

Is There an Association between Variceal Bleed and *Helicobacter pylori* Infection in Cirrhotic Patients with Portal Hypertension?

A prospective cohort study

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ABSTRACT: Objectives: This study aimed to determine the association between *Helicobacter pylori* infection and variceal bleeding as well as rebleeding in cases of cirrhosis with portal hypertension. **Methods:** This prospective cohort study included patients with bleeding oesophageal varices and was conducted at the Department of Surgery, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry, India, from August 2016 to July 2018. **Results:** A total of 190 patients were assessed for eligibility, of which 159 patients were included in this study. Among the 159 patients, 124 (78.0%) had alcohol-related liver disease and eight had hepatitis B virus-related liver disease. Seven patients with varices had bled neither at presentation nor during the follow-up period. A total of 78 (49.1%) patients were *H. pylori* infected. The primary outcome, which was correlation between prevalence of *H. pylori* and the incidence of bleeding/rebleeding from varices as well as encephalopathy found that patients with oesophageal varices (adjusted risk [AR] = 0.714) and *H. pylori* infection (AR = 0.682) had a lower risk of variceal rebleeding. Among *H. pylori*-negative patients, pepsinogen I was higher in patients with rebleeding (30.7 versus 14.4 ng/mL; $P < 0.001$). The secondary outcome, which was correlation of the site of bleeding with *H. pylori* infection and the association of the ratio of pepsinogen I/II with bleeding showed that among *H. pylori*-positive patients, the ratio of pepsinogen I/II was higher in patients with rebleeding (2.9 versus 1.3 ng/mL; $P = 0.023$). **Conclusion:** *H. pylori* infection was associated with a lower risk of rebleeding in cases of cirrhosis with portal hypertension. Irrespective of the status of the *H. pylori* infection, rebleeding was associated with increased levels of gastric acid output, as demonstrated by the level of pepsinogen.

Keywords: Pepsinogen; Hepatic Encephalopathy; Gastric Acid; Helicobacter Pylori; India.

ADVANCES IN KNOWLEDGE

- This study found that rebleeding episodes in patients with oesophageal varices were significantly less in cases with *Helicobacter pylori* infection.
- A comparison between the oesophageal and gastric varices found that the risk of rebleeding was higher in the latter.
- Child–Pugh class B and C patients were documented as having a higher risk of rebleeding.
- Pepsinogen levels are also directly correlated with the risk of rebleeding; higher levels were associated with an increased risk of rebleeding.

APPLICATION TO PATIENT CARE

- The findings of the present study suggest that the routine eradication of *H. pylori* infection might not be necessary for patients with bleeding oesophageal varices, as the presence of *H. pylori* infection is found to be associated with a lower risk of rebleeding.
- Higher pepsinogen levels are associated with increased acid output, which in turn is associated with an increased risk of rebleeding; thus it can be postulated that acid reduction measures may be necessary to reduce the risk of rebleeding.

HELICOBACTER PYLORI INFECTION IS A universal bacterial infection that remains a common cause of morbidity and mortality.^{1–3} It is now known that *H. pylori* infection is associated not only with chronic gastritis and peptic ulcer disease but also with mucosa-associated lymphoid tissue lymphoma and gastric adenocarcinoma.² Bleeding from varices is one of the most common causes of upper gastrointestinal (UGI) bleeding and is at times fatal in patients with liver cirrhosis.⁴ Oesophageal varices cause the oesophagogastric junction patulous

to increase acid reflux into the oesophagus, thus increasing the risk of bleeding.⁵ The prevalence of *H. pylori* infection is significantly less in patients with gastro-oesophageal reflux disease (GERD) compared to those without GERD, indicating a possible low acid output with *H. pylori*. In Sakamoto *et al.*'s prospective analysis, they proposed a possible negative correlation between variceal bleeding and rebleeding and *H. pylori* infection due to a possible reduction in the gastric acid output.⁴ However, the proposed negative association has not been clearly established.

