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A Risk Assessment of Gastric Cancer and Precancerous Condition Using Serum Pepsinogen and H. Pylori Antibody Test

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Objectives: We aimed to determine serum PGs (serum pepsinogens) and H. Pylori IgG in atrophic gastritis and gastric cancer patients and evaluate the gastric cancer risk.

Method: We enrolled 40 gastric cancer patients, 40 chronic atrophic gastritis patients and 40 healthy control subjects. Serum PGI, PGII, and H. pylori IgG levels were measured by ELISA. The PGI to PGII ratio was calculated.

Results: The mean age of the subjects was 60±10.9 years, We found that 52.6% (n=60) were male. H. Pylori IgG was positive in 67 subjects. The serum PGI and PGR levels were significantly decreased in gastric cancer and atrophic gastritis groups compared to the healthy control. According to classification ABC (D), group D had higher proportion of atrophic gastritis cases, group C had higher proportion of gastric cancer cases than others. Additionally, we evaluated all subjects by giving one point to each of the age ≤40, positive family history of gastric cancer, positive previous gastric disease history, PGI ≤75.07 ng/ml, PGR ≤6.25, or two point to each of PGI ≤35.25 ng/ml, and PGR ≤5.27, with score ranging between 0-7. As score increased, the risk of atrophic gastritis or gastric cancer increased.

Conclusion: A combination of methods involving PGs and other risk factors may predict the probability of gastric cancer and could identify individuals who may need upper endoscopy.

Keywords: Biological marker, Cancer screening, Atrophic gastritis, Screening test, Stomach neoplasm.

Introduction

Cases of gastric cancer have been declining worldwide in recent years on the contrary, they have increased in the last decade in Mongolia [1]. According to data of the International Agency for Research on Cancer, Mongolia had the highest rate (32.5 new cases per 100,000 population) of gastric cancer in the world, followed by Japan (100'000:31.6) and South Korea (100'000:27.9) for both sexes in 2020. Also, Mongolia (100'000:24.6) led the mortality for gastric cancer, while Japan

(100'000:8.2) and South Korea (100'000:8.2) ranked at 34th and 56th, respectively [2]. Japan and South Korea successfully implemented national screening program for early detection of gastric cancer [3-5] leading to lower mortality rates. In Mongolia, over 80% of gastric cancer cases are diagnosed during the late stage [6]. But a screening program has not been introduced to decrease the gastric cancer rate. Gastric cancer is the end of a long and multistep process, including atrophic gastritis, intestinal metaplasia, and low and high grade dysplasia [7]. These malignant lesions should be the targets for primary prevention of cancer. Several studies have revealed that serum pepsinogens (PGs) level reflects, indirectly, histological and functional characteristics of the gastric mucosa [8-10]. Human PGs, which are protein-digestive enzymes secreted as proenzymes by chief cells, are classified according to biochemical and immunological properties, into two types: pepsinogen I (PGI) and pepsinogen II (PGII) [9]. In some developed countries, H. Pylori IgG and pepsinogens (PGs) have been studied as non-invasive serological evaluation of gastric cancer and precancerous gastric lesions, and a variety of cut-off values have been suggested [11]. A Japanese study group (Miki et al.) developed the ABC (D) screening method using combination of H. Pylori IgG and PGs (PGI <70ng/ml and PGI to PGII ratio (PGR) <3.0 as positive PGs) for atrophic marker to stratify high risk patients for gastric cancer [12]. Gantuya B et al (2019) conducted cross-sectional study to evaluate serum pepsinogens and H. Pylori for 752 non-cancer dyspeptic patients and 51 gastric cancer patients. Their study reveals that serum PGI and PGR were significantly decreased in the gastric cancer group compared to low-risk patients and PGII was significantly increased in high risk group more than low risk and the gastric cancer group. They considered that PGs not only a prognostic tool for gastric atrophy but also it can be a prediction tool for corpus chronic gastritis and PGR <2.2 and PGI <28ng/ml were the best cut-off point to predict gastric cancer patients compared to non-cancer dyspeptic patients[13]. It is known that serum PGI and PGII are associated with age and sex from previous studies. In a study published in 2016, conducted on 6596 healthy individuals, the PGI, PGII and PGR ratio were higher in males than in females and the serum PGI and PGII levels gradually increased with age [14]. The study differs from the previous study assessing the association between serum pepsinogen levels and the development of gastric cancer that has taken into account other confounding factors, including age and sex, and living areas compared with healthy gastric mucosa subjects. Therefore, we aimed to conduct a case-control study to determine serum PGs and H. Pylori IgG for atrophic gastritis and gastric cancer patients and compare the gastric cancer risk to the healthy gastric mucosa.

