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【 ORIGINAL ARTICLE 】

Negative Association between the Occurrence of Esophageal Candidiasis and Reflux Esophagitis

Kyoichi Adachi[1], Eiko Okimoto[1], Utae Sakamoto[1], Yuko Matsubara[1], Akihiko Oka[2], Norihisa Ishimura[2] and Shunji Ishihara[2]

Abstract:

Objective Reflux esophagitis (RE) is caused by gastroesophageal acid reflux, whereas the heterotopic gastric mucosa (HGM) of the cervical esophagus often shows acid secretion. This study investigated whether an intra-esophageal acidic condition in patients with RE or HGM prevents the occurrence of esophageal candidiasis.

Materials We enrolled 5,221 adults (males/females: 3,260/1,961, mean age 54.8±9.8 years) who underwent an esophagogastroduodenoscopy (EGD) examination as part of a medical checkup. The presence of esophageal candidiasis, RE, and/or HGM in the cervical esophagus was endoscopically determined, and the risk factors for esophageal candidiasis were investigated.

Results The EGD findings revealed esophageal candidiasis, RE, and HGM of the cervical esophagus in 176 (3.4%), 1,119 (21.4%), and 367 (7.0%) patients, respectively. A multiple logistic regression analysis showed that an older age, habitual alcohol consumption, and comorbidities (poorly controlled diabetes mellitus, bronchial asthma with steroid therapy, autoimmune disease with immunosuppressive treatment, and/or malignant disease with chemotherapy) were significant risk factors, whereas RE was negatively correlated with esophageal candidiasis. HGM of the cervical esophagus was not significantly related to its occurrence.

Conclusion Esophageal candidiasis was found in 3.4% of the subjects who underwent EGD for a medical checkup. RE was negatively correlated with esophageal candidiasis, whereas HGM of the cervical esophagus did not show such an association.

Key words: esophagus, candida, heterotopic gastric mucosa, reflux esophagitis, endoscopy

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Introduction

Esophageal candidiasis is the most common esophageal infection and it is frequently observed in patients administered immunosuppressants as well as in those with underlying conditions such as diabetes mellitus, malignant disease, or acquired immune deficiency syndrome (1, 2). An adequate pH level for Candida colony formation ranges from 5.0 to 6.5, whereas esophageal candidiasis rarely occurs in an intra-esophageal acidic condition. Proton pump inhibitor (PPI) usage has been shown to induce esophageal candidiasis as the intra-esophageal pH rises due to the elevated pH of the gastroesophageal reflux contents (2).

Heterotopic gastric mucosa (HGM) of the cervical esophagus is often detected incidentally by esophagogastroduodenal endoscopy (EGD), with a prevalence in adults who undergo such an examination ranging from 1.1% to 10% (3). Although often asymptomatic, it has been reported to occasionally induce symptoms, such as coughing, sore throat, hoarseness, or esophageal complications, including ulcers, stenosis, or perforation (4, 5). These reports also noted that such symptoms and esophageal complications can be caused by acid secretion from the affected mucosa. Weickert et al. performed a histological investigation of HGM cases and classified the histologic types as oxyntic

[1]Health Center, Shimane Environment and Health Public Corporation, Japan and [2]Second Department of Internal Medicine, Shimane University Faculty of Medicine, Japan
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Correspondence to Dr. Kyoichi Adachi, adachi@kanhokou.or.jp

(24%), cardiac (15%), and mixed (61%) (6). Thus, cervical esophageal tissues in 85% of affected individuals are considered to show acid secretion, since oxyntic-type HGM is composed of acid-secreting parietal cells. Acid secretion from the HGM of the cervical esophagus may have a protective function in preventing the occurrence of esophageal candidiasis. However, to the best of our knowledge, no study has investigated the relationship between cervical esophageal HGM and esophageal candidiasis has been presented.

Reflux esophagitis (RE) is primarily caused by gastroesophageal reflux of gastric acidic contents, and the intraesophageal environment in affected individuals is likely more acidic than that in unaffected individuals (7, 8). As a result, the presence of RE is considered to be negatively associated with esophageal candidiasis, although this has yet to be established. The present retrospective study was performed to clarify the prevalence of esophageal candidiasis in individuals who underwent EGD examination as part of a medical checkup, as well as the effects of the presence of RE and HGM of the cervical esophagus on its occurrence.

