



FREQUENCY OF ALARMING FEATURES IN PATIENTS WITH UPPER GASTROINTESTINAL MALIGNANCY

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Name of Author:

¹Fazeela, ²Hafeezullah Shaikh, ³Raheela Khalid, ⁴Ajit Kumar Khemchandani

Affiliation: ¹Gastroenterology, Dow University of Health Sciences, Karachi, Pakistan.

²Gastroenterology, Dow University of Health Sciences, Karachi, Pakistan.

³Gastroenterology, Dow University of Health Sciences, Karachi, Pakistan.

⁴Gastroenterology, Dow University of Health Sciences, Karachi, Pakistan.

Corresponding Author:

Dr. Fazeela

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Abstract: Objective: To evaluate the frequency of alarming features in patients with upper gastrointestinal malignancy at a tertiary care gastroenterology unit, and to explore their association with age, sex and tumour site, including factors independently associated with dysphagia. **Methodology:** This Cross-sectional research was conducted at the Department of Gastroenterology, DUHS, Ojha Campus, Karachi, from August 2024 to February 2024. Patients aged 18 years or older were consecutively sampled for a total of 153 who were histologically proven to have an upper gastrointestinal malignancy. Eight ominous characteristics were noted as either being present or absent. The data were analysed by the chi-square test, Fisher's exact test and binary logistic regression test with a p-value of <0.05. **Results:** The median age was 50 (37.0–55.0) years, and 81 patients (52.9%) were men. Weight loss (75.2%) and dysphagia (64.1%) were the most frequent alarming features. Dysphagia was more frequent in women ($p = 0.020$) and remained independently associated with female gender (adjusted OR 2.38, $p=0.015$). Heartburn ($p = 0.005$) and gastro-oesophageal reflux disease ($p < 0.001$) increased with age. **Conclusion:** Alarming features were frequently present in patients with confirmed upper gastrointestinal malignancy, with weight loss and dysphagia predominating and overt bleeding uncommon. Dysphagia was independently more frequent in women, and reflux-related features became commoner with advancing age. These observations characterise the symptom pattern of proven disease in a local tertiary care population.

Keywords: Stomach Neoplasms, Esophageal Neoplasms, Deglutition Disorders, Weight Loss, Dyspepsia, Gastroesophageal Reflux; Endoscopy, Gastrointestinal

INTRODUCTION

Upper gastrointestinal (GI) malignancies are one of the most fatal solid malignancies in clinical practice, mainly carcinomas of the oesophagus and stomach, and they are responsible for a significant proportion of the cancer mortality in the world [1]. They have a multifactorial pathogenesis, in which chronic *Helicobacter pylori* (*H. pylori*) infection plays an

important role by inducing a sequence of events leading to gastric carcinoma, including atrophic gastritis and intestinal metaplasia, and dietary habits, tobacco, and environmental exposures play an additional, although less well-understood, role, especially when dietary factors are limited in low- and middle-income populations [2,3]. In Pakistan, delayed presentation and unequal access to screening

endoscopy exacerbate this burden, and data from the hospital in Karachi revealed a significant incidence of premalignant and malignant upper gastrointestinal lesions, though there was a greater male incidence with a preponderance of older individuals [4].

In routine clinical practice, gastroenterologists rely on a familiar pattern of symptoms to identify which dyspeptic patients may harbour an occult malignancy that warrants urgent endoscopy [5]. The traditional red flags include dysphagia, unintentional weight loss, gastrointestinal bleeding (haematemesis and melaena), persistent vomiting, iron deficiency anaemia and a palpable epigastric mass, and more recently, the guidelines for dyspepsia have included these in addition to age criteria as markers for rational use of upper GI endoscopy [5]. While heartburn and gastro-oesophageal reflux disease (GERD) are common and often insignificant, they can also be associated with or mistaken for malignant disease, so they may be confused in clinical triage at the initial encounter [6].

The diagnostic performance of alarm features has been examined extensively, yet the evidence remains inconsistent. A large systematic review concluded that, taken individually, these features possess only modest discriminatory power for upper GI malignancy, with wide variation in reported sensitivity and specificity [7]. Database and cohort studies have nonetheless confirmed that the presence of alarm features meaningfully raises the probability of significant endoscopic and malignant findings and that unexplained weight loss and dysphagia carry the strongest associations and tend to accompany more advanced disease [8,9,10,11]. On the other hand, in people without alarm signs, the yield of endoscopy is low, thereby favouring a more selective approach [12]. However, reports of malignancy developing many years after an interval of symptoms in younger patients highlight the fact that this time frame can be misleading [13,14].

