Prognostic factors associated with mortality in patients with gastric fundal variceal bleeding

Keishi Komori, Masaru Kubokawa, Eikichi Ihara, Kazuya Akahoshi, Kazuhiko Nakamura, Kenta Motomura, Akihide Masumoto

AIM
To determine the prognostic factors associated with mortality in patients with gastric fundal variceal (GFV) bleeding.

METHODS
In total, 42 patients were endoscopically diagnosed with GFV bleeding from January 2000 to March 2014. We retrospectively reviewed the patients' medical records and assessed their history, etiology of liver cirrhosis, disease conditions, treatment options for GFV bleeding, medications administered before and after onset of GFV bleeding, blood test results (hemoglobin, albumin, and bilirubin concentrations), and imaging results (including computed tomography and abdominal ultrasonography). We also assessed the prognostic factors associated with short-term mortality (up to 90 d) and long-term mortality in all patients.
RESULTS
Multivariate analysis showed that prophylactic administration of antibiotics was an independent prognostic factor associated with decreases in short-term mortality (OR = 0.08, 95% CI: 0.01-0.52) and long-term mortality (OR = 0.27, 95% CI: 0.08-0.91) in patients with GFV bleeding. In contrast, concurrent hepatocellular carcinoma (HCC) and regular use of proton pump inhibitors (PPI) were independent prognostic factors associated with increases in short-term mortality (HCC: OR = 15.4, 95% CI: 2.08-114.75; PPI: OR = 12.76, 95% CI: 2.13-76.52) and long-term mortality (HCC: OR = 7.89, 95% CI: 1.98-31.58; PPI: OR = 10.91, 95% CI: 2.86-41.65) in patients with GFV bleeding. The long-term overall survival rate was significantly lower in patients who regularly used PPI than in those who did not use PPI ($p = 0.0074$).

CONCLUSION
Administration of antibiotics is associated with decreased short- and long-term mortality, while concurrent HCC and regular PPI administration are associated with increased short- and long-term mortality.

Key words: Antibiotics; Gastric varices; Gastric fundus; Proton pump inhibitors; Hemorrhage

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Core tip: Bleeding from gastric fundal varices is associated with high mortality. This study aimed to clarify the prognostic factors associated with short- and long-term mortality of patients with gastric fundal variceal (GFV) bleeding and, in particular, to determine the effect of prophylactic antibiotic administration on the outcome in patients with GFV bleeding. Antibiotic administration was associated with decreases in short- and long-term mortality in patients with GFV bleeding; concurrent hepatocellular carcinoma and use of a proton pump inhibitor were independent factors associated with an increase in short- and long-term mortality.

INTRODUCTION
Gastric varices occur in 20% to 60% of patients with portal hypertension[1,2], and the incidence of acute bleeding in patients with gastric varices reportedly ranges from 3% to 36%[2,3]. Although the incidence of gastric variceal bleeding is lower than that of esophageal variceal bleeding, gastric variceal bleeding is much more life-threatening. In particular, gastric fundal variceal (GFV) bleeding is a serious condition associated with high mortality[1,4]. Thus, it is important to determine the prognostic factors associated with mortality in patients with GFV bleeding and the risk factors for GFV bleeding, which have not been previously evaluated[1,2,4]. In contrast, risk factors for esophageal variceal bleeding have been investigated in several prospective trials; an increased risk of esophageal variceal bleeding is associated with a high Child-Pugh classification, increased variceal size, and the presence of red wale markings, while the risk of esophageal variceal bleeding is decreased in patients taking beta blockers[5,6].

Approximately 20% of patients with cirrhosis who develop acute variceal bleeding are affected by subsequent bacterial infections within 48 h after the onset of bleeding[7]. However, whether prophylactic administration of antibiotics to patients with GFV bleeding is associated with a decreased risk of rebleeding and/or decreased mortality is controversial[7,9].

We performed this retrospective study to identify the prognostic factors associated with mortality in patients with GFV bleeding and to determine whether prophylactic administration of antibiotics positively affects patients with GFV bleeding.

MATERIALS AND METHODS

Patient characteristics
This retrospective study included 42 patients (29 males, 13 females; mean age, 64.9 years; range, 48-82 years) endoscopically diagnosed with GFV bleeding from January 2000 to March 2014. The patients had either type 2 gastroesophageal varices or type 1 isolated gastric varices based on the classification developed by Sarin et al.[1]. We retrospectively reviewed the patients’ medical records and assessed their history, etiology of liver cirrhosis, disease conditions, treatment options for GFV bleeding, medications administered before and after onset of GFV bleeding, blood test results (hemoglobin, albumin, and bilirubin concentrations), and imaging results (including computed tomography and abdominal ultrasonography). Whether prophylactic antibiotics should be administered to patients with GFV bleeding is still controversial; therefore, the decision regarding whether to administer prophylactic antibiotics was made by the attending doctors in our hospital. In total, 23 of 42 patients were administered intravenous prophylactic antibiotics within
48 h after the onset of GFV bleeding. We determined the prognostic factors associated with short- and long-term mortality in all patients with GFV bleeding. Short-term mortality was calculated as the death rate up to 90 d after the onset of GFV bleeding, while long-term mortality was calculated as the overall death rate. Rebleeding was defined as recurrence of GFV bleeding within 90 d after the initial treatment.

