

Factors Related to Peptic Ulcer Diseases in Cirrhotic Patients

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ABSTRACT

Background: Due to the extreme risk of death after variceal hemorrhage, endoscopic screening for varices has been recommended in cirrhotic patients since 1998. Previous studies revealed a higher incidence of peptic ulcer diseases in cirrhotic patients than those of general population. However, the pathogenesis of peptic ulcers in liver cirrhosis remains inconclusive.

Objective: To investigate for clinical and epidemiological factors that might play role in the pathogenesis of peptic ulcer diseases in cirrhosis and to evaluate for the incidence of peptic ulcers in asymptomatic cirrhotic patients who underwent endoscopic screening.

Patients and Methods: 114 cirrhotic patients without any evidence of liver cancer were recruited into the study consecutively from the Gastroenterological clinic for endoscopic screening. Patient history and their clinical data were collected. Biochemical tests were done prior to the study. Doppler ultrasound was used to assess the portal vein velocity and portal vein size by a single radiologist. Study patients underwent endoscopic examination for any abnormalities including esophageal and gastric varices and the presence of peptic ulcers. The presence of *Helicobacter pylori* infection was confirmed by two of the three positive tests of Urease test, histology or ¹⁴C Urea breath test. Statistical analysis of continuous variables was done with student t-test or non-parametric test as appropriate. Chi-square or Fisher exact test was used for analysis of discrete variables. P-value <0.05 was considered to be statistically significant. Multivariate logistic regression analysis was performed further for factors with p-value <0.20.

Results: Peptic ulcers were detected in 45/114 (39.5%) cases. Comparing between peptic ulcer and non peptic ulcer groups, there was no statistically difference in mean ages, sex, history of regular alcohol drinking, smoking, NSAID use, portal vein velocity and portal vein size among the two groups except *Helicobacter pylori* infection (p = 0.02) and Child Pugh class (p = 0.08). Multivariate logistic regressioon analysis showed that *Helicobacter pylori* infection (OR 3.22; 95%CI 1.3-7.5), and Child-Pugh class B (OR 2.71; 95%CI 1.1-6.9) or class C (OR 3.85; 95% CI 1.3-11.3) were independently associated with the presence of peptic ulcer diseases in these patients.

Conclusions: Helicobacter pylori infection and advanced stages of liver cirrhosis are the two important factors associated with peptic ulcers in cirrhotic patients. Comparing with the general population, peptic ulcer diseases are more common in asymptomatic cirrhotic patients who underwent endoscopic screening for varices.

Key words : peptic ulcer, cirrhotic patients

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BACKGROUND

From previous reports, the mortality rate in cirrhotic patients after first variceal hemorrhage could reach $20-35\%^{(1-3)}$. Endoscopic screening for varices has been recommended in cirrhotic patients since $1998^{(4)}$. In a recent meeting⁽⁵⁾, it is recommended to perform endoscopy in all cirrhotic patients to detect varices, in such patients the use of nonselective beta blocker could reduce the risk of first variceal bleeding by 11% and risk of death by $9\%^{(6)}$.

The incidence of peptic ulcer in cirrhotic patients has been reported at 5-20%, comparing to with 2-4% among those of the general population⁽⁷⁾. The pathogenesis of peptic ulcers in cirrhosis remains inconclusive. From one report, *Helicobacter pylori* increases the risk of peptic ulcer in these patients by 2.70 times⁽⁸⁾ but following study⁽⁹⁾ did not confirm this finding. In one study, HVPG >12 increased the incidence of GU in cirrhotic patients⁽¹⁰⁾. The HVPG of cirrhotic patients with and without GU were different. $(15.5 \pm 5.0 \text{ mmHg} \text{ vs } 17.3 \pm 4.4 \text{ mmHg}; \text{ p} = 0.01)^{(10)}$. The relationship between peptic ulcer in these patients with other factors, e.g. age, sex, and portal hypertensive gastropathy remain controversial and have never been studied.

