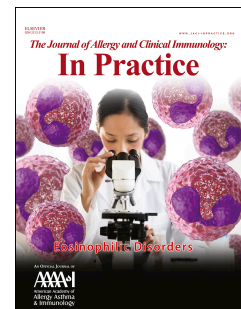


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Comparison of Non-esophageal Eosinophilic Gastrointestinal Disorders with Eosinophilic Esophagitis: A Nationwide Survey

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Comparison of Non-esophageal Eosinophilic Gastrointestinal Disorders with Eosinophilic Esophagitis: A Nationwide Survey

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Disclosure of potential conflict of interest

The authors declare no conflicts of interest associated with this manuscript.

ABSTRACT

BACKGROUND: Eosinophilic esophagitis (EoE) has increased rapidly and has been well characterized. However, no nationwide survey has been conducted regarding non-esophageal eosinophilic gastrointestinal disorders (non-EoE EGIDs), and they remain poorly understood.

OBJECTIVE: To compare the clinical features and natural histories of non-EoE EGIDs and EoE by using the same questionnaire, for all ages.

METHODS: We conducted a nationwide hospital-based survey of patients who visited hospitals from January 2013 through December 2017. We randomly selected 10,000 hospitals that performed endoscopy. We analyzed the demographics, symptoms, gastrointestinal histology, treatments and natural histories of EoE and non-EoE EGIDs.

RESULTS: A total of 2,906 hospitals responded to the questionnaire. We identified 1,542 patients, and obtained detailed data for 786 patients, consisting of 39% EoE and 61% non-EoE EGIDs. The clinical characteristics were analyzed for patients who met the "definite" criteria that excluded comorbidities. Non-EoE EGIDs showed no gender difference, while EoE was male-predominant. Tissue eosinophilia was often seen in the small intestine (62%) and stomach (49%). The frequency of hypoproteinemia was high (27%) in childhood. Children also had more serious symptoms and complications than adults: restriction of daily life activity ($P=.009$), failure to grow/weight loss ($P=.008$), and surgery ($P=.01$). For both diseases the most common natural history was the continuous type: 66% (95% CI: 58–74) in EoE and 64% (95% CI: 55–72) in non-EoE EGIDs.

CONCLUSIONS:

The percentage of persistent patients with non-EoE EGIDs was almost same as with EoE. Complications were more frequent in children than in adults.

Highlights Box

1. What is already known about this topic?

Unlike for eosinophilic esophagitis (EoE), the prevalence, putative phenotypes and natural courses of non-esophageal eosinophilic gastrointestinal disorders (non-EoE EGIDs) remain poorly understood.

(23/35words)

2. What does this article add to our knowledge?

Continuous type was 64% (95%CI: 55-72) in non-EoE EGIDs and 66% (95%CI: 58-74) in EoE. Restriction of activity, weight loss, surgery and hypoproteinemia in non-EoE EGIDs were more frequent in pediatric patients than adult patients.

(35/35 words)

3. How does this study impact current management guidelines?

Most non-EoE EGIDs were persistent and severe, especially in children. These findings will promote development of treatment strategies that do not inhibit growth and have fewer long-term side effects.

(34/35 words)

Key words:

Eosinophilic gastrointestinal disorders; Eosinophilic esophagitis (EoE); Non-esophageal eosinophilic gastrointestinal disorders (non-EoE-EGIDs); Eosinophilic gastritis (EG);

109 Eosinophilic gastroenteritis (EGE); Eosinophilic colitis (EC); Natural history;

110 Treatment; Nationwide survey (9/10)

111

112

113 *Abbreviations used*

114 *CI* *Confidence interval*

115 *EC* *Eosinophilic colitis*

116 *EE* *Eosinophilic enteritis*

117 *EG* *Eosinophilic gastritis*

118 *EGE* *Eosinophilic gastroenteritis*

119 *EGIDs* *Eosinophilic gastrointestinal disorders*

120 *EoE* *Eosinophilic esophagitis*

121 *GI tract* *Gastrointestinal tract*

122 *IQR* *Interquartile range*

123 *Non-EoE EGIDs* *Non-esophageal eosinophilic gastrointestinal disorders*

124

INTRODUCTION

Eosinophilic gastrointestinal disorders (EGIDs) are characterized by massive eosinophil infiltration into the gastrointestinal (GI) tract, causing chronic inflammation and dysfunction.¹ EGIDs are divided into eosinophilic esophagitis (EoE) and non-EoE EGIDs. Non-EoE EGIDs are further subgrouped into eosinophilic gastritis (EG), eosinophilic gastroenteritis (EGE), eosinophilic enteritis (EE) and eosinophilic colitis (EC), based on the GI site of the eosinophil infiltration.² The prevalence of EGIDs—especially that of EoE—has increased rapidly during the last two decades.^{3,4}

The clinical features of EoE have been well characterized. EoE occurs more often in males and is persistent in nature.^{3,5} The underlying mechanism is generally considered to be a Th2 immune response driven by a non-IgE-mediated food allergy.^{3,6-8} Clinical guidelines have been established to treat this persistent inflammatory disorder.⁹⁻¹¹

On the other hand, most previous studies of non-EoE EGIDs were case series studies, and only a few surveys have been conducted.^{4,12, 13} Large-scale studies are needed to fully clarify the prevalence, putative phenotypes, age related symptoms and natural courses of non-EoE EGIDs. Knowledge of the pathogenesis and natural history of these diseases will help us develop effective treatment strategies.

Accordingly, we used a single questionnaire to conduct a nationwide survey of patients of all ages in Japan to compare non-EoE EGIDs with EoE.

METHODS

Study design and data collection

This was a medical record survey of EGIDs in Japan that was nationwide, cross-sectional, hospital-based and retrospective. It was conducted from April 2018 through January 2019. We used a list of hospitals that perform GI tract endoscopy, had more than 20 beds and at least one of the departments of internal medicine, surgery and pediatrics. There were 11,117 hospitals that met these criteria, from among which we randomly selected 10,000 hospitals (the details of that selection process are described in the Methods section in this article's Online Repository at www.jaci-inpractice.org). We sent each hospital a first survey that asked the number of patients with EGIDs who visited the hospital from January 2013 through December 2017, regardless of the body site of eosinophil infiltration. Next, we sent a questionnaire as a second survey (see the Methods section in this article's Online Repository at www.jaci-inpractice.org) to the hospitals that responded, in which we asked for information on the patients' diagnosis, sex, age, symptoms, serious complications, laboratory findings, macroscopic abnormal endoscopic findings, tissue eosinophil counts in gastrointestinal biopsies, treatments and natural history patterns. The attending physicians at each hospital answered the questionnaire based on the data in the patients' medical records. We analyzed the received data. The Ethics Committee of the National Center for Child Health and Development had approved the study protocol (Reference Number #1736).

