

Observational Study

Factors associated with complicated erosive esophagitis: A Japanese multicenter, prospective, cross-sectional study

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Abstract

AIM

To assess the clinical characteristics of patients with complicated erosive esophagitis (EE) and their associated factors.

METHODS

This prospective, cross-sectional study included patients diagnosed with EE by upper gastrointestinal endoscopy between October 2014 and March 2015 at 106 Japanese hospitals. Data on medical history, general condition, gastrointestinal symptoms, lifestyle habits, comorbidities, and endoscopic findings were collected using a standard form to create a dedicated database. Logistic regression analysis was used to calculate adjusted odds ratios (aOR) and 95%CI for the association with complicated EE.

RESULTS

During the study period, 1749 patients diagnosed with EE, 38.3% of whom were prescribed proton pump inhibitors (PPIs) were included. Of them, 143 (8.2%) had EE complications. Esophageal bleeding occurred in 84 (4.8%) patients, esophageal strictures in 45 (2.6%) patients, and 14 (0.8%) patients experienced both. Multivariate analysis showed that increased age (aOR: 1.05; 95%CI: 1.03-1.08), concomitant use of psychotropic agents (aOR: 6.51; 95%CI: 3.01-13.61), and Los Angeles grades B (aOR: 2.69; 95%CI: 1.48-4.96), C (aOR: 15.38; 95%CI: 8.62-28.37), and D (aOR: 71.49; 95%CI: 37.47-142.01) were significantly associated with complications, whereas alcohol consumption 2-4 d/wk was negatively associated (aOR: 0.23; 95%CI: 0.06-0.61). Analyzing associated factors with each EE complication separately showed esophageal ulcer bleeding were associated with increased age (aOR: 1.05; 95%CI: 1.02-1.07) and Los Angeles grades B (aOR: 3.60; 95%CI: 1.52-8.50), C (aOR: 27.61; 95%CI: 12.34-61.80), and D (aOR: 119.09; 95%CI: 51.15-277.29), while esophageal strictures were associated with increased age (aOR: 1.07; 95%CI: 1.04-1.10), gastroesophageal reflux symptom (aOR: 2.51; 95%CI: 1.39-4.51), concomitant

use of psychotropic agents (aOR: 11.79; 95%CI: 5.06-27.48), Los Angeles grades C (aOR: 7.35; 95%CI: 3.32-16.25), and D (aOR: 20.34; 95%CI: 8.36-49.53) and long-segment Barrett's esophagus (aOR: 4.63; 95%CI: 1.64-13.05).

CONCLUSION

Aging and severe EE were common associated factors, although there were more associated factors in esophageal strictures than esophageal ulcer bleeding. Despite the availability and widespread use of PPIs, EE complications are likely to remain a problem in Japan owing to the aging population and high-stress society.

Key words: Complication; Erosive esophagitis; Proton pump inhibitor; Esophageal ulcer bleeding; Esophageal stricture

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Core tip: This nationwide prospective survey in Japan evaluated the clinical characteristics of complicated erosive esophagitis (EE) and its associated factors at the time of proton pump inhibitors (PPIs) availability in real-world clinical settings. Our results indicate that aging and severe EE were common associated factors, although there were more associated factors in esophageal strictures than esophageal ulcer bleeding, indicating that pathophysiology of esophageal strictures was more complex than esophageal ulcer bleeding. Despite the availability and widespread use of PPIs, EE complications are likely to remain a problem in Japan owing to the aging population and high-stress society.

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INTRODUCTION

The prevalence of erosive esophagitis (EE) was previously considered much lower in Asian countries, including Japan, than in Western countries^[1]. In recent years, however, the prevalence of EE has increased in Japan^[2,3]. The major esophageal complications of EE include ulcer bleeding and strictures. Although death from EE is uncommon, these complications are associated with significant morbidity and mortality rates^[4].

