# Internal Medicine Section

# Relationship of *Helicobacter pylori*Infection with Various Components of Metabolic Syndrome in Dyspeptic Patients: A Cross-sectional Study from Western Maharashtra, India

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### **ABSTRACT**

Introduction: Helicobacter pylori (H. pylori), despite its high prevalence in the Indian population, has been subjected to limited studies concerning its potential role as a risk factor for Metabolic Syndrome (MetS) and Insulin Resistance (IR). Proposed mechanisms include inflammatory mediators, atherogenic lipid profiles, and vasoconstriction.

**Aim:** To determine the association between *H. pylori* infection and MetS components, focusing on Highly sensitive C-Reactive Protein (hs-CRP) levels, to enhance understanding and management of these conditions.

Materials and Methods: This cross-sectional study was conducted at the Department of Medicine, Dr. D.Y. Patil Medical College, Hospital and Research Centre, Pimpri, Pune, Maharashtra, India spanning from September 2017 to August 2019. This study involved 100 dyspeptic patients aged 18 years or older undergoing upper Gastrointestinal (GI) endoscopy. Data collection included fasting/postprandial blood parameters, serum lipids, hs-CRP, and *H. pylori* detection via both rapid urease test and Histopathological Examination (HPE). Physical

assessments covered height, weight, Waist Circumference (WC), and blood pressure. MetS was evaluated using the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria. Statistical analysis employed unpaired t-tests, Chi-square tests, and Fisher-Exact tests using IBM Statistical Package for Social Sciences (SPSS) version 21.0.

**Results:** The study of 100 dyspeptic patients, predominantly females, revealed a significant association between *H. pylori* infection and MetS (p-value<0.001). *H. pylori* infection was associated with elevated fasting glucose (90.24%) and triglycerides (90.24%) (p-value<0.001). Additionally, individuals with *H. pylori* infection exhibited higher inflammatory markers (p-value 0.0029).

**Conclusion:** The above findings underscore the potential role of *H. pylori* as a risk factor for MetS and highlight the need for further research to elucidate mechanisms and implications for preventive strategies and clinical management, offering avenues for improved patient care and outcomes, particularly in addressing cardiovascular health.

**Keywords:** Cardiovascular complications, Inflammatory mediators, Insulin resistance

# INTRODUCTION

The MetS with IR constitutes key factors contributing to cardiovascular diseases, a significant cause of global mortality [1]. MetS encompasses a cluster of diabetes and cardiovascular elements, including elevated blood pressure, low High-Density Lipoprotein (HDL) levels, increased serum Triglycerides (TG) levels, central obesity, and hyperglycaemia [2]. While lifestyle and dietary changes are attributed to the high prevalence of MetS, they alone do not account for all MetS cases, necessitating the exploration of alternative emerging risk factors [3].

H. pylori, a spiral-shaped, microaerophilic, gram negative bacterium, is among the most common infections worldwide, especially prevalent in developing countries. H. pylori prevalence varies, reaching up to 80% in developing countries, while it is around 30% in developed nations [4]. A causal factor in various Gl illnesses, including chronic gastritis, gastric ulcerations, and MALToma (Mucosa-associated lymphoid tissue-lymphoma), H. pylori is classified as a class I carcinogen, capable of inducing chronic gastric inflammation and cancer [5]. Associations between H. pylori infection and extradigestive pathologies, such as atherosclerotic vascular diseases and coronary artery diseases, have been indicated previously [6].

However, the relationship between *H. pylori* infection and MetS/IR remains controversial, with limited studies conducted in the Indian population, despite a prevalence exceeding 60% [7,8]. Some epidemiological studies support a significant association between *H. pylori* infection, MetS, and IR [7,8]. Postulated mechanisms, including an increase in systemic inflammatory mediators and markers, the presence of an atherogenic lipid profile, and factors of vasoconstriction, offer hypothetical explanations for this role [9]. A study conducted in the Indian population suggested that *H. pylori* induce oxidative and inflammatory damage to beta-pancreatic cells, leading to IR [10]. Another study revealed that postmenopausal Indian women are predisposed to coronary artery disease due to a high prevalence of diabetes, IR, hs-CRP levels, and low HDL-cholesterol, postulating a high prevalence of occult *H. pylori* infections in such study groups [11].

