Age and Alarm Symptoms Predict Upper Gastrointestinal Malignancy among Patients with Dyspepsia

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ABSTRACT

Background: *Upper gastrointestinal (UGI) malignancy is one of the major causes of cancer related death. Endoscopy in dyspeptic patients above 45 years, or those with alarm symptoms may detect this condition. There were only limited data in Indonesia about age and alarm symptoms to predict UGI malignancy. This study was aimed to determine the prevalence of UGI malignancy among dyspepsia patients and to develop a simple clinical prediction model.*

Method: *A cross-sectional study to 390 patients with dyspepsia underwent endoscopy in Endoscopy Unit of Sanglah Hospital Denpasar between July 2012 and June 2013 was conducted. Demography and alarm symptoms were documented. Chi-square and logistic regression test analysis were conducted to analyze variables associated with UGI malignancy.*

Results: *Twenty (5.13%) of 390 patients with dyspepsia had UGI malignancy. Of the 20 patients, 65% were gastric cancer and 30% were esophageal cancer. The mean age was 59 ± 12 years. Variables associated with UGI malignancy were weight loss (OR = 8.2), dysphagia (OR = 6.2), age > 45 years old (OR = 5.6), gastrointestinal bleeding (OR = 5.5), persistent vomiting (OR = 5.4), and anemia (OR = 4.9). Using a simplified rule of age > 45 years and the presence of any alarm symptom, sensitivity was 85% and specificity was 67.57%.*

Conclusions: *UGI malignancy was found in 5.13% of patients with dyspepsia who underwent endoscopy. Simple clinical prediction model states that age above 45 years and alarm symptoms may be used as a screening tool to predict UGI malignancy.*

Keywords: *dyspepsia, alarm symptoms, upper GI malignancy, clinical prediction model*

ABSTRAK

Latar belakang: *Keganasan saluran cerna bagian atas merupakan salah satu penyebab terbanyak kematian terkait kanker. Endoskopi pada pasien dispepsia di atas usia 45 tahun atau mereka dengan tanda bahaya dapat mendeteksi kondisi ini. Saat ini hanya ada sedikit data di Indonesia mengenai usia dan gejala tanda bahaya dalam memprediksi keganasan saluran cerna bagian atas. Penelitian ini bertujuan untuk menentukan prevalensi keganasan saluran cerna pada pasien dispepsia dan untuk mengembangkan contoh prediksi klinis sederhana.*

Metode: *Suatu penelitian potong-lintang dilakukan terhadap 390 pasien dispepsia yang menjalani prosedur pemeriksaan endoskopi di Unit Endoskopi Rumah Sakit Sanglah Denpasar antara bulan Juli 2012 sampai Juni 2013. Faktor demografi dan gejala tanda bahaya didokumentasikan. Analisis Chi-square dan tes regresi logistik dilakukan untuk menganalisa variabel yang berhubungan dengan keganasan saluran cerna bagian atas.*

Hasil: *Dua puluh (5.13%) dari 390 pasien dispepsia menderita keganasan saluran cerna bagian atas. Dari 20 pasien, 65% dengan kanker lambung, dan 30% dengan kanker esofagus. Rerata usia adalah 59 ± 12 tahun. Variabel yang berhubungan dengan keganasan saluran cerna bagian atas adalah penurunan berat badan (RO = 8.2), disfagia (RO = 6.2), usia > 45 tahun (RO = 5.6), perdarahan saluran cerna (RO = 5.5), muntah yang persisten (RO = 5.4), dan anemia (RO = 0.49). Dengan menggunakan aturan prediksi sederhana usia > 45 tahun dan adanya tanda bahaya, sensitivitas mencapai 85% dan spesifisitas mencapai 67.57%.*

Simpulan: *Keganasan saluran cerna bagian atas dijumpai pada 5.13% pasien dispepsia yang menjalani prosedur pemeriksaan endoskopi. Contoh prediksi klinis sederhana menyatakan usia di atas 45 tahun dan adanya tanda bahaya dapat digunakan sebagai alat penapis untuk memprediksi keganasan saluran cerna bagian atas.*

Kata kunci: *dispepsia, tanda bahaya, keganasan saluran cerna bagian atas, contoh prediksi klinis*

