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ORIGINAL ARTICLE

The impact of COVID-19 on Japanese patients with eosinophilic gastrointestinal disorders during the vaccination era

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Abstract

Background: Eosinophilic gastrointestinal disorders (EGIDs) are chronic allergic diseases categorized as eosinophilic esophagitis (EoE) and non-EoE EGIDs. Few studies regarding the association between EGIDs and coronavirus disease 2019 (COVID-19) have been reported. Although most Japanese individuals received the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine, the incidence of COVID-19 remained high in 2022. This study examines the incidence of COVID-19 in patients with EGIDs during the vaccination era.
Methods: Patients with EGIDs who visited our department between October and December 2022 were enrolled in the study. The incidence and severity of COVID-19 prior to October 1, 2022 were determined. Patients who reported having COVID-19 also reported their hospitalization history, intensive care unit admissions, and EGID flares. The number of SARS-CoV-2 vaccinations received and treatment for EGIDs were obtained from the patients' medical records.
Results: Of 111 patients with EGIDs (65 with EoE and 46 with non-EoE EGIDs) included in this study, 31 (28%) patients reported having COVID-19, including 14 (22%) with EoE and 17 (37%) with non-EoE EGIDs. Fifty-nine (84%) patients received two or more vaccinations, and 11 (16%) patients received no vaccinations. COVID-19 was mild in all but one patient who had moderate symptoms. COVID-19 was not associated with EGID flares. EGID treatments and an unvaccinated status were not associated with an increased risk of COVID-19.
Conclusion: COVID-19 was mild in patients with EGIDs and not associated with EGIDs flares during the vaccination era. There was a relatively high incidence of COVID-19 among patients with non-EoE EGIDs.

Introduction

Eosinophilic gastrointestinal disorders (EGIDs) are chronic, immune-mediated allergic diseases characterized by marked eosinophilic infiltration of the gastrointestinal tract and symptoms such as dysphagia, heartburn, abdominal pain, nausea/vomiting, and diarrhea.[1–5] EGIDs can be divided into eosinophilic esophagitis (EoE) and non-eosinophilic esophagitis (non-EoE) EGIDs, including eosinophilic gastritis (EoG), eosinophilic duodenitis (EoD), eosinophilic enteritis (EoN), and eosinophilic colitis (EoC).[6] The incidence and prevalence of EoE have been increasing in Western and Asian countries, including Japan.[3,7,8] However, the incidence and prevalence of non-EoE EGIDs are low.[3,5,8] EoE and non-EoE EGIDs have a similar pathogenesis including a type 2 inflammatory response,[5,9] and EGID treatments include acid-suppressive drugs such as proton pump inhibitors (PPIs) and potassium competitive acid blockers (P-CABs),

systemic or topical corticosteroid therapy, an elimination diet, anti-allergic agents such as montelukast, and biologics.[2–5,10]

Since January 2020, more than 21 million people have been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and approximately 44 000 have died of coronavirus disease 2019 (COVID-19) in Japan as of September 2022.[11] COVID-19 affects public health, and risk factors for severe outcomes of COVID-19 include older age, obesity, chronic lung disease, and diabetes.[12,13] Since the SARS-CoV-2 vaccine was introduced, the global incidence and mortality rate of COVID-19 have decreased. However, in 2022, the incidence of COVID-19 in Japan remained high[11] and affected social activities.

Associations between COVID-19 and gastrointestinal diseases including inflammatory bowel disease (IBD)[14,15] have been reported, although few reports regarding COVID-19 in patients with EGIDs[16,17] have appeared. No study regarding COVID-19 in patients with EGIDs has been performed in Japan. We examined the incidence of COVID-19 among Japanese patients with EGIDs during the vaccination era.

Methods

Patients. Patients who visited our department between October and December 2022, were diagnosed with EGIDs, and continuously underwent treatment were included. Patients diagnosed as having EGIDs after October 2022 were excluded from the study. The study protocol was approved by the Ethics Committee of Osaka Metropolitan University Graduate School of Medicine (protocol number: 2020-151) and was performed in accordance with the principles of the Declaration of Helsinki. The study information was disclosed on the department's website, and patients had the opportunity to opt out.

