Appropriateness Guidelines and Predictive Rules to Select Patients for Upper Endoscopy: A Nationwide Multicenter Study

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OBJECTIVES: **Selecting patients appropriately for upper endoscopy (EGD) is crucial for efficient use of endoscopy. The objective of this study was to compare different clinical strategies and statistical methods to select patients for EGD, namely appropriateness guidelines, age and/or alarm features, and multivariate and artificial neural network (ANN) models.**

METHODS: **A nationwide, multicenter, prospective study was undertaken in which consecutive patients referred for EGD during a 1-month period were enrolled. Before EGD, the endoscopist assessed referral appropriateness according to the American Society for Gastrointestinal Endoscopy (ASGE) guidelines, also collecting clinical and demographic variables. Outcomes of the study were detection of relevant findings and new diagnosis of malignancy at EGD. The accuracy of the following clinical strategies and predictive rules was compared: (i) ASGE appropriateness guidelines (indicated vs. not indicated), (ii) simplified rule (≥45 years or alarm features vs. <45 years without alarm features), (iii) logistic regression model, and (iv) ANN models.**

RESULTS: **A total of 8,252 patients were enrolled in 57 centers. Overall, 3,803 (46%) relevant findings and 132 (1.6%) new malignancies were detected. Sensitivity, specificity, and area under the receiver-operating characteristic curve (AUC) of the simplified rule were similar to that of the ASGE guidelines for both relevant findings (82%/26%/0.55 vs. 88%/27%/0.52) and cancer (97%/22%/0.58 vs. 98%/20%/0.58). Both logistic regression and ANN models seemed to be substantially more accurate in predicting new cases of malignancy, with an AUC of 0.82 and 0.87, respectively.**

CONCLUSIONS: **A simple predictive rule based on age and alarm features is similarly effective to the more complex ASGE guidelines in selecting patients for EGD. Regression and ANN models may be useful in identifying a relatively small subgroup of patients at higher risk of cancer.**

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INTRODUCTION

The increasing reliance by physicians on endoscopy and the appreciation by the general public that upper endoscopy (EGD) is useful for diagnosis, surveillance, or exclusion of important gastroduodenal diseases have led to an increasing demand for open-access endoscopy (1). To optimize the use of finite resources in an open-access system, the appropriate selection of patients for EGD is crucial (2,3).

For this purpose, official guidelines for the appropriate use of EGD have been proposed by the American Society for

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Gastrointestinal Endoscopy (ASGE) and by EPAGE (European Panel on the appropriateness of Gastrointestinal Endoscopy) (2,4). Observational studies have shown a substantial rate of inappropriate EGD indications, which in turn has been associated with a lower diagnostic yield for relevant findings (5–13). However, the validity of these expert-derived guidelines has never been tested in a randomized study or compared with alternative strategies (14).

A more empirical approach to select patients for EGD is to build up predictive rules on the basis of multivariate statistical methods, with previous studies producing conflicting results (15,16). Alternatively, a very simple prediction rule based on the association between alarm features or age ≥45 years and the detection of relevant findings, in particular cancer, has been successfully implemented in patients with dyspepsia (17,18). However, its accuracy in selecting nondyspeptic patients for EGD is largely unknown.

Recently, artificial neural networks (ANNs) have been developed to predict clinical outcomes with a higher degree of accuracy as compared with multivariate models. ANN has been shown to be effective in predicting upper and lower gastrointestinal (GI) bleeding (19,20).

The aim of this study was to compare all these different available options to select patients for EGD examinations referred to open-access Endoscopy Units.

METHODS

A cross-sectional, prospective, multicenter study involving 56 open-access Endoscopy Units, uniformly distributed throughout Italy (SIED Appropriateness Project) was conducted between October 2007 and February 2008.

A local study coordinator assumed responsibility for each center, and all clinical investigators were experienced endoscopists (with more than 15 years experience with standard methods). According to the protocol, all patients referred to the participating centers for open-access EGD during 1 month were prospectively enrolled. EGDs were performed according to predefined weekly schedules, the referring physicians being unaware of the purpose of the study. All patients gave written informed consent for endoscopy. Data were collected uniformly according to a previously defined protocol that included the following four steps: (i) patient evaluation including personal medical history. The following variables were systematically collected: age and sex; presenting symptoms (such as dyspepsia, reflux, atypical reflux manifestations, anemia, weight loss, dysphagia, vomiting, GI bleeding, family history of gastric cancer); preprocedure endoscopic diagnosis (previous EGD); concomitant therapy (proton pump inhibitors, other antisecretory/antiacid drugs, nonsteroidal anti-inflammatory drugs/anti-cyclooxygenase-2/aspirin); (ii) determination of the indication category specified by the ASGE guidelines, on the basis of the information provided by both the patient and the referring physician; type of specialty practiced by the referring physician (primary care physicians, gastroenterologists or other specialists); (iii) performance of EGD; and (iv) reporting of the endoscopic findings, including selection of a standard diagnosis from a predefined list. The initial two steps were performed by an investigating gastroenterologist before endoscopy. Endoscopic findings were reported with internationally accepted terminology and definitions. Data quality assurance was assessed by a random review of 5% of the procedures.