Statistical analysis
The Kaplan-Meier method, log-rank test, and Breslow test were used for survival analyses. Cox regression analysis was used to analyze prognostic factors for mortality. Parameters with P values of < 0.10 in the univariate analysis were included in the multivariate analyses. Student’s t-test was used to compare variables between two groups, and Fisher’s exact test was used to compare two categorical variables. All statistical analyses were performed using SPSS version 12.0 (SPSS Inc., Chicago, IL). A P value of < 0.05 was considered statistically significant.

Table 1  Baseline demographics and characteristics of patients with gastric fundal variceal bleeding

| Parameters                                                                 | n (%)                               |
|---------------------------------------------------------------------------|-------------------------------------|
| Sex ratio (F/M)                                                            | 13/29                               |
| Mean age (yr)                                                              | 64.9 ± 11.6                         |
| Mean follow-up period (d)                                                 | 631 ± 109.6                         |
| History                                                                   |                                     |
| Smoking (presence/absence)                                                | 21/21 (50)                          |
| Alcohol (presence/absence)                                                | 20/22 (47.6)                        |
| Disease conditions                                                        |                                     |
| Child-Pugh classification (A/B/C)                                         |                                      |
| Hepatocellular carcinoma (presence/absence)                               | 14/28 (33.3)                        |
| Hepatic encephalopathy (presence/absence)                                 | 6/36 (14.3)                         |
| Form of gastric fundal varices (F1-F2/F3)                                 | 4/38                                 |
| Concurrent esophageal varices (presence/absence)                          | 30/12 (71.4)                        |
| Previous treatment of gastric varices (presence/absence)                  | 1/41 (2.4)                          |
| Etiology of liver cirrhosis                                               |                                     |
| Hepatitis B                                                               | 5 (11.9)                            |
| Hepatitis C                                                               | 18 (42.9)                           |
| Alcoholic                                                                 | 12 (28.6)                           |
| Others                                                                    | 7 (16.6)                            |
| Treatment of gastric fundal varices                                       |                                     |
| Success of initial treatment (total success/total failure)                | 39/3 (92.9)                         |
| Endoscopic treatment (EIS) (success/failure)                              | 30/1 (96.7)                         |
| Nonendoscopic treatment (success/failure)                                 | 8/1 (11.1)                          |
| Not applicable                                                            | 1/1 (50)                            |
| Antibiotics (presence/absence)                                            | 23/19 (54.8)                        |
| Blood transfusion (presence/absence)                                      | 38/4 (90.5)                         |
| Rebleeding after initial treatment (presence/absence)                     | 10/32 (23.8)                        |
| Medications administered before admission                                 |                                     |
| NSAIDs (presence/absence)                                                 | 5/37 (11.9)                         |
| Anticoagulants (presence/absence)                                         | 1/41 (2.4)                          |
| Proton pump inhibitors (presence/absence)                                 | 14/28 (33.3)                        |
| Blood test results                                                        | 1/1 (50)                            |
| Hemoglobin (g/dL)                                                         | 8.7 ± 1.8                           |
| Albumin (g/dL)                                                            | 2.54 ± 0.44                         |
| Bilirubin (mg/dL)                                                         | 1.98 ± 1.44                         |

Results are presented as mean ± SEM, if applicable. EIS: Endoscopic injection sclerotherapy; NSAIDs: Non-steroidal anti-inflammatory drugs.