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Serum pepsinogen is an indirect marker of gastric acid output. It helps in quantifying the gastric acid output and establishing the gastric mucosal atrophy caused by *H. pylori*. In *H. pylori*-negative patients, pepsinogen (PG) I correlates with the maximal acid output, whereas in *H. pylori*-positive cases, a ratio of PG I and II correlates better with the maximal gastric acid output.⁵ On analysis of the results, the authors reported a direct correlation of PG I and PG I/II ratio with acid secretion irrespective of *H. pylori* status, whereas there was no direct correlation between PG II and acid secretion.⁵ *H. pylori*, being an ammonia-producing organism, may increase the incidence of hepatic encephalopathy in patients with cirrhosis.^{5,6} A few reports have recommended eradication therapy, suggesting that *H. pylori* increases the incidence of hepatic encephalopathy.^{5,6} Considering the possible negative association of *H. pylori* infection with the incidence of rebleeding, *H. pylori* eradication to prevent the risk of hepatic encephalopathy needs to be considered with utmost caution. The current study was carried out to determine the role of *H. pylori* infection in reducing variceal bleeding and rebleeding in patients with cirrhosis and portal hypertension.

Methods

This prospective cohort study was conducted at the Department of Surgery, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Pondicherry, India, from August 2016 to July 2018. All patients with a diagnosis of bleeding oesophageal varices during the study's period were included. Patients with non-variceal causes of UGI bleeding; patients on drugs that reduce acid output, such as proton pump inhibitors (PPI), in the six weeks preceding the study; and patients who had received *H. pylori* eradication in the preceding three months were excluded from the study.

Cirrhosis and portal hypertension were diagnosed using ultrasonography and upper gastrointestinal endoscopy (UGIE), respectively. Liver cirrhosis was diagnosed by the presence of altered liver echoes on ultrasonography.⁷ The presence of oesophageal or gastric varices was taken as an indicator of portal hypertension. During endoscopy, biopsies for *H. pylori* diagnosis were performed at four different sites of the stomach—two at the antrum and two at the corpus.⁸ One biopsy each from the corpus and antrum was used for rapid urease testing for *H. pylori*, which was conducted with a solution prepared and standardised at the authors' institute. The second set of biopsies from the corpus and antrum was sent

for histopathological examination of *H. pylori* using Giemsa stain. If fresh or altered blood was found in the stomach, biopsies were performed during subsequent follow-up endoscopy, as the presence of blood in the stomach is known to affect the results of *H. pylori* testing.^{9,10} Patients were considered positive for *H. pylori* infection if either the urease or histopathology was positive or both were positive. Patients were considered negative for *H. pylori* only if both the tests were negative. Endoscopic variceal band ligation or sclerotherapy was done as per the standard protocol. Approximately 5 mL of blood was collected from the patients in a fasting state by venepuncture and the serum was separated by centrifugation. The samples were labelled and stored at -20°C. The samples were analysed for serum PG I and II levels using separate enzyme-linked immunosorbent assay kits for each of the subtypes (Ray Biotech Inc., Peachtree Corners, Georgia, USA).¹¹ Bleeding/rebleeding was defined as either haematemesis or melena or both.⁴ Hepatic encephalopathy was diagnosed based on the presence of clinical symptoms, including loss of orientation to time and place, agitation, the presence of asterixis, stupor or coma, the improvement of these features with standard treatment for hepatic encephalopathy and the absence of any other cause of neurological impairment in the patient's history and also during follow-up.¹² Portal hypertensive gastropathy (PHG) was defined as changes in the mucosa of the stomach in patients with portal hypertension.¹³ The changes included friability of the gastric mucosa and the presence of ecstasic vessels that had a mosaic pattern in endoscopy. Patients were followed-up for bleeding/rebleeding, incidence and development of hepatic encephalopathy at three-month intervals up to nine months, till the end of the study or till the patient's death, whichever occurred first.

The primary outcome measures were the prevalence of *H. pylori* infection in patients with oesophageal/gastric/gastro-oesophageal varices due to liver cirrhosis with portal hypertension and the correlation of *H. pylori* infection with the incidence of bleeding/rebleeding from varices and with encephalopathy. The secondary outcome measures included the correlation of the site of bleeding with *H. pylori* infection and the determination of the association of PG I and PG II and PG I/II ratio with variceal bleeding and *H. pylori* infection.