Definition of EGIDs. The diagnosis of EGIDs was based on the international criteria for EoE[1–3] and the criteria of the Japan Intractable Disease Information Center for eosinophilic gastroenteritis.[3–5] EoE was defined based on esophageal symptoms, such as dysphagia, food impaction, or heartburn, paired with eosinophil infiltration of the esophageal mucosa of ≥15 eosinophils/high-power field (eos/hpf).[1–3] Non-EoE EGIDs were diagnosed when pathological eosinophil infiltration of ≥20 eos/hpf was observed in the stomach, duodenum, small intestine, or colon via biopsy paired with gastrointestinal symptoms including nausea/vomiting, abdominal pain, or diarrhea.[3–5] Secondary causes of tissue eosinophilia were excluded during the diagnosis of EGIDs. EGIDs were divided into EoE and non-EoE EGIDs, including EoG, EoD, EoN, and EoC, based on the location of eosinophil infiltration.[6]

COVID-19 and SARS-CoV-2 vaccination. Patients reported diagnoses of COVID-19, which were confirmed via nasopharyngeal swab-based polymerase chain reaction or an antigen-based test prior to October 1, 2022. Patients who reported having COVID-19 also reported the onset, severity, symptoms (such as fever, throat pain, fatigue, cough, and anosmia/ageusia), hospitalization history, intensive care unit admissions, breakthrough infection, and EGID flares. The number of SARS-CoV-2 vaccinations received prior to October 1, 2022 and EGID treatments were recorded from the patients' medical records.

Data collection. The patients' clinical characteristics and EGID-related treatments were obtained from their medical records. Patient demographics included age, sex, body mass index (BMI), alcohol consumption, smoking habits, allergic diseases, and comorbidities (including diabetes mellitus, hypertension, hyperlipidemia, cancer, chronic lung disease, chronic kidney disease, and cerebrovascular disease). EGID symptoms, peripheral eosinophil counts, and EGID-related treatments (including PPI/P-CAB, systemic or topical corticosteroids, an elimination diet, and montelukast) were also collected from the medical records. EGID-related treatments were defined as those administered when COVID-19 was diagnosed or at any time during the past 1 year if COVID-19 was not diagnosed.

Statistical analysis. Data are expressed as number and percentage, mean and standard deviation (SD), or median and interquartile range. Statistical analyses of the categorized values were performed using Fisher's exact test, and multiple logistic regression analysis was used to determine the factors associated with COVID-19 in patients with EGIDs. The factors were divided into sex (male or female); EGID type (EoE or non-EoE EGIDs); absence or presence of hypertension or chronic kidney disease; SARS-CoV-2 vaccination status; and use of PPI/P-CAB, montelukast, or systemic or topical corticosteroids. The 95% confidence interval (CI) was calculated for each odds ratio (OR). Statistical significance was set at $P = 0.05$. All statistical analyses were performed using R software (version 3.6.2; The R Foundation for Statistical Computing).

Results

Patients. Of the 111 patients included in the study, 66 (59%) had EoE and 46 (41%) had non-EoE EGIDs (Table 1). None of the patients canceled their hospital visits during the study period. Ninety-one (82%) patients had allergic diseases, including atopic dermatitis ($n = 11$), asthma ($n = 25$), allergic rhinitis ($n = 33$), hay fever ($n = 55$), and food allergies ($n = 27$). Comorbidities included diabetes ($n = 14$), hypertension ($n = 14$), hyperlipidemia ($n = 10$), and chronic kidney disease ($n = 3$). Other comorbidities included cerebellar vascular disease ($n = 1$), autoimmune hepatitis ($n = 1$), immunoglobulin G4-related disease ($n = 1$), eosinophilic dermatitis ($n = 1$), eosinophilic granular polyangiitis ($n = 1$), chronic myeloid leukemia ($n = 1$), and idiopathic thrombocytopenia ($n = 1$). No chronic lung disease was observed. Ninety-one (82%) patients were treated with PPI/P-CAB, 18 (16%) with systemic corticosteroids (1–20 mg prednisolone/day), nine (8%) with topical corticosteroids (100–800 μg fluticasone/day), and 26 (23%) with montelukast (10 mg/day). All patients with EGIDs were categorized as having clinical remission.

