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ORIGINAL ARTICLE

Retrospective Cohort Study

Yield of alarm features in predicting significant endoscopic findings among hospitalized patients with dyspepsia

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Abstract

BACKGROUND

Dyspepsia is a very prevalent upper gastrointestinal tract symptoms complex. Some of these symptoms might arise from serious underlying diseases, so the promotion of evidence-based guidelines could potentially better align evaluation and treatment.

AIM

To determine the value of alarm features as a predictive factor for significant endoscopic findings (SEFs) among hospitalized patients presenting with dyspepsia.

METHODS

We conducted a retrospective case-control study including information about 6208 endoscopic procedures performed for hospitalized patients. Patients were divided into two groups, with and without SEFs, and compared to elucidate the ability of the different alarm features to predict SEFs.

RESULTS

During the study, 605 patients fulfilled the inclusion criteria. When the demographics and clinical characteristics of the two groups were compared, tachycardia ($P < 0.05$), normocytic anemia, ($P < 0.05$), leukocytosis ($P < 0.05$), and hypoalbuminemia ($P < 0.05$) documented on admission prior to endoscopy were strong predictors of SEFs. Among the alarm features, upper gastrointestinal bleeding, persistent vomiting, odynophagia [odds ratio (OR) = 3.81, $P < 0.05$; OR = 1.75, $P = 0.03$; and OR = 7.81, $P = 0.07$, respectively] were associated with SEFs.

Unexplained weight loss was strongly associated with malignancy as an endoscopic finding (OR = 2.05; $P < 0.05$). In addition, long-term use of anti-aggregate medications other than aspirin ($P < 0.05$) was correlated to SEFs.

CONCLUSION

Novel predictors of SEFs were elucidated in this study. These parameters could be used as an adjunctive in decision making regarding performing upper endoscopy in hospitalized patients with dyspepsia.

Key Words: Dyspepsia; Endoscopy; Weight loss; Anti-aggregate medications; Persistent vomiting; Odynophagia

Core Tip: Dyspepsia is a common symptom complex necessitating medical consultation. Alarm features usually guide the necessity of performing upper endoscopy in the outpatient settings. Upper endoscopy and data regarding alarm features in hospitalized patients with dyspepsia are lacking. We found that tachycardia, persistent vomiting, normocytic anemia, upper gastrointestinal bleeding, leukocytosis, and hypoalbuminemia were strongly associated with significant endoscopic findings. Unexplained weight loss and abnormal computed tomography findings were strongly associated with malignancy. This is the first study exploring alarm features in hospitalized patients with dyspepsia. Our findings might guide physicians in prioritizing hospitalized patients for upper endoscopy performance.

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INTRODUCTION

Dyspepsia is a medical term used to describe a wide range of upper gastrointestinal symptoms associated with difficult digestion. According to Rome IV criteria, dyspepsia is defined as any combination of early satiation, postprandial fullness, epigastric pain, and epigastric burning, occurring at least 3 days per week for 3 months and severe enough to disturb usual activities[1]. The prevalence of dyspepsia in the Western world is approximately 20% to 25%, thus creating a very high economic and social impact for the health care service[2]. The incidence of dyspepsia approaches 1.5%[3]. Dyspepsia is subdivided based on underlying etiology into organic and functional dyspepsia. Organic dyspepsia is a result of peptic ulcer, gastroesophageal reflux disease, gastric or esophageal cancer, pancreatic or biliary disorders, intolerance to food or drugs, and other infectious or systemic diseases. However, functional dyspepsia refers to dyspeptic symptoms present after ruling out organic pathology[4]. The use of alarm features, which constitute recent onset dyspepsia, unexplained weight loss, dysphagia, persistent vomiting, odynophagia, upper gastrointestinal bleeding (UGIB), iron deficiency anemia, epigastric mass or lymphadenopathy, and a family history of upper gastrointestinal malignancy, as a predictive factor for endoscopic finding is a matter of dispute[5,6]. Significant endoscopic findings (SEFs) are defined as peptic ulcer disease (PUD), erosive esophagitis class B or higher, malignancy, stricture, or findings requiring specific therapy[7]. A previous study evaluated the yield of alarm features in predicting SEFs in the outpatient setting and showed that age > 55 years and classical alarm features were associated with SEFs[8].

Our study evaluated the alarm features as a predictive factor for SEFs among hospitalized patients presenting with dyspepsia.

MATERIALS AND METHODS

Study design

This was a retrospective case-control study using a database of Galilee Medical Center in Nahariya, Israel. All patients between the ages of 18 years and 94 years, who underwent upper endoscopy as part of hospitalization at the Galilee Medical Center for investigating dyspepsia during 10 years beginning at January 1, 2012 through December 31, 2021, were found eligible and included in the study. Exclusion criteria were patients who underwent endoscopy due to a cause other than investigating dyspepsia, and patients with proven pre-procedure upper gastrointestinal diagnosis.

