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ORIGINAL ARTICLE

Correlation between anxiety and decreased quality of life in patients with non-esophageal eosinophilic gastrointestinal diseases

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Abstract

Background and Aim: Mental status such as anxiety and depression in patients with non-esophageal eosinophilic gastrointestinal diseases (non-EoE EGIDs) has not been studied. The aim of this study was to evaluate whether patients with non-EoE EGIDs had mental disorders and decreased mental-health-related quality of life (QOL) similar to those in patients with disorders of gut–brain interaction (DGBI).
Methods: We enrolled patients with non-EoE EGIDs and DGBI visiting the Osaka Metropolitan University Hospital, and the measures listed below were compared between the groups. We collected data using the following questionnaires: hospital anxiety and depression scale, and short form (SF)-8 including mental component summary (MCS)-8.
Results: We evaluated 21 and 17 patients with non-EoE EGIDs and DGBI, respectively. The anxiety score was not significantly different between the groups. The proportion of patients with possible anxiety was not significantly different between the groups (19.0% *vs* 33.3%). These results show that patients with non-EoE EGIDs had anxiety that might be equivalent to that of patients with DGBI. The depression score and proportion of patients with possible depression in the non-EoE EGID group tended to be lower than those in the DGBI group. MCS-8 scores were not significantly different between the non-EoE EGID and DGBI groups, which might imply an equivalent decrease in mental-health-related QOL in both groups of patients. In patients with non-EoE EGIDs, the anxiety score had a significant inverse association with the MCS-8 score.
Conclusions: Patients with non-EoE EGIDs may have anxiety that correlates with decreased mental-health-related QOL.

Introduction

Eosinophilic gastrointestinal diseases (EGIDs) are chronic allergic diseases of the gastrointestinal (GI) tract and involve pathological eosinophilic infiltration.[1] EGIDs are divided into two subtypes: eosinophilic esophagitis (EoE) and non-EoE EGIDs.[2] In non-EoE EGIDs, the stomach, small intestine, and colon are involved. In patients with non-EoE EGIDs, type 2 helper T-cell (Th2)-mediated immune response including the activation of eosinophils and mast cells leads to clinical symptoms such as nausea, vomiting, abdominal pain, and diarrhea. Food allergens are the triggers of inflammatory response; however, the exacerbating factors of non-EoE EGIDs have not yet been studied.

In other allergic diseases such as bronchial asthma, atopic dermatitis, and allergic rhinitis, psychological stress is one of exacerbating factors.[3–5] We recently reported that in a mouse model of non-EoE EGIDs, psychological stress exacerbated eosinophilic enteritis (EoN) via the corticotropin-releasing hormone (CRH)–mast cell axis and increased ileal permeability.[6] Anxiety disorders are one of the background characteristics that lead to the generation of hypersensitivity to psychological stress. In the GI tract, psychological stress increases peripheral CRH mainly released by eosinophils as a consequence of neuroimmune reactions.[7,8] CRH activates mast cells and induces degranulation by binding to the CRH receptor on mast cells, which can lead to increased intestinal permeability,[9] which has the potential to increase the flux of food allergens into the mucosa, exacerbating EGIDs.

In disorders of gut–brain interaction (DGBI), psychological stress is a well-known exacerbating factor, which is associated with anxiety and depression. The representative diseases of DGBI are irritable bowel syndrome (IBS) and functional dyspepsia (FD). A previous systematic review showed that the

prevalence of depression or anxiety was higher in patients with FD compared to healthy controls.[10] The quality of life (QOL) is reduced in IBS as well as in FD, and anxiety and depression are particularly associated with a lower QOL.[11,12] Accordingly, we hypothesized that mental disorders such as anxiety and depression might be associated with non-EoE EGIDs similar to DGBI. To the best of our knowledge, there are very few studies that report on the mental status of patients with non-EoE EGIDs. Only one report found that concomitant psychiatric diseases such as anxiety and depression were common in patients with non-EoE EGIDs evaluated in the United States.[13] Moreover, there is no comparative study investigating the mental status of patients with non-EoE EGIDs and DGBI. The aim of this study was to evaluate whether patients with non-EoE EGIDs have anxiety and depression and decreased mental-health-related QOL similar to patients with DGBI.

Methods

Study design and participants. This was a single-center, retrospective observational study. We enrolled consecutive patients with non-EoE EGIDs and DGBI visiting the Osaka Metropolitan University Hospital between November 2021 and July 2022, and the parameters listed below were compared between the groups. The inclusion criteria were as follows: outpatients suffering from non-EoE EGIDs and DGBI, above 20 years of age, and answered the questionnaires. The exclusion criteria were as follows: history of abdominal surgery, patients who were enrolled in other clinical trials, patients who did not undergo endoscopy and biopsy, not available for filling the questionnaire, and missing data in the questionnaire. Patients with eosinophilic infiltration of the GI tract due to other diseases such as parasitic infection, autoimmune disorders, including eosinophilic granulomatosis with polyangiitis, inflammatory bowel diseases, hypereosinophilic syndrome, and drug hypersensitivity reaction were also excluded.

