Original Article

Comparison of Nonesophageal Eosinophilic Gastrointestinal Disorders with Eosinophilic Esophagitis: A Nationwide Survey

Mayu Yamamoto, MD[a], Saori Nagashima, MD[a], Yoshiyuki Yamada, MD, PhD[b], Takatsugu Murakoshi, MD, PhD[c], Yasuyuki Shimoyama, MD, PhD[d], Sakuma Takahashi, MD, PhD[e], Hideyuki Seki, MD, PhD[f], Takashi Kobayashi, MD, PhD[g], Yuichi Hara, MD[h], Hiromi Tadaki, MD, PhD[i], Norihisa Ishimura, MD, PhD[j], Shunji Ishihara, MD, PhD[j], Yoshikazu Kinoshita, MD, PhD[j,k], Hideaki Morita, MD, PhD[l], Yukihiro Ohya, MD, PhD[m], Hirohisa Saito, MD, PhD[l], Kenji Matsumoto, MD, PhD[l], and Ichiro Nomura, MD, PhD[a,m] *Tokyo, Gunma, Kagawa, Hokkaido, Aichi, Fukuoka, Kanagawa, Shimane, and Himeji, Japan*

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.

What does this article add to our knowledge? Continuous type was 64% (95% confidence interval [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.

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.

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 perform endoscopy. We analyzed the demographics, symptoms, gastrointestinal histology, treatments, and natural histories of EoE and non-EoE EGIDs.

RESULTS: A total of 2906 hospitals responded to the questionnaire. We identified 1542 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, whereas EoE was male-predominant. Tissue eosinophilia was often seen in the small intestine (62%) and stomach (49%). The frequency of

[a]Division of Eosinophilic Gastrointestinal Disorders, National Research Institute for Child Health and Development, Tokyo, Japan
[b]Division of Allergy and Immunology, Gunma Children's Medical Center, Gunma, Japan
[c]Department of Gastroenterology, Tokyo Metropolitan Children's Medical Center, Tokyo, Japan
[d]Department of Gastroenterology and Hepatology, Gunma University Graduate School of Medicine, Gunma, Japan
[e]Department of Gastroenterology, Kagawa Prefectural Central Hospital, Kagawa, Japan
[f]Department of Gastroenterology, KKR Sapporo Medical Center, Hokkaido, Japan
[g]Department of Gastroenterology, Fujita Health University Bantane Hospital, Aichi, Japan
[h]Department of Gastroenterology, Fukuoka Sanno Hospital, Fukuoka, Japan
[i]Department of Pediatrics, National Hospital Organization Yokohama Medical Center, Kanagawa, Japan
[j]Department of Gastroenterology, Shimane University Hospital, Shimane, Japan
[k]Department of Medicine, Steel Memorial Hirohata Hospital, Himeji, Japan
[l]Department of Allergy and Clinical Immunology, National Research Institute for Child Health and Development, Tokyo, Japan
[m]Allergy Center, National Center for Child Health and Development, Tokyo, Japan

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Corresponding authors: Ichiro Nomura, MD, PhD, Division of Eosinophilic Gastrointestinal Disorders, National Research Institute for Child Health and Development, 2-10-1, Okura, Setagaya-ku, Tokyo 157-8535, Japan. E-mail: nomura-i@ncchd.go.jp; or: Kenji Matsumoto, MD, PhD, Department of Allergy and Clinical Immunology, National Research Institute for Child Health and Development, 2-10-1, Okura, Setagaya-ku, Tokyo 157-8535, Japan. E-mail: matsumoto-k@ncchd.go.jp.
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Abbreviations used

CI- Confidence interval
EC- Eosinophilic colitis
EE- Eosinophilic enteritis
EG- Eosinophilic gastritis
EGE- Eosinophilic gastroenteritis
EGIDs- Eosinophilic gastrointestinal disorders
EoE- Eosinophilic esophagitis
FPIAP- Food protein—induced allergic proctocolitis
GI tract- Gastrointestinal tract
hpf- High-power field
IQR- Interquartile range
Non-EoE EGIDs- Non—esophageal eosinophilic gastrointestinal disorders

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% confidence interval [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 the same as those with EoE. Complications were more frequent in children than in adults. **(J Allergy Clin Immunol Pract 2021;9:3339-49)**

Key words: *Eosinophilic gastrointestinal disorders; Eosinophilic esophagitis (EoE); Non—esophageal eosinophilic gastrointestinal disorders (non-EoE EGIDs); Eosinophilic gastritis (EG); Eosinophilic gastroenteritis (EGE); Eosinophilic colitis (EC); Natural history; Treatment; Nationwide survey*

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 2 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 1 of the departments of internal medicine, surgery, and pediatrics. There were 11,117 hospitals that met these criteria, among which we randomly selected 10,000 hospitals (the details of the 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 GI 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 4 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 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 $\geq$15 eosinophils/high-power field (hpf), with the 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 1 or more GI tract biopsies below the esophagus, with tissue eosinophilia and digestive tract symptoms. We used Pesek's criteria for tissue eosinophilia of the GI tract: stomach $\geq$30 eosinophils/hpf, small intestine $\geq$50 eosinophils/hpf, and colon $\geq$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, treatments, 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 1 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, whereas 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[2]; and (e) extensive disease:

