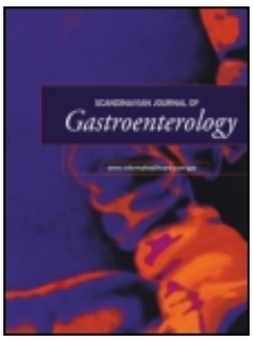

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ORIGINAL ARTICLE

A comprehensive evaluation of fasting serum gastrin-17 as a predictor of diseased stomach in Chinese population

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Abstract

Background and aim. Fasting serum gastrin-17 (FsG17) is considered as a noninvasive biomarker reflecting the structure and functional status of gastric mucosa, but its clinical utility remains unclear. This study aimed to evaluate FsG17 comprehensively: establish the ranges and cut-off points of FsG17 levels in different gastric diseases, identify their influencing factors, and investigate the accuracy of FsG17 for identifying diseased stomach. ***Methods.*** The study included 4064 participants from Northern China between 2008 and 2013. FsG17 and serum *Helicobacter pylori* IgG antibody levels were measured by enzyme-linked immunosorbent assay. Diagnostic accuracy was assessed by receiver operator characteristic curves. Multivariate logistic regression analysis was performed to determine the best predictors of gastric histopathological conditions. ***Results.*** Median FsG17 levels in healthy, non-atrophic, atrophic, and cancerous stomachs were 1.8, 4.0, 3.8, and 6.1 pmol/l, respectively. Age, smoking status, alcohol consumption, *H. pylori* infection, and predominant lesion site were factors that affected FsG17 levels. The optimal cut-off values for FsG17 were 3.0 pmol/l (sensitivity of 59.3% and specificity of 67.3%) for discriminating between healthy stomach and diseased stomach and 10.7 pmol/l (sensitivity of 37% and specificity of 83.7%) for discriminating between cancerous stomach and cancer-free stomach; the screening accuracy was higher (sensitivity of 50.0% and specificity of 83.0%) for gastric cancer in the corpus. Multivariate analysis showed that FsG17, gender, age, and *H. pylori* infection were independent predictors of cancerous stomach. ***Conclusion.*** With the progression from health stomach to malignancy, FsG17 levels significantly increased and were influenced by other factors. FsG17 combined with age, gender, and *H. pylori* infection could distinguish between cancerous stomach and cancer-free stomach. The results will enhance our understanding of the potential clinical utility of FsG17.

Key Words: *diseased stomach, gastric cancer, gastrin-17, Helicobacter pylori*

Introduction

Recently, serological tests for detection and screening of gastric diseases have attracted increased attention because the techniques are easy, accessible, less time-consuming, inexpensive, and noninvasive compared with routine practices, such as endoscopy and histological investigation [1]. Of the numerous potential serological markers, the most widely used ones are those which specifically reflect the structure and function of gastric mucosa and are commonly referred to as stomach-specific biomarkers [2].

Gastrin, an important gastrointestinal hormone secreted by the G cells located in the gastric antral mucosa, stimulates gastric acid secretion, promotes proliferation/growth, and inhibits apoptosis of gastrointestinal epithelial cells [3]. The gastrin gene is located on human chromosome 17q21 and encodes

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a 101 amino acid polypeptide [4]. A series of post-translational modifications of the gene product result in a number of biologically active peptides. About 95% of bioactive gastrin is α-amidated gastrin, of which 80–90% is gastrin-17 (G17) and 5–10% is gastrin-34 [5].

Serum G17 (sG17) concentration depends on intragastric acidity and the number of G cells in the gastric antrum and normally increases after food stimulation. Although studies of sG17 as a biomarker for screening gastric cancer have been conducted since the 1990s [6], the clinical utility of sG17 testing remains unclear. One study reported that lower sG17 levels after food stimulation were associated with atrophy of the antral mucosa [7], and other studies suggested that fasting sG17 (FsG17) tests might not be useful in screening for atrophic gastritis or gastric cancer [8,9].

Currently, the ranges and cut-off points of FsG17 levels for different gastric diseases are not established, thus affecting its potential clinical utility. In addition, FsG17 levels are affected by various physiological stimuli and pathological states, such as age, sex, *Helicobacter pylori* infection, and risk behavior, and few studies have taken these factors into account. There are few reports that tried to establish the ranges and cut-off points of FsG17 levels. Therefore, a comprehensive evaluation of the correlation between FsG17 and stomach diseases will help determine its potential clinical utility.

