solids or fluids, retrosternal pain independent of eating), earlier episodes of food impaction and reflux symptoms (heartburn, acid eructation, regurgitation), history of atopy (allergic rhinitis/conjunctivitis, allergic asthma, atopic dermatitis, food allergy and family history of atopic diseases), prior PPI use and its effect (or lack of effect) in improving symptoms were recorded.

Blood samples were taken for complete blood count including absolute peripheral eosinophils (normal count 50–300 / μ L) and serum immunoglobulin E (IgE; levels above 100 IU/mL were considered elevated).

EGD was performed with the patient under conscious sedation with 1 mg/kg disoprivan as an intravenous bolus followed by further, smaller administrations. A standard videogastroscope (GIF-Q180; Olympus Optical Europe, Hamburg, Germany) was used. Two biopsy samples were obtained from the oesophagus from each of the positions, distal (3 cm above the Z-line), middle and proximal; any highly conspicuous features were biopsied in addition. Standard biopsies from the antrum (two samples), the corpus (two samples) and the duodenum (one sample) were taken with standard biopsy forceps. The Los Angeles classification was used to describe erosive oesophagitis and the Prag classification was used for Barrett oesophagus; biopsies of areas suspected of showing the latter were placed in separate biopsy sample tubes. Samples were sent to the histopathological laboratory in separate tubes, respectively for distal, middle and

proximal oesophagus and other specific lesions, antrum, corpus and duodenum.

Formalin-fixed, paraffin-embedded biopsy samples were stained with haematoxylin and eosin for histological examination. Gastritis grading was performed to the up-dated Sydney classification.¹⁸ For a positive diagnosis of EoE, the histological criterion of elevated intraepithelial eosinophils (>15 per HPF of 0.55 mm² in areas of peak density) in at least one biopsy had to be fulfilled. Further histological conspicuities such as eosinophilic microabscesses, aggregates of eosinophils in the epithelial surface layer and degranulation of eosinophils were additionally documented.¹⁹

Statistical calculations were performed with SAS Version 9.4 (SAS Institute Inc., Cary, North Carolina, USA). The description of the clinical characteristics has the form mean $\pm$ s.d. for continuous variables or n (%) for variables with discrete levels. The univariate comparisons of the two groups (EoE and GERD patients) were performed by using the *t*-test (Welch test, Satterthwaite's approximation to compute the degree of freedom) for metric parameters. Binary variables were compared by Fisher's exact test.

To find a simple means of clinical differentiation between EoE and GERD before oesophagogastrroduodenoscopy, we examined the power of eight clinical and two laboratory-related variables that we had identified as relevant in an earlier study.¹¹ These were: history of atopy, weight loss, history of food impaction, dysphagia, PPI-refractory symptoms, eructation/regurgitation, chest pain with or without swallowing/odynophagia, peripheral eosinophilia (peripheral eosinophilia) and IgE elevation. Patient's age and sex were also included.

After the univariate analysis of these characteristics, we conducted a logistical regression analysis to take account of the correlations between them. The goodness of fit of different models was compared by using the reclassification rate and the corresponding areas (AUCs) under the ROC curves. Having identified the most clearly significant and predictive characteristics for distinguishing between EoE and GERD, we reduced stepwise the number of markers (from 10 to 6, then to 4), in order to develop a model that embodied the best compromise between the smallest possible loss of sensitivity and specificity in detecting EoE on the one hand and the requirement to construct a simple and practicable marker constellation.

All statistical decisions were made on a two-tailed basis with a significance criterion of $P < 0.05$ and without α adjustment.

RESULTS

Patient population

The analysis of demographic variables revealed clear differences between the EoE and GERD patients. The EoE patients were significantly younger and were more likely to be male. Details are shown in Table 1.

