

Contents lists available at [ScienceDirect](http://ScienceDirect.com)

## International Journal of Gerontology

journal homepage: [www.ijge-online.com](http://www.ijge-online.com)

## Original Article

Clinical Characteristics of Elderly Patients with Refractory Gastroesophageal Reflux Disease<sup>☆</sup>Ying-Nan Li<sup>1</sup>, Xiao-Ning Zhao<sup>2</sup>, Ting-Ting Li<sup>1</sup>, Chang-Zheng Wang<sup>1</sup>, Wei-Hua Wang<sup>1</sup>, Lei Tian<sup>3</sup>, Ben-Yan Wu<sup>1\*</sup><sup>1</sup> Department of Geriatric Gastroenterology, <sup>2</sup> Department of Geriatric Cardiology, <sup>3</sup> Institute of Geriatrics and Gerontology, Chinese PLA General Hospital, Beijing, China

## ARTICLE INFO

## Article history:

Received 2 March 2014

Received in revised form

3 August 2014

Accepted 16 March 2015

Available online 27 May 2016

## Keywords:

gastroesophageal reflux disease, geriatrics, human characteristics, proton pump inhibitors

## SUMMARY

**Background:** Gastroesophageal reflux disease (GERD) is a common upper gastrointestinal disease, and almost 30% of GERD patients do not respond well to proton pump inhibitor (PPI) therapy. The aim of this study is to evaluate the clinical characteristics of elderly GERD patients who either respond to or resist PPI therapy.**Methods:** A total of 198 patients (75.9 ± 6.4 years, 73.7% males) with GERD receiving PPI treatment were enrolled in this study. Enrolled patients were requested to complete a questionnaire and a personal interview concerning their demographics, comorbidities, symptoms, and endoscopic findings.**Results:** Among the 198 enrolled patients, 135 responded to PPI once or twice daily (Group R), while 63 failed to respond to PPI twice daily (Group F). Cross-group differences were detected for body mass index ( $p = 0.042$ ), family status ( $p = 0.028$ ), depression (0.7% vs. 7.9%,  $p = 0.03$ ), compliance (77% vs. 60%,  $p = 0.015$ ), and hiatal hernia (6.7% vs. 17.5%,  $p = 0.019$ ).**Conclusion:** PPI failure appears to be significantly influenced by body mass index, family status, depression, compliance, and hiatal hernia of GERD patients.Copyright © 2016, Taiwan Society of Geriatric Emergency & Critical Care Medicine. Published by Elsevier Taiwan LLC. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## 1. Introduction

Gastroesophageal reflux disease (GERD) is a chronic and common upper gastrointestinal disease, the incidence of which in European and American countries is in the range of 10–20%<sup>1</sup>. Several studies have demonstrated that over 40% of the US adult population report GERD-related symptoms at least once a month and 20% once a week<sup>2–4</sup>. In China, the prevalence of GERD symptoms is about 9%<sup>5</sup>. Although not a life-threatening disease, GERD has a significant impact on patients' health and quality of life.

At present, proton pump inhibitors (PPIs) still represent the cornerstone of treatment for both erosive esophagitis (EE) healing and symptom relief. However, studies have shown that up to 40% of

GERD patients reported either partial or complete lack of response of their symptoms to a standard PPI dose once or twice daily<sup>6</sup>.

When PPI therapy failed, physicians are often inclined to increase the dose of PPI or change to an alternative for symptomatic relief. However, this therapeutic strategy frequently results in a less satisfactory symptomatic relief, and the majority of patients continue to experience GERD symptoms. To explore the underlying mechanisms that are accounted for PPI failure, a lot of research has been carried out and several mechanisms have been proposed, including lifestyle, adherence to and compliance with treatment, esophageal hypersensitivity, ultrastructural and functional changes in the esophageal epithelium, etc<sup>6</sup>. However, only a few studies have focused on elderly GERD patients. As a special population, elderly patients show a lack of typical reflux symptoms and are more likely to suffer from severe diseases and esophageal complications. Moreover, some available treatments for GERD may be more dangerous to the elderly patients<sup>7</sup>. In this study, we compared the clinical characteristics of elderly GERD patients who failed to

<sup>☆</sup> Conflicts of interest: All contributing authors declare that they have no conflicts of interest.

