

***Helicobacter pylori* infection in patients with liver cirrhosis: prevalence and association with portal hypertensive gastropathy**

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Abstract

Background The role of *Helicobacter pylori* (*H. pylori*) in the pathogenesis of portal hypertensive gastropathy (PHG) in cirrhotic patients is poorly defined. The aim of this study was to investigate the prevalence of *H. pylori* infection and its association with PHG in patients with liver cirrhosis.

Methods Seroprevalence of *H. pylori* was tested in 70 cirrhotic patients with PHG (cases) and 70 cirrhotic patients without PHG (controls) using an anti-*H. pylori* IgG ELISA. All patients underwent upper gastrointestinal endoscopy to assess the severity of PHG and grade of varices.

Results The presence of *H. pylori* was observed in 31 (44.3%) cirrhotic patients with PHG (cases) compared to 19 (27.1%) cirrhotic patients without PHG (controls). The risk estimate showed a significant association between *H. pylori* and PHG in cirrhotic patients ($P=0.034$, OR 2.134, 95% CI 1.052-4.327). Out of the 31 patients with PHG and *H. pylori* infection, 19 had severe PHG and 12 had mild PHG while 5 patients had severe PHG and 34 had mild PHG in the group of *H. pylori* negative patients. The difference was statistically significant ($P<0.001$, OR 10.767, 95% CI 3.293-35.205). Of the 70 patients with PHG, 24 had severe PHG and of these 18 (75%) were in Child C compared to 6 (25%) in Child B.

Conclusion There is significant association between *H. pylori* infection and PHG in cirrhotic patients which is also related to severity of PHG. Thus, *H. pylori* needs to be eradicated in cirrhotic patients with PHG.

Keywords Portal hypertensive gastropathy (PHG), *Helicobacter pylori* (*H. pylori*), cirrhosis
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Introduction

Cirrhosis is a major health problem with high incidence and prevalence worldwide. It is associated with alterations in the gastrointestinal mucosa, with increased risk for peptic ulcer disease [1]. Portal hypertensive gastropathy (PHG) is one of the clinically important gastric mucosal lesions because it may cause acute or chronic gastrointestinal blood loss leading to anemia. It is characterized by endoscopic appearance of the gastric mucosa that is classically described

as a mosaic-like pattern that resembles snake skin, with or without red spots [2]. The prevalence of PHG varies widely; frequencies from 4% to 98% have been recorded in studies of patients with portal hypertension [3]. The prevalence of PHG is shown to be closely associated with the severity of cirrhosis assessed by Child-Pugh classification, being more common in Child-Pugh C than in Child-Pugh A patients [4]. Several pathophysiological mechanisms have been postulated for PHG. They include increased serum gastrin [5] leading to increased acid secretion, alteration in blood flow [6,7], decreased secretion of prostaglandin in the gastric mucosa [8] and the presence of *Helicobacter pylori* (*H. pylori*) infection [9].

Infection by *H. pylori* is highly prevalent, especially in low socioeconomic strata of developing countries [10], being responsible for lesions like gastroduodenal erosions and ulcers. In patients with liver cirrhosis, their prevalence is controversial [11-13], as well as the existence of associations with PHG. Knowledge of the prevalence of infection by *H. pylori* in patients with liver cirrhosis and the study of the association with PHG, could be useful to better understand

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Conflict of Interest: None

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the pathogenesis of PHG and the evaluation of possible additive effect on production of PHG, when the two conditions are present. A meta-analysis by Vergara *et al* [14] which included seven studies that assessed the prevalence of *H. pylori* infection and endoscopic lesions associated with cirrhosis, concluded that infection by *H. pylori* was present in 60.7% of the patients with increased risk of developing peptic ulcer. However, in another study, Batmanabane *et al* [15] from India concluded that PHG does not provide a favorable environment for colonization by *H. pylori*, suggesting no contribution of the bacteria in the pathogenesis of PHG.

