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Serum Interleukin-8, High-Sensitivity C-Reactive Protein and Gastrin-17 in Helicobacter Pylori-Positive Dyspepsia: A Cross-Sectional Case–Control Study from Al-Najaf, Iraq

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Abstract

Background: Helicobacter pylori (H. pylori) infection contributes to mucosal and systemic inflammation in dyspeptic patients. We aimed to characterize serum interleukin-8 (IL-8), high-sensitivity C-reactive protein (hs-CRP) and Gastrin-17 (G-17) in relation to H. pylori stool antigen, and to evaluate their combined diagnostic value, in Iraqi adults with dyspepsia.

Methodology: This cross-sectional case–control study enrolled 170 adults at the Digestive Diseases Centre, Al-Najaf Al-Ashraf, between October 2025 and May 2026: H. pylori-positive dyspepsia (n = 60), H. pylori-negative dyspepsia (n = 60), and healthy controls (n = 50). H. pylori was detected by stool-antigen ELISA. Serum IL-8, hs-CRP, G-17, pepsinogen I (PG-I) and II (PG-II) were quantified by ELISA. Group comparisons, Spearman correlation, multivariable linear regression, and ROC analysis (DeLong test) were performed.

Results: H. pylori-positive participants exhibited significantly higher IL-8 (71.4 ± 20.9 pg/mL), hs-CRP (median 8.0 mg/L), G-17 (14.1 pmol/L) and PG-II, and a lower PG-I/PG-II ratio, than H. pylori-negative dyspepsia and controls (all $p < 0.001$). Stool-antigen optical density correlated with IL-8 ($\rho = 0.490$, $p < 0.001$). After adjustment for age, sex, BMI, smoking and NSAID use, H. pylori positivity independently predicted IL-8 ($\beta = 21.34$), $\log_{10}$ hs-CRP ($\beta = 0.51$) and $\log_{10}$ G-17 ($\beta = 0.18$). A combined biomarker panel achieved an AUC of 0.947 (95% CI 0.905–0.989).

Conclusion: Serum IL-8, hs-CRP and G-17 are coordinately elevated in H. pylori-positive dyspepsia and, in combination, show promising diagnostic performance that warrants prospective external validation.

الإنترلوكين-8 المصلي والبروتين المتفاعل C عالي الحساسية والغاسترين-17 في عسر الهضم الإيجابي للملوية البوابية: دراسة مقطعية حالة–شاهد من النجف، العراق

هديل على حسين وحوراء ناصر جعفر رفيش

الخلاصة

المقدمة

تُسهم عدوى الملوية البوابية (Helicobacter pylori) في إحداث التهاب مخاطي وجهازي لدى مرضى عسر الهضم. هدفت هذه الدراسة إلى توصيف مستويات الإنترلوكين-8 (IL-8) والبروتين المتفاعل C عالي الحساسية (hs-CRP) والغاسترين-17 (G-17) في المصل بالعلاقة مع مستضد الملوية البوابية في البراز، وتقييم القيمة التشخيصية المجتمعة لهذه المؤشرات في البالغين العراقيين المصابين بعسر الهضم.

المرضى وطرق العمل

دراسة مقطعية حالة–شاهد شملت 170 بالغًا في مركز أمراض الجهاز الهضمي بمدينة الصدر الطبية في النجف الأشرف، خلال الفترة من تشرين الأول 2025 إلى أيار 2026: 60 مريضًا بعسر الهضم إيجابي الملوية البوابية، و60 مريضًا بعسر الهضم سلبي الملوية البوابية، و50 من الأصحاء كمجموعة ضابطة. كُشفت الملوية البوابية بواسطة فحص مستضد البراز بطريقة الإليزا. قِيست تراكيز IL-8 و hs-CRP و G-17 والبيبسينوجين I (PG-I) والبيبسينوجين II (PG-II) في المصل بالإليزا. أُجريت المقارنات بين المجموعات وارتباطات سبيرمان وانحدار خطي متعدد المتغيرات وتحليل منحنى ROC (اختبار ديلونغ).

النتائج

أظهر المشاركون إيجابيو الملوية البوابية ارتفاعًا معنويًا في IL-8 (71.4 ± 20.9 بيكوغرام/مل) و hs-CRP (الوسيط 8.0 ملغم/لتر) و G-17 (14.1 بيكومول/لتر) و PG-II، مع انخفاض نسبة PG-I/PG-II، مقارنة بالمجموعتين الأخريين (جميعها $p < 0.001$). ارتبطت الكثافة البصرية لمستضد البراز إيجابيًا بـ IL-8 ($\rho = 0.490$، $p < 0.001$). وبعد تعديل العمر والجنس ومؤشر كتلة الجسم والتدخين واستخدام مضادات الالتهاب اللاستيرويدية، تنبأت إيجابية الملوية البوابية باستقلالية بمستويات IL-8 ($\beta = 21.34$) و hs-CRP اللوغاريتمي ($\beta = 0.51$) و G-17 اللوغاريتمي ($\beta = 0.18$). حقّقت لوحة المؤشرات الحيوية المجتمعة AUC قيمته 0.947 (مجال الثقة 95% 0.905–0.989).

الاستنتاج

ترتفع مستويات IL-8 و hs-CRP و G-17 في المصل بصورة متّسقة لدى مرضى عسر الهضم إيجابيي الملوية البوابية، وتُظهر هذه المؤشرات مجتمعةً أداءً تشخيصيًا واعدًا يستحق التحقق المستقبلي الخارجي.

1. Introduction

Helicobacter pylori is a Gram-negative, spiral-shaped bacterium that colonises the gastric epithelium of an estimated 4.4 billion people worldwide (Hooi et al., 2017). Despite a gradual decline in some high-income countries, prevalence remains very high in much of the Middle East and North Africa, with Iraq among the most heavily affected populations, where adult seroprevalence exceeds 50% in most published series (Li et al., 2023; Malfertheiner et al., 2023). The infection is the principal cause of chronic gastritis and peptic-ulcer disease, and the International Agency for Research on Cancer classifies H. pylori as a Group I human carcinogen because of its causal link to non-cardia gastric adenocarcinoma and gastric MALT lymphoma (Crowe, 2019; Malfertheiner et al., 2022). Most infected individuals remain asymptomatic, but a sizeable minority develop dyspeptic symptoms —epigastric pain, postprandial fullness, early satiety, nausea and bloating — that produce significant functional impairment and consume substantial healthcare resources (Stanghellini et al., 2016; Moayyedi et al., 2017). Distinguishing H. pylori-associated dyspepsia from H. pylori-negative functional dyspepsia is clinically important because the two conditions diverge in prognosis and treatment: eradication therapy benefits the former but not the latter, and recent international guidelines such as the Maastricht VI/Florence Consensus reaffirm a test-and-treat strategy in high-prevalence populations (Malfertheiner et al., 2022). The molecular biology that connects H. pylori to dyspeptic mucosal disease has been progressively clarified. CagA-positive strains, through their type-IV secretion system, trigger NF-κB-mediated expression of interleukin-8 (CXCL8) in gastric epithelial cells (Backert and Tegtmeyer, 2017; Crowe, 2019), with consequent neutrophilic infiltration and amplification of the inflammatory cascade (Outlioua et al., 2020). Sustained mucosal IL-6 release drives the hepatic synthesis of acute-phase reactants, including hs-CRP (Du Clos and Mold, 2004). In parallel, mucosal inflammation alters G-cell physiology and the antral/corpus secretory balance: gastrin-17 rises in non-atrophic antral gastritis, while pepsinogen I declines (and PG-II rises) as gastric atrophy progresses, lowering the PG-I/PG-II ratio (Agréus et al., 2012; Miftahussurur and Yamaoka, 2016; Syrjänen, 2016). These mechanistic links provide a strong rationale for evaluating IL-8, hs-CRP, gastrin-17 and the pepsinogens as a coordinated, non-invasive biomarker panel. Non-invasive testing is especially relevant in low- and middle-resource settings, where endoscopic capacity is limited and the burden of H. pylori is high (Li et al., 2023; Malfertheiner et al., 2023). The H. pylori stool-antigen test (HpSA) has emerged as a low-cost, reliable, point-of-care option for primary diagnosis and post-treatment follow-up, with pooled sensitivity and specificity above 90% in meta-analyses (Best et al., 2018). Combining HpSA with a panel of inflammatory and gastric-function biomarkers could in principle allow clinicians to identify, in a single laboratory visit, both the presence of infection and a snapshot of mucosal inflammatory burden. Although individual biomarker associations have been reported in several countries, integrated data from Iraqi dyspeptic populations remain scarce, and few studies have examined the combined diagnostic performance of IL-8, hs-CRP and Gastrin-17 in conjunction with semi-quantitative HpSA optical density. The novelty of the present work lies in (i) the simultaneous measurement of three pathophysiologically complementary biomarkers, (ii) correlation analysis with stool-antigen burden in infected participants, and (iii) construction and evaluation of a combined diagnostic panel in an Iraqi setting. We therefore aimed to (1) compare serum IL-8, hs-CRP, Gastrin-17, PG-I, PG-II and the PG-I/PG-II ratio across H. pylori-positive dyspepsia, H. pylori-negative dyspepsia, and healthy controls; (2) examine the correlation of H. pylori stool-antigen optical density with these biomarkers and with clinical symptom scores in infected participants; (3) evaluate, by multivariable regression, whether H. pylori positivity independently predicts each biomarker after adjustment for relevant confounders; and (4) assess the

