# Seroprevalence, symptom associations, and biomarker dynamics of *Helicobacter pylori* in dyspeptic patients from Kerman, Iran: A focus on CagA status

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## Abstract

**Introduction:** Infection with *Helicobacter pylori*, especially strains positive for the cytotoxin-associated gene A (CagA), is a well-recognized etiological factor in the carcinogenesis of gastric cancer; however, its relationship with serum cancer biomarker levels in non-cancerous individuals remains unclear.

**Objective:** This research was intended to assess the relationship between the status of *H. pylori* infection, CagA seropositivity, and levels of cancer antigens (CEA, CA19-9, and CA125) in dyspeptic patients without cancer diagnosis.

**Material and Methods:** We randomly selected 91 participants with digestive symptoms (70 *H. pylori* IgG-positive and 21 IgG-negative) and determined their CagA status using ELISA. Then, 50 CagA-positive and 10 CagA-negative patients were selected for the cancer biomarker sub-analysis using the electrochemiluminescence immunoassay.

**Results:** *H. pylori* IgG positivity and higher quantitative IgG titers were strongly associated with stomach pain, bloating, and belching ($p<0.001$). Anti-CagA IgG correlated significantly with stomach pain, belching, prior endoscopy, and a history of gastric ulcer. We did not observe significant differences in mean levels of CEA ($p = 0.25$), CA19-9 ($p = 0.90$), or CA125 ($p = 0.15$) between CagA-positive and

CagA-negative groups. Gender showed no significant association with biomarker levels, while age demonstrated a significant correlation with CEA levels (p=0.003); younger patients exhibited higher rates of abnormal CEA levels.

**Conclusion:** This study showed no significant association between *H. pylori* infection and CagA status and increased levels of cancer biomarkers in dyspeptic patients without a history of cancer. These results enhance the understanding of the complex relationship between *H. pylori* infection and cancer biomarker expression.

**Keywords**: CagA seropositivity, Cancer biomarkers, Dyspepsia, *Helicobacter pylori*, IgG-positive

## 1. Introduction

*Helicobacter pylori* is a gram-negative, spiral-shaped bacterium that resides within the gastric mucosa, affecting approximately 50% of the global population. It is a major contributor to chronic gastritis and peptic ulcer disease and is implicated in the pathogenesis of gastric cancer. While *H. pylori* is a primary driver of gastric pathology, other factors, including nutritional status and dietary composition, can also significantly influence gastric mucosal integrity and histological outcomes [1]. Strains of *H. pylori* that are cytotoxin-associated gene A (CagA)-positive are associated with more severe clinical manifestations and a heightened risk of developing gastric adenocarcinoma. The International Agency for Research on Cancer has classified *H. pylori* as a Group I carcinogen, emphasizing that CagA-positive strains pose the greatest oncogenic threat [2].

Serum tumor markers, including carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), and cancer antigen 125 (CA125), are glycoproteins that have been used in clinical practice for cancer diagnosis, monitoring treatment response, and detecting recurrence [3]. While these biomarkers are elevated in various malignancies, including gastric cancer, they can also be increased in benign conditions, limiting their specificity for cancer detection. Recent studies have suggested that *H. pylori* infection may influence levels of these biomarkers even in non-cancerous individuals, but the findings have been inconsistent [4,5]. The relationship between CagA-positive *H. pylori* infection and the modulation of cancer biomarker levels is still not fully elucidated. While some studies have reported elevated levels of markers, such as CEA, AFP, and CA724, in *H. pylori*-infected individuals, no significant association has been reported regarding the others (CA199, CA153, and CA125) [5,6]. This discrepancy highlights the need for further investigation into the potential influence of *H. pylori* virulence factors on cancer biomarker expression.