Patients and definitions

We set four patient inclusion criteria based on the following definitions. 1) "Doctor-diagnosed EGIDs" cases from the first survey were used to calculate the prevalence of EGIDs patients regardless of the site of eosinophil infiltration. 2) "Doctor-diagnosed EoE and non-EoE EGIDs" cases from the second survey were used

to calculate the rates (%) of EoE and non-EoE EGIDs. 3) "Definite EoE and non-EoE EGIDs" were meant to strictly exclude other diseases and were analyzed to identify the clinical features and treatments. EoE was defined according to the international guideline as an esophageal biopsy showing ≥ 15 eosinophils/high-powered field (hpf), with presence of esophageal dysfunction, but no other GI tract eosinophilia.^{9,10} Because no diagnostic criteria for non-EoE EGIDs had been established, we defined non-EoE EGIDs as one or more GI tract biopsy below the esophagus, with tissue eosinophilia and digestive tract symptoms. We used Pesek's criteria for tissue eosinophilia of the GI tract: stomach ≥ 30 eosinophils/hpf, small intestine ≥ 50 eosinophils/hpf, and colon ≥ 60 eosinophils/hpf.⁴ 4) "Definite EoE and non-EoE EGIDs cases observed for more than six months" were analyzed to clarify their natural histories.

Separately, "probable EoE and non-EoE EGIDs" means patients who did not satisfy inclusion criterion 3). They were similarly analyzed for their clinical features, treatment and natural histories.

In Japan, the pathology departments of many hospitals use microscope eyepieces with a field of view of 22, and the area of one field of view of $\times 400$ is often 0.237 mm^2 .

In this study, patients over the age of 18 years were defined as adults, while those under 18 were defined as children.

Classification of non-EoE EGIDs

We defined EG, EGE, EE, EC and extensive disease as follows: a) EG: tissue eosinophilia restricted to the stomach, or the stomach and esophagus; b) EGE: tissue eosinophilia presenting diffusely in the stomach and small intestine, and may or may not be present in the esophagus; c) EE: tissue eosinophilia restricted to the small intestine;

d) EC: tissue eosinophilia restricted to the colon;¹⁴ and e) extensive disease: none of the above, but with tissue eosinophilia presenting more diffusely in the GI tract, such as in the colon and other sections of the GI tract.

Treatments

The attending physicians extracted the information on treatments (systemic glucocorticoids, swallowed inhaled corticosteroids, elimination of causal foods, antacid treatments, anti-histamines/anti-leukotrienes, or immune-modulating drugs) from the patients' medical records. Because no symptom score had been established for non-EoE EGIDs, our questionnaire listed the following categories for the effect of treatment: "disease remission" (i.e., no recurrence after discontinuation of an effective treatment), "complete disappearance of symptoms," "partial improvement of symptoms," "no effect" and "unknown." Each attending physician selected one. "Disease remission" and "complete disappearance of symptoms" were collectively defined as "symptom resolution," which was used to calculate the "symptom resolution rate" of each treatment.

Natural histories

With reference to an earlier paper on EGE's natural history,¹⁵ we classified the natural history of non-EoE EGIDs into the following four types. "Continuous type": duration of symptoms or treatment was six months or more. "Single-flare type": duration of symptoms and treatment was less than six months, with no recurrence after the initial flare. "Intermittent type": symptoms recurred multiple times, and no treatment was needed during the intervals. "Unable to classify": none of the above. A pattern

diagram of the natural histories is shown in Q27 of the questionnaire in this article's Online Repository at www.jaci-inpractice.org. Each attending physician selected the applicable type.

Statistical analysis

Statistical analyses were performed using the SPSS software (version 23.0, IBM Corporation). Continuous variables were analyzed using the Mann–Whitney *U* test (nonparametric test, two groups) or the Kruskal–Wallis test (nonparametric test, three or more groups). Categorical variables were analyzed using the chi–square test or Fisher's exact test. $P < .05$ was considered to be statistically significant. Logistic regression analysis was performed using JMP 14 software (SAS Institute).

RESULTS

Study population, prevalence of EGIDs and percentages of EoE and non-EoE EGIDs

Figure 1 shows the flow chart and the numbers of patients in this survey. A total of 2,906 hospitals replied to the first survey (response rate: 29%), and 1,542 patients were identified as having "doctor–diagnosed EGIDs." Detailed data were obtained for 786 patients with EGIDs from the second survey: 549 adults (≥ 18 y.o.: 70%), 225 children (29%) and 12 age unknown (1.5%). The percentages of EoE and non-EoE EGIDs in all ages were 39% (310 patients) and 61% (476 patients), respectively. The percentages in adults were 54% (295 patients) and 46% (254 patients), while in children they were 6% (13 patients) and 94% (212 patients). Finally, we identified 153 "definite EoE patients" and 151 "definite non-EoE EGIDs patients" who met all the criteria.

Gender, and the age at disease onset

EoE showed male predominance (80%). The peak age at onset was 35-49 y, and 95% of the patients were adults (Table I, Figure 2A). Non-EoE EGIDs showed no gender difference. The peak age at onset was 0-14 y followed by the 50s, and 58% of the patients were adults (Table I, Figure 2B). To statistically show that there is a difference in the sex ratio between EoE and non-EoE, logistic regression analysis was performed using the presence/absence of EoE in the entire EGIDs population as the dependent variable, and gender as the explanatory variable. Adjustment was made for age. The results showed that the odds ratio for men to women for gender was 4.05 (95% confidence interval (CI): 2.16–7.58, $P<.0001$, Figure 2C). This shows that there was a significant gender difference between EoE and non-EoE in EGIDs.

Clinical characteristics of EGIDs

The most frequent presenting symptom of EoE was dysphagia (82%). Endoscopy revealed abnormal macroscopic findings in 98% of the patients. Non-EoE EGIDs had various digestive symptoms, such as abdominal pain (74%), diarrhea (44%) and vomiting (34%) (Table I). Restriction of daily life activity was reported for 51% of non-EoE EGIDs patients but only 12% of EoE ($P<.001$) (Figure 3A). As parameters that represent the severity of illness, growth failure/weight loss, surgery and hypoproteinemia were more frequent with non-EoE EGIDs than EoE (Figure 3A). Blood eosinophilia ($>500/\mu\text{L}$) was seen in 63% of non-EoE EGIDs but only 22% of EoE ($P<.001$). In non-EoE EGIDs, eosinophil infiltration was most frequently seen in the small intestine (62%), followed by the stomach (49%). The majority of patients with

eosinophil infiltration in the esophagus and stomach had abnormal macroscopic findings. However, about 1/3 of patients with eosinophil infiltration in the small intestine or colon had no abnormal macroscopic findings (Table I).

Comparison of adult (≥ 18 y.o.) and pediatric patients (< 18 y.o.) with non-EoE EGIDs

Bloody stools occurred in some pediatric non-EoE EGIDs patients (30%) and significantly more frequently than in adults ($P < .001$). Pediatric non-EoE EGIDs patients had more severe symptoms and complications than adults: restriction of daily life activity (65%, $P < .009$), growth failure/significant weight loss (13%, $P = .008$) and more cases of surgery (10%, $P = .01$). Hypoproteinemia was also detected in 27% of the children.

Childhood, in a nutshell, is a long time. Especially up to about 4 years of age, chronic food-protein-induced enterocolitis syndrome (FPIES), food-protein-induced enteropathy (FPE) and food-protein-induced allergic proctocolitis (FPIAP), which often occur in infancy, can be diagnosed as non-EoE-EGID pathologically. For this reason, we have divided childhood into two age groups: 0~4 years and 5~17 years (Figure 3B, Table II). In particular, the 5~17 y.o. group had a high rate of restriction of daily life activity (70%), which was considered to be the greatest interference with the quality of life. Hypoproteinemia was more prevalent in the 0~4 y.o. group (50%).

