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Helicobacter pylori Infection and Peptic Ulcer Disease in Patients with Liver Cirrhosis

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Background/Aims : We investigated the prevalence and relationship of peptic ulcer disease and *Helicobacter pylori* infection to liver cirrhosis.

Methods : We examined 288 patients with liver cirrhosis, 322 patients with non-ulcer dyspepsia, and 339 patients with peptic ulcer disease. Rapid urease test and Wright-Giemsa staining were used for diagnosis of *H. pylori* infection.

Results : The prevalence of peptic ulcer disease in patients with cirrhosis was 24.3%. The prevalence of peptic ulcer disease in patients with cirrhosis divided into Child-Pugh classes A, B, and C was 22.3%, 21.0%, and 31.3%, respectively (p〉0.05). The prevalence of *H. pylori* infection in the patients with cirrhosis, non-ulcer dyspepsia, and peptic ulcer without chronic liver disease were 35.1%, 62.4%, and 73.7%, respectively (p〈0.001). The prevalence of *H. pylori* infection did not differ depending on whether there was peptic ulcer (35.6%) or not (34.9%) in patients with liver cirrhosis (p〉0.05). The prevalence of *H. pylori* infection in patients with hepatitis virus-related liver cirrhosis and in the patients with alcohol-related liver cirrhosis was 42.5% and 22.0%, respectively (p〈0.001). The prevalence of *H. pylori* infection in patients with Child-Pugh classes A, B, and C liver cirrhosis was 51.5%, 30.5%, and 20.0%, respectively (p〈0.001).

Conclusions : Factors other than *H. pylori* may be involved in the pathogenesis of peptic ulcer disease in the setting of liver cirrhosis.

Key Words : *Helicobacter pylori;* Liver cirrhosis; Peptic ulcer

INTRODUCTION

Chronic liver disease and its complications are major health problems. Peptic ulcer disease is one of the most frequently observed complications in patients with liver cirrhosis. Although the incidence and prevalence of peptic ulcer disease appear to be increased in cirrhosis, the underlying mechanism of peptic ulcer disease in cirrhosis is unclear[1-3]. In the general population, *Helicobacter pylori* infection is central to the pathogenesis of peptic ulcer disease[4, 5]. However, the role of *H. pylori* infection in the pathogenesis of peptic ulcer disease in cirrhotic patients still remains to be elucidated. Many studies have suggested a role for *H. pylori* infection in the pathogenesis of peptic ulcer disease in cirrhotic patients, but several studies have found no relationship[6-24]. Moreover, there is debate concerning the relationship between *H. pylori* infection and the etiology or severity of cirrhosis.

The aim of this study was to define the prevalence of peptic

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Table 1. The prevalence of *H. pylori* infection in patients with liver cirrhosis, non-ulcer dyspepsia, and peptic ulcer disease

(%)	LC* (n=288)	NUD† (n=322)	PUD‡ (n=339)
	101/288 (35.1%)§	201/322 (62.4%)	250/339 (73.7%)
According to the presence of PU‖			
without PU	76/218 (34.9%)		
with PU	24/70 (35.6%)¶		
According to the etiology of cirrhosis			
HBV#	63/145 (43.4%)		
HCV**	9/24 (37.5%)		
HBV + HCV	2/5 (40.0%)		
Alcoholic	24/109 (22.0%)††		
Cryptogenic	2/5 (40.0%)		
According to the Child-Pugh class			
A	53/103 (51.5%)		
B	32/105 (30.5%)		
C	16/80 (20.0%)		

*Liver Cirrhosis, †Non-Ulcer Dyspepsia, ‡Peptic Ulcer Disease, ‖ Peptic Ulcer, # Hepatitis B Virus, **Hepatitis C Virus
§ $p<0.001$ (LC vs. NUD, LC vs. PUD), ¶ $p<0.001$ (PU with LC vs. PU without LC), †† $p<0.001$ (alcohol vs. viral etiology)

ulcer disease and *H. pylori* infection in patients with liver cirrhosis. We additionally evaluated the relationship between *H. pylori* infection and the etiology or severity of cirrhosis.

MATERIALS AND METHODS

The study population included 288 consecutive Korean patients (229 men and 59 women, 49.3±11.1 years of age) with newly diagnosed liver cirrhosis presenting at Chuncheon Sacred Heart Hospital, Hallym University Medical Center, Chuncheon, Korea, between January 2000 and December 2004. 322 age- and sex-matched non-ulcer dyspepsia patients (259 men and 63 women, 49.0±10.0 years of age) without chronic liver disease were drawn to serve as a control group. Additionally, 339 age- and sex-matched peptic ulcer patients (272 men and 67 women, 48.1±11.5 years of age) without chronic liver disease were selected as a reference group. Those patients who had taken antibiotics, proton pump inhibitors, or non-steroidal anti-inflammatory drugs within 2 weeks before entry, and those patients who had a history of gastric surgery, were excluded.

