

## Risk factors for proton pump inhibitor refractoriness in Chinese patients with non-erosive reflux disease

Xiao-Ping Niu, Bao-Ping Yu, Yun-Dong Wang, Zhen Han, Shao-Fen Liu, Chi-Yi He, Guo-Zheng Zhang, Wan-Chun Wu

Xiao-Ping Niu, Zhen Han, Shao-Fen Liu, Chi-Yi He, Guo-Zheng Zhang, Wan-Chun Wu, Department of Gastroenterology, Yijishan Hospital, Wannan Medicine College, Wuhu 241001, Anhui Province, China

Bao-Ping Yu, Yun-Dong Wang, Department of Gastroenterology, Renmin Hospital, Wuhan University, Wuhan 430060, Hubei Province, China

**Author contributions:** Yu BP designed and supervised the study; Han Z instructed the study; Niu XP conceived and designed the study, collected and compiled the patient data, performed the scale survey, wrote the manuscript and gave final approval of the version to be published; Wang YD and Liu SF performed the scale survey and the questionnaire on patient general status and lifestyle; He CY compiled the data and performed the statistical analysis; Wu WC and Zhang GZ collected the cases and enrolled the patients.

**Correspondence to:** Bao-Ping Yu, MD, Department of Gastroenterology, Renmin Hospital, Wuhan University, No. 99 Zhangzhidong Road, Wuchang District, Wuhan 430060, Hubei Province, China. [baopingyu@yahoo.cn](mailto:baopingyu@yahoo.cn)

Telephone: +86-27-88041911 Fax: +86-27-88042292

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### Abstract

**AIM:** To analyze risk factors for refractoriness to proton pump inhibitors (PPIs) in patients with non-erosive reflux disease (NERD).

**METHODS:** A total of 256 NERD patients treated with the PPI esomeprazole were enrolled. They were classified into symptom-free and residual symptoms groups according to Quality of Life in Reflux and Dyspepsia (QoLRad) scale. All subjects completed questionnaires on psychological status (self-rating anxiety scale; self-rating depression scale) and quality of life scale (Short Form 36). Multivariate analysis was used to determine the predictive factors for PPI responses.

**RESULTS:** According to QoLRad, 97 patients were confirmed to have residual reflux symptoms, and the remaining 159 patients were considered symptom free. There were no significant differences between the two groups in lifestyle factors (smoking and alcohol consumption), age, *Helicobacter pylori* infection, and hiatal hernia. There were significant differences between the two groups in relation to sex, psychological distress including anxiety and depression, body mass index (BMI), and irritable bowel syndrome (IBS) ( $P < 0.05$ ). Logistic regression analysis found that BMI  $< 23$ , comorbid IBS, anxiety, and depression were major risk factors for PPI resistance. Symptomatic patients had a lower quality of life compared with symptom-free patients.

**CONCLUSION:** Some NERD patients are refractory to PPIs and have lower quality of life. Residual symptoms are associated with psychological distress, intestinal disorders, and low BMI.

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**Key words:** Risk factors; Refractoriness; Proton pump inhibitors; Non-erosive reflux disease

**Core tip:** Non-erosive reflux disease (NERD) is significantly more refractory to proton pump inhibitor (PPI) treatment than erosive esophagitis is, although the reason is unclear at present. Here, we investigated the risk factors for refractoriness to PPI treatment in patients with NERD. Our results demonstrate that some NERD patients are refractory to standard doses of PPIs and have a lower quality of life. Residual symptoms are associated with psychological distress, intestinal disorders, and low body mass index. Recognition of this might hold the key to improving long-term management of NERD.