All clinical variables except for the symptoms 'weight loss' and 'chest pain with or without swallowing/

odynophagia' differed significantly between the two groups. Atopic co-morbidities also differed: in the EoE group, allergic diseases were reported significantly more frequently (75% of patients) than in the GERD group (13%), and the detailed history of atopic disorders showed significant differences for all the allergic diatheses. Significant differences were also seen for peripheral eosinophilia, in respect of both the number of patients affected and the absolute value. IgE levels were elevated

Table 1 | Demographic and baseline characteristics and final diagnosis

	EoE (N = 104)	GERD (N = 98)	P*
Age [years]	42.7 ± 13.5 (22–74)	55.5 ± 15.9 (20–92)	<0.0001
Age <50	79 (76%)	30 (31%)	<0.0001
Male subjects	82 (78%)	55 (56%)	0.0010
Race			
Caucasian	103 (99%)	96 (98%)	0.6122
Asian	1 (1%)	2 (2%)	
Symptoms			
Weight loss	5 (4.8%)	9 (9.2%)	0.2731
Dysphagia	80 (76.9%)	18 (18.4%)	<0.0001
History of food impaction	78 (75.0%)	10 (10.2%)	<0.0001
Eructation/regurgitation	16 (14.4%)	75 (79%)†	<0.0001
PPI-refractory symptoms	73 (70.2%)	16 (17%)‡	<0.0001
Chest pain ± swallowing/odynophagia	17 (16.3%)	21 (21.4%)	0.3736
Odynophagia	17 (16%)	21 (21%)	0.3736
History of atopic disease§			
Any	78 (75%)	13 (13.3%)	<0.0001
Allergic rhinoconjunctivitis	73 (73.1%)	7 (7.1%)‡	<0.0001
Allergic asthma	17 (16.5%)	2 (2.0%)	0.0005
Atopic dermatitis	12 (11.8%)	3 (3.1%)	0.0298
Food allergy	17 (16.5%)	1 (1.0%)	<0.0001
Family history of atopic disease	40 (39.2%)	5 (5.1%)	<0.0001
Laboratory values			
Peripheral eosinophils	574 ± 452 (81–2155)†	195 ± 123 (50–570)‡	<0.0001
Elevated peripheral eosinophils¶	42 (41.6%)†	3 (3.1%)‡	<0.0001
IgE level	320 ± 145 (10–4500)	148 ± 54 (7–3610)**	0.0236
Elevated IgE level (>100 U/L)††	65 (62.5%)	24 (25.0%)**	<0.0001
Medication: ≥4 weeks PPI treatment	104 (100%)	90 (91.8%)	0.0026
Final diagnosis for GERD patients			
Erosive reflux disease	–	68 (69.4%)	–
LA A		33 (33.7%)	
LA B		28 (28.6%)	
LA C		7 (7.1%)	
NERD		21 (21.4%)	
Barrett's oesophagus		9 (9.2%)	

Mean ± s.d. (range) or n (%) are shown, as appropriate.

* Fisher's exact test.

† Three patients' values missing.

‡ One patient's value missing.

§ Multiple mentions possible.

¶ >500 cells/μL.

** Two patients' samples haemolysed.

†† >100 kU/L.

significantly more frequently in EoE than in GERD, and accordingly the IgE concentrations also differed significantly. Use of PPI did not differ significantly between the two groups.

Logistical regression analysis

To find the best possible marker constellation, we first carried out a logistical regression analysis of all clinical characteristics (including age and sex) and laboratory findings – 10 characteristics in all (Table 2). For each variable, the odds ratio for a patient with either GERD or EoE in fact having EoE (the more serious indication) was determined. The 10 characteristics were explored individually as possible criteria for distinguishing between EoE and GERD. Using these, good distinction could be made between the EoE and the GERD patients, with a correct result in 94.4% of cases (Table 2, column 3). Six of these clinical variables were clearly associated with a higher odds ratio for the patient's having EoE (Table 2, column 3). These were the clinical variables 'history of atopy', 'history of FI', dysphagia and PPI-refractory symptoms, and the laboratory variables peripheral eosinophilia and IgE. Age and sex also contributed, though less strongly, to the differentiation between EoE and GERD (Table 2, column 3).