We selected the following two types of endoscopic lesions at EGD as the main outcomes of the study: (i) relevant finding (any finding that directly affects therapeutic decisions and prognosis, as listed in **Appendix A**) (5–12) and (ii) new diagnosis of malignancy (cancer or lymphoma). When there was more than one endoscopic diagnosis, the most severe diagnosis was adopted. Histology was required to confirm all malignancies. Although this was an endoscopic study, in which the centers were not directly involved in cancer treatment, a postendoscopic follow-up was attempted for all the new cases of malignancy. Postsurgical staging was required in the operated patients.

According to the study design, the accuracy of the following clinical and predictive rules were compared:

1. *Appropriateness of the indication*: The ASGE guidelines were used to assess the appropriateness of each examination before the procedure (4). Referrals for EGDs were classified into those "generally indicated" (appropriate) and those "generally not indicated" (inappropriate).
2. *Simplified predictive rule*: According to this option, all EGDs performed in patients ≥45 years and/or in those with at least one alarm symptom (dysphagia, weight loss, anemia, GI bleeding, vomiting), or a family history of gastric cancer were considered to be indicated, whereas those performed in patients <45 years without alarm features were classified as not indicated.
3. *Predictive model (logistic regression analysis)*: Stepwise multiple logistic regression analysis was used to identify significant predictor variables for each of the considered outcomes. The prediction model was built using SPSS version 15.0 (M.J. Norusis, Chicago, IL) stepwise logistic regression analysis on the exploratory sample population with an entry criterion of $P < 0.3$. The stepwise procedure added the independent variables to the model one at a time. In the final model, variables were removed if the retention criterion of $P < 0.05$ was not met. The study population was randomly divided into an exploration group and a validation group. A total of 20 predictor demographic and clinical variables were included in the building process. Once the model was established using the exploratory group, parameter estimates were applied to the validation group to test the predictive accuracy of the model.
4. *Predictive model (ANN) methodology*: Advanced intelligent systems based on the novel coupling of ANNs and evolutionary algorithms were used. Supervised ANNs were applied (21) to develop a model able to predict with a high degree of accuracy the diagnostic class starting from available clinical data. Supervised ANNs are networks that learn by examples, calculating an error function during the training phase and adjusting connection strengths, to minimize the error function. Further details are reported in **Appendix B**.

Each of the two outcomes (relevant finding and new malignancy) served as the reference standard for determining the accuracy of

Table 1. EGD indication in the study population

Main indication	*n* (%)
Dyspepsia without reflux[a]	2,489 (30)
Dyspepsia with reflux[a]	1,075 (13)
Reflux[a]	1,175 (14)
Atypical manifestations of reflux[a]	129 (2)
Alarm features[b]	2,236 (27)
Portal hypertension assessment	324 (4)
Suspicion at RX	73 (1)
Operative endoscopy	121 (1)
Follow-up benign/precancerous/malignant	381 (5)
Duodenal biopsy	166 (2)
EGD for other medical/surgical conditions	74 (1)
Cancer of unknown origin	10 (0.1)

EGD, upper endoscopy; GI, gastrointestinal; RX, radiology.
[a]Excluding cases with simultaneous presence of alarm features.
[b]In 695 (35%) patients, alarm symptoms (anemia, dysphagia, weight loss, GI bleeding, vomiting), or a family history of gastric cancer were reported to be associated with dyspepsia, reflux, or vomiting. In other cases, it was the only symptom reported.

the different strategies. In particular, if a relevant endoscopic finding or a new malignancy was detected and the EGD was classified as indicated according to one of the four strategies (i.e., "generally indicated" by the ASGE guidelines), the EGD was considered to be a true positive. If the EGD was classified as indicated but no relevant finding or new malignancy was diagnosed, the EGD was considered a false-positive result.

We estimated the sensitivity, specificity, and positive and negative predictive values with 95% confidence intervals for each strategy. Areas under the receiver-operating characteristic curves (AUCs) were calculated and compared for clinical and statistical rules with a nonparametric approach using a paired design (22). Odds ratio was used for the association between study variables and the selected outcome. Chi-squared test was used to assess the statistical significance of differences among proportions. All *P* values involve hypothesis tests against a two-sided alternative. Differences were considered significant at a 5% probability level. We also reported in **Appendix C**, the distribution of clinical features in the discordant pairs of predictions (i.e., indicated for the ASGE guidelines and not indicated according to the logistic regression model) among the different strategies to identify areas of main uncertainty.

RESULTS

A cohort of 8,252 (men: 47%; mean age: 57 years, range 18–99 years) patients was enrolled. Primary care physicians, gastroenterologists, and other specialties were the referring physicians in 4,704 (57%), 1,402 (17%), and 2,146 (26%) cases, respectively. Overall, 6,106 (74%) were outpatients, the remaining being hospitalized. Study EGD was the first endoscopy in 5,364 (65%) patients, being a control EGD in the remaining 2,888 cases. In the previous EGD, 1,591 patients (55%) had a previously relevant endoscopic diagnosis.