diagnostic performance — both individually and as a combined panel — of these biomarkers for distinguishing H. pylori-positive from H. pylori-negative dyspepsia.

2. Materials and Methods

2.1 Study Design and Setting

This was a single-centre, observational, cross-sectional, case–control study conducted at the Digestive Diseases Centre, Al-Sadr Medical City, Al-Najaf Al-Ashraf, Iraq, during the period from October 2025 to May 2026. The reporting follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (von Elm et al., 2007).

2.2 Ethical Approval

The study protocol was reviewed and approved by the Research Ethics Committee of the Faculty of Veterinary Medicine, University of Kufa, Al-Najaf Al-Ashraf, Iraq. All participants provided written, informed consent before enrolment. The study was conducted in accordance with the Declaration of Helsinki and its later amendments.

2.3 Participants

Adult patients (≥18 years) attending the outpatient gastroenterology clinic with dyspeptic complaints for at least one month were considered for inclusion. Functional and organic dyspepsia were assessed using Rome IV criteria (Stanghellini et al., 2016). Of 210 screened adults, 170 were enrolled and stratified into three groups based on H. pylori stool antigen testing and clinical presentation: H. pylori-positive dyspepsia (n = 60), H. pylori-negative dyspepsia (n = 60), and 50 age- and sex-comparable healthy controls without dyspeptic symptoms recruited from companions of patients and hospital staff. The full enrolment and analytical flow are summarised in Fig.1.

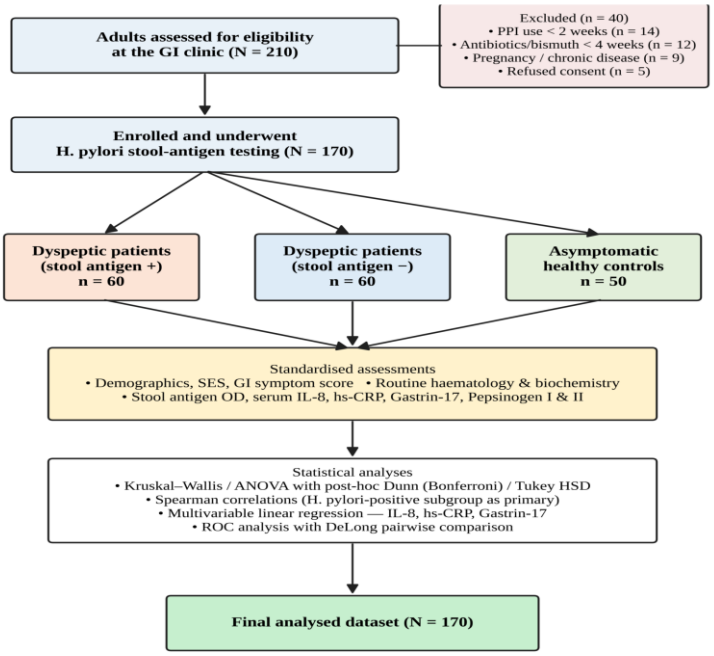

Figure1: Flow Diagram of Study Enrolment and Analytical Workflow (STROBE-compliant). Of 210 adults screened, 40 were excluded according to predefined criteria, leaving 170 participants stratified into three groups based on H. pylori stool-antigen status and dyspeptic symptoms.

Inclusion criteria: age 18–60 years; dyspepsia ≥1 month for the dyspeptic groups; no recent gastrointestinal interventions.

Exclusion criteria: proton-pump inhibitor (PPI) use within the preceding 2 weeks; antibiotic, bismuth or H_2-receptor antagonist use within 4 weeks; previous gastric surgery; known gastric malignancy; chronic hepatic, renal or autoimmune disease; pregnancy and lactation; active infection or systemic inflammatory disorder unrelated to H. pylori; alarm symptoms requiring urgent endoscopy unless completed.

2.4 Sample-Size Estimation

The sample size was calculated using G*Power 3.1.9.7. For a one-way ANOVA across three groups, assuming a medium effect size ($f = 0.30$), $\alpha = 0.05$ and statistical power = 0.95, the required sample was 144 participants. The actual enrolment ($n = 170$) provided power > 0.97 for the primary comparison of serum IL-8.

2.5 Clinical Assessment

A structured interviewer-administered questionnaire captured demographic information (age, sex, residence, education, occupation), anthropometric measurements (height, weight, body mass index [BMI]), socioeconomic data (family size, crowding index [persons/room], household drinking-water source, monthly income strata), behavioural risk factors (smoking, alcohol), past medical and drug history (gastritis, peptic ulcer, NSAID use, PPI use, antibiotic use), and family history of gastric disease.

Dyspeptic symptoms — epigastric pain, heartburn, nausea, vomiting, bloating, early satiety, postprandial fullness, loss of appetite and weight loss — were each rated on a 4-point Likert-type scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe), with the total symptom score derived as the sum of the nine items. Symptom duration was recorded in months. This approach follows the framework used in validated dyspepsia symptom instruments such as the Glasgow Dyspepsia Severity Score (el-Omar et al., 1996). Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer (Seca 213, Seca GmbH, Hamburg, Germany), and body weight to the nearest 0.1 kg using a calibrated digital scale, with participants in light clothing and without shoes. BMI was calculated as weight (kg) ÷ height $(m)^2$.

2.6 Specimen Collection and Processing

A morning fasting venous blood sample (8 mL) was drawn from each participant. Two millilitres were dispensed into an EDTA tube for complete blood count, two millilitres into a sodium-citrate tube for the erythrocyte sedimentation rate, and the remaining 4 mL into a plain serum-separator tube. After clot retraction at room temperature for 30 minutes, sera were separated by centrifugation at 3,000 × g for 10 minutes, aliquoted, and stored at −40 °C until batch analysis. A fresh stool specimen was collected in a labelled sterile container, transported within 2 hours to the laboratory, and either tested immediately or stored at −20 °C for up to one week before analysis.

2.7 Helicobacter pylori Stool-Antigen Testing

H. pylori infection status was determined by quantitative detection of H. pylori-specific antigens in stool using a commercial sandwich enzyme-linked immunosorbent assay (ELISA) kit (Human H. pylori Antigen ELISA, Sunlong Biotech Co., Ltd., Hangzhou, China). Optical density (OD) was read at 450 nm with a reference wavelength of 630 nm on an automated microplate reader. A specimen was classified as positive when the OD exceeded the manufacturer's cut-off (sample OD ≥ negative-control mean OD + 0.15, per kit insert). The continuous OD value was retained as a semi-quantitative index of antigen burden. The HpSA assay has been

validated extensively for the non-invasive diagnosis of active H. pylori infection, with sensitivity and specificity above 90% when manufacturer instructions are followed (Best et al., 2018).