RESULTS

Demographic and clinical characteristics of patients
The baseline demographic and clinical characteristics of patients with GFV bleeding included in the present study are summarized in Table 1. All patients developed GFV bleeding as a complication of liver cirrhosis, the etiology of which was hepatitis B (n = 5), hepatitis C (n = 18), alcoholic liver cirrhosis (n = 12), and other etiologies including nonalcoholic steatohepatitis and primary biliary cirrhosis (n = 7). The preserved liver function was assessed according to the Child-Pugh classification[10], 4 patients were classified as grade A, 20 as grade B, and 18 as grade C. Fourteen patients had concurrent hepatocellular carcinoma (HCC). With respect to the initial hemostatic procedure for GFV bleeding, endoscopic injection sclerotherapy with cyanoacrylate glue was performed in 31 patients, and nonendoscopic treatments including balloon-occluded retrograde transvenous obliteration and simple intubation with a Sengstaken-Blakemore tube were performed in 9 patients (of whom success was achieved in 8). No hemostatic procedures could be applied to two patients because of their very poor general condition. Thirty-eight patients underwent blood transfusion. Rebleeding occurred in 10 patients, all of whom underwent a second hemostatic procedure (endoscopic injection sclerotherapy in 8 patients, balloon-occluded retrograde transvenous obliteration in 1, and surgical treatment in 1). The mean hemoglobin, albumin, and bilirubin concentrations were 8.70 ± 1.80, 2.54 ± 0.44, and 1.98 ± 1.40 mg/dL, respectively. Oral medications administered before admission included proton pump inhibitors (PPI) (n = 14 patients), nonsteroidal anti-inflammatory drugs (n = 5 patients), and anticoagulants (n = 1 patient). As for PPI, either lansoprazole (15 mg or 30 mg o.m.) or omeprazole (10 mg o.m.) was administered continuously for at least 1 mo by the primary doctors. In contrast, intravenous antibiotics including ciprofloxacin (n = 8), cefazolin sodium (n = 5), cefmetazole sodium (n = 5), ceftriaxone sodium (n = 4), and sulbactam/amoxicillin (n = 1) were administered to 23 patients for 3 to 4 d within 48 h after the onset of GFV bleeding to prevent infection after the hemostatic procedure according to the attending doctors in our hospital.

Prognostic factors associated with short-term mortality in patients with GFV bleeding
We performed a univariate analysis to determine which prognostic factors were associated with short-
term mortality in patients with GFV bleeding. The success of the initial treatment and administration of antibiotics were associated with decreased short-term mortality, while concurrent HCC, regular use of PPI, and rebleeding were associated with increased short-term mortality (Table 2). In the multivariable analysis, prophylactic administration of antibiotics was an independent prognostic factor for decreased short-term mortality, while concurrent HCC and regular use of PPI were independent prognostic factors for increased short-term mortality (Table 2).

**Prognostic factors associated with long-term mortality in patients with GFV bleeding**

Similarly to the results for short-term mortality, univariate analysis revealed that the success of the initial treatment was associated with decreased long-term mortality, while concurrent HCC, the Child-Pugh classification (C vs B vs A), regular use of PPI, and rebleeding were associated with increased long-term mortality (Table 3). An elevated bilirubin concentration and nonsteroidal anti-inflammatory drug use tended to be associated with increased long-term mortality; however, these associations were not statistically significant (Table 3). Univariate analysis revealed a tendency for prophylactic administration of antibiotics to be associated with decreased long-term mortality. Multivariable analysis indicated that prophylactic administration of antibiotics was an independent prognostic factor for decreased long-term mortality, while the presence of concurrent HCC and regular use of PPI were independent prognostic factors for increased long-term mortality (Table 3). Multivariate analysis did not identify either the bilirubin concentration or nonsteroidal anti-inflammatory drug use as a prognostic factor for mortality. Interestingly, regular use of PPI was an independent prognostic factor associated with increases in both short- and long-term mortality, whereas prophylactic administration of antibiotics was an independent prognostic factor associated with decreases in both short- and long-term mortality.

**Effects of prophylactic administration of antibiotics on mortality in patients with GFV bleeding**

We performed a subanalysis to assess whether prophylactic administration of antibiotics was associated with decreased mortality in patients with GFV bleeding. The 42 patients were divided into two groups: the antibiotic group (n = 23) and the nonantibiotic group (n = 19). There were no significant differences in the baseline demographics or characteristics of the antibiotic and nonantibiotic groups (Table 4). The survival curves of both groups are shown in Figure 1; there was no statistically significant difference between the two groups (P = 0.071).

**Effects of regular PPI use on mortality in patients with GFV bleeding**

We performed a subanalysis to assess whether regular PPI use was associated with increased mortality in patients with GFV bleeding. Regular PPI use was associated with increased mortality in patients with GFV bleeding, whereas prophylactic administration of antibiotics was associated with decreased mortality in patients with GFV bleeding. The 42 patients were divided into two groups: the PPI group (n = 19) and the non-PPI group (n = 23). There were no significant differences in the baseline demographics or characteristics of the PPI and non-PPI groups (Table 4). The survival curves of both groups are shown in Figure 1; there was no statistically significant difference between the two groups (P = 0.071).