Treatments for EGIDs

The treatments for EoE were mainly antacid treatments. The frequencies of use of a proton pump inhibitor and swallowed inhaled corticosteroids were 84% and 24% (Table

III). The symptom resolution rates were 40% with antacid treatments and 57% with swallowed inhaled corticosteroids.

The treatments for non-EoE EGIDs were anti-histamines/anti-leukotrienes in 44%, antacid treatment in 42%, systemic glucocorticoids in 40%, and elimination of the causal food in 19%. Half of the patients received combination therapy. The symptom resolution rates were 55% with systemic glucocorticoids and 52% with elimination of the causal food, and low with the other treatments. Thirty-two percent of patients underwent long-term administration of systemic glucocorticoids (12 weeks or more); the median treatment period was 22 months, and the median maintenance dose was 5 mg/day.

In pediatric non-EoE EGIDs patients (Table II), 48% were treated by eliminating the causal food and 28% were treated with systemic glucocorticoids. The symptom resolution rates were comparable (52% and 53%, respectively).

In adult non-EoE EGIDs patients, 48% were treated with systemic glucocorticoids; almost all patients underwent long-term administration.

Comparison of disease localization of non-EoE EGIDs

There were 35 patients with EG, 35 with EGE, 36 with EE, 20 with EC and 25 with extensive disease (Table IV). The age at diagnosis was significantly younger in EC (median 14 y.o.) and significantly older in EGE (median 46 y.o.). Vomiting was most frequently seen in EG, EGE and EE (43%, 43% and 42%, respectively), and bloody stools were most frequent in EC (45%). The laboratory findings and natural histories did not differ significantly between the five groups.

The natural histories of EGIDs

The rates of each natural history pattern in EoE were: continuous type, 66% (95% CI: 58–74); single-flare type: 14% (9–22); and intermittent type: 14% (9–22). The respective rates for non-EoE EGIDs were 64% (55–72), 19% (13–27) and 7% (3–13) (Figure 4). Only 9.2% (8/87) of continuous-type EoE and 14% (11/79) of continuous-type non-EoE EGIDs achieved disease remission. The "duration of symptoms or treatment period" for the continuous type was a median 41 months (IQR 22.75–74) for EoE and 40.5 months (IQR 20.85–81) for non-EoE EGIDs.

When the natural history of non-EoE EGIDs was classified according to age, 46% of patients aged 0~4 years were the single-flare type, which was suspected to be related to infantile-onset non-IgE-mediated gastrointestinal food allergies. During the 5~17-year period, 75% were the continuous type (Figure 4, TABLE II).

A detailed comparison was made of the natural histories of the three non-EoE EGIDs types (Table E1 in this article's Online Repository at www.jaci-inpractice.org). Males were more prevalent than females in the continuous type, and 81% (43/53) of all male non-EoE EGIDs patients were classified as continuous. Forty-six percent of the continuous-type patients were treated long-term with systemic glucocorticoids, with a median administration period of 29.5 months and a median maintenance dose of 5 mg/day.

A similar comparison was made of the natural histories of the three EoE types (see Table E2 in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

This nationwide hospital-based questionnaire survey of EGIDs generated new findings that contribute greatly to our current knowledge regarding non-EoE EGIDs.

Earlier surveys that calculated the prevalence using the ICD-9 code in the United States database reported estimated prevalences of 56.7/100,000 for EoE, 6.3/100,000 for EG, 8.4/100,000 for EGE and 3.3/100,000 for EC.^{16,17} Thus, the estimated rates in the United States were 76% for EoE and 24% for non-EoE EGIDs. A Japanese nationwide survey (Kinoshita's survey) of 1,078 gastroenterology teaching hospitals targeted mainly adult patients from 2004 through 2009 and reported rates of 15% for EoE and 85% for non-EoE EGIDs.¹³ These data reveal a large discrepancy in the rates between the United States and Japan, with the percentage of non-EoE EGIDs among all EGIDs being much higher in Japan. It remains unclear whether the cause of this discrepancy is genetic or environmental.

Our current survey found rates of 39% EoE and 61% non-EoE EGIDs across all patient ages. If we limit the age of onset to include only adults, 54% of the cases were EoE in our survey from January 2013 through December 2017. That is a large increase compared with the 15% of adults with EoE in Kinoshita's survey from 2004 through 2009. Therefore, the rate of EoE in adults in Japan seems to have increased rapidly in the last decade. Possible reasons for that change are increased awareness of the disease by clinicians, increases in allergic diseases such as allergic rhinitis and food allergies, westernization of the Japanese diet and reduced prevalence of *Helicobacter pylori*.¹⁸

When we looked at the distributions of sex and the age at onset, we found marked differences between EoE and non-EoE EGIDs (Figures 2A and 2B). The peak age of onset and male predominance in EoE were similar to in Western countries,³ suggesting a shared pathogenetic mechanism between the two regions. Non-EoE EGIDs showed no

gender imbalance. Logistic regression analysis found a significant difference in gender distribution between EoE and non-EoE EGIDs. Two peaks were seen for the age at onset of non-EoE-EGIDs: 0-14 y.o. and the 50s (Figure 2B), i.e., children and adults. Those two groups may have different pathogenetic mechanisms.

In this survey, the health effects appeared to be more severe with non-EoE EGIDs than EoE, with higher likelihoods for restriction of daily life activity, growth failure/weight loss, surgery and hypoproteinemia (Figure 3A). Non-EoE EGIDs manifested various digestive symptoms and blood eosinophilia, consistent with previous retrospective studies at various institutions.^{4,15,19,20} Pediatric patients had more severe restriction of daily life activity and serious complications such as growth failure and surgery than adult patients. In particular, 70% of the 5~17 y.o. group had restrictions of daily life activity, and 50% of the 0~4 y.o. group had hypoproteinemia (Figure 3B). The persistence of this chronic inflammation in the digestive tract seems to be deleterious to children's nutrition, growth and development. The adult non-EoE EGIDs patients were often treated with systemic glucocorticoids, as in previous studies.^{13,15,19} In contrast, the pediatric patients were often treated by food elimination, and the symptom resolution rate was comparable to that with systemic glucocorticoids (Table II). The clinical guidelines for EoE recommend elemental, empiric or targeted elimination diets as initial therapy.^{10,21,22} However, for non-EoE EGIDs the efficacy of food elimination treatments was found to be limited in retrospective studies and case reports.^{4,23,24} Half of continuous-type non-EoE EGIDs were treated by long-term administration of systemic glucocorticoids.

The non-EoE EGIDs were divided into EG, EGE, EE and EC based on the site of eosinophil accumulation (Table IV). In terms of the age at diagnosis, EGE patients were

the oldest, while EC patients tended to be younger at diagnosis, possibly because of inclusion of patients diagnosed with EC due to prolonged FPIAP. Regarding the symptoms, EC patients had less vomiting (10%) and more bloody stools (45%). None of the EE or EC patients had eosinophilic infiltration of the esophagus, whereas 49% of the EGE patients did.

