Effect of *Helicobacter pylori* Infection on Esophagogastric Variceal Bleeding in Patients with Liver Cirrhosis and Portal Hypertension

Yoshihiro Sakamoto, [1)2)]MD., Kazuhiko Oho, [3)]MD.PhD., Atsushi Toyonaga,[4)]MD.PhD.,
Masafumi Kumamoto, MD.PhD.,[1)2)] Tsuyoshi Haruta,MD., Hiroto Inoue, MD., Keigo Emori, MD., Osamu Tsuruta, MD.PhD., Michio Sata,MD.PhD.

1) Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine. 2) Division of GI Endoscopy, Digestive Disease Center, Kurume University Hospital. 3) Division of Gastroenterology, Yanagawa Hospital. 4) Unit of Gastroenterology and GI Endoscopy, Yasumoto Hospital.

Corresponding author: Yoshihiro Sakamoto, MD.
Division of Gastroenterology, Department of Medicine,
Kurume University School of Medicine.
Address: 67 Asahi-machi, Kurume city,
Fukuoka-ken, 830-0011 Japan
Tel: +81-(942)-35-3311, Ext.3714
Fax: +81-(942)-34-2623
E-mail: yoshihirosakamoto3@gmai.com

Abstract

Background and Aims: Bleeding from esophageal and gastric varices is a fatal event in patients with liver cirrhosis and portal hypertension. However, the effects of *Helicobacter pylori* (*H. pylori*) infection on esophagogastric variceal bleeding are not known. The present study was aimed to elucidate the role of *H. pylori* infection in esophagogastric variceal bleeding.

Methods: The subjects were 196 cirrhotic patients who were admitted to the Kurume University Hospital to treat their esophagogastric varices consisted of 95 with acute bleeding and 101 with nonbleeding but high risk of bleeding. For the diagnosis of *H. pylori* infection, a ^{13}C-urea breath test was used, and serum pepsinogen (PG) I and II levels and the PG I/II ratio were also measured.

Results: Esophagogastric variceal bleeding was seen in 34.9% (n = 30) of the *H. pylori*-infected patients (n = 86) and in 59.1% (n = 65) of the noninfected patients (n = 110) (P < 0.0007). There was no significant difference in the infection rate between the bleeding sites of the esophagus and the stomach. The serum PG I and II levels and the PG I/II ratio were 65.6 ng/dL, 14.7 ng/dL, and 4.4, respectively, for the bleeding patients (n = 95), and 43.7 ng/dL, 17.7 ng/dL, and 3.1 for the nonbreeding patients (n = 101). Thus, the nonbreeding patients had significantly higher rate of *H. pylori* infection and lower acid secretion than bleeding patients (0.001). In addition, multivariate logistic regression analysis showed a significant negative association between *H. pylori* infection and esophagogastric variceal bleeding.

Conclusions: These results suggest that *H. pylori* infection has a protective effect against esophagogastric variceal bleeding through the induction of gastric mucosal atrophy and concomitant hypoacidity.

Introduction

Esophagogastric variceal bleeding still remains a major problem in patients with liver cirrhosis and portal hypertension. Today, it is well known that *H. pylori* infection causes histological gastritis including gastric mucosal atrophy[1,2] and primarily peptic ulcer disease.[3,4] There were the studies on relationships between *H. pylori* infection and peptic

ulcer,[5–8] chronic atrophic gastritis, portal hypertensive gastropathy,[9,10] thrombocytopenia (postinfection antibody production),[11] and hepatic encephalopathy (ammonia production caused by urease activity of *H. pylori*)[12] in the patients with liver cirrhosis and portal hypertension. However, the role of *H. pylori* infection is not well understood in variceal bleeding. Bleeding due to variceal rupture is thought to involve mucosal damage caused by *H. pylori* infection. In this context, the present study was conducted to elucidate the effect of *H. pylori* infection on esophagogastric variceal bleeding in patients with cirrhotic portal hypertension.

Methods

Study subjects. A total of 228 Japanese patients with esophagogastric varices was referred from different hospitals and treated for acute bleeding in 110 and for prophylactic purpose in 118 with red color (RC) signs[13–15] between November 2001 and December 2006 at Kurume University Hospital.

Written informed consent was obtained from all patients. No patients refrained from the treatments for emergency and prophylactic purposes. Endoscopic variceal ligation (EVL) or endoscopic injection sclerotherapy (EIS) with 5% ethanolamine oleate was performed for bleeding from esophageal varices.