Furthermore, the eradication of *H. pylori* infection has shown potential for improving IR and serum lipid profiles, suggesting it could impede the development of MetS and IR if treated [9]. Diagnosis of *H. pylori* infection should be based on clinical, biochemistry laboratory findings, microbiological detection, and HPEs. Although upper gastro-oesophago-duodenoscopic examination is invasive, time-consuming,

and expensive, it remains crucial for determining the clinical prognosis. The severity of precancerous lesions and tissue inflammation is frequently diagnosed through histological examinations, with HPE considered the "gold standard method" for diagnosing *H. pylori* infection, boasting sensitivity and specificity exceeding 95% [12].

This study aims to determine the prevalence and association of MetS in dyspeptic patients infected with *H. pylori*. Furthermore, it seeks to explore the relationship between *H. pylori* infection and various metabolic parameters, including blood glucose profile, high sensitivity CRP levels, lipid profile, and blood pressure measurements. Given the lack of research investigating these associations in dyspeptic patients specifically infected with *H. pylori*, this study addresses a significant gap in the literature. Understanding these relationships is crucial for elucidating the underlying mechanisms and developing targeted interventions for better management of metabolic health in *H. pylori*-infected individuals.

### MATERIALS AND METHODS

The present was a cross-sectional study, conducted at the Department of Medicine, Dr. D.Y. Patil Medical College, Hospital, and Research Centre, Pimpri, Pune, September 2017 to August 2019. Before the commencement of the investigation, the Institute's Scientific and Ethics Committee approval was obtained (Ethical committee clearance number: IESC/PG/044/17). Participants were given written consent forms in their own languages, ensuring they understood the study's goals, procedures, and potential risks.

Inclusion criteria: Individuals aged 18 years or older, presenting dyspeptic symptoms and undergoing upper GI endoscopy at the institute were included in the study.

Exclusion criteria: Individuals with chronic liver or renal disease, significant GI procedures history, cancer, recent antacid drug use, psychiatric problems, thyroid disorders, diabetes under treatment, or persistent alcoholism were excluded from the study.

Sample size was calculated by considering the prevalence of *H. pylori* infection among patients with dyspeptic symptoms as 58.8% from the study by Satpathi P et al., with a confidence interval of 95% Cl and an acceptable difference of 10%; the minimum sample size was 94. The software used was winPepi version 11 [13].

## **Study Procedure**

Data collection utilised a pretested proforma designed for the study, covering parameters such as Fasting Blood Sugar (FBS) and Postprandial Blood Sugar levels (PPBS), glycosylated haemoglobin, serum fasting lipids, Hs-CRP, upper Gl endoscopy, and HPE of biopsy samples for *H. pylori* detection. Physical examination encompassed height, weight, WC, and blood pressure measurements.

Blood samples were obtained after a 12-hour overnight fasting period for laboratory investigations. MetS evaluation utilised NCEP ATP III criteria for Asian Indians [14]. Esophagogastroduodenoscopy (OGD scopy) was performed after a minimum 8-hour fasting period, with specimens collected from fixed locations of the gastric antrum and corpus. Patients were categorised into *H. pylori*-positive and *H. pylori*-negative groups based on histopathological and rapid urease test results.

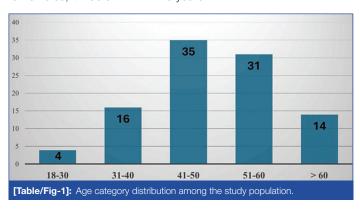
# STATISTICAL ANALYSIS

Statistical analysis was conducted using IBM SPSS version 21.0, expressed data as counts, percentages, and/or mean  $\pm$  SD. Two-tailed tests with a 95% confidence interval and a significance level of 0.05 were employed (p-value 0.05). Unpaired t-tests, Chi-square tests, and Fisher Exact tests were used to determine statistical significance.

# **RESULTS**

In this study, the majority of the participants were females. Out of 100 participants, 69 (69%) were females, and 31 (31%) were males.

The highest prevalence of dyspeptic symptoms was observed in the age group of 41-50 years, age distribution is shown in [Table/ Fig-1]. The mean age of all participants was 49.81±11.10 years. Specifically, the mean age for males was 44.39±11.03 years, while for females, it was 52.24±11.10 years.



In the investigation, the distribution of *H. pylori* across genders revealed that 19 males (46.34%) and 22 females (53.66%) tested positive for *H. pylori*. Among the 41 individuals with *H. pylori* positivity, 37 patients (90.24%) were diagnosed with MetS. A positive family history of obesity was found in three patients (7.31%) with *H. pylori* infection. The study identified associations between *H. pylori*, MetS, and a family history of obesity among individuals with dyspeptic symptoms, with statistical significance (p-value<0.05) and odds ratios of 27.13 and 0.21, respectively [Table/Fig-2].

