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Research Article

A Study on Association of Helicobactor Pylori Infection in Different Clinico-Pathological Pattern of Gastric Adenocarcinomas and A Comparison Among Various Methods of its Detection

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ABSTRACT

Background: Gastric adenocarcinoma is a major global health concern, particularly in developing countries where Helicobacter pylori infection is highly prevalent. Accurate detection of H. pylori in gastric carcinoma specimens is essential for understanding its association and guiding management.
Aim: To determine the prevalence of H. pylori colonization in different histological variants of gastric adenocarcinoma and to compare the diagnostic performance of rapid urease test, haematoxylin & eosin, modified Giemsa, and immunohistochemistry.
Materials and Methods: This prospective observational study was conducted in the Department of Pathology, Nil Ratan Sircar Medical College and Hospital, Kolkata, from February 2016 to July 2017. Fifty endoscopic biopsy specimens diagnosed as gastric adenocarcinoma were included. All cases were evaluated using rapid urease test, haematoxylin & eosin, modified Giemsa stain, and immunohistochemistry. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated. Chi-square test was applied, and $p < 0.05$ was considered statistically significant.
Results: The mean age was 43.18 ± 13.8 years, with male predominance (62%). Intestinal type (60%) was more common than diffuse type (40%), and the antrum was the most frequent site (56%). H. pylori positivity was detected in 42% by RUT, 62% by haematoxylin & eosin, 72% by modified Giemsa stain, and 92% by immunohistochemistry. Immunohistochemistry showed 100% sensitivity and specificity, followed by modified Giemsa stain (78.26% sensitivity, 100% specificity). rapid urease test demonstrated the lowest sensitivity (43.63%).
Conclusion: H. pylori infection is highly prevalent in gastric adenocarcinoma. IHC is the most sensitive diagnostic modality, while modified Giemsa offers a reliable alternative in routine practice.

Keywords: *H. pylori, stomach cancer, detection method.*

INTRODUCTION

Gastric carcinoma remains one of the most common malignancies worldwide and constitutes a major global health burden [1]. It ranks among the leading cancers in Asia, being the second most common in males and the third most common in females [2]. Gastric carcinoma is a heterogeneous disease with complex and incompletely understood pathogenesis. Histologically, gastric adenocarcinoma accounts for more than 90% of all gastric cancers and represents the predominant subtype [3].

The aetiology of gastric carcinoma is multifactorial; however, infection with Helicobacter pylori plays a central role. The prevalence of H. pylori infection varies significantly between developing and developed nations, exceeding 80% in many developing countries compared to approximately 30% in developed regions [4-6]. Indian studies report prevalence rates ranging from 50–90% across different regions. In recognition of its carcinogenic potential, the International Agency for Research on Cancer classified H. pylori as a Group I human carcinogen in 1994. [7]

Geographically, the highest incidence of gastric carcinoma is observed in East Asia, South America, and Central Europe, collectively accounting for nearly 70% of global cases [8]. Males are affected more frequently than females [8]. Carcinogenesis involves the accumulation of genetic alterations, including oncogene activation and tumour suppressor gene inactivation. Environmental risk factors include high dietary salt intake, consumption of smoked or pickled foods, tobacco use, and alcohol consumption. In contrast, diets rich in fresh fruits and vegetables, vitamin C, carotenoids, and green tea appear to exert protective effects.

Chronic *H. pylori* infection, particularly with strains expressing virulence factors such as cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA), plays a critical role in the early stages of gastric carcinogenesis, especially in distal (non-proximal) gastric cancers[9,10]. The infection is also associated with chronic gastritis, peptic ulcer disease, mucosa-associated lymphoid tissue (MALT) lymphoma, immune thrombocytopenic purpura, and iron deficiency anaemia. [11-12]

The histological progression of intestinal-type adenocarcinoma follows a well-recognized cascade: chronic superficial gastritis progresses to atrophy, intestinal metaplasia, dysplasia, and eventually invasive adenocarcinoma [13]. Persistent inflammation may also contribute to diffuse-type adenocarcinoma. Although H. pylori does not invade gastric tissue directly, it induces intense inflammation and immune responses. Its role in carcinogenesis is mediated both by direct oncogenic effects and by the creation of a chronic pro-carcinogenic microenvironment.