INTRODUCTION

Upper gastrointestinal (UGI) malignancy has been estimated globally to happen in about 1.4 million new cases in 2008.[1] Gastric cancer itself is the world's second leading cause of cancer mortality.[1,2] GLOBOCAN estimates that 1.1 million cancer deaths occurred worldwide in 2008 is due to UGI malignancy.[1] Greater than 50% of the world's new cases of gastric cancer, and greater than 70% of newly diagnosed esophageal cancer worldwide occur in Asian countries. World Health Organization South-East Asia region (WHO SEARO) recorded 67,000 new cases of gastric cancer in 2008 with 15,000 (22%) of them came from Indonesia. Although the incidence of gastric cancer in Indonesia is very low, morbidity and mortality rates of gastric cancer in Asia remain the highest in the world. Of 740,000 deaths worldwide which happened due to gastric cancer, 13,500 deaths occurred in Indonesia.[3] UGI malignancy frequencies are varied.[4-6]

Endoscopy is the standard examination to diagnose UGI malignancy.[7] Nevertheless, a prompt endoscopy for every dyspeptic patient cannot be a practical approach because it is not cost-effective and increases the workload of healthcare workers.[8] Therefore, American Gastroenterology Association (AGA) recommends dyspeptic patients over 55 years, or those with alarm features such as weight loss, dysphagia, gastrointestinal (GI) bleeding, anemia, or persistent vomiting should undergo endoscopy.[9] A study stated that alarm symptoms increased the risk of UGI malignancy to 5-6-fold.[10] Of these patients, more than 80% had alarm symptoms.[11,12]

While there are clinical features that should alert clinicians to the possibility of UGI malignancy, the effectiveness of these alarm features are unclear.[13,14] Moreover, the majority of study was conducted in Europe, North America, or East Asia.[6,8,10,11,14] Conclusions from Western or East Asia studies may not be applicable in Indonesia as the prevalence of UGI diseases remarkably differs. There has been no study of the effectiveness of age and alarm features for predicting UGI cancers among dyspeptic patients in Indonesia. The aim of this study was to determine the prevalence of UGI malignancy among dyspepsia patients who underwent endoscopy and to develop a simple clinical prediction model for UGI malignancy.

METHOD

This study is a cross-sectional study from endoscopy record of patient with dyspepsia. Three hundred ninety patients with dyspepsia underwent UGI endoscopy in Endoscopy Unit of Sanglah Hospital Denpasar between July 2012 and June 2013. The inclusion criteria were all patients with dyspepsia who had agreed to undergo UGI tract endoscopy examination. Exclusion criteria were patients with age under 17 years old and patients with documented chronic liver disease.

The data were documented from the medical records and questionnaire. Data acquired consisted of demographic data, presenting symptoms, and alarm symptoms. Alarm symptoms included were weight loss, dysphagia, GI bleeding, anemia, and persistent vomiting. In addition, reports of available laboratory and endoscopy investigations were also obtained. Identified histological data on biopsies of the UGI mucosa were also collected.

Unintentional weight loss was defined as ≥ 10% loss of body weight in recent 6 months. Dysphagia was perception of an impediment to the normal passage of swallowed material. GI bleeding translated as any evidence of hematemesis and/ or melena. Persistent vomiting included if there was at least 7 to 10 days of protracted vomiting, while anemia was defined as hemoglobin values lower than 10 g/dL. UGI malignancy was defined as any histologically

confirmed esophageal, gastric or duodenal cancer detected during endoscopy.

SPSS version 17 software was used in statistical analysis of this study. Age was summarized as mean and standard deviation (SD). Sex and each alarm symptoms were summarized as counts and percentages. Test for differences in age between patients with and without UGI malignancy were done using the independent samples T-test or the Mann-Whitney U-test as appropriate. Test for sex and each alarm symptoms were performed using Chi-square or Fisher's exact test as appropriate.

We estimated significant variables using bivariate analysis. Backward stepwise selection in a multivariate logistic regression was made for statistically significant factors. Subsequently, using an automated backward-stepwise multivariable method, we achieved the final model that only comprised the predictors with a multivariable $p < 0.05$. Once the variables included in the model were defined, we examined the calibration of the model by performing Hosmer-Lemeshow goodness-of-fit test. Based on regression model findings, we decided to report diagnostic accuracy measures using the area under the receiver operating characteristic (ROC) curve or AUC and its 95% confidence intervals (CI). Using histology as the gold standard for diagnosis of UGI malignancies, we calculated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of risk-prediction model based on selected age classification model and alarm symptoms. We also calculated diagnostic odds ratio (OR), and their related 95% confidence intervals for age, sex, and each of alarm symptoms using multivariable adjusted logistic regression models.

