



Serum Pepsinogen, Gastrin-17, and Interleukin-17 as Biomarkers of Helicobacter pylori-Associated Gastric Mucosal Injury

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Abstract

Background: Helicobacter pylori causes progressive gastric mucosal injury, highlighting the need for accurate noninvasive biomarkers reflecting glandular dysfunction and inflammation. **Aims of the study:** This study aimed to evaluate serum pepsinogen, gastrin-17, and interleukin-17 as biomarkers of H. pylori-associated gastric mucosal injury and severity. **Methodology:** This case-control study included 135 participants (90 patients with H. pylori-associated gastric mucosal injury and 45 matched controls) recruited at Al-Habbobi Teaching Hospital during January 2025–April 2026. Patients underwent endoscopy, Sydney-protocol biopsies, histopathology, and rapid urease testing. Fasting serum was stored at -80°C and analyzed in duplicate for PGI, PGII, G-17, and IL-17 using ELISA; the PGI/PGII ratio was calculated. Major gastrointestinal, systemic, pregnancy-related, medication-related, and surgical confounders were excluded. Routine hematological and biochemical tests supported characterization and quality control. **Result:** Groups were demographically comparable (all $P > 0.05$). Among patients, moderate gastritis predominated (41.1%), while active inflammation, atrophy, and intestinal metaplasia occurred in 61.1%, 20.0%, and 15.6%, respectively. Compared with controls, patients had lower PGI and PGI/PGII ratios but higher PGII, G-17, and IL-17 (all $P < 0.001$). Biomarker alterations progressed with histological severity. IL-17 correlated most strongly with severity ($r = 0.711$) and achieved the best individual discrimination ($\text{AUC} = 0.931$). The combined model provided 95.6% sensitivity and 93.3% specificity ($\text{AUC} = 0.972$), supporting complementary diagnostic value for injury. **Conclusions:** Serum PGI, PGII, the PGI/PGII ratio, G-17, and IL-17 effectively reflected H. pylori-associated gastric mucosal injury. IL-17 and the PGI/PGII ratio showed the strongest severity associations, while their combined assessment provided excellent diagnostic accuracy and may support noninvasive patient stratification.

Keyword: Helicobacter pylori; Pepsinogen; Gastrin-17; Interleukin-17; Gastric mucosal injury.

Introduction:

Helicobacter pylori is a Gram-negative, spiral-shaped bacterium which is one of the most common chronic bacterial infections in the world and is a pathogen of gastric mucosa. While the prevalence of its presence has decreased in some parts of the world, about half of the world's population is still infected, with the highest prevalence in developing countries and with socioeconomically disadvantaged groups (Hooi et al., 2017). Infection is usually acquired in childhood and if eradication therapy is not effective can survive for life. *H. pylori* infection has been identified as the main cause of chronic active gastritis, and is closely related to peptic ulcer disease, gastric mucosa-associated lymphoid tissue lymphoma, and gastric adenocarcinoma (Malfertheiner et al., 2022; Sugano et al., 2015).

The severity and clinical consequences of *H. pylori* infection are determined by the interplay of bacterial virulence factors, host immune responses, environmental factors and the site of gastritis. Chronic colonization leads to the development of ulceration and the infiltration of neutrophils, lymphocytes, plasma cells and macrophages into the gastric lamina propria. Chronic non-atrophic gastritis can be followed by a sequence of events known as the Correa cascade, which includes glandular atrophy, intestinal metaplasia, dysplasia and gastric adenocarcinoma in susceptible individuals (Correa, 1992). Diagnosis of inflammation, activity, atrophy and intestinal metaplasia in gastric biopsies continues to be based on histopathology of endoscopic biopsies, e.g. according to the updated Sydney classification and/or the Operative Link on Gastritis Assessment (OLEGA) classification (Rugge et al., 2007). However, endoscopy is invasive, relatively costly and cannot be used for large scale screening or repeated patient surveillance. Thus, gastric mucosal structure and inflammatory activity would be of clinical value to have reliable circulating biomarkers (Dixon et al., 1996).