Table 2  Factors associated with 90-d mortality related to gastric fundal variceal bleeding

| Parameters                                      | Univariate analysis | Multivariate analysis |
|-------------------------------------------------|---------------------|-----------------------|
|                                                  | β       | P value | R | HR (95%CI) | β | P value | R | HR (95%CI) |
| Sex (M/F)                                       | 0.2393 | 0.7354 | 0 | 1.27 (0.32-5.09) |   |         |   |           |
| Age (yr)                                        | 0.0291 | 0.3215 | 0 | 1.03 (0.97-1.09) |   |         |   |           |
| History                                         |         |         |   |           |   |         |   |           |
| Smoking                                         | 0.5698 | 0.4208 | 0 | 1.77 (0.44-7.08) |   |         |   |           |
| Alcohol                                         | 0.1163 | 0.8624 | 0 | 0.89 (0.24-3.32) |   |         |   |           |
| Disease conditions                              |         |         |   |           |   |         |   |           |
| Child-Pugh classification (C/B/A)               | 0.7513 | 0.1991 | 0 | 2.12 (0.67-6.67) |   |         |   |           |
| Hepatocellular carcinoma                       | 1.6422 | 0.0209 | 0.23 | 5.17 (1.28-20.8) | 2.3041 | 0.0092 | 0.28 | 10.01 (1.77-56.74) |
| Hepatic encephalopathy                         | 0.8163 | 0.3115 | 0 | 2.26 (0.47-10.99) |   |         |   |           |
| Form of GFV (F2 or F3/F1)                      | −0.263 | 0.8046 | 0 | 0.77 (0.10-6.16) |   |         |   |           |
| Concurrent esophageal varices                   | −0.233 | 0.7422 | 0 | 0.79 (0.20-3.17) |   |         |   |           |
| Etiology of liver cirrhosis (non-viral/viral)   | −1.215 | 0.1302 | −0.07 | 0.30 (0.06-1.43) |   |         |   |           |
| Treatment of GFV                                |         |         |   |           |   |         |   |           |
| Success of initial treatment                    | −2.176 | 0.0081 | −0.28 | 0.11 (0.02-0.57) |   |         |   |           |
| Initial treatment (non-EIS/EIS/none)            | 0.0253 | 0.9726 | 0 | 1.03 (0.24-4.36) |   |         |   |           |
| Antibiotics                                      | −1.637 | 0.0413 | −0.18 | 0.19 (0.04-0.94) | −2.5412 | 0.0086 | −0.28 | 0.08 (0.01-0.52) |
| Blood transfusion                               | 3.1861 | 0.4892 | 0 | 1.96 (0.32-14.68) |   |         |   |           |
| Rebleeding after initial treatment              | 1.5956 | 0.0177 | 0.24 | 4.94 (1.32-18.42) |   |         |   |           |
| Medications before admission                    |         |         |   |           |   |         |   |           |
| NSAIDs                                          | 0.5802 | 0.4697 | 0 | 1.79 (0.37-8.61) |   |         |   |           |
| Proton pump inhibitors                          | 1.5316 | 0.0306 | 0.2 | 4.63 (1.15-18.53) | 2.5465 | 0.0053 | 0.29 | 12.76 (2.13-76.52) |
| Blood test results                              |         |         |   |           |   |         |   |           |
| Hemoglobin (g/dL)                               | −0.012 | 0.9458 | 0 | 0.99 (0.70-1.39) |   |         |   |           |
| Albumin (g/dL)                                  | −1.429 | 0.0951 | −0.11 | 0.24 (0.04-1.28) |   |         |   |           |
| Bilirubin (mg/dL)                               | 0.1916 | 0.3572 | 0 | 1.21 (0.81-1.82) |   |         |   |           |

1P < 0.05. Hazard risk ratios were calculated using a Cox proportional hazard model. HR: Hazard risk ratio; GFV: Gastric fundal varices; EIS: Endoscopic injection sclerotherapy; NSAIDs: Nonsteroidal anti-inflammatory drugs.
patients with GFV bleeding. The 42 patients were divided into 2 groups: the non-PPI group (n = 28) and the PPI group (n = 14). The serum albumin concentration in the non-PPI group was significantly higher than that in the PPI group (Table 5). The survival curves of both groups are shown in Figure 2; the overall survival rate in the non-PPI group was significantly higher than that in the PPI group (P = 0.0074).

**DISCUSSION**

Gastric varices are classified based on their location within the stomach and their relationship with esophageal varices. The most common type of gastric varices

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**Table 3** Factors associated with overall survival related to gastric fundal variceal bleeding