In the present study, we used data on a large population to establish the ranges and cut-off points of FsG17 levels in different gastric diseases, to identify their influencing factors, and to investigate the accuracy of FsG17 for discriminating between the normal gastric mucosa, nonmalignant lesions, and the malignant lesion (i.e. gastric cancer).

Materials and methods

Study population

A total of 4064 participants were recruited from Liaoning Province in China. Among them, 3839 participants were from the Zhuanghe Gastric Cancer Study, which is a population-based, combined serologic/endoscopic screening program for gastric diseases, conducted in Zhuanghe County. The study population selection and recruitment process has been previously reported [10,11]. Between 2008 and 2013, 7837 participants were recruited in the Zhuanghe Gastric Cancer Study, and gastric endoscopy with biopsies was conducted on 4993 participants; among them, FsG17 measurements were available for 3839 patients. In addition, in order to increase the sample size for gastric cancer cases, we also included 225 histopathologically confirmed gastric cancer cases who were referred for routine outpatient elective gastric endoscopy with biopsies from 2008 to 2013 at the First Affiliated Hospital of China Medical University in Shenyang. Information on age, sex, and lifestyle (smoking and alcohol consumption) were obtained by interviewer-administered questionnaires.

This study was approved by the Human Ethics Review Committee of the First Affiliated Hospital of China Medical University (Shenyang, China). Written informed consent was obtained from each participant in accordance with the Declaration of Helsinki and its later revision.

Histopathological assessment

Mucosal biopsies were obtained from the gastric body, angulus, antrum, and, if applicable, lesion site. Biopsies were processed by routine methods. Briefly, biopsies were oriented, fixed in 95% ethanol, embedded in paraffin blocks, and then sectioned and stained with hematoxylin and eosin at local study centers. Histopathological alterations of each stained section were independently evaluated by two gastrointestinal pathologists using standard criteria from the updated Sydney System for Gastritis [12] and World Health Organization (WHO) classifications for the cancerous stomach (CS). Each participant was assigned a global diagnosis based on the most severe lesion found among all biopsy specimens.

The participants were classified as: (i) healthy stomach (HS, without evidence of *H. pylori* infection or active gastritis, $n = 1071$); (ii) non-atrophic stomach (NAS, with active non-atrophic gastritis, gastric erosion, or ulcer, $n = 1544$); (iii) atrophic stomach (AS, atrophic gastritis with or without intestinal metaplasia, $n = 1200$); and (iv) CS, $n = 249$.

Serological measurements

A 5-ml fasting venous blood sample was collected from each participant. All samples were centrifuged immediately at $3500 \times g$ for 10 min, and a serum aliquot (400 μl) was frozen within 3 h after taking blood. Samples were stored at -80°C until analysis. FsG17 levels and *H. pylori* immunoglobulin G (IgG) antibodies were measured with enzyme-linked immunosorbent assays (Gastrin-17 ELISA and *H. pylori* IgG ELISA kits; Biohit, Helsinki, Finland) in the same aliquot according to the manufacturer's protocol, blinded to the histopathological diagnosis. Duplicate negative and positive controls were included in each 96-well plate. Any serum sample with a definitive

reading of 34 enzyme immune units or higher (the kit-recommended cut-off limit) was considered *H. pylori* seropositive. Samples that yielded implausible values were retested. The mean intra-assay coefficients of variation were 15% for FsG17 and 11% for anti-*H. pylori* IgG.

Statistical analysis

All statistical analyses were performed with SPSS 18.0 (SPSS Inc., Chicago, IL, USA). The distribution of baseline characteristics was tested using the chi-squared test. FsG17 concentrations are represented as the median (with 25–75 percentiles). Medians were compared between two groups using the Mann–Whitney U-test. Receiver operator characteristic curves were used to determine the corresponding cut-off points when the pathologic diagnosis was treated as the "gold standard". Multivariate logistic regression analysis was performed to determine the best predictors of gastric histopathological conditions, and the area under the curve (AUC) was used to evaluate the discriminatory performance of the predictors. Observations with missing data were excluded from analysis. For all tests, a two-sided significance level of $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics of the study participants

The selected sociodemographical characteristics and risk behaviors of the study participants by histopathological conditions are presented in Table I. There were increasing proportions of males and older participants as the histopathological conditions progressed from HS, NAS, AS to CS. The distributions of smoking and drinking status were similar across different histopathological conditions ($p > 0.05$); also, *H. pylori* seropositivity was similar among patients with NAS, AS or CS ($p > 0.05$).