At the molecular level, H. pylori activates pathways such as hepatocyte growth factor (HGF)/c-Met signalling, promoting invasive tumour growth. Early epigenetic changes, including E-cadherin methylation, have been linked to infection. The CagA protein interacts intracellularly with host signalling pathways, enhancing mitogenic and proliferative responses.[14] Given its pathogenic significance and high prevalence in developing countries, accurate detection of *H. pylori* is essential. Eradication following endoscopic resection of early gastric carcinoma has been shown to reduce recurrence rates. Diagnostic methods include endoscopic tests—rapid urease test (RUT), histopathology, special stains (modified Giemsa, toluidine blue), immunohistochemistry, PCR, and culture—and non-endoscopic methods. Molecular techniques, though sensitive, are costly and less feasible for routine use in resource-limited settings.

Histopathology offers distinct advantages by enabling simultaneous assessment of bacterial presence and associated morphological changes such as inflammation, atrophy, metaplasia, and malignancy. Many diagnostic tests require discontinuation of proton pump inhibitors prior to evaluation, as medications may reduce test sensitivity. Routine histochemical stains like hematoxylin–eosin and modified Giemsa remain cost-effective, accessible, and practical tools for detection.

Aims and Objectives

This study aims to document the prevalence of Helicobacter pylori colonization in different variants of gastric adenocarcinoma and to evaluate various staining methods, including immunohistochemistry, for its detection.

MATERIALS AND METHODS

Study Design and Setting

This prospective observational study was conducted in the Department of Pathology in collaboration with the Department of Gastroenterology at Nil Ratan Sircar Medical College and Hospital, Kolkata, from February 2016 to July 2017. Ethical clearance was obtained from the Institutional Ethics Committee, and written informed consent was secured from all participants prior to inclusion in the study.

Study Population and Specimen Collection

Upper gastrointestinal endoscopic biopsy specimens were collected from consecutive patients diagnosed with gastric adenocarcinoma. Discontinuation of proton pump inhibitors at least two weeks prior to endoscopy was ensured. Patients receiving chemotherapy, those undergoing eradication therapy for *Helicobacter pylori* infection, metastatic carcinoma involving the stomach and those with oesophageal carcinoma extending into the stomach were excluded from the study. A

detailed clinical history was obtained from each participant, including demographic profile, socioeconomic status, present and past illness, family history, smoking habits, and use of proton pump inhibitors (PPIs). All patients underwent upper gastrointestinal endoscopy using an Olympus CLV-160 video gastroscope in the Department of Endoscopy. During the endoscopic procedure, biopsy samples were obtained and subjected to Rapid Urease Test (RUT) in the endoscopy suite.

Histopathological Processing
Biopsy specimens were fixed in 10% neutral buffered formalin within 30 minutes of collection and not beyond 48 hours (optimal fixation time: 12–24 hours). Tissue processing was performed using an automated tissue processor following standard protocols. Specimens were dehydrated in graded alcohol (80%, 90%, and absolute alcohol), cleared in xylene, and impregnated in molten paraffin wax at 65°C in two successive baths.

Paraffin blocks were prepared using metal moulds and rapidly cooled. Sections of 4–5 µm thickness were cut using a rotary microtome after cooling the blocks on ice. Sections were mounted on glass slides coated with Mayer's egg albumin and incubated at 60°C for two hours to ensure proper adhesion.

Haematoxylin and Eosin (H&E) Staining
Sections were de-paraffinized in xylene, rehydrated through descending grades of alcohol, and stained with Harris haematoxylin followed by differentiation in 1% acid alcohol and bluing in ammonia water. After counterstaining with eosin, sections were dehydrated, cleared in xylene, and mounted with DPX. Histopathological evaluation included tumour typing, grading, and assessment for H. pylori.

Modified Giemsa (MG) Staining
Modified Giemsa staining was performed on selected sections for detection of *H. pylori*. Slides were de-paraffinized, fixed in methanol, and sequentially treated with Solution I (containing eosin and buffer) and Solution II (containing Azure A and methylene blue). After rinsing in distilled water, slides were air-dried and mounted. Known H. pylori-positive gastric tissue served as control.

