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ABOUT COVER

Editorial board member of *World Journal of Gastroenterology*, Dr. Naoki Hashimoto was awarded his medical degree from Kobe University in 1975 and his PhD from Hyogo Medical College in 1984. Over the last 10 years, his scientific interest has remained focused on topics related to reflux of duodenal contents inducing esophageal carcinogenesis, with his research efforts including both experimental and clinical approaches. His practical expertise encompasses biomedical imaging, surgical treatment and chemoradiotherapy for advanced esophageal cancer, and he practices in the Kindai University's Department of Surgery. He is the recipient of many academic honors, from such esteemed groups as European Conference on General Thoracic Surgery in 2012 and World Organization for Specialized Studies of Diseases of the Esophagus (OESO) in 2013 and 2015. His academic career embodies a continual pursuit towards conducting more innovative, translational and enduring research.

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ORIGINAL ARTICLE

Observational Study

Predictive value of alarm symptoms in patients with Rome IV dyspepsia: A cross-sectional study

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Author contributions: Wei Z-C, Pan Y-L, Wang J-H and Liu N designed the research; Wei Z-C, Yang Q, Yang Q and Yang J performed the research; Tantai X-X, Xing X and Xiao C-L contributed analytic tools; Wei Z-C and Yang Q analyzed the data; Wei Z-C, Pan Y-L, Wang J-H and Liu N wrote the paper.

Institutional review board statement: The study was approved by the ethics committee of the Second Affiliated Hospital of Xi'an Jiaotong University.

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STROBE statement: The guidelines

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Abstract

BACKGROUND

No studies have evaluated the predictive value of alarm symptoms for organic dyspepsia and organic upper gastrointestinal (GI) diseases based on Rome IV criteria in the Chinese population.

AIM

To evaluate the predictive value of alarm symptoms for dyspeptic patients based on Rome IV criteria.

METHODS

We performed a cross-sectional study of dyspepsia patients who met the inclusion and exclusion criteria at two academic urban tertiary-care centers from March 2018 to January 2019. Basic demographic data, dyspeptic information, alarm symptoms, lifestyle, examination results, family history and outpatient cost information were collected. Dyspepsia patients with normal findings on upper GI endoscopy, epigastric ultrasound and laboratory examination and without *Helicobacter pylori*-associated dyspepsia were classified as functional dyspepsia.

RESULTS

A total of 381 patients were enrolled in the study, including 266 functional dyspepsia patients and 115 organic dyspepsia patients. There were 24 patients

with organic upper GI disease among patients with organic dyspepsia. We found that based on the Rome IV criteria, alarm symptoms were of limited value in differentiating organic dyspepsia and organic upper GI diseases from functional dyspepsia. Age (odds ratio (OR) = 1.056, P = 0.012), smoking (OR = 4.714, P = 0.006) and anemia (OR = 88.270, P < 0.001) were independent predictors for organic upper GI diseases. For the comparison of epigastric pain syndrome, postprandial distress syndrome and epigastric pain syndrome combined with postprandial distress syndrome, the results showed that there were statistically significant differences in anorexia (P = 0.021) and previous visits (P = 0.012). The ClinicalTrials.gov number is NCT 03479528.

CONCLUSION

Most alarm symptoms had poor predictive value for organic dyspepsia and organic upper GI diseases based on Rome IV criteria. Gastroscopic screening should not be based solely on alarm symptoms.

Key words: Rome IV; Dyspepsia; Alarm symptoms; Prediction

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Core tip: Dyspepsia is a symptom complex referable to the upper gastrointestinal tract. Based on the Rome IV criteria, alarm symptoms were of limited value in differentiating organic dyspepsia and organic upper gastrointestinal diseases from functional dyspepsia, and gastroscopic screening should not be based solely on alarm symptoms. Age, smoking and anemia were the independent predictors for organic upper gastrointestinal diseases. The clinical characteristics of patients with epigastric pain syndrome, postprandial distress syndrome and the two combined were not significantly different.

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INTRODUCTION

Dyspepsia is a clinical symptom originating from the upper gastrointestinal (GI) tract. Dyspepsia can be divided into functional dyspepsia (FD) and organic dyspepsia. FD is a very common functional GI disorder in clinical treatment[1,2]. It is a clinical syndrome that is characterized by chronic or recurrent gastroduodenal symptoms, without any organic or metabolic disease that may explain the symptoms[3-5]. FD has a high incidence in the population. Dyspepsia is present in approximately 20% of the general population worldwide[6], and a recent study showed that FD was present in 11% of the general population in Italy[7]. FD dramatically reduces a patient's quality of life, and it also imposes a severe financial burden due to frequent clinical visits, prolonged drug use and long time off work[8,9].

Clinical diagnosis of the underlying cause of dyspepsia based on symptoms alone is believed to be unreliable[10,11], but a range of alarm symptoms are suggested to indicate an elevated risk of serious illness[12]. Alarm symptoms may indicate underlying malignancy or significant pathology, such as a stricture or ulcer[13]. However, according to the results of previous studies, the sensitivity of alarm symptoms to predict upper GI malignancies is not satisfactory[13-15]. The predictive effect of alarm symptoms requires further research.

FD is a type of dyspepsia that has no organic, metabolic or systemic disease to explain its symptoms, but only a few studies have rigorously diagnosed FD by laboratory examination, epigastric ultrasound and upper GI endoscopy to exclude related diseases[16,17], especially in cross-sectional studies. Further research is needed to rigorously diagnose FD through laboratory examination, epigastric ultrasound and upper GI endoscopy.

In 2016, the Rome IV criteria for dyspepsia were introduced. The Rome IV criteria

of the STROBE statement have been adopted in preparing the manuscript.

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redefined the frequency and severity of each dyspeptic symptom in patients with dyspepsia, but the effectiveness of the Rome IV criteria still needs to be confirmed by relevant studies[18]. At present, no study has assessed the predictive effect of alarm symptoms according to the Rome IV criteria. Here, we carried out a study to evaluate the predictive value of alarm symptoms in dyspeptic patients based on Rome IV.

