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ORIGINAL ARTICLE

Significance of Serological Gastric Biopsy in Different Gastric Mucosal Lesions: an Observational Study

Zhiping Dong [1], Xuan Zhang [1], Xi Chen [2], Jingzhe Zhang [3]

[1] *Department of General Surgery, Shanghai TCM-Integrated Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, China*
[2] *Department of Infectious Disease, Shanghai TCM-Integrated Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, China*
[3] *Department of Surgery, Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, China*

SUMMARY

Background: **Screening and timely treatment of precancerous gastric cancer diseases or of gastric cancer in the early stages has important significance in reducing the incidence and mortality of gastric cancer. Gastroscopy and histopathological biopsy are still the gold standards for the diagnosis of gastric diseases. But the application of gastroscopy for the screening and diagnosis of gastric diseases is limited. In recent years, serum pepsinogen (PG), gastrin, and *Helicobacter pylori (H. pylori*) IgG antibodies have become indicators for "serological biopsy" of the gastric mucosa.**
Methods: **From January 2016 to January 2018, a total of 2,394 patients with digestive tract symptoms underwent gastroscopy. According to the endoscopic examination and pathological diagnosis, there were four case groups: 1,376 cases of chronic non-atrophic gastritis, 708 cases of chronic atrophic gastritis, 265 cases of gastric ulcer, and 45 cases of gastric cancer. Serological gastric biopsies were performed and analyzed.**
Results: **The serum levels of PGI in the chronic atrophic gastritis group was significantly lower than that in the chronic non-atrophic gastritis group, gastric ulcer group, and gastric cancer group ($p < 0.05$). The serum levels of PGII and G-17 in the gastric cancer group were significantly higher than those in the chronic non-atrophic gastritis group, chronic atrophic gastritis group, and gastric ulcer group ($p < 0.05$). The PGR in the gastric cancer group was significantly lower than that in the chronic non-atrophic gastritis group, chronic atrophic gastritis group, and gastric ulcer group ($p < 0.05$). The *H. pylori* positive rates in the chronic atrophic gastritis group and gastric cancer group were higher than those in the chronic non-atrophic gastritis group and gastric ulcer group ($p < 0.05$).**
Conclusions: **Serological gastric biopsy is closely correlated to gastric mucosal disease and can be used as a screening tool in gastric disease.**
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Correspondence:
Jingzhe Zhang
Department of Surgery
Longhua Hospital Affiliated to
Shanghai University of
Traditional Chinese Medicine
No. 725 Wanping South Road, Xuhui District
Shanghai 200032
China
Phone: +86 21 64385700
Fax: +86 21 65461538
Email: zhangxuan201903@163.com

KEY WORDS

pepsinogen, gastrin-17, *Helicobacter pylori,* gastric mucosal lesions

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LIST OF ABBREVIATIONS

PG - pepsinogen
PGI - pepsinogen I
PGII - pepsinogen II
G-17 - gastrin-17
PGR - PGI/PGI
H. pylori IgG - *Helicobacter pylori* IgG