In this study, we investigated the age, sex, *Helicobacter pylori* infection, portal vein velocity, Child-Pugh class and common risk factors for peptic ulcer in the cirrhotic patients. Furthermore, this study can evaluate the incidence of peptic ulcer in Ramathibodi hospital during the study period.

PATIENTS AND METHODS

One hundred and fourteen consecutive cirrhotic patients presented at the Ramathibodi hospital between September 2002 and October 2003 were included in this study. All patients were older than 15 years and had evidence of liver cirrhosis from clinical symptoms, biochemical, radiological and histological tests⁽¹¹⁾. Patients who had history of taking proton pump inhibitor, sucralfate, H₂ blocker, bismuth containing compounds within 2 weeks, corticosteroid, anticoagulant and those with history of gastric or esophageal surgery, vagotomy, pyloric stenosis, varices eradication procedures, evidence of liver cancer, uncorrected thrombocytopenia and coagulopathy (platlets <50,000, INR >2.5) were excluded from the study.

Informed consents were obtained from all patients

before the study and the study protocol was approved by the Ramathibodi Hospital Ethical Committee.

All patients were examined by a doctor at Gastroenterological clinic for history, physical examinations and biochemical tests. The severity of cirrhosis was assessed by the Child-Pugh classification⁽¹²⁾. The etiology of cirrhosis was defined as alcoholic if there was a daily ethanol taking more than 80 g/day for at least 10 years and as viral if HBsAg or antibody to hepatitis C virus were positive.

All patients were sent for doppler ultrasound of upper abdomen (ATL model HDI 5000), which were carried out by a single experienced radiologist to assess the portal vein velocity and portal vein size. In previous reports, the portal vein velocity inversely correlated with hepatic venous portal gradient (HVPG) and signified the degree of portal hypertension⁽¹⁰⁾.

Subsequently, esophagogastroduodenoscopies were performed by a single endoscopist. Any abnormal findings including of esophageal varices, gastric varices, degree of portal hypertensive gastropathy and peptic ulcer were recorded. The severity of hypertensive gastropathy, esophageal varices and gastric varices were graded as previously grading systems⁽¹³⁻¹⁶⁾. Peptic ulcer was diagnosed when a crater with fibrin coated base >3 mm was observed^(17,18).

Helicobacter pylori infection was determined by two positive tests of three following tests : ^{14}C Urea breath test, Urease test (CLO test) and histology .

Statistical Analysis

Descriptive statistics are expressed as number (%) for categorical data, mean (SD) or median (range) are appropriated for continuous data. Statistical analysis of continuous variables was performed by student t-test or non-parametric test as appropriate. Chi-square or Fisher exact test was used for analysis of discrete variables. P-value <0.05 was considered to be statistically significant. Multivariate logistic regression analysis was performed and with p-value <0.20 was considered significant.

RESULTS

One hundred and fourteen patients were enrolled in this study, fifty eight patients (50.9%) were men with mean (\pm SD) age of 56.4 \pm 11.9 (range 17-87 years). The causes of cirrhosis were alcohol in 40 (35.1%), HBV infection in 27 (23.7%), HCV in 21 (18.4%),





Figure 1 Esophageal varices in Child Pugh classes

HCV and alcohol in 7 (6.1%), HBV and alcohol in 5 (4.4%), NASH in 2 (1.8%), HBV and HCV in 1 (0.9%) and other causes in 10 (8.8%). There were 50 (43.9%), 38 (33.3%) and 26 (22.8%) in Child-pugh class A, B and C groups respectively.

Regular smoking were found in 29 patients (25.4%). Daily alcoholic consumption were found in 57 patients (50%). History of NSAID and herbal medicine use within 30 days were identified in 9 (7.9%) and 14 (12.3%) patients respectively.

