

Prevalence of Clinically Significant Endoscopic Findings in Dyspeptic Patients with Alarm Features

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ABSTRACT

Background: Dyspepsia is common in clinical practice. Esophagogastroduodenoscopy (EGD) is generally recommended in dyspeptic patients with alarm features (AF) including (I) age ≥ 55 years, (II) evidence of gastrointestinal blood loss, (III) unexplained weight loss, (IV) dysphagia, and (V) persistent vomiting. The predictive value of AF remains uncertain.

Aims: To evaluate EGD findings in dyspeptic patients with AF and to assess the diagnostic role of abdominal ultrasonography (US) in endoscopy-negative dyspeptic patients with AF.

Methods: Between March 2012 and January 2013, consecutive dyspeptic patients were screened for the presence of AF. EGD was performed in 227 dyspeptic patients with AF. Significant EGD findings were defined as any lesion(s) other than normal and non-erosive gastritis. Patients with known intraabdominal malignancy, previous gastric surgery and previous EGD were excluded. EGD findings among dyspeptic patients without AF who underwent EGD during the same period of time was retrospectively collected to compare with the study population. Abdominal US was performed in all endoscopy-negative patients.

Results: Peptic ulcer disease and erosive gastroduodenitis were found in 18.5% and 44.1% of patients respectively. *H. pylori* infection was found in 52.9% (117/221). GI tumors were encountered in 6.1% (cancer of the esophagus 1, cancer of the stomach 8, gastric lymphoma 2, GIST 2, metastatic squamous cell cancer of the 1). Significant findings were found in 69.2% (157/227) of patients; and this was significantly higher than in the AF-negative dyspeptic cohort. (69.2% vs 21.3%, $p < 0.001$). Among 5 AF, persistent vomiting seemed to have the highest predictive value, especially for peptic ulcer (60%). Male sex, GI blood loss, vomiting, age ≥ 55 with GI blood loss, GI blood loss with weight loss and *H. pylori* infection were associated with significant EGD findings. In those 70 patients with negative EGD, US was performed in 64 patients and was normal in 51.6% and positive in 48.4% (fatty liver 14, gallstones 13, lymphadenopathy 1, cholangiocarcinoma 1, hemangioma 1, intrahepatic duct dilatation 1).

Conclusions: The presence of AF in a dyspeptic patient has a high predictive value for clinically significant EGD findings. The most common lesion was erosive gastroduodenitis. The usefulness of US in EGD-negative dyspeptic patients with AF remains unclear.

Key words : Dyspepsia, alarm features, erosive gastroduodenitis

[*Thai J Gastroenterol* 2013; 14(2):80-86.]

INTRODUCTION

Dyspepsia is a common complaint in the general population worldwide. In Western countries, the prevalence of dyspepsia is estimated to be 25-40%⁽¹⁾. In Thailand, a multicenter survey from referral centers reported prevalence of functional dyspepsia and functional bloating, according to the Rome I criteria, to be 5% and 37% respectively. Whereas a population-based study in the central region of Thailand revealed a 65.98% prevalence of dyspepsia was⁽²⁾. Causes of dyspepsia include a variety of benign disorders (e.g. gastroenteritis, peptic ulcer disease) as well as malignant conditions (e.g. gastric cancer)

Esophagogastroduodenoscopy (EGD) is the most accurate method for diagnosing most conditions associated with dyspepsia. However, EGD involves some discomfort, social inconvenience, and considerable cost. Efforts to identify those patients who are likely to benefit from EGD have been widely discussed and evaluated, but the conclusion remains controversial and varies among groups of experts from different countries^(1,6). The American Gastroenterological Association currently recommends EGD in all patients with alarm symptoms⁽¹⁾. Similarly, the Thailand Consensus for the management of Dyspepsia and *Helicobacter pylori* 2010 recommends endoscopy in patients with alarm symptoms (dysphagia, evidence of gastrointestinal (GI) blood loss, unexplained weight loss, persistent vomiting) or patients over the age of 55⁽⁴⁾.

The value of alarm features in predicting an underlying malignancy in patients with dyspepsia is unclear. Systematic review of the literatures to establish the accuracy of alarm features revealed varied sensitivity and specificity. Most of these studies originated from the Northern America and European countries where the incidence of upper GI malignancy is low. In addition, these studies evaluated alarm features for predicting upper GI malignancy, not for other significant upper GI diseases such as peptic ulcer disease^(1,5-8). Unfortunately, data from Asian countries, particularly from Thailand, to evaluate the performance of alarm features for identifying patients with upper GI malignancy and peptic ulcer disease are scant.

