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ORIGINAL ARTICLE

Clinical value of serum pepsinogen levels for the diagnosis of esophageal squamous cell carcinoma

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Abstract

Objective Pepsinogens have been previously studied as markers of gastric atrophy. The objective of this study was to investigate the clinical significance of the serum levels of pepsinogen (PG) I and II, as well as the pepsinogen I/II ratio (PGR) in the diagnosis of esophageal squamous cell carcinoma.

Methods A retrospective data analysis of patients who underwent gastroscopy and PG examination in Renmin Hospital was performed. The subjects were grouped into cancer and healthy control groups, and the differences in the serum levels of PGI and PGII, as well as the PGRs were compared. The receiver operating curve and the area under the curve (AUC) were also compared between the groups.

Results A total of 351 Chinese patients were enrolled in the study, 209 with esophageal squamous cell carcinoma and 142 healthy controls. Overall, the levels of PGI ($P < 0.0001$) and PGII ($P = 0.0007$), as well as the PGR ($P = 0.007$) of the cancer group were lower than those of the control group. Male subjects in the cancer group had lower PGI ($P < 0.0001$), PGII ($P < 0.0001$), and ($P = 0.0138$). The subjects < 65 years old in the cancer group showed lower PGI ($P < 0.0001$), PGII ($P = 0.001$), and PGR ($P = 0.0087$).Overall, these results show that the levels of PGI (AUC 0.64) and PGII (AUC 0.60) have a predictive ability for discriminating esophageal carcinoma. Moreover, in males < 65 years old, PGI (AUC 0.73) and PGII (AUC 0.69) also showed to have a predictive ability for discriminating esophageal carcinoma.

Conclusion Serum PG levels in patients with esophageal squamous cell carcinoma, especially in males aged < 65 years old, are lower than those in healthy people. PGI and PGII are useful for screening esophageal squamous cell carcinoma.

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Key words: pepsinogen; esophageal squamous cell carcinoma; screening

Pepsinogens (PG) are a class of endopeptidases that are secreted by the gastric epithelium and released into the circulation [1]. PGI is secreted by oxyntic glands located in the gastric fundus and body, whereas PGII is secreted by all gastric and duodenal glands. Serum PG has been used as a biomarker of gastric inflammation and mucosal status [2].

A low serum PGI concentration and a low serum pepsinogen I/II ratio (PGR) are suggestive of the presence of extensive intestinal metaplasia and atrophic gastritis, which are recognized as a risk factor for gastric cancer. Serum PG testing has, therefore, been proposed to identify individuals with higher risk for gastric cancer who could benefit from gastric cancer screening using upper endoscopy [3–4].

Esophageal cancer is the eighth most common cancer and the sixth most common cause of cancer death worldwide; it has a poor prognosis and survival rate due to its late clinical presentation with advanced disease, with less than 15% patients surviving more than 5 years [5–6]. The esophageal squamous cell carcinoma (ESCC) rates are the highest in the so-called "esophageal cancer belt," which includes Iran, Central Asia, and North-Central China. Within China, the rates in the Hebi and Hunyuan counties have been reported to range from 1.4 to 140 per 100,000 people [7].

Previous studies have found an association between chronic atrophic gastritis and ESCC [8–11]. One meta-analysis reports a two to threefold increased risk for developing ESCC in patients with chronic atrophic gastritis, while another concludes that PGI serum level could aid in the early detection of ESCC [12–13]. However, other studies have concluded that there is little or no evidence for an association of PG values with ESCC risk [14–15].

This study analyzes the clinical significance of the

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differences between the serum levels of PGI and PGII, as well as the PGR in ESCC patients versus healthy controls in Wuhan, China.

Materials and methods

Study participants, questionnaire and biological sample collection

A retrospective analysis was performed using the data collected from July 2015 to December 2016 in Renmin Hospital, Wuhan, China. A total of 351 Chinese patients who underwent gastroscopic examination for suspected esophageal diseases were enrolled into the study and their serum samples were subsequently collected. Among the 351 patients, 226 were males and 125 were females, and the ages of the patients ranged from 32 to 89 years old. According to endoscopic and pathological findings, 209 patients had ESCC, whereas 142 patients were free of any esophageal disease (control group).

All subjects did not receive antibiotics, acid suppressants, or mucosal protective agents within a month prior to examination. The exclusion criteria for the patients included moderate to severe gastric diseases, other esophageal diseases or findings, gastrointestinal or non-gastrointestinal cancer, and previous gastrointestinal surgeries. The design and conduct of the study were approved by the hospital ethics committee, the endoscopic center, and the gastroenterology department. All subjects provided written informed consent.