MATERIALS AND METHODS

Study design

This cross-sectional study was conducted at two academic urban tertiary-care centers (the Second Affiliated Hospital of Xi'an Jiaotong University and the Affiliated Hospital of Northwest University), which provide medical services to the whole of northwest China from March 2018 to January 2019. Patients who visited the gastroenterology clinics and completed upper GI endoscopy and epigastric ultrasounds during the study period were initially screened. Furthermore, patients with dyspeptic symptoms who met the Rome IV criteria were further selected. Patients who met the inclusion criteria and exclusion criteria were eventually included in our study. Oral informed consent was obtained from all included patients. The ethics committee of the Second Affiliated Hospital of Xi'an Jiaotong University approved this study. This study protocol was registered at ClinicalTrials.gov (NCT03479528). In addition, there was no funding received.

Inclusion criteria

Inclusion criteria: (1) Age was ≥ 18 years; (2) The chief complaint was dyspeptic symptoms that met the Rome IV criteria (at least one of the following symptoms was present: Bothersome postprandial fullness at least 3 d per week, bothersome early satiation at least 3 d per week, bothersome epigastric pain at least 1 d a week, bothersome epigastric burning at least 1 d a week; symptoms must have been present for at least 3 mo in the previous 6 mo); (3) Patients visited the gastroenterology clinics and completed upper GI endoscopy and epigastric ultrasounds during the study period; and (4) routine blood examination, liver function test and *Helicobacter pylori* (*H. pylori*) test were conducted within the last 6 mo (to ensure that these diagnostic tests were conducted after the onset of dyspeptic symptoms).

Exclusion criteria

Exclusion criteria: (1) History of esophageal cancer, gastric ulcer, gastric cancer or other types of organic upper GI disease, disease of the pancreas or biliary tract or metabolic disorders (thyroid dysfunction, diabetes mellitus); (2) Pregnancy, pregnancy preparation, lactation; (3) History of abdominal surgery; (4) Severe nervous system diseases, mental illness or severe liver, kidney, heart or respiratory related dysfunction; (5) Abnormal liver function, including nonalcoholic steatohepatitis, hepatitis B or hepatitis C related hepatitis; (6) Current antidepressant, steroid or nonsteroidal anti-inflammatory drug use; (7) Patients only or predominantly had reflux-related symptoms; and (8) Patients who were reluctant to participate in this study.

Data collection

All related data were obtained through a clinic visit and telephone consultation. We collected the basic demographic data (name, age, height, weight, gender, marriage), dyspeptic information (dyspeptic symptoms, duration, frequency per week), alarm symptoms [including weight loss and its extent[19], anemia (hemoglobin < 130 g/L for men and hemoglobin < 120 g/L for women), dysphagia, melena, vomiting, anorexia], lifestyle data (including spicy foods, smoking and smoking amount, drinking and alcohol consumption, sleep quality, daily exercise duration), examination results (*H. pylori*, upper abdominal B ultrasound, upper GI endoscopy), family history and outpatient cost information. All questionnaire data were imported into the database by a trained researcher.

Definitions of FD

FD was diagnosed strictly by laboratory examination, abdominal ultrasound and upper GI endoscopy. As Rome IV criteria redefined the frequency and severity of each dyspeptic symptom in patients with dyspepsia, the dyspeptic symptoms of the included patients were all severe enough to impact usual activities, and the

questionnaire included the frequency of dyspepsia. The presence or absence of Rome IV-defined FD, epigastric pain syndrome (EPS) and postprandial distress syndrome (PDS) were decided by the questionnaire according to the Rome IV criteria[18,20] (see Supplementary Table 1). There was no evidence of abnormal results of upper GI endoscopy, epigastric ultrasound, laboratory examination or *H. pylori*-associated dyspepsia[21,22]. *H. pylori*-associated dyspepsia was defined as the relief of dyspepsia symptoms after eradication of *H. pylori*[18].

Definitions of organic dyspepsia

Dyspepsia can be divided into FD and organic dyspepsia. Organic dyspepsia occurs when clinical or laboratory tests reveal underlying organic disease that may be the cause of these symptoms[23,24]. Organic dyspepsia was caused by abnormal results of upper GI endoscopy, epigastric ultrasound, laboratory examination and *H. pylori*-associated dyspepsia in this study. We regarded hepatic cyst (< 5 cm)[25], hepatic hemangioma (< 5 cm)[26], fatty liver, gallbladder wall roughness, cholesterol crystal and gallbladder polyps (< 1 cm)[27] as normal epigastric ultrasound, and gallstone was regarded as abnormal epigastric ultrasound. Abnormal routine blood tests (anemia) were regarded as abnormal laboratory examination.

Definition of organic upper GI disease

All patients underwent complete upper GI endoscopy, and the physicians who performed upper GI endoscopy maintained a blind method for data collection. The findings were recorded using the endoscopic reporting system. Researchers reviewed these endoscopic reports and recorded the patient's endoscopic diagnosis. Upper GI endoscopy or biopsy pathology indicated that organic diseases were classified as organic upper GI disease, while upper GI endoscopy and biopsy pathology showed no evidence of organic disease were classified as nonorganic upper GI diseases. Organic upper GI diseases included gastric ulcer, gastric cancer, duodenal ulcer and esophagus cancer. Endoscopic chronic gastritis and duodenitis are considered nonorganic upper GI diseases[18]. Gastric erosion, duodenal erosion, Barrett's esophagus and esophageal candidiasis were asymptomatic findings and were also regarded as nonorganic diseases of the upper GI diseases.

Statistical analysis

EpiData3.1 software was used to input data, and statistical analyses were performed by EmpowerStats and SPSS 20.0 software. Categorical variables were expressed as counts and percentages and analyzed using chi-square tests or Fisher's exact test. Continuous variables were expressed as the mean ± standard deviation and analyzed using a *t*-test or Kruskal–Wallis test. Variables were first evaluated with univariate analysis, variables with $P < 0.10$ in univariate analysis were then included in the multivariate analysis (logistic regression analysis), and exact logistic regression was conducted by SAS software when appropriate. Data were presented with odds ratios (OR) and 95% confidence intervals (CI). $P < 0.05$ was considered statistically significant. We used the area under the receiver operating characteristic curve to judge the predictive value of independent risk factors.

RESULTS

Baseline of patient characteristics

Between March 2018 and January 2019, a total of 381 patients who met the inclusion and exclusion criteria were collected in this study, including 266 FD patients, 115 organic dyspepsia patients and 24 organic upper GI disease patients (Figure 1). The mean age was 49.9 ± 13.0 years, and 231 (60.6%) patients were female. The baseline characteristics of all participants are shown in Table 1. Among the 381 people who met the Rome IV criteria, there were 224 with chronic gastritis, 120 with gastric erosion, 9 with gastric ulcers and 8 with Barrett's esophagus and others. The results of upper GI endoscopy are shown in Figure 2, and the results of epigastric ultrasounds are shown in Supplementary Figure 1. The results of routine blood tests are shown in Supplementary Figure 2.