Acute bleeding from gastric fundal varices was treated by endoscopic Histoacryl (n-butyl-2-cyanoacrylate [CA]; B. Braun, Melsungen, Germany) glue injection. Following the successful CA glue injection, additional balloon-occluded retrograde transvenous obliteration (B-RTO)[16] was performed for the prevention of rebleeding and recurrence of isolated fundal gastric varices with gastrorenal shunt.[17] The majority of the patients with nonbleeding but high risk for esophageal variceal bleeding was treated by EVL or EIS and for fundal gastric variceal bleeding was treated by B-RTO.[17,18]

Thirty-two patients of 15 bleeders and 17 nonbleeders were excluded from the study because of the followings: (i) patients using drugs for portal hypertension such as propranolol ($n = 5$); (ii) patients using anticancer agents or non-steroidal anti-inflammatory drugs (NSAIDs) ($n=6$); (iii) patients who had received treatment to eradicate *H. pylori* ($n = 12$); (iv) patients who had gastrectomy ($n = 5$); and (v) terminally ill patients with liver cirrhosis and hepatocellular carcinoma (HCC) ($n = 4$).

The patients on propranolol were excluded from the study because, besides *H. pylori*, the propranolol is one of the factors that could affect the history of variceal bleeding episode.

Therefore, 196 esophagogastric variceal patients with 95 bleeders and 101 nonbleeders were enrolled and retrospectively studied. Blood samples were collected from patients with acute bleeding after their condition stabilized and their biochemistry test results improved, and they were moved from the intensive care unit (ICU) to the general ward. These samples were used for evaluation.

Endoscopy. Esophagogastroduodenoscopy was performed in all patients. Two endoscopists independently evaluated the endoscopic findings of varices according to The General Rules for Recording Endoscopic Findings of Esophagogastric Varices proposed by The Japan Society for Portal Hypertension (2nd Edition).[13]

In the present study, endoscopic variceal Forms (F) were divided into two categories of large variceal Form F_2 and small variceal Form < F_2, and similarly severe RC sign RC_2 and mild RC sign < RC_2, respectively, according to the Japanese endoscopic gradings[13] of esophagogastric varices.

H. pylori ***screening***. The diagnostic accuracy of the ^{13}C-urea breath test (UBT) is > 95% in studies. The UBT is an accurate, practical, and readily available test.[19] Serology is a widely available and inexpensive noninvasive test, but the diagnostic accuracy is low (80–84%).[20]

Then, a UBT was used for the diagnosis of *H. pylori* infection, and it was generally performed at admission. For patients with acute bleeding, this test was performed after the patients were improved and moved from the ICU to the general ward. If the patients were taking proton pump inhibitor (PPI), a washout period of 2 weeks at least was used to avoid bias.[21,22]

Serum pepsinogen I and II and pepsinogen I/II ratio. Serum pepsinogen (PG) I and II levels and the PG I/II ratio were measured as indices of gastric acid secretion. The blood samples were collected for these measurements at the same time as the samples for other biochemistry tests.

Multivariate logistic regression analysis. The dependent variable was presence or absence of variceal bleeding, and the covariates were age, sex, etiology of liver cirrhosis, concurrent HCC, Child-Pugh score[23,24] variceal Form, RC sign status, *H. pylori* infection status, and presence or absence of peptic ulcer.

Statistical analysis. Results are expressed as mean SD for quantitative data. The Mann–Whitney *U*-test was used to test for significance when interval measurements were present. Comparisons between risk factors for variceal bleeding were based on univariate analysis using Pearson's χ^2 test or Fisher's exact test.

Significant predictive factors were entered into a multivariate logistic regression model and examined for the significance of the likelihood ratio using a stepwise procedure with backward elimination. All hypothesis testing was done at the 0.05 level of significance using a two-sided test. All analyses were performed using SPSS version 1.0 J (SPSS Inc., Chicago, IL, USA).

Results

Patients. There was no significant difference between the bleeding and nonbleeding groups in sex ratio, etiology of liver cirrhosis, variceal Form and RC sign, peptic ulcer, serum ammonia, hepatic functional reserve assessed by Child-Pugh score, and the number of patients with concurrent HCC except age and platelet count. In the bleeding group, the mean age was younger and the platelet count was more in number than those in nonbleeding group. HCC was a single nodule 3 cm or less and had been controlled by nonsurgical treatment such as percutaneous radiofrequency ablation mostly or percutaneous ethanol injection in both groups (Table 1).

Endoscopy. There was no significant difference in the endoscopic prevalence of peptic ulcer, variceal Form, and RC signs between the two groups of esophagogastric- variceal bleeding and nonbleeding in the patients studied (Table 1). The incidence of peptic ulcer showed no difference between the two groups of *H. pylori* infected and noninfected (Table 2). The lack of a firm association between *H. pylori* prevalence and ulcer frequency in cirrhotic patients argues against a pivotal role of *H. pylori* in the etiology of ulcers in patients with liver cirrhosis and portal hypertension.[6,7]

H. pylori ***infection rate in cirrhotic patients with esophagogastric varices.*** UBT was performed on all 196 patients with cirrhotic portal hypertension and esophagogastric varices. Among these patients, 86 were infected with *H. pylori*, resulting in an infection rate of 43.9%. There was no significant difference in the *H. pylori* infection rate by age, sex, etiology of liver cirrhosis, platelet count, variceal Form, RC sign, serum ammonia, rate of concurrent HCC, or liver functional reserve assessed by the Child-Pugh score (Table 2).

