

RAPID COMMUNICATION

Serum pepsinogen levels and their influencing factors: A population-based study in 6990 Chinese from North China

Li-Ping Sun, Yue-Hua Gong, Lan Wang, Yuan Yuan

Li-Ping Sun, Yue-Hua Gong, Lan Wang, Yuan Yuan, Cancer Institute, First Affiliated Hospital, China Medical University, Shenyang 110001, Liaoning Province, China

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Correspondence to: Dr. Yuan Yuan, Cancer Institute, First Affiliated Hospital, China Medical University, 155 Nanjing North Street, Shenyang 110001, Liaoning Province, China. yyuan@mail.cmu.edu.cn

Telephone: +86-24-83282153 Fax: +86-24-83282292

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Abstract

AIM: To explore the essential characteristics of serum pepsinogen (PG) levels in Chinese people, by analyzing the population-based data on the serum levels of PG I and II and the PG I/II ratio, and their influencing factors in Chinese from North China.

METHODS: A total of 6990 subjects, who underwent a gastric cancer screening in North China from 1997 to 2002, were collected in this study. Serum pepsinogen levels were measured by enzyme-linked immunosorbent assay (ELISA). *H pylori* status was determined by histological examination and *H pylori*-IgG ELISA. The cut-off point was calculated by using receiving operator characteristics (ROC) curves. Factors linked to serum PG I/II ratio were identified using a multivariate logistic regression.

RESULTS: The serum PG I and PG II levels were significantly higher in males than in females (95.2 $\mu\text{g/L}$ vs 79.7 $\mu\text{g/L}$, $P < 0.01$; 12.1 $\mu\text{g/L}$ vs 9.4 $\mu\text{g/L}$, $P < 0.01$), PG I/II ratio was significantly lower in males than in females (7.9 vs 8.3, $P < 0.01$). The PG I/II ratio decreased significantly in the aged groups following the progression of gastric mucosa from normal to non-atrophic and atrophic lesions (10.4, 8.8, and 6.6, respectively). The serum PG I and II levels were significantly higher in patients with *H pylori* infection than in those without *H pylori* infection (88.7 $\mu\text{g/L}$ vs 81.4 $\mu\text{g/L}$, $P < 0.01$; 11.4 $\mu\text{g/L}$ vs 8.4 $\mu\text{g/L}$, $P < 0.01$), while the PG I/II ratio was significantly lower in patients with *H pylori* infection than in those without *H pylori* infection (7.7 vs 9.6, $P < 0.01$). For patients with atrophic lesions, the area under the PG I/II ROC curve was 0.622. The best cut-off point for PG I/II was 6.9, with a sensitivity of 53.2%, and a specificity of 67.5%. Factors linked to PG

I/II were sensitive to identified PG using a multinomial logistic regression relying on the following inputs: males (OR: 1.151, 95% CI: 1.042-1.272, $P = 0.006$), age ≥ 61 years (OR: 1.358, 95% CI: 1.188-1.553, $P = 0.000$), atrophic lesion (OR: 2.075, 95% CI: 1.870-2.302, $P = 0.000$), and *H pylori* infection (OR: 1.546, 95% CI: 1.368-1.748, $P = 0.000$).

CONCLUSION: The essential characteristics of serum PG levels in Chinese are significantly skewed from the normal distribution, and influenced by age, sex, gastric mucosa lesions and *H pylori* infection. PG I/II ratio is more suitable for identifying subgroups with different influence factors compared with PG I or PG II alone.