Proenzymes of pepsin in serum are called serum pepsinogens and are functional and morphological markers of gastric mucosa. Pepsinogen I (PGI) is secreted mainly in the gastric corpus and fundus, while pepsinogen II (PGII) is secreted in the whole stomach and the proximal duodenum. It is important to note that an active inflammation may lead to an increase in PGII, whereas a progressive loss of corpus glands may lead to a decrease in PGI and PGI/PGII ratio. Therefore, reduction of PGI level and PGI/PGII ratio have been suggested as serological markers of corpus atrophy and increased gastric cancer risk (Miki, 2006; Zagari et al., 2017). But the threshold for diagnosis is different depending on the characteristics of the population, the type of assay platform, proton pump inhibitors use and the prevalence and distribution of gastric atrophy (Sipponen et al., 2002; Nasrollahzadeh et al., 2011).

Another possible gastric mucosal function marker is gastrin-17 (G-17) which is produced primarily by antral G cells. It is affected by the integrity of the antral gland, intragastric acidity, fasting status and acid suppressive therapy. A low G-17 level may be a sign of atrophy of the antrum or of increased acid production, while a high concentration may reflect corpus atrophy and hypochlorhydria, which is a result of the loss of negative feedback from acid (Storskrubb et al., 2008). Hence, PGI, PGII, PGI/PGII ratio and G-17 may give complementary information regarding the site and severity of gastric mucosal lesions. However, previous validation studies have shown different diagnostic accuracy and it has been recommended that serological markers be used in addition to, but not as a substitute for, histological assessment (McNicholl et al., 2014; Koivurova et al., 2021).

Immune mediators can also contribute to a more effective identification of active mucosal injury, in addition to the glandular biomarkers. Interleukin-17A (IL-17) is the main cytokine secreted by T-helper-17 cells, and has recently been identified as a key mediator of *H. pylori*-induced inflammation. The expression of gastric IL-17 is upregulated by infection and is able to activate epithelial cells to induce the production of IL-8 and other chemokines, leading to recruitment of neutrophils and maintenance of mucosal inflammation (Mizuno et al., 2005). The IL-23/IL-17 axis is involved in the increasing and sustaining of the Th17 response in infected gastric tissue (Caruso et al., 2008). Furthermore, *H. pylori*-activated dendritic cells are able to produce IL-17, both in an IL-1 β -dependent and an IL-23-dependent

manner, and virulence factors linked to the Cag pathogenicity island may enhance this response (Khamri et al., 2010). Experimental and human data also correlate the rise in IL-17 with an influx of neutrophils and greater gastric disease (Shiomi et al., 2008; Serrano et al., 2013).

Although these individual markers have been shown to be associated with *H. pylori* infection, very little information exists about how these markers are associated together with histologically scored *H. pylori*-induced mucosal damage. The use of IL-17 with functional gastric markers (pepsinogens and G-17) might enhance the ability to differentiate infection from gastric mucosal damage of clinical significance. The present study was therefore designed to assess the levels of serum PGI, PGII, PGI/PGII ratio, G-17 and IL-17 in the patients with *H. pylori* infection and their relations with presence and histopathological severity of gastric mucosal damage.

Methodology:

This case-control study was carried out in the Gastroenterology and Endoscopy Unit, Thi-Qar, Iraq from January 2025 to April 2026. A total of 135 participants (90 patients with confirmed gastric mucosal injury due to *H. pylori* infection and 45 apparently healthy individuals for age and sex) were enrolled in the study. The patients with dyspeptic symptoms had an upper gastrointestinal endoscopy performed and gastric biopsy was taken from both antrum and corpus following the revised Sydney protocol. Histopathological examination along with rapid urease test confirmed the infection of *H. pylori*. An experienced, blinded gastrointestinal pathologist classified gastric mucosal injury as mild, moderate, or severe. Those who had undergone gastric surgery or gastric malignancy, autoimmune gastritis, inflammatory bowel disease, chronic liver/kidney disease, recent gastrointestinal bleeding, pregnancy, or had taken antibiotics, proton pump inhibitors, bismuth compounds, corticosteroids, or immunosuppressive agents within the previous four weeks were excluded. The overnight fasted venous blood samples were collected from each participant, allowed to clot, centrifuged for 10 minutes at 3,000 rpm and the separated serum was kept at -80°C until analyzed. Concentrations of serum pepsinogen I (PGI), pepsinogen II (PGII), gastrin-17 (G-17) and interleukin-17 (IL-17) were measured by commercially available sandwich enzyme-linked immunosorbent assay (ELISA) kits, following the manufacturer's instructions. A PGI/PGII ratio was subsequently determined as another measure of gastric mucosal integrity. Complete blood count, C-reactive protein and basic biochemical investigations were performed in a routine manner to describe the study population and rule out important systemic disease. All laboratory analyses were done in duplicate by experienced technician who had no knowledge of the clinical and histopathological data and adequate quality control measures were put in place to ensure analytical accuracy and reproducibility throughout the study.