Immunohistochemistry (IHC)
Immunohistochemical detection of H. pylori was carried out using a polymer-based detection system and ready-to-use polyclonal primary antibodies. Sections of 3 µm thickness were mounted on poly-L-lysine-coated slides and incubated overnight at 37°C, followed by heat incubation at 65–70°C for one hour.

After deparaffinization and rehydration, antigen retrieval was performed using Tris-EDTA buffer (pH 9) in a pressure cooker. Endogenous peroxidase activity was blocked using hydrogen peroxide. Slides were incubated sequentially with power block, primary antibody (1 hour), super enhancer, and polymer label. Visualization was achieved using diaminobenzidine (DAB) chromogen, followed by counterstaining with haematoxylin. Sections were dehydrated, cleared, and mounted with DPX.

Statistical Analysis:
The collected data were entered into microsoft excel sheet and analysed by using graph pad version 5 .Test of proportion and chi-square statistics were used as test of significance to compare proportion between study groups. A p value of < 0.05 was considered as significant. The sensitivity, specificity, positive predictive value and negative predictive value were compared between rapid urease test, H&E, special stains and immunohistochemistry.

RESULT:
Present study was undertaken at the Department of pathology, Nil Ratan Sircar Medical College & hospital, Kolkata in collaboration with Endoscopy unit, Department of Surgery. A total number of (n=50) patients of either sexes were included in this study. The age of the participants varied between 30-90 years with a mean age group of 43.18±13.8 years. Majority of the patients are male consisting of 62% of cases. Male: female was 1.7:1. The distribution of cases according to their site of occurrence, histological variant and growth pattern is depicted in **Table 1**. Site wise distribution shows highest number of cases in antral region (56%) followed by body and lowest incidence in fundus (06%). According to Lauren's classification the cases were divided into intestinal and diffuse type. Analysis revealed comparatively higher incidence of intestinal type (60%) than that of diffuse type (40%). Majority of the tumours were ulcero-proliferative type (86%).

Table 1: Distribution of cases based on various parameters

Parameters	No of cases	Percentage (%)
Site:		
Antral	28	56
Fundus	03	06
Body	19	38
Histological variant:		
Intestinal	30	60

Diffuse	20	40
Growth pattern:		
Ulcero-proliferative	43	86
Polypoidal	01	02
Annular stenosing	06	12

Applying rapid urease test, 21 (42%) H. pylori positive cases were detected. In contrast to RUT, detection of H. pylori by staining with H&E shows higher rate of detection (62%). H. pylori positive cases (n=31) were detected out of which 15(30%) were intestinal type of gastric adenocarcinoma and 16(32%) cases were diffuse type as shown in **Table 2.** MG stain was superior to H&E stain in accurate of detection of H. pylori .Out of (n=50) participants studied, H. pylori positive cases were 36(72%) and 14 (28%) cases turned out to be negative.

Table2: Outcome of various tests done to detect H. pylori infection in the study population

Type of test with result	Intestinal type (n=30)	Diffuse type (n=20)	Total (n=50)
H. pylori [Rapid Urease test]			
Positive	17 (34%)	04 (8%)	21 (42%)
Negative	13 (26%)	16 (32%)	29 (58%)
H. pylori [H & E Test]			
Positive	15 (30%)	16 (32%)	31 (62%)
Negative	15 (30%)	04 (8%)	19 (38%)
H. pylori [Anti H. pylori antibody]			
Positive	30 (60%)	16 (32%)	46 (92%)
Negative	0	04 (8%)	04 (8%)

When the individual tests were compared with each other it was found that the results obtained with H&E and RUT in detection of H. pylori show significant difference (p value <0.05). The results obtained with MG and RUT also showed a significant difference (p value <0.05) and comparison between MG and H&E shows very significant difference (p <0.0001) as shown **Table 3**.

