



Are alarm symptoms valuable in predicting upper gastrointestinal malignancy?

Alarm semptomları üst gastrointestinal maligniteyi öngörmeye değerli midir?

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ABSTRACT • Background and Aims: The diagnostic utility of alarm symptoms in predicting upper gastrointestinal cancers is uncertain. In our study, we aimed to investigate the predictive value of alarm symptoms in the diagnosis of upper gastrointestinal cancers. **Materials and Methods:** This prospective observational study included patients with at least one or more alarm symptoms of upper gastrointestinal cancers who underwent esophagogastroduodenoscopy. Patients under 18 years of age and over 80 years of age were excluded. Patients were divided into two groups as under and over 45 years of age. Demographic characteristics, presenting complaints, alarm symptoms, endoscopy and pathology results were evaluated prospectively. **Results:** A total of 325 patients were included in the study, 62.5% of whom were female, with a mean age of 50.8 ± 15.8 years. The most common alarm symptoms were new-onset dyspepsia over 45 years of age (48.6%), weight loss (34.8%) and iron deficiency anemia (31.1%), respectively. In our study, malignancy was diagnosed in 8 patients (2.5%), 6 of whom were male, and all of whom were over 45 years of age. The alarm symptoms with the highest sensitivity were weight loss (75%) and iron deficiency anemia (50%), while the alarm symptoms with the highest specificity were palpable abdominal/epigastric mass or abnormal lymphadenopathy (96.5%) and upper gastrointestinal bleeding (96.2%). **Conclusion:** The sensitivity and specificity of alarming features in predicting upper gastrointestinal cancers is limited and other methods need to be developed to define the at-risk population.

Key words: Alarm features, alarm symptoms, dyspepsia, malignancy, upper gastrointestinal malignancy

ÖZET • Giriş ve Amaç: Alarm semptomlarının üst gastrointestinal kanserlerini öngörmedeki tanılabilirliği belirsizdir. Çalışmamızda, alarm semptomlarının üst gastrointestinal kanserlerinin tanısında öngörücü değerini araştırmayı amaçladık. **Gereç ve Yöntem:** Bu prospektif gözlemsel çalışmaya, üst gastrointestinal sistem kanserlerine yönelik en az bir veya daha fazla alarm semptomu olan ve özofagogastroduodenoskopi yapılan hastalar dahil edildi. On sekiz yaş altı ve 80 yaş üstü hastalar çalışma dışı bırakıldı. Hastalar 45 yaş altı ve üstü olarak iki gruba ayrıldı. Hastaların demografik özellikleri, başvuru şikayetleri, alarm semptomları, endoskopi ve patoloji sonuçları prospektif olarak değerlendirildi. **Bulgular:** Çalışmaya %62,5'i kadın, yaş ortalamaları 50,8 ± 15,8 yıl olan toplam 325 hasta dahil edildi. En sık görülen alarm semptomları sırasıyla 45 yaş üzeri başlayan dispepsi (%48,6), kilo kaybı (%34,8) ve demir eksikliği anemisi (%31,1) idi. Çalışmamızda tamamı 45 yaş üstünde olan 6'sı erkek toplam 8 hastaya (%2,5) malignite tanısı konuldu. Malignite tanısında sensitivitesi en yüksek alarm semptomları kilo kaybı (%75) ve demir eksikliği anemisi (%50), spesifitesi en yüksek alarm semptomları ise palpable abdominal/epigastrik kitle veya anormal lenfadenopati (%96,5) ve üst gastrointestinal sistem kanaması (%96,2) idi. **Sonuç:** Üst gastrointestinal kanserleri öngörmeye alarm bulgularının duyarlılığı ve özgüllüğü sınırlıdır ve risk altındaki popülasyonu tanımlamak için başka yöntemlerin geliştirilmesine ihtiyaç vardır.

