

Value of Alarm Features in Dyspepsia for Predicting Significant Organic Lesions in Endoscopy

I PERVEEN^a, M SAHA^b, MB SALAM^c

Abstract

Background: For a long older age and the presence of alarm features are regarded as indications for prompt endoscopy in patients with dyspepsia. We aimed to find out the value of alarm features in diagnosing serious organic upper gastrointestinal lesions in patients with dyspepsia.

Material & methods: In this observational study clinical variables and endoscopic findings of consecutive patients with dyspepsia were recorded in a semi-structured questionnaire. Univariate and multivariate logistic regression was done stepwise to identify predictors for endoscopic findings. A simplified predictor model was built with the age and the presence of any predictor alarm feature to find out the diagnostic accuracy of this model for the significant endoscopic lesion.

Results: Among 304 patients (M=134, F=170) one or more alarm features were present in 193 cases (63.5%). Significant organic lesions were found in 84(27.6%) cases. Age \geq 45

years (OR 2.608), abdominal lump (OR 4.489) and family history of upper gastrointestinal cancer (OR 3.880) were found as independent predictors of major endoscopic findings. Using a simplified predictor model of age \geq 45 years or the presence of any predictive alarm feature, sensitivity, specificity, positive predictive value, and negative predictive value were 32.4 %, 82.5 %, 79.8% and 36.4% respectively for a significant endoscopic lesion. For upper gastrointestinal cancers, these values were 6%, 100.0%, 100.0% and 47.3% respectively.

Conclusion: The predictive value of the age and the presence of alarm features alone are not optimal for significant endoscopic findings in patients with dyspepsia. A newer and more accurate predictive model is a time demand for organic UGI lesions, especially for malignancies.

Keywords: Dyspepsia, alarm features, predictive value.

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Introduction:

Dyspepsia is a common medical condition.¹⁻³ However, most of the dyspeptic patients do not have a major organic lesion in endoscopy.⁴⁻⁷ Endoscopy is the most accurate way to diagnose most organic lesions responsible for dyspepsia. A randomized controlled trial proved cost effectiveness and less loss of working days associated with initial endoscopy and directed treatment rather than empiric therapy with H₂ receptor blockers.⁸ But, endoscopy is invasive, causes discomfort to patient, and is socially inconvenient and costly. Besides in our

resource limited country it is not widely available. Various guidelines recommend that the elderly patients (>55 years) with dyspepsia and having alarm features (gastrointestinal bleeding, anaemia, early satiation, unexplained weight loss, progressive dysphagia, odynophagia, persistent vomiting, previous oesophagogastric malignancy, previously documented peptic ulcer, and lymphadenopathy) to undergo prompt endoscopy for early diagnosis of serious upper gastrointestinal(UGI) diseases.^{9, 10} A previous study showed that the age and symptoms are poor markers of organic upper GI lesions.⁷ Recently American and Canadian joint guideline¹¹ revisited the age limit (> 60 years) for initial endoscopy and did not recommend endoscopy in under 60 years age group with alarm features except in those who were born and spent their childhood in South East Asia and some countries in South America as chance of upper GI malignancy is more and occurs in early age in these geographical locations.¹²⁻¹⁴ The recommendation was made based on a systemic review¹⁵ and another study¹⁶ that showed that alarm features have limited value in detecting any organic pathology (malignancy, peptic ulcer disease, or

a. Prof. Irin Perveen, Professor of Gastroenterology, Enam Medical College, Dhaka, Bangladesh.

b. Prof. Madhusudan Saha, Professor of Gastroenterology, North East Medical College, Sylhet, Bangladesh.

c. Dr. Md. Badius Salam, Assistant Professor of Radiotherapy, Sir Salimullah Medical College, Dhaka.

Address of Correspondence: Irin Perveen, B-11, 11 Shahid Tajuddin Ahmed Sarani, Magh Bazar, Dhaka-1217, Bangladesh. Phone: +8801552365100, E-mail address: irinperveen@yahoo.com

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esophagitis). Around 10-60% of patients with dyspeptic symptoms present with one or more alarm features.¹³⁻¹⁸ In a Western country only 3% of investigated patients with alarm features were detected to have upper GI malignancy.¹⁷ Besides follow up of patients with alarm features over three years only 4%, 11% and 25% were diagnosed to have malignancy, ulcer and gastritis respectively.¹⁹ On the other hand, a systemic review of studies from Asia is in favour of endoscopic evaluation of patients with dyspepsia older than 35 years even in the absence of red flag signs.¹³ We have limited data regarding the prevalence of alarm features in patients with dyspepsia, as well as the role of alarm features in predicting serious upper GI lesions in patients with dyspepsia. In this observational study we aimed to find out the prevalence of alarm features in patients with dyspepsia and to evaluate the predictive value of alarm features and the age in dyspeptic patients undergoing endoscopic evaluation.

