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LETTER TO THE EDITOR

# Role of *Helicobacter pylori* infection and the risk of cholelithiasis

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## Abstract

This article aims to deepen the understanding of the role of *Helicobacter pylori* (*H. pylori*) infection in the development of cholelithiasis, initiated by the article by Yao *et al*, who investigated the potential link between *H. pylori* infection and the development of cholelithiasis through a multicenter retrospective study on an Asian population of over 70000 participants. They also performed a comprehensive analysis of previously published studies on *H. pylori* and cholelithiasis, finding a positive association therein [odds ratio (OR) = 1.103, $P = 0.049$]. Patients positive for *H. pylori* also had lower levels of total and direct bilirubin, but higher levels of total cholesterol and low-density lipoprotein cholesterol compared to uninfected patients ($P < 0.05$). Cohort studies have confirmed that *H. pylori* is a risk factor for cholelithiasis ($P < 0.0001$), and aggregate analyses of case-control and cross-sectional studies have shown a positive association between *H. pylori* and cholelithiasis in Asia (OR = 1.599, $P = 0.034$), but not in Europe (OR = 1.277, $P = 0.246$). Moreover, *H. pylori* appears to be related to a higher ratio of choledocholithiasis/cholecystolithiasis (OR = 3.321, $P = 0.033$). The authors conclude that *H. pylori* infection is positively correlated with cholelithiasis, particularly with the choledocholithiasis phenotype, especially in Asia, and it is potentially related to bilirubin and cholesterol metabolism.

**Key Words:** *Helicobacter pylori*; *Helicobacter pylori* infection; Cholelithiasis; Proton pump inhibitors; Choledocholithiasis



**Core Tip:** This article discusses the role of *Helicobacter pylori* (*H. pylori*) in cholelithiasis and bilirubin metabolism, highlighting a study by Yao *et al* that suggests an association between *H. pylori* infection and gallstones. While the study provides evidence for this link, it notes that the relationship may vary across populations due to factors like strain differences and geographic prevalence. The article also explores the potential role of proton pump inhibitors in increasing cholelithiasis risk, and emphasizes the need for further research into the gut microbiota's involvement in gallstone pathogenesis.

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## TO THE EDITOR

We read with great interest the article by Yao *et al*[1], in which the authors investigated a large sample of patients in a retrospective study involving several hospital centers in Asia. The results provide statistical evidence of the association between *Helicobacter pylori* (*H. pylori*) infection and the presence of gallstones, suggesting a possible involvement in the metabolism of bilirubin and cholesterol, which appear to be altered by the biological activity of *H. pylori*. The authors also examined additional scientific evidence in the literature, which largely aligns with their findings regarding the Asian population, while a strong association between *H. pylori* and cholelithiasis has not yet been highlighted in Europe. The authors suggest that differences between strains of *H. pylori* may contribute to the varying prevalence of this association worldwide. Moreover, they propose that the lower prevalence of *H. pylori* and the high prevalence of cholelithiasis in Europe compared to Asia may obscure the role of *H. pylori* in the correlation with cholelithiasis, justifying the differences observed so far outside the Asian population. The data from the study also show a higher incidence of *H. pylori* infection in patients with choledocholithiasis compared to those without cholecystolithiasis, supporting the theory that *H. pylori* in the stomach may subsequently invade the biliary tract *via* the common bile duct. This study has focused attention on the role of *H. pylori* in the production of gallstones. Moreover, according to Yao *et al*[1], triglycerides were found to be a possible protective factor. This topic is still highly controversial, as there are published meta-analyses with conflicting results[2,3], and it does not take into consideration other elements of the enterohepatic *Helicobacter* species (*H. bilis, H. pullorum*, and *H. hepaticus*) which have been considered by other researchers as possible etiopathogenetic factors toward cholelithiasis development[4-8]. It would also be interesting to consider the different prevalence rates of *H. pylori* infection and cholelithiasis across continents, given that the study involved only Chinese patients. Additionally, as a further limitation, the study analyzed a sample of patients over the age of 60, excluding a younger category of patients equally affected by cholelithiasis.

Furthermore, we believe that another aspect should be further explored, which could justify the differences found among different populations worldwide. In fact, the high incidence of cholelithiasis in the European continent should necessarily find a cause different from that attributed to *H. pylori*. From our perspective, we consider how the bacterium infected the patient who later developed cholelithiasis. For instance, gastric pH has been investigated in studies suggesting a role in the incidence of cholelithiasis. To justify the differences that have been observed when analyzing the spread of *H. pylori* among populations, it could be hypothesized that the causes of *H. pylori* infection are the actual determinants of cholelithiasis. Indeed, there are studies in which the use of proton pump inhibitors (PPIs) has led to an increased risk of gallstone cholecystitis, likely promoting the growth of enteric organisms within the stomach, including *H. pylori*.

We searched the literature and identified two publications in which a relationship between PPIs and patients operated upon for acute cholecystitis was observed[9,10]. Considering that PPIs are among the most administered drugs worldwide, this element may explain the high incidence of cholelithiasis in the Western world, even though the documented incidence of *H. pylori* infection is different from that in Asia. It is, therefore, hypothesized that PPIs reduce gastric acid secretion, increase gastric pH, reduce bactericidal activity, and allow pathogens to pass through the stomach to the duodenum. This process potentially increases the risk of retrograde migration to the biliary system, thereby elevating the incidence of biliary tract infections and increasing the risk of acute cholecystitis. One study involving 211 PPI users analyzed their stool samples, revealing a significant increase in bacteria, including Enterococcus, Streptococcus, Staphylococcus, and Escherichia coli, some of which are common pathogens in acute cholecystitis[9].

In conclusion, considering the limited statistical significance ($P$ = 0.049), *H. pylori* may not be a direct cause of cholelithiasis, but more likely a factor associated with it. The study by Yao *et al*[1] encourages a deeper investigation into the pathogenic mechanisms of cholelithiasis, seeking correlations with the microbiota.

## FOOTNOTES

**Author contributions:** Fabbri N, Greco S, Pesce A, Virgilio F, Romeo D, and Feo CV contributed to this work; Fabbri N and Romeo D equally contributed as co-corresponding authors; Fabbri N and Greco S wrote and edited the manuscript, contributing equally as co-first authors; Feo CV revised the manuscript.

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