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Clinical Characteristics of Severe Erosive Esophagitis among Patients with Erosive Esophagitis: A Case-control Study

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Abstract

Objective The risk factors associated with severe erosive esophagitis are not well defined in Japan. We aimed to evaluate the risk factors associated with the endoscopic severity of esophageal mucosal injury.

Methods Eighty consecutive Japanese patients with severe erosive esophagitis [Los Angeles (LA) classification grade C or D] who had undergone upper endoscopies in the Gastroenterology Division of Omori Red Cross Hospital between June 2010 and March 2013 were retrospectively analyzed. For each case, a control with mild erosive esophagitis (LA classification grade A or B) who was matched by sex and age was randomly selected during the same period. Among the endoscopic findings, the condition of the gastroesophageal flap valve (GEFV) was graded according to Hill's classification. We identified the risk factors for severe erosive esophagitis using a multivariable logistic regression model.

Results A poor performance status (PS) (odds ratio [OR]=17.1201, 95% confidence interval [CI]=3.0268-140.3121, p=0.0008) and an abnormal GEFV (OR=3.0176, 95% CI=1.0589-9.4939, p=0.0385) were risk factors for severe erosive esophagitis, while the presence of open-type gastric mucosal atrophy (GMA) was inversely associated with severe erosive esophagitis (OR=0.2772, 95% CI=0.1087-0.6675, p=0.0040).

Conclusion Among patients with erosive esophagitis, a poor PS and an abnormal GEFV were associated while GMA was inversely associated with severe erosive esophagitis. Drug therapy alone or in combination with physical therapy may improve the therapeutic effect on severe erosive esophagitis in patients with a poor PS.

Key words: severe erosive esophagitis, risk factor, gastroesophageal flap valve

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Introduction

The prevalence of erosive esophagitis in Japan is estimated to be low compared with findings in Western countries, although recent studies have shown that the number of patients with erosive esophagitis has been increasing in Japan (1).

Previous studies reported that the absence of *Helicobacter pylori* infection, the presence of kyphosis or gibbus in elderly subjects and size of a hiatal hernia tend to be associated with an increased risk of erosive esophagitis (2-4). The majority of cases of erosive esophagitis in Japan were of a mild type. However, in general hospitals, we sometimes experience severe cases of erosive esophagitis with episodes of gastrointestinal bleeding.

In the present case-control study, we evaluated Japanese patients with severe erosive esophagitis and defined the risk factors that contribute to its development. Recognition of the predictors of severe erosive esophagitis is clinically and eco-

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nomically important. In this study, we reviewed the medical records of patients with erosive esophagitis and analyzed the data on their comorbidities, lifestyle habits, medications and endoscopic findings.

Materials and Methods

Patients

Eighty consecutive Japanese patients (53 men, 27 women; median age: 74 years; age range: 40-96 years) with severe erosive esophagitis [Los Angeles (LA) classification grade C or D] who had undergone upper endoscopies in the Gastroenterology Division of Omori Red Cross Hospital between June 2010 and March 2013 were retrospectively analyzed. For each case, a control with mild erosive esophagitis (LA classification grade A or B) who was matched by sex and age was randomly selected from among patients who had undergone endoscopies during the same period and who had no endoscopically observed localized lesions in the upper gastrointestinal tract. The exclusion criteria were an inability to obtain a complete patient profile from the medical records and the refusal of the patient to participate in the study. The patients were also excluded if they had a history of gastric or esophageal surgery and were ineligible for inclusion if they had evident disease or Zollinger-Ellison syndrome or primary esophageal motility disorders, or if they were pregnant or lactating.

Endoscopic diagnosis

Erosive esophagitis was diagnosed based on the Los Angeles classification (5) and was divided into two categories: mild (grades A and B) and severe (grades C and D). Additionally, the presence of Barrett's epithelium was diagnosed based on the Prague C & M criteria (6). Under these criteria, Barrett's epithelium is defined as the macroscopic identification of abnormal columnar esophageal epithelium more than 1 cm in thickness, which is suggestive of a columnar-lined distal esophagus, as determined on a standard endoscopy examination with the pull-out technique. The length of Barrett's epithelium is measured in centimeters using the circumferential extent (the C extent) and the maximum extent (the M extent) above the gastroesophageal junction, identified as the proximal margin of the gastric mucosal folds.