Serum pepsinogen assays

Fasting venous blood (5 mL) was collected from all subjects in the morning, and the serum was obtained for centrifugation. The serum PGI and PGII levels were detected by Siemens Advia 2400 automatic biochemical analyzer and supporting reagents; the PGR was subsequently calculated. The operation was carried out in strict accordance with the instructions by an experienced laboratory scientist. Gastroscopy was performed by a trained gastroenterologist with more than 5 years of experience. The biopsies were fixed in 80% ethanol, embedded in paraffin, cut in 5-μm sections, and stained with hematoxylin and eosin; they were subsequently observed and read independently by 2 pathologists with no previous knowledge of the patients' situations. If there was discrepancy in the diagnosis, a joint review would take place.

Statistical analysis

Statistical analyses were conducted using the GraphPad Prism 6.0 and SPSS 20.0 statistical softwares. The data conforming to the normal distribution were represented as the mean with the standard deviation [x(_) ± s], whereas the data exhibiting skewed distribution were expressed as the median with the inter-quartile range (IQR).

The data of the two groups with normal distribution and variance were compared using the independent sample *t* test, whereas, the two groups with skewed distribution and variance were compared using the Mann-Whitney U rank sum test. The chi-square test was used to compare the ratio or composition ratio of the count data. A *P*-value < 0.05 was considered statistically significant.

The clinical value of PG in the diagnosis of ESCC was analyzed, and the sensitivity and specificity across cut-offs generated the receiver operating characteristic (ROC) curve with the area under the curve (AUC) to determine the inherent ability of the PG test to discriminate between the ESCC and control groups. AUC = 1 means the diagnostic test is perfect in differentiating between the two groups, while AUC = 0.5 means the chance of discrimination of the curve is located on the diagonal line in the ROC space.

Results

Table 1 showed the demographic characteristics of the ESCC and control subjects: the pepsinogen serum medium values in each group, the male-to-female ratio, and the subjects younger and older than 65 years in the ESCC and control groups.

Table 2 compared and analyzes the serum levels of PGI and PGII, as well as the PGR between the ESCC and control groups with respect to all of the patients. The serum levels of PGI (P <0.0001) and PGII (P = 0.0007), as well as the PGR (P = 0.007) in the ESCC subjects were significantly lower than those in the controls.

Table 3 compared the PG serum levels between the male and female groups. It shows that the levels of PGI

Table 1 Demographic characteristics of the esophageal squamous cell carcinoma and control groups

	n	PG I (ng/mL)[1]	PG II (ng/mL)	PGR	Female	Male	< 65[2]	≥ 65[3]
ESCC	209	46.0	11.8	4.1	66	143	125	84
Control group	142	67.0	15.4	4.6	59	83	97	45
Total	351				125	226	222	129

[1] Pepsinogen I, II medium values are expressed in ng/mL

[2] < 65 younger than 65 years old

[3] ≥ 65 equal or older than 65 years old

Proportions of female and male subjects in the ESCC and control groups

Table 2 Serum levels of pepsinogen I and II, as well as pepsinogen I/II ratio in the esophageal squamous cell carcinoma and control groups

	n	PG I (ng/mL)	PG II (ng/mL)	PGR
ESCC	209	46.0 (30.5,89.0)	11.8 (8.1,19.5)	4.1 (3.0,5.4)
Control group	142	67.0 (50.0,91.5)	15.4 (10.5,21.5)	4.6 (3.7,5.4)
Total	351	*P* < 0.0001	0.0007	0.007

ESCC = esophageal squamous cell carcinoma

Pepsinogen I, II, ratio median values are expressed in ng/ml with their inter-quartile range

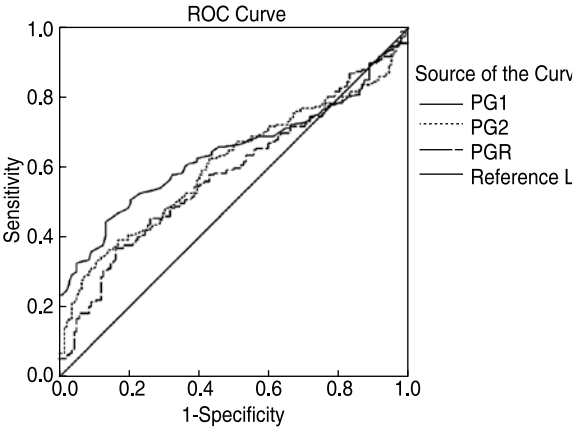
P value < 0.05 is statistically significant

($P < 0.0001$) and PGII ($P = 0.0001$), as well as the PGR ($P = 0.0138$) in the male ESCC group were significantly lower than those in the control group. Within the female subjects, no statistically significant differences were observed.