Data regarding various demographic and clinicopathologic variables were recorded at the time of enrolment, which included age, gender, ultrasonography of the abdomen, findings at UGIE, grade of varices, site of varices and Child-Pugh

Table 1: Factors predicting variceal rebleeding on univariate analysis (N = 152)

Characteristic	Total	n (%)		RR (95% CI)	P value*
		Rebled present	No rebled		
Total	152	58 (38.2)	94 (61.8)		
Male	121	51 (42.1)	70 (57.9)	1.86 (0.9–3.7)	0.045
Female	31	7 (22.6)	24 (77.4)	Ref	
Alcohol-induced cirrhosis	118	50 (42.4)	68 (57.6)	1.80 (0.9–3.4)	0.073
Non-alcohol induced cirrhosis	34	8 (23.5)	26 (76.5)	Ref	
Oesophageal varices	127	44 (34.6)	83 (65.4)	Ref	
Gastric varices	25	14 (56.0)	11 (44.0)	1.61 (1.1–2.5)	0.045
Grade 1/2 oesophageal varices	93	31 (33.3)	62 (66.7)	Ref	
Grade 3/4 oesophageal varices	59	27 (45.8)	32 (54.2)	1.38 (0.9–2.1)	0.124
No PHG	70	28 (40.0)	42 (60.0)	1.13 (0.6–1.9)	0.892
Mild PHG	48	18 (37.5)	30 (62.5)	1.06 (0.6–1.9)	
Severe PHG	34	12 (35.3)	22 (64.7)	Ref	
H. pylori positive	73	20 (27.4)	53 (72.6)	Ref	
H. pylori negative	79	38 (48.1)	41 (51.9)	1.75 (1.1–2.7)	0.009
Child-Pugh's class A	43	3 (7.0)	40 (93.0)	Ref	
Child-Pugh's class B	82	42 (51.2)	40 (48.8)	7.31 (2.4–22.3)	<0.001
Child-Pugh's class C	27	13 (48.1)	14 (51.9)	6.87 (2.2–22.0)	

RR = relative risk; CI = confidence interval; Ref = reference; PHG = portal hypertensive gastropathy; H. = Helicobacter.

*Using Chi-squared test.

Table 2: Multivariate logistic regression showing factors predicting variceal rebleeding.

Variable	AR (95% CI)	P value*
Male gender	1.079 (0.296–3.941)	0.908
Alcoholic cirrhosis	1.276 (0.381–4.272)	0.692
Oesophageal varices	0.714 (0.555–0.920)	0.009
Grade 3/4 varices	1.366 (1.015–1.840)	0.040
Positive H. pylori	0.682 (0.469–0.993)	0.046
Child-Pugh's class B	6.435 (2.131–19.432)	0.001
Child-Pugh's class C	4.814 (1.520–15.254)	0.008

*Dependent variable was the presence or absence of rebleeding.

AR = adjusted risk; CI = confidence interval; H. = Helicobacter.

score at presentation. Considering the prevalence of H. pylori infection in variceal bleeding patients to be 34.9–52%, with an alpha error of 5%, and the power of the study to be 80%, the sample size was calculated

to be 150.^{4,13,14} Considering a 10% dropout rate, a sample size of 165 was determined for the study. The sample size was calculated using OPENEPI® software (www.openepi.com) for Windows 8 (Microsoft Corp., Redmond, Washington, USA).

Statistical analysis was done using the Statistical Package for the Social Sciences (SPSS), Version 19.0 (IBM Corp., Chicago, Illinois, USA). Numerical data such as serum pepsinogen levels and pepsinogen ratios were expressed in the form of medians (interquartile range); categorical data such as gender, aetiology of cirrhosis, location of bleeding varices, portal gastropathy and the Child–Pugh class were expressed in the form of proportions. Numerical data were analysed using the Mann–Whitney U test or the Kruskal–Wallis test, and categorical data were analysed using a Chi-squared test or Fisher's exact test. A P value of less than 0.05 was considered statistically significant.