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Key words: Pepsinogen; Gastric cancer; *Helicobacter pylori*; Screening

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INTRODUCTION

Human pepsinogens (PGs) are inactive pro-enzymes for the specific digestive enzyme--pepsin originating from the gastric mucosa, and can be classified biochemically and immunochemically into pepsinogen I (PG I) and pepsinogen II (PG II). Both of them are secreted by the chief and mucous neck cells of the gastric fundus and corpus. PG II is also secreted by the pylori glands in the antrum and Brunner's glands in the proximal duodenum. PG I and PG II are secreted into the gastric lumen and 1% of them are also leaked into circulating blood^[1,2]. PG levels in blood seem to be related to the morphologic and functional changes in the stomach, and their use as 'serological biopsy' has been reported over 20 years before^[3-5]. Recently, more and more investigators are concerned about the relationship between serum PG levels and gastric precancerous diseases, gastric carcinogenesis, and the significance of them being a marker for the screening of gastric cancer (GC). In most Western countries, the focus has been on the

identification of individuals for intervention studies, whereas in Japan the use of PG levels is to identify those for endoscopic examination and those at risk for GC^[6-10]. However, the limited knowledge about their characteristics in different populations and the significant differences in methodologies may prejudice the assessment of consistency. For instance, different cut-off values are used for the positive definition when either PG I levels or both PG I and PG II levels are considered^[11-13]. Furthermore, due to few cohort studies have been done in Chinese, the population-based data on serum PG levels and their influencing factors, such as age, sex, the presence of different gastric diseases and *H pylori* infection, are limited^[14,15].

In the present study, we measured the serum PG I, PG II levels in residents from the Zhuanghe County, Liaoning Province, in North China, in order to investigate the essential characteristics of serum PG levels in Chinese, which is expected to provide a valuable reference for large-scale surveys of gastric cancer.

MATERIALS AND METHODS

Subjects

A total of 6990 subjects (3455 men and 3535 women), who underwent gastric cancer screening in North China from 1997 to 2002, were enrolled in this study. Their mean age was 48.84 years, ranging 11-82 years. Information about gender, age and other factors was obtained by means of a questionnaire administered to each subject. The study was approved by the Human Ethics Review Committee of China Medical University. Written informed consent was obtained from participants in accordance with the Declaration of Helsinki and its later revision.

Serum pepsinogen level

Approximately 5 mL fasting blood was collected from each participant and kept at 4°C for 24 h. The blood was centrifuged at 3000 r/min for 10 min and the serum aliquot was stored immediately at -20°C and then shifted to an environment at -70°C for the determination of various parameters. Serum PG concentration was measured by enzyme-linked immunosorbent assay (ELISA) with PG I /PG II ELISA kits (Biohit Co., Ltd., Finland).

Endoscopic and clinicopathological examinations

Gastrointestinal endoscopy was performed for observing the entire stomach. Experienced endoscopists performed each examination without knowledge about the serological data on the study subjects. Gastric mucosa was examined, and 4 biopsy specimens were obtained from the body, angulus, antrum and lesions, respectively. The biopsies were routinely bathed in 10% formalin, embedded in paraffin, then sectioned and stained in each local center. The stained sections were evaluated independently by two gastrointestinal pathologists. Each subject was assigned a global diagnosis based on the 4 specimens. Microscopic findings were assessed according to the consensus on chronic gastritis at the national symposium^[16] or in combination with the visual analog scale of the updated

Sydney System^[17], including normal mucosa (NOR, $n = 494$), superficial gastritis (SG, $n = 3954$), erosive gastritis and ulcers (GEU, $n = 362$), superficial gastritis accompanying IM (SG-IM, $n = 347$), atrophic gastritis (AG, $n = 870$), gastric polyp (GP, 73 cases), dysplasia (GD, $n = 110$) and GC ($n = 80$).

Identification of *H pylori* infection

Gastric biopsies were evaluated for *H pylori* infection by histological examination. *H pylori* could be found in gastric epithelium or in mucus. Serum immunoglobulin (Ig)G antibodies to *H pylori* were detected by ELISA with *H pylori*-IgG ELISA kit (Biohit Co., Ltd., Finland) in duplicate. Patients whose antibody titer defined by optical density (OD) values according to the manufacturer's protocol, was higher than the cut off value of 42EIU, were regarded as positive for *H pylori* infection.

