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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: The objective of this study was to find the association of H. pylori in patients with variceal bleeding as well as rebleeding in cases of cirrhosis with portal hypertension. ***Methods:*** This was a prospective cohort of patients with bleeding esophageal varices. The primary outcome was correlation between prevalence of H. pylori and the incidence of bleeding/ rebleeding from varices and with encephalopathy. The secondary outcome were correlation between the site of bleeding with H. pylori infection and the association of pepsinogen I & II and the ratio of pepsinogen I/II with bleeding. ***Results:*** A total of 190 patients were assessed for eligibility, out of which 159 patients were included in this study. 124 out of 159 patients (77.9%) had alcohol-related liver disease. 8 out of 159 patients had HBV-related liver disease. 7 patients with varices had neither bled at presentation nor did bleed in the follow-up period. A total of 78 out of 159 (49.05%) patients were H.pylori-infected. Patients with esophageal varices [Adjusted Risk (AR)=0.7] and H.pylori infection (AR=0.7) had a lower risk of variceal rebleeding. Among the patients negative for H.pylori, pepsinogen I was higher in patients with rebleeding (30.7 vs 14.4; p<0.001). Among H.pylori positive patients, the ratio of pepsinogen

I/II was higher in patients with rebleeding (2.9 vs 1.3; 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 H.pylori infection, rebleeding was associated with more gastric acid output demonstrated by the level of pepsinogen.

Keywords: Pepsinogen; hepatic encephalopathy; gastric acid output, Helicobacter pylori

Advances in Knowledge

- In this study, it was found that the rebleeding episodes in patients with esophageal varices were significantly less in patients with *H. pylori* infection.
- When the risk of rebleeding was compared between the esophageal and gastric varices, the latter had higher risk of rebleeding.
- It was also documented that patients with Child-Pugh's class B and C had a higher risk of rebleeding.
- The pepsinogen levels also directly correlated with the risk of rebleeding, higher levels were associated with increased risk of rebleeding.

Application to Patient Care

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

Introduction

Helicobacter pylori infection is an universal bacterial infection of mankind and remains a common cause of morbidity and mortality.[1–3] It is now known that *H. pylori* infection is not only associated with chronic gastritis and peptic ulcer disease but also mucosa-associated lymphoid tissue (MALToma) lymphoma and gastric adenocarcinoma.[2] Bleeding from varices is one of the most common cause of upper gastrointestinal (UGI) bleeding and at times fatal in patients of liver cirrhosis.[4] Esophageal varices by making the esophagogastric junction patulous increase acid reflux into the oesophagus and may lead to high risks for bleeding.[5] Prevalence of *H. pylori* infection in patients with Gastro-Esophageal Reflux Disease (GERD)

is significantly lesser than those who do not have GERD indicating possible low acid output with *H. pylori*. Sakamoto et al. in their prospective analysis, proposed the possible negative correlation between variceal bleeding and rebleeding with *H. pylori* infection due to a possible reduction in the gastric acid output.[4] However, the proposed negative association has not been clearly established.

Serum pepsinogen is an indirect marker of gastric acid output. It helps in quantifying the gastric acid output and to establish 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 between 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] Few reports have suggested that *H. pylori* rises the incidence of hepatic encephalopathy and recommended for eradication therapy. 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. This study was carried out to determine the role of *Helicobacter pylori* infection in reducing the variceal bleeding and rebleeding in patients with cirrhosis and portal hypertension.

Methods

Study Design

This was a prospective cohort study conducted in the Department of Surgery with the approval of Institute Ethics Committee (IEC) of JIPMER, Pondicherry, India. After obtaining a written informed consent, the participants were included in the study and were given the freedom 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.(CTRI ref no-CTRI/2018/04/013357).

Inclusion and exclusion criteria

All patients with a diagnosis of bleeding esophageal varices were included in this study during the period from August 2016 to July 2018. Non-variceal causes of upper gastrointestinal bleeding, patients on drugs that reduce acid output, like proton pump inhibitors (PPI) in the

past 6 weeks, patients who have received *H. pylori* eradication in the past three months were excluded from the study.