We also randomly selected the upper GI endoscopy results of 200 healthy people from the health examination center of the Affiliated Hospital of Northwest University. The upper GI endoscopy results showed that 77% of patients had chronic gastritis, duodenitis, Barrett's esophagus, esophageal candidiasis or gastric erosion, indicating a

Table 1 Baseline characteristics of all participants and univariate analyses of various predictive variables for organic dyspepsia

Characteristics	Full participants, *n* = 381	FD, *n* = 266	Organic dyspepsia, *n* = 115	*P* value
Age in yr	49.9 ± 13.0	49.6 ± 12.9	50.5 ± 13.4	0.706
BMI in kg/m^2	21.9 ± 3.3	21.9 ± 3.5	21.7 ± 2.9	0.682
Gender, M/F	150/231	107/159	43/72	0.603
Race, Han/minority	377/4	262/4	115/0	0.320
Location, Shaanxi/other	324/57	226/40	98/17	0.949
Job category				0.980
Physical	130 (34.1)	90 (33.8)	40 (34.8)	
Mental	96 (25.2)	67 (25.2)	29 (25.2)	
Middle	101 (26.5)	70 (26.3)	31 (27.0)	
Retire	54 (14.2)	39 (14.7)	15 (13.0)	
Marriage				1.000
Never married	19 (5.0)	13 (4.9)	6 (5.2)	
Married	362 (95.0)	253 (95.1)	109 (94.8)	
Daily exercise				0.048
< 1/2 h	27 (7.1)	18 (6.8)	9 (7.8)	
1/2-1 h	96 (25.2)	69 (25.9)	27 (23.5)	
1-2 h	63 (16.5)	35 (13.2)	28 (24.3)	
> 2 h	195 (51.2)	144 (54.1)	51 (44.3)	
Spicy food	206 (54.1)	145 (54.5)	61 (53.0)	0.792
Smoking				0.720
< half pack a day	335 (87.9)	235 (88.3)	100 (87.0)	
> half pack a day	46 (12.1)	31 (11.7)	15 (13.0)	
Alcohol	72 (18.9)	50 (18.8)	22 (19.1)	0.939
Sleep, good/bad	238/143	168/98	70/45	0.672
Outpatient cost				0.060
< 500	2 (0.5)	1 (0.4)	1 (0.9)	
500-1000	46 (12.1)	40 (15.0)	6 (5.2)	
1000-3000	107 (28.1)	76 (28.6)	31 (27.0)	
3000-5000	41 (10.8)	29 (10.9)	12 (10.4)	
> 5000	185 (48.5)	120 (45.1)	65 (56.5)	
Educational level				0.791
Elementary and below	175 (45.9)	122 (45.9)	53 (46.1)	
High school	84 (22.1)	61 (22.9)	23 (20.0)	
College	109 (28.6)	73 (27.4)	36 (31.3)	
Postgraduate and above	13 (3.4)	10 (3.8)	3 (2.6)	
Previous visits				0.443
0	106 (27.8)	80 (30.1)	26 (22.6)	
1	72 (18.9)	49 (18.4)	23 (20.0)	
2	32 (8.4)	20 (7.5)	12 (10.4)	
≥ 3	171 (44.9)	117 (44.0)	54 (47.0)	
Weight loss				0.238

No	277 (72.7)	199 (74.8)	78 (67.8)	
< 7 lb	50 (13.1)	30 (11.3)	20 (17.4)	
≥ 7 lb	54 (14.2)	37 (13.9)	17 (14.8)	
Anemia, yes/no	31/350	0/266	31/84	< 0.001
Anorexia, yes/no	94/287	66/200	28/87	0.923
Vomiting, yes/no	22/359	14/252	8/107	0.485
Melena, yes/no	23/358	16/250	7/108	1.000
Dysphagia, yes/no	3/378	1/265	2/113	0.218
Family history				0.204
None	331 (86.9)	235 (88.3)	96 (83.5)	
Esophagus cancer	13 (3.4)	10 (3.8)	3 (2.6)	
Gastric cancer	24 (6.3)	15 (5.6)	9 (7.8)	
Other	13 (3.4)	6 (2.3)	7 (6.1)	
Alarm symptoms				0.004
No	161 (42.3)	125 (47.0)	36 (31.3)	
Yes	220 (57.7)	141 (53.0)	79 (68.7)	
Number of alarm symptoms				0.001
0	161 (42.3)	125 (47.0)	36 (31.3)	
1	139 (36.5)	96 (36.1)	43 (37.4)	
2	59 (15.5)	37 (13.9)	22 (19.1)	
3	18 (4.7)	7 (2.6)	11 (9.6)	
4	4 (1.0)	1 (0.4)	3 (2.6)	

Values are expressed as the mean ± standard deviation or *n* (%). BMI: Body mass index; M: Male; F: Female; FD: Functional dyspepsia.

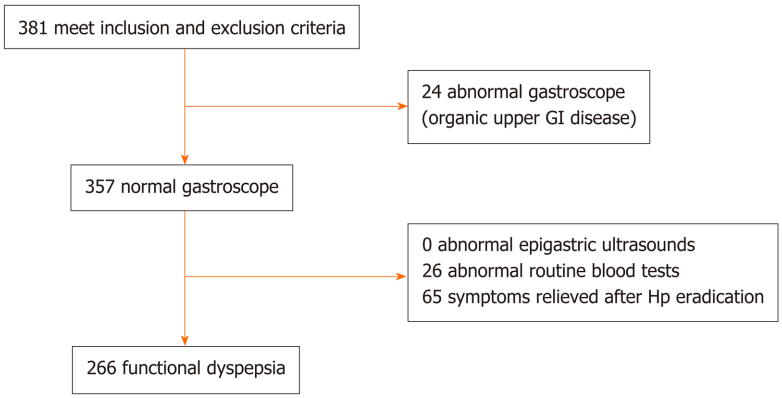

Figure 1 Flow chart of the study. GI: Gastrointestinal; Hp: *Helicobacter pylori*.

high proportion of patients in the general population (Supplementary Table 2). These data further supported our decision to treat chronic gastritis, duodenitis, Barrett's esophagus, esophageal candidiasis or gastric erosion as functional diseases.