RESULTS

Between July 2012 and June 2013, 390 patients with dyspepsia underwent UGI endoscopy. Mean age of patients was 48.8 ± 14.1 years, and 228 (58.5%) patients were above the age of 45 years. The most frequent age group was between 41-50 years (25.9%). There were 220 (56.4%) male and 170 (43.6%) female patient. Of these, 318 (81.5%) patients had at least one alarm symptoms. GI bleeding (27.9%), weight loss (17.9%), and anemia (16.7%) were the commonest alarm symptoms found in all patients (Figure 1; Table 1).

Table 1. Demographic characteristics and distribution of alarm symptoms in all dyspeptic patients

Characteristics	Dyspeptic patients	
	without upper gastrointestinal malignancy n (%)	with upper gastrointestinal malignancy n (%)
Mean age	48.8 ± 14.1	59.0 ± 12.0
Age (years)		
> 45	210 (56.8%)	18 (90%)
≤ 45	160 (43.2%)	2 (10%)
Sex		
Male	208 (56.2%)	12 (60%)
Female	162 (43.8%)	8 (40%)
History of weight loss		
Absent	313 (84.6%)	7 (35%)
Present	57 (15.4%)	13 (65%)
History of GI bleeding		
Absent	274 (74.1%)	7 (35%)
Present	96 (25.9%)	13 (65%)
History of persistent vomiting		
Absent	330 (89.2%)	14 (70%)
Present	40 (10.8%)	6 (30%)
History of dysphagia		
Absent	329 (88.9%)	11 (55%)
Present	41 (11.1%)	9 (45%)
Anemia		
Absent	315 (85.1%)	10 (50%)
Present	55 (14.9%)	10 (50%)

GI: gastrointestinal

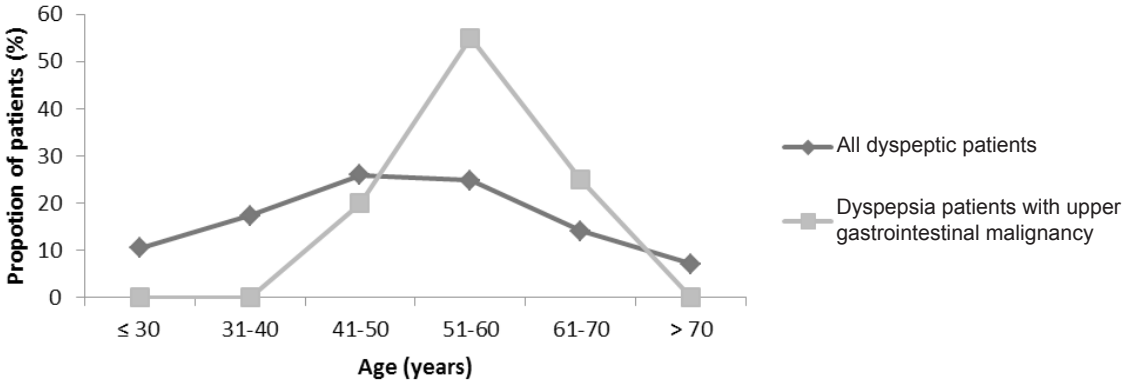

Figure 1. Proportion of all dyspeptic patient and patients with upper gastrointestinal malignancy in this study by age group

A total of 20 UGI cancers were histologicaly confirmed (5.13% prevalence) with 90% occurred in subjects over 45 years of age. If the age of 55 had been taken as the optimal age for screening, 60% cases would have been missed. Patients with UGI malignancy were significantly older (mean age of 59.0 years) and more likely to be male (60%) (Table 1). Patients reporting at least one of the alarm symptoms constituted 95% of patients with UGI malignancies compared to 53.3% in patients without cancer ($p < 0.001$).

Table 2 shows the endoscopic and histological findings in the study participants. Of the 20 patients with cancer, 13 (65%) were diagnosed with gastric cancer, 6 (30%) with esophageal cancer, and 1 (5%) with duodenal cancer. The majority of gastric cancers was adenocarcinomas (61.5%) and was located in the antrum (38.4%). Esophageal cancers were consisted of three adenocarcinomas and three squamous cell types and were located more in the distal-third of the esophagus (83.3%) (Table 2).