Materials and Methods

From April 2024 to March 2025, 5,247 individuals underwent an EGD examination as part of a detailed medical checkup at the Health Center of Shimane Environment and Health Public Corporation. Following the exclusion of 26 patients with a history of esophagectomy (n=1) or gastrectomy (n=25), 5,221 (males/females 3,260/1,961, mean age 54.8±9.8 years) were enrolled in this retrospective study. EGD examinations were conducted by experienced endoscopists who had received Japan Gastroenterological Endoscopy Society certification and/or more than six years of experience with EGD using an EG-L580NW endoscope (FUJIFILM, Tokyo, Japan). All upper endoscopic examinations at our institution were performed under a non-sedated condition and without any anticholinergic drugs, with the endoscope generally inserted in a transnasal manner. Among the present subjects, the numbers of transnasal and peroral EGD were 4,949 (94.8%) and 272 (5.2%), respectively.

Each participant was interviewed by a public health nurse to obtain a precise medical history. Habitual alcohol consumption (≥3 times per week), smoking habits, and comorbidities were recorded. The comorbidities analyzed were poor diabetes mellitus control status (HbA1c ≥7.0%), bronchial asthma with inhaled and/or oral steroid therapy, autoimmune diseases such as rheumatoid arthritis with immunosuppressive treatment, and malignant disease with chemotherapy. None of them was affected by human immunodeficiency virus (HIV) infection. The regular use of antisecretory drugs, an H2 receptor antagonist (H2RA), conventional PPI, or vonoprazan at the time of EGD examination was also noted, although details related to the duration or dosage were not obtained.

Esophageal candidiasis was diagnosed based on typical endoscopic findings of multiple whitish or yellowish plaques (1) (Fig. 1), with severity evaluated using the Kodsi classification (9, 10). The HGM of the cervical esophagus, shown as a salmon-colored patch of columnar epithelium by endoscopic observation using white light imaging (WLI) (4-6), or as a brown-colored patch with narrow band imaging and blue laser imaging (BLI) (Fig. 2), was determined. Positive findings were noted when HGM was observed in the cervical esophageal squamous epithelium by endoscopy with WLI and/or BLI, irrespective of size. In January 2024, the Health Center established a protocol for careful endoscopic examinations and the recording of findings indicating the presence of cervical esophageal HMG; thus, the present one-year study period began in April 2024. Endoscopic findings of RE were evaluated using the Los Angeles (LA) classification (7), with individuals with grades A, B, C, or D diagnosed as positive for RE. Furthermore, those with LA-A or -B were subclassified as mild and those with LA-C or -D as severe. In the present study, the presence of RE was endoscopically determined irrespective of the administration of anti-secretory drugs.

All endoscopic images obtained for each subject were simultaneously reviewed by three expert endoscopists, with findings indicating the presence of esophageal candidiasis, HGM of the cervical esophagus, and RE determined based on decisions made by consensus. When there was inconsistency among the experts, the final diagnosis was decided by a lead endoscopist (K.A.). The present study retrospectively analyzed several endoscopic findings from each subject.

Statistical analyses were conducted using the chi-squared, Fisher's exact, and Mann-Whitney U tests, and univariate and multiple logistic regression analyses were also performed. All calculations were performed using the StatView software program (version 5.0; Abacus Concepts, Berkeley, USA), with a p value <0.05 considered to indicate statistical significance.

This study was performed in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Shimane Environment and Health Public Corporation (no. 201703-202404). Written informed consent indicating that clinical data would be used for a clinical study without the release of individual information was obtained from each participant before performing the medical checkup examination.

Results

Esophageal candidiasis was endoscopically observed in 176 (3.4%) of the 5,221 subjects. Grade 1 and 2 esophageal candidiasis according to the Kodsi classification were noted in 153 (86.9%) and 23 (13.1%) patients, respectively, while none were diagnosed as grade 3 or 4. Furthermore, none of the subjects required any treatment for related symptoms. There were 2,014 (38.5%) subjects with habitual alcohol drinking and 888 (17.0%) with a current smoking habit. Comorbidities were noted in 328 (6.3%), including poor