| Parameters                              | Univariate analysis | Multivariate analysis |
|-----------------------------------------|---------------------|-----------------------|
|                                         | \( \beta \)         | \( R \)               | \( HR (95\%CI) \)       | \( \beta \)         | \( P \) value | \( R \)               | \( HR (95\%CI) \)       |
| Sex (F/M)                               | 0.1107              | 0.8404                | 0.12 (0.38-3.28)        | 0.1507              | 0.5056       | 0.98 (0.94-1.03)       |
| Age (yr)                                | 0.0152              | 0.5056                | 1.76 (0.60-5.18)        | 0.3031              | 0.5991       | 1.35 (0.49-3.74)       |
| History                                 | 0.3076              | 0.5991                | 1.35 (0.49-3.74)        | 0.3031              | 0.5991       | 1.35 (0.49-3.74)       |
| Disease conditions                      |                     |                       |                        |                    |              |                       |
| Child-Pugh classification (C/B/A)       | 0.9924              | 0.0366                | 1.12 (0.38-3.28)        | 1.12 (0.38-3.28)    | 0.0366       | 2.70 (1.06-6.84)       |
| Hepatocellular carcinoma                | 1.8351              | 0.0013                | 6.27 (2.05-19.17)       | 2.0666              | 0.0035       | 7.89 (1.98-31.58)      |
| Hepatic encephalopathy                  | 0.5089              | 0.4391                | 1.66 (0.46-6.04)        | 0.5089              | 0.4391       | 1.66 (0.46-6.04)       |
| Form of GFV (F2 or F3/F1)               | 0.3475              | 0.7379                | 1.42 (0.18-10.85)       | 0.3475              | 0.7379       | 1.42 (0.18-10.85)      |
| Concurrent esophageal varices           | −0.098              | 0.8596                | 0.91 (0.31-2.67)        | −0.098              | 0.8596       | 0.91 (0.31-2.67)       |
| Etiology of liver cirrhosis (non-viral/viral) | −0.086              | 0.8688                | 0.92 (0.33-2.54)        | −0.086              | 0.8688       | 0.92 (0.33-2.54)       |
| Treatment of GFV                        | −2.176              | 0.0281                | 0.11 (0.02-0.57)        | −2.176              | 0.0281       | 0.11 (0.02-0.57)       |
| Initial treatment (non-EIS/EIS/none)    | 0.0390              | 0.9096                | 1.05 (0.32-3.50)        | 0.0390              | 0.9096       | 1.05 (0.32-3.50)       |
| Antibiotics                             | −0.81               | 0.0512                | 0.44 (0.16-1.25)        | −0.81               | 0.0512       | 0.44 (0.16-1.25)       |
| Blood transfusion                       | 0.5432              | 0.0612                | 1.72 (0.22-13.18)       | 0.5432              | 0.0612       | 1.72 (0.22-13.18)      |
| Rebleeding after initial treatment      | 1.3669              | 0.0087                | 3.92 (1.41-10.89)       | 1.3669              | 0.0087       | 3.92 (1.41-10.89)      |
| Medications administered before admission |                     |                       |                        |                    |              |                       |
| NSAIDs                                  | 1.0131              | 0.0877                | 2.75 (0.86-8.81)        | 1.0131              | 0.0877       | 2.75 (0.86-8.81)       |
| Proton pump inhibitors                  | 1.4012              | 0.0084                | 4.06 (1.43-11.52)       | 1.4012              | 0.0084       | 4.06 (1.43-11.52)      |
| Blood test results                      | −0.062              | 0.6398                | 0.94 (0.72-1.22)        | −0.062              | 0.6398       | 0.94 (0.72-1.22)       |
| Hemoglobin (g/dL)                       | −0.181              | 0.0915                | 0.34 (0.10-1.19)        | −0.181              | 0.0915       | 0.34 (0.10-1.19)       |
| Albumin (g/dL)                          | 0.3065              | 0.0514                | 1.36 (0.99-1.85)        | 0.3065              | 0.0514       | 1.36 (0.99-1.85)       |
| Bilirubin (mg/dL)                       | −0.062              | 0.6398                | 0.94 (0.72-1.22)        | −0.062              | 0.6398       | 0.94 (0.72-1.22)       |

\( ^1 P < 0.05 \). Hazard risk ratios calculated using a Cox proportional hazard model. GFV: Gastric fundal varices; EIS: Endoscopic injection sclerotherapy; NSAIDs: Nonsteroidal anti-inflammatory drugs.

**Figure 1** Overall survival of patients with gastric fundal variceal bleeding who received prophylactic antibiotics within 48 h after admission (antibiotic group, n = 23) vs those who did not (nonantibiotic group, n = 19). The overall survival in the two groups was not significantly different (log-rank test, \( P = 0.071 \)).

**Figure 2** Overall survival of patients with gastric fundal variceal bleeding who used proton pump inhibitors before admission (proton pump inhibitor group, n = 14) vs those who did not (non-proton pump inhibitor group, n = 28). The overall survival rate was significantly higher in the non-PPI than PPI group (Breslow test, \( P = 0.0074 \)). PPI: Proton pump inhibitor.
are lesser curve varices connecting to esophageal varices, which originate from the deep submucosal veins arising from the left gastric vein\cite{1,4,12,17}; gastric varices within the fundus are comparatively less common. Fundus varices originate from dilations of the short gastric and posterior gastric veins or direct anastomotic veins between the gastric and retroperitoneal veins, which are frequently associated with large gastrorenal shunts\cite{4,11}. Varices on the lesser curve can be treated by conventional injection sclerotherapy with generally satisfactory hemostatic results\cite{1,4,20}. In contrast, fundus varices require more complex treatments such as devascularization, shunting, splenectomy, transjugular intrahepatic portosystemic shunting, balloon-occluded retrograde transvenous obliteration, and endoscopic cyanoacrylate injection\cite{1,3,4,12,17}. Hence, GFV bleeding is a more serious condition associated with higher mortality than is lesser curve variceal bleeding\cite{1,4,14,18,19}. Determination of the prognostic factors associated with mortality of patients with GFV bleeding is thus very important and was the focus of the present study.

