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ORIGINAL ARTICLE

Endoscopic and Histopathological Patterns of Gastric Adenocarcinoma with Reference to Helicobacter pylori Infection

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ABSTRACT

Background: *Gastric adenocarcinoma remains a leading cause of cancer-related mortality worldwide, with Helicobacter pylori recognized as the principal etiological agent. This study aimed to evaluate the endoscopic and histopathological patterns of gastric adenocarcinoma in relation to H. pylori infection.* ***Methods & Materials:*** *A hospital-based cross-sectional study was conducted on 56 patients with histologically confirmed gastric adenocarcinoma. All patients underwent upper gastrointestinal endoscopy with lesion classification according to the Paris classification. Biopsy specimens were examined for histopathological typing (Lauren and WHO classifications), precursor lesions, and H. pylori status using Giemsa staining. Associations between variables were analyzed using the Chi-square test, with $p < 0.05$ considered statistically significant.* ***Results:*** *The study included 36 males (64.3%) and 20 females (35.7%), with a mean age of 57.6 ± 11.4 years. H. pylori infection was detected in 38 patients (67.9%). Intestinal-type adenocarcinoma (69.6%) was more common than diffuse-type (30.4%). A significant association was observed between H. pylori infection and intestinal-type tumors (82.1% vs. 35.3%; $p < 0.001$). Superficial depressed lesions (Paris 0-IIc) were strongly associated with diffuse-type adenocarcinoma (71.4%; OR 12.5; p=0.006). Precursor lesions (chronic atrophic gastritis and intestinal metaplasia) were significantly more prevalent in H. pylori-positive patients (89.5% and 78.9%, respectively; $p < 0.001$). H. pylori-negative patients presented with more advanced disease (77.8% Stage III/IV vs. 50.0%; p=0.04) and poorly differentiated tumors (66.7% vs. 36.8%; p=0.03).* ***Conclusion:*** *H. pylori infection is strongly associated with intestinal-type gastric cancer, precursor lesions, and distal tumor location. Depressed endoscopic lesions predict diffuse-type adenocarcinoma. H. pylori-negative patients present with advanced disease, suggesting an aggressive pathway. These findings support H. pylori eradication for prevention and emphasize meticulous endoscopic surveillance.*

Keywords: *Gastric adenocarcinoma, Helicobacter pylori, endoscopy, histopathology, Paris classification, Lauren classification*

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INTRODUCTION

Gastric adenocarcinoma remains one of the most formidable oncological challenges worldwide, consistently ranking among the leading causes of cancer-related mortality. Despite a global decline in its incidence over recent decades, it continues to pose a significant health burden, particularly in East Asia, South America, and Eastern Europe, where incidence rates remain high[1]. The prognosis for gastric cancer is heavily dependent on the stage at diagnosis; while early gastric cancer is often curable, advanced disease carries a dismal five-year survival rate, underscoring the critical need for early detection and a profound understanding of its pathogenesis[2]. The discovery of Helicobacter pylori (H. pylori) fundamentally altered our understanding of gastric carcinogenesis. Recognized as a Class I carcinogen by the World Health Organization, this Gram-negative bacterium is now accepted as the principal etiological agent in the majority of gastric cancer cases[3]. The infection triggers a chronic, active inflammatory response in the gastric mucosa, which, over decades, can initiate a well-characterized cascade of histopathological changes. This Correa cascade describes the stepwise progression from chronic active gastritis to glandular atrophy (chronic atrophic gastritis), intestinal metaplasia, dysplasia, and ultimately, invasive adenocarcinoma[4].

