

# Diagnostic value of serum pepsinogen I, pepsinogen II, and gastrin-17 levels for population-based screening for early-stage gastric cancer

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## Abstract

**Objective:** Diagnosing gastric cancer (GC) at early stages is important for reducing its mortality. This study evaluated the diagnostic value of serum pepsinogen (PG) I, PGII, and gastrin-17 (G17) levels in screening for early-stage GC.

**Methods:** Serum levels of PGI, PGII, and G17 were measured in patients with upper digestive tract symptoms or GC family histories, and the PGI to PGII ratio (PGR) was calculated. Receiver operator characteristic curves were used to determine the thresholds of PGI, PGR, and G17 for GC diagnosis.

**Results:** Among the 949 patients examined by gastroscopy, 13 (1.37%) had GC, including five cases of early-stage GC and eight cases of progressive GC. PGI, PGR, and G17 showed good specificity and sensitivity for early-stage and progressive GC. The optimal thresholds of PGI, G17, and PGR were 71.85 µg/L, 15.65 pmol/L and 5.04 for the diagnosis of early-stage GC, respectively, and were 42.55 µg/L, 20.55 pmol/L, and 2.79 for the diagnosis of progressive GC, respectively.

**Conclusion:** Combining PG and G17 serum levels with gastroscopy could be a promising approach to screen for early-stage GC.

## Keywords

Pepsinogen I (PGI), pepsinogen II (PGII), gastrin-17 (G17), gastroscopy, gastric cancer, screening

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## Introduction

Gastroscopy followed by examinations of biopsy specimens is the gold standard for diagnosing gastric cancer (GC). A disadvantage of this method is that it is invasive and causes discomfort and pain, making it an undesirable procedure for diagnostics. Several attempts have been made to detect precancerous lesions and early-stage GC in high incidence areas by examining serum levels of pepsinogen (PG) and gastrin-17 (G17), which could offer an effective and non-invasive alternative to traditional gastroscopy for diagnosing GC.<sup>1-3</sup> A recent study showed that low PGI levels and a low PGI/II ratio were correlated with high G-17 levels and increased risk of GC.<sup>4</sup> Additionally, PGI, PGII, and G17 serum levels were significantly decreased in dyspeptic patients after the eradication of *Helicobacter pylori*.<sup>5</sup> These results suggest a correlation between PGI, PGII, and G17 levels. However, early-stage GC is difficult to diagnose due to patients being either asymptomatic or having nonspecific symptoms.

GC usually develops to advanced stages and metastasizes before symptoms occur, leading to a high mortality rate. GC diagnoses should be made as early as possible so that prompt treatment can be instituted. To address this issue, we surveyed 20,000 local residents, and measured PG and G17 serum levels in patients with upper digestive tract symptoms or with family histories of GC, and then compared these results with other diagnostic methods such as gastroscopy, narrow-band imaging (NBI), chromoendoscopy, and biopsy.

## Subjects and methods

### Participants

Approximately 20,000 residents of six villages in three counties were surveyed

between January 2014 and September 2016. Serum levels of PGI, PGII, and G17 in citizens between 40 and 69 years old with upper digestive tract symptoms (abdominal distension, abdominal pain, acid regurgitation, heartburn, nausea, and loss of appetite) or family histories of GC ( $n=2,500$ ) were measured. The exclusion criteria were as follows: (1) long-term or recent use of antibiotics, acid-suppressive drugs, including H<sub>2</sub> receptor antagonists and proton-pump inhibitors, and non-steroidal anti-inflammatory drugs; (2) a history of surgery for GC; (3) a history of treatment for *H. pylori* infection; and (4) complications associated with severe heart, lung, and kidney diseases. This study was approved by the Ethical Committee of Qinghai Provincial People's Hospital (Xining, China) in October 2013. All participants volunteered to participate in this study and signed informed consent forms prior to entering the study.

### Screening procedures

The demographics (including name, age, gender, history of digestive tract diseases, drug use, GC surgery, family history of GC, diet, and lifestyle) of participants were obtained by paper-and-pencil questionnaires. Fasting blood samples (5 mL) were collected and separated by centrifugation for 5 minutes at 500 ×g, and then stored at -80°C. Serum levels of PGI, PGII, and G17 were detected using ELISA kits (Biohit, Helsinki, Finland) following the manufacturer's instructions; these results were also used to calculate the PGI to PGII ratio (PGR). Participants with serum PGI (80–165 µg/L), PGII (3–15 µg/L), or G17 (1–15 pmol/L) were further examined by gastroscopy according to national diagnostic standards.

