

Relationship between *Helicobacter pylori*-positivity in the gallbladder and stomach and effect on gallbladder pathologies

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Abstract

Objective: *Helicobacter pylori* commonly occurs in the stomach, but localizations outside the stomach and related diseases have also been investigated. However, the relationship between *H. pylori* and gallstones remains controversial. We aimed to investigate the relationships between *H. pylori* in the stomach and the gallbladder and gallstones.

Methods: This prospective case-control study included patients who underwent cholecystectomy because of gallstones, pancreatic head cancer, or hepatic resection. The patients were separated into two groups according to the detection of *H. pylori* in gallbladder samples using Giemsa staining. Stomach *H. pylori* status was based on previous gastroscopy.

Results: The study enrolled 60 patients, comprising 27 patients with gallstones and 33 without. There was no significant difference in the incidence of gallstones between patients with or without *H. pylori* in the stomach or gallbladder. Furthermore, the presence of *H. pylori* in the stomach was measured in 14 patients and was significantly correlated with *H. pylori* in the gallbladder.

Conclusion: The current study showed no relationship between the occurrence of gallstones and the presence of *H. pylori* in either the gallbladder or the stomach. In contrast to previous reports, this suggests that *H. pylori* does not play a role in the development of gallstones.

Keywords

Biliary stone, gallstone, gastritis, general surgery, hepato-pancreatic biliary surgery, *Helicobacter pylori*

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Introduction

Gallstones occur in patients worldwide, but are especially common in western countries.¹ Several factors have been reported to play roles in the formation of gallstones, including bacterial infections in the gallbladder and bile ducts.² Gallstones also cause various clinical conditions, such as acute cholecystitis, chronic cholecystitis, jaundice related to bile duct obstruction, and acute pancreatitis.³

Helicobacter pylori is a Gram-negative bacillus thought to infect more than half the global population. *H. pylori* has primarily been identified in the stomach and has been related to several diseases, including duodenal ulcer, chronic gastritis, non-Hodgkin's lymphoma of the stomach, and gastric adenocarcinoma.⁴⁻⁸ However, increasing numbers of studies have investigated localizations of *H. pylori* outside the stomach and diseases potentially related to such infections.⁹ *H. pylori* was first described in the gallbladder mucosa in patients with gallstones 1996, and a relationship between *H. pylori* and gallstone formation was reported, as in the stomach.¹⁰ However, despite subsequent reports of a relationship between *H. pylori* and chronic cholecystitis, no mechanism has yet been identified.^{11,12} Importantly in this regard, it remains unclear if *H. pylori* reaches the gallbladder and biliary tree via an ascending route from the duodenum, or via the portal venous system.^{13,14}

Given the conflicting reports regarding the relationship between *H. pylori* infections and gallstone formation, this study aimed to investigate the relationships between *H. pylori* in the stomach and gallbladder and the occurrence of gallstones.

Methods

Patients

This prospective, case-control study reviewed a total of 732 patients who underwent

cholecystectomy for any reason at Istanbul Training and Research Hospital between September 2015 and May 2018. Exclusion criteria were cholecystectomy performed because of acute cholecystitis, pregnancy, and patients who did not wish to participate in the study. Indications for cholecystectomy in the included patients were gallstones, pancreatic head cancer, or hepatic resection. Patients were ordered according to the date of cholecystectomy and 60 patients were chosen at random using the www.random.org website. Written informed consent was obtained from each patient and the study protocol was approved by the local Ethics Committee.

Gallbladders excised during cholecystectomy were placed in 10% buffered formaldehyde solution and sent to the pathology laboratory for routine pathology examination and investigation of *H. pylori* using Giemsa staining (Figure 1). The patients were then separated into two groups according to the presence or absence of *H. pylori* in the gallbladder. Patient records included information on age, sex, pathology report and *H. pylori* status in the stomach if gastroscopy had been applied preoperatively, gallbladder wall thickness, cholesterosis, intestinal metaplasia, activation, and pyloric metaplasia.

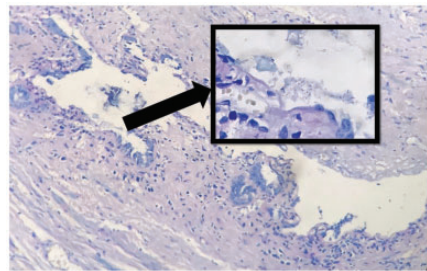


Figure 1. Gallbladder biopsy stained for *H. pylori* using Giemsa staining (magnification $\times 100$). Box shows representative *H. pylori* staining (magnification $\times 400$).

