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Original Article

The diagnostic value of serum pepsinogen I, pepsinogen II and the pepsinogen I/II ratio combined with *Helicobacter pylori* tests in patients with early gastric cancer

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Abstract: Objective: To explore the diagnostic value of serum pepsinogen I (PGI), pepsinogen II (PGII), and the PG I/II ratio combined with *Helicobacter pylori* (Hp) tests for early gastric cancer screening. Methods: A total of 270 patients who underwent gastroscopy from October 2016 to October 2019 were recruited and divided into three groups: the gastric cancer group (n=90), the chronic gastritis group (n=90), and the healthy control group (n=90). The clinical data were retrospectively analyzed, and the serum levels of PGI and PGII, the PG I/II ratio and Hp infection were determined. Results: The serum PGI level and the PG I/II ratio were lower in the gastric cancer group than they were in the chronic gastritis and healthy control groups, and lower in the chronic gastritis group than in the healthy control group (P<0.001). The serum PGII levels were higher in the gastric cancer and the chronic gastritis groups than they were in the healthy control group (P<0.001). A receiver operator characteristic curve analysis revealed that PGI and the PG I/II ratio are essential in diagnosing gastric cancer. The sensitivity of PGI and the PG I/II ratio for gastric cancer were 0.656 and 0.622, respectively; the specificity of PGI and the ratio were 0.889 and 0.911, respectively. Moreover, the Hp infection rate was higher in the gastric cancer group than in the chronic gastritis and healthy control groups (P<0.01), and higher in the chronic gastritis group than in the healthy control group (P<0.001). The PGI level and PG I/II ratio in the Hp positive group were lower than they were in the Hp negative group (P<0.001). In addition, the PGI level and the PG I/II ratio in the early gastric cancer group were higher than they were in the advanced gastric cancer group (P<0.05), but no statistically significant difference was found in the PGII levels (P>0.05). The Hp infection rate in the advanced gastric cancer group was higher than it was in the early gastric cancer group (P<0.05). Conclusion: The serum levels of PGI and PGII combined with Hp tests have a certain diagnostic value and may be serological markers for early gastric cancer.

Keywords: Serum pepsinogen, *Helicobacter pylori*, early gastric cancer, diagnostic value

Introduction

A common clinical malignancy, gastric cancer is the third leading cause of cancer-related mortality globally, with 1.3 million cases worldwide in 2015, and the disease is closely related to lifestyle and diet [1-3]. Gastric cancer has one of the high mortality rates among all cancers [4, 5]. In China, a high-incidence country in East Asia, the incidence of gastric cancer ranks second among tumors [6, 7]. At present, surgery is the main method of treatment [8]. However, surgical treatment alone for advanced gastric cancer (AGC) shows poor efficacy with a low surgical resection rate, a low 5-year survival rate, and high rates of postoperative recurrence and metastasis [9]. As a result, early diagnosis and treatment are significant factors in the prognosis of gastric cancer [10]. Studies have shown that the development and progression of gastric cancer is a multi-step process involving gastric mucosal inflammation, atrophy, intestinal metaplasia and carcinogenesis. Chronic atrophic gastritis, considered to be a precancerous lesion, accounts for two-thirds of all of gastritis cases and is closely related to *Helicobacter pylori* (Hp) infection [11-13]. Diagnoses of atrophic gastritis and gastric cancer require gastroscopy and endoscopic biopsy. However, endoscopic biopsy has a limited applicability for the screening of early gastric cancer (EGC) due to its invasive nature, which makes it

unsuitable for large-scale screening. Therefore, exploring effective, convenient, inexpensive, noninvasive serum markers for the detection of EGC has become a new research direction [14].

The expression levels of serum pepsinogen (PG), a digestive protease secreted by the gastric mucosa, can reflect the morphology and function of different areas of the gastric mucosa, and a change in the PG levels can reflect the severity of gastric mucosal atrophy [15]. One study showed that PG levels, known as "serological biopsy," are noninvasive diagnostic markers of chronic atrophic gastritis [16]. However, there is a controversy in the cut-off values of PG for the screening of gastric cancer in various regions [17]. Based on the previous research findings, this study investigated the diagnostic value of PGI, PGII, and the PG I/II ratio combined with Hp tests in patients with gastric cancer in this region.