Methods:

This observational study was conducted in the Gastroenterology units of Enam Medical college, Savar and North East Medical College, Sylhet from 2018 through 2019. Ethical approval was taken from the Institutional Review Board of the respective institutions. Consecutive patients more than 18 years presenting with dyspepsia at least weekly were enrolled in the study. Patients with significant co-morbid illness, suspected or diagnosed cases of UGI malignancy by other imaging studies, having previous inconclusive biopsy reports (with endoscopy in the recent past) or suffering from upper GI malignancy, or, patients in the surveillance programme for peptic ulcer and Barrett's oesophagus were excluded. Informed consent was taken from individual patients. Patients unwilling to participate or who failed to complete investigations were excluded from the study. Demographic data, dyspeptic symptoms, alarm symptoms, physical findings and investigation reports were recorded in a semi-structured questionnaire (some questions were predetermined, while others were not).

Study definitions:

An alarm feature was defined as any one of the following features: upper gastrointestinal bleeding, iron deficiency anaemia, unintentional/unexplained weight loss, early satiety, progressive dysphagia, odynophagia, persistent

vomiting, personal or family history of GI malignancy, history of gastric surgery, previously documented peptic ulcer, upper abdominal lump/lymphadenopathy and recent onset of dyspepsia in a patient \geq 45 years of age.

Significant endoscopic lesions included oesophageal erosion/ulcer, Mallory-Weiss Tear, oesophageal carcinoma, stricture, achalasia, gastric erosion/ulcer, gastric polyp, vascular ectasia, gastric cancer, duodenal erosion/ulcer, polyp, cancer, gastric outlet obstruction. During evaluation of the predictive value of dysphagia and odynophagia only oesophageal, gastro-oesophageal junctional and cardiac lesion were included. For evaluating the predictive value of a lump in the abdomen lesions producing abdominal lumps were included (gastric outlet obstruction, gastric or duodenal large benign tumours and malignancies). Non erosive gastritis, non-erosive duodenitis, non-erosive oesophagitis, small hiatus hernia and small submucosal tumours (<1cm) were not included in significant endoscopic lesions during analysis.

Statistical Issue: Anticipating a prevalence of different alarm symptoms in patients with dyspepsia not exceeding 50% and the prevalence to be estimated within 5 percentage points of the true value with 90% confidence, table 1b, page 26 showed that for $P=.50$ and $d=0.05$, a sample size of 271 patients with dyspepsia would be needed.²⁰ We included 304 patients with dyspepsia.

The statistical analysis was performed with an SPSS 22.0 program (SPSS Inc., Chicago, IL, USA) and MedCalc online data calculator. A Student's *t*-test was used to compare the distributions of continuous data and Pearson's chi-square test was performed for categorical data with a P value set at .05 or less. The univariate logistic regression was done with each predictor variable (age \geq 45 years, male sex, tobacco use and alarm symptoms) to see the association with a significant endoscopic lesion. Multivariate logistic regression was done with predictor factors having P value <0.1 in the univariate analysis to find out the association with a significant endoscopic lesion. Similar statistical analyses were done for detecting predictor factors of Upper GI malignancy. A simplified predictor model was developed with factors showing positive association (OR >1.5 , $P<0.2$) in the multivariate logistic regression analysis

with a significant endoscopic lesion or upper GI malignancy to find out pooled sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

Results:

A total of 304 participants (male=134, female=170) with a mean age of 37.47±14.088 (range 18-83 years) were studied without a significant difference in the mean age (P.079) between the sexes. Dyspeptic symptoms are summarized in table 1. The number of symptoms was significantly more in females (4.42±2.008) than in males (3.02±1.464, P.000). Around 76% presented with 2-5 symptoms and approximately 18% with six or more dyspeptic symptoms. More frequent dyspeptic symptoms were upper abdominal pain (45.7%), upper abdominal burning (36.2%) and anorexia (45.7%).

