Risk Factors for Resistance to Proton Pump Inhibitor Maintenance Therapy for Reflux Esophagitis in Japanese Women over 60 Years

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Key Words

Proton pump inhibitor • *Helicobacter pylori* • Reflux esophagitis • Lumbar kyphosis • Hiatus hernia

Abstract

Aim: The aim of this study was to evaluate risk factors for proton pump inhibitor (PPI) resistance in older Japanese female patients with reflux esophagitis evaluated by physicians. **Methods:** The study included 462 Japanese female patients aged over 60 years with reflux esophagitis who received PPI maintenance therapy for more than 6 months. **Results:** The characteristics of all 462 patients were: age: 76.4 ± 7.6 years, height: 147.2 ± 6.1 cm, weight: 49.9 ± 8.4 kg and body mass index: 24.0 ± 3.5 . The reflux esophagitis grades were A in 69.5%, B in 15.8%, C in 9.1% and D in 5.6%. *Helicobacter pylori* was positive in 60.6%. Regarding PPI maintenance therapy for clinical symptoms evaluated by the attending physicians, 66.7% were 'good control', 26.8% were 'reasonable control' and 6.5% were 'bad control: resistant'. PPI maintenance therapy was less effective in patients with more severe reflux esophagitis of grades C and D (OR: 0.027; 95% CI: 0.010–0.077) and negative *H. pylori* infection status (OR: 4.470; 95% CI: 1.631–12.247). Lumbar kyphosis and hiatus hernia were risk factors for severity grading of reflux esophagitis. **Conclusions:** PPI maintenance therapy evalu-

ated by attending physicians indicated that reflux esophagitis severity and negative *H. pylori* status were risk factors for treatment resistance.

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Introduction

Reflux esophagitis is a common disease not only in Western countries but also in Oriental countries, including Japan [1–4]. The prevalence of reflux esophagitis, especially severe esophagitis of grades C and D, is high in aged Japanese women [5–7]. Previous studies have suggested that risk factors for esophagitis in aged Japanese women are lumbar kyphosis, short height, hiatus hernia and negative *Helicobacter pylori* infection status [8, 9], whereas high body weight and lifestyle in addition to aging are important risk factors in Western countries [10–13].

Medication with a proton pump inhibitor (PPI) is the first choice of treatment for reflux esophagitis [14–19], and several studies in Japan have indicated factors for a poor response to PPI in reflux esophagitis [8, 9]. These studies demonstrated that severe esophagitis of grades C and D, negative *H. pylori* infection status and negative chronic gastritis are important factors in reflux esophagitis for a poor response to PPI. However, few studies have

Table 1. Background characteristics of patients

	Total (n = 462)
Age	76.4 ± 7.6
≥60 to <70 years	89 (19.3)
≥70 to <80 years	201 (43.5)
≥80 years	172 (37.2)
Height, cm	147.2 ± 6.1
Weight, kg	49.9 ± 8.4
BMI	24.0 ± 3.5
<25	344 (74.9)
≥25	115 (25.1)
Severity of past erosive reflux esophagitis (Los Angeles grade)	
Grade A	321 (69.5)
Grade B	73 (15.8)
Grade C	42 (9.1)
Grade D	26 (5.6)
<i>H. pylori</i> infection	
Negative	182 (39.5)
Positive	280 (60.6)
Hiatus hernia	
Negative	164 (36.2)
Positive	289 (63.8)
Lumbar kyphosis	
Negative	240 (52.3)
Positive	219 (47.7)
Effects of PPI	
Good control	308 (66.7)
Reasonable control	124 (26.8)
Bad control	30 (6.5)

Values represent number with the percentage in parentheses or mean ± SD. BMI was not correctly measured in 3 patients. Hiatus hernia was not evaluated with endoscopic examination in 9 patients. Lumbar kyphosis was not evaluated in 3 patients.

focused on older Japanese women regarding PPI therapy for reflux esophagitis. The effects of PPI maintenance treatment on reflux esophagitis have been evaluated by several methods, including endoscopic examination [8, 9], pH monitoring [20] and questionnaires [21, 22], and the risk factors for a poor response to PPI maintenance therapy in reflux esophagitis did not differ significantly between these evaluation methods.