In this study, a comparison of age, Body Mass Index (BMI), and WC between patients with and without *H. pylori* infection in both males and females was made. The findings revealed that among *H. pylori*-positive patients, there were higher values for WC in both males and females compared to *H. pylori*-negative patients, and these differences were statistically significant (p-value<0.05) [Table/Fig-3].

It was observed that among H. pylori-positive patients, FBS was significantly higher compared to *H. pylori*-negative patients, with a statistically significant difference (p-value<0.05). Furthermore, it was noted that among *H. pylori*-positive patients, there were slightly higher systolic blood pressure (SBP) {130 (120-140) vs 128 (118.25-143.5) mmHg} compared to *H. pylori*-negative patients, but these differences were not statistically significant (p-value>0.05). The comparison of lipid profiles between the two groups revealed that among H. pylori-positive patients, there were slightly higher levels of TG compared to H. pylori-negative patients, with a statistically significant difference (p-value<0.05). Conversely, HDL levels in H. pylori-positive patients were lower compared to v-negative patients, showing a statistically significant difference. H. pylori-positive patients also exhibited slightly higher CRP {3.7 (2.06-4.83) vs 2.6 (2-3.1)} compared to H. pylori-negative patients, with a statistically significant difference (p-value<0.05) [Table/Fig-4].

It was observed that *H. pylori*-positive patients had a higher prevalence of MetS (37, 90.24%) compared to *H. pylori*-negative patients (25.42%). Furthermore, *H. pylori*-positive patients showed a greater proportion of individuals with higher FBS (37, 90.24%) and TG (37, 90.24%) compared to *H. pylori*-negative patients, which was statistically significant, with odds ratios of 14.48 and 29.73, respectively [Table/Fig-5]. There was no significant difference when it comes to abdominal obesity, HDL, and blood pressure.

### DISCUSSION

The findings of this study shed light on several important aspects of the relationship between *H. pylori* infection and MetS. Notably, this study revealed a higher prevalence of dyspepsia in the 41-60 years age group, with a mean age of 49.81±11.10 years for all participants. This contrasts with the notably higher mean participant age of 59.2

		H.pylori positive	H.pylori negative	Total		Significance			
Parameters		n (%)	n (%)	n	χ²	df	p-value	Odds ratio	95 % CI
Male		19 (50)	19 (50)	38			0.450*	1.00	0.0.440
Gender	Female	22 (35.48)	40 (64.52)	62	2.05	1	0.152*	1.82	0.8- 4.13
IVIELADORIC	Present	37 (71.15)	15 (28.85)	52			0.004*	07.40	8.28-
	Absent	4 (8.33)	44 (91.67)	48	40.72	1	<0.001*	27.13	88.76
Family history of Obesity	Present	3 (15.79)	16 (84.21)	19	0.40	1	0.013*	0.21	0.00.0.70
	Absent	38 (46.91)	43 (53.09)	81	6.16				0.06-0.78

[Table/Fig-2]: Association of gender, Metabolic syndrome (MetS) and family history of obesity with *H.pylori* infection among patients with dyspeptic symptoms. n=Frequency of individuals in that category, %=Percentage of individuals in that category (Row percentage), \*Chi-square test, p<0.05 is considered significant, X²=Chi-square value, df=Degree of freedom Cl=Confidence interval

	H.pylori positive		H.pylori	negative	Significance			
Parameters	Median	IQR	Median	IQR	U	df	p-value	
Age in years (Male)	45	41.25-48	51	39.25-59	106.50		0.03#	
Age in years (Female)	58	45-61	50.50	46.50-53	325.50		0.09#	
Body Mass Index (BMI) (Male)	27.49	3.01	27.93	2.98	0.453	36	0.65*	
BMI (Female)	25.74	24.63-28.39	27.59	25.18-30.65	360		0.23#	
Waist Circumference (WC) (Male)	95	90.50-98	84	82.50-88	32.50		<0.001#	
WC (Female)	92	87 -96	80	75.50-84	63		<0.001#	

[Table/Fig-3]: Comparison of age, Body Mass Index (BMI) and Waist Circumference (WC) among patients with and without *H.pylori* infection. IQR: Interquartile range, "Unpaired T-test applied, values given are Mean and SD., "Mann-Whitney test applied, p<0.05 is considered significant, df=degree of freedom