Materials and methods

General data

A total of 270 patients aged 40 to 80 years who underwent gastroscopy in Weihai Central Hospital from October 2016 to October 2019 were enrolled. Among the patients, there were 90 cases of confirmed gastric cancer with an average age of 56.9±11.2, 90 cases of chronic gastritis with an average age of 56.9±10.3 years, and 90 cases of normal gastroscopy results (the healthy control group) with an average age of 56.6±9.1 years. A written informed consent was obtained from each of the patients, and the ethical approval for the study was granted by the Ethics Committee of Weihai Central Hospital.

Inclusion and exclusion criteria

The included patients, aged 18 years and older, were diagnosed with gastric cancer and chronic gastritis using the diagnostic criteria issued by the Ministry of Health of the People's Republic of China in 2010 and the Chinese Society of Gastroenterology in 2000, respectively [18, 19]. Patients with incomplete clinical data, severe malnutrition, or other tumors were excluded. Patients with history of gastric diseases and those with mental illnesses, cerebrovascular diseases, or those unable to cooperate with the study were also excluded.

Grouping

According to their Hp infection status, the 270 patients were also divided into an Hp positive group and an Hp negative group. The clinical and pathological staging were evaluated using the 7th edition of the Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) staging system [20]. According to the pathologic findings of the gastric biopsies, the 90 patients with gastric cancer were further classified into an EGC group (n= 43) and an AGC group (n=47).

Methods

Measurement of blood samples: Fasting venous blood (5 mL) was collected from each subject at 8 o'clock in the morning and stored in ethylenediaminetetraacetic acid tubes in the refrigerator at 4°C for 15 minutes. Then the plasma was separated by centrifugation at 3300 rpm/min from each sample, and stored in the refrigerator at -20°C after adding 40 μL of phosphate buffer solution containing a protease inhibitor. Subsequently, the PGI, PGII and Hp levels were measured using enzyme-linked immunosorbent assay kits (Raybiotech, Inc., Guangzhou, China), following the manufacturer's instructions.

Statistical analysis

SPSS 22.0 software was used to process the data. Continuous variables were expressed as the mean ± standard deviation ($\bar{x}$ ± SD). Paired t-tests were adopted for the inter-group comparisons if the data had a normal distribution and a homogeneity of variance, and a rank sum test was used if not. One-way ANOVA was used for the multigroup comparisons so as to determine whether there were differences, and the Bonferroni method was used for the post hoc comparisons if there were differences. $P<0.05$ was considered statistically different.

Results

Baseline information

There were no significant statistical differences in the sex, age, or combined diseases among the three groups ($P>0.05$), suggesting that the three groups were comparable. See **Table 1**.

Table 1. Baseline information

Patient data	Gastric cancer group	Chronic Gastritis group	Healthy control group	χ^2/F	P
Sex (male/female)	57/33	53/37	51/39	0.862	0.650
Age (year)	56.9±11.2	56.9±10.3	56.6±9.1	0.040	0.961
Combined diseases					
Type 2 Diabetes Mellitus (n, %)	10 (11.11)	11 (12.22)	12 (13.33)	0.207	0.902
Hypertension (n, %)	35 (38.89)	28 (31.11)	26 (28.89)	2.246	0.325
Hyperlipidemia (n, %)	19 (21.11)	17 (18.89)	16 (17.78)	0.333	0.846
Obesity (n, %)	12 (13.33)	10 (11.11)	9 (10.00)	0.510	0.775
Smoking (n, %)	27 (30.00)	24 (26.67)	26 (28.89)	0.254	0.881

Table 2. Comparison of PGI, PGII, and the PG I/II ratio among the three groups

Group	Cases	PGI (ng/mL)	PGII (ng/mL)	PG I/II Ratio
Gastric cancer group	90	81.20±5.56***,###	15.23±2.32***	5.40±0.47***,###
Chronic Gastritis group	90	86.29±7.87***	15.34±2.69***	5.71±0.51***
Healthy control group	90	97.29±9.03	14.39±2.09	6.81±0.36
F		30.291	27.92	241.071
P		<0.001	<0.001	<0.001

Note: Compared with the healthy control group, ***P<0.001; Compared with the chronic gastritis group, ###P<0.001. PGI, Pepsinogen I; PGII, Pepsinogen II; Hp, *Helicobacter pylori*.