INTRODUCTION

The main gastric diseases are chronic non-atrophic gastritis, chronic atrophic gastritis, gastric ulcer, and gastric cancer. Chronic atrophic gastritis and gastric ulcer are precancerous gastric cancer diseases and play an important role in the occurrence and development of intestinal-type gastric cancer. Gastric cancer is a common digestive tract malignant tumor; there were nearly one million new cases of gastric cancer globally in 2012, and of malignant tumors, it has the third highest mortality rate, resulting in a heavy medical burden worldwide [1]. Screening and timely treatment of precancerous gastric cancer diseases or of gastric cancer in the early stages has important significance in reducing the incidence and mortality of gastric cancer. Gastroscopy and histopathological biopsy are still the gold standards for the diagnosis of gastric diseases. Because gastroscopy is affected by factors such as professional technical support and patient compliance and tolerance, the application of gastroscopy for the screening and diagnosis of gastric diseases is limited. In recent years, serum pepsinogen (PG), gastrin, and *Helicobacter pylori* (*H. pylori*) IgG antibodies have become indicators for "serological biopsy" of the gastric mucosa. By virtue of its advantages, such as simple and easy detection, non-invasive operation, objective and reliable results, and good subject compliance, serological biopsy has become a research hotspot. Serum pepsinogen is an inactive precursor of pepsin, which was first discovered by Schwann. [2] Pepsinogen can be classified as either pepsinogen I (PGI) or pepsinogen II (PGII), according to its biochemical and immunological characteristics. The PG level is used as an indicator of the inflammation and acid secretion function of the gastric mucosa. The PGI/PGII ratio (PGR) is used as an indicator of lesions and the function of the gastric mucosa [3]. Gastrin is secreted by antral G cells and cells of the proximal duodenal mucosa. Its level reflects the morphology and function of the gastric mucosa at different sites. Some studies have shown that serum PGI, PGII, the PGR, and gastrin-17 (G-17) levels have important clinical value in the preliminary screening and examination of gastric diseases [4,5]. *H. pylori* is the most common bacterial pathogen that causes chronic infection in humans. Globally, approximately 50% of the population is infected, and most are asymptomatic carriers. There are differences in *H. pylori* infections among different ethnic groups, with prevalence rates of 30%, 39%, and 60% in the United States, Japan, and South Korea, respectively [6]. *H. pylori* is not only a pathogen of chronic gastritis and gastric ulcer but has also been included by the World Health Organization as a type I carcinogen, mainly involved in the early stages of the occurrence and development process of gastric cancer. The gastric cancers caused by *H. pylori* include gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue lymphoma [7]. "Serological biopsy" of the gastric mucosa refers to the detection of serum PG, G-17, and *H. pylori* IgG antibodies. The aim of the present study is to determine the expression of "serological biopsy" indicators of the gastric mucosa in the serum of patients with different gastric mucosal lesions and to investigate the clinical significance of "serological biopsy" of the gastric mucosa for the diagnosis and screening of gastric diseases.

MATERIALS AND METHODS

Patients

A total of 2,394 patients were selected as the objects of the study. The patients underwent gastroscopy and received a definite diagnosis of chronic non-atrophic gastritis, chronic atrophic gastritis, gastric ulcer, or gastric cancer at the Shanghai Hospital of Integrated Traditional Chinese and Western Medicine Affiliated to Shanghai University of Traditional Chinese Medicine from January 2016 to January 2018. Among them, there were 1,222 males and 1,172 females, ranging in age from 21 to 86 years with a mean age of 52 ± 14 years. All patients were asked about their medical history in detail and signed a written informed consent form. The study protocol was approved by the Ethics Committee of the Shanghai Hospital of Integrated Traditional Chinese and Western Medicine Affiliated to Shanghai University of Traditional Chinese Medicine and was conducted following the principles of the Declaration of Helsinki.
Inclusion criteria: This study included patients diagnosed with chronic non-atrophic gastritis, chronic atrophic gastritis, gastric ulcer, or gastric cancer by astroscopic and histopathological examinations; the patients had not taken any antacids, hormones, and gastric mucosal protective agents within one month prior to the diagnosis and had not taken any antibiotics or non-steroidal anti-inflammatory drugs with two weeks prior to the diagnosis.
Exclusion criteria: This study excluded patients with a previous history of gastric surgery, patients with severe cardiopulmonary dysfunction, patients with malignancies in other organs, pregnant or nursing women, and patients with a history of mental illness.

Experimental analysis

Serum PGI, PGII, and G-17 detection: In the early morning, 3 mL of fasting venous blood was collected, and the serum was separated and quickly frozen. The specimens were cryostored at -80°C for later tests. A

Roche C501 automatic biochemistry analyzer was used to detect PGI and PGII using a latex-enhanced immunoturbidimetric assay. The PGI antibody and PGII antibody kits were provided by Eiken Chemical Co., Ltd. (Japan). An Anthos microplate reader was used to detect G-17 using an enzyme-linked immunosorbent assay (ELISA), and the kits were purchased from CanAg Diagnostics Co., Ltd (Beijing). Special personnel were utilized to conduct the assays according to the kit instructions and to complete detection.

Serum *H. pylori* IgG qualitative detection: The antibody test kits were purchased from Beijing Zhongjian Antai Diagnosis Technology Co., Ltd. After the serum thawed to room temperature, the kit was placed on a stand, one drop of serum was dropped into the sample well, and three to four drops of sample diluent were added. As an indicator of quality control, a red line appeared in each well; for positive samples, a detection line appeared five minutes after adding diluent to the sample, indicating the presence of *H. pylori* in the serum sample.

