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Helicobacter pylori as a Risk Factor for Digestive Malignancies

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Abbreviations:
Helicobacter pylori: H. pylori;
OR: odds ratio;
aOR: adjusted odds ratio;
CI: confidence interval;
CEA: carcinoembryonic antigen;
CA 19-9: carbohydrate antigen 19-9;
EPV: events per parameter;
GERD: gastroesophageal reflux disease;
IQR: interquartile range;
VIF: variance inflation factor.

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Rezumat

Helicobacter pylori - factor de risc pentru cancerele digestive

Context: Helicobacter pylori este un carcinogen recunoscut, clasificat în Grupa 1, fiind principalul factor patogen implicat în adenocarcinomul gastric. Deşi rolul său în carcinogeneza gastrică este bine caracterizat, potențiala sa influență oncogenă sistemică asupra neoplaziilor digestive extragastrice rămâne un subiect de cercetare clinică. *Obiectiv:* Obiectivul principal al acestui studiu a fost evaluarea asocierii dintre seropozitivitatea pentru H. pylori şi prezența neoplaziilor gastrice sau colonice. Un obiectiv secundar, explorator, a vizat evaluarea asocierii dintre seropozitivitatea pentru H. pylori şi rezultatul chirurgical (rezecție R0 versus intervenție non-R0/non-curativă) într-un lot distinct de pacienți operați pentru cancer digestiv.
Metode: Am realizat un studiu transversal retrospectiv pe un eşantion de 330 de pacienți, evaluați în perioada februarie 2023 şi mai 2025, stratificați în funcție de statusul serologic pentru H. pylori, determinat prin testarea anticorpilor anti-H. pylori. Au fost utilizate modele de regresie logistică pentru a analiza asocierile dintre seropozitivitatea anti-H. pylori şi diferite tipuri de neoplazii. O analiză exploratorie a inclus un lot separat de 60 de pacienți operați pentru cancer digestiv între aprilie 2023 şi decembrie 2025.
Rezultate: Seropozitivitatea pentru H. pylori a fost asociată cu prezența cancerului gastric (aOR 4,00; IC 95% 1,59–11,5; p = 0,005), precum şi a cancerului de colon (aOR 3,47; IC 95% 1,58–8,12; p = 0,003). Asocierile s-au menținut în analizele de sensibilitate, inclusiv în regresia Firth. Cancerul de colon a fost mai frecvent la pacienții cu sângerări gastrointestinale oculte (17,3% față de 7,7%; OR brut 2,50; IC 95% 1,20–5,26). În subgrupul chirurgical, format din 60 de pacienți operați pentru neoplazii digestive, seropozitivitatea nu a fost asociată cu rezecția curativă (OR pentru intervenția non-curativă 0,99; IC 95% 0,35–2,74).
Concluzii: Seropozitivitatea pentru H. pylori a fost asociată cu o prevalență crescută a neoplaziilor gastrice şi colorectale, cea mai puternică asociere fiind observată în cazul cancerului gastric. Deoarece serologia nu confirmă o infecție activă, iar designul studiului a fost de tip transversal, aceste rezultate trebuie interpretate ca asocieri, şi nu ca dovezi de cauzalitate sau de beneficiu preventiv al terapiei de eradicare.

Cuvinte cheie: Helicobacter pylori, cancer gastric, cancer de colon, cancer esofagian, carcinogeneză

Abstract

Background: Helicobacter pylori is a recognized Group 1 carcinogen and the primary pathogenic driver of gastric adenocarcinoma. Although its role in gastric carcinogenesis is well characterized, its potential systemic oncogenic influence on extra-gastric digestive malignancies remains under clinical investigation. *Objective:* The main objective of this study was to assess whether anti-H. pylori seropositivity was associated with the presence of gastric or colonic neoplasms. A secondary, exploratory objective was to evaluate whether anti-H. pylori seropositivity was associated with the surgical outcome (R0 resection versus non-R0/non-curative surgery) in a separate series of patients operated on for digestive cancer.
Methods: We conducted a retrospective cross-sectional study of 330 patients evaluated between February 2023 and May 2025 stratified by anti-H. pylori serological status, assessed using anti-H. pylori antibody testing. Logistic regression models were used to investigate associations between anti-H. pylori seropositivity and different types of neoplasms. An exploratory analysis included a separate series of 60 patients operated on for digestive cancer between April 2023 and December 2025.
Results: Anti-H. pylori seropositivity was associated with the presence of both gastric cancer (aOR 4.00, 95% CI 1.59-11.5, p = 0.005) and colon cancer (aOR 3.47, 95% CI 1.58-8.12, p = 0.003). The associations were consistent in sensitivity analyses, including Firth penalized regression. Occult gastrointestinal bleeding, a likely manifestation of the tumour, was more frequent in patients with colon cancer (17.3 % vs 7.7%; crude OR 2.50, 95% CI 1.20-5.26). In the surgical series of 60 patients who underwent surgery for digestive neoplasms, seropositivity was not associated with curative resection (OR for non-curative surgery 0.99, 95% CI 0.35-2.74).
Conclusions: Anti-H. pylori seropositivity was associated with an increased prevalence of gastric and colonic neoplasia, with the strongest association observed for gastric cancer. Because serology does not confirm active infection and the study design was cross-sectional, these findings should be interpreted as associations rather than evidence of causality or preventive benefit from eradication therapy.

Keywords: Helicobacter pylori, gastric cancer, colon cancer, esophageal cancer, carcinogenesis, surgical outcomes

Introduction

Gastrointestinal malignancies represent a major global public health challenge. Their reported annual incidence is nearly 5 million cases, with approximately 3.5 million deaths each year (1). These tumors account for more than 30% of all fatal cancers worldwide, with an estimated proportion of 36.3%, making the identification of modifiable risk factors a priority for clinical and public health strategies (1,2). H. pylori is a chronic bacterial infection with worldwide endemicity and a well-established association with gastric adenocarcinoma (3). However, certain digestive cancers are projected to increase by nearly 95% by 2050 (4). Therefore, the potential contribution of this organism to gastrointestinal cancer burden warrants renewed investigation (5). Understanding the effects of H. pylori infection is important for developing effective prevention strategies against the growing global cancer burden (3).

