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Utility of Red Flag Symptoms in Prediction of Malignancy in Elderly Patients with Dyspepsia

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Abstract

Introduction: *The elderly vulnerable population is increasing world-wide. Dyspeptic symptoms are common in the general population; with frequencies ranging from 10% to 45%. Red flags or alarm symptoms can be useful to predict malignancy in elderly patients undergoing upper GI endoscopy.*

Aim: *To evaluate the efficacy of red flag symptoms for prediction of abnormal endoscopic findings, especially malignancy, in elderly population with upper GI symptoms.*

Materials and Method: *We evaluated 288 consecutive eligible elderly patients undergoing routine upper GI endoscopy (UGIE) for dyspepsia over a period of 1 year, for presence of red flag or alarm symptoms (vomiting, dysphagia, weight loss, blood loss and abdominal lump). Significant co-morbidities were excluded.*

Results: *Mean age of the patients was 66.81 ±5.32 years. Epigastric pain/discomfort (38.88%) was the most common dyspeptic symptom. Presence of acute (melena or GI bleed) or chronic blood loss, in the form of iron deficiency anemia was the most common (26.38%) alarm (red flag) symptom in the study population. Unintentional weight loss was seen in 20.48% patients, persistent / delayed vomiting was seen in 11.8% while, abdominal lump was present in 2.77% patients. The most common benign findings were gastritis in 38.88% patients, GERD in 17.7% patients, duodenal ulcer in 12.84% and gastric ulcer in 2.08% patients*

Overall, 13.19% patients had findings of malignancy on upper GI endoscopy in the form of esophageal malignancy in 8.33% cases, gastric malignancy in 3.12% patients and GE junction malignancy in 1.73%.

Conclusion: *The red flag symptom of dysphagia had the highest sensitivity, specificity, positive as well as negative predictive value for occurrence of esophageal malignancy. Finding of significant lesion may be higher in elderly population.*

Keywords: *Red flags, alarm symptoms, dyspepsia, elderly, upper GI endoscopy.*

Introduction

Dyspepsia is an umbrella term, encompassing one or more of the following episodic or persistent symptoms, viz. post-prandial fullness, easy satiety and epigastric pain or burning sensation[1]. Dyspepsia remains a very commonly encountered problem[2] with majority of patients rarely seeking medical advice, only about one fifth of patients consult their general practitioner[3].

Elderly population worldwide has shown a rising trend. By 2050, global life-expectancy at birth is projected to increase by almost eight years, climbing from 68.6 years in 2015 to 76.2 years in 2050. The oldest population in some Asian and Latin countries is being predicted to quadruple by 2050. According to population census 2011, there are about 104 million elderly persons (aged 60 years or more) in India. 9.9% population of the state of Maharashtra belongs to this age-group. Though the patho-physiology of dyspepsia is not expected to change in the elderly; malignant diseases and use of medications for co-morbidities is common in the elderly[4].

Certain symptoms have been earmarked over several years as "red flags" or pretenders of organic pathology in patients with dyspepsia. The investigation of choice for dyspepsia is UGIE, which allows for detection and characterization of benign as well as malignant lesions of esophagus, stomach and duodenum.

Considering this fragile elderly population and their special requirements, we endeavor to elucidate the utility of red flag symptoms to predict abnormal upper GI endoscopy findings in elderly population.

Material and Methods

Consecutive elderly patients (aged 60 years or more) with upper GI symptoms, which included dyspeptic symptoms (e.g., postprandial fullness, early satiety, localized epigastric pain, diffuse epigastric pain, belching, nocturnal/fasting pain, abdominal distention) and/or gastro-esophageal symptoms (heartburn, regurgitation etc), attending the out-patient department over a one year period (February 2014-January 2015) were included in this study. Informed consent was taken. The study was approved by the institutional ethics committee.

