Evaluation of the Relationship Between Alarm Symptoms and Pathological Findings in Upper Gastrointestinal System Endoscopy

Ozan Akıncı[1] , Emre Tunç[2]

[1]Department of General Surgery, İstanbul Kartal Dr. Lütfi Kırdar City Hospital, İstanbul, Turkey
[2]Department of General Surgery, Şırnak State Hospital, Şırnak, Turkey

Abstract

Objective: Dyspeptic symptoms constitute the majority of outpatient gastrointestinal consultations, yet most patients have no detectable malignancy or major upper gastrointestinal pathology. Alarm symptoms allow for an accurate selection of priority patients for endoscopy. This study examines the relationship between upper gastrointestinal alarm symptoms and histopathological findings.

Methods: The study prospectively evaluated 260 cases who underwent upper gastrointestinal endoscopy due to dyspepsia and alarm symptoms between July 2021 and January 2022. Patients' age, gender, symptoms, endoscopy reports, and histopathological findings of endoscopic biopsies were recorded. The correlation between alarm symptoms and malignancy was analyzed statistically.

Results: Male/female ratio was 57% to 43%, and the mean age was 41.50 years. Of these cases, 53.80% (n = 140) had at least 1 alarm symptom, while 46.10% (n = 120) had no alarm symptoms. Anemia was the most common alarm symptom, corresponding to 27.69% (n = 72) of the cases. Those with alarm symptoms had a higher incidence of malignancy ($P < .001$). The incidence of malignancy was significantly higher in patients aged ≥45 years and in patients with anemia, dysphagia, weight loss, melena, family history of gastric cancer, positive abdominal mass, and lymphadenopathy ($P < .05$). The malignancy rate was significantly higher in patients with 3 or more alarm symptoms ($P < .05$). Anemia and weight loss were found to be predictive factors for gastric cancer.

Conclusion: The risk of malignancy was higher in patients aged ≥45 years and in patients with anemia, dysphagia, weight loss, melena, family history of gastric cancer, abdominal mass, and lymphadenopathy symptoms and signs. In the presence of ≥3 alarm symptoms, the sensitivity was 100%.

Keywords: Alarm symptom, endoscopy, gastric cancer, malignancy

Introduction

Upper gastrointestinal system malignancies (UGSM) are one of the most common causes of cancer-related deaths.[1-3] The fact that the prognosis depends on the spread of the disease at the time of diagnosis reveals the importance of early diagnosis and treatment.[4] The early detection of premalignant lesions and the development of organ-preserving treatment methods have enabled endoscopy to play a leading role in the management of UGSM.[5]

Dyspepsia is defined as recurrent or persistent pain or discomfort centered in the upper abdomen. Guidelines recommend that dyspeptic patients over 55 years of age and patients with alarm symptoms (anemia, progressive dysphagia, weight loss, persistent vomiting, anorexia, bleeding, family history of gastrointestinal system (GIS) cancer, lymphadenopathy (LAP), and abdominal mass) undergo prompt endoscopy to rule out peptic ulcer disease, esophagogastric malignancy, and other rare upper GIS diseases.[6,7] On the other hand, the Asian guidelines recommend endoscopy in new-onset dyspeptic patients over 40 years of age in areas of high prevalence and over 45 and 50 years in areas of intermediate and low prevalence, respectively.[8] Turkey is considered an intermediate-risk country.[9] However, more than half of dyspeptic patients do not have an apparent structural abnormality, a condition called "functional" or "non-ulcer" dyspepsia.[5] Hence, performing endoscopy on all dyspeptic patients is very costly, and it is crucial to treat the low-risk patient empirically and perform endoscopy immediately in high-risk patients.[10]

This study aimed to investigate the correlation of alarm symptoms with endoscopic-histopathological findings and evaluate their predictive value, especially for malignancy.