Despite this copious literature from around the world, most studies have described alarm features in unselected dyspeptic patients and not in patients who have already been proven to have an upper gastrointestinal malignancy. Therefore, there is little information and virtually none in our own setting of how often each individual alarm feature occurs in patients with proven disease. Local documentation of this pattern will enable physicians to identify the subset of cases in their population that are more likely to present with red flag symptoms and prompt them to refer patients for timely endoscopy to improve an important evidence-based practice gap in their region. The present study was therefore conducted to determine the frequency of alarming features in patients with upper gastrointestinal malignancy at a tertiary care gastroenterology unit.

MATERIALS AND METHODS

This cross-sectional descriptive study was conducted after obtaining approval from the CPSP and ethical clearance from the institutional ERC (Ref: IRB-3944/DUHS/Approval/2025/287), and written informed consent was taken from every participant before enrolment. Patients of either sex aged 18 years or above who had an endoscopic lesion suspicious of upper gastrointestinal malignancy that was subsequently confirmed as malignant on histopathology, and who were willing to consent, were recruited through non-probability consecutive sampling. Patients with secondary or metastatic deposits from a known non-gastrointestinal primary, recurrent malignancy already receiving oncological treatment, previous upper gastrointestinal surgery likely to alter symptom presentation, or incomplete records and inconclusive histopathology were excluded. Upper gastrointestinal malignancy denoted a malignant neoplasm of the oesophagus, stomach or duodenum confirmed on histopathological examination of endoscopic biopsy specimens reported by a consultant histopathologist, and the anatomical location of the tumour was documented as the oesophagus, stomach or duodenum. The alarming features assessed for every patient comprised dyspepsia, dysphagia, melaena, haematemesis, vomiting, heartburn, weight loss amounting to at least 5% of usual body weight over the preceding six months, and gastro-oesophageal reflux disease, each recorded as present or absent on the basis of a focused history, physical examination and baseline investigations. The sample size of 153 was determined for a single population proportion at a 95% C.I, taking the anticipated proportion of malignant cases presenting with at least one alarming feature as (92%)¹¹ and an absolute precision of 4.3%. Data were collected by a single trained investigator using a structured proforma to minimise interobserver variation, with demographic details and the presence or absence of each alarming feature obtained at presentation, while the tumour site and endoscopic findings were extracted from the endoscopy and histopathology records and verified against the medical record, while histological type was recorded where available but was not analysed because it was not available for all participants. Data were analysed using SPSS-26. The normality of continuous variables was assessed with the Shapiro–Wilk test; normally distributed variables are presented as mean $\pm$ SD and skewed variables as median (IQR). Alarming features were reported as frequencies and percentages. Proportions were compared with the Pearson Chi-square test, and the Fisher exact test (Fisher–Freeman–Halton for the 3×2 site comparisons) was applied where an expected cell count was below five. Factors associated with dysphagia were examined by

binary logistic regression, with variables showing a univariate $p \leq 0.25$ entered into the multivariable model. A $p \leq 0.05$ was considered statistically significant.

RESULT

A total of 153 patients with histologically confirmed upper gastrointestinal malignancy were analysed. The median age was 50.0 years (IQR 37.0 to 55.0), and 25 patients (16.3%) were aged 60 years or above. Men formed a slight majority at 81 (52.9%), while 72 (47.1%) were women, and 91 participants (59.5%) resided in urban areas. The median body mass index was 25.0 kg/m² (IQR 21.0 to 28.0). The malignancy was located in the stomach in 115 patients (75.2%), the oesophagus in 34 (22.2%) and the duodenum in 4 (2.6%). The median family monthly income was PKR 30 000 (IQR 20 000 to 50 000), and the median duration of symptoms was 0.2 years (IQR 0.2 to 0.5). A family history of upper gastrointestinal malignancy was present in 44 patients (28.8%), while diabetes mellitus and hypertension were each recorded in 18 (11.8%) and smoking in 31 (20.3%), as shown in **Table I**.

Table II shows the distribution of each of the eight alarming features. The most common symptom was weight loss (75.2%), followed by dysphagia (64.1%) and vomiting (49.7%). Sixty-five patients (42.5%) reported dyspepsia, 54 (35.3%) reported heartburn, and 40 (26.1%) reported GORD. Melaena was seen in 28 patients (18.3%), while haematemesis was the least common feature, seen in only 12 patients (7.8%).

As shown in **Table III**, on stratification by age, heartburn was more common in patients aged 60 years or older than in younger patients (60.0% versus 30.5%, $p = 0.005$), and gastro-oesophageal reflux disease, similarly, showed a higher prevalence in the older age group (56.0% versus 20.3%, $p < 0.001$). By gender, females were more likely to have dysphagia compared to males (73.6% vs 55.6%, $p = 0.020$). Weight loss was different across the anatomical sites between the oesophageal, gastric and duodenal groups ($p = 0.007$, Fisher–Freeman–Halton exact test), with no patient in the small duodenal group reporting this feature, and this comparison should be interpreted with caution given the small duodenal subgroup ($n = 4$), as shown in **Table IV**.

