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ORIGINAL ARTICLE

The new modified ABCD method for gastric neoplasm screening

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Abstract

Background The ABCD screening method was developed for risk stratification of gastric cancer. It is unclear whether the ABCD method can predict the risk of gastric neoplasms, including gastric adenomas, as observed for gastric cancer. We aimed to devise a modified ABCD method for predicting gastric neoplasms.

Methods We reviewed 562 patients who had undergone upper gastrointestinal tract endoscopy and whose serum IgG anti-*Helicobacter pylori* antibody, gastrin, and pepsinogen (PG) I and PG II data were available. Patients were classified into the following four groups: *H. pylori* antibody negative and normal PG level (group A), *H. pylori* antibody positive and normal PG level (group B), *H. pylori* antibody positive and low PG level (group C), and *H. pylori* antibody negative and low PG level (group D).

Results The PG I/PG II ratio was lower in patients with gastric neoplasms than in patients without these lesions (gastric adenoma vs gastric cancer vs no neoplasm, 3.7 ± 2.0 vs 3.8 ± 1.8 vs 4.9 ± 2.1, $P < 0.001$). The optimal cutoff values of the PG I/PG II ratio for predicting gastric neoplasms were 3.1 for *H. pylori* antibody negative patients and 4.1 for *H. pylori* antibody positive patients. A higher group grade was associated with a significantly higher proportion of gastric neoplasms [odds ratio (95 % confidence interval), group A, reference; group B, 1.783 (1.007–3.156); group C, 3.807 (2.382–6.085); and group D, 5.862 (2.427–14.155)].

Conclusions The modified ABCD method using two different cutoff values according to the *H. pylori* antibody status was useful for predicting the presence of gastric neoplasms. This method might be a supplementary screening tool for both gastric adenoma and gastric cancer. However, further studies will be required to provide a definitive conclusion.

Keywords ABCD method · IgG anti-*Helicobacter pylori* antibody · Pepsinogen · Gastric cancer · Gastric adenoma

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Introduction

Gastric cancer is one of the major causes of cancer-related death worldwide, and almost 990,000 cases of gastric cancer are detected annually [1]. The prognosis of patients with gastric cancer depends on the tumor stage [2–4]. In Korea and Japan, a mass screening program that uses upper gastrointestinal tract endoscopy and gastric fluoroscopy has been introduced for the early detection of gastric cancer [5, 6]. However, upper gastrointestinal tract endoscopy and gastric fluoroscopy are costly and inconvenient for people undergoing screening. In addition, gastric cancer is diagnosed in many patients without them undergoing periodic gastric cancer screening in Korea despite this nationwide cancer screening program [7].

In Japan, the ABCD screening method, which combines the detection of serum IgG anti-*Helicobacter pylori* antibody and the measurement of serum pepsinogen (PG) levels, has been developed for risk stratification of gastric

cancer [8, 9]. Because the ABCD screening method requires only blood sampling, it is much simpler and less invasive than upper gastrointestinal tract endoscopy or gastric fluoroscopy. This screening method is based on two well-known risk factors, namely, *H. pylori* infection and atrophic gastritis. The first risk factor, *H. pylori* infection, is evaluated on the basis of the IgG anti-*H. pylori* antibody status. The second risk factor, atrophic gastritis, is assessed by serum PG I and PG II levels. The serum PG status is usually defined as "atrophic" when both criteria of a serum PG I level of 70 ng/mL or lower and a PG I/PG II ratio of 3.0 or lower are simultaneously fulfilled, as proposed by Miki et al. [9, 10]. Then, individuals are classified into four groups as follows: (1) IgG anti-*H. pylori* antibody negative and normal PG level (group A), (2) IgG anti-*H. pylori* antibody positive and normal PG level (group B), (3) IgG anti-*H. pylori* antibody positive and atrophic PG status (group C), and (4) IgG anti-*H. pylori* antibody negative and atrophic PG status (group D). Previous studies demonstrated that the risk of gastric cancer was higher in group C or group D than in group A or group B [8, 11, 12].