We also examined the gastroesophageal junction to assess the geometry of the gastroesophageal flap valve (GEFV). The GEFV is formed by the sling musculature of the gastric cardia, which is located in the gastric cardia portion maintaining the acute angle of His (7) and which plays an important role as a gate against retrograde gastric flow (8-11). The GEFV condition was assessed using still images of the retroflex view of the gastric cardia and was graded I through IV according to Hill's classification (Figure) (12). We defined GEFV grades I and II as a normal GEFV and grades III and IV as an abnormal GEFV (13-15). Furthermore, on endoscopy, the gastric mucosal atrophy (GMA) was classified as closed or open type according to the Kimura-Takemoto classification (16).

Endoscopic images from these patients were retrieved from the endoscopic filing system (Olympus Medical Systems, Tokyo, Japan). All digital endoscopic images were independently and retrospectively reviewed by two trained endoscopists to investigate the endoscopic findings, including the findings related to GMA, the GEFV, erosive esophagitis, and Barrett's epithelium. If there was any inconsistency in the assessment of the digital endoscopic images, a final diagnosis was decided upon by a joint review of the images.

Patient profiles

We obtained complete patient information at the time of the initial diagnosis from each patient's medical records, including the age; sex; performance status (PS); the presence or absence of a gibbus; symptoms of heartburn, which was defined as a burning feeling rising from the stomach or the lower part of the chest towards the neck; signs of gastrointestinal bleeding such as hematemesis or tarry stool; body mass index (BMI); current regular drinking habits and current smoking habits; blood parameters, such as hemoglobin (Hb) and C-reactive protein (CRP); the presence of concomitant diseases under medical treatment; and medications. The PS was assessed using the Eastern Cooperative Oncology Group (ECOG) scale of performance status, where PS 0 means normal activity; PS 1 means certain symptoms, but still nearly fully ambulatory; PS 2 means spending <50% of daytime in bed; PS 3 means spending $\geq$50% of daytime in bed; and PS 4 means completely bedridden (17).

Statistical analyses

The statistical analyses included a chi-squared test with or without Yates' correction or Fisher's exact test to compare percentages and a Mann-Whitney U-test to compare continuous data. Various risk factors were also evaluated simultaneously using multiple logistic regression. The level of significance was defined as $p<0.05$. All of the statistical analyses were performed using the StatView software program (ver. 5.0) and JMP software program (ver. 11.2; SAS Institute, Cary, USA) and EZR (Saitama Medical Center, Jichi Medical University, Japan) (18).

Ethics

The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the Omori Red Cross Hospital.

Results

Clinical characteristics of the patient profiles

A comparison of the patient profiles between the case group (with severe erosive esophagitis) and the control group (with mild erosive esophagitis) is shown in Table 1.

