

# Prevalence and Association of *Helicobacter pylori* Infection in Gastric Disease at Dr. Cipto Mangunkusumo General National Hospital 2010–2021

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## ABSTRACT

**Background:** Several studies showed contrasting associations between *Helicobacter pylori* infection and organic gastric disorders. We aim to determine the association between *H. pylori* infection and gastroesophageal reflux disease (GERD), gastric polyp, and gastric cancer in an Indonesian national referral hospital.

**Method:** Data was collected from patients referred to Cipto Mangunkusumo General National Hospital, Jakarta, Indonesia, from 2010 to 2021, with complete *H. pylori* test and endoscopy from electronic medical records. Chi-square analysis were performed to determine the association with a significant *p*-value of  $< 0.05$ .

**Results:** Three hundred and fourteen consecutive patients were enrolled, with a median age of 51.0 (16–85), and 131 (41.7%) of them were males. The prevalence of *H. pylori* infection in organic gastric disease was 7.6% ( $n = 24$ ) with 0.3% ( $n = 1$ ) of them having gastric cancer, 3.2% gastric polyp ( $n = 10$ ), and 4.1% ( $n = 13$ ) GERD. A proven association between *H. pylori* infection and GERD was observed (RR = 26.42; 95% CI: 76.12–114.05;  $p = 0.000$ ) and esophagitis (RR = 2.44; 95% CI: 1.71–3.49;  $p = 0.000$ ). However, no significant association was found between *H. pylori* infection and gastric cancer (RR = 4.07; 95% CI: 0.26–64.09;  $p = 0.28$ ), and gastric polyp (RR = 1.16; 95% CI: 0.61–2.22;  $p = 0.65$ ).

**Conclusion:** Our study suggested an association between *H. pylori* infection in GERD and esophagitis patients. An insignificant association was observed between *H. pylori* infection and gastric cancer, and gastric polyp.

**Keywords:** *Helicobacter pylori*, esophagitis, GERD, gastric polyps, gastric cancer

## ABSTRAK

**Latar belakang:** Beberapa studi menunjukkan adanya korelasi antara *Helicobacter pylori* dengan gangguan organik lambung. Penelitian ini dilakukan untuk mengetahui adanya korelasi antara *Helicobacter pylori* dengan kanker lambung, polip lambung, dan gastroesophageal reflux disease (GERD).

**Metode:** Penelitian retrospektif dilakukan RSUPN Dr. Cipto Mangunkusumo pada rentang tahun 2010–2021 dengan data rekam medis pasien yang melakukan pemeriksaan *H. pylori* dan terdiagnosis satu dari tiga kelainan lambung (kanker lambung, polip lambung, GERD). Dilakukan analisis univariat dan bivariat dengan chi square untuk menemukan asosiasi ( $p < 0.05$ ).

**Hasil:** Dari total 314 data pasien yang memenuhi kriteria inklusi, dengan median umur 51.0 (16–85), dan 131 (41.7%) adalah pria. Secara keseluruhan, prevalensi *H. pylori* positif pada kelainan organik usus yaitu 7.6% ( $n = 24$ ) dengan 0.3% ( $n = 1$ ) kanker lambung, 3.2% ( $n = 10$ ) polip lambung, dan 4.1% ( $n = 13$ ) GERD. Ditemukan korelasi bermakna antara *H. pylori* dengan GERD ( $RR = 26.42$ ; 95% CI: 76.12–114.05;  $p = 0.000$ ) dan *H. pylori* dengan esofagitis ( $RR = 2.44$ ; 95% CI: 1.71–3.49;  $p = 0.000$ ). Namun tidak ditemukan korelasi bermakna antara *H. pylori* dan kanker lambung ( $RR = 4.07$ ; 95% CI: 0.26–64.09;  $p = 0.28$ ), dan polip lambung ( $RR = 1.16$ ; 95% CI: 0.61–2.22;  $p = 0.65$ ).

**Simpulan:** Terdapat adanya korelasi bermakna antara infeksi *H. pylori* dengan GERD dan esofagitis. Tidak ditemukan adanya korelasi bermakna antara infeksi *H. pylori* dengan kanker lambung dan polip lambung.

**Kata kunci:** *Helicobacter pylori*, esofagitis, GERD, kanker lambung, polip lambung

## INTRODUCTION

*Helicobacter pylori* is a gram-negative bacterium that colonizes the stomach.<sup>1</sup> *H. pylori* can reach the mucous protective layer on the upper part of the gastric mucosa and survive in extremely acidic conditions. The flagella helps to avoid the location of acid pH by chemotaxis. The large amounts of urea produced by *H. pylori* would subsequently become ammonia and carbon dioxide, which would neutralize its inhabited areas.<sup>2</sup>

Most common *H. pylori* manifestations are mainly gastroduodenal disturbances, such as peptic ulcer, mucosa-associated lymphoid tissue lymphoma, and gastric cancer.<sup>3</sup> Record stated that gastric cancer has the third-highest disease burden in the world.<sup>4</sup> This statement correlated with the fact that since 1994, *Helicobacter pylori* has been classified as a class I carcinogen by the International Agency for Research on Cancer (IARC), a subdivision of the World Health Organization (WHO).

