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Association between *Helicobacter pylori* infection and the types of tumor markers among Yemeni gastric cancer patients: a case-control study

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Abstract

Objectives This study aims to investigate the relationship between *H. pylori* infection and types of tumor markers (CEA and CA19-9) among Yemeni gastric cancer patients, comparing the frequency of these markers in patients with and without *H. pylori* infection.

Results Serum CEA and CA19-9 levels were measured among 85 patients with *H. pylori* infection (cases) and 85 without (controls). The median CEA levels were 7.05 ng/mL in *H. pylori* positive group and 7.14 ng/mL in negative group. The median CA19-9 levels were 33 U/mL in *H. pylori* positive group and 32 U/mL in negative group. No significant differences were found in the serum levels of CEA ($p = 0.44$) or CA19-9 ($p = 0.94$) between the two groups. However, a significant association was observed between *H. pylori* infection and gastric cancer site in cardia and fundus regions ($p = 0.047$). This study found no significant association between *H. pylori* infection and types of tumor markers (CEA and CA19-9) among Yemeni gastric cancer patients. However, the significant association between *H. pylori* infection and site of gastric cancer in cardia and fundus regions needs further investigations to reveal the associated mechanisms.

Keywords *Helicobacter pylori*, Gastric cancer, Tumor markers, Yemen

Introduction

Gastric cancer continues to pose a serious global health challenge, ranking as the fifth most common cancer and the third leading cause of cancer-related deaths worldwide [1, 2]. Among the various risk factors, *Helicobacter pylori* (*H. pylori*) infection stands out as one of the most significant, having been classified as a Group 1 carcinogen by the International Agency for Research on Cancer [1, 3]. The prevalence of *H. pylori* infection varies across different regions, with developing countries experiencing higher rates due to issues such as inadequate sanitation and overcrowded living conditions [4–6] .

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The crude global prevalence of *H. pylori* infection has demonstrated a notable decline over recent decades, decreasing from 52.6% before 1990 to 43.9% among adults between 2015 and 2022. However, *H. pylori* infection rate remains relatively high in in children and adolescents, with a prevalence of 35.1% observed during the same period [7]. In Yemen, the prevalence of *H. pylori* infection is particularly high, with studies suggesting that around 70% of the population is affected. This widespread occurrence highlights the significant burden of *H. pylori* in the region [8–10]. While the role of *H. pylori* in the development of gastric cancer is well established, the relationship between the infection and specific types of tumor markers remains an area of ongoing research. Some studies have indicated that tumor markers like carcinoembryonic antigen (CEA) and carbohydrate antigen 19 – 9 (CA19-9) may be linked to *H. pylori* infection, possibly serving as indicators of gastric cancer risk [11–15]. However, the prevalence of specific types of tumor markers in patients with and without *H. pylori* infection has not been thoroughly examined.

H. pylori has multiple virulence factors (e.g. type IV secretion system and the CagA toxin) which may help *H. pylori* infection to progress to gastric carcinoma [16, 17]. Studies reported serum CEA to have excellent diagnostic efficacy in gastric cancer and other gastrointestinal tumors [18]. CA724 showed no diagnostic value in gastrointestinal tumors [19] .

In a recent cross-sectional study conducted in Yemen, Saeed et al., 2023, assessed serum tumor markers in individuals infected with *H. pylori* who had not yet developed gastric cancer [20]. However, they did not address whether the type of tumor markers differs in relation to *H. pylori* infection. Therefore, this study aims to fill this gap by comparing tumor marker profiles between *H. pylori*-infected and non-infected gastric cancer patients which may enhance our understanding of the disease and allow early detection and management of the disease in regions with a high prevalence of *H. pylori*.

Methods

Study design and population

This case-control study was conducted in Sana'a, Yemen, on 21th January 2022 to 25th December 2023. The study involved 170 patients diagnosed with gastric cancer at the National Oncology Center in Sana'a city, Yemen. Patients were divided into two groups: 85 gastric cancer patients infected with *H. pylori* (case group) and 85 gastric cancer patients not infected with *H. pylori* (control group). The inclusion criteria for participants were a confirmed diagnosis by a biopsy sent to histopathology lab to determine the type of gastric cancer and computed tomography (CT) scan to determine the cancer stage as well as laboratory testing for *H. pylori* infection using the stool antigen test. Exclusion criteria included patients with a history of gastric surgery, other malignancies, or those who had received antibiotic treatment for *H. pylori* eradication in the last six weeks or proton-pump inhibitors within the last two weeks. In addition, patients with diarrhea were also excluded.