Esophagogastric variceal bleeding and **H. pylori** ***infection.*** Variceal bleeding in patients with *H.pylori* infection (Fig. 1): There was variceal bleeding in 34.9% ($n = 30$) of the *H. pylori*-infected patients ($n = 86$) and in 59.1% ($n = 65$) of the noninfected-patients ($n = 110$). Therefore, esophagogastric variceal bleeding was observed in significantly fewer patients with *H. pylori* infection than those without ($P = 0.0007$).

H. pylori infection in patients with variceal bleeding (Fig. 2): Of 95 patients with esophagogastric variceal bleeding, 31.6% ($n = 30$) were infected with *H. pylori*. Of 101 patients without bleeding,

H. pylori ***infection rate by the site of variceal bleeding.*** In the 95 patients with gastroesophageal variceal bleeding, the *H. pylori* infection rate was 36.0% ($n = 9$) for esophageal variceal bleeding, 25.8% ($n = 8$) for gastric cardiac variceal bleeding, and 33.3% ($n = 13$) for gastric fundal variceal bleeding. There was no significant difference in the infection rate by bleeding site (Fig. 3).

Serum PG level. In 196 subjects, the serum PG I and II levels and the PG I/II ratio were 65.6 ng/dL, 14.7 ng/dL, and 4.4 ng/dL, respectively, for the bleeding group ($n = 95$), and 43.7 ng/dL, 17.7 ng/dL ($P = 0.083$), and 3.1 ng/dL for the nonbleeding group ($n = 101$). There was a significant difference in the PG I level ($P < 0.001$) but not in the PG II level ($P = 0.083$). The PG I/II ratio was significantly higher in the bleeding group than the nonbleeding group ($P < 0.001$) (Fig. 4). Therefore, the patients with esophagogastric variceal bleeding had significantly more gastric acid secretion.

Multyivariate logistic regression analysis. To examine whether the prognostic significance of *H. pylori* infection, variceal Form and variceal RC sign was independent

of the other factors, a multivariate logistic regression analysis was carried out and we found that the prognostic parameters of those three were independent risk factors of variceal bleeding. However, *H. pylori* infection was negative risk factor for esophagogastric variceal bleeding (Table 3).

Discussion

The following risk factors have been reported for bleeding because of esophagogastric variceal rupture. The systemic factors are hepatic functional reserve, ascites, concurrent HCC, endotoxemia, and stress.[25] The local factors are esophagitis, peptic erosion or ulcer, variceal size and RC sign,[13,14,25] alcohol, use of an NSAID, or anticancer agent.

The hemodynamic factors are portal pressure exceeding 12 mm Hg,[26,27] and high intravariceal pressure with variceal wall tension (LaPlace equation[28]). However, there has not been any report on the relationship between *H. pylori* infection and variceal bleeding. In gastric mucosa of patients with liver cirrhosis and portal hypertension, there is portal hypertensive gastropathy including a decrease in blood flow,[29] prostaglandin E2 synthesis,[30] potential difference,[31] and mucus secretion.[32,33] Consequently, gastric mucosa weakens and tends to be easily injured.

We initially speculated that when inflammation from *H. pylori* infection is added to the surface mucosa of varices, mucosal breaks can occur easily and become a trigger for variceal bleeding.[1,7] However, the incidence of esophagogastric variceal bleeding was significantly lower than expected in patients infected with *H. pylori*. In other words, our results indicate that *H. pylori* infection has a protective effect and not a promotive effect on variceal bleeding. Our results also show that there is no difference in the *H. pylori* infection rate between the bleeding sites of the esophagus and the stomach. It means that the incidence of esophageal variceal bleeding is also low in the *H. pylori*-infected patients. Some investigators have found that a vast majority of the esophageal variceal bleeding was at the distal esophagus near the esophagogastric junction,[34] and that patients with esophageal varices have a decreased esophageal acid clearance.[35,36] From a viewpoint of acidrelated concerns, it has been reported that the prevalence of *H. pylori* infection is significantly lower in patients with than without gastroesophageal reflux disease.[37] In addition, another report has found that *H. pylori* infection inhibits reflux

esophagitis by inducing atrophic gastritis.[38] These findings suggest that gastric acid is possibly involved in esophageal bleeding because of variceal rupture. However, further studies are necessary to examine the effects of gastroesophageal reflux and esophageal motility dysfunction on bleeding because of esophageal variceal rupture in patients with no history of endoscopic treatment for varices.[39,40]

