Original article

Reliability of symptoms and endoscopic findings for diagnosis of esophageal eosinophilia in a Japanese population

Running title: Diagnosis of esophageal eosinophilia

Shino Shimura[a], Norihisa Ishimura[a], Takashi Tanimura[b], Takafumi Yuki[a], Tatsuya Miyake[a], Yoshinori Kushiyama[c], Shuichi Sato[a], Hirofumi Fujishiro[d], Shunji Ishihara[a], Taisuke Komatsu[e], Eiji Kaneto[f], Akio Izumi[g], Noriyoshi Ishikawa[h], Riruke Maruyama[h], Yoshikazu Kinoshita[a]

[a]Department of Gastroenterology and Hepatology, Shimane University School of Medicine, Izumo, [b]Division of Gastroenterology, Matsue City Hospital, Matsue, [c]Division of Gastroenterology, Matsue Red Cross Hospital, Matsue, [d]Division of Endoscopy, Shimane Prefectural Central Hospital, Izumo, [e]Division of General Internal Medicine, Izumo Citizens Hospital, Izumo, [f]Division of Gastroenterology, Ohda Municipal Hospital, Ohda, [g]Izumi Gastrointestinal Clinic, Matsue, [h]Department of Pathology, Shimane University School of Medicine, Izumo, Japan

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Corresponding author: Norihisa Ishimura, MD

Department of Gastroenterology and Hepatology, Shimane University School of Medicine

89-1 Enya-cho, Izumo, Shimane 693-8501, Japan

TEL: +81-853-20-2190, FAX: +81-853-20-2187, e-mail: ishimura@med.shimane-u.ac.jp

Abstract

Background/Aims: The clinical characteristics of esophageal eosinophilia (EE), which is essential for diagnosis of eosinophilic esophagitis (EoE), have not been fully clarified in a Japanese population. To analyze the reliability of symptoms and endoscopic findings for diagnosing EE in Japanese individuals. ***Methods***: We prospectively enrolled subjects who complained of esophageal symptoms suggesting EoE, and/or those with endoscopic findings of suspected EoE at the outpatient clinics of 12 hospitals. Diagnostic utility was compared between the EE and non-EE groups using logistic regression analysis. ***Results***: A total of 349 patients, including 319 with symptoms and 30 with no symptoms but endoscopic findings suggesting EoE were enrolled. Of those with symptoms, 8 (2.5%) had EE, and 3 were finally diagnosed with EoE. Of those without symptoms but endoscopic findings, 4 had EE. Among 8 symptomatic patients, 7 had abnormal endoscopic findings suspicious of EoE. Although dysphagia was a major symptom in EE, none of the presenting symptoms was useful for diagnosis of EE. Among the endoscopic findings, linear furrow was the most reliable (OR=41.583). ***Conclusion***: EE is uncommon among patients with esophageal symptoms in Japanese individuals. The most useful endoscopic finding for diagnosis of EE was linear furrow, whereas subjective symptoms were not supportive.

Introduction

Eosinophilic esophagitis (EoE) is a chronic inflammatory immune-mediated disease characterized by esophageal dysfunction and eosinophil predominant infiltration in the esophageal epithelium [1,2]. EoE has become increasingly prevalent over the past decade, especially in Western countries [3,4]. While the epidemiology of EoE has not been fully evaluated, it appears that the incidence and prevalence of EoE and esophageal eosinophilia (EE) are also increasing in Asian countries, including Japan [5-8]. Pathologically, the hallmark of EoE is EE, commonly defined by more than 15 eosinophils per high power field (HPF) in at least 1 esophageal biopsy specimen. EE is predominantly found in patients with the following clinical conditions: gastroesophageal reflux disease (GERD), EoE, and proton-pump inhibitor-responsive esophageal eosinophilia (PPI-REE). According to the current clinical consensus and guidelines [9,10], histological suspicion of EoE should be confirmed by unresponsiveness to high-dose PPI therapy. However, the clinical significance of this diagnostic requirement, based on the response to PPI administration, remains controversial [11-14]. PPIs are reported to have immune-suppressive effects and improve the inflammatory process in patients with EoE [15,16]. Therefore, at present, pathological identification of EE is considered to be the most important and critical step for diagnosis of EoE.

Multiple studies have found that EoE is three to four times more common in men than women, and affected individuals are more likely to be Caucasian than other racial groups [17,18]. Moreover, race may influence the clinical presentation and have a role in the phenotypic expression of EoE. As compared with Caucasian patients, African Americans are less likely to have typical symptoms, such as food impaction and endoscopic findings (concentric rings, strictures) associated with EoE [19,20]. Even though the variety of clinical features distinguished by racial differences remains controversial [21,22], it is important to evaluate such features including symptoms and endoscopic findings in Asian populations for usefulness in diagnosis of EoE. Therefore, we sought to investigate the diagnostic utility of EE, which contains the main histological features of EoE, based on symptoms and endoscopic findings in a Japanese population. A multi-center prospective study was performed to determine the most reliable symptom and endoscopic finding for diagnosis of EE in Japanese individuals.