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## INTRODUCTION

Gastroesophageal reflux disease (GERD) is caused by abnormal reflux of gastric contents into the esophagus and is characterized by specific symptoms such as heartburn and acid regurgitation. An epidemiological survey has found that GERD is a common condition with a prevalence of 10%-20% in Western Europe and North America<sup>[1]</sup>. The prevalence of GERD in China is lower than that in Western countries, but appears to be increasing<sup>[2,3]</sup>. However, only about one-third to one-half of patients with GERD has endoscopically positive findings such as erosions and ulcers, whereas others with GERD symptoms have no obvious mucosal breaks during endoscopic examination. Therefore, GERD includes erosive esophagitis (EE) and endoscopy-negative reflux disease, which is also known as non-erosive reflux disease (NERD)<sup>[4,5]</sup>. At present, the most effective drug therapy for GERD is proton-pump inhibitors (PPIs)<sup>[6]</sup>. PPI treatment results in sustained acid reduction for symptom control in the majority of patients. However, 17%-32% of patients with GERD in primary care trials have experienced persistent, troublesome heartburn or regurgitation despite standard-dose PPI treatment, and the majority of them have even experienced refractory symptoms at higher doses<sup>[7-10]</sup>. Studies have shown that EE and NERD have different responses to PPIs because their pathogenesis is distinct<sup>[11-13]</sup>. In addition, NERD is significantly more refractory than EE to PPI treatment<sup>[14,15]</sup>. However, a recent meta-analysis has reported that NERD has the same response rate to PPIs as EE has, and the previously reported low response rate in patients with NERD was likely the result of inclusion of patients with upper gastrointestinal symptoms who did not have reflux disease<sup>[16,17]</sup>.

PPI failure has become a common clinical dilemma in gastrointestinal clinics and has been increasingly encountered at the primary care level as well. It is likely to be an expensive clinical problem because patients tend to utilize health care resources repeatedly, such as clinic visits, diagnostic studies, and prescription medication. A previous observation has shown that non-acid reflux contributes to poor effectiveness of PPIs in both NERD and EE patients<sup>[18]</sup>. However, most previous studies regarding PPI responses and the natural course of EE and NERD were based on Western countries; there have been few reports from Eastern Asian countries, including China<sup>[14,19]</sup>. In addition, the risk factors that affect the response of patients with NERD to PPIs are unclear at present<sup>[20,21]</sup>. To the best of our knowledge, there has been no report on the risk factors for response to PPIs in patients with NERD

in China. Here, we investigated the risk factors for refractoriness to PPI treatment in patients with NERD and propose a potential treatment strategy for them.

## MATERIALS AND METHODS

### Patient selection

Patients with NERD receiving PPI (esomeprazole) maintenance treatment were consecutively enrolled from May 2008 to August 2010. We enrolled 256 patients with reflux symptoms who were assessed by a locally validated GERD questionnaire, the Chinese GerdQ<sup>[22]</sup>. All patients were positive for ambulatory 24-h esophageal pH monitoring (DeMeester score > 14.27). All patients had undergone endoscopy at his/her first visit to exclude erosive reflux disease. All patients with NERD recruited for our study were using standard-dose esomeprazole for at least 6 mo.

### Exclusion criteria

According to the recent Rome III Criteria, patients with functional heartburn whose typical symptoms were associated with neither abnormal pH testing nor a positive symptom index were excluded<sup>[23,24]</sup>. Patients were excluded if there was a history of gastrointestinal surgery, Barrett's esophagus, peptic ulcer, or gastroduodenal cancer, and if they could not accurately express their condition or were unwilling to accept the scale survey.

### Assessments

The patients' medical records were screened for gastrointestinal morbidity, years since the first episode, and comorbidity (unclear what to deliver). Information was obtained regarding age, sex, smoking, alcohol use, *Helicobacter pylori* (*H. pylori*) infection, body mass index (BMI), comorbid irritable bowel syndrome (IBS), and hiatal hernia. The BMI was categorized using 23 and 25 kg/m<sup>2</sup> as a cut-off point in accordance with the WHO recommendation for Asia. IBS was diagnosed using a questionnaire based on the Rome III Criteria. All patients were asked to complete the following questionnaires.

### Quality of life in reflux and dyspepsia

The reflux version of quality of life in reflux and dyspepsia (QoLRad) is a disease-specific instrument, including 25 items combined into five dimensions: emotional distress, sleep disturbance, vitality, food/drink problems, and physical/social functioning. The recall period refers to the last week. QoLRad outcome has been shown to reflect treatment response and impact of symptoms<sup>[25]</sup>. A 7-point scale was used to assess item severity or frequency (1 = a great deal/all of the time; 2 = a lot/most; 3 = a moderate amount/quite a lot; 4 = some; 5 = a little; 6 = hardly any; 7 = none). The lower the scores were, the more severe the impact on daily functioning. Patients scoring  $\geq 6$  on all dimensions were considered symptom free, and those scoring < 6 on at least one dimension as having residual symptoms.