\* Correspondence to: Ben-Yan Wu, Department of Geriatric Gastroenterology, Chinese PLA General Hospital, 28, Fuxing Road, Beijing, China.

E-mail address: [benyanwu301@126.com](mailto:benyanwu301@126.com) (B.-Y. Wu).

respond to PPI twice daily with those who responded to PPI at least once daily.

## 2. Materials and methods

### 2.1. Patients

GERD patients who had received PPI (omeprazole/esomeprazole 20 mg, lansoprazole 30 mg, rabeprazole 10 mg, or pantoprazole 40 mg) once or twice daily for at least 3 months were enrolled in this study. Prior to PPI treatment, patients reported at least three incidences of heartburn or acid regurgitation per week.

Patients were then categorized into two groups: those who responded to PPI once and/or twice daily (Group R) and those who failed to respond to PPI twice daily (Group F). Group R patients reported that their heartburn and acid regurgitation symptoms were relieved, the EE was downgraded by one or more level regardless of symptoms, or the time of pathological acid reflux was decreased by  $\geq 30\%$  regardless of symptoms after receiving PPI treatment once or twice a day for the past 3 months. However, Group F patients continued to suffer from heartburn and acid regurgitation at least three times a week for the past 3 months, the EE was unimproved or exacerbated regardless of symptoms, or the time of pathological acid reflux was decreased by  $< 30\%$  regardless of symptoms despite receiving PPI twice daily.

All patients' clinical data including their demographics, comorbidities, medications, symptoms, compliance with treatment (if patients took the PPI daily), and adherence to treatment (if patients took the PPI before a meal) were collected via a questionnaire, and their endoscopic findings were also recorded.

#### 2.1.1. Inclusion criteria

Patients who were older than 65 years and had typical symptoms of heartburn and acid regurgitation, or were definitely diagnosed with EE by endoscopy or nonerosive reflux disease by 24-hour gastroesophageal pH monitoring test despite typical symptoms were included.

#### 2.1.2. Exclusion criteria

Patients who had a history of gastric or esophageal surgery or peptic ulcer, and were unable to fulfill the questionnaire or provide the information requested by the protocol were excluded.

This study was approved by the medical ethics committee of the Chinese PLA General Hospital, Beijing, China.

### 2.2. Procedure

Patients meeting the inclusion criteria were requested to fill up a questionnaire with data regarding their demographics, comorbidities, medications, and symptoms related to GERD, and were interviewed about their compliance with treatment (if patients took the PPI daily) and adherence to treatment (if patients took the PPI before a meal).

### 2.3. Demographics

All patients enrolled in this study completed a questionnaire with information regarding age, sex, weight, height, body mass index (BMI), family status (single, married, divorced, or widowed), and current smoking and alcohol-drinking status. BMI was calculated using each individual's weight and height. The patients' comorbidities, such as hypertension, diabetes mellitus, chronic obstructive pulmonary disease, ischemic heart disease, renal

failure, depression, *Helicobacter pylori* infection, and asthma, were also recorded, together with their medications.

### 2.4. Evaluation of GERD-related symptoms

Patients' atypical reflux symptoms, such as chest pain, epigastric pain, cough, sleep disturbance, abdominal distension, and dysphagia were recorded.

### 2.5. Compliance with and adherence to therapy

Patients were interviewed whether they took PPI according to the prescribed dose in the past 3 months. Compliance was assessed by asking the patients whether they kept taking the PPI at the prescribed dose during the past 3 months. Adherence was evaluated by confirming whether the patients took the PPI half an hour before a meal or not. Patients who took the PPI with or after a meal were considered to be nonadherent, while those who did not take PPI at the prescribed dose were considered to be noncompliant.

### 2.6. Endoscopic findings

Patients' upper endoscopic findings were needed to evaluate the degree of esophageal mucosal breaks and the presence of hiatal hernia. The degree of esophageal mucosal breaks was categorized according to the Los Angeles classification, which is presented in [Table 1](#).

### 2.7. Statistical methods

SPSS 20.0 statistical analysis software (IBM SPSS Statistics, Armonk, New York, United States) was used for data analysis. Continuous variables, such as age, weight, and height, were reported as mean  $\pm$  standard deviation. Normality of distribution of continuous variables was assessed using the Kolmogorov–Smirnov test (cutoff at  $p = 0.05$ ). Continuous variables were compared between groups using independent-samples *t* test. Categorical variables were expressed in frequency (%). The comparison of categorical variables between groups used the chi-square test. Multiple logistic regression was used to model variables. Odds ratios were estimated with 95% confidence intervals. All tests were two sided and considered significant at  $p < 0.05$ .