The following information was obtained from the medical records as background characteristics: age, gender, body mass index (BMI), duration of sleep, current cigarette smoking status (presence or absence), current alcohol drinking status (presence or absence), disease duration, outpatient period, and concomitant allergic diseases such as allergic rhinitis, bronchial asthma, and atopic dermatitis. We also obtained information about medications received such as systemic, swallowed topical, and inhaled steroids, thioprine, montelukast, histamine H_1 receptor antagonists (H_1RA), histamine H_2 receptor antagonists (H_2RA), proton pump inhibitors (PPI), potassium competitive acid blockers (P-CAB), prokinetics, 5-hydroxytryptamine 3 (5-HT_3) receptor antagonists, loperamide, laxatives, probiotics, benzodiazepines, 5-hydroxytryptamine 1A (5-HT_{1A}) receptor agonists, and noradrenergic and specific serotonergic antidepressants (NaSSAs). Chronic maintenance treatment was defined as EGID-directed and/or DGBI-directed therapy for ≥1 year.

Questionnaires to evaluate anxiety, depression, health-related QOL, and clinical symptoms. We collected data using the following questionnaires and compared the results between the groups: hospital anxiety and depression scale (HADS) and short form (SF)-8 including physical component summary (PCS)-8 and mental component summary (MCS)-8 to evaluate health-related QOL. On the HADS, a score ≥11 was considered possible anxiety and/or depression. Furthermore, a score ≥8 was considered probable anxiety and/or depression. Clinical symptoms were evaluated by the modified frequency scale for gastroesophageal reflux disease (mFSSG) and the gastrointestinal symptom rating scale (GSRS).

Definition of non-EoE EGIDs. Patients with non-EoE EGIDs were those who had pathological eosinophilic infiltration with more than 20/high power field (HPF) (×400) in the biopsy specimens from the GI tract except the esophagus, and GI symptoms which were relevant to the organs that demonstrated eosinophilic infiltration.[14] Patients who had symptoms derived from the upper GI tract, such as nausea, vomiting, and epigastralgia, underwent esophagogastroduodenoscopy (EGD). Patients who had symptoms derived from the lower GI tract, such as diarrhea and lower abdominal pain, underwent colonoscopy (CS). Only one patient underwent double balloon enteroscopy to evaluate the diseases in the small intestine. During endoscopy, biopsy specimens were taken and eosinophil counts were carried out by institutional pathologists. All patients with EGIDs had undergone endoscopy within 2 years of answering the questionnaires. Non-EoE EGIDs were divided into subtypes based on the organs involved with abnormal eosinophils as follows: eosinophilic gastritis (EoG), eosinophilic duodenitis (EoD), EoN including jejunitis (EoJ) and ileitis (EoI), and eosinophilic colitis (EoC).[2] Non-EoE EGIDs patients with eosinophilic infiltration of more than 15/HPF were defined as having "eosinophilic involvement" as well as the definition of EoE.[15,16]

Definition of DGBI. DGBI were diagnosed using the Rome IV criteria. DGBI were divided into subtypes as follows: nonerosive reflux disease (NERD), FD with epigastric pain syndrome (FD-EPS), FD with postprandial distress syndrome (FD-PDS), IBS with predominant diarrhea (IBS-D), and IBS with predominant constipation (IBS-C). All eligible patients with DGBI had undergone endoscopy and biopsy to evaluate eosinophilic infiltration of the GI tract within 2 years of answering the questionnaire. Then, all patients with DGBI were confirmed not to have non-EoE EGIDs. In patients with non-EoE EGIDs, we assumed they had concomitant DGBI when they met the criteria of DGBI without abnormal eosinophilic infiltration of the GI organs that were responsible for the symptoms.

Statistical analysis. Data are expressed as numbers for categorical variables, and median with interquartile range for continuous variables. For categorical variables, the Chi-square test was used for comparison. Continuous variables were compared by the Mann–Whitney *U* test. Spearman's rank correlation coefficients were calculated for correlation analyses. Multivariate regression analysis was performed to investigate the risk factor of decreased mental-health-related QOL. Statistical analyses were performed using the software EZR (version 1.37; Saitama Medical Center, Jichi Medical University, Saitama, Japan).[17]

Results

Background characteristics. The flowchart of the participants is shown in Figure 1. We included 42 patients with non-EoE EGIDs and 27 patients with DGBI. From the non-EoE EGIDs group, 21 patients were excluded for the following reasons: not available for the questionnaire ($n = 18$), missing data in the questionnaire ($n = 1$), or enrolled in other clinical trials ($n = 2$). From the DGBI group, 10 patients were excluded for the following reasons: not available for the questionnaire ($n = 1$) and not undergone endoscopy and biopsy ($n = 9$). Accordingly, we evaluated 21 patients with non-EoE EGIDs and 17 patients with DGBI.