Because reflux of acidic gastric contents into the esophagus plays a major role in the pathogenesis of EE, acid suppression is currently the most effective therapeutic approach. During the last two decades,

many pharmacological studies and large clinical trials have shown the superiority of proton pump inhibitors (PPIs) over other drugs, including antacids, prokinetics, and H₂-receptor antagonists^[5]. PPIs are now considered the mainstay of anti-reflux treatment and are extensively prescribed, not only by gastroenterologists and general practitioners but also by non-GI specialists^[6]. Although the ready availability and widespread use of PPIs have altered the presentation of complicated EE, little is known about its epidemiology. This nationwide prospective survey in Japan therefore evaluated the frequency of complicated EE and its associated factors at the time of PPI availability in real-world clinical settings.

MATERIALS AND METHODS

Study design

This multicenter, prospective, cross-sectional survey was conducted between October 2014 and March 2015 by members of the Gastroesophageal Reflux Disease (GERD) Society, a Japanese GERD study group, at 106 centers located throughout Japan. These centers included 26 university hospitals, 76 public hospitals, and four national hospitals. This study included all patients with a final diagnosis of EE. The demographic and clinical characteristics of these patients were evaluated, including medical history, general condition, gastrointestinal (GI) symptoms, lifestyle habits, comorbidities, and endoscopic findings. Each hospital recorded detailed information on EE patients and sent this information to a central database. This study was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Research issued by the Ministry of Health, Labour and Welfare of Japan, and was approved by the ethics committee of each center and of Kawasaki Medical School, Kurashiki, Japan (Study Number: 1883). This study was registered at the University Hospital Medical Information Network (UMIN registration ID: UMIN000014157).

Inclusion and exclusion criteria

All consecutive patients aged ≥ 50 years with a final diagnosis of EE were enrolled in this study. EE was defined as mucosal breaks on the esophagus and categorized as Los Angeles (LA) classification grades A, B, C and D^[7]. All included patients provided written informed consent. EE patients were excluded if they had a history of malignancy, GI resection, gastrostomy, or endoscopic resection (including endoscopic mucosal resection or endoscopic submucosal dissection).

Endoscopic findings

EE-related complications, including esophageal ulcer bleeding, strictures, and perforation, were recorded. The endoscopic extent of gastric mucosal atrophy was classified as described^[8]. Long-segment Barrett's

esophagus was diagnosed by endoscopic identification of columnar epithelium extending more than 3 cm into the esophagus without histological evidence of intestinal metaplasia. Concurrent findings during endoscopy, such as hiatus hernia, gastritis, or gastroduodenal ulcers were also recorded. The judging panel consisted of four endoscopic specialists (KH, TJ, KN, and KI) qualified by the Japan Gastroenterological Endoscopy Society made the final diagnosis of EE complications. If the panel could not reach a consensus diagnosis on EE-related complications, the patient in question was excluded from those with EE-related complications (Figure 1).

Data collection

Each doctor who participated in this research study conducted face-to-face interviews with all participants using a questionnaire made for this study. Information obtained *via* the questionnaire included patient characteristics, EE treatment, concomitant drugs, comorbidities, and lifestyle, including alcohol consumption, smoking status, and general condition (nasogastric feeding, bedridden, or both). Other patient characteristics included sex, age, height, body weight, and GI symptoms at the time of the endoscopy. Height and body weight were used to calculate body mass index. Reflux symptoms were based on patient reports of heartburn and acid regurgitation. If patients complained of reflux symptoms, the duration of each symptom was determined. Upper GI symptoms were based on patient reports of epigastric pain, epigastric burning, heavy stomach feeling, and early satiety. Lower GI symptoms were based on patient reports of abdominal fullness, constipation, and diarrhea. Infection with *Helicobacter pylori* (*H. pylori*) was defined as at least one positive result on the following tests: histology, culture, rapid urease tests using endoscopic biopsy specimens, *H. pylori*-specific antibody in patient serum, urea breathing test, or stool antigen test. Patients were classified as never smokers, ex-smokers or current smokers. Regarding alcohol intake, patients were classified as never drinkers, ex-drinkers or current drinkers. Patients classified as current drinkers were subclassified by weekly frequency of drinking as less than once, two to four times, or five or more times.