Anahtar kelimeler: Alarm özellikleri, alarm semptomları, dispepsi, malignite, üst gastrointestinal malignite

INTRODUCTION

Gastrointestinal (GI) tract cancers are the most common cancer group and constitute approximately one fourth of the total cancer incidence and one third of cancer-related deaths in developing countries (1). Upper GI cancers account for approxi-

mately 35% of all GI cancers and approximately 1.5 million people die from upper GI cancers worldwide every year (2). As in all solid cancers, the most important factor determining the survival time of the patient in GI cancers is early di-

agnosis (3). Early diagnosis has been found to be associated with less morbidity, and treatment cost as well as increasing the chance of curative treatment (3). However, the majority of patients with cancer are asymptomatic in the early stages of the disease. On the other hand, when cancer-related symptoms occur in patients, the disease is usually diagnosed at an advanced stage and the disease prognosis worsens (3). Therefore, screening programs are needed for early diagnosis of cancer in high-risk populations before the onset of advanced symptoms and ideally before metastasis. Although endoscopic screening is recommended in high-risk individuals for early diagnosis of upper GI tract cancers, routine screening programs are not implemented. Therefore, questioning of risk factors and alarm symptoms of malignancy by physicians is of great importance for early diagnosis.

Upper GI cancers are usually seen in the elderly. Therefore, guidelines recommend that patients with alarming symptoms, especially at older ages, should be investigated for upper GI cancer (4-6). Alarm symptoms are symptoms thought to be associated with serious GI diseases and are predictive of important pathologies such as underlying malignancy, gastrointestinal stricture or ulcer (7,8). However, conflicting results have been found in studies on the sensitivity of alarm symptoms in predicting upper GI tract cancers (8-10). In this study, we aimed to investigate the association of alarm symptoms with the diagnosis of upper GI malignancy and to evaluate their predictive value, especially in terms of malignancy.

MATERIALS and METHODS

In this prospective, single-center observational study, patients who applied to Karadeniz Technical University School of Medicine, Gastroenterology Outpatient Clinic between 01.01.2020 and 01.01.2021 and underwent endoscopy due to one

or more alarm symptoms of upper GI tract cancers were included. Patients between 18 and 80 years of age who gave consent for the study were included in the study. Demographic characteristics, alarm symptoms and comorbid diseases were recorded before endoscopy was performed. Alarm symptoms for upper GI cancers were considered as new-onset dyspepsia over 45 years of age, progressive dysphagia and/or odynophagia, weight loss (unexplained weight loss of more than 5 kg in 2 months), upper gastrointestinal bleeding (hematemesis, melena and fecal occult blood positivity), family history of esophageal or gastric cancer, palpable abdominal or epigastric mass or abnormal lymphadenopathy, persistent vomiting and iron deficiency anemia (5). Patients with previous upper GI cancer, known liver and pancreatic disease, history of esophageal or gastric surgery, voluntary weight loss and patients without alarm symptoms were excluded.

Written informed consent for upper endoscopy and the study was obtained from all patients before the procedure. All patients underwent upper GI endoscopy under conscious sedation by experienced gastroenterologists. In case of suspected malignancy, multiple biopsy specimens were obtained from the suspicious lesion and sent for histologic confirmation. Biopsy specimens were interpreted by an expert pathologist who was completely blinded to alarm symptoms. The study protocol was approved by the Karadeniz Technical University Ethics Committee, with the approval number 24237859-215 and date of 28.01.2020. The study protocol complied with the ethical guidelines of the Declaration of Helsinki.

Statistical Analysis

SPSS 23.0 statistical package program was used for data analysis. Descriptive statistics of the evaluation results were given as number and percentage for categorical variables and mean, standard deviation, minimum, maximum for numerical

variables. The conformity of the measured data to normal distribution was evaluated by One-Sample Kolmogorov Smirnov test. Comparisons of the measured data between two independent groups were evaluated by Student-t Test when the normal distribution condition was met and Mann Whitney U test when it was not. Chi-square test was used to analyze the differences between the rates of categorical variables in independent groups. Statistical significance level was accepted as $p < 0.05$.