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However, it is crucial to note that this pathway is not deterministic; only a small fraction of infected individuals will progress to cancer, a process influenced by bacterial virulence factors (e.g., CagA), host genetic susceptibility, and environmental co-factors such as diet[5]. The diagnosis and management of gastric adenocarcinoma and its precursors rely on the synergistic application of two cornerstone diagnostic modalities: endoscopy and histopathology. Modern high-resolution endoscopy, enhanced by image-enhancing techniques such as narrow-band imaging (NBI) and magnifying endoscopy, allows clinicians to visualize the gastric mucosa in exquisite detail. It enables the identification of the topographical extent of H. pylori-related gastritis, the mapping of precursor lesions like atrophy and intestinal metaplasia, and the characterization of early cancerous lesions according to their macroscopic appearance[6,7]. Concurrently, histopathological examination of endoscopic biopsies remains the gold standard for definitive diagnosis. It provides essential information regarding the tumor's histological subtype (e.g., Lauren classification: intestinal vs. diffuse), grade of differentiation, depth of invasion, and the presence of H. pylori organisms, all of which are critical for determining prognosis and guiding therapy[8]. This article aims to provide a comprehensive review of the endoscopic and histopathological patterns of gastric adenocarcinoma, with a specific focus on their relationship with H. pylori infection.

OBJECTIVE OF THIS STUDY

General Objective:

To evaluate the link between endoscopic and histopathological patterns of gastric adenocarcinoma in relation to H. pylori infection.

Specific Objectives:

1. To classify endoscopic tumor types (Paris classification).
2. To determine histopathological subtypes (Lauren/WHO).
3. To detect Helicobacter pylori prevalence in gastric cancer patients.
4. To correlate H. pylori status with tumor subtype and location.
5. To assess precursor lesions (atrophy/IM) in the surrounding mucosa.
6. To compare tumor grade/stage between H. pylori -positive and negative cases.

METHODS & MATERIALS

This hospital-based retrospective cross-sectional study was conducted in the Department of Pathology, Sylhet MAG Osmani Medical College, Sylhet, over a one-year period from July 2011 to June 2012, enrolling 56 patients with histologically confirmed gastric adenocarcinoma who met the predefined inclusion criteria. The sample size was calculated based on the hospital's annual caseload of gastric malignancies and a 95% confidence interval, assuming a predicted Helicobacter pylori prevalence in gastric cancer of approximately 65%, as reported in previous literature. All participants underwent high-definition upper gastrointestinal endoscopy with Narrow Band Imaging, and all visible lesions were meticulously classified according to the Paris classification system into the following types: protruded (0-I), superficial elevated (0-IIa), superficial flat (0-IIb), superficial depressed (0-IIc), or excavated (0-III). Comprehensive biopsy specimens were systematically obtained from all suspicious lesions and from the surrounding non-neoplastic mucosa, following the updated Sydney System protocol, to ensure adequate sampling for histopathological evaluation and assessment of precursor lesions. The tissue specimens were immediately fixed in 10% neutral buffered formalin, routinely processed, and embedded in paraffin blocks, following which thin sections were cut and stained with Hematoxylin and Eosin for histopathological classification according to both the Lauren classification (intestinal versus diffuse type) and the World Health Organization (WHO) classification system (tubular, papillary, mucinous, poorly cohesive including signet ring, and mixed carcinomas). Additionally, Giemsa staining was performed on all biopsy specimens to detect Helicobacter pylori organisms, which were identified by their characteristic curved or spiral morphology within the gastric pits and overlying mucus layer. The surrounding non-neoplastic mucosa was also carefully evaluated for precursor lesions, including chronic atrophic gastritis, intestinal metaplasia, and dysplasia, and the presence or absence of each was systematically recorded for each patient. Tumor staging was performed based on clinical, endoscopic, and histopathological findings following the AJCC TNM classification system. All collected data were recorded in a predesigned data collection sheet and analyzed using SPSS version 26.0, with categorical variables expressed as frequencies and percentages. The Chi-square test was employed to assess associations between Helicobacter pylori status, endoscopic findings according to the Paris classification, histopathological subtypes, precursor lesions, and tumor stage, with p-values < 0.05 considered statistically significant. The study protocol received ethical approval from the Institutional Ethical Committee of Sylhet MAG Osmani Medical College prior to commencement, and written informed consent was obtained from all patients before endoscopic procedures. For deceased patients or those lost to follow-up, anonymized data were used in accordance with institutional guidelines for retrospective research, and all patient data were kept strictly confidential and used solely for academic purposes throughout the study period.