Not only gastric conditions, hepatopancreatobiliary disorders may also cause the symptoms of dyspepsia. This concern may be particularly important in Thailand in which the incidence of choledocholithiasis, hepatocellular carcinoma and cholangiocarcinoma are higher than in the Western countries⁽⁹⁻¹⁴⁾. There-

fore, we speculate that upper abdominal ultrasonography (US) may have some diagnostic utility in endoscopy-negative dyspeptic patients, particularly those with alarm features⁽¹⁵⁻¹⁷⁾.

This study was aimed to evaluate EGD findings in dyspeptic patients with alarm features, and to assess the utility of abdominal US in endoscopy-negative dyspeptic patients with alarm features.

METHODS

Patients

Patients with dyspeptic symptoms attending Rajavithi Hospital, Bangkok, Thailand a tertiary care hospital between March 2012 and January 2013 were consecutively evaluated. Study patients were at least 18 years of age, provided written informed consent, and had one or more alarm features: (I) age \geq 55 years, (II) evidence of gastrointestinal blood loss, (III) unexplained weight loss, (IV) dysphagia, and (V) persistent vomiting.

Exclusion criteria were history of upper GI surgery, history of intraabdominal malignancy, EGD in the previous 6 months, recent use of medications likely related to dyspepsia and peptic ulcer disease (including NSAIDs, aspirin, penicillin, sulphonamides, macrolides, doxycycline, tetracycline, metformin, estrogen, corticosteroid, digoxin, potassium, bisphosphonate, theophylline) within 1 month prior to the onset of dyspepsia, and patients with contraindication for EGD.

Methods

Baseline assessments included age, medical history, physical examination, medication use. Dyspeptic symptoms and alarm feature(s) were recorded. EGD was performed and endoscopic findings were recorded. Clinically significant findings were defined as lesions that could be responsible for the presenting dyspeptic symptoms. Non-erosive gastritis was not considered a clinically significant finding. If EGD findings were normal or only non-erosive gastritis, patients were further evaluated with upper abdominal US to search for other causes of the dyspeptic symptoms. EGD findings among dyspeptic patients without AF who underwent EGD during the same period of time were retrospectively collected to compare with the study population.

Statistical analysis

The estimated sample size of 288 patients was calculated based on an estimated prevalence of clinically significant findings of 23%. Since in this study we performed upper abdominal US in endoscopy-negative patients, we estimated the prevalence of clinically significant findings at 25%, with a margin of error of 0.05. Categorical variables were summarized as percentage while continuous variables were summarized as median (range) or mean (SD). To compare the variables between the study group and the comparison group (dyspeptic patients without alarm features), Chi-square or Fisher exact test was used for categorical variables and Student's *t*-test or Mann-Whitney U test was used for continuous variables depending on the distribution. Data analyses were performed by using SPSS version 16.0 (SPSS Inc. Chicago IL, USA).

RESULTS

Patients

Between March 2012 and January 2013, a total of 925 patients were screened at the outpatient Inter-