Iran has a high prevalence of *H. pylori* infection, with reported rates ranging from 55% to 70% in the general population [7]. In our previous study, we reported an overall *H. pylori* seroprevalence of 58.1% among Iranian dyspeptic patients, with CagA seropositivity rates of 52.9% and 61.9% in *H. pylori* IgG-

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positive and IgG-negative patients with severe symptoms, respectively [8]. Previous research in Iran has predominantly concentrated on the seroprevalence of *H. pylori* and the prevalence of CagA-positive strains. However, there has been a lack of investigation into the correlation between *H. pylori* infection and the levels of cancer biomarkers in dyspeptic patients who do not have a cancer diagnosis.

This research seeks to address this gap by investigating the possible relationship between *H. pylori* infection, CagA status, and serum concentrations of CEA, CA19-9, and CA125 in Iranian patients experiencing dyspepsia without a prior cancer diagnosis. Understanding this connection is vital for interpreting cancer biomarker results in the context of *H. pylori* infection and for developing suitable screening strategies for high-risk groups.

## 2. Materials and Methods

### *2.1. Study design and population*

This cross-sectional study was conducted on dyspeptic patients who presented to gastroenterology clinics in Kerman, Iran, between January 2016 and December 2017. The study obtained ethical clearance from the Ethics Committee at Kerman University of Medical Sciences (Approval Code: IR.KMU.REC.1397.154), and all participants provided written informed consent prior to their involvement.

Participants were included if they were aged 17-72 years and reported symptoms of digestive disorders, including bloating, abdominal pain, belching, or gastritis. Exclusion criteria included a history of cancer, previous *H. pylori* eradication therapy, use of antibiotics or proton pump inhibitors in the previous four weeks, pregnancy, and severe comorbidities, such as hepatic or renal failure. Accordingly, 659 patients were selected for the study, including 253 males and 406 females, with a mean age of 40.9±12 and 40.2±11, respectively.

### *2.2. Laboratory assays and statistical analysis*

The participants' *H. pylori* infection status and CagA IgG levels were determined using a commercial ELISA kit (Monobind Inc., USA) according to the manufacturer's instructions. We also detected anti-CagA IgG antibodies using a commercial ELISA kit (Euroimmun, Germany), according to the manufacturer's instructions. Also, the correlation of these factors with gender and age was analysed and reported in our previous publication [8]. Here, we evaluated the correlation of these factors' prevalence with patients' clinical symptoms.

### *2.3. Cancer biomarker measurement*

Based on the findings of *H. pylori* seroprevalence [8], we randomly selected 91 participants using a computer-generated random number sequence in SPSS software from the initial cohort of 659 patients for evaluation of their cancer biomarker levels. Among these 91 participants, 70 samples were *H. pylori* IgG-positive, and 21 samples were IgG-negative. For the CagA sub-analysis, we selected 50 CagA-

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positive patients and 10 CagA-negative controls (a 5:1 case-to-control ratio) to ensure adequate statistical power while conserving limited serum samples and resources. The 10 CagA-negative controls were randomly selected from the total pool of 41 CagA-negative patients.

We measured CEA, CA19-9, and CA125 levels using electrochemiluminescence immunoassay (ECLIA) on a Cobas e 411 analyser (Roche Diagnostics, Germany). In line with the guidelines provided by the manufacturer, the cutoff values for normal levels were defined as follows: CEA <5 ng/mL, CA19-9 <37 U/mL, and CA125 <35 U/mL.

### *2.4. Statistical Analysis*

Data were analyzed using SPSS version 21.0 (IBM Corp., USA). Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables were presented as frequencies and percentages. The Student's t-test was used to compare mean biomarker levels between groups. Chi-square tests were employed to assess associations between categorical variables. Logistic regression analyses were employed to control for potential confounding variables. A p-value <0.05 was regarded as statistically significant.