Table V shows that female gender was independently associated with the outcome of dysphagia even after the adjustment, with an odds ratio of 2.38 ($p = 0.015$). Age of 60 years or older and smoking and family history were not associated on univariate screening and were not included in the final model.

Table I: Baseline Characteristics of Study Participants (n=153)		
Characteristics		
Age in years, Median (IQR)		50.0 (37.0–55.0)
Body Mass Index (kg/m ²), Median (IQR)		25.0 (21.0–28.0)
Family monthly income (PKR), Median (IQR)		30000 (20000–50000)
Duration of symptoms (years), Median (IQR)		0.2 (0.2–0.5)
Frequency %		
Gender	Male	81 (52.9%)
	Female	72 (47.1%)
Residential status	Urban	91 (59.5%)
	Rural	62 (40.5%)
Anatomical Location	Oesophagus	34 (22.2%)
	Stomach	115 (75.2%)
	Duodenum	4 (2.6%)
Age ≥60 years		25 (16.3%)
Family History of Upper GI Malignancy		44 (28.8%)
Diabetes Mellitus		18 (11.8%)
Hypertension		18 (11.8%)
Smoking (current)		31 (20.3%)

Table II: Distribution of Alarming Features (n=153)	
Alarming Features	n (%)
Dyspepsia	65 (42.5)
Dysphagia	98 (64.1)
Melaena	28 (18.3)
Haematemesis	12 (7.8)
Vomiting	76 (49.7)
Heartburn	54 (35.3)
Weight loss	115 (75.2)
Gastro-oesophageal reflux disease	40 (26.1)

Table III: Comparison of Alarming Features with Age and Gender (n=153)			
Alarming Features	Age Groups		P-value
	<60 yr (n=128)	≥60 yr (n=25)	
Dyspepsia	50 (39.1%)	15 (60.0%)	0.053
Dysphagia	83 (64.8%)	15 (60.0%)	0.644
Melaena	26 (20.3%)	2 (8.0%)	0.255
Haematemesis	9 (7.0%)	3 (12.0%)	0.416
Vomiting	60 (46.9%)	16 (64.0%)	0.117
Heartburn	39 (30.5%)	15 (60.0%)	0.005
Weight loss	94 (73.4%)	21 (84.0%)	0.264
Gastro-oesophageal reflux disease	26 (20.3%)	14 (56.0%)	<0.001
Alarming Features	Gender		P-value
	Male (n=81)	Female (n=72)	
Dyspepsia	35 (43.2%)	30 (41.7%)	0.847
Dysphagia	45 (55.6%)	53 (73.6%)	0.020
Melaena	16 (19.8%)	12 (16.7%)	0.622
Haematemesis	9 (11.1%)	3 (4.2%)	0.111
Vomiting	42 (51.9%)	34 (47.2%)	0.568
Heartburn	33 (40.7%)	21 (29.2%)	0.135
Weight loss	61 (75.3%)	54 (75.0%)	0.965
Gastro-oesophageal reflux disease	24 (29.6%)	16 (22.2%)	0.298

“Values are n (%). p-values from the Pearson chi-square test, with the Fisher exact test used where an expected cell count was below five (melaena and haematemesis by age group). $p < 0.05$ was considered statistically significant.”

Table IV: Comparison of Alarming Features with Anatomical Site (n=153)				
Alarming Features	Oesophagus (n=34)	Stomach (n=115)	Duodenum (n=4)	P-value
Dyspepsia	11 (32.4%)	52 (45.2%)	2 (50.0%)	0.397
Dysphagia	25 (73.5%)	72 (62.6%)	1 (25.0%)	0.115
Melaena	5 (14.7%)	21 (18.3%)	2 (50.0%)	0.239
Haematemesis	2 (5.9%)	9 (7.8%)	1 (25.0%)	0.386
Vomiting	17 (50.0%)	58 (50.4%)	1 (25.0%)	0.745
Heartburn	11 (32.4%)	42 (36.5%)	1 (25.0%)	0.880
Weight loss	26 (76.5%)	89 (77.4%)	0 (0.0%)	0.007
Gastro-oesophageal reflux disease	6 (17.6%)	33 (28.7%)	1 (25.0%)	0.430

“Values are n (%). p-values from the Fisher–Freeman–Halton exact test, applied because the small duodenal subgroup (n=4) produced expected cell counts below five in these 3×2 comparisons. $p \leq 0.05$ was considered statistically significant.”