### Diagnosis and grouping

Participants diagnosed by gastroscopy were further divided into five groups based on gastroscopic and histopathological results: (1) non-atrophic gastritis; (2) atrophic gastritis; (3) peptic ulcer; (4) early-stage GC; and (5) progressive GC.

### Statistical analysis

All statistical analyses were performed with SPSS Statistics for Windows, Version 17.0 (SPSS Inc., Chicago, IL, USA). The data are expressed as mean  $\pm$  SD. Differences were compared by one-way analysis of variance (ANOVA) for continuous variables, followed by the least significant difference (LSD) post-hoc test for multiple comparisons, or by the Chi-squared test for categorical data. The optimal serum PGI, PGII, and G17 levels for diagnosing GC were determined by receiver operating characteristic (ROC) curves.  $P < 0.05$  was considered statistically significant.

## Results

### Gastroscopic results of participants at a high risk for GC

Among the 20,000 local residents surveyed, 2,500 had upper digestive tract symptoms (including abdominal distension, abdominal pain, acid regurgitation, heartburn, nausea, and loss of appetite) or family

histories of GC, indicating that they had a high risk of GC. Among them, 1,096 were men and 1,404 were women, with an average age of  $50.66 \pm 11.34$  years. Additionally, 949 (37.96%) underwent gastroscopy and 649 (25.96%) underwent biopsy diagnoses. The gender, age, and ethnic distributions of participants examined by gastroscopy are shown in Tables 1 and 2. Only 13 of these 949 participants (1.37%) had GC, including five cases of early-stage GC (38.5%) and eight cases of progressive GC (61.5%). We performed endoscopic submucosal dissection (ESD) in cases of early-stage GC, and all showed good recovery in postoperative follow-up.

### Serum PGI, PGII, and G17 levels in each group

PGI and PGR levels were lower in the atrophic gastritis, early-stage GC, and progressive GC groups compared with the non-atrophic gastritis group as a control ( $P < 0.05$ ). G17 levels were higher in those with early-stage GC and progressive GC ( $P < 0.05$ ). The progressive GC group had lower PGI and PGR levels and higher G17 levels than the early-stage GC group ( $P < 0.05$ , Table 3).

### ROC curves for the diagnostic cutoffs of PGI, PGR, and G17 in GC

ROC curves of PGI, PGR, and G17 for early-stage GC diagnosis are shown in

**Table 1.** Histological diagnoses by gastroscopy.

Pathological type	Number (%)	Gender (male/female)	Age (years)
Non-atrophic gastritis	239 (25.18)	95/144	$48.48 \pm 7.38$
Atrophic gastritis	500 (52.69)	231/269	$45.02 \pm 8.11$
Peptic ulcer	197 (20.76)	113/84	$51.76 \pm 7.98$
Early-stage GC	5 (0.53)	3/2	$54.40 \pm 9.91$
Progressive GC	8 (0.84)	2/6	$50.25 \pm 8.99$
Total	949 (100)	443/506	$49.83 \pm 8.40$

Note: GC, gastric cancer.

**Table 2.** Ethnic distribution of participants examined by gastroscopy.

Pathological types	Han	Hui	Tu	Tibetan
Non-atrophic gastritis	126	93	17	3
Atrophic gastritis	360	118	14	8
Peptic ulcer	109	73	15	0
Early-stage GC	2	3	0	0
Progressive GC	3	5	0	0
Total	600	292	46	11

Note: GC, Gastric Cancer.

**Table 3.** Serum PGI, PGII, PGR, and G17 levels in different groups ( $\bar{x} \pm s$ ).

Group	n	PGI ( $\mu\text{g/L}$ )	PGII ( $\mu\text{g/L}$ )	PGR	G17 ( $\mu\text{g/L}$ )
Non-atrophic gastritis	239	103.89 $\pm$ 37.45	13.37 $\pm$ 7.68	9.18 $\pm$ 4.10	14.99 $\pm$ 7.12
Atrophic gastritis	500	68.73 $\pm$ 16.98*	13.48 $\pm$ 8.48	7.03 $\pm$ 4.55*	12.29 $\pm$ 6.00
Peptic ulcer	197	130.52 $\pm$ 44.09*	16.58 $\pm$ 7.34*	8.98 $\pm$ 4.03	11.95 $\pm$ 5.40*
Early-stage GC	5	70.00 $\pm$ 12.35*	20.86 $\pm$ 7.74*	3.74 $\pm$ 1.40*	18.03 $\pm$ 4.52*
Progressive GC	8	38.39 $\pm$ 2.77*##	20.73 $\pm$ 8.09*	2.05 $\pm$ 0.59*##	25.15 $\pm$ 3.76*##

Note: GC, gastric cancer; PGI, pepsinogen I; PGII, pepsinogen II; PGR, PGI to PGII ratio; G17, gastrin-17. \* $P < 0.05$  vs. the non-atrophic gastritis group; ## $P < 0.05$  vs. the early-stage GC group.