Statistical analysis

Data were analyzed using IBM SPSS Statistics for Windows, Version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive statistics were given as mean \pm standard deviation (SD), median (maximum, minimum), number (n), and percentage (%). Conformity of the data to a normal distribution was assessed using the Kolmogorov–Smirnov test. Quantitative independent data were analyzed using the Mann–Whitney U-test. Qualitative independent data were analyzed by the χ^2 test, or by Fisher's test if the χ^2 test conditions were not met. A value of $P < 0.05$ was accepted as statistically significant.

Results

A total of 60 patients were included in the final evaluation (34 women, 26 men, mean age 56.0 ± 11.7 years). The study was limited to 60 patients because of financial restrictions. Twenty-seven patients had gallstones and 33 did not. Group 1 comprised 52 patients without *H. pylori* in the gallbladder and Group 2 comprised eight patients with *H. pylori* in the gallbladder. There was no significant difference between the groups in terms of age, sex, wall thickness, presence of gallstones, rate of intestinal metaplasia, rate of activation, rate of previous stomach biopsy, or rate of gastritis in previous stomach biopsy (Table 1).

Fourteen patients underwent preoperative gastroscopy and biopsy for *H. pylori* detection. There was no significant difference between patients with and without *H. pylori* in the stomach in relation to the detection of gallstones.

Out of five patients with *H. pylori*-positive gastritis (confirmed by biopsy), four were also positive for *H. pylori* on gallbladder biopsy, while all nine patients negative for *H. pylori* gastritis were also negative for gallbladder *H. pylori*, suggesting a significant

correlation between stomach and gallbladder *H. pylori* status ($P = 0.005$) (Table 2)

In relation to the possible route of spread, 24 of the 33 patients without gallstones, including four of the five patients with *H. pylori* in the gallbladder, had a history of preoperative endoscopic retrograde cholangiography (ERCP), compared with only 2 of the 27 patients who underwent cholecystectomy because of gallbladder stones.

Discussion

Many recent studies have investigated the occurrence of *H. pylori* outside the stomach, e.g., in the skin, nose, and gallbladder,^{9,15} while other studies have evaluated the statuses of other *Helicobacter* strains within the gallbladder.^{10,11}

Fatemi et al. compared *Helicobacter* strains between patients without gallstones and those with acute cholecystitis and chronic cholecystitis associated with gallstones. *H. pylori* was observed at a significantly higher rate in cases with acute cholecystitis associated with gallstones compared with the other cases, and there was no relationship with other *Helicobacter* strains.¹⁶ A meta-analysis that reviewed studies of the relationship between *H. pylori* and gallstones and cholecystectomy reported that *H. pylori* was more common in patients with chronic cholecystitis and gallstones compared with the control group (24.98% vs. 8.28%, $P < 0.05$).¹⁷ Another meta-analysis also demonstrated a relationship between *H. pylori* in the gallbladder and cholelithiasis.¹⁸ Zhou et al.¹⁴ found *H. pylori* in 20% of chronic cholecystitis cases, and also emphasized that gallbladder metaplasia and pre-malignant lesions such as adenomyomatosis were more frequent in patients positive for gallbladder *H. pylori*. In another study, Hassan et al.¹⁹ reported that *H. pylori* infection aggravated potentially precancerous mucosal lesions.

Table 1. Characteristics of patients according to gallbladder *H. pylori* status.

	Gallbladder <i>H. pylori</i> (-)			Gallbladder <i>H. pylori</i> (+)			P value
	Mean \pm SD or n	Percentage (%)	Median	Mean \pm SD or n	Percentage (%)	Median	
Age	55.8 \pm 12.1		58	57.4 \pm 9.6		60	0.524
Sex							
Female	29	55.8%		5	62.5%		0.721
Male	23	44.2%		3	37.5%		
Wall thickness (mm)	3.8 \pm 3.3		3	3.1 \pm 1.1		3	0.508
Gallstones							
Absent	28	53.8%		5	62.5%		0.647
Present	24	46.2%		3	37.5%		
Cholesterosis							
Absent	44	84.6%		8	100.0%		0.582
Present	8	15.4%		0	0.0%		
Intestinal metaplasia							
Absent	47	90.4%		7	87.5%		>0.95
Present	5	9.6%		1	12.5%		
Activation							
Absent	38	73.1%		6	75.0%		0.909
Present	14	26.9%		2	25.0%		
Pyloric metaplasia							
Absent	39	75.0%		8	100.0%		0.182
Present	13	25.0%		0	0.0%		
Previous stomach biopsy							
Absent	40	76.9%		6	75.0%		0.222
Present	10	23.1%		4	25.0%		
Gastritis							
Absent	1	8.3%		0	0.0%		>0.95
Present	9	91.7%		4	100.0%		