The classification of H. pylori as a Group I carcinogen reflects its role in chronic inflammation, which provides the biological basis for gastric carcinogenesis (6). Two primary mechanisms have been described: 1) chronic inflammation and 2) strain-dependent virulence factors, such as CagA and VacA (7). Recent work suggests that extracellular vesicles play an important role in intercellular communication during this inflammatory process along the gastrointestinal tract (8). Although recent findings have provided additional insight into these mechanisms, the exact immunopathological pathways through which H. pylori mediates its effects remain incompletely understood. Clinical interventions have primarily focused on eradication and primary prevention at the level of the gastric mucosa, leaving the remaining gastrointestinal tract comparatively under-investigated (9).

Considerable scientific uncertainty remains regarding the role of H. pylori in extra-gastric malignancies, including its potential systemic effects. Some evidence supports possible associations with colorectal and pancreatic cancers; however, findings remain inconsistent and often conflicting across populations (9-11). A major limitation of the existing literature is that many studies examine individual

malignancy sites rather than providing a comprehensive assessment of the potential effects of H. pylori across different segments of the digestive tract (9, 12). Without integrated data on H. pylori and digestive tract neoplasia, it remains difficult to determine whether this organism functions as a generalizable risk marker for digestive neoplasia. Additional observational evidence is therefore needed to clarify these complex associations through integrated multi-site analyses (9,12,13).

The purpose of this retrospective cross-sectional study was to assess the relationship between anti-H. pylori seropositivity and gastrointestinal malignancies. The main objective was to evaluate whether anti-H. pylori seropositivity was associated with the presence of gastric and colon cancer in a hospital-based sample. Secondary, exploratory objectives were to describe the association with esophageal cancer and with the surgical outcome in a separate surgical series.

Methods

Study Design and Population

This retrospective, cross-sectional, study included a cohort of 330 patients evaluated in a single medical center between February 2023 and May 2025. Patients were classified according to the presence or absence of anti-H. pylori antibodies. Because H. pylori status was determined by serological testing, the exposure variable in this study reflects anti-H. pylori seropositivity rather than confirmed active infection. The comparison group comprised patients from the same source population in whom esophageal, gastric and colon cancer were excluded by upper endoscopy, colonoscopy and imaging. Eleven of them had other known or suspected malignancies (hepatocellular carcinoma, pancreatic, duodenal, bladder or ovarian tumors, a gastrointestinal stromal tumor, a previously operated colon cancer, liver metastases or malignant ascites); they were retained in the main analysis and excluded in a sensitivity analysis. Patient selection is shown in *Fig. 1.*

Inclusion and Exclusion Criteria

Patients were included if they met all of the following criteria:

- age ≥18 years;
- documented anti-H. pylori serology result (positive, negative or indeterminate) and a confirmed or excluded diagnosis of oesophageal, gastric or colon cancer;
- sufficient diagnostic evaluation (clinical, endoscopic, imaging, and/or histopathological) to confirm or exclude malignancy;

Patients were excluded if they had:

- missing or incomplete data regarding anti-H. pylori serological status or oncological diagnosis;

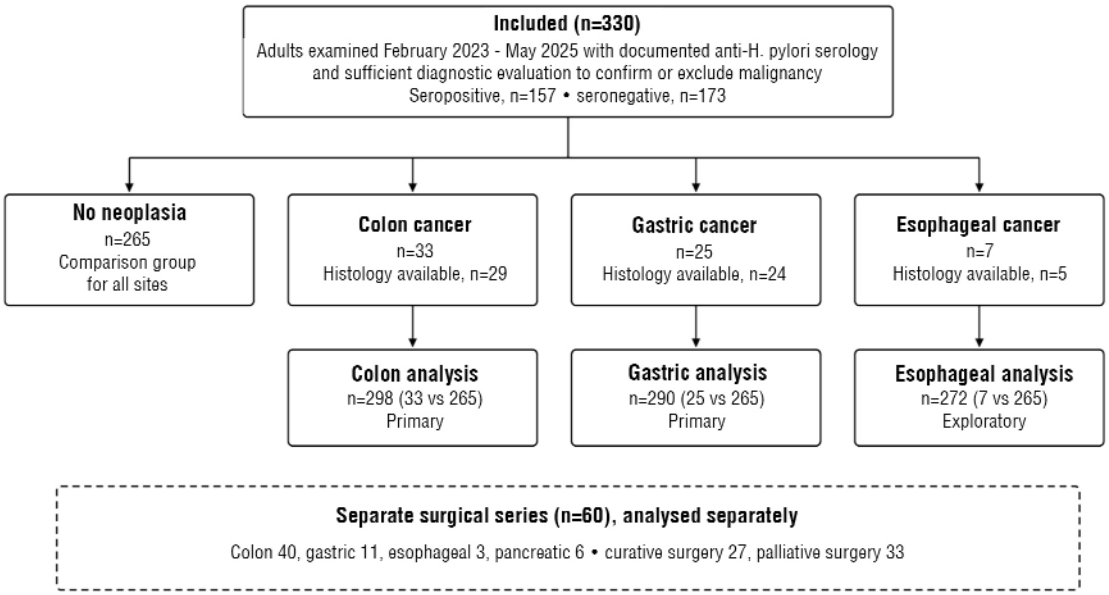


Figure 1. Flow diagram of the study population. The number of patients screened and excluded before inclusion was not recorded

- insufficient diagnostic workup;
- major confounding gastrointestinal conditions (e.g., inflammatory bowel disease);
- inconsistent or contradictory clinical records.

Exposure and Outcome Definitions

Anti-H.pylori serology was performed in the hospital laboratory by detection of serum IgG antibodies. Serology was performed as part of the same diagnostic evaluation as the investigations for malignancy; the exact interval between them was not recorded. Information on previous eradication therapy was not recorded.