To obtain a clinical marker constellation without age and sex as anamnestic parameters, we used only these six variables for a second step of logistic regression. Slightly different odd ratios were obtained, but the discriminatory power was only slightly reduced (92.3%; Table 2, column 4). History of food impaction proved not to be significant ($P \geq 0.05$), so this was omitted in a subsequent analysis, which yielded a correct assignment degree of 87.7% (Table 2, column 5). Clinically, however, dysphagia is a relatively frequent complaint, and EoE patients have often become accustomed to it and only report it when questioned very specifically. In contrast, food impaction is experienced as more dramatic and is therefore reported spontaneously by patients, so the calculation was repeated including history of food impaction instead of dysphagia. This yielded a slightly better rate of correct assignment, 89.7% (Table 2, column 6).

Considering the practical constraints of clinical routine, an assessment of a marker constellation using weighting factors of the linear function of the logistical regression equation is impractical. Therefore, we simplified the model in steps, proceeding from the assumption that only the number of clinical characteristics considered relevant plays a material role. Results for various levels of simplification are shown in Table 3.

Table 2 | Odd ratios and beta values for selected clinical and laboratory parameters from different models to distinguish between EoE and GERD

	Univariate contingency tables	All characteristics (beta/OR)	Logistic regression with clinical and laboratory parameters		
			Only univariate significance (beta/OR)	Significant in logistic regression (beta/OR)	Significant in logistic regression but with FOOD IMPACTION instead of dysphagia (beta/OR)
Weight loss	0.5 [0.16–1.55]	−0.4815/0.62	–	–	–
History of atopy	19.6 [9.4–40.8]	3.2135/24.87	3.3491/28.48	3.5230/33.89	2.7150/15.10
History of food impaction	26.4 [12–58.2]	0.8986/2.46	1.5479/4.70	–	2.3579/10.57
PPI-refractory symptoms	11.9 [6.0–23.6]	2.4792/11.93	2.0271/7.59	2.2851/9.83	2.1612/8.68
Dysphagia	14.8 [7.47–29.4]	3.5001/33.12	3.0228/20.55	3.4975/33.03	–
Pain swallowing/odynophagia	0.72 [0.35–1.46]	0.3445/1.41	–	–	–
IgE elevation	2.72 [2.7–9.2]	2.4437/11.52	2.1686/8.75	2.6765/14.54	1.6019/4.96
Peripheral eosinophilia	5.00 [2.72–9.2]	3.4340/31.00	2.9884/19.85	3.4592/31.79	2.1239/8.36
Age (≤ 50 / > 50)	7.16 [3.83–13.34]	−0.0548/0.947	–	–	–
Sex (male yes/no)	2.91 [1.57–5.40]	1.0303/2.80	–	–	–
Correctly assigned	Maximum = 82%	184/195 = 94.4%	180/195 = 92.3%	171/195 = 87.7%	175/195 = 89.7%

Cohort: 104 EoE and 98 reflux patients (see text). In the first column, 95% confidence intervals are included.

Table 3 | Assignment using various marker constellations

Marker set	N	EoE (n, %)	GERD (n, %)	TOTAL (n/%)	AUC	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
10-marker set (atopy, food impaction, dysphagia, PPI-refractory symptoms, peripheral eosinophilia, IgE, weight loss, pain swallowing/odynophagia, age, sex)	195	95 (94.1)	89 (94.7)	184 (94.4)	0.983	94.1	94.7	95.0	93.7
6-marker set (atopy, food impaction, dysphagia, PPI-refractory symptoms, peripheral eosinophilia, IgE)	195	99 (98.0)	75 (79.8)	174 (89.2)	0.972	98.0	79.8	97.4	97.4
5-marker set (atopy, food impaction, PPI-refractory symptoms, peripheral eosinophilia, IgE)	195	94 (93.1)	81 (86.2)	175 (89.7)	0.952	93.1	86.2	87.8	92.05
5-marker set (atopy, dysphagia, PPI-refractory symptoms, Peripheral eosinophilia, IgE)	195	97 (96.0)	76 (80.9)	173 (88.7)	0.964	96.0	80.9	84.3	95.0
4-marker set (atopy, food impaction, PPI-refractory symptoms, IgE)	197	95 (91.3)	82 (86.3)	177 (88.9)	0.9456	91.3	86.3	90.5	85.3
4-marker set (atopy, food impaction, PPI-refractory symptoms, peripheral eosinophilia)	199	86 (85.1)	87 (90.6)	173 (87.8)	0.9474	85.1	90.6	88.0	90.1

