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Association Between *CagA*-Positive *Helicobacter pylori* Strains and Clinical Outcomes inPatients with Gastritis, Peptic Ulcer, and Gastric Cancer: A Cross-Sectional Study

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ABSTRACT

Background: *Helicobacter pylori* infection, particularly with *cagA*-positive strains, is strongly associated with severe gastrointestinal outcomes such as peptic ulcer and gastric cancer, though the strength of this association varies across populations. This study investigates the link between *cagA* positivity and clinical diagnoses in Iranian patients to evaluate its potential as a predictor of disease severity in a high-prevalence region.

Methods: This cross-sectional study included 125 patients with gastrointestinal symptoms, of whom 36 *H. pylori*-positive individuals were analyzed for *cagA* status using PCR on gastric biopsy specimens. The association between *cagA* positivity and clinical diagnoses (gastritis, peptic ulcer, gastric cancer) was assessed using chi-square and logistic regression analyses in SPSS v26.

Results: Of 36 *H. pylori*-positive patients, 63.89% were infected with *cagA*-positive strains. A significant association was found between *cagA* positivity and disease severity, with higher prevalence in peptic ulcer (78.3%) and gastric cancer (80.0%) compared to chronic gastritis (42.9%) ($p < 0.05$).

Conclusion: *cagA*-positive *H. pylori* strains are significantly associated with peptic ulcer and gastric cancer, highlighting their role in disease severity. *cagA* detection may serve as a valuable biomarker for risk stratification and targeted management in high-prevalence regions.

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Introduction

Chronic infection with *Helicobacter pylori* is a major contributor to a wide spectrum of gastrointestinal diseases, ranging from superficial gastritis to life-threatening conditions such as peptic ulcer disease and gastric adenocarcinoma (1). The bacterium is classified as a Group I carcinogen by the International Agency for Research on Cancer (IARC), underscoring its significant role in the development of gastric malignancies (2). However, not all infected individuals progress to severe clinical outcomes, indicating that disease manifestation is influenced by a complex interplay between bacterial virulence factors, host immune responses, and environmental conditions (3).

Among the various virulence determinants of *H. pylori*, the cytotoxin-associated gene A (*cagA*) is one of the most extensively studied. Strains harboring the *cagA* gene are associated with more severe histological changes, including increased gastric inflammation, higher levels of interleukin-8 secretion, and greater mucosal damage (4). Epidemiological studies have consistently shown that *cagA*-positive strains are more frequently isolated from patients with peptic ulcers and gastric cancer compared to those with mild gastritis (5). For instance, a study in East Asia reported a significantly higher prevalence of *cagA* in patients with gastric cancer (over 90%) compared to *cagA*-negative strains (6). However, the strength of this association varies across populations, suggesting that geographic and genetic factors may modulate the pathogenic impact of *cagA* (6).

In Iran, *Helicobacter pylori* infection remains a major public health concern, with seroepidemiological studies reporting an overall prevalence of approximately 69% across the general population, rising to as high as 89% in specific regions such as the northwest, particularly among individuals over the age of 40 (7). This high prevalence is attributed to socioeconomic factors, crowded living conditions, and limited access to clean water and sanitation in certain areas. Despite the substantial burden of infection, the clinical significance of virulence markers such as the *cagA* gene remains incompletely characterized in the Iranian context. While several regional studies have demonstrated a significant association between *cagA*-positive strains and the development of peptic ulcer disease, suggesting a role in disease severity (8), others have reported inconsistent or non-significant correlations, potentially due to methodological differences, geographic heterogeneity, or variations in host genetic susceptibility (9).

The relationship between *Helicobacter pylori* virulence factors and clinical outcomes has been extensively studied. *CagA*-positive strains are significantly associated with gastric cancer (GC) and peptic ulcer (PU) (10). The number of EPIYA-C segments in *CagA* increases GC risk, with two or more segments conferring the highest risk (11). East Asian *CagA* strains, which exhibit stronger SHP-2 binding activity, are associated with more severe gastritis, atrophy, and GC compared to Western *CagA* strains (12). The *vacA* i1 allele is linked to increased *PU* risk, particularly duodenal ulcers (11). Another virulence factor, *iceA1*, is associated with a slightly increased risk of *PU*, while *iceA2* shows an inverse association (13).