We extracted information about all endoscopic procedures performed at the gastroenterology unit, patients' medical records, indications, and findings. Then patients were divided into two groups, with and without SEFs, and compared to elucidate the ability of the different alarm features to predict SEFs. Of the 6208 patients, 605 fulfilled the inclusion criteria (174 patients with SEFs while 431 without); and 5603 patients were excluded due to referral causes other than dyspepsia such as iron deficiency anemia, UGIB, liver cirrhosis, post-operative abdominal pain mainly mini gastric bypass, investigation of weight loss, or other constitutional symptoms.

Ethics

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the human research committee of each institution (Approval No. 0189-21-NHR). Written informed consent was waived by the local ethical committees due to the retrospective non-interventional nature of the study.

Study variables

Main dependent variable: SEFs defined as having PUD, erosive esophagitis class B or higher, malignancy, stricture, or findings requiring specific therapy.

Main independent variables: (1) Alarming signs included recent onset dyspepsia, unexplained weight loss, dysphagia, persistent vomiting, odynophagia, UGIB, iron deficiency anemia, epigastric mass or lymphadenopathy and a family history of upper gastrointestinal malignancy. Patients were categorized according to their alarm features. First, if they had alarm features or not. Second, if they did, which type of alarm features they had; (2) Patient age in years; and (3) Extracted data included demographics, sex, medications (proton pump inhibitors, non-steroidal anti-inflammatory drugs, aspirin, statin, anticoagulant, anti-aggregate), family history of upper gastrointestinal malignancy, physical finding including blood pressure and pulse, palpable mass or lymphadenopathy, laboratory parameters including complete blood count, C-reactive protein (CRP), liver function test, albumin, radiologic findings (if available), relevant anamnestic information such as duration and quality of symptoms.

Statistical analysis

Continuous variables are reported as the mean ± standard deviation. Categorical variables are reported as the frequencies and percentages. Univariate analysis - comparisons of continuous data of the two groups were conducted using the independent samples *t*-test or Wilcoxon rank-sum test, considering the size of the compared groups and distribution of variables. Categorical data were compared using χ^2 test or Fisher's exact test (if expectancy < 5). Ordinal data were compared using the Mann-Whitney test.

To test the predictive value of alarm features, we calculated the sensitivity and specificity of each one. Multivariable logistic regression models with a backward stepwise method were performed to assess the association of the alarm features with SEFs, while adjustments were made to other variable factors by reporting the *P* value, odds ratio (OR), and confidence interval (CI) for OR. The other variables were chosen to be included in the logistic regression equation as independent variables if they were found to be statistically significant in the univariate analysis with $P < 0.1$. A threshold for statistical significance was set at a $P < 0.05$. All analyses were performed by an experienced statistician using the statistical analysis software IBM SPSS statistics software 3, version 27.0 (Armonk, NY, United States).

RESULTS

Baseline and clinical and laboratory characteristics

The mean age was 58.2 ± 19 years and the median age was 60 years. Sex was approximately equally divided, 49.2% females and 50.8% males. The duration of dyspeptic symptoms was less than 1 month before the endoscopy in 62% of patients. Only 10% had the symptoms for 3 months or more. Among the 605 upper endoscopies performed, 28.8% had significant findings. The most common was PUD (15.2%), followed by malignancy (6.9%) and erosive esophagitis class B or higher (5.6%) (Table 1).

Comparing parameters of those with and without SEFs, we found several parameters to be significantly associated with SEFs, including duration of symptoms ($P < 0.05$) and tachycardia ($P < 0.05$). Notably, patients with SEFs tended to have hypotension when blood pressure was measured at presentation ($P < 0.05$; Table 2). Regarding laboratory findings among patients with and without SEFs, three laboratory parameters were significantly associated with SEFs: normocytic anemia, leukocytosis, and hypoalbuminemia defined as albumin < 3.5 mg/dL ($P < 0.05$; Table 3). In Table 4, we depict the correlation of regular medication use during the dyspeptic period before endoscopy with endoscopic findings. The regular use of anti-aggregates, with the exclusion of aspirin, was more common among patients with SEFs compared to those with normal endoscopy, with borderline statistical significance ($P < 0.05$).

Yield of alarm features and imaging findings in predicting SEFs

By performing univariate analyses of alarm features and imaging findings associated with SEFs, we found that UGIB at presentation as an alarm feature was strongly associated with SEFs ($P < 0.05$). Epigastric mass or lymphadenopathy, dysphagia, odynophagia, and iron deficiency anemia were specific in predicting SEFs (99.8%, 94.4%, 99.3%, and 91.2% respectively), with low sensitivities and insignificant *P* values. By contrast, none of the other alarms featured were statistically sensitive in predicting SEFs (Table 5). Regarding imaging findings among our 605 patients, imaging modalities were performed in 415 patients. Normal abdominal computed tomography (CT) was shown to be associated with normal endoscopy ($P < 0.05$). However, CT with suspicion of space-occupying lesion (SOL), metastatic disease, or bowel wall thickening was strongly associated with SEFs ($P < 0.05$; Table 6).