There have been many reports regarding the natural history of EoE. It is known that its chronic nature progresses over time and leads to fibrostenosis. However, there are few reports on non-EoE EGIDs. In a prospective study of 43 adult patients in France,¹⁵ 42% were the single-flare type, 37% were the intermittent type and 21% were the persistent type. In a Swiss study of mainly adult patients, 30% were the single-flare type, 30% were the intermittent type and 40% were the persistent type.²⁵ In our study of 124 non-EoE EGIDs cases, 64% (95%CI: 55–72) were the continuous type. Furthermore, the rate was almost the same (61%) for 325 "probable" cases, confirming the reproducibility of the data. Based on the above, we think non-EoE EGIDs frequently persist for a long time. About half of the continuous type were pediatric patients. Patients with growth failure, weight loss and hypoproteinemia were mostly this type (Table E1). When the childhood years were stratified, the continuous type accounted for 75% of the 5~17 y.o. patients (Figure 4).

Compared to EoE, non-EoE-EGIDs had a wider variety of symptoms, with more extensive involvement of the gastrointestinal tract.²⁶ For continuous-type non-EoE EGIDs, long-term treatment is preferable. Treatments that cause fewer side effects are needed, especially for children in the growing stage.

Study limitations

This study has a number of limitations. First, this was a retrospective cross-sectional survey. Thus, there might be some cases in which the medical records were incomplete. Second, until recently, diagnostic criteria had not been established for non-EoE EGIDs, and we were unable to rule out the possibility that "doctor-diagnosed" patients might include patients with other diseases. For this reason, for selection of subjects for detailed analysis we adopted Pesek's strict criteria⁴ to avoid inclusion of other diseases. This resulted in a smaller sample size, but we were able to analyze patients who had been accurately diagnosed. Furthermore, since the demographics and natural history were very similar for both "definite (n=151)" and "probable (n=325)" non-EoE EGIDs patients, we do not think that the "definite" patients were biased cases (Table E3). Third, the treatment effect was judged by the attending physician, which means that there was no standardization. Fourth, the pathology departments of many hospitals in Japan use microscope eyepieces with a field of view of 22, and the area of one field of view of x400 is often 0.237 mm². However, this may vary among hospitals. In this national survey, we were unable to verify the microscope equipment used to determine the eosinophil count or the area of one field of view, so this point represents a limitation of this study. Finally, we analyzed the natural history of patients who were followed up in the hospital for more than six months. Therefore, patients with a single-flare type who stopped visiting the hospital within six months were not included in that analysis of the natural history, and their number might be underestimated. Some patients may have moved or sought care at another hospital, thus not allowing complete categorization of the natural history.

CONCLUSIONS

Both EoE and non-EoE EGIDs are chronic inflammatory diseases caused by eosinophil infiltration of the GI tract. However, their clinical demographics differed noticeably, suggesting that they may have different etiologies. The age at onset of non-EoE EGIDs showed two peaks: 0~14 y.o. and in the 50s. This bimodal distribution and the greater severity of symptoms documented in the pediatric patients suggest different etiologies in adult and pediatric patients. Future studies regarding the risk factors for non-EoE EGIDs are required to elucidate their pathogenesis.

Most non-EoE EGIDs cases were the continuous type, and they rarely resolved over time.

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533 gastrointestinal tract. *Pediatr Allergy Immunol* 2020; 31 Suppl 24:25-7.

534

535 **Tables and their legends****TABLE I.** Clinical characteristics of EoE and non-EoE EGIDs

Characteristic	EoE n = 153	non-EoE EGIDs n = 151	P value
Sex, n (%)			<.001*
Male	123 (80)	75 (50)	
Female	30 (20)	72 (48)	
Age at diagnosis (y), median (IQR)	46 (38-54)	31 (12-50)	<.001*
Adult, n (%)	145 (95)	88 (58)	<.001*
Child, n (%)	8 (5)	60 (40)	
Symptoms, n (%)			
Dysphagia	126 (82)	27 (18)	<.001*
Appetite loss	42 (27)	82 (54)	<.001*
Vomiting	30 (20)	52 (34)	.004*
Abdominal pain	36 (24)	112 (74)	<.001*
Diarrhea	9 (6)	67 (44)	<.001*
Bloody stools	0 (0)	23 (15)	<.001*
Ascites	0 (0)	20 (13)	<.001*
Restriction of daily life activity	19 (12)	77 (51)	<.001*
Serious complications, n (%)			
Growth failure/weight loss	1 (0.7)	10 (7)	.005*
Surgery	1 (0.7)	7 (5)	.03*
Shock	0 (0)	1 (0.7)	.31
Laboratory findings	n	n	
Blood eosinophilia (>500/ μ L), n (%)	139 33 (22)	149 95 (63)	<.001*
Eosinophil count (/ μ L), median (IQR)	139 298 (171-485)	149 756 (318-1,725)	<.001*
Hypoproteinemia, n (%)	133 0 (0)	139 32 (21)	<.001*
Abnormal macroscopic findings in endoscopy, n (%)			
Esophagus	150 (98)	30 (20)	<.001*
Stomach	12 (8)	66 (44)	<.001*
Small intestine	2 (1)	62 (41)	<.001*
Colon	1 (0.7)	33 (22)	<.001*
Eosinophil infiltration site, n (%)			
Esophagus	153 (100)	33 (22)	<.001*
Stomach	0 (0)	74 (49)	<.001*
Small intestine	0 (0)	93 (62)	<.001*
Colon	0 (0)	45 (30)	<.001*

536 EoE, eosinophilic esophagitis; EGIDs, eosinophilic gastrointestinal disorders; IQR, interquartile range.

537 Adult ≥ 18 y.o.; Child <18 y.o. Hypoproteinemia: total protein <6 g/dL or albumin <3 g/dL. If the patient's

538 age is two years or younger, total protein or albumin should be below the 2.5th percentile for the same age

539 group. * $P < .05$ (Mann–Whitney U test, chi-square test or Fisher's exact test).

540

TABLE II. Clinical characteristics, treatment, and disease course of adult and pediatric patients with non-EoE EGIDs

