

## Retrospective Study

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

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**Institutional review board statement:** This study was reviewed and approved by the ethics committee of Aso Iizuka Hospital. It was conducted in accordance with the ethical principles of the Declaration of Helsinki and in compliance with good clinical practice.

**Informed consent statement:** This was a retrospective study using routinely collected data, and the results had no impact on the participants. Patients were not required to give informed consent for the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent. The information regarding this study has been posted on the website of Aso Iizuka Hospital at ([http://aih-net.com/shared/oshirase/rinri\\_201604-008.html](http://aih-net.com/shared/oshirase/rinri_201604-008.html)).

**Conflict-of-interest statement:** The authors declare no conflict of interest.

**Data sharing statement:** No additional data are available.

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Manuscript source: Unsolicited manuscript

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Received: September 23, 2016

Peer-review started: September 26, 2016

First decision: December 2, 2016

Revised: December 13, 2016

Accepted: December 21, 2016

Article in press: December 21, 2016

Published online: January 21, 2017

### Abstract

#### 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.

Komori K, Kubokawa M, Ihara E, Akahoshi K, Nakamura K, Motomura K, Masumoto A. Prognostic factors associated with mortality in patients with gastric fundal variceal bleeding. *World J Gastroenterol* 2017; 23(3): 496-504 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v23/i3/496.htm> DOI: <http://dx.doi.org/10.3748/wjg.v23.i3.496>

## INTRODUCTION

Gastric varices occur in 20% to 60% of patients with portal hypertension<sup>[1,2]</sup>, and the incidence of acute bleeding in patients with gastric varices reportedly ranges from 3% to 36%<sup>[2,3]</sup>. 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<sup>[1,4]</sup>. 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<sup>[1,2,4]</sup>. 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<sup>[5,6]</sup>.

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<sup>[7]</sup>. The guidelines of major gastrointestinal societies recommend the administration of short-term prophylactic antibiotics as standard treatment for all patients with cirrhosis who develop variceal bleeding, irrespective of the presence or absence of actual infection<sup>[8]</sup>. However, whether this treatment strategy should be applied to all patients with variceal bleeding remains unclear. In particular, whether prophylactic administration of antibiotics to patients with GFV bleeding is associated with a decreased risk of rebleeding and/or decreased mortality is controversial<sup>[7,9]</sup>.

We performed this retrospective study to identify the prognostic factors associated with mortality in patients with GFV bleeding and 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*<sup>[1]</sup>. 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

**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)	4/20/18
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	
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.

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.

### Ethical considerations

This study was reviewed and approved by the ethics committee of our hospital. It was conducted in accordance with the ethical principles of the Declaration of Helsinki and in compliance with good clinical practice.

## 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<sup>[10]</sup>; 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/ampicillin (*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-

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

Parameters	Univariate analysis				Multivariate analysis			
	$\beta$	<i>P</i> value	R	HR (95%CI)	$\beta$	<i>P</i> value	R	HR (95%CI)
Sex (F/M)	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 <sup>1</sup>	0.23	5.17 (1.28-20.8)	2.3041	0.0092 <sup>1</sup>	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 <sup>1</sup>	-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 <sup>1</sup>	-0.18	0.19 (0.04-0.94)	-2.5412	0.0086 <sup>1</sup>	-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 <sup>1</sup>	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 <sup>1</sup>	0.2	4.63 (1.15-18.53)	2.5465	0.0053 <sup>1</sup>	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)				

<sup>1</sup>*P* < 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.

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 2 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).

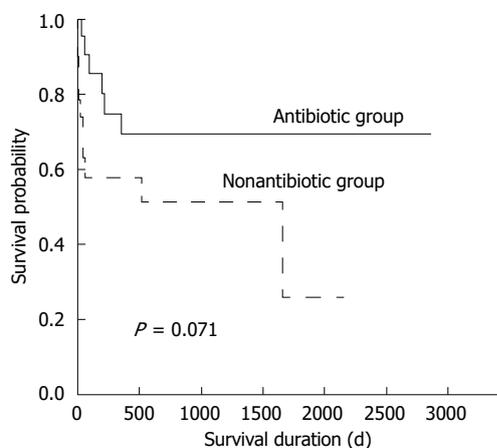
### Effects of regular PPI use on mortality in patients with GFV bleeding

We performed a subanalysis to assess whether regular PPI use was associated with increased mortality in