Multivariable logistic regression analysis of parameters associated with SEFs

Multivariable logistic regression analysis was performed. Multiple models were conducted to assess parameters predicting SEFs, and each SEF alone (PUD, esophagitis, and malignancy). The variables included in the equation were

Table 1 Basic demographics of the study population

Features	*n* of 605	%
Age, mean ± SD (58.2 ± 19), median = 60		
< 60 years	294	48.6
≥ 60 years	311	51.4
Sex		
Female	297	49.2
Male	307	50.8
Duration of symptoms		
< 30 days	330	62.6
30-59 days	75	13.2
60-89 days	11	7.3
≥ 90 days	14	9.3
Control without alarm features	92	15.2
Patients with alarm features	513	84.8
Alarm features		
Upper GI bleeding	144	23.8
Unexplained weight loss	137	22.6
Persistent vomiting	124	20.5
Iron deficiency anemia	50	8.3
Dysphagia	37	6.1
Odynophagia	5	0.8
Epigastric mass or lymphadenopathy	1	0.2
Endoscopic finding		
Patients without endoscopic finding	431	71.2
Patients with any endoscopic finding	174	28.8
Peptic ulcer disease	92	15.2
Erosive esophagitis class B or higher	34	5.6
Malignancy	42	6.9
Stricture	1	0.2
Finding requiring specific therapy	15	2.5
Medications		
PPIs	173	29
Statins	191	32.3
Aspirin	111	18.8
Anticoagulant	39	6.6
Anti-aggregate	30	5.1
NSAIDs	23	3.9

GI: Gastrointestinal; NSAIDs: Non-steroidal anti-inflammatory drugs; PPI: Proton pump inhibitors; SD: Standard deviation.

Table 2 Patients' clinical and demographics characteristics at presentation in both groups with and without significant endoscopic findings, *n* (%)

Patients' clinical characteristics	Total, *n* = 605	SEFs, *n* = 174	No SEFs, *n* = 431	*P* value
Sex				0.08[1]
Female	297 (49.2)	94 (54)	203 (47.2)	
Male	307 (50.8)	80 (46)	227 (52.8)	
Duration of symptoms				0.01[2]
< 30 days	330 (62.2)	106 (70.2)	224 (59.6)	
30-59 days	75 (14.2)	20 (13.2)	55 (14.6)	
60-89 days	39 (7.4)	11 (7.3)	28 (7.4)	
≥ 90 days	83 (15.7)	14 (9.3)	69 (18.4)	
Pulse				0.001[2]
Bradycardia	51 (8.5)	10 (5.8)	41 (9.5)	
Normal pulse	524 (86.9)	146 (84.4)	378 (87.9)	
Tachycardia	28 (4.6)	17 (9.8)	11 (2.6)	
Blood pressure				0.08[2]
Hypotension	61 (10.1)	24 (13.9)	37 (8.6)	
Normal BP	417 (69.3)	116 (67.1)	301 (70.2)	
Hypertension	124 (20.6)	33 (19.1)	91 (21.2)	

[1]Pearson χ^2 test.
[2]Mann-Whitney test.
BP: Blood pressure; SEFs: Significant endoscopic findings.

those statistically significant in the univariate analyses or alarm features with $P < 0.1$. The variables entered step 1 for each of the following models were blood pressure, pulse, unexplained weight loss, persistent vomiting, odynophagia, UGIB, iron deficiency anemia, age younger than 45, anti-aggregate medication, albumin, normocytic anemia, leukocytosis, CRP, duration of symptoms, CT showing suspected SOL or metastatic disease or lymphadenopathy (a united variable of the three was created). Table 7 presents the last step for each model, achieved using the backward stepwise method. For the 1st model dependent factor was SEF.

The last step for this model included UGIB (OR = 3.48; $P < 0.001$), normocytic anemia (OR = 2.06; $P = 0.003$), leukocytosis (OR = 1.83; $P = 0.02$) hypoalbuminemia (OR = 1.78; $P = 0.05$), duration of symptoms (OR = 0.99; $P = 0.04$), CT with above-mentioned findings (OR = 7.83; $P < 0.001$). The second model dependent variable was also SEFs, but the model did not include the duration of symptoms, as one of the variables had missing information for 78 patients which affects our sample size thus an identical model without this variable was conducted. The last step showed a correlation between tachycardia (> 100 heartbeats/min) at admission and SEFs (OR = 3.11; $P = 0.01$) in addition to the above-mentioned associations in the first model (Table 7).

Multivariable logistic regression analyses of parameters associated with each SEF alone

The third model's main dependent variable was PUD. An inverse correlation between unexplained weight loss and PUD finding in endoscopy was found (OR = 0.31; $P = 0.009$). Patients with unexplained weight loss were three times less likely to have PUS found on upper gastrointestinal endoscopy for dyspeptic symptoms investigation. The alarm features showing a direct correlation in models 1 and 2 were similarly shown when compared with PUD as a sole endoscopic finding. The fourth model determined erosive esophagitis class B or higher endoscopic finding as the dependent variable. In the last step of this model, odynophagia raised the probability of erosive esophagitis (OR = 21.03, $P = 0.004$). In addition, the chronic use of anti-aggregate medication was also found to be directly correlated to this finding raising the probability by 3.9 times (OR = 3.94, $P = 0.01$). The last model determined malignancy as an endoscopic finding to be the main dependent variable. The last step of this model showed two main variables correlated to finding a malignancy, unexplained weight loss before hospitalization (OR = 2.05; $P = 0.07$), and abnormal CT findings (OR = 39.68; $P < 0.001$) (Table 7).