We found that prophylactic administration of antibiotics was an independent prognostic factor associated with a decrease in short- and long-term mortality of patients with GFV bleeding. Furthermore, the long-term overall survival rate tended to be higher in the antibiotic group than in the nonantibiotic group. Although several studies have determined the prognostic factors for mortality in patients with GFV bleeding\cite{4,20}, only a few studies have reported antibiotic therapy as a favorable prognostic factor. In some studies, bacterial infection in patients with cirrhosis who developed bleeding was associated with early mortality and failure to control bleeding\cite{21}, and antibiotic therapy prevented rebleeding of both esophageal varices\cite{22,23} and gastric varices\cite{22}. Goulis et al\cite{24} reported that bacterial infection has a close relationship with gastrointestinal bleeding and hypothesized that bacterial infection/endotoxemia triggers a cytokine cascade with release of vasoactive substances, thus increasing variceal pressure, impairing primary hemostasis, and inducing variceal bleeding. It has also been reported that bacterial infection is an independent clinical factor associated with failure of primary hemostasis of gastrointestinal bleeding and with early rebleeding\cite{25,26}. Hence, we conducted a subanalysis to determine the risk factors associated with GFV rebleeding. However, multivariate analysis showed that prophylactic administration of antibiotics was not associated with a risk of GFV rebleeding (data not shown). Prophylactic administration of antibiotics might play a role in improving the mortality of patients with GFV bleeding, independent of GFV rebleeding; further studies are necessary to clarify this.

We found that concurrent HCC and regular use of PPI were independent prognostic factors associated with an increase in short- and long-term mortality in patients with GFV bleeding. It is reasonable to expect...
concurrent HCC to negatively affect mortality. In general, patients with HCC present with more severe liver dysfunction and liver-related complications than those without HCC, leading to increased mortality in patients with concurrent HCC[27]. In contrast, we did not expect that regular use of PPI would be associated with increased mortality. PPI treatment is beneficial and recommended in patients with cirrhosis who undergo endoscopic band ligation for esophageal variceal bleeding[28]. However, regular use of PPI is associated with increased mortality in patients with cirrhosis[29]. In contrast, we did not expect that regular use of PPI would be associated with increased mortality. PPI treatment is beneficial and recommended in patients with cirrhosis who undergo endoscopic band ligation for esophageal variceal bleeding[28]. However, regular use of PPI is associated with increased mortality in patients with cirrhosis[29].

Additionally, PPI themselves might have direct adverse effects on patients with GFV bleeding. Further studies are required to clarify the effect of PPI on patients with GFV bleeding.

There are a few limitations to the present study. First, this was a retrospective study carried out in a single hospital. Second, because of the rarity of GFV bleeding, the study had a relatively small sample size despite a >14-year study period. We cannot deny the possibility that the study period affected the statistical analysis.

In conclusion, this study is the first to reveal that prophylactic administration of antibiotics to patients with GFV bleeding is significantly associated with a decrease in short-term mortality and that regular use of PPI before and after the onset of GFV bleeding is associated with an increase in both short- and long-term mortality. Large-scale prospective studies are required to determine whether the mortality of patients with GFV bleeding is actually reduced by the prophylactic administration of antibiotics and increased

Table 5 Baseline demographics and characteristics of patients in the proton pump inhibitors vs non-proton pump inhibitors group