Two or more SARS-CoV-2 vaccinations (Corminaty or COVID-19 Vaccine Moderna) were received by 97 (87%) patients, whereas no SARS-CoV-2 vaccination was received by 14 (13%) patients. Among the 97 patients who received vaccinations, there was no severe adverse event, such as anaphylaxis.

Table 1 Patient characteristics

	$n = 111$
Age	47.8 ± 14.8
Sex, male	50 (45%)
BMI (kg/m^2)	23.8 ± 4.5
Alcohol consumption	26 (23%)
Active smoker	12 (11%)
EoE	65 (59%)
Non-EoE EGIDs (EoG/EoD/EoN/EoC)	46 (17/24/7/19*)
Allergic diseases	91 (82%)
Comorbidities	
Diabetes mellitus	14 (13%)
Hypertension	14 (13%)
Hyperlipidemia	10 (9%)
Chronic kidney diseases	3 (3%)
Others	7 (6%)
Symptoms	
Dysphagia/food impaction	42 (38%)
Reflux symptoms	23 (21%)
Abdominal pain	43 (39%)
Diarrhea	16 (14%)
Nausea/vomiting	13 (12%)
Peripheral eosinophil counts, per μl	357 [167–653]
Number of vaccinations, none/1/2/≥3	14/0/15/82
Treatments	
Systemic steroid therapy	18 (16%)
Topical steroid therapy	9 (8%)
PPI/P-CAB	91 (82%)
Montelukast	26 (23%)

*Includes 14 with EoG and EoD; 3 with EoG, EoD, and EoC; 3 with EoD and EoN; and 1 with EoN and EoC.
Data are presented as number (%) or mean ± standard deviation.
BMI, body mass index; EGIDs, eosinophilic gastrointestinal disorders; EoC, eosinophilic colitis; EoD, eosinophilic duodenitis; EoE, eosinophilic esophagitis; EoG, eosinophilic gastritis; EoN, eosinophilic enteritis; P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor.

Incidence of COVID-19 and patient characteristics. Seven peaks of COVID-19 were detected between January 2020 and September 2022 in Japan (Fig. 1). Thirty-one (28%) patients reported having COVID-19 prior to the study, including two who were diagnosed in September 2021 during the fifth wave of the pandemic and 29 who were diagnosed in 2022 during the sixth or seventh wave of the pandemic. The incidence of COVID-19 in patients with non-EoE EGIDs (37%) was higher than in patients with EoE (22%), although the difference was not statistically significant ($P = 0.083$) (Fig. 2). Fever was reported by most patients (81%) with COVID-19, followed by throat pain (42%) and fatigue (26%) (Table 2). The severity of COVID-19 was mild in 30 patients and moderate in 1 patient. Two patients reported hospitalization, one with moderate symptoms who had pneumonia but did not require oxygen, and one with comorbidities. No intensive care unit admissions were reported. Twenty-six (84%) patients who reported COVID-19 diagnoses received two or more vaccinations, while five (16%) patients received no vaccinations.

One patient with COVID-19 had transient diarrhea, though no EGID flares were observed at the time of diagnosis.

No patients with EoE canceled endoscopic examinations due to COVID-19, and no patient developed esophageal stricture or other symptoms as a result of canceled endoscopy.

Factors associated with COVID-19. Patients with non-EoE EGIDs had a relatively high crude OR (2.14) and multiple-adjusted OR (1.90) compared to those with EoE (Table 3). Systemic corticosteroid therapy, topical corticosteroid therapy, PPI/P-CAB use, and an unvaccinated status were not associated with COVID-19.

Discussion

In this study, 31 (28%) patients with EGIDs reported COVID-19 diagnoses that occurred prior to October 1, 2022. Ninety-seven (87%) patients received two or more vaccinations. Thirty (97%) patients with COVID-19 reported mild symptoms, while one reported moderate symptoms. No EGIDs flares were associated with COVID-19. A higher incidence of COVID-19 was observed in patients with non-EoE EGIDs than in those with EoE, though no factors were found to be associated with COVID-19. These findings suggest that EGIDs and their treatments do not affect COVID-19 infection and are not associated with severe outcomes of COVID-19 or EGID flares.