Statistical analysis:

IBM SPSS Statistics 27.0 (IBM Corp., Armonk, NY, USA) and MedCalc Statistical Software 22.0 (MedCalc Software Ltd, Ostend, Belgium) were used for statistical analysis. The normality of the data was tested by the Shapiro-Wilk test. Data are presented as mean $\pm$ standard deviation (SD) for normally distributed data, median (interquartile range) for non-normally distributed data, and as frequencies and percentages for categorical data. Independent-samples t-test and Mann-Whitney U test were used, as appropriate, to compare between two groups. Multiple group comparisons were done by one-way analysis of variance (ANOVA) with Tukey's post hoc test or by Kruskal-Wallis test followed by Dunn's multiple-comparison correction. Pearson's or Spearman's correlation coefficients were used to assess associations between serum biomarkers and the degree of histopathological severity, depending on the distribution of the data. Multivariable logistic regression analysis was used to determine the independent factors associated with *Helicobacter pylori*-related gastric mucosal injury, while adjusting for potential confounding factors. Multiple linear regression analysis was also performed to identify factors associated with the severity scores of the histopathology. The diagnostic usefulness of each biomarker and their

combined predictive model was assessed using receiver operating characteristic (ROC) curve analysis, and the area under the curve (AUC), 95% confidence intervals (CI), optimal cut-off values, sensitivity, specificity, positive (PPV) and negative (NPV) predictive value were calculated. All statistical tests were performed two-tailed and a P-value <0.05 was deemed statistically significant.

Ethical approval:

The Research Ethics Committee of the College of Medicine, University of Thi-Qar, Iraq, has reviewed and approved the study protocol according to ethical principles of the Declaration of Helsinki (2013 revision). All participants gave written informed consent before enrollment in the study, in which the aims and methods were explained in detail. All of the above was done voluntarily, and the participants were told they could withdraw from the study at any time without it impacting their medical care. Data collected were anonymized and treated with confidentiality throughout the study, to ensure participants' privacy.

Results:

Comparison of age, sex, BMI, smoking, NSAID use, and family history between the study groups

Demographic and clinical parameters were similar in the patients with gastric mucosal injury and healthy controls. No statistically significant differences were observed in age (45.6 ± 11.4 vs. 43.8 ± 10.9 years; $P = 0.364$), male sex (55.6% vs. 53.3%; $P = 0.801$), or BMI (25.9 ± 3.8 vs. 25.2 ± 3.4 kg/m²; $P = 0.281$). In contrast, current smoking, family history of gastric disease and NSAID use did not differ significantly between patients and controls (all $P > 0.05$). These results suggest good baseline comparability and suggest that the subsequent biomarker comparisons were not greatly affected by demographic or clinical imbalances.

Table1: Baseline Demographic and Clinical Characteristics of Patients with Gastric Mucosal Injury and Healthy Controls

Variable	Controls (n=45)	Patients (n=90)	P-value
Age (years)	43.8 ± 10.9	45.6 ± 11.4	0.364
Male, n (%)	24 (53.3)	50 (55.6)	0.801
BMI (kg/m ²)	25.2 ± 3.4	25.9 ± 3.8	0.281
Current smoker, n (%)	13 (28.9)	31 (34.4)	0.522
NSAID use, n (%)	6 (13.3)	15 (16.7)	0.609
Family history of gastric disease	5 (11.1)	13 (14.4)	0.597

Distribution of gastritis severity, active inflammation, premalignant lesions, and bacterial density in the patient group

In 37 patients (41.1%) moderate chronic gastritis was the most common histopathological category, mild gastritis in 28 patients (31.1%) and severe gastritis in 25 patients (27.8%). The number of patients with active inflammation was 55 (61.1%) of the total, showing that there was considerable active mucosal inflammatory activity. Eighteen (20.0%) patients were diagnosed with atrophic gastritis and 14 (15.6%) patients with intestinal metaplasia. In terms of density of *H. pylori*, 39 patients (43.3%) had a moderate density, 26 (28.9%) a mild density, and 25 (27.8%) a severe density. In general, the results show a wide range of mucosal damage, with moderate gastritis and active inflammation being predominant histopathological changes.