Outcomes were primary malignant neoplasms of the esophagus, stomach and colon; rectal tumors were not recorded separately. A histopathological diagnosis was available for 58 of the 65 cases: colon, 27 adenocarcinomas, 1 malignant polyp and 1 unspecified colonic neoplasm; stomach, 19 adenocarcinomas, 3 gastrointestinal stromal tumors and 2 lymphomas; esophagus, 4 adenocarcinomas and 1 squamous cell carcinoma. In the remaining 7 cases (4 colon, 1 gastric, 2 esophageal), the diagnosis was based on clinical, endoscopic and imaging findings, in accordance with the inclusion criteria. The gastric outcome was therefore pathogenetically heterogeneous; because the association with H. pylori is established mainly for adenocarcinoma, an analysis restricted to gastric adenocarcinoma was prespecified as a sensitivity analysis. Occult gastrointestinal bleeding was recorded as the positive or negative result of the fecal occult blood test documented in the medical record and hypoanabolic syndrome as documented by the attending physician. Two patients had an indeterminate (borderline) serology result; because the test was performed and reported, they met the inclusion criteria and were classified as seronegative because they did not meet the laboratory criterion for positivity. Sex was not recorded for one patient, who was assigned to the more frequent category (male). A complete-case analysis excluding all three gave similar estimates (aOR 3.39 for colon and 3.93 for gastric cancer; (*Supplementary Table S1*)

Study Endpoints

Three analytical substudies were conducted:

1. Identification of the association with colon cancer (primary);
2. Identification of the association with gastric cancer (primary);
3. 3. Analysis of the association between anti-H. pylori seropositivity and the surgical outcome, classified as curative resection (R0) or non-R0/non-curative surgery, in a surgical cohort consisting of 60 patients operated on for digestive cancer at the same hospital between April 2023 and December 2025 (exploratory).

The dependent variable in the first two analyses was the presence or absence of neoplasia (binary outcome). For the surgical series analysis, the dependent variable was the type of surgery achieved. Curative resection was defined as resection performed in the absence of distant metastases and with R0 margins on final histopathology. All other procedures were classified as non-curative: resections with R1 or R2 margins, resections in the presence of distant metastases (including resection of the primary tumor with synchronous metastases) and palliative procedures without tumor resection, such as bypass or stoma formation. Because the classification depended on final histopathology, it reflects the result of surgery rather than the preoperative treatment intent. Classification was based on operative reports, multidisciplinary team decisions and histopathology reports.

Variables Analyzed

Independent variables included:

- demographic factors: age, sex, area of residence;
- lifestyle factors: smoking status, alcohol consumption;
- clinical and paraclinical parameters: obesity, anemia, occult gastrointestinal bleeding, hemorrhoids, colonic polyps;
- anti-H. pylori serological status.

Control of Confounding

Confounding variables, defined as factors potentially related to both the exposure and the outcome, were identified using predefined clinical criteria. Age, sex, and smoking status were selected as primary confounders because they are established risk factors for digestive cancer and are associated with H. pylori seroprevalence. These variables were entered simultaneously in a single model for each site; no data-driven covariate selection was performed. Tumor markers, anemia, occult bleeding and hypoanabolic syndrome were not considered confounders. Adjusted odds ratios (aORs) were used to control for confounding in the multivariable logistic regression models.

Statistical Analysis

Statistical analysis was performed using R software

(version 4.5.3, R Foundation for Statistical Computing). Univariable logistic regression models were used to assess the association between each predictor and the presence of neoplasia. Multivariable logistic regression models including age, sex and smoking status simultaneously were constructed to estimate the association of anti-H. pylori seropositivity with each cancer site (33 colon and 25 gastric cancers; 8.3 and 6.3 events per parameter). Results were reported as odds ratios, 95% confidence intervals and p values. Model discrimination, calibration and collinearity were assessed and, given the small number of events, Firth's penalized regression was used as a sensitivity analysis for small-sample bias. The associations of seropositivity with gastric and colon cancer were the primary analyses; all other analyses were exploratory. Further sensitivity analyses are listed in *Supplementary Table S1*.

Results

Overall Cohort Characteristics

A total of 330 patients were included (*Fig. 1*). Anti-H. pylori seropositivity was present in 157 patients (47.6%), while 173 patients (52.4%) were seronegative. Within the overall cohort, 65 patients (19.7%) were diagnosed with esophageal, gastric or colon cancer, whereas 265 patients (80.3%) formed the comparison group, defined by the absence of the three target cancers (esophageal, gastric and colon) rather than of any malignancy (*Table 1*). The predefined site-specific neoplasia endpoints analyzed in the overall cohort were esophageal neoplasm, n = 7 (2.1%) gastric neoplasm, n = 25 (7.6%) and colonic neoplasm, n = 33 (10.0%).

The overall cohort was slightly male-predominant, including 174 men (53%) and 156 women (47%). The mean age was approximately 64 years, with a standard deviation of approximately 12 years. Most patients were rural residents, accounting for 208 cases (63%), whereas 122 patients (37%) lived in urban areas.

Smoking was more frequent among patients with neoplasia than in the comparison group (46% vs. 34%), showing a borderline but non-significant association (p = 0.067). Alcohol consumption did not differ between patients with cancer and the comparison group (34% vs. 35%; p = 0.85). Clinical and paraclinical data showed that hypoanabolic syndrome was significantly more frequent in patients with malignant disease than in the comparison group (80% vs. 53%; p < 0.001) (*Table 2*). Similarly, anemia was more prevalent among patients with malignant disease (46% vs. 32%; p = 0.028), as was occult gastrointestinal bleeding (48% vs. 32%; p = 0.021) (*Table 3*).

Table 1. Baseline characteristics of the overall cohort

Variable	Overall (N=330)	Comparison group (N=265)	Esophageal, gastric or colon cancer (N=65)	p value
Sex, n (%)				0.19
Female	156 (47)	130 (49)	26 (40)	
Male	174 (53)	135 (51)	39 (60)	
Age (years)				0.14
Mean (SD)	64 (12)	64 (12)	66 (11)	
Median (Q1-Q3)	66.5 (56-73)	65 (55-73)	68 (62-74)	
Residence, n (%)				0.38
Rural	208 (63)	164 (62)	44 (68)	
Urban	122 (37)	101 (38)	21 (32)	
Smoking, n (%)				0.067
No	210 (64)	175 (66)	35 (54)	
Yes	120 (36)	90 (34)	30 (46)	
Alcohol consumption, n (%)				0.85
No	215 (65)	172 (65)	43 (66)	
Yes	115 (35)	93 (35)	22 (34)	

Comparison group: patients without the three target cancers (esophageal, gastric or colon); 11 had other known or suspected tumors. Values n (%). p values from Pearson's chi-square test or Fisher's exact test for expected counts below five; age compared with the Wilcoxon rank-sum test.