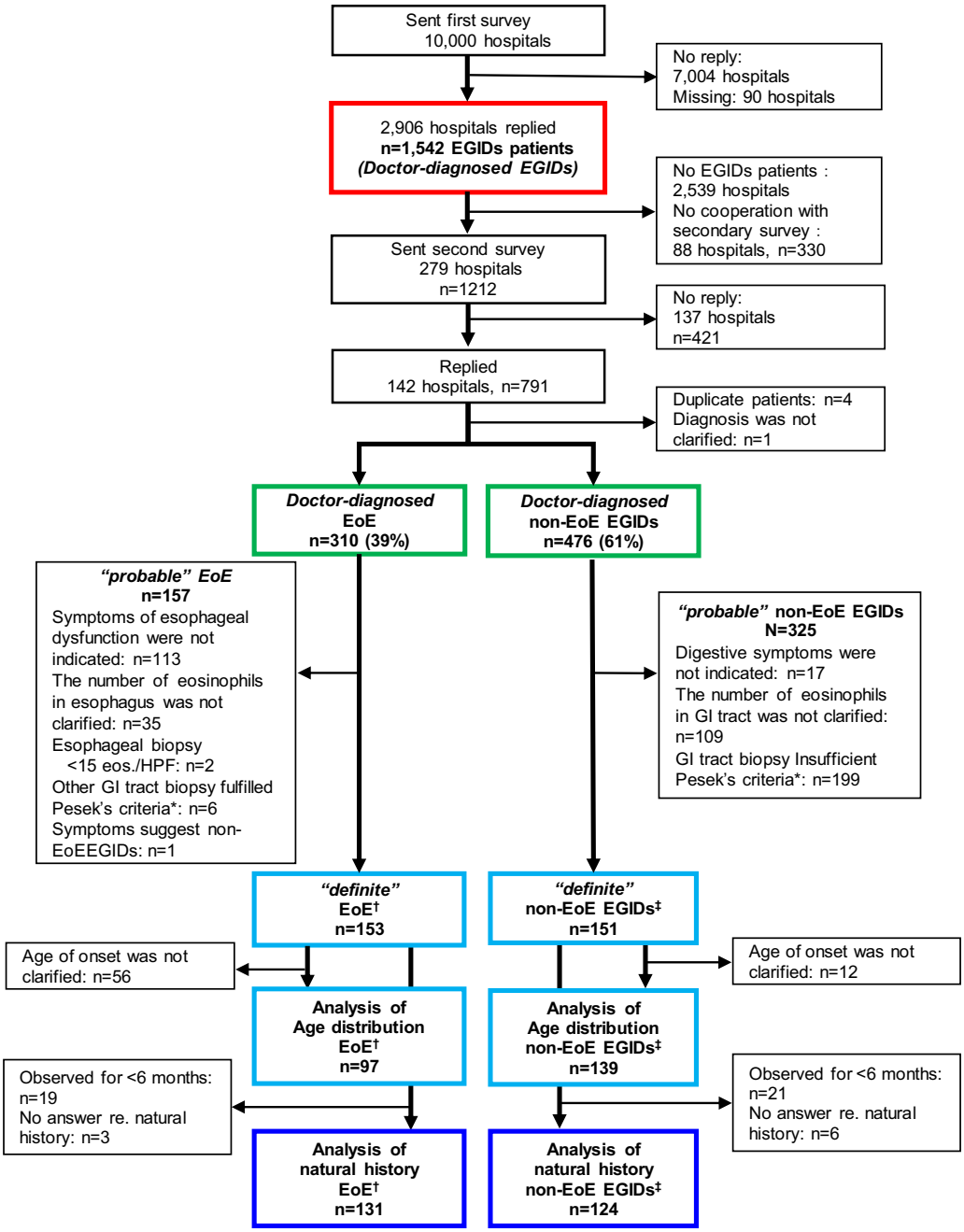


FIGURE 1. Flow chart of the study. *Pesek's criteria: stomach ≥30 eosinophils/HPF; small intestine ≥50 eosinophils/HPF; and colon ≥60 eosinophils/HPF. †Esophageal biopsy ≥15 eosinophils/HPF and indicated symptoms of esophageal dysfunction. ‡GI tract biopsy fulfilled Pesek's criteria and indicated digestive symptoms. *EGIDs*, Eosinophilic gastrointestinal disorders; *EoE*, eosinophilic esophagitis; *GI*, gastrointestinal; *HPF*, high-power field.

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, antihistamines/antileukotrienes, 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" (ie, 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,"

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/μL), n (%)	139	33 (22)	149	95 (63)	**<.001**
Eosinophil count (/μL), median (IQR)	139	298 (171-485)	149	756 (318-1725)	**<.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**

EGIDs, Eosinophilic gastrointestinal disorders; *EoE*, eosinophilic esophagitis; *IQR*, interquartile range; *y.o.*, years old.
Bold indicates statistical significance ($P < .05$ [Mann-Whitney *U* test, χ^2 test, or Fisher's exact test]).
*Adult ≥18 y.; child <18 y. Hypoproteinemia: total protein <6 g/dL or albumin <3 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.

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,[14] we classified the natural history of non-EoE EGIDs into the following 4 types. "Continuous type": duration of symptoms or treatment was 6 months or more. "Single-flare type": duration of symptoms and treatment was less than 6 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.

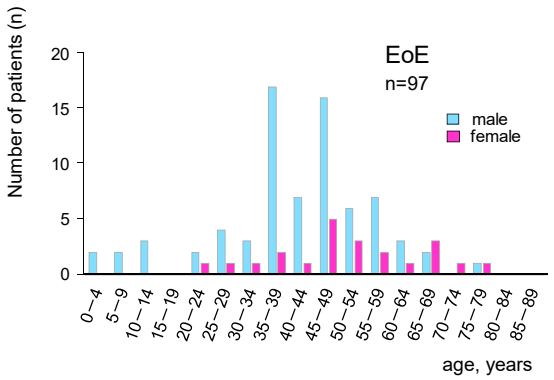
Statistical analysis

Statistical analyses were performed using the SPSS software (version 23.0; IBM Corporation, Armonk, NY). Continuous variables were analyzed using the Mann-Whitney *U* test (nonparametric test, 2 groups) or the Kruskal-Wallis test (nonparametric test, 3 or more groups). Categorical variables were analyzed using the χ^2 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, Cary, NC).

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 2906 hospitals replied to the first survey (response rate: 29%), and 1542 patients were identified as having "doctor-diagnosed EGIDs." Detailed data were obtained for 786 patients with EGIDs from the second survey: 549 adults (≥18 years old [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),



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Independent variable	Odds ratio	95% CI Lower	95% CI Upper
Gender	4.05	2.16	7.58
Age	1.04	1.02	1.05

FIGURE 2. Distribution of age at onset of EGIDs. (**A**) EoE; (**B**) non-EoE EGIDs. Analysis of patients who satisfied the "definite" criteria was performed. (**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; $P < .0001$). *CI*, Confidence interval; *EGIDs*, eosinophilic gastrointestinal disorders; *EoE*, eosinophilic esophagitis.

whereas 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 to 49 years, and 95% of the patients were adults (Table I, Figure 2, *A*). Non-EoE EGIDs showed no gender difference. The peak age at onset was 0 to 14 years followed by the 50s, and 58% of the patients were adults (Table I, Figure 2, *B*). 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 EGID 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 2, *C*). 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 patients with non-EoE EGIDs but only 12% of patients with EoE ($P < .001$) (Figure 3, *A*). 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 3, *A*). Blood eosinophilia (>500/μL) 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, approximately one-third 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 patients with non-EoE EGIDs (30%) and significantly more frequently than in adults ($P < .001$). Pediatric patients with non-EoE EGIDs 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 approximately 4 years of age, chronic food protein–induced enterocolitis syndrome, food protein–induced enteropathy, and food protein–induced allergic proctocolitis (FPIAP), which often occur in infancy, can be diagnosed as non-EoE EGIDs pathologically. For this reason, we divided childhood into 2 age groups: 0-4 years and 5-17 years (Figure 3, *B*; 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%, respectively (Table III). The symptom resolution rates were 40% with antacid treatments and 57% with swallowed inhaled corticosteroids.