Endoscopic findings: Gastroduodenal ulcer was diagnosed in 45 patients (39.5%), 34 (29.8%) patients with gastric ulcer, 5 patients (4.4%) with duodenal ulcer and 6 patients (5.3%) had both lesions. Esophageal varices were identified in 57 patients (50%) which were grade 1 in 45 patients, grade 2 in 24 patients (21.1%) and grade 3 in 6 patients (5.3%) (Figures 1). Compare to those with Child-Pugh class A, the incidence of grade 2 esophageal varices was higher in Child-Pugh class B and C (p = 0.037). Gastric varices were found in 22 (19.3%) as GOV1 in 13 patients (11.4%), GOV2 in 5 patients (4.4%) and IGV1 in 4 patients (3.5%). Hypertensive gastropathy were mild in 54 patients (47.4%) and severe in 26 patients (22.8%).

Helicobacter pylori infection: Rapid urease test (CLO test) were positive in 56 patients (49.1%), histologic findings were positive in 58 patients (50.9%) and ¹⁴C Urea breath test were positive in 57 patients (50%). 56 of the patients (49.1%) had two or more positive



Figure 2 Median value of portal vein velocity in each Child Pugh classes

test for Helicobacter pylori infection.

Doppler ultrasound findings: The median (range) of portal vein velocity was 9.6 (-24.2, 28.4) cm/sec and the mean (\pm SD) of portal vein size was 11.1 (\pm 3.3) mm. There was no correlation between the median portal vein velocity and the severity of liver cirrhosis as denoted by the Child-Pugh scores. However, the portal vein velocity of class C patients was lower than those of the patients with class A and B. [6.5 (-18.7, 20.6) cm/sec vs 9.3 (-24.2, 28.4) cm/sec, p = 0.89] (Figure 2).

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| | With peptic ulcer ⁽⁴⁵⁾ | Without peptic ulcer ⁽⁶⁹⁾ | p-value |
|------------------------------------|-----------------------------------|---|---------|
| Age | | | 0.574 |
| <20 | 0 | 6 | |
| 21-40 | 2 | 38 | |
| 41-60 | 24 | 23 | |
| >60 | 19 | 2 | |
| Sex | | | 0.73 |
| Male | 22 (48.9%) | 36 (52.2%) | |
| Female | 23 (51.1%) | 33 (47.8%) | |
| Etiology of cirrhosis ⁺ | | | |
| HBV | 10 (22.2%) | 24 (34.8%) | 0.152 |
| HCV | 14 (31.1%) | 15 (21.7%) | 0.261 |
| Alcoholic | 18 (40.0%) | 34 (49.3%) | 0.331 |
| Nash | 1 (2.2%) | 1 (1.4%) | 0.759 |
| Other | 4 (8.8%) | 6 (8.7%) | 0.97 |
| Smoking | | | 0 524 |
| Yes | 10 (22.2%) | 19 (27.5%) | 0.021 |
| No | 35 (77.8%) | 50 (72.5%) | |
| Alcohol | | | 0.338 |
| Ves | 20 (44 4%) | 37 (53.6%) | 0.550 |
| No | 25 (55.6%) | 32 (46 4%) | |
| | 20 (00.070) | 32 (10.170) | 0.524 |
| NSAID | 5 (11 10/) | 4 (5 00/) | 0.524 |
| Yes | 5(11.1%) | 4(5.8%) | |
| INO | 40 (88.9%) | 65 (94.2%) | |
| Herbal Medicine | | | 0.759 |
| Yes | 5 (11.1%) | 9 (13%) | |
| No | 40 (88.9%) | 60 (87%) | |
| Ascites | | | 0.416 |
| Yes | 17 (37.8%) | 21 (30.4%) | |
| No | 28 (62.2%) | 48 (69.6%) | |
| Child pugh class | | | 0.08 |
| A | 14 (31.1%) | 36 (52.2%) | |
| В | 18 (40.0%) | 20 (29.0%) | |
| С | 13 (28.9%) | 13 (18.8%) | |
| Total bilirubin | $3.004 \pm 4.824*$ | $2.101 \pm 2.17*$ | 0.176 |
| Albumin | $30.687 \pm 8.040 *$ | $34.428 \pm 8.177 *$ | 0.017 |
| Platelets | $118,244.4 \pm 60,154*$ | 131,966.7 ± 98,400* | 0.731 |
| PHG | | | 0.581 |
| No | 14 (31 1%) | 20 (29 0%) | 0.501 |
| Mild | 23 (51.1%) | 31(44.9%) | |
| Severe | 8 (17.8%) | 18 (26.1%) | |
| Ilelieskaster mileri | | 10 (2011/0) | 0.024 |
| Dositivo | 28 (62 20/) | 28(40.69/) | 0.024 |
| 1 USILIVE Nagativa | 20 (02.2%) 17 (27.80/) | 20 (40.0%) | |
| Dertelassin sole site (see (see) | 1 / (3 / .070) | ті (<i>J7.</i> † <i>/</i> 0 <i>)</i> 10.2 (.24.2.26.2)* | 0.20 |
| Portal vein velocity (cm/sec) | U (-19.8, 28.4)* | 10.2 (-24.2, 20.2)* | 0.29 |
| Portal vein size (mm) | $10.97 \pm 3.299 **$ | $11.188 \pm 3.340 **$ | 0.93 |