FsG17 levels across gastric histopathological conditions

As shown in Table II, FsG17 levels tended to increase as the histopathological conditions progressed from HS, NAS, AS to CS. The lowest level of FsG17 was observed in the HS group among the four groups ($p < 0.001$). The FsG17 level in the CS group was significantly higher than that in the cancer-free groups ($p < 0.001$). There were no statistically significant differences in FsG17 levels between the NAS and AS groups ($p = 0.223$), or between intestinal and diffuse type of gastric cancers ($p = 0.719$). Figure 1 shows the distribution of FsG17 levels among cancer-free participants and gastric cancer patients. Gastric cancer patients tended to have higher FsG17 levels and 69.1% had FsG17 levels ≥3.0 pmol.

FsG17 levels by their influencing factors according to different gastric histopathological conditions

FsG17 levels by sex, age, smoking/drinking status, *H. pylori* seropositivity, lesions site, and histological type of gastric cancer according to different gastric

Table I. Selected sociodemographical characteristics and risk behaviors of the study participants by histopathological conditions.

	HS	NAS	AS	CS	
Characteristics	$n = 1071$ (%)	$n = 1544$ (%)	$n = 1200$ (%)	$n = 249$ (%)	p-Value*
Sex					< 0.001
Male	345 (32.2)	630 (40.8)	602 (50.2)	166 (66.7)	
Female	726 (67.8)	914 (59.2)	598 (49.8)	83 (33.3)	
Age (years)					
<60	813 (75.9)	1221 (79.1)	818 (68.2)	106 (42.6)	< 0.001
≥60	258 (24.1)	323 (20.9)	382 (31.8)	143 (57.4)	
Current smoker					0.383
No	563 (52.6)	862 (55.8)	657 (54.8)	39 (15.7)	
Yes	508 (47.4)	680 (44.0)	542 (45.2)	36 (14.5)	
Missing		2 (0.1)	1 (0.1)	174 (69.9)	
Alcohol consumption					0.674
No	597 (55.7)	889 (57.6)	684(57.0)	46 (18.5)	
Yes	474 (44.3)	653 (42.3)	515(42.9)	29 (11.6)	
Missing			2(0.1)	174 (69.9)	
H. pylori seropositivity					0.051
Negative	1071 (100.0)	586 (38.0)	510 (42.5)	79 (31.7)	
Positive		958 (62.0)	690 (57.5)	125 (50.2)	
Missing				45 (18.1)	

Abbreviations: HS = healthy stomach; NAS = non-atrophic stomach; AS = atrophic stomach; CS = cancerous stomach.
*p-Value from the chi-squared test.

Table II. FsG17 levels by different gastric histopathological conditions.

	Amount	G17 (pmol/l)[$]	*p*-Value
HS	1071	1.8 (0.8–3.9)	
NAS	1544	4.0 (1.4–9.4)	< 0.001[⋆]
AS	1201	3.8 (1.5–8.3)	< 0.001[⋆], 0.223[#]
CS	249	6.1 (2.6–15.8)	< 0.001[⋆#$]
Intestinal type	105	5.0 (2.2–14.4)	
Diffuse type	104	5.9 (2.7–14.4)	0.719[&]

Abbreviations: G17 = gastrin-17; HS = healthy stomach; NAS = -non-atrophic stomach; AS = atrophic stomach; CS = cancerous stomach.
[$]Values are medians (25–75 percentiles).
[⋆]*p*-Value: compared with HS.
[#]*p*-Value: compared with NAS.
[$]*p*-Value: compared with AS.
[&]*p*-Value: compared with intestinal type.

histopathological conditions are shown in Table III. We found that: (i) *age*: FsG17 levels were higher in participants ≥60 years compared with those <60 years ($p = 0.024$) in the HS group; (ii) H. pylori *infection and smoking*: in cancer-free disease groups (i.e. NAS and AS), *H. pylori* infected participants or smokers had higher levels of FsG17 compared to those without *H. pylori* infection ($p < 0.001$) or nonsmokers ($p < 0.001$); whereas in the CS group, higher FsG17 levels were observed in those without *H. pylori* infection ($p = 0.037$) or nonsmokers ($p = 0.018$); (iii) *alcohol consumption*: in cancer-free groups (i.e. HS, NAS, and AS), FsG17 levels were significantly higher in participants who consumed alcohol than those who did not ($p = 0.006$, $p < 0.001$, $p < 0.001$, respectively); (iv) *predominant lesion site*: in the CS group, FsG17 levels were higher in participants with corpus-predominant lesions than those with antrum-predominant lesions ($p = 0.006$).

