Value of Serum Gastrin-17 Combined with Pepsinogen I, II and *Helicobacter pylori* C14 Detection in Early Diagnosis of Gastric Cancer

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Wang *et al.*: Study For the Early Screening of Gastric Carcinoma

To conduct a study on the value of serum gastrin-17 plus pepsinogen I, II and *Helicobacter pylori* C14 breath test in the early screening of gastric carcinoma. The clinical data of 96 patients with epigastric distress requiring gastroscopic pathological examination from January 2019 to June 2020 were analyzed retrospectively. 49 patients diagnosed with chronic superficial gastritis and chronic atrophic gastritis were included in the gastritis group, and 47 patients diagnosed with early gastric carcinoma were included in the gastric carcinoma group; the serum levels of gastrin-17, pepsinogen I, pepsinogen II, and pepsinogen ratio, as well as *Helicobacter pylori* positive rate, were compared between the two groups. The diagnostic value of various indicators and their combination was analyzed by the receiver operating characteristic curve. The patients in the gastric carcinoma group had a higher level of gastrin-17 than the gastritis group (p<0.05), whereas the patients in the gastric carcinoma group had a lower level of pepsinogen ratio than the gastritis group (p<0.05); for the early stage of gastric carcinoma, the diagnostic results of *Helicobacter pylori* positive, pepsinogen I, and pepsinogen II showed moderate consistency with the gold standard (p<0.05), the diagnostic results of serum gastrin-17 and pepsinogen ratio for the early stage of gastric carcinoma showed good consistency with the gold standard (p<0.05), and the diagnostic results of the combination of various indicators showed superior consistency with the gold standard (p<0.05); the positive rate of *Helicobacter pylori* detected by serum gastrin-17, pepsinogen I and pepsinogen II levels, pepsinogen ratio, and C14 breath test showed a moderate screening value for the early stage of gastric carcinoma (p<0.05), and the combination of various indicators embraced high screening value (p<0.05). Serum gastrin-17 combined with pepsinogen I, II, and *Helicobacter pylori* C14 shows a high application value for early screening of gastric carcinoma. Its advantage lies in convenient operation, good repeatability, and wide application. Moreover, it can provide a necessary reference for the screening and early diagnosis of gastric carcinoma.

Key words: Gastric carcinoma, serum gastrin-17, pepsinogen I, pepsinogen II, *Helicobacter pylori*

Gastric Cancer (GC) is one of the most often diagnosed cancers around the world. In China, GC comes in second in terms of mortality behind other malignancies, and its incidence comes in second when compared to other types of malignant tumors[1-3]. Early GC mostly lacks specific manifestations and tends to be confused with chronic superficial gastritis, leaving its clinical diagnosis difficult. Most of them have progressed to the intermediate and advanced stages of GC when patients present with significant manifestations followed by gastroscopy, thus losing the timing of surgical treatment[4-6]. The combined detection of serum Gastrin-17 (G-17), Pepsinogen (PG) I, and PGII has been applied in gastric precancerous lesions and GC screening in Japan[7,8]. Serological screening for GC diagnosis in China is still in its infancy. GC is one of the most often diagnosed cancers around the world. *Helicobacter pylori* (*H. pylori*) infection is the first type of carcinogenic factor recognized by the World Health Organization as an independent risk factor for the development and progression of GC. Our hospital intended to improve the accuracy

of early diagnosis of GC by combined detection of serological detection and *H. pylori* infection. The diagnostic value was analyzed in this study. Specific studies are described below.

MATERIALS AND METHODS

General data:

From January 2019 to June 2020, the clinical data of 96 patients with epigastric distress who needed a gastroscopic pathological examination were reviewed retrospectively.

Inclusion criteria: Patients at our hospital were diagnosed with early GC, chronic superficial gastritis, or chronic atrophic gastritis after a gastroscopic pathological examination; adult patients aged ≥18 y and patients with complete relevant examinations and clinical data in our hospital.

Exclusion criteria: Patients complicated with other malignant tumors; patients who failed to tolerate gastroscopy; patients with a history of anti-*H. pylori* therapy and gastric acid secretion inhibitors, gastric mucosal protective agents, anticoagulants, antibiotics, and other drugs 2 w before admission; patients with clotting disorder or hemorrhagic disorder and hemorrhagic diathesis and patients who were free of being fully diagnosed by gastroscopic pathological examination.