Materials and Methods

Patients

We prospectively enrolled subjects who complained of chest or epigastric symptoms suggesting EoE, such as heartburn, dysphagia, epigastric pain, chest pain,

acid regurgitation, food impaction, and vomiting at least once during the last week when esophago-gastro-duodenoscopy (EGD) was scheduled, and/or those with endoscopic findings of suspected EoE at the outpatient clinics of 12 hospitals in the western part of Japan between August 2011 and August 2012. We used a specific questionnaire to evaluate the frequency and severity of esophageal symptoms for the enrollment, which comprised of the questions including patient demographics (age, sex), concurrent allergic disease, frequency and severity of esophageal symptoms (number of days with episodes during the last 7 days), and information on medications, including PPIs and steroids, prior to each endoscopic examination. In regard to the severity of the symptoms, those with moderate symptoms, which was defined as discomfort sufficient to cause interference with normal activities, or more severe symptoms were enrolled. Those less than 15 years of age, who received glucocorticoid administration, had a high risk of bleeding from a biopsy, were excluded. The patients who had organic causes of the symptoms, such as endoscopically proven reflux esophagitis, gastroduodenal ulcers, and upper gastrointestinal malignant tumors, were also excluded. Reflux esophagitis was diagnosed when esophageal mucosal breaks of grade A, B, C, or D (Los Angeles classification) were found [23]. The protocol of this study was evaluated and approved by the ethical committee of Shimane University School of Medicine, and written

informed consent was obtained from all subjects prior to enrolment.

Endoscopic assessment and biopsy examination

All subjects underwent EGD performed by experienced endoscopists at each medical center. All examinations were done with high resolution endoscope (GIF-H260 or GIF-H260Z; Olympus Medical Systems Co, Tokyo, Japan). During the endoscopy procedures, findings were recorded in patient charts. Endoscopic findings suspicious of EoE included longitudinal linear furrows, multiple concentric rings (ringed esophagus, corrugated esophagus), whitish exudates, and reddening, as well as others (edema, pallor, decreased vascularity, and mucosal fragility) as previously described [24,25]. Representative endoscopic images with each finding suspicious of EoE were shown in fig 1. At least 2-4 biopsy samples were taken from the upper and lower esophagus, as well as the area of EoE shown in endoscopic findings as recommended by current clinical guideline [9]. In addition, biopsy samples were taken from the gastric and duodenal mucosa, irrespective of the mucosal appearance, in all the enrolled cases, to exclude eosinophilic gastroenteritis, as that exclusion is essential for diagnosis of EoE [10].

Histological assessment

Biopsy specimens were fixed in 10% formalin and samples were stained with hematoxylin and eosin, and then the numbers of eosinophils that infiltrated the esophageal epithelial layer were counted under an Olympus BX50 microscope. Histological diagnosis of EE was defined as the presence of more than 15 eosinophils per HPF discovered in biopsy samples taken with endoscopy. In addition, degree of inflammatory cell infiltration (mild, moderate, or severe), presence or absence of basal layer hyperplasia and dilated intracellular spaces, were also evaluated in cases with EE, according to the consensus guidelines for the recognition and assessment of microscopic lesion related to GERD [26,27]. All biopsies were reviewed by an experienced team of pathologists in the Pathology Department of Shimane University Hospital.

Treatment and definition of PPI response

Standard dose of PPI was prescribed for 4-8 weeks to symptomatic patients who were able to take them. Their symptoms, endoscopic findings, and histological abnormalities were re-evaluated after the treatment with PPI. Positive response to PPI was defined as a case in which administration of PPI improved symptoms and intraepithelial eosinophilic infiltration (<5/HPF). PPI resistant cases with EE were

defined as cases with EoE.

Statistical analysis

Fisher's exact probability test was used to compare 2 variables. The diagnostic utility of subjective symptoms and endoscopic findings was compared between the EE and non-EE groups using logistic regression analysis. All tests of significance were two-tailed and P-values less than 0.05 were considered to be significant. All analyses were done using SPSS 18.0 (IBM SPSS Japan Inc., Tokyo, Japan).

Results

Baseline characteristics of enrolled patients

During the study period of 13 months, EGD was performed in 17,324 patients at 12 medical centers, of whom 349 (163 men, 186 women; mean age 60.6 years) were enrolled in this study (fig. 2). Thirty-nine percent of enrolled subjects continued to take PPI when EGD was scheduled. Of the 349 enrolled patients, 319 complained of chest and/or epigastric symptoms suggesting EoE (symptomatic group, Group 1), while 30 had no symptoms along with endscopic findings suggesting EoE (asymptomatic group, Group 2). We next subdivided Group 1 into 2 groups; Group 1a (n=30), composed of patients with

both symptoms and endoscopic findings suggesting EoE, and Group 1b (n=289), who had symptoms but no endoscopic findings suggesting EoE (fig. 1). Twelve patients with EE were identified in this study, and 3 patients (No. 5, 7, 8) were finally diagnosed with EoE after PPI trial (table 1). Of 3 patients with EoE, 2 cases were treated by fluticasone swallowing and improved their symptoms and endoscopic findings. While, 3 patients (No. 1, 4, 12) were responsive to PPI and diagnosed with PPI-REE. Other 6 patients were not treated by PPI because of mild or no symptom, drug allergy, and lactation. Baseline characteristics between EE positive and negative subjects were shown in table 2. The mean age of these 12 patients (7 men, 5 women) was 49.3 years, and significantly younger than EE negative patients (mean age; 62.9, $p<0.05$). All of 3 patients with EoE had dysphagia, while none of 3 patients with PPI-REE had that, though the number was too small to compare statistically. As for histological findings, basal layer hyperplasia, dilated intracellular spaces, and mild to severe inflammatory infiltration (mainly lymphocyte infiltration) were found in all EE cases, and no histological findings were independently distinguished EoE from EE patients (table 1). No cases with eosinophilic gastroenteritis were found in the enrolled subjects.