Comparisons of the FsG17 levels between different gastric histopathological conditions stratified by their influencing factors

When we compared the FsG17 levels between different gastric histopathological conditions stratified by selected characteristics (Table IV), we found that (i) among *H. pylori* seronegative participants, FsG17 differed significantly between HS and the diseased stomachs ($p < 0.001$) and between CS and cancer-free stomachs ($p < 0.001$). In *H. pylori*

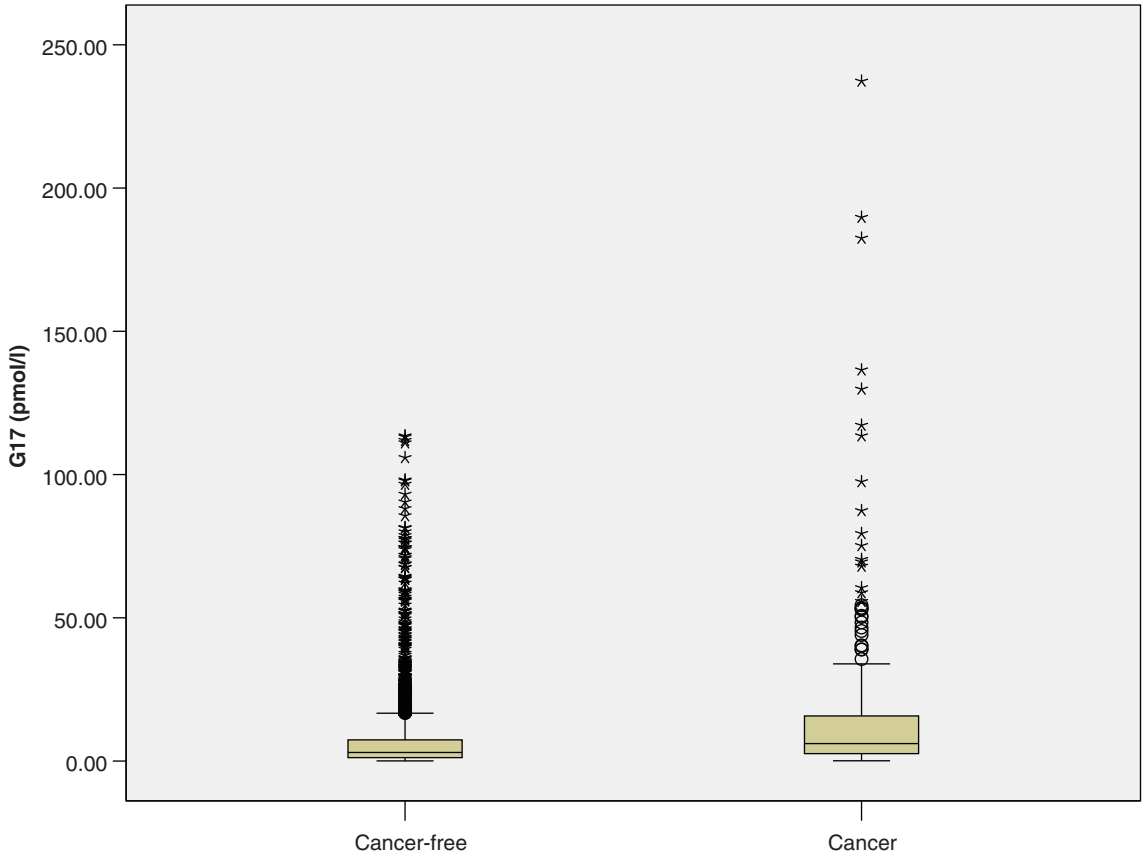

Figure 1. The distribution of FsG17 levels among cancer-free participants and gastric cancer patients. Abbreviations: FsG17 = fasting serum gastrin-17; G17 = gastrin-17.

Table III. FsG17 levels by their influencing factors according to different gastric histopathological conditions.