Table 2. Gallstones and *H. pylori* status according to presence of *H. pylori* in stomach biopsy

		Stomach <i>H. pylori</i> (-)		Stomach <i>H. pylori</i> (+)		P value
		n	Percentage (%)	n	Percentage (%)	
Gallstones	Absent	4	44.4%	3	60.0%	<0.95
	Present	5	55.6%	2	40.0%	
Gallbladder <i>H. pylori</i> status	Absent	9	100.0%	1	20.0%	0.005
	Present	0	0.0%	4	80.0%	

In contrast to many studies, a retrospective study¹⁵ of 45 cases including cholecystectomy samples detected *H. pylori*-positivity in the gallbladder in 40% of patients without gallstones and 20% of those with gallstones.

However, this difference was not significant and no relationship could be established between *H. pylori*-positivity and the occurrence of gallstones. Moreover, no *H. pylori* gallbladder infection was noted in 10

patients with ulceration of the gallbladder.¹⁵ Similarly, the current study found no relationship between *H. pylori*-positivity in the gallbladder and gallstones, or the development of cholesterosis, intestinal metaplasia, pyloric metaplasia, and activation.

Previous studies reported that *H. pylori* was more prevalent in eastern countries and showed no sex difference, but was related to age, with a particular increase in colonization rates above the age of 70 years.^{20–22} The mean age of the patients with gallbladder *H. pylori*-positivity in the current study was 57.4 years, which was not significantly different from that of the patients who were *H. pylori*-negative in the gallbladder.

There is currently insufficient evidence regarding the route whereby *H. pylori* settles in the gallbladder. It may reach the gallbladder via an ascending route from the duodenum or via the portal circulation system.^{23,24} A meta-analysis of patients undergoing ERCP reported that the procedure could result in contamination of the gallbladder with *Helicobacter* strains via the ascending pathway from the duodenum, leading to false-positive results.¹⁷ In the current study, although four out of the five patients with *H. pylori* in the gallbladder without gallstones underwent preoperative ERCP, thus supporting its possible spread via the ascending pathway, no conclusions can be drawn about the route of spread in patients with gallstones who did not undergo ERCP.

An extensive retrospective study²⁵ that evaluated the relationship between the presence of *H. pylori* antibodies in the blood and gallstones found no relationship between the rates of gallstones in *H. pylori*-positive patients overall, but a significant negative correlation was observed in individuals aged <45 years. The same study identified a significant relationship between gallbladder polyps and *H. pylori*-positivity.²⁵ Helaly et al.²⁶ reported a significant relationship between *H. pylori*-positivity in the stomach

and the gallbladder, while another study also found a strong association between gallbladder and stomach *H. pylori*-positivity.¹⁴ The current study found no significant relationship between the occurrence of gallstones and stomach *H. pylori*-positivity in patients with stomach biopsy results, but did confirm a significant relationship between stomach and gallbladder *H. pylori*-positivity.

This study had some limitations owing to its small size and limited variation, which meant that it was not possible to examine subgroups of patients with cancers of the hepatobiliary system and pre-malignant lesions because of the low patient numbers. In addition, *H. pylori* status was not measured in the bile ducts, thus limiting the information available in relation to the route of *H. pylori* spreading.

In contrast to several previous studies, the current results suggested that the rates of gallbladder *H. pylori*-positivity, as well as stomach *H. pylori*-positivity, were similar in patients with and without gallstones. However, there was a significant relationship between stomach and gallbladder *H. pylori* statuses. Although further studies with larger series are required, the present results indicate that *H. pylori* infection does not contribute to the development of gallstones.


Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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References