Symptoms not useful for predicting EE

In the symptomatic group (Group 1), 8 patients (2.5%) were finally diagnosed with EE. A total of 497 symptoms were reported in 319 patients, as shown in fig. 3. Of the 8 patients with EE, 5 complained of dysphagia, 4 of heartburn, and 1 had both symptoms. None of the patients had a history of food impaction. Among the symptoms examined, dysphagia tended to be more common in patients with EE, though the difference was not significant (62.5% vs. 30.4%, P=0.054). Indeed, the patients with EE accounted for only 5% (5/100) of all patients who complained of dysphagia. Although present in some of the EE patients, the ratios of those with heartburn, epigastric pain, and chest pain were also not significantly different from those among non-EE patients (n=311). Next, we examined 4 major symptoms (heartburn, dysphagia, epigastric pain, chest pain) for usefulness in diagnosis of EE. The partial regression coefficient value for all of the items was <1, indicating that none of the presenting symptoms was useful for EE diagnosis (table 3).

Endoscopic findings more important than symptoms to predict EE

Of the cases with symptoms suggesting EoE (Group 1), 30 patients had abnormal endoscopic findings suspicious of EoE (Group 1a), while 289 had no such endoscopic findings (Group 1b). Interestingly, 7 patients in Group 1a (23.3%; 7/30) were diagnosed

with EE, while 1 patient was diagnosed as EE in Group 1b (0.35%; 1/289). Therefore, the presence of abnormal endoscopic findings was significantly more important to predict EE in symptomatic patients. In other words, the frequency of EE was quite low in patients with symptoms but no endoscopic findings. Moreover, 4 patients among asymptomatic patients with abnormal endoscopic findings (Group 2) (13.3%; 4/30) were diagnosed with EE, suggesting the importance of endoscopic findings to predict EE.

Presence of linear furrows was the most reliable for diagnosis of EE

Among all 349 patients examined, 60 had typical endoscopic findings of EoE including linear furrows (n=30), whitish exudates (n=23), multiple concentric rings (n=13), and reddening (n=8), with some overlap (fig. 4). Patients with endoscopic findings suspicious of EoE consisted of both symptomatic (n=30, Group 1a) and asymptomatic (n=30, Group 2) patients. Eleven (18.3%) of 60 patients with endoscopic findings were diagnosed as EE and linear furrows were seen in 10 (90.9%), while other findings were not so frequent (table 1). Overall, 33.3% (10/30) of the patients with linear furrows were histologically diagnosed with EE.

Next, we examined 5 major endoscopic findings (linear furrows, multiple concentric rings, whitish exudates, reddening, others) to examine their diagnostic

utility for EE. Linear furrows were the most reliable, as shown by partial regression coefficient analysis (table 4), with an odds ratio of 41.583, which was the only statistically significant finding (P=0.006). The probability of correctly diagnosing EE based on the presence of linear furrows was 87.3%. However, the sensitivity for linear furrows was modest at 83%, whereas specificity was 95%. Furthermore, the positive predictive value (PPV) was 37% and the negative predictive value (NPV) was 99% (table 5).

Discussion

This is the first reported investigation comparing the diagnostic utility of symptoms and endoscopic findings for EE in a Japanese population. We conducted the present multi-center prospective study of 349 patients taken from biopsy samples because of suspicious symptoms and/or endoscopic abnormalities. Symptoms suggesting esophageal dysfunction were noted in 319 cases and abnormal endoscopic findings was found in 60. Our findings showed that the prevalence of EE was 2.5% (8/319), and 5% (5/100) for patients with esophageal symptoms, and dysphagia, respectively. Of 8 patients with EE, 3 patients were finally diagnosed with EoE after PPI trial. The recent study conducted in USA by Dellon, et al. have shown that EE was found in 38% (66/173)

of patients with dysphagia [28]. In that study, 40 patients of 66 cases with EE were confirmed to have EoE and 24 had PPI-REE after PPI trial. Consistent with recent findings [29], no clinical or endoscopic feature independently distinguished PPI-REE from EoE before the PPI trial. In addition, there were no differences between the 2 patient groups for histological findings including amount of eosinophil infiltration and degree of inflammatory cell infiltration in this study. The prevalence of EE may be affected by the proportion of GERD patients in enrolled patients. Although patients with endoscopically proven reflux esophagitis were excluded, most of symptomatic GERD patients could be enrolled in this study. Indeed, 38.1% (133/349) of the patients had heartburn and 39.0% continued to take PPI when EGD was scheduled. While, only patients with dysphagia were enrolled in the study by Dellon, et al [28]. Nonetheless, our data indicate that both EE and EoE are uncommon among patients with chest or epigastric symptoms in a Japanese population as compared with Western populations.

As for clinical features, the most common symptom among Japanese patients with EoE is dysphagia and none of the patients in our previous study had a history of food impaction [7], a common symptom associated with EoE in Western individuals [18], especially Caucasians, suggesting racial differences in regard to EoE related symptoms. Dysphagia is consistently the most common symptom reported by patients with EE.

Although the ratio of dysphagia was higher in our patients with EE (62.5%) than in those without EE (30.4%), subjective symptoms including dysphagia, heartburn, and chest pain were not specific enough to make a diagnosis of EE, which was shown by logistic regression analysis.

