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Alimentary Tract

Can clinical features stratify use of endoscopy for dyspeptic patients with high background prevalence of upper gastrointestinal cancer?☆

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ABSTRACT

Background: Whether clinical features can stratify priority of endoscopy remains controversial for dyspeptic patients with high background prevalence of upper gastrointestinal cancer.
Aim: To examine the predictive performance of clinical features for cancerous lesions in dyspeptic patients in Taiwan.
Methods: Between April 2008 and July 2009, 2530 consecutive dyspeptic outpatients underwent prospective evaluation with standardized questionnaire and then upper gastrointestinal endoscopy. Performance of using age thresholds and alarm symptoms to predict malignancy was determined. Independent risk factors associated with malignancy and those with negative endoscopic findings were identified.
Results: Malignant lesions were found in 31 patients (1.2%) and were independently associated with age, male gender, gastrointestinal bleeding, weight loss, and alcohol consumption. Any symptom of weight loss, bleeding and dysphagia, or simply age >45 years predicted 97% of cancer cases, with the sensitivity, specificity, positive and negative predictive values being 96.8%, 29.3%, 1.7%, and 99.9%, respectively. This strategy achieved a low negative likelihood ratio (0.11) and a high diagnostic odds ratio (12.45). Negative endoscopic finding (n = 1377, 54.4%) was independently associated with younger age, female gender, no use of non-steroidal anti-inflammatory drug, and no tobacco or alcohol consumption.
Conclusions: Absence of weight loss, dysphagia, and gastrointestinal bleeding predicts low likelihood of malignancy in dyspeptic Taiwanese patients aged <45 years.

1. Introduction

Dyspepsia, defined as various upper abdominal symptoms thought to originate from the gastroduodenal region [1,2], is a common chief complaint for either primary care visit or gastroenterology referral [3,4]. Because structural diseases at upper gastrointestinal (UGI) tract such as peptic ulcer, erosive esophagitis, luminal stricture, and malignancy may manifest with dyspepsia [5–9], esophagogastroduodenoscopy (EGD) is the diagnostic procedure of choice to distinguish patients with organic from those with functional dyspepsia [2]. Nevertheless, a prompt endoscopy for every dyspeptic patient cannot be a practical approach because the high prevalence (10–20%) will render the required cost and workload unaffordable to any healthcare systems [10–12]. Diagnostic yield and cost effectiveness will also be low on account of a large portion of investigated dyspepsia being functional [13–15]. How to utilise EGD in the management of uninvestigated dyspepsia remains controversial around the world.

Risk stratification based on simple clinical parameters is convenient, inexpensive and non-invasive, and hence an attractive strategy to direct the priority of further investigation. Practice guidelines from international academic associations have endorsed using alarm symptoms with or without age thresholds, usually set at 50–55 years, to select dyspeptic patients for endoscopy [16–20]. The predictive performance of using alarm features to predict UGI pathology has been extensively studied, but the results were inconsistent [5,21,22]. Moreover, the majority of previous research was conducted in Europe or North America. For example, only one out of the 15 studies included in the systemic review and meta-analysis performed by Vakil et al. came from Asia (Hong Kong) [5]. Conclusions from Western studies may not be applicable in Asian countries where prevalence of UGI diseases remarkably differs.

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The predictive performance of using age threshold and alarm symptoms to stratify indications of endoscopic investigation remains controversial for dyspeptic patients with high background prevalence of UGI malignancy. Some studies suggested lowering age threshold to 40–45 years [6–8], whilst others refuted this strategy and recommended prompt endoscopy regardless of clinical features [9]. In order to elucidate the role of clinical presentation in managing dyspeptic patients, prospective data regarding endoscopic findings in relation to clinical features is fundamental but remains strikingly sparse from Asia. By prospectively investigating consecutive patients with uninvestigated dyspepsia in an ethnic Chinese population, this study set to assess the performance of clinical features for predicting malignancy in a country with high prevalence of UGI cancers.