Data collection

Demographic and clinical data were collected using a structured questionnaire developed specifically for this study. It was administered through face-to-face interviews and medical record reviews. Information collected included age, gender, socioeconomic status, education level, smoking status, dietary habits, and family history of gastric cancer. All patients were freely participated and withdrawal without given any reasons.

Laboratory tests

H. pylori infection was determined using a stool antigen test (Abon Biopharm, Hangzhou Co. Ltd, China). Blood samples were collected from all participants, centrifuged to obtain serum, and stored at -20 °C until analysis. Tumor markers, carcinoembryonic antigen (CEA) and carbohydrate antigen 19 – 9 (CA19-9), were measured using electrochemiluminescence immunoassay (ECLIA) kits according to the manufacturer's instructions (Elecsys, Roche Company, Germany). The levels of these tumor markers were analyzed to determine their frequency in both the *H. pylori* positive and negative groups. Laboratory investigations were done at One Lab laboratory, Sana'a city, Yemen.

Statistical analysis

Data were analyzed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) and compared using the Student's t-test or Mann-Whitney U test, depending on the distribution. Categorical variables, including the types of tumor markers, were expressed as frequencies and percentages, and compared using the chi-square test or Fisher's exact test when appropriate. The association between *H. pylori* infection and the types of tumor markers (CEA and CA19-9) was assessed using logistic regression analysis, adjusting for potential confounders such as age, gender, and socioeconomic status. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. A *P*-value of < 0.05 was considered statistically significant.

Results

Demographic characteristics of gastric cancer patients

The demographic characteristics are summarized in Table 1. The mean age of participants was 56.05 ± 13.145 years, with a majority (62.4%) in the 30–60 age group.

Table 1 Demographic characteristics of gastric cancer patients in Sana'a, Yemen (2022–2023)

Characteristic	Cases (H. pylori positive)	Controls (H. pylori negative)	Total	*P*-value
Age groups (years)				
≤ 30	3 (3.5%)	2 (2.4%)	5 (2.9%)	0.20
30–60	58 (68.2%)	48 (56.5%)	106 (62.4%)	
≥ 61	24 (28.2%)	35 (41.2%)	59 (34.7%)	
Mean ± STD*	54.68 ± 13.101	57.41 ± 13.124	56.05 ± 13.145	
Gender				
Males	60 (70.6%)	63 (74.1%)	123 (72.4%)	0.61
Females	25 (29.4%)	22 (25.9%)	47 (27.6%)	
Socioeconomic Status				
Low	56 (65.9%)	57 (67.1%)	113 (66.5%)	0.84
Moderate	27 (31.8%)	27 (31.8%)	54 (31.8%)	
High	2 (2.4%)	1 (1.2%)	3 (1.8%)	
Education Level				
Illiterate	40 (47.1%)	35 (41.2%)	75 (44.1%)	0.65
Primary	23 (27.1%)	30 (35.3%)	53 (31.2%)	
Moderate	18 (21.2%)	15 (17.6%)	33 (19.4%)	
High	4 (4.7%)	5 (5.9%)	9 (5.3%)	
Total	85 (100%)	85 (100%)	170 (100%)	

*STD: standard deviation

Table 2 Association of *H. pylori* infection with tumor marker types (CEA and CA19-9) in gastric cancer patients in Sana'a, Yemen (2022–2023)

Tumor marker	Cases (H. pylori +)	Controls (H. pylori -)	Mann-Whitney	*P*-value
CEA	7.05 (0.18–529)	7.14 (0.18–3019)	3364	0.44
CA19-9	33 (0.3-29852)	32 (0.65–513)	3590	0.94

Values are presented as Median (range), CEA = Carcinoembryonic Antigen, CA19-9 = Carbohydrate Antigen 19 – 9

There were no statistically significant differences between the groups in terms of age, gender, socioeconomic status, or education level ($P > 0.05$ for all variables).