Table-I

<i>Profile of Dyspeptic symptoms among study population</i>		
Dyspeptic symptoms	Number (%)	Duration (days) (mean)
Heart burn	68(22.4)	3-5460(389.3)
Regurgitation	33(10.9)	3-5460(463.9)
Dysphagia	29(9.5)	4-1825(186.2)
Abdominal pain	139(45.7)	3-4380(351.7)
Abdominal burning	110(36.2)	3-4380(395.2)
Postprandial fullness	112(36.8)	12-4380(451.9)
Early satiety	19(6.2)	30-3650(354.4)
Nausea	111(36.5)	3-4380(260.4)
Vomiting	92(30.3)	3-1095(114.0)
Anorexia	111(36.5)	3-4380(341.8)
Belching	56(18.4)	3-3560(186.8)

One or more organic lesions were present in 205(67.4%) cases (table 2). Significant endoscopic lesions were present in 84(27.6%) cases and 56(29.0%) patients with alarm features. At least one alarm feature was present in 193(63.5%) cases (table 3). The mean number of alarm features was 1.37(range 1to 8). More prevalent alarm features were anaemia (n=78, 25.7%), persistent vomiting (n=73, 24.0%) and unexplained weight loss (n=64, 21.1%). In the reproductive age group (18-49 years), mild anaemia was considered insignificant in females when a comparison was made for the significant

Table-II

<i>Endoscopic Findings in study population</i>		
Findings		Number (%)
Oesophageal lesion	Ulcer ^a	1(0.3)
	Reflux Oesophagitis ^b	7(2.3)
	Mallory Weiss Tear ^a	1(0.3)
	Moniliasis ^{a, b}	1(0.3)
	Hiatus hernia	11(3.3)
	Carcinoma/Junctionaltumour ^{a,b}	2(0.6)
	Barrette's oesophagus ^a	2(0.6)
Gastric Lesion	Non-erosive Gastritis	111(36.5)
	Erosive gastritis ^a	9(2.9)
	Gastric Ulcer ^a	9(2.9)
	Congestive gastropathy ^a	1(0.3)
	Vascular ectasia ^a	1(0.3)
	Carcinoma ^{a,c}	8(2.6)
	Polyp ^{a, c}	6(1.8)
	Sub-mucosal tumour ^c	14(4.6)
	Gastro-jejunosotomy ^a	2(0.6)
Gastric outlet obstruction ^a	8(26.3)	
Duodenal lesion	Non-erosive Duodenitis	2(0.6)
	Duodenal ulcer ^a	15(4.9)
	Chronic Duodenal ulcer ^a	7(2.1)
	Chronic DUD in remission	11(3.3)
	Duodenal polyp ^a	1(0.3)

NB. a: considered as significant lesion while calculating sensitivity, specificity, PPV & NPV

b: Lesions considered for evaluation of dysphagia/odynophagia
c: considered for producing symptom of lump in abdomen.

endoscopic lesion. Moderate to severe anaemia was significantly more in female subjects (M=4, F=19, P.000).

Sensitivity, specificity, PPV and NPV of individual alarm features for significant endoscopic lesions were, 0-64.3%, 72.3-78.2%, 0-46.4% and 73.2-99.6% respectively (table 3). The presence of any alarm feature in dyspepsia was not predictive of any significant endoscopic lesion (OR 0.715, P .203). In the univariate regression analysis "age ≥45 years" (P0.001, OR 2.365) was found more significantly associated with significant endoscopic lesions than "recent onset of symptom in ≥45years (P0.228, OR 1.568)". Therefore, in the multivariate analysis, we included "age ≥45 years" instead of "recent onset of symptoms in e"45 years". In the multivariate logistic regression (with alarm symptoms having P <0.1 in the univariate analysis, age ≥45 years and male sex), family history of GI cancer (OR 3.880, P .007), abdominal lump (OR 4.489, P .001) and age e"45 years (OR 2.608, P

.004) were found as important predictors of the significant endoscopic lesion (table IV).

A simplified predictor model was built using factors showing a positive association with the significant endoscopic lesion in the multivariate analysis (OR >1.5, P < 0.2; age ≥45 years, male sex, abdominal lump, and family history of upper GI cancer) (table 4). Only 67/207 patients had a significant endoscopic lesion in this model. The sensitivity, specificity, PPV and NPV of this predictor model were 32.4 %, 82.5 %, 79.8% and 36.4% respectively (table VI).

The prevalence of upper GI malignancy in patients with dyspepsia was only 2.5% (n=10) in our study. Eight

(80%) patients with malignancy were ≥45 years. The prevalence of malignancy was not significantly different in patients with or without alarm symptoms (4.3% vs. 1.7%, P .325). The sensitivity, specificity, PPV and NPV of any alarm feature for upper GI malignancy were 5.2%, 100%, 100% and 37.8% respectively. A simplified predictor model using factors having a positive association with Upper GI malignancy (P < 0.45, OR > 2 in the multivariate logistic regression analysis) (age ≥45 years, anaemia, unexplained weight loss, fever and abdominal lump) (table 5) had a sensitivity, specificity, PPV and NPV of 6%, 100.0%, 100.0% and 47.3% respectively for upper GI malignancy (table VI). Only 10/165 patients had upper GI malignancy in this model.