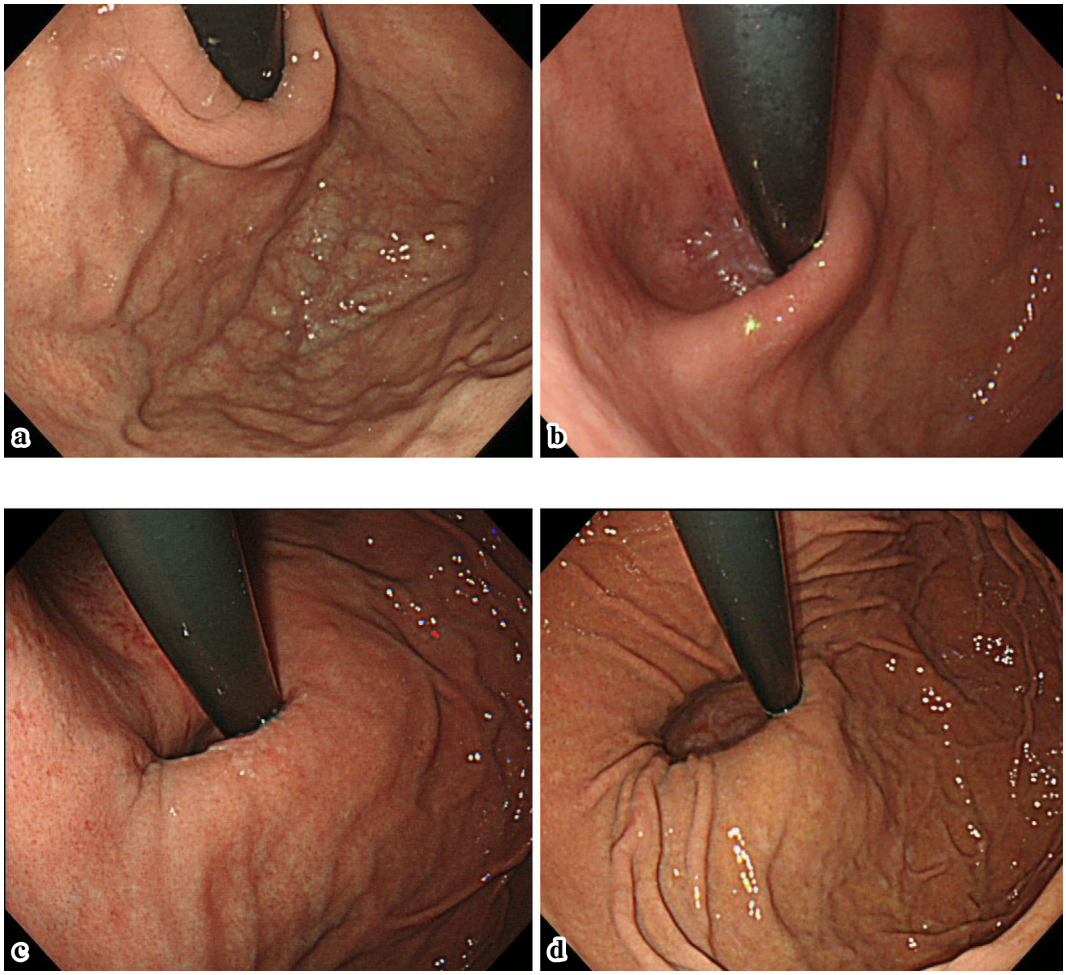

Figure. **Retroflexed view of the gastroesophageral flap valve. (a) Grade I. The prominent fold of tissure along the lesser curvature was closely apposed to the endoscope. (b) Grade II. The fold was present but there would be periods of opening and rapid closing around the endoscope. (c) Grade III. The fold was not prominent and the endoscope was not gripped tightly by the ridge. (d) Grade IV. There was no fold and the lumen of the esophagus gaped open, allowing the squamous epithelium to be viewed below.**

The subjects were 27 females and 53 males, and the median (range) age was 74.0 (40.0-96.0) years in both the case and control groups. The results of a univariate analysis of the clinical factors showed that there were significantly more patients with a poor general condition, or PS 3 or 4 ($p< 0.0001$); having a gibbus ($p=0.0375$); and having a low BMI ($p=0.0191$) in the case group than in the control group. There was no significant difference in the prevalence of heartburn symptoms between the two groups, but patients with signs of gastrointestinal bleeding were predominant in the case group. The prevalence of current regular drinking and current smoking habits was not significantly different between the two groups. Regarding the blood parameters, anemia and a mounting inflammatory reaction were significantly more frequent in the case group than in the control group.

Prevalence of comorbidities

The prevalence of comorbidities in patients with severe erosive esophagitis and the control group is shown in Table 2. There was no difference in the prevalence of comorbidities between the two groups, other than for dementia, which was more frequently present in the case group than in the control group.

Prevalence of medication-associated risk factors

The findings regarding the daily use of medicine are shown in Table 3. Only proton pump inhibitor (PPI) use was predominant in the case group, whereas other medications did not significantly differ in use between the groups. Patients using PPIs were found in both groups. PPI treatment might change the grade of esophagitis from severe to mild. Patients with severe esophagitis treated by PPIs were considered extremely intractable cases among those with erosive esophagitis.