Table 3 Patients' blood test, *n* (%)

CBC	Total (%), *n* = 605	SEFs, *n* = 174	No SEFs, *n* = 431	*P* value
Normal CBC	234 (38.7)	39 (22.4)	195 (45.2)	< 0.001[1]
Abnormal CBC	371 (61.3)	135 (77.6)	236 (54.8)	
Normocytic anemia	194 (32.1)	83 (47.7)	111 (25.8)	< 0.001[1]
Microcytic anemia	87 (14.4)	28 (16.1)	59 (13.7)	0.52[1]
Macrocytic anemia	3 (0.5)	1 (0.6)	2 (0.5)	1.0[3]
Leukocytosis	134 (22.1)	52 (29.9)	82 (19)	0.005[1]
Leukopenia	8 (1.3)	2 (1.1)	6 (1.4)	1.0[3]
Thrombocytosis	18 (3.0)	7 (4.0)	11 (2.6)	0.427[1]
Thrombocytopenia	14 (2.3)	6 (3.4)	8 (1.9)	0.24[3]
CRP				
CRP normal, < 5	289 (47.9)	83 (47.7)	206 (48.0)	1.00[1]
CRP abnormal	314 (52.1)	91 (52.3)	223 (52.0)	
Albumin				
Hypoalbuminemia	102 (17.2)	47 (28.0)	55(12.9)	< 0.001[2]
Normal albumin	489 (82.3)	118 (70.2)	371 (87.1)	
Hyperalbuminemia	3 (0.5)	3 (1.8)	0 (0)	
Liver function test				
Normal	554 (91.7)	157 (90.2)	397 (92.3)	0.416[1]
Hepatocellular enzymes elevated	39 (6.5)	13 (7.5)	26 (6.0)	0.58[1]
Cholestatic enzymes elevated	22 (3.6)	9 (5.2)	13 (3.0)	0.231[1]

[1]Pearson χ^2 test.
[2]Mann-Whitney test.
[3]Fisher exact test.
CBC: Complete blood count; CRP: C reactive protein; SEFs: Significant endoscopic findings.

Table 4 Correlation between regular medication use during dyspeptic symptom period, *n* (%)

Drug	Total (%), *n* = 605	SEFs, *n* = 174	No SEFs, *n* = 431	*P* value
PPI	173 (29)	48 (28.2)	125 (29.6)	0.77[1]
NSAIDs	23 (3.9)	9 (5.3)	14 (3.3)	0.35[1]
Aspirin	111 (18.8)	27 (15.9)	84 (19.9)	0.29[1]
Statin	191 (32.3)	54 (31.8)	137 (32.4)	0.92[1]
Anticoagulant	39 (6.6)	10 (5.9)	29(6.9)	0.72[1]
Anti-aggregate	30 (5.1)	13 (7.6)	17 (4)	0.05[1]

[1]Pearson χ^2 test.
NSAIDs: Non-steroidal anti-inflammatory drugs; PPI: Proton pump inhibitors; SEFs: Significant endoscopic findings.

DISCUSSION

The fear of missing a significant organic underlying cause for dyspeptic symptoms leads to the overuse of endoscopy regardless of age and alarm features, especially among hospitalized patients. In our study sample, the most common alarm feature was UGIB. A total of 145 of 605 patients (24%) had it at presentation. Among them, 45% had SEFs on examination. In both univariate and multivariate analyses, UGIB was found to be strongly correlated to SEFs. Supporting our finding, a retrospective study reviewing 1000 consecutive endoscopies performed at rural South African hospitals showed that UGIB was similarly the most prevalent alarm feature[9], and it showed a statistically significant correlation

Table 5 Association of alarm features with significant endoscopic findings, *n* (%)

Alarm features	Total (%), *n* = 605	SEFs, *n* = 174	No SEFs, *n* = 431	*P* value
Unexplained weight loss	137 (22.6)	35 (20.1)	102 (23.7)	0.391[1]
Dysphagia	37 (6.1)	13 (7.5)	24 (5.6)	0.453[1]
Persistent vomiting	124 (20.5)	40 (23.0)	84 (19.5)	0.373[1]
Odynophagia	5 (0.8)	2 (1.1)	3 (0.7)	0.629[3]
Upper GI bleeding	145 (24)	67 (38.5)	78 (18.1)	< 0.001[1]
IDA	50 (8.3)	12 (6.9)	38 (8.8)	0.516[1]
Epigastric mass or lymphadenopathy	1 (0.2)	0	1 (0.2)	1.000[3]

[1]Pearson χ^2 test.
[3]Fisher's exact test.
GI: Gastrointestinal; IDA: Iron deficiency anemia.