The definition of dyspepsia refers to any condition or disease in which there are upper abdominal symptoms including upper abdominal pain or discomfort, loss of appetite, heartburn, regurgitation, bloating, early satiety or belching. The investigation of alarm features in this study included the following five alarm features – persistent vomiting, dysphagia, weight loss (more than 5 kg), acute or chronic blood loss (melena, hematemesis, iron deficiency anemia), and abdominal lump.

Patients presenting with at least two weeks duration of dyspeptic symptoms were included. Detailed history was taken and a thorough physical examination was performed. Patients underwent trans-abdominal US and routine blood tests like, CBC, LFT, KFT & FBS before the UGIE. Detailed evaluation with respect to presence of red flags was obtained and the patients were subjected to the upper GI endoscopy after obtaining informed consent.

Patients with significant co-morbidities (CKD, CLD, CCF, pre-existing malignancies), those with recent (within past 1 month) use of antibiotics, those with concurrent NSAIDs use, those who have undergone previous abdominal surgeries, those with known malignancies (past/present) were excluded from the study. Indoor admitted patients (to some other hospital) were also excluded from the study.

Results

A total of 288 patients were included in the study during the study period. Out of these 288 cases, 178 (61.81%) patients were male and 102 (38.19%) were female. The male to female ratio was 1.61:1. Mean age of the patients was 66.81 ±5.32 years.

Table-1: Prevalence of upper GI symptoms in the elderly

Sr. no.	Upper GI symptom	Prevalence (n)	Prevalence (%)
1	Heartburn	82	28.47
2	Reflux	15	5.20
3	Epigastric discomfort	112	38.88
4	Postprandial fullness	53	18.40
5	Abdominal bloating	67	23.26
6	Belching	42	14.58
7	Early satiety	39	13.54
8	Anorexia	27	9.37
9	Nausea	30	10.41

Amongst all the elderly patients, included in the study, epigastric pain/discomfort (38.88%) was the most common dyspeptic symptom, while 28.47% of the patients had heartburn, 23.26% patients had abdominal bloating, 18.4% patients had post-prandial fullness, 14.58% had belching, 13.54% patients had early satiety, while 10.41%, 9.37% and 5.2% patients had nausea, anorexia and reflux, respectively.

Table-2: Prevalence of red flag symptoms in the elderly

Sr. no.	Red flag symptom	Prevalence (n)	Prevalence (%)
1.	Vomiting	55	19.09
2.	Dysphagia	34	11.80
3.	Unexplained weight loss	59	20.48
4.	Acute or chronic blood loss	76	26.38
5.	Abdominal lump	8	2.77

Presence of acute (melena or GI bleed) or chronic blood loss, in the form of iron deficiency anemia was the most common (26.38%) alarm (red flag) symptom in the study population. Unintentional weight loss was seen in 20.48% patients, persistent / delayed vomiting was seen in 11.8% while, abdominal lump was present in only 8 (2.77%) patients.

Table-3: Upper GI endoscopy findings in the elderly

Sr. no.	Upper GIE findings	Prevalence (n)	Prevalence (%)
1.	Erosive GERD	51	17.70
2.	Hiatus hernia	30	10.41
3.	Gastritis	112	38.88
4.	Duodenitis	47	16.31
5.	Gastric ulcer	23	7.98
6.	Duodenal ulcer	37	12.84
7.	Esophageal malignancy	24	8.33
8.	GE junction malignancy	05	1.73
9.	Gastric malignancy	09	3.12
10.	Esophageal / gastric varices	06	2.08

187 out of 288 (64.93%) patients had 1 or more findings on upper GI endoscopy. The most common benign findings were gastritis in 112 (38.88%) patients, GERD in 51 (17.7%) patients, duodenitis in 47 (16.31%) cases, duodenal ulcer in 37 (12.84%), hiatus hernia in 30 (10.41%) patients. Gastric ulcer was seen in 06 (2.08%) patients, while 06 (2.08) patients had gastro-esophageal varices.