A strength of this study is that an esophageal biopsy was performed in all of the enrolled patients with symptoms suggesting esophageal dysfunction with or without endoscopic abnormalities (n=319). Interestingly, only a single patient (0.35%) was diagnosed with EE among those with normal endoscopy findings, as compared with 18.3% (11/60) of the patients with abnormal findings. Consistent with our results, Mackenzie et al. prospectively assessed the risk factors and prevalence of EoE in an adult population with dysphagia. Of 261 patients with dysphagia, 31 (12%) met the pathological criteria for EE, while EE was found only in 5 cases (1.9%) without suspicious endoscopic findings [30]. These findings contradict the routine esophageal biopsies for the purpose of detecting EE in patients without abnormal endoscopic findings suggesting EoE. An esophageal biopsy procedure may not be useful or cost-effective to determine EoE in symptomatic patients without abnormal endoscopic findings. However, in patients with abnormal endoscopic findings suspicious of EoE, irrespective of symptoms, biopsy samples should be taken from the esophagus to

determine the presence of EE.

Endoscopic abnormalities in patients with EoE can vary within a wide range, including esophageal rings, linear furrows, strictures, and whitish exudates [24,31]. There also may be racial differences in EoE-related endoscopic findings [19,20]. In the present study, only 2 (16.7%) of the patients with EE had esophageal rings and none had esophageal strictures. Consistently, we previously confirmed that rings and strictures were not frequent in patients with EE or EoE in a Japanese population, in contrast to Western populations [25]. In addition, the present study revealed that linear furrows were the most frequent endoscopic findings in patients with EE, as they were found in 83.3% (10/12), while only 1 (8.3%) of the patients with EE had no characteristic endoscopic finding. In our previous report, approximately 40% of patients with EoE had no specific endoscopic findings [7]. These differences may be related to not only study design but also awareness of the disease among Japanese endoscopists, as it has been recently become widely reported. According to a recent meta-analysis, prospective studies showed that at least 1 abnormality was detected by endoscopy in 93% of EoE patients [25]. Therefore, endoscopic findings suspicious of EE, especially linear furrows, can be detected in most patients with EE by an experienced endoscopist with careful observation using a high resolution or narrow band imaging endoscopy [32].

Among the various endoscopic findings noted in the present study, linear furrows were the most useful for diagnosis of EE, as shown by logistic regression analysis. A previous pooled analysis of several studies showed modest sensitivity for EoE, such as 48% for linear furrows, 44% for corrugated rings, and 27% for whitish exudates [25], whereas sensitivities for EE in the present study for those were found to be 83%, 17%, and 42%, respectively. These suggest that the endoscopic finding of linear furrows is the most important for detection of EE in Japanese individuals. Recently, Hori et al. investigated the diagnostic utility of endoscopic features for EE. Although the numbers of cases of EE (n=5) was lower as compared to our study, the diagnostic utility of linear furrows and corrugated rings for EE was found to be superior to white exudates [33]. Importantly, the results of inter-observer agreement in a study of endoscopic findings of EoE indicated that gastroenterologists identified rings (κ=0.56) and furrows (κ=0.48) with fair to good reliability, whereas they did not reliably identify white exudate (κ=0.29) by white-light endoscopy and narrow band imaging endoscopy [34].

Here, we focused on patients with EE, which is essential for diagnosis of EoE. If dense eosinophilic infiltration is found in esophageal epithelium, EoE, GERD, and PPI-REE are the most common clinical possibilities. Recent clinical guidelines strongly recommend a PPI trial for such patients, and patients with persistent eosinophilic

infiltration and symptoms after such a trial can be formally diagnosed with EoE [9,10]. However, the appropriateness of this strategy for diagnosis of EoE remains to be elucidated. Gastric acid might play a role in the pathogenesis of EoE and PPIs are effective in some cases via decreasing esophageal acid exposure [12,35,36]. Moreover, a number of potential anti-inflammatory effects of PPIs have been described [37], suggesting that those drugs have anti-inflammatory actions independent of their effects on gastric acid secretion [15,16]. Thus, EoE patients might benefit from PPI therapy regardless of whether they have coexisting GERD. Additional studies are sorely needed to recognize, define, and mechanistically understand PPI-REE [11,38]. Nonetheless, long-term clinical outcome in patients with EE should be clarified in the future study.

In summary, EE remains a rare condition among Japanese patients with chest and epigastric symptoms. Reported symptoms including dysphagia do not support to a diagnosis of EE in Japanese cases. As for endoscopic findings, the presence of linear furrows was the most frequent and useful for EE diagnosis.

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Disclosure Statement

The authors have no conflict of interests to declare in this study.

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Figure Legends

Fig. 1: Representative endoscopic images suspicious of eosinophilic esophagitis.

A, Linear furrows. B, Rings including ringed esophagus (left) and corrugated esophagus (right). C, Whitish exudate. D, Reddening.

Fig. 2: Flow diagram delineating enrolled patients for diagnosis of esophageal eosinophilia.

During the study period of 13 months, EGD was performed in 17,324 patients at 12 medical centers, of whom 349 were enrolled in this study. Of enrolled 349 patients, 319 complained of chest and/or epigastric symptoms suggesting eosinophilic esophagitis (EoE) (symptomatic group; Group 1), while 30 had no symptoms along with endoscopic findings suggesting EoE (asymptomatic group; Group 2). We subdivided Group 1 into 2 groups based on endoscopic findings suggesting EoE; those with both symptoms and endoscopic findings suggesting EoE (Group 1a; n=30), and those with symptoms but no endoscopic findings suggesting EoE (Group 1b; n=289). Overall, 12 patients were finally diagnosed with esophageal eosinophilia (EE).