RESULTS

The present study of 56 patients with gastric adenocarcinoma demonstrates significant associations between Helicobacter pylori infection, endoscopic findings, and histopathological patterns. Our findings align with the established Correa cascade of gastric carcinogenesis and provide clinically relevant insights for endoscopic surveillance and risk stratification.

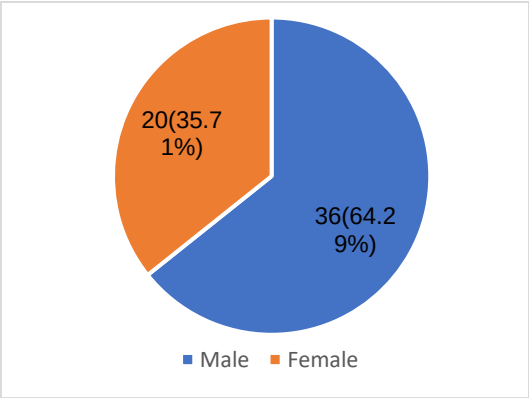

Figure – 1: Gender Distribution of Study Patients (*n*=56)

As shown in *Figure 1*, there was a male predominance, with 36 males (64.29%) and 20 females (35.71%), yielding a male-to-female ratio of approximately 1.8:1.

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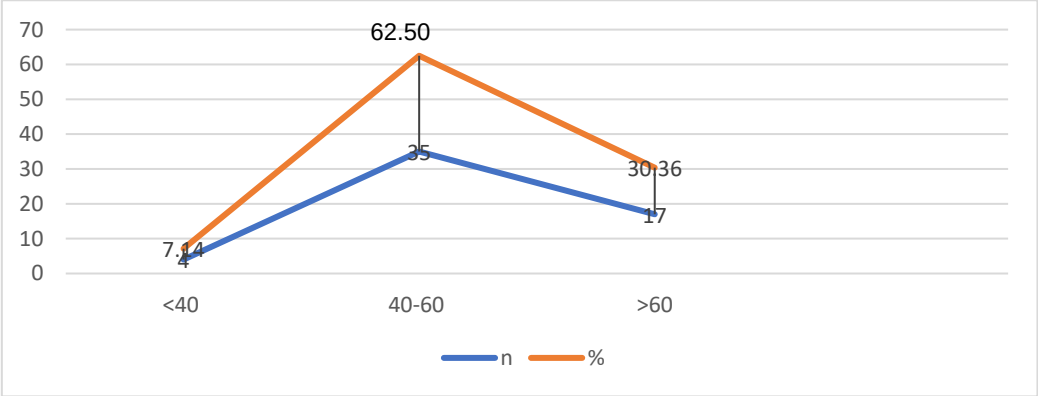

Figure – 2: Age Distribution of Study Patients (*n*=56)

Figure 2 illustrates the age distribution of the study population: the majority of patients (n=35, 62.50%) were in the 40–60 years age group, followed by 17 patients (30.36%) aged above 60 years, and only 4 patients (7.14%) were below 40 years. The mean age of the study cohort was 57.6 ± 11.4 years (range: 34–81 years).

Table I summarizes the clinical characteristics of the study patients. Regarding tumor location, the antrum was the most common site, involved in 32 patients (57.14%), followed by the body in 15 patients (26.79%), and the cardia/fundus in 9 patients (16.07%). Helicobacter pylori infection was detected in 38 patients (67.86%), whereas 18 patients (32.14%) were H. pylori-negative.