Table-III

Alarm features: Prevalence, sensitivity, specificity, PPV and NPV for significant endoscopic lesion

Alarm Features	Prevalence(%)	Sensitivity%	Specificity%	PPV%	NPV%
Age > 45 years	98(32.2)	39.8	78.2	46.4	73.2
Anaemia	78(25.7)	35.9	75.2	33.3	77.3
Fever	33(10.9)	39.4	73.8	15.5	90.9
Unexplained weight loss	64(21.1)	40.6	75.8	31	82.7
Progressive Dysphagia	28(9.2)	32.1	72.8	10.7	91.4
Progressive Odynophagia	10(3.3)	50.0	73.1	6.0	97.7
Persistent vomiting	73(24.0)	31.5	73.6	27.4	77.3
Early satiety	19(6.2)	47.4	73.7	10.7	95.5
GI bleeding	27(8.9)	33.3	72.9	10.7	91.8
Lump in abdomen	28(9.2)	64.3	76.1	21.4	95.5
Past documented PUD	33(10.9)	36.4	73.4	14.3	90.5
Past H/O upper GI cancer*	1(0.3)	0	72.3	0	99.6
Family H/O GI cancer*	21(6.9)	57.1	74.8	14.5	95.9
Any alarm feature	193(63.5)	29.0	74.8	66.7	37.7

Table-IV

Multivariate logistic regression showing important predictor factors for significant endoscopic lesions

Factors	B	P	OR	95.0% CI for OR
Age ≥45 years	.959	.004*	2.608	1.359-5.006
Male sex	.520	.106	1.682	.896-3.185
Tobacco use	-.032	.918	.968	.521-1.798
Unexplained weight loss	.324	.353	1.382	.698-2.739
Early satiety	.257	.617	1.293	.445-3.758
F/H of GI malignancy	1.356	.007*	3.880	1.444-10.428
Anaemia	-.136	.710	.873	.426-1.768
Abdominal lump	1.502	.001*	4.489	1.846-10.913
Indicator	-1.874	.000	.154	

Table-V*Multivariate logistic regression analysis showing important predictor factors for UGI malignancy.*

Factors	B	P	OR	95.0% CI for OR
Age \geq 45 years	1.301	.188	3.674	.530-25.495
Anaemia	.781	.408	2.185	.343-13.914
Fever	.864	.335	2.374	.409-13.778
Persistent vomiting	.248	.799	1.281	.190-8.632
Early satiety	.564	.544	1.757	.284-10.871
Unexplained weight loss	.893	.324	2.443	.414-14.411
Abdominal lump	3.457	.000	31.721	5.796-173.590
Indicator	-6.601	.000	.001	

Table-VI*Sensitivity, specificity and predictive values of predictor models for significant endoscopic lesions^a and upper GI malignancy^b*

	Significant endoscopic lesions	Upper GI Malignancy
Sensitivity	32.4% (26- 39.2)	6% (2.9-10.9)
Specificity	82.5 % (73.4- 89.5)	100.0% (97.4-100)
Positive predictive value	79.8% (71.0-86.4)	100%
Negative predictive value	36.4 % (33.4 - 39.5)	47.3 % (46.3-48.3)

a-Age \geq 45 years or any alarm symptoms (Male sex, abdominal lump, and family history of upper GI cancer)b-Age \geq 45 years or any alarm symptoms (anaemia, fever, weight loss& abdominal lump)**Table-VII***Distribution of patients having age \geq 45 years or any alarm symptom ^a predictive of significant endoscopic lesion*

	Significant endoscopic lesion	No significant endoscopic lesion
Age \geq 45 or predictor alarm symptoms	67	80
Age <45 years or no alarm symptoms	17	140

Sensitivity, Specificity, PPV& NPV of age \geq 45 years or any alarm symptoms ^a were 32.4% (26- 39.2), 82.5 % (73.4- 89.5), 79.8% (71.0-86.4), &36.4 % (33.4 – 39.5) respectively for significant upper GI lesions^a Alarm symptoms (Male sex, family H/O malignancy, weight loss, abdominal lump)**Table-VIII***Distribution of patients having age \geq 45 years or any alarm symptom ^a predictive of malignant lesion in endoscopy*

	Upper GI Malignant lesion	No Upper GI Malignant lesion
Age \geq 45 or predictor alarm symptoms	10	181
Age <45 years or no predictor alarm symptoms	0	113