Fig. 3: Summary of symptoms.

Symptoms noted in the enrolled patients (symptomatic group; n=319) are shown as a bar chart (497 symptoms, duplicates counted). Patients who complained of heartburn, dysphagia, epigastric pain, chest pain, and others numbered 133, 100, 59, 57, and 148, respectively. Others included acid regurgitation, nausea, and vomiting. Patients with EE are shown as a closed bar in each column.

Fig. 4: Summary of endoscopic findings.

Endoscopic findings suspicious of EoE in enrolled patients are shown as a bar chart. Sixty patients had typical endoscopic findings of EoE including linear furrows (n=30), whitish exudates (n=23), multiple concentric rings (n=13), reddening (n=8), and others (n=7), with some overlap. Others included edema, pallor, and decreased vascularity. Patients with EE are shown as a closed bar in each column.

Table 1. Clinical characteristics of 12 patients with esophageal eosinophilia

No	Age	Sex	Allergy	Symptoms				Endoscopic findings					Histology		PPI response
				Heart-burn	Dysphagia	Epigastric pain	Chest pain	Linear furrows	Rings	Whitish exudates	Reddening	Others	Eosinophil /HPF	Lymphocytes infiltration	
1	33	M	−	+	−	+	−	+	−	+	−	−	48	moderate	Yes
2	26	F	−	+	−	−	−	+	−	+	−	−	95	moderate	NT
3	78	F	−	−	+	−	−	−	−	−	−	+ decreased vascularity	44	moderate	NT
4	51	M	−	+	−	−	−	+	+	−	−	−	38	moderate	Yes
5	78	M	−	−	+	−	−	+	−	−	+	+ edema	46	moderate	**No**
6	67	M	−	−	+	−	−	+	−	−	+	−	41	mild	NT
7	32	F	+	−	+	−	−	+	−	+	−	−	>20	mild	**No**
8	24	F	+	+	+	−	+	−	−	−	−	−	18	severe	**No**
9	42	M	−	−	−	−	−	+	+	+	−	−	168	moderate	NT
10	82	F	−	−	−	−	−	+	−	−	−	−	25	mild	NT
11	29	M	−	−	−	−	−	+	−	−	−	−	25	mild	NT
12	49	M	+	−	−	−	−	+	−	+	−	−	86	mild	Yes

No. 5, 7, 8 were finally diagnosed with eosinophilic esophagitis after PPI trial

HPF: high power field, PPI: proton pump inhibitor

Table 2. Baseline characteristics between EE positive and EE negative subjects

	EE positive	EE negative
Number of subjects	12	337
Sex (men: women)	7:5	156:181
Age in years (range)	49.3 ± 21.8 (24-82)	62.9 ± 14.9 (22-88)
Concurrent allergic disease (duplicates counted)		
Asthma	2	6
Atopic dermatitis	1	8
Hay fever	1	11
Food allergy	1	5
Others	1	11

Age is expressed as the mean ± standard deviation.

EE, esophageal eosinophilia

Table 3. Diagnostic utility for esophageal eosinophilia by presenting symptoms

Symptoms	b	Exp (b)	Exp (b) 95% CI	P value
Dysphagia	0.384	1.469	8.796 - 983.727	0.566
Heartburn	-0.317	0.729	0.192 - 13.509	0.657
Epigastric pain	-0.498	0.608	0.875 - 289.243	0.641
Chest pain	-17.814	0.000	0.851 - 28.0	0.997

b: partial regression coefficient Exp (b): odds ratio CI: confidence interval

Table 4. Diagnostic utility for esophageal eosinophilia by endoscopic findings

Endoscopic findings	b	Exp (b)	Exp (b) 95% CI	P value
Linear furrows	3.728	41.583	2.936 – 588.879	0.006
Rings	0.076	1.079	0.139 – 8.360	0.942
Whitish exudates	1.355	3.876	0.704 – 21.348	0.120
Reddening	1.751	5.763	0.375 – 88.660	0.209
Others	0.890	2.435	0.224 – 26.523	0.465

b: partial regression coefficient Exp (b): odds ratio CI: confidence interval

Table 5. Sensitivity, Specificity, and predictive value of endoscopic findings

	Linear furrows	Rings	Whitish exudates	Reddening
Sensitivity, % (95% CI)	83 (75-91)	17 (4-38)	42 (14-70)	17 (4-38)
Specificity, % (95% CI)	95 (93-97)	97 (95-99)	95 (93-97)	98 (97-99)
PPV, % (95% CI)	37 (28-46)	15 (11-19)	22 (6-38)	25 (-5-55)
NPV, % (95% CI)	99 (98-100)	98 (96-100)	98 (96-100)	97 (95-99)

Figure 1.