Although the ABCD screening method has been validated in some studies performed exclusively in Japan [8, 11–14], some questions remain unanswered. The first issue is the optimal PG cutoff value for determining atrophic gastritis. Several studies used the same criteria proposed by Miki et al. for defining atrophic PG status [8, 11–14]; however, Miki et al. [10] determined the PG cutoff value on the basis of endoscopically diagnosed atrophic gastritis rather than histologically confirmed atrophic gastritis. Therefore, the best PG cutoff value for optimal grouping in the ABCD method as well as for predicting histologic atrophic gastritis may differ somewhat from the value proposed by Miki et al. The second issue is whether the applicability of the ABCD method can be extended to predict the risk of gastric neoplasms including gastric adenomas as well as just gastric cancers. This may be an important issue at present because endoscopic resection has become increasingly used for the treatment of early gastric neoplasms including early gastric cancers and gastric adenomas [7].

To answer the aforementioned questions, we set two study aims. The first aim was to devise a modified ABCD method using the optimal PG cutoff value for gastric cancer risk stratification. The second aim was to ensure that the modified ABCD method could be applied for predicting gastric neoplasms rather than only gastric cancer.

Methods

Patients

We retrospectively reviewed consecutive patients who had undergone upper gastrointestinal tract endoscopy and whose serum IgG anti-*H. pylori* antibody, gastrin, and PG I and PG II data were available at Severance Hospital in Seoul, Korea, between May 2012 and August 2014. Patients with gastric neoplasms other than gastric adenoma and gastric cancer (i.e., gastric lymphoma, neuroendocrine tumor) were excluded from the study. Therefore, patients could be classified into three groups according to the disease status as follows: no neoplasm, gastric adenoma, and gastric cancer. We collected the following data from the patients' medical records: age, sex, presence of any gastric lesions and their location on upper gastrointestinal tract endoscopy, IgG anti-*H. pylori* antibody status, and the levels of serum gastrin, PG I, and PG II. This study was approved by the Institutional Review Board of Severance Hospital (IRB 4-2013-0722).

Serological tests

H. pylori infection was determined using enzyme-linked immunosorbent assay kits (Chorus *Helicobacter pylori* IgG; DIESSE Diagnostica Senese, Monteriggioni, Italy). Subjects with levels of 12.0 AU/mL or higher were classified as having *H. pylori* infection. Those with levels below 12.0 AU/mL were regarded as being *H. pylori* negative. The sensitivity and specificity of this assay for *H. pylori* infection were 89 % and 100 %, respectively. The levels of PG I and PG II were measured using latex agglutination turbidimetric immunoassay kits (HiSens pepsinogen-I LTIA and HiSens pepsinogen-II LTIA; HBI, Anyang, Korea).

Modification of the ABCD method

Similarly to the original ABCD method, we also classified patients into four groups as follows: (1) IgG anti-*H. pylori* antibody negative and normal PG level (group A), (2) IgG anti-*H. pylori* antibody positive and normal PG level (group B), (3) IgG anti-*H. pylori* antibody positive and low PG level (group C), and (4) IgG anti-*H. pylori* antibody negative and low PG level (group D). Low PG level, however, was defined in a different manner. First, we determined the variables that significantly differed among patients according to the disease status. Among the variables of "both PG I and PG I/PG II ratio," "PG I," and "PG I/PG II ratio," only the significant PG variables were selected for determining low PG levels in the modified ABCD method. Second, the optimal PG cutoff value was identified using the receiver operating characteristic (ROC) curve and the Youden index for predicting the presence of gastric neoplasms. Third, we determined the PG cutoff values in the IgG anti-*H. pylori* antibody positive and IgG anti-*H. pylori* antibody negative subgroups because *H. pylori* infection affects gastric atrophy and PG level, and

reliable PG cutoff values may differ according to the *H. pylori* infection status [15–17].