RESULTS

A total of 325 patients, 203 female (62.5%) and 122 male (37.5%), with alarm symptoms of upper GI tract cancers were included in the study. The

mean age of the patients was 50.8 ± 15.8 years. Patients were divided into two groups as under and over 45 years of age. Comorbid diseases were significantly higher in the group older than 45 years. Although smoking, alcohol and NSAID use were higher in the group over 45 years of age, this increase was not statistically significant. Among the alarm symptoms, weight loss and persistent vomiting were statistically significantly higher in the patients under 45 years of age than in the patients over 45 years of age, whereas the incidence of other alarm symptoms was similar between the groups. Demographic characteristics, comorbidities, habits and alarm symptoms of the study patients at admission are shown in Table 1.

Table 1 Demographic characteristics of the patients and alarm symptoms at admission

	Total n (%)	Under 45 Years Old n (%)	Over 45 Years Old n (%)	p
Number of patients, n (%)	325 (100)	109 (33.5)	216 (66.5)	
Female	203 (62.5)	69 (21.2)	134 (41.3)	
Male	122 (37.5)	40 (12.3)	82 (25.2)	
Comorbidities				
Hypertension	103 (31.7)	7 (2.1)	96 (29.5)	< 0.001
Diabetes mellitus	41 (12.6)	2 (0.6)	39 (12)	< 0.001
Cardiovascular disease	28 (8.6)	0 (0)	28 (8.6)	< 0.001
Chronic kidney disease	18 (5.5)	3 (0.9)	15 (4.6)	0.074
Cerebrovascular disease	11 (3.4)	1 (0.3)	10 (3.1)	0.030
Unhealthy lifestyle				
Smoking	45 (13.8)	16 (4.9)	29 (8.9)	0.758
Alcohol use	14 (4.3)	4 (1.2)	10 (3.1)	0.688
Alarm symptoms				
New-onset dyspepsia over 45 years of age	158 (48.6)	0 (0)	158 (73.1)	< 0.001
Weight loss	113 (34.8)	52 (47.7)	61 (28.2)	< 0.001
Iron deficiency anemia	101 (31.1)	33 (30.3)	68 (31.5)	0.824
Family history of upper GI cancer	64 (19.7)	26 (23.9)	38 (17.6)	0.180
Progressive dysphagia and/or odynophagia	51 (15.7)	17 (15.6)	34 (15.7)	1.000
Persistent vomiting	26 (8)	17 (15.6)	9 (4.2)	< 0.001
History of upper GI bleeding	13 (4)	4 (3.7)	9 (4.2)	1.000
Palpable abdominal or epigastric mass or abnormal lymphadenopathy	11 (3.4)	4 (3.7)	7 (3.2)	1.000

GI: Gastrointestinal. $p < 0.05$ was considered statistically significant.

Endoscopy and Pathology Results

The most common endoscopic findings were gastritis (82.8%), normal endoscopic findings (9.5%) and esophagitis (7.3%). Biopsy samples were obtained from 286 (88%) patients during endoscopy. The most common histopathologic findings were chronic gastritis in 262 patients (80.6%) and intestinal metaplasia in 27 patients (8.3%). Intestinal metaplasia was statistically significantly higher in the group over 45 years of age (11.1%) than in the group under 45 years of age (2.8%), while no significant difference was found between the groups in terms of other pathologic findings. The histopathologic findings of the endoscopic biopsy specimens are summarized in Table 2.