The treatments for non-EoE EGIDs were antihistamines/antileukotrienes 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 (prednisolone equivalent).

In pediatric patients with non-EoE EGIDs (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).

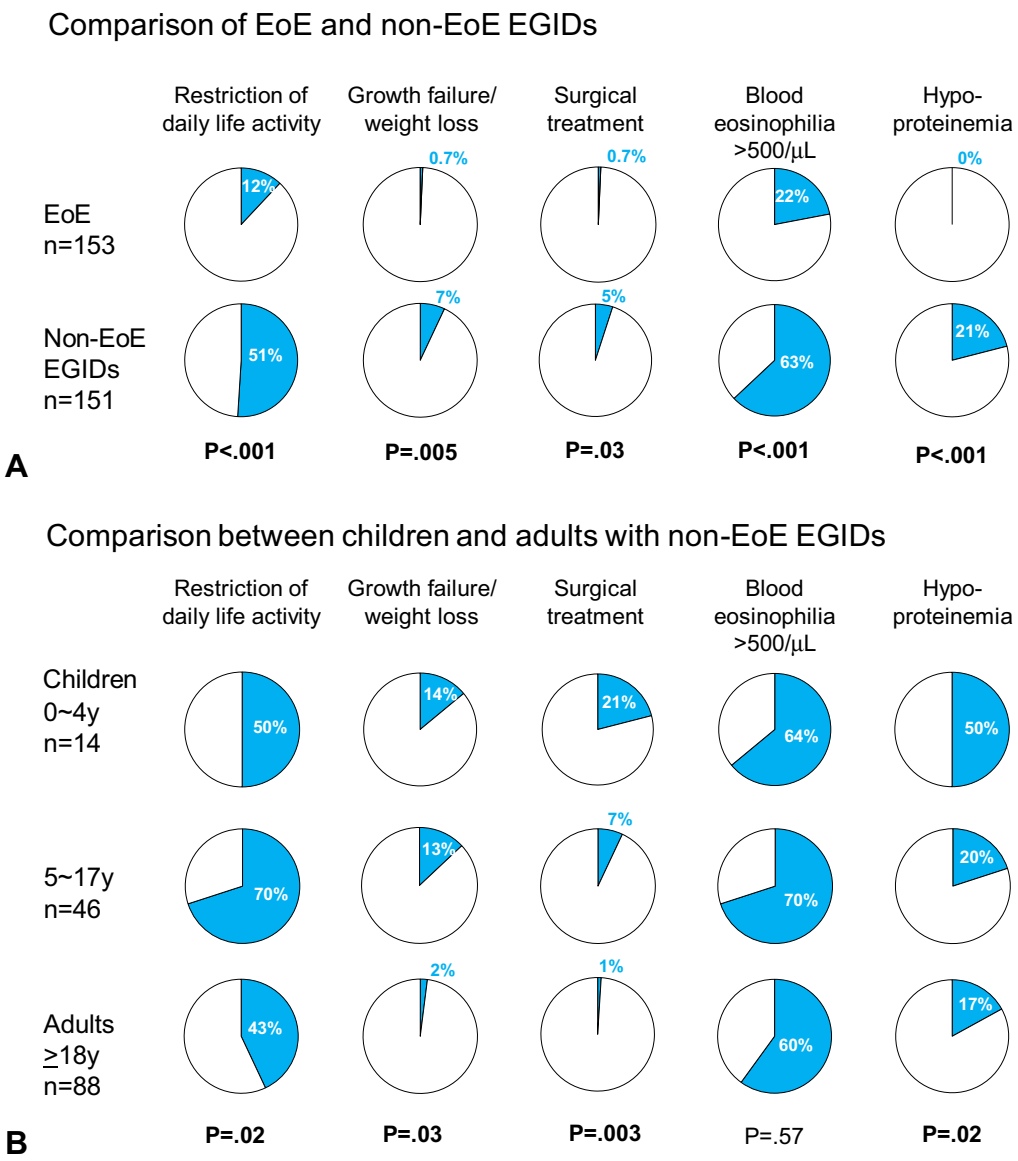

FIGURE 3. Comparison of clinical parameters that represent the severity of illness. Percentages of the patients who experienced restriction of daily life activity, complications, and abnormality of laboratory data are shown. (**A**) Comparison between EoE and non-EoE EGIDs. (**B**) Comparison between children 0-4 years old, 5-17 years old, 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. *EGIDs*, Eosinophilic gastrointestinal disorders; *EoE*, eosinophilic esophagitis.

In adult patients with non-EoE EGIDs, 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 5 groups.

The natural histories of EGIDs

The rates of each natural history pattern in EoE were as follows: 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

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

	Child			Adult	
	0-4 y	5-17 y	0-4 y vs 5-17 y	≥18 y	Child vs Adult
Characteristic	n = 14	n = 46	*P* value	n = 88	*P* value
Age at diagnosis (y), median (IQR)	1.5 (0-2)	12 (9-13.75)	**<.001**	47 (36-59)	**<.001***
Sex, n (%)			.41		.08
Male	6 (43)	29 (63)		39 (44)	
Female	6 (43)	17 (37)		47 (53)	
Symptoms, n (%)					
Dysphagia	4 (29)	4 (9)	.06	19 (22)	.20
Vomiting	1 (7)	22 (48)	**.006**	27 (31)	.33
Abdominal pain	2 (14)	39 (85)	**<.001**	70 (80)	.12
Diarrhea	7 (50)	16 (35)	.31	43 (49)	.21
Bloody stools	8 (57)	10 (22)	**.01**	5 (6)	**<.001***
Ascites	0 (0)	8 (17)	.09	12 (14)	.96
Restriction of daily life activity	7 (50)	32 (70)	.18	38 (43)	**.009***
Severe complications, n (%)					
Growth failure, significant weight loss	2 (14)	6 (13)	.91	2 (2)	**.008***
Surgery	3 (21)	3 (7)	.10	1 (1)	**.01***
Laboratory findings					
Blood eosinophilia (>500/μL), n (%)	9 (64)	32 (70)	.71	53 (60)	.32
Eosinophil count (/μL), median (IQR)	769 (431-1519)	726 (448-1577)	.82	752 (278-1815)	.74
Hypoproteinemia, n (%)	7 (50)	9 (20)	**.02**	15 (17)	.16
Eosinophil infiltration site, n (%)					
Esophagus	1 (7)	11 (24)	.17	20 (23)	.69
Stomach	4 (29)	21 (46)	.26	49 (56)	.09
Small intestine	6 (43)	26 (57)	.37	58 (66)	.12
Colon	7 (50)	9 (20)	**.02**	29 (33)	.41
Treatment, n (%)					
Systemic glucocorticoids	1 (7)	16 (35)	**.04**	42 (48)	**.02***
Elimination of causal food	9 (64)	20 (43)	.17	0 (0)	**<.001***
Antacid treatment	2 (14)	19 (41)	.06	39 (44)	.26
Antihistamines, antileukotriens	3 (21)	30 (65)	**.004**	33 (38)	**.04***
Combined treatment, n (%)	3 (21)	28 (61)	**.01**	42 (48)	.64
Symptom resolution by any treatment, n (%)	7 (63)	24 (57)	.89	31 (43)	**.05***
Symptom resolution per treatment modality, n (%)					
Systemic glucocorticoids	1 (100)	8 (50)	.35	23 (55)	.11
Elimination of causal food	5 (56)	10 (50)	.29	0 (0)	**<.001***
Antacid treatment	1 (50)	4 (21)	.85	8 (21)	.87
Antihistamines, antileukotriens	0 (0)	6 (20)	.15	5 (15)	.33
Long-term administration of systemic glucocorticoids (>12 wk), n (%)	1 (7)	8 (17)	.35	40 (45)	**<.001***
Administration period (mo), median (IQR)	29	12.5 (2.88-37.5)	.39	25 (6.5-52)	.33
Maintenance administration amount (mg), median (IQR), prednisolone equivalent	4	8.75 (5-19.25)	1.00	5 (2.5-5)	.07
Natural history, n (%)*			**<.001**†		**.02***,†
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)	