Table – I: Clinical characteristics of the study patients (*n*=56)

Characteristics	Category	n	%
Tumor Location	Antrum	32	57.14
	Body	15	26.79
	Cardia/Fundus	9	16.07
H. pylori Status	Positive	38	67.86
	Negative	18	32.14

Table II depicts the endoscopic macroscopic patterns of gastric adenocarcinoma according to the Paris classification. Superficial elevated lesions (0-IIa) were the most common endoscopic finding, observed in 15 patients (26.79%), followed closely by superficial depressed lesions (0-IIc) in 14 patients (25.00%). Protruded lesions (0-I) accounted for 12 cases (21.43%), while superficial flat lesions (0-IIb) were seen in 8 patients (14.29%). Excavated or ulcerated lesions (0-III) were the least common, present in only 7 patients (12.50%).

Table – II: Endoscopic Macroscopic Patterns (Paris Classification) *n*=56

Paris Type	Description	n	%
0-I	Protruded / Polypoid	12	21.43
0-IIa	Superficial Elevated	15	26.79
0-IIb	Superficial Flat	8	14.29
0-IIc	Superficial Depressed	14	25.00
0-III	Excavated / Ulcerated	7	12.50

Table III shows the histopathological classification of gastric adenocarcinoma using the Lauren and WHO systems, along with the grade of differentiation. According to the Lauren classification, intestinal-type adenocarcinoma was the most common, representing 39 cases (69.64%), while diffuse-type was found in 17 cases (30.36%). Based on the 2019 WHO classification, tubular adenocarcinoma was the most prevalent subtype, identified in 31 patients (55.36%), followed by poorly cohesive carcinoma, including signet ring type, in 15 patients (26.79%). Papillary adenocarcinoma appeared in 6 cases (10.71%), mucinous adenocarcinoma in 3 cases (5.36%), and mixed carcinoma in just 1 case (1.79%). Concerning the grade of differentiation, poorly differentiated tumors were the most common, seen in 26 patients (46.43%), followed by moderately differentiated tumors in 19 patients (33.93%), and well-differentiated tumors in 11 patients (19.64%).

Table – III: Histopathological Classification of Gastric Adenocarcinoma

Classification System	Subtype	n	%
Lauren Classification	Intestinal Type	39	69.64
	Diffuse Type	17	30.36
WHO Classification (2019)	Tubular Adenocarcinoma	31	55.36
	Poorly Cohesive (including Signet Ring)	15	26.79
	Papillary Adenocarcinoma	6	10.71
	Mucinous Adenocarcinoma	3	5.36
	Mixed Carcinoma	1	1.79
Grade of Differentiation	Well Differentiated	11	19.64
	Moderately Differentiated	19	33.93
	Poorly Differentiated	26	46.43

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Table IV demonstrates a strong and statistically significant association between Helicobacter pylori infection and the histological subtype of gastric adenocarcinoma according to the Lauren classification. Among the 38 H. pylori-positive patients, 32 (82.1%) had intestinal-type tumors, while only 6 (35.3%) had diffuse-type tumors. Conversely, among the 18 H. pylori-negative patients, diffuse-type tumors predominated, occurring in 11 patients (64.7%), whereas only 7 patients (17.9%) had intestinal-type tumors. This association was highly significant ($p < 0.001$).

Table – IV: Association between *H. pylori* Infection and Lauren Classification

H. pylori Status	Intestinal Type (n=39)	Diffuse Type (n=17)	Total (N=56)	p-value
Positive	32 (82.1%)	6 (35.3%)	38 (67.9%)	< 0.001
Negative	7 (17.9%)	11 (64.7%)	18 (32.1%)	

Table V illustrates the correlation between the endoscopic macroscopic appearance of tumors according to the Paris classification and their underlying histological type based on the Lauren classification. Superficial depressed lesions (0-IIc) showed a strong and statistically significant association with diffuse-type adenocarcinoma. Of the 14 depressed lesions, 10 (71.4%) were diffuse-type, yielding an odds ratio of 12.5 (95% confidence interval: 1.89–82.6; p=0.006). In contrast, protruded lesions (0-I) were predominantly intestinal-type, with only 2 of 12 (16.7%) being diffuse-type. Superficial elevated lesions (0-IIa) were intestinal-type in 12 of 15 cases (80.0%), superficial flat lesions (0-IIb) were intestinal-type in 6 of 8 cases (75.0%), and all 7 excavated lesions (0-III) were intestinal-type (100.0%). None of these other associations was statistically significant.