2. Methods and materials

2.1. Study patients and settings

This prospective observational study was conducted in a regional hospital (Lotung Poh-Ai Hospital, Ilan, Taiwan), which provided open-access service to endoscopy that did not require referral to specialists first. During the period between April 2008 and July 2009, consecutive adult outpatients who presented with uninvestigated dyspepsia and received EGD for primary investigation were screened for eligibility. Dyspepsia was defined as subjective upper abdominal discomfort thought to originate from the UGI tract [2]. Patients were excluded if any one of the following criteria was present: (1) age less than 18 years old, (2) UGI endoscopy not performed, (3) endoscopy indicated for following up a known structural lesion (including findings revealed on prior endoscopic or radiographic exams) or for surveillance, (4) previous surgery involving UGI tract, and (5) failure to provide written informed consent. The study protocol was approved by institutional review board of the Lotung Poh-Ai hospital.

All study participants were systemically evaluated before endoscopy. The presence of dyspepsia was measured by the Hong Kong Index, an investigative tool for dyspepsia that was developed and validated in ethnic Chinese populations [23,24], and has been used in our research [25]. The 12 common UGI symptoms encompassed in the Hong Kong Index were epigastralgia, upper abdominal bloating, upper abdominal dull ache, epigastralgia before a meal, epigastralgia when anxious, vomiting, nausea, belching, acid regurgitation, heartburn, feeling of acidity in the stomach, and loss of appetite. All patients were interviewed to determine the presence of alarm symptoms including dysphagia, symptoms suggestive of UGI bleeding, persistent vomiting, and unintended body weight loss. The weight loss was defined as loss >5% of original body weight in 3 months. Demographic and anthropometric data, medical history, use of tobacco and alcohol, recent medication (focused on aspirin and NSAID), and family history were also obtained.

2.2. Interpretation of endoscopic findings and outcome assessment

EGD was carried out with standard electronic videoendoscope (GIF-Q240 or GIF-Q260; Olympus, Tokyo, Japan) by experienced endoscopists with a minimum of 2000 prior exams. In order to control inter-observer variability, one investigator (YCH) reviewed electronically archived images of all participants, and if interpretation of endoscopic findings was different from the initial diagnosis, another investigator (YZH) independently examined the stored imaged and settled the disagreement. Both investigators were blinded to clinical data when reviewing endoscopic pictures.

Primary outcome of this study was histopathologically confirmed UGI malignancy. Secondary outcome was negative endoscopic finding and was defined as absence of any structural lesion that might account for dyspeptic symptoms. For the purpose of this study, peptic ulcers were mucosal ulcerations larger than 0.5 cm in diameter. If ulcer scars led to apparent luminal narrowing, they were regarded as structural lesions accounting for dyspepsia, but merely mucosal scarring or fold tractions were not considered responsible for symptoms. Erosive esophagitis was classified according to the Los Angles classification [26]. *Helicobacter pylori* status was evaluated by rapid urease test or histology at the discretion of treating physicians.

2.3. Statistical analysis

Continuous variables were expressed with median along with inter-quartile ranges and categorical variables with percentage of occurrence. Mann–Whitney test was used to compare sets of continuous variables and Fisher's exact test for comparisons of proportions. For each predictive model, the sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, and diagnostic odds ratio (DOR) were determined. The DOR was defined as positive likelihood ratio (PLR) divided by negative likelihood ratio (NLR), i.e. PLR/NLR [5,27]. Factors possibly predictive of endoscopic outcomes were evaluated by stepwise multivariate logistic regression. Adjusted odds ratio (aOR) with 95% confidence interval (CI) was computed. The receiver operating characteristic (ROC) curve of the regression model for cancer prediction was built. All statistical tests were two-tailed and conducted by using commercial software (Stata, version 9.1; Stata Corp, College Station, TX, USA), with a p value less than 0.05 defined as statistically significant.

3. Results

3.1. Clinical characteristics and endoscopic findings of the study population

Amongst 2530 dyspeptic patients included into analysis, peptic ulcer and reflux esophagitis constituted the major causes of organic dyspepsia, and 31 (1.23%) cases of UGI cancers (23 gastric and 8 esophageal cancers) were found (Fig. 1). The majority of cancers were diagnosed at an advanced stage, with only 5 (5/23 or 21.7%) gastric and 2 (2/8 or 25%) esophageal cancers being early (depth of invasion confined to submucosal layer). Clinical characteristics of participants were summarized in Table 1. Patients with UGI cancer were significantly older, male-predominant, and having higher prevalence of diabetes mellitus, cigarette smoking as well as alcohol drinking. Approximately half (n = 16, 51.6%) of the cancer patients reported at least one alarm symptom (Fig. 2).