The aim of this study was to evaluate the risk factors for a poor response during PPI maintenance therapy of more than 6 months, with a focus on older Japanese women who most frequently suffer from severe reflux esophagitis. With this aim, the characteristics of reflux esophagitis in older Japanese women were analyzed, and the PPI responses were evaluated by the attending medical physicians as 'good control', 'reasonable control' and 'bad control'.

Patients and Methods

Patients

This study included 462 female Japanese patients aged over 60 years with endoscopic reflux esophagitis who received PPI maintenance therapy for more than 6 months. The maintenance therapy was conducted with 10 mg omeprazole, 15 mg lansoprazole or 10 mg rabeprazole once per day. The patients were recruited from 25 hospitals, including Saga Medical School in Saga Prefecture, from March to April 2009. Those patients who had received surgical operation of the upper gastrointestinal tract were excluded from the present study. The patients were interviewed directly by their attending physicians regarding the effects of the PPI maintenance therapy on their clinical symptoms. Finally, the attending physicians evaluated the satisfaction with the PPI maintenance therapy by choosing from three answers: 'good control', 'reasonable control' or 'bad control'. A consensus meeting for evaluation criteria was held 3 times before the present study, and 'good control' and 'reasonable control' were defined as sensitive to PPI maintenance therapy, and 'bad control' was defined as resistant to PPI maintenance therapy. Lumbar kyphosis was diagnosed by the attending physicians with radiographic examination. A self-administered questionnaire was designed to collect the demographic data including age, weight, height, smoking and alcohol intake. Before the start of the PPI therapy, the patients received an endoscopic examination for diagnosis of hiatus hernia and reflux esophagitis according to the Los Angeles classification [23], and the worst severity was recorded if the patients received endoscopic examinations several times before PPI therapy. All the patients were tested for *H. pylori* infection using a urine test kit to detect anti-*H. pylori* immunoglobulins (Otsuka Pharmaceuticals, Tokyo, Japan). The present study was performed with approval from the Ethics Committee of the Saga Medical School.

Statistical Analysis

The patients' background characteristics were evaluated by the t test, χ^2 test or ANOVA. Univariate and multivariate conditional logistic regression analyses with the proportional hazard model plus regression procedure were used to obtain crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs). Factors with values of $p < 0.05$ in the univariate analyses were included in the multivariate analyses, and stepwise selection was employed with Statistical Analysis System (SAS) software version 9.1 (SAS Institute, Cary, N.C., USA). Differences were considered significant if the probability of the difference occurring by chance was less than 5 in 100 ($p < 0.05$).

Results

Table 1 shows the background characteristics of the patients. The mean age was 76.4 ± 7.6 years. The proportions of the age ranges were as follows: ≥ 60 to <70 years 19.3%, ≥ 70 to <80 years 43.5% and ≥ 80 years 37.2%. The patients had a height of 147.2 ± 6.1 cm, a weight of 49.9 ± 8.4 kg and body mass index (BMI) of 24.0 ± 3.5 . The proportions of the grades of erosive reflux esophagitis

Table 2. Comparisons of background with age

	60–69 years (n = 89)	70–79 years (n = 201)	>80 years (n = 172)	p value
Mean height $\pm$ SD, cm	150.9 $\pm$ 4.5	148.1 $\pm$ 5.2	144.2 $\pm$ 6.4	<0.01
Mean weight $\pm$ SD, kg	54.8 $\pm$ 9.4	50.4 $\pm$ 7.4	46.7 $\pm$ 7.6	<0.01
Mean BMI $\pm$ SD	24.1 $\pm$ 3.5	23.0 $\pm$ 3.3	22.4 $\pm$ 3.1	<0.01
Los Angeles classification (A + B vs. C + D)	84/5	173/28	137/35	<0.01
<i>H. pylori</i> infection				
Positive, %	67	59.2	58.5	NS
Hiatus hernia				
Positive, %	44.3	61.7	74.3	<0.01
Lumbar kyphosis				
Positive, %	12.5	38.5	76.4	<0.01
PPI effects (resistant/effective)	2/87	15/186	13/159	NS

NS = Not significant; resistant = bad control; effective = reasonable + good control.