Table 2: Endoscopic and Histopathological Characteristics of Helicobacter pylori-Associated Gastric Mucosal Injury among Patients

Variable	n (%)
Mild chronic gastritis	28 (31.1)
Moderate chronic gastritis	37 (41.1)

Severe chronic gastritis	25 (27.8)
Active inflammation	55 (61.1)
Intestinal metaplasia	14 (15.6)
Atrophic gastritis	18 (20.0)
H. pylori density Mild	26 (28.9)
Moderate	39 (43.3)
Severe	25 (27.8)

Comparative assessment of pepsinogens, PGI/PGII ratio, gastrin-17, and IL-17 concentrations between the study groups

Patients exhibited significantly lower serum PGI concentrations than controls (61.5 ± 18.4 vs. 81.9 ± 15.8 ng/mL; $P < 0.001$), whereas PGII was significantly elevated (18.6 ± 5.1 vs. 10.7 ± 2.9 ng/mL; $P < 0.001$). Consequently, the PGI/PGII ratio was markedly reduced in patients (3.45 ± 1.14 vs. 7.72 ± 1.63 ; $P < 0.001$). Serum G-17 and IL-17 concentrations were also significantly higher among patients than controls (9.61 ± 3.25 vs. 5.42 ± 1.94 pmol/L and 28.7 ± 8.6 vs. 12.5 ± 4.8 pg/mL, respectively; both $P < 0.001$). The results suggest that there is dual gastric glandular dysfunction and increased inflammatory activation in patients with gastric mucosal damage.

Table 3: Serum Gastric Functional and Inflammatory Biomarkers in Patients with Mucosal Injury and Healthy Controls

Biomarker	Controls	Patients	P-value
Pepsinogen I (ng/mL)	81.9 ± 15.8	61.5 ± 18.4	<0.001
Pepsinogen II (ng/mL)	10.7 ± 2.9	18.6 ± 5.1	<0.001
PGI/PGII ratio	7.72 ± 1.63	3.45 ± 1.14	<0.001
Gastrin-17 (pmol/L)	5.42 ± 1.94	9.61 ± 3.25	<0.001
IL-17 (pg/mL)	12.5 ± 4.8	28.7 ± 8.6	<0.001

Severity-dependent alterations in pepsinogens, PGI/PGII ratio, gastrin-17, and IL-17 among patients with gastritis

Serum biomarker levels have increased in a linear fashion as the histopathological severity has increased. PGI declined from 68.4 ± 16.1 in mild gastritis to 60.8 ± 14.8 in moderate and 49.7 ± 13.2 in severe disease, whereas PGII increased from 15.6 ± 4.1 to 18.4 ± 4.3 and 22.7 ± 5.4 , respectively. Consequently, the PGI/PGII ratio decreased markedly across the severity categories (4.42 ± 1.12 , 3.28 ± 0.94 , and 2.34 ± 0.71). In contrast, G-17 increased from 7.3 ± 2.4 to 12.6 ± 3.3 , while IL-17 rose from 20.4 ± 5.8 to 38.9 ± 7.8 . All trends showed statistical significance ($P < 0.001$), indicating a progressive decrease in gastric function and inflammatory activation according to increasing mucosal injury.

Table 4: Serum Biomarker Profiles According to the Histopathological Severity of Gastric Mucosal Injury

Marker	Mild	Moderate	Severe	P-value
PGI	68.4 ± 16.1	60.8 ± 14.8	49.7 ± 13.2	<0.001
PGII	15.6 ± 4.1	18.4 ± 4.3	22.7 ± 5.4	<0.001
PGI/PGII ratio	4.42 ± 1.12	3.28 ± 0.94	2.34 ± 0.71	<0.001
Gastrin-17	7.3 ± 2.4	9.8 ± 2.9	12.6 ± 3.3	<0.001
IL-17	20.4 ± 5.8	28.5 ± 6.2	38.9 ± 7.8	<0.001

Direction and strength of associations between gastric functional markers, IL-17, and increasing histopathological severity

All evaluated biomarkers were significant with respect to histopathological severity. There was a moderate inverse correlation between PGI and increasing mucosal injury ($r = -0.596$; $P < 0.001$), and a moderate positive correlation between PGII and increasing mucosal injury ($r = 0.548$; $P < 0.001$). The inverse association between PGI and PGII was the most significant ($r = -0.689$; $P < 0.001$). G-17 was positively correlated with disease severity ($r = 0.621$; $P < 0.001$) and IL-17 had the highest overall positive correlation ($r = 0.711$; $P < 0.001$). These results suggest that progressive mucosal damage is associated with progressive decrease in the functional indexes of the stomach and a progressive increase in secretory and inflammatory activity.

