Diagnosis of gastric adenocarcinoma using a scoring system: Combined assay of serological markers of *Helicobacter pylori* infection, pepsinogen I and gastrin

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Abstract: This study was carried out to develop a scoring system for the diagnosis of gastric adenocarcinoma (GAC). A total of 686 subjects, 150 patients with GAC, 182 with gastric ulcer, 127 with duodenal ulcer, and 227 subjects with negative findings, were enrolled. Analysis of the likelihood ratio (LR) showed that patients with advanced age, ulcer in the stomach, low serum levels of pepsinogen I (PGI), low PGI $\times$ gastrin values, and low PGI/gastrin ratio were likely to have GAC. Of these indicators, the serum PGI level had the greatest weight, with a LR of 7.59 for the group with a level <30 ng/ml. A scoring system combining serum PGI level, *Helicobacter pylori* seropositivity, and gastric ulcer status was derived, using a logistic regression model. This scoring system was found to be better than any one-parameter criterion for diagnosing GAC after evaluation by the area under the receiver operating characteristic curve (0.84; 95% confidence interval, 0.81–0.88) or by specificity-fixed sensitivity (sensitivity 0.82 at specificity 0.72, sensitivity 0.87 at specificity 0.66, sensitivity 0.96 at specificity 0.44). This scoring system may be potentially useful as a new model for the noninvasive diagnosis of GAC in the future.

Key words: pepsinogen I, *H. pylori*, gastric adenocarcinoma, scoring system

Introduction

Gastric adenocarcinoma (GAC) is one of the most common cancers worldwide.¹ The diagnosis of GAC is based mainly on endoscopy combined with histologic examination. The invasiveness of endoscopy generally makes it non-feasible for the screening of asymptomatic subjects. Except in Japan, where mass screening programs are successfully performed, the majority of GAC are found at an advanced stage and the patients have a poor prognosis.² Various tumor markers have been evaluated for the early diagnosis of GAC; however, their low sensitivity and specificity precludes their clinical use for the early detection of this disease.^{3–5}

Previous reports have shown that serum pepsinogen I (PGI) levels are low in patients with atrophic gastritis and GAC,^{6–9} but that serum gastrin levels are elevated in these patients.^{10,11} A combination of these two markers may significantly improve the diagnostic ability for detecting severe atrophic gastritis and, probably, GAC.¹² Recently, it has been reported that *Helicobacter pylori* infection is also associated with GAC.^{13,14} However, serum levels of gastrin and PGI were reported to be affected by *H. pylori* infection.^{15,16} The complex interaction among these factors indicates that using any one-parameter criterion for the diagnosis of GAC would usually be inadequate, and a combined assay of *H. pylori* seropositivity and serum levels of PGI and gastrin may be needed.

In this study, a scoring system using these three serologic markers, as well as other clinical variables, was developed. The predictive power and diagnostic value of the proposed system are potentially useful as a new model for the noninvasive diagnosis of GAC in the future.

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Materials and methods

Subjects

Between January 1992 and June 1993, a total of 686 subjects who underwent endoscopic examination in the National Taiwan University Hospital were enrolled in the present study. They were free from major cardiopulmonary, hepatobiliary, and renal diseases. None of them had received gastric surgery, or were receiving ongoing treatment with antibiotics, acid reducing agents, or nonsteroidal antiinflammatory drugs. One hundred and fifty of the 686 subjects were diagnosed histologically as having GAC. The non-GAC controls (536 subjects) consisted of 227 negative controls with normal gastric mucosa or minimal gastritis (determined by endoscopy after the exclusion of macroscopic abnormalities, including intestinal metaplasia, atrophic gastritis, erosions, ulcers, polyps, and tumors in the stomach and duodenal bulb), 182 patients with endoscopically and histologically confirmed benign gastric ulcer, and 127 patients with endoscopically verified duodenal ulcer (Table 1). Two hundred and forty patients with peptic ulcer had endoscopic evidence of antral gastritis.