Liver cirrhosis was diagnosed using a combination of clinical, biochemical, radiologic, and histologic methods. The severity of cirrhosis was scored according to the Child-Pugh classification. Etiology of the cirrhosis was defined as alcoholic if viral markers (HBsAg, anti-HCV) were negative and there was a history of ethanol intake of over 60 g/day for 5 years or more.

All the enrolled patients underwent upper gastrointestinal endoscopy with 4 biopsies taken from the antrum (within 2 cm from the pylorus) and 4 biopsies taken from the gastric body (greater curvature side of the midbody). Endoscopy was performed using an Olympus videoscope GIF 240 (Olympus Optical Co., Ltd., Tokyo, Japan). Endoscopic diagnosis of peptic ulcer disease was made when a distinct ulcer crater with fibrin-coated base larger than 5 mm was observed. The diagnosis of gastric ulcer was always confirmed by multiple biopsies of the ulcer.

Four biopsy specimens 2 from the antrum and 2 from the gastric body were used to identify *H. pylori*, using the rapid urease test (CLOtest®, Ballard Medical Products, UT, USA or ProntoDry®, Medical Instruments Co., Herford, Germany). Four other specimens 2 from the antrum and 2 from the gastric body were used for determining *H. pylori* presence (hematoxylin-eosin & Wright-Giemsa staining). The presence of *H. pylori* infection was determined by positivity of rapid urease test and/or histology (Wright-Giemsa staining).

This study was approved by the Hospital's Ethics Committee, and informed consent for endoscopy was obtained from all the patients.

The demographic and clinical characteristics were analyzed statistically using the chi-square test and Spearman correlation test, as appropriate. A value of $p<0.05$ was considered to be statistically significant. Statistical calculation was made with the help of SPSS statistical package for Windows version 8.0.0. (SPSS Inc, Chicago, IL, USA).

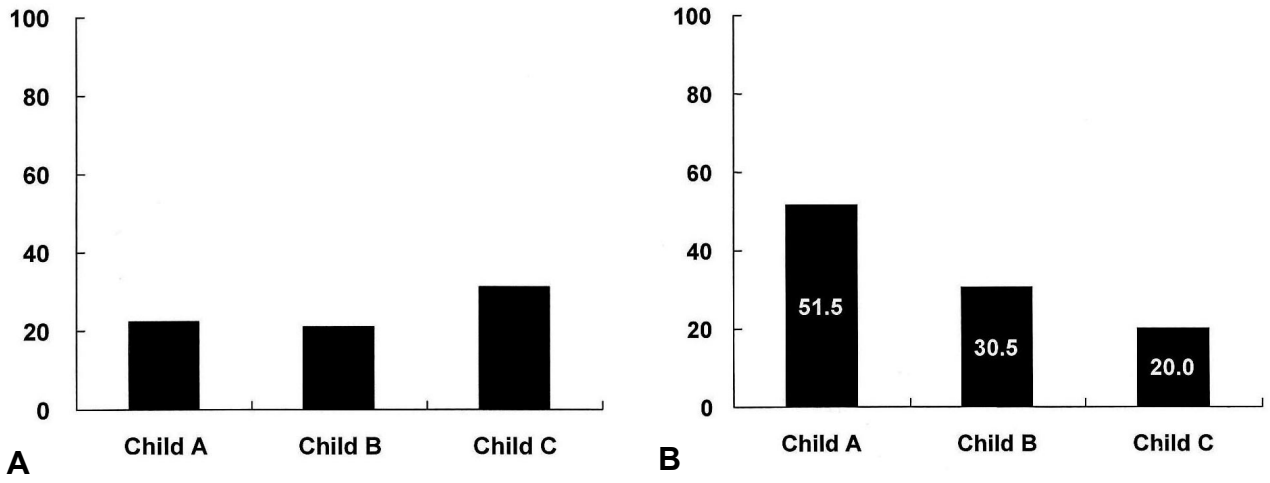

Figure 1. The prevalence of peptic ulcer (A) and *H. pylori* infection (B) in patients with liver cirrhosis. (A) The prevalence of peptic ulcer disease in cirrhotic patients is not significantly different according to Child-Pugh class (p〉0.05). (B) A negative correlation is demonstrated between the prevalence of *H. pylori* infection and the severity of liver cirrhosis according to Child-Pugh class (Spearman's rho=-0.267, p〈0.001).

RESULTS

The etiologies of the 288 cirrhosis patients were: Hepatitis B virus (HBV)-related in 145, Hepatitis C virus (HCV)-related in 24, HBV and HCV-related in 5, alcohol-related in 109, and cryptogenic in 5 patients.