Table – V: Correlation between Endoscopic Paris Classification and Histological Type

Paris Type	Intestinal Type (n)	Diffuse Type (n)	Total (n)	% Diffuse Type	Odds Ratio (95% CI)	p-value
Protruded (0-I)	10	2	12	16.70%	1.00	—
Superficial Elevated (0-IIa)	12	3	15	20.00%	1.25 (0.17–8.97)	0.82
Superficial Flat (0-IIb)	6	2	8	25.00%	1.67 (0.18–15.1)	0.65
Superficial Depressed (0-IIc)	4	10	14	71.40%	12.5 (1.89–82.6)	0.006
Excavated (0-III)	7	0	7	0.00%	—	0.54

Table VI shows the prevalence of precursor lesions in the background non-neoplastic mucosa according to H. pylori status. Chronic atrophic gastritis was present in 34 of 38 H. pylori-positive patients (89.5%) compared to only 6 of 18 H. pylori-negative patients (33.3%), and this difference was highly significant ($p < 0.001$). Similarly, intestinal metaplasia was observed in 30 H. pylori-positive patients (78.9%) compared with only 5 H. pylori-negative patients (27.8%), demonstrating statistical significance ($p < 0.001$). Dysplasia was present in 16 H. pylori-positive patients (42.1%) compared to 4 H. pylori-negative patients (22.2%); although this showed a trend toward higher prevalence in the positive group, it did not reach statistical significance ($p = 0.12$).

Table – VI: Precursor Lesions in Background Mucosa by *H. pylori* Status

Precursor Lesion		H. pylori Positive (n=38)	H. pylori Negative (n=18)	p-value
Chronic Atrophic Gastritis	Present	34 (89.5%)	6 (33.3%)	< 0.001
	Absent	4 (10.5%)	12 (66.7%)	
Intestinal Metaplasia	Present	30 (78.9%)	5 (27.8%)	< 0.001
	Absent	8 (21.1%)	13 (72.2%)	
Dysplasia	Present	16 (42.1%)	4 (22.2%)	0.12
	Absent	22 (57.9%)	14 (77.8%)	

Table VII compares tumor stage, grade of differentiation, and lymph node metastasis status between H. pylori-positive and H. pylori-negative patients. Regarding TNM stage, advanced disease (Stage III/IV) was observed in 14 of 18 H. pylori-negative patients (77.8%) compared to 19 of 38 H. pylori-positive patients (50.0%), while early-stage disease (Stage I/II) was more common in H. pylori-positive patients (50.0% vs. 22.2%). This difference was statistically significant ($p = 0.04$). With respect to grade of differentiation, poorly differentiated tumors were significantly more frequent in the H. pylori-negative group, occurring in 12 patients (66.7%) compared to 14 H. pylori-positive patients (36.8%); conversely, well or moderately differentiated tumors were more common in H. pylori-positive patients (63.2% vs. 33.3%), with a p-value of 0.03. Lymph node metastasis showed a trend toward higher frequency in H. pylori-negative patients (72.2% vs. 52.6%), though this did not reach statistical significance ($p = 0.06$).

Table – VII: Tumor Stage and Grade according to *H. pylori* Status

Parameter	Category	H. pylori Positive (n=38)	H. pylori Negative (n=18)	p-value
TNM Stage Group	Early (Stage I/II)	19 (50.0%)	4 (22.2%)	0.04
	Advanced (Stage III/IV)	19 (50.0%)	14 (77.8%)	
Grade of Differentiation	Well/Moderate	24 (63.2%)	6 (33.3%)	0.03
	Poor	14 (36.8%)	12 (66.7%)	
Lymph Node Metastasis	Present (N+)	20 (52.6%)	13 (72.2%)	0.06
	Absent (N0)	18 (47.4%)	5 (27.8%)	