Assignment was based upon fulfilment of at least three (in the 10-marker set) or at least two (in the other sets) of the respective criteria listed indicating EoE. Sensitivity and specificity refer to recognition of EoE (the more serious complaint) among the set of EoE/ GERD patients. For details see text.

Figure 1 provides a survey of the quality criterion of AUC and the reduction of the resubstitution rate that we have used for assessment of the reduced prediction model, and thus how the diagnostic value of the models changes in step with the simplification. The first ROC analysis was carried out with the sets of variables described above and indicated in Table 2: first all 10, then the six that showed significance in the univariate analysis, then the latter set with 'history of food impaction replacing dysphagia'. The corresponding ROC curves are shown in Figure 1. The reduction of the number of variables from 10 through 6 to 5; the latter set corresponded to the six-membered set but with omission of either history of food impaction or dysphagia.

Although, as expected, the area under the curve decreases in step with the reduction in numbers of observables, the discriminatory power nonetheless remains clear. Each marker is one of the variables in the chosen set.

We then carried out a further simplification, reducing the number of markers in the set to four (Table 3). The resulting ROC curves are also shown in Figure 1. The largest AUC value was given by the marker constellation 'peripheral eosinophilia, atopy, food impaction, PPI-refractory symptoms'. The decrease in AUC when peripheral eosinophilia was chosen as a laboratory variable in place of IgE was minimal (legend to Figure 1).

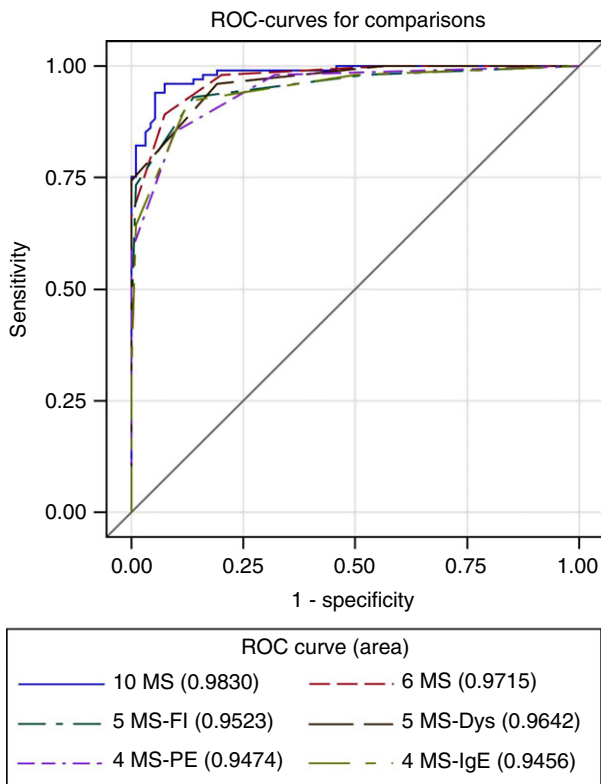


Figure 1 | ROC analysis and area under the curve for assignment using as markers.

- all 10 markers (10 MS),
- the six markers that showed significance in univariate analysis (6 MS),
- the five-marker sets defined in Table 3 (5 MS–food impaction, 5 MS–dysphagia),
- the four-marker sets defined in Table 3 (4 MS–PE = peripheral eosinophilia, atopy, food impaction, PPI-refractory symptoms; 4 MS–IgE = IgE, atopy, food impaction, PPI-refractory symptoms). In each case, the area under the curve is shown (see also text).