Materials and Methods

Study subjects

The case-control study was conducted between January 2022 and January 2023 at the Institute of Medical Sciences. The study enrolled 40 patients who attended the gastrointestinal endoscopy clinic and had confirmed gastric cancer by histology at the National Center of Cancer of Mongolia. Besides, we selected 40 chronic atrophic gastritis and 40 healthy control subjects matched by age (±2), sex, and living areas with gastric cancer and atrophic gastritis patients. Exclusion criteria were as follows: age <18, pregnancy, recent use of proton pump inhibitor or H2 receptor blockers, history of H. Pylori eradication within three months, history of gastric surgery or malignancy of cancers. After the exclusion of 6 subjects, 36 subjects with gastric cancer, 40 subjects with chronic atrophic gastritis, and 38 healthy subjects were included.

Gastrointestinal endoscopy

Gastrointestinal endoscopy was performed at the National Cancer Center of Mongolia in accordance with the national standard MNS5747-1:2007 using EVIS Exera III endoscope. After 10-hour fasting, simethicone solution was used to improve the visibility of the mucosa, followed by 10% lidocaine spray. Endoscopies were initially performed using white light. Subsequently, narrow-band imaging was activated to see if any further evaluation was required.

Measurement of serum biomarkers using GastroPanel

Serum PGI, PGII, and H. Pylori IgG levels were measured using Gastro Panel enzyme-linked immunosorbent assay kit (Biohit, Helsinki, Finland). To obtain more accurate analysis results, the biomarkers concentration was used for the average value of the results of a triplicate analysis repeated twice. The fasting blood samples were collected into serum tubes from all subjects. The blood samples from gastric cancer patients were collected before surgery and other therapies. The blood samples were centrifuged at 2000 rpm for 10 minutes, and the supernatant was stored at -70°C freezer until testing. The plasma

concentrations of PGI, PGII, and H.pylori IgG were determined by following the protocol in accordance with the instruction of the manufacturer. First, the blank solutions, calibrators, controls and diluted samples were pipetted into microplate wells at a volume of 100 µl. Each sample was pipetted into 3 microplate wells. The microplates were incubated at room temperature for 60 minutes while shaking at 750 rpm. Microplate strips were automatically washed three times with 350 µl of diluted buffer and gently tapped on a clean towel. Subsequently, 100 µl of specific conjugate solutions were pipetted into each microplate wells and incubated at room temperature for 60 minutes while shaking at 750 rpm. Microplate strips were automatically washed three times using a BIOBASE-EL10A reader with 350 µl of diluted buffer and gently tapped on a clean towel. After that, 100 µl of substrate solutions were pipetted into each microplate wells and incubated for 30 minutes at ambient temperature avoiding exposure to light. Finally, 100 µl of stop solutions were pipetted into microplate wells. The absorbance of the microplate wells was measured at 450 nm using a BIOBASE-EL10A microplate reader (Biobase Biodustry, Shandong, China). Also, PGI to PGII ratio (PGR) was calculated.

Statistical Analysis

Descriptive statistics, including frequency, percentages and mean were calculated to describe baseline characteristics. The Chi-squared test was used to analyze differences between categorical variables, ANOVA test used to compare means between study groups. Serum levels of biomarkers were presented as medians and differences assessed using Kruskal-Wallis test depending on assumptions of skewed distribution. The diagnostic accuracy and cut-off values were assessed by ROC curves and the Youden index and the risk expressed by odds ratio (OR) and 95% confidence intervals (95%CI) based on logistic regression analysis. Differences with $p<0.05$ were considered to be statistically significant.