	HS (n = 1071)		NAS (n = 1544)		AS (n = 1200)		CS (n = 249)	
Influencing factors	G17 (pmol/l)[§]	p-Value⋆	G17 (pmol/l)[§]	p-Value⋆	G17 (pmol/l)[§]	p-Value⋆	G17 (pmol/l)[§]	p-Value⋆
Sex								
Male	1.7 (0.7–3.7)	0.133	4.6 (1.4–10.3)	0.335	3.9 (1.6–8.2)	0.352	5.5 (2.6–14.5)	0.226
Female	1.8 (0.9–4.0)		3.9 (1.4–8.9)		3.4 (1.4–8.4)		7.5 (2.7–17.1)	
Age (years)								
<60	1.6 (0.8–3.6)	0.024	4.0 (1.4–9.4)	0.567	3.8 (1.4–8.2)	0.464	6.2 (2.7–17.2)	0.242
≥60	2.0 (0.8–5.2)		4.6 (1.6–9.1)		3.7 (1.6–8.4)		5.8 (2.4–14.4)	
Current smoker								
No	1.7 (0.7–3.8)	0.138	3.3 (1.1–8.4)	< 0.001	3.2 (1.3–7.7)	< 0.001	5.0 (2.7–16.1)	0.018
Yes	1.8 (0.8–4.0)		5.1 (1.9–10.8)		4.4 (1.8–8.9)		3.3 (1.6–5.1)	
Alcohol consumption								
No	1.6 (0.7–3.5)	0.006	3.4 (1.2–8.7)	< 0.001	3.2 (1.3–7.2)	< 0.001	4.1 (2.6–13)	0.832
Yes	2.0 (0.9–4.4)		5.1 (1.8–10.4)		4.8 (1.9–9.9)		4.4 (2.1–10.6)	
H. pylori seropositivity								
Negative	1.8 (0.8–3.9)		2.8 (1.1–7.3)	< 0.001	2.5 (1.1–6.3)	< 0.001	6.2 (2.5–24.4)	0.037
Positive			5.0 (1.8–10.4)		4.9 (2.2–9.2)		4.7 (2.4–11.8)	
Lesions site								
Corpus			3.9 (1.5–9.2)	0.989	5.5 (1.6–11.0)	0.156	10.0 (3.0–27.6)	0.006
Antrum			4.0 (1.5–9.1)		3.6 (1.6–8.2)		4.7 (2.2–13.3)	
Histological type of gastric cancer								
Intestinal							5.0 (2.2–14.4)	0.719
Diffuse							5.9 (2.7–14.4)	

Abbreviations: FsG17: Fasting serum gastrin-17; G17 = gastrin-17; HS = healthy stomach; NAS = non-atrophic stomach; AS = atrophic stomach; CS = cancerous stomach.
[§]FsG17 values are medians (25–75 percentiles).
⋆p-Value for comparisons of FsG17 levels between different sexes, age groups, smoking statuses, alcohol consumption statuses, *H. pylori* infection statuses, predominant lesion sites, and histological types of gastric cancer; [#]: compared with other groups combined; [$]: compared with the NAS group.

seropositive individuals, FsG17 levels showed no significant differences among the different stomach condition groups. (ii) Among nonsmokers, FsG17 levels differed significantly between HS and the diseased stomachs ($p < 0.001$) and between CS and cancer-free stomachs ($p = 0.001$). Also, significant differences were observed between HS and other diseased stomachs ($p < 0.001$) for smokers, but no significant differences were observed between the different diseased stomachs. Similar results were found for alcohol consumption. (iii) Regardless of the location of the predominant lesion (corpus vs. antrum), there were significant differences ($p < 0.05$) in FsG17 levels between different gastric histopathological conditions except when NAS was compared with AS.

Accuracy of FsG17 in discriminating between gastric histopathological conditions

Accuracy of FsG17 levels in discriminating between HS versus diseased stomach, and cancer-free stomach versus CS is shown in Table V.

In order to discriminate the diseased stomach from HS, the optimal cut-off value of FsG17 was 3.0 pmol/l, with an AUC of 0.659 (95% confidence interval

Table IV. Comparison of p-Values of the FsG17 levels between different gastric histopathological conditions stratified by their influencing factors.

		H. pylori		Smoking		Alcohol consumption		Lesions site	
Comparisons	Overall	Seronegative	Seropositive	No	Yes	No	Yes	Corpus	Antrum
HS versus NAS	<0.001	<0.001	NA	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
HS versus AS	<0.001	<0.001	NA	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
HS versus CS	<0.001	<0.001	NA	<0.001	0.008	<0.001	0.001	<0.001	<0.001
NAS versus AS	0.223	0.298	0.755	0.833	0.072	0.239	0.593	0.373	0.266
NAS versus CS	<0.001	<0.001	0.372	0.001	0.082	0.063	0.802	<0.001	0.033
AS versus CS	<0.001	<0.001	0.371	0.001	0.209	0.02	0.899	0.003	0.009

Abbreviations: HS = healthy stomach; NAS = non-atrophic stomach; AS = atrophic stomach; CS = cancerous stomach; NA = not applicable.