Figure 1a and b, with early-stage GC as the disease group ( $n = 5$ ) and non-atrophic gastritis, atrophic gastritis, and peptic ulcers as references ( $n = 936$ ). For PGI, the area under the ROC curve (AUC) was 0.625 and the optimal threshold was 71.85  $\mu\text{g/L}$  (sensitivity: 80%; specificity: 59%). For PGR, the AUC was 0.828 and the optimal threshold was 5.04 (sensitivity: 100%; specificity: 70.4%). For G17, the AUC was 0.755 and the optimal threshold was 15.65 pmol/L (sensitivity: 80%; specificity: 69.3%) (Table 4).

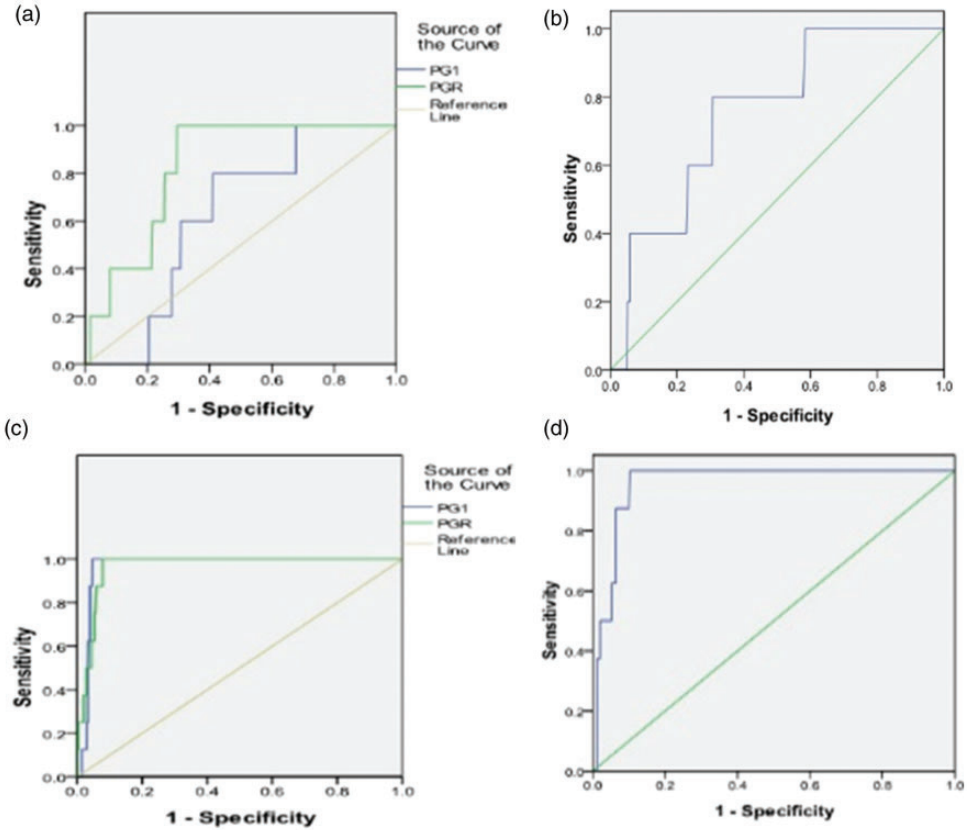
ROC curves of PGI, PGR, and G17 for diagnosing progressive GC are shown in Figure 1c and d, with progressive GC as the disease group ( $n = 8$ ) and non-atrophic gastritis, atrophic gastritis, and peptic ulcers as references ( $n = 936$ ). For PGI, the AUC was 0.966 and the optimal threshold was 42.55  $\mu\text{g/L}$  (sensitivity: 100%; specificity: 95.3%). For PGR, the AUC was 0.964 and the optimal threshold was 2.79 (sensitivity: 100%; specificity: 92.1%). For G17,

the AUC was 0.958 and the optimal threshold was 20.55 pmol/L (sensitivity: 100%; specificity: 89.7%) (Table 5).

## Discussion

ELISA showed that GC patients were associated with low serum PGI and PGR levels but high G17 levels; serum PGI, PGR, and G17 levels showed good specificity and sensitivity for diagnosing both early-stage and progressive GC, consistent with previous studies.<sup>6,7</sup> Therefore, PGI and G17 levels as well as PGR could be important indicators of the severity/aggressiveness of GC.