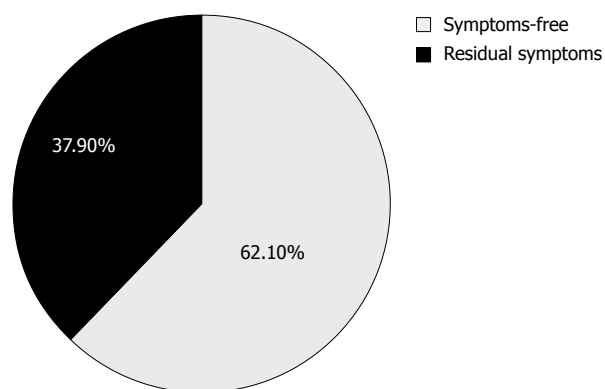


Figure 1 Effectiveness of proton pump inhibitor in 256 patients with non-erosive reflux disease.

Table 1 Self-rating anxiety scale and self-rating depression scale scores in the two groups of patients

Group	n	SAS score	SDS score	SAS%	SDS%
Residual symptoms	97	42.68 ± 6.21	52.36 ± 6.93	46.39% (45/97)	50.52% (49/97)
Symptom-free	159	31.17 ± 6.15	43.13 ± 5.27	10.06% (16/159)	8.18% (13/159)
Control	52	30.74 ± 8.18	35.32 ± 6.71	0.00% (0/20)	1.90% (1/52)

Self-rating anxiety scale (SAS) grades:  $F = 104.54, P < 0.001$ ; Self-rating depression scale (SDS) grades:  $F = 143.91, P < 0.001$ ; SAS%:  $\chi^2 = 52.30, P < 0.001$ ; SDS%:  $\chi^2 = 79.58, P < 0.001$ .

### Zung self-rating anxiety scale and Zung self-rating depression scale

The scores of the 20 items in the self-rating depression scale (SDS) and self-rating anxiety scale (SAS) were added and multiplied by 1.25. The nearest integer was taken as the standard score. An SDS standard score  $\geq 53$  indicated the presence of depression. An SAS standard score  $\geq 50$  indicated the presence of anxiety<sup>[26]</sup>.

### Quality of life scale (Short Form 36, SF-36)

This 36-question survey measured generic quality of life in eight dimensions<sup>[27]</sup>: physical functioning (PF), role limitations-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitations-emotional (RE), and mental health (MH). Summary physical component score (PCS) and mental component score (MCS) were also calculated from patient responses. Raw scores were converted to a scale of 0 to 100, with higher scores indicating higher levels of health or wellbeing.

### Data analysis

The ages of the patients were categorized into deciles. Descriptive statistics (mean and SD) and additional analyses were calculated using SPSS version 14.0. Mean values were compared using Student's *t* test and analysis of variance, and two-sided *P* values of 0.05 were considered statistically significant. Ninety-five percent confidence intervals and two-tailed *P* values were calculated for the

Table 2 Lifestyle characteristics of two groups of patients

Variables	Residual symptoms (n = 97)	Symptom-free (n = 159)	t/ $\chi^2$	P value
Age (yr)	59.3 ± 11.2	57.1 ± 12.7	1.28	0.203
Sex (male/female)	38/59	97/62	0.92	0.016
Alcohol consumption	19%	26%	0.44	0.509
Smoking	37%	32%	9.93	0.062
<i>Helicobacter pylori</i> positive	59%	62%	11.52	< 0.001
BMI (kg/m <sup>2</sup> )			6.19	0.045
$\geq 25$	37	86		
23–24.9	30	38		
< 23	30	35		
Comorbid IBS	37%	12%	36.44	< 0.001
Hiatal hernia	9%	8%	1.75	0.186

BMI: Body mass index; IBS: Irritable bowel syndrome.

ORs. Multivariate logistic regression analysis was carried out using determinants with *P* values  $\leq 0.1$ .