1. Stinton LM and Shaffer EA. Epidemiology of gallbladder disease: cholelithiasis and cancer. *Gut Liv* 2012; 6: 172–187.
2. Maurer KJ, Carey MC and Fox JG. Roles of infection, inflammation, and the immune system in cholesterol gallstone formation. *Gastroenterol* 2009; 136: 425–440.
3. Leong RW and Sung JJ. *Helicobacter* species and hepatobiliary diseases. *Aliment Pharmacol Ther* 2002; 16: 1037–1045.
4. Parsonnet J, Friedman GD and Vandersteen DP. *Helicobacter pylori* infection and the risk of gastric carcinoma. *N Engl J Med* 1991; 325: 1127–1131.
5. Correa P and Houghton J. Carcinogenesis of *Helicobacter pylori*. *Gastroenterol* 2007; 133: 659–672.
6. Marshall BJ and Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* 1984; 1: 1311–1315.
7. Veldhuyzen van Zanten SJ and Sherman PM. *Helicobacter pylori* infection as a cause of gastritis, duodenal ulcer, gastric cancer and nonulcer dyspepsia: a systematic over-view. *Can Med Assoc J* 1994; 150: 177–185.
8. Parsonnet J, Hansen S, Rodriguez L, et al. *Helicobacter pylori* infection and gastric lymphoma. *N Engl J Med* 1994; 330: 1267–1271.
9. Testerman TL and Morris J. Beyond the stomach: an updated view of *Helicobacter pylori* pathogenesis, diagnosis, and treatment. *World J Gastroenterol* 2014; 20: 12781–12808.
10. Kawaguchi M, Saito T, Ohno H, et al. Bacteria closely resembling *Helicobacter pylori* detected immunohistologically and genetically in resected gallbladder mucosa. *J Gastroenterol* 1996; 31: 294–298.
11. Moricz AD, Melo M, Castro AM, et al. Prevalence of *Helicobacter* spp in chronic cholecystitis and correlation with changes on the histological pattern of the gallbladder. *Acta Cir Bras* 2010; 25: 218–224.
12. Apostolov E, Al-Soud WA, Nilsson I, et al. *Helicobacter pylori* and other *Helicobacter* species in gallbladder and liver of patients with chronic cholecystitis detected by immunological and molecular methods. *Scand J Gastroenterol* 2005; 40: 96–102.
13. Mishra RR, Tewari M and Shukla HS. Association of *Helicobacter pylori* infection with inflammatory cytokine expression in patients with gallbladder cancer. *Indian J Gastroenterol* 2013; 32: 232–235.
14. Zhou D, Guan WB, Wang JD, et al. A comparative study of clinicopathological features between chronic cholecystitis patients with and without *Helicobacter pylori* infection in gallbladder mucosa. *PLoS One* 2013; 8: e70265.
15. Patnayak R, Reddy V, Jena A, et al. *Helicobacter pylori* in cholecystectomy specimens-morphological and immunohistochemical assessment. *Clin Diagn Res* 2016; 10: EC01-3. doi: 10.7860/JCDR/2016/14802.7716.
16. Fatemi SM, Doosti A, Shokri D, et al. Is there a correlation between *Helicobacter pylori* and enterohepatic *Helicobacter* species and gallstone cholecystitis? *Middle East J Dig Dis* 2018; 10: 24–30.
17. Cen L, Pan J, Zhou B, et al. *Helicobacter Pylori* infection of the gallbladder and the risk of chronic cholecystitis and cholelithiasis: a systematic review and meta-analysis. *Helicobacter* 2018; 23. doi: 10.1111/hel.12457.
18. Zhou D, Zhang Y, Gong W, et al. Are *Helicobacter pylori* and other *Helicobacter* species infection associated with human biliary lithiasis? A meta-analysis *PLoS ONE* 2011; 6: e27390.
19. Hassan EH, Gerges SS, El-Atrebi KA, et al. The role of *H. pylori* infection in gall bladder cancer: clinicopathological study. *Tumour Biol* 2015; 36: 7093–7098.
20. Bulajic M, Maisonneuve P, Schneider-Brachert W, et al. *Helicobacter pylori* and the risk of benign and malignant biliary tract disease. *Cancer* 2002; 95: 1946–1953.
21. Leja M, Axon A and Brenner H. Epidemiology of *Helicobacter pylori* infection. *Helicobacter* 2016; 21: 3–7.
22. Apostolopoulos P, Vafiadis-Zouboulis I, Tzivras M, et al. *Helicobacter pylori* (*H pylori*) infection in Greece: the changing prevalence during a ten-year period and its antigenic profile. *BMC Gastroenterol* 2002; 2: 11.
23. Pellicano R, Ménard A, Rizzetto M, et al. *Helicobacter* species and liver diseases:

- association or causation? *Lancet Infect Dis* 2008; 8: 254–260.
24. Tiwari SK, Khan AA, Ibrahim M, et al. *Helicobacter pylori* and other *Helicobacter* species DNA in human bile samples from patients with various hepato-biliary diseases. *World J Gastroenterol* 2006; 12: 2181–216.
 25. Xu MY, Ma JH, Yuan BS, et al. Association between *Helicobacter pylori* infection and gallbladder diseases: a retrospective study. *J Gastroenterol Hepatol* 2017; 27: 1207–1212.
 26. Helaly GF, El-Ghazzawi EF, Kazem AH, et al. Detection of *Helicobacter pylori* infection in Egyptian patients with chronic calculous cholecystitis. *Br J Biomed Sci* 2014; 71: 13–18.