This study was approved by the Institute Ethics Committee of JIPMER prior to the commencement of the study (JIP/IEC/2016/27/885). Participants were included in the study after obtaining written, informed consent, and they were allowed the freedom

Table 3: Correlation of various factors with *Helicobacter pylori* infection

Characteristic	Total	n (%)		P value*
		<i>H. pylori</i> present	<i>H. pylori</i> absent	
Total	159	78 (49.1)	81 (50.9)	
Male	127	62 (48.8)	65(51.2)	0.905
Female	32	16 (50.0)	16 (50.0)	
Alcohol-induced cirrhosis	124	59 (47.6)	65(52.4)	0.62
Non-alcohol induced cirrhosis	35	19 (54.3)	16 (45.7)	
Oesophageal varices	133	68 (51.1)	65 (48.9)	0.237
Gastric varices	26	10 (38.5)	16 (61.5)	
Grade 1/2 oesophageal varices	100	52 (52.0)	48 (48.0)	0.334
Grade 3/4 oesophageal varices	59	26 (44.1)	33 (55.9)	
No PHG	75	40 (53.3)	35 (46.7)	0.223
Mild PHG	49	19 (38.8)	30 (61.2)	
Severe PHG	35	19 (54.3)	16 (45.7)	
Child-Pugh's class A	48	31 (64.6)	17 (35.4)	0.026
Child-Pugh's class B	83	37 (44.6)	46 (55.4)	
Child-Pugh's class C	28	10 (35.7)	18 (64.3)	

H. = *Helicobacter*; PHG = portal hypertensive gastropathy.

*Using Chi-squared test.

to withdraw at any point of time during the study. All the provisions of the Declaration of Helsinki were followed in the study. The study was registered at www.ctri.gov.in (Clinical Trials Registry-India ref no: CTRI/2018/04/013357).

Results

A total of 190 patients were assessed for eligibility during the study period; some patients were excluded and a final sample size of 159 patients were included in the study. The total number of males and females was 127 and 32, respectively. Overall, 124 patients (78.0%)

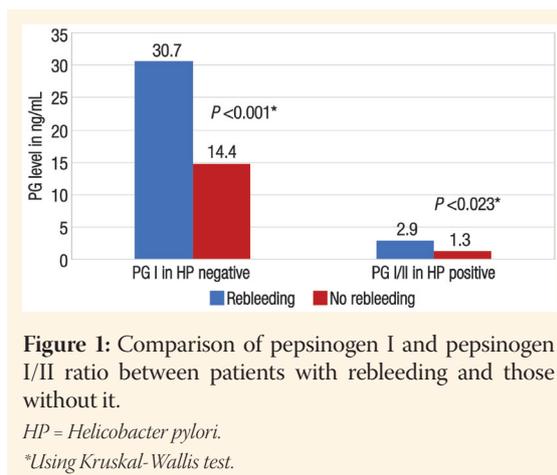


Figure 1: Comparison of pepsinogen I and pepsinogen I/II ratio between patients with rebleeding and those without it.

HP = *Helicobacter pylori*.

*Using Kruskal-Wallis test.

had alcohol-related liver disease, eight patients had hepatitis B virus-related liver disease and only one patient had hepatitis C virus-related liver disease. The aetiology of cirrhosis in 26 patients (16.4%) was not known (idiopathic). In total, 30 patients were lost to follow-up, and 11 patients died during the course of the study. The median follow-up period was nine months. Seven patients with varices had bled neither at presentation nor during the follow-up period. Therefore, the analysis was carried out with 152 patients. On univariate analysis, male gender (relative risk [RR] = 1.86; $P = 0.045$), gastric varices (RR = 1.61; $P = 0.045$), *H. pylori*-negative status (RR = 1.75; $P = 0.009$) and Child–Pugh class B and C ($P = 0.001$) were found to be significantly associated with rebleeding episodes [Table 1].