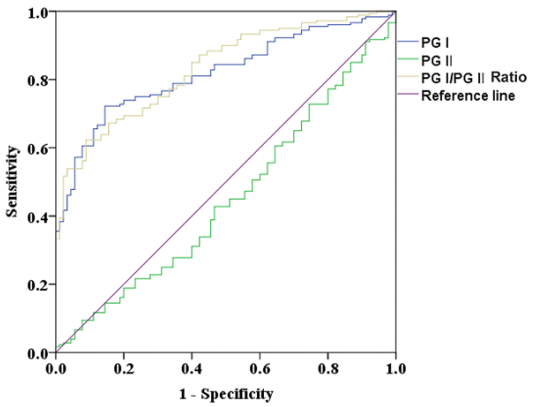

Figure 1. ROC curves for PGI, PGII and the PG I/II ratio in patients with gastric cancer. ROC, receiver operator characteristic; PGI, Pepsinogen I; PGII, Pepsinogen II.

Comparison of PGI, PGII, and the PG I/II ratio among the three groups

The serum PGI level and the PG I/II ratio were lower in the gastric cancer group than they were in the chronic gastritis and healthy control groups, and lower in the chronic gastritis group than in the healthy control group (P<0.001). The serum PGII levels were higher in the gastric cancer and chronic gastritis groups than in the healthy control group (P<0.001). See **Table 2**.

Comparison of the receiver operator characteristic curves for PGI, PGII, and the PG I/II ratio in the patients with gastric cancer

The receiver operator characteristic (ROC) analysis for PGI, PGII and the PG I/II ratio in the patients with gastric cancer demonstrated that the biomarkers (including PGI and the PG I/II ratio), but not PGII, are diagnostically significant in detecting gastric cancer. The area under curve (AUC), cut off value, Youden's index, and the sensitivity and specificity of PG I were 0.819, 87.617, 0.545, 0.656 and 0.889, while those of the PG I/II ratio were 0.832, 5.894, 0.533, 0.622 and 0.911, respectively. See **Figure 1**.

Comparison of the Hp infection rates among the three groups and of PGI, PGII, and the PG I/II ratio in the Hp positive and Hp negative groups

The Hp infection rate was higher in the gastric cancer group than it was in the chronic gastritis and healthy control groups (P<0.01), and it was higher in the chronic gastritis group than it was in the healthy control group (P<0.001). The PGI and PG I/II ratio in the Hp positive group were lower than the corresponding values in the Hp negative group (P<0.001). See **Tables 3** and **4**.

Table 3. Comparison of the Hp infection rates among the three groups

Group	Cases	Hp (+)	Hp (-)
Gastric cancer group	90	74 (82.22)***,##	16 (17.78)
Chronic Gastritis group	90	57 (63.33)***	33 (36.67)
Healthy control group	90	24 (26.67)	66 (73.33)
χ^2		58.741	
P		<0.001	

Note: Compared with the healthy control group, ***P<0.001; Compared with the chronic gastritis group, ##P<0.01. PGI, Pepsinogen I; PGII, Pepsinogen II; Hp, *Helicobacter pylori*.

Table 4. Comparison of PGI, PGII, and the PG I/II ratios in the Hp positive and the Hp negative groups

Group	Cases	PGI (ng/mL)	PGII (ng/mL)	PG I/II Ratio
Hp positive group	155	83.41±7.11	15.02±2.43	5.53±0.50
Hp negative group	115	94.80±9.98	14.92±2.47	6.58±0.60
t		10.423	0.802	15.702
P		<0.001	0.289	<0.001

Note: PGI, Pepsinogen I; PGII, Pepsinogen II; Hp, *Helicobacter pylori*.

Table 5. Comparison of PGI, PGII and the PG I/II ratios in the EGC and AGC groups

Subgroup	Cases	PGI (ng/mL)	PGII (ng/mL)	PG I/II Ratio
EGC group	43	82.45±5.28	15.32±2.46	5.38±0.79
AGC group	47	79.23±4.98	15.19±2.23	5.21±0.54
t		7.892	1.098	4.980
P		<0.001	0.239	<0.001

Note: PGI, Pepsinogen I; PGII, Pepsinogen II; Hp, *Helicobacter pylori*; EGC, early gastric cancer; AGC, advanced gastric cancer.

Table 6. Comparison of the Hp infection rate in the EGC and AGC groups

Subgroup	Cases	Hp (+)	Hp (-)
EGC group	43	31 (72.09)	12 (27.91)
AGC group	47	43 (91.49)	4 (8.51)
χ^2		5.780	
P		0.016	

Note: Hp, *Helicobacter pylori*; EGC, early gastric cancer; AGC, advanced gastric cancer.