Table 3: Comparative assessment between various tests outcome for detecting H. Pylori

RUT	H & E				MG			
	Positive	**Negative**	**Sub Total**	**P value**	**Positive**	**Negative**	**Sub total**	**P value**
Positive	**19**	**02**	**21**	**0.004**	**19**	**02**	**21**	**0.0237**
Negative	**12**	**17**	**29**		**17**	**12**	**29**	
Total	**31**	**19**	**50**		**36**	**14**	**50**	
H & E	**MG**				**IHC**			
	Positive	**Negative**	**Sub Total**	**P value**	**Positive**	**Negative**	**Sub total**	**P value**
Positive	**31**	**0**	**31**	**<0.0001**	**31**	**0**	**31**	**0.0168**
Negative	**05**	**14**	**19**		**15**	**04**	**19**	
Total	**36**	**14**	**50**		**46**	**04**	**50**	

MG	IHC			
	Positive	**Negative**	**Sub Total**	**P value**
Positive	**36**	**0**	**36**	**0.0043**
Negative	**10**	**04**	**14**	
Total	**46**	**04**	**50**	

RUT: Rapid urease test, **H & E:** Haematoxylin and Eosin, **MG:** Modified Geimsa stain, **IHC**: Immunohistochemistry
Agreement of outcome with various detection methods were compared with outcome and mentioned in **Table 4**. Analysis reveals amongst the four immunohistochemistry is the superior method of detection of H. pylori. MG was more sensitive (78.26%) to H&E though specificity is equal.

Table: 4 Comparative analysis of the various stains used to detect H. pylori infection

Various stains	Sensitivity	Specificity	PPV	NPV
RUT	43.63%	66.66%	90.47%	13.79%

H&E	67.39%	100%	100%	21.53%
MG	78.26%	100%	100%	38.59%
IHC	100%	100%	100%	100%

RUT: Rapid urease test, **H & E:** Haematoxylin and Eosin, **MG:** Modified Geimsa stain, **IHC**: Immunohistochemistry**, PPV:** Positive predictive value, **NPV:** Negative predictive value

The comparison between two histological variant of adenocarcinoma revealed intestinal type was more prevalent than diffuse type. Male predominance was seen. Distal type was more common than proximal and morphologically, ulcero-proliferative growth pattern was predominant as depicted in **Table 5**.

Table 5: Comparison between two histologic variants of gastric adenocarcinoma

Parameters	Intestinal type (N= 30)	Diffuse type (N= 20)	P value
Age	54.69 ± 14.3	49.29 ± 11.6	
Site1 (fundus)	01	02	
Site 2 (body)	13	06	
Site 3 (antrum)	16	12	
RUT + ve	17	4	0.0183
H&E +ve	15	16	0.0411
MG +ve	20	16	0.3533
IHC +ve	30	16	0.0210

RUT: Rapid urease test, **H & E:** Haematoxylin and Eosin, **MG:** Modified Geimsa stain, **IHC**: Immunohistochemistry

DISCUSSION:

Pathologists have been trying to establish the association of H. pylori infection with gastric adenocarcinoma for decades. A correct and reliable histological diagnosis of H. pylori infection is essential for proper evaluation. The sensitivity and yield of the histological diagnostic tests for H. pylori depends not only on the number or site of endoscopic biopsies but also on the staining technique and experience of pathologists [15]

In the present study, a comparison between RUT and other three histological methods (haematoxylin & eosin, Modified Giemsa and IHC) for detection of H. pylori in endoscopic biopsies diagnosed as gastric adenocarcinoma was done. In the present study the mean age of the study participants was 43.18±13.70 years. Most cases of gastric malignancy occurs over 50 years of age. Incidences was predominantly found over the age group of 45 years in the current study. Similar kind of findings was evident i.e. patient below 30 years of age were very uncommon with this disease in the study of Nakamura et al [16] However Mysorekar et al. [17] reported that maximum occurrence of H. pylori gastritis was in the third and fourth decade of life which is inconsistent with the present study.

In this study majority of the patients were male 31(62%). The findings of Moayyedi et al [18] reported that clinically H. pylori infection was more prevalent in men (29%) than women (26%) but the difference remained statistically insignificant. Not only H. pylori infection, male predominance was also found with gastric adenocarcinoma. As in the present study male: female is 1.38:1 which was consistent with study of S. Pentti et al.[19]

Histological subtype:

Parsonnet et al [20] found a significant association of H. pylori infection with histological type of gastric carcinoma with a prevalence of 89% in intestinal type compared with 32% in diffuse type. The present study was consistent with another previous study of Forman D et al [21] with a higher prevalence of intestinal type. Whitiling JL et al [22] did a retrospective study and showed that mostly the growths are antral in H. pylori infection. In present study out of 50 cases 28 cases (56%) were antral at location. Mishra V et al. [23] found that there was association of H. pylori infection more in distal adenocarcinoma than proximal (73.6% vs 48.6%). The present study(56% vs 38%) is consistent with the statistics of previous one .