Prediction of organic dyspepsia

For the comparison between FD and organic dyspepsia, there were 266 FD and 115 organic dyspepsia. In univariate analysis, there were statistically significant differences between FD and organic dyspepsia in daily exercise ($P = 0.048$), anemia ($P < 0.001$), alarm symptoms ($P = 0.004$) and number of alarm symptoms ($P = 0.001$). Then in the multivariate logistic regression analysis, outpatient cost was analyzed together

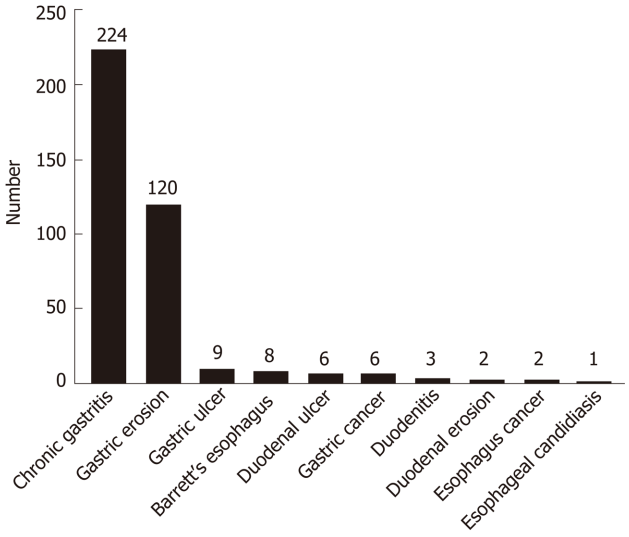

Figure 2 Endoscopy results.

with daily exercise, anemia, alarm symptoms and number of alarm symptoms. All anemia patients always had organic dyspepsia with complete separation, and exact logistic regression analysis was used. Anemia (OR = 137.700, 95%CI: 30.206-∞, P < 0.001) was still an independent predictor of organic dyspepsia (Table 1). These data suggested that most alarm symptoms had poor predictive value for organic dyspepsia based on Rome IV criteria. Moreover, there was no difference in outpatient cost between patients with FD and those with organic dyspepsia.

Prediction of organic upper GI diseases

There were 266 FD and 24 organic upper GI disease cases. Univariate analysis demonstrated that smoking (P = 0.024), anemia (P < 0.001), alarm symptoms (P = 0.038) and number of alarm symptoms (P = 0.009) were significant predictors of organic upper GI diseases. In multivariate analysis, age together with smoking, anemia, alarm symptoms and number of alarm symptoms were analyzed. Anemia belonged to organic upper GI diseases, there was complete separation, and exact logistic regression analysis was used. In multivariate regression analysis, age (OR = 1.056, P = 0.012), smoking (OR = 4.714, P = 0.006) and anemia (OR = 88.270, P < 0.001) were independent predictors for organic upper GI diseases (Table 2).

Additionally, the receiver operating characteristic curve was used to evaluate the predictive value of these independent risk factors. When the three criteria (age, smoking and anemia) were used together, the area under the receiver operating characteristic curve was 0.788 (P < 0.001, 95%CI: 0.692-0.884). These data suggested that most alarm symptoms had poor predictive value for organic dyspepsia based on Rome IV criteria, and age, smoking and anemia had certain predictive value for organic dyspepsia. Moreover, there was no difference in outpatient cost between FD patients and patients with organic upper GI diseases.

Comparison of EPS and PDS

FD was prevalent in 266 of the population who underwent complete upper GI endoscopy according to the Rome IV criteria. Among the 266 patients with dyspepsia, 174 individuals only presented with EPS, 31 individuals only met the criteria for PDS, and the remaining 61 individuals presented with both EPS and PDS. For the comparison of EPS, PDS and EPS combined with PDS, univariate analysis showed that there were statistically significant differences in anorexia (P = 0.021) and previous visits (P = 0.012), and the clinical characteristics of patients with EPS, PDS and EPS combined with PDS were not significantly different. Characteristics of patients with EPS, PDS and EPS combined with PDS are shown in Table 3.

DISCUSSION

To our knowledge, our study is the first to research the predictive value of alarm

Table 2 Univariate and multivariate analysis of various predictive variables for organic upper gastrointestinal diseases

Characteristics	FD, *n* = 266	Organic upper GI disease, *n* = 24	Univariate analysis	Multivariate analysis		
			P value	OR	95%CI	*P* value
Age in yr	49.6 ± 12.9	54.8 ± 14.8	0.071	1.056	1.012-1.101	0.012
BMI in kg/m^2	21.9 ± 3.5	21.5 ± 2.1	0.635			
Gender, M/F	107/159	10/14	1.000			
Race, Han/minority	262/4	24/0	1.000			
Location, Shaanxi/other	226/40	19/5	0.553			
Job category			0.629			
Physical	90 (33.8)	8 (33.3)				
Mental	67 (25.2)	4 (16.7)				
Middle	70 (26.3)	9 (37.5)				
Retire	39 (14.7)	3 (12.5)				
Marriage			0.136			
Never married	13 (4.9)	3 (12.5)				
Married	253 (95.1)	21 (87.5)				
Daily exercise			0.128			
< 1/2 h	18 (6.8)	0 (0)				
1/2-1 h	69 (25.9)	3 (12.5)				
1-2 h	35 (13.2)	6 (25.0)				
> 2 h	144 (54.1)	15 (62.5)				
Spicy food	145 (54.5)	14 (58.3)	0.719			
Smoking			0.024			
< half pack a day	235 (88.3)	17 (70.8)				
> half pack a day	31 (11.7)	7 (29.2)		4.714	1.569-14.16	0.006
Alcohol	50 (18.8)	5 (20.8)	0.788			
Sleep, good/bad	168/98	16/8	0.827			
Outpatient cost			0.363			
< 500	1 (0.4)	0				
500-1000	40 (15.0)	1 (4.2)				
1000-3000	76 (28.6)	7 (29.2)				
3000-5000	29 (10.9)	1 (4.2)				
> 5000	120 (45.1)	15 (62.5)				
Educational level			0.789			
Elementary and below	122 (45.9)	12 (50.0)				
High school	61 (22.9)	5 (20.8)				
College	73 (27.4)	7 (29.2)				
Postgraduate and above	10 (3.8)	0				
Previous visits			0.637			
0	80 (30.1)	9 (37.5)				
1	49 (18.4)	4 (16.7)				
2	20 (7.5)	3 (12.5)				
≥ 3	117 (44.0)	8 (33.3)				