Table 5: Correlations Between Serum Biomarkers and Histopathological Severity of Gastric Mucosal Injury

Variable	r	P-value
PGI	-0.596	<0.001
PGII	0.548	<0.001
PGI/PGII ratio	-0.689	<0.001
Gastrin-17	0.621	<0.001
IL-17	0.711	<0.001

Adjusted associations of pepsinogens, PGI/PGII ratio, gastrin-17, and IL-17 with the likelihood of mucosal injury

After multivariate logistic regression, all of the biomarkers assessed were found to be significant factors related to gastric mucosal injury. Each 1-ng/mL increase in PGI was associated with 5% lower adjusted odds of injury (aOR = 0.95, 95% CI: 0.92–0.98; $P = 0.002$), whereas each 1-ng/mL increase in PGII was associated with 17% higher odds (aOR = 1.17, 95% CI: 1.08–1.28; $P < 0.001$). A one-unit increase in the PGI/PGII ratio corresponded to 52% lower odds (aOR = 0.48, 95% CI: 0.31–0.73; $P < 0.001$). G-17 and IL-17, on the other hand, were associated with 26% and 18% increased adjusted odds per unit increase, respectively. These results corroborate the independent contributions of functional derangements of the stomach and inflammatory activation to the development of mucosal damage.

Table 6: Multivariable Logistic Regression of Biomarkers Associated with Gastric Mucosal Injury

Variable	Adjusted OR	95% CI	P-value
PGI	0.95	0.92–0.98	0.002
PGII	1.17	1.08–1.28	<0.001
PGI/PGII ratio	0.48	0.31–0.73	<0.001
Gastrin-17	1.26	1.10–1.45	0.001
IL-17	1.18	1.09–1.29	<0.001

ROC-derived cut-offs, sensitivity, and specificity of individual biomarkers and the combined diagnostic model

The diagnostic performance of PGI and PGII was good (AUC 0.818 and 0.845, respectively) with optimal cut-off concentrations of ≤ 69.5 ng/mL for PGI and ≥ 14.8 ng/mL for PGII, respectively. G-17 had very good discrimination (AUC = 0.889), 86.7% sensitivity and 82.2% specificity at ≥ 7.20 pmol/L. PGI/PGII ratio had excellent accuracy (AUC = 0.914) and IL-17 was the strongest single marker (AUC = 0.931) with 91.1% sensitivity and 88.9% specificity at cutoff ≥ 20.5 pg/mL. The gastric functional and inflammatory markers with the combined model yielded the highest diagnostic performance (AUC = 0.972), with 95.6% sensitivity and 93.3% specificity, suggesting that the combination of gastric functional and inflammatory markers significantly enhances the ability of detecting mucosal injury.

Table 7: Diagnostic Performance of Serum Biomarkers for Detecting Helicobacter pylori-Associated Gastric Mucosal Injury

Marker	AUC	95% CI	Cut-off	Sensitivity	Specificity
PGI	0.818	0.746–0.884	≤ 69.5	77.8%	75.6%
PGII	0.845	0.777–0.901	≥ 14.8	81.1%	77.8%
PGI/PGII ratio	0.914	0.861–0.959	≤ 4.60	88.9%	86.7%
Gastrin-17	0.889	0.827–0.938	≥ 7.20	86.7%	82.2%
IL-17	0.931	0.883–0.972	≥ 20.5	91.1%	88.9%
Combined model	0.972	0.944–0.992	—	95.6%	93.3%

Independent contributions of gastric functional and inflammatory biomarkers to variation in the histopathological severity score

All the evaluated markers were found to be independent predictors of histopathological severity by multiple linear regression. PGI was inversely associated with severity ($\beta = -0.281$; standardized $\beta = -0.292$; $P < 0.001$), whereas PGII showed a positive association ($\beta = 0.214$; standardized $\beta = 0.231$; $P = 0.001$). The PGI/PGII ratio was a strong inverse predictor ($\beta = -0.337$; standardized $\beta = -0.348$; $P < 0.001$), while G-17 independently increased with severity ($\beta = 0.258$; standardized $\beta = 0.249$; $P < 0.001$). The best independent predictor was IL-17 with the highest standardized coefficient ($\beta = 0.416$; standardized $\beta = 0.438$; $t = 7.16$; $P < 0.001$). These results suggest that inflammatory activation and loss of gastric functional integrity are key factors in exacerbating gastric mucosal damage.