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

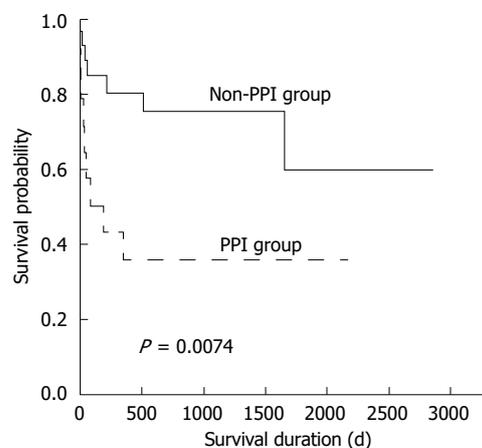
Parameters	Univariate analysis				Multivariate analysis			
	$\beta$	P value	R	HR (95%CI)	$\beta$	P value	R	HR (95%CI)
Sex (F/M)	0.1107	0.8404	0	1.12 (0.38-3.28)				
Age (yr)	0.0152	0.5056	0	0.98 (0.94-1.03)				
History								
Smoking	0.5678	0.3014	0	1.76 (0.60-5.18)				
Alcohol	0.3031	0.5591	0	1.35 (0.49-3.74)				
Disease conditions								
Child-Pugh classification (C/B/A)	0.9924	0.0366 <sup>1</sup>	0.15	2.70 (1.06-6.84)				
Hepatocellular carcinoma	1.8351	0.0013 <sup>1</sup>	0.29	6.27 (2.05-19.17)	2.0666	0.0035 <sup>1</sup>	0.26	7.89 (1.98-31.58)
Hepatic encephalopathy	0.5089	0.4391	0	1.66 (0.46-6.04)				
Form of GFV (F2 or F3/F1)	0.3475	0.7379	0	1.42 (0.18-10.85)				
Concurrent esophageal varices	-0.098	0.8596	0	0.91 (0.31-2.67)				
Etiology of liver cirrhosis (non-viral/viral)	-0.086	0.8688	0	0.92 (0.33-2.54)				
Treatment of GFV								
Success of initial treatment	-2.176	0.0081 <sup>1</sup>	-0.22	0.11 (0.02-0.57)				
Initial treatment (non-EIS/EIS/none)	0.0496	0.9356	0	1.05 (0.32-3.50)				
Antibiotics	-0.81	0.0512	-0.07	0.44 (0.16-1.25)	-1.3103	0.0341 <sup>1</sup>	-0.16	0.27 (0.08-0.91)
Blood transfusion	0.5432	0.6012	0	1.72 (0.22-13.18)				
Rebleeding after initial treatment	1.3669	0.0087 <sup>1</sup>	0.22	3.92 (1.41-10.89)				
Medications administered before admission								
NSAIDs	1.0131	0.0877	0.1	2.75 (0.86-8.81)	1.2391	0.1184	0.07	3.45 (0.73-16.35)
Proton pump inhibitors	1.4012	0.0084 <sup>1</sup>	0.22	4.06 (1.43-11.52)	2.3901	0.0005 <sup>1</sup>	0.32	10.91 (2.86-41.65)
Blood test results								
Hemoglobin (g/dL)	-0.062	0.6398	0	0.94 (0.72-1.22)				
Albumin (g/dL)	-1.081	0.0915	-0.09	0.34 (0.10-1.19)				
Bilirubin (mg/dL)	0.3065	0.0514	0.13	1.36 (0.99-1.85)	0.4224	0.0535	0.13	1.53 (0.99-2.34)

<sup>1</sup>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.



Antibiotic	23	17	17	17	17	17	17	Number at risk
Nonantibiotic	19	11	10	10	9	9	9	Number at risk

**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).



Non-PPI	28	23	22	21	21	21	21	Number at risk
PPI	14	5	5	5	5	5	5	Number at risk

**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.

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

**Table 4** Baseline characteristics of patients with gastric fundal variceal bleeding in the antibiotic vs nonantibiotic group

Parameters	Antibiotic group (n = 23)	Non-antibiotic group (n = 19)	P value
Sex ratio (F/M)	5/18	8/11	0.1925
Mean age (yr)	64.4 ± 13.07	65.47 ± 9.83	0.7673
History			
Smoking (presence/absence)	12/11	9/10	1
Alcohol (presence/absence)	12/11	8/11	0.5512
Disease conditions			
Child-Pugh classification (A/B/C)	2/13/8	2/7/10	NA
Hepatocellular carcinoma (presence/absence)	7/16	7/12	0.7483
Hepatic encephalopathy (presence/absence)	1/22	5/14	0.0754
Form of gastric fundal varices ( F2-F3/F1)	21/2	17/2	1
Concurrent esophageal varices (presence/absence)	17/6	13/6	0.7422
Previous treatment of GV (presence/absence)	0/23	1/18	0.4524
Etiology of liver cirrhosis			
Non-viral/viral	9/14	10/9	0.5347
Treatment of gastric fundal varices			
Success of initial treatment (success/failure)	22/1	17/2	0.5813
Antibiotics (presence/absence)	23/0	0/19	< 0.0001 <sup>a</sup>
Blood transfusion (presence/absence)	22/1	16/3	0.3129
Medications before admission			
NSAIDs (presence/absence)	2/21	3/16	0.6440
Anticoagulant (presence/absence)	0/23	1/18	0.4524
Proton pump inhibitors (presence/absence)	8/15	6/13	1
Blood test results			
Hemoglobin (g/dL)	8.97 ± 1.99	8.30 ± 1.63	0.2472
Albumin (g/dL)	2.56 ± 0.47	2.50 ± 0.39	0.6125
Bilirubin (mg/dL)	1.89 ± 1.41	2.09 ± 1.49	0.6616