Gastroscopy: After blood was drawn for the detection of "serological biopsy" indicators of the gastric mucosa, gastroscopy was carried out within three days. Gastroscopic biopsy was performed according to the standards of the Sydney System (1990). Biopsies were taken from five sites on the gastric mucosa: the lesser and greater curvatures of the antrum, the lesser and greater curvatures of the gastric corpus, and the gastric angle. If other suspicious lesions were encountered, biopsies were taken at the sites of the suspicious lesions. According to the histopathological diagnosis determined from the gastroscopy biopsies, the patients were divided into four groups - chronic non-atrophic gastritis, chronic atrophic gastritis, gastric ulcer, and gastric cancer - for comparative analysis.

Statistical analysis

SPSS 19.0 statistical software was used to carry out the data analysis. The count data are expressed as the number of cases or rate (%), and the χ^2 test was used. The measurement data are expressed as the mean ± standard deviation ($\bar{x} \pm SD$), and the *t*-test was used. A difference with $p < 0.05$ was considered statistically significant.

RESULTS

A total of 2,394 patients were selected for the study. The patients underwent gastroscopy and received a definite diagnosis of chronic non-atrophic gastritis, chronic atrophic gastritis, gastric ulcer, or gastric cancer at our hospital from January 2016 to January 2018. Among them, there were 1,222 males and 1,172 females, ranging in age from 21 to 86 years with a mean age of 52 ± 14 years. See Table 1 - 5 for the general information regarding each group of patients.

Comparison of Serum PGI, PGII, PGR, and G-17 among the four groups of patients

The PGI expression level in the chronic atrophic gastritis group was significantly lower than those in the chronic non-atrophic gastritis group and gastric ulcer group ($p < 0.05$). The PGI expression level in the gastric cancer group was lower than those in the chronic non-atrophic gastritis group and gastric ulcer group, but the differences were not statistically significant ($p > 0.05$). The PGII expression level in the gastric cancer group was significantly higher than in the chronic non-atrophic gastritis group, chronic atrophic gastritis group, and gastric ulcer group ($p < 0.05$). The PGR in the gastric cancer group was lower than in the chronic non-atrophic gastritis group, chronic atrophic gastritis group, and gastric ulcer group ($p < 0.05$). The PGR in the chronic atrophic gastritis group was lower than in the chronic non-atrophic gastritis group and gastric ulcer group, but the differences were not statistically significant ($p > 0.05$). The G-17 expression level in the gastric cancer group was significantly higher than in the chronic non-atrophic gastritis group, chronic atrophic gastritis group, and gastric ulcer group ($p < 0.05$). The G-17 expression level in the chronic atrophic gastritis group was significantly higher than those in the chronic non-atrophic gastritis group and gastric ulcer group ($p < 0.05$). See Table 6.

Comparison of serum *H. pylori* IgG antibody positivity rates among the four groups of patients

The *H. pylori* IgG antibody positivity rates for the gastric cancer group and chronic atrophic gastritis group were both significantly higher than those for the chronic non-atrophic gastritis group and gastric ulcer group ($p < 0.05$), but the difference in the *H. pylori* IgG antibody positivity rates between the gastric cancer group and chronic atrophic gastritis group was not statistically significant ($p > 0.05$). The difference in the *H. pylori* IgG antibody positivity rates between the chronic non-atrophic gastritis group and gastric ulcer group was not statistically significant ($p > 0.05$). See Table 7.

DISCUSSION

"Serological biopsy" of the gastric mucosa refers to the assessment of gastric mucosal lesions and digestive functions by detecting the serum indicators PGI, PGII, PGR, G-17, and *H. pylori* IgG. Pepsinogen is an inactive precursor of pepsin. According to its biochemical and immunological characteristics, human pepsinogen can be divided into two subtypes - PGI and PGII. PGI is secreted by chief cells and mucous neck cells of the gastric fundic glands and is abundantly stored in the gastric corpus. In addition to being secreted by the gastric fundic glands, PGII can also be secreted by the pyloric glands (in the antrum of the pylorus) of the stomach and Brunner's glands of the duodenum. Most of the secreted pepsinogen enters the glandular cavity where it is con-

Table 1. Age information of the patients (years).