Table 8: Multiple Linear Regression Analysis of Biomarkers Predicting Histopathological Severity of Gastric Mucosal Injury

Variable	β	Standard Error	Standardized β	t	P-value
PGI	-0.281	0.052	-0.292	-5.37	<0.001
PGII	0.214	0.061	0.231	3.51	0.001
PGI/PGII ratio	-0.337	0.074	-0.348	-4.56	<0.001
Gastrin-17	0.258	0.069	0.249	3.74	<0.001
IL-17	0.416	0.058	0.438	7.16	<0.001

Discussion:

The present study showed that there is a correlation between the changes of the gastric functional and inflammatory biomarkers in H pylori-associated gastric mucosal injury patients. Patients had significantly increased pepsinogen II (PGII), gastrin-17 (G-17) and interleukin-17 (IL-17) levels and decreased pepsinogen I (PGI) and PGI/PGII ratio. The changes were increasingly marked with increasing severity of the histopathology. In addition, together the biomarker model was the best discriminator of mucosal injury compared to any individual biomarker, and IL-17 and the PGI/PGII ratio had the strongest associations with mucosal injury.

Demographic and clinical features of the patients and controls in the present study were similar (Table 1). The age, sex, BMI, smoking habits, NSAID use and gastric disease history were not significantly different between the groups. This comparability decreases the likelihood that the differences observed in the biomarkers were due to a baseline difference rather than the damage to the mucosa that is caused by H. pylori. This matching is important especially because of variability in pepsinogen levels by age, sex, smoking, renal function and acid suppressive drugs. However, other factors such as proton-pump inhibitor use, diet, and bacterial virulence and infection duration should be kept in mind.

Histopathological data in Table 2 revealed that the most common type of gastritis was moderate chronic gastritis followed by mild and severe gastritis. Active inflammation was identified in 61.1% of patients suggesting most of the patients had active bacterial injury from neutrophils rather than passive bacterial colonization. Twenty percent of patients were found to have atrophic gastritis and 15.6% of patients were found to have intestinal metaplasia. These results suggest that a significant fraction had developed from non-atrophic inflammation to structural damage of the glands and mucosal abnormalities that are precursors to development of malignancy. The presence of gastric atrophy and intestinal metaplasia is now deemed to be important in gastric carcinogenesis and risk stratification based on their severity and extent is recommended (Shah et al., 2021; Pimentel-Nunes et al., 2019).

As shown in Table 3, serum PGI level was significantly reduced in the patients compared to the controls while PGII was significantly increased in the patients. PGI is secreted mainly by chief and mucous-neck cells in the corpus and fundus, so that progressive damage to these cells or their atrophy will decrease the blood level of PGI. In contrast, PGII is synthesized in a larger area of the stomach and proximal duodenum, and is generally elevated with active mucosal inflammation. Therefore, patients with a very low PGI/PGII ratio have an overall decrease in the amount of PGI/PGII, which is due to the decrease in corpus gland and inflammatory stimulation.

The results herein are consistent with those of Zhou et al. who found increased levels of PGII and G-17 and decreased PGI/PGII ratio in *H. pylori*-positive individuals (Zhou et al., 2022). In addition, Bang et al. conducted a systematic review and meta-analysis of the accuracy of serum pepsinogen testing for the diagnosis of chronic atrophic gastritis and gastric neoplasia that demonstrated that the accuracy of the testing ranged by population and assay thresholds, but was clinically useful (Bang et al., 2019). Likewise, Dondov et al. found the ratios of PGI to PGII and PGI to PGI+PGII, which were significantly decreased in patients with atrophic gastritis and gastric cancer, were better discriminators than PGI alone (Dondov et al., 2022).