The background characteristics of the patients are shown in Table 1. Patients with non-EoE EGIDs were significantly younger than those with DGBI. Gender, BMI, sleep period, proportion of current cigarette smoking, and proportion of current alcohol drinking were not significantly different between patients in the non-EoE EGIDs and DGBI groups. The numbers in each subtype of non-EoE EGIDs were 6 EoG, 12 EoD, 1 EoN (EoJ), 11 EoC, and 6 with esophageal involvement. The numbers of each subtype in the DGBI group were 9 NERD, 16 FD (14 FD-EPS and 12 FD-PDS), and 3 IBS (2 IBS-D and 1 IBS-C). Disease duration and outpatient period for those with DGBI were significantly longer than those in non-EoE EGIDs group. The proportion of concomitant allergic diseases such as allergic rhinitis, bronchial asthma, and atopic dermatitis was not significantly different between the groups.

The proportion having chronic maintenance treatment was not significantly different between the groups. Regarding the medication received, most types of drugs (except one) were not significantly different. The proportion of patients who had montelukast was significantly higher in the non-EoE EGIDs group compared to the DGBI group.

Clinical symptoms. The results of clinical symptoms are shown in Table 2. The total score of mFSSG was not significantly different between patients with non-EoE EGIDs and DGBI. Additionally, the score of reflux and dyspepsia were not significantly different between the groups. The total score of GSRS was not different between patients with non-EoE EGIDs and DGBI. Moreover, the score of regurgitation, abdominal pain, indigestion, diarrhea, and constipation was not significantly different between the groups. Accordingly, the extent of clinical symptoms was not significantly different between the groups.

Eosinophil counts in the upper GI tract. The results of eosinophil counts in the upper GI tract are shown in Figure 2. Eosinophil counts of the esophagus, stomach, and duodenum were not statistically different between the non-EoE EGIDs and DGBI groups (Fig. 2a–c). Among patients with non-EoE EGIDs, two patients had ≥15 eosinophils/HPF in the esophagus (Fig. 2a), three patients had ≥20 eosinophils/HPF in the stomach (Fig. 2b), and five patients had ≥20 eosinophils/HPF in the duodenum (Fig. 2c). These results indicated that few patients of non-EoE EGIDs had histopathological activity. In other words, most patients had histopathological remission in response to the medications. All patients with DGBI had eosinophil counts less than the cut-off value for the definition of EGIDs (Fig. 2a–c).

Anxiety and depression. Anxiety scores in patients with non-EoE EGIDs were not significantly different those in patients with DGBI (7.0 [5.0–9.0] *vs* 6.0 [5.0–11.0], $P = 0.906$; Fig. 3a). The proportion of possible patients with anxiety was not significantly different between the groups (19.0% *vs* 33.3%, $P = 0.716$; Fig. 3b). The proportion of possible plus probable patients with anxiety was not significantly different between the groups (42.9% *vs* 53.3%, $P = 1.0$; Fig. 3c). These results showed that patients with non-EoE EGIDs had anxiety that might be equivalent to that of patients with DGBI.

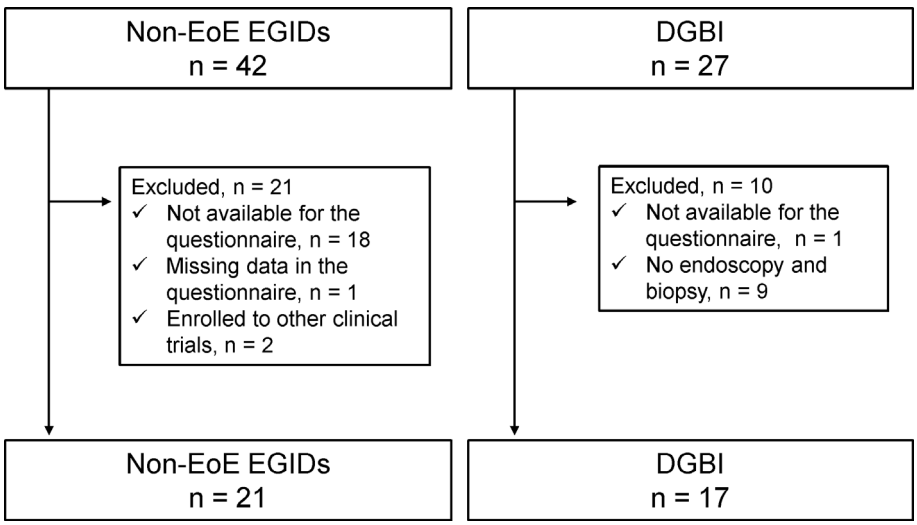

Figure 1 Flow chart of the study participants. DGBI, disorders of gut–brain interaction; EGIDs, eosinophilic gastrointestinal diseases; EoE, eosinophilic esophagitis.