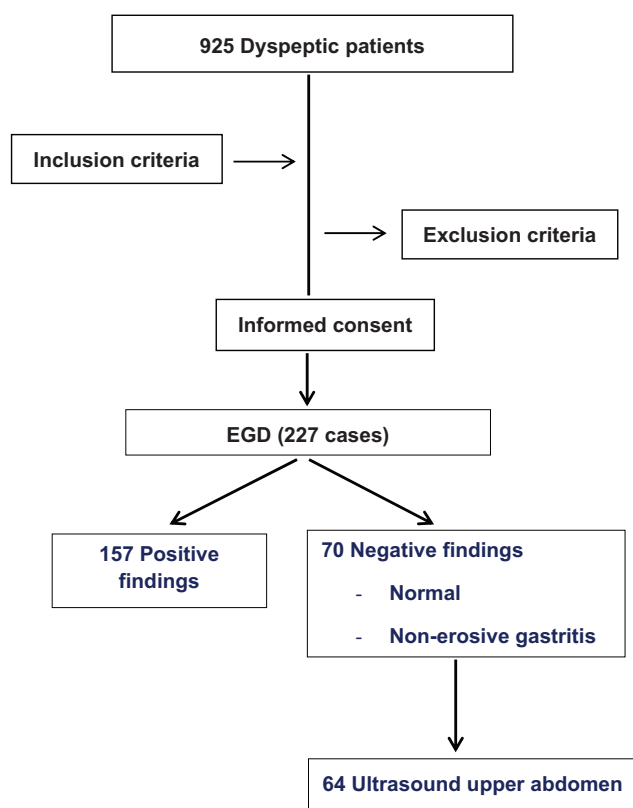


Figure 1. Study flow chart

nal Medicine and GI Clinics; 227 patients met the inclusion and exclusion criteria and were enrolled into the study. All 227 patients underwent EGD and provided adequate clinical information for the analysis. There were 85 men (37.4%) and 142 women (62.6%), with a mean age of 58.55 ± 13.78 years and a median age of 61 years (range 21-87 years). Thirty percent of patients were < 55 years old and 70% of patients were ≥ 55 . The mean duration of dyspeptic symptoms was 31.14 ± 1.27 weeks, with a median duration of 8 weeks (range 1 day-30 years). Each of the alarm features, namely (I) age ≥ 55 years, (II) evidence of gastrointestinal blood loss, (III) unexplained weight loss, (IV) dysphagia, and (V) persistent vomiting were noted in 70%, 33.9%, 46.3%, 4%, and 4.4% of patients, respectively.

Prevalence of clinically significant findings at endoscopy

Clinically significant findings were found in 69.2% (157/227) of patients, while negative findings were observed in 30.8% (70/227). Sixty-seven non-erosive gastritis (29.5%) and 3 normal EGD (1.3%) were noted. Among clinically significant EGD lesions, erosive gastritis was most commonly found (34.4%). Malignancies were found in 14 of 227 patients (6.1%) (Table 1). The prevalence of clinically significant EGD findings in dyspeptic patients with AF was significantly higher than the AF-negative dyspeptic cohort in our study (69.2% versus 21.3%, respectively; $p < 0.001$) (Table 2).

The prevalences of EGD findings are summarized in Table 3. Of the 5 alarm features, persistent vomiting appeared to have the highest predictive value, as significant EGD findings were detected in 100% of such patients.

Normal EGD was more common in dyspeptic patients age ≥ 55 years or those with weight loss compared to other alarm features (Table 3). Further analysis for patients with age ≥ 55 years or weight loss without other alarm features revealed more cases of normal EGD (45.9% and 43.3% respectively), although gastric adenocarcinoma was detected in 1.4% in patients age ≥ 55 years alone and 3.3% in patients with weight loss alone without other alarm features (Table 4). Patients with more than one alarm feature had higher prevalence of significant EGD findings compare to patients with a single alarm feature (Table 3, 4).

In patients who presented with weight loss, tu-

Table 1. Results of endoscopic finding in dyspeptic patients with alarm features.

Endoscopic finding	N (%)
CA esophagus	1 (0.4%)
Erosive gastritis	78 (34.4%)
Erosive gastroduodenitis	20 (8.8%)
Erosive duodenitis	2 (0.9%)
Gastric ulcer	30 (13.2%)
Duodenal ulcer	9 (4%)
Peptic stricture	3 (1.3%)
PHG	1 (0.4%)
Gastric tumors	13 (5.7%)
- Adenocarcinoma	8 (3.5%)
- Lymphoma	2 (0.9%)
- GIST	2 (0.9%)
- Metastatic squamous cell carcinoma	1 (0.4%)
Non-erosive gastritis	67 (29.5%)
Normal	3 (1.3%)

mors were more common in those with weight loss $\geq 5\%$ from baseline, compared with others weight loss $< 5\%$ from baseline (Table 5).

Tests for the presence of *H. pylori* infection, either a rapid urease test or histology staining, were performed in 97.4% (221/227) of patients, and were positive in 52.9% (117/221), negative in 47.1% (104/221). The prevalence of *H. pylori* infection was significantly higher in patients with positive EGD findings, compared to those with negative EGD findings (80.3% vs. 55.8%, $p < 0.001$) (Table 6).

Male sex, GI blood loss, vomiting, age ≥ 55 with GI blood loss, GI blood loss with weight loss, and *H. pylori* infection were associated with positive EGD findings (Table 7).

Upper abdominal ultrasonography (US) was performed in 64 patients (91.4% of endoscopy-negative patients), with negative studies in 33 of 64 (51.6%).

Table 2. Baseline characteristics and EGD findings between alarm feature positive and negative groups.

	With alarm feature	Without alarm feature	p-value
Sex (male)	85/227 (37.4%)	29/80 (36.3%)	0.894
Mean age	58.5 \pm 13.8	42.1 \pm 8.4	<0.001
Significant EGD findings	157/227 (69.2%)	17/80 (21.3%)	<0.001

Table 3. Alarm features and diagnosis.