End-points

The primary end-point was the clinical characteristics of patients with EE-related complications, including esophageal ulcer bleeding and strictures. The secondary end-point was to clarify the factors associated with complicated EE.

Statistical analysis

Continuous variables are reported as mean and SD, whereas categorical variables are reported as percentages. Student's *t*-tests were used to compare two independent groups. The χ^2 test (with Yates correction,

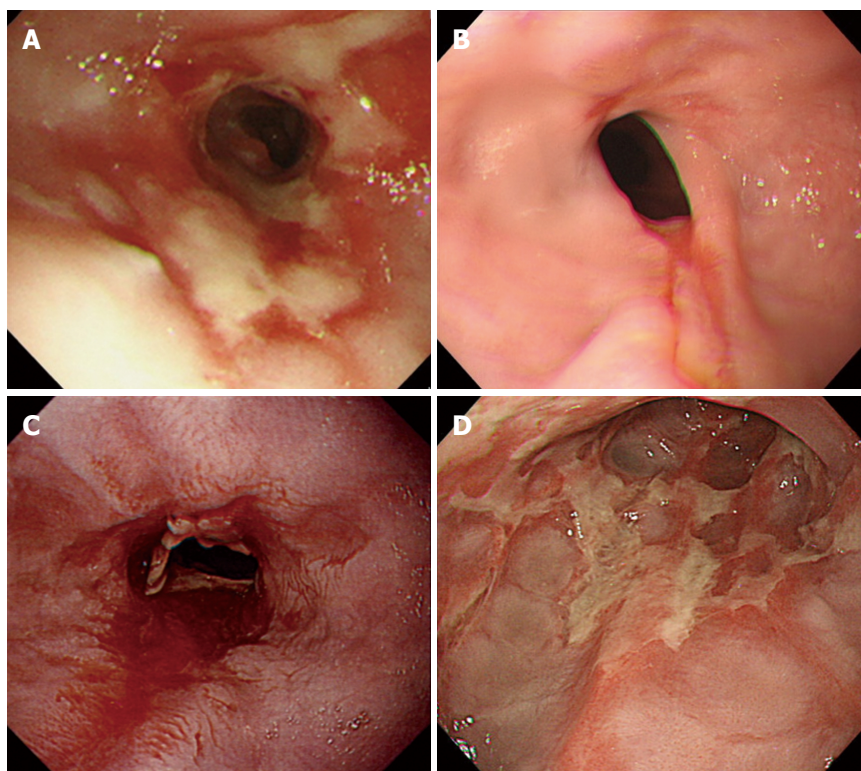


Figure 1 Endoscopic images of typical cases with erosive esophagitis-related complications. A and C: Esophageal stricture with ulcer bleeding; B and D: Esophageal stricture with ulcer.

if required) was used to compare percentages. Logistic regression analysis was used to calculate odds ratios (ORs) and 95% CIs for the association with complications of EE. Multivariate logistic regression analysis included all factors determined by univariate analysis to be associated with complications. OR was regarded as an estimate of the relative risk of factors associated with complicated EE. Statistical significance was defined at $P < 0.05$. All statistical analyses were performed using JMP 12.0.1 and SAS 9.4 (SAS Institute, Cary, NC, United States).

RESULTS

Participant description

During the study period between October 2014 and March 2015, 1817 were diagnosed with EE. Of them, 68 (3.7%) were excluded for the following reasons: age < 50 years (61 patients), insufficient data (four patients), history of GI surgery (two patients), and lack of esophageal mucosal breaks (one patient). The study cohort therefore consisted of 1749 participants (1044 men and 705 women, mean age 68.0 ± 9.6). Of these patients, 995, 508, 162, and 84 were diagnosed with LA grades A, B, C, and D, respectively. Of the 1,749 patients with EE, 143 (8.2%) had complications, including 84 (4.8%) with esophageal ulcer bleeding, 45 (2.6%) with esophageal strictures, and 14 (0.8%) with both.