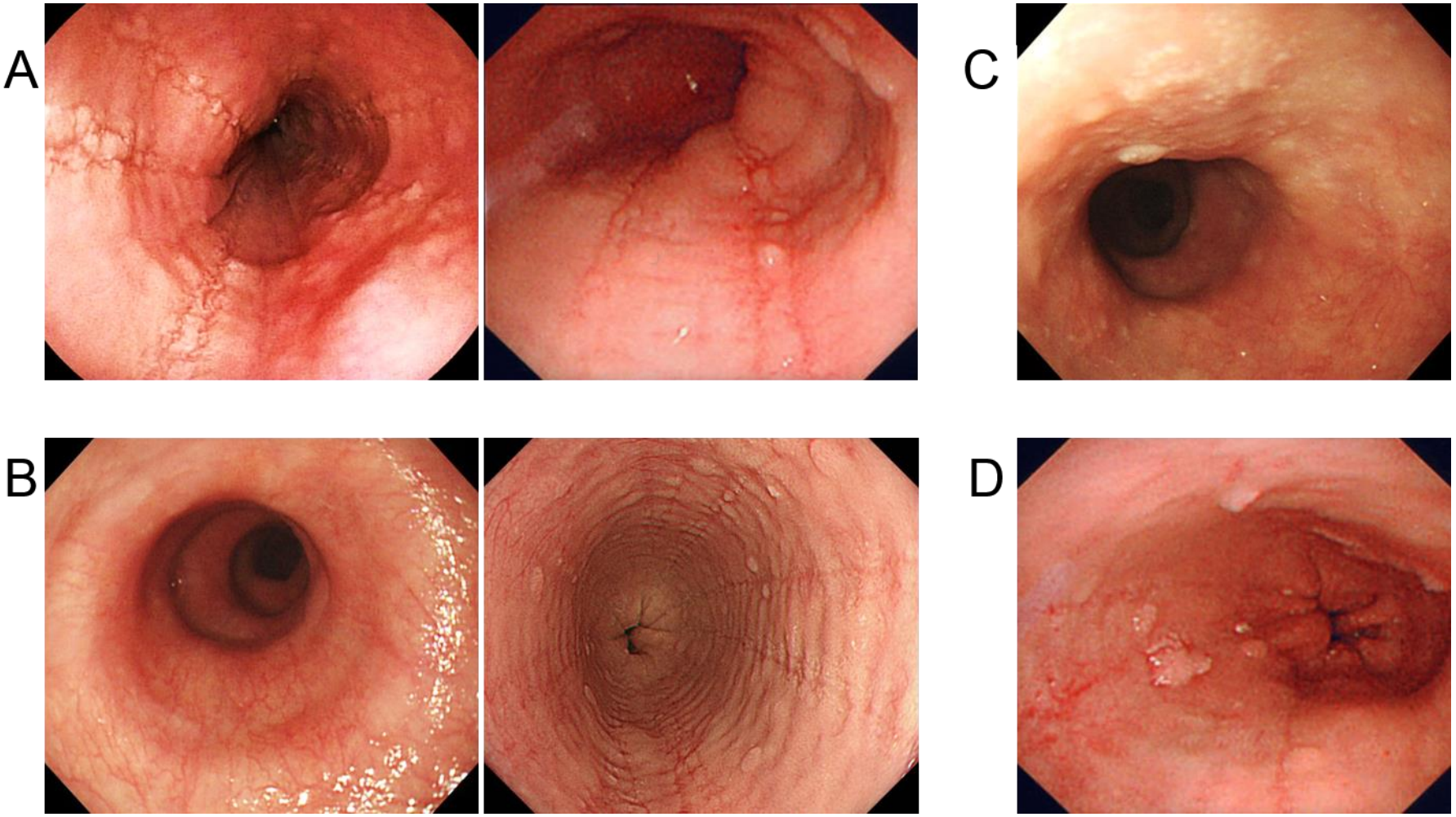


Figure 2.