Diagnosis	1 AF					2 AF			3 AF
	A (N=159)	B (N=77)	C (N=105)	D (N=9)	E (N=10)	A+B (N=42)	A+C (N=63)	B+C (N=32)	A+B+C (N=21)
Tumor	4.4%	11.7%	6.7%	11.1%	20%	9.5%	6.4%	12.5%	9.6%
Peptic ulcer disease	18.9%	39%	14.3%	11.1%	60%	42.9%	19.1%	34.3%	38.1%
Erosive gastroduodenitis	43.4%	36.4%	48.6%	55.5%	20%	33.4%	46%	37.4%	33.3%
PHG	0.6%	1.3%	0%	0%	0%	2.4%	0%	0%	0%
Normal /Non-erosive gastritis	32.7%	11.7%	30.5%	22.2%	0%	11.9%	28.6%	15.6%	19%

AF = alarm features

A=age ≥ 55 ; B=GI blood loss; C=weight loss; D=dysphagia; E=vomiting

Peptic ulcer disease includes gastric ulcer, duodenal ulcer and peptic stricture

Erosive gastroduodenitis includes gastritis, duodenitis and gastroduodenitis

Table 4. Diagnosis in dyspeptic patients aged ≥ 55 without other alarm features and in those with weight loss without other alarm features.

	Age ≥ 55 (N=72)	Weight loss (N=30)
Gastric adenocarcinoma	1.4%	3.3%
Peptic ulcer disease	11.1%	0%
Erosive gastroduodenitis	41.7%	53.4%
Normal/Non-erosive gastritis	45.9%	43.3%

Erosive gastroduodenitis includes gastritis, duodenitis and gastroduodenitis

Table 5. Significant vs. non-significant weight loss and diagnosis.

Diagnosis	% Weight loss from base line	
	<5% (N=37)	≥5% (N=68)
Tumor	2.7%	8.9%
Peptic ulcer disease	18.9%	11.8%
Erosive gastroduodenitis	56.8%	44.1%
Normal/Non-erosive gastritis	21.6%	35.3%

Erosive gastroduodenitis includes gastritis, duodenitis and gastroduodenitis

Table 6. *H. pylori* infection and diagnosis.

Diagnosis	<i>H. pylori</i> infection		<i>p</i> -value
	Positive (N=117)	Negative (N=104)	
Tumor	7.7%	4.8%	0.001
Peptic ulcer disease	22.2%	13.5%	0.001
Erosive gastroduodenitis	50.4%	37.5%	0.001
Normal/Non-erosive gastritis	19.7%	44.2%	0.001
Significant findings	80.3%	55.8%	<0.001

Erosive gastroduodenitis includes gastritis, duodenitis and gastroduodenitis

Table 7. Predictors of clinically significant endoscopic findings.

Predictor	Positive EGD findings (N=157)	Negative EGD findings (N=70)	<i>p</i> -value
Sex (male)	45.2%	20%	<0.001
Mean of symptom duration (weeks)	23.6±75.0	48.0±199.3	0.182
Mean age	58.4±14.3	58.8±12.6	0.862
Age ≥ 55 years	68.2%	74.3%	0.433
GI blood loss	43.3%	12.9%	<0.001
Weight loss	46.5%	45.7%	1.000
Weight loss ≥ 5%	60.3%	75%	0.185
Dysphagia	4.5%	2.9%	0.725
Vomiting	6.4%	0%	0.034
Age ≥ 55 with GI blood loss	23.6%	7.1%	0.008
Age ≥ 55 with weight loss	28.7%	25.7%	0.131
GI blood loss with weight loss	17.2%	7.1%	0.004
Age ≥ 55 with GI blood loss with weight loss	10.8%	5.7%	0.057
<i>H. pylori</i> infection	61.8%	33.3%	<0.001

Significant US findings that subsequently led to modification of patients' management were noted in 16 of 64 patients (25%). A case of cholangiocarcinoma was detected by upper abdominal ultrasonography (Table 8).

DISCUSSION

The results in this study indicated that there was a high prevalence of clinically significant upper GI findings in dyspeptic patients with alarm features. Clini-

Table 8. Upper abdominal ultrasonographic findings in endoscopy-negative patients.

Ultrasonographic findings	N (%)
Negative	33 (47.1%)
Gallstone	13 (18.6%)
Fatty liver	14 (20%)
Cholangiocarcinoma	1 (1.4%)
Hemangioma	1 (1.4%)
Intraabdominal LN enlargement	1 (1.4%)
Intrahepatic duct dilatation	1 (1.4%)
Loss follow up	6 (8.6%)

cally significant findings were observed in 157 of 227 patients (69.2%), which was higher than previous studies from the UK being (23%)⁽⁷⁾ and Canada (58%)⁽⁸⁾. The differing results could be due to different alarm features used to enroll patients into the UK study, whereas the Canadian study included uninvestigated dyspepsia patients also. Importantly, the resulted figures were significantly higher than in the alarm features-negative dyspeptic cohort, usefulness of the alarm features.