Endoscopic findings

The endoscopic findings are shown in Table 4. Esophageal complications were observed only in the severe group: 15 (18.8%) had bleeding, 7 (8.8%) had stenosis, and 27

Table 1. Clinical Characteristics of the Patients with Severe EE (n=80) and with Mild EE as the Control (n=80).

	Sever EE (n=80)	Control (n=80)	p value
Age: median (range) in years	74.0 (40.0-96.0)	74.0 (40.0-96.0)	1.0000
Sex: male; n (%)	53 (66.25)	53 (66.25)	1.0000
PS: n (%)			
0	39 (48.8)	63 (78.8)	
1	15 (18.8)	11 (13.8)	
2	5 (6.3)	3 (3.8)	0.0002
3	11 (13.8)	0	
4	10 (12.5)	3 (3.8)	
PS 3 or 4: n (%)	21 (26.3)	3 (3.8)	<0.0001
Gibbus: n (%)	19 (23.8)	9 (11.3)	0.0375
Heartburn symptoms: n (%)	42 (52.5)	42 (52.5)	1.0000
Gastrointestinal bleeding signs: n (%)	30 (37.5)	4 (5.0)	<0.0001
BMI: median (range)	21.9 (14.6 - 35.5)	23.0 (16.4 - 36.0)	0.0191
Current smoker: n (%)	29 (36.3)	20 (25.0)	0.1227
Brinkman index: mean (range)	301.5 (0 - 2,880)	235 (0 - 1,660)	0.3830
Heavy drinker: n (%)	19 (23.8)	16 (20.0)	0.5662
Blood examination			
Hb: mean (median) (g/dL)	11.7 (12.1)	13.2 (14.1)	0.0013
CRP (mg/dL)	2.330 (0.825)	0.384 (0.070)	<0.0001

BMI: Body mass index

CRP: C-reactive protein

Table 2. Prevalence of Comorbidities in Patients with Severe EE and the Control Group.

Comorbidities	Sever EE (n=80)	Control (n=80)	p value
Diabetes: n (%)	18 (22.5)	19 (23.8)	0.8513
Hypertension: n (%)	28 (35.0)	33 (41.3)	0.4157
Asthma: n (%)	3 (3.8)	2 (2.5)	0.6496
Chronic renal failure: n (%)	4 (5.0)	4 (5.0)	1.0000
Chronic heart failure: n (%)	6 (7.5)	7 (8.8)	0.7723
Ischemic heart disease: n (%)	5 (6.3)	1 (1.3)	0.0960
Cerebrovascular disease: n (%)	14 (17.5)	12 (15.0)	0.6682
Gastroduodenal ulcer: n (%)	16 (20.0)	17 (21.3)	0.8451
COPD: n (%)	5 (6.3)	1 (1.3)	0.0960
Neurodegenerative disease: n (%)	6 (7.5)	6 (7.5)	1.0000
Dementia: n (%)	10 (12.5)	2 (2.5)	0.0163
Arrhythmia: n (%)	2 (2.5)	4 (5.0)	0.4053
Depression: n (%)	5 (6.3)	8 (10.0)	0.3854
Osteoporosis: n (%)	6 (7.5)	4 (5.0)	0.5136
Liver cirrhosis: n (%)	3 (3.8)	1 (1.3)	0.3112

COPD: chronic obstructive pulmonary disease

(33.8%) had an ulcer. The prevalence of Barrett's epithelium was significantly higher in the case group than in the control group (p<0.0001). A total of 58 (72.5%) patients had no atrophic gastritis (GMA closed type) in the case group, and this proportion was significantly higher (p=0.0001) than in the control group (34 patients, 42.5%). In addition, the prevalence of an abnormal GEFV (Hill grade III or IV) was significantly higher in the severe group (71 patients, 88.8%) than in the case group (50 patients, 62.5%; p=0.0001).

Clinical factors associated with severe erosive esophagitis

The results of the multiple logistic regression analysis of the clinical factors associated with severe erosive esophagitis

Table 3. Prevalence of Medicational Risk Factor in Patients with Severe EE and the Control Group.