Table 2. Clinical and laboratory characteristics by neoplasia status

Variable	Overall	Comparison Group	Esophageal, gastric or colon cancer	p value
Hypoanabolic syndrome	193 (58%)	141 (53%)	52 (80%)	<0.001
Anemia	114 (35%)	84 (32%)	30 (46%)	0.028
Hemorrhoids	122 (37%)	103 (39%)	19 (29%)	0.15
Diverticula	35 (11%)	31 (12%)	4 (6%)	0.19
Diabetes mellitus	40 (12%)	31 (12%)	9 (14%)	0.63
Obesity	23 (7%)	20 (8%)	3 (5%)	0.59
Gastric ulcer	39 (12%)	37 (14%)	2 (3%)	0.015
Duodenal ulcer	21 (6%)	21 (8%)	0 (0%)	0.019
Hepatic steatosis	65 (20%)	58 (22%)	7 (11%)	0.043

Comparison group: patients without the three target cancers (esophageal, gastric or colon); 11 had other known or suspected tumors. Values n (%). p values from Pearson's chi-square test or Fisher's exact test for expected counts below five.

Table 3. Additional gastrointestinal conditions and tumor markers comparison by neoplasia status

Variable	Overall	Comparison group	Esophageal, gastric or colon cancer	p value
Gastritis	109 (33%)	103 (39%)	6 (9%)	<0.001
Atrophic gastritis	7 (2.1%)	7 (2.6%)	0 (0%)	0.35
Pangastritis	8(2.4%)	8(3.0%)	0 (0%)	0.36
GERD	6 (2%)	6 (2%)	0 (0%)	0.60
Irritable bowel syndrome	12 (4%)	12 (5%)	0 (0%)	0.13
Anti-H. pylori seropositivity	157 (48%)	110 (42%)	47 (72%)	<0.001
Elevated CEA	32 (10%)	8 (3%)	24 (37%)	<0.001
Elevated CA 19-9	46 (14%)	19 (7%)	27 (42%)	<0.001
Occult bleeding	117 (35%)	86 (32%)	31 (48%)	0.021

Comparison group: patients without the three target cancers (esophageal, gastric or colon); 11 had other known or suspected tumors. Values n (%). p values from Pearson's chi-square test or Fisher's exact test for expected counts below five.

Anti-H. pylori seropositivity was markedly more frequent in patients with neoplasia than in the comparison group. Among patients with oncological disease, 47 of 65 cases (72%) were anti-H. pylori seropositive, compared with 110 of 265 patients (42%) in the comparison group (p<0.001).

Conversely, gastritis was documented less frequently among patients with cancer than in the comparison group (9% vs. 39%; p < 0.001). Gastric ulcer, duodenal ulcer, gastroesophageal reflux disease, atrophic gastritis and pangastritis were primarily documented in the comparison group. These conditions probably reflect the clinical indications for serology and represent differential diagnoses rather than coexisting malignant processes; their high prevalence in the comparison group is addressed in the limitations.

Baseline Characteristics According to Anti-H. pylori Serological Status

A gender difference in anti-H. pylori seropositivity was observed at baseline. Seropositivity was more frequent among male patients than among female patients. Among the 174 male subjects, 93 were seropositive (53.4%), whereas 64 of 156 female subjects were seropositive (41.0%). This difference was statistically significant (p = 0.024).

Lifestyle-related variables were associated with anti-H. pylori seropositivity. Among smokers, 77 of 120 patients (64.2%) were anti-H. pylori seropositive, compared with 80 of 210 non-smokers (38.1%), yielding a statistically significant association (p < 0.001). Anti-H. pylori seropositivity was also more frequent among alcohol-consuming patients. Sixty-nine of 115 alcohol-consuming patients (60%) were seropositive, compared with 88 of 215 non-alcohol-consuming patients (41%), indicating a statistically significant association (p = 0.001). Smoking and alcohol consumption largely overlapped (103 of 120 smokers consumed alcohol). The associations of seropositivity with sex and smoking supported their inclusion as confounders.

Colon Neoplasia Analysis

The colon neoplasm analysis included 298 patients: 265 in the comparison group and 33 with colon cancer. The univariable logistic regression model showed that anti-H. pylori seropositivity was significantly associated with higher odds of colon neoplasm. Among anti-H. pylori-seronegative patients, 10 of 165 had colon neoplasm (6.1%), compared with 23 of 133 anti-H. pylori-seropositive patients (17.3%). The odds of colon neoplasm were more than three times higher in the anti-H. pylori-seropositive cohort than in seronegative patients (crude OR 3.24, 95% CI 1.52-7.38; p = 0.003).

Table 4. Univariable logistic regression for colon neoplasia

Predictor	OR (95% CI)	p value
Anti-H. pylori seropositivity	3.24 (1.52–7.38)	0.003
Occult bleeding	2.50 (1.20–5.26)	0.014
CEA positive	38.5 (15.0–108)	<0.001
CA 19-9 positive	6.47 (2.68–15.2)	<0.001
Hemorrhoids	1.89 (0.91–3.96)	0.087
Other variables	NS	

The univariable logistic regression model also identified occult gastrointestinal bleeding as significantly associated with colon neoplasia. Specifically, 18 of 104 patients with occult bleeding (17.3%) had colon neoplasia, compared with 15 of 194 patients without occult bleeding (7.7%) (crude OR 2.50, 95% CI 1.20-5.26; p=0.014). Tumor markers and manifestations of disease were not considered risk factors or confounders. Other variables did not demonstrate statistically significant associations with colon cancer (*Table 4*).