The Relationship Between the Presence of Malignancy and Alarm Symptoms

Of a total of 325 patients with alarm symptoms for upper GI malignancy, 8 (2.5%) were found to have malignancy [7 (2.2%) gastric cancer, 1 (0.3%) esophageal cancer]. Of the patients with cancer, 6 were male and 2 were female with a mean age of 62.75 ± 10.45 years (range 50-78 years). While cancer was detected in 6 of the 122 male patients

(4.9%), cancer was detected in only 2 of the 203 female patients (0.98%) ($p = 0.005$). One patient had only weight loss and one had only iron deficiency anemia. Other patients had more than one alarm symptom. The type of malignancy, demographic characteristics and alarm symptoms of patients with malignancy are summarized in Table 3.

The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of alarm symptoms for detecting malignancy were calculated separately. Among the alarm symptoms, unexplained weight loss (75%) and iron deficiency anemia (50%) had the highest sensitivity for predicting cancer, while palpable abdominal/epigastric mass or abnormal lymphadenopathy (LAP) (96.5%), upper GI bleeding (96.2%) and persistent vomiting (92.4%) had the highest specificity, respectively (Table 4).

DISCUSSION

We prospectively evaluated the endoscopic and histopathologic results of patients with alarm symptoms for upper GI cancers and found upper GI cancer in 2.5% of patients. Similar to our study, the incidence of upper GI cancer in patients with

Table 2 The histopathologic findings of the endoscopic biopsy specimens

Histopathologic Findings	Total n (%)	Age Group		p
		Under 45 Years Old n (%)	Over 45 Years Old n (%)	
Chronic gastritis	262 (80.6)	86 (26.5)	176 (54.1)	0.684
Intestinal metaplasia	27 (8.3)	3 (0.9)	24 (7.4)	0.018
Normal	9 (2.7)	4 (1.2)	5 (1.5)	0.490
Gastric cancer	7 (2.2)	0 (0)	7 (2.2)	0.100
Hyperplastic polyp	5 (1.5)	1 (0.3)	4 (1.2)	0.667
Eosinophilic duodenitis	2 (0.6)	2 (0.6)	0 (0)	0.112
Low-grade dysplasia	2 (0.6)	1 (0.3)	1 (0.3)	1.000
High-grade dysplasia	1 (0.3)	0 (0)	1 (0.3)	1.000
Esophageal cancer	1 (0.3)	0 (0)	1 (0.3)	1.000
Barrett's esophagus	1 (0.3)	0 (0)	1 (0.3)	1.000

Table 3 Type of malignancy, demographic characteristics and alarm symptoms of patients with malignancy

Patient No	1	2	3	4	5	6	7	8
Gender (Female/Male)	F	M	M	F	M	M	M	M
Age	52	69	78	74	50	65	54	60
Malignancy type								
1. Esophageal cancer								
2. Stomach cancer	1	2	2	2	2	2	2	2
New-onset dyspepsia over 45 years of age	-	-	-	+	-	-	+	+
Upper GI bleeding	-	-	-	-	-	-	+	-
Iron deficiency anemia	-	-	+	-	+	-	+	+
Progressive dysphagia and/or odynophagia	+	-	-	+	-	+	-	-
Persistent vomiting	-	-	+	+	-	-	-	-
Weight loss	+	+	-	+	-	+	+	+
Family history of upper GI cancer	-	-	-	-	-	-	-	-
Palpable abdominal/epigastric mass or abnormal lymphadenopathy	-	-	-	-	-	-	-	-

F: Female, M: Male, GI: Gastrointestinal.

Table 4 Sensitivity, specificity, positive predictive value, and negative predictive value of the alarm symptoms for predicting malignancy

Alarm Symptoms	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
New-onset dyspepsia over 45 years of age	37.5	51.1	1.9	97.0
GI bleeding	12.5	96.2	7.7	97.8
Iron deficiency anemia	50.0	69.4	4.0	98.2
Progressive dysphagia and/or odynophagia	37.5	84.9	5.9	98.2
Persistent vomiting	25.0	92.4	7.7	98.0
Significant weight loss	75.0	66.2	5.3	99.1
Family history of upper GI cancer	0	79.8	0	96.9
Palpable abdominal/epigastric mass or	0	96.5	0	97.5