Patients with organic dyspepsia (both peptic ulcers and reflux esophagitis), as compared with those with negative endoscopy, were older, had higher BMI, higher proportions of tobacco smoking, alcohol drinking, betel nut chewing, and recent aspirin or NSAID use. Prevalence of alarm symptom was similar between patients with benign organic lesions and those without structural diseases, except in peptic ulcer patients who were more likely to present with over GI bleeding (Table 1).

3.2. Clinical factors independently associated with UGI malignancy and those with negative endoscopic findings

Multivariate logistic regression analysis identified age (aOR, 1.05 per year; 95% CI, 1.02–1.07), male gender (aOR, 6.76; 95% CI, 1.97–23.24), alcohol drinking (aOR, 3.78; 95% CI, 1.72–8.30), UGI bleeding (aOR, 2.98; 95% CI, 1.28–6.91) and unintended weight loss

Table 1
Comparison of clinical characteristics amongst dyspeptic patients with different endoscopic findings.

Variable	All patients (n = 2530)	Cancer (n = 31)	Peptic ulcer (n = 346)	Reflux esophagitis (n = 885)	Negative (n = 1377)
Age (year)	51 [39, 64]	63 [49, 74]*	56 [43, 69]*	52 [41, 65]*	49 [37, 62]
Age > 45 years, n (%)	1613 (63.8%)	28 (90.3%)*	255 (73.7%)*	597 (67.5%)*	818 [59.4%]
Male gender, n (%)	1155 (45.7%)	28 (90.3%)*	211 (61.0%)*	537 (60.7%)*	468 (34.0%)
BMI (kg/m^2)	23.1 [20.8, 25.6]	22.7 [19.7, 25.4]	23.7 [20.8, 26.4]*	23.9 [21.6, 26.7]*	22.6 [20.4, 24.9]
Cigarette smoker, n (%)	536 (21.2%)	15 (48.4%)*	117 (33.9%)*	247 (27.9%)*	206 (15.0%)
Alcohol drinker, n (%)	451 (17.8%)	15 (48.4%)*	93 (26.9%)*	233 (26.3%)*	159 (11.5%)
Betel nut chewer, n (%)	100 (4.0%)	1 (3.2%)	20 (5.8%)*	59 (6.7%)*	29 (2.1%)
Diabetes mellitus, n (%)	255 (10.1%)	7 (22.6%)*	51 (14.74%)	103 (11.64%)	111 (8.06%)
Hypertension, n (%)	561 (22.2%)	7 (22.6%)	90 (26.01%)	246 (27.8%)	251 (18.2%)
Chronic viral hepatitis, n (%)	309 (12.2%)	6 (19.4%)	30 (8.7%)	106 (12.0%)	179 (13.0%)
Family with UGI cancer, n (%)	153 (6.0%)	4 (12.9%)	24 (6.9%)	48 (5.4%)	91 (6.6%)
Aspirin or NSAID use, n (%)	566 (22.37%)	7 (22.6%)	106 (30.6%)*	220 (24.9%)*	269 (19.5%)
Any alarm symptoms, n (%)	683 (27.0%)	16 (51.6%)*	114 (32.9%)*	245 (27.7%)	348 (25.3%)
UGI bleeding, n (%)	239 (9.4%)	8 (25.8%)*	61 (17.6%)*	80 (9.0%)	114 (8.3%)
Weight loss, n (%)	247 (9.8%)	8 (25.8%)*	39 (11.3%)	88 (9.9%)	124 (9.0%)
Dysphagia, n (%)	97 (3.8%)	3 (9.7%)	5 (1.4%)*	40 (4.5%)	51 (3.7%)
Persistent vomiting, n (%)	205 (8.1%)	1 (3.2%)	21 (6.1%)	73 (8.2%)	116 (8.4%)

* $p < 0.05$ as compared with patients with negative endoscopy; peptic ulcers and reflux esophagitis coexisted in 109 patients. BMI, body mass index; UGI, upper gastrointestinal; NSAID, non-steroidal anti-inflammatory drug.

(aOR, 2.96; 95% CI, 1.27–6.90) were independent risk factors associated with malignancy (Table 2). The area under the ROC curve for malignancy was 0.85 with a 95% CI between 0.80 and 0.91. Based on the curve, we determined the optimal cutoff score of this model to be −3.65. Subgroup analyses according to anatomical site (esophageal versus gastric) or invasion depth (advanced versus early) were not possible because of the limited case number.