 Table 1 Factors related to peptic ulcer in cirrhotic patients by univariate analysis

(*median (range), (** mean + 1SD)

HBV and HCV = 1, HBV and alcohol = 5, HCV and alcohol = 7

| | OR (95%CI) | SE | p-value |
|---------------------|-------------------|------|---------|
| H. Pylori infection | 3.22 (1.38-7.51) | 1.39 | 0.007 |
| Child pugh | | | |
| Class A | 1.0 | | |
| Class B | 2.71 (1.07-6.91) | 1.29 | 0.036 |
| Class C | 3.85 (1.30-11.37) | 2.12 | 0.015 |

 Table 2
 Factors related to peptic ulcer in cirrhotic patients by multivariate logistic regression analysis

Univariate analysis (Table1): *Helicobacter py-lori* infection (p = 0.02) and albumin (p = 0.017) were important factors for the presence of peptic ulcer. Multivariate logistic regression analysis was performed further for the factors with p < 0.2. There was no statistically difference in mean ages, sex, history of regular alcohol drinking, smoking, NSAID use, portal vein velocity and portal vein size between the two groups. Multivariate logistic regression analysis (Table2) : *Helicobacter pylori* infection (OR 3.22; 95%CI 1.38-7.51, p = 0.007), Child's Pugh class B (OR 2.71; 95%CI 1.07-6.91, p = 0.036) and class C (OR 3.85; 95%CI 1.30-11.37, p = 0.015) independently associated with the presence of peptic ulcer disease in cirrhotic patients.

DISCUSSION

The result of this study is consistence with previous reports that the prevalence of peptic ulcer disease in cirrhotic patients was higher than those without liver cirrhosis (39.5% vs 10% (data from internal review of dyspepsia patients presented at Ramathibodi hospital during the study period))

In a recent meta analysis⁽⁸⁾, *Helicobacter pylori* infection has been found to be an independent risk factor of peptic ulcer in cirrhotic patients. In this study, we also found Child Pugh class B and C were risk factors associated with presence of peptic ulcer. Although we found no correlation between the portal vein velocity in each Child Pugh class, the portal vein velocity in Child Class C was lower than those of the Child Pugh classes A and B. Since portal vein velocity is inversely correlated with portal hypertension⁽¹⁰⁾.

In theory, the portal hypertension may involve in pathogenesis of peptic ulcer by causing splanchnic congestion, altering normal reparative processes of gastroduodenal mucosa and impairing gastric mucosal secretion, thus lead to increasing susceptibility towards acid and pepsin secretion.