Table 2. Frequency of relevant findings (any able to impact clinical management) and malignancy in the study population

Relevant finding	Whole population (*N* = 8,252), *n* (%)
Esophagus	
Peptic esophagitis	1,118 (13.5)
Varices	427 (5.2)
Barrett's esophagus[a]	150 (1.8)
Micotic esophagitis	67 (0.8)
Cancer[b]	76 (1)
Foreign body	28 (0.3)
Peptic stricture	15 (0.2)
Mallory–Weiss	16 (0.2)
Anastomotic stricture	7 (0.1)
Caustic lesion	7 (0.1)
Caustic stricture	4 (0.05)
Stomach	
Erosive gastritis	989 (12.0)
Hypertensive gastropathy	307 (3.7)
Polyp	228 (2.8)
Peptic ulcer	219 (2.7)
Cancer[b]	111 (1.3)
Stomitis	81 (1.0)
Fundus varices	39 (0.5)
Anastomotic ulcer	28 (0.3)
Gastric antral vascular ectasia	24 (0.3)
Angiodysplasia	20 (0.2)
Lymphoma[b]	17 (0.2)
Foreign body	20 (0.2)
Anastomotic stricture	7 (0.1)
Menetrier's syndrome	2 (0.002)
Duodenum	
Erosive duodenitis	340 (4.1)
Duodenal ulcer	300 (3.6)
Signs of malabsorption	84 (1)
Cancer[b]	15 (0.2)
Ampulloma	4 (0.05)

Overall, relevant findings were detected in 3,803 patients. Some patients (864 cases) presented with more than 1 relevant finding, so that the overall sum of the different diagnoses is more than 3,803.
[a]There was a new diagnosis of Barrett's in 50 (0.6%) cases. Of those, only 10 (20%) patients were <45 years without alarm symptoms.
[b]There was a new diagnosis in 38, 88, and 6 cases of esophageal, gastric, and duodenal malignancies, respectively. In all, 2 cases of gastric lymphomas and 130 cancers were reported at histology.

A main clinical symptom/sign was reported in 7,104 (86%) cases (**Table 1**). In detail, an alarm feature was present in 2,236 (27%) cases, anemia, dysphagia, weight loss, GI bleeding, a family history

Table 3. Postendoscopic follow-up for patients diagnosed with a new case of malignancy at study EGD

Main indication	No. patients (%; 95% CI)
Not operated	42[a] (52; 42, 63)
Palliative surgery	11[b] (14; 6, 21)
Curative surgery	27 (34; 23, 44)
Localized stage[c]	7 (8; 3, 15)
Regional/distant stage	20 (25; 16, 34)

CI, confidence interval; EGD, upper endoscopy.
A detailed follow-up was available in 80 patients.
[a]In all, there were 32 cases for metastatic disease and 10 for surgical risk.
[b]Palliative surgery was the only available option because of metastatic progression.
[c]i.e., N0.

of gastric cancer, and vomiting being present in 9.3, 5, 4.1, 7.1, 1.7, and 4.3%, respectively (in some cases, more than one alarm symptom was present). Dyspepsia without reflux, dyspepsia with reflux, and only typical and atypical reflux symptoms (all without alarm symptoms) represented the main presenting symptoms in 2,489 (30%), 1,075 (13%), 1,175 (14%), and 129 (2%) patients, respectively. EGD indications in the remaining 1,148 (14%) patients without dyspepsia/reflux or alarm symptoms are listed in **Table 1**. Concomitant therapy with proton pump inhibitor was reported by 2,626 (32%) patients, other antisecretory/antiacids being used by 948 (11%). Concomitant therapy with nonsteroidal anti-inflammatory drug/anti-cyclooxygenase-2/aspirin was reported in 719 (9%) cases.

As shown in **Table 2**, detection of relevant findings was reported in 3,803 (46%) patients. Malignancy (cancer or lymphoma) was diagnosed in 215 (2.6%) cases (**Table 2**). It was a new diagnosis in 132 (1.6%) patients (130 cancers and 2 gastric lymphomas), whereas it was an already diagnosed malignancy (excluded from further analysis) in 83 (0.9%) patients. The mean age of those with a new malignancy was 71 years (range: 38–96 years), 76 (57%) of them being men. Postendoscopic follow-up was available for 80 (61%) patients, and is reported in **Table 3**.

Accuracy of appropriateness guidelines

EGD indication was included in the ASGE guidelines in 7,983 (97%) patients, the remaining 269 cases being excluded from further analysis within this strategy. EGD indication was classified as appropriate according to the ASGE criteria in 6,389 (80%) patients, being inappropriate in the remaining 1,594.