*Helicobacter pylori* infection affects 60.3% of the world's population, and its prevalence is particularly high in developing countries.<sup>3</sup> However, the relationship between *H. pylori* infection and the occurrence of organic gastric disease in specific developing countries has not been much discussed. This study focuses on *H. pylori* infection in Indonesia, one of the developing countries.<sup>5</sup> The study aims to determine the prevalence and relationship of *H. pylori* infection in patients with organic diseases of the gastric (gastroesophageal reflux disease/GERD, gastric polyps, and gastric cancer) in Indonesia with a sample of patients undergoing endoscopy at RSUPN Dr. Cipto Mangunkusumo, Jakarta, Indonesia, from 2010 to 2021.

## METHODS

### Research design and population

The study was conducted at Dr. Cipto Mangunkusumo, the General National Hospital in Indonesia. In this study, a total sampling method was carried out with a total of 338 patient records obtained from electronic medical records. Using a minimal sample equation from the previous study we had a minimal sample of 66.<sup>6</sup> In this study, the *Helicobacter pylori*-negative group consists of 274 patients, with 22 patients excluded due to incomplete medical records. The *Helicobacter pylori*-positive group consists of 64 patients, with two patients excluded due to incomplete medical records.

The inclusion criteria are patients who are  $\geq 18$  years of age, undergo an examination of *H. pylori*, and undergo an endoscopic examination. The inclusion diagnosis is that the patient has one of three gastric diseases (gastric cancer, gastric polyps, or GERD) and has a complete medical record. The exclusion is a patient who has already been diagnosed with *H. pylori* before or already finished *H. pylori* therapy outside Dr. Cipto Mangunkusumo General Hospital. The study was conducted with the approval of the Universitas Indonesia Ethics Committee with protocol number 20-07-0753 using secondary data in the form of medical records. Electronic medical record data is collected from patients performing endoscopy and colonoscopy examinations at the Digestive Endoscopic Center, Dr. Cipto Mangunkusumo General National Hospital in 2010–2021 who underwent *H. pylori* examination through both histopathological biopsy and urea breath test.

The diagnosis of gastric cancer and gastric polyps is established through endoscopy and histopathology examination with biopsy. The diagnosis of gastritis and GERD is established through anamnesis and physical examination. The diagnosis of esophagitis, hiatal hernia, and peptic ulcers is established through an endoscopy examination. The diagnosis of *H. pylori* is obtained through a urea breath test and histopathological examination with biopsy.

### Statistical Analysis

Statistical analysis is done using IBM SPSS version 25. The method of analysis used is chi-square analysis to determine the significance value of  $p < 0.05$  and 95% CI.

### RESULT

Out of a total of 314 patients meeting the inclusion criteria, there were 131 male (41.7%) and 183 (58.3%) female patients. No significant differences were found between sex and the incidence of *H. pylori* infection ( $p = 0.152$ ). There were 62 (19.74%) patients with a positive diagnosis of *H. pylori* infection and 252 (80.25%) patients with *H. pylori* negative. The demographics of patients are shown in Table 1.

Table 1. Distribution of cases

Gastric Disease	<i>H. pylori</i> Positive	<i>H. pylori</i> Negative
Peptic ulcer		
Present	14 (22.6)	43 (17.1)
Absent	48 (77.4)	209 (82.9)
Hiatal hernia		
Present	6 (9.7%)	24 (9.5%)
Absent	56 (90.3)	228 (90.5)
Esophagitis		
Present	30 (48.4)	50 (19.8)
Absent	32 (51.6)	202 (80.2)
Gastritis		
Present	60 (96.8)	226 (89.7)
Absent	2 (3.2)	26 (10.3)
GERD		
Present	13 (21.0)	2 (0.8)
Absent	49 (79.0)	250 (99.2)
Gastric cancer		
Present	1 (1.6)	1 (0.4)
Absent	61 (98.4)	251 (99.6)
Gastric polyps		
Present	10 (16.1)	35 (13.9)
Absent	52 (83.9)	217 (86.1)

In the chi-square bivariate test in Table 2, the variables that have significance with *H. pylori* infection are the incidence of esophagitis (RR = 2.44; 95% CI: 1.71–3.49;  $p < 0.001$ ) and GERD (RR = 26.42; 95% CI:

6.12–114.05;  $p = 0.000$ ). For the gender variable (RR = 1.40; 95% CI: 0.90–2.18;  $p = 0.15$ ), no significance was found. Similarly, there is no association found between *H. pylori* infection with gastric cancer (RR = 4.12; 95% CI: 0.26–64.09;  $p = 0.28$ ) and gastric polyps (RR = 1.19; 95% CI: 0.61–2.22;  $p = 0.65$ ). Gastritis, hiatal hernias, and peptic ulcers are included in the variable as some of the diseases that are widely found in endoscopy and colonoscopy but are not one of the three organic gastric diseases that fall into the inclusion criteria. The results obtained have no significance with the results of each RR analysis (RR = 1.08; 95% CI: 1.01–1.148;  $p = 0.08$ ), (RR = 1.02; 95% CI: 0.43–2.38;  $p = 1.00$ ), and (RR = 1.32; 95% CI: 0.78–2.27;  $p = 0.31$ ).

Table 2. Analysis of chi-square

Variables	P Value	Relative Risk	CI 95%
Gender	0.15	1.40	0.90–2.18
Gastritis	0.08	1.08	1.01–1.148
Peptic ulcer	0.31	1.32	0.78–2.27
Esophagitis*	<0.001*	2.44	1.71–3.49
Hiatal hernia	1.000	1.02	0.43–2.38
GERD*	<0.001*	26.42	6.12–114.05
Gastric polyp	0.65	1.16	0.61–2.22
Gastric cancer	0.28	4.07	0.26–64.09

\*significant,  $p$ -value < 0.05

### DISCUSSION

*Helicobacter pylori* is one of the most common bacteria in the world. A study reported that *H. pylori* infection is associated with the host's genetic susceptibility, environmental factors where the host lives, and the genetic diversity affecting the strain of *H. pylori* itself.<sup>7</sup> A study showed that several habits such as eating food with fingers, washing hands before eating, or drinking alcohol, may affect the increase of *H. pylori* prevalence.<sup>8</sup> Other socio-cultural risk factors including salary, source of water, history of medicine, and smoking were also associated with the increased prevalence in Indonesia.<sup>9</sup>

GERD is one of the most common gastrointestinal diseases.<sup>10</sup> Based on the Montreal classification, GERD is defined as a condition in which reflux from the gastric content leads to unwanted symptoms or complications.<sup>11</sup> The pathophysiology of GERD begins with the failure of the lower esophageal sphincter, which can be caused by various factors such as hernia hiatus, obesity, pregnancy, drugs, and smoking.<sup>2</sup>

Globally, an increase in GERD incidence is expected to occur.<sup>12</sup> The best treatment for *H. pylori* infection in GERD patients is still debatable, and there is still insufficient agreement on the association between *H. pylori* infection and GERD. *H. pylori* has

been identified as a protective factor in GERD by multiple studies.<sup>13</sup> It is thought that there may be a link between *H. pylori* and GERD because the frequency of GERD has been rising in developing nations while the prevalence of *H. pylori* infection has been dropping.

In this study, we have found there is a positive association between *H. pylori* infection with esophagitis and GERD. According to other studies with the same outcome, *H. pylori* infection is related to the severity of GERD and is less common in people with severe GERD than it is in people with mild GERD.<sup>14</sup> A study by Fatin et al in Turkey showed that there is a positive association between *H. pylori* infection with GERD, with *H. pylori* infection found in 82.4% of patients with GERD based on the study.<sup>14</sup> Jie et al in their study concluded that the prevalence of *H. pylori*-positive was higher among patients with GERD and peptic ulcers.<sup>15</sup> Other research, however, demonstrates no connection between GERD and *H. pylori*. A cross-sectional study conducted in Iran for 7 years with more than 1900 participants showed there was no association between *H. pylori* infection and erosive GERD.<sup>16</sup>

*Helicobacter pylori* can induce esophagitis in GERD through one of the following three potential mechanisms: (1) *H. pylori* infection becomes a predisposition to GERD by increasing the secretion of gastric acid; (2) *H. pylori* infection may result in esophageal damage by infecting the columnar-type epithelium of the gaster that lines the distal or as part of Barrett's esophagus; or (3) *H. pylori* infection may lead to indirect damage to the esophagus. One study showed no statistically significant differences between esophagitis and reflux in patients with and without *H. pylori* infection.<sup>17</sup>

A randomized controlled trial (RCT) by Yan Xue showed that no association was found between *H. pylori* and GERD or erosive esophagitis.<sup>13</sup> A meta-analysis showed that the long-term use of PPI is associated with an increased risk of gastric atrophy. The exact mechanism is still unknown. One of the theories is the concurrent use of PPI can change the distribution of organisms in the corpus, resulting in active chronic corpus gastritis with atrophy.<sup>18</sup> Since many GERD patients use PPI medicines for a sufficiently long period, this is considered to be an association between *H. pylori* and GERD.