## 3. Results

### 3.1. Demographics

A total of 261 patients with GERD were recruited, while 63 patients were lost to follow up. Ultimately, a total of 198 patients meeting the inclusion criteria were included in the study; of them, 135 fully responded to PPI once or twice daily (Group R) and 63 failed to respond to PPI twice daily (Group F).

Patients' characteristics are listed in [Table 2](#). The mean age of the patients was  $75.9 \pm 6.4$  years and male patients accounted for

**Table 1**  
Los Angeles classification of esophagitis.

Grade A	One (or more) mucosal break no longer than 5 mm that does not extend between the tops of two mucosal folds
Grade B	One (or more) mucosal break more than 5 mm long that does not extend between the tops of two mucosal folds
Grade C	One (or more) mucosal break that is continuous between the tops of two or more mucosal folds but involves $< 75\%$ of the circumference
Grade D	One (or more) mucosal break that involves at least 75% of the esophageal circumference

**Table 2**  
Comparison of clinical characteristics between groups.

Characteristics	Group R (n = 135)	Group F (n = 63)	p
Age (y)	76.03 ± 6.27	75.62 ± 6.56	0.673
Sex (male, %)	75.6	69.8	0.395
Weight (kg)	74.89 ± 9.66	76.27 ± 8.27	0.329
Height (cm)	170.85 ± 7.95	169.6 ± 8.98	0.324
BMI	25.76 ± 2.32	26.5 ± 2.49	0.042
Present smoker	11 (8.1)	9 (14.3)	0.182
Present drinker	25 (18.5)	13 (20.6)	0.725
Family status			0.028
Married	91 (67.4)	30 (47.6)	0.008
Divorced	6 (4.4)	5 (7.9)	0.505
Widowed	38 (28.1)	28 (44.4)	0.023

Data are presented as mean ± SD or n (%).

BMI = body mass index; SD = standard deviation.

73.7%. There was no significant difference between Groups R and F, in terms of smoking and drinking habits. However, a significantly higher BMI was observed for patients in Group F compared with that in Group R. Furthermore, statistically significant difference was also detected in family status of patients between the two groups: there were a higher proportion of married patients and a lower proportion of widowed patients in Group R than in Group F.

### 3.2. Comorbidities and medications

Patient comorbidities of the two groups are shown in Table 3. The proportion of patients with diabetes mellitus in Group F was higher than that in Group R. A higher proportion of patients with depression was also observed in Group F. However, no significant difference was observed in patients with hypertension, chronic obstructive pulmonary disease, ischemic heart disease, renal failure, *H. pylori* infection, and asthma between the two groups. In terms of medications, more patients took calcium channel blockers (CCBs) and benzodiazepines in Group F than those in Group R, but there was no evident difference in the number of patients taking nitrates, aspirin, and clopidogrel between the two groups.

### 3.3. Atypical GERD symptoms

Atypical GERD symptoms are listed in Table 4. A number of symptoms differed significantly between the two groups. The proportions of patients with symptoms of cough and sleep disturbance were significantly higher in Group F than in Group R

**Table 3**  
Comparison of comorbidities and medications between groups.

Comorbidities and medications	Group R (n = 135)	Group F (n = 63)	p
<b>Comorbidities</b>			
Hypertension	71 (52.6)	40 (63.5)	0.150
Diabetes mellitus	15 (11.1)	19 (30.2)	0.001
COPD	68 (50.4)	33 (52.4)	0.792
Ischemic heart disease	52 (38.5)	27 (42.9)	0.561
Renal failure	7 (5.2)	5 (7.9)	0.663
Depression	1 (0.7)	5 (7.9)	0.030
<i>Helicobacter pylori</i> infection	47 (34.8)	24 (38.1)	0.654
Asthma	11 (8.1)	9 (14.3)	0.182
<b>Medications</b>			
Calcium channel blockers	55 (40.7)	37 (58.7)	0.018
Nitrates	45 (33.3)	25 (39.7)	0.384
Benzodiazepines	52 (38.5)	37 (58.7)	0.008
Aspirin	58 (43)	28 (44.4)	0.845
Clopidogrel	18 (13.3)	11 (17.5)	0.444

Data are presented as n (%).