The prevalence of *H. pylori* infection in patients with cirrhosis, patients with non-ulcer dyspepsia without chronic liver disease, and peptic ulcer disease patients without chronic liver disease, were 35.1% (101/288), 62.4% (201/322), and 73.7% (250/339), respectively. The prevalence of *H. pylori* infection in patients with cirrhosis was significantly lower than in non-ulcer dyspepsia (p〈0.001) or peptic ulcer disease patients without chronic liver disease (p〈0.001) (Table 1).

The point prevalence of peptic ulcer disease in patients with cirrhosis was 24.3% (36 gastric ulcer, 31 duodenal ulcer, 3 gastric and duodenal ulcer). The prevalence of *H. pylori* infection was 35.6% in peptic ulcer disease patients with liver cirrhosis and 73.7% in peptic ulcer disease patients without chronic liver diseases (p〈0.001). The prevalence of *H. pylori* infection did not differ in patients with liver cirrhosis, whether peptic ulcer was present (35.6%) or no (34.9%) (p〉0.05) (Table 1).

The prevalence of *H. pylori* infection in patients with HBV-related, HCV-related, HBV- and HCV-related, alcohol-related, and cryptogenic liver cirrhosis was 43.4%, 37.5%, 40.0%, 22.0%, and 40.0%, respectively. The prevalence of *H. pylori* infection in patients with hepatitis virus-related liver cirrhosis (42.5%) was significantly higher than that in patients with alcohol-related liver cirrhosis (22.0%, p〈0.001) (Table 1).

As shown in Table 1, the prevalence of *H. pylori* infection in patients with Child-Pugh class A, B, and C liver cirrhosis was 51.5%, 30.5%, and 20.0%, respectively. A negative correlation was noted between the prevalence of *H. pylori* infection and the severity of liver cirrhosis according to Child-Pugh class (Spearman's rho=-0.267, p〈0.001). The prevalence of peptic ulcer disease in cirrhotic patients according to Child-Pugh class A, B, and C was 22.3%, 21.0%, and 31.3%, respectively (p〉0.05) (Figure 1).

DISCUSSION

Although the point prevalence of peptic ulcer disease in patients with liver cirrhosis is high, reaching 24.3%, the exact mechanism remains to be determined. The high prevalence of peptic ulcer disease in patients in our study with liver cirrhosis is consistent with previous reports[1-3, 6-8].

The role of *H. pylori* infection in the pathogenesis of peptic ulcer disease has been extensively evaluated in non-cirrhotic patients[4, 5]. The increased rate of peptic ulcer disease in patients with cirrhosis has been explained in some studies, by higher rates of gastric colonization with *H. pylori*[6, 7, 14-18, 23, 24]. However, other studies have found no relationship between *H. pylori* infection and peptic ulcer disease in cirrhosis[9-12, 18-20]. For a proper interpretation of the studies investigating the prevalence of *H. pylori* infection in patients with liver cirrhosis, several factors, such as diagnostic methods, etiology of liver cirrhosis, and geographic and racial differences in *H. pylori* prevalence should be considered.

In our study, the prevalence of *H. pylori* infection in patients with liver cirrhosis was 35.1%. Previous studies have reported a wide range (39~89%) in the prevalence of *H. pylori* infection in

patients with liver cirrhosis, most of them somewhat higher than our study[7, 8, 12, 14, 17, 18]. Moreover, the prevalence of *H. pylori* infection in cirrhotic patients in our study was significantly lower than that in the control and reference groups, a finding that was different from that found by many groups[6, 7, 13-18, 23, 24]. It was consistent with the results of others[19, 20]. This relatively low prevalence of *H. pylori* infection in cirrhotic patients in our study can be explained by the enrollment of more than 50% of Child-Pugh B and C cirrhotic patients in our study. Although those who took antibiotics within 2 weeks before entry were excluded, those who had a history of extensive but remote use of antibiotics were included. Therefore, inclusion of decompensated cirrhotic patients with a history of extensive but remote use of antibiotics due to various reasons might affect the prevalence of *H. pylori*.

The relatively low prevalence of *H. pylori* infection in cirrhotic patients in our study can also be partially explained by the difference in the diagnostic methods used in the setting of *H. pylori* infection. In general, studies that use serologic tests (IgG to *H. pylori*) report higher prevalence than the studies that use the rapid urease test, histology, or urea breath test for detection of *H. pylori* infection (76.2~89% vs. 39~59.7%). If *H. pylori* infection and liver cirrhosis have the same risk factors, but *H. pylori* infection cannot easily persist in the stomach of cirrhotic patients, serologic determination of *H. pylori* infection may lead to confounding results. The 2007 Maastricht Consensus Report on *H. pylori* diagnosis and treatment does not recommend serological determination of *H. pylori* infection in routine clinical practice. It also recommends that the primary diagnosis of *H. pylori* infection should be established by rapid urease test and/or histology[25-28].