The results in Table 4 showed a gradual increase in PGI as the severity of the mucosal injury increased, but PGII increased with severity of the mucosal injury. As such, the PGI/PGII ratio was found to be lower for severe injury compared with the mild injury (4.42 compared to 2.34). The negative correlation between histological severity and PGI as well as PGI/PGII ratio, while the positive correlation with PGII, were confirmed by the correlation analysis in Table 5. The PGI/PGII ratio below 3 was also correlated with an increase in gastric precursor lesions by ninefold by Sánchez-López et al. (Sánchez-López et al., 2024). Another indication for the usefulness of the PGI/PGII ratio was the finding of Ye et al. that it is a good predictor of active and *H. pylori*-associated gastritis (Ye et al., 2024).

The decrease in PGI noted in the current study is in contrast to the results of Zhou et al. who noted the higher the urea-breath-test, the higher the PGI concentration. The difference could be due to differences in disease stages. The early non-atrophic infection might lead to increased mucosal permeability and release of both PGI and PGII as a result of inflammation. In severe corpus injury, however, the loss of chief and mucous-neck cells causes a decrease in PGI production and PGII may continue to be high due to continued inflammatory stimulation. The number of individuals with histologically confirmed mucosal damage (atrophy and intestinal metaplasia) was greater in the current study than in the study by Zhou et al., which included a larger number of people with infection, but no definite diagnosis of glandular atrophy. Inconsistency may also be due to ethnic differences, densities of bacteria, distribution of gastritis, suppression of acid and differences in assays (White & Banks, 2022).

There was a progressive increase in serum G-17 from mild to severe mucosal injury and this value was significantly higher in patients. G-17 is secreted mainly by antral G cells, and is controlled by gastric acidity. If the gastritis or atrophy is of the corpus-dominant type, then acid production is decreased and this will not provide the normal negative feedback on the G cells, leading to a compensatory increase in gastrin production (hypergastrinemia). So the higher G-17 seen in this study could be due to a problem with the corpus acid secretory function. Combining G-17 with pepsinogens could be useful to identify

people with premalignant gastric mucosal alterations, White and Banks noted (Rugge et al., 2021). Rugge et al. further pointed out the influence of the topography of the gastritis, glandular atrophy, and functional alterations in the gastric secretion (Rugge et al., 2021).

Both the positive correlation of G-17 with histopathological severity and its association with progressive functional impairment support the potential use of G-17 as a marker of progressive functional impairment. However, results from the G-17 have not been reproduced in other studies. Dondov et al. compared the G-17 in the control, atrophic gastritis and gastric cancer groups, and concluded no significant difference was observed; however, the G-17 in models showed some improvement in diagnosis of atrophy (Dixon et al., 2019). Sánchez-López et al. also found poor correlation between the serological biomarkers classifications and histopathology (Sánchez-López et al., 2024). The differences could be the result of the site of the atrophy. Hypochlorhydria may cause the G-cells to decrease, which in turn could cause a decrease in the G-17, and the atrophy of the corpus could increase. The grouping of antral, corpus and multifocal gastritis may thus make it difficult to detect the location-specific effects. Other conditions, such as, but not limited to, the status of the patient's fasting, and use of proton pump inhibitors, and autoimmune gastritis, can affect circulating G-17.

Most notable inflammatory markers were the high levels of IL-17 in patients. It increased with severity of injury from 20.4pg/mL (mild injury) to 38.9pg/mL (severe injury) and was most strongly correlated with the histopathological severity. The production of IL-17 is primarily by activated Th17 cells and the stimulation of gastric epithelial expression of IL-8 and other chemokines. These mediators promote neutrophil recruitment and play a role in oxidative stress, gastric epithelia disruption and chronic gastric inflammation. Dixon et al. referred to the dual role of Th17 responses in *H. pylori* infection: protective (anti-microbial) and inflammatory (tissue injuring) activities (Dixon et al., 2019). The role of the IL-23/IL-17 axis in neutrophilic inflammation and gastrointestinal mucosal damage was also highlighted by Dewayani et al (Dewayani et al., 2021).

Current findings are supported by Bagheri et al. who reported higher level of Th17 activity and expression level of IL-17A in PUD patients with *H. pylori* infection compared with those with uncomplicated gastritis (Bagheri et al., 2018). This implies that hyperactivity of IL-17 could go along with more severe gastric pathology. Kang et al. also showed that gastric carcinogenic effect of *H. pylori* was mediated by inflammatory and oxidative pathways activated by the IL-17A receptor (IL-17RC) (Kang et al., 2023). Thus, the increasing levels of serum IL-17 with increasing severity groups might be the evidence of a biologically active pathway whereby the continued infection leads to the recruitment of immune cells, damage to the epithelium, and finally to premalignant progression.