Among the patients with red flag sign, 69.23% had significant benign abnormal endoscopic findings. Presence of red flags had a sensitivity of 35.19%, specificity of 74.3%, PPV of 69.23% and NPV of 41.11% for detection of benign upper GI lesions.

38 (13.19%) patients had findings of malignancy on upper GI endoscopy in the form of esophageal malignancy in 24 (8.33%) cases, gastric malignancy in 9 (3.12%) patients and GE junction malignancy in 5 (1.73%, all adenocarcinoma). For purpose of analysis GEJ and gastric cancers were clubbed together (n=5+9=14).

Table-4: Red flag symptoms as predictors of esophageal malignancy in elderly

Red flag symptom	Esophageal malignancy +nt (n=24)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	χ2-value (p value)
Vomiting (n=55)	14	58.33	84.47	25.45	95.71	26.09 (p=0.0001,S)
Dysphagia (n=34)	19	79.17	94.32	55.88	98.03	114.10 (p=0.0001,S)
Unexplained weight loss(n=59)	16	66.67	83.71	27.12	96.51	34.28 (p=0.0001,S)
Acute or chronic blood loss(n=76)	11	45.83	75.38	14.47	93.87	5.08 (p=0.024,S)
Abdominal lump(n=8)	1	4.16	97.35	12.50	91.79	0.18 (p=0.66,NS)

(S= Significant, NS= Not significant)

Presence of dysphagia was highly significantly associated with the occurrence of esophageal malignancy, while presence of abdominal lump was not associated with the occurrence of esophageal malignancy. The red flag of dysphagia had the highest sensitivity (79.17%), specificity (94.32%), positive (55.88%) as well as negative predictive value (98.03%) for occurrence of esophageal malignancy.

Table-4: Red flag symptoms as predictors of GEJ and gastric malignancy in elderly

Red flag symptom	Gastric and GEJ malignancy (n=14)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	χ2-value (p value)
Vomiting (n=55)	10	71.43	83.58	18.18	98.28	26.08 (p=0.0001,S)
Dysphagia (n=34)	3	21.43	88.69	8.82	95.67	1.30 (p=0.25,NS)
Unexplained weight loss(n=59)	10	71.43	82.12	16.95	98.25	23.44 (p=0.0001,S)
Acute or chronic blood loss(n=76)	11	78.57	76.28	14.47	98.58	20.63 (p=0.0001,S)
Abdominal lump(n=8)	7	50	99.64	87.50	97.50	121.5 (p=0.0001,S)

(S= Significant, NS= Not significant)

In case of GEJ and gastric malignancy, presence of abdominal lump, though rare, had the highest specificity of 99.64. The red flag of "acute or chronic blood loss" had the highest sensitivity (78.57%) for occurrence of these malignancies.

Discussion

Elderly patients represent a vulnerable and ever increasing subset of world population. The needs and psycho-social needs of these patients are different than the working population of the young and middle age. 10% of overall[5] patients consulting a general practitioner because of dyspepsia report one or more alarm symptom.

Alarm symptoms have been variously evaluated for predicting upper GI endoscopy findings. However, co-relation is at best tenuous for minor upper GI endoscopy findings. Jones et al.[6] studied 7,62,325 patients aged 15 or older. The association of four alarm symptoms (hematuria, hemoptysis, dysphagia, rectal bleeding) with either cancer or non-cancer diagnoses within 90 days, was 22.6% (21% to 24.3%) for dysphagia. In another study, Jones et al.[7] observed 5999 new diagnoses of dysphagia, 150 males had esophageal cancer (PPV = 5.7%, 4.9% to 6.7%) and 81 in females (PPV=2.4%, 1.9 to 3.0%). Bai Y et al.[8] did a database review of 102,665 patients. They found that among the 4362 patients with malignancy, 52% had alarm features. Among those with alarm features, 14.8% were found to have upper GI malignancy. Overall, 4.2% patients had upper GI malignancies. Prevalence of malignancies increased from 0.6% in patients <35 years old to 18% in those >75 years old. Presence of dysphagia had a positive likelihood ratio >10 for malignancy prediction. All the four alarm features had a very high specificity (ranging from 95.3% to 97.8%) and NPV (ranging from 95.8% to 96.9%). In our study the NPV of these five "red flags" ranged from 91.79 to 98.03%. Similarly, the specificity was high and ranged from 83.71 to 97.35%.