Group	Cases	Min	Max	P25	M	P75	χ^2	p
Chronic non-atrophic gastritis	1,376	21	65	39	48	52	379	< 0.0001
Chronic atrophic gastritis	708	28	86	48	55	64		
Gastric ulcer	265	25	83	39	45	52		
Gastric cancer	45	35	81	60	65	70		

Test methods: Kruskal-Wallis test.

Table 2. Comparison of ages between any two groups.

Comparison group	χ^2	p
Chronic non-atrophic gastritis to chronic atrophic gastritis	277.91	< 0.0001
Chronic non-atrophic gastritis to gastric ulcer	3.15	0.3695
Chronic non-atrophic gastritis to gastric cancer	91.32	< 0.0001
Chronic atrophic gastritis to gastric ulcer	153.17	< 0.0001
Chronic atrophic gastritis to gastric cancer	18.87	0.0003
Gastric ulcer to gastric cancer	94.36	< 0.0001

Test methods: Nemenyi test.

Table 3. Gender information regarding the patients.

Group	Cases	Male	Female	χ^2	p
Chronic non-atrophic gastritis	1,376	611	765	59.45	< 0.0001
Chronic atrophic gastritis	708	420	288		
Gastric ulcer	265	159	106		
Gastric cancer	45	32	13		

Test methods: χ^2 test.

Table 4. Comparison of gender between any two groups.

Comparison group	χ^2	p
Chronic non-atrophic gastritis to chronic atrophic gastritis	41.62	< 0.0001
Chronic non-atrophic gastritis to gastric ulcer	21.70	< 0.0001
Chronic non-atrophic gastritis to gastric cancer	12.55	0.0004
Chronic atrophic gastritis to gastric ulcer	0.04	0.8479
Chronic atrophic gastritis to gastric cancer	2.45	0.1175
Gastric ulcer to gastric cancer	2.01	0.1565

Test methods: χ^2 test.

Table 5. Body mass index information regarding the patients.

Group	Cases	Thin	Normal	Overweight	Obese	χ^2	p
Chronic non-atrophic gastritis	1,376	105	958	281	32	2.00	0.5722
Chronic atrophic gastritis	708	57	501	138	12		
Gastric ulcer	265	31	172	59	3		
Gastric cancer	45	6	30	8	1		

Test methods: Kruskal-Wallis test.

Table 6. PGI, PGII, PGI/PGII, and G-17 expression levels in the four groups of patients.

Group	n	PGI (ng/mL)	PGII (ng/mL)	PGI/PGII	G-17 (pmol/L)
Chronic atrophic gastritis	708	40.38 ± 15.72	9.20 ± 4.98 ▵	3.92 ± 1.35 ▵	11.80 ± 3.55 ▵
Chronic non-atrophic gastritis	1,376	53.31 ± 12.83 *	8.77 ± 3.83 ▵	4.89 ± 1.25 ▵	4.89 ± 1.25 ▵
Gastric ulcer	265	65.15 ± 18.97 *	11.70 ± 5.6 ▵	5.80 ± 1.74 ▵	3.92 ± 1.35 ▵
Gastric cancer	45	46.57 ± 13.65	15.95 ± 6.27	2.60 ± 0.86	18.60 ± 6.86

Note: * - indicates $p < 0.05$ when compared with the chronic atrophic gastritis group; ▵ - indicates $p < 0.05$ when compared with the gastric cancer group.

Table 7. Comparison of the serum *H. pylori* IgG antibody positivity rates among the four groups of patients.