	Child			Adult	
	0-4y n = 14	5-17y n = 46	0-4y vs 5-17y P value	≥18y n = 88	
Age at diagnosis (y), median (IQR)	1.5 (0-2)	12 (9-13.75)	<.001*	47 (36 – 59)	
Sex, n (%)			.41		
Male	6 (43)	29 (63)		39 (44)	
Female	6 (43)	17 (37)		47 (53)	
Symptoms, n (%)					
Dysphagia	4 (29)	4 (9)	.06	19 (22)	
Vomiting	1 (7)	22 (48)	.006*	27 (31)	
Abdominal pain	2 (14)	39 (85)	<.001*	70 (80)	
Diarrhea	7 (50)	16 (35)	.31	43 (49)	
Bloody stools	8 (57)	10 (22)	.01*	5 (6)	
Ascites	0 (0)	8 (17)	.09	12 (14)	
Restriction of daily life activity	7 (50)	32 (70)	.18	38 (43)	
Severe complications, n (%)					
Growth failure, significant weight loss	2 (14)	6 (13)	.91	2 (2)	
Surgery	3 (21)	3 (7)	.10	1 (1)	
Laboratory findings					
Blood eosinophilia (>500/μL), n (%)	9 (64)	32 (70)	.71	53 (60)	
Eosinophil count (/μL), median (IQR)	769 (431-1,519)	726 (448-1577)	.82	752 (278 – 1,815)	
Hypoproteinemia, n (%)	7 (50)	9 (20)	.02*	15 (17)	
Eosinophil infiltration site, n (%)					
Esophagus	1 (7)	11 (24)	.17	20 (23)	
Stomach	4 (29)	21 (46)	.26	49 (56)	
Small intestine	6 (43)	26 (57)	.37	58 (66)	
Colon	7 (50)	9 (20)	.02*	29 (33)	
Treatment, n (%)					
Systemic glucocorticoids	1 (7)	16 (35)	.04*	42 (48)	
Elimination of causal food	9 (64)	20 (43)	.17	0 (0)	
Antacid treatment	2 (14)	19 (41)	.06	39 (44)	
Anti-histamines, Anti-leukotriens	3 (21)	30 (65)	.004*	33 (38)	
Combined treatment, n (%)	3 (21)	28 (61)	.01*	42 (48)	
Symptom resolution by any treatment, n (%)	7 (63)	24 (57)	.89	31 (43)	
Symptom resolution per treatment modality, n (%)					
Systemic Glucocorticoids	1 (100)	8 (50)	.35	23 (55)	
Elimination of causal food	5 (56)	10 (50)	.29	0 (0)	
Antacid treatment	1 (50)	4 (21)	.85	8 (21)	
Anti-histamines, Anti-leukotriens	0 (0)	6 (20)	.15	5 (15)	
Long-term administration of systemic Glucocorticoids (>12w), n (%)	1 (7)	8 (17)	.35	40 (45)	
Administration period (months), median (IQR)	29	12.5 (2.88-37.5)	.39	25 (6.5 – 52)	
Maintenance administration amount (mg), median (IQR)	4	8.75 (5-19.25)	1.00	5 (2.5 – 5)	
Natural history, n (%)			<.001*		
Continuous type	5 (38)	30 (75)		44 (65)	
Single flare type	6 (46)	1 (3)		16 (24)	

Intermittent type	1 (8)	2 (5)	6 (9)
Unable to classify	1 (8)	6 (15)	2 (3)

Continuous type: duration of symptoms or treatment period $\geq$ six months; single-flare type: duration of symptoms and treatment period <6 months, and no relapse; intermittent type: symptoms relapsed multiple times. * $P < .05$ (Mann–Whitney U test, chi-square test, or Fisher's exact test). †Statistical analysis excluding "unable to classify."

TABLE III. Treatment data for EoE and non-EoE EGIDs

Characteristic	EoE n = 153	non-EoE EGIDs n = 151	P value
Treatment, n (%)			
Systemic glucocorticoids	10 (7)	60 (40)	<.001*
Swallowed inhaled corticosteroid	37 (24)	6 (4)	<.001*
Elimination of causal food	4 (3)	29 (19)	<.001*
Antacid treatments	128 (84)	63 (42)	<.001*
Anti-histamines, anti-leukotrienes	10 (7)	67 (44)	<.001*
Immune-modulating drug	0 (0)	7 (5)	.007*
Combined treatment	40 (26)	76 (50)	<.001*
Symptom resolution by any treatment, n (%)	73 (48)	64 (50)	.35
Symptom resolution per treatment modality, n (%)			
Systemic glucocorticoids	5 (50)	33 (55)	<.001*
Swallowed inhaled corticosteroid	21 (57)	0 (0)	<.001*
Elimination of causal food	1 (25)	15 (52)	<.001*
Antacid treatments	51 (40)	14 (22)	<.001*
Anti-histamines, anti-leukotrienes	3 (30)	11 (16)	.03*
Immune-modulating drug	- -	1 (14)	.31
Long-term administration of systemic glucocorticoids (>12 wk), n (%)	10 (7)	49 (32)	<.001*
Administration period (months), median (IQR)	16 (9-43.5)	22 (5-44)	.97
Maintenance administration dose (mg), median (IQR)	3.5 (1.25-5)	5 (2.75-7.75)	.11

EoE, eosinophilic esophagitis; EGIDs, eosinophilic gastrointestinal disorders; IQR, interquartile range. * $P < .05$ (Mann–Whitney U test, chi-square test, or Fisher's exact test).

TABLE IV. Clinical characteristics and natural history of disease localization of each non-EoE EGID

Characteristic	EG n = 35	EGE n = 35	EE n = 36	EC n = 20	Extensive disease n = 25	P-value
Sex, n (%)						.62
Male	18 (51)	18 (51)	16 (44)	8 (40)	15 (60)	
Female	15 (43)	17 (49)	20 (56)	11 (55)	9 (36)	
Age at diagnosis (y), median (IQR)	23 (10.5-49.5)	46 (13-59.75)	21 (12-46.8)	14 (4-43.5)	38 (22-51)	.02*
Adult, n (%)	18 (51)	23 (66)	18 (50)	9 (45)	20 (80)	.12
Child, n (%)	17 (49)	11 (31)	16 (44)	11 (55)	5 (20)	
Symptoms, n (%)						
Dysphagia	9 (26)	8 (23)	3 (8)	1 (5)	6 (24)	.13
Vomiting	15 (43)	15 (43)	15 (42)	2 (10)	5 (20)	.03*
Abdominal pain	26 (74)	29 (83)	30 (83)	12 (60)	15 (60)	.10
Diarrhea	10 (29)	17 (49)	19 (53)	9 (45)	12 (48)	.29
Bloody stools	3 (9)	2 (6)	6 (17)	9 (45)	3 (12)	.001*
Ascites	4 (11)	6 (17)	4 (11)	5 (25)	1 (4)	.29
Restriction of daily life activity	20 (57)	20 (57)	22 (61)	8 (40)	7 (28)	.07
Growth failure or significant weight loss	3 (9)	4 (11)	1 (3)	1 (5)	1 (4)	.60
Laboratory findings						
Blood eosinophilia (>500/ μ L), n (%)	28 (80)	22 (63)	18 (50)	12 (60)	15 (60)	.13
Eosinophil count (/ μ L), median (IQR)	957 (625-2,287)	764 (277-2,856)	589 (225-1,296)	972 (351-1,600)	546 (402-1,380)	.22
Hypoproteinemia, n (%)	9 (26)	10 (29)	4 (11)	4 (20)	5 (20)	.43
Eosinophil infiltration site, n (%)						
Esophagus	9 (26)	17 (49)	0 (0)	0 (0)	7 (28)	<.001*
Stomach	35 (100)	29 (83)	0 (0)	0 (0)	10 (40)	<.001*
Small intestine	0 (0)	35 (100)	36 (100)	0 (0)	22 (88)	<.001*
Colon	0 (0)	0 (0)	0 (0)	20 (100)	25 (100)	<.001*
Natural history, n (%)						.96
Continuous type	20 (63)	18 (64)	17 (59)	8 (53)	16 (76)	
Single-flare type	5 (16)	5 (18)	7 (24)	4 (27)	3 (14)	
Intermittent type	3 (9)	2 (7)	1 (3)	2 (13)	1 (5)	
Unable to classify	4 (13)	3 (11)	4 (14)	1 (7)	1 (5)	

EG, eosinophilic gastritis; EGE, eosinophilic gastroenteritis; EE, eosinophilic enteritis; EC, eosinophilic colitis.