Richter J[9] reviewed 3,667 patients undergoing upper GI endoscopy for dyspeptic symptoms and found that 33.6% patients had normal findings, 23% had GERD, 20% had gastritis, 19% ulcers, and 2% of the patients had malignancy. However, Lockhart[10], found presence of malignancy in 33% of elderly patients with dyspepsia. We found that 13.19% elderly patients with dyspepsia had findings of malignancy in the form of esophageal malignancy in 8.33%, gastric malignancy in 3.12% and GE junction malignancy in1.73%. The prevalence and incidence of esophageal cancer is increased in the elderly, partly due to higher frequency of chronic esophagitis and prolonged smoking and/or alcohol abuse. Similarly, the

prevalence and incidence of gastric cancer is also increased, partly due to a higher frequency of gastric ulcers and prolonged exposure to H. pylori, which leads to atrophic gastritis and mucosal metaplasia.

Kapoor et al.[11] evaluated a cohort of 1785 patients with a mean age of 59 years. Occurrence of cancer was seen in 3.8%; and serious benign pathology in 12.8%. Dysphagia (odds ratio (OR) 3.1), weight loss (OR 2.6), and age >55 years (OR 9.5) were found to be significant predictive factors for cancer but the value of other accepted alarm features was more limited.

Meineche-Schmidt et al. observed the consequence of such alarm symptoms prospectively over a period of 3 years. During this period patients with alarm symptoms were found to have a malignancy in 4%, peptic ulcers in 11% and minor gastrointestinal diseases in 25% of cases [5].

Murray et al.[12] studied 200 patients and found that dysphagia had a sensitivity, specificity, positive predictive value and negative predictive value of 98.4%, 9.3%, 11.8% and 98.0% respectively in predicting the occurrence of esophageal malignancy (seen in 11% patients with dysphagia). Age >60 years, male gender and shorter (<8weeks) duration of symptoms were associated with a higher risk of malignancy. In our study, dysphagia had the highest sensitivity (79.17%), specificity (94.32%), positive (55.88%) as well as negative predictive value (98.03%) for occurrence of esophageal malignancy. Overall, these red flags in our study had a sensitivity of 84.21%, specificity of 76.4%, PPV of 35.16% and NPV of 96.95% for detection of upper GI malignancy.

Conclusion

Dyspepsia is a very common problem in general practice. 25 to 40% of adults in the general population have dyspeptic symptoms. Red flag signs are important predictor of having abnormal endoscopic findings. Use of alarm symptoms could be helpful in prioritizing the resources like UGIE, by helping in predicting ominous diseases.

However, these alarm symptoms, other than few like recent onset dysphagia with weight loss, need further refining and incorporation in predictive models for clinical use.

This study was carried out in a tertiary care setup and hence may include a selection bias. The H.pylori infection status was not available for this study. Inclusion of rare "red flag" of abdominal lump might have affected the statistical analysis of other red flags. The present study only included patients who were referred for endoscopy. So, a referral bias may have crept in the study. A larger population based study could further clarify the matter.

In conclusion, for dyspeptic elderly patients, alarm features, except for dysphagia, were less accurate for prediction of malignancy. However, due to wide availability and relatively low cost for upper GI endoscopy in India, as compared to Western countries, prompt endoscopy may be recommended in this vulnerable population, especially those with these "red flags".

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