Medications	Sever EE (n=80)	Control (n=80)	p value
PPI: n (%)	25 (31.3)	14 (17.5)	0.0428
NSAIDs: n (%)	14 (17.5)	8 (10.0)	0.1684
Steroids: n (%)	5 (6.3)	1 (1.3)	0.0960
Bisphosphonates: n (%)	5 (6.3)	4 (5.0)	0.7315
Calcium blockers: n (%)	16 (20.0)	24 (30.0)	0.1441
ACE inhibitors: n (%)	19 (23.8)	19 (23.8)	1.0000
β-blockers: n (%)	5 (6.3)	2 (2.5)	0.2462
Nitrites: n (%)	4 (5.0)	3 (3.8)	0.6991
Xanthines: n (%)	2 (2.5)	0 (0)	0.1547
Sulfonylureas: n (%)	7 (8.8)	7 (8.8)	1.0000
Anti-thrombotic medicines including low-dose aspirin: n (%)	20 (25.0)	19 (23.8)	0.8539
Cerebral nerve and antipsychotic drugs: n (%)	16 (20.0)	15 (18.8)	0.8415

PPI: proton pump inhibitor

ACE: angiotensin-converting enzyme

Table 4. Endoscopic Findings

Endoscopic findings	Sever EE (n=80)	Control (n=80)	p value
Esophageal complications			
Bleeding: n (%)	15 (18.8)	0	<0.0001
Stenosis: n (%)	7 (8.8)	0	0.0068
Ulcer: n (%)	27 (33.8)	0	<0.0001
GMA open type: n (%)	22 (27.5)	46 (57.5)	0.0001
Hill's grade: n (%)			
I	0	2 (2.5)	<0.0001
II	9 (11.2)	28 (35.0)	
III	27 (33.8)	31 (38.8)	
IV	44 (55.0)	19 (23.7)	
Hill's grades III and IV: n (%)	71 (88.8)	50 (62.5)	0.0001
Barrett's epithelium: n (%)	56 (70.0)	22 (27.5)	<0.0001

GMA: gastromucosal atrophy

are shown in Table 5. After adjustments for clinical factors, a poor PS (odds ratio [OR] = 17.1201, 95% confidence interval [CI] = 3.0268-140.3121, p=0.0008) and an abnormal GEFV (OR = 3.0176, 95% CI = 1.0589-9.4939, p=0.0385) were found to be risk factors for severe erosive esophagitis, while the presence of open-type GMA was inversely associated with severe erosive esophagitis (OR = 0.2772, 95% CI = 0.1087-0.6675, p=0.0040). Signs of gastrointestinal bleeding (OR = 4.3351, 95% CI = 1.2074-18.5115, p= 0.0239), CRP (OR = 1.8122, 95% CI = 0.3251-0.8621, p= 0.0053) and a prevalence of Barrett's epithelium were also significantly associated with severe erosive esophagitis (OR = 9.6271, 95% CI = 3.9626-25.7395, p <0.0001).

Discussion

This study examined the presence of severe erosive esophagitis and the risk factors associated with its severity through a retrospective case-control study matched by age and sex. Based on the results of the multivariate analysis, a poor PS and an abnormal GEFV (Hill grade III or IV) showed a strong association with severe erosive esophagitis. In contrast, the presence of open-type GMA was inversely related to severe erosive esophagitis (OR, 0.2772).

Several reasons may explain the finding that a poor PS was related to severe erosive esophagitis. For example, poor PS patients are kept in the supine position for a long time, causing delayed gastric emptying, which may increase the likelihood of gastroesophageal reflux. Previous studies have

Table 5. Multiple Logistic Regression Analysis Using Parameters with a p value of Less than 0.1 Identified from Univariate Regression Analysis.

Clinical factors	Odds ratio	95% CI	p value
PS 3 and 4	17.1201	3.0268 - 140.3121	0.0008
Hill's grades III and IV	3.0176	1.0589 - 9.4939	0.0385
GMA: open type	0.2772	0.1087 - 0.6675	0.0040
Gastrointestinal bleeding signs	4.3351	1.2074 - 18.5115	0.0239
CRP	1.8122	0.3251 - 0.8621	0.0053
Barrett's epithelium: n (%)	9.6271	3.9626 - 25.7395	<0.0001
Gibbus	0.2796	0.0528 - 1.2856	0.1027