The mean sensitivity and specificity of appropriateness guidelines for the detection of relevant findings were 88 and 27%, respectively, and the AUC was 0.55. Positive and negative predictive values were 51 and 72%, respectively.

Mean sensitivity, specificity, and AUC for the detection of new cases of malignancy were 98%, 20%, and 0.58, respectively. Positive and negative predictive values were 2 and 99.8, respectively.

Of the three patients with an inappropriate indication diagnosed with a malignancy, the inappropriateness was referred to atrophic gastritis surveillance (one patient with gastric cancer, 48 years, T3 N1 M0), metastatic cancer of unknown origin (one patient with gastric cancer, 50 years, T4 N1 M1), and symptoms considered

Table 4. Univariate analysis of the associations between the main clinical variables and the detection of relevant findings, and new cases of malignancy (cancer and lymphoma) in the study population

Clinical variable	Prevalence (%)	OR relevant findings (95% CI)	OR new malignancy (95% CI)
Age (years)			
≥45	73	1.51330[a] (1.4–1.7)	8.15[a] (4–18)
<45	27		
Sex			
Male	47	1.76[a] (1.6–1.9)	1.64[b] (1.1–2.3)
Female	53		
Setting			
In-patient	26	1.6[a] (1.4–1.8)	4.2[a] (3–6)
Outpatient	74		
Previous EGD			
No	65	0.72[a] (0.6–0.8)	4.06[a] (2.5–7)
Yes	35		
Relevant finding at previous EGD			
Yes	19	2.76[a] (2.5–3.1)	0.15[a] (0.06–0.4)
No	81		
Anemia			
Yes	9	1.13 (0.8–1.3)	3.6[a] (2.4–5.3)
No	91		
Weight loss			
Yes	4	1.31[b] (1–1.6)	14.6[a] (10–21)
No	96		
Dysphagia			
Yes	5	1.21 (0.99–1.5)	8.7[a] (6–13)
No	95		
Bleeding			
Yes	7	3.5[a] (2.9–4.2)	1.89[b] (1.13–3.2)
No	93		
Family history of cancer			
Yes	2	0.6[b] (0.4–0.9)	1.76 (0.6–2.8)
No	98		
Dyspepsia			
Yes	49	0.79[a] (0.7–0.9)	0.58[b] (0.4–0.8)
No	51		
Reflux			
Yes	29	1.161330[b] (1.05–1.3)	0.37[a] (0.2–0.6)
No	71		
Atypical reflux			
Yes	4	0.72[b] (0.6–0.9)	0.17 (0.02–1.3)
No	96		

Table 4 continued on following page

Table 4. Continued

Clinical variable	Prevalence (%)	OR relevant findings (95% CI)	OR new malignancy (95% CI)
Vomiting			
Yes	4	0.92 (0.7–1.1)	5.5[a] (3.6–8.6)
No	96		
Alarm symptom			
Yes	26	1.49[a] (1.3–1.6)	8.75[a] (5.9–13)
No	74		
Alarm symptom/age ≥45 years			
Yes	78	1.64[a] (1.4–1.8)	9.28[a] (3.4–25.15)
No	22		
PPI therapy			
Yes	32	1.03 (0.93–1.1)	0.99 (0.7–1.4)
No	68		
Antisecretory/antiacid therapy[c]			
Yes	43	1.04 (0.95–1.13)	0.81 (0.45–1.17)
No	57		
NSAIDs/anti-COX2/aspirin			
Yes	9	1.41 (0.97–1.33)	1.01 (0.6–1.8)
No	91		
Appropriateness			
Yes	80	2.7[a] (2.4–3)	10.92[a] (3.5–34)
No	20		
Specialist			
Yes	43	1.57[a] (1.4–1.7)	3.95[a] (2.7–5.8)
No	57		

CI, confidence interval; COX2, cyclooxygenase-2; EGD, upper endoscopy; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; PPI, proton pump inhibitor.
[a]<0.001.
[b]<0.05.
[c]Also including PPI.

Table 5. (a) Multivariate analysis for the detection of relevant findings and (b) new cases of malignancy (cancer and lymphoma) in the study population

(a)

Clinical variable	Relevant finding OR (95% CI)
Bleeding	3.51 (2.9–4.2)
Relevant finding at previous EGD	2.76 (2.5–3.1)
Appropriateness	2.7 (2.4–3)
Male sex	1.77 (1.6–1.9)
Age ≥45 years	1.55 (1.4–1.7)
Alarm symptoms	1.39 (1.2–1.6)
Weight loss	1.32 (1–1.6)
Reflux	1.16 (1.05–1.3)
PPI therapy	1.03 (0.93–1.1)

(b)

Clinical variable	New malignancy OR (95% CI)
Weight loss	15.23 (9.3–24.8)
Dysphagia	9.39 (5.7–15.6)
Alarm features	8.78 (5.2–14.8)
Age ≥45 years	8.09 (2.6–23.8)
Age ≥45 years or alarm features	7.63 (2.3–24.7)
Vomiting	5.64 (3.2–10.1)
Anemia	3.66 (2.2–6.1)
Bleeding	1.91 (0.5–6.4)
Male sex	1.63 (1–2.6)
Reflux	0.37 (0.2–0.6)

CI, confidence interval; EGD, upper endoscopy; OR, odds ratio; PPI, proton pump inhibitor.

functional in a 51-year-old patient complaining of dyspepsia in the previous month, eventually diagnosed with gastric cancer (T3 N3 M0) at EGD.