Group	n	Positive for *H. pylori* IgG antibody (n)	*H. pylori* IgG antibody positive rate (%)
Chronic non-atrophic gastritis	1,376	253	18.39
Gastric ulcer	265	61	23.02
Chronic atrophic gastritis	708	458	64.69 * ▵
Gastric cancer	45	32	71.11 * ▵

Note: * - indicates $p < 0.05$ when compared with the chronic non-atrophic gastritis group; ▵ - indicates $p < 0.05$ when compared with the gastric ulcer group.

verted into pepsin; only 1% of the pepsinogen enters the blood circulation. The level of serum pepsinogen reflects the state of gastric acid levels and gastric mucosal inflammation. Combined detection of PGI and PGII expression levels can determine the degree of gastric mucosal damage and changes in gastric functions, playing a role in the "serological biopsy" of the gastric mucosa [8]. PGI expression levels are related to mucosal function of the gastric fundus and the gastric corpus, indicating whether or not the gastric mucosal glands have atrophied. When the gastric fundic glands undergo atrophy, the number of chief cells decreases, and PGI levels are reduced. When atrophic gastritis is accompanied with intestinal metaplasia and the gastric antral glands extend toward the gastric corpus and when pseudopyloric gland metaplasia of the gastric fundus appears, the PGII levels increase. Changes in serum PGI and PGII levels and the PGR can indicate lesions in different parts of the gastric mucosa and the degree of lesion severity. The data and results of the present study showed that the serum PGI level of patients in the chronic atrophic gastritis group was significantly lower than those of patients in the chronic non-atrophic gastritis group, gastric ulcer group, and gastric cancer group ($p < 0.05$). In this study, chron-

ic atrophic gastritis was not divided into chronic atrophic gastritis of the gastric fundus and chronic atrophic gastritis of the gastric corpus for a further comparison of PGI levels. A study has shown that regardless of whether the etiology of atrophic gastritis is caused by autoimmunity or *H. pylori* infection, PGI levels are reduced (< 25 μg/L). For the diagnosis of moderate to severe atrophic gastritis of the gastric body, the sensitivity is 84% and specificity is 95% [9]. Miki et al. [10] hypothesized that PGI could be a marker for chronic atrophic gastritis and gastric cancer, and they used PG ≤ 70 ng/mL and PGR ≤ 3 as critical values. The research results showed that for the diagnosis of moderate to severe atrophic gastritis, the sensitivity was 80% and the specificity is 70%. The positive predictive value for diagnosing gastric cancer was 1.4%, which was higher than that obtained for the barium meal examination (0.8%). Because gastric cancer is more prone to occur in the gastric corpus in Japanese patients, PGI expression levels are obviously reduced due to gland destruction and mucosal atrophy in Japanese patients with chronic atrophic gastritis and gastric cancer. Gastric cancer is more prone to occur in the gastric antrum in Chinese patients; the scope of gland destruction by early tumors is smaller, the reduction in PGI levels is not obvious, and PGI expression levels in Chinese patients with gastric cancer are often higher than those in Chinese patients with chronic atrophic gastritis. In the present study, the PGI expression level in the gastric cancer group was higher than that in the chronic atrophic gastritis group and lower than those in the chronic non-atrophic gastritis group and gastric ulcer group, but the differences were not statistically significant. The PGI level in the gastric ulcer group was higher than those in the other groups; a large amount of PGI enters the blood circulation mainly due to an increase in the number of chief and parietal cells in patients with peptic ulcers, which causes an increase in the serum PGI of patients with peptic ulcers. Some studies have confirmed that the serum PGI and PGII expression levels in patients with gastric ulcers are significantly higher than those in healthy controls, the serum PGI and PGII expression levels in patients with gastric ulcers in an active phase are higher than those in patients with gastric ulcers in a cicatricial phase, and a high serum PGI level is a reliable indicator for peptic ulcer screening [11-13]. PGII secretion sites are widely distributed, and the correlation of PGII secretion with mucosal lesions of the gastric fundus is higher than that of the gastric antrum. An increase in PGII is mainly related to atrophy of the fundic gland ducts, intestinal metaplasia, pseudopyloric gland metaplasia, and dysplasia. The data and results of the present study showed a significantly higher PGII level in the gastric cancer group ($p < 0.05$), while the PGR for this group was significantly lower than those for the other groups ($p < 0.05$). This result was consistent with the results of previous studies. In a study on the detection of serum PGI and PGII in 450 cases of gastric cancer, 111 cases of chronic atrophic gastritis, and 961 healthy controls, the PGII levels of patients with gastric cancer and chronic atrophic gastritis were higher than those of the healthy controls, and the PGR of patients with gastric cancer and chronic atrophic gastritis were lower. High PGII and low PGR are considered to be reliable serological indicators for gastric cancer screening [14].