EGIDs, Eosinophilic gastrointestinal disorders; *EoE*, eosinophilic esophagitis; *IQR*, interquartile range.
Bold indicates statistical significance ($P < .05$ [Mann-Whitney *U* test, χ^2 test, or Fisher's exact test]).
*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.
†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**
Antihistamines, antileukotrienes	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**
Antihistamines, antileukotrienes	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 (mo), median (IQR)	16 (9-43.5)	22 (5-44)	.97
Maintenance administration dose (mg), median (IQR), prednisolone equivalent	3.5 (1.25-5)	5 (2.75-7.75)	.11

EGIDs, Eosinophilic gastrointestinal disorders; *EoE*, eosinophilic esophagitis; *IQR*, interquartile range.
Bold indicates statistical significance ($P < .05$ [Mann-Whitney *U* test, χ^2 test, or Fisher's exact test]).

(interquartile range [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 GI food allergies. During the 5- to 17-year period, 75% were the continuous type (Figure 4, Table II).

A detailed comparison was made of the natural histories of the 3 non-EoE EGID types (Table E1, available 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 patients with non-EoE EGIDs 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 (prednisolone equivalent).

A similar comparison was made of the natural histories of the 3 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 International Classification of Diseases (9th Revision) code in the United States database reported the estimated prevalence 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.[15,16] 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 1078 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*.[17]

When we looked at the distributions of sex and the age at onset, we found marked differences between EoE and non-EoE EGIDs (Figure 2, *A* and *B*). The peak age of onset and male predominance in EoE were similar to in Western countries,[3] suggesting a shared pathogenetic mechanism between the 2 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 2, *B*), that is, children and adults. Those 2 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 3, *A*). Non-EoE EGIDs manifested various digestive symptoms and blood eosinophilia, consistent with previous retrospective studies at various institutions.[4,14,18,19] Pediatric patients had more severe restriction of daily life activity and serious complications such as growth

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/μL), n (%)	28 (80)	22 (63)	18 (50)	12 (60)	15 (60)	.13
Eosinophil count (/μL), median (IQR)	957 (625-2287)	764 (277-2856)	589 (225-1290)	972 (351-1616)	546 (402-1380)	.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)	

EC, Eosinophilic colitis; *EE*, eosinophilic enteritis; *EG*, eosinophilic gastritis; *EGE*, eosinophilic gastroenteritis; *EGID*, eosinophilic gastrointestinal disorder; *EoE*, eosinophilic esophagitis; *IQR*, interquartile range.

Bold indicates statistical significance ($P < .05$ [Mann-Whitney *U* test, χ^2 test, or Fisher's exact test]).

*Hypoproteinemia: total protein <6 g/dL or albumin <3 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.

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 3, *B*). The persistence of this chronic inflammation in the digestive tract seems to be deleterious to children's nutrition, growth, and development. The adult patients with non-EoE EGIDs were often treated with systemic glucocorticoids, as in previous studies.[13,14,18] 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.[10,20,21] However, for non-EoE EGIDs, the efficacy of food elimination treatments was found to be limited in retrospective studies and case reports.[4,22,23] 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, patients with EGE were the oldest, whereas patients with EC tended to be younger at diagnosis, possibly because of inclusion of patients diagnosed with EC due to prolonged FPIAP. Regarding the symptoms, patients with EC had less vomiting (10%) and more bloody stools (45%). None of the patients with EE or EC had eosinophilic infiltration of the esophagus, whereas 49% of the patients with EGE 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,[14] 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.[24] 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. On the basis of 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, available in this article's