According to the results of the gastroscopic pathological examination, 49 patients diagnosed with chronic superficial gastritis and chronic atrophic gastritis among the 96 patients were included in the gastritis group, and 47 patients diagnosed with early GC were included in the GC group. Patients in the gastritis group were 33 y-71 y of age, with an average of (49.65±8.96) y; the maximum diameter of lesions was 1.1-2.13 cm, with an average of (1.61±0.26) cm; there were 16 patients with chronic superficial gastritis and 33 patients with chronic atrophic gastritis. Patients in the GC group were 36 y-70 y of age, with an average of (50.14±8.71) y; the maximum diameter of lesions was 1.0-2.16 cm, with an average of (1.64±0.31) cm.

Methods:

Serological tests: All patients had 3 ml of blood drawn from the cubital vein under fasting conditions, which were then allowed to stand for 20 min before being placed in a centrifuge and centrifuged at 3000 r/min for 10 min to obtain serum for testing. Serum samples were measured for G-17, PGI, and PGII levels by immune enzyme-linked immunosorbent assay, and the PGI-to-PGII Ratio (PGR) was calculated.

C14 breath test: 2 h after fasting or feeding, all patients were given one urea 14C capsule with a cup of water orally. The insufflation nozzle and accumulator card were opened after 15 min of sitting quietly, and the insufflation nozzle was loaded with the accumulator card in the direction indicated by the arrow. Later, the patient began to insufflate smoothly with an insufflation nozzle and blow as long as possible, and the air could be exchanged in the middle but the suck-back was prohibited. The insufflation was maintained for about 1-3 min until the indicator changed from orange-red to yellow. The accumulator card was inserted into the instrument card slot to read the automatic measurement result on the instrument.

Diagnostic criteria: In our hospital, all patients had a gastroscopic pathological examination, and the laboratory results were accepted as the gold standard. The serological positive criterion was described as; PGI <70 μg/l, PGII >15 μg/l, PGR <7 and G-17 >7 pmol/l[9,10].

Methodology:

The serum levels of G-17, PGI, and PGII as well as the positive rate of *H. pylori* were compared between the two groups. The consistency between the diagnostic results of various indicators and their combination for early GC and the gold standard was analyzed. The diagnostic efficacy indicators (sensitivity, specificity and accuracy) were calculated. The Receiver Operating characteristic (ROC) curve parameter and Area under the Curve (AUC) were utilized to analyze the diagnostic value of various indicators and their combination.

Statistical analysis:

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) 21.0 software. Enumeration data were compared using Chi-Square (χ^2) test and expressed as n (%); measurement data were compared using t-test and expressed as ($\bar{x}\pm s$); AUC grading criteria was displayed below; AUC >0.9 signified a high diagnostic value, 0.7<AUC≤0.9 indicated a moderate diagnostic value, 0.5≤AUC≤0.7 suggested a low diagnostic value, and AUC <0.5 was deemed

as the absence of diagnostic value basically; the consistency was analyzed by kappa, with grading criteria; excellent for 0.8<kappa≤1.0, good for 0.6<kappa≤0.8, moderate for 0.4≤kappa≤0.6, and poor for kappa<0.4; p<0.05 indicated statistically significant differences. p<0.05 suggested a statistically significant difference.

RESULTS AND DISCUSSION

In this section, we will discuss the comparison of serological indicators, positive rate of *H. pylori*, consistency and diagnostic efficacy indicators, and analysis of diagnostic value in detail.

As shown in Table 1, the patients in the GC group had higher levels of G-17 and PGI than the gastritis group (p<0.05), whereas the patients in the GC group had lower levels of PGII and PGR than the gastritis group (p<0.05).

As shown in Table 2, the positive rate of *H. pylori* was reported at a higher rate in the GC group

(68.09 %) compared to what was observed in the gastritis group (22.45 %) (p<0.05).

As shown in Table 3, the diagnostic results of *H. pylori* positive, PGI, and PGII for the early stage of GC showed a moderate consistency with the gold standard (p<0.05), and the diagnostic results of serum G-17 and PGR for the early stage of GC showed good consistency with the gold standard (p<0.05); the diagnostic results of the combination of various indicators showed a superior consistency with the gold standard (p<0.05) and the combined diagnosis exhibited the highest diagnostic efficacy, with a sensitivity of 89.36 %, a specificity of 95.92 %, and an accuracy of 92.71 %.

As shown in Table 4, the positive rate of *H. pylori* detected by serum G-17, PGI, PGII, and PGR levels, and C14 breath test showed a moderate diagnostic value for the early stage of GC (p<0.05), and the combination of various indicators embraced high diagnostic value (p<0.05). ROC curve is displayed in fig. 1.