The prevalence of *H. pylori* infection among cirrhotic patients with portal hypertension was found to be 49.1%. Patients with *H. pylori* infection were found to have less rebleeding episodes than those without it (adjusted risk [AR] = 0.682, 95% confidence interval [CI] = 0.469–0.993; $P = 0.046$). Patients belonging to Child–Pugh class B (AR = 6.435, 95% CI = 2.131–19.432; $P = 0.001$) and Child–Pugh class C (AR = 4.814, 95% CI = 1.520–15.254; $P = 0.008$) had higher rebleeding episodes compared to patients in Child–Pugh class A [Table 2].

A total of seven out of 11 patients who had encephalopathy were *H. pylori* infected (RR = 1.83); however, this difference was not statistically significant ($P = 0.363$). The site of variceal bleeding in patients was independent of *H. pylori* status ($P = 0.237$) [Table 3]. Among patients negative for *H. pylori* infection, rebleeding was significantly associated with higher levels of PG I (30.7 versus 14.4 ng/mL; $P < 0.001$). Among patients positive for *H. pylori* infection, rebleeding was associated with a higher ratio of PG I/II (2.9 versus 1.3 ng/mL; $P = 0.023$) [Figure 1].

Discussion

The presence of *H. pylori* was considered a topic of interest for the present study because some researchers have postulated that mucosal inflammation resulting from *H. pylori* infection might weaken the mucosa and may trigger bleeding from varices. In contrast, others have suggested that by causing atrophic gastritis and reducing acid output from the stomach, it might reduce variceal bleeding episodes.^{4,5}

In the present study, the prevalence of *H. pylori* infection among cirrhotic patients with portal hypertension was 49.1%. Many studies have been published on the prevalence of *H. pylori* infection and its association with cirrhosis and portal hypertension, albeit with conflicting results.^{15–18} While some studies have found that *H. pylori* infection is more prevalent among cirrhotic patients compared to the general population, others have found no such difference. Previous studies have shown the prevalence of *H. pylori* infection in a similar population to be 67–83.3%.^{15,16} The present study found that the prevalence of *H. pylori* infection was lower among cirrhotic patients compared to the general population. Previous studies have shown that viral cirrhotic patients have a higher prevalence of *H. pylori* infection than those with other aetiologies of cirrhosis.^{19,20} However, in the present study, the majority of the patients had alcohol-induced cirrhosis (78.0%) with associated PHG (52.8%), which probably accounted for the lower prevalence of *H. pylori*, as studies have shown that PHG does not favour *H. pylori* colonisation.¹³ In the present study, as expected, patients belonging to Child–Pugh class B and C had higher rebleeding episodes compared to Child–Pugh class A; this can act as a confounding factor when correlating with *H. pylori*. However, multivariate analysis revealed *H. pylori* infection to be a protective factor.

In the present study, *H. pylori* infected patients were found to have lesser rebleeding episodes than those patients without it (AR = 0.682, 95% CI = 0.469–0.993; $P = 0.046$). This supports the theory that *H. pylori* infection, when present, leads to gastritis and reduces acid output, which is a protective action against variceal bleeding. Sakamoto *et al.*, in their cross-sectional study, found that patients with *H. pylori* infection had a significantly lower risk of bleeding from varices compared to patients without *H. pylori* infection (odds ratio = 0.475; $P = 0.019$).⁴ Gastric acid is believed to be responsible for variceal rupture and bleeding. In the current study, among *H. pylori*-positive individuals, in whom PG I/II ratio correlates closely with gastric acid output, it was found that the median of the PG I/II ratio was significantly

higher among patients with rebleeding than among those without it (2.9 versus 1.3 ng/mL; $P = 0.023$). Among *H. pylori* negative individuals, in whom PG I correlates closely with gastric acid output, it was found that the median of PG I was significantly higher among patients with rebleeding compared to those without it (30.7 versus 14.4 ng/mL; $P < 0.001$). This shows that, both in the presence and absence of *H. pylori* infection, patients with rebleeding episodes had higher pepsinogen levels, probably reflecting more gastric acid output, compared to those who had no rebleeding.