## 3. Results

### *3.1. Participant characteristics*

The prevalence of general anti-*H. pylori* IgG was 58.1%. In this study, males showed a seroprevalence of 54.5%, while females had a higher rate of 60.3%. This factor exhibited a positive correlation with age, but the effect of sex was not significant. Additionally, the prevalence of the anti-CagA IgG antibody was found to be 52.9% in seropositive patients and 61.9% in seronegative patients for general *H. pylori* IgG. The demographic characteristics and *H. pylori* IgG and anti-CagA IgG seroprevalence were reported in our previous publication [8].

### *3.2. Association of the patient's clinical symptoms and their age, gender, and H. Pylori status*

The p-values, presented in Table 1, indicate whether the correlation between the patient's clinical symptoms and their age, gender, and *H. Pylori* status is significant or not. Based on the results, a significant correlation was found between age group and history of endoscopy, such that patients in the 31 to 40 age group had the highest history of endoscopy. In comparison, the 10 to 20 age group had the lowest history. *H. pylori* IgG shows a statistically significant association with three symptoms: burping, bloating, and stomachache. Specifically, among individuals who were positive for *H. pylori* infection, 62.7% reported belching, 72.6% reported bloating, and 83% reported stomach pain. However, gender and steroid medication use showed no statistically significant associations with any listed symptoms at the p <0.05 level.

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Additionally, according to the t-test analyses (Table 2), symptoms like stomach pain, bloating, and belching are strongly associated with higher anti-*H. pylori* IgG levels. A history of endoscopy and stomach ulcer also correlates with elevated IgG, suggesting a link between *H. pylori* infection and these clinical features. However, steroid use showed no significant association with IgG levels. Notably, the consistently low p-values ($p < 0.001$) for key symptoms underscore the clinical relevance of IgG titers in assessing *H. pylori*-related symptomatology.

Table 2 also shows the relationship between the clinical symptoms and anti-CagA IgG levels. Based on the results, there was a significant correlation between stomach pain, belching, history of endoscopy, and history of stomach ulcer with anti-CagA IgG level. However, the association of bloating and a history of steroid drug use with this factor was insignificant.

### *3.3. Association of the H. pylori seroprevalence and cancer biomarker levels*

The study population consisted of 91 dyspeptic patients with dyspeptic symptoms, including 70 *H. pylori* IgG-positive and 21 IgG-negative individuals. Among the 91 participants tested for anti-CagA antibodies, 50 were positive, including 37/70 in the *H. pylori* IgG-positive group and 13/21 in the *H. pylori* IgG-negative group with dyspeptic symptoms. Three participants showed borderline results and were included in the positive group for subsequent analysis. For the cancer biomarker sub-analysis, we selected 50 CagA-positive patients and 10 CagA-negative controls (a 5:1 ratio).

Based on the t-test analysis, we failed to observe a statistically significant correlation between *H. pylori* infection status and abnormal levels of any cancer biomarker (CA125: $p = 0.640$; CA19-9: $p = 0.283$; CEA: $p = 0.190$). Similarly, no statistically significant association was detected between CagA status and abnormal biomarker levels (Table 3).

### *3.4. Association between demographic factors and cancer biomarkers*

Furthermore, the Chi-square test did not show a significant association between gender and the cancer biomarkers for any of the biomarkers (CA125: $p = 0.543$; CA19-9: $p = 0.472$; CEA: $p = 0.140$). Regarding age, we found no significant associations for CA125 ($p = 0.289$) or CA19-9 ($p = 0.798$). However, a significant correlation existed between age groups and the CEA biomarker ($p=0.003$). In the 10-20 year age group, 50% of samples had levels higher than normal. This is when, in the 41-50 year age group, 87.5% of samples had levels within the normal range.

## 4. Discussion

*H. pylori* is a Gram-negative, spiral-shaped bacterium that colonizes the human gastric mucosa and is considered a principal factor for chronic gastritis, peptic ulcer disease, and the development of gastric malignancies, including adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma.