The best criteria for the presence of EoE, taking into account both their simplicity and their practicability in clinical routine and of the smallest possible loss of resolving power as reflected in AUC, along with the smallest loss of AUC are thus the following:

- History of atopy + history of food impaction + PPI-refractory symptoms + IgE (two or more of these).
- History of atopy + history of food impaction + PPI-refractory symptoms + peripheral eosinophilia (two or more of these).

By using the first of these marker constellations, a sensitivity in detecting EoE of 91.3% and a specificity of 86.3% were achieved. The second gave respectively 85.1% and 90.6%. Use of the first constellation led to

positive and negative predictive values of 90.5% and 85.3%; if the second was used, these were respectively 88.0% and 90.1%; full details are given in Table 3. As the difference between these was found to be minimal, the choice between these two 4-marker constellations can be made according to the information available in a given clinical situation.

DISCUSSION

The diagnosis of EoE still represents a major challenge, especially against the background of the more highly prevalent GERD²⁰ and its overlapping clinical symptoms. In an earlier paper,¹¹ we investigated a marker set comprising history of food impaction, PPI-refractory heartburn and peripheral eosinophilia, and showed that it is possible to distinguish pre-endoscopically between EoE and GERD, with high reliability. However, the conclusions of that paper were limited because of possible selection bias and for methodological reasons.

The present study was prospective and we reduced the initial set of 10 markers to four parameters: history of atopy, history of food impaction, PPI-refractory symptoms and either IgE or peripheral eosinophilia. The reduced sets showed excellent ability to predict EoE and distinguish EoE from GERD. Both sets were similarly capable to implement peripheral eosinophilia and IgE in respect to their individual contributions to the proposed scoring model; no significant difference was seen according to the criterion of AUC. This observation is important for clinical practice, as a complete blood count, including peripheral eosinophils, is easier, quicker and cheaper than an IgE determination—meaning that the marker set including peripheral eosinophilia is in favour because of its rapid availability before performance of EGD.

The other three markers in the set (PPI-refractory symptoms, history of food impaction, history of atopy) are easily recorded as part of the patient's medical history, and they differed significantly between the two patient groups. It should be mentioned here that all the EoE patients in our specialised out-patient department had already been treated with a PPI by their physician and had not responded to this either clinically or histologically, so that PPI-REE was excluded. More detailed examination of these patients revealed that they had been told they were suffering from heartburn, while in fact – as closer questioning revealed – these EoE patients did not have the typical symptoms of heartburn. For this reason, we have replaced the term 'PPI-refractory heartburn'¹¹ by 'PPI-refractory symptoms' in our routine medical workup.

Our results show that a simple marker set, combining clinical features and a laboratory variable (either peripheral eosinophilia or IgE), is able to help distinguish between EoE and GERD patients, in the absence of EGD, with high accuracy. This is of practical importance, as EoE is often prone to long diagnostic delays owing to the lack of clinical distinguishing characteristics of EoE and GERD resulting in improper biopsy technique during EGD.

To date, only few studies have been directed towards the clinical identification and differentiation of EoE and GERD, or of EoE and non-EoE cases, among adults or children. Mulder *et al.*²¹ investigated retrospectively 163 EoE and GERD cases (adult and paediatric), looking for clinical, endoscopic and histological features; on the basis of a scoring system, they developed a logistical regression model that incorporated the variables male sex, dysphagia, history of food impaction, absence of pain/heartburn, endoscopic linear furrowing and white papules. Their ROC analysis yielded an AUC of 0.858. This scoring system represented a combination of clinical and endoscopic parameters to differentiate between EoE and GERD.

In a prospective study, Aceves *et al.*²² observed that dysphagia and anorexia/early satiety were reported more frequently among 35 children with EoE than among 27 children with GERD. Furthermore, these symptoms correlated with the endoscopic and histological findings. As a broad spectrum of symptoms was observed in these children, the results of this study imply a major challenge to the precision with which medical history are obtained.