Sensitivity, Specificity, PPV& NPV of age \geq 45 years or any alarm symptom^a were 6% (2.9-10.9), 100.0 % (97.4-100), 100% and 47.3 % (46.3-48.3) respectively for UGI malignancy

a: Alarm symptoms (anaemia, fever, abdominal lump, weight loss)

Discussion

Globally the pooled prevalence of uninvestigated dyspepsia (UD) is around 21% when reflux symptoms (heartburn and regurgitation) are included in dyspeptic symptoms.²¹ In Bangladesh the prevalence of dyspeptic symptoms varies between 2.5%-20.4% in the general population when symptoms occur at least weekly basis.^{1, 22, 23} Around 44-65% of our dyspeptic patients have one or more organic lesions in upper GI endoscopy; however, the prevalence of serious organic lesions is low.^{4, 5} H. pylori infection, infection-associated dyspeptic symptoms and related endoscopic lesions are prevalent in Bangladesh.²⁴ In the present study majority (n=197, 64.8%) of the patients were below 40 years which is consistent with previous studies.^{4, 5, 14} Like previous studies upper abdominal pain (45.7%) and or burning (36.2%) were the most prevalent dyspeptic symptoms.^{1, 5, 17, 25} Around 63.5% of our patients had one or more alarm symptoms. Lower prevalences^{13, 14, 25, 26, 27, 28} as well as higher prevalences^{17, 26, 30} of alarm symptoms in patients with dyspepsia were also reported by investigators. This variation may be due to the study population involved (tertiary vs. primary), health care facilities available, local prevalence of a disease and study design (retrospective vs. prospective). In our study the sensitivity, specificity, PPV and NPV of alarm features for any significant endoscopic lesion varied from 0- 64.3%, 72.3 -78.2%, 0-46.4% and 73.2-99.63% respectively. Collectively for any alarm feature these figures were 29.0%, 74.8%, 66.7% and 37.7% respectively. A study from Cambodia reported a sensitivity, specificity, PPV & NPV of alarm features 14%, 96%, 20% & NPV 93% respectively for organic dyspepsia.²⁶ The sensitivity of most of the alarm features in our study was more in comparison to the Nigerian population¹⁷ despite excluding less serious lesions (non-erosive gastritis, duodenitis) during analysis in our study.

Some studies reported limited value of alarm symptoms in the diagnosis of upper GI malignancy or significant organic lesions.^{15, 17-19} Only 31.0% of subjects with dyspepsia and alarm features had no endoscopic lesion and the endoscopic diagnostic yield was 69.0% in the present study. These findings are consistent with studies from Nigeria (28.6%)¹⁵, China (35%)²⁷ and India (35%)¹⁴, but in contrast with the study from the UK (73%) and Cambodia (79%).^{6, 26} Kapoor et al. considered

gastritis and duodenitis as normal findings.⁶ When we excluded non-erosive gastritis and duodenitis during analysis 71.2% patients with dyspepsia having alarm features had normal endoscopic findings and the finding is consistent with Kapoor et al.⁶ A multicentric database study by Wallace et al. reported a sensitivity, specificity, PPV and NPV of 87%, 26%, 23% and 88% respectively for major endoscopic lesions (cancer, ulcer or stricture) using a simplified clinical prediction rule with age > 45 years, male sex, anaemia and bleeding in patients with dyspepsia.⁷ In our model using age > 45 years, male sex, abdominal lump, unexplained weight loss and family history of upper GI cancer we found a sensitivity, specificity, PPV and NPV of 32.4 %, 82.5 %, 79.8% and 36.4% respectively for significant upper GI lesions. In the Chinese population, the pooled sensitivity and specificity of the alarm features (dysphagia, weight loss, GI bleeding and persistent vomiting) were 13.4% and 96.6%, respectively²⁵ whereas in the Nigerian population the pooled sensitivity, specificity, PPV and NPV of alarm features (recent onset of symptoms in more than 45 years, odynophagia, progressive dysphagia, UGI bleeding, recurrent vomiting and unexplained weight loss) were 65%, 49%, 71% and 41% respectively.¹⁷

In the present study only eight (4.3%) patients with dyspepsia and alarm features had upper GI malignancy. Malignancy was 2.5 times more prevalent in dyspeptic patients with alarm features than without alarm features (1.7% VS 4.3%, P .325) which is far less than the report from India^{14, 27}, China²⁴ and Ghana.³² On the other hand in Taiwan & Shanghai 50.7-72.2% of patients with gastric cancer had no alarm symptoms.^{33, 34} A recent study did not recommend urgent endoscopy (2-week wait referral) in uncomplicated dyspepsia as the diagnostic yield of gastric or oesophageal malignancy is very low.³⁵ However another study concluded that the combination of age and gender provides better discrimination than the age alone in patients with uncomplicated dyspepsia.³⁶