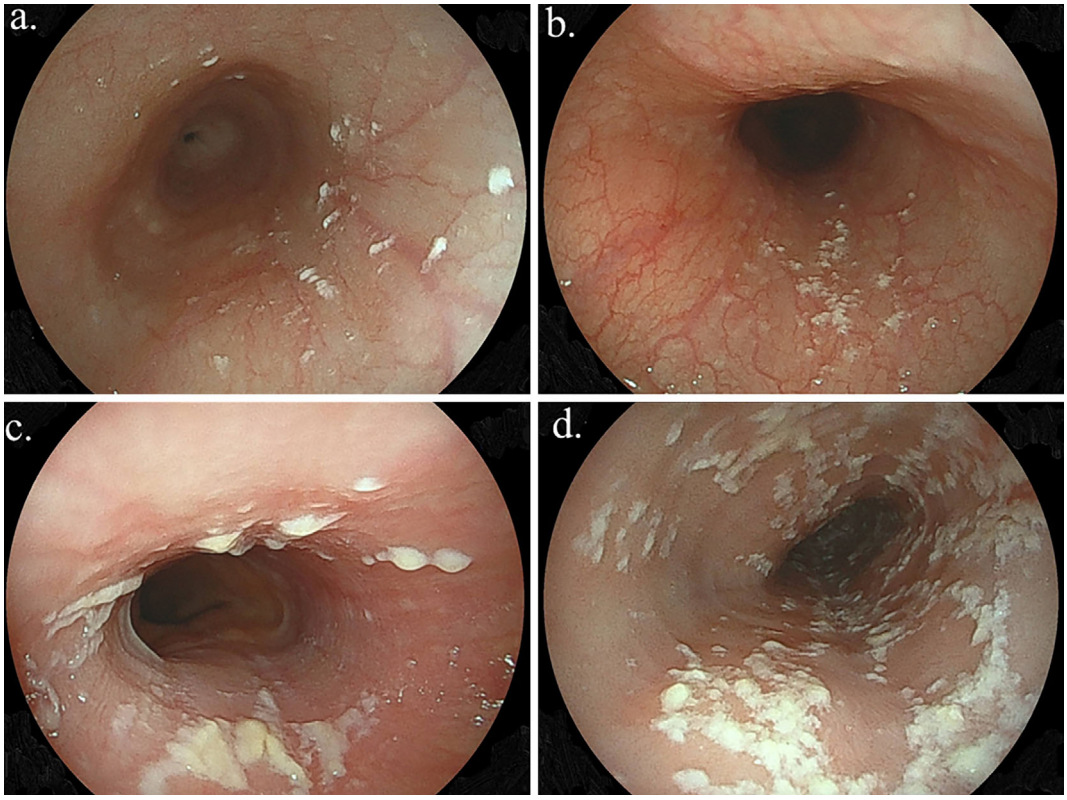

Figure 1. **Endoscopy images showing esophageal candidiasis. Multiple whitish plaques were also observed. a, b: Plaques ≤2 mm were observed and diagnosed as grade 1 according to the Kodsi classification. c, d: Plaques >2 mm were observed and diagnosed as grade 2, according to the Kodsi classification.**