Hypoproteinemia: total protein <6 g/dL or albumin <3 g/dL. If the patient's age is two years or younger, total protein or albumin should be below the 2.5th percentile for the same age group. * P <.05 (Mann-Whitney U test, chi-square test, or Fisher's exact test).

Figure legends

FIGURE 1. Flow chart of the study.

EGIDs, eosinophilic gastrointestinal disorders; EoE, eosinophilic esophagitis; HPF, high-powered field. *Pesek's criteria: stomach ≥ 30 eosinophils/HPF; small intestine ≥ 50 eosinophils/HPF; and colon ≥ 60 eosinophils/HPF. †Esophageal biopsy ≥ 15 eosinophils/HPF and indicated symptoms of esophageal dysfunction. ‡GI tract biopsy fulfilled Pesek's criteria and indicated digestive symptoms.

FIGURE 2. Distribution of age at onset of EGIDs.

A) EoE, B) non-EoE EGIDs. Analysis was performed of patients who satisfied the "definite" criteria. C) Logistic regression analysis was performed for the presence/absence of EoE in all EGIDs. The results showed that the odds ratio for men to women for gender was 4.05 (95% CI: 2.16–7.58; $P < .0001$).

FIGURE 3. Comparison of clinical parameters that represent the severity of illness.

Percentages of the patients who experienced restriction of daily life activity, complications, and abnormality of laboratory data are shown. A) Comparison between EoE and non-EoE EGIDs. B) Comparison between children 0~4 y, 5~17 y and adults with non-EoE EGIDs. Hypoproteinemia: total protein < 6.0 g/dL or serum albumin < 3.0 g/dL. If the patient's age is 2 years or younger, total protein or albumin should be below the 2.5th percentile for the same age group.

FIGURE 4. The natural histories of EoE and non-EoE EGIDs.

The pie chart shows the number of patients and their percentages (95% confidence interval) for each natural history type. Continuous type: duration of symptoms or treatment period ≥ 6 months. Single-flare type: duration of symptoms and treatment period < 6 months, and no relapse. Intermittent type: symptoms relapsed multiple times, and no treatment in the intervals. Non-EoE-EGIDs were further classified as 0~4 y, 5~17 y and ≥ 18 y.

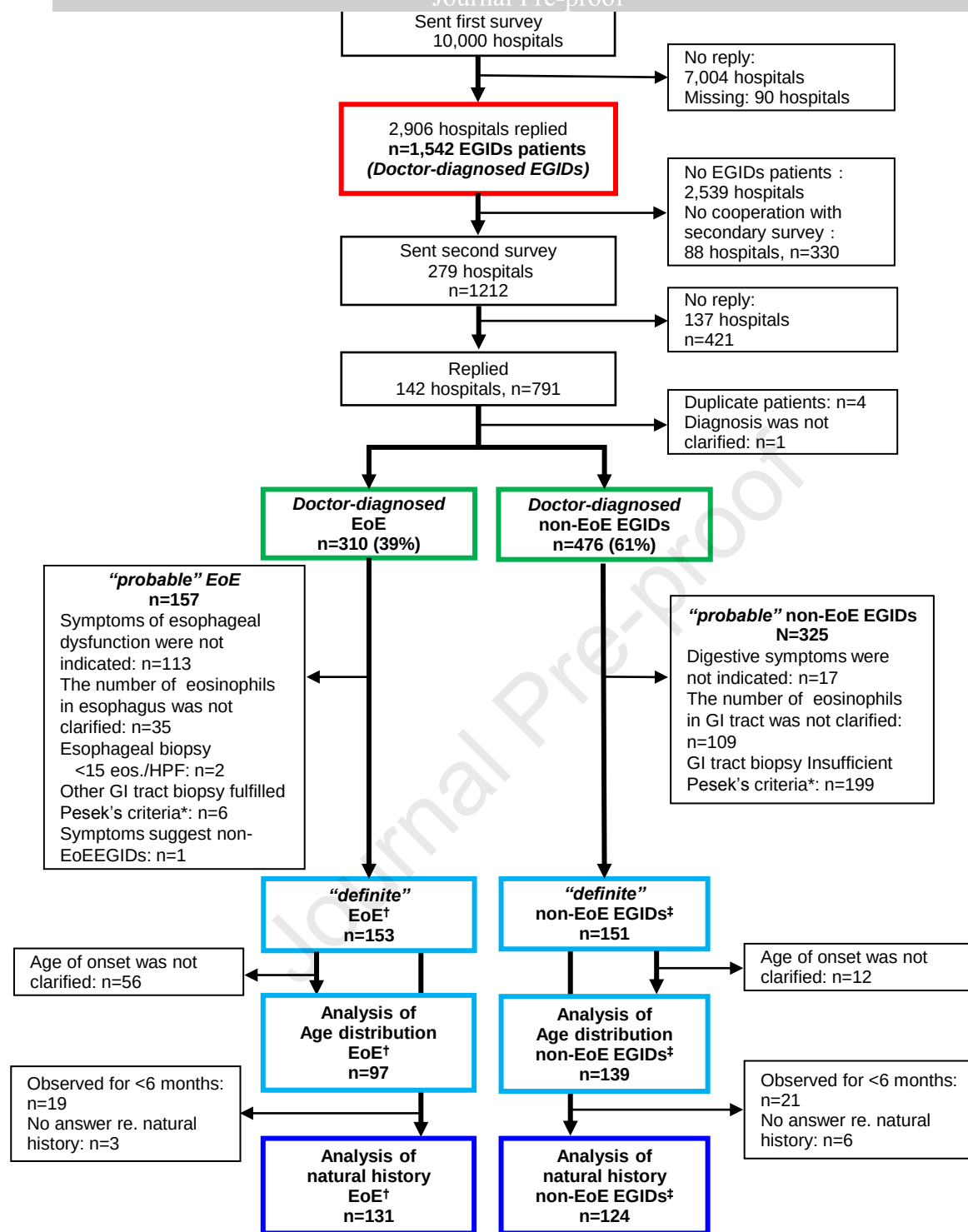


FIGURE 1. Flow chart of the study.