Gastrin is a peptide hormone produced by G cells of the pyloric glands and cells of the proximal duodenal mucosa; 80 - 90% of gastrin is G-17, which plays a role in promoting the secretion of gastric acid by parietal cells and in promoting the proliferation and differentiation of gastric mucosal cells. Serum gastrin secretion levels are mainly affected by factors such as the number of G cells in the gastric antrum, the pH level in the gastral cavity, food intake (protein is the best stimulus), vagus nerve stimulation, pulling of the gastric antrum, antacid consumption, and gastrin-stimulating cytokines (bombesin). In addition, the site where gastric mucosal atrophy occurs is also an important factor affecting serum gastrin levels. When gastric mucosal atrophy is limited to the gastric antrum, serum PGI and the PGR are normal, while the serum G-17 level is reduced. For patients with gastric mucosal atrophy, serum PGI or the PGR is reduced, while the serum G-17 level is significantly increased. A high gastrin level is closely related to the occurrence of gastric cancer; gastrin participates in processes such as gastric cancer cell proliferation, infiltration, invasion, and angiogenesis. Some scholars found that G-17 levels gradually increased as gastric mucosal atrophy, dysplasia, and gastric cancer progressed [15-17]. In the present study, the serum G-17 expression level in the gastric cancer group was significantly higher than those in the chronic non-atrophic gastritis group, chronic atrophic gastritis group, and gastric ulcer group ($p < 0.05$). Hypergastrinemia is deemed to be a risk factor for the occurrence of gastric cancer and has a certain significance in the screening and diagnosis of gastric diseases, but it is mostly detected in combination with pepsinogen, indicating the site and scope of diseases [18]. Serum gastrin levels are related to the type of gastric cancer and the site of carcinogenesis. In the present study, the included gastric cancer samples were mainly intestinal-type gastric cancer, and the gastrin level in the gastric cancer group was consistent with those of previous studies [19], but the effect of the type of gastric cancer pathology on serum gastrin levels awaits further study.

H. pylori is a microaerophilic gram-negative bacillus that was discovered by Australian scientists Warren and Marshall, who isolated and cultivated *H. pylori* from the gastric mucosa of patients with chronic gastritis [20]. *H. pylori* infection is one of the main pathogenic factors of gastric diseases. The colonization of *H. pylori* leads to an abnormal acid environment in the stomach, which can cause an increase in carcinogenic substances, such as nitrosamine, in the stomach. Excessive repair of gastric mucosal cells affects gene expression, and atrophy, intestinal metaplasia, dysplasia, and carcinogenesis are

prone to occur in the gastric mucosa. A study showed that *H. pylori* infection is closely related to the occurrence of gastric ulcers, gastric lymphoma of mucosa-associated lymphoid tissue, and gastric cancer [21]. In the present study, the *H. pylori* IgG positivity rates for the gastric cancer group, chronic atrophic gastritis group, and gastric ulcer group were significantly higher than for the chronic non-atrophic gastritis group ($p < 0.05$) by the chi-square test. In a previous study, the serum PG levels of 4,160 cases of *H. pylori* IgG-positive gastritis and 323 cases of *H. pylori* IgG-negative gastritis were observed; the *H. pylori* IgG-positive group had a higher PGII level than that of the *H. pylori* IgG-negative group and a lower PGR than that of the *H. pylori* IgG-negative group. PG levels were used as an effective serological indicator for assessing *H. pylori*-associated gastritis [22]. The results of the present study showed that the chronic atrophic gastritis group and gastric cancer group had higher *H. pylori* IgG positivity rates than those of the chronic non-atrophic gastritis group and gastric ulcer group and that the PGRs of the chronic atrophic gastritis group were lower than those of the chronic non-atrophic gastritis group and gastric ulcer group. These results are consistent with those from previous research. It was found in a study on the relationship between serum *H. pylori* IgG levels and PG and G-17 in a healthy population that serum *H. pylori* IgG levels correlated positively with PGI, PGII, and G-17 but correlated negatively with the PGR [23]. Intestinal gastric cancer results mostly from the progression of chronic non-atrophic gastritis, chronic atrophic gastritis, intestinal metaplasia, and dysplasia. After *H. pylori* eradication therapy, the inflammatory activity of the gastric mucosa can improve. This treatment can be used to delay or even prevent gastric mucosa atrophy, intestinal metaplasia, and dysplasia [24]. In recent years, studies regarding the "non-reversible point" of *H. pylori* eradication therapy timing deemed that carrying out eradication therapy in the gastric mucosal atrophy or mild intestinal metaplasia phase can effectively reverse gastric mucosal atrophy or mild intestinal metaplasia and is more effective in preventing further progression of gastric mucosal lesions into gastric cancer. Serum *H. pylori* IgG levels and serum PG levels are also affected by factors such as the *H. pylori* strain, host genetic factors, and infection site. Most relevant studies indicate that a polypeptide that directly stimulates chief cells is secreted in the early stage of *H. pylori* infection and that, in turn, stimulates the secretion of PGII, not PGI. In the progression to a pre-gastric cancer lesion or the gastric cancer stage, the pepsin gene in gastric mucosal cells mutates, and the cells lose the ability to secrete PGI; however, PGII is produced by mature gland cells and is widely distributed, and therefore, changes in PGII levels are not obvious, leading to a corresponding decrease in the PGR [25].