Table 1 Background characteristics

Variable	Non-EoE EGIDs ($n = 21$)	DGBI ($n = 17$)	*P*-value
Age, years	48 (33–57)	57 (49–68)	0.024
Male, *n* (%)	5 (23.8)	8 (47.1)	0.247
BMI, kg/m^2	21.1 (19.7–23.9)	23.0 (20.0–24.4)	0.504
Sleep period, h	6.0 (6.0–7.0)	5.5 (5.0–6.0)	0.123
Current cigarette smoking, *n* (%)	2 (9.5)	3 (17.6)	0.800
Current alcohol drinking, *n* (%)	8 (38.1)	7 (41.2)	1.000
Subtype of non-EoE EGIDs (EoG/EoD/EoN/EoC/esophageal involvement), *n* (%)	6 (28.6)/12 (57.1)/1 (4.8)/11 (52.4)/6 (28.6)	0 (0.0)/0 (0.0)/0 (0.0)/0 (0.0)/0 (0.0)	N/A
Subtype of DGBIs (NERD/FD/IBS), *n* (%)	5 (23.8)/1 (4.8)/0 (0.0)	9 (52.9)/16 (94.1)/3 (17.6)	N/A
Disease duration, months	34 (23–44)	53 (42–84)	<0.01
Outpatient period, months	30 (15–39)	50 (29–71)	0.014
Concomitant allergic diseases			
Allergic rhinitis, *n* (%)	4 (19.0)	5 (29.4)	0.716
Bronchial asthma, *n* (%)	6 (28.6)	1 (5.9)	0.170
Atopic dermatitis, n (%)	2 (9.5)	1 (5.9)	1.000
Having chronic maintenance treatment, *n* (%)	17 (81)	17 (100)	0.170
Medication			
No medications, *n* (%)	1 (4.8)	0 (0.0)	1.000
Systemic steroid, *n* (%)	3 (14.3)	0 (0.0)	0.308
Swallowed topical steroid, *n* (%)	1 (4.8)	0 (0.0)	1.000
Inhaled steroid, *n* (%)	3 (14.3)	1 (5.9)	0.758
Thioprine, *n* (%)	1 (4.8)	0 (0.0)	1.000
Montelukast, *n* (%)	12 (57.1)	0 (0.0)	<0.01
H_1RA, *n* (%)	3 (14.3)	1 (5.9)	0.758
H_2RA, *n* (%)	0 (0.0)	1 (5.9)	0.915
PPI, *n* (%)	10 (47.6)	8 (47.1)	1.000
P-CAB, *n* (%)	4 (19.0)	3 (17.6)	1.000
Prokinetics, *n* (%)	0 (0.0)	4 (23.5)	0.069
5-HT_3 receptor antagonist, *n* (%)	2 (9.5)	0 (0.0)	0.564
Loperamide, *n* (%)	1 (4.8)	1 (5.9)	1.000
Laxative, *n* (%)	2 (9.5)	1 (5.9)	1.000
Probiotics, *n* (%)	7 (33.3)	2 (11.8)	0.241
Benzodiazepine, *n* (%)	1 (4.8)	2 (11.8)	0.849
5-HT_{1A} receptor agonist, *n* (%)	0 (0.0)	1 (5.9)	0.915
NaSSA, *n* (%)	0 (0.0)	1 (5.9)	0.915

Data are expressed as median (IQR) for continuous variables and as numbers (percentage) for categorical variables.

BMI, body mass index; DGBI, disorders of gut–brain interaction; EGID, eosinophilic gastrointestinal disorder; EoC, eosinophilic colitis; EoD, eosinophilic duodenitis; EoE, eosinophilic esophagitis; EoG, eosinophilic gastritis; EoN, eosinophilic enteritis; H_1RA, histamine H_1 receptor antagonist; H_2RA, histamine H_2 receptor antagonist; IBS, irritable bowel syndrome; NaSSA, noradrenergic and specific serotonergic antidepressant; NERD, non-erosive reflux disease; P-CAB, potassium competitive acid blocker; PPI, proton pump inhibitor.

The depression scores in patients with DGBI tended to be high compared to those in non-EoE EGID patients; however, there was no statistically significant difference (4.0 [3.0–7.0] *vs* 6.0 [3.0–11.0], $P = 0.188$; Fig. 3d). The proportion of possible patients with depression in DGBI tended to be higher than in non-EoE EGID patients (14.3% *vs* 33.3%, $P = 0.461$; Fig. 3e). The proportion of possible plus probable patients with depression in DGBI tended to be higher compared to that in non-EoE EGID patients (23.8% *vs* 53.3%, $P = 0.247$; Fig. 3f).