Studies reported that gastrointestinal bleeding, anaemia, dysphagia, weight loss and increasing age are positive predictors of upper GI malignancy.^{6, 26-28, 30, 31, 37, 38} In the present study only age >45 years (OR 9.067), unintentional weight loss (OR 6.103), early satiety (OR 7.446) and abdominal lump (OR 54.800) were found as important predictors for UGI malignancy in the univariate logistic regression. In the multivariate regression

abdominal lump only stood out as a predictor factor for malignancy. A simplified predictor model with age \leq 45 years, anaemia, unexplained weight loss, fever and the abdominal lump had a specificity and PPV of 100.0% for UGI malignancy at the expense of very low sensitivity (6%). Wallace et al.⁷ by using a simplified clinical prediction rule with age $>$ 45 years, male sex, anaemia and bleeding found a PPV of 3% and NPV of 99% for cancers. In an Indian study altogether, alarm features had a sensitivity and specificity of 92% and 81.2% respectively for predicting malignancy.²⁷

Meta-analyses showed that the individual alarm feature had a low sensitivity ($<$ 50%) and low PPV for an underlying UGI cancer.^{15, 38} In western countries low prevalence ($<$ 0.5%) of upper GI malignancy questions the high NPV of all individual alarm feature for diagnosing UGI cancer in patients with dyspepsia.^{15, 38} Inclusion of age and gender did not dramatically improve the accuracy of alarm features. So, the authors suggested symptom combination of alarm features together with physical signs can improve diagnostic accuracy.¹⁵ Although the absolute chance of missing malignancy is low in the absence of alarm features, up to 25% of malignancies will be missed, if endoscopy is restricted for patients with dyspepsia having alarm features to strictly follow the guidelines.^{38- 40} In our study 20% of patients with malignancy had no alarm features. In China (48%)²⁵ and India (44%)¹⁴ this constituted around half of the patients with malignancy.

A meta-analysis showed that in Asia the overall malignancy detection rate is 1.3% (95% CI: 0.80-2.10) and 17.8% (95% CI: 10.90-29.00) patients with UGI malignancy are younger than 45 years and 3.0% (95% CI: 2.50-3.50) are younger than 35 years.¹³ The diagnostic accuracy at age $>$ 35 years (DOR: 9.41, 95% CI: 7.89-11.21; AUC = 0.82) is better than that at age $>$ 45 years (DOR: 3.50, 95% CI: 2.32-5.27; AUC = 0.70).¹⁸ In our study 20% of patients with malignancy were below 45 years and 10% were below 35 years which is consistent with a study from India.¹⁴ In a study from Singapore the cumulative frequencies of gastric cancer were 1.15 of 1000 endoscopies in patients less than 45 years old and 9.6/1000 endoscopies in patients greater than 45 years of age.²⁸

This is a prospective study, therefore unlikely to be biased by the patients' recall.

As the study was done in tertiary care centers data might be potentially biased by the pre-selection of higher risk patients. Besides the sample size was small and the study was not population based. So, the results might not be representative of the community. We failed to do occult blood tests of stools and tests for *H. pylori* due to a lack of feasibility.

In conclusion, alarm features are highly prevalent in patients with dyspepsia in our population, but the diagnostic value of alarm features is not optimal to accept as an indication for endoscopy. Age, male sex and certain alarm features though predictive of significant endoscopic lesion, sensitivity is low. The sensitivity of alarm features is very low for upper GI malignancy despite high predictive value and specificity. A newer and more accurate predictive model is a time demand for organic UGI lesions, especially for malignancies. We recommend that decision for endoscopy is to be individualized depending on clinical presentation and there should be no age bar for endoscopy. Further studies are required at the community level involving a larger sample size to find out the true prevalence of alarm features in dyspepsia and to find out the predictive value of alarm features for a significant organic lesion in endoscopy.

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References

1. Perveen I, Rahman MM, Saha M. Upper gastro-intestinal symptoms in general population of a district in Bangladesh. *J Enam Med Col*, 2014;4(2):79-88.
2. Ghosal UC, Sing R, Chang FY, Hou X, Wong BCY, Kachintorn U. Epidemiology of uninvestigated and functional dyspepsia in Asia: facts and fiction. *J NeurogastroenterolMotil* 2011;17: 235 -244.[PMC free article][PubMed]
3. Heading RC. Prevalence of upper gastrointestinal symptoms in general population: A systemic review. *Scand J Gastroenterol Suppl.* 1999; 231: 3-8.
4. Ghosh DK, Barua UK, Saha SK, Ghosh CK, Rahman M, Alam MR. Endoscopic evaluation of dyspeptic patients. *Bangladesh Med J* 2013;42(3):82-84.
5. Nessa A, Hossain MR, Rahman MH, Rahman SMM, Al Mamun A, Khan JM. Evaluation of 105 cases of dyspepsia by upper gastrointestinal endoscopy and ultrasonography