Ethics

The study was approved by the Research Ethics Committee of Mongolian National University of Medical Sciences on January 21, 2022 (Approval № 2022/3-01). This study was performed according to the Helsinki Declaration and all subjects signed informed consent to participate.

Results

1. Basic characterisitics and serum PGIs level

The mean age of the subjects was 60±10.9 years, 52.6% (n=60) were male. Proportions of family history of gastric cancer and previous history of gastric disease were significantly higher in the gastric cancer group compared to the atrophic gastritis and healthy control groups ($p<0.05$, $p<0.05$). H. Pylori was positive in 67 (58.8%) subjects according to an H. Pylori IgG assay and there was no difference between study groups (Table 1). The median of serum PGI was 74.32 ng/ml (17.65 to 223.94) for healthy controls, 56.52 ng/ml (4.23 to 209.28) for atrophic gastritis and 46.94 ng/ml (6.52 to 212.67) for gastric cancer patients. The serum PGI level was significantly decreased in gastric cancer and atrophic gastritis groups compared to the healthy control ($p<0.05$, $p<0.05$). The median of PGR was 5.77 (1.71 to 12.87), 5.03 (0.60 to 13.73), and 3.76 (0.58 to 8.71) for healthy controls, atrophic gastritis, and gastric cancer patients. The PGR was significantly lower in the gastric cancer group compared with the healthy control ($p<0.01$). There were no significant differences in the serum PGII level between the study groups (Figure 1).

Table 1. Baseline characteristics of the study subjects

Characteristics	Healthy control, (n=38)	Atrophic gastritis(n=40)	Gastric cancer (n=36)	Total (n=114)	*p value*
Age[a], mean±SD	59.9±11.6	58.7±10.8	61.5±10.3	60±10.9	-
Sex[a], male (%)	20 (52.6)	21 (52.5)	19 (52.8)	60 (52.6)	-
Body mass index kg/m^2, mean±SD	27.5±5.1	27.3±4.6	26.4±4.8	27.0±4.8	*0.574*[b]
Blood type 0(I), (%) A(II), (%) B(III), (%) AB(IV), (%)	 10 (47.6) 5 (23.8) 6 (28.6) -	 8 (33.3) 6 (25.0) 9 (37.5) 1 (4.2)	 10 (31.3) 5 (15.6) 12 (37.5) 5 (15.6)	 28 (36.4) 16 (20.8) 27 (35.1) 6 (7.8)	*0.799*[c]

Family history of gastric cancer (%)	7 (18.4)	4 (10.0)	13 (36.1)	24 (21.1)	*0.018*[d]
History of previous gastric disease (%)	6 (15.8)	10 (25.0)	19 (52.8)	35 (30.7)	*0.002*[d]
H.pylori IgG >30EIU (%)	24 (63.2)	22 (55.0)	21 (58.3)	67 (58.8)	*0.764*[d]

[a]Age and sex are matched between study groups;
[b]p-value calculated with the ANOVA test;
[c]p-value was calculated with the Chi-square test, excluded AB blood type;
[d]p-value was calculated with the Chi-square test;