It is well known that *H. pylori* infection can cause chronic atrophic gastritis.[1,2] Gastric mucosal atrophy is progressive and decreases gastric acid secretion in patients with chronic *H. pylori* infection. Serum PG is a biochemical index of gastric acid secretory capacity.[41,42] PG I level reflects acid secretion of the gastric corpus and PG II level mainly reflects acid secretion of the entire stomach. In the present study, the PG I level and the PG I/II ratio, which were serum markers for gastric atrophy, were significantly lower for the nonvariceal bleeding group. Then, it can be suggested that patients with lower acid secretion caused by *H. pylori* infection had significantly lower incidence of variceal bleeding.

Iijima *et al*.[43,44] examined PG as a biomarker and found that gastric acid secretion was lower in the *H. pylori* positive patients, and that eradication of *H. pylori* resulted in recovery of gastric acid secretion. Based on the results of the present study, it is suggested that the chronic atrophic gastritis progressed because of chronic *H. pylori* infection and the total serum PG level and the PG I/II ratio decreased. These results involved decrease in gastric acid secretion via chronic atrophic gastritis, particularly corpus gastritis,[45] in *H. pylori*-infected patients.

Therefore, normal acid secretory capacity in patients without *H. pylori* infection can be a relatively aggressive factor for mucosa on varices in patients with cirrhotic portal hypertension. Consequently, *H. pylori* infection is considered to be a protective factor against esophagogastric variceal bleeding by decreasing gastric acid secretion.

In addition, a multivariate logistic regression analysis showed that *H. pylori* infection was a negative risk factor of esophagogastric variceal bleeding. Conclusively the patients with *H.pylori* infection have significantly lower incidence of esophagogastric variceal bleeding.

J. Hart *et al*.[46] reported that aspirin-induced gastric erosion was inhibited in *H. pylori*-infected patients. R. Nishiki *et al*.[34] showed that the frequency of esophageal variceal bleeding was significantly lowered by long-term use of PPI. It should be noted that "The long-term administration of PPI reduces treatment failures such as rebleeding after esophageal band ligation" was reported with a randomized, controlled trial by Hidaka *et al*.[47] The results of these reports, in part, support our results.

In our study, it was suggested that gastric acid was more closely involved in esophagogastric variceal bleeding than inflammation from *H. pylori* infection. Therefore, strong inhibitors of gastric acid secretion such as PPI might effectively inhibit esophagogastric variceal bleeding. However, there are still important questions which need to be answered. How effective is *H. pylori* infection as a protective factor against esophagogastric variceal bleeding? If *H. pylori* infection has a protective effect, what are the pros and cons of *H. pylori* eradication in cirrhotic patients with esophagogastric varices? A large series of prospective randomized controlled study is necessary to examine this point.

In summary, the present study clearly demonstrated that the frequency of esophagogastric variceal bleeding was significantly lower in patients with *H. pylori* infection than those without.

Thus, our results suggest that *H. pylori* infection has a protective effect against esophagogastric variceal bleeding through the induction of atrophic gastritis and concomitant hypoacidity in patients with liver cirrhosis and portal hypertension.

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Figure legends

Figure 1. Esophagogastric variceal bleeding in patients with and without *H. pylori* infection(n=196).

Esophagogastric variceal bleeding was seen in 34.9% (n=30) of the *H. pylori* infected patients but in 59.1% (n=65) of the non-infected patients. The infected patients had significantly lower incidence of esophagogastric variceal bleeding ($p< 0.0007$).

Figure 2. *H. pylori* infection in patients with and without esophagogastric variceal bleeding(n=196).

H. pylori infection was detected in 31.6% (n=30) of the patients with esophagogastric variceal bleeding and in 55.4% (n=56) of the patients without bleeding. The non-bleeding patients had significantly higher *H. pylori* infection rate ($p<0.001$).

Figure 3. *H. pylori* infection and site of esophagogastric variceal bleeding(n=95).