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Affecting over half of the global population, *H. pylori* demonstrates pronounced geographical, demographic, and socioeconomic variations in its prevalence and pathogenic outcomes [9,10]. However, the present study specifically focused on the clinical symptoms and CagA seroprevalence in a dyspeptic cohort from Kerman, Iran, and did not evaluate socioeconomic variables.

Our previous study from Kerman uncovered a seroprevalence of general anti-*H. pylori* IgG of 58.1% among dyspeptic patients. Notably, while females exhibited a slightly higher rate (60.3%) than males (54.5%), the difference was not statistically significant. Also, an age-dependent increase in seropositivity was observed [8], aligning with patterns documented both within Iran and across global regions experiencing a high burden of infection [11]. This prevalence is substantial, though it aligns with other Iranian studies where seropositivity rates among dyspeptic patients are. For example, *H. pylori* infection has been reported at 41.5% in Southern regions [12], 72.8% in the northeast [13], and 57% in the southwest [14]. According to a systematic review by Eshraghian (2014), the total prevalence of *H. pylori* infection across Iran, regardless of age and time period, varied between 30.6% and 82%. In contrast, the overall prevalence of *H. pylori* infection in other Eastern Mediterranean nations (Kingdom of Saudi Arabia, Egypt, United Arab Emirates, Libya, Oman, Tunisia, and Lebanon), irrespective of age and time, ranged from 22% to 87.6% [15].

Our study identified belching, bloating, and stomach pain as symptoms significantly associated with anti-*H. pylori* IgG positivity. This triad represents established dyspeptic complaints linked with *H. pylori*-induced gastritis and matches the pattern described in broader Iranian and international literature [16]. The specificity of these associations is supported by mechanistic insights; *H. pylori* induces chronic gastric inflammation, mucosal dysfunction, and altered gastric motility, manifesting clinically as pain, distension, and excessive gas production [17,18]. Notably, both Iranian and Western clinical guidelines now advocate noninvasive *H. pylori* testing in patients presenting with these symptoms, especially in moderate-to-high prevalence regions [19].

Our cohort study on the Kerman participants reported an anti-CagA IgG prevalence of 52.9% in patients seropositive for general anti-*H. pylori* IgG, and a surprisingly higher rate (61.9%) in seronegative patients with severe dyspeptic symptoms. This discordance has been interpreted as evidence that anti-CagA IgG can persist longer in serum than general anti-*H. pylori* IgG or that sole CagA positivity may reflect a recently cleared general infection or a more intense host response to virulent CagA-positive strains [8]. CagA positivity has major implications for clinical and epidemiological research. First, the detection of anti-CagA antibodies in seronegative individuals is increasingly recognized as a diagnostic window for prior or ongoing infection with virulent strains, even when anti-*H. pylori* IgG has waned. Second, regional studies (including Iranian meta-analyses) report CagA positivity rates in *H. pylori*-infected patients ranging from 46.9% [20] to 70% [21], which support our findings in Kerman and signal a pronounced burden of more virulent *H. pylori* lineages in the Middle East [22].

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The correlation between anti-CagA IgG levels and specific clinical features was significant for stomach pain, belching, history of endoscopy, and prior stomach ulcer. This pattern follows previous reports and underscores the importance of CagA status in the prediction of more severe or complicated presentations of *H. pylori* infection [23]. CagA positivity marks more virulent strains and is mechanistically associated with increased inflammatory and carcinogenic potential in the gastric mucosa. Numerous mechanistic and clinical studies show that CagA triggers SHP2-ERK/MAPK, PI3K/Akt, NF-κB, and JAK/STAT signaling pathways, promoting cellular proliferation, mucosal damage, and precancerous changes [24–26]. Clinically, CagA serology thus provides a strong noninvasive biomarker for stratifying at-risk dyspeptic patients, and, in conjunction with endoscopic and histopathologic findings, may guide optimized surveillance and early interventions.