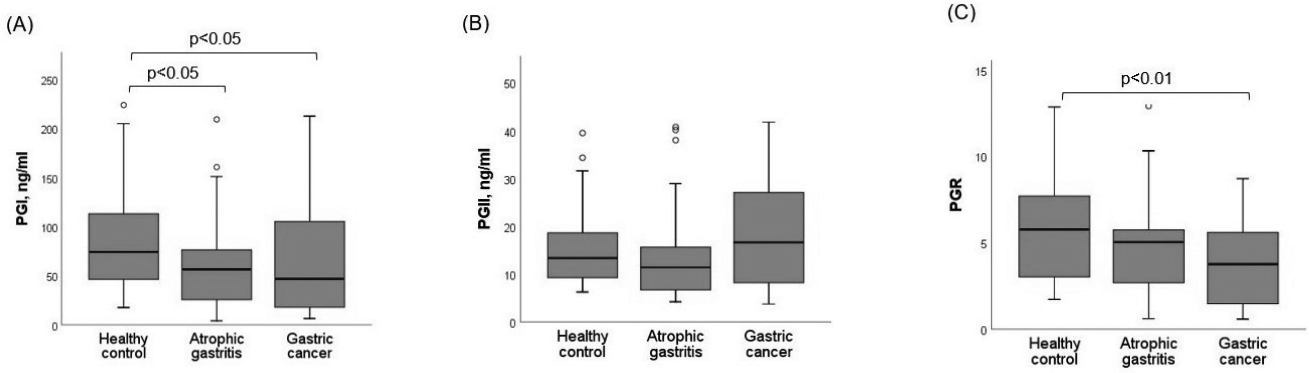

Figure 1. The comparison of the serum PGI (A), PGII (B), and PGR (C) levels between study groups. The p-value was calculated with the Kruskal-Wallis test.

The corresponding ROC curves of PGI and PGR were developed to predict atrophic gastritis and gastric cancer. The optimal cut off value of PGI was ≤35.25 ng/ml (AUC 64.3, 95% CI 51.3-77.2, p<0.05) for gastric cancer and PGI was ≤75.07 ng/ml (AUC 65.2, 95% CI 53.0-77.3, p<0.05) for atrophic gastritis. Also, the optimal cut off value of PGR was ≤5.27 (AUC 71.6, 95% CI 69.6-82.8, p<0.01) for gastric cancer and PGR was ≤6.25 (AUC 62.7, 95% CI 50.1-75.3, p<0.05) for atrophic gastritis.

2. Risk evaluation of ABC(D) method

Japanese researchers developed the ABC(D) method which is a combination of H. Pylori IgG and PGs (PGI<70ng/ml and PGR<3.0 as positive PGs) for atrophic marker to stratify high risk patients of gastric cancer[12]. We modified PGs criteria based on our cut-off values: PGI<35.25ng/ml and PGR<5.27 as positive PGs for gastric cancer vs healthy control groups, PGI<75.07ng/ml and PGR<6.25 as positive PGs for atrophic gastritis vs healthy control groups. After modification, we split participants into four groups: group A, H. Pylori (-), PGs (-); group B, H. Pylori (+), PGs (-); group C H. pylori (+), PGs (+); group D, H. Pylori (-), PGs (+). Prevalence of gastric cancer was significantly different among all groups (p<0.05). According to the classification of atrophic gastritis patients and healthy controls, 11 (14.1%) were categorized as group A, 12 (15.4%) as group B, 34 (43.6%) as group C, and 21 (26.9%) as group D (p<0.05). Group D had a higher proportion of atrophic gastritis cases than group A, B and C (OR 5.04, 95% CI 1.13-22.50, p<0.05). According to the classification of gastric cancer patients and healthy controls, 18 (24.3%) were categorized as group A, 34 (45.9%) as group B, 11 (14.9%) as group C, 11 (14.9%) as group D (p<0.05). Groups C had higher proportion of gastric cancer cases than group A, B and D (OR 6.19, 95% CI 1.04-36.78, p<0.05) (Table 2).