Table V: Regression Analysis of Factors Associated with Dysphagia (n=153)

Predictor	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Age ≥60 years (vs <60)	0.81 (0.34–1.96)	0.645	—	—
Female (vs male)	2.23 (1.13–4.42)	0.021	2.38 (1.19–4.76)	0.015
Oesophageal site (vs gastric/duodenal)	1.75 (0.75–4.08)	0.195	1.97 (0.83–4.70)	0.125
Smoking (vs none)	1.23 (0.53–2.84)	0.632	—	—
Family history (vs none)	1.12 (0.54–2.34)	0.761	—	—

“Odds ratios from binary logistic regression for the presence of dysphagia. Variables with a univariate $p < 0.25$ (female sex and oesophageal site) were entered into the multivariable model; a dash denotes variables not entered. $p < 0.05$ was considered statistically significant.”

DISCUSSION

Upper gastrointestinal malignancy is still a late diagnosis with a high mortality rate and weight of symptoms leading to endoscopy referral [1,15]. A well-defined set of alarm features is used by clinicians as indicators of which patients with dyspepsia should have urgent investigation [5]. However, they have been questioned, as a large systematic review revealed that the sensitivity and specificity of individual alarm features are quite variable among populations and have low discriminatory power for malignancy [7]. A large proportion of this evidence is derived from unselected dyspeptic populations instead of proven cancer patients. In the present study, the frequencies of each of the alarm features were examined in a group of children with a confirmed diagnosis of disease on histological examination to describe the local patterns of presentation.

The median age of 50 years and slight male predominance reported here are consistent with those reported in other areas for upper gastrointestinal cancer [4,16]. There were age and gender variations between centres and tumour types, with a similar mean age being described in a Karachi series of oesophageal carcinoma, with a female preponderance [17]. Weight loss was the most prevalent alarm feature, reported by 75.2% of patients, like the 76% observed in a prospective series of malignant patients [9] and with cohort data which associated unexplained weight loss with important endoscopic findings [10]. This concordance confirms that weight loss is a reliable indicator of malignancy, not a random occurrence.

Dysphagia (64.1%) was the second most common symptom, consistent with other studies which show that dysphagia and weight loss are most associated with malignant and advanced disease [11]. Dysphagia is also the major presenting complaint reported in Pakistani studies of oesophageal carcinoma [16,18]. Dyspepsia and heartburn were intermediate (15.6%), vomiting (15.6%) and melaena (18.3%) were uncommon, while haematemesis (7.8%) was very

rare. The incidence of overt bleeding was also relatively low, reflecting the results of other studies of databases in which overt bleeding was a rare but important mode of presentation [8].

Gastro-oesophageal reflux disease was documented in 26.1% of patients, a proportion above the pooled global prevalence of around 14% estimated in a large meta-analysis [19], this is not surprising in a population with an upper gastrointestinal disease. Reflux symptoms can be like malignant symptoms and can lead to delayed diagnosis when confused with benign disease [6]. The dominance of gastric tumours and of distal subsites is consistent with the noncardia pattern seen across many developing populations, where *H. pylori* is the principal pathway [2,15]. These mechanisms help explain why dyspeptic and reflux-type symptoms featured prominently in the cohort.

Stratified analysis identified two associations that were statistically significant. Dysphagia occurred more commonly in women than in men, and the trend remained true in the regression model, with female gender having an adjusted odds ratio of 2.38 for dysphagia. This finding could be attributed to a meta-analysis that showed gastric cancers occurred more often in women, and women more frequently had distal and diffuse tumours, which might affect symptom presentation [20]. Like the higher prevalence of reflux with age, heartburn and reflux disease is significantly more prevalent in patients older than 60 years [19]. Weight loss also differed among tumour sites, with the tiny subgroup of duodenal tumours having limits to interpretation.

The main advantage of the study is that the patients had a confirmed malignancy with a histological diagnosis and the use of a single trained investigator and a standardised proforma, eliminating the diagnostic uncertainty seen in unselected dyspeptic samples. There are some caveats, however, to the findings. Because of the single-centre and cross-sectional design, generalisability is limited, and the consecutive sampling technique might cause selection bias. Histological type was known but not included in

the regression. Duodenal and elderly subgroups were small, making it difficult to make precise estimates involving them. There are ongoing calls for additional local data like this [12,21].

Collectively, the results indicate that alarm features are prevalent in cases with confirmed upper gastrointestinal malignancy, most manifested as weight loss and dysphagia and less commonly as frank bleeding. The pattern follows the general literature, and the local pattern is supplemented with setting-specific detail. Knowing the frequency of each feature in a proven disease can help local physicians have greater confidence in the features that warrant prompt endoscopic evaluation [5,7].

CONCLUSION

Alarming features were common among patients with confirmed upper gastrointestinal malignancy, with weight loss and dysphagia the most frequent and overt gastrointestinal bleeding the least. Dysphagia was independently more frequent in women, while heartburn and gastro-oesophageal reflux disease increased with age. These findings describe how alarm features present in established disease within this population.

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