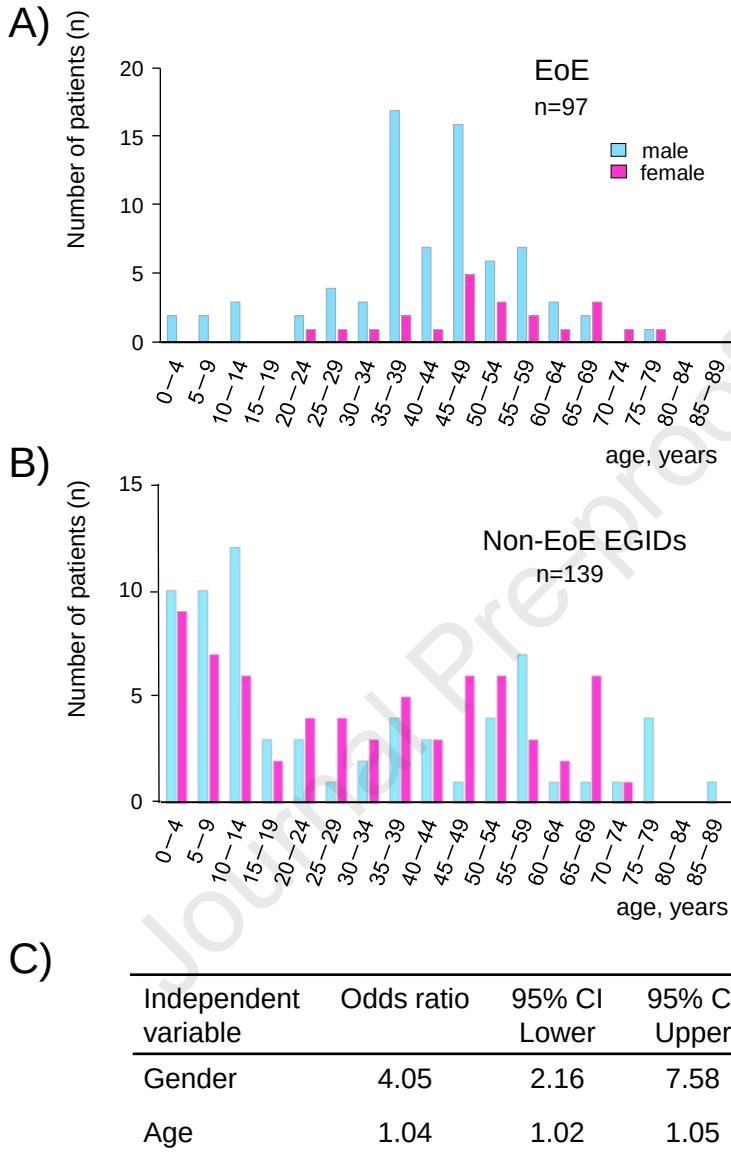
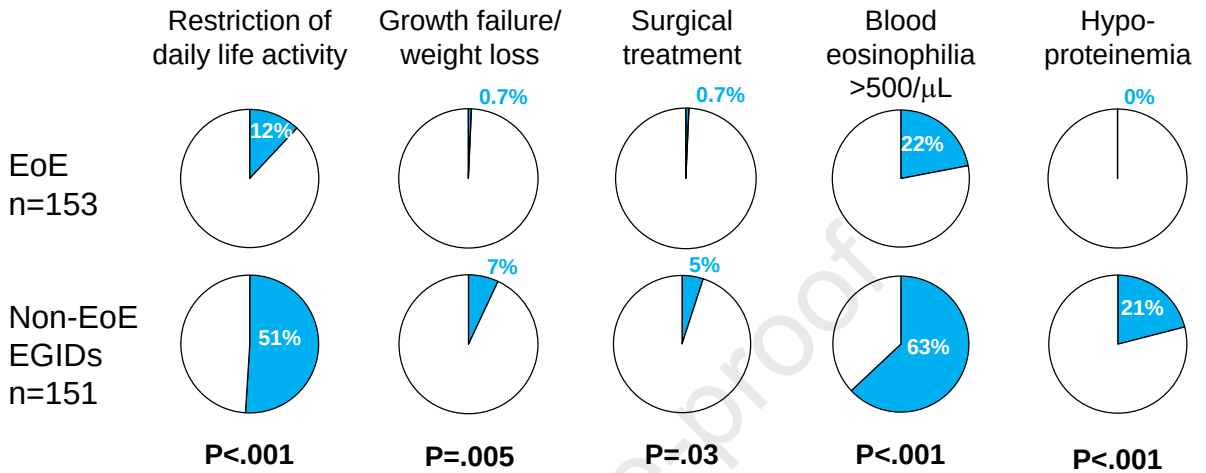


FIGURE 2. Distribution of age at onset of EGIDs.

A) Comparison of EoE and non-EoE EGIDs



B) Comparison between children and adults with non-EoE EGIDs

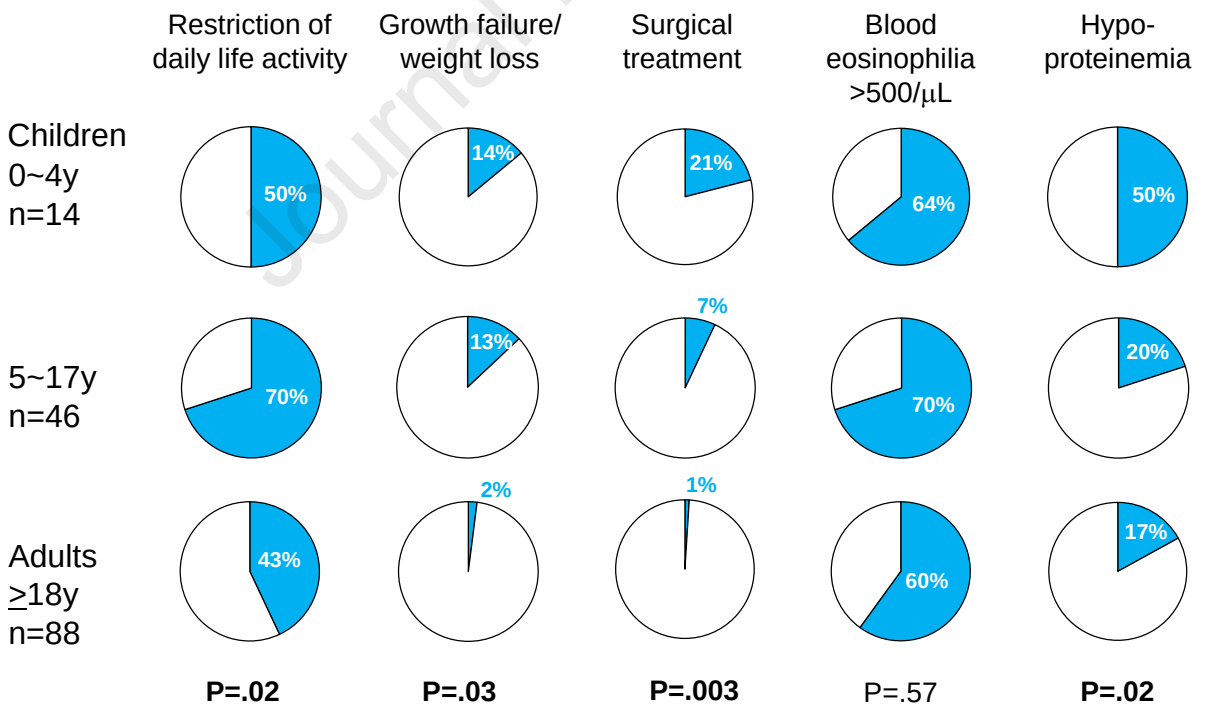


FIGURE 3. Comparison of clinical parameters that represent the severity of illness.