Study Procedure

Cirrhosis and portal hypertension was diagnosed using ultrasonography and UGIE respectively. Liver cirrhosis was diagnosed by the presence of altered liver echoes on ultrasonography.[7] Presence of esophageal or gastric varices was taken as an indicator of portal hypertension. During the endoscopy, biopsies were taken from the stomach at four different sites for *H. pylori* diagnosis i.e., two from the antrum and two from the corpus.[8] One biopsy each from corpus and antrum were used for rapid urease testing (RUT) for *H. pylori*, which was done with a solution prepared and standardized in our institute. One more biopsy from 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 taken 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 any one of 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 (EVL) or sclerotherapy were done as per the standard protocol. About 5 ml of blood sample was collected from the patients in fasting state by venepuncture and the serum was separated by centrifugation. The samples were labelled and stored at -20^0C. The samples were analyzed for serum pepsinogen I and II[11]levels using separate ELISA kits for each of the subtypes (Ray Biotech, Inc. USA). Bleeding/rebleeding was defined as either hematemesis/melena or both.[4] Hepatic encephalopathy was diagnosed based on presence of clinical symptoms including loss of orientation to time and place, agitation, the presence of asterixis, stupor or coma and these features improving with standard treatment for hepatic encephalopathy and the absence of any other cause of neurological impairment from 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 were friability of the gastric mucosa and the presence of ecstatic vessels which had a mosaic pattern in endoscopy. Patients were followed up for bleeding/rebleeding, incidence and development of hepatic encephalopathy at three monthly intervals up to 9 months or till the end of study or patient's death whichever was earlier.

Outcome measures

The primary outcome measures was the prevalence of *H. pylori* infection in patients with esophageal/gastric/gastroesophageal 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 correlation of the site of bleeding with *H. pylori* infection and to determine the association of PG I and PG II and PG I /PG II ratio with variceal bleeding and *H. pylori* infection.

Data collection and Statistical Analysis

Data regarding various demographic and clinicopathologic variables were recorded at the time of enrolment which included age, gender, ultrasonography of abdomen, findings at upper GI endoscopy, grade of varices, site of varices and Child-Pugh's score at presentation. Considering the prevalence of *H. pylori* infection in variceal bleeding patients ranging from 34.9% to 52%,[4,13,14] with the alpha error of 5% and power of the study to be 80%, the sample size was calculated to be 150. Considering a 10% drop out rate, the sample size of 165 was taken for the study. The sample size was calculated using OPENEPI® software for Windows 8.

Statistical analysis was done using SPSS 19.0 software for windows. Numerical data such as serum pepsinogen levels and pepsinogen ratios were expressed in the form of Median [Interquartile range (IQR)] and categorical data such as gender, aetiology of cirrhosis, location of bleeding varices, portal gastropathy and Child-Pugh's class were expressed in the form of proportions. Numerical data were analysed using the Mann-Whitney U test or Kruskal-Wallis test and categorical data were analysed using Chi-square test or Fisher's exact test. A *p* value of less than 0.05 was considered statistically significant.

Results

This study was conducted from August 2016 to July 2018. A total of 190 patients were assessed for eligibility and among those patients, 159 patients as per inclusion criteria were included in the study. In the present study, total number of males and females was 127 and 32 respectively. 124 out of 159 patients (77.9%) had alcohol-related liver disease. 8 out of 159 patients had HBV-related liver disease and only one patient had HCV-related liver disease. The aetiology of cirrhosis in 26 patients (16.35%) was not known (idiopathic). Thirty patients were lost to follow up. Eleven patients died during the course of the study. The median follow-up period was 9 months. 7 patients with varices had neither bled at presentation nor did bleed in the follow-up period. Therefore, the analysis was carried out with 152 patients. On univariate

analysis, male gender (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's class B and C (p=0.001) were significantly associated with rebleeding episodes (Table 1). The prevalence of *H. pylori* infection among cirrhotic with portal hypertension was found to be 49.05%. In the present study, patients with *H. pylori* infection were found to have lesser rebleeding episodes than those patients without it [Adjusted Risk (AR) =0.682; p=0.046; CI =0.47 - 0.99](Table 2). 7 out of 11 patients who had encephalopathy were *H. pylori* infected [Relative risk (RR) =1.83], however, this difference was not statistically significant (p=0.363).The site of variceal bleeding in patients were independent of *H. pylori* status (Table 3). Among patients negative for *H. pylori* infection, rebleeding was significantly associated with higher levels of PG I (30.7 vs 14.4; p<0.001). Among patients positive for *H. pylori* infection, rebleeding was associated with a higher ratio of PG I/II (2.9 vs. 1.3; p=0.023)[Figure 1].