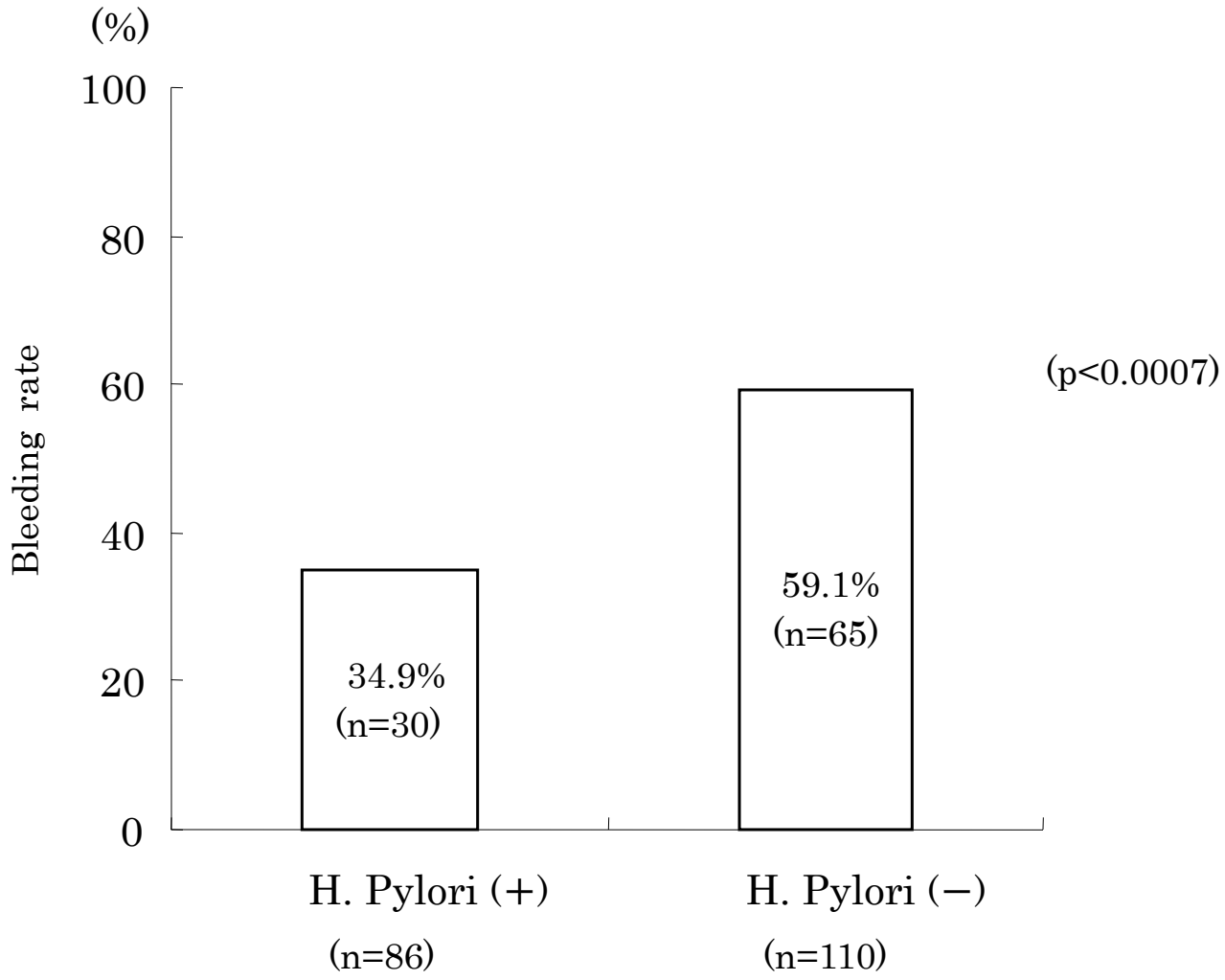
When the *H. pylori* infection rate was examined by the site of esophagogastric variceal bleeding, there was no significant difference in the infection rate among the three bleeding sites of esophagus, gastric cardia, and gastric fundus($p<0.001$).

Figure 4. Serum PG Ⅰ, PGⅡ and PG Ⅰ/Ⅱ ratio in patients with and without esophagogastric variceal bleeding(n=196).

Gastric acid secretion was examined using serum pepsinogen as a biomarker. Serum pepsinogen level was, in turn, examined by the presence or absence of esophagogastric variceal bleeding. The PG Ⅰ level and PG Ⅰ/Ⅱ ratio were significantly higher in bleeding group, which means higher gastric acid secretion in patients with esophagogastric variceal bleeding. In other words, the non-bleeding group had significantly lower acid secretion compared to the bleeding group($p<0.001$).