COPD = chronic obstructive pulmonary disease.

**Table 4**  
Comparison of atypical GERD symptoms between groups.

Symptoms	Group R (n = 135)	Group F (n = 63)	p
Cough	18 (13.3)	17 (27)	0.019
Dysphagia	8 (5.9)	6 (9.5)	0.358
Chest pain	28 (20.7)	15 (23.8)	0.626
Epigastric pain	34 (25.2)	22 (34.9)	0.157
Sleep disturbance	46 (34.1)	31 (49.2)	0.042
Abdominal distension	19 (14.1)	12 (19)	0.370

Data are presented as n (%).

GERD = gastroesophageal reflux disease.

( $p = 0.019$  and  $p = 0.042$ , respectively). For other symptoms, such as dysphagia, chest pain, epigastric pain, and abdominal distension, no significant difference was observed between the two groups.

### 3.4. Adherence to and compliance with treatment

The proportions of compliant patients in Groups R and F were 77% and 60%, respectively, which were statistically significant ( $p = 0.015$ ).

### 3.5. Endoscopic findings

Endoscopic findings are presented in Table 5. The morbidity of hiatal hernia was significantly lower in Group R than in Group F ( $p = 0.019$ ).

There were no patients with EE Grade D (Los Angeles grade) in both groups. Although no significant difference was observed in patients with EE Grades A and B between the two groups ( $p = 0.541$  and  $p = 0.251$ , respectively), there were fewer patients with EE Grade C in Group F ( $p = 0.021$ ).

### 3.6. Multiple logistic regression analysis

As shown in Table 6, BMI, hiatal hernia, and depression significantly increased the odds of being a PPI nonresponder, while compliance with treatment showed the opposite trend. Family status was another significant risk factor for nonresponse to PPI therapy: married patients were less likely to be nonresponders compared with those who were widowed. However, hypertension, diabetes mellitus, CCBs, benzodiazepines, sleep disturbance, and Los Angeles grade of EE were not significant risk factors.

## 4. Discussion

According to the Montreal definition, GERD is defined as the presence of acid-reflux-related symptoms, or esophageal mucosal damage, caused by the abnormal reflux of gastric contents into the esophagus<sup>1</sup>. Previous studies have shown that multiple factors contribute to the development of GERD. In elderly patients, GERD becomes more common and severe. Elderly patients tended to have more risk of acid-related disorder due to having more comorbidities

**Table 5**  
Endoscopic findings.

Endoscopic findings	Group R (n = 135)	Group F (n = 63)	p
Los Angeles grade of EE			0.015
Grade A	23 (17)	13 (20.6)	0.541
Grade B	12 (8.9)	9 (14.3)	0.251
Grade C	1 (0.7)	5 (7.9)	0.021
Hiatal hernia	9 (6.7)	11 (17.5)	0.019

Data are presented as n (%).

EE = erosive esophagitis.

**Table 6**  
Odds ratios for PPI failure of patients by multiple logistic regression analysis.

Characteristics	OR	95% CI	p
BMI	1.345	0.530–0.715	0.036
Family status	0.707	0.506–0.987	0.042
Compliance with treatment	0.636	0.333–0.917	0.020
Diabetes mellitus	0.871	0.321–2.619	0.871
Depression	2.046	12.812–29.683	0.035
Calcium channel blockers	0.763	0.382–1.523	0.443
Benzodiazepines	0.704	0.356–1.392	0.313
Cough	1.392	0.724–2.673	0.321
Sleep disturbance	1.135	0.578–2.229	0.713
LA grade of EE	0.943	0.800–1.112	0.484
Hiatal hernia	2.196	0.760–0.945	0.016

BMI = body mass index; CI = confidence interval; EE = erosive esophagitis; LA = Los Angeles; OR = odds ratio; PPI = proton pump inhibitor.

and taking medications such as nonsteroidal anti-inflammatory drugs, etc.<sup>8</sup>. Our study presents a comprehensive evaluation of the clinical characteristics of elderly GERD patients who respond to or are refractory to PPI therapy.