Methods

This randomized prospective study included 260 cases who underwent upper GIS endoscopy between July 13, 2021, and January 31, 2022. Ethics committee approval was obtained from Kartal Dr Lutfi Kirdar City Hospital Clinical Research Ethics Committee (Date: 12.07.2021, approval number: 2021/514/205/5). Patients under 18 years of age with a history of previous upper GIS surgery, a known diagnosis of UGSM, a history of cirrhosis, esophageal variceal bleeding, and history of caustic agent use were excluded from the study.

The patients were questioned for the presence of alarm symptoms. Alarm symptoms were determined as anemia, dysphagia, weight loss, anorexia, melena, hematemesis, family history of UGSM, vomiting, abdominal mass, and lymphadenopathy.[6,11] Also, ≥45 years of age was considered as a risk factor.[8] Patients' age, gender, alarm symptoms, endoscopy reports,

and histopathological results of endoscopic biopsies were recorded and evaluated.

The distribution of alarm symptoms, the correlation of pathology results with the presence of any alarm symptoms and with individual alarm symptoms, the relationship between the number of alarm symptoms and malignancy, and the sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) of alarm symptoms were analyzed.

Statistical Analysis

Statistical Package for the Social Sciences software version 21.0 program was used for data analysis. Descriptive statistics were presented as the number of observations and percentages and compared with Pearson's Chi-square and Fisher's exact tests in 2 × 2 tables. The relationship between alarm symptoms and malignancy was examined; variables associated with malignancy were determined and introduced into multivariate logistic regression analysis as independent variables. Sensitivity, specificity, PPV, and NPV for malignancy were analyzed. A P-value below .05 was considered statistically significant.

Results

The mean age of 260 individuals included in the study was 41.5 years, and 42.7% were ≥45 years old. Fifty-seven percent of the patients were male, and 43% were female. At least 1 alarm symptom was observed in 53.8% (n = 140) of the cases, while 46.1% (n = 120) had no alarm symptoms. Anemia was the most common alarm symptom, corresponding to 27.69% (n = 72) of the cases. This was followed by dysphagia, anorexia, and melena (Table 1).

Investigation of any statistical relationship between the presence of alarm symptoms and the pathology results revealed that there was a significant relationship between the presence of alarm symptoms and the presence of malignancy, and the incidence of malignancy was higher in those with alarm symptoms ($P < .05$) (Table 2).

Anemia was the most common alarm symptom observed in chronic gastritis-, *Helicobacter pylori*-, and intestinal

Table 1. Distrubution of Alarm Symptoms and Risk Factors

	n	%
≥45 years old	111	42.69
Anemia	72	27.69
Dysphagia	44	16.92
Weight loss	20	7.69
Anorexia	27	10.38
Melena	26	10.00
Hematemesis	9	3.46
Family history of UGSM	13	5.00
Vomiting	8	3.08
Abdominal mass	4	1.54
LAP	2	0.77

UGSM, upper gastrointestinal system malignancy; LAP, lymphadenopathy.

Table 2. Alarm Symptoms—Pathology Findings Relationship

	Alarm Symptom				
	Yes		No		
	n	%	n	%	*p*
Malignancy	16	11.43	0	0.00	**<.001**
Chronic gastritis	79	56.43	93	77.50	**<.001**
Acute gastritis	14	10.00	13	10.83	.826
Intestinal metaplasia	9	6.43	14	11.67	.138
Helicobacter pylori	50	35.71	52	43.33	.210

Chi-square test.

metaplasia-positive cases (62%, 56%, and 44%, respectively). In acute gastritis, the most common alarm symptom was hematemesis (50%). There was no significant relationship between alarm symptoms and chronic gastritis, acute gastritis, intestinal metaplasia, and *H. pylori* ($P > .05$).