Table V. Accuracy of FsG17 levels in discriminating between healthy stomach versus diseased stomach, and cancer-free stomach versus cancerous stomach.

Comparisons		Cut-off value	AUC (95% CI)	Sensitivity	Specificity	YD	*p*-Value
HS versus diseased stomach*	Overall	3.0	0.659 (0.641–0.677)	59.3%	67.3%	0.266	< 0.001
	H. pylori seronegative	3.3	0.599 (0.576–0.622)	45.9%	70.4%	0.163	< 0.001
	Non-smoking	3.0	0.629 (0.603–0.654)	54.1%	69.3%	0.234	< 0.001
	Smoking	2.8	0.680 (0.653–0.707)	66.0%	64.4%	0.304	< 0.001
	Non-drinking	3.0	0.638 (0.613–0.663)	54.5%	70.4%	0.249	< 0.001
	Drinking	4.2	0.671 (0.644–0.699)	54.9%	73.6%	0.285	< 0.001
Cancer-free stomach§ versus CS	Overall	10.7	0.665 (0.633–0.698)	37.0%	83.7%	0.207	< 0.001
	H. pylori seronegative	4.4	0.748 (0.698–0.798)	62.0%	70.5%	0.325	< 0.001
	Non-smoking	11.9	0.691 (0.617–0.764)	35.9%	87.5%	0.234	< 0.001
	Non-drinking	11.9	0.632 (0.560–0.704)	28.3%	87.4%	0.156	0.002
	Corpus lesion	10.7	0.713 (0.646–0.781)	50.0%	83.0%	0.330	< 0.001
	Antrum lesion	11.0	0.612 (0.558–0.665)	30.8%	83.8%	0.146	< 0.001

Abbreviations: AUC = area under the curve; CI = confidence interval; HS = healthy stomach; CS = cancerous stomach; YD = Youden's indx.
*Diseased stomach includes non-atrophic stomach, atrophic stomach, and cancerous stomach.
§Cancer-free stomach includes healthy stomach, non-atrophic stomach, and atrophic stomach.

[CI]: 0.641–0.677), and a sensitivity of 59.3% and specificity of 67.3%. In stratified analysis, the AUCs for those who were *H. pylori*-negative, smokers, non-smokers, drinkers, and non-drinkers were 0.599, 0.629, 0.680, 0.638, and 0.671, with corresponding optimal cut-off points of 3.3, 3.0, 2.8, 3.0, and 4.2 pmol/l, respectively.

In order to discriminate the CS from the cancer-free stomach, the optimal cut-off value of FsG17 was set at the cut-off value to maximize specificity given specificity >70%. Overall, the optimal cut-off value of FsG17 was 10.7 pmol/l, with an AUC of 0.665 (95% CI: 0.633–0.698), a sensitivity of 37%, and a specificity of 83.7%. In stratified analysis, the AUCs for those who were *H. pylori*-negative, nonsmokers, non-drinkers, those who is predominant in the corpus, and those who is predominant in the antrum were 0.748, 0.691, 0.632, 0.713, and 0.612, with corresponding optimal cut-off points of 4.4, 11.9, 11.9, 10.7, and 11.0 pmol/l, respectively.

Table VI. Summary of logistic regression analyses for predictors of diseased stomach or cancerous stomach.

Dependent variable	Predictors	OR (95% CI)	*p*-Value
Diseased stomach *	Gender (male)	1.789 (1.498, 2.137)	< 0.001
	Smoking	1.308 (1.039, 1.646)	0.022
	FsG17	1.022 (1.013, 1.032)	< 0.001
Cancerous stomach	Intercept (constant)		
	Gender (male)	1.758 (1.079, 2.864)	0.024
	Age	1.131 (1.094, 1.170)	< 0.001
	H. pylori seropositivity	3.367 (2.012, 5.650)	< 0.001
	FsG17	1.015 (1.001, 1.030)	0.041

Abbreviations: FsG17 = fasting serum gastrin-17; CI = confidence interval; OR = odds ratio.
*Diseased stomach includes non-atrophic stomach, atrophic stomach, and cancerous stomach.