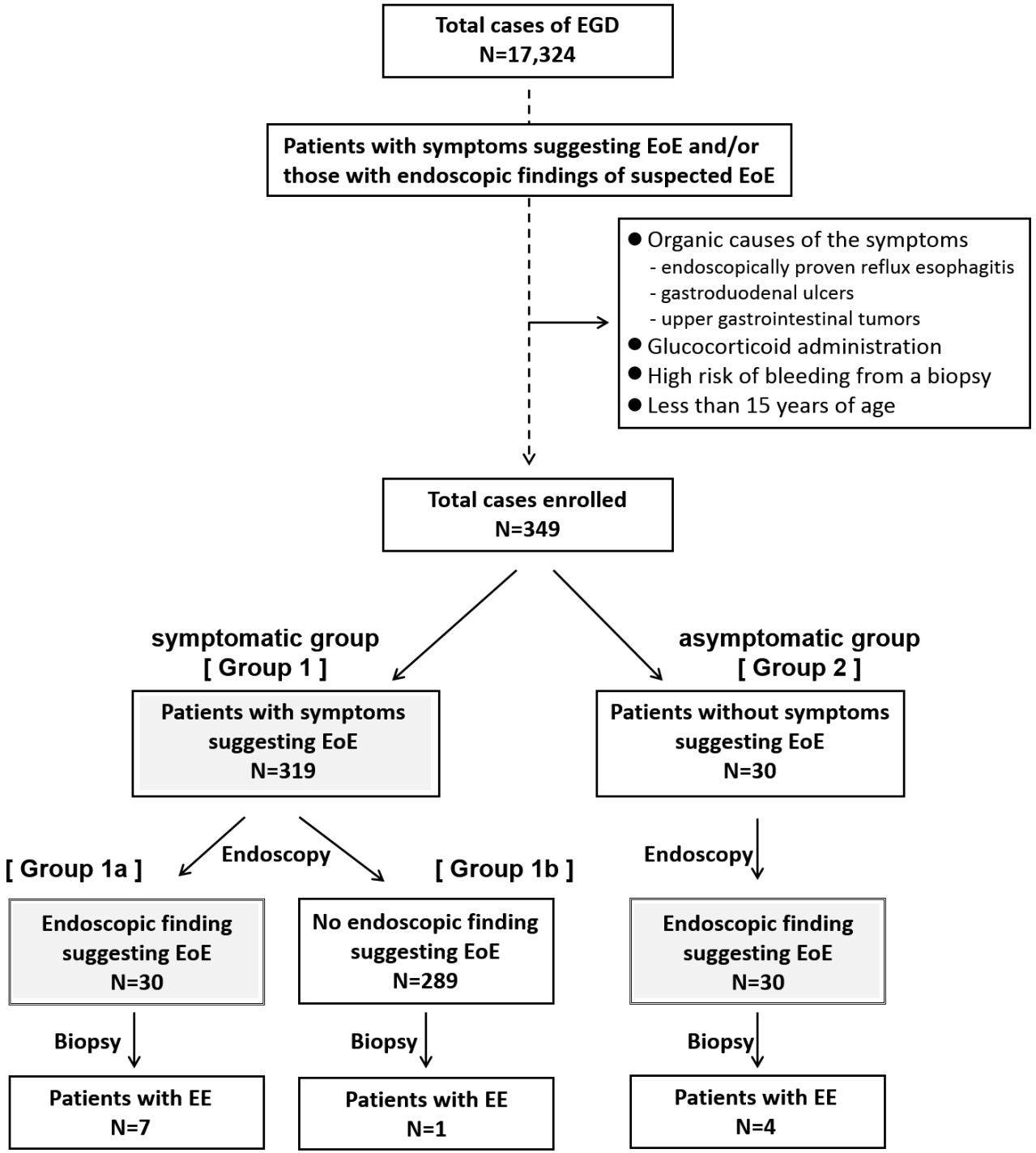

Total cases of EGD
N=17,324
Patients with symptoms suggesting EoE and/or those with endoscopic findings of suspected EoE
Organic causes of the symptoms
- endoscopically proven reflux esophagitis
- gastroduodenal ulcers
- upper gastrointestinal tumors
Glucocorticoid administration
High risk of bleeding from a biopsy
Less than 15 years of age
Total cases enrolled
N=349
symptomatic group
[Group 1]
asymptomatic group
[Group 2]
Patients with symptoms suggesting EoE
N=319
Patients without symptoms suggesting EoE
N=30
Endoscopy
[Group 1a]
[Group 1b]
Endoscopy
Endoscopic finding suggesting EoE
N=30
No endoscopic finding suggesting EoE
N=289
Endoscopic finding suggesting EoE
N=30
Biopsy
Biopsy
Biopsy
Patients with EE
N=7
Patients with EE
N=1
Patients with EE
N=4

Figure 3.