TABLE 1: COMPARISON OF SEROLOGICAL INDICATORS IN THE TWO GROUPS ($\bar{x}\pm s$)

Group	n	G-17 (pmol/l)	PGI (µg/l)	PGII (µg/l)	PGR
Gastritis	49	9.13±2.97	169.65±21.26	16.03±6.78	11.01±3.42
GC	47	18.74±4.85	73.21±14.13	19.27±7.69	3.76±1.01
t		11.762	26.061	2.192	14.530
p		≤0.001	≤0.001	0.031	≤0.001

**TABLE 2: COMPARISON OF THE POSITIVE RATE OF *H. pylori* IN THE TWO GROUPS n (%)**

Group	n	Positive	Negative
Gastritis	49	11 (22.45)	38 (77.55)
GC	47	32 (68.09)	15 (31.91)
73.21±14.13		20.204	
χ^2		≤0.001	

TABLE 3: DIAGNOSTIC CONSISTENCY OF VARIOUS INDICATORS AND DIAGNOSTIC EFFICACY INDICATORS (%)

Indicators	Sensitivity	Specificity	Accuracy	Positive predictive value	Negative predictive value	Kappa	p
PGR	82.98	85.71	84.38	84.78	84	0.687	≤0.001
Serum PGI	80.85	81.63	81.25	80.85	81.63	0.625	≤0.001
Serum PGII	59.57	83.67	71.88	77.78	68.33	0.435	≤0.001
Serum G-17	87.23	87.76	87.5	87.23	87.76	0.75	≤0.001
H. pylori	61.7	93.88	78.13	90.63	71.88	0.559	≤0.001
Combination	89.36	95.92	92.71	95.45	90.38	0.854	≤0.001

TABLE 4: STATISTICS OF ROC CURVE OF DIAGNOSTIC VALUE

Indicators	AUC	Standard error	p	95 % confidence interval	
				Lower limit	Upper limit
PGR	0.843	0.043	≤0.001	0.759	0.928
Serum PGI	0.812	0.046	≤0.001	0.722	0.903
Serum PGII	0.716	0.054	≤0.001	0.611	0.821
H. pylori	0.778	0.05	≤0.001	0.681	0.875
Serum G-17	0.875	0.039	≤0.001	0.798	0.952
Combination	0.926	0.031	≤0.001	0.866	0.987
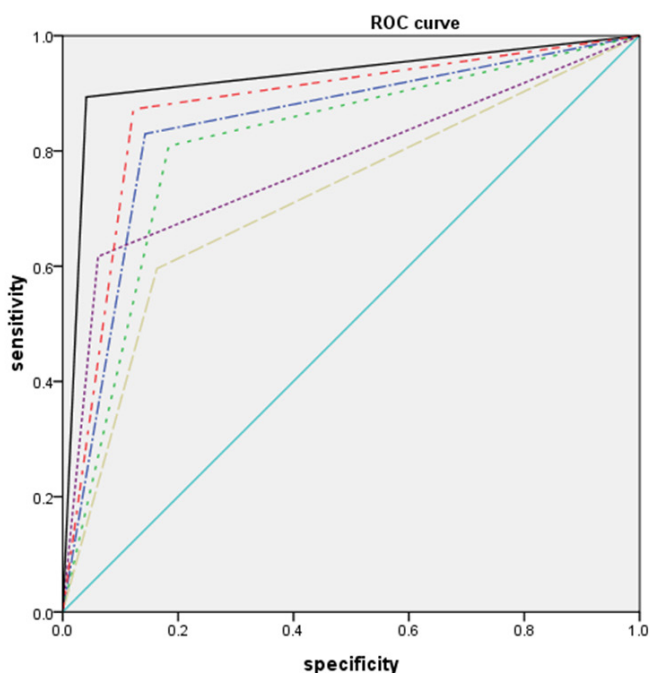
Fig. 1: ROC curve of diagnostic value
Note: (—··—): PGR; (·····): Serum PGI; (— —): Serum PGII; (·····): Hp; (——): Union; (— —): Serum G-17 and (——): Reference line