Table 2. ABCD risk group defined by pepsinogen test and H.pylori antibody

ABCD Category	Healthy control vs Atrophic gastritis[a]		Healthy control vs Gastric cancer[b]	
	Frequency	OR (95% CI)	Frequency	OR (95% CI)
Group A (H.pylori IgG negative, PGs negative)	18.4% vs 10.0%	ref	28.9% vs 19.4%	ref

Group B (H.pylori IgG positive, PGs negative)	26.3% vs 5.0%	0.95 (0.25-3.71)	57.9% vs 33.3%	0.75 (0.24-2.37)
Group C (H.pylori IgG positive, PGs positive)	36.8% vs 50.0%	3.34 (0.80-13.94)	5.3% vs 25.0%	6.19 (1.04-36.78)
Group D (H.pylori IgG negative, PGs positive)	18.4% vs 35.0%	5.04 (1.13-22.5)	7.9% vs 22.2%	3.21 (0.63-16.38)

[a]PGs criteria based on our cut-off values: PGI<75.07ng/ml and PGR<6.25 as positive PGs
[b]PGs criteria based on our cut-off values: PGI<35.25ng/ml and PGR<5.27 as positive PGs

3. Risk evaluation of scoring system based on risk factors and serum PGs

By logistical regression analysis, a positive history of previous gastric disease (OR 5.96, 95% CI 2.00-17.73), PGI≤35.25 ng/ml (OR 4.69, 95% CI 1.40-15.73), PGR ≤6.25 (OR 4.80, 95% CI 1.52-15.10) is a significantly increased gastric cancer risk. Also, PGI≤75.07 ng/ml (OR 2.75, 95% CI 1.02-7.42), PGR ≤6.25 (OR 4.27, 95% CI 1.42-12.8) is a significantly increased atrophic gastritis risk (Table 3). In addition, we evaluated all subjects by assigning one point to each of the following satisfied criteria: the age ≤40, positive family history of gastric cancer, positive previous gastric disease history, PGI ≤75.07 ng/ml, PGR ≤6.25, or two points to each individual whose PGI ≤35.25 ng/ml, and PGR ≤5.27, with total scores ranging from 0 to 7. As scores increased, the risk of atrophic gastritis or gastric cancer increased. Scores 0 to 2, 3 to 4, 5 to 7 were classified into three categories, corresponding to low, medium, high risk, respectively. According to this classification, 29 (25.4%) subjects were classified into the low-risk category, 40 (35.1%) subjects into medium-risk category, and 45 (39.5%) subjects into high-risk category. For the atrophic gastritis patients, 17 (42.5%) were classified into medium-risk category (OR 4.49, 95% CI 1.38-14.58) and 17 (42.5%) were classified into high-risk category (OR 7.69, 95% CI 2.16-27.43). Whereas 11 (30.6%) patients with gastric cancer were classified into medium-risk category (OR 4.35, 95% CI 1.13-16.85), 21 (58.3%) were classified into high-risk category (OR 14.25, 95% CI 3.60-56.43) (Table 3).

Table 3. Logistic regression of some risk factors and score based risk groups defined by pepsinogen test and risk factors

Variables	Healthy control n (%)	Atrophic gastritis		Gastric cancer	
		n (%)	OR (95% CI)	n (%)	OR (95% CI)
Positive family history of gastric cancer	6 (15.8%)	4 (10.0%)	2.03 (0.54-7.60)	13 (36.1%)	0.40 (0.14-1.16)
Positive previous gastric disease history	7 (18.4%)	10 (25.0%)	1.78 (0.58-5.49)	19 (52.8%)	5.96 (2.00-17.73)
PGI ≤75.07 ng/ml	19 (50.0%)	30 (75.0%)	2.75 (1.02-7.42)	24 (66.7%)	1.82 (0.68-4.87)
PGI ≤35.25 ng/ml	5 (13.2%)	14 (35.0%)	2.75 (0.83-9.14)	17 (47.2%)	4.69 (1.40-15.73)
PGR ≤6.25	21 (55.3%)	34 (85.0%)	4.27 (1.42-12.8)	31 (86.1%)	4.80 (1.52-15.1)
PGR ≤5.27	19 (50.0%)	29 (72.5%)	2.00 (0.74-5.41)	27 (75.0%)	1.84 (0.63-5.35)
Score based category[a]					
Low-risk (0-2)	19 (50.0%)	6 (15.0%)	ref	4 (11.1%)	ref
Medium-risk (3-4)	12 (31.6%)	17 (42.5%)	4.49 (1.38-14.58)	11 (30.6%)	4.35 (1.13-16.85)
High-risk (5-7)	7 (18.4%)	17 (42.5%)	7.69 (2.16-27.43)	21 (58.3%)	14.25 (3.60-56.43)

[a]One point when the age ≤40, positive family history of gastric cancer, positive previous gastric disease history, PGI ≤75.07 ng/ml, PGR ≤6.25, or two points when PGI ≤35.25 ng/ml, and PGR ≤5.27, with total scores ranging from 0 to 7.