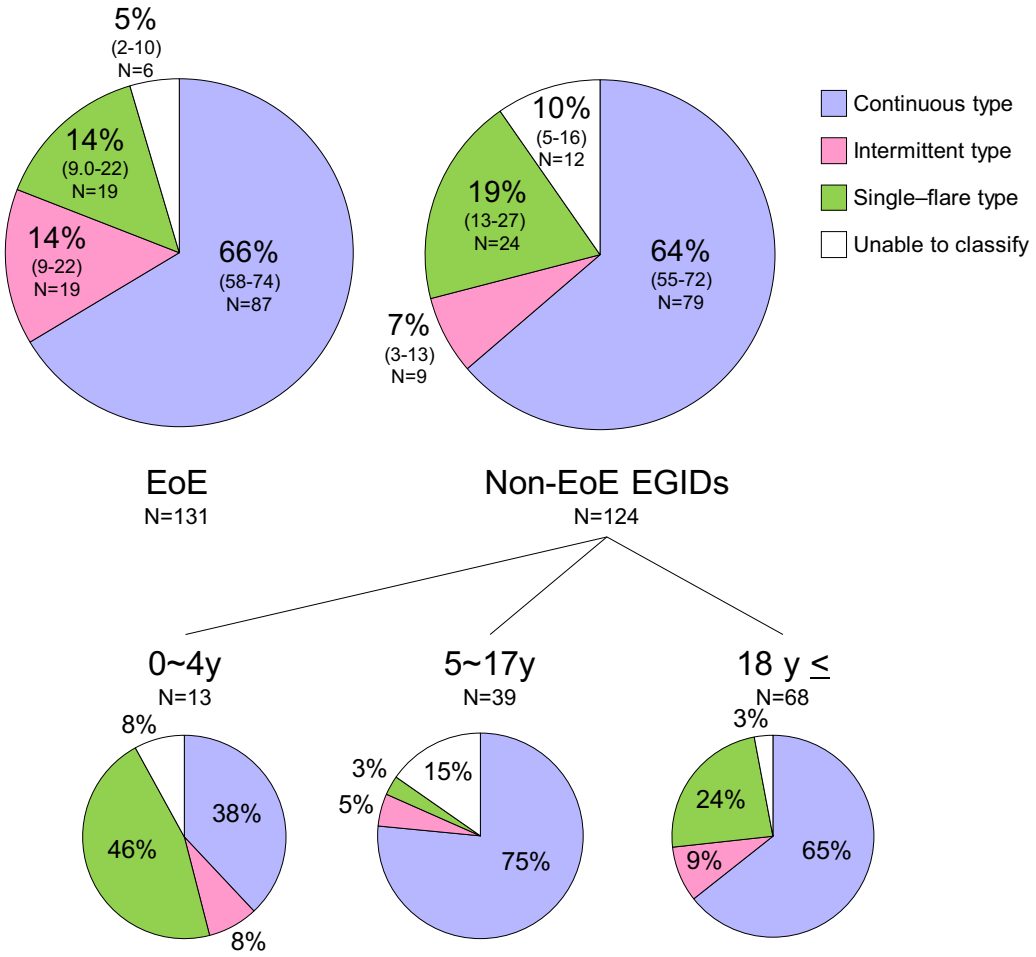

FIGURE 4. The natural histories of EoE and non-EoE EGIDs. The pie chart shows the number of patients and their percentages (95% confidence interval) for each natural history type. Continuous type: duration of symptoms or treatment period ≥6 months. Single-flare type: duration of symptoms and treatment 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 years, 5-17 years, and ≥18 years. *EGIDs*, Eosinophilic gastrointestinal disorders; *EoE*, eosinophilic esophagitis.

Online Repository at www.jaci-inpractice.org). When the childhood years were stratified, the continuous type accounted for 75% of the 5-17 y.o. patients (Figure 4).

Compared with EoE, non-EoE EGIDs had a wider variety of symptoms, with more extensive involvement of the GI tract.[25] 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 criteria[4] 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, as the demographics and natural history were very similar for both "definite (n = 151)" and "probable (n = 325)" patients with non-EoE EGIDs, we do not think that the "definite" patients were biased cases (Table E3, available in this article's Online Repository at www.jaci-inpractice.org). 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 1 field of view of ×400 is often 0.237 mm^2. 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 1 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 6 months. Therefore, patients with a single-flare type who stopped visiting the hospital within 6 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 2 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.

Acknowledgments

We thank the many Japanese doctors who replied to our survey. The facilities that cooperated with the second survey are shown in Table E4 in this article's Online Repository at www.jaci-inpractice.org. We thank Shuichi Ito MD, PhD, Department of Pediatrics, Yokohama City University Graduate ack-School of Medicine, for providing 2 physician-researchers to our research group; Masashi Mikami MSc of the Clinical Research Center for his kind help and critical advice regarding biostatistics; the doctors of the EGIDs research group for their invaluable advice from professional perspectives; and Chihiro Usami and Keiko Sasagawa for their excellent office work.

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ONLINE REPOSITORY

METHODS

First survey: how we selected 10,000 hospitals from 11,117

To stay within the research budget, it was necessary to limit the number of hospitals to 10,000 or less. Excel's table sorted 11,117 facilities by location, north to south. We numbered each facility, from 1 to 11,117. All facilities whose number ended in 5 were deleted. That eliminated 1,112 facilities. Next, 5 facilities with numbers that were multiples of 2000 were deleted. Finally, the first survey was sent to 10,000 facilities.

Distribution of the patients shown on a map of Japan

The number of patients in each prefecture was determined from each patient's address, not from the hospital's address for the definite patients.

RESULTS

Analysis of "probable" EoE and non-EoE EGIDs

"Probable" EoE and non-EoE EGIDs were patients who did not satisfy inclusion criterion 3 (Figure 1 in the main text). They were analyzed for their clinical features (Table E3). However, this "probable group" may contain diseases other than EGID, so care must be taken when interpreting it.

The numbers of patients and the EoE/non-EoE EGID ratios shown on a map of Japan (Figure E1)

Shimane Prefecture had the highest number of patients with EoE (n = 60), whereas Tokyo, which has approximately one-tenth of the national population, had as few as 8 patients. (B) Non-EoE EGID was most common in Gunma Prefecture (n = 40), followed by Aichi and Kagawa Prefectures (n = 16). Tokyo was also low with n = 6. (C) The EoE/non-EoE EGID ratio was calculated only for the prefectures where there were 7 or more cases of each of EoE and non-EoE EGID. Yellow indicates a higher proportion of EoE, whereas green indicates a higher ratio of non-EoE EGID.

There are many hospitals in the Tokyo metropolitan area, and they tend to attract patients from all over Japan. Thus, many patients were reported from hospitals in Tokyo, but most of them had addresses in other prefectures. Okinawa Prefecture did not report any cases of non-EoE EGID, but the ratio was produced by substituting 1 patient.