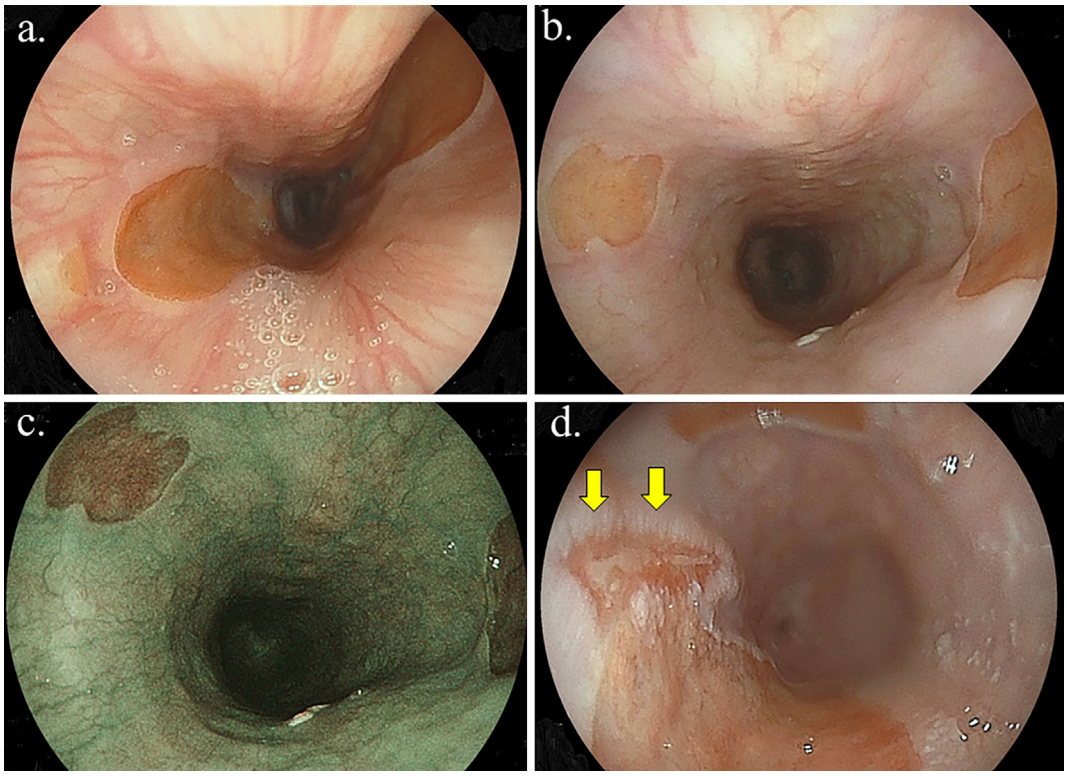

Figure 2. **Endoscopy images showing HGM in cervical esophagus. a, b, c: Typical images of HGM (a, b: white light image showing salmon-colored patch of columnar epithelium in the cervical esophagus. c: A blue laser image showing brown-colored patch (b and c from same case). d: HGM of the cervical esophagus and mucosal injury (yellow arrows) in the adjacent esophageal mucosa.**

Table 1. Characteristics of Cases with and without Esophageal Candidiasis.

	Esophageal candidiasis		p value
	Positive	Negative	
Male/female	114 (64.8)/62 (35.2)	3,146 (62.4)/1,899 (37.6)	0.516
Age, years, mean±SD	57.1±10.4	54.7±9.7	0.005
Habitual alcohol drinking*, positive/negative	97 (55.1)/79 (44.9)	1,917 (38.0)/3,128 (62.0)	<0.001
Current smoker, positive/negative	34 (19.3)/142 (80.7)	854 (16.9)/4,191 (83.1)	0.407
Comorbidities**, positive/negative	19 (10.8)/157 (89.2)	309 (6.1)/4,736 (93.9)	0.012
Diabetes mellitus***, positive/negative	9 (5.5)/155 (94.5)	185 (3.9)/4,582 (96.1)	0.298
Bronchial asthma, positive/negative	6 (3.4)/170 (96.6)	85 (1.7)/4,960 (98.3)	0.086
Autoimmune disease, positive/negative	4 (2.3)/172 (97.7)	28 (0.6)/5,017 (99.4)	0.004
Malignant disease, positive/negative	0 /176 (100)	14 (0.3)/5,031 (99.7)	
Antisecretory drug usage, positive/negative	20 (11.4)/156 (88.6)	416 (8.2)/4,629 (91.8)	0.142
H2 receptor antagonist, n=50	1 (0.6)	49 (1.0)	
Proton pump inhibitor****, n=285	11 (6.3)	274 (5.4)	
Vonoprazan, n=101	8 (4.5)	93 (1.8)	
HGM*****, positive/negative	17 (9.7)/159 (90.3)	350 (6.9)/4,695 (93.1)	0.165
Reflux esophagitis, positive/negative	28 (15.9)/148 (84.1)	1,091 (21.6)/3,954 (78.4)	0.069
Mild reflux esophagitis******, n=999	28 (15.9)	971 (19.2)	
Severe reflux esophagitis******, n=120	0 (0)	120 (2.4)	

Numbers in parentheses indicate percentage.

*Alcohol consumption three or more times per week

**Diabetes mellitus (HbA1c ≥7.0%), bronchial asthma with steroid therapy, autoimmune disease with immunosuppressive therapy, malignant disease with chemotherapy

***Diabetes mellitus positive when HbA1c ≥7.0% (4,931 cases examined for HbA1c level)

****Conventional proton pump inhibitor, excluding vonoprazan

*****Heterotopic gastric mucosa of cervical esophagus

******Mild reflux esophagitis (LA-A and -B), severe reflux esophagitis (LA-C and -D)

control of diabetes mellitus (n=194, 3.7%), bronchial asthma with steroid therapy (n=91, 1.7%), autoimmune diseases with immunosuppressive therapy (n=32, 0.6%), and malignant diseases with chemotherapy (n=14, 0.3%). Antisecretory drugs were prescribed to 436 (8.4%) patients, while the use of H2RA, conventional PPI, and vonoprazan was noted in 50 (1.0%), 285 (5.5%), and 101 (1.9%) patients, respectively. Endoscopic findings revealed HGM of the cervical esophagus in 367 patients (7.0%), with no significant difference in the detection rate between transnasal and peroral EGD (7.1% vs. 6.3%, p=0.606). RE was endoscopically observed in 1,119 (21.4%) patients, with 999 classified as mild and 120 as severe.