Patients belonging to Child-Pugh's class B (Adjusted Risk=6.4; p=0.001; CI=2.13-19.43) and Child-Pugh's class C [Adjusted Risk=4.8; p=0.008; CI=1.52-15.25] had higher rebleeding episodes compared to patients in Child-Pugh's class A.

Discussion

The presence of *H. pylori* came into interest because a few researchers have postulated that mucosal inflammation resulting from *H. pylori* infection might weaken the mucosa and may trigger bleeding from varices whereas a few others have suggested that by causing atrophic gastritis and reducing acid output from the stomach, it might reduce variceal bleeding episodes.[4,5]

The prevalence of *H. pylori* infection among cirrhotic with portal hypertension in the present study was 49.05%. Many studies have been published on the prevalence of *H. pylori* infection and its association with cirrhosis and portal hypertension with conflicting results.[15-18] Whereas a few studies have found that *H. pylori* infection is more prevalent among cirrhotic when compared to the general population, some have found no difference. Previous studies have shown the prevalence of *H. pylori* in similar population to be 67%[15] to 83.3%.[16] In the present study, it was found that the prevalence of *H. pylori* infection among cirrhotic was lower than the general population. It has been shown in previous studies that viral cirrhotic have a higher prevalence of *H. pylori* than other aetiologies of cirrhosis.[19,20] However, in the present study, the majority of the patients were alcoholic cirrhotic (78%) with associated PHG (52.9%) and

hence probably lower prevalence of *H. pylori,* as studies have shown that PHG does not favor *H. pylori* colonization.[13] In the present study patients belonging to Child-Pugh's class B and Child-Pugh's class C had higher rebleeding episodes in comparison to Child-Pugh's class A, as expected and this can act as an confounding factor when correlating with *H. pylori.* However, multivariate analysis showed *H. pylori* infection as a protective factors.

In the present study, *H. pylori* infected patients were found to have lesser rebleeding episodes than those patients without it [AR=0.682; p=0.046; CI =0.47 - 0.99]. This supports the theory that *H. pylori* infection when present leads to gastritis and reduces acid output which is protective 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 as compared to patients without *H. pylori* infection[OR=0.475; p=0.019].[4] It is thought that gastric acid is responsible for variceal rupture and bleeding. In the present 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 PG I/II ratio was significantly higher among patients with rebleeding than those without it (2.9 vs 1.3; p=0.023). Among *H. pylori* negative individuals in whom PG I correlates closely with gastric acid output, we found that the median of PG I was significantly higher among patients with rebleeding than those without it (30.7 vs 14.4; p<0.001). This shows that both in the presence or 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 were almost similar among patients positive or negative for *H. pylori* infection. Though gastric acid reflux into the lower oesophagus is a physiological phenomenon, in case of cirrhotic, it is postulated that this refluxed gastric acid causes breaks in the epithelium covering the esophageal varices causing variceal rupture and triggering a bout of hematemesis. *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 few 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]

We found no difference in the risk of development of hepatic encephalopathy among those with or without *H. pylori* infection. 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%). On comparing, hepatic encephalopathy against *H. pylori* infection, 7 patients who were *H. pylori* positive had hepatic encephalopathy against 4 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] Results of the present study were in concordance with this study probably because patients with only overt hepatic encephalopathy were included in this study, similar to the present study. A systematic review of 20 studies was conducted in China to determine the association between the risk of hepatic encephalopathy with that of *H. pylori* infection. [22] They found that the prevalence of *H. pylori* infection was higher in patients with hepatic encephalopathy than those without it.[22] Considering the low prevalence of hepatic encephalopathy in the present study, the effect of *H. pylori* could have been masked by the lower prevalence of hepatic encephalopathy.