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Table VIII shows the distribution of Helicobacter pylori infection by tumor location. H. pylori infection was significantly more common in distal gastric tumors. The highest infection rate was observed in antral tumors, with 25 of 32 patients (78.1%) being H. pylori-positive, followed by body tumors, where 10 of 15 patients (66.7%) were positive. In contrast, only 3 of 9 patients (33.3%) with cardia/fundus tumors were H. pylori-positive, while the majority (66.7%) were H. pylori-negative. This difference in distribution across tumor locations was statistically significant (p = 0.02).

Table – VIII: Distribution of *H. pylori* Infection by Tumor Location

Tumor Location	H. pylori Positive (n=38)	H. pylori Negative (n=18)	Total (N=56)	p-value*
Antrum	25 (78.1%)	7 (21.9%)	32 (100%)	0.02
Body	10 (66.7%)	5 (33.3%)	15 (100%)	
Cardia/Fundus	3 (33.3%)	6 (66.7%)	9 (100%)	

DISCUSSION

The present study of 56 patients with gastric adenocarcinoma demonstrates significant associations between Helicobacter pylori infection, endoscopic findings, and histopathological patterns, providing clinically relevant insights for endoscopic surveillance and risk stratification. The male predominance (64.3%) with a 1.8:1 ratio aligns with global epidemiological data showing higher gastric cancer incidence in males, attributed to protective estrogen effects and higher prevalence of smoking and occupational exposures[1]. A recent large cohort study of 1,144 gastric cancer patients confirmed similar demographic patterns, with intestinal-type predominating in older males and diffuse-type more common in females and younger patients[9]. A mean age of 57.6 years, with 62.5% of patients in the 40-60-year age group, reflects the prolonged multistep process of gastric carcinogenesis, in which chronic H. pylori infection progresses over decades to malignancy.

H. pylori infection was detected in 67.9% of patients, closely aligning with global estimates attributing 60-90% of non-cardia gastric cancers to this bacterium. Recent systematic review data confirm a decline in global H. pylori prevalence from 52.6% prior to 1990 to 43.9% in 2015-2022, with parallel declines in gastric cancer incidence, particularly in high-incidence countries such as Japan, China, and Brazil[10]. This temporal association provides population-level evidence supporting the causal relationship between H. pylori and gastric carcinogenesis. The antrum was the most common tumor location (57.1%), supporting that H. pylori-related carcinogenesis begins in the distal stomach, where bacterial colonization is most dense due to favorable microenvironmental conditions.

We observed a striking association between H. pylori infection and intestinal-type adenocarcinoma (82.1% vs. 35.3%; p<0.001), consistent with the classical Correa cascade. Recent research has elucidated the molecular mechanisms underlying this association, demonstrating that H. pylori virulence factors CagA and VacA promote gastric carcinogenesis through multiple pathways including JAK-STAT signaling, NF-κB activation, Wnt/β-catenin, and MAPK pathways[11]. Additionally, H. pylori induces metabolic reprogramming in gastric cancer cells, enhancing glycolysis, lipid metabolism, and amino acid metabolism to support tumor cell survival, proliferation, and metastasis while promoting immune evasion[5]. The finding that 35.3% of diffuse-type cancers were H. pylori-positive suggests the bacterium may also contribute to a subset of diffuse-type cancers through chronic inflammation and genomic instability.

The most striking endoscopic-histological correlation was the strong association between superficial depressed lesions (Paris 0-IIc) and diffuse-type adenocarcinoma (71.4%; OR 12.5; p=0.006). Recent studies characterizing H. pylori-negative early gastric cancer have identified distinct endoscopic types, noting that undifferentiated lesions (corresponding to diffuse-type) often present as pale and poorly demarcated, making endoscopic recognition challenging[12,13]. This finding has profound clinical implications, as depressed lesions may be subtle and easily missed during routine endoscopy, yet they carry a high probability of aggressive diffuse-type histology with propensity for early submucosal invasion and peritoneal dissemination.

