Achieving Macroscale Liquid Superlubricity Using Lubricant Mixtures of Glycerol and Diols

haitao yu
Qingdao 971 hospital https://orcid.org/0000-0002-6288-4126
Haigang Pang
Qingdao 971 Hospital
Gang Yuan
Qingdao 971 hospital
Dongfang Dong
Qingdao 971 hospital
Ying Lu
Qingdao 971 hospital
Yue Lun
Qingdao 971 hospital
Zhen Li
Qingdao 971 hospital
Qunying Wang
Qingdao 971 Hospital
Wenzhu Dong (wzhdong7@126.com)
Qingdao 971 hospital

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Abstract

Background

We aimed to assess a serological biopsy using five stomach-specific circulating biomarkers pepsinogen I (PGI), PGII, PGI/II ratio, anti- *Helicobacter pylori (H. pylori)* antibody, and gastrin-17 (G-17) for identifying high-risk individuals and predicting risk of developing gastric cancer (GC).

Results

In the cross-sectional analysis, PGII, the PG ratio, G17, anti- *H. pylori* IgG were associated with the presence of CAG, and the five biomarkers combined prediction is more effective than single factor prediction (0.692 vs 0.54, 0.604, 0.616, 0.629).

Conclusion

The combination of pepsinogens, G17 and anti-H. pylori antibodies for serological analysis is helpful to screen CAG high-risk individuals from the general population and recommend that these people should carry out further endoscopy and biopsy.

Introduction

Gastric cancer (GC) is one of the most common cancers worldwide, and nearly half of new cases and deaths in the world occur in China[1]. Chronic atrophic gastritis (CAG) is an extremely important precancerous in the evolution of gastric cancer[2]. Early diagnosis and monitoring of CAG is of great significance for early detection and treatment of gastric cancer. Currently, endoscopic biopsy histology is the gold standard for the diagnosis of chronic atrophic gastritis[3]. However, gastroscopy use is limited by its invasiveness, high costs and an insufficient supply of skilled endoscopists and endoscopy facilities. Therefore, there is an urgent need for a method to identify CAG in the general individuals.

Recent decades, the examination of gastric biomarkers have been used to diagnose CAG non-invasively, including pepsinogen I (PGI), PGII, the PGI/II ratio, anti- *H. pylori* antibodies, and gastrin-17 (G-17)[3-8]. Miki[9] established the ABC method, which combines anti- *H. pylori* antibodies with the measurement of serum PG levels, to identify individuals at high risk for future GC development. Tu[10] *et al* also evaluated a serological biopsy composed of the five stomach-specific circulating biomarkers to stratify individuals' risk of developing GC. However, the practical utility is controversial due to highly varied accuracy in different regions of the world.

Therefore, in order to better understand the relationship between these gastric serological biomarkers and CAG, this study examined the levels of PGI, PGII, the PGI/II ratio, anti- *H. pylori* antibodies, and G-17 in patients with CAG and chronic nonatrophic gastritis (CNAG). The value of these serum biomarkers in the diagnosis of CAG was preliminarily analyzed to provide further clinical evidence for better prediction rule.

Materials And Methods

Study populations

A total of 186 subjects who came to the 971 hospital for a screening gastroscopy as part of a routine health check-up, were prospectively enrolled in this study from January 2020 to October 2020. The subjects were divided into CAG and CNAG according to endoscopic pathology. Exclusion criteria were a history of *H. pylori* eradication, previous gastric surgery, treatment with proton pump inhibitors or H2 blockers within the previous 2 weeks, serious systemic disease, pregnancy, a history of cancer of any type, and those taking anti-secretory or anti-coagulant drugs. A fasting blood sample was obtained from each patient before endoscopy.

Serological measurements and endoscopic and histopathological examinations

Details on the serological measurements and endoscopic and his[1]topathological examination procedures were previously described (18,19). Serum PGI, PGII, and G-17 concentrations in morning fasting blood samples were measured using enzyme-linked immunosorbent assays (ELISAs; Pepsinogen I ELISA; Pepsinogen II ELISA and Gastrin-17 ELISA kit, Snibe Diagnostic, shenzhen, China), serum anti-*H. pylori* IgG were measured using colloidal gold immunochromatography assay (GICA, anti-*H. pylori kit,* HUIAN, shenzhen, China) .