The site of variceal bleeding was almost similar among patients positive or negative for *H. pylori* infection. Though gastric acid reflux into the lower oesophagus is a physiological phenomenon, in cases of cirrhotic patients, it is postulated that this refluxed gastric acid causes breaks in the epithelium covering the oesophageal varices, which in turn causes variceal rupture and triggers a bout of haematemesis. *H. pylori*, by causing chronic atrophic gastritis and reducing gastric acid output, in turn, reduces gastric acid reflux into the lower oesophagus and hence is protective against variceal rupture. This is supported by some previous studies, which have shown that long-term PPI therapy in patients with liver cirrhosis can reduce variceal bleeding rates probably due to the same mechanism.²¹

The present study found no difference in the risk of development of hepatic encephalopathy between those with *H. pylori* infection and those without it. The prevalence of hepatic encephalopathy in the present study was relatively low. The total number of patients who had hepatic encephalopathy in the present study was 11 (6.9%); seven patients who were *H. pylori* positive were found to have hepatic encephalopathy compared to four patients who were *H. pylori* negative. However, this difference was not statistically significant. Calvet *et al.* conducted a prospective study and found that *H. pylori* was not independently associated with the development of hepatic encephalopathy.¹² The results of the present study are consistent with the aforementioned study probably because patients with only overt hepatic encephalopathy were included in both the studies. A systematic review of 20 studies by Hu *et al.* was conducted in China to determine the association between the risk of hepatic encephalopathy and that of *H. pylori* infection.²² The review found that the prevalence of *H. pylori* infection was higher in patients with hepatic encephalopathy than those without it.²² In the present study, the effect of *H. pylori* could have been masked by the lower prevalence of hepatic encephalopathy.

The strengths of the present study are that it is one of a very small number of studies on the association between *H. pylori* infection and variceal bleeding and the only prospective study evaluating the association between *H. pylori* infection and variceal rebleeding. The limitations are that the study included only patients with overt hepatic encephalopathy, excluding those with minimal hepatic encephalopathy and subclinical hepatic encephalopathy, which could have resulted in the underdiagnosis of hepatic encephalopathy in the studied patients. The present study showed that *H. pylori* has an inverse relationship with episodes of rebleeding from oesophago-gastric varices in cirrhotic patients with portal hypertension; hence, eradication of *H. pylori* may not be recommended routinely.

Conclusion

This prospective analytical study found that the rebleeding episodes were significantly less among those who had *H. pylori* infection compared to those without it. Compared to gastric varices, oesophageal varices were found to have a significantly lower risk of rebleeding. Location of the bleeding varices was not found to be significantly different between *H. pylori* positive and negative patients. Patients belonging to the Child–Pugh class B and C and those with grade 3/4 varices had higher rebleeding episodes. Irrespective of the *H. pylori* infection status, patients with rebleeding had higher levels of pepsinogen, indicating high gastric acid output. Furthermore, there was no difference in the level of serum pepsinogen between *H. pylori* positive and negative patients. The present study did not find an association between *H. pylori* infection and encephalopathy. *H. pylori*-infected patients were found to have significantly less rebleeding episodes, with no significant increase in the incidence of encephalopathy. Hence, routine *H. pylori* eradication may not be recommended for all cirrhotic patients with portal hypertension, as the present study showed that *H. pylori* was protective against variceal bleeding episodes. Consequently, eradication of *H. pylori* might precipitate variceal bleeding episodes and may only be considered for symptomatic *H. pylori* infections.

AUTHORS' CONTRIBUTION

SS and VK conceptualised and designed the study. SV was responsible for the data collection. SV and VB were responsible for the investigation. BG, EA, SM and VK contributed to the validation of the study. SM designed the methodology. SV, BG, EA, VK and TM were involved in data analysis and interpretation. SS, VK, VB and TM supervised the work. SV drafted

the initial manuscript. SS, BG, EA, SM, VK, VB and TM were involved in drafting and revising the manuscript. All authors approved the final version of the manuscript.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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