Discussion

Gastric cancer is a disease that has a major global impact, with an estimated 1 million new cases annually. The third most common cause of cancer-related mortality is the a result of its high prevalence and late diagnosis stage [15]. Accurate non-invasive tests would be extremely useful in order to detect gastric neoplasm in an early phase. In clinical practice, there is currently no reliable biomarker for detecting this cancer. According to our results, atrophic gastritis and gastric cancer patients were associated with a low level of PGI and PGR. Previous studies have shown that the low precancerous lesions with a variety of cut-off values [12, 13, 16, 17]. In our study, the optimal cut-off value of PGI was ≤75.07 ng/ml with 75% sensitivity, 50% specificity and ≤35.25 ng/ml with 47.2% sensitivity, 86.8% specificity for atrophic gastritis and gastric cancer, respectively. These findings were approximately similar to other studies which suggested a PGI cut off ≈70 ng/ml and ≈30 ng/ml for atrophic gastritis and gastric cancer, respectively [12, 16, 17]. PGI sensitivity for gastric cancer (47.2%) in our result is consistent with previous studies showing that sensitivity is lower (36.8%-62.3%) for cancer than the assessment of gastric atrophy [8, 18, 19]. In contrast, PGR has better sensitivity for the assessment of atrophic gastritis and gastric cancer in this study (85% and 75.0%) than previous studies (73.5-87.1%) [8, 19]. PGR cut-off values (≤6.25 for atrophic gastritis, ≤5.27 for gastric cancer), were quite higher in our result than some studies suggested [12, 16]. But similar results were reported in a study by Cao Q et al (2007). For the best discrimination of atrophic gastritis, the cut-off values of PGI and PGR were 82.3 microg/L and 6.05, respectively [17]. ParkCH et al (2016) modified the ABCD method for gastric neoplasm screening. Their finding was similar to our result, a higher group grade was associated with a significantly higher proportion of gastric neoplasms [odds ratio (95 % CI), 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)]. They conclude that 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 [20]. Cai Q et al (2019) comprised seven variables, including age, sex, PGR, G-17 level, H. Pylori infection, pickled food and fried food, with scores from 0 to 25 to stratify high-risk population in China. According to their results, the observed prevalence rates of gastric cancer in the derivation cohort at low-risk (≤11), medium-risk (12–16) or high-risk (17–25) group were 1.2%, 4.4%, and 12.3%, respectively ($p<0.001$) [17]. In this study, we created a risk prediction scoring system with a score ranging from 0 to 7, based on variables age, family history of gastric cancer, prior disease history, PGI and PGR levels. Our findings revealed that medium-risk (3-4 score) or high-risk (5-7 score) categories have more prevalence of patients with atrophic gastritis and gastric cancer. So, we recommended that patients who were classified into medium-risk or high-risk category should go through further examination, such as upper endoscopy. Our study had several limitations. Due to the small number of subjects, subjects with atrophic gastritis and gastric cancer were not classified into different clinical classifications. Previous studies reported that a low level of serum PGI and PGR were more related to corpus atrophy and diffuse type gastric cancer [13, 21]. Because of these reasons, future studies need to be conducted with a larger number of subjects and determine risks into different clinical classifications, including antrum or corpus atrophy, intestinal metaplasia, and diffuse or intestinal-type gastric cancer.

Conclusion

In conclusion, a combination of methods involving PGs and other risk factors may predict the probability of gastric cancer and could identify individuals who may need upper endoscopy.

Conflict of Interest

The authors declare that no competing interests exist. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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