Weight loss			0.380			
No	199 (74.8)	16 (66.7)				
< 7 lb	30 (11.3)	5 (20.8)				
≥ 7 lb	37 (13.9)	3 (12.5)				
Anemia, yes/no	0/266	5/19	< 0.001	88.27	15.486-∞	< 0.001
Anorexia, yes/no	66/200	9/15	0.222			
Vomiting, yes/no	14/252	3/21	0.156			
Melena, yes/no	16/250	3/21	0.200			
Dysphagia, yes/no	1/265	1/23	0.159			
Family history			0.627			
None	235 (88.3)	22 (91.7)				
Esophagus cancer	10 (3.8)	0				
Gastric cancer	15 (5.6)	2 (8.3)				
Other	6 (2.3)	0				
Alarm symptoms			0.038			
No	125 (47.0)	6 (25.0)				
Yes	141 (53.0)	18 (75.0)				
Number of alarm symptoms			0.009			
0	125 (47.0)	6 (25.0)				
1	96 (36.1)	10 (41.7)				
2	37 (13.9)	4 (16.7)				
3	7 (2.6)	3 (12.5)				
4	1 (0.4)	1 (4.2)				

Values are expressed as the mean ± standard deviation or *n* (%). BMI: Body mass index; M: Male; F: Female; FD: Functional dyspepsia; OR: Odds ratio; CI: Confidence interval.

symptoms in patients with Rome IV dyspepsia. For patients with dyspepsia, it is very important to identify early digestive tract diseases, and the ability of alarm symptoms to identify severe upper digestive tract diseases is limited, meaning that further study is necessary[13,19,28]. In this study, patients with dyspepsia symptoms who met the Rome IV criteria were collected to evaluate the predictive value of alarm symptoms for dyspepsia.

FD was diagnosed strictly by laboratory examination, abdominal ultrasound and upper GI endoscopy. In the exclusion criteria of our study, we excluded patients with liver dysfunction, diabetes mellitus, thyroid dysfunction and other organic or metabolic diseases that were treated primarily as nondyspeptic diseases in clinical practice. In addition, severe abnormalities of white blood cells or platelets were considered as having other serious diseases and were excluded. Mild abnormalities of white blood cells or platelets were considered as normal results without causing any symptoms. Therefore, abnormal routine blood tests refer to anemia in this study.

In this cross-sectional study, we were unable to determine whether dyspeptic symptoms were relieved after treatment for anemia. As anemia is likely to explain dyspeptic symptoms and FD was diagnosed strictly by laboratory examination, abdominal ultrasound and upper GI endoscopy in this study, all anemia was considered organic disease regardless of whether it was proven to actually be associated with dyspeptic symptoms. Therefore, we not only evaluated the predictive value of alarm symptoms for organic dyspepsia, but also evaluated the predictive value of alarm symptoms for organic upper GI diseases to make the results more accurate. The results of this study showed that anemia was the only independent risk factor for organic dyspepsia and organic upper GI diseases among alarm symptoms based on the Rome IV criteria. Therefore, based on the Rome IV criteria, most alarm symptoms were of limited value in predicting organic dyspepsia and organic upper GI

Table 3 Characteristics of patients with epigastric pain syndrome and postprandial distress syndrome

Characteristics	EPS, *n* = 174	PDS, *n* = 31	EPS and PDS, *n* = 61	*P* value
Age in yr	49.2 ± 12.7	49.1 ± 12.7	50.8 ± 13.5	0.638
BMI in kg/m^2	22.3 ± 3.5	21.2 ± 2.7	21.3 ± 3.8	0.062
Gender, M/F	70/104	14/17	23/38	0.788
Race, Han/minority	170/4	31/0	61/0	0.742
Location, Shaanxi/other	147/27	28/3	51/10	0.733
Job category				0.172
Physical	59 (33.9)	11 (35.5)	20 (32.8)	
Mental	49 (28.2)	8 (25.8)	10 (16.4)	
Middle	44 (25.3)	10 (32.3)	16 (26.2)	
Retire	22 (12.6)	2 (6.5)	15 (24.6)	
Marriage				0.615
Never married	7 (4.0)	2 (6.5)	4 (6.6)	
Married	167 (96.0)	29 (93.5)	57 (93.4)	
Daily exercise				0.993
< 1/2 h	12 (6.9)	2 (6.5)	4 (6.6)	
1/2-1 h	47 (27.0)	7 (22.6)	15 (24.6)	
1-2 h	24 (13.8)	4 (12.9)	7 (11.5)	
> 2 h	91 (52.3)	18 (58.1)	35 (57.4)	
Spicy food	94 (54.0)	22 (71.0)	29 (47.5)	0.100
Smoking				0.225
No	149 (85.6)	24 (77.4)	46 (75.4)	
< half pack a day	11 (6.3)	2 (6.5)	3 (4.9)	
half pack-one pack a day	5 (2.9)	1 (3.2)	2 (3.3)	
> one pack a day	9 (5.2)	4 (12.9)	10 (16.4)	
Alcohol	29 (16.7)	9 (29.9)	12 (19.7)	0.265
Sleep, good/bad	115/59	18/13	35/26	0.393
Outpatient cost				0.672
< 500	1 (0.6)	0	0	
500-1000	30 (17.2)	5 (16.1)	5 (8.2)	
1000-3000	51 (29.3)	10 (32.3)	15 (24.6)	
3000-5000	18 (10.3)	4 (12.9)	7 (11.5)	
> 5000	74 (42.5)	12 (38.7)	34 (55.7)	
Educational level				0.166
Elementary and below	76 (43.7)	11 (35.5)	35 (57.4)	
High school	37 (21.3)	10 (32.3)	14 (23.0)	
College	53 (30.5)	10 (32.3)	10 (16.4)	
Postgraduate and above	8 (4.6)	0	2 (3.3)	
Previous visits				0.012
0	59 (33.9)	13 (41.9)	8 (13.1)	
1	36 (20.7)	3 (9.7)	10 (16.4)	
2	12 (6.9)	3 (9.7)	5 (8.2)	