Additionally, to avoid the effects of concomitant DGBI in patients with non-EoE EGIDs, we excluded six patients with concomitant DGBI and re-analyzed the data ($n = 15$, non-EoE EGIDs). As a result, we obtained similar results. Anxiety scores in patients with non-EoE EGIDs were not significantly different from those in patients with DGBI (6.5 [4.8–8.3] *vs* 6.0 [5.0–11.0], $P = 0.842$). The depression score in patients with DGBI tended to be high compared to that in non-EoE EGID patients; however, there was no statistically significant difference (3.5 [3.0–5.3] *vs* 6.0 [3.3–10.0], $P = 0.136$).

Health-related QOL. The results of SF-8 are shown in Table 3. PCS-8 scores in the DGBI group tended to be lower than those in the non-EoE EGID group; however, there was no statistical difference (47.7 [42.0–54.2] *vs* 44.4 [40.9–47.2], $P = 0.078$; Fig. 4a).

MCS-8 scores in patients with non-EoE EGIDs were not significantly different from those in patients with DGBI (46.6

Table 2 Clinical symptoms

Variable	Non-EoE EGIDs ($n = 21$)	DGBI ($n = 17$)	*P*-value
mFSSG			
Total score	13.0 (7.0–24.0)	17.0 (11.0–25.0)	0.860
Reflux	7.0 (3.0–13.0)	7.0 (4.0–9.0)	0.444
Dyspepsia	6.0 (4.0–11.0)	9.0 (4.0–16.0)	0.369
GSRS			
Total score	29.0 (24.0–36.0)	33.0 (28.0–39.0)	0.332
Regurgitation	3.0 (2.0–4.0)	4.0 (2.0–5.0)	0.405
Abdominal pain	5.0 (3.0–10.0)	6.0 (5.0–9.0)	0.411
Indigestion	8.0 (5.0–9.0)	7.0 (6.0–11.0)	0.626
Diarrhea	5.0 (3.0–11.0)	6.0 (3.0–9.0)	0.867
Constipation	5.0 (3.0–9.0)	6.0 (5.0–11.0)	0.099

Data are expressed as median (IQR).
DGBI, disorders of gut–brain interaction; EGID; eosinophilic gastrointestinal disorder; EoE, eosinophilic esophagitis; GSRS, gastrointestinal symptom rating scale; IQR, interquartile range; mFSSG, modified frequency scale for the symptoms of gastroesophageal reflux disease.

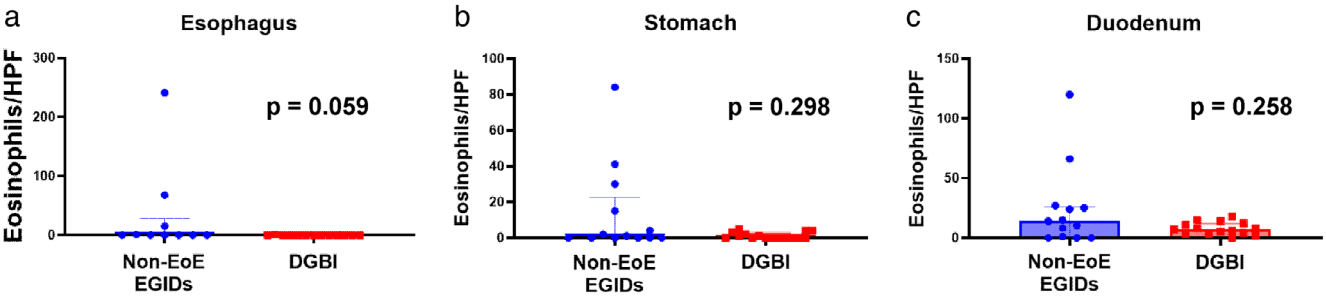

Figure 2 Eosinophil counts in the upper gastrointestinal tract: (a) esophagus, (b) stomach, and (c) duodenum. DGBI, disorders of gut–brain interaction; EGIDs, eosinophilic gastrointestinal diseases; EoE, eosinophilic esophagitis; HPF, high power field.

[40.7–49.8] *vs* 47.4 [38.7–50.1], $P = 0.862$; Fig. 4b), which might imply that mental-health-related QOL in patients with non-EoE EGIDs was decreased to a degree equivalent to that in patients with DGBI. In patients with non-EoE EGIDs, anxiety score had a significant inverse association with MCS-8 ($P < 0.01$, $r = -0.598$; Fig. 4c). On the other hand, the depression score was not significantly associated with MCS-8 ($P = 0.112$, $r = -0.357$; Fig. 4d). These results showed that anxiety but not depression was associated with decreased mental-health-related QOL in patients with non-EoE EGIDs.

Next, we performed multivariate regression analysis. In clinical characteristics, patients with non-EoE EGIDs were significantly younger than those with DGBI. Therefore, we included age and anxiety score as explanatory variables in the multivariate regression analysis to investigate the association with MCS-8 score as an objective variable. As a result, the MCS-8 score was significantly associated with the anxiety score ($P < 0.01$) but not age ($P = 0.893$). In summary, anxiety was an independent risk factor for decreased mental-health-related QOL.