Laboratory methods

Fasting blood samples, obtained from all subjects on the morning of their first endoscopy, were stored at -70°C until examination. IgG antibodies against *H. pylori* were tested using an enzyme-linked immunosorbent assay (ELISA) (HEL-p test; AMRAD, Victoria, Australia). The antigen was an inactivated

native antigen of *H. pylori*. The manufacturer's state that this assay has a sensitivity of 96% and a specificity of 93%. The serum level of PGI was determined with a commercial radioimmunoassay kit (Sorin Biomedica, Saluggia, Italy), was the serum level of gastrin (Incstar Corp., Stillwater, Minn.). Serum PGI and gastrin levels were expressed as means $\pm$ SD.

Statistical analysis

Evaluation of single diagnostic test (one-parameter criterion). Various laboratory and clinical characteristics of the study subjects were evaluated with regard to their diagnostic value in GAC. As some test results were repeated on continuous scales, the likelihood ratios (LRs), calculated by dividing the proportion of GAC patients with a given result by the proportion of non-GAC subjects with the same result, were employed in this study instead.¹⁷ Ninety-five percent confidence intervals (CI) for the LRs were also determined.¹⁸ The posterior odds (and hence the posterior probability) of having GAC for a subject with a result "x" were calculated by the following formula:¹⁷

Posterior odds of GAC at x = (prior odds) $\times$ (LR at x)

Construction of a scoring system. A binary logistic model was used to examine how GAC occurrence depends on laboratory results and any covariates of interest. A forward stepwise algorithm was employed to select the significant predictors. The variables evaluated were: sex (male/female); age (categorized into five 10-year levels); ulcer in the stomach (yes/no); *H. pylori* seropositivity (yes/no); serum PGI; serum

Table 1. Demographic data, *H. pylori* seropositivity, and serum levels of pepsinogen I and gastrin in gastric adenocarcinoma (GAC) cases and non-GAC subjects

	GAC cases (<i>n</i> = 150)	Non-GAC subjects (<i>n</i> = 536)		
		GU (<i>n</i> = 182)	DU (<i>n</i> = 127)	NC (<i>n</i> = 227)
Age in years (range)	59.2 $\pm$ 14.7 (24–87)	59.5 $\pm$ 12.3 (26–88)	48.1 $\pm$ 12.3* (18–83)	46.6 $\pm$ 13.5* (18–79)
Sex ratio Male/Female	102/48	131/51	82/45	87/140**
<i>H. pylori</i> positivity (%)	91/150 (60.7)	148/182 (81.3)	108/127 (85.0)	129/227 (56.8)
Serum PGI in ng/ml (range)	61.9 $\pm$ 36.9 (4.6–207.2)	101.9 $\pm$ 53.9* (9.2–271)	94.1 $\pm$ 36.7* (18.5–254)	66.0 $\pm$ 24.0 (19.2–140)
Serum GS in pg/ml (range)	62.2 $\pm$ 29.0 (12.6–184)	62.0 $\pm$ 28.8 (21–233)	57.7 $\pm$ 17.9 (33.7–161)	69.8 $\pm$ 33.9 (18.1–245)

* $P < 0.005$ vs GAC by Student's *t*-test; ** $P < 0.005$ vs GAC by chi-square test with Yate's correction

GAC, Gastric adenocarcinoma; GU, gastric ulcer; DU, duodenal ulcer; NC, negative control; PGI, pepsinogen I; GS, gastrin; *H. pylori* positivity, no. of subjects with positive IgG antibody to *H. pylori*/no. subjects examined