Predictors for gastric histopathological conditions

Multivariate logistic regression analyses (Table VI) showed significant relations between the presence of a diseased stomach and sex (male vs. female, odds ratio [OR] = 1.789, $p < 0.001$), smoking (OR = 1.308, $p = 0.022$), FsG17 (OR = 1.022 per unit increase, $p < 0.001$); as for the presence of a CS, the ORs for male, age (per year increase), *H. pylori* seropositivity, and FsG17 (per unit increase) were 1.758 ($p = 0.024$), 1.131 ($p < 0.001$), 3.367 ($p < 0.001$), and 1.015 ($p < 0.001$), respectively.

Discussion

In the present study, we performed a comprehensive evaluation of the correlations between FsG17 levels and different stomach diseases. This mainly includes establishment of the ranges and cut-off points of FsG17 levels in different gastric diseases, identification of their influencing factors, and investigation of the accuracy of FsG17 in discriminating between the normal gastric mucosa, nonmalignant lesions, and the malignant lesion. To our knowledge, this is the first study to report a comprehensive evaluation of FsG17 using a large Chinese population.

We began by focusing on the ranges and cut-off points of FsG17 levels in different gastric histopathological conditions, because little is known, affecting

its application. In previous reports, FsG17 levels in the health stomach were in the range of 2.4 to 8.9 pmol/l [13-15]. The wide range might be due to different definitions of "healthy stomach" in different studies, and we defined the status as stomach with no evidence of *H. pylori* infection, no inflammation or metaplastic or atrophic changes in the available endoscopic biopsies, and no presence of any gastric lesions on endoscopy. We found that among the 1071 participants with HS, the median value of FsG17 was 1.8 pmol/l (25–75% quartiles, 0.8–3.9 pmol/l). As far as we know, this is the first study to report on the baseline level of FsG17 from a Chinese population, which provides a valuable reference for clinical practice.

We also compared the FsG17 levels between disease groups. Along with the progression from HS, NAS, AS to CS, FsG17 levels increased gradually (1.8, 4.0, 3.8, and 6.0 pmol/l, respectively). Significant differences were observed between HS and all the diseased stomach groups ($p < 0.001$) and between CS and cancer-free stomach ($p < 0.001$), but not between NAS and AS groups ($p = 0.226$). These results suggest that FsG17 could be a potential biomarker to distinguish between the HS and the stomach with different gastric diseases, especially with CS. Several studies have demonstrated that gastrin is an important growth factor that plays a significant role in the carcinogenesis of gastrointestinal malignant tumors [16-20]. Although the mechanism of gastrin on cell proliferation is still unclear, there is accumulating evidence that hypergastrinemia promotes cell proliferation and resistance to cell apoptosis [21], which may contribute to the development of gastric atrophy and remodeling of the gastric mucosa.

Based on the understanding of different FsG17 levels with different gastric histopathological conditions, we further examined the influence of a variety of factors on FsG17 levels. Our data showed that age, smoking status, alcohol consumption, *H. pylori* infection, and predominant lesion site were influencing factors for FsG17 levels in different gastric diseases. FsG17 levels were positively associated with age and were much higher in participants over 60 years compared with those below 60 years in the HS group but not in any of the disease groups.

Currently, few studies have examined the association between sex or age and FsG17 levels. Our previous study showed that FsG17 level was markedly higher in ≥60 years and no significant difference between gender groups, which are similar to the results of present study [22]. In addition, Nie et al. reported greater FsG17 levels among females but no statistical difference between age groups [23]. The reason for the difference might be the difference of the gastric mucosal status of the study population. In the present study, we classified gastric mucosal status according to histopathological evaluation, which is more reliable for the investigation of associations between FsG17 and its potential influencing factors.

To date, most studies, including our own previous study [10], suggest that FsG17 levels are positively associated with *H. pylori* infection [13,24,25]. However, other studies have reported different results. For example, Nie et al. reported that sG17 levels were higher in *H. pylori*-negative participants than in *H. pylori*-positive participants [23], and Cao et al. found that *H. pylori* infection had no influence on sG17 levels in gastric cancer patients [26]. In cancer-free disease groups (NAS and AS), FsG17 levels were much higher among *H. pylori* seronegative patients compared with *H. pylori* seropositive patients, whereas the association was the opposite in patients with gastric cancer. The dynamic trends along disease progression in *H. pylori* seronegative participants were similar to the overall trends. However, no significant differences were observed between any *H. pylori* seropositive participants. Based on the data from the present study, we hypothesize that, in different stages of gastric mucosal lesions, characterized by inflammation, atrophy, and malignancy, FsG17 levels show different trends of change with *H. pylori* infection status. Therefore, it is necessary to clarify the association of *H. pylori* infection with FsG17 levels stratified by gastric disease.