Serum PG and G17 levels have been established as useful markers for detecting early-stage cancers.<sup>8</sup> Decreased serum PGI and PGR levels indicate the progression of gastric mucosal atrophy from the pylorus to the gastric body and fundus.<sup>9,10</sup> Additionally, the progression from non-atrophic gastritis to atrophic gastritis, high-grade intraepithelial neoplasia, and



**Figure 1.** Receiver operating characteristic (ROC) curves for diagnosing gastric cancer (GC). (a) ROC curves of pepsinogen (PG) I and the PGI to PGII ratio (PGR) for diagnosing early-stage GC. (b) ROC curves of gastrin-17 (G17) for diagnosing early-stage GC. (c) ROC curves of PGI and PGR for diagnosing progressive GC. (d) ROC curves of G17 for diagnosing progressive GC.

**Table 4.** The optimal thresholds and AUCs of PGI, PGR, and G17 for diagnosing early-stage GC.

Group	PGI		PGR		G17	
	Threshold (µg/L)	AUC (95%CI)	Threshold	AUC (95%CI)	Threshold (pmol/L)	AUC (95%CI)
Early-stage GC	71.85 (80%, 59%)	0.625 (0.477–0.773)	5.04 (100%, 70.4%)	0.828 (0.732–0.925)	15.65 (80%, 69.3%)	0.755 (0.582–0.927)

Note: GC, gastric cancer; AUC, area under the curve; PGI, pepsinogen I; PGR, PGI to PGII ratio, G17, gastrin-17.

progressive GC is associated with progressive atrophy of the gastric mucosal glands, decreased number of chief cells, and impaired secretory function, resulting in decreased PGI levels. This atrophy

accompanied by gland metaplasia can increase PGII levels, while intestinal metaplasia and GC decrease PGI levels. Thus, measuring PG levels, particularly PGI and PGR, is valuable for diagnosing

**Table 5.** The optimal thresholds and AUCs of PGI, PGR, and G17 for diagnosing progressive GC.

Group	PGI		PGR		G17	
	Threshold ( $\mu\text{g/L}$ )	AUC (95%CI)	Threshold	AUC (95%CI)	Threshold ( $\text{pmol/L}$ )	AUC (95%CI)
Progressive GC	42.55 (100%, 95.3%)	0.966 (0.952–0.981)	2.79 (100%, 92.1%)	0.964 (0.943–0.986)	20.55 (100%, 89.7%)	0.958 (0.933–0.983)

Note: GC, gastric cancer; AUC, area under the curve; PGI, pepsinogen I; PGR, PGI to PGII ratio, G17, gastrin-17.

precancerous lesions to improve the detection rate of early-stage GC.<sup>11,12</sup>

Gastrin is a gastrointestinal hormone secreted by G cells of the gastric antrum, and its levels are primarily affected by the number and function of G cells, as well as by negative feedback regulation from gastric acid. G17 regulates the secretion of gastric acid and the growth of gastric mucosa. Previous studies have shown that G17 levels are significantly increased in GC patients, and gastrin can promote the growth and proliferation of cancer cells.<sup>8,13</sup>

In this study, we found that PG and G17 serum levels in combination with gastroscopy was a powerful approach to diagnosing early-stage GC. Owing to the lack of original data from each participant, we could not subgroup the 949 participants based on different physiological indexes that could affect serum PGI, PGII, and G17 levels. Additionally, only five early-stage and eight progressive GC patients were included in the final analysis of thresholds of the serum levels. Furthermore, the demographic information of participants was obtained from questionnaires, which may have introduced survey errors. These are the primary limitations of this study and should be addressed in future studies.

ROC curve analysis showed that the optimal thresholds of PGI and PGR for diagnosing early-stage GC were higher than what had been reported in previous studies, while the optimal G17 thresholds were lower, which could be attributable to the high attitude of Qinghai Province and

the particular diet and lifestyle of local residents. To determine the optimal thresholds for serum PGI, PGII, and G17 levels for diagnosing GC in other regions of China, multicenter studies involving a larger number of participants with diverse ethnic backgrounds and from low-, middle-, and high-altitude areas will be required. To our knowledge, this is the first study of large-scale screening for GC patients in high altitude areas where there is a lack of accessibility to medical equipment and staff. Establishing reliable PGI, PGII, and G17 thresholds for populations at high altitude will greatly help diagnose GC at earlier stages in these areas.

#### Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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