Clinical characteristics in EE patients with and without complications

Table 1 shows the clinical characteristics of the 143 EE patients with complications and the 1606 without complications. The presence of complications was associated with older age, female sex, and being bedridden. The percentage of EE patients with reflux-related symptoms was higher in patients who had complications than in those without complications (Table 2), although their duration of heartburn symptoms did not differ significantly ($P = 0.226$). Other GI symptoms, including epigastric pain, epigastric burning, and constipation, were more frequent in EE patients with than without complications (Table 2). There were a higher percentage of current drinkers (two to four times per week frequency) among patients with uncomplicated EE than with complicated EE. Smoking status did not differ significantly in these two groups (Table 1). Patients with EE complications had more severe EE on endoscopy than those without complications (Table 3). The frequency of endoscopic gastric mucosal atrophy, defined by the Kimura-Takemoto classification (C1-O3), was similar in the two groups. The rates of hiatal hernia and Barrett's epithelium were higher in patients with than without EE-related complications. Assessments of comorbidities showed that cerebral infarction, dementia, and kyphosis occurred more frequently in EE patients with than without complications (Table 1), and that patients with complications used more

Table 1 Demographic and clinical characteristics of erosive esophagitis patients with and without complications *n* (%)

	With complications (<i>n</i> = 143)	Without complications (<i>n</i> = 1606)	<i>P</i> value
Sex (M/F)	74/69	970/636	0.043
Age (years old)	74.4 ± 11.0	67.4 ± 9.2	< 0.001
BMI (kg/m ²)	23.2 ± 3.8	23.8 ± 3.5	0.074
General condition (tube-fed/bedridden/tube-fed + bedridden)	0/8/0	1/5/1	< 0.001
Consultation behavior (outpatient/inpatient/emergency patient)	90/26/27	1511/83/12	< 0.001
Smoking (never/current smoker/ex-smoker)	94/16/33	955/234/417	0.311
Duration of smoking cessation (yr)	16.8 ± 13.7	14.5 ± 13.3	0.359
Alcohol drinking			< 0.001
Never	76 (53.1)	711 (44.3)	
Current			
< 1 d per week	10 (7.0)	199 (12.4)	
2-4 d per week	4 (2.8)	192 (12.0)	
> 5 d per week	38 (26.6)	432 (26.9)	
Ex-drinker	15 (10.5)	72 (4.5)	
Duration of drinking cessation (yr)	8.8 ± 9.7	9.0 ± 10.8	0.957
Comorbidities			
Hypertension	71 (49.7)	724 (45.1)	0.293
Diabetes mellitus	26 (18.2)	282 (17.6)	0.851
Hyperlipidemia	33 (23.1)	391 (24.3)	0.734
Cerebrovascular disease	22 (15.4)	83 (5.2)	< 0.001
Liver cirrhosis	4 (2.8)	30 (1.9)	0.441
Ischemic cardiac disease	13 (9.1)	85 (5.3)	0.058
Collagen disease	6 (4.2)	34 (2.1)	0.111
Dementia	13 (9.1)	11 (0.7)	< 0.001
Kyphosis	11 (7.7)	36 (2.2)	< 0.001
PPI treatment status			0.001
Never	20 (27.4)	395 (50.4)	
Continuation therapy	40 (54.8)	251 (32.1)	
On-demand therapy	2 (2.7)	35 (4.5)	
Cessation	11 (15.1)	102 (13.0)	
Concomitant medication			
Antithrombogenic	31 (21.7)	216 (13.5)	0.007
Aspirin	12 (8.4)	97 (6.0)	0.265
Antiplatelet agent	15 (10.5)	89 (5.5)	0.017
Anticoagulant agent	8 (5.6)	60 (3.7)	0.271
Antihypertensive drug	58 (40.6)	615 (38.3)	0.594
NSAID	17 (11.9)	91 (5.7)	0.003
Psychotropic	16 (11.2)	40 (2.5)	< 0.001