Our study showed that poor compliance with treatment is the most important reason for PPI treatment failure among GERD patients. According to a large population-based survey, only 55% of the GERD patients took their PPIs as prescribed. In contrast, 37% took their PPI only for  $\leq 12$  d/mo<sup>9</sup>. For elderly patients, it is more common to take medicine irregularly. Since GERD is primarily a symptom-driven disease, many patients continue to take medications as long as they experience symptoms, but tend to forget to take PPI when symptoms are resolved, leading to discontinuation of treatment<sup>10</sup>.

Over decades, ample evidence has accumulated that psychological factors are associated with gastrointestinal diseases<sup>11</sup>. Our study clearly demonstrated that depression is associated with unsatisfactory PPI treatment to GERD patients. In our study, five of six patients with depression failed to respond to PPI therapy, which indicated that psychological state and stress played important roles in the treatment of GERD patients. Does psychological distress result in symptomatology or do symptoms result in psychological distress? Psychological state has an impact on perception, rather than on causal mechanisms. Patients could become hypervigilant, resulting in perception of symptoms. Exacerbation and increased symptom perception might cause more elevated levels of psychological distress. Thus, a vicious circle in which these two pathways reinforce each other can be envisioned<sup>11</sup>.

In this study, we also found that obese patients are more likely to be refractory to PPI therapy. Several studies have shown that obese patients experience more esophageal acid exposure than nonobese patients<sup>12–14</sup>. A mechanically defective lower esophageal sphincter was shown to be more frequent in patients with a higher BMI, and obese patients were more than two times more likely to have a defective lower esophageal sphincter compared with patients of normal weight<sup>13</sup>. Moreover, obesity may also alter the pharmacokinetics of acid-suppressive therapies, including distribution (e.g., poor blood flow in adipose tissue, obesity-related changes in plasma concentrations of binding proteins, and variations in lipophilicity of drugs), metabolism (e.g., fatty liver disease, common in obese patients, slowing the enzymatic metabolism of drugs), and elimination (e.g., increased glomerular filtration rates and tubular secretion, associated with obesity, accelerating the elimination of some drugs)<sup>15–17</sup>.

In addition, we observed that hiatal hernia was another important reason for PPI failure in elderly GERD patients. The presence of a hiatal hernia impairs the function of the lower esophageal sphincter and may also impair the clearance of refluxed

acid from the distal esophagus<sup>18</sup>. The prevalence of hiatal hernia appears to increase with age<sup>19</sup>. Indeed, a large percentage of elderly patients with reflux esophagitis have hiatus hernia.

Another important observation of our study was the influence of the family status. In this study, patients who were divorced or widowed were more likely to be refractory to PPI therapy. A plausible explanation is that elderly patients who are divorced or widowed usually live on their own and suffer from a lack of care from children or friends. Due to their insufficient self-care capability and memory loss, these patients tend to have a life of poor quality and do not always comply with PPI therapy. Moreover, psychological problems caused by loneliness, such as depression, dread, pessimism, etc., would also contribute to the PPI failure. Therefore, it is important to pay more attention to the psychological well-being as well as medication of elderly GERD patients.

Adverse effects of drugs on the esophagus should also be taken into consideration. Many widely used medications, such as nitroglycerins, anticholinergics,  $\beta$ -adrenergic agonists, aminophyllines, benzodiazepines, and CCBs can induce lower esophageal sphincter relaxation<sup>20</sup>. The effect of benzodiazepines on lower esophageal sphincter had been reported by Rushnak and Leevy<sup>21</sup> in 1980. Similarly, CCBs have been proved to be associated with impaired esophageal motility and increase of esophageal exposure to gastric acid. Our study showed that more patients took CCBs and benzodiazepines in Group F than in Group R. PPIs might be less effective or not effective at all when combined with treatment using the drugs listed above. Therefore, elderly GERD patients need to be made aware of the interactions between PPIs and these drugs.

Several problems still exist in our study: The samples in this study was not so abundant as we expect that we did not divide the groups of responders into two groups (fully responders and partly responders). Furthermore, the effect of PPI therapy was evaluated by subjective symptoms and not by objective indicators such as GERD questionnaire scores. If these issues were taken care of, the results of this study would have been more convincing.

## 5. Conclusion

Our study provides a comprehensive evaluation of the clinical characteristics of elderly GERD patients who are refractory to PPI therapy. We found that PPI failure appeared to be significantly associated with the patients' BMI, family status, compliance with treatment, depression, and hernia. These clinical findings are very valuable for an effective management of patients with GERD refractory to PPI therapy.