The incidence of malignancy was significantly higher in cases aged ≥45 years, with anemia, dysphagia, weight loss, melena, family history of gastric cancer, abdominal mass, and LAP-positive

Table 3. The Relationship of Risk Factors and Alarm Symptoms with Malignancy

	Malignancy				
	Yes		No		*p*
	n	%	n	%	
≥45 years old	14	87.50	97	39.75	**<.001**
Male/female	9/7	6.08/6.25	139/105	93.9/93.7	>.05
Anemia	14	(87.50)	58	(23.77)	**<.001**
Dysphagia	6	37.50	38	15.57	**.035**
Weight loss	13	81.25	7	2.87	**<.001**
Anorexia	4	25.00	23	9.43	.070
Melena	5	31.25	21	8.61	**.014**
Hematemesis	1	6.25	8	3.28	.441
Family history of UGSM	5	31.25	8	3.28	**<.001**
Vomiting	2	(12.50)	6	(2.46)	.080
Abdominal mass	4	25.00	0	0.00	**<.001**
LAP	2	12.50	0	0.00	**.004**
1 alarm symptom	0	0.00	41	16.80	.084
2 alarm symptoms	0	0.00	32	13.11	.232
≥3 alarm symptoms	16	100.00	49	20.08	**<.001**

Chi-Square test.
UGSM, upper gastrointestinal system malignancy; LAP, lymphadenopathy.

Table 4. Results of Multiple Logistic Regression Analysis of Alarm Symptoms

	B	SE	Sig.	Exp(B)	95% CI for EXP(B)	
					Lower	Upper
≥45 years old	0.684	1.180	0.562	1.982	0.196	20.017
Anemia	3.968	1.463	**0.007**	52.876	3.006	930.124
Dysphagia	1.297	0.977	0.184	3.657	0.539	24.808
Weight loss	6.025	1.435	**0.000**	413.468	24.821	6887.687
Melena	−1.112	1.296	0.391	0.329	0.026	4.167
Family history of UGSM	0.739	1.524	0.628	2.093	0.106	41.497
Constant	−8.028	1.911	0.000	0.000		

Multiple logistic regression analysis.
UGSM, upper gastrointestinal system malignancy; SE, standard error.

cells ($P < .05$). Patients with ≥3 alarm symptoms also had a statistically significantly higher malignancy rate ($P < .05$). Gender, anorexia, hematemesis, vomiting, and the presence of 1 or 2 alarm symptoms were not significantly associated with malignancy ($P > .05$) (Table 3).

After examining the relationship between alarm symptoms and malignancy, significant variables were included in the model as independent variables. Abdominal mass, LAP, and "3 or more alarm symptoms" variables were excluded because they distorted the model. Examination of the effect of alarm symptoms variables on malignancy determined anemia and weight loss parameters

Table 5. Sensitivity, Specificity, PPD, and NPD Values of Alarm Symptoms and Risk Factors in Terms of Malignancy

	Sensitivity	Specificity	PPV	NPV
≥45 years old	87.50	60.25	12.61	98.66
Anemia	87.50	76.23	19.44	98.94
Dysphagia	37.50	84.43	13.64	95.37
Weight loss	81.25	97.13	65.00	98.75
Anorexia	25.00	90.57	14.81	94.85
Melena	31.25	91.39	19.23	95.30
Hematemesis	6.25	96.72	11.11	94.02
Family history of UGSM	31.25	96.72	38.46	95.55
Vomiting	12.50	97.54	25.00	94.44
Abdominal mass	25.00	100.00	100.00	95.31
LAP	12.50	100.00	100.00	94.57
1 alarm symptom	0.00	83.20	0.00	92.69
2 alarm symptoms	0.00	86.89	0.00	92.98
≥3 alarm symptoms	100.00	79.92	24.62	100.00

PPV, positive predictive values; NPV, negative predictive values; LAP, lymphadenopathy; UGSM, upper gastrointestinal system malignancy.

to be predictive factors for malignancy (Table 4). The risk of malignancy increased 52.876 times in patients with anemia and 413.468 times in those with weight loss. Age, dysphagia, melena, and family history of gastric cancer variables were found to be insignificant ($P < .05$).