Statistical analysis

All statistical analyses were performed using SPSS 11.5 software (SPSS Inc. Chicago, USA). The distribution of variables was tested by "Kolmogorov-Smirnov". The relation between two continuous variables was assessed by Spearman's correlation coefficient. The median of variables was compared between two groups by the Mann-Whitney *U* test and multiple comparisons by the Kruskal-Wallis test. The receiving operating characteristics (ROC) curve for each evaluation was used to extract the corresponding cut-off point, which can be used to discriminate different histological patterns of patients. For that purpose, the area under each ROC curve was used to measure the discriminatory ability of the model. The resulting value of the cut-off point for each evaluation was applied to the determination of the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of the test. Consequently, 95% confidence interval was calculated. Different variables influencing the values of PG I, PG II and PG I / II ratio were identified with multivariate logistic regressions adjusted by the histological diagnosis. The value was shown as the median. A two-sided *P* value of less than 0.05 was considered statistically significant.

RESULTS

Basic population data on PG levels in Chinese

Among the 6990 subjects analyzed, the serum levels of PG I and PG II and the PG I / II ratio were significantly skewed from the normal distribution. The median value was 86.9 µg/L, 10.6 µg/L and 8.1 µg/L, respectively.

PG levels in different gender groups

The gender was significantly correlated with the serum PG I and PG II level ($r = -0.178$, $r = -0.147$, $P = 0.000$). The PG I and PG II levels were significantly higher in males than in females, while the PG I / II ratio was significantly lower in males than in females (Table 1).

PG levels in different age groups

All the objects were assigned to four groups based on their

Table 1 Serum PG levels in different gender groups (median)

Gender	Cases (n)	PG I (μg/L)	PG II (μg/L)	PG I / II
Male	3455	95.2	12.1	7.9
Female	3535	79.7	9.4	8.3
P value		0.000	0.000	0.000

Table 2 Serum PG levels in different age groups (median)

Age (yr)	Cases (n)	PG I (μg/L)	PG II (μg/L)	PG I / II
A (≤ 40)	1813	86.6 ^a	9.9	8.7
B (41-50)	2225	86.9 ^b	10.6 ^d	8.3 ^f
C (51-60)	1840	88.6 ^c	11.3 ^e	7.8 ^g
D (≥ 61)	1112	84.0	10.9	7.0 ^h

PG I: ^a*P* = 0.017, ^b*P* = 0.031, ^c*P* = 0.019 vs D group; PG II: ^d*P* = 0.018 vs A group, ^e*P* = 0.010 vs B group; PG I / II: ^f*P* = 0.003 vs A group, ^g*P* = 0.002 vs B group, ^h*P* = 0.002 vs C group.

age: group A (≤ 40 years of age), group B (41-50 years of age), group C (51-60 years of age) and group D (≥ 61 years of age), respectively. The serum PG levels were compared between different groups (Table 2). The serum PG II level increased with age (correlation coefficient: 0.065, *P* = 0.000), while the PG I / II ratio decreased with age (correlation coefficient: -0.104, *P* = 0.000).

The PG I value increased in groups A (86.6 μg/L), B (86.9 μg/L) and C (88.6 μg/L), though the difference was not significant (*P* = 0.754, *P* = 0.683, respectively). The PG I value in group D (84.0 μg/L) was significantly lower than that in groups C (*P* = 0.017), B (*P* = 0.031) and A (*P* = 0.019). The PG II value in groups A (9.9 μg/L), B (10.6 μg/L) and C (11.3 μg/L) increased significantly in the sequence indicated (*P* = 0.018, *P* = 0.010, respectively). There was no significant difference in the PG II level between groups D (10.9 μg/L) and C (*P* = 0.803). The PG I / II ratio in groups A (8.7), B (8.3), C (7.8) and D (7.0) decreased significantly in the sequence indicated (*P* = 0.003, *P* = 0.002, *P* = 0.002, respectively).

