Association of Helicobacter Pylori and Portal Hypertensive Gastropathy in Patients with Cirrhosis of Liver
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Abstract
Portal hypertensive gastropathy (PHG) is a common endoscopic finding in patients of cirrhosis of liver. The cause and pathogenesis of PHG in cirrhotic patients is poorly understood. Some studies showed, association of Helicobacter pylori (H. Pylori) with portal hypertensive gastropathy in cirrhosis of liver, but the evidence is not robust. The aim of this study was to assess the association of H. pylori infection and PHG in patients with cirrhosis of liver. This case control study was conducted in the Department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, from April 2016 to August 2018. A total of 230 patients with cirrhosis of liver were included in this study. There were 115 cirrhotic patients with PHG as cases and 115 cirrhotic patients without PHG as controls. Upper gastrointestinal Endoscopy and 13C Urea Breath Test (UBT) was done in both cases and controls. In this study, out of 230 cases, 147 (63.91%) found to have H. pylori infection. Among cirrhotic patients with PHG case, 77 (66.95%) was positive in UBT. Out of these 77 UBT positive cases, 55 had mild PHG whereas 22 cases had severe form of PHG. Among 38 cases of cirrhosis with PHG who had negative UBT, 23 had mild PHG and 15 cases had severe form of PHG. The risk of positive urea breath test was not statistically significant in cirrhotic patients with PHG in comparison with cirrhotic patients without PHG (P=0.337, OR 1.303, 95% CI 0.759-2.235). In this study, statistically significant association was not found between H. Pylori and PHG in cirrhotic patients.

Keywords: Cirrhosis of liver, helicobacter pylori (H. Pylori), portal hypertensive gastropathy (PHG)

INTRODUCTION
Portal hypertension is a common condition in cirrhosis of liver. When hepatic venous pressure gradient (HVPG) >5mmHg is called portal hypertension.1 Cirrhosis of liver, non-cirrhotic portal fibrosis and extra hepatic portal vein obstruction are common causes of portal hypertension. Gastrointestinal haemorrhage, hepatic encephalopathy, hepato-renal syndrome, ascites are common complications of portal hypertension.2 Liver cirrhosis and portal hypertensive gastropathy patients are very prone to develop acute or chronic GI bleeding.3,4 Prevalence of portal hypertensive gastropathy in cirrhotic patients is approximately 9-80%.5,6,7,8 Portal hypertensive gastropathy causes change in the mucosa of the stomach in patients with portal hypertention. The most common cause of this is cirrhosis of liver. Mucosal changes occur in PHG including friability of mucosa and the presence of erratic blood vessels.9 PHG is common both in cirrhotic and non-cirrhotic portal hypertension. The endoscopic findings of PHG is mosaic-like pattern of gastric mucosa.10 Whole of the stomach can be involved in portal hypertensive gastropathy (PHG). Not only mucosal changes but also the severity mosaic pattern and red spots increase bleeding risk.11,12 Numerous mechanisms are involved in the development of PHG. High gastrin level causes huge amount of acid secretion and altered blood flow, reduced prostaglandin secretion and the presence of H. pylori infection.13,14,15,16

In PHG gastric mucosal ability to regenerate has lost.17 Another study showed increased susceptibility of portal
hypertensive gastropathy by bile acid and *H. pylori* infection. 

*H. pylori* is a gram negative organism is found in gastric mucosa or between the epithelial and mucous layer of stomach. In developing country the prevalence of *H. pylori* is higher than the developed countries. The prevalence and association of *H. pylori* in cirrhosis of liver is under debate. *H. pylori* infection is one of the most common cause of peptic ulcer disease. In cirrhosis of liver *H. pylori* may have a role in developing PHG.

Sensitivity and specificity of serological test to diagnose *H. pylori* is very low. Other than *H. pylori*, no bacteria is found to be involved in the development of PHG.

PHG does not provide a favorable environment for colonization by *H. pylori*, suggesting no contribution of the bacteria in the pathogenesis of PHG.

Urea breath test (UBT) which is widely used to diagnose *H. pylori* infection. UBT relies on bacterial hydrolysis of orally administered urea tagged with a carbon isotope. Hydrolysis of urea generates ammonia and tagged CO2 which can be detected in breath samples. The specificity of UBT is about 95%. Sensitivity is about 80-95%.

Association of *H. pylori* with PHG is still now a debating issue. The mucosal lesion of stomach and several extra-gastric conditions are associated with *H. pylori* infection.

Unexplained vitamin B12 deficiency, Idiopathic thrombocytopenic purpura (ITP) and Iron deficiency anaemia (IDA) is associated with *H. pylori* infection. *H. pylori* is associated with portal hyperensive gastropathy eradication of *H. pylori* may be beneficial in the management of PHG, if *H. pylori* infection is still present.