≥ 3	67 (38.5)	12 (38.7)	38 (62.3)	
Weight loss				0.637
No	133 (76.4)	24 (77.4)	42 (68.9)	
< 7 lb	20 (11.5)	2 (6.5)	8 (13.1)	
≥ 7 lb	21 (12.1)	5 (16.1)	11 (18.0)	
Anorexia, yes/no	34/140	10/21	22/39	0.021
Vomiting, yes/no	11/163	0/31	3/58	0.535
Melena, yes/no	9/165	4/27	3/58	0.236
Dysphagia, yes/no	0/174	1/30	0/61	0.117
Family history				0.743
None	151 (86.8)	28 (90.3)	56 (91.8)	
Esophagus cancer	7 (4.0)	1 (3.2)	2 (3.3)	
Gastric cancer	10 (5.7)	2 (6.5)	3 (4.9)	
Other	6 (3.4)	0	0	

Values are expressed as the mean ± standard deviation or *n* (%). BMI: Body mass index; M: Male; F: Female; EPS: Epigastric pain syndrome; PDS: Postprandial distress syndrome.

diseases.

A systematic review reported that the global prevalence of FD among adults ranged between 1.8% and 57% according to the Rome criteria used to define FD. Among patients with dyspepsia, more than 70% had FD[29]. In our study, among patients with dyspepsia, the prevalence of FD was 69.8% (266/381) according to the Rome IV criteria, and the rate of patients who were diagnosed with FD was slightly lower. The reason may be that the dyspeptic patients included had completed an upper GI endoscopy, an abdominal ultrasonography, a routine blood examination, a liver function test and an *H. pylori* test within the last 6 mo. Many FD patients with incomplete data were excluded.

Our data suggested that age was the independent predictor for organic upper GI diseases (OR = 1.056, P = 0.012). In a study by Gracie *et al*[30] of the Rome III criteria, the age of organic upper GI diseases patients were older than of FD patients. In a prospective cross-sectional study of 839 patients, there was a significant difference in age between patients with FD and those with organic upper GI diseases[31]. Our research results also showed that, based on the Rome IV criteria, smoking was an independent risk factor for organic upper GI diseases (OR = 4.714, P = 0.006, 95%CI: 1.569-14.16). FD epidemiological data indicated that smoking was a factor associated with the pathophysiology of FD[32]. In an observational study, smoking was an independent predictor of organic dyspepsia, while Faintuch *et al* showed that smoking status was associated with organic dyspepsia. Several reports suggested that smoking was a risk factor for gastric or duodenal ulcer based on multivariable logistic regression analyses. Overall, the results in our study were remarkably comparable to those of other studies.

The relationship between clinical features and dyspepsia was not consistent[33-36]. In this study, gender, BMI, race, location, marriage, spicy food, alcohol, sleep, daily exercise, educational level, outpatient cost and previous visits were not independent risk factors for organic dyspepsia and organic upper GI diseases, which may be related to the diverse clinical characteristics and the limited number of patients. No consistent results had been obtained on the relationship between FD and clinical characteristics in previous studies, which still needed to be confirmed by further clinical studies[37-39].

Our study had some limitations. First, in our study, FD was diagnosed strictly by laboratory examination, abdominal ultrasound and upper GI endoscopy. The study inclusion criteria were very rigorous. Although our study was conducted at two centers, the relatively small sample size also limited the evidence strength of the results. The study population was mainly from northwest China. In the future, it still needs to be confirmed by larger sample studies from multicenters all over China. Second, because our study mainly compared FD with organic dyspepsia and FD with organic upper GI diseases, we only counted the number of patients with relief of dyspeptic symptoms after eradication of *H. pylori* (*H. pylori*-associated dyspepsia) as a

part of organic dyspepsia but did not further count the number of patients with no relief of dyspeptic symptoms after eradication of *H. pylori* and the rate of *H. pylori* infection in FD. To our knowledge, no study has been conducted to assess the prevalence of *H. pylori* in FD after excluding *H. pylori*-associated dyspepsia based on the Rome IV criteria making this a good direction for future research. Third, relevant data on psychological factors were not collected, which might be an important influencing factor and can be the next research direction.

In conclusion, most alarm symptoms had poor predictive value for organic dyspepsia and organic upper GI diseases based on Rome IV criteria, and gastroscopic screening should not be based solely on alarm symptoms. The clinical characteristics of patients with EPS, PDS and EPS combined with PDS were not significantly different.

ARTICLE HIGHLIGHTS

Research background

No studies have evaluated the predictive value of alarm symptoms for organic dyspepsia and organic upper gastrointestinal (GI) diseases based on Rome IV criteria in the Chinese population.

Research motivation

Previous studies have shown that the sensitivity of alarm symptoms for predicting cases with upper GI malignancies is unsatisfactory. The predictive value of alarm symptoms requires further research.

Research objectives

To evaluate the predictive value of alarm symptoms of dyspeptic patients based on Rome IV criteria.

Research methods

We performed a cross-sectional study of dyspepsia patients who met the inclusion and exclusion criteria from March 2018 to January 2019.

Research results

Based on the Rome IV criteria, alarm symptoms were of limited value in differentiating organic dyspepsia and organic upper GI diseases from functional dyspepsia.

Research conclusions

Most alarm symptoms had poor predictive value for organic dyspepsia and organic upper GI diseases based on Rome IV criteria. The clinical characteristics of patients with epigastric pain syndrome, postprandial distress syndrome and the two combined were not significantly different.

Research perspective

Gastroscopic screening of dyspepsia patients should not be based solely on alarm symptoms. In the future, the predictive value of alarm symptoms still needs to be confirmed by larger sample studies from multicenters all over China.