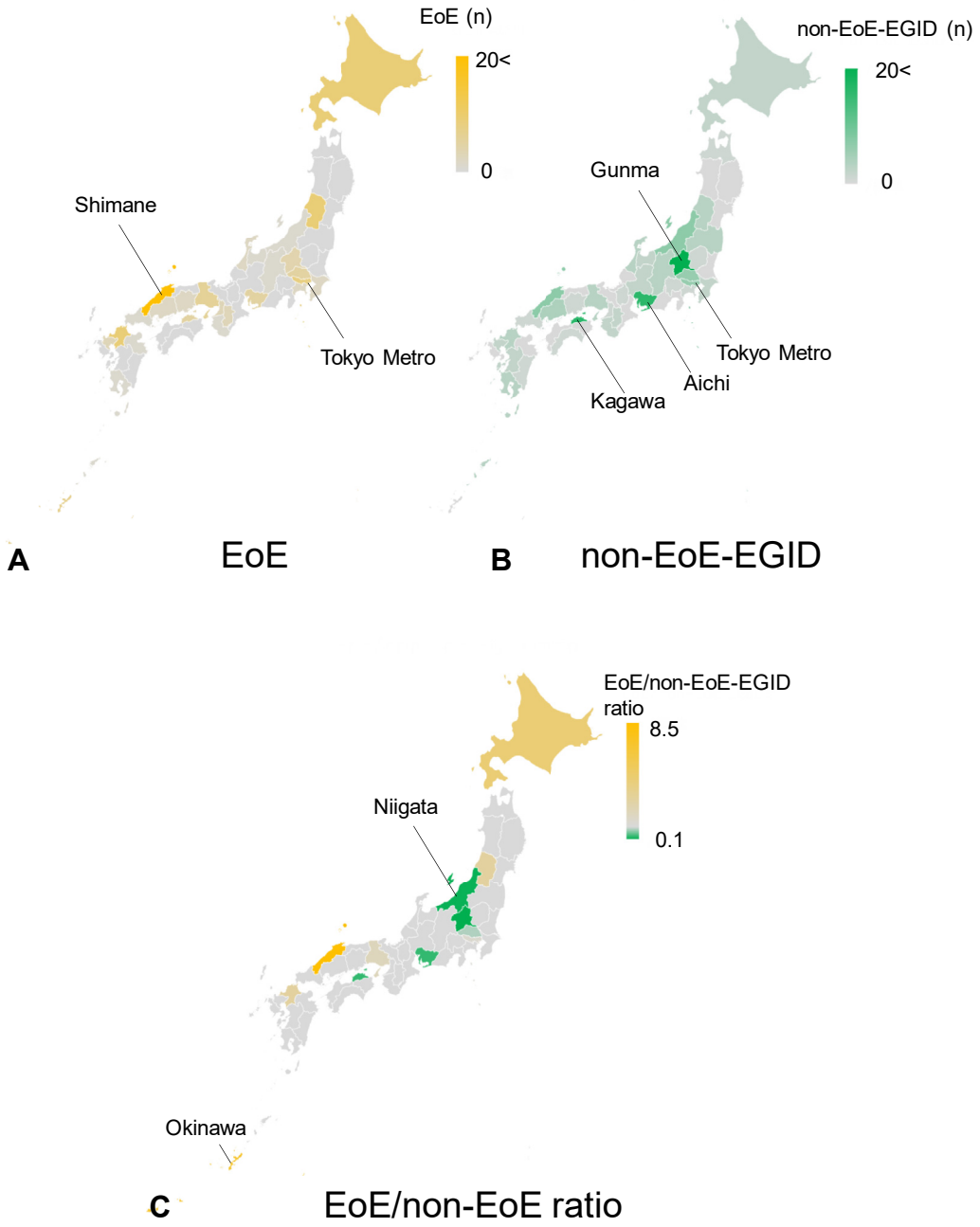

FIGURE E1. The numbers of patients and the EoE/non-EoE EGID ratios shown on a map of Japan. For the definite patients, the number of patients in each prefecture was determined based on each patient's address, not the address of the hospital. (**A**) The number of patients with EoE in each prefecture. (**B**) The number of patients with non-EoE EGIDs in each prefecture. (**C**) EoE/non-EoE EGID ratio.

TABLE E1. Clinical characteristics and treatments of each natural history of non-EoE EGIDs

Characteristic	Continuous type (n = 79)	Single-flare type (n = 24)	Intermittent type (n = 9)	*P* value
Sex, n (%)				
Male	43 (54)	9 (38)	1 (11)	**.04**
Female	34 (43)	14 (58)	7 (78)	
Age at diagnosis (y), median (IQR)	27 (12-43.5)	36 (8.5-53.5)	36 (10-52)	.79
Adult, n (%)	44 (56)	16 (67)	6 (67)	.26
Child, n (%)	35 (44)	7 (29)	3 (33)	
Symptoms, n (%)				
Dysphagia	15 (19)	3 (13)	2 (22)	.72
Vomiting	31 (39)	4 (17)	3 (33)	.12
Abdominal pain	57 (72)	18 (75)	8 (89)	.55
Diarrhea	36 (46)	11 (46)	3 (33)	.78
Bloody stools	10 (13)	5 (21)	3 (33)	.22
Ascites	11 (14)	4 (17)	0 (0)	.44
Restriction of daily life activity	39 (49)	15 (63)	5 (56)	.52
Growth failure, significant weight loss	6 (8)	1 (4)	0 (0)	.60
Laboratory findings				
Blood eosinophilia (>500/μL), n (%)	51 (65)	17 (71)	3 (33)	.13
Eosinophil count (/μL), median (IQR)	856 (341-1,719)	774 (502-1,983)	428 (306-672)	.20
Hypoproteinemia, n (%)*	14 (18)	5 (21)	0 (0)	.35
Eosinophil infiltration site, n (%)				
Esophagus	19 (24)	3 (13)	1 (11)	.36
Stomach	40 (51)	11 (46)	6 (67)	.56
Small intestine	48 (61)	15 (63)	4 (44)	.61
Colon	24 (30)	7 (29)	3 (33)	.97
Long-term administration of systemic glucocorticoids (>12 wk), n (%)	36 (46)	5 (21)	2 (22)	.05
Administration period (m), median (IQR)	29.5 (13.5-62.3)	3.5 (2.6-4.5)	8 (6.5-9.5)	**.005**
Maintenance dose (mg), median (IQR)	5 (2.5-6)	5 (3-12.5)	12.5 (8.8-16.3)	.42

EGIDs, Eosinophilic gastrointestinal disorders; *EoE*, eosinophilic esophagitis; *IQR*, interquartile range.
Bold indicates statistical significance ($P < .05$ [Mann-Whitney *U* test, χ^2 test, or Fisher's exact test]).
*Hypoproteinemia: total protein <6 g/dL or albumin <3 g/dL. Continuous type: duration of symptoms or treatment period ≥6 months. Single-flare type: duration of symptoms and treatment period <6 months, with no relapse. Intermittent type: symptoms relapsed multiple times, but no treatment was given in the periods of remission.

TABLE E2. Clinical characteristics of each natural history type of EoE

Characteristic	Continuous type (n = 87)	Single-flare type (n = 19)	Intermittent type (n = 19)	*P* value
Sex, n (%)				.88
Male	69 (79)	15 (79)	16 (84)	
Female	18 (21)	4 (21)	3 (16)	
Age at diagnosis (y), median (IQR)	46 (38.5-54.5)	48 (39.5-54.5)	44 (38.5-49)	.58
Adult, n (%)	82 (94)	17 (90)	19 (100)	.37
Child, n (%)	5 (6)	2 (11)	0 (0)	
Symptoms, n (%)				
Dysphagia	78 (90)	13 (68)	16 (84)	.057
Sometimes	61 (70)	11 (58)	12 (63)	
Always	15 (17)	1 (5)	4 (21)	
Inability to swallow solid foods	2 (2)	1 (5)	0 (0)	
Vomiting	19 (22)	4 (21)	1 (5)	.25
Abdominal pain	15 (17)	6 (32)	5 (26)	.31
Diarrhea	4 (4)	2 (11)	2 (11)	.46
Activity restriction	13 (15)	3 (16)	1 (5)	.51
Laboratory findings				
Blood eosinophilia (>500/μL), n (%)	21 (24)	4 (21)	3 (16)	.72
Eosinophil count (/μL), median (IQR)	300 (197-497)	272 (148-579)	351 (258-407)	.76
Eosinophil count in esophageal tissue (/HPF), median (IQR)	48 (26-86)	60 (38-97)	63 (39-84)	.39

EoE, Eosinophilic esophagitis; *IQR*, interquartile range.