2.8 Serum Biomarker Assays

Interleukin-8 (IL-8/CXCL8) was quantified by sandwich ELISA (Human IL-8 ELISA kit, Sunlong Biotech Co. Ltd., Hangzhou, China; or an equivalent CE-marked kit from Elabscience Biotechnology Co. Ltd., Wuhan, China, both used in regional Iraqi research laboratories). Sensitivity was < 10 pg/mL; intra- and inter-assay coefficients of variation were < 10%.

High-sensitivity C-reactive protein (hs-CRP) was measured by a quantitative sandwich ELISA (DRG Diagnostics, Marburg, Germany), with a detection limit of approximately 0.1 mg/L.

Gastrin-17 (G-17) was measured by quantitative sandwich ELISA (Sunlong Biotech Co. Ltd., China); the assay measures the amidated G-17 form secreted by antral G-cells.

Pepsinogen I (PG-I) and **Pepsinogen II (PG-II)** were each quantified by sandwich ELISA (Sunlong Biotech, China). The PG-I/PG-II ratio was calculated by division.

All ELISA assays were performed in duplicate following manufacturer protocols, with absorbance read on an automated ELISA microplate reader (Stat Fax 2100, Awareness Technology, Palm City, FL, USA), and washing performed on a Stat Fax 2600 microplate washer. Standard curves were constructed from manufacturer-supplied calibrators, and quality-control material was run with every plate.

2.9 Haematological, Biochemical and Inflammatory Parameters

The complete blood count (haemoglobin, white-blood-cell count, neutrophils, lymphocytes, platelets, red-cell distribution width [RDW]) was determined on an automated haematology analyser (Sysmex XN-550, Sysmex Corporation, Kobe, Japan; or Mindray BC-5300, Mindray Medical International, Shenzhen, China). Derived inflammatory ratios were calculated as: neutrophil-to-lymphocyte ratio (NLR) = neutrophils / lymphocytes; platelet-to-lymphocyte ratio (PLR) = platelets / lymphocytes; and systemic immune-inflammation index (SII) = (platelets × neutrophils) / lymphocytes. The erythrocyte sedimentation rate (ESR) was determined by the Westergren method using citrated whole blood, read at 1 hour. Liver-function tests (ALT, AST, ALP, total bilirubin), renal-function tests (urea, creatinine) and fasting plasma glucose were measured on an automated clinical-chemistry analyser (Mindray BS-240, Mindray, Shenzhen, China; or Cobas c311, Roche Diagnostics, Mannheim, Germany). Stool occult blood was tested by an immunochromatographic faecal-immunochemical test (FIT) following the manufacturer's instructions.

2.10 Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA) and R version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria) with the pROC, psych and car packages. The distribution of continuous variables was assessed by the Shapiro–Wilk test. Normally distributed variables were summarised as mean ± standard deviation (SD) and compared by one-way analysis of variance (ANOVA) with Tukey's HSD post-hoc test; non-normally distributed variables were summarised as median (interquartile range, Q1–Q3) and compared by the Kruskal–Wallis test with Dunn–Bonferroni post-hoc adjustment. Categorical variables were summarised as n (%) and compared by Pearson's χ^2 or Fisher's exact test. Effect sizes were reported as eta-squared (η^2) for ANOVA, epsilon-squared (ε^2) for Kruskal–Wallis, and Cramér's V for χ^2. Spearman's rank-order correlation (ρ) was used for inter-variable association, with 95% confidence intervals derived by Fisher's z-transformation. Multivariable linear regression with H. pylori positivity, age, sex,

BMI, smoking and NSAID use as covariates was used to identify independent predictors of each biomarker; hs-CRP and Gastrin-17 were $\log_{10}$-transformed to satisfy normality of residuals, and the absence of multicollinearity was confirmed by variance-inflation factors < 2. Diagnostic performance of biomarkers in distinguishing H. pylori-positive from H. pylori-negative dyspepsia was assessed by receiver-operating-characteristic (ROC) curve analysis. The area under the curve (AUC) with the Hanley–McNeil 95% CI was reported, and pairwise AUC comparisons were performed using the non-parametric DeLong test. Optimal cut-off values were derived by maximising Youden's J index. A combined biomarker panel was generated as the predicted probability from a multivariable logistic-regression model containing IL-8, hs-CRP and Gastrin-17. A two-sided p-value < 0.05 was considered statistically significant.

3. Results

3.1 Baseline Characteristics

Of 210 adults screened, 170 met the eligibility criteria and were stratified into three groups (Fig.1, Table1). The groups were comparable in age (mean 36.3 ± 9.9, 36.2 ± 9.0, and 34.4 ± 8.8 years; p = 0.470), sex distribution (p = 0.361), residence, smoking, alcohol use, family size and crowding index. BMI was modestly higher in the dyspeptic groups than in controls ($p < 0.001$, $\eta^2 = 0.086$), and socioeconomic stratum differed significantly (p = 0.001, V = 0.231), with H. pylori-positive participants more frequently belonging to the lower stratum — a pattern consistent with the established socioeconomic gradient of H. pylori transmission.

Table1: Baseline Demographic, Anthropometric and Socioeconomic Characteristics of The Study Participants (N = 170).

Variable	H. pylori$^+$ Dyspepsia (n=60)	H. pylori$^-$ Dyspepsia (n=60)	Healthy Controls (n=50)	Test	p-value	Effect size
Age, years	36.33 ± 9.89	36.23 ± 9.04	34.36 ± 8.84	ANOVA	0.470	$\eta^2 = 0.009$
Sex – Female, n (%)	40 (66.7)	33 (55.0)	28 (56.0)	χ^2	0.361	V = 0.109
Sex – Male, n (%)	20 (33.3)	27 (45.0)	22 (44.0)			
BMI, kg/m²	26.81 ± 3.17	26.52 ± 4.12	24.24 ± 3.58	ANOVA	<0.001	$\eta^2 = 0.086$
Residence – Rural	14 (23.3)	20 (33.3)	20 (40.0)	χ^2	0.165	V = 0.146
Residence – Urban	46 (76.7)	40 (66.7)	30 (60.0)			
Smoking – Yes	9 (15.0)	14 (23.3)	10 (20.0)	χ^2	0.510	V = 0.089
Alcohol – Yes	0 (0.0)	3 (5.0)	0 (0.0)	χ^2	0.061	V = 0.181
Family size	6.00 (5.00–7.00)	6.00 (4.00–7.00)	6.00 (4.25–6.75)	K-W	0.533	$\varepsilon^2 = 0.007$
Crowding index	2.00 (1.48–2.50)	2.00 (1.33–2.75)	2.00 (1.42–2.92)	K-W	0.993	$\varepsilon^2 = 0.000$
Socioeconomic – Low	26 (43.3)	14 (23.3)	5 (10.0)	χ^2	0.001	V = 0.231

Variable	H. pylori⁺ Dyspepsia (n=60)	H. pylori⁻ Dyspepsia (n=60)	Healthy Controls (n=50)	Test	p-value	Effect size
Socioeconomic – Middle	24 (40.0)	25 (41.7)	25 (50.0)			
Socioeconomic – High	10 (16.7)	21 (35.0)	20 (40.0)			
Data: mean ± SD (One-way ANOVA), median (Q1–Q3) (Kruskal–Wallis, K-W), n (%) (χ^2 or Fisher's exact). Effect sizes: η^2 (ANOVA), ε^2 (K-W), Cramér's V (χ^2). BMI, body-mass index. $p < 0.05$ significant.						