Contrary to this, recent experiments indicate that the role of IL-17 signaling is not exclusive and pathogenic. Brackman et al. showed increased inflammation in the gastric mucosa, lymphoid follicle formation, decrease in mucin production and changes in the mucosa barrier function after *H. pylori* infection in IL-17 receptor A deficient mice (Brackman et al., 2024). The same research group then demonstrated that, in the context of epithelial IL-17RA signaling, excessive inflammatory response and maintenance of gastric epithelial homeostasis were prevented (Brackman et al., 2024). More recent studies also suggested that the normal activation of IL-17 could also be protective against *H. pylori*-induced gastric carcinogenesis in susceptible models (Brackman et al., 2024).

The seemingly opposing observations might indicate context dependent function of the IL-17 pathway. Regulatory IL-17 signaling may be protective against infection, facilitate immunoglobulin secretion, mediate epithelial repair, and promote barrier integrity. On the other hand, chronic or high levels of IL-17 can promote recruitment of neutrophils to promote ongoing tissue damage. Thus, higher IL-17 levels in the serum should be seen as markers of immune stimulation and disease severity, and not necessarily as markers of general harmful effects of IL-17. Other mediators that have been shown to be induced during infection (e.g., extracellular-matrix regulatory proteins, barrier modifying proteins) can further impact the association between bacterial colonization and mucosal inflammation (Xie et al., 2024).

Multivariable logistic regression analysis presented in Table 6 indicated that PGI and PGI/PGII ratio were inversely related to gastric mucosal injury whereas PGII, G-17 and IL-17 were positively independent factors for gastric mucosal injury. An increase of one unit of IL-17 corresponded with a 18% increase in the adjusted odds of mucosal injury and a decrease of one unit of PGI/PGII corresponded with a decrease in the adjusted odds of mucosal injury of approximately 52%. The results are in line with the complementary role of inflammatory and gastric function biomarkers (Xie et al., 2024).

But PGI and PGII are mathematically and biologically related with each other and PGI/PGII ratio. When all three are modeled in the same regression, there can be some multicollinearity in the model, and unstable estimates of the adjusted parameters. The variance inflation factors and tolerance values should thus be looked at. The two models that would be preferable for publication would be: a) a model with PGI and PGII in the model, and a b) a model with the ratio of PGI/PGII but without PGI and PGII as separate variables. The other factors that may be considered as potential confounders should also be included, such as age, sex, BMI, smoking, and use of proton-pump inhibitors or NSAIDs (White & Banks, 2022).

The research outcomes for PGI, PGII and G-17 showed good diagnostic performance of the ROCs in these cases and very good in the case of G-17. The PGI/PGII ratio and IL-17 were excellent discrimination with IL-17 having the highest individual AUC. The overall model achieved an AUC of 0.972, and had a sensitivity of 95.6% and specificity of 93.3%. This improvement is biologically logical as the markers included are different components of mucosal injury, which are PGI (corpus gland integrity), PGII (inflammatory stimulation), G-17 (acid-secretory feedback), and IL-17 (immune-mediated inflammation) (Caruso et al., 2008).

However, the overall diagnostic accuracy is greater than the external biomarker studies that have been reported. This difference could be due to the comparison of patients with healthy controls; however, in patients that are actually in clinical practice, there are symptomatic patients with other gastric pathologies. Keeping the same dataset for deriving and evaluating cut-offs also can lead to optimism and overestimate accuracy. Therefore, internal validation, calibration analysis and evaluation of the combined model in an independent cohort is needed before the combined model can be used in a clinical setting (Bang et al., 2019).

Conclusion:

In conclusion, the serum levels of PGI, PGII, the PGI/PGII ratio, G-17, and IL-17 seem to be complementary with each other in providing information about gastric mucosal injury caused by *H. pylori*. IL-17 and the PGI/PGII ratio were the best single variables and a combination of these three with PGI/PGII, PGI and PGII enhanced discriminatory power. These biomarkers could, however, be used as a tool to stratify individuals for risk and not as a substitute for endoscopy and histopathology. Validation by multiple centers involving symptomatic disease controls, and standardized documentation of location of gastritis, use of proton-pump inhibitors, virulence factors of bacteria and gastric atrophy, is needed.

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