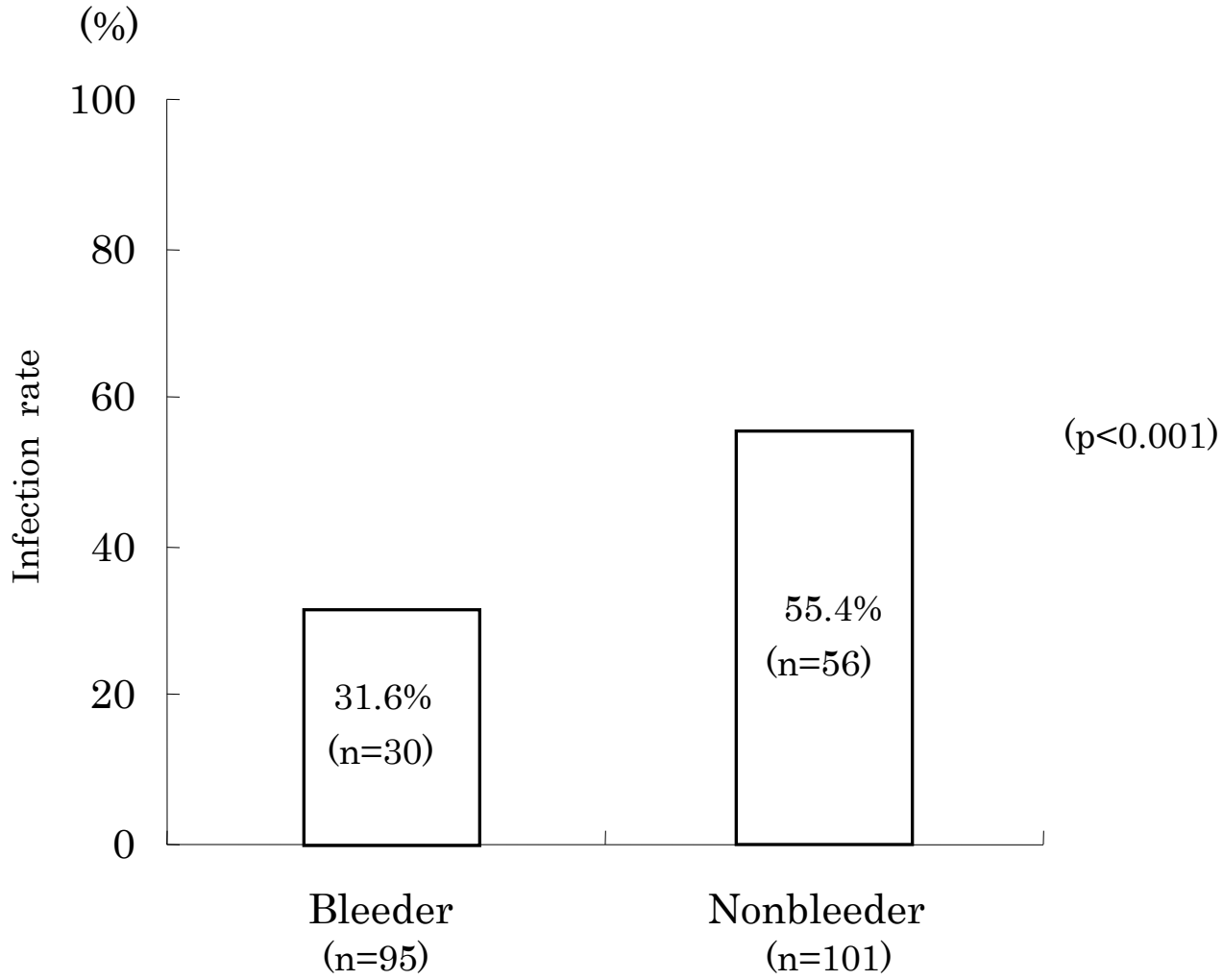
PG, pepsinogen.

Figure 1. Esophagogastric variceal bleeding in patients with and without *H. pylori* infection(n=196)