Table 6 Correlation between radiologic findings during hospitalization and endoscopic findings, *n* (%)

Imaging modality	Total (%), *n* = 605	SEFs, *n* = 174	No SEFs, *n* = 431	OR	95%CI	*P* value
Imaging modality not performed	188 (31.2)	64 (37)	124 (28.8)	1.45	0.99-2.1	0.051
Imaging modality performed	415 (68.8)	109 (63)	306 (71.2)			
CT	345 (57)	*n* = 100	*n* = 245			
Normal abdominal CT	214(62)	31 (31)	183 (74.7)	6.57	3.94-11	< 0.001
CT shows suspected PUD	5 (0.8)	2 (2.0)	3 (1.2)	1.65	0.27-100	0.59
CT shows suspected SOL	35 (10.1)	26 (26.0)	9 (3.7)	9.21	4.13-20.54	< 0.001
CT shows bowel wall thickening	60 (17.4)	25 (25.0)	35 (14.3)	2	1.12-3.56	0.02
CT shows stricture	5 (0.8)	2 (2.0)	3 (1.2)	1.65	0.27-10	0.59
CT shows metastatic disease	12 (2.0)	9 (9.0)	3 (1.2)	8	2.11-30.13	0.002
CT shows distended stomach	9 (1.5)	5 (5.6)	4 (1.6)	3.17	0.83-12.1	0.09
CT shows lymphadenopathy	8 (1.3)	3(3.0)	5 (2.0)	1.48	0.35-6.33	0.59
US	113 (18.7)	*n* = 19	*n* = 94			
Normal abdominal US	110 (97.3)	19 (100)	91 (96.8)	0		1
US shows cholecystitis	3 (2.7)	0 (0.0)	3 (3.2)			

CI: Confidence interval (calculated on the basis of univariate logistic regression); CT: Computerized tomography; OR: Odds ratio; SEFs: Significant endoscopic findings; SOL: Space-occupying lesion; US: Ultrasound.

with major endoscopic findings.

By contrast, in a retrospective study reviewing 3926 patients who underwent endoscopy for symptoms of dyspepsia, there was a positive correlation between alarm features and advanced stages of gastric cancers, except for gastrointestinal bleeding[10]. Moreover, persistent vomiting was also found to be correlated with SEFs and specifically PUD. In support of this, a cross-sectional study of 4664 dyspeptic patients who underwent endoscopy found that persistent vomiting and UGIB are strong predictors for upper gastrointestinal malignancy in patients aged below 50-years-old[11]. Conversely, a prospective observational study on 221 dyspeptic patients undergoing upper gastrointestinal endoscopy who were referred by primary care physicians found that persistent vomiting did not predict SEFs[12]. Nevertheless, this has limited value in contradicting our findings since their subjects were primary care patients only.

Although not commonly described among our sample, 5 of 605 patients (0.8%) suffered from odynophagia at presentation. Its prediction power for SEFs as a cluster and PUD as a sole endoscopic finding had borderline significance. However, it was shown to be a strong predictor of erosive esophagitis class B or higher ($P < 0.05$). Furthermore, it was the only alarm feature statistically significant in predicting erosive esophagitis in the multivariate prediction model. A retrospective study reviewing 159 endoscopic findings in adults with dyspepsia and alarm features implied a significant correlation between odynophagia and abnormal endoscopic findings[13].

Table 7 Five models presenting the correlation between alarm features and other variables found significant in our univariate analysis and significant endoscopic findings

Model	Variables	*P* value	OR	95%CI for OR	
1	Dependent variable: Significant endoscopic finding				
	Persistent vomiting	0.09	1.59	0.93	2.73
	Odynophagia	0.08	12.65	0.72	222.1[1]
	UGIB	< 0.001	3.48	2.07	5.86
	Normocytic anemia	0.003	2.06	1.28	3.29
	Leukocytosis	0.02	1.83	1.11	3.04
	Low albumin	0.05	1.78	1.01	3.15
	Duration of symptoms	0.04	0.99	0.99	1.00
	Abnormal CT[2]	< 0.001	7.83	4.21	14.54
2	Dependent variable: Significant endoscopic finding (duration of symptoms not included)				
	Persistent vomiting	0.03	1.75	1.05	2.91
	Odynophagia	0.07	7.81	0.85	72.07
	UGIB	< 0.001	3.22	1.97	5.27
	Normocytic anemia	< 0.001	2.36	1.51	3.69
	Leukocytosis	0.01	1.83	1.13	2.98
	Hypoalbuminemia	0.04	1.77	1.04	3.01
	Abnormal CT[2]	< 0.001	8.64	4.82	15.49
	Tachycardia	0.01	3.11	1.26	7.69
3	Dependent variable: Peptic ulcer disease				
	Unexplained weight loss	0.009	0.31	0.13	0.75
	Persistent vomiting	0.04	1.92	1.05	3.75
	UGIB	< 0.001	3.81	2.22	6.52
	Normocytic anemia	< 0.001	3.12	1.77	5.48
	Leukocytosis	0.03	1.92	1.06	3.48
	Abnormal CT[2]	0.04	2.29	1.03	5.10
	tachycardia	0.03	2.85	1.14	7.17
4	Dependent variable: Erosive esophagitis class B or higher				
	Odynophagia	0.004	21.03	2.69	164.3[1]
	Anti-aggregate medications	0.01	3.94	1.37	11.33
	Leukocytosis	0.003	2.99	1.45	6.17
5	Dependent variable: Malignancy as an endoscopic finding				
	Unexplained weight loss	0.07	2.05	0.95	4.41
	Abnormal CT[2]	< 0.001	39.68	11.81	133.33

[1]We suggest that upper limit of 95% confidence interval for odds ratio of odynophagia is high unproportionate due to the small number of patients with odynophagia in comparison to the sample size. The rest of the models' main dependent factor is each significant endoscopic finding with the above-mentioned variables.