3.2 Clinical Symptom Profile

All nine individual dyspeptic symptoms and the total symptom score were graded higher in H. pylori-positive dyspepsia than in H. pylori-negative dyspepsia, and both exceeded healthy controls Table2, overall Kruskal–Wallis $p < 0.001$ for every item). The largest effect sizes were for total symptom score ($\varepsilon^2 = 0.586$) and symptom duration ($\varepsilon^2 = 0.677$). Gastritis/peptic-ulcer history ($p = 0.008$) and NSAID use ($p = 0.018$) were more frequent in dyspeptic groups, and PPI and antibiotic washouts were complete.

Table2: Clinical Symptom Profile, Gastrointestinal Risk Factors and Medication Use Across the Three Study Groups.

Variable	H. pylori⁺ (n=60)	H. pylori⁻ (n=60)	Controls (n=50)	Test	p-value	Effect size
Epigastric pain	2.00 (1.00–2.00)	1.00 (0.00–2.00)	0.00 (0.00–0.00)	K-W	<0.001	$\varepsilon^2 = 0.235$
Heartburn	1.00 (0.00–2.00)	1.00 (0.75–2.00)	0.00 (0.00–0.75)	K-W	<0.001	$\varepsilon^2 = 0.133$
Nausea	1.00 (1.00–2.25)	1.00 (0.00–2.00)	0.00 (0.00–0.00)	K-W	<0.001	$\varepsilon^2 = 0.286$
Vomiting	1.50 (1.00–2.00)	1.00 (0.00–2.00)	0.00 (0.00–0.00)	K-W	<0.001	$\varepsilon^2 = 0.215$
Bloating	1.00 (1.00–2.00)	1.00 (0.00–2.00)	0.00 (0.00–0.00)	K-W	<0.001	$\varepsilon^2 = 0.263$
Early satiety	1.00 (1.00–2.00)	1.00 (0.00–2.00)	0.00 (0.00–1.00)	K-W	<0.001	$\varepsilon^2 = 0.137$
Postprandial fullness	1.00 (1.00–2.00)	1.00 (0.00–2.00)	0.00 (0.00–1.00)	K-W	<0.001	$\varepsilon^2 = 0.122$
Loss of appetite	1.00 (1.00–2.00)	1.00 (0.00–2.00)	0.00 (0.00–0.00)	K-W	<0.001	$\varepsilon^2 = 0.259$
Weight loss	1.00 (1.00–2.00)	1.00 (0.00–2.00)	0.00 (0.00–0.00)	K-W	<0.001	$\varepsilon^2 = 0.160$
Total symptom score	13.00 (10.75–15.00)	10.50 (9.00–13.00)	3.00 (2.00–5.00)	K-W	<0.001	$\varepsilon^2 = 0.586$
Symptom duration (mo)	9.00 (4.00–12.00)	4.00 (2.00–6.75)	0.00 (0.00–0.00)	K-W	<0.001	$\varepsilon^2 = 0.677$
Gastritis/PU history – Yes	13 (21.7)	12 (20.0)	1 (2.0)	χ^2	0.008	V = 0.239

Variable	H. pylori⁺ (n=60)	H. pylori⁻ (n=60)	Controls (n=50)	Test	p-value	Effect size
NSAID use – Yes	11 (18.3)	11 (18.3)	1 (2.0)	χ^2	0.018	V = 0.218
Symptoms rated 0–3 Likert. K-W, Kruskal–Wallis; PU, peptic ulcer; NSAID, non-steroidal anti-inflammatory drug.						

3.3 Hematological, Hepatic, Renal and Inflammatory Parameters

Total WBC, neutrophils, platelets, NLR, PLR, SII index and ESR were sequentially highest in H. pylori-positive dyspepsia, intermediate in H. pylori-negative dyspepsia, and lowest in controls Table3, with ESR showing the largest gradient ($\eta^2 = 0.394$, $p < 0.001$). Hepatic, renal and glycaemic markers did not differ across groups.

Table3: Hematological, Inflammatory, Hepatic and Renal Laboratory Parameters Across the Three Study Groups.

Variable	H. pylori⁺ (n=60)	H. pylori⁻ (n=60)	Controls (n=50)	Test	p-value	Effect size
Haemoglobin, g/dL	12.73 (12.04–13.50)	13.18 (12.43–14.59)	13.30 (12.54–14.29)	K-W	0.012	$\varepsilon^2 = 0.053$
WBC, cells/µL	7755 ± 1680	6788 ± 1451	6442 ± 1130	ANOVA	<0.001	$\eta^2 = 0.129$
Neutrophils, cells/µL	4576 ± 1312	4438 ± 963	3751 ± 1119	ANOVA	<0.001	$\eta^2 = 0.087$
Lymphocytes, cells/µL	2082 ± 594	2332 ± 499	2324 ± 541	ANOVA	0.021	$\eta^2 = 0.045$
Platelets, ×10³/µL	295.97 ± 62.85	260.49 ± 57.70	244.75 ± 43.69	ANOVA	<0.001	$\eta^2 = 0.129$
NLR	2.19 (1.58–2.85)	2.01 (1.44–2.30)	1.60 (1.25–2.03)	K-W	<0.001	$\varepsilon^2 = 0.088$
PLR	147.6 (114.8–176.2)	117.7 (90.8–138.9)	106.6 (87.2–130.0)	K-W	<0.001	$\varepsilon^2 = 0.125$
SII index	657,541 (426,146–956,610)	466,067 (370,758–648,133)	378,911 (275,171–518,061)	K-W	<0.001	$\varepsilon^2 = 0.157$
ESR, mm/h	28.70 ± 13.01	18.82 ± 8.43	9.72 ± 4.53	ANOVA	<0.001	$\eta^2 = 0.394$
ALT, U/L	27.00 (21.00–32.25)	27.00 (18.00–33.50)	25.00 (15.25–36.00)	K-W	0.790	$\varepsilon^2 = 0.003$
AST, U/L	25.57 ± 10.60	28.30 ± 10.30	26.04 ± 9.67	ANOVA	0.302	$\eta^2 = 0.014$
ALP, U/L	92.0 ± 24.8	79.0 ± 26.0	82.3 ± 29.2	ANOVA	0.024	$\eta^2 = 0.044$
Urea, mg/dL	29.75 ± 8.90	32.73 ± 10.68	31.36 ± 9.51	ANOVA	0.247	$\eta^2 = 0.017$
Creatinine, mg/dL	0.85 ± 0.18	0.81 ± 0.15	0.85 ± 0.16	ANOVA	0.336	$\eta^2 = 0.013$
Fasting glucose, mg/dL	96.0 (85.0–104.8)	89.5 (81.3–105.8)	94.0 (81.0–108.0)	K-W	0.664	$\varepsilon^2 = 0.005$
NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; ESR, erythrocyte sedimentation rate.						

3.4 Serum and Stool Biomarker Levels

All five gastric and inflammatory biomarkers differed significantly across groups Table4, Fig.2. H. pylori-positive participants exhibited markedly higher stool-antigen OD (median 0.90 vs 0.06 vs 0.05), IL-8 (71.4 ± 20.9 pg/mL), hs-CRP (median 8.0 mg/L), Gastrin-17 (median 14.1 pmol/L) and PG-II (12.4 ± 5.1 ng/mL), and lower PG-I (95.8 ± 28.1 ng/mL) and PG-I/PG-II ratio (median 7.3) than the other two groups. Stool antigen did not differ between H. pylori-negative dyspepsia and controls (p = 0.326), confirming analytic specificity.

Table4: Serum and Stool Biomarker Levels Across the Three Study Groups, With Overall and Pairwise Post-Hoc Comparisons.