CI: confidence interval

suggested that the normal cardia is more competent in the supine position than in the upright position, and the progression from a normal lower esophageal sphincter (LES) to one that is completely defective correlates with dysfunction of the GEFV. In poor PS patients with an abnormal GEFV, the protective effect of the LES in the supine position may be impaired. Furthermore, the LES has been shown to be commonly defective in poor PS patients, regardless of body position, and subsequent bipositional reflux, which predominates in the supine position, causes severe esophageal mucosal damage (19, 20). Gastric fluid would consequently be able to flow back into the esophagus in the supine position but could not be cleared effectively within a short period, resulting in longer esophageal acid exposure and therefore greater mucosal damage (19, 20).

Gastrointestinal bleeding signs, CRP positivity, and Barrett's epithelium were not causes of severe esophagitis but might instead be considered a result. CRP positivity in particular might reflect the inflammation of the esophageal mucosa and/or severe erosive esophagitis coupled with a poor PS, possibly leading to aspiration pneumonia caused by acid reflux. The presence of a gibbus, a low BMI, and comorbid dementia, which were predominant in cases of severe erosive esophagitis in the univariate analysis, might be reflective of a poor PS as well.

Hill's classification is useful as an endoscopic predictor of the severity of esophagitis because of the high reproducibility of the findings. Previous studies have reported a correlation between hiatal hernia and erosive esophagitis. However, the endoscopic diagnosis of a hiatal hernia is poorly reproducible and depends largely on the distension of the stomach. Previous reports have suggested that an abnormal GEFV configuration may serve as an independent factor predicting a poor response to PPI therapy (21, 22). The results of our survey showed that PPI use was more frequent in the severe erosive esophagitis group, suggesting the possibility of PPI resistance and that mucosal healing is limited with PPI therapy alone. In addition, Chang et al. demonstrated that the prevalence of acid reflux in the supine position correlated more closely with loosening of the GEFV than the upright position (23). It was speculated that, in the abnormal GEFV group, the gastric contents were able to reflux more easily in the supine position, with a lower gravity effect, due to attenuation of the collar sling musculature of the flap valve (24). Drug therapy either alone or in combination with physical therapy may improve the therapeutic effect on severe erosive esophagitis in patients with a poor PS. In accordance with the findings of previous reports (24-27), we showed that the presence of GMA was negatively correlated with the severity of erosive esophagitis. This may be due to *Helicobacter pylori* infection, which prevents erosive esophagitis through the induction of atrophic gastritis and reduced acid secretion (28).

In the present study, lifestyle-related factors, such as smoking, drinking habits, and obesity, were less closely associated with the severity of erosive esophagitis in the multiple logistic regression analysis than other factors. In previous reports (29-39), these parameters were found to be risk factors for erosive esophagitis, but the roles of lifestyle risk factors in erosive esophagitis are still poorly defined and remain controversial (40-44). Thus, lifestyle-related factors might be risk factors for erosive esophagitis (and especially mild erosive esophagitis, such as LA grade A or B) but may not be related to the severity of erosive esophagitis. In addition, even if patients drink or smoke excessively and are obese, their erosive esophagitis may not be severe unless their PS becomes poor. Another reason for the poor relationship between lifestyle profiles and the severity of erosive esophagitis might be that our study did not include super-obese patients but did include relatively old patients and patients with a poor PS who did not smoke or drink.

Several limitations associated with the present study warrant mention. First, this was a retrospective study, and there might have been bias in reviewing the findings of the endoscopic photographs. Second, the presence of *H. pylori* was not determined, although the presence of GMA reflects *H. pylori* infection. Therefore, the evaluation of GMA compensates for this limitation to a certain degree. Third, this study was an age-matched case-control study, which might have prevented age from being identified as a significant risk factor, although esophagitis is common in the elderly.

In conclusion, among patients with erosive esophagitis, a poor PS and an abnormal GEFV were associated while GMA was inversely associated with severe erosive esophagi-

tis. The endoscopic findings regarding the GEFV and GMA as well as the PS are therefore useful for predicting the risk of erosive esophagitis. However, a longitudinal follow-up study in a large cohort may be needed to further evaluate the risk factors and clarify the path to prevention.

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

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