Table 3. Univariate analyses of risk factors for resistance to PPI maintenance therapy

	Effective (n = 432)	Resistant (n = 30)	OR	95% CI
Mean age $\pm$ SD, years	76.3 $\pm$ 7.7	77.9 $\pm$ 6.1	0.971	0.924–1.021
Mean height $\pm$ SD, cm	147.2 $\pm$ 6.1	146.8 $\pm$ 6.7	1.010	0.951–1.073
Mean weight $\pm$ SD, kg	49.8 $\pm$ 8.4	50.5 $\pm$ 8.0	0.990	0.948–1.034
Mean BMI $\pm$ SD	23.0 $\pm$ 3.5	23.4 $\pm$ 3.0	0.967	0.873–1.071
Los Angeles classification (A + B vs. C + D)	388/43	6/25	0.022	0.008–0.061*
<i>H. pylori</i> infection				
Positive, %	63.3	20.0	6.991	2.766–17.272*
Hiatus hernia				
Positive, %	62.9	66.7	0.846	0.386–1.853
Lumbar kyphosis				
Positive, %	46.5	65.5	0.458	0.208–1.007

* p < 0.01.

were grade A in 69.5% (n = 321), grade B in 15.8% (n = 73), grade C in 9.1% (n = 42) and grade D in 5.6% (n = 26). The ratio of *H. pylori* infection was 60.6%, endoscopic hiatus hernia was complicated in 63.8% and the ratio of lumbar kyphosis was 47.7%. Regarding PPI maintenance therapy for clinical symptoms, 66.7% of all patients were categorized as 'good control', 26.8% as 'reasonable control' and 6.5% as 'bad control'.

Table 2 shows the patients' characteristics divided into three age groups of 60–69 years, 70–79 years and >80 years. The height, weight and BMI decreased in an age-related manner. The ratios of severe reflux esophagitis of grades C and D, hiatus hernia and kyphosis significantly increased with age. Aging did not influence

the therapeutic evaluation of PPI or the *H. pylori* infection ratio.

The categorizations of the PPI effects (resistant vs. sensitive) evaluated by the attending physicians are shown in table 3. PPI maintenance therapy was more effective in patients with mild reflux esophagitis of grades A and B, and was also more effective in *H. pylori*-positive than in *H. pylori*-negative patients. Other factors including age, height, weight, BMI, hiatus hernia and lumbar kyphosis had no influence on PPI maintenance therapy. The patients were prescribed three different PPI in the present study for maintenance therapy of reflux esophagitis, 10 mg omeprazole, 15 mg lansoprazole or 10 mg rabeprazole (data are not shown in table 3). The effect was not differ-

Table 4. Multivariate logistic regression analyses of risk factors for resistance to PPI maintenance therapy

Variable	OR	95% CI	p value
Los Angeles classification (A + B vs. C + D)			
LA: C + D	0.027	0.010–0.077	<0.01
<i>H. pylori</i> infection			
Positive	4.470	1.631–12.247	<0.01

LA = Los Angeles.

Table 5. Comparison between two Los Angeles (LA) classification groups: A + B vs. C + D

	LA: A + B (n = 394)	LA: C + D (n = 68)	p value
Mean age $\pm$ SD, years	75.9 $\pm$ 7.7	79.2 $\pm$ 6.3	<0.01
Mean height $\pm$ SD, cm	147.5 $\pm$ 5.9	145.1 $\pm$ 6.8	<0.01
Mean weight $\pm$ SD, kg	50.1 $\pm$ 8.5	48.8 $\pm$ 8.0	NS
Mean BMI $\pm$ SD	23.0 $\pm$ 3.6	23.2 $\pm$ 3.2	NS
<i>H. pylori</i> infection			
Positive, %	63.6	38.2	<0.01
Hiatus hernia			
Positive, %	61.3	79.7	<0.01
Lumbar kyphosis			
Positive, %	43.5	74.2	<0.01

NS = Not significant.

Table 6. Comparison between two lumbar kyphosis groups: positive vs. negative

	Positive (n = 219)	Negative (n = 240)	p value
Mean age $\pm$ SD, years	80.6 $\pm$ 6.3	72.6 $\pm$ 6.7	<0.01
Mean height $\pm$ SD, cm	144.3 $\pm$ 5.9	149.7 $\pm$ 5.1	<0.01
Mean weight $\pm$ SD, kg	48.0 $\pm$ 8.0	51.6 $\pm$ 8.4	<0.01
Mean BMI $\pm$ SD	23.0 $\pm$ 3.4	23.0 $\pm$ 3.6	NS
Los Angeles classification (A + B vs. C + D)	169/50	222/18	<0.01
<i>H. pylori</i> infection			
Positive, %	57.3	63.8	NS
Hiatus hernia			
Positive, %	78.2	49.4	<0.01

Lumbar kyphosis was not evaluated in 3 patients. NS = Not significant.

ent among these three PPI: omeprazole versus lansoprazole versus rabeprazole, sensitive 116, 153 and 163 patients, and resistant 8, 15 and 7 patients, respectively.