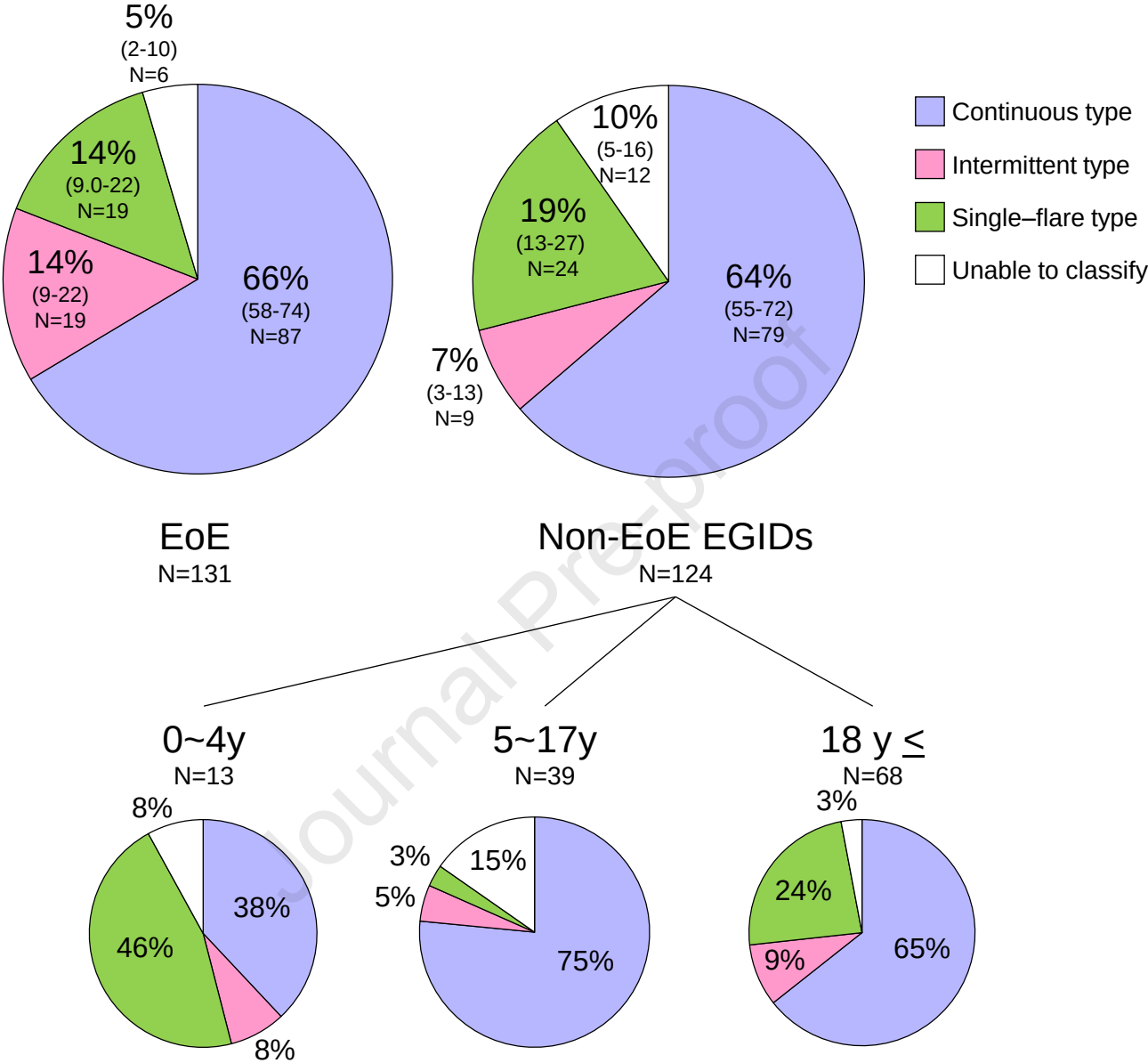


FIGURE 4. The natural histories of EoE and non-EoE EGIDs.

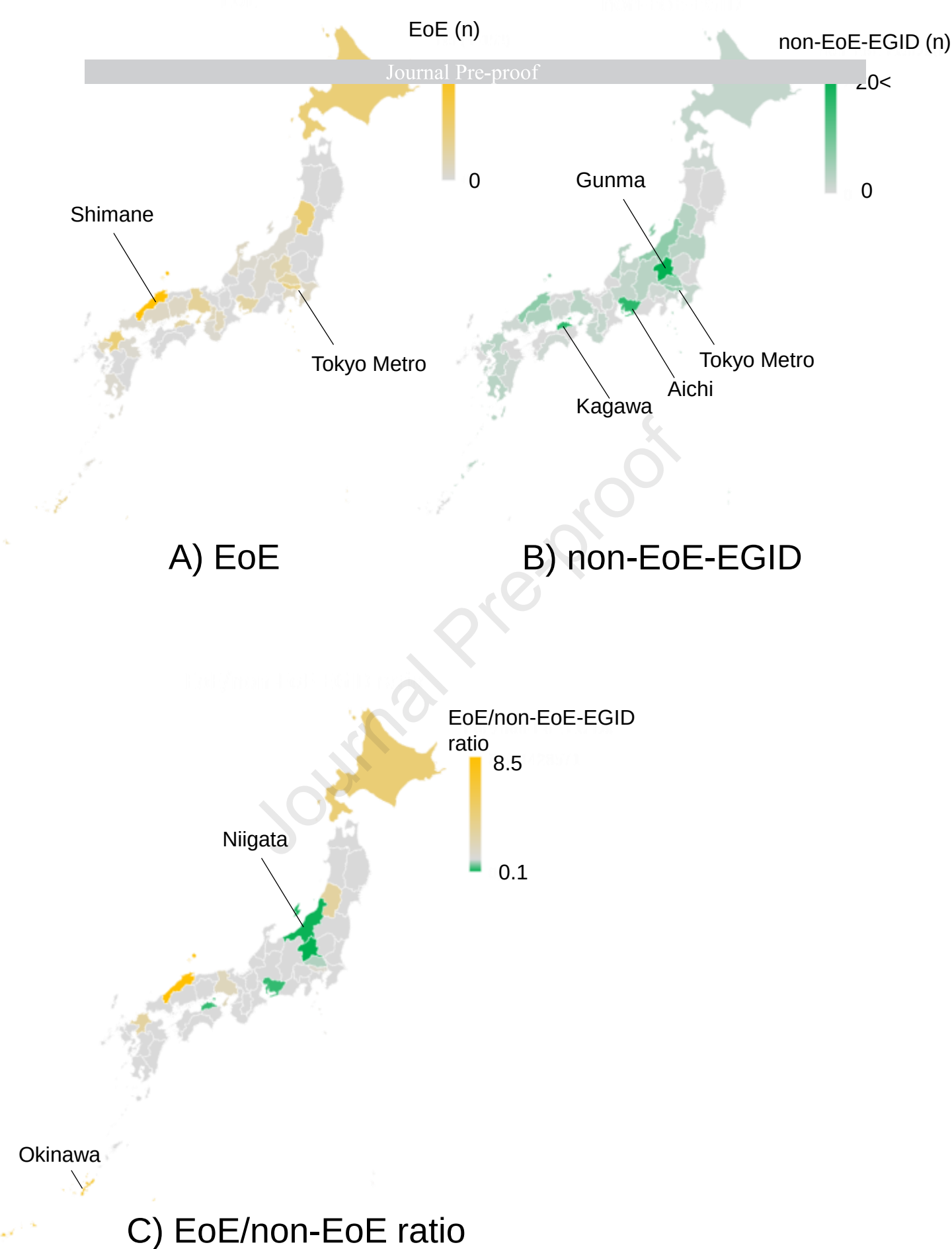


FIGURE E1. The numbers of patients and the EoE/non-EoE-EGID ratios shown on a map of Japan.