Independent predictors for negative endoscopic findings were younger age (aOR, 0.98 per increment of year; 95% CI, 0.98–0.99), female gender (aOR, 2.21; 95% CI, 1.85–2.64), no use of aspirin or NSAID (aOR, 1.31; 95% CI, 1.07–1.61), no cigarette smoking (aOR, 1.47; 95% CI, 1.17–1.84), and no alcohol consumption (aOR, 1.92; 95% CI, 1.52–2.45). Presence or absence of any alarm symptom was not independently associated with benign organic dyspepsia.

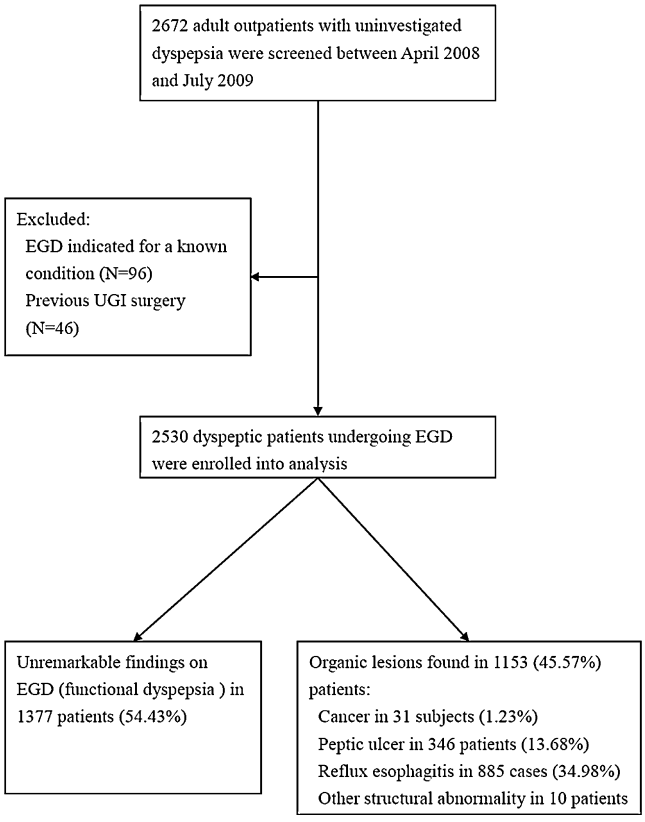

Fig. 1. Flow diagram of patient enrollment. Peptic ulcers and reflux esophagitis were not mutually exclusive and they coexisted in 109 patients (4.31%); EGD, esophagogastroduodenoscopy; UGI, upper gastrointestinal.

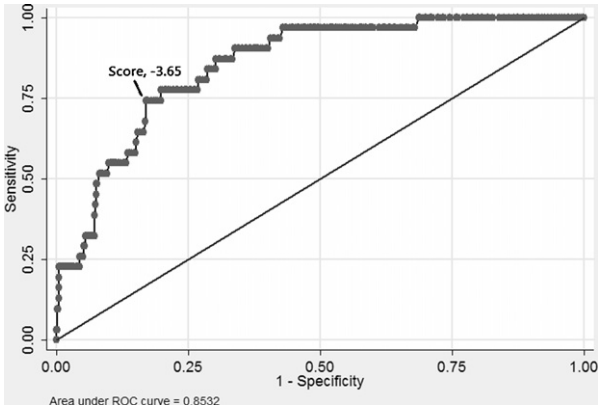

Fig. 2. Receiver operating characteristic curve for the upper gastrointestinal malignancy predicted by the regression model built on independent clinical factors. The model is 0.05 × age (years) + 1.91 × male gender + 1.08 × weight loss + 1.33 × alcohol drinking + 1.09 × gastrointestinal bleeding − 9.14. The area under curve is 0.853 with a 95% confidence interval of 0.797–0.909. The optimal cutoff value is −3.65.

3.3. Predictive performance of clinical features for UGI malignancy

The prevalence of UGI malignancy amongst dyspeptic patients rose with age, from 0.5% in the age group of 30–35 years to nearly 3% in patients aged 75 years and older (Supplementary figure). However, the youngest cancer patient was 30 years old, and there were 3 (9.7% of all cancer cases) and 8 (25.8% of all cancer cases)

Table 2
Independent risk factors associated with upper gastrointestinal cancer by multivariate logistic regression analysis.