Statistical analysis

Continuous variables are presented as the mean with the standard deviation and were compared by using the *t* test or analysis of variance. When the significance was identified via analysis of variance, the Bonferroni correction was used for post hoc analysis. Categorical variables are presented as the sample number with the proportion and were compared by using the χ^2 test or Fisher's exact test. To determine the PG cutoff values, the ROC curve and the Youden index were used. In addition, the Cochran-Armitage trend test was performed for trend analysis of the proportion of gastric neoplasms according to the ABCD grouping. Finally, logistic regression analysis was performed to evaluate whether the modified ABCD method could predict the presence of gastric neoplasms under adjustment for possible confounding variables, including age and sex. A *P* value below 0.05 was considered significant for group comparisons. All statistical analyses were performed using the statistical software program SPSS for Windows (version 18.0; SPSS, Chicago, IL, USA), except for the Cochran-Armitage trend test, for which the analysis was performed using R (version 2.15.3; R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

A total of 584 patients who had undergone upper gastrointestinal tract endoscopy and whose serum IgG anti-*H. pylori* antibody, gastrin, and PG I and PG II data were available were identified. Of these, 15 patients with extranodal marginal zone B-cell lymphoma and seven patients with gastric neuroendocrine tumors were excluded. The remaining 562 patients were retrospectively analyzed in the study. The mean age of the patients was 59 years, and 48.6 % of the patients were men (Table 1). Gastric adenomas and cancers were detected in 51 patients (9.1 %) and 131 patients (23.3 %), respectively. The remaining 380 patients (67.6 %) did not exhibit gastric adenoma or gastric cancer on endoscopy, and these patients formed the no neoplasm (control) group.

Laboratory tests according to the disease status

The patient demographics and the results of laboratory tests according to disease status are presented in Table 2. Patients in the gastric adenoma and gastric cancer groups

Table 1 Baseline patient and lesion characteristics

Variable	Value
No. of patients	562
Mean age ± SD (years)	58.5 ± 12.5
Sex	
Male	273 (48.6 %)
Female	289 (51.4 %)
Disease	
No neoplasm[a]	380 (67.6 %)
Gastric adenoma	51 (9.1 %)
Gastric cancer	131 (23.3 %)
Depth of invasion[b]	
Mucosa	79 (60.3 %)
Submucosa	21 (16.0 %)
Proper muscle	11 (8.4 %)
Subserosa	6 (4.6 %)
Serosa	14 (10.7 %)
Histology[b]	
Differentiated	80 (61.1 %)
Undifferentiated	51 (38.9 %)
Tumor location[c]	
Upper third	17 (9.3 %)
Middle third	53 (29.1 %)
Lower third	112 (61.5 %)

SD standard deviation

[a] This category included patients with dyspepsia

[b] This variable was calculated on the basis of the number of patients with gastric cancer

[c] This variable was calculated on the basis of the number of patients with gastric adenoma and cancer

were older than those in the no neoplasm group (gastric adenoma vs gastric cancer vs no neoplasm, 64.5 ± 8.8 years vs 60.4 ± 11.0 years vs 57.0 ± 13.0 years, *P* < 0.001). In addition, the proportion of men was higher in the gastric adenoma and gastric cancer groups than in the no neoplasm group (gastric adenoma vs gastric cancer vs no neoplasm, 64.74 % vs 71.84 % vs 38.4 %, *P* < 0.001).