We used bivariate analysis to determine which variables were suitable for multivariate analysis. Male was not different to female of having UGI cancers ($p = 0.740$). On the other hand, relations between age and each alarm symptoms with UGI malignancy were found. Each predictor variable (age > 45, weight loss, dysphagia, anemia, bleeding, and persistent vomiting) was significant in the bivariate analysis (Table 3).

Table 2. Endoscopic and histologic findings in study population

Criteria	n (%)
Upper gastrointestinal endoscopy	
No malignancy	370 (94.9%)
Esophageal malignancy	6 (1.5%)
Gastric malignancy	13 (3.3%)
Duodenal malignancy	1 (0.3%)
Cancer morphology	
Esophageal SCC	3 (50%)
Adenocarcinoma	3 (50%)
Gastric	
Adenocarcinoma	8 (61.5%)
Signet ring cell carcinoma	3 (23.1%)
Others (GIST, MALT lymphoma)	2 (15.4%)
Duodenal	
Adenocarcinoma	1 (100%)
Cancer topography	
Esophageal middle-third	1 (16.7%)
Esophageal lower-third	5 (83.3%)
Gastric	
Cardia	2 (15.4%)
Corpus	3 (23.1%)
Antrum	5 (38.4%)
Diffuse	3 (23.1%)
Duodenal	
D1	1 (100%)

SCC: squamous cell carcinoma; GIST: gastrointestinal stromal tumor; MALT: mucosa-associated lymphoid tissue); D1: duodenum part 1

Multivariate analysis found that age (> 45 years), weight loss, dysphagia, bleeding, anemia, and persistent vomiting were significant predictors of having an upper GI malignancy (Table 4). The accuracy

Table 3. Bivariate analysis of variables predict UGI malignancy

Characteristic	Dyspeptic patients without UGI malignancy		Dyspeptic patients with UGI malignancy		p*
	Frequency	%	Frequency	%	
Age (± SD)	48.8 ± 14.1		59.0 ± 12.0		0.002
Sex					
Male	208	56.2	12	60	0.740
Female	162	43.8	8	40	
History of weight loss					
Absent	313	84.6	7	7	< 0.001
Present	57	15.4	13	65	
History of gastrointestinal bleeding					
Absent	274	74.1	7	35	< 0.001
Present	96	25.9	13	65	
History of persistent vomiting					
Absent	330	89.2	14	70	0.010
Present	40	10.8	6	30	
History of dysphagia					
Absent	329	88.9	11	55	< 0.001
Present	41	11.1	9	45	
Anemia					
Absent	315	85.1	10	50	< 0.001
Present	55	14.9	10	50	

*p values are calculated using independent sample T-test for age and Chi-square tests for variables to compare the distribution of the variables between patient with and without UGI malignancy; UGI: upper gastrointestinal

of the multivariate model was shown in Figure 2. The Hosmer-Lemeshow test showed p = 0.902 which informed that this multivariate model had a good calibration. ROC analysis presented AUC 0.91 (95% CI = 0.852-0.978) indicated that this model had good statistic quality.

Table 4. Multivariate analysis of variables predict upper gastrointestinal malignancy

Variables	Coefficient	p	OR (95% CI)
History of weight loss	2.101	< 0.001	8.17 (2.63-25.44)
History of GI bleeding	1.712	0.006	5.54 (1.64-18.70)
Persistent vomiting	1.696	0.019	5.45 (1.32-22.50)
History of dysphagia	1.830	0.004	6.23 (1.82-21.31)
Anemia	1.585	0.011	4.88 (1.44-16.55)
Age > 45 years	1.726	0.037	5.62 (1.11-28.51)
Constant	-7.141	< 0.001	0.001

GI: gastrointestinal; CI: confidence interval

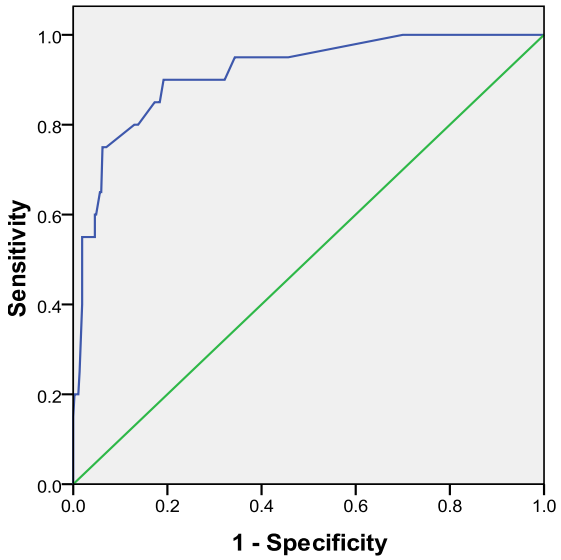

Figure 2. ROC curve showing the relationship between sensitivity and specificity of the prediction rule for major upper gastrointestinal pathology. The diagonal line represents a model which has zero predictive value. C statistic (area under the ROC curve) = 0.91