*H. pylori* is also considered to be the leading cause of gastritis and peptic ulcers, which can develop into gastric cancer and gastric mucosa-associated lymphoid tissue (MALT) lymphoma. Gastritis caused by *H. pylori* occurs as a result of a decrease in the production

of somatostatin, which regulates gastrin, resulting in hypergastrinemia.<sup>19</sup> If not addressed immediately, this will result in inflammation of the gastric mucosa and atrophy, which can increase the risk of gastric ulcers and non-cardia adenocarcinomas.

A study in Iran showed that *H. pylori* is isolated in 60–80% of cases of peptic ulcers.<sup>20</sup> The frequency of duodenal ulcers is higher than that of gastric ulcers, with the majority of patients being male. The virulence factors of *H. pylori*, which are gene A (*cagA*) and cytotoxin A (*vacA*), are considered to be the factors that induce the process of apoptosis in cells and result in the death of the host cell on the epithelium of the gaster. It also leads to the dysregulation of the pathway of mitogen-activated protein kinases (MAPKs).

Keikha et al's meta-analysis showed a significant correlation between the occurrence of peptic ulcers and *vacA* and *cagA*-positive strains of *H. pylori* (RR = 1.63; 95% CI: 1.39–1.91;  $p = 0.00$ ).<sup>21</sup> The ability of *cagA/vacA*-positive bacteria to withstand gastric acid conditions and evade the immune system is a distinctive trait that links them to peptic ulcers.<sup>22</sup> All strains of *H. pylori* include the *vacA* gene, but only 50% of them also contain the *vacA* toxin, which is the functional protein. For the bacteria to thrive in the mucous layer, the *vacA* protein creates a channel on the bacterial membrane that draws various ions and metabolites into the cytoplasm.

*CagA* is a protein that has high immunity; some studies stated that the *cagA*-positive strain has been associated with more severe inflammation, increased degrees of atrophy, and a greater likelihood of developing into adenocarcinoma compared with the *cagA*-negative strain. *CagA* will bind to the membrane cell when it enters the host cell, then pass through the tyrosine phosphorylation process that will change the cell morphology and affect a variety of other intracellular processes that then result in inflammation.<sup>4</sup>

The researchers discovered a link between *H. pylori* infection and hiatal hernia, which is a contributing factor to Gastroesophageal Reflux Disease (GERD) and is connected with the development of esophagitis.<sup>23</sup> Another study found that the incidence of hiatal hernias without infection with *H. pylori* was higher compared to hiatal hernias with *H. pylori* (91 versus 31;  $p < 0.0001$ ).<sup>17</sup>

*Helicobacter pylori* is an etiological agent for gastric adenocarcinoma, which then, more than 50% of the time, becomes gastric cancer. Other factors are thought to influence the carcinogenesis in the *H. pylori* infection process, such as smoking. A study in

East Asia showed that smoking at the time of research increased the risk of non-cardiac gastric cancer, but only in subjects who harbored antibodies to the *H. pylori* virus, specifically CagA-positive *H. pylori*. This implies that smoking status is an additional risk factor for gastric cancer incidence in regions with high *H. pylori* prevalence, such as East Asia, and that quitting smoking may be a useful tactic to lower the risk of gastric cancer.<sup>24</sup>

Infection with *H. pylori* results in damage to the gastric mucous membrane, causing atrophic gastritis that then turns into intestinal metaplasia, dysplasia, and gastric cancer. However, in this study, significant correlations were found only in esophagitis and GERD. There are some limitations to this study, especially in the number of samples. Data from 2010–2014 is difficult to find through electronic medical records, and not all patients undergoing endoscopy are examined for *Helicobacter pylori*. This study did not include GERD patients who did not go through endoscopy examination, thus selection bias may occur as a limitation.

The strength of this study lies in the way it diagnoses gastric cancer and gastric polyps through endoscopy and *H. pylori* infection through tissue histopathological examination. The study used immunohistochemistry to diagnose *H. pylori* on a gastric biopsy because it has high sensitivity and specificity, especially in patients who have just started therapy.<sup>25</sup>

## CONCLUSION

This study found a significant correlation between *Helicobacter pylori* infection and the occurrence of esophagitis and GERD. No significant correlation was found between *H. pylori* infection and the occurrence of gastric cancer or gastric polyps. This may occur due to a lack of data on patients with *H. pylori* infection. Research with more samples is recommended for further research.

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