Serum gastrin levels did not differ among the three groups (*P* = 0.312). PG I levels also did not differ among the three groups (*P* = 0.102). Although the PG II level was higher in the gastric cancer group than in the no neoplasm group (*P* < 0.001), it did not differ between the gastric adenoma and no neoplasm groups (*P* > 0.999). Both the gastric adenoma group and the gastric cancer group displayed significantly lower values of the PG I/PG II ratio than did the no neoplasm group (gastric adenoma vs gastric cancer vs no neoplasm, 3.7 ± 2.0 vs 3.8 ± 1.8 vs 4.9 ± 2.1, *P* < 0.001). In addition, the prevalence of IgG anti-*H. pylori* antibody positive status was higher in the gastric adenoma and gastric cancer groups than into the no

Table 2 Demographics and results of laboratory tests according to the disease status

Variable	No neoplasm (n = 380)	Gastric adenoma (n = 51)	Gastric cancer (n = 131)	P	P^a		
					No neoplasm vs gastric adenoma	No neoplasm vs gastric cancer	Gastric adenoma vs gastric cancer
Age (years)	57.0 ± 13.0	64.5 ± 8.8	60.4 ± 11.0	<0.001	<0.001	0.019	0.131
Sex				<0.001			
Male	146 (38.4 %)	33 (64.7 %)	94 (71.8 %)				
Female	234 (61.6 %)	18 (35.3 %)	37 (28.2 %)				
Gastrin (pg/mL)	82.3 ± 153.8	115.1 ± 132.5	97.9 ± 196.3	0.312			
PG I (ng/mL)	64.9 ± 40.3	58.6 ± 52.8	72.6 ± 51.1	0.102			
PG II (ng/mL)	15.5 ± 11.7	16.4 ± 11.4	20.2 ± 12.7	<0.001	>0.999	<0.001	0.149
PG I/PG II ratio	4.9 ± 2.1	3.7 ± 2.0	3.8 ± 1.8	<0.001	<0.001	<0.001	>0.999
IgG anti-*Helicobacter pylori* antibody				<0.001			
Negative	192 (50.5 %)	17 (33.3 %)	35 (26.7 %)				
Positive	188 (49.5 %)	34 (66.7 %)	96 (73.3 %)				

Values are presented as the mean with the standard deviation or as the number with the proportion.

PG pepsinogen

[a] Results of post hoc analysis using the Bonferroni correction

neoplasm group (gastric adenoma vs gastric cancer vs no neoplasm, 66.7 % vs 73.3 % vs 49.5 %, P < 0.001).

Comparison of laboratory tests according to the IgG anti-*H. pylori* antibody status

Figure 1 shows the results of laboratory tests for the IgG anti-*H. pylori* antibody negative and the IgG anti-*H. pylori* antibody positive subgroups in the no neoplasm, gastric adenoma, and gastric cancer groups. Serum gastrin levels did not differ between the IgG anti-*H. pylori* antibody negative and IgG anti-*H. pylori* antibody positive subgroups (Fig. 1a). Although serum PG I levels were higher in the IgG anti-*H. pylori* antibody positive subgroup than in the IgG anti-*H. pylori* antibody negative subgroup in patients who had neither gastric adenoma nor gastric cancer, it did not differ according to the IgG anti-*H. pylori* antibody status in patients with either the gastric adenoma group or the gastric cancer group (Fig. 1b). Serum PG II levels, however, were higher in the IgG anti-*H. pylori* antibody positive subgroup than in the IgG anti-*H. pylori* antibody negative subgroup in all three groups (Fig. 1c). In addition, the PG I/PG II ratio was lower in the IgG anti-*H. pylori* antibody positive subgroup than in the IgG anti-*H. pylori* antibody negative subgroup in all three groups (Fig. 1d).

Determination of cutoff values for the PG I/PG II ratio

Because PG I levels did not differ among the no neoplasm, gastric adenoma, and gastric cancer groups, as shown in Table 2, we chose only the PG I/PG II ratio rather than

PG I level as the variable for determining low PG levels in the modified ABCD method. In patients with IgG anti-*H. pylori* antibody negative status, the optimal cutoff value for the PG I/PG II ratio was 3.1 (Fig. 2a). The optimal cutoff values for the PG I/PG II ratio for predicting gastric neoplasms were 3.1 for patients with IgG anti-*H. pylori* antibody negative status and 4.1 for patients with IgG anti-*H. pylori* antibody positive status (Fig. 2b).