Associations between EGIDs and COVID-19 have been reported in previous studies. Three studies conducted in Italy during the initial pandemic period with a high mortality rate failed to identify COVID-19 with EGIDs,[18–20] suggesting that the Th-2 inflammatory response or peripheral eosinophils may protect against SARS-CoV-2 infection. Since the first case of an EoE patient with COVID-19 was reported,[21] two studies regarding COVID-19 in patients with EGIDs have been conducted. Qeadan reported that the in-hospital mortality rate was lower among patients with EGIDs who were exposed to or positive for COVID-19 than among matched controls.[16] The Surveillance Epidemiology of Coronavirus Under Research Exclusion for EoE/EGID database includes 94 patients with COVID and EGIDs. EoE was observed in 80% of the patients, with a median age of 21 years, and clinical remission was observed in 54% of the patients. PPI was administered to 52% of patients, topical corticosteroid therapy to 51% of patients, and systemic corticosteroids to 2% of patients, and an elimination diet was prescribed in 36% of patients. COVID-19 infection was mild in 70% of patients, asymptomatic in 15%, moderate in 12%, and severe in 2%. Three patients were hospitalized and none required intensive care unit admission. No patient died. One patient had an EGID flare.[17] The authors concluded that patients with EGIDs may not have an increased risk of severe COVID-19 and that COVID-19 does not lead to EGID flares.[17]

Although no clear associations between severe outcomes of COVID-19 and EGDIs were identified in the current study or in previous reports, this study has several strengths. First, the study period included the vaccination era. Second, the proportion of patients with non-EoE EGIDs who were administered systemic steroids was higher in our study. As this is the first study regarding the association between COVID-19 and EGIDs in Japan, it provides important clinical data.

The Ministry of Health, Labor, and Welfare reported approximately 21 million cases of COVID-19 as of the end of