All data are expressed as means $\pm$ SD

gastrin; the product $\text{PGI} \times \text{gastrin}$; and the ratio $\text{PGI}/\text{gastrin}$. Each of the last four factors were categorized into four levels. The significance level for entering the model was set at a type 1 error of 0.05. The analysis was performed by the SAS/LOGISTIC program.¹⁹ After the final model was selected, the "intercept" estimated from the model was subtracted by logarithm (prior odds of GAC), that is, $\log(150/536) = -1.27$.²⁰ All the parameters in the model were then exponentiated, rescaled, and rounded to serve as clinically useful scores. The scores corresponding to each level of the diagnostic criteria for a subject can be multiplied together to produce a composite score. This composite score also represents the model-based LR of being a GAC case for that particular subject.²⁰ Based on this scoring formula, any subject could be classified into a "case" or a "non-case" category if his/her composite score (or LR) was greater or less than one. A desired level of sensitivity (or specificity) can also be achieved by varying the cut-off point for the composite score.

Evaluation of the scoring system. To evaluate the predictive power of the scoring system, GAC cases and non-GAC subjects in this study were separately grouped into five categories according to their composite scores derived from the model. The expected number of subjects in each category was calculated and compared to the, observed number. The goodness-of-fit test of Hosmer and Lemeshow was applied.²¹

To compare the diagnostic values of the scoring system with any one-parameter criterion, areas under the receiver operating characteristic (ROC) curves (AUC) were used as the performance indices.²² The AUCs were calculated by the trapezoid rule.²² A non-parametric statistical test was used for the comparison.²³ With regard to discrete diagnostic tests, we fixed the specificity at the level of the discrete test and compared the estimated sensitivity of the scoring system with the sensitivity of the discrete test.²⁴ The sensitivity of the scoring system at a particular level of specificity was estimated by linear intrapolation if required.

Results

Clinical and laboratory characteristics

As shown in Table 1, patients with GAC were significantly older than the patients with duodenal ulcer ($P < 0.005$) and the negative controls ($P < 0.005$). Female predominance was noted only in the negative controls (male/female, 87/140, $P < 0.005$ vs GAC). No significant difference in *H. pylori* seropositivity was observed between GAC cases and non-GAC subjects. The serum PGI levels were significantly

higher in patients with gastric ulcer (101.9 ± 53.9 ng/ml) and duodenal ulcer (94.1 ± 36.7 ng/ml) than in those with GAC (61.9 ± 36.9 ng/ml) ($P < 0.005$). Serum gastrin levels in GAC cases were not significantly different from those in patients with gastric or duodenal ulcer, or the negative controls.

Diagnosis of gastric adenocarcinoma (GAC) with a single parameter

The LRs of diagnosing GAC by clinical characteristics and/or laboratory results are shown in Table 2. Subjects with advanced age, ulcer in the stomach, low levels of serum PGI, low $\text{PGI} \times \text{gastrin}$ values, and low $\text{PGI}/\text{gastrin}$ ratios were likely to have GAC. Of these variables, serum PGI level had the greatest weight, with LRs ranging from 7.59 to 0.56.

Table 2. Likelihood ratios (LR) with 95% confidence intervals (CI) of subjects being gastric adenocarcinoma cases by clinical characteristics and laboratory results

	GAC cases	Non-GAC subjects	LR	95% CI
Sex				
Female	48	236	0.73	0.56–0.94
Male	102	300	1.21	1.06–1.39
Age (years)				
≤ 40	24	122	0.70	0.47–1.05
41–50	15	126	0.43	0.26–0.70
51–60	30	127	0.84	0.59–1.20
61–70	48	124	1.38	1.05–1.83
> 70	33	37	3.19	2.07–4.91
Ulcer in the stomach				
No	25	354	0.25	0.18–0.36
Yes	125	182	2.45	2.14–2.82
<i>H. pylori</i>				
Negative	59	151	1.40	1.10–1.78
Positive	91	385	1.84	0.73–0.97
PGI (ng/ml)				
≤ 30	34	16	7.59	4.31–13.37
31–50	29	77	1.35	0.91–1.98
51–80	48	195	0.88	0.68–1.14
> 80	39	248	0.56	0.42–0.75
Gastrin (pg/ml)				
≤ 40	32	81	1.41	0.98–2.04
41–60	54	207	0.93	0.73–1.18
61–80	31	129	0.86	0.61–1.22
> 80	33	119	0.99	0.70–1.39
$\text{PGI} \times \text{gastrin}$ value				
≤ 2000	45	48	3.35	2.33–4.82
2001–4000	50	181	0.99	0.76–1.27
4001–6000	25	151	0.59	0.40–0.87
> 6000	30	156	0.69	0.49–0.97
$\text{PGI}/\text{gastrin}$ ratio				
≤ 0.6	43	53	2.90	2.02–4.15
0.61–1.20	48	188	0.91	0.70–1.18
1.21–1.80	36	138	0.93	0.68–1.28
> 1.80	23	157	0.52	0.35–0.78