If *H. pylori* infection is found to contribute to the pathogenesis of PHG, then eradication of *H. pylori* should be beneficial in the management of PHG bleeding which usually results in anemia.

This study was undertaken to determine the prevalence of *H. pylori* infection in cirrhosis patients with PHG, to find out any association of *H. pylori* infection with PHG and to correlate the severity of PHG with the colonization of *H. pylori*.

Materials and methods

This retrospective case control study was conducted in the Department of Medical Gastroenterology, Government Medical College, Thiruvananthapuram, Kerala, from June 2011-November 2012. 70 consecutive cirrhotic patients with endoscopic diagnosis of PHG were enrolled as cases and consecutive 70 matched cirrhotic patients without PHG were enrolled as controls. The diagnosis of cirrhosis was made by a combination of ultrasound abdomen, liver function tests (prothrombin time and serum albumin), and presence of esophageal or fundal varices and by a liver histology in ambiguous cases. The clinical profile of these patients was noted from the medical records, and informed consent was obtained from all patients. Patients with primary or secondary hepatic malignancy, with a history of gastric surgery, with peptic ulcer found in upper gastrointestinal (GI) endoscopy, recent acute variceal bleeding (maximum 2 weeks), patients with intake of antibiotics (up to 1 month) or prior therapy for eradication of *H. pylori* were excluded. The severity of liver cirrhosis was assessed using the Child-Pugh classification. All patients underwent upper GI endoscopy to assess grade of varices and the severity of PHG. Esophageal varices were graded from grade I to grade IV using classification of Paquet [16]. The severity of PHG was graded according to McCormack’s classification into two classes: mild and severe [17]. Mild PHG comprises snake-skin or mosaic pattern or fine pink speckling, and severe PHG comprises cherry red spots with or without spontaneous bleeding. All patients were screened for *H. pylori* prevalence using a commercial ELISA kit (anti-*H. pylori* IgG ELISA).

The Medical college Research Council and the Ethics Committee approved the study.

Statistics

Statistical analysis was made with the SPSS Statistics

versions 18.0. Chi-square test was used to analyze the relation between different variables. The Odds Ratio was used to investigate the strength of the associations. The confidence interval was considered as 95%. A P-value of less than 0.05 was considered to be significant.

Results

Out of the 70 cirrhotic patients with PHG (cases), 50 were males and 20 were females (mean age 54.80±10 years). Of the 70 cirrhotic patients without PHG (controls) 46 were males and 24 were females (mean age 52.09±10.3 years). The other patient characteristics were comparable among cases and controls (Table 1).

The presence of *H. pylori* infection was observed in 31 (44.3%) cirrhotic patients with PHG (cases) compared to 19 (27.1%) cirrhotic patients without PHG (controls). When both cases and controls are taken together, a proportion of *H. pylori* infection was observed in 50 out of a total of 140 patients (35.71%). The risk estimate showed a significant association between *H. pylori* and PHG in cirrhotic patients (P=0.034, OR 2.134, 95% CI 1.052-4.327) (Fig. 1).

Out of the 31 patients with PHG and *H. pylori* infection, 19 had severe PHG and 12 had mild PHG while 5 patients had severe PHG and 34 had mild PHG in the group of *H. pylori*-negative patients. The difference was statistically significant (P<0.001, OR 10.767, 95% CI 3.293-35.205) (Fig. 2).

Out of the 70 patients with PHG, 24 had severe PHG and of these 18 (75%) were in Child C compared to 6 (25%) in Child B (Fig. 3).