Continuous type: duration of symptoms or treatment period ≥6 months. Single-flare type: duration of symptoms and treatment period <6 months, with no relapse. Intermittent type: symptoms recurred multiple times, and no treatment was needed during the intervals. Mann-Whitney *U* test, χ^2 test, or Fisher's exact test.

TABLE E3. Clinical characteristics of EoE and non-EoE EGIDs with "probable*" criteria

Characteristic	EoE (n = 157)	non-EoE EGIDs (n = 325)
Sex, n (%)		
Male	121 (78)	164 (52)
Female	35 (22)	154 (48)
Age at diagnosis (y), median (IQR)	45 (38-52)	22.5 (11-46)
Adult, n (%)	150 (97)	166 (52)
Child, n (%)	5 (3)	152 (48)
Symptoms, n (%)		
Dysphagia	33 (21)	34 (10)
Vomiting	10 (6)	90 (28)
Abdominal pain	10 (6)	248 (76)
Diarrhea	3 (2)	173 (53)
Bloody stools	1 (0.6)	64 (20)
Ascites	2 (1)	42 (13)
Activity restriction	8 (5)	199 (61)
Severe complications, n (%)		
Growth failure, significant weight loss	0 (0)	25 (8)
Surgery	2 (1)	5 (2)
Shock	0 (0)	3 (1)
Laboratory findings		
Blood eosinophilia (>500/μL), n (%)	25 (16)	174 (54)
Eosinophil count (/μL), median (IQR)	270 (172-466)	568 (208-2295)
Hypoproteinemia (total protein <6 g/dL, albumin <3 g/dL), n (%)	2 (1)	57 (18)
Abnormal macroscopic findings in endoscopy, n (%)		
Esophagus	153 (97)	28 (9)
Stomach	17 (11)	90 (28)
Small intestine	5 (3)	105 (32)
Colon	3 (2)	86 (26)

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

*"Probable group" may contain diseases other than EGID, so care must be taken when interpreting it.

TABLE E4. Facilities that cooperated with the second survey

Name of facility	Prefecture	Medical department	No. of patients
KKR Sapporo Medical Center	Hokkaido	Gastroenterology	22
Sapporo Medical University Hospital	Hokkaido	Gastroenterology	3
Rumoi City Hospital	Hokkaido	Gastroenterology	2
Sapporo Kyoritsu Gorinbashi Hospital	Hokkaido	Gastroenterology	1
Asahikawa-Kosei General Hospital	Hokkaido	Surgery	1
Abashiri-Kosei General Hospital	Hokkaido	Pediatrics	1
Engaru-Kyosei General Hospital	Hokkaido	Internal medicine	1
Date Red Cross Hospital	Hokkaido	Pediatrics	1
Arai Hospital	Hokkaido	Gastroenterology	1
Nemuro City Hospital	Hokkaido	Internal medicine	1
Aomori Prefectural Central Hospital	Aomori	Gastroenterology	6
Iwate Prefectural Iwai Hospital	Iwate	Gastroenterology	2
Iwate Medical University Hanamaki Onsen Hospital	Iwate	Internal medicine	1
Miyagi Children's Hospital	Miyagi	Gastroenterology	3
Yamagata University Hospital	Yamagata	Gastroenterology	18
Ohara General Hospital	Fukushima	Pediatrics	5
Fukushima Medical University Hospital	Fukushima	Pediatrics	1
Fukushima Seibu Hospital	Fukushima	Surgery	1
Iwaki City Medical Center	Fukushima	Gastroenterology	1
Gunma University Hospital	Gunma	Gastroenterology/Hepatology	40
Gunma Children's Medical Center	Gunma	Allergy infection immunity, respiratory department	25
Takasaki General Medical Center	Gunma	Gastroenterology	2
National Hospital Organization Numata Hospital	Gunma	Surgery	2
Gunma Chuo Hospital	Gunma	Surgery	1
Takasaki Central Hospital	Gunma	Surgery	1
Keiaido Hospital	Gunma	Surgery	1
Saitama Red Cross Hospital	Saitama	Gastroenterology	5
Jichi Medical University Saitama Medical Center	Saitama	Gastroenterology	3
Todachuo General Hospital	Saitama	Pediatrics	2
TMG Asaka Medical Center	Saitama	Surgery	1
Chichibu Hospital	Saitama	Internal medicine	1
Tokorozawa Central Hospital	Saitama	Surgery	1
Park Hospital	Saitama	Internal medicine	1
Seirei Sakura Citizen Hospital	Chiba	Internal medicine	2
Abiko Toho Hospital	Chiba	Gastrointestinal surgery	1
The Jikei University Kashiwa Hospital	Chiba	Gastroenterology/Hepatology	1
Tokyo Metropolitan Children's Medical Center	Tokyo	Gastroenterology	70
NTT Medical Center Tokyo	Tokyo	Gastroenterology	36
National Center for Child Health and Development	Tokyo	Allergy center	19
Tokyo Metropolitan Ohtsuka Hospital	Tokyo	Internal medicine/Gastroenterology	9
Toho University Omori Medical Center	Tokyo	Pediatrics	8
Juntendo University Nerima Hospital	Tokyo	Gastroenterology	2
Musashimurayama Hospital	Tokyo	Gastroenterology	2
Teikyo University Hospital	Tokyo	Pediatrics	1
Juntendo University Nerima Hospital	Tokyo	Pediatrics	1
Nippon Medical School Tama Nagayama Hospital	Tokyo	Pediatrics	1
Minamitama Hospital	Tokyo	Internal medicine	1
Tokai University Hospital	Kanagawa	Gastroenterology	3

(continued)