Table 4 compared PG serum levels between different ages in the ESCC and control groups.

Subjects were divided into an elderly group (≥ 65 years old) and a young–middle-aged group (< 65 years old). Upon analyzing the elderly group, the serum levels of PGI ($P < 0001$) and PGII ($P = 0.001$) and the PGR ($P = 0.0087$) in the ESCC group were found to be significantly lower than those in the control group. Within the elderly group, no statistically significant differences were observed.

Fig. 1 analyzed the clinical value of the levels of PGI and PGII, as well as the PGR in the diagnosis of ESCC in the totality of the subjects. Table 5 showedthe corresponding cut-off values for the sensitivity, specificity, and the AUC.



In this ROC curve the sensitivity (true positive rate) is plotted in function of the 1-specificity (false positive rate) for different cut-off points. Each point of the pepsinogen I, II, ratio values from the overall group on the ROC curve represent a sensitivity/specificity pair corresponding to a particular decision threshold.

Fig. 1 Receiver operating characteristic curve of pepsinogen I, II, ratio levels in the diagnosis of esophageal squamous cell carcinoma in the overall subject

The best cut-off value for PGI was 42.7 ng/mL (sensitivity 44.5%, specificity 86.6%) with the AUC = 0.64 (95% CI: 0.58–0.69, $P = 0.000$). For PGII, the best cut-off value was 8.9 ng/mL (sensitivity 31.1%, specificity 90.8%) with the AUC=0.60 (95% CI: 0.55–0.65, $P = 0.000$). Whereas, the best cut-off value for PGR was 3.5 ng/mL (sensitivity 37.8%, specificity 81.6%) with the AUC = 0.5 (95% CI:

Table 3 Serum levels of pepsinogen I and II, as well as pepsinogen I/II ratio in the esophageal squamous cell carcinoma and control groups classified by gender

	Male				Female			
	n	PG I (ng/mL)[1]	PG II (ng/mL)	PGR	*n*	PG I (ng/mL)[1]	PG II (ng/mL)	PGR
ESCC	143	43.0 (26.0, 86.0)	11.5 (7.7, 18.6)	4.2 ± 1.8	66	52.0 (38.0, 113.3)	13.0 (9.7, 20.4)	4.5 ± 2.1
Control group	83	73.0 (55.0, 101.0)	16.7 (11.9, 21.7)	4.4 (3.6,5.8)	59	59.0 (43.0, 81.0)	12.1 (9.4, 21.4)	4.6 ± 1.4
	226	*P* < 0.0001	*P* < 0.0001	*P* < 0.0138	125	*P 0.3582*	0.6961	0.604

In the male and female groups pepsinogen I and II in ESCC and control group are represented by the median with inter-quartile range.

PGR in the ESCC male and female ESCC and control group are represented by the mean with standard deviation

P value < 0.05 is statistically significant

Table 4 Serum levels of pepsinogen I and II, as well as pepsinogen I/II ratio in the esophageal squamous cell carcinoma and control groups classified by age

	< 65 years				≥ 65 years			
	n	PG I (ng/mL)[1]	PG II (ng/mL)	PGR	*n*	PG I (ng/mL)[1]	PG II (ng/mL)	PGR
ESCC	125	42.0 (27.0, 72.5)	10.6 (7.5, 16.4)	4.2 ± 1.6[2]	84	58.5 (38.0, 119.0)	13.4 (9.4, 30.4)[1]	4.0 (3.0, 6.1)[1]
Control group	97	65.0 (48.5, 84.0)	13.7 (10.2, 19.5)	4.5(3.7, 5.4)[1]	45	75.0 (54.0, 113.0)	20.8 ± 9.0[2]	4.6 ± 1.8[2]
	222	*P* < 0.0001	0.001	0.0087	129	*P* 0.101	0.063	0.383

[1] Data with non-symmetric distribution represented by the median with inter-quartile range

[2] Data with symmetric distribution represented by the mean with standard deviation

P value < 0.05 is statistically significant

Table 5 Cut-off values, sensitivity, specificity, and area under the curve of levels of pepsinogen I and II, as well as pepsinogen I/II ratio in the diagnosis of esophageal squamous cell carcinoma in the overall group