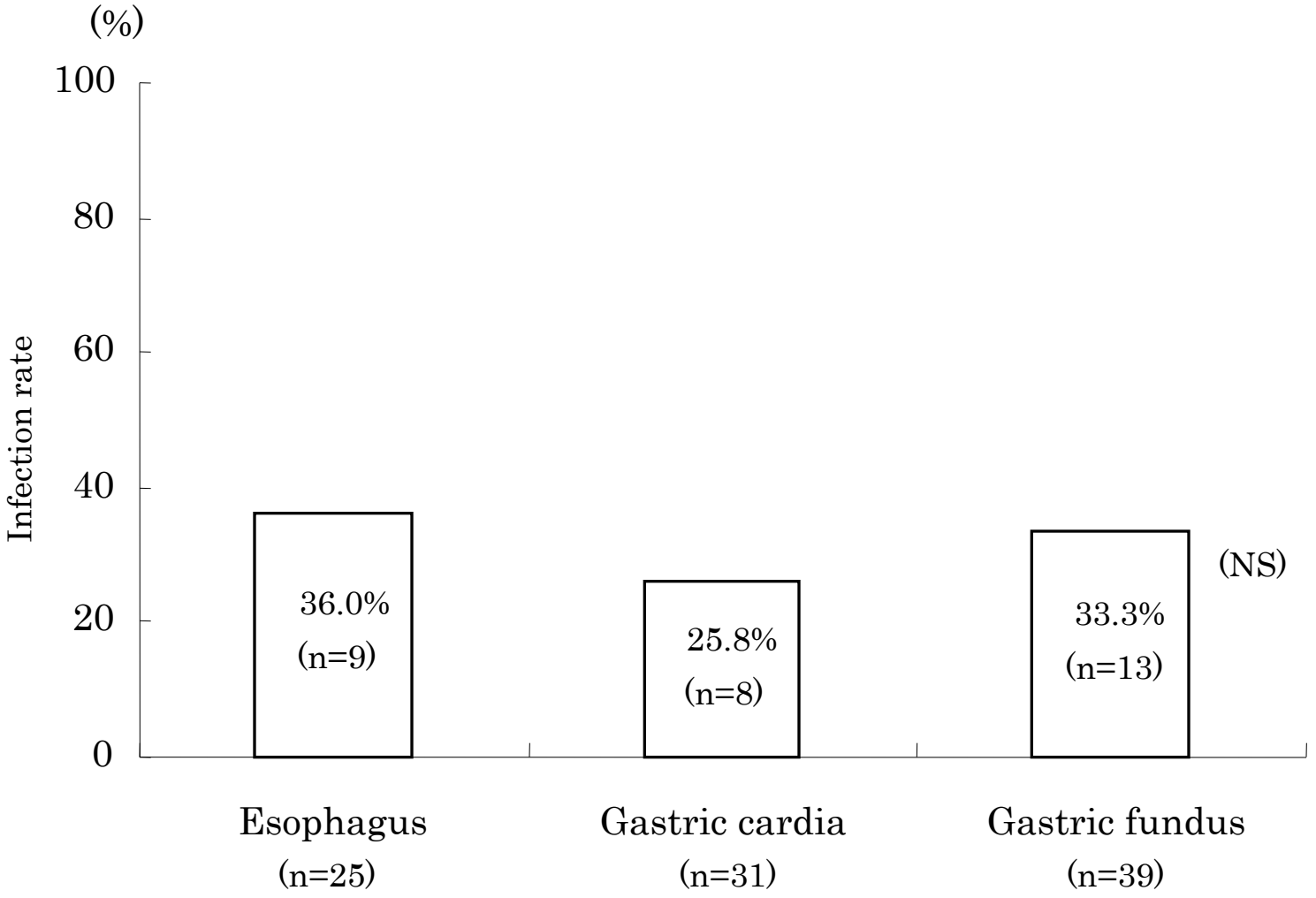
H. pylori, helicobacter pylori.

Figure 2. *H. pylori* infection in patients with and without esophagogastric variceal bleeding (n=196)



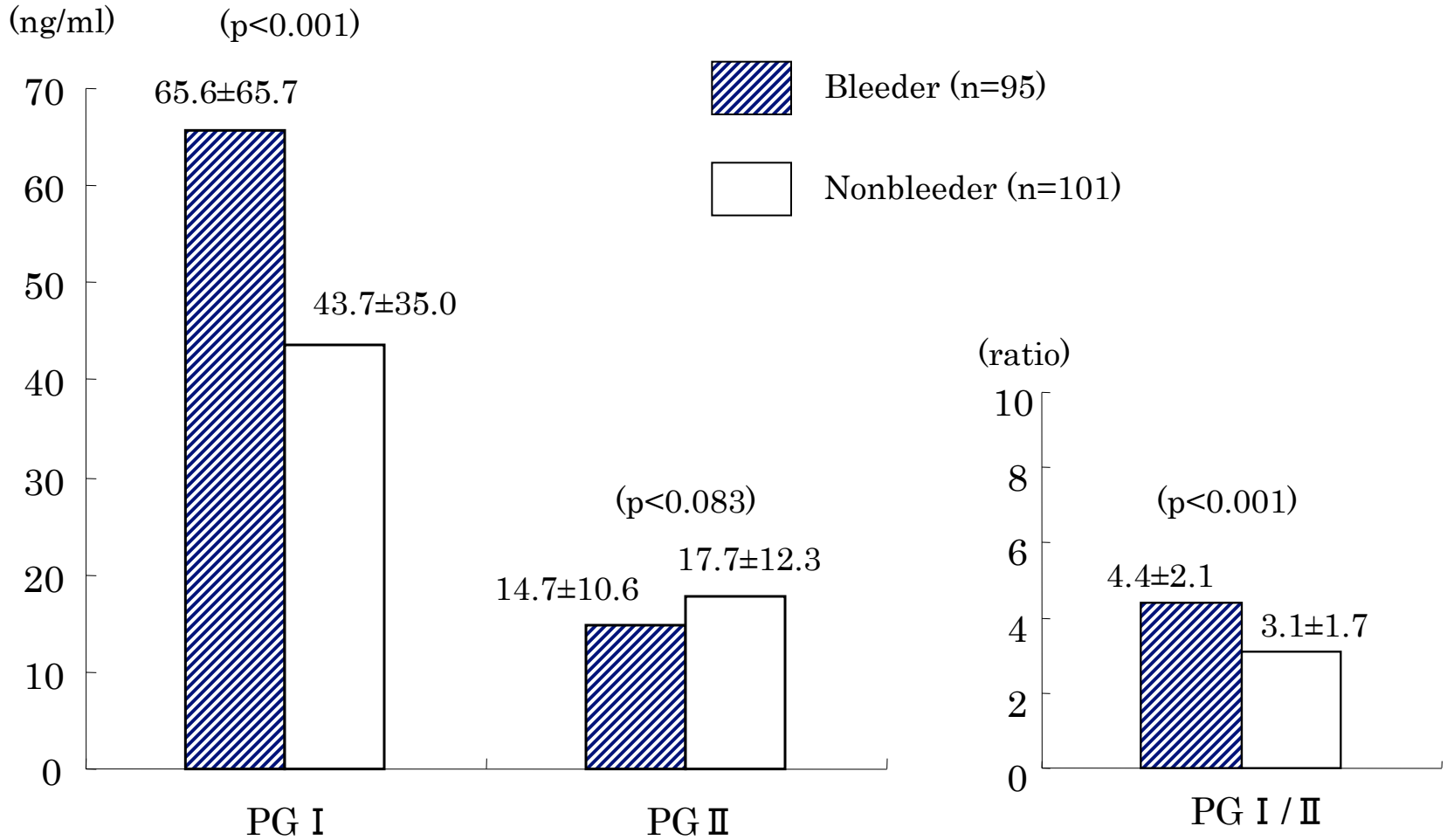
H. pylori, helicobacter pylori.