Upper GI malignancies were found in 6.1% in our study, higher than 0.8% and 3.8% in previous studies^(5,7), but lower than the study in China (14.8%)⁽³⁾. In patients ≥ 55 years without other alarm features, tumors were detected in 1.4%, higher than in the studies from Canada (0.53% in patients age ≥ 50 years) and from the UK (0.3%)^(8,7). This may be partly due to variations in the prevalence of upper GI malignancy in different populations. Gastric cancer is more common in Asia than in the USA or European countries⁽⁵⁾. In addition, most studies did not define the severity or the duration of the alarm features, accounting for the differing results.

Persistent vomiting appeared to have the highest predictive value in our study. This observations is different from the study from China and UK in which dysphagia and weight loss were strong predictors for cancer^(3,7). Only 4% of our study population had dysphagia, compared with 22.2% and 34% in China and the UK. In addition, tumors were found 11.1% in patients with dysphagia in our study. A 10% chance for detecting cancers is relatively high, considering the potential consequences of cancer disease.

Non-significant findings were found more com-

monly in patient's age ≥ 55 years without other alarm features, when compared to those with other alarm features. Nonetheless, tumors were detected in 1.4% of this population. Thus consider that endoscopy should be performed in older dyspeptic patients in this country.

Among patients with weight loss, clinically significant findings were equally observed in those with weight loss $\geq 5\%$ from baseline, compared to those with weight loss $< 5\%$ from baseline. However, GI tumors were more common in those with a higher degree of weight loss. These findings suggest that the degree of weight loss is not a reliable predictor for the overall significant EGD findings, but it raises the suspicion of upper GI malignancies

H. pylori infection was significantly higher in patients with positive EGD findings, compare with those with negative EGD findings. However, tumors were detected in 4.8% of patients with negative *H. pylori* infection. This finding suggested that empirical treatment for *H. pylori* or "*H. pylori* test and treat" approach, should not be chosen in dyspeptic patients with alarm features, especially in the areas with relatively high prevalence of upper GI malignancies, as such approach may delay the diagnosis of malignancy. Prompt EGD is the appropriate management.

With regard to the diagnostic role of abdominal US in endoscopy-negative dyspeptic patients with alarm features, negative studies were noted in about half of our patients. Approximately 25% of patients had positive findings on US (e.g. gallstones, lymphadenopathy, and bile duct abnormalities), which subsequently led to changes in their management, including one case of cholangiocarcinoma. These observations suggest that upper abdominal US is useful selected population with dyspepsia and alarm features, particularly in Thailand in which the prevalence of hepatobiliary cancers is high. Further pre-specified studies with larger sample size are required to assess the role of US for dyspeptic patients. In clinical practice, careful history taking and physical examination is the key for identifying dyspeptic patients who are likely to benefit from US.

Our study has many interesting aspects and advantages. To our knowledge, no reports from Thailand on the performance of alarm features for predicting EGD findings in dyspeptic patients have been published. Most studies assessing this question were from Western countries where the prevalence of upper GI

and hepatobiliary malignancies is lower than in Asia. Our study is first in Thailand aiming to assess the prevalence of significant EGD findings in dyspeptic patients with alarm features. Moreover, we further evaluated the performance of each individual alarm feature, and also preliminarily evaluated the role of upper abdominal US for those with non-significant findings, as we consider that such queries are relevant to our clinical settings. In addition, our study is a prospective design. Most previous studies with larger sample size are retrospective^(3,5-7).

Those were some limitations. Firstly, our sample size was relatively small. Therefore, there was not enough statistical power to detect differences among the alarm features. Secondly, due to resource limitations, the study did not designate patients without alarm features to undergo EGD, so we could not thoroughly evaluate the diagnostic accuracy of alarm features.

In conclusion, the presence of alarm features in dyspeptic patients is a good predictor for clinically significant EGD findings. The most common lesion was erosive gastroduodenitis. GI blood loss appears to be a strong predictor for the overall significant EGD findings, whereas vomiting, dysphagia, and $\geq 5\%$ weight loss seem to be significant alarming symptoms for GI malignancies. The usefulness of US in EGD-negative dyspeptic patients with alarm features remains unclear, as most studies revealed negative or irrelevant findings.

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