Accuracy of the simplified predictive rule

When coupling the 6,027 (73%) patients ≥45 years with the 2,236 patients presenting with an alarm symptom or a family history of gastric cancer, EGD appeared to be indicated in 6,422 (78%) patients.

Mean sensitivity, specificity, and AUC for the detection of relevant findings were 82%, 26%, and 0.52, respectively. Positive and negative predictive values were 49 and 63%, respectively. Sensitivity and specificity in dyspeptic and nondyspeptic patients (excluding patients with alarm features) were 72% (95% confidence interval (95% CI): 70, 75) and 37% (95% CI: 35, 39), and 76% (95% CI: 74, 79) and 29% (95% CI: 26, 31), respectively.

Mean sensitivity, specificity, and AUC for the detection of new cases of malignancy were 97%, 22%, and 0.58, respectively. Positive and negative predictive values were 2 and 99.8%, respectively. Sensitivity and specificity in dyspeptic and nondyspeptic patients (excluding patients with alarm symptoms) were 81% (95% CI: 64, 98) and 33% (95% CI: 32, 35), and 100% (95% CI: 100, 100) and 27% (95% CI: 25, 28), respectively.

Four patients <45 years without alarm symptoms were diagnosed with a new malignancy. One of them (41 years of age), complaining of dyspepsia with reflux resistant to empiric proton pump inhibitor therapy, was diagnosed with a gastric lymphoma. The remaining three, all complaining of dyspepsia resistant to empiric treatment, were diagnosed with gastric cancer at 41 (T2 N1 M0), 43 (T1 N1 M0), and 44 years of age (T1 N1 M0), respectively.

Accuracy of the logistic regression model

The association between each of the included variables and the selected endoscopic outcomes at univariate and multivariate analyses are shown in **Tables 4** and **5**.

Table 6. Estimates of accuracy of the different strategies in selecting EGD referrals for the detection of (a) relevant findings and (b) new malignancies

Strategy	Rate of EGDs indicated (%)	NNT	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV% (95% CI)	NPV% (95% CI)	AUC (95% CI)
(a)							
ASGE guidelines	80	2	88 (87, 89)	27 (25, 28)	51 (50, 52)	72 (70, 74)	0.55 (0.53, 0.57)
Age 45 years/ alarm features	78	2	82 (81, 83)	26 (24, 27)	49 (47, 50)	63 (61, 65)	0.52 (0.5, 0.54)
Multivariate model	39	1.6	53 (52, 55)	74 (72, 75)	64 (62, 66)	64 (63, 65)	0.69** (0.68, 0.70)
ANN model	73	1.8	84 (83, 85)	36 (34, 37)	54 (52, 55)	72 (70, 74)	0.66* (0.64, 0.67)
(b)							
ASGE guidelines	80	50	98 (95, 100)	20 (19, 21)	2 (1.6, 2.4)	99.8 (99.7, 100)	0.58 (0.54, 0.63)
Age ≥45 years/ alarm features	78	50	97 (93, 99)	22 (21, 23)	2 (1.6, 2.3)	99.8 (99.5, 100)	0.58 (0.54, 0.62)
Multivariate model	12	11	60 (53, 67)	89 (88, 90)	9 (7, 11)	99 (99, 99.4)	0.82* (0.78, 0.86)
ANN model	19	14	83 (77, 90)	82 (81, 83)	7 (6, 9)	99.6 (99.3, 99.8)	0.87** (0.83, 0.89)

ANN, artificial neural network; ASGE, American Society for Gastrointestinal Endoscopy; CI, confidence interval; EGD, upper endoscopy; NNT, number needed to scope; NPV, negative predictive value; PPV, positive predictive value.
We also reported the rate of EGDs classified as indicated (true+false positives) for each strategy and the number of EGD to be performed to detect 1 finding (NNT), to provide an estimate of the endoscopic workload.
*$P<0.05$ as compared with the ASGE guidelines and age 45 years/alarm features.
**$P<0.05$ as compared with all the other strategies.

Mean sensitivity, specificity, and AUC of the logistic regression model for the detection of relevant findings were 53%, 74%, and 0.69, respectively. Positive and negative predictive values were 64 and 64%, respectively.

Mean sensitivity, specificity, and AUC for the detection of new cases of malignancy were 60%, 89%, and 0.82, respectively. Positive and negative predictive values were 9 and 99%, respectively.

Accuracy of the ANN model

The following variables were selected from the ANN algorithm for the prediction of relevant findings: age ≥45 years, sex, alarm symptoms, in-patient setting, typical and atypical reflux, and the presence of relevant findings at previous EGD.