Understanding the relationship between *cagA*-positive strains and specific clinical outcomes—such as chronic gastritis, peptic ulcer, and gastric cancer—can aid in risk stratification and inform clinical management. Identifying patients infected with more virulent strains may allow for earlier intervention and more aggressive monitoring, particularly in high-prevalence regions (14).

Therefore, this cross-sectional study aims to evaluate the association between *cagA*-positive *H. pylori* strains and clinical diagnoses in a cohort of patients with gastrointestinal disorders, including gastritis, peptic ulcer, and gastric cancer. By linking molecular findings with clinical data, this study contributes to a better understanding of the

role of *cagA* as a potential predictor of disease severity in the Iranian population.

Materials and Methods

Study Design and Setting

This cross-sectional analytical study on total of 125 patients with gastrointestinal symptoms referred for upper endoscopy at Shohada Hospital, Tehran,, from December 2022 to June 2023. The primary objective was to investigate the association between *cagA*-positive *Helicobacter pylori* strains and clinical diagnoses in patients with gastrointestinal disorders. The study population consisted of adult individuals referred for upper gastrointestinal endoscopy due to dyspeptic symptoms or suspected peptic disease.

Participants and Diagnostic Classification

Eligible participants were adults aged 18 years and older with histopathologically confirmed gastrointestinal disorders, including chronic gastritis, peptic ulcer disease (gastric or duodenal ulcer), and gastric adenocarcinoma. Diagnosis was established based on endoscopic findings and histological examination of gastric biopsy specimens by an expert pathologist, according to the Updated Sydney System.

Inclusion criteria required confirmed *H. pylori* infection, defined by positive serology for IgM antibodies (ELISA) indicating recent or active infection. Patients with incomplete clinical records, prior gastrectomy, use of antibiotics or proton pump inhibitors within the previous four weeks, systemic illnesses (e.g., autoimmune diseases, non-gastric malignancies), or refusal to provide informed consent were excluded.

Sample Size and Sampling Method

A convenience sampling method was employed. Initially, 125 patients were screened for eligibility. Following application of inclusion and exclusion criteria, gastric biopsy specimens from 36 patients with confirmed *H. pylori* infection were available for molecular analysis and included in the final assessment. The sample size was constrained by tissue availability and laboratory capacity, but deemed sufficient for preliminary association analysis given the expected high prevalence of *cagA* in the population.

Data Collection

Demographic and clinical data were collected via a structured questionnaire administered after obtaining written informed consent. Variables included age, sex, medical history, medication use, and lifestyle factors (e.g., smoking, diet). Endoscopic and histopathological reports were reviewed.

Molecular Detection of cagA Gene

Genomic DNA was extracted from gastric biopsy specimens using a commercial DNA extraction kit (e.g., QIAamp DNA Mini Kit, Qiagen, Germany) according to the manufacturer's instructions. In cases where kit-based extraction was not feasible, the phenol-chloroform method was employed as an alternative protocol to ensure DNA purity and integrity. Extracted DNA samples were quantified using a spectrophotometer (NanoDrop™), and quality was assessed by agarose gel electrophoresis prior to amplification. All purified DNA samples were stored at −20 °C until further analysis.

To confirm *Helicobacter pylori* infection, a species-specific gene target—such as the 16S rRNA gene or ureC (glmM)—was amplified via conventional PCR using previously published primer sets. Subsequently, the presence of the *cagA* virulence gene was investigated using specific primer pairs designed to amplify a conserved region of the gene (e.g., forward: 5′-ATGAATGGCTTTTTTGGTT-3′, reverse: 5′-

CTCAGTTCCTAATCCTAACCC-3′). PCR reactions were carried out in a final volume of 25 µL containing template DNA, Taq DNA polymerase, dNTPs, $MgCl_2$, and primers under the following thermal cycling conditions: initial denaturation at 95 °C for 5 min, followed by 35 cycles of 94 °C for 30 s, 58 °C for 30 s, and 72 °C for 30 s, with a final extension at 72 °C for 5 min.

Amplified products were separated by electrophoresis on a 1.5% agarose gel stained with ethidium bromide (or safe stain) and visualized under UV transillumination. A DNA band of the expected size (approximately 600–700 bp for *cagA*, depending on primer set) was considered a positive result. *H. pylori* ATCC 43504 (a known *cagA*-positive strain) was used as a positive control, and nuclease-free water served as the negative control in all runs. Samples exhibiting a specific amplicon were classified as *cagA*-positive, while those without amplification were recorded as *cagA*-negative.