Analysis of 91 dyspeptic patients revealed no significant association between *H. pylori* serostatus and abnormal levels of cancer markers CA125, CA19-9, or CEA. Also, we did not find a statistically significant association between anti-CagA IgG status and abnormal levels of CA125, CA19-9, or CEA. These observations may reflect the relatively small sample size of our biomarker sub-cohort (50 cases and 10 controls). Although *H. pylori* (notably CagA-positive strains) is a recognized class I carcinogen and a critical driver of gastric cancer (GC) risk, the utility of "routine" serum tumor markers (CEA, CA19-9, CA125) for early detection or risk prediction of gastric malignancy remains equivocal in this context. Studies have shown that these markers, while valuable in advanced and metastatic cancer (especially for surveillance and prognosis), lack sensitivity and specificity for early GC in high-risk, *H. pylori*-infected populations [27,28]. However, other studies acknowledge that chronic, symptomatic *H. pylori* infection, especially when long-term and associated with precancerous changes, may be linked to moderately increased tumor marker levels, warranting further stratification by duration and clinical presentation [5,29]. Besides, all participants of our study tested for cancer biomarkers were, according to the self-report, free of any cancer and suspicious symptoms of it until the date of testing. Therefore, the lack of a significant association between the level of anti-*H. pylori* IgG antibody and anti-CagA antibody with cancer biomarkers might be attributed to the fact that all investigations were performed in healthy individuals.

While this study provides valuable insights, several limitations should be acknowledged. The biomarker sub-analysis was constrained by a limited sample size, particularly the 10 CagA-negative controls, which may reduce statistical power and introduce a risk of Type II error; therefore, the null findings regarding cancer biomarkers should be viewed as preliminary rather than definitive. Additionally, socioeconomic factors were not collected, and the single-center design in Kerman, Iran, may limit generalizability. Furthermore, the inherent non-specificity of serum tumor markers (CEA, CA19-9, CA125) should be noted. Despite these limitations, this study offers valuable preliminary data on the interplay between *H. pylori* CagA status and cancer biomarkers, laying the groundwork for future larger, multicenter investigations.

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## 5. Conclusion

This study demonstrates that serologic evidence of *H. pylori* exposure, including quantitative IgG titers and anti-CagA status, is closely associated with key dyspeptic symptoms and a greater likelihood of prior endoscopic assessment, but is not accompanied by changes in general cancer biomarkers CA125, CA19-9, or CEA in a symptomatic outpatient population. These results support the use of targeted serologic testing and symptom-driven endoscopy for patient triage while discouraging routine reliance on CA125, CA19-9, or CEA for *H. pylori*–related diagnostic or prognostic purposes; longitudinal studies integrating endoscopic, histologic, and gastric-specific biomarkers are recommended to refine screening and surveillance algorithms.

**Aknowledgment**

Not applicable

**Ethical approval**

The study was approved by the Ethics Committee of Kerman University of Medical Sciences (Code: IR.KMU.REC.1397.154). All participants provided written informed consent.

**Conflict of interest**

The authors declare that they have no conflicts of interest.

**Authors' contribution**

1. Study concept and design: Sadegh Afzali (lead: conceptualization); Mojtaba Alimolaei (contributed to methodology and study design).
2. Acquisition of data: Sadegh Afzali and Faranak Saeidnia (both responsible for investigation); Shirin Soltani (provided resources to support data collection).
3. Analysis and interpretation of data: Sadegh Afzali (formal analysis and primary interpretation); Sadegh Khorrami (validation and interpretation support).
4. Drafting of the manuscript: Shirin Soltani (writing —original draft).
5. Critical revision of the manuscript for important intellectual content: Mojtaba Alimolaei and Sadegh Khorrami (writing — review & editing).
6. Statistical analysis: Sadegh Afzali (formal/statistical analysis).
7. Administrative, technical, and material support: Faranak Saeidnia and Sadegh Khorrami (resources and technical/material support).
8. Study supervision: Mojtaba Alimolaei (overall supervision).

All authors reviewed and approved the final manuscript.

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366

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