Estimates of ANN sensitivity, specificity, and AUC for relevant findings were 84%, 36%, and 0.66, respectively. Positive and negative predictive values were 54 and 72%, respectively.

The following variables were selected for the prediction of new malignancy: age ≥45 years, weight loss, dysphagia, GI bleeding, vomiting, reflux, use of nonsteroidal anti-inflammatory drugs/ anti-cyclooxygenase-2/aspirin, and the presence of relevant findings at previous EGD.

Estimates of ANN sensitivity, specificity, and the AUC for new malignancy were 83%, 82%, and 0.87, respectively. Positive and negative predictive values were 7 and 99.6%, respectively.

Comparison among the different strategies

As shown in **Table 6** and **Figure 1**, there was no statistically significant difference in accuracy (AUC values) for both relevant findings and new malignancy between the ASGE criteria and the simplified rule (age ≥45/alarm symptoms), whereas both of them were less accurate than the logistic regression and the ANN models for both relevant findings and cancer detection. The ANN model also seemed to be statistically significantly more accurate than the logistic regression model for new malignancy, whereas the logistic regression model was more accurate than the ANN model for relevant findings.

DISCUSSION

Our study shows that a simple prediction rule based on age and alarm features is as accurate as the ASGE guidelines in selecting patients for EGD. It is noted that this is true not only for benign relevant findings but also for new cases of malignancy. The validity of this approach is indirectly confirmed by the selection of age and most of the alarm features as independent predictors at both multivariate and ANN analyses. It could be argued that dyspepsia is the most frequent indication for EGD, and that the accuracy of age and alarm features has already been widely described in dyspeptic patients (i.e., Maastricht criteria) (18). However, we have shown that such accuracy is similar in both dyspeptic and nondyspeptic patients, most of the latter presenting with reflux, suggesting the possibility of using a simplified rule also in nondyspeptic patients. This is clearly related to the intimate association between older age and a higher risk of cancer, which is independent from the clinical presentation of the upper GI symptoms (18,23).

It seems to be clinically relevant to offer a simple alternative to the ASGE guidelines. Such guidelines are quite complex, consisting of 9 general indications and more than 20 specific indications

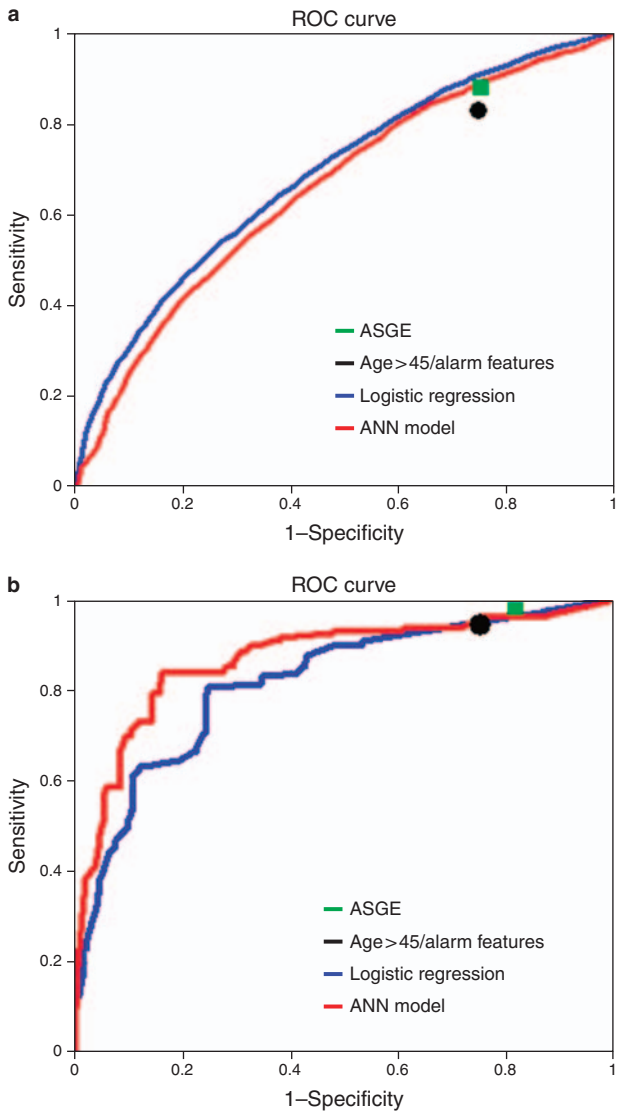

Figure 1. (**a**) Receiver-operating characteristic (ROC) curve for logistic regression and ANN models for relevant findings and (**b**) new cases of malignancy. We also reported the accuracy values for the ASGE criteria and the simplified rule (age 45/alarm features). The ROC represents the relationship between sensitivity and specificity for the prediction of each of the considered outcomes. ANN, artificial neural network; ASGE, American Society for Gastrointestinal Endoscopy.