Biomarker	H. pylori^{+} (n=60)	H. pylori^{-} (n=60)	Controls (n=50)	Overall p	P^{+} vs P^{-}	P^{+} vs HC	P^{-} vs HC
HpSA OD value	0.90 (0.71–1.19)	0.06 (0.04–0.09)	0.05 (0.03–0.06)	<0.001	<0.001	<0.001	0.326
IL-8, pg/mL	71.42 ± 20.88	49.38 ± 14.98	29.93 ± 9.64	<0.001	<0.001	<0.001	<0.001
hs-CRP, mg/L	8.02 (3.65–12.12)	2.62 (1.20–4.14)	1.38 (0.74–1.92)	<0.001	<0.001	<0.001	0.002
Gastrin-17, pmol/L	14.10 (8.20–20.02)	8.95 (5.88–12.68)	5.35 (3.45–7.80)	<0.001	0.003	<0.001	<0.001
PG-I, ng/mL	95.81 ± 28.12	115.27 ± 24.83	125.04 ± 26.62	<0.001	<0.001	<0.001	0.136
PG-II, ng/mL	12.37 ± 5.09	7.31 ± 2.65	4.98 ± 2.05	<0.001	<0.001	<0.001	0.002
PG-I/PG-II	7.28 (5.83–12.21)	15.44 (12.41–21.66)	25.84 (19.15–35.45)	<0.001	<0.001	<0.001	<0.001

HpSA, H. pylori stool antigen; OD, optical density; PG, pepsinogen. Post-hoc by Dunn–Bonferroni or Tukey HSD as appropriate.

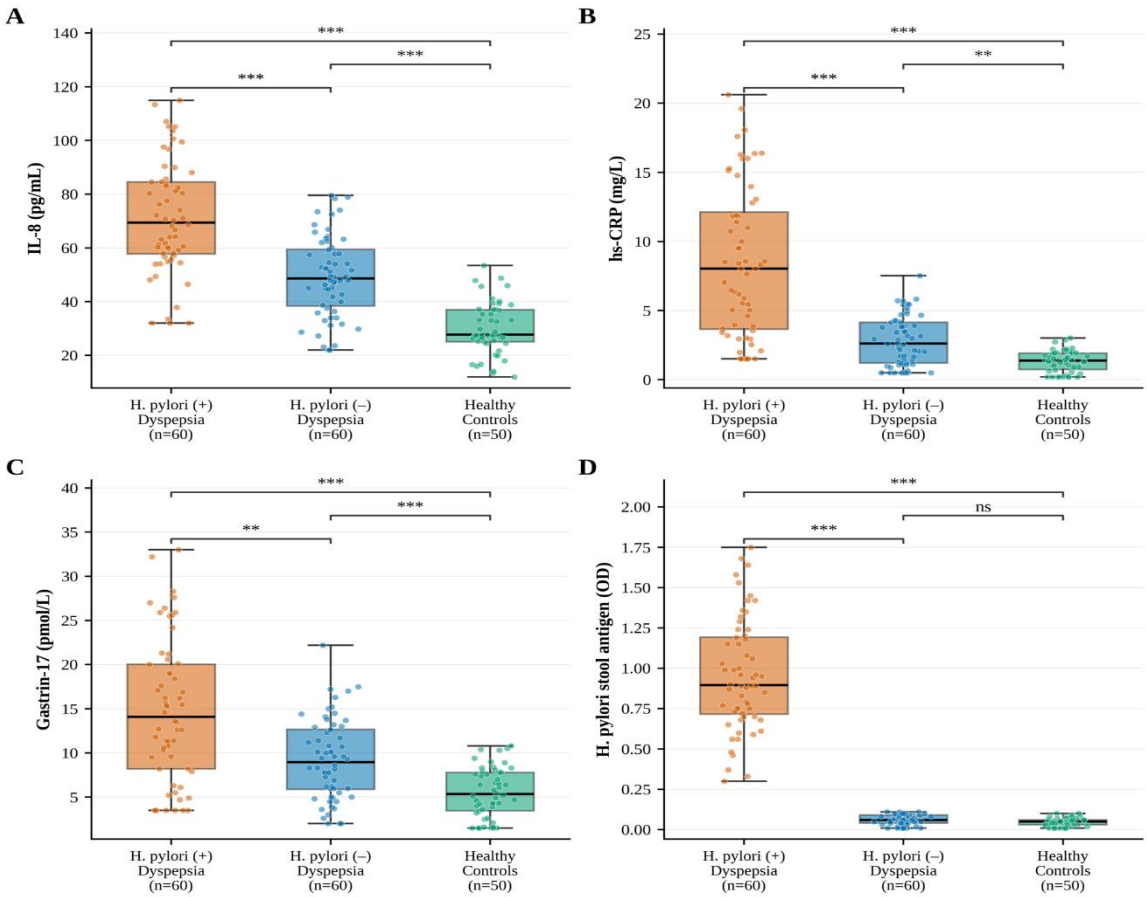

Figure2: Distribution of The Four Key Biomarkers Across the Three Study Groups. Box Plots (Median, IQR; Whiskers = 1.5 × IQR) With Jittered Individual Data Points for (A) IL-8, (B) hs-CRP, (C) Gastrin-17, and (D) H. pylori stool-antigen optical density. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$, ns = not significant.

3.5 Correlation Analysis

In the H. pylori-positive subgroup, stool-antigen OD correlated positively with serum IL-8 ($\rho = 0.278$, $p = 0.032$) and PG-I/PG-II ratio ($\rho = 0.274$, $p = 0.034$), and negatively with PG-II ($\rho = -0.302$, $p = 0.019$; Table5, Fig.3). Across the full dyspeptic cohort, correlations were stronger and uniformly significant for IL-8, hs-CRP, Gastrin-17 and ESR (all $\rho > 0.32$, $p < 0.001$), reflecting the between-group infection signal. The correlation matrix (Fig.4) shows the expected biological clustering, with positive intercorrelations between inflammatory and gastric markers and an inverse cluster for PG-I and the PG-I/PG-II ratio.

Table5: Spearman Rank Correlations of H. Pylori Stool-Antigen Optical Density with Serum Biomarkers and Clinical Symptom Scores.

Variable	H. pylori⁺ ρ	H. pylori⁺ 95% CI	p	Cohort ρ	Cohort 95% CI	p
IL-8, pg/mL	0.278	(0.025, 0.496)	0.032	0.490	(0.341, 0.616)	<0.001
hs-CRP, mg/L	−0.079	(−0.326, 0.178)	0.548	0.422	(0.263, 0.559)	<0.001
Gastrin-17, pmol/L	0.166	(−0.092, 0.403)	0.205	0.367	(0.201, 0.512)	<0.001
PG-I, ng/mL	0.006	(−0.249, 0.259)	0.966	−0.342	(−0.491, −0.173)	<0.001
PG-II, ng/mL	−0.302	(−0.516, −0.052)	0.019	0.373	(0.208, 0.518)	<0.001
PG-I / PG-II ratio	0.274	(0.022, 0.494)	0.034	−0.439	(−0.573, −0.281)	<0.001
Total symptom score	0.151	(−0.107, 0.390)	0.250	0.264	(0.089, 0.423)	0.004
Epigastric pain	0.174	(−0.084, 0.410)	0.184	0.232	(0.055, 0.395)	0.011
Bloating	−0.121	(−0.364, 0.137)	0.358	0.016	(−0.164, 0.195)	0.863
Postprandial fullness	−0.009	(−0.263, 0.245)	0.944	0.185	(0.006, 0.352)	0.044
Symptom duration	−0.094	(−0.340, 0.164)	0.475	0.252	(0.077, 0.413)	0.005
NLR	−0.083	(−0.330, 0.175)	0.529	0.140	(−0.040, 0.311)	0.128
SII index	−0.048	(−0.299, 0.208)	0.714	0.245	(0.069, 0.407)	0.007
ESR, mm/h	−0.084	(−0.331, 0.173)	0.522	0.322	(0.152, 0.474)	<0.001

Spearman's rank correlation; 95% CI by Fisher's z-transformation. Cohort = full dyspeptic cohort, n = 120