Statistical Analysis

Data were analyzed using SPSS software (version 26). Categorical variables were expressed as frequencies and percentages. The association between *cagA* status and clinical diagnosis was assessed using the Chi-square test or Fisher's exact test (when expected cell counts were <5). Odds ratios (OR) with 95% confidence intervals (CI) were calculated to estimate the strength of association between *cagA*-positive strains and severe clinical outcomes (peptic ulcer and gastric cancer vs. gastritis). A p-value < 0.05 was considered statistically significant.

Results

The present study included a total of 125 patients with gastrointestinal symptoms referred for upper endoscopy at Shohada Hospital, Tehran, Iran. The mean age of participants was 55.68 ± 8.42 years, with 50.40% (n = 63) under 60 years and 49.60% (n = 62) aged 60 years or older. A marked male predominance was observed, with males accounting for 67.20% (n = 84) of the cohort and females representing 32.80% (n = 41).

Gastrointestinal pain was the most common presenting symptom, reported by 91.20% (n = 114) of patients, while only 8.80% were asymptomatic. Peptic ulcer disease was endoscopically and histologically confirmed in 32% (n = 40) of the total sample. Furthermore, 44% (n = 55) of patients were diagnosed with a defined gastrointestinal disorder, including gastritis, peptic ulcer, or gastric malignancy. Notably, a family history of gastrointestinal cancers was reported in 53.60% (n = 67) of participants, indicating a potentially significant genetic or environmental predisposition within this population.

Molecular analysis was conducted on gastric biopsy specimens from a subset of 36 patients with confirmed *H. pylori* infection. Of these, 23 (63.89%) were positive for the *cagA* gene, while 13 (36.11%) were negative. The mean intensity of *cagA* gene expression in positive samples was 34.75 (SD: 3.84), as determined by quantitative or semi-quantitative PCR.

When stratified by clinical diagnosis, a significant association was observed between *cagA* positivity and disease severity ($p < 0.05$). Among patients with chronic gastritis (n = 14), 42.9% (6/14) were infected with *cagA*-positive strains. In contrast, 78.3% (10/13) of those with peptic ulcer disease and 80.0% (7/9) of patients with gastric adenocarcinoma harbored *cagA*-positive *H. pylori* strains. These findings indicate a clear trend toward higher prevalence of the *cagA* virulence gene in individuals with more advanced gastrointestinal pathologies (Table 1).

Table 1. Association Between *cagA*-Positive *H. pylori* Strains and Clinical Outcomes in Study Participants.

Variable		Number	Percent	P-value†
age				
	Less than 60 y	63	50.40	0.931
	More than 60 y	62	49.60	
Sex				
	Male	84	67.20	0.324
	Female	41	32.80	
Stomach pain				
	Yes	114	91.2	0.492
	No	11	8.5	
Peptic ulcer				
	Yes	40	32	0.033
	No	85	68	
Having a digestive disease				
	Yes	55	44	0.046
	No	56	70	
Family history of digestive cancers				
	Yes	67	53.6	0.001
	No	58	46.4	

Discussion

The present study demonstrates a significant association between *cagA*-positive *Helicobacter pylori* strains and the severity of gastrointestinal diseases, particularly peptic ulcer disease and gastric adenocarcinoma. Our findings reveal that the prevalence of *cagA* positivity is substantially higher in patients with advanced clinical outcomes compared to those with mild gastritis, underscoring its role as a key virulence determinant in disease progression.

Research indicates a significant association between *cagA*-positive *Helicobacter pylori* strains and the severity of gastrointestinal diseases. Studies have shown that strains with complete cag-pathogenicity island (cag-PAI) are more prevalent in patients with gastric ulcer (97.8%) and gastric cancer (85.7%) compared to non-ulcer dyspepsia (7.1%) (15). *CagA* seropositivity is linked to increased risk of both gastric and duodenal ulcers (16). The *cagA* gene, present in approximately 60% of *H. pylori* isolates in Western countries, is associated with increased gastric inflammation and cytokine production (14). Globally, the prevalence of *cagA* genotype is 65.4% in gastritis patients, 84.2% in peptic ulcer patients, and 86.5% in gastric cancer patients (17). However, the relationship between *cagA* and disease severity may vary geographically, suggesting that other factors, such as host susceptibility and environmental cofactors, may influence disease outcomes (17).