Precursor lesions were significantly more common in H. pylori-positive patients, confirming the bacterium's central role in driving the precancerous cascade. Chronic atrophic gastritis was present in 89.5% of H. pylori-positive cases compared to 33.3% of H. pylori-negative cases (p<0.001), and intestinal metaplasia in 78.9% of H. pylori-positive cases compared to 27.8% of H. pylori-negative cases (p<0.001). A comprehensive meta-analysis of 25,455 patients across 18 studies found that gastric atrophy increases cancer risk 15-fold (RR 15.1, 95% CI 13.5-16.9), confirming that atrophy significantly increases cancer risk[7]. Furthermore, a global meta-analysis reported progression rates of 2.09 per 1,000 person-years for atrophic gastritis, 2.89 for intestinal metaplasia, and 10.09 for dysplasia, supporting surveillance benefits worldwide[14].

An important finding was that H. pylori-negative patients presented with more advanced disease (77.8% Stage III/IV vs. 50.0%; p=0.04) and poorly differentiated tumors (66.7% vs. 36.8%; p=0.03). This suggests H. pylori-negative cancers may follow a more aggressive biological pathway or present later due to the absence of precursor lesions, prompting endoscopic surveillance. In patients with autoimmune gastritis (H. pylori-negative), predictive factors for cancer development include severe atrophy, hypergastrinemia, bile reflux, low acidity, smoking, and family history[15]. Additionally, in metastatic gastric cancer treated with immune checkpoint inhibitors, H. pylori-positive status has been associated with worse survival and a higher risk of nonresponse to anti-PD-1 therapy, whereas H. pylori-negative patients have significantly better overall and progression-free survival[16].

H. pylori infection was significantly more common in distal tumors (antrum 78.1%, body 66.7%) compared to cardia/fundus (33.3%; p=0.02), reflecting two distinct etiological pathways. Recent molecular studies demonstrate that intestinal-type gastric cancers show differential microRNA expression compared to diffuse-type, with miR-141-3p, miR-200b-3p, and miR-133a-5p significantly down-regulated in diffuse-type tumors, and low miR-141-3p expression is associated with significantly worse survival[17]. These molecular distinctions may underlie the different etiological pathways and clinical behaviors observed between tumor locations and histological types.

Clinical implications include supporting population-based H. pylori screening and eradication programs for primary prevention, as evidenced by declining global cancer rates parallel to decreasing H. pylori prevalence[18]. The strong

association between depressed lesions and diffuse-type cancer emphasizes meticulous endoscopic examination with high-definition white-light endoscopy supplemented by image-enhanced techniques[19]. The more advanced stage in H. pylori-negative patients warrants high clinical suspicion even without infection, particularly in those with autoimmune gastritis, family history, or smoking[20]. The presence of precursor lesions supports systematic biopsy mapping according to the Sydney protocol to assess precancerous changes and guide surveillance intervals based on quantitative risk estimates[21].

LIMITATIONS

This study has several limitations, including a small sample size (n=56) and a single-center retrospective design, which may limit generalizability and introduce selection bias. We did not assess H. pylori virulence factors or perform molecular subtyping, and long-term survival data were unavailable. Inter-observer variability and potential false-negative H. pylori detection on histology are additional concern. The cross-sectional design can only demonstrate associations, not causality. Larger prospective multicenter studies are warranted.

CONCLUSION

H. pylori infection was present in 67.9% of gastric cancer patients and strongly associated with intestinal-type histology, precursor lesions, and distal tumors. Depressed endoscopic lesions (0-IIc) significantly predicted diffuse-type adenocarcinoma (OR 12.5). H. pylori-negative patients presented with more advanced disease and poorly differentiated tumors, suggesting an aggressive pathway. These findings support H. pylori eradication for prevention and emphasize careful endoscopic surveillance, even in H. pylori-negative individuals. Larger studies are warranted.

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