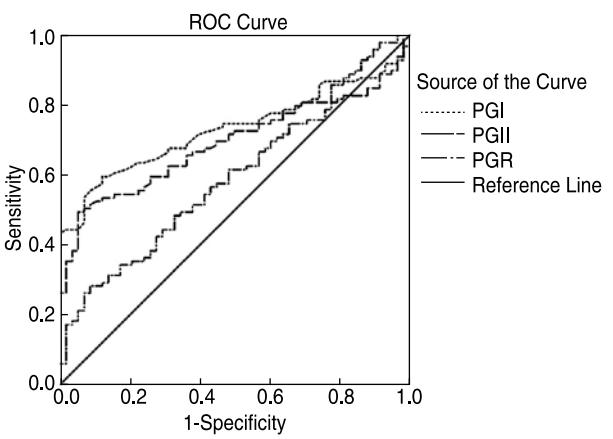
	Cut-off[1]	Sensitivity	95%CI	Specificity	95%CI	AUC[2]
PGI	42.7	44.5	37.6–51.5	86.6	79.9–91.75	0.64
PGII	8.9	31.1	24.8–37.8	90.8	84.8–95.0	0.60
PGR	3.5	*37.8*	31.2–44.7	81.6	74.3–87.6	0.58

[1] Pepsinogen I, II, ratio cut-off values for sensitivity and specificity calculated with the Jordan Index

[2] Area under the curve generated after the receiver operating characteristic curve

0.53–0.63, P = 0.001), indicating that its capacity to discriminate between ESCC and normal subjects is no better than the chance level. The ROC and the AUC demonstrate that PGI and PGII serum levels have a predictive ability in discriminating ESCC from normal subjects, and PGI has a greater discrimination capacity than PGII. To assess the difference between the two AUC values, the z test was performed (z = 0.83, two tailed P = 0.40) and it found that the difference was not statistically significant.

Fig. 2 showed the analysis of the clinical values of PGI and PGII serum levels and the PGR in the young–middle-aged male group. Table 6 showed the corresponding cut-off values for the sensitivity and specificity and the AUC. The best cut-off value for PGI was 50.5 ng/mL (sensitivity 60.6%, specificity 84.4%) with the AUC = 0.73 (95% CI: 0.65–0.80, P = 0.000). For PGII, the best cut-off value was 10.1 ng/mL (sensitivity 50.5%, specificity 93.1%) with



In this ROC curve the sensitivity (true positive rate) is plotted in function of the 1-specificity (false positive rate) for different cut-off points. Each point of the pepsinogen **I**, **II**, ratio values from the young-middle aged male group on the ROC curve represent a sensitivity/specificity pair corresponding to a particular decision threshold.

Fig. 2 Receiver operating characteristic curve of pepsinogen I, II, ratio levels in the diagnosis of esophageal squamous cell carcinoma in the young-middle aged male group

Table 6 Cut-off values, sensitivity, specificity, and area under the curve of levels of pepsinogen I and II, as well as pepsinogen I/II ratio in the diagnosis of esophageal squamous cell carcinoma in the young–middle-aged male group

	Cut-off[1]	Sensitivity	95%CI	Specificity	95%CI	AUC[2]
PGI	50.5	60.6	50.2–70.2	84.4	72.5–92.6	0.73
PGII	10.1	50.5	40.2–60.7	93.1	81.0–97.1	0.69
PGR	3.5	*34.3*	25.0–44.5	81.0	68.5–90.1	0.59

[1] Pepsinogen I, II, ratio cut-off values for sensitivity and specificity calculated with the Jordan Index

[2] Area under the curve generated after the receiver operating characteristic curve

the AUC=0.69 (95% CI: 0.61–0.76, P = 0.000). The best cut-off value for PGR was 3.5 ng/mL (sensitivity 34.3%, specificity 81%) with the AUC=0.59 (95% CI: 0.53–0.63, P = 0.001), indicating that its capacity to discriminate between ESCC and normal young–middle-aged male subjects is no better than the chance level. The ROC and AUC values demonstrate that among the young–middle-aged male subjects, PGI and PGII have a predictive ability for discriminating patients with ESCC from normal subjects and that PGI has a greater discrimination capacity than PGII. To assess the difference between these two AUC values, the z test was performed (z = 1.04, two tailed P = 0.29) and it showed that the difference was not statistically significant.