Table 1 Clinical characteristics of cases and controls

	Cases	Controls
Total number	70	70
Males	50 (71.4%)	46 (65.7%)
Females	20 (28.6%)	24 (34.3%)
Etiology alcohol	34 (48.6%)	37 (52%)
HBV	15 (21.4%)	18 (25%)
HCV	8 (11%)	9 (12.8%)
Biliary	1 (1.4%)	1 (1.4%)
NASH	11 (15.7%)	8 (11.4%)
AIH	1 (1.4%)	3 (4.3%)
Child A	8 (11.4%)	3 (4.3%)
Child B	31 (44.3%)	37 (52.9%)
Child C	31 (44.3%)	30 (42.9%)
Ascites	50 (71.4%)	41 (58.6%)
Encephalopathy	12 (17.1%)	11 (15.7%)

HBV, hepatitis B virus; HCV, hepatitis C virus; NASH, non alcoholic steatohepatitis; AIH, auto immune hepatitis

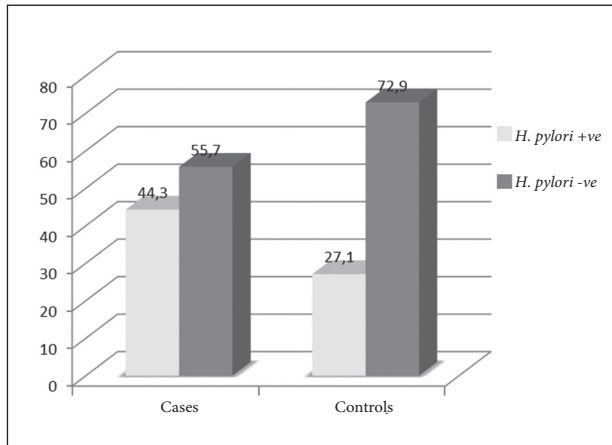


Figure 1 Significant association between *Helicobacter pylori* (*H. pylori*) and portal hypertensive gastropathy in cirrhosis patients (P=0.034, OR 2.134 95% CI, 1.052 to 4.327)

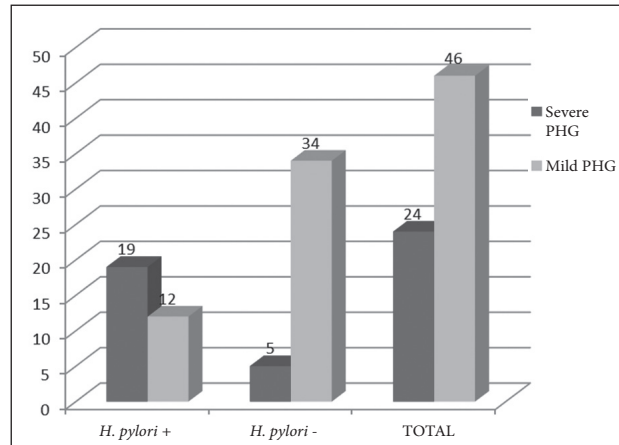


Figure 2 Association of *Helicobacter pylori* (*H. pylori*) with severity of portal hypertensive gastropathy (PHG) (P<0.001 OR 10.767, 95% CI 3.293-35.205)

Discussion

In recent years, gastric mucosal lesions have been recognized as an important complication of portal hypertension. A variety of terms including erosive gastritis, acute gastric erosions, and vascular ectasia have been coined to describe these lesions. Because the pathological change is characterized by vascular ectasia rather than mucosal inflammation, the term congestive gastropathy was coined by McCormack *et al* [17]. Currently, PHG is the preferred term, and is clinically significant because of its significant risk for both chronic occult and overt GI bleeding in cirrhotic patients leading to anemia and decompensation of cirrhosis. This gastric manifestation of portal hypertension is found in up to 50% of cirrhotic patients and accounts for one third of bleeding events in these patients [18]. The overall prevalence of PHG ranges from 20% to 98% of patients with known cirrhosis, in various studies [2,4]. This discrepancy is perhaps related to several factors: patient selection; absence of uniform diagnostic criteria and classification; and differences in inter- and intra-observer interpretation of endoscopic lesions [17]. Several studies [19,20] have shown a higher prevalence in patients with high Child-Pugh scores, patients with esophageal varices or with a history of esophageal varices treatment (sclerotherapy or ligation). However, these studies have been inconclusive and have generally failed to identify variables that predict for the presence of PHG. In general, most patients with PHG have a mild form of the disease. In a previous review, mild PHG was reported to be present in 60% of patients, while severe PHG was present in up to 46% of cases [2]. In most of cases (30-60%), PHG remains stable. Interestingly, however, PHG may also fluctuate, which suggests that it is a dynamic entity. It has been reported to progress from mild to severe in up to 30% of the cases and it regress or disappear in up to 20% of cases [21].