CONCLUSION

In summary, serum PGI, PGII, PGR (PGI/PGII), G-17, and *H. pylori* IgG detection methods are simple, convenient, and fast, the results are stable, and diagnoses are accurate; serological biopsy is a simple and effective non-invasive screening method for gastric diseases. Existing clinical practice has confirmed that the serological biopsy of the gastric mucosa can provide a basis for the screening, diagnosis, and treatment of gastric diseases. In physical health examinations and clinical examinations, this method can be used to carry out preliminary screening on the population, and then, gastroscopy and pathological diagnosis of gastric mucosal biopsies can be performed on the high-risk population, which can conserve medical resources and improve the efficiency of gastroscopy. Therefore, this method is worthy of broad clinical promotion.

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Declaration of Interest:
The authors declare that they have no conflicts of interest.

References:

1. Samloff IM. Pepsinogens I and II: purification from gastric mucosa and radioimmunoassay in serum [J]. Gastroenterology, 198, 82(1): 26-33 (PMID: 7053333).

2. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015;65(2): 87-108 (PMID: 25651787).

3. Hosseini M, Amoueian S, Attaranzadeh A, et al. Serum gastrin 17, pepsinogen I and pepsinogen II in atrophic gastritis patients living in North-East of Iran. J Res Med Sci 2013;18(3):225-9 (PMID: 23930120).

4. He CY, Sun LP, Gong YH, Xu Q, Dong NN, Yuan Y. Serum pepsinogen II:a neglected but useful biomarker to differentiate between diseased and normal stomachs. J Gastroenterol Hepatol 2011;26(6):1039-46 (PMID: 21303408).

5. Sun L, Tu H, Liu J, et al. A comprehensive evaluation of fasting serum gastrin-17 as a predictor of diseased stomach in Chinese population. Scand J Gastroenterol 2014;49(10):1164-72 (PMID: 25157583).

6. Watari J, Chen N, Amenta PS, et al. Helicobacter pylori associated chronic gastritis, clinical syndromes, precancerous lesions, and pathogenesis of gastric cancer development. World J Gastroenterol. 2014;20:5461-73 (PMID: 24833876).

7. Roesler BM, Costa SC, Zeitune JM. Eradication Treatment of Helicobacter pylori Infection: Its Importance and Possible Relationship in Preventing the Development of Gastric Cancer. ISRN Gastroenterol 2012;2012:935410 (PMID: 22778979).

8. Korstanje A, den Hartog G, Biemond I, Lamers CB. The serological gastric biopsy: a non-endoscopical diagnostic approach in management of the dyspeptic patient significance for primary care based on a survey of the literature. Scand J Gastroenterol Suppl. 2002;37(236):22-6 (PMID:12408500).

9. Sipponen P, Ranta P, Helske T, et al. Serum levels of amidated gastrin-17 and pepsinogen I in atrophic gastritis: an observational case-control study. Scand J Gastroenterol. 2002;37:785-91 (PMID: 12190091).