## Acknowledgments

This study was supported by the Scientific Innovation Fund of Chinese PLA General Hospital (12KMM21). Ying-Nan Li and Xiao-Ning Zhao were in charge of design of the study and the analysis and interpretation of data; all authors contributed to data collection, and Ying-Nan Li fulfilled the final manuscript.

## References

1. Vakil N, van Zanten SV, Kahrilas P, et al. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus paper. *Am J Gastroenterol*. 2006;101:1900–1920.
2. Fass R, Fennerty M, Vakil N. Nonerosive reflux disease—current concepts and dilemmas. *Am J Gastroenterol*. 2001;96:303–314.
3. Locke 3rd GR, Talley NJ, Fett SL, et al. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. *Gastroenterology*. 1997;112:1448–1456.
4. Nebel OT, Fornes MF, Castell DO. Symptomatic gastroesophageal reflux: incidence and precipitating factors. *Am J Dig Dis*. 1976;21:953–956.

5. Pan GZ, Xu GM, Guo HP, et al. Epidemiology of the symptoms of patients with gastroesophageal reflux disease in Beijing and Shanghai. *Chin J Digest*. 1999;19:223–226.
6. Cicala M, Emerenziani S, Guarino MP, et al. Proton pump inhibitor resistance, the real challenge in gastro-esophageal reflux disease. *World J Gastroenterol*. 2013;19:6529–6535.
7. Soumekh A, Schnoll-Sussman FH, Katz PO. Reflux and acid peptic diseases in the elderly. *Clin Geriatr Med*. 2014;30:29–41.
8. Franceschi M, Di Mario F, Leandro G, et al. Acid-related disorders in the elderly. *Best Pract Res Clin Gastroenterol*. 2009;23:839–848.
9. The Gallup Organization. *Gallup Study of Consumers' Use of Stomach Relief Products*. Princeton, NJ: The Gallup Organization; 2000.
10. Fass R, Shapiro M, Dekel R, et al. Systematic review: proton-pump inhibitor failure in gastro-oesophageal reflux disease—where next? *Aliment Pharmacol Ther*. 2005;22:79–94.
11. Van der Velden AW, De Wit NJ, Quartero AO, et al. Maintenance treatment for GERD: residual symptoms are associated with psychological distress. *Digestion*. 2008;77:207–213.
12. El-Serag HB, Ergun GA, Pandolfino J, et al. Obesity increases oesophageal acid exposure. *Gut*. 2007;56:749–755.
13. Ayazi S, Hagen JA, Chan LS, et al. Obesity and gastroesophageal reflux: quantifying the association between body mass index, esophageal acid exposure, and lower esophageal sphincter status in a large series of patients with reflux symptoms. *J Gastrointest Surg*. 2009;13:1440–1447.
14. Crowell MD, Bradley A, Hansel S, et al. Obesity is associated with increased 48-hours esophageal acid exposure in patients with symptomatic gastroesophageal reflux. *Am J Gastroenterol*. 2009;104:553–559.
15. Blouin RA, Warren GW. Pharmacokinetic considerations in obesity. *J Pharm Sci*. 1999;88:1–7.
16. Jacobson BC. Body mass index and the efficacy of acid-mediating agents for GERD. *Dig Dis Sci*. 2008;53:2313–2317.
17. Barak N, Ehrenpreis ED, Harrison JR, et al. Gastro-oesophageal reflux disease in obesity: pathophysiological and therapeutic considerations. *Obes Rev*. 2002;3:9–15.
18. Huang X, Zhu HM, Deng CZ, et al. Gastroesophageal reflux: the features in elderly patients. *World J Gastroenterol*. 1999;5:421–423.
19. Amano K, Adachi K, Katsube T, et al. Role of hiatus hernia and gastric mucosal atrophy in the development of reflux esophagitis in the elderly. *J Gastroenterol Hepatol*. 2001;16:132–136.
20. Tutuian R. Adverse effects of drugs on the esophagus. *Best Pract Res Clin Gastroenterol*. 2010;24:91–97.
21. Rushnak MJ, Leevy CM. Effect of diazepam on the lower esophageal sphincter. A double-blind controlled study. *Am J Gastroenterol*. 1980;73:127–130.