GI: Gastrointestinal; PPV: Positive predictive value; NPV: Negative predictive value.

alarm symptoms has been reported between 0.5% and 4.7% in previous studies (7,10,11). In a study including 4664 patients in which age and alarm symptoms were evaluated in predicting upper GI cancer in patients with dyspepsia, a higher cancer prevalence was reported in patients with alarm symptoms compared to those without alarm symptoms (OR 22.3, 95% CI 10.5- 47.4; $p < 0.001$) (7). The incidence of upper GI cancers may vary be-

tween countries. In studies conducted in countries where upper GI cancers are relatively common and in which the role of alarm symptoms in the diagnosis of upper GI cancer was investigated, cancer prevalence rates (14.8% - 22.3%) much higher than our study were reported (9,12,13). This difference may be due to differences in the prevalence of upper GI cancer and *Helicobacter pylori* between regions or differences in study designs.

The incidence of upper GI cancers increases with age and most cases occur in individuals over 45 years of age (7,12). In our study, all patients with malignancy were over 45 years of age (mean age 62.75 years). In addition, the finding of intestinal metaplasia, which is a precancerous lesion, was statistically significantly higher in patients over 45 years of age than in patients 45 years and younger ($p=0.018$). In various studies similar to our study, it has been reported that the probability of cancer development in young patients is very low even if there is an alarm finding (7,14). Therefore, in the American College of Gastroenterology (ACG) and Canadian Association of Gastroenterology (CAG) guidelines, routine endoscopy is not recommended in dyspeptic patients under the age of 60 years only for the presence of alarm symptoms in order to exclude upper GI malignancies (4). In these guidelines, it was emphasized that the incidence of malignancy in patients under 60 years of age is very low ($< 1\%$), the positive predictive value of alarm features is low and endoscopy is not cost-effective even in the presence of alarm symptoms (6). On the other hand, in a meta-analysis including Asian dyspeptic patients, it was reported that 17.8% (95% CI: 10.90 - 29.00) of cancer patients were under the age of 45 years and 3.0% (95% CI: 2.50 - 3.50) were under the age of 35 years, and the optimal age threshold for endoscopy screening in Asia was suggested as 35 years (6). Recently, in a prospective observational study conducted by Kumari et al. in patients under 60 years of age with alarm features, they reported organic lesions (65.3%), including malignancy (15.6%) in a significant proportion of patients (12). Unlike American guidelines, European and Asian guidelines recommend immediate upper GI endoscopy to exclude malignancy in patients of any age presenting with dyspeptic and/or alarm symptoms (4,5). Therefore, patient age, geography, ethnic characteristics, family history, cost, procedure-related morbidity and mortality

should be taken into consideration when deciding on endoscopy in patients with alarm symptoms.

The presence of alarm symptoms has been an important determinant in prioritizing endoscopic evaluation of patients presenting with dyspepsia, as these factors are believed to indicate a higher likelihood of malignancy. In our study, the most common alarm symptoms were new-onset dyspepsia over 45 years of age (48.6%), weight loss (34.8%) and iron deficiency anemia (31.1%). In the study by Meineche-Schmidt et al. the most common alarm symptoms were dysphagia (28.6%), weight loss (27.6%) and fecal occult blood positivity (14.5%) (15). In another study by Bai et al. involving 15 235 patients with alarm symptoms, the most common alarm symptoms were reported as GI bleeding (33.2%), persistent vomiting (28%) and dysphagia (22.2%) (13). New-onset dyspepsia over forty-five years of age is considered an alarm symptom in areas with high prevalence of *Helicobacter pylori* (5,13). Therefore, the most common alarm symptom in our study differs from the literature data. In high-risk countries for *Helicobacter pylori* infection, the age limit accepted as the alarm symptom of dyspepsia should be kept low. In this way, we think that the early diagnosis of GI malignancies can be increased.