(4). It is noted that only a minority of the EGDs in our study—i.e., 17%—were prescribed by gastroenterologists, showing that, after the implementation of an open-access system, most of the referrals come from primary care physicians or other specialists. A simple prediction rule based on age and alarm features would seem more suitable to non-GI physicians as compared with the more complex ASGE guidelines.

It could be argued that although we confirmed the high sensitivity of the ASGE guidelines for both relevant findings and cancer, both the simplified rule and the ASGE criteria seemed to be hampered by low specificity. However, the relatively high prevalence of relevant endoscopic findings reduces the importance of specificity in this setting, so that the positive predictive value is still close to 50%. For this reason, the substantial improvement in specificity achieved by logistic regression and ANN models only marginally increases the positive predictive value.

The simplified clinical rule seemed to have a very high sensitivity for malignancy, so that its negative predictive value was practically equal to that of the other options. In detail, one case of cancer would be detected for every 50 EGDs performed in patients ≥45 years or with alarm features, whereas 457 EGDs in patients <45 years without alarm features would have been required to detect one cancer. Moreover, to detect a cancer does not necessarily correlate with saving a life. Our data on the stage of presentation of gastroesophageal cancers were very dismal. Only one-third of the patients underwent a surgery with curative intent, and <10% had a cancer in a localized stage. This would mean that more than 5,700 EGDs in patients <45 years without alarm symptoms would be required to detect one cancer in a localized stage. Moreover, none of the patients <45 years without any alarm symptoms were found to have a cancer in a localized disease in our series. It could be argued that no cancer in patients <45 years would have been missed if we had considered as indicated all the initial EGDs performed in those without alarm symptoms and the successive endoscopies in those with a previous relevant endoscopic finding. However, in this case only 3% of all the study EGDs would have been considered as "not indicated," such a marginal rate questioning on the usefulness of a widespread implementation of a clinical strategy. Different from relevant findings, the higher specificity of both logistic regression and ANN models substantially affected the positive predictive value, because of the low prevalence of malignancy. In detail, these models identified a relatively small subgroup of population—between 12 and 19% of all the population—at higher risk for malignancy that may need a prioritized EGD.

Despite the high accuracy of malignancy for both clinical strategies and predictive models, it could be argued that a few cancers would be ineludibly missed when adopting any of these strategies to select access to EGD. Conversely, such malignant lesions would be detected when performing an initial endoscopic examination of any patient independently of the presenting complaint. Ultimately, it is an individual decision of any health system whether to adopt or not adopt any filter to select access for EGD, as well as for any other medical procedure. The rationale behind adopting a filter is that the resources saved by not performing the inappropriate procedures may be shifted in a more effective and efficient manner to other medical procedures in which a higher diagnostic yield is expected because of the appropriateness of the indication (13).

The main limitation of our study was that we did not randomize patients according to the ASGE criteria and the simplified prediction rule. However, it is unlikely that systematic bias could have altered the collection of the patient age and the presence of alarm symptoms.

In conclusion, our study showed that a simple rule based on age and alarm features may be as accurate as the more complex ASGE guidelines in predicting endoscopic outcome in an unselected EGD population. Regression and ANN models may be useful to prioritize patients at higher risk of malignancy.

CONFLICT OF INTEREST

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Appropriateness of upper endoscopy (EGD) indication according to the American Society for Gastrointestinal Endoscopy (ASGE) guidelines has been related to a higher diagnostic yield for relevant endoscopic findings and to a favorable cost-effectiveness profile.
- ✓ Accuracy of the ASGE guidelines has never been compared with other predictive rules to select patients for EGD.

WHAT IS NEW HERE

- ✓ In this multicenter, prospective study that included 8,252 patients, accuracy of a simplified rule on the basis of age and alarm symptoms was similar to that of the ASGE guidelines for both relevant findings and cancer, without any difference between dyspeptic and nondyspeptic patients.
- ✓ Both logistic regression and artificial neural network (ANN) models seemed to be substantially more accurate in predicting new cases of malignancy, mainly because of higher specificity.
- ✓ A simple rule based on age and alarm features may be as accurate as the more complex ASGE guidelines in predicting endoscopic outcome.
- ✓ Regression and ANN models may be useful to prioritize patients at higher risk of malignancy.

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ENDOSCOPY

APPENDIX A

List of the endoscopic findings regarded as relevant for the purpose of this study
Esophagus
Peptic esophagitis
Varices
Barrett's esophagus
Micotic esophagitis
Cancer
Foreign body
Peptic stricture
Mallory–Weiss
Anastomotic stricture
Caustic lesion
Caustic stricture
Stomach
Erosive gastritis
Hypertensive gastropathy
Polyp
Peptic ulcer
Cancer
Stomitis
Fundus varices
Anastomotic ulcer
Gastric antral vascular ectasia
Angiodysplasia

Continued
Lymphoma
Foreign body
Anastomotic stricture
Menetrier's syndrome
Duodenum
Erosive duodenitis
Duodenal ulcer
Signs of malabsorption
Cancer
Ampulloma

APPENDIX B

Methodology of the artificial neural networks (ANNs)

Preprocessing methods and experimental protocols

Data preprocessing was performed using two different resampling criteria of the global dataset.