The characteristics of the patients with and without esophageal candidiasis are shown in Table 1. Subjects with esophageal candidiasis were significantly older than those without, while significantly greater numbers were also affected by habitual alcohol consumption and/or comorbidities. Among the comorbidities investigated, autoimmune disease with immunosuppressive treatment was a significant risk factor for esophageal candidiasis. In contrast, gender, current smoking habits, poor control of diabetes mellitus, bronchial asthma with steroid therapy, malignant disease with chemotherapy, use of antisecretory drugs, and presence of HGM were not significantly correlated with esophageal candidiasis. The prevalence of esophageal candidiasis tended to be lower in patients with mild RE and was not seen in any affected by severe RE.

The results of the univariate and multiple logistic regression analyses for esophageal candidiasis occurrence are presented in Table 2. A univariate logistic regression analysis indicated that an older age, habitual alcohol consumption, autoimmune disease with immunosuppressive treatment, and vonoprazan use were significant risk factors for esophageal candidiasis. Thus, multivariate logistic regression analyses were performed by including the factors of age, habitual drinking, comorbidities, and antisecretory drug use, in addition to HGM of the cervical esophagus and reflux esophagitis. The findings showed that reflux esophagitis was negatively associated with esophageal candidiasis, while the presence of HGM in the cervical esophagus did not show such an association.

Discussion

The most common infection of the esophagus is esophageal candidiasis, which is mainly caused by *Candida albicans*, *C. glabrata*, and *C. tropicalis* (1). Some patients require treatment for esophageal symptoms such as swallowing dysfunction or severe candidiasis, with the latter possibly inducing candidemia or candidiasis in other organs. Nevertheless, esophageal candidiasis is incidentally diagnosed in many asymptomatic cases based on EGD findings, while its incidence in the general population has been re-

Table 2. Logistic Regression Analysis for Presence of Esophageal Candidiasis.

	Odds ratio	95% CI	p value
Univariate analysis			
Male	1.110	0.810-1.520	0.516
Age	1.025	1.010-1.041	0.015
Habitual alcohol drinking	2.003	1.481-2.711	<0.001
Current smoker	1.175	0.802-1.721	0.407
Diabetes mellitus*	1.438	0.723-2.861	0.301
Bronchial asthma**	2.060	0.887-4.780	0.093
Autoimmune disease***	4.167	1.446-12.012	0.008
H2 receptor antagonist****	0.606	0.083-4.414	0.621
Conventional proton pump inhibitor****	1.191	0.639-2.222	0.582
Vonoprazan****	2.553	1.218-5.348	0.013
HGM*****	1.434	0.860-2.393	0.167
Reflux esophagitis	0.686	0.455-1.033	0.071
Multivariate analysis			
Age	1.018	1.002-1.035	0.029
Habitual alcohol drinking	1.979	1.456-2.689	<0.001
Comorbidities[1]	1.781	1.078-2.943	0.024
Antisecretory drug usage[2]	1.086	0.661-1.784	0.746
HGM*****	1.349	0.805-2.259	0.256
Reflux esophagitis	0.634	0.419-960	0.031

*Diabetes mellites (HbA1c ≥7.0%)

**Bronchial asthma with steroid therapy

***Autoimmune disease with immunosuppressive therapy

****Odds ratio, calculated in comparison with no anti-secretory drug usage

*****Heterotopic gastric mucosa of the cervical esophagus

[1]Diabetes mellitus (HbA1c ≥7.0%), bronchial asthma with steroid therapy, autoimmune disease with immunosuppressive therapy, malignant disease with chemotherapy

[2]Regular usage of H2 receptor antagonist, conventional proton pump inhibitor, or vonoprazan

ported to range from 0.3% to 5.2% (1, 2). In the present study, esophageal candidiasis was endoscopically diagnosed in 3.4% of individuals who underwent an EGD examination as part of a medical checkup; the prevalence rate was considered to be similar to that of the general population in Japan. HIV infection, diabetes mellitus, malignant disease, and use of antibiotics or immunosuppressive agents have been demonstrated as risk factors for esophageal candidiasis (1, 2).