PGI, Pepsinogen I

Diagnosis of gastric adenocarcinoma (GAC) with the scoring system

The scoring system derived from the logistic regression model is shown in Table 3. The background score was 7.2 for every subject. Presence of ulcer in the stomach, absence of *H. pylori* infection, and lower serum levels of PGI were associated with increased scores.

Table 4 shows the predictive power of this scoring system: The expected number of subjects in each category as predicted by the model was in close agreement with the observed number (goodness-of-fit test $P = 0.1841$). The performance of the scoring system as compared to various one-parameter criteria is shown in Table 5. The AUC of the scoring system was 0.84 (95% CI 0.81–0.88), with a sensitivity of 0.82 at specificity 0.72, sensitivity 0.87 at specificity 0.66, and sensitivity 0.96 at specificity 0.44. The scoring system was better than any one-parameter criterion, as evaluated by AUC or by specificity-fixed sensitivity. This superiority reached a significant level, except

Table 5. Comparison of performance of the scoring system and various one-parameter criteria

Diagnostic test or clinical characteristics	AUC (95% CI) ^a	Sensitivity/ Specificity
Scoring system	0.84 (0.81–0.88)	0.82/0.72 0.87/0.66 0.96/0.44
One-parameter criterion		
PGI	0.66 (0.61–0.71)*	–
Gastrin	0.53 (0.47–0.58)*	–
PGI × gastrin value	0.65 (0.60–0.71)*	–
PGI/gastrin ratio	0.62 (0.57–0.67)*	–
Age	0.65 (0.60–0.71)*	–
<i>H. pylori</i> seropositivity	–	0.39/0.72*
Ulcer in stomach	–	0.83/0.66
Sex	–	0.68/0.44*

* $P < 0.0001$, compared with scoring system

AUC, Areas under receiver operating characteristics (ROC) curves; 95% CI, 95% confidence interval; PGI, pepsinogen I

when compared to the variable of the presence of ulcer in the stomach.

Table 3. Scoring system^a derived from the logistic regression model

Terms	Score
Background score	7.2
Ulcer in the stomach	
No	0.1
Yes	1.4
Pepsinogen I (ng/ml)	
≤30	2.0
31–50	0.4
51–80	0.2
>80	0.1
<i>H. pylori</i>	
Negative	1.8
Positive	1.0

^a Scores corresponding to each level of the diagnostic results for a subject can be multiplied together to produce a composite score, which is also the likelihood ratio for being a GAC case for the subject under evaluation

Table 4. Observed (*Obs*) vs expected (*Exp*) number of GAC cases and non-GAC subjects by composite score category^a

Composite score category	GAC cases Obs (Exp)	non-GAC subjects Obs (Exp)	Total
≤0.25	6 (7.1)	234 (232.9)	240
0.26–0.50	11 (6.2)	77 (81.8)	88
0.51–2.00	41 (42.6)	146 (144.4)	187
2.01–4.00	43 (39.9)	57 (60.1)	100
≥4.00	49 (50.6)	22 (20.4)	71
Total	150 (146.3)	536 (539.7)	686