Comparison of Hp infection rate, PGI, PGII, and the PG I/II ratio in the EGC and AGC groups

The PGI and PG I/II ratio in the EGC group were higher than they were in AGC group (P<0.05), but no statistically significant difference was found in the PGII level (P>0.05). The Hp infection rate was higher in the AGC group than it was in the EGC group (P<0.05). See **Tables 5** and **6**.

Discussion

With the increased incidence of gastric cancer in China and the huge difference between the prognoses of EGC and medium and advanced gastric cancer, the early diagnosis of gastric cancer plays a crucial role in clinical practice. At present, endoscopic biopsy is still the gold standard for diagnosing gastric cancer [14]. Due to the large population and invasive nature of gastroscopic biopsy, it is difficult and expensive to conduct mass screenings for gastric cancer. Hence exploring suitable serum markers to replace gastroscopic biopsy has become a new research direction. One study found that PG, a digestive protease secreted by the gastric mucosa is of great value in diagnosing atrophic gastritis and gastric cancer [21]. Previous studies have shown that if the atrophic gastric glands are replaced by intestinalized epithelial or pyloric glands, the PG levels will be decreased due to the reduction of the glands. In the process, the PGI level is reduced significantly, but the PGII level remains relatively stable or slightly increases; the PG I/II ratio shows a downward trend because there is a much higher level and a greater decrease of PGI [22, 23]. In this study, we identified similar results, namely that the PGI level and the PG I/II ratio in the gastric cancer group (showing a greater decrease) and the chronic gastritis group were lower than they were in the healthy control group, but the PGII levels in the gastric cancer and the chronic gastritis groups were slightly higher than the levels in the healthy control group. The results are consistent with the findings reported by Iguchi et al., suggesting that the PG levels are useful serological markers to some degree [24]. A previous study found that the sensitivity and specificity of PGI were 0.67 and 0.47 respectively in the diagnosis of gastric cancer. Also, it was reported that the AUCs of the PGI and PG I/II ratio were 0.78 and 0.79 respectively in the diagnosis of gastric

atrophy [25, 26]. Furthermore, another two studies found that the PG I/II ratio is significantly associated with the mortality rate of gastric atrophy and gastric cancer if the ratio <3 [27, 28]. In this study, the diagnostic cut-off values of PGI and the PG I/II ratio were 87.617 and 5.894, which are different from the above results. This may be due to the various regions and relatively small sample size, thus, we will expand the sample size and further explore the optimal cut-off value for diagnosing gastric cancer in this region.

Infection with Hp has been proven to be the major cause of gastric diseases and gastric cancer. After Hp eradication, the recurrence rate is still high. [29]. Currently, the Hp infection rate in China is still higher than it is in other developed countries [30]. Recently, Hp infection has been found to cause abnormal secretions of PGI and PGII. After Hp eradication, there is a decrease in the PGI and PGII levels and an increase in the PG I/II ratio [31]. Moreover, a positive correlation between the serum levels of PGI and PGII and Hp infection and a negative correlation between the ratio and Hp infection have been found [32]. Previous studies have shown that the PG I/II ratio after eradication treatment increases in Hp-infected patients [33, 34]. In this study, the infection rate of Hp in gastric cancer was higher than it was in the chronic gastritis and healthy control groups; the PGI level and the PG I/II ratio of the Hp positive patients were lower than they were in the Hp negative patients; the PGI level and PG I/II ratio decreased after infection with Hp. A study of Hp infection in gastric cancer showed that Hp-infected patients have a higher risk of developing gastric cancer [29]. Moreover, it was reported that Hp infection is correlated with the prognosis of gastric cancer [35]. In this study, the infection rate of Hp in the AGC group was higher than it was in the EGC group; the PGI level and the PG I/II ratio in the EGC group were higher than they were in the AGC group. The results suggest that Hp infection plays a critical role in the progression of gastric cancer and has an effect on the levels of serum PG.

The sample size in our single-center study was small, so we will use larger sample sizes and perform a multi-center clinical trial to get a more precise conclusion in the future.

In summary, the serum levels of PGI and PGII combined with Hp testing have a certain diagnostic value and are potential serological markers for the detection of EGC.

Disclosure of conflict of interest

None.

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