[2]Abnormal contrast tomography is a variable we created which consists of contrast tomography showing suspected space-occupying lesion, lymphadenopathy or a metastatic disease.

The first model solely includes duration of symptoms as one of the variables. CI: Confidence interval; CT: Computed tomography; OR: Odds ratio; UGIB: Upper gastrointestinal bleeding.

Regarding unintended weight loss, which was the second most described alarm feature, reported by 137 of 605 patients (22.6%), there were conflicting findings. On one hand it was shown to have borderline power in predicting malignancy (OR = 2.048, 95%CI: 0.951-4.412; P = 0.067) as shown in our multivariate model describing malignancy as an endoscopic finding (Table 7). In a recent cross-sectional descriptive study of 372 patients, weight loss predicted SEFs in 85.7% of patients[14]. A prospective study enrolling 900 patients reported a 76% sensitivity and 90.8% specificity for weight loss in predicting malignancy[15]. On the other hand, in our multivariate PUD model, it was shown to be inversely related to SEFs. A study challenging the diagnostic value of alarm features among patients with dyspepsia found that patients with esophageal cancers and upper gastric cancers detected on endoscopy when investigating dyspeptic symptoms had the highest ratio of alarm features, mostly unintended weight loss and dysphagia[10].

In contrast to the above-mentioned alarm features, iron deficiency anemia and dysphagia were not significant in either our univariate or multivariate analysis in predicting SEFs (Tables 4 and 7). Conversely to our finding regarding dysphagia, a cross-sectional study of 3414 patients referred to tertiary gastrointestinal clinics, who underwent upper gastrointestinal endoscopy for the investigation of dyspeptic symptoms, found that dysphagia significantly predicted abnormal endoscopic findings in both univariate and multivariate regression models[16]. The discrepancies might result from a small percentage of dysphagia among our participants (6%), which can be attributed to the fact that a patient with dysphagia in primary care would be referred to endoscopy urgently and diagnosed there (as described in the three mentioned studies), thus making it a less common and significant among our hospitalized patients. This further emphasizes the differences between outpatients and inpatients with dyspepsia. These data strengthen our initial hypothesis of the different variables (if present) predicting ability in general and among the different patient settings at the time of presentation specifically inpatient and outpatient settings.

Concerning vital signs and the laboratory results of our sample, a strong correlation between normocytic anemia, leukocytosis, hypoalbuminemia, and tachycardia on admission with SEFs was depicted throughout our study in univariate and multivariate analyses. They were found to be significant in both SEFs as a cluster models (Table 7, models 1 and 2) and PUD (Table 7, model 3). Supporting our finding is a retrospective study of 329 patients[17], which depicts the prevalence of hypoalbuminemia in patients presenting with non-variceal UGIB and its correlation with a complicated course. More significantly a 5-year prospective study[18], which developed and applied a scoring model for predicting risk of malignancy in patients with dyspepsia. The model included a combination of alarm features with hypoalbuminemia, low hemoglobin, and age. It was applied on 2324 patients with impressive area under the curve of 0.9 (0.88-0.93) in receiver operating characteristic curve, and sensitivity of 92.5% of a score of 2 in predicting upper gastrointestinal malignancy. This suggests and further emphasizes the importance of creating a new algorithm that combines demographic and clinical data, specifically the above-mentioned alarm features and lab results and implements it in our management of dyspeptic patients. Additional parameters might also be important.

Furthermore, while investigating the regular medications of our patients' sample, a statistically significant link between the use of anti-aggregates other than aspirin (as aspirin was tested separately to refrain bias as its correlation with PUD is established in the literature[19,20]), and SEFs were found with erosive esophagitis in model 4 multivariate study. A study in which a magnetically controlled capsule endoscopy was used for assessment of antiplatelet therapy-induced gastrointestinal injury showed that nearly all patients receiving antiplatelet therapy despite being at low risk for bleeding developed gastrointestinal injury[21]. By contrast, statins which were our sample's most used medications reported in 191 patients of 605 (32%), were not linked to SEFs. Moreover, a previous study suggested a protective role against endoscopic lesions, especially in aspirin consumers or patients with cardiovascular diseases, which might also explain the lack of correlation between our sample's aspirin users and SEFs[22].

Age as a risk factor for SEFs is highly contested in literature, and is continuously changing even geographically. Our study continued with this trend not showing any significance in any division proposed by multiple studies and guidelines[23-27]. First, we divided our sample to below and above the age of 60, followed by a division to below and above the age of 45 which also failed to show statistical significance. CT findings including SOL, lymphadenopathy, wall thickening, and metastasis, were unsurprisingly correlated with SEFs and malignancies.