Until now, a variety of etiological factors have been

investigated to illustrate the pathogenesis of PHG. The pathogenesis of PHG is complex, and many controversies exist. Many factors including splanchnic blood flow, humoral factors, local disturbances in the regulation of vascular tone, and portal pressure have been examined to elucidate the underlying mechanisms [22,23]. PHG is thought to be a vascular disorder, and is associated with changes in splanchnic blood flow. It is postulated that PHG develops as a result of vascular congestion induced by blockade of gastric blood drainage rather than by hyperemia [24]. However, increased permeability of the gastric mucosa microvessels mediated by endothelin-1, involvement of prostaglandins and overexpression of nitric oxide synthase have also been implicated in gastric mucosal change. In another study of inducible nitric oxide synthase (iNOS) induction by *H. pylori* and PHG by Arafa *et al* [25] found that *H. pylori* infection and PHG independently induced significant iNOS protein expression in the gastric mucosa of cirrhotic patients resulting

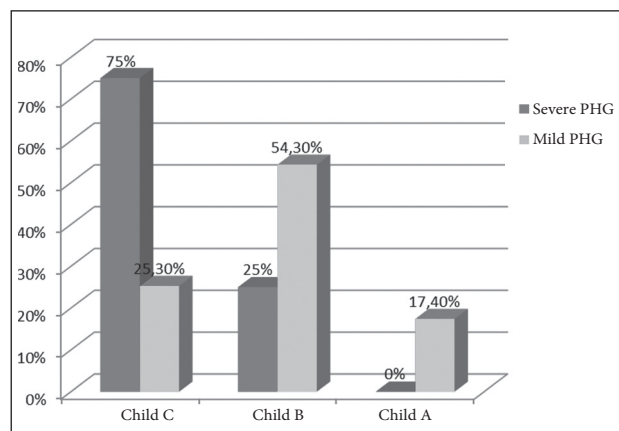


Figure 3 Association between severity of portal hypertensive gastropathy (PHG) and Child class

in decreased gastric prostaglandin production. Expression of iNOS was dependent on the endoscopic severity of PHG as well as the severity of associating chronic gastritis. *H. pylori* infection is well documented to be associated with many gastric mucosal lesions and peptic ulcers; however, its role in the development of PHG is conflicting.

Anti-*H. pylori* IgG serology has been shown to be an accurate method for prediction of the *H. pylori* status in the normal population [26]. The present study shows that patients with liver cirrhosis have a 35.7% seroprevalence of *H. pylori*, comparable with the data reported by Batmanabane *et al* [15]. While evaluating the effects of eradication of *H. pylori* in patients with liver cirrhosis, Lo *et al* [27] observed a prevalence of 52% of the bacteria and in another study by Quritox *et al* [28] in hepatitis C patients found a prevalence of *H. pylori* in 70.2% and 47.5% in cirrhotic patients and patients without cirrhosis respectively.