Figure 3. *H. pylori* infection and site of esophagogastric variceal bleeding (n=95)



H. pylori, helicobacter pylori. NS, not significant.

Figure 4. Serum PG Ⅰ and Ⅱ levels and PG Ⅰ/Ⅱ ratio in patients with and without esophagogastric variceal bleeding (n=196)



PG, pepsinogen

Table 1. Characteristics of patients studied (n=196)

	Variceal Bleeding		P
	Yes	No	
Number of patients	95	101	
Mean age, year±SD	61.6±10.4	64.4±8.9	P<0.025
Sex , male	53	63	NS
Etiology of cirrhosis			
HCV 138	67	71	NS
HBV 31	15	16	NS
Alcohol 18	8	10	NS
Others 9	5	4	NS
Platelet count ($\times 10^4/mm^3$)	8.4±4.0	7.1±2.9	P<0.001
Variceal Form (Small/Large)	14/81	15/86	NS
Red Color sign (Mild/Severe)	23/72	25/76	NS
Peptic ulcer	8	9	NS
NH_3 (μmol/dL)	63.4±31.1	63.2±30.5	NS
Child-Pugh score	6.6±1.5	6.4±1.5	NS
HCC nonsurgically controlled	6	6	NS

HCV, hepatitis C virus. HBV, hepatitis B virus. NH_3, serum ammonia.
HCC, hepatocellular carcinoma. NS , not significant.

Table 2. *H. pylori* infection in patients with esophagogastric varices (n=196)

	H. pylori infection		P
	(+)	(−)	
Number of patients	86	110	
Mean age, year ± SD	64.7±8.5	62.5±10.8	NS
Sex, male	47	69	NS
Etiology of liver cirrhosis			
HCV 138	62	76	NS
HBV 31	14	17	NS
Alcohol 18	7	11	NS
Others 9	3	6	NS
Platelet count ($\times 10^4/mm^3$)	8.3±3.1	7.6±4.2	NS
Variceal Form (Small/Large)	19/67	21/80	NS
Red Color sign (Mild/Severe)	27/59	29/89	NS
Peptic ulcer	9	8	NS
NH_3 (μmol/dL)	66.8±34.2	60.3±27.5	NS
Child-Pugh score	6.5±1.4	6.5±1.5	NS
HCC nonsurgically controlled	6	6	NS

H. pylori, helicobacter pylori. HCV, hepatitis C virus. HBV, hepatitis B virus. NH_3, serum ammonia . HCC, hepatocellular carcinoma. NS, not significant.

Table 3. Esophagogastric variceal bleeding *and H. pylori* infection

— Multivariate logistic regression analysis —

Dependent variable : Presence or absence of variceal bleeding

Covariate : Age, sex, etiology of cirrhosis, association of HCC, Child-Pugh score, variceal Form, variceal RC sign, *H. pylori* infection, and peptic ulcer

	P value	Odds ratio	95% Confidence interval
Large variceal Form	0.001	1.832	1.229 – 2.584
Positive *H. pylori*	0.019	0.475	0.255 – 0.886
Severe RC sign	0.046	1.979	1.013 – 3.864

H. pylori, helicobacter pylori. HCC, hepatocellular carcinoma. RC, red color.