Relationship between gastric neoplasms and the modified ABCD grouping

Using the cutoff values for the PG I/PG II ratio derived from the ROC curves and the Youden index, we classified the patients into four groups as shown in Table 3. In patients without gastric neoplasms, the numbers of patients in groups A, B, C, and D were 179, 76, 112, and 13, respectively. In patients with gastric neoplasms, the numbers of patients in groups A, B, C, and D were 37, 32, 98, and 15, respectively. Of the 182 patients with gastric neoplasms, 113 (62.1 %) were in group C or group D. The Cochran-Armitage trend test confirmed that a higher group grade was associated with a significantly higher proportion of gastric neoplasms (P_{trend} <0.001).

To compare the screening capacity between the original ABCD method and the modified ABCD method, numbers of patients who were classified by the original ABCD grouping are shown in Table S1. In patients with gastric neoplasms, the numbers of patients in groups A, B, C, and D were 40, 86, 44, and 12, respectively. Compared with the classification by the modified ABCD method, fewer
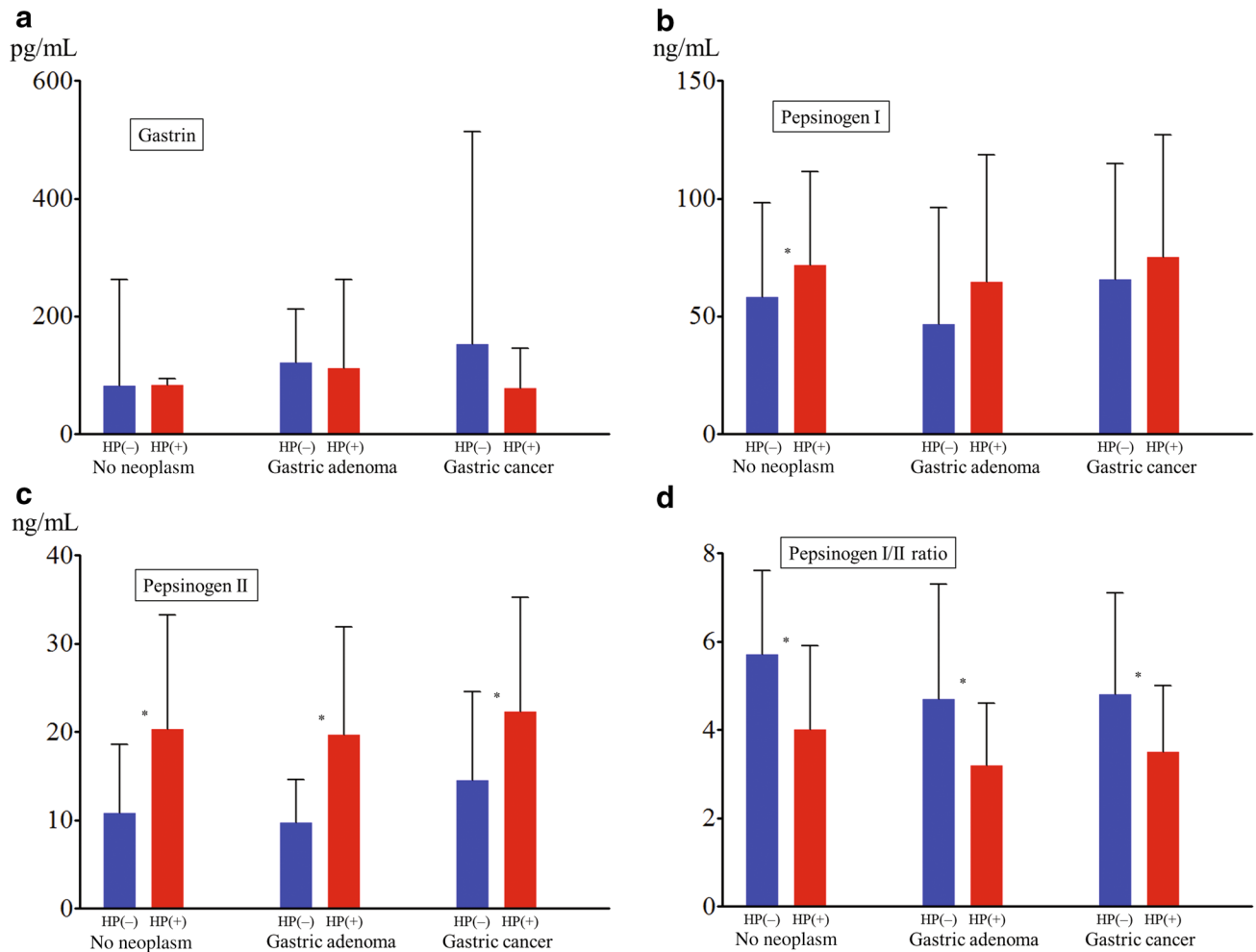
a