10. Miki K, Morita M, Sasajima M, Hoshina R, Kanda E, Urita Y. Usefulness of gastric cancer screening using the serum pepsinogen test method. Am J Gastroenterol 2003;98(4):735-9 (PMID: 12738449).

11. Pomytkina TE. [The serum content of gastrin-17 and pepsinogen-1 in patients with duodenal ulcerative disease in occupational contact with Nitrogenous compounds]. Klin Lab Diagn 2009; 11(11):16-9 (PMID: 20030266).

12. Yang J, Li CX, Dai YY, Peng F, Weng XM, Ji MX. [Expression and significance of trefoil factor 1 protein and serum pepsinogen in benign and malignant gastric ulcers]. Zhonghua Yi Xue Za Zhi 2012;92(22):1540-3 (PMID: 22944057).

13. Zhang XM, Li JX, Zhang GY, Li XH, Gu H. The value of serum pepsinogen levels for the diagnosis of gastric diseases in Chinese Han people in midsouth China. BMC Gastroenterol 2014;14:3 (PMID: 24383519).

14. Dinis-Ribeiro M, da Costa-Pereira A, Lopes C, et al. Validity of Serum Pepsinogen I/II Ratio for the Diagnosis of Gastric Epithelial Dysplasia and Intestinal Metaplasia during the Follow-Up of Patients at Risk for Intestinal-Type Gastric Adenocarcinoma. Neoplasia 2004;6(5):449-56 (PMID: 15548353).

15. Copps J, Murphy RF, Lovas S. The production and role of gastrin-17 and gastrin-17-gly in gastrointestinal cancers. Protein Pept Lett 2009;16(12):1504-18 (PMID: 20001914).

16. Tu H, Sun L, Dong X, et al. Serum anti-Helicobacter pylori immunoglobulin G titer correlates with grade of histological gastritis, mucosal bacterial density, and levels of serum biomarkers. Scand J Gastroenterol. 2014;49:259-66 (PMID: 24329006).

17. Kidd M, Tang LH, Modlin IM, et al. Gastrin-mediated alterations in gastric epithelial apoptosis and proliferation in a mastomys rodent model of gastric neoplasia. Digestion 2000;62(2-3):143-51 (PMID: 11025361).

18. Agréus L, Kuipers EJ, Kupcinskas L, et al. Rationale in diagnosis and screening of atrophic gastritis with stomach-specific plasma biomarkers. Scand J Gastroenterol. 2012;47:136-47 (PMID: 2224 2613).

19. Zagari RM, Rabitti S, Greenwood DC, Eusebi LH, Vestito A, Bazzoli F. Systematic review with meta-analysis: diagnostic performance of the combination of pepsinogen, gastrin-17 and anti-Helicobacter pylori antibodies serum assays for the diagnosis of atrophic gastritis. Aliment Pharmacol Ther. 2017;46:657-67 (PMID: 28782119).

20. Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet 1984; 1(8390):1311-5 (PMID: 6145023).

21. Keck JW, Miemyk KM, Bulkow LR, et al. Helicobacter pylori infection and markers of gastric cancer risk in Alaska Native persons: a retrospective case-control study. Can J Gastroenterol Hepatol 2014;28(6):305-10 (PMID: 24945184).

22. Kitamura Y, Yoshihara M, Ito M, et al. Diagnosis of Helicobacter pylori-induced gastritis by serum pepsinogen levels. J Gastroenterol Hepatol. 2015;30:1473-7 (PMID: 25974661).

23. Shan JH, Bai XJ, Han LL, Yuan Y, Sun XF. Changes with aging in gastric biomarkers levels and in biochemical factors associated with infection in asymptomatic Chinese population. World J Gastroenterol 2017;23:5945-53 (PMID: 28932086).

24. Liu KS, Wong IO, Leung WK. Helicobacter pylori associated gastric intestinal metaplasia: Treatment and surveillance. World J Gastroenterol 2016;22(3):1311-20 (PMID: 26811668).

25. Lorente S, Doiz O, Trinidad Serrano M, Castillo J, Lanas A. Helicobacter pylori stimulates pepsinogen secretion from isolated human peptic cells. Gut 2002;50:13-8 (PMID: 11772960).