Gastroscopy with sampling of gastric biopsies was defined as the gold standard for definitive diagnosis. Endoscopic biopsies were obtained from the antrum and corpus, all along the greater curvature (one biopsy from both sites). Biopsy specimens were routinely fixed in neutral formalin and processed in paraffin. Tissue sections were stained with HE, Alcian blue and modified Giemsa (*H pylori* stain) methods.

Statistical analyses

SPSS 19.0 was used to carry out statistical analysis. The normal distribution measurement data is expressed as mean±standard deviation, the average between the two groups is compared by t test, and the counting data is expressed by rate or percentage, and the comparison is $\chi 2$ test.

H. pylori serological antibody results was classified as negative and positive. The other biomarkers (PGI, PGII, the PGI/II ratio, G-17) were categorized according to quartiles of their distributions in the study cohort. For the cross-sectional analysis, odds ratios (ORs) with 95% confidence intervals (95% confidence intervals (CIs)) were calculated using logistic regression.

In the risk prediction modeling analysis, receiver operator characteristic curves with corresponding C statistics (area under the curve, AUC) based on logistic models were used to measure the discriminatory performance of combination of predictors where the pathology diagnosis was considered the “gold standard”. A *P* value<0.05 (two-sided) was considered statistically significant.

Results

1. Selected baseline characteristics of the study participants

Selected characteristics of the study participants in the cross-sectional analysis are summarized in Table 1. There was no significant difference in age and sex between the two groups, (P>0.05).

Table 1. Selected baseline characteristics of the study participants

Groups	Cases	Sex(female/male)	Age(years)
CAG	73	25/48	59.96±7.87
CNAG	113	48/65	58.17±6.94
t/χ2		1.26	-1.63
P value		0.26	0.1

2. Cross-sectional associations of gastric biomarkers between CNAG and CAG

As shown in Table 2, the five gastric biomarkers were statistically analyzed between the two groups, in which PGII, the PG ratio, G17, anti- *H. pylori* IgG were statistically significant (P<0.05), while PGI was not statistically significant (P=0.476). There was a dose-response relationship between higher PG II levels or lower PGI/II ratios and the incidence of CAG, and a J-shaped association between G-17 and the incidence of CAG.

Table 2. Cross-sectional associations of gastric biomarkers levels between CNAG and CAG

Biomarkers	CNAG(n=113)	CAG(n=73)	OR(95%CI)	P value
PGI(ng/ml)				
Q1(≤56.97)	29(15.59)	17(9.14)	Reference	0.476
Q2(56.97-73.22)	30(16.13)	16(8.60)	0.91(0.388-2.134)	
Q3(73.22-92.34)	30(16.13)	17(9.14)	0.967(0.416-2.248)	
Q4(>92.34)	24(12.90)	23(12.37)	1.635(0.714-3.741)	
PGII(ng/ml)				
Q1(≤7.0)	34(18.28)	12(6.45)	Reference	0.028
Q2(7.0-10.52)	32(17.20)	15(8.06)	1.328(0.54-3.265)	
Q3(10.52-16.29)	26(13.98)	21(11.29)	2.288(0.955-5.484)	
Q4(>16.29)	21(11.29)	25(13.44)	3.373(1.403-8.11)	
PGI/II ratio				
Q1(≤5.345)	24(12.90)	22(11.83)	Reference	0.03
Q2(5.345-7.11)	23(12.37)	24(12.90)	1.138(0.505-2.568)	
Q3(7.12-9.11)	31(16.67)	16(8.60)	0.563(0.244-1.299)	
Q4(>9.11)	35(18.82)	11(5.91)	0.343(0.141-0.836)	
G17(pmol/L)				
Q1(≤2.85)	37(19.89)	9(4.84)	Reference	0.009
Q2(2.85-5.59)	29(15.59)	18(9.68)	2.552(1.001-6.508)	
Q3(5.6-12)	21(11.29)	25(13.44)	4.894(1.929-12.42)	
Q4(>12)	26(13.98)	21(11.29)	3.321(1.313-8.4)	
Anti-H.pylori IgG				
Negative	74(39.78)	37(19.89)	1.846(1.012-3.367)	0.045
Positive	39(20.97)	36(19.35)		

3. Receiver-operator characteristic curves of five biomarkers for discriminating of CAG

As shown in Table 2, the PG ratio, G17, anti- *H. pylori* IgG are closely related to the occurrence of CAG, and previous studies have shown that PGI is also an important predictor of CAG[10]. Therefore, we propose a prediction model based on the five biomarkers to identify high-risk populations who may suffer from CAG using the cross-sectional data. The five biomarkers combined yielded a C statistic of 0.692 (95%

CI=0.616–0.768). Furthermore, combined prediction is more effective than single factor prediction (0.692 vs 0.54, 0.604, 0.616, 0.629).