The strengths of the study are that it is one of the very few studies on the association of *H. pylori* infection with variceal bleeding and the only prospective study evaluating the association of *H. pylori* infection on variceal rebleeding. Limitations are that we included only patients with overt hepatic encephalopathy leaving those with minimal hepatic encephalopathy and subclinical hepatic encephalopathy which could have resulted in underdiagnosis of hepatic encephalopathy in the study patients. The present study showed that *H. pylori* has an inverse relationship with rebleeding episodes from esophagogastric varices in patients of cirrhosis with portal hypertension and hence, eradication of *H. pylori* may not be recommended routinely.

Conclusion

In this prospective analytical study, it was found that the rebleeding episodes were significantly lesser among those who had *H. pylori* infection than those without it. Esophageal varices compared to gastric varices were found to have a significantly lesser risk of rebleeding. Location of bleeding varices was not found to be significantly different between patients positive or negative for *H. pylori* infection. Patients belonging to Child-Pugh's class B and C and those with grade 3/4 varices had a higher rebleeding episodes. Irrespective of *H. pylori* infection status, patients with rebleeding had higher level of pepsinogen indicating high gastric acid output and there was no difference in the level of serum pepsinogen between patients positive or negative *H. pylori* infection. The present study did not find an association between *H. pylori* infection and encephalopathy. *H. pylori* infected patients were found to have

significantly lesser rebleeding episodes with no significant increase in the incidence of encephalopathy. Hence, routine *H. pylori* eradication may not be recommended for all patients with cirrhosis with portal hypertension as the present study showed *H. pylori* was protective against variceal bleeding episodes and eradication of *H. pylori* might precipitate variceal bleeding episodes and can only be considered for symptomatic *H. pylori* infection.

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Authors' Contribution

SS and VK conceptualized and designed the study. SV was responsible for the data collection. SV and VB were responsible for the investigation in the study. BG, EA, SM and VK contributed to the validation in the study. SM designed the methodology in the study. 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.

Conflicts of Interest

The authors declare no conflicts of interest.

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Table 1: Factors predicting variceal rebleeding on univariate analysis

Characteristics	Total	Rebleed present (%)	No Rebleed (%)	Relative risk (CI)	P value*
Total (n)	152	58(38.1%)	94(61.8%)		
Male	121	51(42.1%)	70(57.9%)	1.86 (0.9-3.7)	0.045
Female	31	07(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	08(23.5%)	26(76.4%)	Ref	
Esophageal varices	127	44(34.6%)	83(65.4%)	Ref	
Gastric varices	25	14(56%)	11(44%)	1.61 (1.1-2.5)	0.045
Grade 1/2 esophageal varices	93	31(33%)	62(66.7%)	Ref	
Grade 3/4 esophageal varices	59	27(45.8%)	32(54.2%)	1.38 (0.9-2.1)	0.124
No PHG	70	28(40%)	42(60%)	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	0.009
***H.pylori* Negative**	79	38(48.1%)	41(51.9%)	1.75 (1.1-2.7)	
Child's Class A	43	03(7%)	40(93%)	Ref	<0.001
Child's Class B	82	42(51.2%)	40(48.8%)	7.31 (2.4-22.3)	
Child's Class C	27	13(48.1%)	14(51.9%)	6.87 (2.2-22)	

*Chi-Square test. [PHG-Portal Hypertensive Gastropathy]; CI-Confidence Interval.