	Coefficient (β)	Adjusted odds ratio	95% CI of aOR	p
Age (year)	0.05	1.05	1.02–1.07	<0.001
Male gender	1.91	6.76	1.97–23.24	0.002
UGI bleeding	1.09	2.98	1.28–6.91	0.011
Weight loss	1.08	2.96	1.27–6.90	0.012
Alcohol drinker	1.33	3.78	1.72–8.30	0.001

UGI, upper gastrointestinal; the constant of this regression function is −9.14; p value of the Hosmer and Lemshow test was 0.947.

Table 3
Description of cancer patients younger than 50 years without alarm symptoms.

Patient	Age	Gender	Location	Invasion depth	Drinking	Smoking
A	30 years	Male	Gastric	Advanced	Yes	No
B	45 years	Female	Gastric	Advanced	No	No
C	45 years	Male	Esophageal	Early	Yes	Yes
D	47 years	Male	Esophageal	Early	Yes	Yes
E	49 years	Male	Gastric	Advanced	Yes	No

Table 4
Performance of different age thresholds with alarm symptoms in predicting upper gastrointestinal cancers amongst patients with uninvestigated dyspepsia.

Age thresholds and alarm symptoms	Sensitivity	Specificity	Accuracy	PPV	NPV	LR (+)	LR (−)	DOR	Spared EGD versus missed cancer	Spared EGD per one missed cancer
Symptom D, B, W, V	51.6%	73.3%	73.0%	2.3%	99.2%	1.93	0.66	2.92	1832:15	122.1
Symptom D, B, W	48.4%	79.6%	79.2%	2.9%	99.2%	2.37	0.65	3.65	1989:16	124.3
Age > 50 years	74.2%	47.0%	47.4%	1.7%	99.3%	1.4	0.55	2.55	1175:8	146.9
Age > 50 years or D, B, W, V	83.9%	34.5%	35.1%	1.6%	99.4%	1.28	0.47	2.72	861:5	172.2
Age > 50 years or D, B, W	83.9%	37.9%	38.5%	1.6%	99.5%	1.35	0.42	3.21	947:5	189.4
Age > 45 years	90.3%	36.6%	37.2%	1.7%	99.7%	1.42	0.27	5.26	914:3	304.7
Age > 45 years or D, B, W, V	96.8%	26.1%	27.0%	1.6%	99.8%	1.31	0.12	10.92	653:1	653
Age > 45 years or D, B, W	96.8%	29.3%	30.1%	1.7%	99.9%	1.37	0.11	12.45	731:1	731
Age > 40 years	93.5%	27.1%	27.9%	1.6%	99.7%	1.28	0.24	5.33	676:2	338
Age > 40 years or D, B, W, V	96.8%	19.3%	20.2%	1.5%	99.8%	1.20	0.17	7.06	482:1	482
Age > 40 years or D, B, W	96.8%	21.6%	22.5%	1.5%	99.8%	1.23	0.15	8.2	539:1	539
#Regression scores ≧−3.65	71.0%	82.2%	82.0%	4.7%	99.6%	3.99	0.35	11.4	2062:9	229.1

Alarm symptom: D, dysphagia; B, bleeding; W, weight loss; V, vomiting; PPV, positive predictive value; NPV, negative predictive value; LR (+), likelihood ratio for a positive test; LR (−), likelihood ratio for a negative test; EGD, esophagogastroduodenoscopy; DOR, diagnostic odds ratio; # the regression model is 0.05 × age (years) + 1.91 × male gender + 1.08 × weight loss + 1.09 × gastrointestinal bleeding + 1.33 × alcohol drinking − 9.14.

cancer patients younger than 45 and 50 years, respectively. If the age threshold had been set at 45 and 50 years, 1 (3.2%) and 5 (16.1%) cancer patients with simple dyspepsia would have been missed (Table 3).

Predictive performance of different strategies with clinical features for UGI cancer was summarized in Table 4. PLR was low for all strategies, ranging between 1.20 and 3.99, whilst NLR varied considerably from 0.11 to 0.66. The multivariate model built on independent risk factors was more specific with higher PPV than any strategy using age/alarm symptoms, however at the expense of sensitivity. Using the regression model to select patients for endoscopy would have spared 2062 exams but missed 9 cancers. Collectively, age threshold at 45 years along with dysphagia, weight loss, or UGI bleeding resulted in the lowest NLR (0.11) and highest DOR (12.45). The cancer missing rate of this strategy was 0.04% (1/2530). Vomiting as an alarm symptom reduced specificity but did not increase sensitivity.