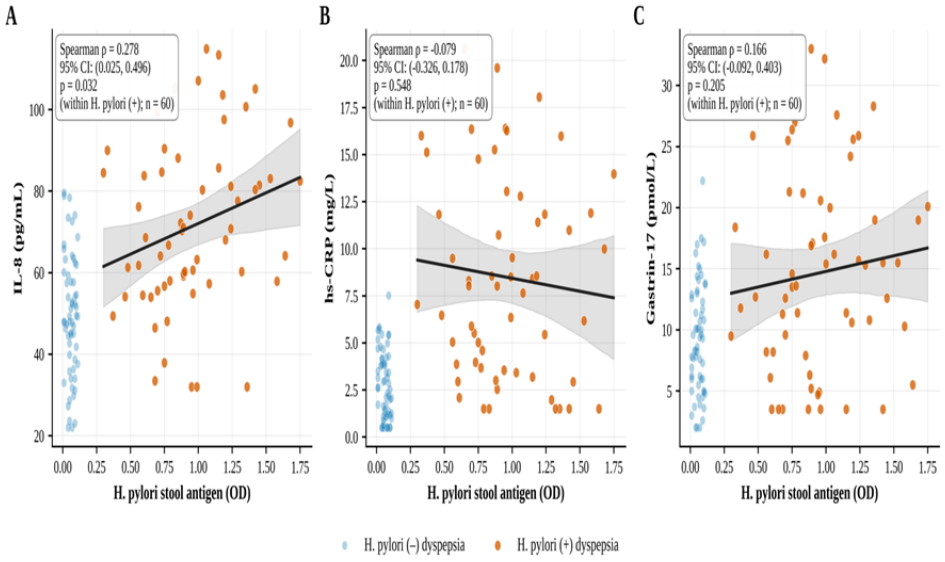

Figure3: Within-Positive-Subgroup Associations Between H. Pylori Stool-Antigen Burden and Circulating Biomarkers. Scatter Plots of Stool-Antigen OD vs (A) IL-8, (B) hs-CRP and (C) Gastrin-17, restricted to the H. pylori-positive subgroup (n = 60). Solid lines, OLS fits; shaded bands, 95% bootstrap CI.

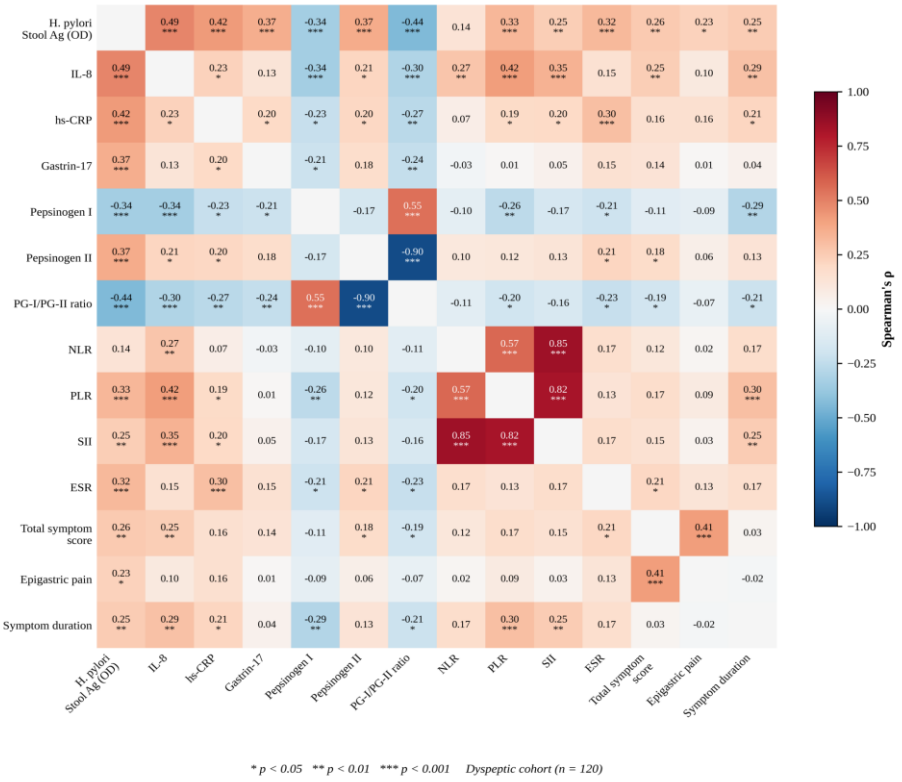

Figure4: Spearman Correlation Matrix of Biomarkers, Inflammatory Indices and Symptom Variables in The Dyspeptic Cohort (N = 120). Cells display Spearman's ρ with significance stars (* p < 0.05, ** p < 0.01, *** p < 0.001). Colour intensity reflects magnitude and sign (red, positive; blue, negative).

3.6 Multivariable Regression

After adjustment for age, sex, BMI, smoking and NSAID use, H. pylori positivity remained independently associated with higher IL-8 (β = 21.34 pg/mL, p < 0.001), $\log_{10}$ hs-CRP (β = 0.51, p < 0.001) and $\log_{10}$ Gastrin-17 (β = 0.18, p < 0.001) (Table6, Fig.6). Smoking was an additional independent predictor of hs-CRP (β = 0.19, p = 0.022). Adjusted R^2 was highest for hs-CRP (0.367), intermediate for IL-8 (0.254) and lowest for Gastrin-17 (0.096). All variance-inflation factors were < 1.16.

Table6: Multivariable Linear Regression Analyses of Factors Independently Associated with Serum IL-8, Hs-CRP (Log_{10}) And Gastrin-17 (Log_{10}) In The Dyspeptic Cohort (N = 120).

Outcome	Predictor	β (unstd.)	95% CI	p-value	Adj. R^2
IL-8 (pg/mL)	H. pylori positivity	21.337	(14.644, 28.030)	<0.001	0.254
	Age (per year)	0.051	(−0.304, 0.406)	0.776	
	Male sex (vs female)	−6.015	(−13.304, 1.275)	0.105	
	BMI (per kg/m²)	0.219	(−0.696, 1.134)	0.636	
	Current smoking	0.805	(−8.263, 9.874)	0.861	
	NSAID use	−1.497	(−10.151, 7.158)	0.733	

Outcome	Predictor	β (unstd.)	95% CI	p-value	Adj. R^2
hs-CRP (log_{10})	H. pylori positivity	0.505	(0.383, 0.628)	<0.001	0.367
	Age (per year)	0.001	(−0.006, 0.007)	0.797	
	Male sex	−0.017	(−0.150, 0.117)	0.806	
	BMI	−0.016	(−0.033, 0.001)	0.061	
	Current smoking	0.194	(0.028, 0.360)	0.022	
	NSAID use	−0.088	(−0.247, 0.070)	0.273	
Gastrin-17 (log_{10})	H. pylori positivity	0.175	(0.077, 0.274)	<0.001	0.096
	Age	−0.003	(−0.008, 0.002)	0.269	
	Male sex	0.018	(−0.089, 0.125)	0.741	
	BMI	−0.002	(−0.016, 0.011)	0.739	
	Current smoking	−0.126	(−0.259, 0.007)	0.064	
	NSAID use	−0.023	(−0.150, 0.104)	0.721	
Multivariable OLS regression. hs-CRP and Gastrin-17 log_{10}-transformed. All VIFs < 1.16.					