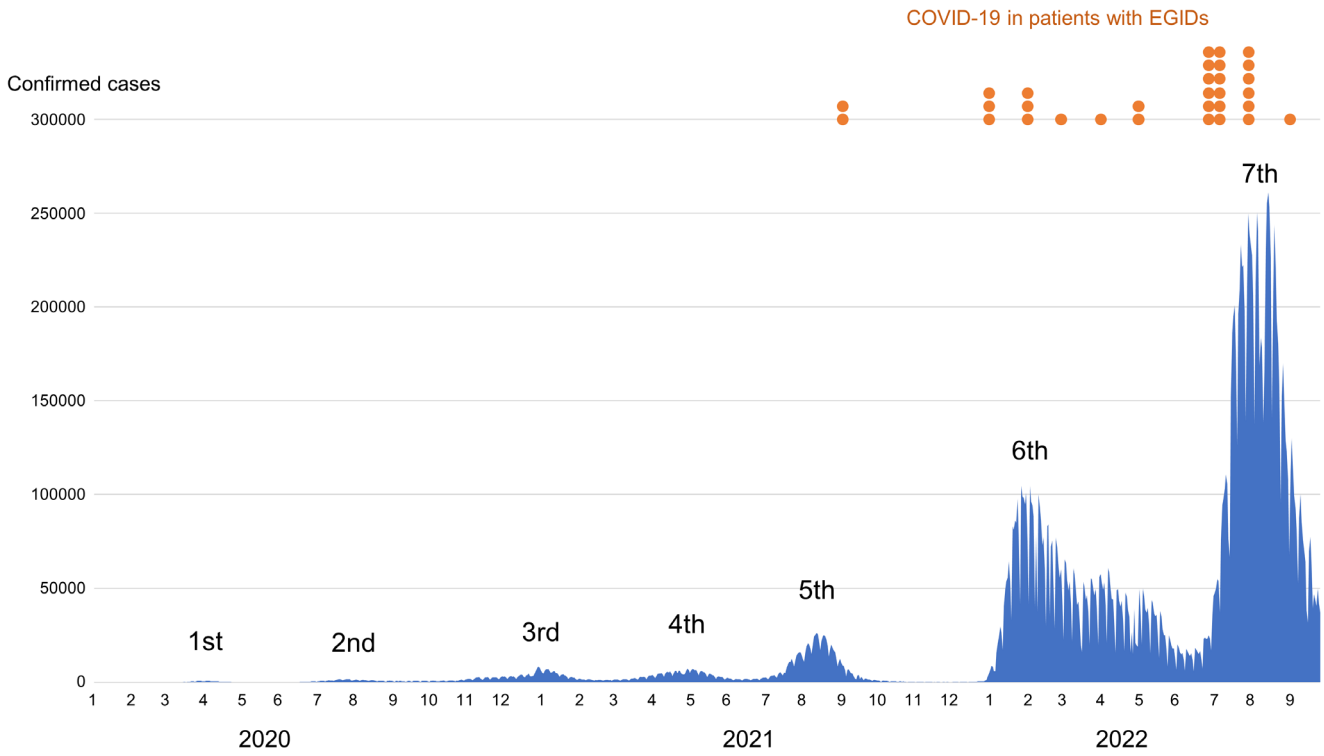

Figure 1 Incidence of coronavirus disease 2019 (COVID-19) in Japan and onset of COVID-19 in the current study. Seven waves of the COVID-19 pandemic have been observed in Japan. The orange circles represent the patients with eosinophilic gastrointestinal disorders (EGIDs) diagnosed as having COVID-19. The onset was during the fifth wave in 2021 in two patients and during the sixth and seventh waves in 2022 in 29 patients.

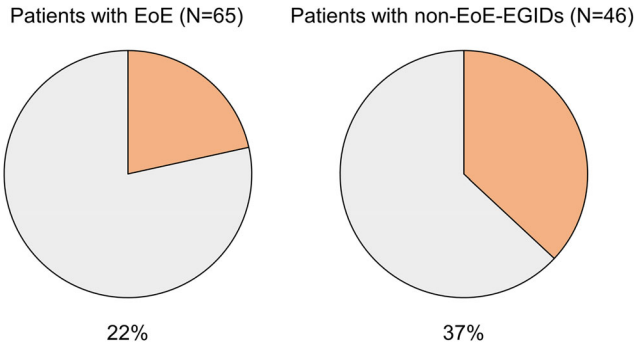

Figure 2 Incidence of coronavirus disease 2019 (COVID-19) in patients with eosinophilic esophagitis (EoE) and non-eosinophilic esophagitis eosinophilic gastrointestinal disorders (non-EoE EGIDs). A higher incidence of COVID-19 was observed in patients with non-EoE EGIDs than in those with EoE. , COVID-19+; , COVID-19−.

September 2022[11]; therefore, approximately 16% of the general Japanese population had been diagnosed with COVID-19. The higher incidence of COVID-19 in the current study (28%) may be due to the fact that patients with EGIDs may prefer to be tested for SARS-CoV-2.

Ninety-seven (87%) patients with EGIDs were vaccinated for SARS-CoV-2, and 73% received at least three vaccinations, suggesting that patients with EGIDs desired the SARS-COV-2 vaccination despite their allergic comorbidities. Approximately 77% of Japanese individuals received the SARS-CoV-2 vaccination at least twice, including 68% who received it at least three times as of the end of September 2022.[22] Therefore, the vaccination rates among patients with EGIDs are similar to those of the general population.

In the current study, the incidence of COVID-19 in patients with non-EoE EGIDs was higher than that in patients with EoE. However, the cause of this finding remains unknown. The human receptor for SARS-COV-2, angiotensin converting enzyme-2 (ACE2), is expressed in several human tissues including the gastrointestinal tract.[23,24] Binding of the SARS-CoV-2 spike protein to ACE2 and proteolytic cleavage by transmembrane serine protease 2 (TMPRSS2), a cellular serine protease, facilitates the virus' entry into cells.[23] Therefore, the SARS-CoV-2 virus may penetrate the enterocytes of patients with non-EoE EGIDs. However, Chiang et al. reported that the expressions of ACE2 and TMPRSS2 were low in the esophagus of patients with EoE[25]; however, they did not examine the expressions of ACE-2 and TMPRSS2 in the inflamed or non-inflamed intestinal mucosa of patients with non-EoE EGIDs. Therefore, additional studies are necessary.