An early stage of GC is a common malignancy in the digestive system[11,12]. Recently, the incidence of GC shows an upward trend gradually in China, and there is a tendency to progress towards younger. Abnormal changes in serum G-17, PGI, and PGII levels are observed during the formation and progression of GC. First discovered by Edkins, G-17 is amidated gastrin secreted by antral G-cells G-17[13,14], a polypeptide hormone, has the capability of promoting the proliferation and differentiation of gastric mucosal cells and stimulating gastric acid secretion physiologically. G-17 expression in humans accounts for >90 % of the total G-17[15,16], which is a sensitive index reflecting the secretory function of gastric antrum in clinical practice, is proven to be a mirror of the atrophy state of the gastric antrum and a promoter of the formation and progression of GC. An abnormal rise in serum G-17 is found in patients with early GC, and its rise degree is associated with the location and clinical stage of GC tissues. Increased serum G-17 is more prominent in GC patients occurring in the fundus and body. The detection of serum G-17 levels can thus provide crucial information for the early diagnosis of GC. Under the influence of gastric acid, PG, an inactive precursor, is transformed to pepsin. Through the capillaries of the gastrointestinal mucosa, about 1 % of PG enters the blood stream[17,18]. According to its immunocompetence and biochemical characteristics, PG is divided into two subtypes; PGI and PGII. PGI is mainly secreted by the mucous neck cells of chief cells in the fundic glands, and a few PGI are secreted by the pyloric glands of the antrum and Brunner's glands of the proximal duodenum, and its content in the serum

is relatively stable. Since it can reflect the capacity of the gastric body mucosa to secrete acid, PG is clinically known as "serological biopsy". PGI and PGII maintain dynamic balance in a normal state. After carcinogenesis, the PGI level reduces abnormally while the PGII level rises abnormally. As a result, the detection of the expression levels of two subtypes of PG in serum serves as an important reference for the early diagnosis of GC. As a common method, the C14 breath test shows high diagnostic accuracy for *H. pylori* infection. Currently, *H. pylori* infection is clinically recognized as an independent risk factor for GC, and *H. pylori* positivity indicated the presence of increased risk of GC[19,20].

The results of this study showed the patients in the GC group had a higher level of G-17 and PGII than the gastritis group, whereas the patients in the GC group had a lower level of PGI than the gastritis group; it was proven that patients with early GC may present with abnormal changes in serum G-17, PGI, PGII, and PGR levels. The diagnostic results of *H. pylori* positive, PGI, and PGII for the early stage of GC showed a moderate consistency with the gold standard (p<0.05), and the diagnostic results of serum G-17 and PGR for the early stage of GC showed good consistency with the gold standard (p<0.05); the diagnostic results of the combination of various indicators showed a superior consistency with the gold standard; it was obvious that apart from the combination of various indicators, various diagnostic efficacy indicators and consistency of serum G-17 were optimal, followed by PGR. It was suggested that the combination of various indicators could improve the consistency of serological indicators and *H. pylori* C14 detection for the early diagnosis of GC, with a sensitivity of 89.36 %, a specificity of 95.92 %, and an accuracy of 92.71 %. Moreover, among all indicators, the accuracy, sensitivity, and specificity of serum G-17 and serum C-14 alone and their consistency with the gold standard were far higher in the early diagnosis of GC. It was shown by the ROC curve that the serum levels of G-17, PGI, PGII, and the positive rate of *H. pylori* detected by the C14 breath test showed a moderate diagnostic value for the early stage of GC, whereas the combination of various indicators exhibited a relatively high value for screening the early GC; it was a reminder of us that the combination of serum G-17, PGI, PGII levels and the positive rate of *H.*

pylori detected by C14 breath test has the potential to upgrade the diagnostic value for the early stage of GC, and serum G-17 alone among all indicators showed the highest value for screening early GC, followed by PGR.

In summary, serum G-17 combined with PGI, PGII, and *H. pylori* C14 shows a quite high screening value for the early stage of GC, and the combination of various indicators can play a complementary and mutually corrected role.

The combination of serum G-17, PGI, II, and *H. pylori* C14 has a high applicability value for early GC screening. Its benefits include ease of use, high reproducibility, and a wide range of applications. Furthermore, it can serve as a valuable resource for GC screening and early diagnosis. The results of this study revealed that patients with early GC had higher levels of G-17 and PGII than those with gastritis, but lower levels of PGI than those with gastritis; it was also shown that patients with early GC may have aberrant changes in serum G-17, PGI, PGII, and PGR levels. It served as a reminder to us that the combination of serum G-17, PGI, PGII levels, and the positive rate of *H. pylori* detected by the C14 breath test has the potential to improve the diagnostic value for early-stage GC, with serum G-17 alone showing the highest value for early-stage GC screening, followed by PGR. In conclusion, serum G-17 in combination with PGI, PGII, and *H. pylori* C14 has a relatively good screening value for early-stage GC, and the combination of diverse indicators can play a complementary and mutually corrected role.

Ethical approval:

This study has been reviewed and approved by the Medical Ethics Committee of West China Fourth Hospital, Sichuan University. All the patients were informed about this study and signed the informed consent form.

Conflict of interests:

The authors declared no conflict of interest.

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