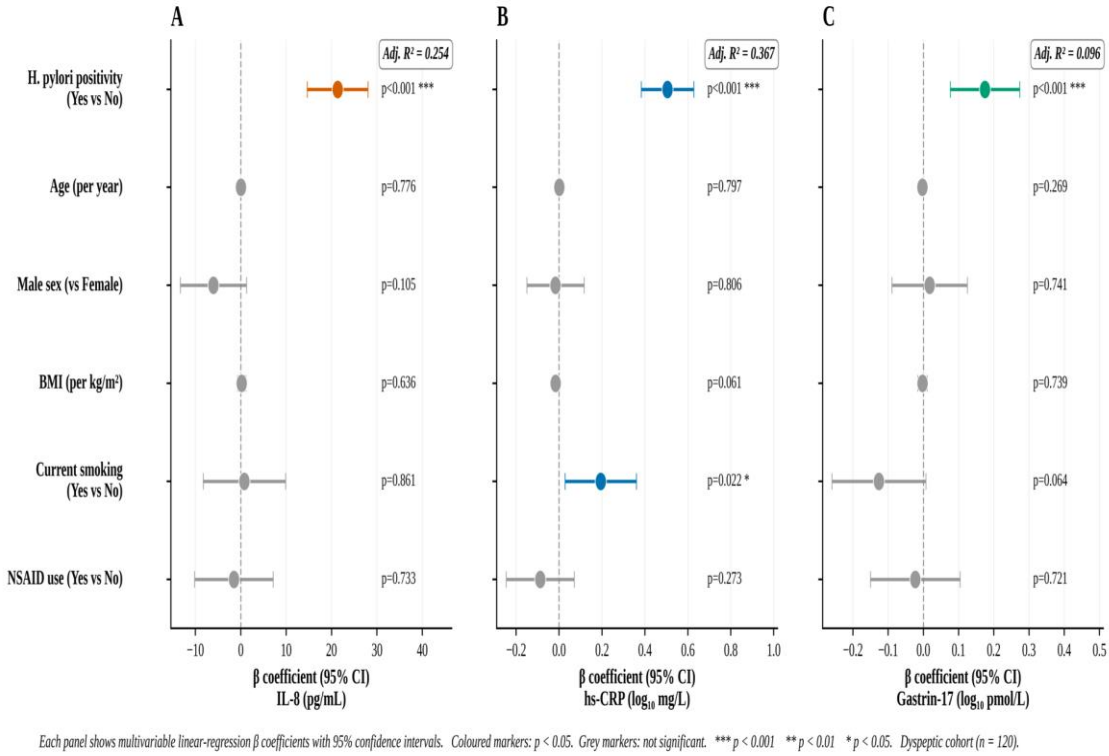

Figure6: Forest Plot of Multivariable Linear Regression: Independent Predictors of (A) IL-8, (B) hs-CRP (log_{10}) and (C) Gastrin-17 (log_{10}) in the dyspeptic cohort (n = 120). Markers, β coefficients; horizontal bars, 95% CI. Colored markers denote $p < 0.05$; grey denotes non-significant.

3.7 Diagnostic Performance

Individually, hs-CRP showed the highest area under the curve (AUC 0.837), followed by IL-8 (0.806) and Gastrin-17 (0.700) (Table7, Fig.5). A combined panel of the three biomarkers produced an AUC of 0.947 (95% CI 0.905–0.989) with 100% specificity and 89.2% overall accuracy. DeLong testing confirmed that the combined panel significantly outperformed every individual marker (all $p < 0.001$).

Table7: Diagnostic Performance of Serum Biomarkers — Individually and As A Combined Panel for Distinguishing H. Pylori-Positive from H. Pylori-Negative Dyspepsia (N = 120).

Biomarker	AUC	95% CI	Cut-off	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)	Accuracy (%)
IL-8 (pg/mL)	0.806	(0.727–0.884)	54.90	81.7	68.3	72.1	78.8	75.0
hs-CRP (mg/L)	0.837	(0.764–0.909)	5.89	61.7	98.3	97.4	72.0	80.0
Gastrin-17 (pmol/L)	0.700	(0.607–0.794)	15.30	48.3	91.7	85.3	64.0	70.0
Combined panel	0.947	(0.905–0.989)	0.737*	78.3	100.0	100.0	82.2	89.2

ROC analysis; cut-off by Youden's J. *Cut-off for combined panel = predicted probability scale (0–1) from multivariable logistic-regression. DeLong test: combined panel vs each individual marker, all $p < 0.001$.

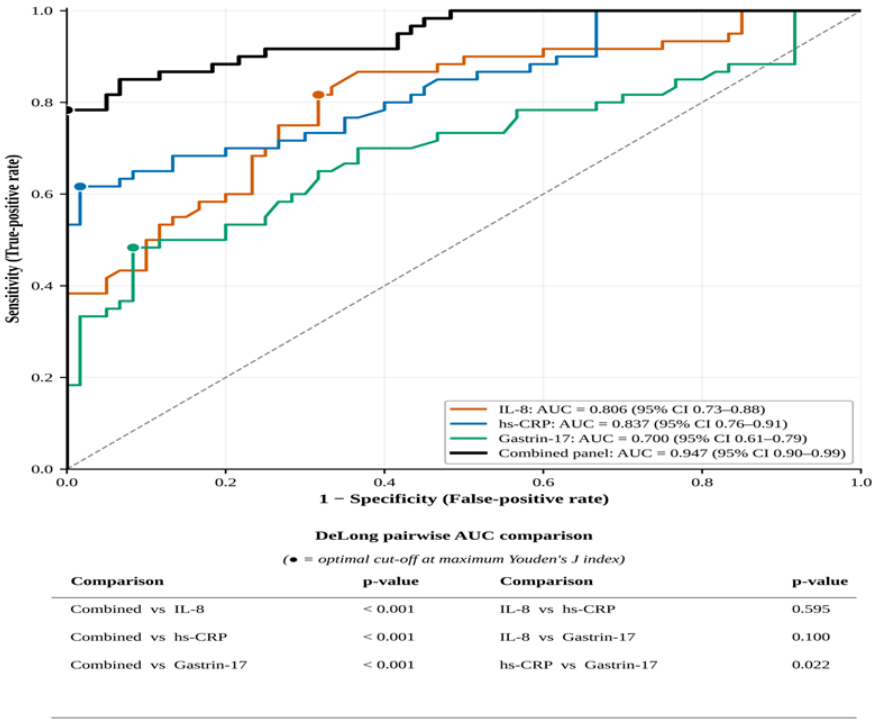

Figure5: Receiver-Operating-Characteristic (ROC) Curves for Serum Biomarkers — Alone and As A Combined Panel — Discriminating H. Pylori-Positive from H. Pylori-Negative Dyspepsia. AUC with Hanley–McNeil 95% CI shown for each; coloured dots mark the Youden-optimal cut-off.

4. Discussion

In this cross-sectional study of 170 adults from Al-Najaf Al-Ashraf, Iraq, participants with H. pylori-positive dyspepsia had significantly higher circulating IL-8, hs-CRP and Gastrin-17, together with a lower PG-I/PG-II ratio, than H. pylori-negative dyspeptic patients and healthy controls. After adjustment for age, sex, BMI, smoking and NSAID use, H. pylori positivity remained an independent predictor of each of the three primary biomarkers, and a combined IL-8 + hs-CRP + Gastrin-17 panel discriminated H. pylori-positive from H. pylori-negative dyspepsia with an AUC of 0.947. These observations extend prior work on individual biomarkers by showing that, in an Iraqi clinical setting, the three markers behave in a coherent and biologically plausible pattern reflecting both local mucosal inflammation and systemic acute-phase activation.

4.1 Demographic and Socioeconomic Context

The three groups were comparable in most baseline variables. The two that differed — BMI and socioeconomic status — are themselves both linked to H. pylori ecology. A higher proportion of H. pylori-positive participants belonged to the lower socioeconomic stratum, consistent with the well-documented socioeconomic gradient of H. pylori transmission worldwide and in the Iraqi context (Hussein, 2010; Li et al., 2023; Malfertheiner et al., 2023). National Iraqi seroprevalence has been estimated at 50–80% in adults, among the highest globally (Hussein, 2010; Ford et al., 2020; Li et al., 2023), reflecting overcrowding, suboptimal sanitation infrastructure in some districts, and intra-familial spread.

4.2 Mechanistic Interpretation of the Biomarker Pattern

The cardinal molecular event linking H. pylori to mucosal IL-8 release is delivery of the cytotoxin-associated gene A (CagA) effector through the type-IV secretion system (T4SS) into gastric epithelial cells, activating the NF-κB and AP-1 transcription factors and the ERK1/2-MAPK cascade (Backert and Tegtmeyer, 2017; Crowe, 2019; Outlioua et al., 2020). IL-8 is a potent neutrophil chemoattractant, and its mucosal release drives the neutrophilic infiltration that defines acute H. pylori gastritis. Although IL-8 is primarily produced locally, a fraction enters the systemic circulation in proportion to mucosal disease severity (Outlioua et al., 2020). Our finding of a moderate positive correlation between stool-antigen optical density and serum IL-8 ($\rho = 0.490$ across the dyspeptic cohort and $\rho = 0.278$ within infected participants) is consistent with this mechanism and aligns with international reports from Moroccan, Iranian and Turkish cohorts demonstrating elevated IL-8 in H. pylori-infected patients (Razavi et al., 2015; Bagheri et al., 2018; Outlioua et al., 2020).