pg/mL

b

ng/mL

c

ng/mL

d

Fig. 1 Laboratory tests for gastrin (**a**), pepsinogen (PG) I (**b**), PG II (**c**), and the PG I/PG II ratio (**d**) according to the IgG anti-*Helicobacter pylori* antibody status. *HP(+)* and *HP(−)* denote IgG anti-*H. pylori* antibody positive and IgG anti-*H. pylori* antibody negative, respectively
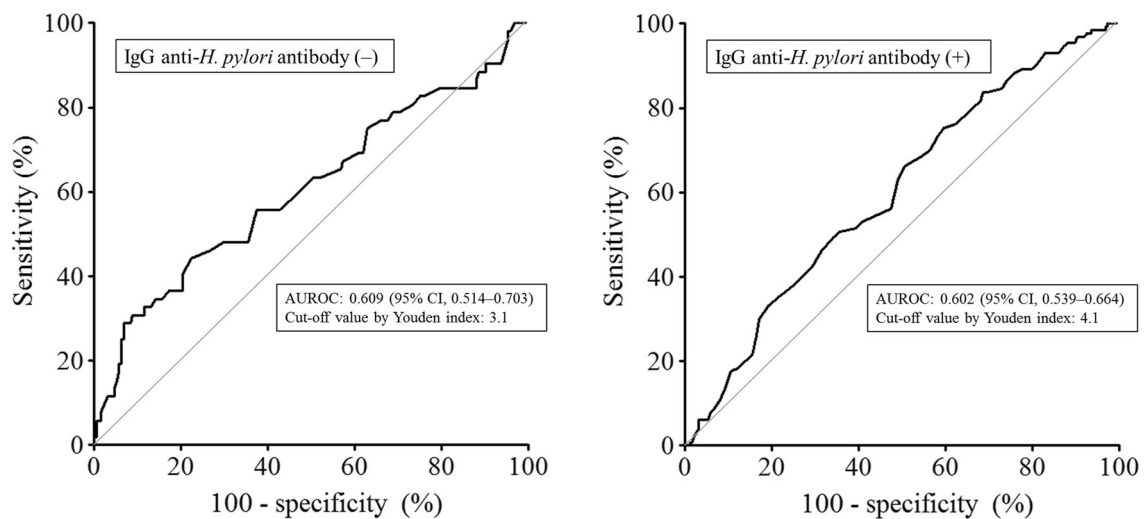

Fig. 2 Receiver operating characteristic curves for predicting gastric neoplasms based on the pepsinogen (PG) I/PG II ratio in patients with IgG anti-*Helicobacter pylori* antibody negative status (**a**) and IgG

anti-*H. pylori* antibody positive status (**b**). Gastric neoplasms included gastric adenoma and gastric cancer. *AUROC* area under the receiver operating characteristic curve, *CI* confidence interval