To the best of our knowledge, in Bangladesh no such study has been carried out. So this study was carried out to find out the association of *H. pylori* infection with PHG in patients with cirrhosis of liver.

**MATERIAL AND METHODS**

This case control study was conducted in the Department of Gastroenterology, BSMMU, Dhaka, Bangladesh during the period of April 2016 to August 2018. A total of 230 patients with cirrhosis of were included in this study. There were 115 cirrhotic patients with PHG as cases and 115 cirrhotic patients without PHG as controls. Patients with age < 18 years, peptic ulcer disease found in upper gastrointestinal endoscopy, patients with intake of proton pump inhibitors, bismuth compounds, antibiotics (within 2 weeks), *H. pylori* eradication within past 2 month, patients on NSAIDs or history of gastric surgery were excluded from the study.

**DATA COLLECTION**

At first, stable cirrhotic patients were selected for study as per inclusion and exclusion criteria. After proper counseling an informed written consent was taken from every participant. Information about demographic and clinical profile and laboratory parameters was collected on the predesigned data sheet. Detailed clinical history including history of jaundice, drug abuse, alcohol intake, blood transfusion, haematemesis, melaena etc was elicited from the participants. General physical and systemic examination was done for presence of ascites, splenomegaly and other peripheral signs of liver cirrhosis such as jaundice, palmar erythema, spider naevi, alopecia, gynaecomastia, testicular atrophy etc. Complete blood count, liver function tests including serum bilirubin, aminotransferase (ALT, AST) enzymes level ANA, 24 hours’ urinary copper, prothrombin time, serum albumin, viral markers (HBsAg, Anti-HCV), renal function test and imaging by abdominal ultrasound was done.

Endoscopy of upper gastrointestinal tract was performed in a single endoscopy unit using a video endoscope (OLYMPUS GIF-H190) at gastroenterology department of BSMMU to identify the presence of portal hypertensive gastropathy, assess its severity and also oesophageal or fundal varices. Upper GI endoscopy was done by single endoscopist to avoid interobserver variability. The severity of PHG was graded according to McCormack’s classification and the severity of liver cirrhosis was assessed by using Child-pugh classification.

UBT was performed to identify *H. pylori* infection at gastroenterology department of BSMMU in accordance with the manufacturer’s recommendations (HCBT-01, Headway Urea Breath Analyzer, China). UBT was done after an abstinence of proton pump inhibitor, antibiotics, bismuth compounds for two weeks and fasting for 6 hours on the day of procedure.

**STATISTICAL ANALYSIS**

After collection of data, all data were checked and cleaned. After cleaning, the data were entered into computer and statistical analysis of the results being obtained using Statistical Packages for Social Sciences (SPSS). Numerical variables were expressed as mean and standard deviation, whereas categorical variables were expressed in percentage. Numerical variables were compared using student’s t test.
and categorical variables were analyzed by Chi-square test. The risk was expressed in odd’s ratio with 95% confidence interval (CI). P value of less than 0.05 was considered statistically significant.

**ETHICAL CONSIDERATION**

Before starting this study, the research protocol was submitted to the institutional review board of BSMMU, Dhaka and IRB clearance was taken. All participants were informed about the objectives, methodology and purpose of the study in easily understandable way. Informed written consents were obtained from all participants without any influences prior to sample collection.

**RESULTS**

This case control study was conducted in the Department of Gastroenterology, BSMMU, Dhaka, Bangladesh during the period of April 2016 to August 2018. A total of 230 patients with cirrhosis were included in this study. There were 115 cirrhotic patients with PHG as cases and 115 cirrhotic patients without PHG as controls.

Table I shows the age distribution of the study patients according age-group in patients of cirrhosis with or without PHG. Most of the patients were of age more than 40 years in both groups. The mean age was 54.37 years for cases and 52.03 years for controls. The age difference among the cases and controls was not significant.

Table I: Distribution of the patients according to age in two groups

| Age (years) | Cases (n=115) n (%) | Controls (n=115) n (%) | p value |
|-------------|---------------------|------------------------|---------|
| 21 – 30     | 2 (1.7)             | 4 (3.5)                |         |
| 31 – 40     | 12 (10.4)           | 20 (17.4)              |         |
| 41 – 50     | 31 (27.0)           | 31 (27.0)              |         |
| 51 – 60     | 37 (32.2)           | 32 (27.8)              |         |
| >60         | 33 (28.7)           | 28 (24.3)              |         |

Mean±SD 54.37±10.97 52.03±11.05 0.109ns

Ns= not significant
Unpaired t test was done to measure the level of significance

Table II shows the gender distribution of cases ad controls. There were 88 (76.5%) male and 27 (23.5%) female patients of cirrhosis with PHG and 83(72.2%) of male and 32 (27.8%) of female cirrhotic patients of cirrhosis without PHG. There was no significant gender difference in cases and controls.