The elevation of hs-CRP in our infected participants (median 8.0 mg/L vs 2.6 mg/L vs 1.4 mg/L) reflects the downstream hepatic acute-phase response driven by IL-6, itself induced by H. pylori-stimulated macrophages and dendritic cells (Du Clos and Mold, 2004). Smoking emerged as an additional independent predictor of hs-CRP — a finding compatible with the established cumulative effect of cigarette smoke on systemic inflammation (Du Clos and Mold, 2004). Gastrin-17 is secreted by antral G-cells and is regulated by intraluminal pH and by the inflammatory milieu in the antrum. In non-atrophic H. pylori-induced antral gastritis, G-cell hyperplasia and mucosal inflammation typically produce a moderate elevation of fasting G-17; with progression to antral atrophy, G-17 declines (Agréus et al., 2012; Miftahussurur and Yamaoka, 2016). Our patients showed elevated G-17 (median 14.1 pmol/L), compatible with a predominantly non-atrophic antral pattern at this point in the disease trajectory. The reduced PG-I/PG-II ratio in H. pylori-positive participants is the most clinically informative element of the pepsinogen profile. PG-I derives mainly from corpus chief and mucous-neck cells, while PG-II is produced throughout the stomach and the duodenum (Agréus et al., 2012; Miftahussurur and Yamaoka, 2016;

Syrjänen, 2016). In active H. pylori infection, PG-II rises disproportionately because of inflammation throughout the gastric mucosa, depressing the PG-I/PG-II ratio — the analytic basis of the so-called serological biopsy or GastroPanel approach to non-invasive screening for atrophic gastritis (Syrjänen, 2016). The PG-I/PG-II ratio of approximately 7.3 in our infected group, compared with 25.8 in controls, fits this paradigm.

4.3 Systemic Inflammatory Haematological Indices

NLR, PLR and SII index were progressively higher across controls → H. pylori-negative → H. pylori-positive dyspepsia, reinforcing the same inflammatory gradient observed with hs-CRP. These low-cost indices have recently attracted interest as accessible markers of low-grade systemic inflammation in H. pylori infection (Farah and Khamisy-Farah, 2020) and may complement biomarker panels in resource-limited settings.

4.4 Comparison with Iraqi and Regional Studies

The pattern we observed is broadly consistent with several Iraqi reports. Hussein and colleagues, in studies of Iraqi adults from northern governorates, documented H. pylori prevalences in the 50–70% range and highlighted the contribution of crowded living conditions (Hussein, 2010). Iraqi work on inflammatory cytokines in H. pylori-positive patients has likewise reported elevation of pro-inflammatory mediators relative to non-infected dyspeptics (Al-Ezzy, 2018), and Iraqi cohorts examining hs-CRP in H. pylori-positive patients have similarly shown significantly higher CRP values than controls, although absolute levels vary with assay platform and patient case-mix (Naser and Al-Mussawi, 2020). Iraqi work on the pepsinogen panel and Gastrin-17 has been comparatively limited, but the few available series indicate a depressed PG-I/PG-II ratio and elevated G-17 during the non-atrophic phase of infection — observations our findings extend (Salman et al., 2022).

Beyond Iraq, the results align with international evidence. Iranian and Turkish series have reported significantly higher serum IL-8 and hs-CRP in H. pylori-positive dyspeptics than negatives (Razavi et al., 2015; Bagheri et al., 2018); Moroccan and Egyptian studies have demonstrated similar gradients with additional variation linked to CagA status (Outlioua et al., 2020; Sayed et al., 2021); and the Maastricht VI/Florence and Kyoto consensus working groups support the integration of pepsinogens and gastrin-17 into non-invasive risk stratification for gastric mucosal disease (Crowe, 2019; Malfertheiner et al., 2022).

4.5 Diagnostic Implications

The combined biomarker panel (IL-8 + hs-CRP + Gastrin-17) achieved an AUC of 0.947 with 100% specificity at the chosen threshold, meaningfully outperforming each individual marker. This is the principal incremental finding. However, this represents apparent (in-sample) performance, and the cut-off was selected to maximise Youden's J in the same dataset, which introduces optimism bias. The panel must therefore be regarded as a hypothesis-generating tool requiring prospective external validation before clinical deployment.

If validated, such a panel could support a stratified test-and-treat strategy in primary-care settings in regions of high H. pylori prevalence, in line with Maastricht VI/Florence Consensus recommendations (Malfertheiner et al., 2022), by helping to triage which dyspeptic patients should proceed to endoscopy and which may reasonably be treated empirically.

4.6 Strengths and Limitations

Strengths. The study applied a rigorous three-group design with healthy controls, ensured strict 2-week PPI and 4-week antibiotic washout periods, and used multiple complementary biomarkers spanning local mucosal (IL-8, G-17, pepsinogens) and systemic (hs-CRP, NLR, PLR, SII, ESR) inflammation. All analyses report effect sizes

and 95% confidence intervals; multivariable regression adjusted for relevant confounders; ROC comparisons were performed with the appropriate DeLong test; and the reporting follows STROBE guidance.

Limitations. Several limitations should be acknowledged. First, the cross-sectional case–control design precludes causal inference and does not capture longitudinal change after eradication. Second, the study was conducted at a single referral centre, limiting external generalisability. Third, although the HpSA test is well validated, endoscopic histology and the urea breath test were not performed on all participants, so the gold-standard confirmation is partial. Fourth, CagA, VacA and dupA virulence genotyping was not performed, which would have allowed deeper mechanistic interpretation of the IL-8 signal. Fifth, the ROC and cut-off derivation used in-sample data only; cross-validation and external validation are needed. Sixth, dietary salt, Vitamin C and other micronutrient covariates that may modulate gastric inflammation were not measured. Finally, the modest sample size limited subgroup analyses.

Conclusion

In adults presenting with dyspepsia at a single Iraqi gastroenterology centre, H. pylori infection — as detected by stool antigen — was independently associated with significantly higher circulating IL-8, hs-CRP and Gastrin-17, and with a lower PG-I/PG-II ratio, than H. pylori-negative dyspepsia or healthy controls. A panel combining IL-8, hs-CRP and Gastrin-17 discriminated infected from non-infected dyspeptic patients with high apparent accuracy. Because these findings derive from a cross-sectional single-centre design and the diagnostic cut-off was internally derived, prospective external validation, ideally with endoscopic and histological reference standards, is required before the panel can be recommended for routine clinical use. Until such validation is available, the present data should be interpreted as supporting — but not yet establishing — the integrated use of these biomarkers as a non-invasive adjunct in the assessment of H. pylori-related dyspepsia in Iraqi populations.

Declarations

Ethics Approval and Consent to Participate

The study protocol was reviewed and approved by the Research Ethics Committee of Faculty of Veterinary Medicine, University of Kufa, Al-Najaf Al-Ashraf, Iraq. Written informed consent was obtained from every participant before enrolment. All procedures were performed in accordance with the Declaration of Helsinki and its subsequent amendments.

Consent for Publication

Not applicable; no individually identifying participant data are presented.

Availability of Data and Materials

The de-identified datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contributions

HAH conceived and designed the study, recruited participants, performed laboratory analyses, analysed the data and drafted the manuscript. HNJR supervised the project, contributed to study design, supervised the laboratory

work, contributed to data interpretation, and revised the manuscript critically for important intellectual content. Both authors read and approved the final manuscript.

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Trial Registration

Not applicable (observational, non-interventional study).

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