REFERENCES

1 **Parkman HP**, Camilleri M, Farrugia G, McCallum RW, Bharucha AE, Mayer EA, Tack JF, Spiller R, Horowitz M, Vinik AI, Galligan JJ, Pasricha PJ, Kuo B, Szarka LA, Marciani L, Jones K, Parrish CR, Sandroni P, Abell T, Ordog T, Hasler W, Koch KL, Sanders K, Norton NJ, Hamilton F. Gastroparesis and functional dyspepsia: excerpts from the AGA/ANMS meeting. *Neurogastroenterol Motil* 2010; **22**: 113-133 [PMID: 20003077 DOI: 10.1111/j.1365-2982.2009.01434.x]

2 **Tack J**, Carbone F. Functional dyspepsia and gastroparesis. *Curr Opin Gastroenterol* 2017; **33**: 446-454 [PMID: 28832359 DOI: 10.1097/MOG.0000000000000393]

3 **Tack J**, Talley NJ, Camilleri M, Holtmann G, Hu P, Malagelada JR, Stanghellini V. Functional gastroduodenal disorders. *Gastroenterology* 2006; **130**: 1466-1479 [PMID: 16678560 DOI: 10.1053/j.gastro.2005.11.059]

4 **Talley NJ**, Vakil NB, Moayyedi P. American gastroenterological association technical review on the evaluation of dyspepsia. *Gastroenterology* 2005; **129**: 1756-1780 [PMID: 16285971 DOI: 10.1053/j.gastro.2005.09.020]

5 **Saito YA**, Locke GR, Almazar AE, Bouras EP, Howden CW, Lacy BE, DiBaise JK, Prather CM, Abraham BP, El-Serag HB, Moayyedi P, Herrick LM, Szarka LA, Camilleri M, Hamilton FA, Schleck CD, Tilkes KE, Zinsmeister AR, Talley NJ. Polymorphisms of 5-HTT LPR and GNβ3 825C>T and Response to Antidepressant Treatment in Functional Dyspepsia: A Study from The Functional Dyspepsia Treatment Trial. *Am J Gastroenterol* 2017; **112**: 903-909 [PMID: 28291238 DOI: 10.1038/ajg.2017.52]

6 **Feld L**, Cifu AS. Management of Dyspepsia. *JAMA* 2018; **319**: 1816-1817 [PMID: 29715342 DOI: 10.1001/jama.2018.3435]

7 **Zagari RM**, Law GR, Fuccio L, Cennamo V, Gilthorpe MS, Forman D, Bazzoli F. Epidemiology of functional dyspepsia and subgroups in the Italian general population: an endoscopic study. *Gastroenterology* 2010; **138**: 1302-1311 [PMID: 20074574 DOI: 10.1053/j.gastro.2009.12.057]

8 **El-Serag HB**, Talley NJ. Health-related quality of life in functional dyspepsia. *Aliment Pharmacol Ther* 2003; **18**: 387-393 [PMID: 12940923 DOI: 10.1046/j.1365-2036.2003.01706.x]

9 **Moayyedi P**, Mason J. Clinical and economic consequences of dyspepsia in the community. *Gut* 2002; **50** Suppl 4: iv10-iv12 [PMID: 11953338 DOI: 10.1136/gut.50.suppl_4.iv10]

10 **Thomson AB**, Barkun AN, Armstrong D, Chiba N, White RJ, Daniels S, Escobedo S, Chakraborty B, Sinclair P, Van Zanten SJ. The prevalence of clinically significant endoscopic findings in primary care patients with uninvestigated dyspepsia: the Canadian Adult Dyspepsia Empiric Treatment - Prompt Endoscopy (CADET-PE) study. *Aliment Pharmacol Ther* 2003; **17**: 1481-1491 [PMID: 12823150 DOI: 10.1046/j.1365-2036.2003.01646.x]

11 **Kapoor N**, Bassi A, Sturgess R, Bodger K. Predictive value of alarm features in a rapid access upper gastrointestinal cancer service. *Gut* 2005; **54**: 40-45 [PMID: 15591502 DOI: 10.1136/gut.2004.039438]

12 **Talley NJ**, Silverstein MD, Agréus L, Nyrén O, Sonnenberg A, Holtmann G. AGA technical review: evaluation of dyspepsia. American Gastroenterological Association. *Gastroenterology* 1998; **114**: 582-595 [PMID: 9496950 DOI: 10.1016/s0016-5085(98)70542-6]

13 **Vakil N**, Moayyedi P, Fennerty MB, Talley NJ. Limited value of alarm features in the diagnosis of upper gastrointestinal malignancy: systematic review and meta-analysis. *Gastroenterology* 2006; **131**: 390-401; quiz 659-60 [PMID: 16890592 DOI: 10.1053/j.gastro.2006.04.029]

14 **Fransen GA**, Janssen MJ, Muris JW, Laheij RJ, Jansen JB. Meta-analysis: the diagnostic value of alarm symptoms for upper gastrointestinal malignancy. *Aliment Pharmacol Ther* 2004; **20**: 1045-1052 [PMID: 15569106 DOI: 10.1111/j.1365-2036.2004.02251.x]

15 **Wallace MB**, Durkalski VL, Vaughan J, Palesch YY, Libby ED, Jowell PS, Nickl NJ, Schutz SM, Leung JW, Cotton PB. Age and alarm symptoms do not predict endoscopic findings among patients with dyspepsia: a multicentre database study. *Gut* 2001; **49**: 29-34 [PMID: 11413107 DOI: 10.1136/gut.49.1.29]

16 **Holtmann G**, Talley NJ, Liebregts T, Adam B, Parow C. A placebo-controlled trial of itopride in functional dyspepsia. *N Engl J Med* 2006; **354**: 832-840 [PMID: 16495395 DOI: 10.1056/NEJMoa052639]

17 **von Arnim U**, Peitz U, Vinson B, Gundermann KJ, Malfertheiner P. STW 5, a phytopharmacon for patients with functional dyspepsia: results of a multicenter, placebo-controlled double-blind study. *Am J Gastroenterol* 2007; **102**: 1268-1275 [PMID: 17531013 DOI: 10.1111/j.1572-0241.2006.01183.x]

18 **Stanghellini V**, Chan FK, Hasler WL, Malagelada JR, Suzuki H, Tack J, Talley NJ. Gastroduodenal Disorders. *Gastroenterology* 2016; **150**: 1380-1392 [PMID: 27147122 DOI: 10.1053/j.gastro.2016.02.011]

19 **Hammer J**, Eslick GD, Howell SC, Altiparmak E, Talley NJ. Diagnostic yield of alarm features in irritable bowel syndrome and functional dyspepsia. *Gut* 2004; **53**: 666-672 [PMID: 15082584 DOI: 10.1136/gut.2003.021857]