The accuracy of gastric mucosal biopsy may be affected by various factors: the presence of bacteria other than *H. pylori* that produce urease, the patch distribution of *H. pylori* in gastric mucosa, and the histologic overestimation of *H. pylori* due to the presence of confounding bacteria. Thus, primary diagnosis by gastric mucosa biopsy urease testing and/or histology has some limitations[19]. So the accuracy of diagnostic methods use to detect *H. pylori* infection in our study may affect the result of low prevalence of *H. pylori* infection. The concordance of rapid urease test and histology for the diagnosis of *H. pylori* infection in our study was 255 out of 288 in cirrhotic patients and 293 out of 339 in peptic ulcer patients without chronic liver disease.

The prevalence of *H. pylori* infection in the control group of the present study (62.4%) was slightly lower than the seroprevalence (66.9%) in asymptomatic Korean adults[29]. This discrepancy may be due to the different study groups and diagnostic methods. *H. pylori* infection in the general population correlates with age, social class, education level, overcrowding, bed-sharing, and economic level during childhood[13]. Thus, a valid comparison of the prevalence of *H. pylori* infection in patients with cirrhosis and the general population, a control group matched by prognostic variables (age, socioeconomic status, ethanol intake, etc.) would be required. Although our study used age- and sex-matched control and reference groups, socioeconomic status and ethanol intake were not matched. Consequently, out study may not provide definitive data.

Besides *H. pylori*, other factors may contribute to the increased risk of peptic ulcer in cirrhotic patients[30, 31]. Reduced prostaglandins, decreased gastric acid secretion, elevated serum gastrin concentration, impaired mucus secretion, a reduction in potential difference of the gastric mucosa, and portal hypertensive gastropathy may all play a role in the pathogenesis of peptic ulcer disease in cirrhotic patients[1-3].

Several studies have been previously performed regarding the relationship between the prevalence of *H. pylori* infection and peptic ulcer disease according to the etiology and severity of liver cirrhosis. The present study demonstrated an interesting finding in that the prevalence of *H. pylori* infection in patients with liver cirrhosis varied according to the etiology of cirrhosis (viral *vs.* alcoholic = 42.5 *vs.* 22.0%, $p<0.001$). In Korea, HBV infection is still the leading cause of liver cirrhosis (53%), followed by alcohol (31%) and HCV infection (10%)[32]. Since our study included a relatively small proportion of cirrhotic patients with HCV infection, the fact that the prevalence of *H. pylori* infection in virus-related liver cirrhosis was higher than that in alcohol-related cirrhosis patients may not be generalizable in other countries where the major cause of liver cirrhosis is HCV infection.

It is of interest to note that the prevalence of *H. pylori* infection was related inversely to Child-Pugh classification. Although this observation is consistent with a previous report, which suggested that the prevalence of *H. pylori* infection among cirrhotic patients might be inversely related to the severity of liver cirrhosis, many previous data have noted no relationship between *H. pylori* infection and severity of liver cirrhosis[8, 10, 11, 33, 34]. Several factors, such as diagnostic methods, etiology of liver cirrhosis, proportion of decompensated cirrhosis, and geographic and racial differences in *H. pylori* prevalence, may explain the discrepancy. Based on our study, we hypothesize that the environment of the stomach in cirrhotic patients may not be suitable for the growth of *H. pylori*, and the progression of liver disease may lead to a more hostile milieu to *H. pylori*.

Many studies have argued for the relationship between *H. pylori* and peptic ulcer in cirrhotic patients, but the 'statistically high' (which is at most 2 times higher than control) prevalence of *H. pylori* in cirrhotic patients in those studies cannot explain completely the 'vividly and absolutely high' (which is at least 10 times higher than control) prevalence of peptic ulcer in cirrhotic patients. Our study showed that even though *H. pylori* infection

was decreased in patients with severe liver cirrhosis, peptic ulcer disease was increased. Based on our observations and those of others, we hypothesize that *H. pylori* may not be a main cause of peptic ulcer disease in cirrhotic patients[6].

The followings are major findings of our study: (1) Even though the prevalence of peptic ulcer disease was increased in patients with liver cirrhosis, *H. pylori* infection rate in peptic ulcer disease patients with cirrhosis was significantly lower than that in patients without chronic liver disease. (2) The prevalence of *H. pylori* infection did not differ in patients with liver cirrhosis, whether there was peptic ulcer or no. (3) Although the prevalence of *H. pylori* infection decreased with Child's class progression, the prevalence of peptic ulcer disease did not change. Taking the above major findings into account, we can conclude that *H. pylori* infection may not be one of the main factors in the pathogenesis of peptic ulcer disease in patients with liver cirrhosis.

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