4. Discussion

This is the first prospective research that validates the predictive performance of clinical presentation in stratifying indications for EGD amongst ethnic Chinese patients with uninvestigated dyspepsia. We demonstrated that age threshold at 45 years and alarm symptom of unintended weight loss, UGI bleeding or dysphagia would identify almost all (97%) dyspeptic patients with UGI malignancy. The low NLR (0.11) and high DOR (12.45) suggested that this imperfect strategy could help clinicians identify those at low risk of cancer. The discriminative values of alarm symptoms were further supported by their independent association with malignancy. In addition, clinical factors including age, gender, and information on the use of tobacco, alcohol and ulcerogenic drugs were predictive of a negative endoscopy. Our data indicates that clinical features remain valuable in deciding promptness of endoscopy for dyspeptic patients with high background prevalence of UGI cancers.

Our research revealed that alarm symptoms were present in only half of the patients with UGI malignancy. Furthermore, we reaffirmed that the age threshold for screening patients with simple dyspepsia should be set at 40–45 years in Asia [6–8], approximately one decade earlier than in the West [16–20]. However, not all cancers could be diagnosed unless the cutoff age was lowered to 30 years. In fact, since gastric cancer may infrequently occur in the very young aged less than 30 years [28,29], theoretically the only way to prevent any misdiagnosis is to scope every dyspeptic patient. However, the required workload will prohibitively overwhelm the endoscopic service of any healthcare system, and low-risk patients may thus occupy the access to prompt investigation, ironically resulting in delay diagnosis amongst those at high risk. Applying investigative strategies based on risk stratification represents the attempt to keep balance between timely diagnoses of cancer patients and cost-effective allocation of healthcare resource. How to evaluate the balance remains unknown, but may be indicated by the number of EGD that could be spared versus that of the cancers that would be missed. In this regard, our data suggested that age ≧45 year with symptom of bleeding, weight loss, or dysphagia could guide endoscopic investigation (Table 4). Furthermore, since male gender was an independent risk factor associated with UGI cancer, it appeared plausible to explore how gender would further refine the prediction criteria. Indeed, Marmo et al. have reported in a large prospective multicenter study that age in combination with gender was better than age alone in identifying cancer patients presenting with simple dyspepsia [30]. Nonetheless, the small number of women with UGI cancers in our study limited the statistical power of subgroup analyses for different genders, and regrettably we could not establish different age thresholds according to gender.

The sensitivity and specificity of (any) alarm symptoms to predict UGI cancers ranged widely from 0 to 83% and 40 to 98% respectively in the literature [5,21]. In addition to the regional prevalence of UGI structural lesions, different study designs might also explain the discrepancy. Ideally, a prospective research with pre-specified alarm symptoms is preferred over a retrospective one for the concern of recall bias. A randomly recruited community cohort is superior to a hospital-based cross-sectional sample to reduce bias related to health-seeking behaviour. Adequate cancer cases and hence a large study cohort is essential to develop a robust predictive model. Unfortunately, such an ideal study is

understandably very difficult to conduct and has not been available to our knowledge. Furthermore, the definition of dyspepsia varied across studies and whether reflux symptoms should be included was debatable. With the purpose to reflect daily practice rather than to create a controlled experimental setting, we targeted a broad population with various UGI discomforts instead of a strictly defined patient group with specific symptomatology. Therefore, enrolled patients did not necessarily conform to the Rome III symptomatic criteria for functional dyspepsia and acid regurgitation or heartburn was not excluded. To this end, we adopted the validated Hong Kong Index, which covered and rated a wide range of dyspeptic symptoms [23–25]. Unlike the GerdQ questionnaire that is useful for diagnosis and management of gastroesophageal reflux disease [31], the Hong Kong Index rates symptom severity on a 5-point Likert scale but does not rate the frequency of symptoms.