| Parameters                                      | PPI group (n = 14) | Non-PPI group (n = 28) | P value |
|------------------------------------------------|-------------------|------------------------|---------|
| Sex ratio (F/M)                                | 6/8               | 7/21                   | 0.2980  |
| Mean age (yr)                                  | 61.9 ± 13.36      | 66.4 ± 10.53           | 0.2364  |
| History                                         |                   |                        |         |
| Smoking (presence/absence)                     | 8/6               | 13/15                  | 0.7442  |
| Alcohol (presence/absence)                     | 7/7               | 13/15                  | 1       |
| Disease conditions                              |                   |                        |         |
| Child-Pugh classification (A/B/C)               | 0/6/8             | 4/14/10                | 0.2122  |
| Hepatocellular carcinoma (presence/absence)    | 6/8               | 8/20                   | 0.4899  |
| Hepatic encephalopathy (presence/absence)      | 2/12              | 4/24                   | 1       |
| Form of gastric fundal varices (F2-F3/F1)       | 2/12              | 2/26                   | 0.5902  |
| Concurrent esophageal varices (presence/absence)| 7/7              | 23/5                   | 0.0666  |
| Previous treatment of GV (presence/absence)    | 0/14              | 1/27                   | 1       |
| Etiology of liver cirrhosis                    |                   |                        |         |
| Non-viral/viral                                 | 4/10              | 15/13                  | 0.1905  |
| Treatment of gastric fundal varices             |                   |                        |         |
| Success of initial treatment (success/failure)  | 12/2              | 27/1                   | 0.2537  |
| Antibiotics (presence/absence)                 | 8/6               | 15/13                  | 1       |
| Blood transfusion (presence/absence)           | 13/1              | 25/3                   | 1       |
| Medications before admission                   |                   |                        |         |
| NSAIDs (presence/absence)                      | 4/24              | 1/13                   | 0.6496  |
| Anticoagulants (presence/absence)              | 1/13              | 0/28                   | 0.3333  |
| Proton pump inhibitors (presence/absence)      | 14/0              | 0/28                   | <0.0001 |
| Blood test results                              |                   |                        |         |
| Hemoglobin (g/dL)                              | 8.65 ± 1.59       | 8.68 ± 1.99            | 0.4792  |
| Albumin (g/dL)                                 | 2.34 ± 0.39       | 2.64 ± 0.43            | 0.0314  |
| Bilirubin (mg/dL)                              | 2.00 ± 1.39       | 1.97 ± 1.48            | 0.5238  |

PPI group: patients with gastric fundal variceal (GFV) bleeding who were administered proton pump inhibitors; Non-PPI group: patients with GFV bleeding who did not receive proton pump inhibitors. *P < 0.05. NA: Not applicable; GV: Gastric varices; NSAIDs: Nonsteroidal anti-inflammatory drugs; PPI: Proton pump inhibitors.
REFERENCES
1. Sarin SK, Lahoti D, Saxena SP, Murthy NS, Makwana UK. Prevalence, classification and natural history of gastric varices: a long-term follow-up study in 568 portal hypertension patients. *Hepatology* 1992; 16: 1343-1349 [PMID: 1446800 DOI: 10.1002/hep.1840160607]
2. Hashizume M, Kitano S, Yamaga H, Koyanagi N, Sugimachi K. Endoscopic classification of gastric varices. *Gastrointest Endosc* 1990; 36: 276-280 [PMID: 2365213 DOI: 10.1016/S0016-5107(90)70103-1]
3. Akahoshi T, Hashizume M, Tomikawa M, Kawanaka H, Yamaguchi S, Konishi K, Kinjo N, Maehara Y. Long-term results of balloon-occluded retrograde transvenous obliteration for gastric variceal bleeding and risky gastric varices: a 10-year experience. *J Gastroenterol Hepatol* 2008; 23: 1702-1709 [PMID: 18713295 DOI: 10.1067/msh.2002.119501]
4. Kim T, Shijo H, Kokawa H, Tokumitsu H, Kubara K, Otta K, Akiyoshi N, Iida T, Yokoyama M, Okuda K. Portal hemodynamics in patients with gastric varices. A study in 230 patients with esophageal and/or gastric varices using portal vein catheterization. *Gastroenterology* 1988; 95: 434-440 [PMID: 3391371 DOI: 10.1016/0016-5085(88)90501-X]
5. Feretis C, Dinopoulos C, Benakis P, Kalliakmanis B, Apostolis N, N-butyl-2-cyanoacrylate (Histoacyrl) plus sclerotherapy versus sclerotherapy alone in the treatment of bleeding esophageal varices: a randomized prospective study. *Endoscopy* 1995; 27: 355-357 [PMID: 7588348 DOI: 10.1055/s-2007-1007113]
6. Huang YH, Yeh HZ, Chen GH, Chang CS, Wu CY, Poon SK, Lien HC, Yang SS. Endoscopic treatment of bleeding gastric varices by N-butyl-2-cyanoacrylate (Histoacyrl) injection: long-term efficacy and safety. *Gastrointest Endosc* 2000; 52: 160-167 [PMID: 10922085 DOI: 10.1067/mge.2000.104976]
7. Sarin SK, Sachdev G, Nanda R, Misra SP, Broor SL. Endoscopic sclerotherapy in the treatment of gastric varices. *Br J Surg* 1988; 75: 747-750 [PMID: 3263238 DOI: 10.1016/bjs.1800750809]
8. Sonomura T, Ono W, Sato M, Sahara S, Nakata K, Sanda H, Kawai N, Minamiguchi H, Nakai M, Kishi K. Emergency balloon-occluded retrograde transvenous obliteration of ruptured gastric varices. *World J Gastroenterol* 2013; 19: 5125-5130 [PMID: 23964147 DOI: 10.3748/wjg.v19.i31.5125]
9. Oh SH, Kim SJ, Rhee KW, Kim KM. Endoscopic cyanoacrylate injection for the treatment of gastric varices in children. *World J Gastroenterol* 2015; 21: 2719-2724 [PMID: 25759541 DOI: 10.3748/wjg.v21.i9.2719]
10. Rajorjya N, Tripathi D. Historical overview and review of current day treatment in the management of acute variceal haemorrhage. *World J Gastroenterol* 2014; 20: 6481-6494 [PMID: 24914369 DOI: 10.3748/wjg.v20.i21.6481]
11. Hosking SW, Johnson AG. Gastric varices: a proposed classification leading to management. *Br J Surg* 1988; 75: 195-196 [PMID: 3349325 DOI: 10.1016/bjs.1800750303]
12. Trudeau W, Prindiville T. Endoscopic injection sclerosis in bleeding gastric varices. *Gastrointest Endosc* 1986; 32: 264-268 [PMID: 3488937 DOI: 10.1016/S0016-5107(86)71843-9]
13. Chang CJ, Hou MC, Liao WC, Lee FY, Lin HC, Lee SD. Risk factors of early re-bleeding and mortality in patients with ruptured gastric varices and concomitant hepatocellular carcinoma. *J Gastroenterol* 2012; 47: 531-539 [PMID: 22223176 DOI: 10.1007/s00535-011-0518-3]
21 Vivas S, Rodriguez M, Palacio MA, Linares A, Alonso JL, Rodrigo L. Presence of bacterial infection in bleeding cirrhotic patients is independently associated with early mortality and failure to control bleeding. *Dig Dis Sci* 2001; 46: 2752-2757 [PMID: 11768269]