Table 2: Factors predicting variceal rebleeding on multivariate analysis

Dependent variable: Presence or absence of rebleeding

	Adjusted Risk	P value*	95% Confidence Interval
Male gender	1.079	0.908	0.2955-3.9405
Alcoholic cirrhosis	1.276	0.692	0.3812-4.2715
Esophageal varices	0.714	0.009	0.5550-0.9201
Grade 3/4 varices	1.366	0.040	1.0146-1.8402
Positive *H.pylori*	0.682	0.046	0.4694-0.9926
Child's class B	6.435	0.001	2.1311-19.4315
Child's class C	4.814	0.008	1.5195-15.2538

*Logistic Regression Analysis

Table 3: Correlation of various factors with *H.pylori* infection

Characteristics	Total	*H.pylori* present	*H.pylori* absent	P value*
	159	78(49.05%)	81(50.95%)	
Male	127	62(48.8%)	65(51.2%)	0.905
Female	32	16(50%)	16(50%)	
Alcohol-induced cirrhosis	124	59(47.6%)	65(52.4%)	0.62
Non-alcohol induced cirrhosis	35	19(54.2%)	16(45.7%)	
Esophageal	133	68(51.1%)	65(48.9%)	0.237
Gastric	26	10(38.5%)	16(61.5%)	
Grade 1/2 esophageal varices	100	52(52%)	48(48%)	0.334
Grade 3/4 esophageal 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's Class A	48	31(64.6%)	17(35.4%)	0.026
Child's Class B	83	37(44.6%)	46(55.4%)	
Child's Class C	28	10(35.7%)	18(64.3%)	

*Chi-Square test

[PHG- Portal Hypertensive Gastropathy]

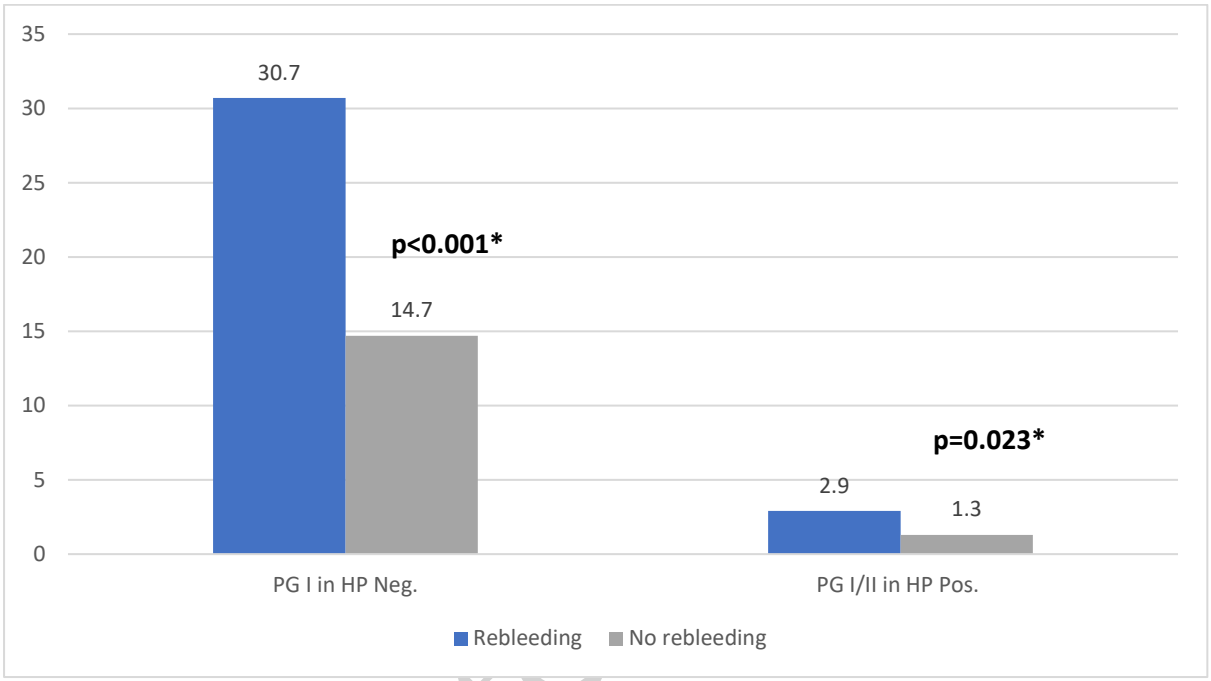

Figure 1: Comparison of Pepsinogen I and Pepsinogen I/II ratio amongst patients with rebleeding against those without it.

HP Neg. - *Helicobacter pylori* uninfected; HP Pos.- *Helicobacter pylori*-infected

*Kruskal –Wallis test