TABLE E4. *(Continued)*

Name of facility	Prefecture	Medical department	No. of patients
Sagamihara National Hospital	Kanagawa	Pediatrics	3
Fujisawa Shounandai Hospital	Kanagawa	Gastroenterology	2
Kawasaki Municipal Ida Hospital	Kanagawa	Gastroenterology	1
Saiseikai Niigata Hospital	Niigata	Gastroenterology	8
Niigata City General Hospital	Niigata	Pediatrics	6
Nagaoka Red Cross Hospital	Niigata	Pediatrics	4
Uonuma Kikan Hospital	Niigata	Gastroenterology	1
Niigata Prefectural Central Hospital	Niigata	Internal medicine	1
Toyama University Hospital	Toyama	Pediatrics	10
Fujikoshi Hospital	Toyama	Surgery	1
Noto General Hospital	Ishikawa	Internal medicine	10
Yawata Medical Center	Ishikawa	Surgery	8
Kanazawa Jouhoku Hospital	Ishikawa	Pediatrics	1
Kanazawa Jouhoku Hospital	Ishikawa	Internal medicine	1
Kanazawa University Hospital	Ishikawa	Pediatrics	1
Asama General Hospital	Nagano	Pediatrics	10
Iida Municipal Hospital	Nagano	Gastroenterology	5
Ina Central Hospital	Nagano	Gastrointestinal surgery	2
Aizawa Hospital	Nagano	Pediatrics, gastroenterology	1
Gifu Prefectural General Medical Center	Gifu	Gastroenterology	8
Gifu Prefectural General Medical Center	Gifu	Pediatrics	1
Nagara Medical Center	Gifu	Pediatrics	1
Sakashita Clinic	Gifu	Internal medicine	1
Mishima Central Hospital	Shizuoka	Internal medicine	1
Fujita Health University Bantane Hospital	Aichi	Gastroenterology	22
Aichi Children's Health and Medical Center	Aichi	Allergy	9
Handa City Hospital	Aichi	Gastroenterology	7
Nagoya City University Hospital	Aichi	Gastroenterology	5
Fujita Health University Hospital	Aichi	Gastroenterology	3
Nagoya City West Medical Center	Aichi	Gastroenterology	1
Fujita Health University Bantane Hospital	Aichi	Pediatrics	1
Konan Kosei Hospital	Aichi	Gastroenterology	1
Mie Chuo Medical Center	Mie	Gastroenterology	10
National Mie Hospital	Mie	Pediatrics	9
Japanese Red Cross Ise Hospital	Mie	Pediatrics	1
Kohka Public Hospital	Shiga	Gastroenterology	3
University Hospital Kyoto Prefectural University of Medicine	Kyoto	Pediatrics	1
Kenporen Osaka Central Hospital	Osaka	Gastroenterology	3
Osaka General Medical Center	Osaka	Pediatrics	3
Saiseikai Senri Hospital	Osaka	Pediatrics	1
Kansai Medical University Medical Center	Osaka	Pediatrics	1
Nagayoshi General Hospital	Osaka	Internal medicine	1
Kindai University Hospital	Osaka	Pediatrics	1
Hyogo Collage of Medicine Hospital	Hyogo	Gastroenterology	11
Kobe University Hospital	Hyogo	Gastroenterology	5
Itami City Hospital	Hyogo	Pediatrics	2
Toyooka Hospital	Hyogo	Gastroenterology	1
Nara Prefecture Seiwa Medical Center	Nara	Gastroenterology	7
Kindai University Nara Hospital	Nara	Pediatrics	3
Nara Prefecture Seiwa Medical Center	Nara	Pediatrics	1
Nara Medical University Hospital	Nara	3rd Department of Internal Medicine	1
Kinan Hospital	Wakayama	Gastroenterology	7
Wakayama Rosai Hospital	Wakayama	Gastroenterology	3
Tottori University Hospital	Tottori	Medicine and clinical science	4

(continued)

TABLE E4. *(Continued)*

Name of facility	Prefecture	Medical department	No. of patients
Tottori University Hospital	Tottori	Pediatrics	2
Tottori Medical Center	Tottori	Pediatrics	1
Shimane University Hospital	Shimane	Gastroenterology	100
National Hospital Organization Hamada Medical Center	Shimane	Gastroenterology	2
Oda Municipal Hospital	Shimane	Gastroenterology	1
Akaiwa Medical Association Hospital	Okayama	Internal medicine	2
Tsuyama Chuo Hospital	Okayama	Pediatrics	1
National Hospital Organization Fukuyama Medical Center	Hiroshima	Gastroenterology	9
Hiroshima City Asa Citizens Hospital	Hiroshima	Gastroenterology	4
Miyoshi Central Hospital	Hiroshima		3
Hiroshima Red Cross Hospital and Atomic-bomb Survivors Hospital	Hiroshima	Pediatrics	1
Yamaguchi Rosai Hospital	Yamaguchi	Gastroenterology	2
Ajisu Dohjin Hospital	Yamaguchi		1
Saiseikai Shimonoseki General Hospital	Yamaguchi	Pediatrics	1
Itsuki Hospital	Tokushima	Internal medicine	1
Kagawa Prefectural Central Hospital	Kagawa	Gastroenterology	24
Kagawa University Hospital	Kagawa	Pediatrics	4
Oozora Hospital	Ehime	Internal medicine	1
Saiseikai Matsuyama Hospital	Ehime	Internal medicine	1
Uwajima Tokushukai Hospital	Ehime	Surgery	1
Kochi Health Sciences Center	Kochi	Pediatrics	1
Kochi Medical School Hospital	Kochi	Pediatrics	1
Fukuoka Sanno Hospital	Fukuoka	Gastroenterology	47
Fukuoka University Chikushi Hospital	Fukuoka	Gastroenterology	6
Wakamatsu Hospital of the University of Occupational and Environmental Health	Fukuoka	Gastroenterology	1
Akimoto Hospital	Fukuoka	Gastrointestinal surgery	1
Abe Hospital	Fukuoka		1
Karatsu Red Cross Hospital	Saga	Internal medicine	4
Karatsu Red Cross Hospital	Saga	Pediatrics	1
Saiseikai Karatsu Hospital	Saga	Internal medicine	1
St.Mary Hospital	Nagasaki	Internal medicine	1
Kumamoto University Hospital	Kumamoto	Gastroenterology	5
Musashigaoka Hospital	Kumamoto	Gastroenterology	1
Arita GI Hospital	Oita	Gastroenterology	5
Miyazaki Konan Hospital	Miyazaki	Internal medicine	1
Miyazaki Prefectural Nobeoka Hospital	Miyazaki	Pediatrics	1
Kagoshima University Hospital	Kagoshima	Gastroenterology	7
Saiseikai Sendai Hospital	Kagoshima	Gastroenterology	4
Kagoshima City Hospital	Kagoshima	Pediatrics	1
Ryusei Hospital	Okinawa	Internal medicine	8