The use of an antisecretory drug such as a PPI has been reported to increase the risk of esophageal candidiasis. Furthermore, the presence of atrophic gastritis, which is mainly induced by a long-term *Helicobacter pylori* infection and is known to cause low gastric acid secretion, was demonstrated to be related to its occurrence (2). An important related factor is considered to be intra-esophageal acidity affected by intragastric acidity; thus, the intra-esophageal acidic condition in cases with RE or HGM might prevent the occurrence of esophageal candidiasis. However, to the best of our knowledge, the effects of either RE or HGM in the cervical esophagus on esophageal candidiasis have not yet been investigated. The present multiple logistic regression analysis findings demonstrated a negative correlation between RE and esophageal candidiasis; thus, an intra-esophageal acidic environment induced by gastroesophageal acid reflux is thought to prevent the overgrowth of Candida in the esophagus. Notably, esophageal candidiasis was not observed in any of the subjects with severe RE, who were found in previous studies to have severe gastroesophageal acid reflux, not only during the day but also at night, compared to those with mild RE (7, 8).

HGM of the cervical esophagus was observed in 7.0% of the subjects who underwent an EGD examination as part of a medical checkup. The prevalence of HGM in the present study is similar to that in previous reports, which noted that 1.1% to 10% of adults who underwent EGD were affected by HGM (3). Although it has also been reported that 85% of patients with HGM have acid secretion ability (6), the present results did not indicate a negative correlation with esophageal candidiasis. Therefore, acid secretion in HGM patients is considered to be insufficient to prevent esophageal candidiasis, although it has been found to be associated with mucosal injury in the adjacent esophageal mucosa (4, 5), as shown in Fig. 2d. In this study, we did not investigate the size and histological type of HGM, which correlates with acid secretion ability. Additional studies are needed to elucidate the details regarding relationship between HGM in the cervical esophagus and esophageal candidiasis.

The present results showed that an older age, habitual al-

cohol consumption, and immunosuppressive treatment for autoimmune diseases were risk factors for esophageal candidiasis. *Candida* organisms in the esophagus originate from the oral cavity, where they are commonly present, although they need to remain in the esophagus for a certain period before development. Therefore, age-related reductions in esophageal motor function and saliva secretion (11-13), which play important roles in washing out esophageal contents and moving them to the stomach, are considered to be related to the increased occurrence of esophageal candidiasis in aged individuals. In addition, a reduced immune response associated with age may be correlated with age-related increases in esophageal candidiasis (14). Heavy alcohol drinking (five or more days within the past 30) has been reported to cause decreased lymphocyte counts and increase the risk of viral and bacterial infections, although the related mechanisms have not been clearly revealed (15). Therefore, the reduced immune response in individuals with habitual drinking (≥3 days per week in the present analysis) may be associated with an increased risk of esophageal candidiasis.

Smoking habits, poor control of diabetes mellitus, steroid therapy for bronchial asthma, chemotherapy for malignant diseases, and antisecretory drug usage have been demonstrated to increase the risk of several infectious diseases, including candidiasis (1, 2). It has been reported that smoking increases the risk of esophageal candidiasis due to its effects on hygiene and the occurrence of oral candidiasis (16); however, this was not shown by the present findings. Esophageal candidiasis was noted more often in patients with poor control of diabetes mellitus or bronchial asthma with steroid therapy than in those without such conditions, although statistical significance was not observed. The number of subjects with malignant disease in present cohort was considered to be too small to determine its influence on esophageal candidiasis development. A univariate logistic regression analysis showed that vonoprazan, a potent acid suppressive drug, was associated with an increased occurrence of esophageal candidiasis, while neither H2RA nor conventional PPI usage was found to be a significant risk factor. Thus, RE is considered to be negatively associated with esophageal candidiasis, while vonoprazan usage for RE increases its occurrence.

The present study is associated with several limitations. It was retrospectively performed using data from a single medical center, and the majority of the subjects were socially active and productive, with relatively few young or elderly individuals. On the other hand, the subjects are considered representative of the general population, as compared with patients who visit a medical clinic for specific symptoms and are affected by disease conditions. Additional analyses are needed to clarify the risk factors for esophageal candidiasis in individuals affected by various diseases.

In conclusion, esophageal candidiasis was noted in 3.4% of individuals who underwent an EGD examination as part of a medical checkup. The presence of RE was found to be negatively associated with its occurrence, whereas HGM of the cervical esophagus did not show a preventive effect.

The authors state that they have no Conflict of Interest (COI).

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