## RESULTS

A total of 256 patients with NERD on PPI treatment were included in the study (mean age 58 years, 53% male). Residual reflux symptoms were investigated by analyzing their impact on QOLRad score. They were divided into the residual symptoms ( $n = 97$ ) and symptom-free ( $n = 159$ ) groups according to QOLRad scores (Figure 1). Scores for SAS and SDS were significantly higher in the residual symptoms than symptom-free group (Table 1).

Demographics, clinical and laboratory findings is summarized in Table 2. We found that there was no significant difference between the two groups with regard to age, smoking, alcohol consumption, *H. pylori* infection, and hiatal hernia. A significant sex difference was observed in the residual symptoms and symptom-free groups. There were more women than men in the residual symptoms than symptom-free group ( $P < 0.05$ ). There were significantly more patients in the residual symptoms group with BMI < 23 and comorbid IBS than in the symptom-free group (Table 2). Multivariate analysis of patient characteristics indicated that the risk factors for residual symptoms were: BMI < 23, comorbid IBS, and mental health problems (anxiety or depression) (Table 3). The SF-36 scores indicated that symptomatic patients had a lower quality of life than those who were symptom free (Table 4).

## DISCUSSION

Patients with NERD experience typical GERD symptoms caused by acid and non-acid reflux, but they do not have visible esophageal injury<sup>[28,29]</sup>. NERD is a more common type of GERD in Asian than in Western populations<sup>[30]</sup>. Patients with NERD are a heterogeneous group including various subpopulations with different mechanisms for their main symptoms: reflux of acidic and non-acidic

**Table 3** Multivariate logistic regression of patient characteristics (*n* = 256)

Variables	$\beta$	SE	Z	P value	B	OR	95%CI
Women	-0.14	0.10	6.25	< 0.001	-0.19	0.66	0.31-0.89
BMI < 23	0.09	0.03	14.12	< 0.001	0.32	1.56	1.37-2.81
Comorbid IBS	0.21	0.06	12.30	< 0.006	0.37	1.33	1.26-2.55
SDS score	0.46	0.29	5.95	< 0.026	0.53	1.56	1.13-2.39
SAS score	1.05	0.32	9.26	< 0.001	0.85	2.17	1.57-2.76

BMI: Body mass index; IBS: Irritable bowel syndrome; SDS: Self-rating depression scale; SAS: Self-rating anxiety scale.

gastric contents, mucosal hypersensitivity, intraesophageal distension by gas, intraduodenal infusion of fat, muscle contractions, and psychological abnormalities. Some studies have reported that the proportion of patients with NERD that responds to a standard dose of PPI is 20%-30%, which is lower than the proportion of patients with EE<sup>[15,17]</sup>. Some NERD patients even use high doses of PPI but cannot completely control the symptoms. For a long time, ineffective drug maintenance treatment has become a common problem in primary care<sup>[31,32]</sup>. These patients tend to utilize repeatedly healthcare resources, such as frequent consultations, referrals, diagnostic tests, and repeat prescriptions, which consume a large amount of medical resources. These patients also bear physical suffering and economic pressure, which seriously affect their quality of life<sup>[33]</sup>. Several studies have demonstrated that the proportion of patients with NERD that respond to a standard dose of PPI is 60%-70%, which is lower than that of patients with EE<sup>[34]</sup>. A recent study has suggested that, in well-defined NERD patients, the estimated complete symptom response rate after PPI therapy is comparable to the response rate in patients with EE. The previously reported low response rate in studies with patients classified as NERD was probably the result of inclusion of patients with upper gastrointestinal symptoms who did not have reflux disease. In the present study, we found that only 62.1% of patients with NERD treated with PPI were symptom free, and 37.9% of patients had residual symptoms and had a significantly lower quality of life.