Random criterion:

We used the so-called 5×2 cross-validation protocol (1). In this procedure, the study sample is randomly divided five times into two subsamples, always different but containing similar distribution of cases and controls: the training subsample (containing the dependent variable) and the testing subsample. During the training phase, ANNs learn a model of data distribution and then, on the basis of such a model, classify subjects in the testing set in a blind manner. Training and testing sets are then reversed, and consequently 10 analyses for every model used are conducted.

Optimized criterion: training with input selection and testing system

The training with input selection and testing system consists an ensemble of two previously described systems: T&T and IS (2). The T&T system is a robust data resampling technique that arranges the source sample into subsamples that all possess a similar probability density function. In this way, data are split into two or more subsamples to train, test, and validate the ANN models more effectively. The IS system is an evolutionary wrapper system that reduces the amount of data while conserving the largest amount of information available in the data set. The combined action of these two systems allows us to solve two frequent problems in managing ANNs. Both systems are based on a Genetic Algorithm, the Genetic Doping Algorithm (GenD) developed at the Semeion Research Centre (3). After this processing, the features that were most significant for the classification were selected, and at the same time the training set and the testing set were created with a function of probability distribution similar to the one that provided the best results in the classification. A supervised Multi-Layer Perceptron, with four hidden units, was then used for the classification task.

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APPENDIX C

Distribution of clinical features among the discordant pairs of predictions among the different strategies for both (a) relevant findings and (b) new cases of cancer

Variable	ASGE vs. simplified rule	ASGE vs. log regression	ASGE vs. ANN	ANN vs. log regression	Simplified rule vs. log regression	Simplified rule vs. ANN
(a)						
Number of discordant pairs	1,849	3,370	1,227	3,155	3,593	2,242
Referring physician (%)						
PCP	63	63	55	64	63	63
Other specialties	16	10	16	9	11	15
Gastroenterologist	21	27	29	26	26	22
Setting (%)						
In-patient	23	23	31	21	23	21
Outpatient	77	77	69	78	77	79
First endoscopy	74	79	65	76	69	67
Previous EGD	26	21	35	24	31	33
Relevant finding at previous EGD	15	5	20	6	8	11
Clinical features (%)						
Anemia	5	13	12	13	12	7
Weight loss	2	4	3	5	4	2
Dysphagia	1	6	3	7	6	2
Bleeding	8	1	4	2	1	2
Family history of cancer	1	2	1	2	2	2
Vomiting	3	7	1	7	7	1
Dyspepsia	60	61	60	55	58	58
Reflux	34	24	25	31	24	30
Atypical reflux	4	4	9	5	4	6
Alarm symptom	18	29	21	31	29	14
PPI therapy	31	37	37	35	33	34
Antisecretory/antiacid therapy	46	47	48	44	43	47
NSAIDs/anti-COX2/aspirin	9	10	8	10	10	7

Continued

Variable	ASGE vs. simplified rule	ASGE vs. log regression	ASGE vs. ANN	ANN vs. log regression	Simplified rule vs. log regression	Simplified rule vs. ANN
(b)						
Number of discordant pairs	1,848	5,252	4,879	716	5,035	4,682
Referring physician (%)						
PCP	72	56	57	36	57	59
Other specialties	13	20	20	20	18	18
Gastroenterologist	15	24	23	45	25	23
Setting (%)						
In-patient	12	25	23	49	25	23
Outpatient	88	75	77	51	75	76
First endoscopy	61	65	63	67	59	57
Previous EGD	39	35	37	33	41	43
Relevant finding at previous EGD	18	21	24	11	23	26
Clinical features (%)						
Anemia	0.9	10	9	19	11	10
Weight loss	0.2	1	0.9	6	1	1
Dysphagia	0.3	3	2	15	3	2
Bleeding	0.4	5	5	27	6	5
Family history of cancer	1	1	1	0.7	2	2
Vomiting	0.7	3	3	13	4	3
Dyspepsia	58	53	53	36	51	52
Reflux	36	31	33	8	29	30
Atypical reflux	4	4	4	1	4	4
Alarm symptom	4	23	20	70	25	22
PPI therapy	36	36	37	31	34	34
Antisecretory/antiacid therapy	49	48	48	41	44	45
NSAIDs/anti-COX2/aspirin	5	9	10	15	10	11

ANN, artificial neural network; ASGE, American Society for Gastrointestinal Endoscopy; COX2, cyclooxygenase-2; EGD, upper endoscopy; log regression: logistic regression model; NSAID, nonsteroidal anti-inflammatory drug; PCP, primary care physician; PPI, proton pump inhibitor.
Strategies were defined as discordant when classifying in an opposite way the same EGD (i.e., indicated for ASGE and not indicated for the regression model).