Therefore, we suggest a new risk stratification model for hospitalized dyspeptic patients based on the alarm features including UGIB, persistent vomiting, odynophagia, and unexplained weight loss. In addition, one vital sign parameter (tachycardia) and three lab values (normocytic anemia, leukocytosis, and hypoalbuminemia) and probably the use of anti-aggregate medications (other than aspirin) for referral to endoscopy.

This study had limitations. First, the homogenous single-center hospitalized patients might have unique features that are not applicable worldwide. Second, this was a retrospective study. However, its strength resides in its relatively large study cohort of patients, suggesting further research with an emphasis on our significant variables and our proposed model should be implemented in clinical research.

CONCLUSION

In this unique research investigating only hospitalized patients with dyspepsia as their main indication for hospitalization, interesting findings have emerged as significant predictors of SEFs. To the best of our knowledge, this is the first time in the English literature that those variables were reported to be predictors of SEFs in hospitalized patients. We suggest implementing a new weighted scoring system that include the above-mentioned variable in determining the need for upper endoscopic examination in hospitalized dyspeptic patients.

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REFERENCES

1 **Futagami S**, Yamawaki H, Agawa S, Higuchi K, Ikeda G, Noda H, Kirita K, Akimoto T, Wakabayashi M, Sakasegawa N, Kodaka Y, Ueki N, Kawagoe T, Iwakiri K. New classification Rome IV functional dyspepsia and subtypes. *Transl Gastroenterol Hepatol* 2018; **3**: 70 [PMID: 30363705 DOI: 10.21037/tgh.2018.09.12]

2 **Talley NJ**. Dyspepsia: management guidelines for the millennium. *Gut* 2002; **50** Suppl 4: iv72-8; discussion iv79 [PMID: 11953354 DOI: 10.1136/gut.50.suppl_4.iv72]

3 **Wallander MA**, Johansson S, Ruigómez A, García Rodríguez LA, Jones R. Dyspepsia in general practice: incidence, risk factors, comorbidity and mortality. *Fam Pract* 2007; **24**: 403-411 [PMID: 17728288 DOI: 10.1093/fampra/cmm050]

4 **Oustamanolakis P**, Tack J. Dyspepsia: organic versus functional. *J Clin Gastroenterol* 2012; **46**: 175-190 [PMID: 22327302 DOI: 10.1097/MCG.0b013e318241b335]

5 **Vakil N**, Moayyedi P, Fennerty MB, Talley NJ. Limited value of alarm features in the diagnosis of upper gastrointestinal malignancy: systematic review and meta-analysis. *Gastroenterology* 2006; **131**: 390-401; quiz 659 [PMID: 16890592 DOI: 10.1053/j.gastro.2006.04.029]

6 **Wallace MB**, Durkalski VL, Vaughan J, Palesch YY, Libby ED, Jowell PS, Nickl NJ, Schutz SM, Leung JW, Cotton PB. Age and alarm symptoms do not predict endoscopic findings among patients with dyspepsia: a multicentre database study. *Gut* 2001; **49**: 29-34 [PMID: 11413107 DOI: 10.1136/gut.49.1.29]

7 **Abdeljawad K**, Wehbeh A, Woolard S, Qayed E. Utility of Alarm Features in Predicting Significant Endoscopic Findings in Outpatients with Dyspepsia. *AJG* 2017; **112**: S668-S669

8 **Abdeljawad K**, Wehbeh A, Qayed E. Low Prevalence of Clinically Significant Endoscopic Findings in Outpatients with Dyspepsia. *Gastroenterol Res Pract* 2017; **2017**: 3543681 [PMID: 28210269 DOI: 10.1155/2017/3543681]

9 **Cheddie S**, Manneh CG, Owczarek BM, Moodley Y. Age is a predictor of significant endoscopic findings in dyspepsia patients in South Africa. *S Afr J Surg* 2020; **58** [DOI: 10.17159/2078-5151/2020/v58n1a2814]

10 **Lee SW**, Chang CS, Yeh HJ, Lien HC, Lee TY, Peng YC. The Diagnostic Value of Alarm Features for Identifying Types and Stages of Upper Gastrointestinal Malignancies. *Gastroenterology Res* 2017; **10**: 120-125 [PMID: 28496533 DOI: 10.14740/gr826w]

11 **Kaosombatwattana U**, Charatcharoenwitthaya P, Pausawasdi N, Maneerattanaporn M, Limsrivilai J, Leelakusolvong S, Kachintorn U. Value of age and alarm features for predicting upper gastrointestinal malignancy in patients with dyspepsia: an endoscopic database review of 4664 patients in Thailand. *BMJ Open* 2021; **11**: e052522 [PMID: 34706958 DOI: 10.1136/bmjopen-2021-052522]

12 **Azzam NA**, Almadi MA, Alamar HH, Almalki LA, Alrashedi RN, Alghamdi RS, Al-hamoudi W. Performance of American Society for Gastrointestinal Endoscopy guidelines for dyspepsia in Saudi population: prospective observational study. *World J Gastroenterol* 2015; **21**: 637-643 [PMID: 25605988 DOI: 10.3748/wjg.v21.i2.637]