Hemorrhoids and colon neoplasia were not significantly associated according to anti-H. pylori serological status. Anti-H. pylori seropositivity was present in 49.5% of patients diagnosed with colonic polyps and in 46.9% of patients without colonic polyps. The association between anti-H. pylori seropositivity and colon neoplasm did not appear to be accompanied by an identifiable relationship between anti-H. pylori seropositivity and non-malignant polypoid lesions.

In the multivariable model including seropositivity, age, sex and smoking (n = 298; 33 events), seropositivity remained associated with colon cancer (aOR 3.47, 95% CI 1.58–8.12; p = 0.003); Firth-penalized estimates were similar (aOR 3.32, 95% CI 1.54–7.60). Age, sex and smoking were not associated with colon cancer. The model had a C statistic of 0.68, a Hosmer-

Table 5. Multivariable logistic regression for colon cancer (n =298, 33 cases)

Predictor	OR (95% CI)	aOR (95% CI)	p value
Anti-H. pylori seropositivity	3.24 (1.52–7.38)	3.47 (1.58–8.12)	0.003
Age, per year	1.02 (0.99–1.06)	1.02 (0.99–1.06)	0.19
Male sex	1.02 (0.49–2.13)	1.16 (0.47–2.81)	0.74
Smoking	0.97 (0.44–2.05)	0.69 (0.26–1.80)	0.44

Reference categories: seronegative, female, non-smoker. OR, crude odds ratio; aOR, odds ratio adjusted for all variables in the table; CI, confidence interval. Firth penalized aOR for anti-H. pylori seropositivity 3.32 (1.54–7.60). C statistic 0.68; Hosmer–Lemeshow p = 0.89; maximum variance inflation factor 1.54; 8.3 events per parameter. Partially adjusted models are shown in Supplementary Table S2 and sensitivity analyses in *Supplementary Table S2*.

Lemeshow p value of 0.89 and a maximum variance inflation factor of 1.54 (*Table 5*). The association was consistent in all sensitivity analyses (aOR range 3.11–3.91; *Supplementary Table S1*). In partially adjusted models, the aOR for seropositivity was 3.22 (95% CI 1.51–7.35) after adjustment for age, 3.26 (95% CI 1.53–7.45) after adjustment for sex and 3.47 (95% CI 1.60-8.04) after adjustment for smoking (*Supplementary Table S2).*

A small subgroup of 20 patients presented with both anti-H. pylori seropositivity and diabetes mellitus. Among these, only 2 cases of colon neoplasia were identified. Given the limited number of cases in this subgroup, no formal statistical analysis was conducted.

Gastric Neoplasia Analysis

The gastric neoplasia analysis included 290 patients: 25 with gastric neoplasia and 265 in the comparison group. Among anti-H. pylori-seronegative patients, 6 of 161 had gastric neoplasia (3.7%), compared with 19 of 129 anti-H. pylori-seropositive patients (14.7%). The odds of gastric neoplasia were approximately 4.5 times higher in patients with anti-H. pylori seropositivity (OR 4.46, 95% CI 1.82-12.6; p = 0.002; *Table 6*).

Anemia was another factor associated with gastric neoplasia. Nine of 190 patients without anemia had gastric cancer, compared with 16 of 100 anemic patients. The odds of gastric neoplasia were 3.83 times higher in anemic patients than in non-anemic patients (95% CI 1.66-9.39; p = 0.002). Most likely, anemia was present as a manifestation of the tumor.

Smoking showed a borderline but non-significant association with gastric neoplasia. Among non-smokers, 12 of 187 were diagnosed with gastric neoplasia, compared with 13 of 103 smokers, corresponding to an OR of 2.11 (95% CI 0.92–4.87; p=0.077). The remaining factors studied in this investigation did not demonstrate a statistically significant relationship with gastric neoplasia. Colonic polyps were less frequent among patients with gastric cancer (OR 0.10, 95% CI 0.005–0.47; p = 0.023), which most likely reflects the more frequent use of colonoscopy in patients investigated for lower gastrointestinal symptoms rather than a protective effect. The remaining factors were not associated with gastric cancer.Specifically, age was not associated with gastric neoplasm (OR 1.00, 95% CI 0.97–1.04; p=0.78); likewise, alcohol consumption was not associated with the disease (OR 0.87, 95% CI 0.34–2.04; p=0.76).

Gastroesophageal reflux disease, atrophic gastritis, and pangastritis were not observed concomitantly with gastric neoplasia in this dataset. Therefore, they were not modeled as predictors of gastric neoplasia and were considered primarily relevant for differential diagnosis.

Table 6. Univariable logistic regression for gastric neoplasia

Predictor	OR (95% CI)	p value
Anti-H. pylori seropositivity	4.46 (1.82–12.6)	0.002
Anemia	3.83 (1.66–9.39)	0.002
CEA positive	8.03 (2.25–26.5)	<0.001
CA 19-9 positive	14.0 (5.65–35.6)	<0.001
Smoking	2.11 (0.92–4.87)	0.077
Colonic polyps	0.10 (0.005-0.47)	0.023

In the multivariable model including seropositivity, age, sex and smoking (n = 290; 25 events), seropositivity remained associated with gastric cancer (aOR 4.00, 95% CI 1.59–11.5; p = 0.005); Firth-penalized estimates were similar (aOR 3.74, 95% CI 1.53–10.3). Age, sex and smoking were not associated with gastric cancer (C statistic 0.69; Hosmer-Lemeshow p = 0.89; maximum variance inflation factor 1.68; *Table 7*). The association was consistent in sensitivity analyses (aOR range 3.67–4.46) and was stronger when the outcome was restricted to the 19 gastric adenocarcinomas (aOR 6.37, 95% CI 1.99–28.4; Firth 5.54, 95% CI 1.84-21.9; *Supplementary Table S1*). The five non-epithelial tumors (three GIST, two lymphomas) were too few to be analysed separately. In partially adjusted models, the aOR for seropositivity was 4.46 (95% CI 1.82–12.6) after adjustment for age, 4.25 (95% CI 1.72–12.1) after adjustment for sex and 4.03 (95% CI 1.60–11.6) after adjustment for smoking (*Supplementary Table S2*).