Antibiotic group: patients with gastric fundal variceal (GFV) bleeding who were administered prophylactic antibiotics; Nonantibiotic group: patients with GFV bleeding patients who did not receive antibiotics. <sup>a</sup>P < 0.05. NA: Not applicable; GV: Gastric varices; NSAIDs: Nonsteroidal anti-inflammatory drugs.

are lesser curve varices connecting to esophageal varices, which originate from the deep submucosal veins arising from the left gastric vein<sup>[1]</sup>; 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 gastrosplenic shunts<sup>[4,11]</sup>. Varices on the lesser curve can be treated by conventional injection sclerotherapy with generally satisfactory hemostatic results<sup>[1,4]</sup>. 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<sup>[1,3,4,12-17]</sup>. Hence, GFV bleeding is a more serious condition associated with higher mortality than is lesser curve variceal bleeding<sup>[1,4,14,18,19]</sup>. 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<sup>[4,20]</sup>, 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<sup>[21]</sup>, and antibiotic therapy prevented rebleeding of both esophageal varices<sup>[22,23]</sup> and gastric varices<sup>[22]</sup>. Goulis *et al.*<sup>[24]</sup> 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<sup>[25,26]</sup>. 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

**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 <sup>a</sup>
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 <sup>a</sup>
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. <sup>a</sup>*P* < 0.05. NA: Not applicable; GV: Gastric varices; NSAIDs: Nonsteroidal anti-inflammatory drugs; PPI: Proton pump inhibitors.

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<sup>[27]</sup>. 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<sup>[28]</sup>. However, regular use of PPI is associated with increased mortality in patients with cirrhosis<sup>[29]</sup>. UK guidelines do not recommend prophylactic administration of PPI to all patients with cirrhosis who have a risk of variceal bleeding unless they have peptic ulcers, a condition associated with an increased risk of variceal bleeding<sup>[8]</sup>. Therefore, whether prophylactic PPI should be administered to patients with cirrhosis remains controversial. The present study provides more evidence that regular use of PPI should not be recommended to all patients with cirrhosis who are at risk of GFV bleeding; the PPI group had increased short- and long-term mortality rates and a significantly lower overall survival rate than did the non-PPI group. It is important to consider how regular PPI use increases the mortality of patients with GFV bleeding. One potential explanation is that regular use of PPI might increase the risk of

bacterial infection. In one study, regular use of PPI in patients with cirrhotic ascites was associated with an increased risk of spontaneous bacterial peritonitis<sup>[30]</sup>, and in another study, PPI treatment tended to be associated with the onset of bacterial infection<sup>[29]</sup>. 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

by regular PPI use.

## COMMENTS

### Background

Because gastric varices have greater blood flow than do esophageal varices, ruptured gastric varices can cause massive hemorrhage and are associated with high mortality. Therefore, it is important to determine the prognostic factors associated with mortality in patients with gastric fundal variceal (GFV) bleeding and the risk factors for GFV bleeding.

### Research frontiers

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 proton pump inhibitors before and after the onset of GFV bleeding is associated with an increase in both short- and long-term mortality.

### Innovations and breakthroughs

Antibiotic administration is associated with a decrease in short- and long-term mortality in patients with GFV bleeding.

### Applications

Administration of antibiotics may be applicable to patients with GFV bleeding, but regular use of proton pump inhibitors in patients with GFV may not.

### Terminology

Cyanoacrylate is a tissue adhesive agent that rapidly hardens upon contact with water. 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.

### Peer-review

This is a retrospective study analyzing the prognostic factors for gastric varices, a relatively unexplored area of research. The main limitation is the small number of patients enrolled; however, the results are promising.

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**P- Reviewer:** Garcia-Olmo D, Goenka MK **S- Editor:** Yu J

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ISSN 1007-9327