20 **Ford AC**, Bercik P, Morgan DG, Bolino C, Pintos-Sanchez MI, Moayyedi P. The Rome III criteria for the diagnosis of functional dyspepsia in secondary care are not superior to previous definitions. *Gastroenterology* 2014; **146**: 932-40; quiz e14-5 [PMID: 24417817 DOI: 10.1053/j.gastro.2014.01.014]

21 **Enck P**, Azpiroz F, Boeckxstaens G, Elsenbruch S, Feinle-Bisset C, Holtmann G, Lackner JM, Ronkainen J, Schemann M, Stengel A, Tack J, Zipfel S, Talley NJ. Functional dyspepsia. *Nat Rev Dis Primers* 2017; **3**: 17081 [PMID: 29099093 DOI: 10.1038/nrdp.2017.81]

22 **Tack J**, Talley NJ. Functional dyspepsia--symptoms, definitions and validity of the Rome III criteria. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 134-141 [PMID: 23399526 DOI: 10.1038/nrgastro.2013.14]

23 **Oustamanolakis P**, Tack J. Dyspepsia: organic versus functional. *J Clin Gastroenterol* 2012; **46**: 175-190 [PMID: 22327302 DOI: 10.1097/MCG.0b013e318241b335]

24 **Tack J**, Janssen P, Masaoka T, Farré R, Van Oudenhove L. Efficacy of buspirone, a fundus-relaxing drug, in patients with functional dyspepsia. *Clin Gastroenterol Hepatol* 2012; **10**: 1239-1245 [PMID: 22813445 DOI: 10.1016/j.cgh.2012.06.036]

25 **Wijnands TF**, Ronot M, Gevers TJ, Benzimra J, Kool LJ, Vilgrain V, Drenth JP. Predictors of treatment response following aspiration sclerotherapy of hepatic cysts: an international pooled analysis of individual patient data. *Eur Radiol* 2017; **27**: 741-748 [PMID: 27180184 DOI: 10.1007/s00330-016-4363-x]

26 **Dong J**, Zhang M, Chen JQ, Ma F, Wang HH, Lv Y. Tumor size is not a criterion for resection during the management of giant hemangioma of the liver. *Eur J Gastroenterol Hepatol* 2015; **27**: 686-691 [PMID: 25923944 DOI: 10.1097/MEG.0000000000000344]

27 **Aloia TA**, Járufe N, Javle M, Maithel SK, Roa JC, Adsay V, Coimbra FJ, Jarnagin WR. Gallbladder cancer: expert consensus statement. *HPB (Oxford)* 2015; **17**: 681-690 [PMID: 26172135 DOI: 10.1111/hpb.12444]

28 **Lee SW**, Chang CS, Yeh HJ, Lien HC, Lee TY, Peng YC. The Diagnostic Value of Alarm Features for Identifying Types and Stages of Upper Gastrointestinal Malignancies. *Gastroenterology Res* 2017; **10**: 120-125 [PMID: 28496533 DOI: 10.14740/gr826w]

29 **Ford AC**, Marwaha A, Sood R, Moayyedi P. Global prevalence of, and risk factors for, uninvestigated dyspepsia: a meta-analysis. *Gut* 2015; **64**: 1049-1057 [PMID: 25147201 DOI: 10.1136/gutjnl-2014-307843]

30 **Gracie DJ**, Bercik P, Morgan DG, Bolino C, Pintos-Sanchez MI, Moayyedi P, Ford AC. No increase in prevalence of somatization in functional vs organic dyspepsia: a cross-sectional survey. *Neurogastroenterol Motil* 2015; **27**: 1024-1031 [PMID: 25931163 DOI: 10.1111/nmo.12578]

31 **Mahadeva S**, Goh KL. Anxiety, depression and quality of life differences between functional and organic dyspepsia. *J Gastroenterol Hepatol* 2011; **26** Suppl 3: 49-52 [PMID: 21443710 DOI: 10.1111/j.1440-1746.2011.06656.x]

32 **Olafsdottir LB**, Gudjonsson H, Jonsdottir HH, Thjodleifsson B. Natural history of functional dyspepsia: a 10-year population-based study. *Digestion* 2010; **81**: 53-61 [PMID: 20029209 DOI: 10.1159/000243783]

33 **Mahadeva S**, Goh KL. Epidemiology of functional dyspepsia: a global perspective. *World J Gastroenterol* 2006; **12**: 2661-2666 [PMID: 16718749 DOI: 10.3748/wjg.v12.i17.2661]

34 **Shaib Y**, El-Serag HB. The prevalence and risk factors of functional dyspepsia in a multiethnic population in the United States. *Am J Gastroenterol* 2004; **99**: 2210-2216 [PMID: 15555004 DOI: 10.1111/j.1572-0241.2004.40052.x]

35 **Koloski NA**, Talley NJ, Boyce PM. Epidemiology and health care seeking in the functional GI disorders: a population-based study. *Am J Gastroenterol* 2002; **97**: 2290-2299 [PMID: 12358247 DOI: 10.1111/j.1572-0241.2002.05783.x]

36 **Aziz I**, Palsson OS, Törnblom H, Sperber AD, Whitehead WE, Simrén M. Epidemiology, clinical characteristics, and associations for symptom-based Rome IV functional dyspepsia in adults in the USA, Canada, and the UK: a cross-sectional population-based study. *Lancet Gastroenterol Hepatol* 2018; **3**: 252-262 [PMID: 29396034 DOI: 10.1016/S2468-1253(18)30003-7]

37 **Aziz I**, Palsson OS, Whitehead WE, Sperber AD, Simrén M, Törnblom H. Epidemiology, Clinical Characteristics, and Associations for Rome IV Functional Nausea and Vomiting Disorders in Adults. *Clin Gastroenterol Hepatol* 2019; **17**: 878-886 [PMID: 29857155 DOI: 10.1016/j.cgh.2018.05.020]

38 **Hammer J**, Führer M. Clinical characteristics of functional dyspepsia depending on chemosensitivity to capsaicin. *Neurogastroenterol Motil* 2017; **29**: 1-12 [PMID: 28547912 DOI: 10.1111/nmo.13103]

39 **Kinoshita Y**, Chiba T; FUTURE Study Group. Characteristics of Japanese patients with chronic gastritis and comparison with functional dyspepsia defined by ROME III criteria: based on the large-scale survey, FUTURE study. *Intern Med* 2011; **50**: 2269-2276 [PMID: 22001450 DOI: 10.2169/internalmedicine.50.5678]

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