Table II: Distribution of the patients according to gender in two groups

| Gender | Cases (n=115) n (%) | Controls (n=115) n (%) | p value |
|--------|---------------------|------------------------|---------|
| Male   | 88 (76.5)           | 83 (72.2)              | 0.450ns |
| Female | 27 (23.5)           | 32 (27.8)              |         |

Ns= not significant
Chi-square test was done for the level of significance.

Table III shows the distribution of study patients according to clinical features. The cases and controls show no significant differences in presentation of clinical features.

Table III: Distribution of the patients according to clinical features in two groups

| Clinical feature | Cases (n=115) n (%) | Controls (n=115) n (%) | p value |
|------------------|---------------------|------------------------|---------|
| Jaundice         | 30 (26.1)           | 19 (16.5)              | 0.096ns |
| Ascites          | 94 (81.7)           | 83 (72.2)              | 0.085ns |
| Leg oedema       | 73 (63.5)           | 61 (53.0)              | 0.109ns |
| Anaemia          | 73 (63.5)           | 63 (54.8)              | 0.180ns |
| Leukonychia      | 10 (8.7)            | 7 (6.1)                | 0.450ns |
| Spider           | 18 (15.7)           | 17 (14.8)              | 1.000ns |
| Splenomegaly     | 62 (53.9)           | 51 (44.3)              | 0.147ns |

ns= not significant
Chi-square test was done to measure the level of significance

Table IV shows the laboratory parameters in cases and controls. The patients of cases and controls had no significant difference in the laboratory finding.

Table IV: Distribution of the patients according to laboratory features in two groups
Table IV: Investigation findings of the patients in two groups

| Investigations                  | Cases (n=115) [mean±SD] | Controls (n=115) [mean±SD] | p value |
|---------------------------------|-------------------------|-----------------------------|---------|
| Hb (g/dl)                       | 10.77 ± 1.40            | 11.08 ± 1.14                | 0.066ns |
| ESR (mm in 1st hour)            | 49.64 ± 16.75           | 45.89 ± 17.55               | 0.098ns |
| TC (No/mm3)                     | 6196.35 ± 2164.04       | 6648.69 ± 1819.77           | 0.088ns |
| Platelet count (per mm3)        | 131426.09 ± 95576.63    | 151464.91 ± 56544.94        | 0.055ns |
| Serum creatinine (mg/dl)        | 1.05 ± 0.27             | 1.00 ± 0.27                 | 0.225ns |
| Na+ (meq/L)                     | 132.62 ± 4.30           | 133.56 ± 4.61               | 0.109ns |
| K+ (meq/L)                      | 3.91 ± 0.44             | 4.02 ± 0.40                 | 0.057ns |
| ALT (U/L)                       | 38.98 ± 21.28           | 36.74 ± 12.48               | 0.331ns |
| AST (U/L)                       | 49.96 ± 26.33           | 48.28 ± 21.77               | 0.600ns |
| S. Bilirubin (mg/dl)            | 1.75 ± 1.08             | 1.48 ± 1.10                 | 0.063ns |
| S. Albumin (g/L)                | 25.11 ± 5.07            | 26.13 ± 3.46                | 0.075ns |
| Prothrombin time                |                         |                             |         |
| Control                         | 11.90 ± 0.16            | 11.88 ± 0.12                | 0.252ns |
| Patient                         | 17.32 ± 3.31            | 16.71 ± 2.61                | 0.119ns |
| INR                             | 1.46 ± 0.29             | 1.41 ± 0.25                 | 0.189ns |

ns=not significant
Unpaired t test was done to measure the level of significance

Table V shows the case and control patients of cirrhosis with different etiology. There were 63 (54.7%) patients in cases and 60 (52.1%) patients in controls with CHBV infection. Chronic hepatitis C virus infection was found in 11 (9.6%) of patients in cases and 14 (12.2%) of patients in controls as a cause of cirrhosis. There was no etiological difference among the cases and controls.

Table V: Distribution of the patients according to etiology in two groups (n=230)

| Etiology   | Cases (n=115) n (%) | Controls (n=115) n (%) | p value |
|------------|---------------------|------------------------|---------|
| HBsAg      | 48 (41.7)           | 43 (37.4)              | 0.500ns |
| HbsAg-Anti-HBc | 15 (13.0)     | 17 (14.7)              | 0.849ns |
| Anti HCV   | 11 (9.6)            | 14 (12.2)              | 0.525ns |

ns=not significant
Chi-square test was done to measure the level of significance

Table VI shows the distribution of cases and controls according to Child-Pugh score. Most of the patients of cases and controls were of Child-Pugh class B and Child-Pugh class C. There were no significant difference in the Child-Pugh class of cases and controls.