Esophageal Neoplasia Analysis

A total of 272 individuals were analyzed to assess esophageal cancer according to anti-H. pylori serological status. The sample consisted of 265 individuals in the comparison group and seven individuals with documented esophageal cancer. Because of the very

Table 7. Multivariable logistic regression models for gastric neoplasia adjusted for age, sex, and smoking

Predictor	OR (95% CI)	aOR (95% CI)	p value
Anti-H. pylori seropositivity	4.46 (1.82–12.6)	4.00 (1.59–11.5)	0.005
Age, per year	1.00 (0.97–1.04)	1.01 (0.97–1.05)	0.74
Male sex	1.71 (0.74–4.17)	1.13 (0.36–3.45)	0.83
Smoking	2.11 (0.92–4.87)	1.44 (0.49–4.57)	0.52

Reference categories: seronegative, female, non-smoker. OR, crude odds ratio; aOR, odds ratio adjusted for all variables in the table; CI, confidence interval. Firth penalized aOR for anti-H. pylori seropositivity 3.74 (1.53–10.3). C statistic 0.69; Hosmer–Lemeshow p = 0.89; maximum variance inflation factor 1.68; 6.3 events per parameter. Partially adjusted models are shown in *Supplementary Table S2* and sensitivity analyses, including restriction to adenocarcinoma, in *Supplementary Table S1*.

low number of esophageal neoplasia cases, these data were considered exploratory and were not used to develop predictive models.

Anti-H. pylori seropositivity was associated with higher odds of esophageal neoplasia in the univariable model, but the association did not reach statistical significance. Among anti-H. pylori-seronegative patients, 2 of 157 had esophageal neoplasia, compared with 5 of 115 anti-H. pylori-seropositive patients. The corresponding crude OR was 3.52 (95% CI 0.74-24.9; p=0.14).

Smoking and alcohol consumption were more frequent among patients with esophageal cancer: 6 of 96 smokers vs 1 of 176 non-smokers (Fisher's exact p = 0.009) and 6 of 99 alcohol consumers vs 1 of 173 non-consumers (p = 0.010). Because 103 of the 120 smokers also consumed alcohol and only seven cases were available, the two exposures could not be separated and the estimates are highly imprecise.

Because of the very low number of esophageal cancer cases in this sample (n = 7), these variables were not included in multivariable logistic regression models. Therefore, these associations should be interpreted as exploratory rather than confirmatory.

Surgical Series Analysis

The surgical analysis was performed in a separate series of 60 patients who underwent surgery for digestive cancer at Târgoviște Emergency Hospital between April 2023 and December 2025 and had documented anti-H. pylori serology. The series comprised colon (n = 40, 67%), gastric (n = 11, 18%), esophageal (n = 3, 5%) and pancreatic (n = 6, 10%) cancers. Pancreatic cancer was represented only in this series and was not an endpoint of the main analyses. Anti-H. pylori sero-positivity was present in 31 patients (52%). Curative resection was achieved in 27 patients (45%) and non-curative surgery in 33 (55%) (*Table 8*).

Table 8. Characteristics of the surgical series according to surgical ou come: R0 resection vs non-R0/non-curative surgery (n=60)

Variable	R0 resection (n=27)	Non-R0 / Non-curative surger (n=33)	p value
Male sex	18 (66.7)	17 (51.5)	0.24
Age, years, mean (SD)	67 (8)	70 (8)	0.14[b]
Smoking	10 (37.0)	12 (36.4)	0.96
Alcohol consumption	10 (37.0)	10 (30.3)	0.58
Anti-H. pylori seropositivity	14 (51.9)	17 (51.5)	0.98
Tumor site			0.99[a]
Colon	18 (66.7)	22 (66.7)	
Gastric	5 (18.5)	6 (18.2)	
Esophageal	1 (3.7)	2 (6.1)	
Pancreatic	3 (11.1)	3 (9.1)	

Values are n (%) unless otherwise stated. Separate series of patients operated on for digestive cancer, not part of the main cohort analyses (see Methods). p values from Pearson's chi-square test, except [a]Fisher's exact test and [b]Wilcoxon rank-sum test. SD, standard deviation.

Table 9. Univariable associations with non-R0/non-curative surgery

Predictor	OR (95% CI)	p value
Pre-existing benign lesions (ref. absent)	8.32(1.38-160)	0.033[a]
Elevated CEA (ref. normal)	3.29 (1.10-10.9)	0.040
Anti-H. pylori seronegativity (ref. seronegative)	0.99 (0.35 – 2.74)	0.98

Outcome coded 1 = non-R0/non-curative surgery, 0 = R0 resection. Odds ratios compare the presence of each factor with its absence (reference category in brackets), with profile-likelihood 95% confidence intervals. [a]Fisher's exact test; other p values from logistic regression. Other variables (sex, age, residence, smoking, alcohol, tumor site, hypoanabolic syndrome, anemia, CA 19-9, AFP, occult bleeding) were not significant.

The prevalence of anti-H. pylori seropositivity did not differ substantially between patients with curative resection and those with non-curative surgery. Among the 27 patients who underwent curative surgery, 14 (51.9%) were anti-H. pylori seropositive. Among the 33 patients who received non-curative surgery, 17 (51.5%) were anti-H. pylori seropositive. The univariable logistic regression model showed no association between anti-H. pylori serological status and the likelihood of undergoing non-curative surgery (OR 0.99, 95% CI 0.35-2.74; p = 0.98).

In addition to anti-H. pylori serological status, two variables were associated with non-R0/non-curative surgery (*Table 9*). The first was a history of pre-existing benign gastrointestinal lesions: eight of the nine patients with such lesions underwent non-curative surgery, compared with 25 of the 51 without them (OR 8.32, 95% CI 1.38-160; Fisher's exact p = 0.033; Tjur R2 0.082). The second was elevated CEA: 16 of 22 patients (73%) with elevated CEA underwent non-curative surgery, compared with 17 of 38(45%) with normal values (OR 3.29, 95% CI 1.10 – 10.9; p = 0.040; Tjur R2 0.074).