The reason why NERD is more refractory than EE to PPIs is unclear at present. Previous observations have shown that the pathogenesis of NERD is associated with age, sex, lifestyle, *H. pylori* infection, BMI, comorbid IBS, and hiatal hernia<sup>[31]</sup>. It has also been shown that patients with NERD often have more psychological problems than those with EE<sup>[35,36]</sup>. A large number of epidemiological investigations have found that anxiety, depression, and chronic stress can lead to NERD<sup>[37]</sup>. Conventional treatment for NERD depends on PPI applications, but it cannot resolve the underlying psychological problems. Patients with NERD are often not satisfied with the treatment. Zerbib *et al.*<sup>[38]</sup> have reported that a no-reflux pattern demonstrated by 24-h pH-impedance monitoring is associated with response to PPIs in patients with

**Table 4** Social functioning-36 scores in residual symptoms and symptom-free groups

Dimensionality	Residual symptoms	Symptom-free	Control	F	P value
PF	91.31 ± 8.73	92.03 ± 7.62	92.31 ± 8.26	0.81	0.3926
RP	80.01 ± 19.12 <sup>1</sup>	89.93 ± 18.93	94.10 ± 12.15	3.90	0.0117
BP	59.00 ± 10.06 <sup>1</sup>	86.22 ± 11.13	89.31 ± 14.81	31.24	< 0.0001
GH	61.25 ± 16.12 <sup>1</sup>	85.28 ± 15.26	83.15 ± 11.32	30.27	< 0.0001
VT	64.46 ± 17.92 <sup>1</sup>	81.30 ± 19.21	90.61 ± 20.13	12.93	< 0.0001
SF	61.53 ± 11.46 <sup>1</sup>	79.23 ± 19.73	80.16 ± 17.23	10.25	< 0.0001
RE	57.64 ± 10.11 <sup>2</sup>	68.17 ± 23.55	82.72 ± 18.19	11.75	< 0.0001
MH	50.96 ± 13.13 <sup>2</sup>	66.21 ± 12.46	89.15 ± 16.28	23.29	< 0.0001

<sup>1</sup>Significant difference between residual symptoms and symptom-free groups and control group; <sup>2</sup>Significant difference among the three groups. PF: Physical functioning; RP: Role limitations-physical; BP: Bodily pain; GH: General health; VT: Vitality; SF: Social functioning; RE: Role limitations-emotional; MH: Mental health.

GERD symptoms. In contrast, absence of esophagitis, presence of functional digestive disorders, and BMI ≤ 25 kg/m<sup>2</sup> are strongly associated with PPI failure.

To date, there has been no report on the risk factors that affect the response of NERD patients to PPI therapy in China. In the present study, we found that there was no significant difference between the symptom-free and residual symptoms groups with regard to age, smoking, alcohol consumption, *H. pylori* infection, and hiatal hernia. However, symptomatic patients differed from symptom-free patients in relation to sex, BMI, comorbid IBS, and psychological distress. These variables were analyzed by multivariate analysis and we found that anxiety, depression, comorbid IBS, and BMI < 23 were independent risk factors associated with residual symptoms, but sex was not a risk factor for residual symptoms. We used the modified BMI criteria as proposed by the WPRO, which considers the smaller body frame of Asians and provides a more accurate reflection of body fat stores, thus avoiding a false perception of not being overweight<sup>[39]</sup>.

In conclusion, our results demonstrate that some NERD patients are refractory to standard doses of PPIs and have a lower quality of life. Residual symptoms are associated with psychological distress, intestinal disorders, and low BMI. Recognition of this might hold the key to improving long-term management of NERD.

## COMMENTS

### Background

Non-erosive reflux disease (NERD) is significantly more refractory than erosive esophagitis to proton pump inhibitor (PPI) treatment, although the reason is unclear at present.

### Research frontiers

Here, the authors report a study of the risk factors for PPI refractoriness in Chinese patients with NERD. The majority of studied cases were sporadic.

### Innovations and breakthroughs

Although a previous observation has shown that non-acid reflux contributes to poor effectiveness of PPIs in NERD patients, there has been no report on the risk factors for response to PPIs in patients with NERD in China. Here, the authors investigated the risk factors for refractoriness to PPI treatment in patients

with NERD and propose a potential treatment strategy for them.

### Applications

The authors found that some NERD patients were refractory to standard doses of PPIs and had a lower quality of life. Residual symptoms were associated with psychological distress, intestinal disorders, and low body mass index. Recognition of this might hold the key to improving long-term management of NERD.

### Terminology

There is no specific, unique terminology that will not be familiar to the majority of readers.

### Peer review

This was a qualitative study with an original approach to establishing the risk factors for refractoriness to PPIs in patients with NERD. This is an important problem in the treatment of these patients. The study was well designed and the results are clearly described.

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