Moreover, we evaluated the correlation between eosinophil counts in the GI tract and mental-health-related QOL. As a result, the MCS-8 score was not significantly associated with eosinophil counts in the esophagus ($P = 0.845$), stomach ($P = 0.125$), and duodenum ($P = 0.225$).

Discussion

In this study, we found that patients with non-EoE EGIDs may have anxiety that correlated with decreased mental-health-related QOL. To the best of our knowledge, this is the first report that showed the correlation between anxiety and QOL in patients with non-EoE EGIDs. Based on these results, we consider that there is a possibility that anxiety may affect the pathophysiology of non-EoE EGIDs. In this study, eosinophil counts of the esophagus, stomach, and duodenum were not different between the non-EoE EGIDs and DGBI groups because many patients with non-EoE EGIDs had medications such as montelukast, systemic steroids, and PPIs. Interestingly, these results may imply that patients with non-EoE EGIDs had anxiety even though histopathological therapeutic effects were attained. In patients who had received no medications, the level of anxiety may be higher than that in patients who had received medications. Moreover, these results were observed even though the disease duration and outpatient period were shorter than those in patients with DGBI.

Regarding QOL, decreased mental-health-related QOL was comparable between the non-EoE EGIDs and DGBI groups. On the other hand, physical-health-related QOL tended to be lower in patients with DGBI compared to that in patients with non-EoE EGIDs. Patients with DGBI had a stronger tendency toward depressive moods than non-EoE EGID patients. Accordingly, the