Association of *H. pylori* infection with tumor marker types

The analysis of tumor marker types (CEA and CA19-9) was conducted in both groups. The median CEA levels were 7.05 ng/mL (range: 0.18–529) in the case group and 7.14 ng/mL (range: 0.18–3019) in the control group. The median CA19-9 levels were 33 U/mL (range: 0.3-29852) in the case group and 32 U/mL (range: 0.65–513) in the control group. However, no significant differences were observed in the prevalence or types of tumor markers between the two groups ($P = 0.44$ for CEA and $P = 0.94$ for CA19-9), as shown in Table 2.

Risk factors for *H. pylori* infection

The analysis of potential risk factors for *H. pylori* infection among gastric cancer patients is presented in Table 3. There were no statistically significant associations between *H. pylori* infection and gender ($P = 0.61$), age group ($P = 0.20$), socioeconomic status ($P = 0.84$), or education level ($P = 0.65$). Additionally, factors such as living in crowded homes, having a family member with *H. pylori* infection, hand hygiene practices, eating from restaurants, and smoking were not significantly associated with *H. pylori* infection ($P > 0.05$ for all).

Association of *H. pylori* infection with the site of gastric cancer

The association between *H. pylori* infection and the site of gastric cancer is summarized in Table 4. A significant association was observed between *H. pylori* infection and cancer in the cardia and fundus region ($P = 0.047$). However, no significant associations were found between *H. pylori* infection and other cancer sites such as the diffuse, body and antrum, body, antrum, or other locations ($P > 0.05$ for all).

Discussion

Although several studies reported an association between tumor markers (CEA and CA19-9) and *H. pylori* infection [21, 22], the results of this study indicate that *H. pylori* infection is not significantly associated with the tumor marker profiles, CEA and CA19-9, in Yemeni gastric cancer patients. Absence of a significant association between *H. pylori* infection and tumor marker expression among gastric cancer patients may be attributed to the heterogeneity of gastric cancer, including morphological

Table 3 Risk factors for getting H. pylori infection among in gastric cancer patients in Sana'a, Yemen (2022–2023)

Risk factor	Cases (H. pylori +)	Controls (H. pylori -)	OR	CI (95%)	χ2	*P*-value
Gender (Male)	60 (70.6%)	63 (74.1%)	0.84	0.43–1.64	0.27	0.61
Age group (31–60 years)	58 (68.2%)	48 (56.5%)	-	-	3.19	0.20
Low socioeconomic status	56 (65.9%)	57 (67.1%)	-	-	0.34	0.84
Illiterate	40 (47.1%)	35 (41.2%)	-	-	1.64	0.65
Living in crowded home	67 (78.8%)	64 (75.3%)	0.82	0.40–1.68	0.3	0.58
Family member with H. pylori	38 (44.7%)	33 (38.8%)	-	-	5.22	0.07
Washing hands before eating	80 (94.1%)	77 (90.6%)	-	-	0.79	0.67
Eating from restaurants	68 (80%)	66 (77.6%)	0.87	0.42–1.81	0.14	0.71
Smoking	58 (68.2%)	55 (64.7%)	0.85	0.45–1.62	0.24	0.63

Table 4 Association of H. pylori with the site of cancer in gastric cancer patients in Sana'a, Yemen (2022–2023)

Site of cancer	H. pylori positive	H. pylori negative	Total	Chi-square (χ2)	*P*-value
Cardia	15 (17.6%)	23 (27.1%)	38 (22.4%)	1.68	0.194
Diffuse	17 (20%)	10 (11.8%)	27 (15.9%)	1.81	0.178
Body and antrum	11 (6.5%)	7 (4.1%)	18 (10.6%)	0.89	0.346
Body	9 (10.6%)	9 (10.6%)	18 (10.6%)	0.00	1.000
Antrum	7 (8.2%)	10 (11.8%)	17 (10%)	0.53	0.467
Cardia and fundus	11 (12.9%)	3 (3.5%)	14 (8.2%)	4.57	0.047*
Cardia and body	6 (7.1%)	6 (7.1%)	12 (7.1%)	0.00	1.000
Fundus and body	4(4.7%)	7(8.2%)	11(6.5%)	0.8	0.5
Fundus	1(1.2%)	7(8.2%)	8(4.7%)	3.3	0.06
Cardia and antrum	1(1.2%)	0(0%)	1(0.6%)	1.0	1
Cardia, fundus and body	2(2.4%)	1(1.2%)	3(1.8%)	0.3	1
Cardia, fundus and antrum	1(1.2%)	2(2.4%)	3(1.8%)	0.3	1
Total	85 (100%)	85 (100%)	170 (100%)		