Table 3 The relationship between gastric neoplasms and the modified ABCD grouping

Variable	Group A: IgG anti-Helicobacter pylori antibody negative and PG I/PG II ratio >3.1	Group B: IgG anti-H. pylori antibody positive and PG I/PG II ratio >4.1	Group C: IgG anti-H. pylori antibody positive and PG I/PG II ratio ≤4.1	Group D: IgG anti-H. pylori antibody negative and PG I/PG II ratio ≤3.1	P	P_{trend}
No neoplasms ($n = 380$)	179 (47.1 %)	76 (20.0 %)	112 (29.5 %)	13 (3.4 %)	<0.001	<0.001
Gastric neoplasms ($n = 182$)	37 (20.3 %)	32 (17.6 %)	98 (53.8 %)	15 (8.2 %)		

Gastric neoplasms included gastric adenoma and gastric cancer

PG pepsinogen

Table 4 Multiple logistic regression model for predicting the presence of gastric neoplasms

Variable	Number	Gastric neoplasms	OR[a]	P
Age (years)			1.030 (1.013–1.048)	0.001
Sex				
Male	273	127 (46.5 %)	3.550 (2.370–5.319)	<0.001
Female	289	55 (19.0 %)	1.000	
IgG anti-Helicobacter pylori antibody status and PG I/PG II ratio				
Group A: IgG anti-H. pylori antibody negative and PG I/PG II ratio >3.1	216	29 (13.4 %)	1.000	
Group B: IgG anti-H. pylori antibody positive and PG I/PG II ratio >4.1	108	21 (19.4 %)	1.783 (1.007–3.156)	0.047
Group C: IgG anti-H. pylori antibody positive and PG I/PG II ratio ≤4.1	210	109 (51.9)	3.807 (2.382–6.085)	<0.001
Group D: IgG anti-H. pylori antibody negative and PG I/PG II ratio ≤3.1	28	23 (82.1 %)	5.862 (2.427–14.155)	<0.001

Gastric neoplasms included gastric adenoma and gastric cancer

OR odds ratio, PG pepsinogen

[a] The 95 % confidence interval is given in *parentheses*

patients with gastric neoplasms were in group C or group D [original ABCD method vs modified ABCD method, 56 (30.8 %) vs 113 (62.1 %), $P < 0.001$].

Finally, we created a multiple logistic regression model to determine the relationship between the ABCD grouping and the proportion of gastric neoplasms after adjustment for confounding variables, including age and sex (Table 4). The prevalence of gastric neoplasms in groups B, C, and D was higher than that in group A [odds ratio (95 % confidence interval), group B, 1.783 (1.007–3.156); group C, 3.807 (2.382–6.085); and group D, 5.862 (2.427–14.155)].

Discussion

The ABCD screening method, which was developed in Japan, can easily be used for risk stratification of gastric cancer because it is simple and less invasive compared with upper gastrointestinal tract endoscopy or gastric fluoroscopy [9]. Considering that gastric cancer is diagnosed in many patients without them undergoing periodic gastric cancer screening in Korea despite there being a national gastric cancer screening program [7], the ABCD method may have a role in gastric cancer screening in regions in which the incidence of gastric cancer is high. Although some studies demonstrated that a higher group grade in the ABCD method was associated with a higher risk of gastric cancer [8, 11, 12], all of those studies focused on only gastric cancer rather than gastric adenoma. Although screening for gastric cancer is important, screening for gastric adenoma is also important. Correa [18] postulated that gastric cancer may be induced from chronic gastritis via intestinal metaplasia and dysplasia. Recently, a dysplasia–carcinoma sequence has been reported to be associated with the development of intestinal-type gastric cancer [8, 19, 20]. When gastric dysplasia is detected by screening, curative removal via endoscopic resection is possible.