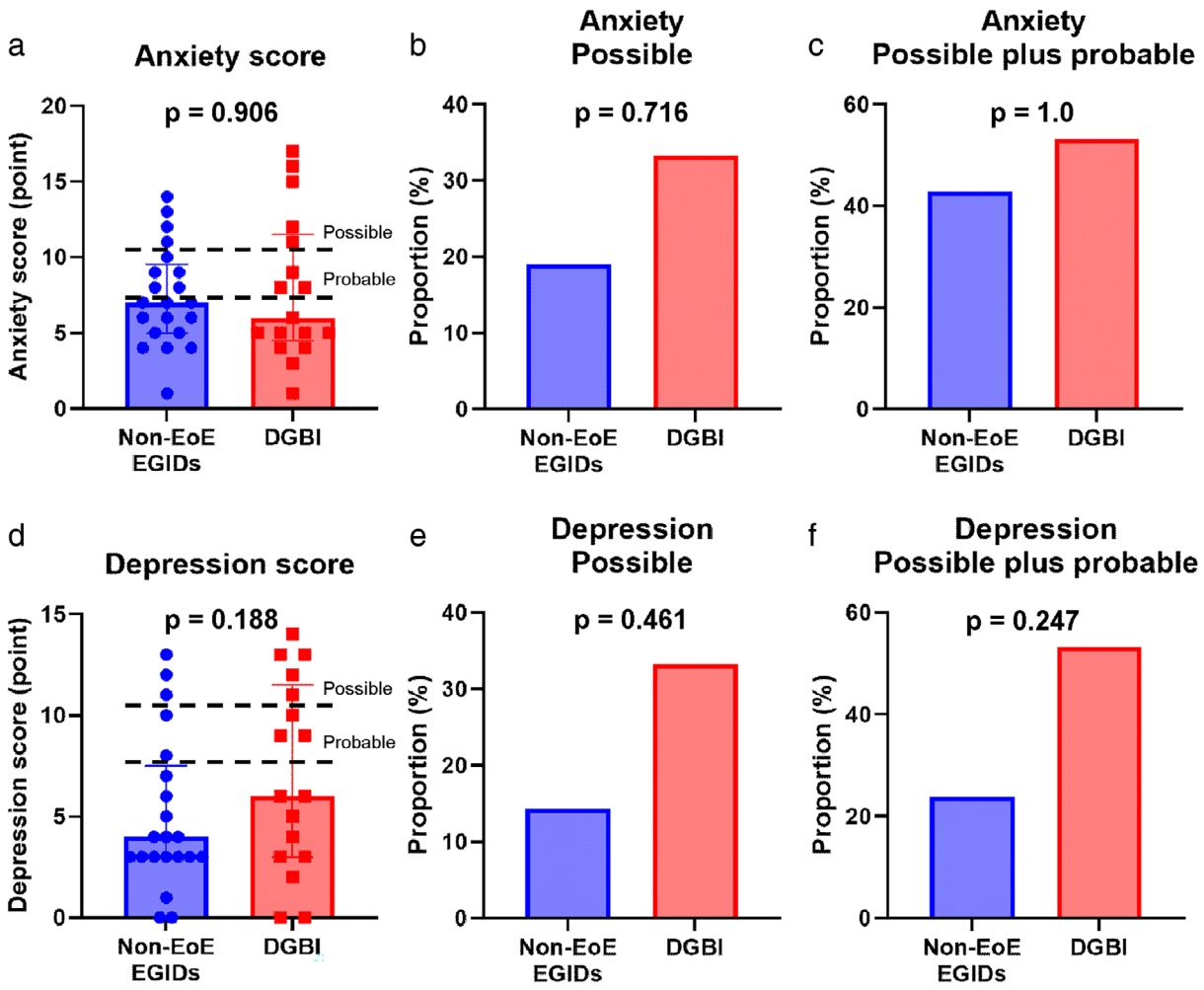

Figure 3 Anxiety and depression: (a) anxiety score, (b) proportion of possible patients with anxiety, and (c) proportion of possible plus probable patients with anxiety. (d) Depression score: (e) proportion of possible patients with depression, and (f) proportion of possible plus probable patients with depression. DGBI, disorders of gut–brain interaction; EGIDs, eosinophilic gastrointestinal diseases; EoE, eosinophilic esophagitis.

Table 3 Health-related QOL

Variable	Non-EoE EGIDs ($n = 21$)	DGBI ($n = 17$)	*P*-value
SF-8			
General health perception	50.3 (40.4–50.3)	40.4 (40.4–50.3)	0.053
Physical functioning	47.8 (41.5–53.5)	47.9 (41.5–47.8)	0.144
Role physical	47.4 (47.4–54.1)	47.4 (40.7–47.4)	0.106
Bodily pain	46.1 (38.2–52.5)	46.1 (38.2–52.5)	1.000
Vitality	53.7 (44.5–53.7)	44.5 (44.5–53.7)	0.091
Social functioning	45.6 (37.7–55.1)	45.6 (37.7–45.6)	0.228
Mental health	44.9 (36.3–50.7)	44.9 (36.3–50.7)	0.530
Role emotional	48.0 (42.2–54.2)	48.0 (42.2–54.2)	0.939
Physical component summary-8	47.7 (42.0–54.2)	44.4 (40.9–47.2)	0.078
Mental component summary-8	46.6 (40.7–49.8)	47.4 (38.7–50.1)	0.862

Data are expressed as median (IQR).
DGBI, disorders of gut–brain interaction; EGID, eosinophilic gastrointestinal disorder; EoE, eosinophilic esophagitis; IQR, interquartile range; QOL, quality of life; SF, short form.

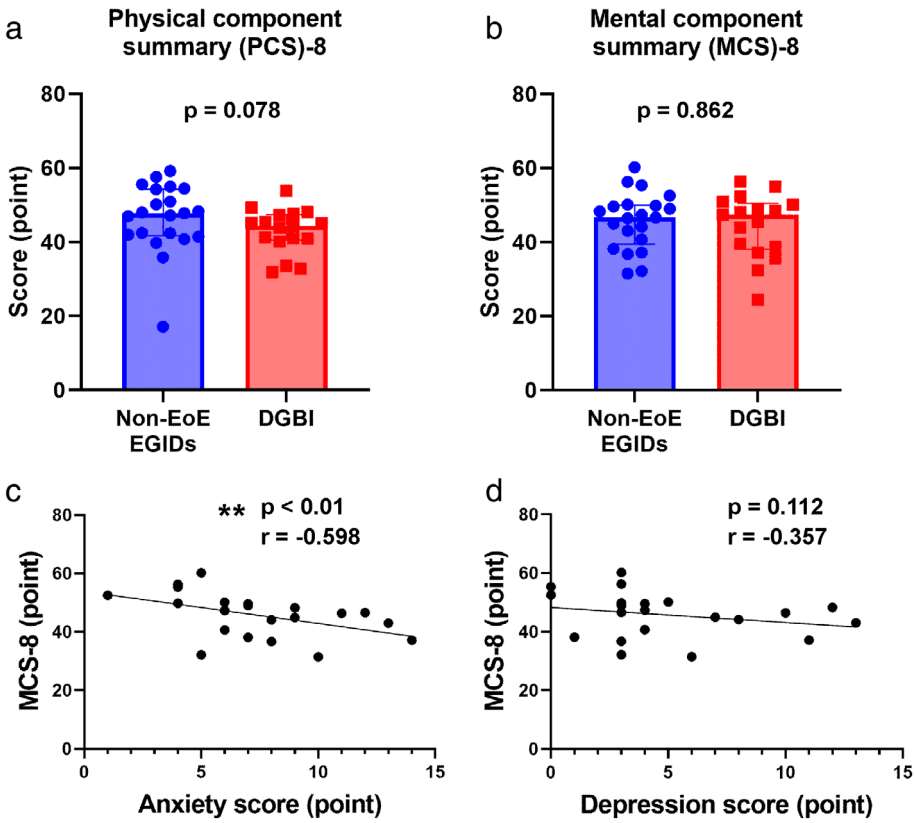

Figure 4 Health-related quality of life and correlation analyses: (a) score of physical component summary (PCS)-8, (b) score of mental component summary (MCS)-8, (c) correlation analysis between MCS-8 and anxiety, and (d) correlation analysis between MCS-8 and depression. DGBI, disorders of gut–brain interaction; EGIDs, eosinophilic gastrointestinal diseases; EoE, eosinophilic esophagitis.