Table VI: Distribution of the patients according to Child pugh score in two groups

| Child Pugh Class | Cases (n=115) n (%) | Controls (n=115) n (%) | p value |
|------------------|---------------------|------------------------|---------|
| A                | 12 (10.4)           | 20 (17.5)              | 0.074ns |
| B                | 48 (41.7)           | 55 (48.2)              |         |
| C                | 55 (47.8)           | 39 (34.2)              |         |

ns= not significant
Chi-square test was done to measure the level of significance

Table VII shows the distribution of cases according to grade of PHG. There were78(67.8%) of patients with mild PHG whereas 37(32.2%) of patients had severe PHG.

Table VII shows the distribution of cases according to grade of PHG.
Table VII: Distribution of cases according to grade of PHG (n=115)

| PHG     | Frequency (n) | Percentage (%) |
|---------|---------------|----------------|
| Mild    | 78            | 67.8           |
| Severe  | 37            | 32.2           |

Table VIII shows distribution of patients according to the test result of UBT. There were 77 (67.0%) patients of case and 70 (60.9%) patients of control with positive UBT. There were 38 (33.0%) patients of case and 45 (39.1%) patients of control had negative UBT. There was no statistically significant difference in test result among the cases and controls with OR 1.303 at 95% CI, 0.759-2.235. Patients with PHG did not have significant increase risk of H.pylori infection.

Table VIII: Distribution of the patients according to $^{13}$C Urea Breath Test in two groups

| $^{13}$C Urea Breath Test | Cases (n=115) | Controls (n=115) | p value  | OR (95% CI) |
|---------------------------|---------------|------------------|----------|-------------|
| Positive                  | 77 (67.0)     | 70 (60.9)        |          | 1.303       |
| Negative                  | 38 (33.0)     | 45 (39.1)        | 0.337ns  | (0.759-2.235) |

ns= not significant
Chi-square test was done to measure the level of significance

Table IX shows the distribution and association of H. pylori with severity of PHG. Out of 77 H. pylori positive patients with PHG, 55 patients had mild PHG whereas 22 patients had severe form of PHG. There were 38 patients with PHG had negative UBT out of which 23 had mild PHG and 15 patients had severe form of PHG. There was no significant association among the patients of H. pylori infection and severity of PHG (p= 0.290).

Table IX: Association of H. pylori with severity of PHG (n=115)

| PHG    | H. pylori | p value |
|--------|-----------|---------|
|        | Positive  | Negative |
|        | (n=77)    | (n=38)  |          |
| Mild(78)| 55 (70.5) | 23 (29.5) | 0.290ns |
In our study, out of 230 patients with cirrhosis, 147 patients were H. pylori positive with overall proportion of H. pylori infection was 63.91%, which was comparable to another study done by Abbas et al. who found a prevalence of H. pylori was 62.1% and Safwat et al. who found prevalence of H. pylori was 60%.

The concern of our study was to find out the association of H. pylori with portal hypertensive gastropathy in cirrhosis of liver. In our study, we had positive UBT in 77 (67.0%) patients of cirrhosis with PHG and 70 (60.9%) patients of cirrhosis without PHG. Thirty-eight patients with PHG had negative UBT out of which 23 had mild PHG and 15 patients had severe form of PHG. There was no significant association of H. pylori with presence of PHG in cirrhotic patients (p= 0.337 with OR 1.303 at 95% CI: 0.759-2.235). Hammad et al. conducted a similar study in Egypt and reported H. pylori infection among 70% cases and 63.3% controls and insignificant association of H. pylori with PHG.

The severity of PHG was mild in 55 H. pylori positive patients and 23 H. Pylori negative patients whereas severe PHG was present in 22 H. pylori positive and 15 H. Pylori negative patients. The severity of PHG and H. Pylori infection had no significant association in cirrhotic patients. These findings were similar as studied by Bahnacy et al. H. pylori positivity decreased when the severity of PHG increased. As there is severe hemorrhagic congestion and oedema of the gastric mucosa in PHG, so it may not provide a favourable environment for the colonization of H. pylori. In contrast Sathar et al. and Safwat et al. had noticed a significant association between H. pylori and severity of PHG (p< 0.001). They had suggested that H. pylori colonization of the stomach of cirrhotic patients likely to be contributory to the pathogenesis of PHG.

CONCLUSIONS
No significant association was found between H. pylori infection and PHG in cirrhotic patients in this study. The data also showed that, severity of PHG was not associated with H. pylori infection. Further prospective studies with a large number of samples are required to see the association of H. pylori with PHG.

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