^a Goodness-of-fit test $\chi^2 = 4.838$, $P = 0.1841$

Discussion

In this study, the demographic data of GAC patients were in line with other series.² Although the seroprevalence (60.7%) of *H. pylori* infection in GAC cases was not significantly different from that in the negative controls (56.8%), the seropositivity of patients with gastric ulcer and duodenal ulcer was higher than that in the GAC cases. This result is in accordance with the hypothesis that *H. pylori* infection may be associated with peptic ulcer, but is not sufficient for gastric carcinogenesis.²⁵ Findings similar to ours have also been reported.^{26–29} The lower serum PGI levels in GAC observed in this study are also consistent with previous reports and thus suggest that PGI may be a potential serologic marker for GAC.^{8,9} Nevertheless, there is a considerable overlapping in PGI between GAC and benign conditions. Various other factors, such as the gastric inflammation induced by *H. pylori* infection, may also increase serum PGI.¹⁶ Therefore, the diagnosis of GAC using this single parameter may not be satisfactory.

Based on our LR analysis, advanced age, ulcer in the stomach, low serum PGI level, low PGI × gastrin values, and low PGI/gastrin ratio were associated with an increased likelihood of having GAC. Serum PGI level less than 30 ng/ml had the highest LR (7.59) and had the greatest weight. This cut-off-point (30 ng/ml) was also mentioned in a previous report on atrophic gastritis.³⁰ However, in contrast to the study of Farinati et al.,¹² neither the PGI × gastrin value nor the PGI/gastrin ratio was better than PGI alone in

predicting the risk for GAC in this study. Gastrin alone was also not of diagnostic value in our study.

In our scoring system, the presence of ulcer in the stomach increased the composite score. This finding should not, however, be interpreted as reflecting gastric cancers arising from pre-existing benign ulcer. It may simply indicate that, in our study, the gastric malignancy was generally of the ulcerative type, rather than of the fungating type. The role played by *H. pylori* in our scoring system also deserves close scrutiny. In our system, negative IgG antibody to *H. pylori* increased the composite score. This apparently paradoxical result may be due to a complex interaction between *H. pylori* seropositivity and age.²⁶ In general, although the prevalence of *H. pylori* infection has been found to increase with age, it tends to decline after an advanced age is reached.^{16,26} The predominance of aged patients and the relatively low *H. pylori* seropositivity in GAC in this study may explain why *H. pylori* seronegativity increased the composite score and, thus, the GAC risk. Further analysis, using tree-structured classification,³¹ may clarify the role played by *H. pylori* in gastric carcinogenesis and thus improve our scoring system.

The markers that predict GAC in this scoring system are clinically simple to use. It is convenient to draw blood and measure the serologic markers of *H. pylori* and PGI. To recognize the presence of gastric ulcer, a non-invasive examination such as double-contrast upper gastrointestinal radiology may be employed. Based on the above methods, any subject can easily be classified as a "GAC suspect" or a "non-GAC subject" if their composite scores are greater or less than one. As this composite score system also represents the model-based LR of having GAC for a particular subject, it may be useful for the targeting of high-risk patients for additional investigation. Furthermore, it may serve as a supplemental means to distinguish a benign from a malignant gastric ulcer when radiology alone is controversial.

PGI was a slightly more favorable marker than others in our study. Nevertheless, the PGI/PGII ratio, rather than PGI alone, has recently been demonstrated to have greater weight for estimating the severity and/or extent of atrophic gastritis, and to be more predictive of gastric cancer.^{9,30,32} Therefore, further investigations to increase the predictive value of our model by combining other serum markers, such as PGII, are mandatory in the future.

This study was a preliminary attempt to analyze the clinical usefulness of various serum markers and demographic characteristics for the diagnosis of GAC from a new perspective. The scoring system we have proposed awaits further evaluation in different clinical settings and in different patient populations.

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