	H.pylori positive		H.pylori	negative	Significance		
Blood parameters	Median	IQR	Median	IQR	U	p-value	
FBS	118	104-125.25	94	90-102	601.50*	<0.001	
SBP	130	120-140	128	118.25-143.5	1203.50*	0.9663	
DBP	80	80-88	82	80-86	1087.50*	0.3819	
TG	188	186-225	142	136.5-180	633*	<0.001	
HDL	42	36-46.50	55	45-60	454*	<0.001	
Highly sensitive C-Reactive Protein (Hs-CRP)	3.7	2.06-4.83	2.6	2-3.1	785.50*	0.0029	

[Table/Fig-4]: Comparison of Fasting Blood Sugar (FBS), blood pressure, serum triglyceride, high density lipoprotein and Highly sensitive C-Reactive Protein (Hs-CRP) among patients with and without *H.pylori* infection.

IQR: Interquartile Range, "Mann-Whitney test, p<0.05 is considered significant, FBS: Fasting blood sugar; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TG: Triglyceride; HDL: High density lipoprotein

	H.pylori positive	H.pylori negative		Significar	ice		
Metabolic Syndrome (MetS) components	n (%)	n (%)	χ²	df	p-value	Odds ratio	95% CI
Abdominal obesity (WC)-High	13 (50)	13 (50)	1.176	1	0.28#	1.643	(0.67-4.04)
Abdominal obesity (WC)-Normal	28 (37.84)	46 (62.16)	1.176				
HDL- Low	19 (38.78)	30 (61.22)	0.00	1	0.66#	0.83	(0.38-1.86)
HDL- Normal	22 (43.14)	29 (56.86)	0.20				
Triglycerides- High	37 (72.55)	14 (27.45)	42.83	-	<0.001#	29.73	(0.00.00.05)
Triglycerides- Low	4 (8.16)	45 (91.84)	42.63		<0.001"	29.73	(9.02-98.05)
Blood pressure- High	25 (46.30)	29 (53.70)	1.00	1	0.24#	1.616	(0.72-3.63)
Blood pressure- Low	16 (34.78)	30 (65.12)	1.36				
Fasting glucose (≥100 mg/dL)	37 (61.67)	23 (38.33)	26.48	1	<0.001#	14.48	(4.55-46.03)
Fasting glucose (≤100 mg/dL)	4 (10)	36 (90)	20.48				

**[Table/Fig-5]:** Association between *H.pylori* infection and Metabolic Syndrome (MetS) components.

n=frequency of individuals in that category, %=percentage of individuals in that category (Row percentage), Waist Circumference (WC) high if ≥ 102 cm in males, ≥ 88 cm in females [14], High density lipoprotein (HDL) is low if < 40 mg/dL in males, < 50 mg/dL in females [14], Triglycerides is high if value ≥150 mg/dL [14], Blood pressure is high if ≥ 130/85 mmHg [14], \*Chi square test applied; X²=Chi square value; df=Degree of freedom; Cl=Confidence interval

years reported in a Chinese study by Chen LW et al., examining the correlation between MetS and *H. pylori* infection [15]. Additionally, a Turkish study by Işıktaş Sayılar E et al., found that the majority of *H. pylori*-infected patients fell within the 40-49 years age group [12]. These variations underscore the importance of considering demographic differences when interpreting findings related to MetS and *H. pylori* infection across diverse populations.

In terms of gender distribution, this study, along with others [12,15-17], observed comparable percentages of males and females. Despite the variations in overall *H. pylori* prevalence reported in

different studies, the lack of statistically significant gender-based differences in *H. pylori* prevalence has been consistently noted [12,15-17]. This highlights the need for further exploration to understand the nuanced factors influencing *H. pylori* infection rates among genders.

Both this study and the study by Liu Y et al., found statistically significant differences in WC between *H. pylori*-positive and -negative patients [18]. This consistency highlights the robustness of the association between *H. pylori* infection and WC across different research studies. Similarly, elevated FBS levels in *H. pylori*-

positive patients were consistent with previous reports by Vaishnav BT et al., emphasising a potential link between *H. pylori* infection and alterations in glucose metabolism [19]. The current study and the reference study were both statistically significant. Furthermore, several studies have associated *H. pylori* infection with IR, with higher haemostatic model assessment for IR values and insulin levels observed in infected individuals [8].

Contrasting findings were observed regarding the relationship between *H. pylori* infection and blood pressure regulation. While this study did not find statistically significant differences in systolic and diastolic blood pressure between *H. pylori*-positive and -negative patients, other studies by Longo-Mbenza B et al., reported elevated blood pressure levels in infected individuals. This highlights the complexity of the relationship between *H. pylori* infection and blood pressure regulation, warranting further investigation [20].