The sensitivity, specificity, PPV, and NPV values for both individual alarm symptoms and the number of alarm symptoms present are shown in Table 5. In the presence of ≥3 alarm symptoms, the sensitivity and NPV were calculated as 100%. The sensitivity of anemia and ≥45 years old was 87.5%.

Discussion

The presence of alarm symptoms not only in upper GIS neoplasms but also in benign conditions, such as peptic ulcer and *H. pylori* infection, has led to controversy over the diagnostic value of these symptoms. Especially, the fact that young UGSM patients also present with dyspepsia rather than alarm symptoms further complicates this issue.[12,13] These controversies have led to many studies determining the diagnostic value of alarm symptoms.[14,15]

In parallel with the literature, the most common alarm symptoms in the patients evaluated in our study were ≥45 years of age, dysphagia, anemia, and weight loss. We found a statistically high risk of malignancy in those with alarm symptoms. Madsen et al[16] reported that the use of endoscopy resources could be optimized, thanks to age (≥45 years), weight loss, nonsteroidal anti-inflammatory drug use, bleeding, and dysphagia findings. Lee et al[17] reported that despite their low sensitivity, the presence of alarm symptoms is helpful for the diagnosis of UGSM, and especially weight loss and dysphagia are associated with advanced gastric cancer. Contrary to these, a study conducted in Nigeria found no correlation between alarm symptoms and endoscopy findings in patients with dyspepsia.[18]

Literature suggests that the presence of at least 1 alarm symptom has a high PPV.[14] Similarly, Khademi et al[5] reported that 66.7% of patients with UGSM had at least 1 alarm symptom, while this rate was 38.9% in patients without cancer. Our study found no statistically significant increase in the incidence of UGSM in individuals with a single alarm symptom. On the other hand, malignancy was detected in all (100%) cases with ≥3 alarm symptoms.

Deciding to whom and when to perform endoscopy primarily requires careful cost–benefit analysis. Such analyses depend on the risk estimation model, but the possibility of overlooking a potentially treatable cancer should be considered if there is a

delay of several months in diagnosis and treatment. Therefore, in Asian societies where gastric cancers and *H. pylori* infection are common, patients over 35 years of age with dyspepsia or alarm symptoms are recommended to be referred for early endoscopic evaluation in the presence of alarm symptoms.[19] In contrast to Asian populations, cost-effectiveness analyses in the United States and Europe, where the incidence of UGSM and *H. pylori* are low, revealed that prompt endoscopy is not beneficial and that the "test and treat" approach is the most cost-effective strategy.[20]

In our study, the parameters with the highest sensitivity for UGSM were age ≥45, anemia, and weight loss. Anemia and weight loss were found to be predictive factors for malignancy. The 3 parameters with the highest PPV were abdominal mass, LAP, and weight loss. Besides, in the presence of ≥3 alarm symptoms, the sensitivity was 100%. Therefore, based on our findings, we think that each alarm symptom should be a warning in making a prompt and early endoscopy decision, and this process should be managed much more immediately in patients with ≥3 alarm symptoms.

Recent studies have indicated that male gender is the most significant risk factor for the development of gastric malignancy in the United States, with a nearly 2:1 male to female dominance.[21] Therefore, male gender appears to represent a predictor factor for gastric cancer. In the present study, in contrast to the literature, no statistically significant difference was found in terms of the incidence of malignancy between males and females.

The limitations of our study are the lack of long-term data on the patients and the unspecified cancer stages and localizations. In addition, only patients ≥45 years of age were categorized in our study. Not including other age ranges is another limitation of the study.

The risk of malignancy was higher in patients aged ≥45 years, with anemia, dysphagia, weight loss, melena, family history of gastric cancer, abdominal mass, and LAP symptoms and signs. In the presence of ≥3 alarm symptoms, the sensitivity was 100%. Anemia and weight loss are predictive factors for UGSM. These risk groups should be carefully determined, and they should undergo prompt endoscopy. Multicenter and large patient-based studies are needed to determine the predictive values of alarm symptoms and create diagnostic algorithms that can more accurately determine the need for endoscopy.

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