A comprehensive and very thorough prospective investigation of 144 EoE and 81 non-EoE cases has been described by Dellon *et al.*²³ In a manner similar to our model, clinical and endoscopic variables implicating EoE were identified. Eight variables (age, sex, dysphagia, food allergy, endoscopic rings, furrows, plaques and hiatal hernia) in a predictive model gave an AUC of 0.944, and 92% of the patients were correctly assigned, with a sensitivity of 84%, a specificity of 97%, and positive and negative predictive values of 93–91%. In that study, not only four symptoms but also four endoscopic signs were included in the prediction. In our study, with four variables, we were able to classify 88% or 89% of the cases correctly, and this was associated with sensitivities and specificities between 86% and 91% and with positive and negative predictive values between 85% and 90% – without knowledge of any endoscopic or histological results.

In our study, we were able to identify a constellation of clinically relevant predictive markers that allow an initial distinction to be made between EoE and GERD on the basis of clinical observations alone. Our model can identify EoE accurately, and it can also reliably screen out non-EoE cases. Thus, if the marker constellation indicates that a patient may have EoE, then the physician should undergo an EGD with adequate biopsy technique to ensure definitive diagnosis of EoE. A recently published calculation²⁴ indicated that patients with EoE have an estimated annual health care cost of up to \$1.4 billion in the USA; it may reasonably be expected that earlier diagnosis could reduce these costs.

A limitation of the present study was that symptoms were only scored as 'present' or 'absent', rather than being scored by the use of scales such as the Dysphagia Score.²⁵ The conduct of the study at a tertiary centre may have led to a degree of selection bias: patients with PPI-REE were not included, as all the patients had already been treated with a PPI and had failed to show any clinical or histological improvement after a PPI treatment; although the clinical outcome of prior PPI therapy is taken account of in our marker constellation, there remains the possibility that the use of this constellation might allow PPI-REE to be missed because patients were under PPI therapy at least for 4 weeks. To resolve the question, which PPI dose and duration is effective in inducing clinical and histological remission further studies including the participation of primary-care units (gastroenterological practices) who would be able to include treatment naïve patients with oesophageal eosinophilia and oesophageal symptoms will be of interest. Further our proposed clinical marker constellation is reserved for adult patients, as children with EoE and GERD present with a symptom constellation much more variable and heterogenous than in adults.

As in our earlier study, the allergy anamnesis was not made by a specialist, and we did not perform specific IgE determinations. Nevertheless, the emphasis of our proposed marker constellation is upon allergy indicators, which can be elicited and classified by any physician.

A further theoretical limitation of our study may be the comparison of EoE patients with GERD (erosive or non-erosive GERD and Barrett's oesophagus) patients alone after a reported PPI therapy in their medical history. However, in view of its high prevalence, the latter group represents the greatest diagnostic challenge. Other disorders with overlapping symptomatology such as non-ulcer dyspepsia, motility disorders of the oesophagus (e.g. achalasia, nutcracker oesophagus), sclerodermy or

Crohn's disease may limit the generalisability and utility of our proposed clinical prediction tool. An extension of the study to test our model under conditions including an independent patient cohort would be desirable.

In summary, we have developed a simple clinical and laboratory-based marker set that is able to help reliably distinguish between EoE and GERD before oesophago-gastroduodenoscopy; the criteria are easily applied and they have a high predictive power. The use of our model may be expected to lead to earlier EGDs with stepwise biopsies that will definitively make the diagnosis of EoE. Moreover, it may lead to the avoidance or reduction of complications through the earlier adoption of anti-inflammatory treatment.

AUTHORSHIP

Guarantor of the article: Dr. U. von Arnim.

Author contributions: UvA, study design, data analysis, data interpretation, manuscript drafting and critical revision; FWR, data management, statistical analysis, data interpretation, critical revision; SM, critical revision; DJ, histology, data interpretation; DR, laboratory analyses; TW critical revision, data interpretation; PM, critical revision.

All authors have approved the final version of the manuscript.

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