BMI: Body mass index; PPI: Proton pump inhibitor; NSAID: Nonsteroidal antiinflammatory drug.

antiplatelet agents (except aspirin), non-steroidal anti-inflammatory drugs, and psychoactive drugs. PPI prescribing differed significantly in the two groups, although previous history of EE did not (Table 1).

Factors associated with complications of EE

Multivariate logistic regression analysis was used to determine the factors associated with EE complications. Six factors were found to be significantly and independently associated with complications: increased age [adjusted odds ratio (aOR): 1.05; 95%CI: 1.03-1.08, $P < 0.001$], concomitant use of psychotropic agents (aOR: 6.51; 95%CI: 3.01-13.61, $P < 0.001$), and LA grades B (aOR: 2.69; 95%CI: 1.48-4.96, $P = 0.001$), C (aOR: 15.38; 95%CI: 8.62-28.37, $P < 0.001$) and D (aOR: 71.49; 95%CI: 37.47-142.01, $P < 0.001$). In contrast, consumption of alcohol two to four times per week showed a significant negative association with EE complications (aOR: 0.23; 95%CI: 0.06-0.61, $P = 0.008$) (Table 4).

Factors associated with esophageal ulcer bleeding

Multivariate logistic regression analysis was used to determine the factors associated with esophageal ulcer bleeding. Four factors were found to be significantly and independently associated with complications: increased age (aOR: 1.05; 95%CI: 1.02-1.07, $P < 0.001$), LA grades B (aOR: 3.60; 95%CI: 1.52-8.50, $P = 0.004$), C (aOR: 27.61; 95%CI: 12.34-61.80, $P < 0.001$) and D (aOR: 119.09; 95%CI: 51.15-277.29, $P < 0.001$).

Factors associated with esophageal strictures

Multivariate logistic regression analysis was used to determine the factors associated with esophageal strictures. Seven factors were found to be significantly and independently associated with complications: increased age (aOR: 1.07; 95%CI: 1.04-1.10, $P < 0.001$), reflux-related symptoms (aOR: 2.51; 95%CI: 1.39-4.51, $P = 0.002$), concomitant use of psychotropic agents (aOR: 11.79; 95%CI: 5.06-27.48, $P < 0.001$), and LA

Table 2 Symptoms at the time of endoscopy of erosive esophagitis patients with and without complications *n* (%)

	With complications (<i>n</i> = 143)	Without complications (<i>n</i> = 1606)	<i>P</i> value
Upper GI symptoms			
Heartburn	86 (60.1)	773 (48.1)	0.006
Regurgitation	54 (37.8)	428 (26.7)	0.004
Epigastric pain	34 (23.8)	261 (16.3)	0.022
Epigastric burning	28 (19.6)	149 (9.3)	< 0.001
Heavy stomach feeling	42 (29.4)	398 (24.8)	0.227
Early satiety	19 (13.3)	136 (8.5)	0.052
Lower GI symptoms			
Abdominal Bloating	10 (7.0)	165 (10.3)	0.210
Constipation	39 (27.3)	277 (17.2)	0.003
Diarrhea	7 (4.9)	117 (7.3)	0.286
Constipation/diarrhea	5 (3.5)	39 (2.4)	0.434

GI: Gastrointestinal.