Comparison between various histochemical stains:

In the present study after assessment of H.pylori by various stains of 50 cases, 31 cases were confirmed by H&E, 36 cases by modified Giemsa and 46 cases by immunohistochemistry (applying NCL Hpp antibody). Rotimi et al [24] after examination of 60 cases, confirmed 30 positive cases by modified Giemsa and 30 by antibody.

Several studies have shown that immunohistochemical staining with specific H. pylori antibodies show the highest sensitivity and specificity in detecting H. pylori. Ali .K. Riba et al. [25] conducted a study to compare a new Novocastra monoclonal antibody, clone UCL3R, to a polyclonal antibody, NCL-HPp, in known cases of H.pylori infection in stomach.They observed that monoclonal method was superior for quality of organism morphology and background staining

.The sensitivity of this two methods are comparable with 96.2% of the cases identified by monoclonal method and 98.5% by the polyclonal method tough the specificity is 100% in both cases.

Wabinga HR et al. [26] studied on African population to demonstrate H. pylori infection and compare immunohistochemistry and modified Giemsa stains for demonstration of H. pylori. In this study IHC was used as gold standard and the performance of Giemsa was evaluated. The present also shows consistency with the above mentioned, showing 100% sensitivity and specificity of IHC in comparison with H&E, Modified Giemsa.

Study of Shukla S et al. [27] compared the sensitivity & specificity of different staining method. Rapid urease test showed a sensitivity of 74.5%, & positive predictive value of 54.3%. Whereas H&E showed sensitivity of 72.5% and a positive predictive value of 100%. Staining with anti NCL-HPp antibody for better sensitivity, showed 100% sensitivity, 100% positive predictive value and negative predictive value of 100%. Present study showed that sensitivity of RUT 43.63%, specificity 66.66%, PPV 90.47% and NPV 13.79%. In case of H&E sensitivity 67.39%, specificity 100%, PPV 100%. Whereas, modified Giemsa and immunohistochemical stain NCL-HPp showed 78.23%&100% sensitivity ,100% specificity in both cases along with 100% positive predictive value.

Therefore, amongst different method IHC is the most sensitive histological method. Coccoid forms were easily seen in immunostaining. However, IHC is superior to histochemical staining in detection of H.pylori in very low population. Early and accurate detection of H. pylori infection in gastric carcinoma patients is crucial, as eradication therapy may reduce recurrence and has important implications for prevention strategies.

Limitation:
First, the sample size was relatively small, which may limit the generalizability of the findings to the broader population. A larger cohort would have strengthened the statistical power and external validity of the observations.

Second, the study was conducted at a single tertiary care centre in Kolkata, which may introduce institutional or regional bias. Variations in demographic, environmental, and socioeconomic factors across different geographic regions of India may influence the prevalence of H. pylori infection and patterns of gastric adenocarcinoma.

Third, IHC was considered the reference standard in this study; however, no molecular methods such as PCR or culture were employed for confirmation. Although IHC demonstrated 100% sensitivity and specificity in the present analysis, the absence of molecular validation may limit definitive conclusions regarding absolute diagnostic accuracy.

Fourth, sampling error is an inherent limitation in endoscopic biopsy-based studies. The patchy distribution of H. pylori colonization, particularly in atrophic or intestinal metaplastic mucosa, may result in under-detection in certain cases.

CONCLUSION:
A high prevalence of H. pylori colonization in patients with gastric adenocarcinoma observed, with intestinal type being more common than diffuse type. Male predominance and distal (antral) localization were notable clinico-pathological findings. Immunohistochemistry emerged as the most sensitive and specific method for detection of H. pylori, followed by modified Giemsa staining and haematoxylin & eosin staining. Rapid urease test demonstrated comparatively lower sensitivity in carcinoma cases. Further large-scale, multicentric studies incorporating molecular techniques are recommended to validate these findings and refine diagnostic algorithms in the Indian context.

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