PG levels and kinds of gastric disease

Along the sequence of NOR→SG→GEU→AG→GC groups, the serum PG I and PG II levels increased and then decreased, while the PG I / II ratio decreased gradually. The PG I and PG II levels in the NOR group were lower than those in other groups, while both of them were the highest in GEU. The PG I / II ratio in the NOR group was higher than that other groups, while it was the lowest in the GC group. Several statistical differences were noticed. The differences in the PG II level and the PG I / II ratio between NOR and other groups were of statistical significance. The differences in the PG I / II ratio between SG and other groups were of statistical significance. The differences in PG I and PG II levels in GEU and other groups were of statistical significance. Compared to SG and GEU groups, the differences in PG II level and the PG I / II ratio were of statistical significance in the AG group, while compared to the GC group, the differences in PG, PG II level and the PG I / II ratio had no statistical

Table 3 Serum PG levels in different gastric disease groups (median)

Gastric disease	Cases (n)	PG I (μg/L)	PG II (μg/L)	PG I / II
NOR	494	79.3	7.4	10.4
SG	3654	86.0	9.4	9.0
GEU	362	102.5	14.4	7.5
SG-IM	1347	89.9	12.8	6.8
AG	870	84.8	13.0	6.5
GP	73	87.5	13.3	6.1
GD	110	96.9	15.9	5.7
GC	80	84.4	11.3	6.4

Table 4 Results of Mann-Whitney U test

Group	P value		
	PG I	PG II	PG I / II
NOR vs SG	0.000	0.000	0.000
NOR vs GEU	0.000	0.000	0.000
NOR vs AG	0.021	0.000	0.000
NOR vs GC	0.892	0.000	0.000
SG vs GEU	0.000	0.000	0.000
SG vs AG	0.173	0.000	0.000
SG vs GC	0.218	0.060	0.000
GEU vs AG	0.000	0.017	0.002
GEU vs GC	0.000	0.023	0.137
AG vs GC	0.422	0.251	0.809

significance (Tables 3 and 4).

As described in Table 3, atrophic diseases including AG and GC could be taken as the “low group” (L), and non-atrophic diseases including SG and GEU as the “middle group” (M), and NOR as the “high group”(H). The SG-IM could be assigned to the L group. The argument for the categorization of GP and GD was different. Both of them could be assigned to the L group too, since the PG I / II ratio decreased along with AG→GC→GP→GD, but there was no significant difference between them (*P* = 0.566). Therefore, the median value of the PG I / II ratio in H (NOR), M (SG + GEU) and L (SG - IM + AG + GC + GP + GD) groups was 10.4, 8.8 and 6.6, respectively, while the corresponding differences between neighboring groups were of statistical significance (*P* = 0.000, *P* = 0.000). More interestingly, it was possible to differentiate three histological groups according to their median PG I / II ratio: > 10 for normal mucosa, < 7 for atrophic mucosa, and an intermediate value for non-atrophic mucosa.

ROC curves were plotted for each of the serum tests as a predictor of atrophy. The results obtained from the ROC curves could discriminate between patients with atrophy, normal and non-atrophy (Figure 1). The areas under the ROC curves for PG I, PG II, and the PG I / II ratio were 0.494, 0.398 and 0.622, respectively, suggesting that the PG I / II ratio was the only useful biomarker for screening atrophy in this population. The best cut-off point of the PG I / II ratio for predicting atrophy was 6.9. The corresponding validity parameters were sensitivity (53.2%), specificity (67.5%), PPV (47.3%), and NPV (72.4%). The accuracy of the PG I / II ratio as a diagnostic test was 62.4%.

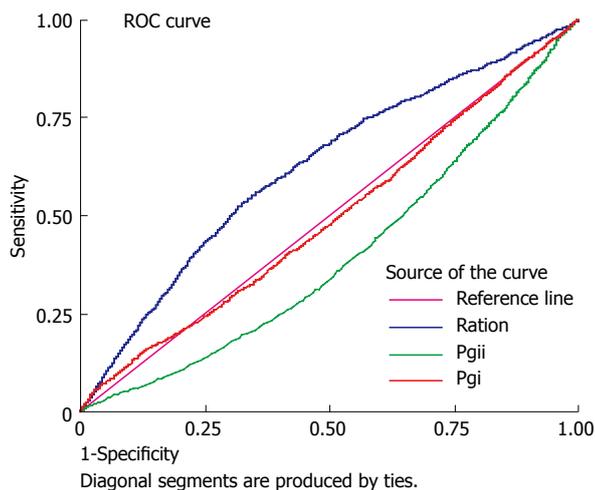


Figure 1 Unadjusted ROC curves for PG I, PG II and the PG I / II ratio to discriminate between patients with atrophic lesions and those with normal or inflammatory gastric mucosa.