22 Hou MC, Lin HC, Liu TT, Kuo BI, Lee FY, Chang FY, Lee SD. Antibiotic prophylaxis after endoscopic therapy prevents rebleeding in acute variceal hemorrhage: a randomized trial. *Hepatology* 2004; 39: 746-753 [PMID: 14999693 DOI: 10.1002/hep.20126]

23 Hou MC, Chen WC, Lin HC, Lee FY, Chang FY, Lee SD. A new “sandwich” method of combined endoscopic variceal ligation and sclerotherapy versus ligation alone in the treatment of esophageal variceal bleeding: a randomized trial. *Gastrointest Endosc* 2001; 53: 572-578 [PMID: 11323581 DOI: 10.1067/mge.2001.114058]

24 Goulis J, Patch D, Burroughs AK. Bacterial infection in the pathogenesis of variceal bleeding. *Lancet* 1999; 353: 139-142 [PMID: 10023916 DOI: 10.1016/S0140-6736(98)06020-6]

25 Bernard B, Cadranel JF, Valla D, Escolano S, Jarlier V, Opolon P. Prognostic significance of bacterial infection in bleeding cirrhotic patients: a prospective study. *Gastroenterology* 1995; 108: 1828-1834 [PMID: 7768389 DOI: 10.1016/0016-5085(95)00146-9]

26 Goulis J, Armonis A, Patch D, Sabin C, Greenslade L, Burroughs AK. Bacterial infection is independently associated with failure to control bleeding in cirrhotic patients with gastrointestinal hemorrhage. *Hepatology* 1998; 27: 1207-1212 [PMID: 9581672 DOI: 10.1002/hep.510270504]

27 Petta S, Di Marco V, Bruno S, Enea M, Calvaruso V, Boccaccio V, Rossi S, Craxì A, Cannà C. Impact of virus eradication in patients with compensated hepatitis C virus-related cirrhosis: competing risks and multistate model. *Liver Int* 2016; 36: 1765-1773 [PMID: 27164508 DOI: 10.1111/liv.13156]

28 Shaheen NJ, Stuart E, Schmitz SM, Mitchell KL, Fried MW, Zacks S, Russo MW, Galanko J, Shrestha R. Pantoprazole reduces the size of postbanding ulcers after variceal band ligation: a randomized, controlled trial. *Hepatology* 2005; 41: 588-594 [PMID: 15726658 DOI: 10.1002/hep.20593]

29 Dultz G, Piiper A, Zeuzem S, Kronenberger B, Waidmann O. Proton pump inhibitor treatment is associated with the severity of liver disease and increased mortality in patients with cirrhosis. *Aliment Pharmacol Ther* 2015; 41: 459-466 [PMID: 25523381 DOI: 10.1111/apt.13061]

30 Min YW, Lim KS, Min BH, Gwak GY, Paik YH, Choi MS, Lee JH, Kim JJ, Koh KC, Paik SW, Yoo BC, Rhee PL. Proton pump inhibitor use significantly increases the risk of spontaneous bacterial peritonitis in 1965 patients with cirrhosis and ascites: a propensity score matched cohort study. *Aliment Pharmacol Ther* 2014; 40: 695-704 [PMID: 25078671 DOI: 10.1111/apt.12875]