The multivariable model including both pre-existing benign lesions and CEA positivity indicated that both associations persisted after mutual adjustment (pre-existing benign lesions: aOR 9.98, 95% CI 1.57-197; p=0.040; elevated CEA: aOR 3.79, 95% CI 1.20-13.2; p=0.028; Tjur R2 0.164; *Table 10*). Anti-H. pylori seropositivity was not associated with the type of surgery achieved (*Table 9*) and was not included in the multivariable model.

Table 10. Multivariable model for non-R0/non-curative surgery

Predictor	Adjusted OR (95% CI)	p value
Pre-existing benign lesions (ref. absent)	9.98 (1.57-197)	0.040
Elevated CEA (ref. normal)	3.79 (1.20-13.2)	0.028
Model R^2 (Tjur)	0.164	

Multivariable logistic regression in the surgical series (n=60; 33 non R0/non-curative procedures, 27 R0 resections); outcome coded 1 = non-R0/non-curative surgery, 0 = R0 resection. Odds ratios compare the presence of each factor with its absence and are adjusted for the other variable in the table; profile-likelihood 95% confidence intervals; p values from Wald tests. CEA, carcinoembryonic antigen.

Discussion

Core Findings

Our study found a positive association between anti-H. pylori seropositivity and gastric and colon cancer consistent with previous reports (14,15). After adjustment for age, gender and smoking, the association persisted, indicating that demographic factors did not explain the observed relationship in this cohort. However, because of the retrospective observational design, these results do not establish causality, the timing of carcinogenesis or the effect of H. pylori eradication.

Gastric Neoplasm: Confirming Established Evidence

The association observed between anti-H. pylori seropositivity and gastric cancer (aOR 4.00 and 6.37 when restricted to adenocarcinoma) aligns with international evidence identifying H. pylori as an established risk factor for gastric adenocarcinoma (23). The aggregated gastric outcome, however, combined tumors with different pathogenesis: adenocarcinoma, gastrointestinal stromal tumors, which have no recognised link with H. pylori and lymphomas, for which the link follows a different mechanism. The stronger association for adenocarcinoma alone (aOR 6.37) is consistent with this idea and the aggregated estimate should be interpreted as referring to a heterogeneous endpoint. From a clinical perspective, the current results support further evaluation of H. pylori testing and treatment strategies aimed at reducing the burden of gastric cancer (24-27).

Colorectal Cancer: Study Contribution

Beyond the stomach, our study provides evidence of an association between anti-H. pylori seropositivity and colon cancer. Although previous studies examining this relationship have yielded mixed results, the present findings add to a growing body of literature suggesting that H. pylori infection, particularly when associated with gastric atrophy and intestinal metaplasia, may be linked to an increased risk of colorectal cancer and its precursor lesions, such as adenomas (15-19,25). Recent studies using national data from Sweden have found that individuals with documented H. pylori infection have a significantly higher CRC incidence than the general population (28). This suggests a possible extra-gastric association, potentially mediated through systemic microbial-host interactions, but it does not prove causality.

H. pylori and Esophageal Neoplasia

The association between H. pylori and esophageal cancer is complex and counterintuitive. Our study found that smoking and alcohol consumption were more frequent among patients with esophageal neoplasia; these estimates were highly imprecise, the two exposures largely overlapped; the results align with published evidence identifying lifestyle factors as established contributors to esophageal carcinogenesis, primarily for squamous cell carcinoma (29). Taken together, findings from multiple meta-analyses suggest that H. pylori does not act as a primary driver of esophageal cancer and that its role, if present, is indirect and context-dependent (30,31). In this setting, our results should be interpreted cautiously and considered exploratory.

Role of Clinical and Lifestyle Factors

No clinically relevant or statistically significant associations were observed between the target cancers and the demographic or lifestyle factors evaluated in the present study. Occult gastrointestinal bleeding was associated with colon neoplasia, most likely as a manifestation of the tumor rather than a risk factor (32). It was also more frequent among patients with anti-H. pylori seropositivity (70/117, 59.8% vs 87/213, 40.8%; p=0.001), which may reflect both the higher prevalence of cancer and benign H. pylori – related lesions such as peptic ulcer among them. For this reason, occult bleeding was not used as a covariate and should not be interpreted as a marker of increased cancer risk in seropositive patients.

Surgical Series: Curative Resection

Anti-H. pylori serological status was unrelated to the type of surgical intervention performed in the surgical series (20-22). Patients undergoing curative and non-curative procedures had equivalent rates of seropositivity (22, 33). Instead, previous benign lesions and elevated CEA were associated with non-curative procedures. Because this series differed from the main cohort and resectability depends strongly on tumour site and stage, this finding should be regarded as exploratory.

Limitations and Strengths

This study has several limitations. Its retrospective cross-sectional design prevents definitive causal inference and may introduce selection bias related to the use of tertiary-care hospital databases. The

number of patients assessed before inclusion was not recorded, so the degree of selection cannot be quantified. In addition, H. pylori status was assessed using anti-H. pylori antibody serology; therefore, the study cannot distinguish active infection from previous exposure and the characteristics of the serological assay were not recorded. We also lacked information on specific H. pylori strains or genotypes that may affect the inflammatory response (34). Event numbers were limited (25 gastric and 33 colon cancers), yielding fewer than 10 events per model parameter, and secondary analyses were exploratory and not corrected for multiplicity. Firth penalized regression reduces small-sample bias but does not address residual confounding by factors that were not recorded (e.g., socioeconomic status, family history or medication use), selection bias, or the lack of temporality; the adjusted odds ratios describe associations with prevalent disease, not prospective risk. The E-values (6.40 and 7.46) suggest that only strong unmeasured confounding could fully explain the associations, without excluding it. The gastric outcome was pathogenetically heterogeneous and the number of non-epithelial tumors was too small for separate analysis. The comparison group excluded esophageal, gastric and colon cancer and included 11 patients with other known or suspected tumors; excluding them did not weaken the associations (aOR 3.57 and 4.13). The surgical series was a distinct population, which limits comparison with the main cohort. In the surgical series, the outcome was defined by final histopathology and therefore reflects the result of surgery rather than the preoperative treatment intent. Nonetheless, the study has two important strengths: integrated examination across multiple cancer sites and application of multivariable models. By contextualizing our findings within recent clinical guidelines and systematic reviews, we provide a rationale for further prospective evaluation of the associations observed in this cohort (10).