PG levels and status of *H pylori* infection

Among the 6990 cases tested, 5285 were positive for *H pylori* infection and 1705 were negative for *H pylori* infection. The PG I and PG II levels in the positive group were significantly higher than those in the negative group (88.7 $\mu\text{g/L}$ vs 81.4 $\mu\text{g/L}$, $P = 0.000$; 11.4 $\mu\text{g/L}$ vs 8.4 $\mu\text{g/L}$, $P = 0.000$, respectively), while the PG I / II ratio in the positive group was significantly lower than that in the *H pylori* group (7.7 vs 9.6, $P = 0.000$).

Determination of independent variables by multivariable logistic regression

A multivariable logistic regression was performed to determine the dependent variables that could explain the variation of biomarkers. The applied model took four variables of gender, age (< 60 years, ≥ 61 years), gastric mucosal lesion (atrophic or non-atrophic), and *H pylori* infection (+, -) as inputs and considered the PG I / II ratio (≤ 7 , > 7) as the outcome. Results from this regression gave a statistical significance ($\chi^2 = 341.535$, $P = 0.000$). Another qualification for this model was its fitting confidence (13.695, $P = 0.250$). The testing result from this model showed a statistical significance in gender ($P = 0.006$), age ($P = 0.000$), atrophic lesion ($P = 0.000$) and *H pylori* infection ($P = 0.000$). Their corresponding risk factors were male (OR: 1.151, 95% CI: 1.042-1.272), age ≥ 61 years (OR: 1.358, 95% CI: 1.188-1.553), atrophic lesion (OR: 2.075, 95% CI: 1.870-2.302) and *H pylori* infection (OR: 1.546, 95% CI: 1.368-1.748) (Table 5). The overall accordance of this model was 64.6%.

DISCUSSION

In this study, we reported for the first time the essential serum PG levels in the Chinese population, including some influence influencing factors such as sex, age, the presence of gastric diseases, and *H pylori* infection.

Studies have reported some conflicting results with regard to the correlation between serum PG level and

Table 5 Multivariable logistic regression of the PG I / II ratio

	<i>n</i>	Coeff.	95% CI	<i>P</i> -values
Gender				
Female	3535	Baseline		
Male	3455	1.151	1.042-1.272	0.006
Age				
< 60 yr	5878	Baseline		
≥ 61 yr	1112	1.358	1.188-1.553	0.000
Gastric mucosal lesions				
Non-atrophy	4510	Baseline		
Atrophy	2480	2.075	1.870-2.302	0.000
<i>H pylori</i>				
<i>H pylori</i> ⁻	1705	Baseline		
<i>H pylori</i> ⁺	5285	1.546	1.368-1.748	0.000

age or sex. For instance, men have higher normal PG I values than women^[18], which is in agreement with the data on blood donors^[19]. In contrast, in 20-70 year old Japanese, serum PG level is dependent on the age and PG I increases gradually with age, while the PG I / PG II ratio decreases significantly^[20]. In our study, the PG I and PG II levels were significantly higher in males than in females. The PG I / II ratio of the males was significantly lower than that of the females. Both PG I and PG II levels increased gradually till the age of 60 years, while the PG I / II ratio showed a significant stage reduction. These findings are in agreement with the reported data^[9]. These different age-dependences therefore require a thorough checking of the characteristically different distribution, and difference among populations in application value for serum PG. Another important aspect needing special attention is the identification of its normal distribution in different age and gender groups by stratification.