*Fisher's Exact test

subtypes (intestinal vs. diffuse) and molecular subtypes (MSI, EBV, TP53 mutation) [23–25]. It could be also attributed to presence of different strains of *H. pylori* that have varying levels of pathogenicity due to genetic diversity (e.g., *cagA* and *vacA* gene variations). Strain differences may influence their role in carcinogenesis and their association with specific tumor markers [26–28].

Furthermore, the considerable variability observed in both CEA and CA19-9 levels underscores significant interpatient differences, which may be attributed to factors such as advanced disease stages in some individuals or the presence of other underlying clinical conditions. This heterogeneity possibly contributes to the lack of statistically significant findings and highlights that tumor marker concentrations in gastric cancer patients are modulated by a complex interaction of tumor burden, histopathological characteristics, and individual patient-specific variables, rather than being determined solely by *H. pylori* infection [29, 30].

Unlike other studies from the West which reported *H. pylori* to be commonly associated with tumors located distally (antrum/pylorus), this study found *H. pylori* to be significantly associated with cardia and funds tumors [31–33]. On the other hand, our result is in agreement with studies from the Asia which reported *H. pylori* to be associated with cardia gastric cancer, suggesting that regional factors such as dietary habits, environmental exposures, or host genetic predispositions may influence tumor site preference in *H. pylori*-associated carcinogenesis [34–36]. Interestingly, other tumor sites such as antrum, body, or combinations did not show significant associations with *H. pylori*. This may suggest evolving tumor migration patterns, multifocal involvement, or variation in disease progression pathways [37, 38].

Moreover, the absence of significant associations between *H. pylori* infection and demographic factors, such as age, gender, socioeconomic status, and education level, is consistent with some previous studies, although others have reported contrasting results [39–41]. In Yemen, the high prevalence of *H. pylori* infection, regardless of these demographic factors, may be due to widespread risk factors such as poor sanitation and inadequate hygiene practices [8, 10].

Limitations

Biopsy-based diagnosis for *H. pylori* was a limitation due to cost and technical issues. Excessive anatomical subgrouping posed another limitation. Due to the ongoing humanitarian crisis and collapsing healthcare infrastructure in our country, many patients present with advanced gastric cancer making reliable Tumor–Node–Metastasis (TNM) staging is often unavailable.

Conclusion and recommendation

Lack of association between *H. pylori* and type of tumor markers implies that the mechanisms driving tumor markers' expression in stomach cancer may be *H. pylori* independent pathways, suggesting that once cancer has developed, the tumor's biological behavior and marker expression are likely influenced by factors beyond the initial infectious trigger. Further studies on the association between *H. pylori* infection and type of tumor markers based on the morphological and molecular gastric cancer subtypes as well as *H. pylori* strains are recommended.

Abbreviations

H. pylori	*Helicobacter pylori*
CA19-9	Carbohydrate antigen 19-9
CEA	Carcinoembryonic antigen
TNM	Tumor-Node-Metastasis

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Author contributions

AMO and AA wrote the main text, ASA and GTA perform the practical part, NMA, KHJ and AAA participated in revision. AMO and NMA perform data analysis. All authors participated in revision and corrections of final drafts.

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Data availability
The data that support the findings of this study are available. Anyone interested can get upon reasonable request from corresponding author.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethics Committee of the Faculty of Medicine and Health Sciences, Sana'a University (Approval No: FMHS/2022/019). Written informed consent was obtained from all participants before enrollment in the study. Participants were assured of the confidentiality of their information and their right to withdraw from the study at any time without any consequences. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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