characteristics regarding depression and physical-health-related QOL might be different between the DGBI and non-EoE EGIDs groups. Patients with DGBI may have impaired somatic activity, as they are likely to have somatization.[18] Importantly, in patients with non-EoE EGIDs, decreased mental-health-related QOL was significantly correlated with the level of anxiety but not depression. Therefore, we consider that anxiety is a more prominent mental status than depression, and anxiety may modulate the disease status of non-EoE EGIDs.

Anxiety and psychological stress have a close relationship, and chronic psychological stress is a risk factor for anxiety.[19] Psychological stress induces the production of not only central CRH but also peripheral CRH. In DGBI, increased intestinal permeability is a key mechanism that increases the flux of the contents of the gut lumen, such as acids, foods, and microbial component, into the mucosa.[20,21] In EGIDs, increased intestinal permeability may be a key mechanism as well, because increased intestinal permeability can lead to an increase in the flux of food allergens into the GI mucosa. Mast cells are key immune cells in not only Th2-mediated allergic response but also in the stress response. Peripheral CRH activates mast cells via the CRH receptor, followed by the release of proteases. Mast cells are also involved in the pathophysiology of DGBI.[22,23] For instance, mast-cell-dependent excitation of visceral nociceptive sensory neuron was observed in IBS.[22] Moreover, in patients with EoE, mast cells may be associated with symptom perception.[24] Taken together, in patients with non-EoE EGIDs, mast cells may be involved in the sequence of not only Th2-mediated immune response but also neuroimmune response.

In clinical practice, it is sometimes difficult to make a differential diagnosis between non-EoE EGIDs and DGBI. We found that both patients with non-EoE EGIDs and DGBI had anxiety, which may be one of the reasons for such difficulties. Clinicians may have similar impressions of patients with non-EoE EGIDs and DGBI when they have anxiety. Moreover, anxiety and psychological stress can increase intestinal permeability, which leads to the exacerbation of GI inflammation. Such pathophysiology may be common in both DGBI and non-EoE EGIDs. This may be a second reason for the difficulties in diagnosis. Therefore, performing endoscopy and assessing the number of GI eosinophils are important to make a correct diagnosis. However, duodenal eosinophils are involved in the pathophysiology of FD, so the cut-off value of GI eosinophils for the definition of non-EoE EGIDs needs to be reconsidered in the future.[23,25] We had previously reported that the endoscopic findings of EoG may be helpful in the diagnosis.[26]

This study has some limitations. Because the sample size was small, the study might be underpowered. This is a critical limitation of this study. In future studies with large numbers of participants, the proportion of patients with anxiety and/or depression may have statistical differences between the groups. However, this study showed that the proportion of patients with anxiety was

relatively high (19.0%). We believe that this information may help clinical practice. Patients with non-EoE EGIDs were younger than those with DGBI. This background characteristic may affect the results. In this study, almost all patients received medications. However, we consider that the effect of medications were limited. Although the administration ratio of montelukast was significantly different between the groups, this kind of drug does not commonly affect mental status.

We included patients taking anti-anxiety drugs and anti-depressants in this study. As shown in Table 1, the proportion of patients taking anti-anxiety drugs such as benzodiazepine and 5-HT_1A receptor agonist was not significantly different between the non-EoE EGIDs and DGBI groups. Moreover, the proportion of patients taking anti-depressant such as NaSSA was not significantly different between the groups. Therefore, we consider that the effect of pre-existing mental conditions and psychotropic drugs may be limited.

Moreover, there is a possibility that the heterogeneity of non-EoE EGIDs may affect the results. To solve this problem, comparison among the subtypes of non-EoE EGIDs may lead to better understanding in future studies.

In conclusion, patients with non-EoE EGIDs may have anxiety that correlate with decreased mental-health-related QOL. In clinical practice, it is important to evaluate the presence of anxiety in patients with non-EoE EGIDs. Further study is warranted to investigate psychological stress in patients with non-EoE EGIDs and to determine whether psychological stress is an exacerbating factor. Treatment with anti-anxiety drug may help increase health-related QOL in patients with non-EoE EGIDs.

Ethics approval and patient consent statement. The study protocol was in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Osaka Metropolitan University Graduate School of Medicine (protocol number 2021-210). The requirement for informed consent from the study subjects was waived because of the retrospective nature of the study design. We disclosed the information of this study on our home page and provided the opportunity to opt out.

Data availability statement. All data generated and/or analyzed during this study are available from the corresponding author on reasonable request.

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