Serum PG is a well-known indicator and "serological biopsy" of corpus mucosa^[21,22]. A cascade of mucosal lesions, from chronic gastritis, atrophy, intestinal metaplasia, to dysplasia has been consistently identified, at least for Lauren's intestinal subtype of GC^[23]. In this study, along with the sequence of NOR→SG→GEU→AG→GC, the serum PG I and PG II levels increased while the PG I / II ratio decreased. When it came to the atrophic lesion from the non-atrophic lesion, both PG I and PG II levels had a trend to go down, suggesting that the PG I / II ratio reflects the development of atrophic lesion on gastric membranes better than either PG I or PG II alone. The PG I / II values for atrophic gastritis were significantly lower than those for NOR and non-atrophic lesions, while there was no difference among these atrophic lesions, suggesting that the PG I / II ratio is an effective parameter for screening individuals at high risk of GC^[9,24-27]. We obtained the best cut-off points of the PG I / II ratio for detecting GC and its precursors by ROC curve with a sensitivity of 53.2% and a specialty of 67.5%, which can be used for further investigation as a screening tool in the first period.

H pylori infection frequently persists lifelong in the host stomach and is associated with a wide spectrum of human gastric and duodenal diseases, ranging from gastritis to duodenal ulcer, GC and MALT lymphoma^[28,29]. In 1994, it was defined as a definite carcinogen by the International

Agency for Research on Cancer^[30]. It was reported that *H pylori* stimulates G cells in the antrum, thus increasing the level of gastrin they secreted^[31]. Gastrin directly stimulates the main cells and is able to stimulate the synthesis and secretion of PGs, especially PG II by increasing the density of calcium-ion flux, cAMP and phosphoinositide inside the main cells. Serum epidemiological studies showed that *H pylori* infection correlates significantly to the elevated serum PG especially PG II, and the reduced PG I / II ratio^[32]. Our previous study revealed that the incidence of *H pylori* infection is 79.3% in Zhuanghe County^[33]. In the present study, the serum PG I and II levels in positive *H pylori* individuals were significantly higher than those in negative *H pylori* individuals, and the PG I / II ratio was lower in positive *H pylori* individuals than in negative *H pylori* individuals, confirming that *H pylori* infection influences the serum PG level in residents of Zhuanghe County.

Multivariable logistic regression with the PG I / II ratio as the outcome showed that the PG I / II levels were significantly affected if the surveyed samples met any one of the following qualifications: male, age > 60 years, atrophic lesion and *H pylori* infection, showing that all these factors should be taken into account in the screening of GC with serum PGs.

In summary, our results from this population-based study provide the essential characteristics of serum PG in Chinese. The PG I / II ratio is more suitable for identifying subgroups with different influencing factors, compared with PG I or PG II alone. This implies that low PG I / II ratio can be used as a serological indicator of gastric atrophic diseases.

COMMENTS

Background

Human pepsinogens (PGs) are inactive pro-enzymes for the specific digestive enzyme--pepsin originating from the gastric mucosa, and can be classified biochemically and immunochemically into pepsinogen I (PG I) and pepsinogen II (PG II). Serum PG levels are related to the morphologic and functional changes in the stomach, and can be used as a 'serological biopsy'.

Research frontiers

In the present study, we investigated the essential characteristics of serum PG in Chinese, which provides a valuable reference for large-scale surveys of gastric cancer in China.

Innovations and breakthroughs

In this study, we analyzed the essential characteristics of serum PG levels and their influencing factors in residents from the Zhuanghe County in North China. Our results that serum PG skewed from the normal distribution significantly, and was influenced by age, sex, the gastric mucosa lesions and *H pylori* infection. The PG I / II ratio was more suitable for identifying subgroups with different influencing factors, compared with PG I or PG II alone.

Applications

The essential characteristics of serum PG in Chinese are described. The PG I / II ratio is more suitable for identifying subgroups with different influence factors and can be used as a serological indicator of gastric atrophic diseases.

Peer review

This paper presents the serum pepsinogen values and their influencing factors in a large group of Chinese from North China, which is of certain importance. However, a large room for improvement in its language.

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