- of hepatobiliary system in a rural setting. *JFMC Bangladesh* 2015; 11(2):25-29.
6. Kapoor N, Bassi A, Sturgess R, Bodger K. Predictive value of alarm features in a rapid access upper gastrointestinal cancer service. *Gut* 2005;54(1):40-45.
 7. Wallace M, Durkalski V, Vaughan J, Palesch Y, Libby E, Jowell P et al. Age and alarm symptoms do not predict endoscopic findings among patients with dyspepsia: a multicenter database study. *GUT*. 2001;49(1):29-34.
 8. Bytzer P, Hansen JM, Schaffalitzky De Muckadell OB. H2-blocker therapy or prompt endoscopy in management of dyspepsia. *Lancet* 1994;343:811-816.
 9. Talley NJ, Vakili NB, Moayyedi P. American Gastroenterological Association technical review on the evaluation of dyspepsia. *Gastroenterology* 2005;129:1756-1780.
 10. Veldhuyzen van Zanten SJ, Bradette M, Chiba N *et al*. Evidence-based recommendations for short- and long-term management of uninvestigated dyspepsia in primary care: an update of the Canadian Dyspepsia Working Group (CanDys) clinical management tool. *Can J Gastroenterol* 2005;19:285-303.
 11. APA Moayyedi, Paul M MB, ChB, PhD, MPH, FACP1; Lacy, Brian E MD, PhD, FACP2; Andrews, Christopher N MD3; Enns, Robert A MD4; Howden, Colin W MD, FACP5; Vakili, Nimish MD, FACP6 and CAG Clinical Guideline: Management of Dyspepsia, *American Journal of Gastroenterology*: July 2017 – Volume 112 – Issue 7 – p 988-1013. Doi: 10.1038/ajg.2017.154
 12. International Agency for Research on Cancer. <http://gco.iarc.fr/today/home> Accessed on 1 January 2018.
 13. Chen SL, Gwee KA, Lee JS, Miwa H, Suzuki H, Guo P et al. Systemic review with meta-analysis: prompt endoscopy as the initial management strategy for uninvestigated dyspepsia in Asia. *Aliment Pharmacol Ther.* 2015;41(3):239-252.
 14. Sumathi B, Navaneethan U, Jayanthi V. Appropriateness of indications for diagnostic upper gastrointestinal endoscopy in India. *Singapore Medical Journal* 2008;49(12): 970-976.
 15. Vakili 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.
 16. Moayyedi P, Talley N, Fennerty MB *et al*. Can the clinical history distinguish between organic and functional dyspepsia? *JAMA* 2006;295:1566-1576.
 17. Odeghe EA, Adeniyi OF, Oyeleke GK, Keshinro SO. Use of alarm features in predicting significant endoscopic findings in Nigerian patients with dyspepsia. *Pan African Medical journal* 2019;34:66. Doi:10.11604/pamj.2019.34.66.18848
 18. Meineche-Schmidt V, Jorgensen T. 'Alarm symptoms' in dyspepsia. How does the general practitioner investigate? *Scand J prim health Care*, 2003;21:224-229.
 19. Meineche-Schmidt V, Jorgensen T. 'Alarm symptoms' in patients with dyspepsia: a three-year prospective study from general practice. *Scand J Gastroenterol*, 2002;37(9): 999-1007. Doi:10.1080/003655202320378167
 20. Lwanga S. K, Lemeshaw S. Sample size determination in health studies. WHO (1991). pp 1-25. [http://www.Whqlibdoc.who.int/publications/9241544058\(p1-p22\).pdf](http://www.Whqlibdoc.who.int/publications/9241544058(p1-p22).pdf)
 21. Ford AC, Marwaha A, Sood R, Moayyedi P. Global prevalence of, and risk factors for, uninvestigated dyspepsia: A meta-analysis. *Gut* 2014
 22. Saha M, Perveen I, Alamgir MJ, Masud MH, Rahman MH. Prevalence and risk factors for gastro-oesophageal reflux disease in the North-Eastern part of Bangladesh. *Bangladesh Med Res Counc Bull* 2012; 38: 105-113.
 23. Perveen I, Rahman MM, Saha M, Rahman MM, Hasan MQ. Prevalence of irritable bowel syndrome and functional dyspepsia, overlapping symptoms, and associated factors in a general population of Bangladesh. *Indian J Gastroenterol* 2014;33(3):265-273. Doi 10.1007/s12664-041-0447-1
 24. Nahar S, Kibria KMK, Hossain ME, Sarker SA, Bardhan PK, Talukder KA et al. Epidemiology of *H. pylori* and its relation with gastrointestinal disorders, A community-based study in Dhaka, Bangladesh. *Journal of GHR* 2018;7(5):2709-2716. Doi: 10.17554/j.issn.2224-3992.2018.07.795
 25. Bai Y, Li ZS, Zou DW, Wu RP, Yao YZ, Jin ZD et al. Alarm features and age for predicting upper gastrointestinal malignancy in Chinese patients with dyspepsia with high background prevalence of *Helicobacter pylori* infection and upper gastrointestinal malignancy: an endoscopic database review of 102,665 patients from 1996 to 2006. *Gut*. 2010;59(6):722-728. Doi:10.1136/gut.2009.1924
 26. Ung B, Chea K, Ung C, Saurine JC, Ko CW. Endoscopic yield of chronic dyspepsia in outpatients: A single-center experience in Cambodia. *JGH Open* 2019; 24(1): 61-68. Doi: 10.1002/jgh3.12210.eCollection 2020 Feb
 27. Shetty A, Balaraju G, Shetty S, Pai CG. Diagnostic utility of alarm features in predicting malignancy in patients with dyspeptic symptoms. *Indian J Gastroenterol* 2021; 40: 183-188.
 28. Wai CT, Yeah KG, Ho KY, Kang JY, Lim SG. Diagnostic yield of upper endoscopy in Asian patients presenting with dyspepsia. *GIE* 2002; 56(4): 548-551. Doi: 10.1067/mge.2002.128493
 29. Lieverman D, Fennerty MB, Morris CD, Hulab J, Eise G, Sonnenberg A. Endoscopic evaluation of patients with dyspepsia: results from the national endoscopic data repository. *Gastroenterol* 2004;127(4):1067-1075.