The results of the multivariate analyses are shown in table 4. The risk factors for resistant to PPI maintenance therapy were severe reflux esophagitis of grades C and D (OR: 0.027; 95% CI: 0.010–0.077) and negative *H. pylori* infection status (OR: 4.470; 95% CI: 1.631–12.247).

Comparisons of the patients' characteristics for several factors including the severity of reflux esophagitis and lumbar kyphosis were carried out. Severe reflux esophagitis was more common in patients with older age, short height, negative *H. pylori* infection, hiatus hernia and lumbar kyphosis (table 5). Complications of lumbar kyphosis were related to older age, short height, low body weight, severe reflux esophagitis and hiatus hernia (table 6).

Discussion

This study targeted elderly women, and the therapeutic effects of PPI maintenance therapy on reflux esophagitis were evaluated by their attending physicians. The results revealed that more severe reflux esophagitis (grades C and D) and negative *H. pylori* infection status were risk factors for treatment resistance in elderly Japanese women with reflux esophagitis. Specifically, PPI maintenance therapy was less effective in patients with severe reflux esophagitis of grades C and D (OR: 0.027; 95% CI: 0.010–0.077) and negative *H. pylori* infection status (OR: 4.470; 95% CI: 1.631–12.247), while body weight, BMI and age were not related to PPI maintenance therapy. These risk factors for older Japanese women were similar to the risk factors demonstrated in previous studies focusing on Japanese patients with reflux esophagitis [8, 9, 20]. Most previous studies evaluated the effects of PPI on reflux esophagitis by endoscopic examination, pH monitoring and questionnaires [8, 9, 20–22, 24–33]. However, the present study indicates that evaluation of the therapeutic effects of PPI by the physicians who take care of reflux patients in daily clinical situations may be convenient and useful compared with evaluation by endoscopy and/or questionnaires.

This study confirmed that negative *H. pylori* infection status was a risk factor for resistance to PPI treatment in patients with reflux esophagitis [8, 9]. The ratio of *H. pylori* infection was still high, up to 60%, in the present study, and the positive rate increases in an age-related manner in Japan [34, 35], indicating that the percentage

of PPI resistance in patients with reflux esophagitis may increase in the near future in Japan. The increased prevalence of reflux esophagitis in aged females was supported by previous reports that the ratio of negative *H. pylori* infection status was high in patients with reflux esophagitis compared with control subjects in Japan [36–42].

The percentage of patients with severe esophagitis of grades C and D was 14.7%, which was higher than the percentages in other studies performed in Japan, but did not differ significantly from those in previous Japanese studies focusing on elderly females [3–7, 43–46], although the prevalence of severe esophagitis in females was the same as that in males in Western countries [47]. The present study further indicated that the risk factors for an increase in severe reflux esophagitis of grades C and D in aged females were lumbar kyphosis, hiatus hernia, negative *H. pylori* infection status, short height and high age, which were compatible with previous reports [3–5, 8, 9].

Although both lumbar kyphosis (positive rate: 47.7%) and hiatus hernia (positive rate: 63.8%) were closely related to the severity of reflux esophagitis, as shown in previous studies [5, 48–50], those studies did not indicate that these two factors were risk factors for PPI resistance. The reason for this discrepancy was not apparent in this study, although negative for *H. pylori* infection might be a more potent risk factor for PPI resistance in older Japanese female patients with reflux esophagitis.

In conclusion, our study demonstrated the risk factors for PPI resistance in older Japanese females with reflux esophagitis based on evaluation by the attending physicians. More severe reflux esophagitis (grades C and D) and negative *H. pylori* infection status were risk factors for treatment resistance in elderly Japanese women with reflux esophagitis. These findings provide an important clinical tool for medical physicians to treat PPI-refractory erosive esophagitis.

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