Consistent with previous research, this study also found higher levels of TG, along with lower HDL levels, in H. pylori-positive patients. This aligns with the findings of a meta-analysis by Shimamoto T et al., which estimated the association between H. pylori infection and the serum lipid profile [21]. This study revealed that H. pylori infection was positively associated with LDL, TC, and TG (Standardised Mean Difference (SMD) (95% CI)=0.11 (0.09-0.12), 0.09 (0.07-0.10), and 0.06 (0.05-0.08), respectively) and negatively associated with HDL (SMD=-0.13 (-0.14 to -0.12)). Also, the association between H. pylori infection and low HDL levels has been consistently observed across diverse populations [22,23], suggesting a potential role of H. pylori in lipid metabolism alterations. Moreover, a meta-analysis by Watanabe J et al., has shown that after the eradication of H. pylori, HDL levels tend to increase, further supporting a link between H. pylori infection and alterations in lipid metabolism [24]. These collective findings underscore the complex interplay between H. pylori infection and lipid metabolism, warranting further exploration and understanding.

Furthermore, this study demonstrated higher levels of hs-CRP in *H. pylori*-positive patients. This finding aligns with a similar study done on 811 patients by Altun E et al., demonstrating elevated hs-CRP levels in *H. pylori*-infected patients [25]. CRP serves as an inflammation marker, and *H. pylori* infection induces a robust inflammatory response in the gastric antrum, leading to increased hs-CRP levels. Elevated hs-CRP is recognised as a risk factor for Coronary Heart Disease (CHD) and stroke. Consequently, it can be inferred that *H. pylori* infection, with its association with heightened hs-CRP levels, may pose a potential risk for metabolic disturbances contributing to the development of CHD. This underscores the importance of understanding the inflammatory aspects of *H. pylori* infection in the context of cardiovascular health.

In this study, all components of MetS were compared between individuals with and without *H. pylori* infection, revealing statistically significant correlations with *H. pylori* positivity. This observation underscores a potential association between *H. pylori* infection and MetS components, including elevated WC, blood pressure (SBP), FBS, TG levels, and reduced HDL levels (p-value<0.05).

Consistent with the findings of this study, a systematic review and meta-analysis by Upala S et al., of six trials reported a statistically significant association between *H. pylori* and MetS with a pooled odds ratio of 1.34 (95% CI 1.17-1.53, I(2)=39%, Pheterogeneity <0.01) [26]. Between the infected and non-infected groups, there were significant differences in FBG, HDL, BMI, TG, and SBP (all p-value<0.05), suggesting a potential role of *H. pylori* infection in the development of MetS components. One more study by Liu Y et al., also reveals similar findings [18].

Regarding the relationship between *H. pylori* infection and diabetes mellitus, this study found significantly higher FBS levels in *H. pylori*-positive patients. According to the findings of a study

by Hosseininasab Nodoushan SA and Nabavi A *H. pylori* is was more common in Type 2 diabetic patients than in healthy individuals or non diabetic patients [27]. The reason is the growth of *H. pylori* infection-induced inflammation and the generation of inflammatory cytokines, as well as numerous hormonal imbalances caused by this bacterium, which are related to diabetes mellitus.

### Limitation(s)

Despite the valuable insights gained from this study, several limitations should be acknowledged. Firstly, the cross-sectional design of the research inherently restricts the establishment of causal relationships, limiting our ability to infer causation between *H. pylori* infection and MetS. Additionally, the study's relatively small sample size might influence the generalisability of the findings to larger populations. The exclusion of individuals with certain medical conditions, such as chronic liver or renal disease, and the focus on dyspeptic patients undergoing upper GI endoscopy could introduce selection bias, affecting the study's external validity. Furthermore, the study's reliance on a single-center setting may limit the generalisability of the results to diverse demographic and geographic contexts. Despite these limitations, the findings contribute valuable information to the existing literature on the potential association between *H. pylori* infection and MetS.

# **CONCLUSION(S)**

In essence, this study underscores the significant association between *H. pylori* infection and MetS components, highlighting its potential as a risk factor. These findings shed light on *H. pylori*'s involvement in metabolic disturbances, inflammation, and subsequent cardiovascular complications, informing preventive strategies and clinical management. Recognising this interplay is crucial for targeted interventions, ultimately enhancing patient outcomes.

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