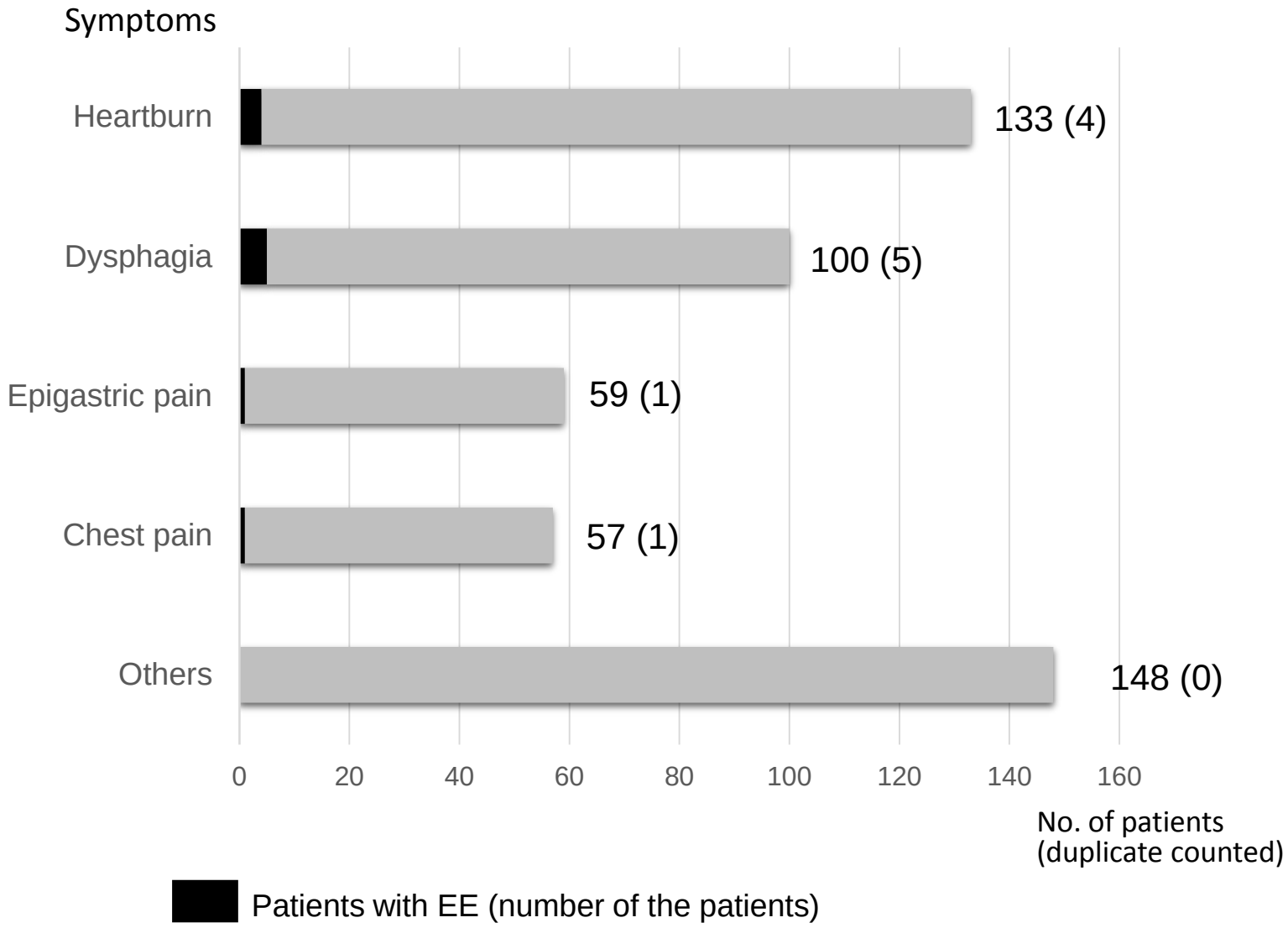
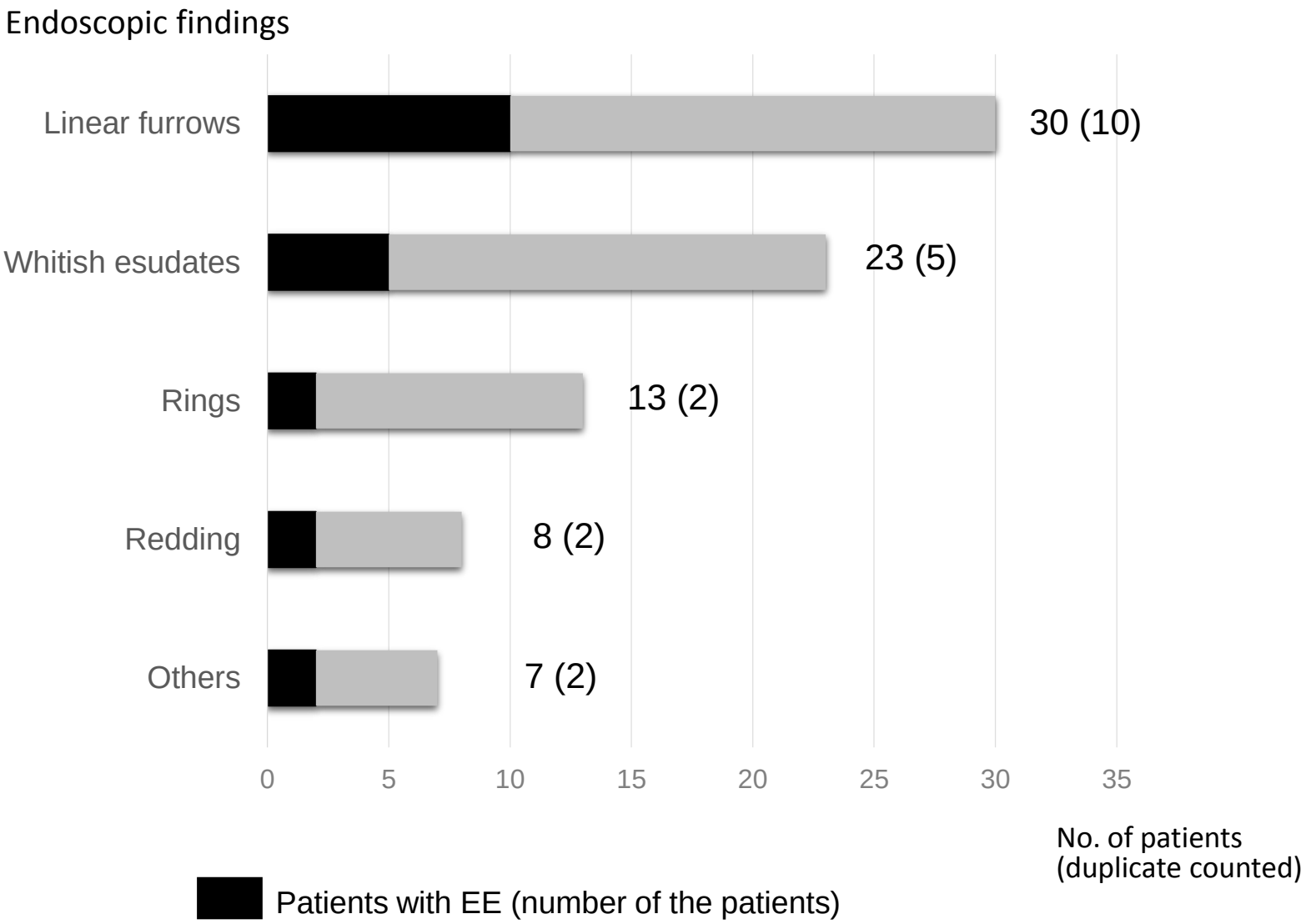

Symptoms
Heartburn
Dysphagia
Epigastric pain
Chest pain
Others
133 (4)
100 (5)
59 (1)
57 (1)
148 (0)
0
20
40
60
80
100
120
140
160
No. of patients
(duplicate counted)
Patients with EE (number of the patients)

Figure 4.


Endoscopic findings
Linear furrows
Whitish esudates
Rings
Redding
Others
30 (10)
23 (5)
13 (2)
8 (2)
7 (2)
0
5
10
15
20
25
30
35
No. of patients
(duplicate counted)
Patients with EE (number of the patients)