We applied the simplified decision rule where the presence of any significant predictor (age > 45 years, weight loss, dysphagia, anemia, bleeding, persistent vomiting) was considered as an indication for endoscopy. Among patients aged more than 45 or those with significant predictors, 20 of 318 (6.29%) had an UGI malignancy (positive predictive value) (Table 4). Among younger patients with no significant predictors, 72 of 72 (100%) had no UGI malignancy (negative predictive value) (Table 4). The sensitivity of the simplified prediction rule was 100% and specificity was 19.5%.

Due to low specificity of first model we tried to specify new criteria combining age and any alarm symptoms (weight loss, dysphagia, GI bleeding, anemia, and persistent vomiting). Instead of using just one marker such as only age older than 45 years or any components of alarm symptoms implied in the classical criteria, we used new criteria that stated "age older than 45 years and any components of alarm symptoms". Using this new model, 17 of 137 (12.41%) had an UGI malignancy (positive predictive value). Negative predictive value of this model was 250 of 253 (98.81%). The sensitivity of the new model was 85% and specificity was 67.57%. Applying these new criteria would have resulted in findings of 17 dyspeptic patients with UGI malignancy.

DISCUSSION

UGI malignancy is still remaining as major health problem. Existing data of every state is different. UGI malignancies has different prevalence, ranging from 0.5 to 9.7% from several endoscopic studies.[4,15] Study in United Kingdom reported prevalence of 2.0 to 3.8%.[16,17] Lower incidence reported from Hongkong which is 0.90%.[18] Records of more than 100,000 patients in China resulted prevalence of 4.2%.[6] Another study in Cipto Mangunkusumo Hospital Jakarta resulted 5.20% cases of UGI malignancy among dyspeptic patients.[12] In this study, the result is 5.13% UGI malignancy among 390 dyspeptic patient underwent endoscopy. This result is greater than most studies but seems to be in accordance with Cipto Mangunkusumo Hospital study. This may be caused by Sanglah Hospital which acts as regional referral hospital from other hospitals, also from Nusa Tenggara. The distribution of UGI malignancy in this study is gastric cancer 3.33%, esophageal cancer 1.54% and duodenal cancer 0.26%. The result of this study is higher compared to study conducted in Singapore and Saudi Arabia where cases found were gastric cancer 0.47% and 0.91%, esophageal cancer 0.06% and 1.49% respectively. But it is still lower than center in Medan which showed incidence of 5.6%.[19] This study shows similarity with other studies conducted in Indonesia. Study in Cikini Hospital Jakarta showed that incidence of gastric cancer in 2005 was 3.9%.[20]

Most gastric cancer in our study was located at antrum (38.4%). This is in accordance with other studies in South-East Asia.[12,21] Gastric cancer is still antral predominant cancer in Asian countries, and though we did not study the association of *Helicobacter pylori* (*H. pylori)* with the gastric

cancer in our study, carcinogenesis-promoting effect of *H. pylori* seems to be responsible for this. In a large prospective nested case-control study, *H. pylori* was strongly associated with distal gastric cancer.[22] Adenocarcinoma constituted most of gastric cancer in our study. This finding was similar with other study which stated that approximately 90% of gastric cancers were adenocarcinomas.[2,5,23,24] Findings of esophageal cancers location in our study were also similar with other study conducted in Jakarta. Retrospective study in Jakarta found lower third part as the most common site of esophageal cancer, as also proved by our study in Bali.[25] This finding probably related to gastroesophageal reflux disease which may turn to Barrett's metaplasia and predispose to malignancy in such location.