Clinical Implications

The clinical implications of these findings are relevant but should be interpreted cautiously. The results support further prospective studies evaluating whether H. pylori testing and eradication strategies may influence the risk of gastric and extra-gastric digestive neoplasms (35). As projections forecast a rising global burden of gastrointestinal cancers by 2050, comprehensive test-and-treat programs may represent important public health interventions; however, these findings should be interpreted cautiously. Whether H. pylori testing and eradication influence the risk of extra-gastric digestive cancers cannot be addressed by this design and requires prospective longitudinal studies (4,35).

Conclusion

In this retrospective cross-sectional study, anti-H. pylori seropositivity was associated with the prevalence of gastric and colonic neoplasia. These associations were numerically stronger for gastric neoplasia and persisted after adjustment for selected confounders. However, because H. pylori status was determined by serology and the study was observational, the results should be interpreted as associations rather than evidence of active infection, causality, or a proven preventive effect of eradication therapy.

The association between anti-H. pylori seropositivity and esophageal neoplasia was not statistically significant, although an elevated odds ratio was observed. Due to the low number of esophageal neoplasms, the results have limited statistical power. Therefore, findings relating to this relationship are exploratory rather than conclusive.

Within the surgical series analysis, anti-H. pylori seropositivity was not associated with curative resection versus non-curative surgery. Further prospective longitudinal studies using tests for active H. pylori infection are needed to clarify the temporal relationship between H. pylori infection and extra-gastric digestive cancers.

Authors' Contributions

Conceptualization, C. R. F., P. T.; Methodology and Investigation, C. R. F., E. A., G. D. E.; Writing - Original Draft, C. R. F., E. A., G. D. E., G. F. T.; Writing - Review and Editing, D. E. G.; Supervision, P. T. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Emergency County Hospital Târgovişte (approval No 13, dated 27 April 2023).

Conflicts of Interest

The authors declare no conflict of interest.

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Data Availability Statement

The data presented in this study are available from the corresponding author upon reasonable request.

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Supplementary Material

Supplementary Table S1. Sensitivity analyses for the association of anti-H. pylori seropositivity with colon and gastric cancer

Analysis	Colon cancer aOR (95% CI)	n / cases	Gastric cancer aOR (95% CI)	n / cases
Main model (*Tables 5* and *7*)	3.47 (1.58–8.12)	298 / 33	4.00 (1.59–11.5)	290 / 25
Firth penalized regression	3.32 (1.54–7.60)	298 / 33	3.74 (1.53–10.3)	290 / 25
Additional adjustment for alcohol consumption[a]	3.53 (1.60–8.29)	298 / 33	3.93 (1.53–11.4)	290 / 25
Additional quadratic term for age	3.30 (1.49–7.78)	298 / 33	4.46 (1.72–13.2)	290 / 25
Comparison group without gastritis or peptic ulcer	3.11 (1.33–7.73)	145 / 33	3.67 (1.39–11.0)	137 / 25
Excluding 11 comparison patients with other known or suspected malignancies[b]	3.57 (1.62–8.35)	287 / 33	4.13 (1.63–11.9)	279 / 25
Excluding 3 patients with indeterminate serology or missing sex	3.39 (1.55–7.93)	295 / 33	3.93 (1.56–11.3)	287 / 25
Histologically confirmed cases only[c]	3.91 (1.68–9.95)	294 / 29	6.37 (1.99–28.4)	284 / 19
Firth penalized regression	—		5.54 (1.84–21.9)	284 / 19
Holm-adjusted p value, main model	0.005		0.005	
E-value, point estimate / lower confidence limit[d]	6.40 / 2.54		7.46 / 2.56	

All models were adjusted for age, sex and smoking; odds ratios refer to anti-H. pylori seropositivity (reference: seronegative), with profile-likelihood 95% confidence intervals. [a]Smoking and alcohol consumption largely overlapped (103 of 120 smokers consumed alcohol). [b]Hepatocellular carcinoma, pancreatic tumor or nodule, gastrointestinal stromal tumor, malignant duodenal tumor, previously operated colon cancer, liver metastases, malignant ascites, and bladder or ovarian tumor. [c]For gastric cancer, restricted to the 19 adenocarcinomas (excluding three gastrointestinal stromal tumors, two lymphomas and one case without histology). [d]Minimum strength of association that an unmeasured confounder would need with both seropositivity and cancer to explain away the estimate (or its lower confidence limit); the outcome was assumed to be rare, so that the odds ratio approximates the risk ratio.

Supplementary Table S2. Partially adjusted logistic regression models

Model	Predictor	aOR (95% CI)	p value
	Colon cancer (n = 298; 33 cases)		
Model A	Anti-H. pylori seropositivity	3.22 (1.51–7.35)	0.003
	Age, per year	1.02 (0.99–1.06)	0.18
Model B	Anti-H. pylori seropositivity	3.26 (1.53–7.45)	0.003
	Male sex	0.93 (0.44–1.95)	0.84
Model C	Anti-H. pylori seropositivity	3.47 (1.60–8.04)	0.002
	Smoking	0.73 (0.32–1.59)	0.44
	Gastric cancer (n = 290; 25 cases)		
Model A	Anti-H. pylori seropositivity	4.46 (1.82–12.6)	0.002
	Age, per year	1.00 (0.97–1.04)	0.80
Model B	Anti-H. pylori seropositivity	4.25 (1.72–12.1)	0.003
	Male sex	1.41 (0.60–3.50)	0.44
Model C	Anti-H. pylori seropositivity	4.03 (1.60–11.6)	0.005
	Smoking	1.54 (0.65–3.65)	0.33

aOR, odds ratio adjusted for the other variable in the same model; CI, confidence interval. Reference categories: seronegative, female, non-smoker. These models were reported in the original version of *Tables 5* and *7*; the simultaneously adjusted models are now shown in *Tables 5* and *7*.