Similar to the findings for *H. pylori*, smoking and drinking had different effects on FsG17 levels in different gastric diseases. The influence of smoking was the most obvious. Smoking is associated with higher gastric acid secretion, which stimulates the vagus nerve and activates the parietal cells to enhance acid output. Derakhshan et al. found that smokers had greater acid secretion than nonsmokers [27]. Wong et al. noted that chronic nicotine administration could lead to increased muscarinic receptor sensitivity, and then elevated basal acid secretion, which decreased gastrin secretion [28]. Additionally, the results from a rat model indicated that nicotine treatment could influence gastrin gene expression in the gastrointestinal tract [29]. The latter study preliminarily discussed the relationship between smoking status and FsG17 levels in different gastric diseases. It is proposed that the linear relationship between the number of cigarettes smoked and FsG17 levels should be further clarified and applied in the evaluation of risk factors and the screening of high gastric cancer risk individuals in the future.

In the present study, corpus-predominant lesions showed higher FsG17 levels compared with antrum-predominant lesions only in the CS group. For the AS

group, although we also found higher FsG17 levels with corpus-predominant lesions, it was not statistically significant. Traditionally, FsG17 levels are considered to reflect mucosal lesions in the gastric antrum because G17 is secreted by G cells in the antrum; however, because of the negative feedback mechanism in the regulation of hydrochloric acid secretion by gastrin, FsG17 levels are also closely related to lesions in the corpus. Many studies have reported that FsG17 levels were higher in atrophic gastritis that was limited to the corpus and lower or the same if the atrophy occurred in both the antrum and the corpus [30-32]. Consistent with these observations, we noted that differences in FsG17 levels between corpus-predominant lesions and antrum-predominant lesions were more significant when mucosal lesions progressed from NAS to AS and to CS. Given the low prevalence (4.9%) of corpus-predominant AS in our study participants, more studies with a larger sample size are needed to verify our findings.

We also evaluated the diagnostic performance of FsG17 levels for discriminating between different gastric diseases. Discriminating between HS versus diseased stomach and cancer-free stomach versus CS is one of the key issues in assessing the risk of serious gastric diseases in clinical practice. Due to cost-effective considerations, the identification of diseased stomach or CS may be helpful in making clinical decisions and rationalizing and optimizing diagnostic, therapeutic, and screening procedures [33,34].

Further, we were able to establish the optimal cut-off FsG17 levels and screening accuracy parameters, such as sensitivity and specificity. As previously reported, sG17, usually in combination with pepsinogens and *H. pylori* antibodies, is applied for the detection of atrophic gastritis and gastric cancer. However, the effectiveness of a screening technique differs significantly at different cut-off values [30,35-37]. The results of the present study demonstrate the potential significance of FsG17 levels in practice. FsG17 could be used to distinguish between the cancer-free stomach and the CS, with higher accuracy for gastric cancer in the corpus. Future research could combine FsG17 with its influencing factors and other serum biomarkers to improve accuracy. Also, since we had a limited number of gastric cancer cases in our screening population, we included hospital-based gastric cancer cases in order to provide a stable estimate of FsG17 levels; future studies with a sufficient sample size of gastric cancer cases are needed to confirm our results.

In conclusion, in this study, we observed an association between FsG17 levels and stomach diseases. FsG17 levels increased gradually from the HS (1.8 pmol/l [25–75% quartiles, 0.8–3.9 pmol/l]) to the AS (3.8 pmol/l [25–75% quartiles, 1.5–8.3 pmol/l]) to the NAS (4.0 pmol/l [25–75% quartiles, 1.4–9.4 pmol/l]) to the CS (6.1 pmol/l [25–75% quartiles, 2.6–15.8 pmol/l]). Age, smoking status, alcohol consumption, and *H. pylori* infection, as well as predominant lesion site were factors that influenced FsG17 levels. The optimal cut-off values of FsG17 was 3.0 pmol/l for discriminating between the healthy and the diseased stomachs and was 10.7 pmol/l for discriminating between the CS and the cancer-free stomach. FsG17 levels, combined with age, gender, and *H. pylori* infection may distinguish between the CS and the cancer-free stomach with higher accuracy. Further studies are needed to investigate the combination of FsG17 with its influencing factors and other serum biomarkers to enhance the clinical utility of FsG17.

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