13 **Odeghe EA**, Adeniyi OF, Oyeleke GK, Keshinro SO. Use of alarm features in predicting significant endoscopic findings in Nigerian patients with dyspepsia. *Pan Afr Med J* 2019; **34**: 66 [PMID: 31762930 DOI: 10.11604/pamj.2019.34.66.18848]

14 **Al-Abachi KT**. Diagnostic value of endoscopy in adult patients with dyspepsia. *Prz Gastroenterol* 2022; **17**: 274-279 [PMID: 36514452 DOI: 10.5114/pg.2021.112250]

15 **Shetty A**, Balaraju G, Shetty S, Pai CG. Diagnostic utility of alarm features in predicting malignancy in patients with dyspeptic symptoms. *Indian J Gastroenterol* 2021; **40**: 183-188 [PMID: 33830441 DOI: 10.1007/s12664-021-01155-x]

16 **Emami MH**, Ataie-Khorasgani M, Jafari-Pozve N. Diagnostic value of alarm symptoms for upper GI malignancy in patients referred to GI clinic: A 7 years cross sectional study. *J Res Med Sci* 2017; **22**: 76 [PMID: 28717373 DOI: 10.4103/jrms.JRMS_450_15]

17 **Tung CF**, Chow WK, Chang CS, Peng YC, Hu WH. The prevalence and significance of hypoalbuminemia in non-variceal upper gastrointestinal bleeding. *Hepatogastroenterology* 2007; **54**: 1153-1156 [PMID: 17629059]

18 **Dutta AK**, Rebekah G, Chowdhury SD, Gangadharan SK, Subramani Y, Sahu MK, Kurien RT, David D, Simon EG, Joseph AJ, Donapati VR, Chacko A. A Simple Pre-endoscopy Score for Predicting Risk of Malignancy in Patients with Dyspepsia: A 5-Year Prospective Study. *Dig Dis Sci* 2018; **63**: 3442-3447 [PMID: 30109577 DOI: 10.1007/s10620-018-5245-7]

19 **Iwamoto J**, Saito Y, Honda A, Matsuzaki Y. Clinical features of gastroduodenal injury associated with long-term low-dose aspirin therapy. *World J Gastroenterol* 2013; **19**: 1673-1682 [PMID: 23555156 DOI: 10.3748/wjg.v19.i11.1673]

20 **Shim YK**, Kim N. [Nonsteroidal Anti-inflammatory Drug and Aspirin-induced Peptic Ulcer Disease]. *Korean J Gastroenterol* 2016; **67**: 300-312 [PMID: 27312830 DOI: 10.4166/kjg.2016.67.6.300]

21 **Pantea M**, Negovan A, Voidăzan S, Macarie M, Mocan S, Bățagă S. Statins and gastroduodenal endoscopic lesions: A case-control study. *Medicine (Baltimore)* 2018; **97**: e13579 [PMID: 30558024 DOI: 10.1097/MD.0000000000013579]

22 **Kumari P**, Machhan P, Sharma B, Sharma R, Bodh V, Kumar R. Dyspepsia with alarm symptoms in patients aged less than 60 years: Is upper gastrointestinal endoscopy justified in Indian scenario? *Indian J Gastroenterol* 2022; **41**: 430-439 [PMID: 36308702 DOI: 10.1007/s12664-022-01275-y]

23 **Black CJ**, Paine PA, Agrawal A, Aziz I, Eugenicos MP, Houghton LA, Hungin P, Overshott R, Vasant DH, Rudd S, Winning RC, Corsetti M, Ford AC. British Society of Gastroenterology guidelines on the management of functional dyspepsia. *Gut* 2022; **71**: 1697-1723 [PMID: 35798375 DOI: 10.1136/gutjnl-2022-327737]

24 **Salkic NN**, Zildzic M, Zerem E, Smajic M, Gegic A, Alibegovic E, Jovanovic P. Simple uninvestigated dyspepsia: age threshold for early endoscopy in Bosnia and Herzegovina. *Eur J Gastroenterol Hepatol* 2009; **21**: 39-44 [PMID: 19086146 DOI: 10.1097/MEG.0b013e328308b300]

25 **Liou JM**, Lin JT, Wang HP, Huang SP, Lee YC, Shun CT, Lin MT, Wu MS. The optimal age threshold for screening upper endoscopy for uninvestigated dyspepsia in Taiwan, an area with a higher prevalence of gastric cancer in young adults. *Gastrointest Endosc* 2005; **61**: 819-825 [PMID: 15933682 DOI: 10.1016/S0016-5107(05)00366-4]

26 **Schmidt N**, Peitz U, Lippert H, Malfertheiner P. Missing gastric cancer in dyspepsia. *Aliment Pharmacol Ther* 2005; **21**: 813-820 [PMID: 15801916 DOI: 10.1111/j.1365-2036.2005.02425.x]

27 **Uehara G**, Nago A, Espinoza R, Vargas G, Astete M, Morán L, Nuñez N, Mayuri C, Valdivia M, Chávez M, Moreno C. [Optimal age for gastric cancer screening in patients with dyspepsia without alarm symptoms]. *Rev Gastroenterol Peru* 2007; **27**: 339-348 [PMID: 18183275]

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