In the normal populations, alcoholic ingestion, smoking and NSAIDs are the important factors related to presence of peptic ulcers. However, in this study all these factors were not play important role. Thai cirrhotic patients may reduce the taking of alcohol, NSAID and smoking when they become sick.

Limitation of Study

The study period was only 14 months so the study patients may not represent all cirrhotic patients. It need further study to confirm our findings.

CONCLUSION

Helicobacter pylori infection and advanced stages of cirrhosis are two important factors associated with peptic ulcers in cirrhosis. Furthermore peptic ulcer diseases are more common in asymptomatic cirrhotic patients who underwent endoscopic screening for varices comparing to those of the non-cirrhotic dyspeptic patients.

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Appendix

1. Diagnostic criteria of liver cirrhosis⁽¹⁰⁾

Clinical criteria

- Esophageal varices
- Splenomegaly and /or changing of peripheral blood morphology from hypersplenism
- Ascites
- Hepatosplenomegaly
- Muscle wasting
- Dermovascular change of cirrhosis e.g. spider angiomas

Laboratory criteria

Hyperbilirubinemia, hypoalbuminemia and coagulopathy in cirrhotic patients

Radiologic/imaging criteria

Ultrasound : Findings of liver nodule, ascites, splenomegaly or vascular change (intraabdominal portosystemic collateral circulation)

CT abdomen : Finding of liver nodule and portal hypertension

Morphologic criteria

Liver biopsy : Histologic finding showed one liver nodule surrounding with fibrous tissue. (in some cases)

2. Child-Pugh Classification⁽¹¹⁾

| Findings | 1 Point | 2 Points | 3 Points |
|---|---------------------------|--------------------------|-----------------------------|
| Serum albumin (g/dL) | > 3.5 | 2.8-3.5 | < 2.8 |
| Serum bilirubin (mg/dL) | < 2.0 (for primary | 2.0-3.0 (for primary | > 3.0 (for primary biliary |
| | biliary cirrhosis, < 4.0) | biliary cirrhosis, 4-10) | cirrhosis, cirrhosis, > 10) |
| Prolongation in prothrombin time (seconds) or INR | 1-4 | 4-6 | > 6 |
| | < 1.7 | 1.7-2.3 | > 2.3 |
| Ascites | None with diuretics | Slight or controlled | Moderate or severe |
| Encephalopathy | None | Mild or moderate | Severe |

Class A = 5-6 points; Class B = 7-9 points; Class C = 10-15 points.

3. Endoscopic findings

- Esophageal varice classified as following⁽¹²⁾
 - F1 : small straight varices
 - F2 : enlarged, tortuous; occupy less than one third lumen
 - F3 : large, coil-shaped: occupy more than one third of lumen
- Gastric varices^(13,14)
 - 1. Gastroesophageal varices

Type 1 (GEV 1) -along lesser curve (usually 2-5 cms in length)

- Type 2 (GEV2) along the greater curve extending toward the gastric fundus
- 2. Isolated gastric varices

Type 1 (IGV1) - isolated cluster of varices in the gastric fundus

- Type 2 (IGV2) isolated gastric varices in the other part of the stomach
- Portal hypertensive gastropathy (International Consensus conference)⁽¹⁵⁾
 - 1. mild : a mosaic-like pattern of small polygonal areas that slightly protrude in the center surrounded by a whitish or yellow depressed border

2. severe

- Red point lesions (RPLs) : red lesions with diameter less than 1 mm
- Cherry red spots (CRSs) : raised red lesion with diameter more than 2 mm
- Black brown spots (BBSs) : flat black or brown spot with irregular border indicate recent bleeding in mucosal layer
- Ulcer⁽¹⁶⁻¹⁷⁾
 - Depend on site of lesions :Gastric ulcer and Duodenal ulcer
 - Ulcer was diagnosed when a crater with fibrin coated base >3 mm