Table 3. ROC curves of five biomarkers for discriminating of CAG

Biomarkers	AUC	Standard error	95%CI	P value
PG□	0.54	0.044	0.454-0.627	0.354
PG□	0.604	0.042	0.521-0.686	0.017
PGI/II ratio	0.616	0.043	0.532-0.7	0.007
G-17	0.629	0.041	0.548-0.71	0.003
Five biomarkers	0.692	0.039	0.616-0.768	<0.001

Discussion

Atrophic gastritis is a disease in which appropriate glands of the gastric mucosa are lost and replaced by connective tissue and/or intestinal epithelium (intestinal metaplasia)[11]. It is a precancerous lesion of gastric cancer and will evolve into gastric cancer: from chronic active gastritis to atrophy gastritis, to intestinal metaplasia, to dysplasia, and finally to invasive carcinoma[2]. A retrospective study[12] showed that about 6% of patients with severe gastric mucosal atrophy developed gastric cancer within 5 years. Therefore, it is important to screen out CAG from the general individuals. Gastroscopy combined with histopathological examination is the gold standard for the detection of atrophic gastritis, but the use of endoscopy as a screening test is costly, uncomfortable and does not have good patient's compliance[13-14]. Therefore, the emergence of non-invasive serological detection method makes up for the application of this disease screening in the asymptomatic population.

Pepsinogens are products of differentiated gastric mucosa. There are two isoforms of PG (PG I and PG II) present in serum[15]. PGI is produced by the chief cells of the gastric fundus , whereas PG II is secreted by cells of the entire stomach and duodenum[16-17]. Previous studies have shown that, low PG I level and low PG I/II ratio could predict the occurrence of CAG[18], and low PG I/II ratio also is a marker for predicting GC, meanwhile elevated PGII levels may be associated with GC and precancerous lesions[10]. In the study, we also found that low PG I/II ratio and elevated PGII levels are CAG risk factors ($P<0.05$), but there is no clear correlation between PGI and CAG occurrence ($P=0.476$).

The level of G17 in serum depends on the acidity in the stomach and the number of G cells[19]. Atrophic gastritis in different site may result in variety of G17 concentrations[20]. One study showed that either low or high G17 could leaded to the incidence of gastric cancer[10], and another study showed that individuals with GC had a higher serum level of G-17 than those without[21]. Also some evidences suggested that low G-17 may be related to atrophic gastritis in the stomach antrum, then high serum G-17 may be an indication of atrophic gastritis limited to the stomach fundus/body[22-24]. In our study, we

divided all the subjects into two groups, and compared with non-atrophic gastritis group, higher G-17 was detected in atrophic gastritis group.

Since the discovery of *H. pylori*, many studies have confirmed that it is associated with gastric cancer and precancerous lesions[25-26]. The present study also showed that *H. pylori* infection was correlated with CAG (P=0.045).

In order to screen gastric cancer and its precancerous lesions more effectively, several studies have tried to establish a variety of methods to identify the high-risk individuals by jointly detecting these serological circulating biomarkers, even commercialized[2,9-10]. However, most of the previous studies are carried out in Europe, the diagnostic reliability of this test remains uncertain[14]. So further evidences are needed to enrich these data in order to establish more accurate prediction rule. In our study, we incorporated the five biomarkers into a prediction model, and the results showed that the combined model could provide more accurate prediction results than the single risk factor model (Table 3). This is similar to the previous studies. The deficiency of this study is that the source of the patients in the single center, and the data is relatively insufficient diversity and representativeness, so that expanded sample size, multi-regional, multi-center clinical studies and further external validation of the usefulness of the prediction model for CAG risk assessment is needed.

In conclusion, our findings support that the combination of pepsinogens, G17 and anti-H. pylori antibodies for serological analysis is helpful to screen CAG high-risk individuals from the general population and recommend that these people should carry out further endoscopy and biopsy. This provides useful data for the establishment of accurate prediction rules for chronic atrophic gastritis.