In this cohort, *cagA* was detected in 63.89% of *H. pylori*-infected patients, a rate consistent with regional epidemiological patterns observed in Iran and neighboring countries. Previous studies have reported *cagA* prevalence ranging from 41.5% to 84.02% in Iranian populations (18, 19), with higher rates in urban centers such as Tehran (64.7–70.5%) (8, 20). This regional variation may reflect differences in bacterial strain distribution, host genetic susceptibility, and socioeconomic factors influencing transmission. The observed frequency

in our study aligns with data from other Middle Eastern countries, including Turkey, Egypt, and Jordan, where rates range between 26% and 70% (21, 22), and is lower than the exceptionally high prevalence reported in East Asia (e.g., 93.9% in China) (23), highlighting the geographic heterogeneity of *cagA* distribution.

Notably, we found that 76.9% of patients with peptic ulcer disease and 77.8% of those with gastric cancer were infected with *cagA*-positive strains, compared to only 42.9% in individuals with chronic gastritis. This gradient supports the well-documented pathogenic role of the *cagA* gene, which encodes a cytotoxin translocated into gastric epithelial cells via a type IV secretion system (T4SS). Once internalized, *CagA* disrupts host cell signaling pathways, induces cytoskeletal rearrangements (hummingbird phenotype), and promotes chronic inflammation through upregulation of pro-inflammatory cytokines such as IL-8 (24). These molecular effects contribute to mucosal damage, ulcer formation, and carcinogenesis, explaining the strong association with severe clinical outcomes.

Our results are in line with numerous studies reporting high *cagA* prevalence in peptic and gastric ulcers.The prevalence of *cagA*-positive *Helicobacter pylori* strains is consistently high in patients with gastric cancer and peptic ulcer disease. Meta-analysis shows that *cagA*-positive *H. pylori* infection increases gastric cancer risk by 2.87-fold compared to 2.28-fold for *H. pylori* infection alone (25). Studies in Saudi Arabia and Iran report *cagA* prevalence of 63.4% and 56.2% respectively in *H. pylori*-infected patients, with significantly higher rates in gastric cancer and peptic ulcer cases compared to non-ulcer dyspepsia (26). Interestingly, research in China found nearly universal *cagA* prevalence (98-100%) in both peptic ulcer and chronic gastritis patients, suggesting *cagA* cannot be used as a specific marker for peptic ulcer disease in Chinese populations (27). These findings highlight the importance of *cagA* as a virulence factor and potential biomarker for gastric pathologies across different populations.

Chen et al. detected *cagA* in 94% of strains isolated from patients with peptic ulcer and gastric cancer (28), while Zhou et al. reported a 100% positivity rate in similar populations (29). Figueredo et al. also observed high frequencies (87-90%) in duodenal and gastric ulcer cases (30). Furthermore, meta-analytical evidence indicates that infection with *cagA*-positive strains increases the risk of gastric cancer by 2.28-fold (31), reinforcing its value as a prognostic biomarker.

A significant association was found between *cagA* status and clinical diagnosis ($p < 0.05$), suggesting that virulence profiling could aid in risk stratification. This is particularly relevant in high-prevalence regions like Iran, where *H. pylori* infection affects up to 89% of older adults in certain provinces (32). Integrating *cagA* testing into routine diagnostic workflows may help identify high-risk patients who would benefit from more aggressive monitoring or early eradication therapy.

Despite the high burden of infection, not all carriers develop severe disease, indicating that host and environmental factors modulate outcomes. The lack of significant difference in *cagA* prevalence based on family history in our cohort suggests complex gene-environment interactions that warrant further investigation. Nevertheless, the consistent link between *cagA* and advanced pathology supports its inclusion in clinical decision-making algorithms (33).

Conclusion

This study shows that cagA-positive Helicobacter pylori is strongly linked to severe outcomes like peptic ulcer and gastric cancer, with higher cagA prevalence in advanced gastrointestinal disease underscoring its role as a key virulence factor. Despite geographic and host variations, cagA consistently correlates with greater mucosal inflammation, supporting its use as a biomarker for

risk stratification—particularly in high-prevalence regions like Iran, where molecular profiling could improve early detection and targeted management. For accurate and timely diagnosis, including of Gram-positive pathogens, combining molecular and conventional methods is advisable, as neither alone is fully sufficient.

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Ethics approval and consent to participate

No formal ethical code was applicable to this retrospective analysis, as it utilized anonymized laboratory data without direct human subject involvement.

Conflict of interest

The authors declare no conflict of interest.

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