Our findings demonstrated that alarm symptoms could not stratify the likelihood of benign organic lesions in patients with uninvestigated dyspepsia, consistent with the existing literature [14,32,33]. Whether an endoscopic diagnosis of benign organic dyspepsia is clinically important is another unsettled issue. Some researchers argued that an endoscopic procedure, even if it revealed nothing abnormal, reassured the patients, improved their quality of life, and cost less than empirical therapy [34,35]. Others considered that empirical treatment with proton pump inhibitor and/or *H. pylori* eradication was indicated with or without endoscopic diagnosis, and argued that an early endoscopy was unnecessary for young patients with uncomplicated dyspepsia since it would not affect the clinical management [12,36]. With the understanding that young individuals with simple dyspepsia are unlikely to have malignant lesions and accordingly should not take the priority of endoscopic investigation, whether they should undergo EGD to uncover organic (most likely benign) lesions depends mainly on the local cost and availability of EGD. Economic models evaluating the pros and cons of endoscopic investigation are urgently needed in Asia to further elucidate the controversy.

The pathogenesis of visceral symptoms and its association with structural abnormality of gastrointestinal organs is complex and has not been elucidated [37]. On one hand, debilitating functional dyspepsia may occur without evidence of any organic derangement [38]; on the other hand, apparent structural lesions may present with no symptoms at all [39]. Therefore, it is possible that endoscopically uncovered mucosal ulcerations may not entirely account for the symptomatology of a dyspeptic subject. The causal relationship should ideally be confirmed by showing healing of the discernible lesions would lead to resolution of symptoms. However, it is difficult to frequently monitor dyspeptic patients by endoscopy. Our study could not examine how symptoms evolved in a dyspeptic patient with positive endoscopic findings after treatment, since the follow-up visits, type of medication, and evaluation of therapeutic responses were not standardized

The prospective design is considered as a major strength of our research. Unlike most previous studies that retrospectively analysed medical records, our research prospectively evaluated symptomatology and relevant clinical history with standardized protocols prior to endoscopy. The comprehensively collected information thus permitted alarm symptom assessed both collectively and individually. In addition, endoscopic diagnoses were carefully established through a consensus process, reducing inter-observer variability. The open-access system to endoscopy service may be regarded as an advantage because it enabled us to recruit patients managed in the primary care setting. Those referred to specialists were probably higher-risk patients who might have already failed empiric therapy and accordingly incurred a selection bias. Finally, endoscopic findings of this cohort were not affected by exposure to proton pump inhibitor. Because the Taiwan National Health Insurance, which covers more than 99% of the entire national population, does not reimburse anti-secretory medications for uninvestigated dyspepsia, patient will not receive proton pump inhibitor until EGD discloses ulcers or esophagitis.

With regard to the limitations of this study, lacking information on the status of *H. pylori* infection prevented us from exploring how *H. pylori* infection would influence management of uninvestigated dyspepsia. Nevertheless, routine checkup of *H. pylori* status in uninvestigated dyspeptic patients is not reimbursed in Taiwan and other Asian countries where 40–50% of the adults are infected [40]. As a result, clinicians in this part of world usually have to decide the indication of EGD without knowing first the *H. pylori* status. Second, the relative small number of cancer patients limited the statistical power for important subgroup analyses on gender (male or female), age (> or <45 years), anatomical location (gastric versus esophageal), and depth of invasion (early versus advanced). Therefore, despite having achieved the primary aim of evaluating the validity of clinical predictors in risk stratification for UGI malignancy, this study could not reach firm conclusions amongst the very young patients and those with specific type of cancers. The small number of early cancers limited the analysis of its association with clinical presentation and is recognized as a major limitation. Previous study has shown that early cancers were more likely to present with simple dyspepsia than the advanced counterparts [8]. Finally, caution is advised to extrapolate findings of our hospital-based research to dyspeptic individuals not seeking medical attention.

In conclusion, combining age threshold set at 45 years and presentation with weight loss, UGI bleeding, or dysphagia would identify the vast majority of (97%) cancer patients in an ethnic Chinese population with uninvestigated dyspepsia. The likelihood ratio for a young patient without any alarm feature to have UGI malignancy is low (0.1). On the other hand, negative endoscopy cannot be predicted by absence of alarm symptoms but is independently associated with age, gender, habit of cigarette smoking or alcohol drinking, and use of ulcerogenic drug. These findings validate the discriminative value of clinical features in identifying dyspeptic patients at low risk of malignancy, and consequently in guiding the priority of endoscopic investigation. Clinicians caring for patients with high background prevalence of UGI cancers should not overlook clinical presentation in deciding the indication of EGD and subsequent management.

Conflict of interest statement

None of the authors reported any conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.dld.2011.10.012.

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