Although generally accepted, and many researches have been done in this area, the diagnostic value of alarm symptoms is still not clear (8,10). In our study, the alarm symptoms with the highest sensitivity were unexplained weight loss (75%) and iron deficiency anemia (50%), and those with the highest specificity were palpable abdominal/epigastric mass or abnormal lymphadenopathy (96.5%), upper GI bleeding (96.2%) and persistent vomiting (92.4%), respectively (Table 4). In our study, the sensitivity of alarm symptoms in predicting malignancy ranged between 12.5% and 75%, specificity between 51.1% and 96.5%, positive predictive value between 1.9% and 7.7%, and negative predictive

value between 96.9% and 90.1%. In a meta-analysis of 57 363 patients, Vakil et al. reported that the overall sensitivity and specificity of alarm features for predicting GI malignancy at endoscopy ranged from 0% to 83% and 40% to 98%, respectively (8). In a recent study by Kumari et al., the sensitivity of alarm features for predicting malignancy was reported to be between 17.4% and 78.3%, specificity between 37.9% and 95.2%, positive predictive value between 16.3% and 40% and negative predictive value between 85.4% and 92.4% (12). Similarly, Lee et al. reported the sensitivity of alarm features for predicting malignancy between 15% and 61%, specificity between 94% and 99%, positive predictive value between 12% and 67% and negative predictive value between 98% and 99% (14). In general, the sensitivity, specificity and positive predictive values of alarm features in predicting malignancy were found to be relatively low and negative predictive values were found to be high. The risk of upper gastrointestinal malignancy is very low in any individual without alarm symptoms.

Gastric and esophageal cancer is 2-3 times more common in the male gender than in the female gender (2,16). In our study, the rate of malignancy was higher in male patients ($p=0.005$). Of the 8 patients with malignancy, 75% were male. In a study by Lee et al. on 3926 patients, 70.7% of the patients were male (14). These data suggest that older men have the highest risk of upper GI malignancy and endoscopy should be considered regardless of the presence of alarm features. The higher prevalence of upper GI malignancy in the male sex compared to the female sex may be due to the higher use of alcohol and tobacco products in the male sex compared to the female sex. Reducing alcohol and tobacco consumption is important in reducing the prevalence of malignancy.

Although there are many studies on the diagnostic value of alarm symptoms on upper GI cancer,

the data obtained cause confusion. Our study was a prospective single-center study conducted in a tertiary care hospital to contribute to the evaluation of the role of alarm symptoms in the diagnosis of upper GI cancer. However, our study had some limitations. First, because the dates of our study coincided with the beginning of the covid 19 pandemic process, there were patients who did not undergo endoscopy among the patients planned to be included in the study, and our number of patients was lower than planned. Another limitation is that although our study was conducted in a tertiary referral center, it is a single-center study. Therefore, the results may not be representative of the community in general.

In conclusion, although alarm symptoms are generally considered as an indication to refer patients for endoscopy, our study showed that alarm symptoms are not of optimal value in the diagnosis of upper GI cancers. Advanced age and male gender were found to be more risky for malignancy in patients with alarm symptoms. The incidence of cancer in patients without alarm symptoms is negligible and medical treatment can be started in these patients without endoscopy. In other words, the absence rather than the presence of alarm symptoms would be more appropriate for follow-up with symptomatic treatment without endoscopy. Since alarm symptoms alone are not sufficient to predict upper GI cancers, each patient should be evaluated individually and multifactorial in terms of further investigation or initiation of symptomatic treatment. There is a need for studies on other risk factors and markers other than the classical generally accepted alarm symptoms that will enable early diagnosis.

Ethics: The study protocol was approved by the Karadeniz Technical University Ethics Committee, with the approval number 24237859-215 and date of 28.01.2020.

Conflicts of Interest: None of the authors have any potential conflicts of interest associated with this research.

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