No factors associated with COVID-19 were identified in this study. However, the association between COVID-19 and EGID treatments have been reported, including those between EGID treatments and SARS-CoV-2 infection or severe outcomes of COVID-19. PPI use has been reported as a risk factor for SARS-CoV-2 infection or severe COVID-19[26]; however, this

Table 2 Characteristics of patients with COVID-19

	$n = 31$
Onset of COVID-19	
Fifth wave	2 (6%)
Sixth wave	10 (32%)
Seventh wave	19 (61%)
Breakthrough infection	26 (84%)
COVID-19 symptoms	
Fever	25 (81%)
Throat pain	13 (42%)
Fatigue	8 (26%)
Cough	5 (16%)
Anosmia and ageusia	5 (16%)
Diarrhea	1 (3%)
Severity of COVID-19	
Mild	30 (97%)
Moderate	1 (3%)
Severe	0 (0%)
Hospitalization	2 (6%)
Intensive care admission	0 (0%)
EGIDs flares	0 (0%)

COVID-19, coronavirus disease 2019; EGIDs, eosinophilic gastrointestinal disorders.

association is controversial, and a meta-analysis confirmed no clear evidence of a positive association between SARS-CoV-2 infection or severe COVID-19 and PPIs.[27,28] Corticosteroid use affects SARS-CoV-2 infection and the severity of COVID-19 in patients with IBD.[14,15] Therefore, several IBD guidelines recommend the administration of prednisolone (≤20 mg).[29,30] In this study, a low dose of prednisolone administered due to clinical remission of EGIDs may have affected the association between COVID-19 and EGIDs. In contrast, inhaled steroids were not associated with COVID-19 outcomes in patients with bronchial asthma.[31,32] Although biologics are not available in Japan, eosinophil depletion drugs may affect the clinical course of COVID-19 as peripheral eosinophils may protect against SARS-CoV-2 infection or severe COVID-19.[33] Taken together, there is no clear evidence that EGID treatments are associated with SARS-CoV-2 infection or COVID-19 severity.

Table 3 Factors associated with COVID-19 in patients with eosinophilic gastrointestinal disorders (EGIDs)

	Crude OR (95% CI)	*P*-value	Multi-adjusted OR (95% CI)*	*P*-value
Age	1.00 (0.97–1.02)	0.724		
Male gender	0.70 (0.30–1.63)	0.405		
Non-EoE EGIDs	2.14 (0.92–4.95)	0.077	1.90 (0.71–5.07)	0.200
Hypertension	1.52 (0.47–4.95)	0.489		
Chronic kidney disease	1.30 (0.11–14.9)	0.833		
Vaccination	0.66 (0.20–2.15)	0.489		
PPI/P-CAB	0.73 (0.26–2.02)	0.541		
Topical corticosteroids	0.30 (0.04–2.50)	0.266	0.38 (0.04–3.27)	0.378
Systemic corticosteroids	1.83 (0.64–5.26)	0.262	1.10 (0.33–3.79)	0.864
Montelukast	1.52 (0.59–3.89)	0.387		

*OR adjusted for non-EoE EGIDs, topical corticosteroids, and systemic corticosteroids.

CI, confidence interval; Non-EoE EGIDs, non-eosinophilic esophagitis eosinophilic gastrointestinal disorders; OR, odds ratio; P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitor.

This study is not without limitations. First, this was a single-center study and the number of patients was low due to the rarity of EGIDs. However, this is the first study to evaluate COVID-19 in more than 100 patients with EGIDs. Second, patients with COVID-19 are often asymptomatic.[34] Patients with asymptomatic COVID-19 may have been missed in this study. Third, several studies have shown the psychological impact of COVID-19 in patients with chronic diseases, such as inflammatory bowel diseases.[35–37] However, no data are available on this issue.

Conclusion

In conclusion, patients with EGIDs who are diagnosed with COVID-19 have mild symptoms, and a diagnosis of COVID-19 was not associated with EGID flares during the vaccination era. Non-EoE EGIDs may be associated with an increased susceptibility to COVID-19.

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