Discussion

Several studies have demonstrated that low PGI serum levels and low PGR are sensitive and specific markers for gastric atrophy [16–17]; later, a consistent association was found between pepsinogen serum levels and the risk of gastric cancer [18]. However, it was not until a Swedish study found an association between chronic gastric atrophy and ESCC that demonstrated patients with pernicious anemia had a relative risk of 3.2 to present ESCC [8]. Many hypotheses have suggested the potential causes of this association, such as that the atrophic mucosa produces less acid, thus allowing more bacteria to proliferate, and that there might be an increased production of acetaldehyde and N-nitroso compounds that may act like risk factors for ESCC [19]. Further studies have demonstrated a two to threefold increased risk of gastric atrophy, ESCC, and gastric adenocarcinoma [10].

Although the incidence of ESCC is not high compared to other carcinomas, the survival rate is low because of late clinical presentation. In China, ESCC has high incidence and mortality rates with a multi-causal association, such as family aggregation [20], poor nutritional status, smoking, low intake of fruits and vegetables, high temperatures, and drinking beverages [21].

Because of the high impact of ESCC on mortality and survival rates, there is a need to find an early detection method for this disease. With the controversial findings of previous studies, we aimed to investigate the clinical association and significance of pepsinogen serum values with the detection of ESCC.

Our results demonstrate that, in general, the serum levels of PGI and PGII, as well as PGR are decreased in ESCC patients compared to non-ESCC patients; however, the difference was only statistically significant within the young–middle-aged male group, and not in the female and ≥ 65 years old groups. A Chinese study demonstrated the associations of the differences in PG serum levels with gender, age, Helicobacter pylori infection, and consumption of alcohol and tobacco [22]. Our study sample is too small and may be susceptible to bias; thus, further studies need to be conducted to validate the causality of these differences in larger sample sizes.

The ROC analysis in this study showed that PGI (AUC = 0.64) has the highest predictive ability for screening ESCC in the totality of the patients. With the optimal cut-off value of 42.7 ng/mL, the sensitivity was 44.5% and the specificity was 86.6%. However, this predictive value is poor in general, especially considering the low sensitivity; thus, there is a large risk for misdiagnosis. The results in this study corroborate those found in previous studies, wherein serum PGI levels patients with severe atrophic gastritis were found to be reduced but PGII levels remained normal or even increased [23], and that there is a correlation between severe gastric mucosal atrophy and a higher risk of ESCC [24].

Based on our analysis, the PGI serum levels in the young–middle-aged male group were found to have a high sensitivity (60.6%) and the highest predictive ability in discriminating ESCC from normal subjects (AUC = 0.73). Even though the AUC from PGI and PGII levels in the overall dataset and the young–middle-aged male groups were different, this difference was not statistically significant.

Some reports have shown that PGR alone is a superior marker of atrophy, but other reports have also shown that serum PGI level is more strongly associated with atrophy [25–26]. In our study, PGR did not present a higher capacity than chance to discriminate patients with ESCC from normal subjects (AUC = 0.58), and this may be due to unknown mechanisms that are unrelated to atrophy. Large-sample multicenter studies are needed to further explore the differences in serum PG levels.

The strengths of this study include the asymptomatic subjects at the time of enrollment in the study, the endoscopy gastroenterologist and the laboratory scientist who performed the assays unaware of the patients' clinical diagnoses, and the calibrated laboratory materials; the measurement of PG serum levels and the accurate classification of the ESCC patients permitted the analysis using cut-off points to generate the ROC and AUC data.

The limitations include the small sample size, the measurement of the biomarkers at only one point during the study, the imperfect correlation between the level of PGI and the PGR, the lack of gastric atrophy diagnosis, and the presence of an unknown confounder that cannot be totally ruled out.

In conclusion, this study suggests that gastric mucosal atrophy with low PG serum levels are closely related to the occurrence of ESCC and that the relationship between gastric mucosal atrophy and esophageal cancer needs further exploration through trials with a larger patient cohort, which also consider factors, such as age, gender, Helicobacter pylori infection, lifestyle habits, and optimal timepoint biomarker measurement.

A serum PG test alone is valuable for the diagnosis of ESCC, but its sensitivity as a marker is low; thus, it is necessary to combine the detection of PG and other tumor markers to come up with a new, fast, and convenient serological detection method for predicting the development of ESCC.

Further investigations should, therefore, be conducted to come up with a method for effectively screening individuals at risk of developing ESCC at an early stage of cancer.

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Ethical Statement

Authors declare that all procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study.

Conflicts of interest

The authors declare no potential conflicts of interest.

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