Table 3 Endoscopic findings of erosive esophagitis patients with and without complications *n* (%)

	With complications (<i>n</i> = 143)	Without complications (<i>n</i> = 1606)	<i>P</i> value
Los Angeles classification			< 0.001
A	19 (13.3)	976 (60.8)	
B	30 (21.0)	478 (29.8)	
C	43 (30.1)	119 (7.4)	
D	51 (35.7)	33 (2.1)	
Gastric mucosal atrophy	82 (57.3)	930 (57.9)	0.464
Hiatal hernia	123 (86.0)	1070 (66.6)	< 0.001
Barrett's epithelium	8 (5.6)	24 (1.5)	< 0.001
<i>H. pylori</i> infection			< 0.001
Positive	10 (7.0)	134 (8.3)	
Negative	31 (21.7)	677 (42.2)	
Unknown	102 (71.3)	795 (49.5)	

H. pylori: *Helicobacter pylori*.**Table 4 Relative risk for complications of erosive esophagitis (multivariable analysis)**

	Odds ratio (95%CI)	<i>P</i> value
Ages	1.05 (1.03-1.08)	< 0.001
Alcohol drinking		
Never	1.00	-
< 1 d per week	0.73 (0.32-1.52)	0.425
2-4 d per week	0.23 (0.06-0.61)	0.008
> 5 d per week	1.32 (0.80-2.14)	0.268
Concomitant medication: psychotropic agent	6.51 (3.01-13.61)	< 0.001
Los Angeles classification grade		
A	1.00	-
B	2.69 (1.48-4.96)	0.001
C	15.38 (8.62-28.37)	< 0.001
D	71.49 (37.47-142.01)	< 0.001

grades C (aOR: 7.35; 95%CI: 3.32-16.25, $P < 0.001$), D (aOR: 20.34; 95%CI: 8.36-49.53, $P < 0.001$) and long-segment Barrett's esophagus (aOR: 4.63; 95%CI: 1.64-13.05, $P = 0.004$).

DISCUSSION

This Japanese, multicenter, prospective, cross-sectional study involving 1749 patients with EE, 38.3% of

whom were prescribed PPIs, showed that 8.2% of these patients had complications, including 4.8% with esophageal ulcer bleeding, 2.6% with esophageal strictures, and 0.8% with both. On multivariate analysis, increased age, concomitant use of psychotropic agents, and severe EE as defined by LA grades B-D was significantly associated with complications. Interestingly, moderate alcohol consumption showed a significant negative association with complications in patients with

EE. Although several studies have evaluated risk factors for EE^[9,10], this study, to our knowledge, is the first multicenter large-scale study to assess factors associated with complicated EE among Japanese patients, the majority of whom were being treated with PPIs.

Obesity, smoking, and age are risk factors for EE^[11-16], with age also being considered an important risk factor for severe EE^[17-19]. Age is associated with increased esophageal exposure to acid, although the severity of reflux symptoms decreases with age. These changes are associated with a progressive decrease in abdominal lower esophageal sphincter (LES) length and esophageal motility^[18]. Increasing EE severity in elderly subjects, such as esophageal ulcer bleeding or stricture, is related to degradation of the gastroesophageal junction and impaired esophageal clearance. Interestingly, this study also found that concomitant treatment with psychotropic agents was an independently associated factor for complicated EE. Long-term use of psychotropic agents, such as clozapine and clomipramine, has been associated with severe esophageal dilation and hypomotility accompanied by lowered visceral sensitivity, leading to excess esophageal exposure to acid and impaired acid clearance, which are considered crucial causes of complicated EE^[20]. Nevertheless, psychotropic agents differed in the ability to influence the pathophysiology of EE^[21,22]. This study, however, did not evaluate the relationships of complicated EE with the duration of use or the type of psychotropic agents, suggesting the need for further studies to clarify these points.

Because the reflux of acidic gastric content into the esophagus leads to symptoms and esophageal mucosal breaks, acid suppression is considered the most effective therapeutic approach, with PPIs being superior to other classes of drug^[5]. PPIs are now considered the mainstay of anti-reflux therapy and are extensively prescribed worldwide. This study found that patients with complicated EE were more likely to be prescribed a PPI than those without complications. Considering the previous studies showing that PPI-resistant EE is observed more frequently in patients with severe EE than those with mild EE^[23,24], it may be the case that patients with PPI-resistant EE tend to also have complications.