Declarations

Competing interests: The authors have declared that no competing interests exist.

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Ethics approval: The study protocol was approved by the ethics committees of the respective institutions (971LL-2019012 by No.971 Hospital).

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Figures

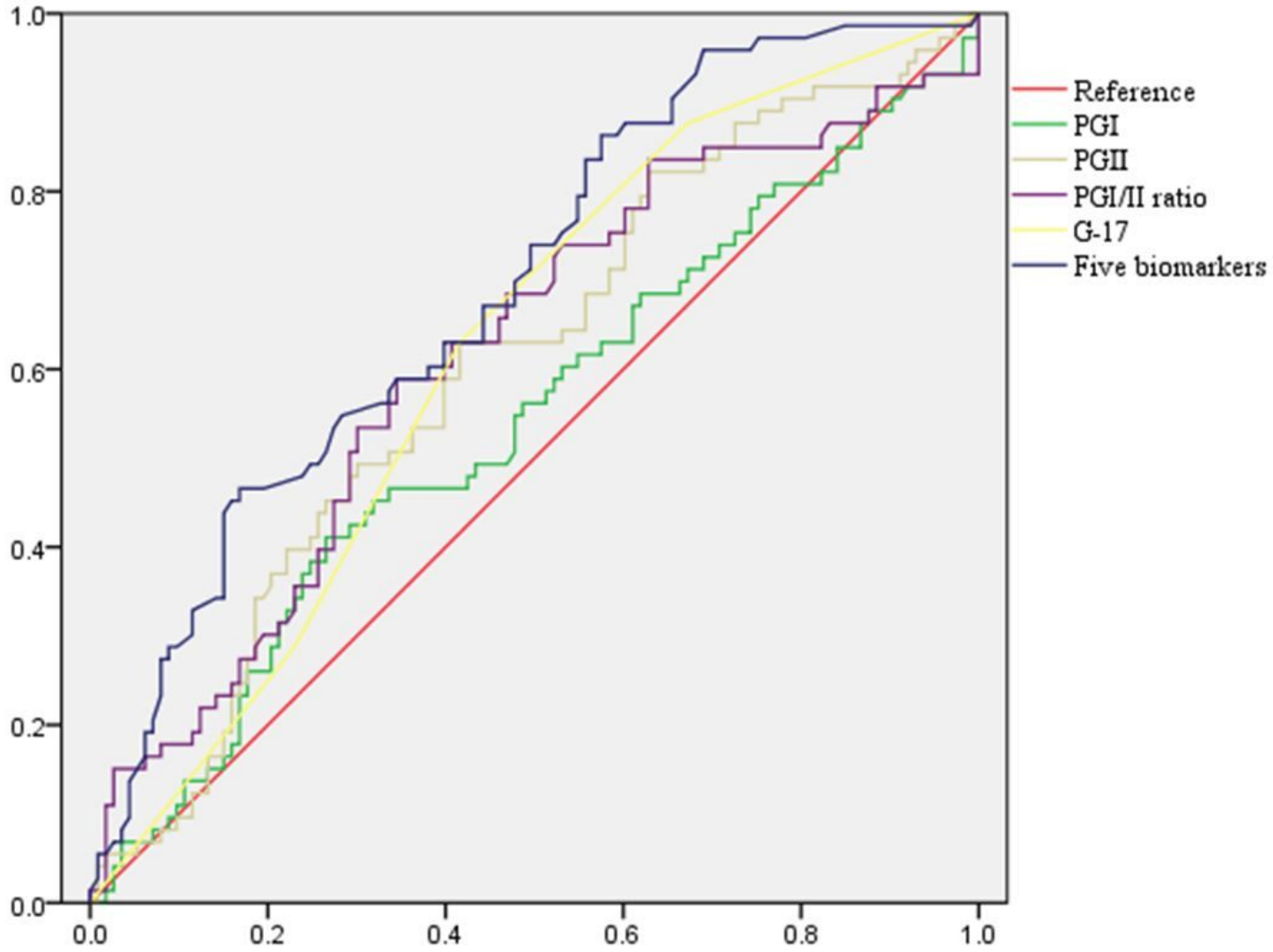

Figure 1

Receiver-operator characteristic curves of PGI, PGII, PGI/II ratio, G-17, and Five biomarkers for chronic atrophic gastritis.