30. 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(2):120-125.
31. GyeduAYorkeJ. Upper GI endoscopy in patient population of Kumasi, Ghana: indications and findings. *Pan Afr Med J* 2014;18: 327.
32. Liou JM, Lin JT, Wang HP, Shun CT, Lin MT, Wu Ms, et al. The optimal age threshold for upper endoscopy for uninvestigated dyspepsia in Taiwan, an area with a higher prevalence of gastric cancer in young adults. *GIE* 2005; 61(7): 819-825. Doi: 10.1016/S0016-5107(05)00366-4
33. Li XB, Liu WZ, Ge ZZ, Chen XY, She Y, Xio SD. Helicobacter pylori "test-and-treat" strategy is not suitable for the management of patients with uninvestigated dyspepsia in Shanghai. *Scandinavian Journal of Gastroenterology* 2005; 40(9): 1028-1031. Doi: 10.1080/00365520510023206
34. Ovid.2. Patel J, McNair A. "Identification of upper gastrointestinal malignancy in patients with uncomplicated dyspepsia referred under the two-week-wait cancer pathway: a single center, 10-year experience", abstract. *European Journal of Gastroenterology & Hepatology* 2020; 32(1): 22-25. Doi:10.1097/MEG.0000000000001556
35. Ovid 1. Marmo R, Rotondano G, Piscopo R, BiancoMACapobianco PR, Cipolletta L. "Combination of age and sex improves the ability to predict upper gastrointestinal malignancy in patients with uncomplicated dyspepsia: a prospective multicentric database study", abstract. *Am J Gastroenterol.* 2005;100(4); 784-91. Doi: 10.1111/j.1572-0241.2005.40085.x
36. Emami MH, Ataei-Khorasgani M, Jafari-Pozvi N. Diagnostic value of alarm symptoms for pper GI malignancy in patients referred to GI clinic: a 7 years cross sectional study. *J Res Med Sd.* 2017;22:76
37. Fransen GA, Janssen MJ, Muris JW, Laheij RJ, Jansen JB. Meta-analysis: the diagnostic of alarm symptoms for upper gastro-intestinal malignancy. *Aliment Pharmacol Ther* 2004;20(10): 1045-1952.
38. HinmarschACheong E, Rees L, Rhodes M. National referral guidelines forcases of suspected upper GI cancer in UK: are they working? *Gut.* 2003;52(supple.VI): A17.
39. Ahmad I, Azam A. To assess the effectiveness of two-week referrals for oesophageal and gastric cancer in accordance with United Kingdom department of health guidelines. *Gut.* 2003; 52(supple.VI): A17.