The mean age of UGI malignancy in this study was 59.0 ± 12.0 years, and 90% patients were above the age of 45 years. Of 20 patients with UGI malignancy, 60% were male and 40% were female. Due to this condition we used the age cut-off at 45 years at Sanglah hospital. This is similar to the recommendation in several studies.[8,9,15,26] Hsu reaffirmed that the age threshold for screening should be set at 40-50 years in Asia.[8] Syam also agreed 45 years as the age cut-off to underwent endoscopy.[26] Talley suggested an age cut-off of 55 years for Western countries and a lower threshold in some countries in the Asia-Pacific region.[9] This higher incidence of UGI malignancy especially gastric cancer observed among men is partially explained by higher *H. pylori* infection rates in male as proved by a large, population-based metaanalysis.[27]

Dyspepsia patients with alarm signs have been found in 19 (95%) patients, including decrease of bodyweight, melena, hematemesis, anemia and dysphagia. Of all dyspeptic patients found, GI bleeding was the most common alarm sign presented (27.9%). This is similar with study conducted in Koja hospital which found GI bleeding as the most common alarm symptoms found.[28] Maconi et al reported that among 92 gastric cancer, 58.7% had uncomplicated dyspepsia and 41.3% had alarm sign.[29]

Alarm symptoms are accepted as an indication for direct endoscopy.[4,9] However, the existing evidence does not consistently support the usefulness of alarm symptoms for this matter.[13] Another study found that 93% of patients had an alarm feature when diagnosis of UGI malignancy was established.[30] In this study, age more than 45 years, weight loss, dysphagia, GI bleeding, persistent vomiting, and anemia were all positively associated with risk of UGI cancers. Of these, weight loss and dysphagia were the most important predictors. Male was not associated with higher risk of UGI malignancy. Some previous studies have also assessed the value of age and alarm symptoms in predicting risk of cancer in dyspeptic patients.[6,16,30] Large samples study in China proposed criteria that stated age and some components of alarm symptoms were valuable in diagnosing UGI malignancy.[6] A meta-analysis by Fransen et al found limited diagnostic values including sensitivity, specificity and predictive values, for each individual alarm symptom.[4] They suggested using alarm symptoms in combination with other factors – such as age, sex, or smoking – might be a better tool for selection of high-risk patients. Kapoor et al., built criteria that said dysphagia or weight loss may increase the opportunity of having UGI malignancy.[16] Khademi et al agreed criteria that combine demographic factors and alarm symptoms as clues to do endoscopy.[5]

In this study, six factors were found significant as predictors for UGI malignancy and then developed as a risk-prediction model. Those factors were age more than 45 years, weight loss, dysphagia, GI bleeding, persistent vomiting, and anemia. Unfortunately male was not significant as predictive factor. Recent study showed that men did not have significantly higher chance of UGI cancers than women.[5] The discriminative values of alarm symptoms were further supported by their independent association with malignancy. This was also proved by group in Taiwan that found weight loss, GI bleeding and dysphagia as predictive factors for UGI malignancy.[8] Among all predictors in study conducted in Sanglah Hospital, weight loss was the strongest predictor of UGI cancers as implied in other study.[5]

Risk-prediction model in our study consisted of age > 45 years and alarm symptoms. Using classical prediction model that states recommendation of endoscopy in subjects older than 45 years or has any components of alarm symptom, yield low specificity. Therefore, classic premise is not a proper tool as a screening test for UGI malignancy. By changing the premise into age older than 45 years and components of alarm symptoms, the specificity increased. New criteria with better sensitivity and specificity proved to be a good diagnostic tool in detection of UGI malignancy. Hsu et al also demonstrated that age threshold of 45 years and alarm symptom would identify almost all dyspeptic patients with UGI malignancy.[8] These criteria that combine age cut-off and any components of alarm symptoms may be used in the future among

primary health care, to suspect patient who most likely need to be further investigated by endoscopy for any condition of UGI malignancy. This new criteria is cost-effective and may save burden of cost due to improper selection of candidate for endoscopy.

The strengths of our study are relatively large sample size collected for one year, simple criteria added in diagnosing UGI malignancy, and the first study in Indonesia as far as we know that prove age and alarm symptoms as beneficial tool in detecting UGI malignancy. Limitations of the study are unavailability of other demographic factors and clinical parameters such as *H. pylori* infection that may relate and add accuracy in diagnosing UGI malignancy and no external validation set.

CONCLUSION

Upper gastrointestinal malignancy was found in small portion of dyspeptic patients. The older the age of patients and alarm symptoms are associated with the risk of upper gastrointestinal malignancy. Simple clinical prediction model states that older age and any components of alarm symptoms may be used as a screening tool for further endoscopy. Prediction strategies are cost-effective and may be useful among primary health care services as indications in predicting potential upper gastrointestinal malignancies which may warrant referral.

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