Our study has merits for being the first study to demonstrate that the presence of gastric neoplasms, including gastric adenoma, could be predicted by the IgG anti-H. pylori antibody status and PG I/PG II ratio. In patients with a higher group grade in the modified ABCD method, more careful and strict screening may be required

for the early diagnosis of both gastric adenoma and gastric cancer.

Another advantage of the modified ABCD method is the use of two different cutoff values for the PG I/PG II ratio according to the IgG anti-*H. pylori* antibody status. Among the four groups in the ABCD method, the risk of group A is distinct from that of group D despite the identical IgG anti-*H. pylori* antibody status between the two groups. IgG anti-*H. pylori* antibody negative status in group A means that patients have never been infected with *H. pylori*. In contrast, IgG anti-*H. pylori* antibody negative status in group D implies prior *H. pylori* infection because *H. pylori* does not survive well in the atrophic or intestinal metaplasia mucosa [12]. Compared with groups A and D, a relatively similar severity of the gastric mucosa was expected in terms of gastric atrophy between groups B and C because significant proportions of patients in both groups may be currently infected with *H. pylori*. In other words, the distribution of the PG I/PG II ratio may differ between patients with IgG anti-*H. pylori* antibody negative status (groups A and D) and those with IgG anti-*H. pylori* antibody positive status (groups B and C). In our study, as expected, the optimal cutoff value for the PG I/PG II ratio did differ between the patients with IgG anti-*H. pylori* antibody negative status and those with IgG anti-*H. pylori* antibody positive status. This new approach may help to increase the screening capacity of the ABCD method for gastric neoplasms.

Although this study was the first to evaluate whether gastric neoplasms could be predicted by the IgG anti-*H. pylori* antibody status and serum PG levels, there are several limitations. First, a few patients who had undergone upper gastrointestinal tract endoscopy were not included because their serum IgG anti-*H. pylori* antibody, gastrin, or PG I and PG II data were unavailable, and a possible selection bias could be a concern. However, we think that this selection bias may not be serious, because tests for serum IgG anti-*H. pylori* antibody, gastrin, and PG I and PG II had been performed only for individuals who had undergone gastrointestinal tract endoscopy for screening purposes or patients in whom gastric neoplasms had been diagnosed. Second, this study was based on nonrepresentative groups of patients. Our results identified 380 patients (67.6 %), 51 patients (9.1 %), and 131 patients (23.3 %) with no neoplasm, gastric adenoma, and gastric cancer, respectively; however, this distribution did not represent the prevalence of gastric adenoma and gastric cancer in the screening population. A population-based cohort study is required to prove the usefulness of the modified ABCD method for gastric neoplasm screening. The third limitation is the cross-sectional design of the study. The study did not include follow-up data; therefore, we could evaluate only the predictive accuracy concerning the presence of gastric neoplasms rather than the risk of gastric cancer development in the future. Our study design, however, helped to include a larger number of gastric cancers compared with previous studies [8, 11–14]. Fourth, data on histologic atrophic gastritis were unavailable in the study. Although we determined the cutoff values for the PG I/PG II ratio using ROC curves for predicting the presence of gastric neoplasms, they should be determined ideally using ROC curves to predict the presence of histologically confirmed atrophic gastritis. To remedy this limitation, we plan to perform a prospective study on the optimal PG cutoff values for histologic atrophic gastritis. Finally, although we demonstrated the usefulness of the modified ABCD method using multiple logistic regression models, external validation is mandatory to provide a definitive conclusion. Further studies on the modified ABCD method are expected.

Despite these limitations, our data may form the basis of a system to suggest a new screening strategy for gastric cancer. The modified ABCD method using two different cutoff values according to the IgG anti-*H. pylori* antibody status was useful for predicting the presence of gastric neoplasms. We believe that the modified ABCD method can be a supplementary screening tool for both gastric adenoma and gastric cancer. However, further studies will be required to provide a definitive conclusion.

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