A Chinese study by Yang *et al* investigated the possible association between *H. pylori* infection and PHG in cirrhotic patients and suggested that *H. pylori* colonization of the stomach of cirrhotic patients was likely to be contributory to the pathogenesis of PHG [29]. In contrast, Balan *et al* reported detection of *H. pylori* in 40% of cirrhotic patients, a figure identical to the prevalence of the organism in the general population. They concluded that *H. pylori* infection is unlikely to be an important factor in the pathogenesis of PHG [30]. A metaanalysis of seven studies by Vergara *et al* [14] that assessed the prevalence of *H. pylori* infection and endoscopic lesions associated with cirrhosis, concluded that infection by *H. pylori* was present in 60.7% of the patients with increased risk of developing peptic ulcer. In another study of 37 patients, Batmanabane *et al* [15] found an overall prevalence of *H. pylori* in 43% of patients with PHG and a decline in *H. pylori* positivity with increasing severity of PHG. They concluded that there was no contribution of the bacteria to the pathogenesis of PHG. On the contrary, our study showed a significant association between *H. pylori* and PHG in cirrhotic patients ($P=0.034$, OR 2.134, 95% CI 1.052-4.327). This result suggests, therefore, that patients with *H. pylori* infection are more than twice as likely to develop PHG as patients without. This study also showed severity of PHG was more associated with *H. pylori* infection ($P<0.001$, OR 10.767, 95% CI 3.293-35.205). Thus, this study demonstrates not only a significant association of *H. pylori* with PHG in cirrhosis but also with the severity of PHG. This positive association is significant compared with previous studies because of the larger study population in this study.

This study suggests that the gastric mucosa in cirrhosis might provide a hospitable environment for the colonization of *H. pylori*, especially when there is severe hemorrhagic congestion and edema of the mucosa. Factors like increased iNOS expression resulting in high reactive oxygen species, impairment of gastric mucosal defence due to PHG in cirrhotic patients might increase virulence of *H. pylori* to produce a synergistic effect between *H. pylori* and PHG. Furthermore, colonization with *H. pylori* strains result in gastric inflammatory response, including interleukin-8, tumor

necrosis factor- α , which may be associated with the sequence of events leading to PHG.

Out of the 24 severe PHG patients, 18 (75%) were in Child C compared to 6 (25%) in Child B. Thus severe PHG was more often seen in patients with advanced liver disease, which is similar to previous studies [4,19]. This observation suggests that liver dysfunction plays an important role in the susceptibility of the gastric mucosa to injury induced by irritants like ethanol, bile salts, aspirin or traditional non-steroid anti-inflammatory drugs, as well as in the development of spontaneous bleeding episodes [31].

As this is a retrospective case control study, further prospective studies with a large number of patients are needed to validate the association of PHG with *H. pylori* infection. One of the major limitations of the study is the absence of histological data, not only for the diagnosis of *H. pylori* infection but also for the differentiation of lesions attributed to *H. pylori* gastritis from lesions due to PHG. Although anti-*H. pylori* IgG ELISA serology is the preferred technique in epidemiological surveys for detection of *H. pylori* infection, its reliability is lower than other diagnostic tools such as histology or the urea breath test [32].

Summary Box

What is already known:

- Portal hypertensive gastropathy (PHG) is one of the clinically important gastric mucosal lesion seen in cirrhotic patients because it may cause acute or chronic gastrointestinal blood loss leading to anemia
- Several pathophysiological mechanisms have been postulated for PHG such as increased serum gastrin, alteration in blood flow and decreased secretion of prostaglandin in the gastric mucosa
- The role of *Helicobacter pylori* (*H. pylori*) in the development of PHG is conflicting
- If *H. pylori* infection is found to contribute to the pathogenesis of PHG, then eradication of *H. pylori* should be beneficial in the management of PHG bleeding

What the new findings are:

- There was significant association between *H. pylori* infection and PHG in cirrhotic patients, also related to severity of PHG
- PHG provides a favorable environment for the colonization of *H. pylori*, leading to a high prevalence of this bacterium in cirrhotic patients with PHG
- Thus, further studies are warranted to show whether routine eradication of *H. pylori* may benefit the treatment of PHG in cirrhosis

In conclusion, there is significant association between *H. pylori* infection and PHG in cirrhotic patients, also related to severity of PHG. PHG provides a favorable environment for the colonization of *H. pylori*, leading to a high prevalence of this bacterium in cirrhotic patients with PHG. Thus, further prospective studies are warranted to show whether routine eradication of *H. pylori* may benefit the treatment of PHG in cirrhosis.

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