This study also found that moderate alcohol drinking was significantly negatively associated with complicated EE. Although this study did not clarify whether the moderate alcohol drinking was a cause or result of complicated EE, several studies have shown that consumption of large amounts of alcohol can promote regurgitation of acid into the esophagus, thereby causing EE, which is inconsistent with our result^[25,26]. Several other studies examining the risk of EE in relation to alcohol consumption have yielded contradictory outcomes. For example, alcohol use has been reported to be a risk factor for EE^[27], but its long-term effects and relationship to pathological reflux have not been

determined. Other studies, however, have suggested that alcohol exposure was not associated with the risk of EE^[28]. EE was recently reported to be significantly associated with psychosocial stress, with the severity of EE correlating with the degree of stress^[29]. Moderate amounts of alcohol may reduce psychosocial stress^[30], explaining the mechanism underlying the negative relationship between moderate alcohol drinking and complicated EE. Additional physiological studies are necessary to assess the influence of moderate amounts of alcohol on the mechanism of EE in more detail.

Analyzing associated factors with each EE complication separately revealed that aging and severe EE were common associated factors, which is consistent with previous studies^[31,32]. In this study we also found that there were more associated factors in esophageal strictures than esophageal ulcer bleeding, indicating that pathophysiology of esophageal strictures was more complex than esophageal ulcer bleeding.

This study had three limitations. First, information about patients' diets was not recorded, even though chocolate and other high-fat foods have been reported to increase the likelihood of EE^[33]. However, the impact of diet on EE was not the focus of this study. Second, this study did not evaluate the rate of drug adherence/compliance^[34]. Rather, we focused on characteristics of complicated EE, based on current Japanese clinical guidelines. Further studies will therefore be necessary to clarify these matters. Third, not only body mass index but also upper arm anthropometry and grip strength are important in the assessment of general nutritional status^[35]. Because we only evaluated general nutritional status with body mass index, further study is necessary to clarify this matter.

In conclusion, the aging of the Japanese population and increasing levels of stress associated with daily life in modern Japan will likely lead to increased rates of EE and associated complications, despite the availability and widespread use of PPIs.

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COMMENTS

Background

The prevalence of erosive esophagitis (EE) was previously considered much lower in Asian countries, including Japan, than in Western countries. In recent years, the prevalence of EE has increased in Japan. The major esophageal complications of EE include ulceration, strictures, and gastrointestinal bleeding. Although proton pump inhibitors (PPIs) have altered the presentation of complicated EE, little is known about its epidemiology.

Research frontiers

The research hotspot is to evaluate the frequency of complicated EE and its associated factors at the time of PPIs availability in real-world clinical settings by the nationwide prospective survey in Japan.

Innovations and breakthroughs

Despite the availability and widespread use of PPIs, EE related complications are likely to remain a problem in Japan. Increased age, concomitant use of psychotropic agents, and severe EE as defined by LA grades B-D were significantly associated with complications, while moderate alcohol consumption showed a significant negative association with complications.

Applications

The aging of the Japanese population and increasing levels of stress associated with daily life in modern Japan will likely lead to increased rates of EE and associated complications, despite the availability and widespread use of PPIs.

Terminology

EE-related complications included esophageal ulcer bleeding, strictures, and perforation. The endoscopic extent of gastric mucosal atrophy was classified by the Kimura-Takemoto classification. Long-segment Barrett's esophagus was diagnosed by endoscopic identification of columnar epithelium extending more than 3 cm into the esophagus without histological evidence of intestinal metaplasia.

Peer-review

Very interesting topic and some of the data provided appear indicative of EE etiologies. To improve the strength of this paper, a more comprehensive review of the international literature (*i.e.*, grey papers) may provide more compelling data to include in your review process. Further a meta-analysis would have added further credence to your findings.

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